MARROW ED8

Pathology

Comprehensive Question Bank

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Cellular Genetics, Adaptations and Injury

Question 1:

How many base pairs the human genome is made of?

a) 3.6 billion

b) 3.2 billion

c) 7.2 billion

d) 4.2 billion

Question 2:

Which of the following describes the non-coding regulatory RNAs?

a) Transcribed from protein-coding regions of DNA and translated to regulatory proteins

b) Transcribed from protein-coding regions of DNA but never translated

c) Transcribed from non-protein-coding regions of DNA and translated to regulatory proteins

d) Transcribed from non-protein-coding regions of DNA but never translated

Question 3:

What is the study of heritable changes in gene expression that are not caused by alterations in DNA sequence?

a) Genomics

b) Phylogenetics

c) Epigenetics

d) Molecular genetics

Question 4:

Micro-RNA are involved during which of the following stages?

a) Pre-transcriptional

b) Post transcriptional

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c) Post translational

d) Replication

Question 5:

Which of the following statements is false about microRNAs?

a) They are coding RNAs

b) They are involved in cell differentiation and carcinogenesis

c) Mature forms of microRNAs are single stranded

d) They can suppress tumor suppressor genes

Question 6:

What is the most common cause of cell injury?

a) Hypoxia

b) Immunologic reactions

c) Drug-induced

d) Nutritional imbalance

Question 7:

Which of the following statements is false?

a) Atrophy is a type of reversible cell injury

b) Plasma membrane blebbing occurs in reversible cell injury

c) On removal of stimulus, necrosis can be reversed

d) Chronic sublethal stimulus can cause cellular aging

Question 8:

Which among the following is not a feature of reversible cell injury?

a) Large amorphous densities in the mitochondria

b) Decrease in ATP generation

c) Swelling of the endoplasmic reticulum

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d) Detachment of ribosomes from granular ER

Question 9:

Which is the most important light microscopic feature of irreversible cell injury?

a) Amorphous densities in mitochondria

b) Cell membrane blebs and loss of microvilli

c) Ribosomal detachment from endoplasmic reticulum

d) Nuclear changes like pyknosis and karyolysis

Question 10:

Thrombosis is initiated by:

a) Platelet activation

b) Endothelial injury

c) Coagulation cascade

d) Vasoconstriction of vessels

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Question 11:

Which of the following statements about cellular adaptations is correct?

a) Hyperplasia involves synthesis of intracellular components

b) Atrophy is defined as decrease in cell size

c) Atrophy is the decrease in number and size of cells

d) Metaplasia is an irreversible replacement of a cell by another cell type

Question 12:

A patient with long-standing hypertension develops left ventricular hypertrophy. Which of the following transcription factors do not play a role in this?

a) GATA4

b) NFAT

c) MEF2

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d) HNF

Question 13:

How does myosin change during muscle hypertrophy?

a) From α-heavy chain to °-heavy chain

b) From °-heavy chain to α-heavy chain

c) From °-light chain to α-light chain

d) From α-light chain to °-light chain

Question 14:

Both physiological hyperplasia and hypertrophy are simultaneously seen in which of the following individuals?

a) A 24-year-old man vigorously training for an athletic race

b) A 35-year-old woman regularly taking combined oral contraceptive pills

c) A 50-year-old man with proliferation of liver cells following transplantation

d) A 24-year-old pregnant woman at 22 weeks of gestation

Question 15:

Which among the following do not usually undergo hyperplasia?

a) Skeletal muscle only

b) Skeletal and heart muscle

c) Heart and smooth muscle

d) Skeletal and smooth muscle

Question 16:

Which of the following is an example of physiological atrophy?

a) Atrophy of the legs of a bedridden patient

b) Atrophy of the arm muscles following a nerve injury

c) Muscle wasting in a child suffering from marasmus

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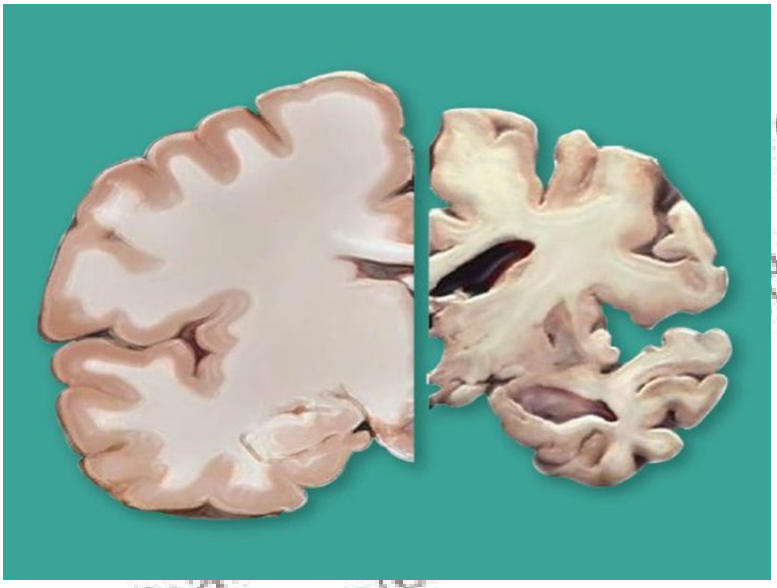
d) Uterine atrophy after delivery by Cesarean-section

Question 17:

The cross-section of the brain of an 84-year-old man with dyslipidemia is given below, in comparison with a normal brain. Which of the following is the most likely pathological change?



a) Malnutrition atrophy

b) Pressure atrophy

c) Denervation atrophy

d) Ischemic atrophy

Question 18:

Which of the following is the most common type of metaplasia?

a) Columnar to squamous epithelium

b) Squamous to columnar epithelium

c) Squamous to transitional epithelium

d) Columnar to transitional epithelium

Question 19:

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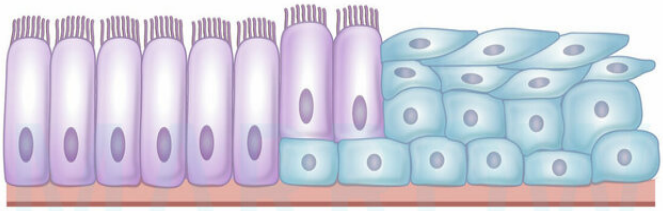
The lining epithelium of the respiratory tract of a middle-aged man who is a chronic smoker shows a change from columnar to stratified squamous epithelium, as depicted in the image below. The change is called:



a) Dysplasia

b) Hypertrophy

c) Atrophy

d) Metaplasia

Question 20:

Which of the following conditions is an example of connective tissue metaplasia?

a) Myositis ossificans

b) Dystrophic calcification

c) Atherosclerotic plaques

d) Keloid

Question 21:

Deficiency in which of the following vitamins can lead to metaplastic transformation in the lung?

a) Vitamin A

b) Vitamin B

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c) Vitamin C

d) Vitamin E

Question 22:

Anaplasia refers to:

a) Lack of differentiation

b) Variation in cell size and shape

c) Replacement of one type of cell by other

d) Disordered arrangement of tumor cells

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Answer Key

Question No.	Correct Option
1	b
2	d
3	c
4	b
5	a
6	a
7	c
8	a
9	d
10	b
11	c
12	d
13	a
14	d
15	b
16	d
17	d
18	a
19	d
20	a

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21	a
22	a

Detailed Explanations

Solution to Question 1:

The human genome is the complete set of nucleic acid sequences for humans and is made up of 3.2 billion base pairs.

It is encoded as DNA within the 23 chromosomes (haploid).

In 2007, a multinational project called Encyclopedia of DNA Elements (ENCODE) concluded that about 80% of the human genome does not code for the proteins. However, they allow for the binding of proteins or are involved in the regulation of gene expression, in a cell type-specific fashion. They are known as functional non-protein-coding genes.

Solution to Question 2:

The non-coding regulatory RNAs are the functional non-protein-coding regions of the DNA, which are transcribed to RNA but are never translated into proteins.

The two important types of non-coding regulatory RNAs are the micro RNA (miRNA) and the long non-coding RNAs (lncRNAs). These RNAs play an important role in the regulation of gene expression.

Solution to Question 3:

Epigenetics is the branch of molecular biology that deals with the study of heritable changes in gene function not involving changes in the DNA sequence.

These heritable changes involve factors that mediate processes such as:

• Histone organization

• DNA methylation

• Chromatin organization

These in turn regulate the genomic organization and gene expression in a cell-type-specific fashion. The dysregulation of these epigenomic factors plays a major role in the development of malignancy.

Green tea catechins have been reported to modulate epigenetic processes. They can reverse DNA methylation of tumor suppressor genes and increase the transcription of these genes.

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Solution to Question 4:

Micro-RNAs (miRNA) act during the post-transcriptional stage.

It is a type of non-coding RNA. The primary function of miRNA is to modulate the translation of target mRNAs into their corresponding proteins. After the target RNA is transcribed from its gene (post-transcriptional), the miRNA may either induce mRNA cleavage or repress its translation. This is referred to as gene silencing.

Small interfering RNAs (siRNAs) are short RNA sequences that can be introduced experimentally into cells. They have functions similar to endogenous miRNA (serve as substrates for the Dicer enzyme and interact with the RNA-induced silencing complex). They may have a therapeutic role in silencing certain oncogenes.

Solution to Question 5:

MicroRNAs (miRNAs) are small noncoding, single-stranded RNAs. They are approximately 22 nucleotides in length.

MicroRNAs mediate inhibition of messenger RNA (mRNA) translation through the action of the RNA-induced silencing complex (RISC). They control normal cell growth, differentiation, and cell survival. miRNA can be of 2 types:

• Tumour-suppressive miRNAs - decrease the translation of oncogenic mRNAs

• Onco-miRNAs - suppress tumor-suppressor genes

Other noncoding RNAs include:

• piwi-interacting RNAs (piRNAs) - involved in post-transcriptional gene silencing

• snoRNAs - involved in maturation of rRNA, assembly of ribosomes and noncoding RNAs

• lncRNAs - regulate the activity of chromatin 'writers', which modify histones and control gene expression

Solution to Question 6:

Hypoxia is the most common cause of cell injury.

Causes of cell injury include:

• Hypoxia

• Physical agents

• Chemical agents and drugs

• Infectious agents

• Immunologic reactions

• Genetic abnormalities

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• Nutritional imbalances

The mechanism of hypoxic cell injury is reduced oxidative respiration. The most common cause of hypoxia is ischemia.

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor with protective effects against hypoxic injury such as:

• Promotion of blood vessel formation

• Stimulation of cell-survival pathways

• Enhancement of anaerobic glycolysis

The cells most sensitive to hypoxia are neurons. The most sensitive neurons include:

• Pyramidal neurons of the hippocampus (especially, area CA1, also known as Sommer's sector)

• Cerebellar Purkinje cells

• Pyramidal neurons in the cerebral cortex

The cells most resistant to hypoxia are fibroblasts.

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Solution to Question 7:

On removal of stimulus, necrosis cannot be reversed. It is an irreversible cell injury.

Cellular adaptations are the reversible responses where the cells achieve an altered steady state in response to physiologic or some pathologic stimuli. They can be reversed if the stimulus causing stress or injury is removed. These cellular adaptations include:

• Hypertrophy

• Hyperplasia

• Atrophy

• Metaplasia

Chronic sublethal stimuli are unable to cause cell death but may lead to certain changes in cells, such as:

• Intracellular accumulations

• Pathological calcifications

• Cellular aging

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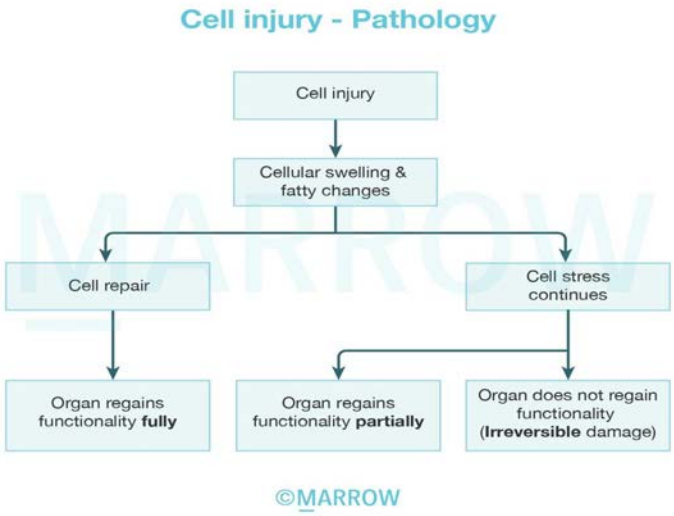

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Solution to Question 8:

Small amorphous densities are seen in the mitochondria in reversible cell injury.

The following changes occur in reversible cell injury:

- Cellular swelling - earliest change
- ATP depletion leads to sodium-potassium pump failure
- Na and water accumulate within the cell causing cellular swelling
- Fatty change -
- Seen in cells involved in or dependent on fat metabolism (liver hepatocytes and myocardial cells)
- Light microscopy - no noticeable changes
- Ultrastructural findings -
- Mitochondrial swelling and small amorphous densities
- Plasma membrane blebs
- Swelling of the endoplasmic reticulum (ER)
- Detachment of ribosomes from granular ER
- Nuclear changes like disaggregation of granular and fibrillar filaments

Note: The formation of large amorphous densities in the mitochondria is a feature of irreversible injury.

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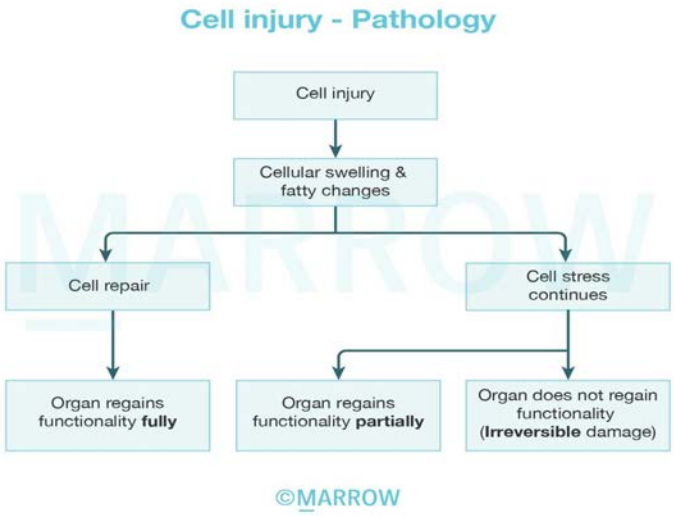

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Solution to Question 9:

Nuclear changes like pyknosis, karyorrhexis, and karyolysis are features of irreversible cell injury visible on light microscopy.

The ultrastructural findings visible on electron microscopy include:

- Large amorphous floccular densities in mitochondria
- Cell membrane blebs and loss of microvilli
- Ribosomal detachment from endoplasmic reticulum

Solution to Question 10:

Thrombosis is initiated by endothelial injury.

Thrombosis is is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system.

Three primary abnormalities, often referred to as Virchow triad, are known to induce thrombosis. They include:

- Endothelial injury - most important factor
- Stasis or turbulent blood flow
- Hypercoagulability of the blood

Solution to Question 11:

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Atrophy is a reduction in the size of an organ or tissue due to a decrease in cell size and number.

Cellular adaptations are reversible changes in the size, number, phenotype, metabolic activity, or functions of cells in response to changes in their environment. There are 4 types:

• Hypertrophy -

• Increase in organ size due to an increase in the size of cells

• Involves synthesis and assembly of intracellular structural components

• Hyperplasia -

• Increase in organ size due to an increase in the number of cells

• It is due to division and proliferation of stem cells

• Atrophy - reduction in organ size due to a decrease in cell size and number.

• Metaplasia - one differentiated cell type (epithelial or mesenchymal) is replaced by another cell type

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Solution to Question 12:

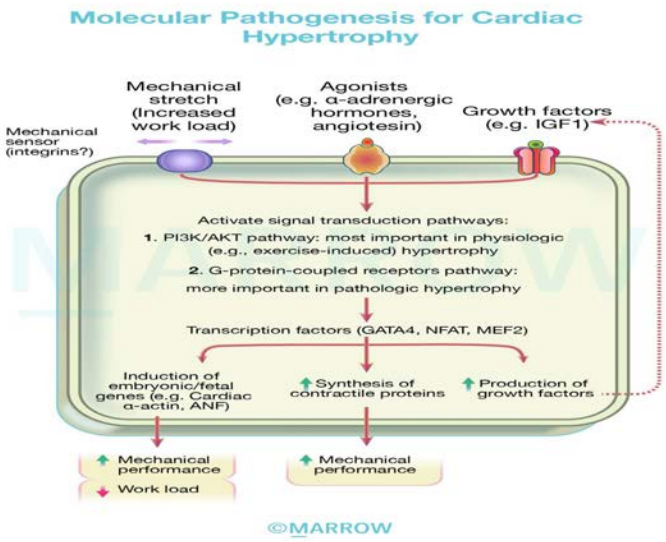
HNF is a transcription factor involved in the development of maturity-onset diabetes of the young (MODY), not the development of cardiac hypertrophy.

The transcription factors involved in cardiac muscle hypertrophy are:

• GATA4 – hypertrophic stimuli result in enhanced DNA-binding activity of GATA-4

• MEF2- increases due to pressure and volume overload

• NFAT (Nuclear Factor for Activated T-cells)



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Solution to Question 13:

During muscle hypertrophy, the α-isoform of the myosin heavy chain is replaced by the °-isoform. It produces slower and more energetically economic contraction.

During hypertrophy, there may occur a switch of contractile proteins from the adult isoforms to the fetal or infantile isoforms.

Solution to Question 14:

Physiological hypertrophy and hyperplasia can be simultaneously seen in the uterus during pregnancy.

In early pregnancy, uterine growth is due to hyperplasia of uterine smooth muscle cells; however, the predominant growth of the uterus during pregnancy occurs after mid-gestation, by way of stretch■induced myometrial hypertrophy.

Simultaneous physiological hypertrophy and hyperplasia also occur in the female breast during puberty and pregnancy.

Option A: Enlargement of skeletal muscles in athletes is an example of physiological hypertrophy.

Option B: Combined oral contraceptive pills causing endometrial hyperplasia is an example of pathological hyperplasia.

Option C: Following transplantation of a liver lobe, the remaining liver cells proliferate so that the organ grows back to its original size (compensatory hyperplasia).

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Solution to Question 15:

Skeletal muscle and heart muscle usually undergo hypertrophy, not hyperplasia.

Examples of physiologic hyperplasia:

• Female breast during puberty and pregnancy (hormonal hyperplasia)

• Uterine smooth muscle during early pregnancy

• Compensatory hyperplasia of liver cells after partial resection

Examples of pathologic hyperplasia:

• Endometrial hyperplasia

• Benign prostatic hyperplasia

Solution to Question 16:

Uterine atrophy following delivery is an example of physiological atrophy.

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Atrophy is defined as a reduction in the size of an organ or tissue due to a decrease in cell size and number.

The following mechanisms are involved in atrophy:

• Decreased protein synthesis due to decreased metabolic activity

• Increased destruction of proteins by the ubiquitin-proteasome pathway

The various types of atrophy are:

Stimulus/type of atrophy	Example
Physiologic atrophy	
Loss of hormonal stimulation	Atrophy of the uterus after p arturitionAtrophy of the end ometrium, vaginal epitheliu m, and breast after menopau se
During embryonic developme nt	Certain structures, like notoc hord and thyroglossal duct
Pathologic atrophy	
Disuse atrophy (decreased w orkload)	Atrophy in a limb that has be en immobilized following a fr acture
Denervation atrophy (loss of nerve supply)	Skeletal muscle atrophy follo wing nerve injury
Ischemic atrophy	Senile atrophy of the brain a nd heart due to atheroscleros is
Inadequate nutrition	Severe muscle wasting in ma rasmus
Pressure atrophy	Atrophy of surrounding unin volved tissues caused by an e nlarging benign tumor

Solution to Question 17:

The given image shows narrowing of gyri and widening of sulci in a senile brain, which is suggestive of senile atrophy. It is due to a gradual decrease in blood supply as a result of atherosclerosis, known as ischemic atrophy.

The various types of pathological atrophy are:

Pathologic atrophy	
Disuse atrophy (decreased w orkload)	Atrophy in a limb that has be en immobilized following a fr acture

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Pathologic atrophy	
Denervation atrophy (loss of nerve supply)	Skeletal muscle atrophy following nerve injury
Ischemic atrophy	Senile atrophy of the brain and heart due to atherosclerosis
Inadequate nutrition	Severe muscle wasting in marasmus
Pressure atrophy	Atrophy of surrounding uninvolved tissues caused by an enlarging benign tumor

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Solution to Question 18:

The most common type of metaplasia is squamous metaplasia, in which the normal columnar cells are replaced by squamous epithelial cells.

The table below shows various types of metaplasia:

GERD: Gastroesophageal reflux disease

Tissue	Metaplasia	Cause
Airways	Squamous metaplasia: Normal pseudostratified epithelium is replaced by the squamous epithelium.	Chronic smoking,Deficiency of retinoic acid
Urinary bladder	Squamous metaplasia: Normal transitional epithelium is replaced by squamous epithelium.	Bladder stones
Esophagus	Columnar metaplasia:Normal squamous epithelium is replaced by the glandular columnar epithelium(Barrett's esophagus)	Chronic GERD
Cervix	Squamous metaplasia: Normal glandular epithelium may be replaced by the squamous epithelium	Low pH of the cervix
Muscle	Connective tissue metaplasia: Formation of bone in the muscle tissue; (myositis ossificans)	Following intramuscular hemorrhage

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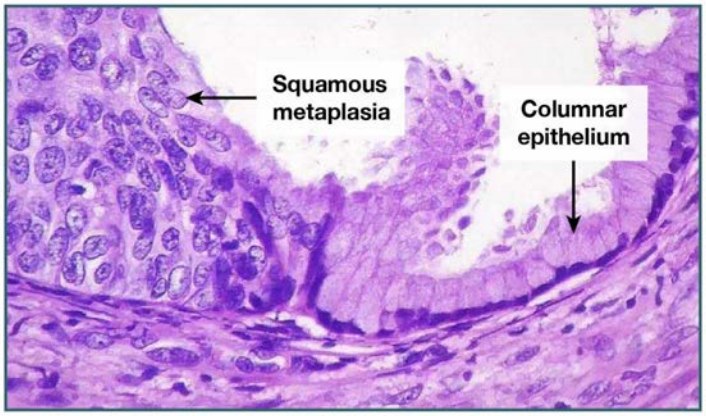
Squamous metaplasia



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Solution to Question 19:

The change described in the question is called metaplasia. It is defined as a reversible change in which one type of differentiated cell is replaced by another type.

The table below shows various types of metaplasia:

GERD: Gastroesophageal reflux disease

Tissue	Metaplasia	Cause
Airways	Squamous metaplasia: Normal pseudostratified epithelium is replaced by the squamous epithelium.	Chronic smoking,Deficiency of retinoic acid
Urinary bladder	Squamous metaplasia: Normal transitional epithelium is replaced by squamous epithelium.	Bladder stones
Esophagus	Columnar metaplasia: Normal squamous epithelium is replaced by the glandular columnar epithelium (Barret's esophagus)	Chronic GERD
Cervix	Squamous metaplasia: Normal glandular epithelium may be replaced by the squamous epithelium.	Low pH of the cervix
Muscle	Connective tissue metaplasia: Formation of bone in the muscle tissue; (myositis ossificans).	After intramuscular hemorrhage

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Solution to Question 20:

Myositis ossificans is an example of connective tissue metaplasia.

It refers to the formation of cartilage, bone, or adipose tissue (mesenchymal tissues) in tissues that normally do not contain these elements.

Myositis ossificans is characterised by bone formation within muscle tissue following traumatic injury to the area. However, this type of metaplasia is less clearly seen as an adaptive response.

Solution to Question 21:

The deficiency of vitamin A (retinoic acid) induces squamous metaplasia in the respiratory epithelium.

Solution to Question 22:

Anaplasia refers to a lack of differentiation.

The term anaplasia means to form backward implying a reversal of differentiation to a more primitive level. The extent to which neoplastic cells resemble normal cells, both morphologically and functionally, is called differentiation.

Anaplasia is an important morphological feature of malignant transformation.

The morphological features of malignancy include:

• Anaplasia

• Pleomorphism - variation in the size and shape of cells

• Increased N: C ratio (nucleus: cytoplasmic ratio) - around 1:4 in normal cells, increases to 1:1 in malignant cells

• Hyperchromasia - coarsely clumped and darkly stained chromatin within irregular nuclei

• Increased mitosis - atypical, bizarre mitotic figures

• Loss of polarity - sheets or large masses of tumor cells grow in an anarchic, disorganized fashion

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Cell Death

Question 1:

Which among the following is false regarding necrosis?

a) It is due to denaturation of protein

b) It is due to enzymatic digestion

c) It is an active process

d) There is swelling of cells

Question 2:

What is the correct sequence of events that occur during necrosis?

a) 1, 2, 3, 4

b) 1, 4, 3, 2

c) 2, 3, 4, 1

d) 4, 3, 2, 1

Question 3:

A 58-year-old man was admitted with sudden, substernal chest pain radiating to his left arm. On examination, he was diaphoretic and dyspneic with an irregular pulse. Despite resuscitative measures, he died within an hour of admission. Autopsy revealed the following gross appearance of the interventricular myocardium. Which of the following microscopic changes is most likely to be present?

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a) Liquefactive necrosis

b) Caseous necrosis

c) Fat necrosis

d) Coagulative necrosis

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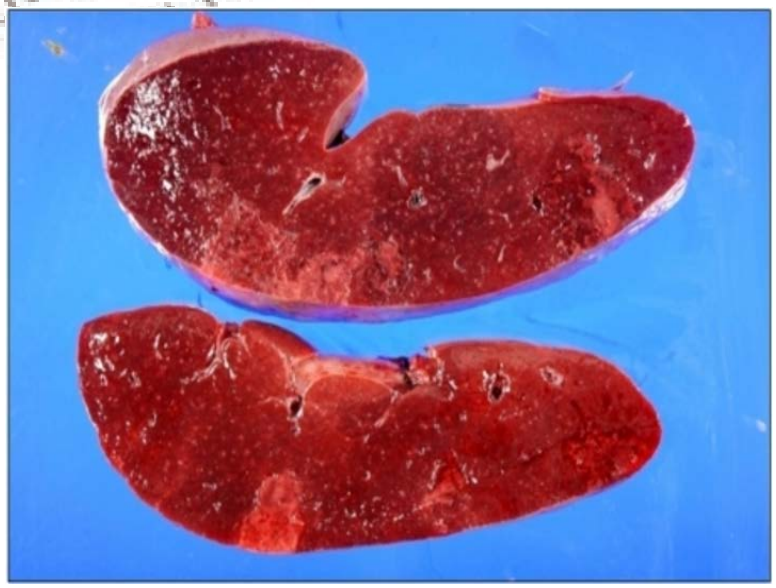
Question 4:

Which of the following is the most common cause of the following pathological change seen in the spleen?



a) Apoptosis

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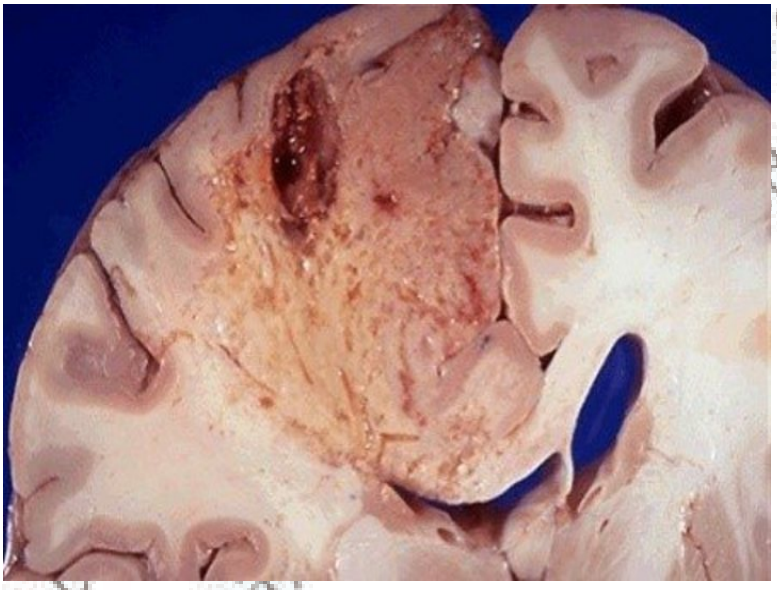
b) Embolization

c) Metastasis

d) Atherosclerosis

Question 5:

A 67-year-old woman died in the hospital 3 days after she was admitted with a sudden onset of right-sided weakness of her body, along with slurring of speech. An autopsy showed the following finding in the brain. What is this pathological change in this lesion?



a) Fibrinoid necrosis

b) Liquefactive necrosis

c) Caseous necrosis

d) Coagulative necrosis

Question 6:

The gross specimen of the pancreas from a patient who died of acute pancreatitis is shown below. What is it suggestive of?

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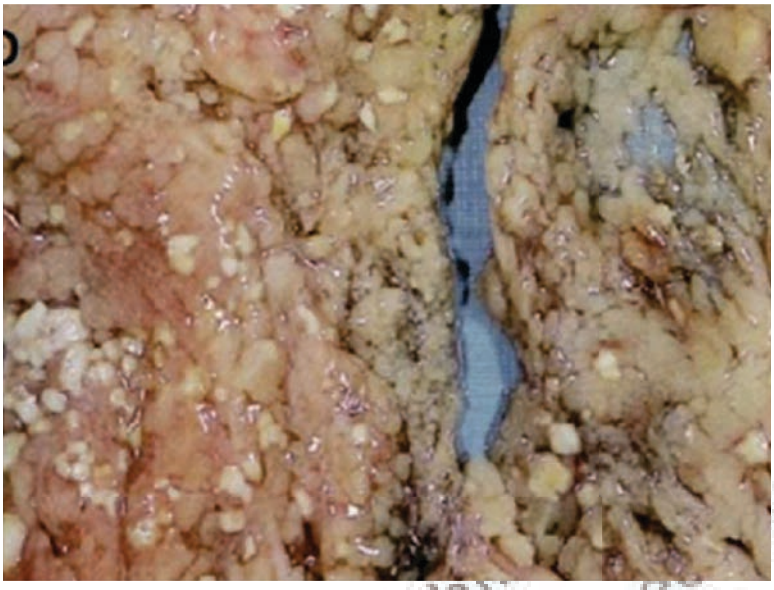

a) Coagulative necrosis

b) Caseous necrosis

c) Fibrinoid necrosis

d) Fat necrosis

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Question 7:

What is the type of necrosis seen in the vessel wall of a patient with polyarteritis nodosa?

a) Fibrinoid necrosis

b) Gangrenous necrosis

c) Fat necrosis

d) Caseous necrosis

Question 8:

Which of the following is involved in recognition and clearance of necrotic cells?

a) Inflammasome

b) Toll-like receptors (TLRs)

c) P selectin

d) Manoreceptor

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Question 9:

In cases of cell injury, all of the following are responsible for the increased eosinophilic staining and glassy homogenous cytoplasm except:

a) Loss of cytoplasmic RNA

b) Denatured protein

c) Increase in glycogen particles

d) Loss of glycogen particles

Question 10:

Which of the following is a true statement about apoptosis?

a) There is enzymatic digestion of cellular contents

b) It is associated with adjacent inflammation

c) Karyolysis is present

d) Plasma membrane remains intact

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Question 11:

Which of the following is not an example of physiological apoptosis?

a) Endometrial cell break-down during menstrual cycle

b) Apoptosis of Müllerian structures in male fetuses

c) Elimination of neutrophils after an acute inflammatory response

d) Atrophy in parenchymal organs following duct obstruction

Question 12:

Which of the following is not an anti-apoptotic protein?

a) BCL-XL

b) BAX

c) BCL- 2

d) MCL-1

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Question 13:

Which of the following is not a stress sensor of apoptosis?

a) Bim

b) Puma

c) Smac

d) Noxa

Question 14:

What are apoptotic bodies made up of?

a) Cytoplasm and organelles

b) Cytoplasm and nuclear fragments

c) Organelles and nuclear fragments

d) Cytoplasm, nuclear fragments and organelles

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Question 15:

Caspase cleaves proteins at:

a) Cysteine residue

b) Cystine residue

c) Aspartic acid residue

d) Asparagine residue

Question 16:

What is the function of FLIP protein in the pathway of apoptosis?

a) Stimulates the extrinsic pathway

b) Stimulates the intrinsic pathway

c) Inhibits the extrinsic pathway

d) Inhibits the intrinsic pathway

Question 17:

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Both intrinsic and extrinsic pathways are seen in:

a) Apoptosis

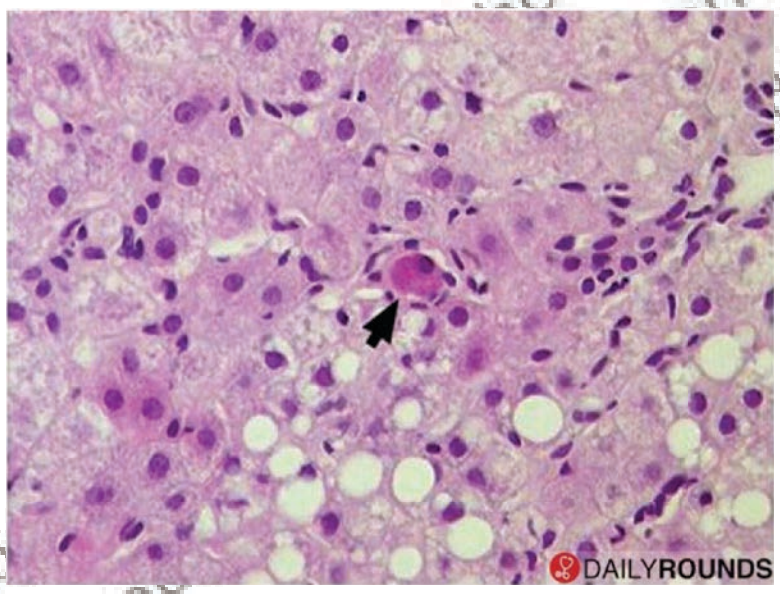
b) Necrosis

c) Necroptosis

d) Pyroptosis

Question 18:

Which of the following pathological changes is represented by the marked structure seen on histopathology of a liver specimen?



a) Apoptosis

b) Granuloma formation

c) Abscess formation

d) Coagulative necrosis

Question 19:

Which of the following features is not true about necroptosis?

a) It is a form of programmed cell death

b) It results in cell swelling

c) There is caspase activation

d) Reduced cellular ATP levels

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Question 20:

All of the following are true about pyroptosis except:

a) There is cell swelling

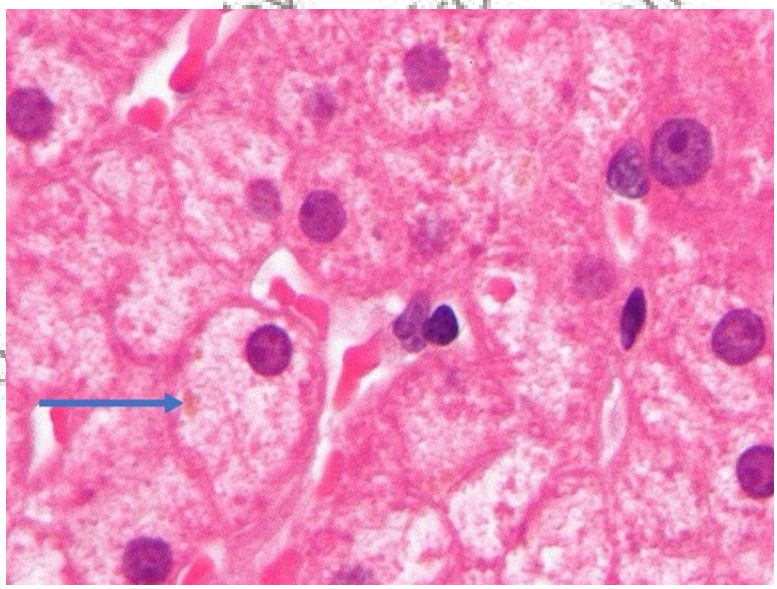
b) There is loss of membrane integrity

c) It is a form of programmed cell death

d) There is involvement of caspase 8

Question 21:

During the autopsy of a 90-year-old woman, a normal-looking liver was noted. The following microscopic appearance of hepatocytes was noted. Which of the following cellular mechanisms is likely responsible for this finding?



a) Nuclear pyknosis

b) Hypertrophy

c) Coagulative necrosis

d) Autophagocytosis

Question 22:

What is the most reliable marker for cellular autophagy?

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a) Atg5

b) RIP3

c) LC3

d) Annexin V

Question 23:

Which of the following forms of cell death is induced by lipid peroxidation?

a) Pyroptosis

b) Necroptosis

c) Ferroptosis

d) Programmed necrosis

Question 24:

Which of the following is not involved in efferocytosis?

a) Epithelial cell

b) Macrophage

c) Fibroblast

d) Free radicals

Question 25:

Which of the following diseases is not caused by an abnormal folded protein?

a) Alzheimer's disease

b) Huntington's disease

c) Parkinson's disease

d) Pompe disease

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Answer Key

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Question No.	Correct Option
1	c
2	b
3	d
4	b
5	b
6	d
7	a
8	a
9	c
10	d
11	d
12	b
13	c
14	d
15	c
16	c
17	a
18	a
19	c
20	d
21	d
22	c
23	c
24	d
25	d

Detailed Explanations

Solution to Question 1:

Necrosis is a passive process, not active.

It is due to denaturation of protein and enzymatic digestion.

Solution to Question 2:

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The sequence of events in necrosis is: cellular swelling → pyknosis → karyorrhexis → karyolysis

Necrosis is defined as the spectrum of morphological changes that follow cell death due to the progressive degradative action of enzymes.

Morphological changes that occur in necrosis are as follows:

Cytoplasmic changes -

• Increased eosinophilic staining on H&E specimens

• Moth-eaten appearance of the cytoplasm - due vacuolated cytoplasmic organelles formed by enzymatic degradation

• Glassy and homogenous cytoplasm - due to loss of glycogen in the cytoplasm

Nuclear changes -

• Pyknosis - nucleus first shrinks and becomes more condensed

• Karyorrhexis - fragmentation of the pyknotic nucleus

• Karyolysis - nucleus fades away leaving behind only the cell membrane or empty cells

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Solution to Question 3:

The given clinical scenario and image showing dead tissue are suggestive of myocardial infarction. It is characterized by coagulative necrosis.

In coagulative necrosis, despite cell death, the outline and architecture of the cells are preserved for a few days. This is because the cell injury is mainly due to the denaturation of all proteins, including the enzymatic proteins. This prevents the proteolysis of the dead cells. Ultimately, these necrotized cells are removed by phagocytosis and the lysosomal action of the enzymes of the leukocytes.

Examples of coagulative necrosis:

• Ischemic injury in all organs, except the brain

• Dry gangrene

Solution to Question 4:

The above image shows a pale, wedge-shaped area of infarction in the spleen.

An infarct is a region of ischaemic necrosis resulting from the obstruction of blood flow, typically due to occlusion of the arterial supply or venous drainage. The most common cause of solid organ infarts is thromboembolism.

The pattern of ischemic necrosis seen in solid organ infarction is coagulative necrosis. However, CNS infarctions are an exception. They cause liquefactive necrosis.

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Solution to Question 5:

This clinical scenario is suggestive of a stroke, which results in ischemic injury to the brain. This results in liquefactive necrosis.

Liquefactive necrosis refers to cell death by enzymatic degradation. The brain contains microglial cells, which contain many enzymes. When these cells are broken down, they release these enzymes, resulting in liquefactive necrosis.

The various types of necrosis are as follows:

Type	Example
Coagulative necrosis	Infarcts in all organs except t he brain
Caseous necrosis	Tuberculosis
Liquefactive necrosi s	AbscessesBrain infarctWet ga ngrene
Fat necrosis	Pancreatitis, Breast
Fibrinoid necrosis	VasculitisAschoff bodiesMali gnant hypertension

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Solution to Question 6:

The given specimen shows yellow nodules with areas of chalky-white deposits, which are suggestive of fat necrosis.

Fat necrosis results from the release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. These enzymes act on surrounding tissue to release fatty acids, which then combine with calcium to produce grossly visible chalky-white areas (fat saponification).

Histologic examination reveals foci of shadowy outlines of necrotic fat cells, with basophilic calcium deposits, surrounded by an inflammatory reaction.

The various types of necrosis include:

Type	Example
Coagulative necrosis	Infarcts in all organs except t he brain
Caseous necrosis	Tuberculosis
Liquefactive necrosi s	AbscessesBrain infarctWet ga ngrene
Fat necrosis	Pancreatitis, Breast
Fibrinoid necrosis	VasculitisAschoff bodiesMali gnant hypertension

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Solution to Question 7:

Immune reactions involving blood vessels, as seen in the case of polyarteritis nodosa, usually show fibrinoid necrosis. Fibrinoid means fibrin-like.

In some immune disorders, the antigen-antibody complexes get deposited in the blood vessels. These complexes result in complement activation (type III hypersensitivity) leading to cell injury. This leads to leakage of fibrin out of the blood vessel, giving a pinkish appearance around the blood vessels.

Fibrinoid necrosis is seen in the following conditions:

- SLE
- Libman-sacks endocarditis
- Arthus reaction
- Serum sickness
- Polyarteritis nodosa
- Post-streptococcal glomerulonephritis
- Malignant hypertension

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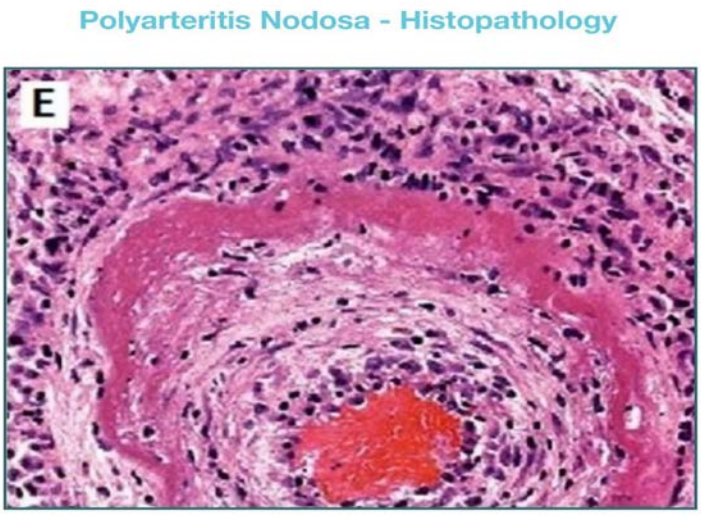

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Solution to Question 8:

Inflammasomes are involved in the recognition and clearance of necrotic cells.

Inflammasomes are involved in pyroptosis, a process of programmed cell death distinct from apoptosis and necrosis. This process is dependent on caspases 1, 4, and 5 and is responsible for killing of infected cells. It occurs in the following sequence:

• Activation of inflammasome complex by infected cells

• This causes activation of caspase-1

• This results in generation of IL-1, which is responsible for fever, inflammation, leukocyte recruitment

Option B: Toll-like receptors (TLR)- recognizes molecules shared by pathogens

Option C: P-selectins - an important role in the initial recruitment of WBCs at the site of inflammation & in platelet recruitment and aggregation at the site of injury.

Solution to Question 9:

In cell injury, there is a loss of glycogen, which leads to a change in cytoplasmic appearance. An increase in glycogen particles is not a feature of cell injury.

In cell injury, the following changes are seen in the cytoplasm:

• Increased eosinophilic staining due to -

• Increase in denatured proteins (which bind to acidic dyes like eosin)

• Loss of cytoplasmic RNA (nucleic acids bind to basic dyes like hematoxylin)

• Glassy, homogeneous appearance - due to loss of glycogen particles

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• Moth-eaten appearance - vacuolated appearance due to enzymatic digestion of cytoplasmic organelles

Solution to Question 10:

The plasma membrane remains intact in apoptosis.

Apoptosis literally means falling-off in Greek. It is a pathway of programmed cell death.

Apoptotic cells break up into fragments called apoptotic bodies. These apoptotic bodies have intact plasma membrane but altered structures. Hence, they are subjected to phagocytosis without eliciting inflammation.

Necrosis is an unprogrammed form of cell death that includes:

• Enzymatic digestion

• Adjacent inflammation

• Karyolysis

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Solution to Question 11:

Atrophy in parenchymal organs after duct obstruction is a pathological cause of apoptosis.

Physiological causes of apoptosis:

• During embryogenesis - Müllerian inhibiting factor causing apoptosis of the Mullerian structures in the male fetus

• Hormone-dependent apoptosis -

• Endometrial cell breakdown during the menstrual cycle

• Regression of the lactating breast after weaning.

• Cell loss in proliferating cell populations - turnover of cells of intestinal crypt epithelium

• Elimination of neutrophils after an acute inflammatory response and lymphocytes at the end of an immune response

Pathological causes of apoptosis:

• DNA damage beyond repair

• Accumulation of misfolded proteins leads to endoplasmic reticulum stress

• Cell injury in certain viral infections (e.g., Councilman bodies in viral hepatitis)

• Pathologic atrophy after duct obstruction in parenchymal organs like pancreas, parotid gland, and kidneys

Solution to Question 12:

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BAX and BAK are pro-apoptotic proteins.

They get inserted into the mitochondrial membrane and result in the formation of channels. This allows proteins from the inner mitochondrial membrane to leak out into the cytoplasm.

On the other hand, antiapoptotic proteins of the BCL2 family, like BCL-2 and BCL-XL limit the escape of proapoptotic mitochondrial proteins.

Solution to Question 13:

Smac, also known as Diablo is not a stress sensor of apoptosis. It is a proapoptotic protein that initiates the caspase cascade by neutralizing IAPs (physiological inhibitors of apoptosis).

Solution to Question 14:

Apoptotic bodies are made up of cytoplasm with tightly packed organelles, and nuclear fragments.

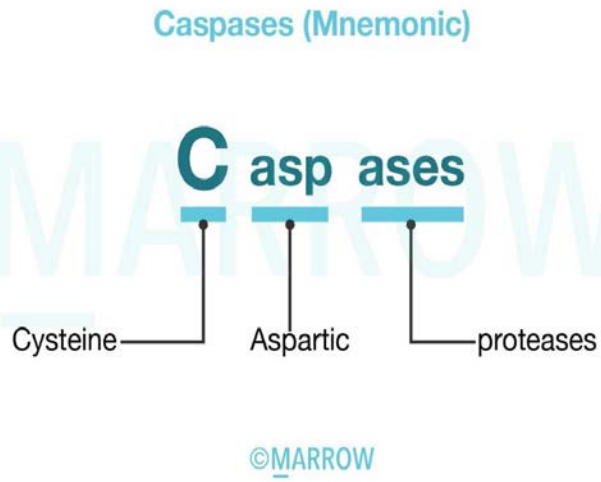
During apoptosis, extensive plasma membrane blebbing occurs, followed by cell fragmentation into apoptotic bodies by a process called budding.

In apoptotic cells, phosphatidylserine, which is normally present on the inner leaflet of the plasma membrane, flips to the outer leaflet. Hence, it gets recognized by tissue macrophages and leads to phagocytosis of the apoptotic bodies.

Annexin V is a marker of apoptosis.

Solution to Question 15:

Caspases are cysteine proteases that cleave proteins at the aspartic acid residue. Hence, the activation of caspases plays a key role in the process of apoptosis.



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The activation of caspases depends on a finely tuned balance between production of pro- and anti-apoptotic proteins.

Two distinct pathways converge on caspase activation:

• The mitochondrial (intrinsic) pathway

• The death receptor (extrinsic) pathway

Solution to Question 16:

FLIP is a cellular protein that inhibits the extrinsic pathway of apoptosis.

It is a caspase antagonist that inhibits the activation of caspases involved in the extrinsic or death receptor pathway. Some viruses produce homologs of this protein. This may play a role in keeping infected cells alive.

There are two pathways that can lead to caspase activation and cause apoptosis of the cell.

APAF-1 - Apoptotic peptidase activating factor-1

TNF - Tumor necrosis factor

Mitochondrialorintrinsicpathway	Death receptororextrinsicpathway
Activation inside the cell	Activation outside the cell
Occurs in response to:DNA damageRadiationInfection	Involved in:Elimination of self-reactive lymphocytesKilling of target cells by cytotoxic T-cells
Involves release of pro-apoptotic proteins (BAX, BAK)They form aBAX-BAKchannel in the mitochondrial membrane	Involves death receptors on cell surfaces (have a death domain)These includeTNF-1and Fas(CD95) of the TNF family
Leakage ofcytochrome-cresults in the formation of Cyt.c-APAF1 complex, followed byapoptosomeformation	FasLon T-cells binds to Fas bind adapter proteins via death domain
Activation ofcaspase 9	Activation ofcaspases 8and10
Both pathways converge into a common pathway that involves the activation of caspases 3, 6, 7 (executioner caspases)	

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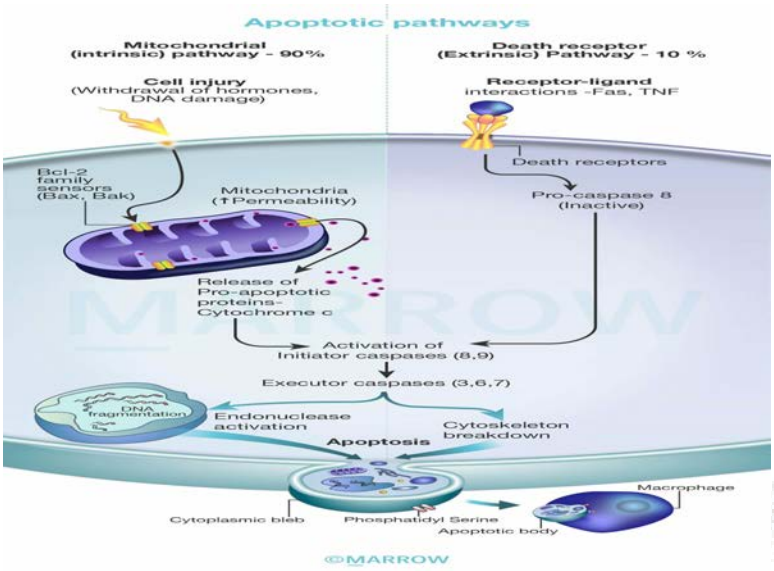

Solution to Question 17:

Intrinsic and extrinsic pathways are both seen in apoptosis.

Apoptosis has two pathways:

APAF-1 - Apoptosis activating factor-1

TNF - Tumor necrosis factor

Mitochondrialorintrinsicpathway	Death receptororextrinsicpathway
Activation inside the cell	Activation outside the cell
Occurs in response to:DNA damageRadiationInfection	Involved in:Elimination of self-reactive lymphocytesKilling of target cells by cytotoxic T-cells
Involves release of pro-apoptotic proteins (BAX, BAK)They form aBAX-BAKchannel in the mitochondrial membrane	Involves death receptors on cell surfaces (have a death domain)These includeTNF-1and Fas(CD95) of the TNF family
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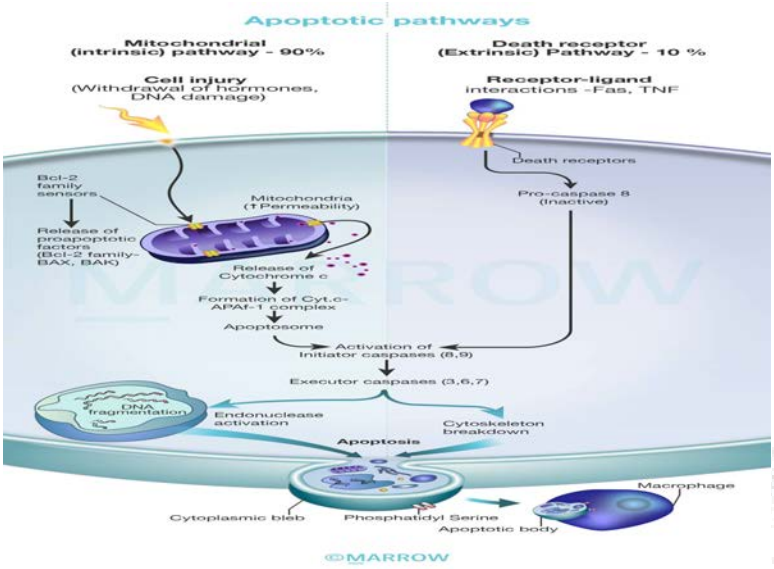

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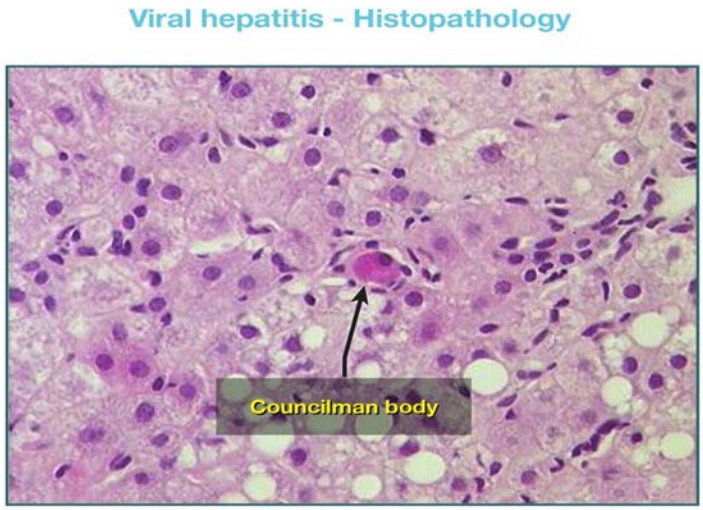
Solution to Question 18:

The above histopathological image shows Councilman or acidophil bodies. They represent hepatocytes undergoing apoptosis.

Councilman bodies are commonly seen in acute viral hepatitis.



Solution to Question 19:

Caspase activation does not occur in necroptosis. It is a caspase-independent form of programmed cell death.

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Necroptosis is a programmed form of necrosis (which is normally an unprogrammed process). Though the activation of this pathway is similar to apoptosis, there is no activation of caspases, which is an important part of apoptosis.

Necroptosis is triggered by the activation of TNFR1 by TNF-α. This induces the recruitment of RIP1 and RIP3 kinase and the formation of a necrosome. The necrosome reduces cellular ATP levels.

Necroptosis occurs in the following conditions:

• Pathological - ischemic brain injury, neurodegenerative diseases, viral infections

• Physiological - formation of the mammalian bone growth plate

The following table lists the differences between apoptosis and necroptosis:

Feature	Apoptosis	Necroptosis
Induction stimuli	Oxidative stress, death recept or ligands, chemotherapy	Viral or chemical exposure, r adiation, endogenous or path ological factors
Morphological chan ges	Nuclear pyknosis, membrane blebbing, generation ofapopt oticbodies	Swelling of cellsand organelle s, loss of membrane integrity
Molecular changes	Cleavage of caspases, DNA fr agmentation	Acidosis, random DNA degra dation, release of cellular pro teins
Clearance	Apoptotic bodies phagocytos ed by neighboring cells and macrophages	Necrotic cells ingested by ma crophages, significant inflam mation

Solution to Question 20:

Caspases 1, 4, and 5 are involved in pyroptosis, not caspase 8.

Pyroptosis is a form of programmed cell death that is different from apoptosis and necrosis. It is involved in the clearance of necrotic and microbe-infected cells. It occurs in the following sequence:

• Activation of the inflammasome complex

• Activation of caspase-1

• Generation of IL-1 - results in fever, inflammation, leukocyte recruitment

Pyroptosis differs from apoptosis by the following features:

• There is cellular swelling

• There is loss of cell membrane integrity

• It is associated with inflammation

• Caspases 1, 4, and 5 are involved

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Solution to Question 21:

The given image shows brownish lipofuscin granules within the liver cells. It is composed of lipid-containing residues of lysosomal digestion that are formed due to autophagocytosis.

Lipofuscin is a wear-and-tear pigment that is due to free radical injury to the tissue. It is prominent in the liver and heart of aging patients or patients with severe malnutrition and cancer cachexia.

Autophagy is a process by which the cell consumes itself. It involves the sequestration of cellular organelles into cytoplasmic autophagic vacuoles (autophagosomes) that fuse with lysosomes, resulting in the digestion of the enclosed material. It occurs in the following conditions:

• As a survival mechanism during nutrient deprivation and stress conditions

• Cancers, inflammatory bowel diseases, neurodegenerative disorders - due to dysregulation

Solution to Question 22:

Microtubule-associated protein light chain 3 (LC3) is a reliable marker for cellular autophagy.

There is increased synthesis of this molecule during autophagy. LC3 plays a role in elongation and closure of the autophagosomal membrane.

Autophagy (self-eating) is the process in which the starved cell eats its own components in an attempt to reduce nutrient demand to match the supply.

Option A: Atg5 protein, although associated with autophagy, is not a reliable marker as there is no differential expression during autophagy initiation.

Option B: RIP3 (receptor associated kinase 3) is a unique kinase involved in necroptosis.

Option D: Annexin V is a marker for cellular apoptosis.

Solution to Question 23:

Ferroptosis is an iron-dependent pathway of cell death that is induced by lipid peroxidation.

It is triggered by an increase in membrane lipid peroxidation in response to the following signals:

• Excessive intracellular levels of iron

• Reactive oxygen species (ROS)

This leads to a loss of selective permeability of the plasma membrane, which ultimately leads to cell death. Unlike necrosis, the process is regulated by specific signals and can, therefore, be prevented by reducing iron levels.

Ferroptosis has been linked to cell death in a variety of human pathologies including:

• Cancer

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• Neurodegenerative diseases

• Stroke

Other forms of cell death that are not dependent on lipid peroxidation include:

• Necroptosis or programmed necrosis - programmed cell death without caspase activation

• Pyroptosis - programmed cell death that is dependent on caspases 1, 4, and 5

Solution to Question 24:

Efferocytosis is a specialized type of phagocytosis, where apoptotic bodies are phagocytosed with the help of macrophages, epithelial cells, and fibroblast cells.

During this process, ligands bind to the apoptotic bodies and send 'eat me' signals. These signals are recognized by receptors present on phagocytes that bind and engulf these cells.

Solution to Question 25:

Pompe disease is a glycogen storage disorder caused by the deficiency of lysosomal acid alpha glucosidase enzyme. It is not due to abnormal folded proteins.

During normal protein synthesis, chaperones in the endoplasmic reticulum (ER) control the proper folding of newly synthesized proteins. Misfolded polypeptides are ubiquitinated and targeted for proteolysis.

Sometimes, unfolded or misfolded proteins accumulate in the ER as a result of inherited mutations or environmental stress. This induces a protective response called the unfolded protein response that increases the production of chaperones. This reduces the levels of misfolded proteins in the cell.

However, when the accumulation of misfolded proteins overwhelms these adaptations, it results in ER stress which leads to the activation of caspases and, ultimately, apoptosis.

Some diseases that occur due to the accumulation of abnormal folded proteins are:

• Alzheimer's disease

• Huntington's disease

• Parkinson's disease

• Prion diseases

• Amyotrophic lateral sclerosis

• Tay-Sachs disease

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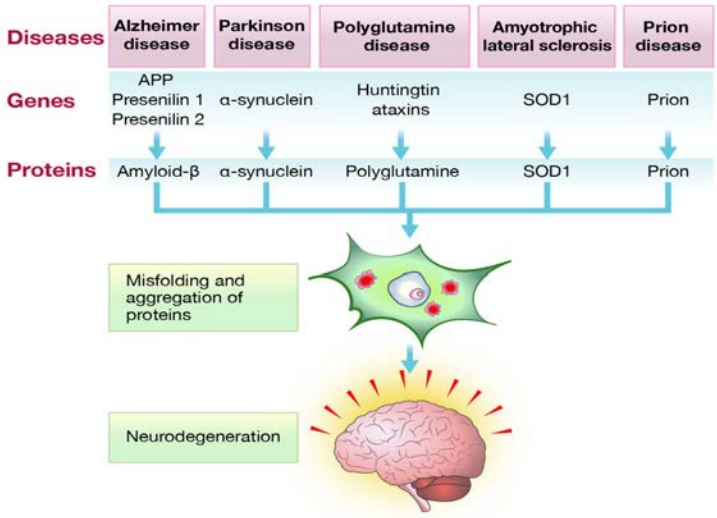

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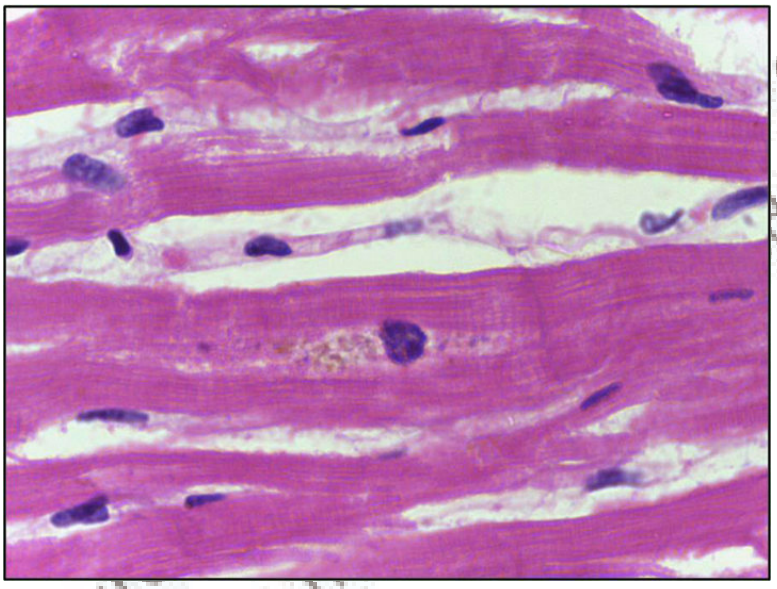
Intracellular Accumulations, Pathological Calcification and Cellular Ageing

Question 1:

The following finding was noted on the cardiac tissue specimen of an 82-year-old man. Which of the following is false about the given finding?



a) It is a tell-tale sign of free radical injury

b) It is injurious to the cell and its function

c) It is derived through lipid peroxidation

d) It can also be seen in liver of aging patients

Question 2:

A pathologist is examining a liver biopsy specimen from a patient with liver disease. The following finding is noted. Which of the following is the most likely cause of this finding?

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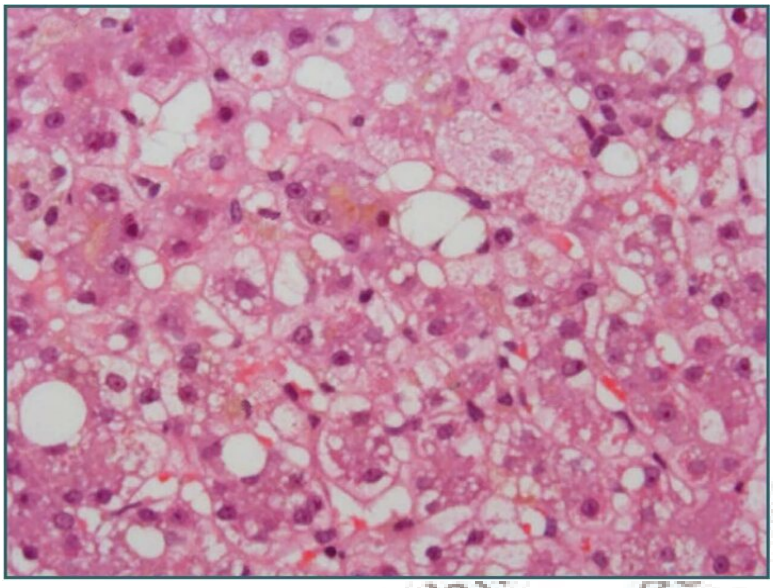

a) Atherosclerosis

b) Hepatitis B

c) Alcoholism

d) Hemolysis

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Question 3:

Which of the following conditions are associated with the intracellular accumulation of cholesterol and cholesterol esters?

a) 1, 2, 5

b) 1, 2, 4

c) 1, 3, 5

d) 2, 3, 4

Question 4:

A 60-year-old male patient presented with backache. Urine examination revealed nephrotic range proteinuria with Bence-Jones proteins. Laboratory reports showed hypercalcemia. Histopathological examination of the bone marrow aspirate showed the findings as given below. The findings seen on histopathology are due to the accumulation of:

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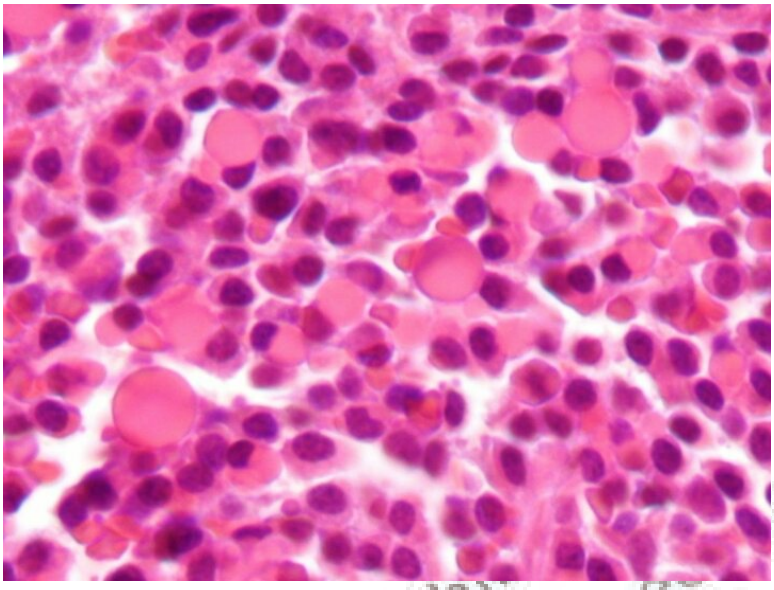

a) Cholesterol

b) Immunoglobulins

c) Lipoproteins

d) Neutrophils

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Question 5:

A 36-year-old man with a history of chronic alcoholism presented with increasing abdominal girth and malaise. On examination, shifting dullness was present and the liver span was 6 cm. Histopathological examination revealed the presence of intracytoplasmic eosinophilic inclusions in hepatocytes. What is the content of these inclusions?

a) Fibronectin filament

b) Keratin filament

c) Desmin filament

d) Vimentin filament

Question 6:

An elderly man diagnosed with squamous cell carcinoma of the lung underwent surgical resection. Histopathological examination of the resected hilar lymph nodes revealed the following finding as given below. Which of the following is the most likely cause for this?

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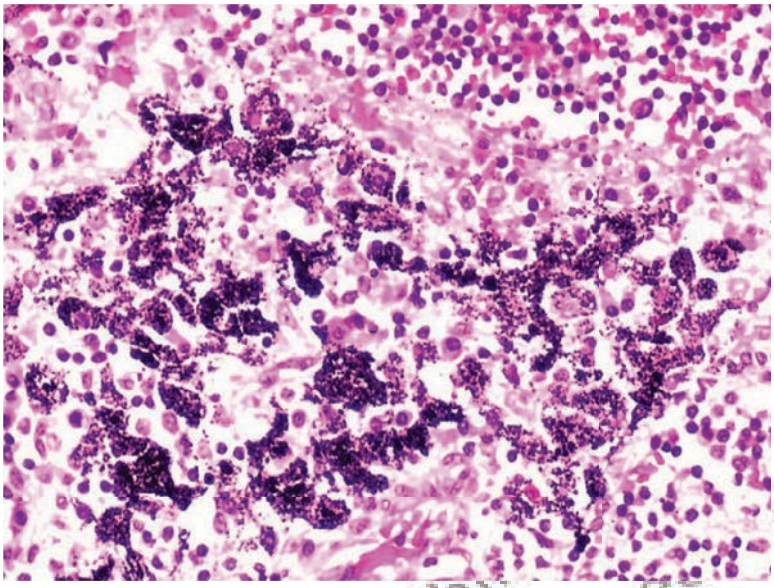

a) Anthracotic pigmentation

b) Metastatic carcinoma

c) Hemosiderosis

d) Accumulation of melanin

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Question 7:

A 58-year-old man died 24 hours after the onset of substernal chest pain radiating to the left arm. On autopsy, an atheromatous plaque was seen obstructing the left anterior descending artery. Which type of calcification is most likely to be seen in this condition?

a) Dystrophic with increased serum calcium

b) Metastatic with increased serum calcium

c) Dystrophic with normal serum calcium

d) Metastatic with normal serum calcium

Question 8:

In which of the following patients would you not expect metastatic calcification?

a) A 55-year-old man with Paget's disease

b) A 75-year-old woman suffering from multiple myeloma

c) A 39-year-old woman diagnosed with sarcoidosis

d) A 60-year-old man with pulmonary tuberculosis

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Question 9:

Which of the following stains is not used in the detection of calcium in tissues?

a) Congo red

b) Von Kossa stain

c) Alizarin Red S

d) Azan stain

Question 10:

Which of the following stains is used for staining melanin?

a) Verhoeff's method

b) Gomori methamine silver stain

c) Masson–Fontana stain

d) Masson trichrome stain

Question 11:

Which of the following is responsible for an increased incidence of cancer in old age?

a) Telomerase reactivation

b) Loss of telomeres

c) Telomerase deactivation

d) Excess shortening of telomeres

Question 12:

Which of the following is false regarding sirtuins?

a) Reduce apoptosis

b) Reduce insulin sensitivity

c) Stimulate protein folding

d) Increased by caloric restriction

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Question 13:

Which fixation technique is used for fat in the histopathological examination?

a) IHC

b) Frozen section

c) Liquid paraffin

d) Formalin fixed

Question 14:

A 56-year-old diabetic male presented with arthralgia and skin pigmentation. On examination, he was found to have hepatomegaly, arthropathy involving small joints, excessive skin pigmentation with a characteristic slate-grey hue, and hypogonadism. As a part of the work-up, liver biopsy was done. Which of the following stains should be used for staining the biopsy specimen?

a) Luxol fast blue stain

b) Toluidine blue stain

c) Alcian blue stain

d) Perls' Prussian blue stain

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Question 15:

A 34-year-old woman is undergoing evaluation for premature cataracts, thinning of skin, alopecia, osteoporosis, and atherosclerosis. She is found to have a hereditary genetic mutation in the WRN gene. This gene encodes which of the following proteins?

a) Deaminase

b) Helicase

c) Oxidase

d) Polymerase

Answer Key

Question No.	Correct Option

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1	b
2	c
3	d
4	b
5	b
6	a
7	c
8	d
9	a
10	c
11	a
12	b
13	b
14	d
15	b

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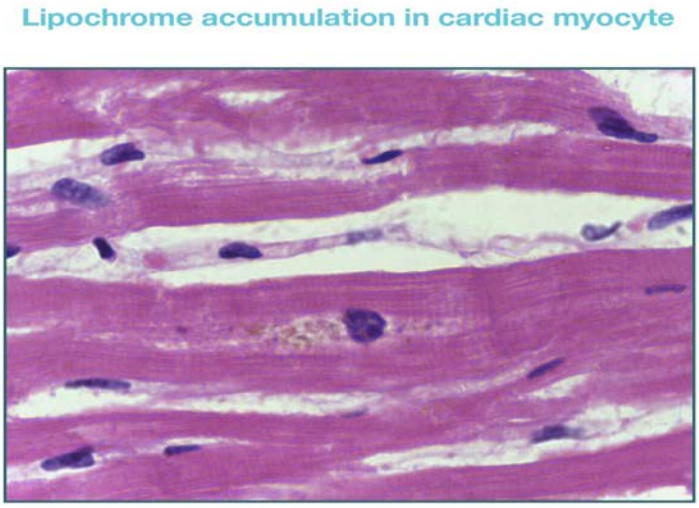
Detailed Explanations

Solution to Question 1:

The given histopathological image shows yellow-brown lipochrome or lipofuscin pigment. It is not injurious to the cell or its functions.



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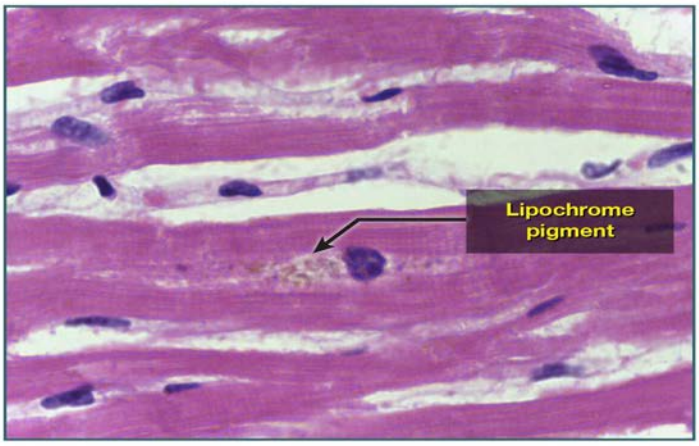
Lipochrome accumulation in cardiac myocyte



Lipofuscin is a wear-and-tear pigment derived from the peroxidation of lipids of subcellular membranes. It is an indicator of free radical injury to the cells.

It is an insoluble, brownish yellow, granular intracellular material that is seen in the liver, brain, and heart due to normal aging. The brown pigment in large amounts can give a characteristic appearance to the tissue called brown atrophy.

It can also be seen in patients with severe malnutrition and cancer cachexia.

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Solution to Question 2:

The given histopathological image shows hepatic macro-vesicular steatosis along with intraparenchymal cholestasis, which is suggestive of fatty liver. This condition can occur due to alcoholism.

The lipid accumulates in the hepatocytes as vacuoles. These vacuoles have a clear appearance on hematoxylin and eosin staining.

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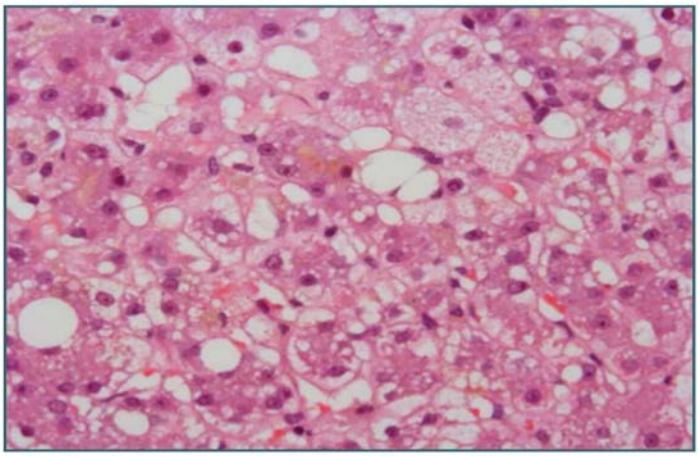
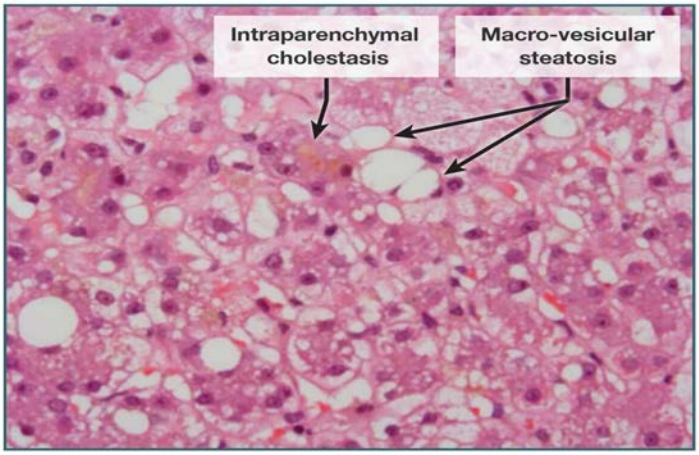
Macro-vesicular steatosis



Macro-vesicular steatosis



A few causes of fatty liver are as follows:

• Alcoholism - most common cause in developed countries

• Non-alcoholic fatty liver disease (NAFLD) - associated with diabetes and obesity

• Toxins

• Malnutrition

• Dyslipidemia

• Anoxia

Fatty change is mostly seen in the liver because it is the major organ involved in fat metabolism. It may also occur in the heart, muscles, and kidneys.

The most common form of lipid accumulation is triglycerides. Other forms of lipid that can be accumulated include cholesterol, cholesterol esters, and phospholipids.

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Solution to Question 3:

Fabry disease and abetalipoproteinemia are not associated with intracellular accumulations of cholesterol and/or cholesterol esters.

The following conditions are associated with the intracellular accumulation of cholesterol and/or cholesterol esters:

• Xanthomas - accumulation of lipid-laden macrophages in the subepithelial connective tissue of the skin and in tendons

• Strawberry gallbladder (cholesterolosis) - accumulation of cholesterol-laden macrophages in the lamina propria of the gallbladder

• Niemann–Pick disease type C - mutations in NPC1 or NPC2 gene results in impaired cholesterol transport inside the cells

• Atherosclerosis - foamy macrophages in the tunica intima of smooth muscles

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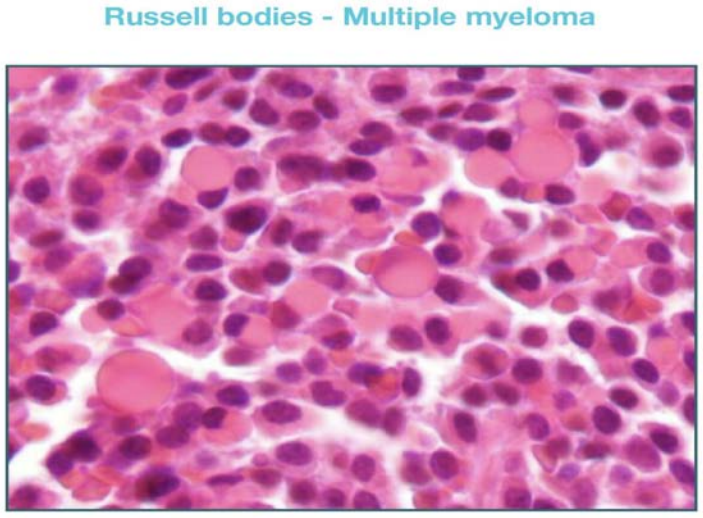
Solution to Question 4:

The given clinical scenario and the histopathological image showing Russell bodies are suggestive of multiple myeloma. These are globular, eosinophilic intracellular accumulations of immunoglobulins.



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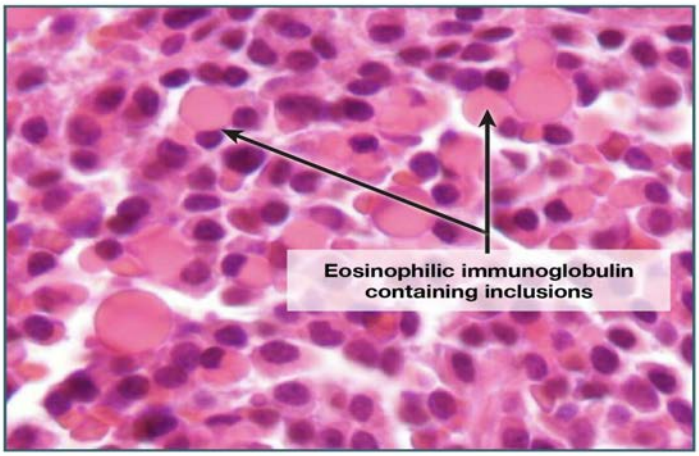
Russell bodies - Multiple myeloma



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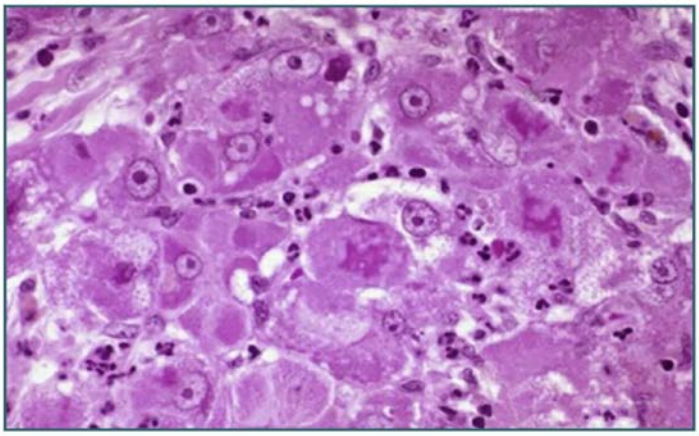
Solution to Question 5:

The given clinical scenario is suggestive of alcoholic liver disease. In this condition, there are intracytoplasmic eosinophilic inclusions called Mallory Denk bodies. They are composed of intermediate keratin filaments.

Mallory bodies are also seen in the following conditions:

- Morbid obesity
- Indian childhood cirrhosis
- Wilson's disease
- Primary biliary cirrhosis

Mallory Denk bodies - Alcoholic liver disease



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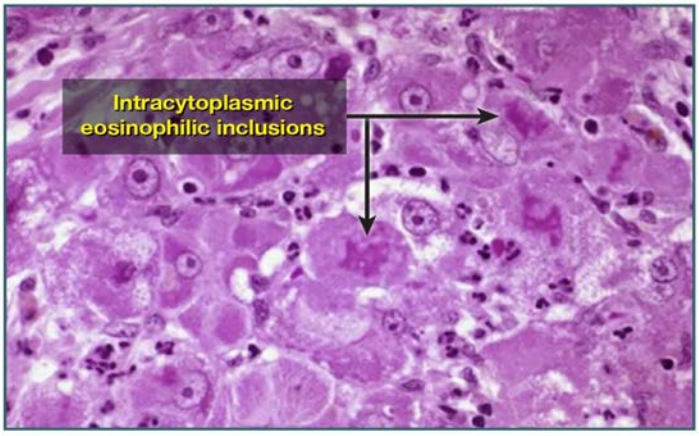
Mallory Denk bodies - Alcoholic liver disease



There are several types of cytoskeletal proteins such as microtubules, thin actin filaments, thick myosin filaments, and intermediate filaments (10 nm).

The intermediate filaments provide a flexible intracellular scaffold that organizes the cytoplasm and resists the forces applied to the cell.

They are divided into five classes:

• Keratin filaments - characteristic of epithelial cells (forms Mallory Denk bodies)

• Neurofilaments - neurons (forms neurofibrillary tangles in Alzheimer's disease)

• Desmin filaments - muscle cells

• Vimentin filaments - connective tissue cells

• Glial filaments - astrocytes

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Solution to Question 6:

The given clinical scenario and histopathological image of the lymph node showing abundant black-colored pigment within the macrophages are characteristic of pulmonary anthracosis.

The black color is due to the deposition of carbon particles. The inhaled carbon particles are engulfed by the lung macrophages and then transported to the hilar lymph nodes, which causes the blackening of the tissues. The carbon dust may also induce fibroblastic reaction or emphysema that may lead to a condition called coal worker's pneumoconiosis.

It is commonly seen in people who work in environments where there is high air pollution with carbon particles, such as coal mines.

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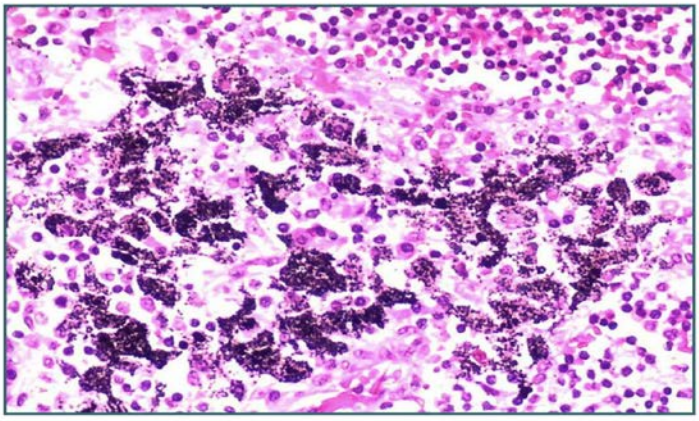
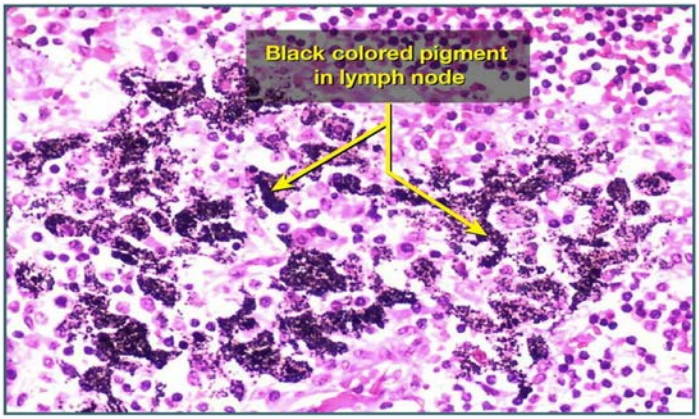
Anthracotic pigmentation - Pulmonary anthracosis



Anthracotic pigmentation - Pulmonary anthracosis



The following images show the accumulation of various types of pigments within cells.

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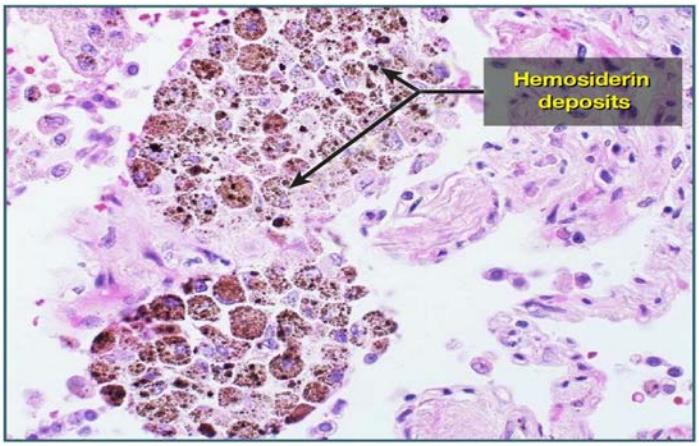
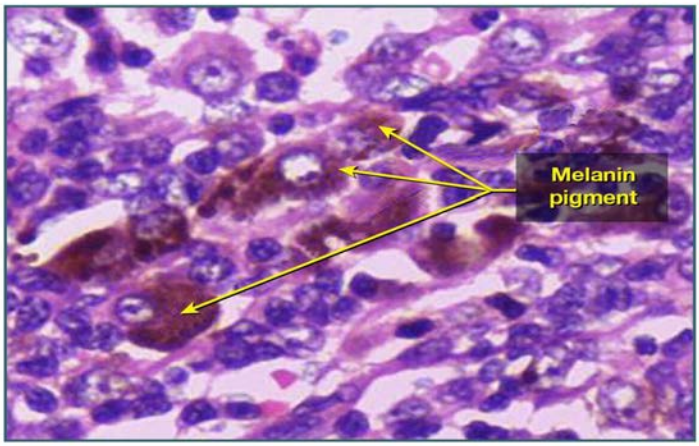
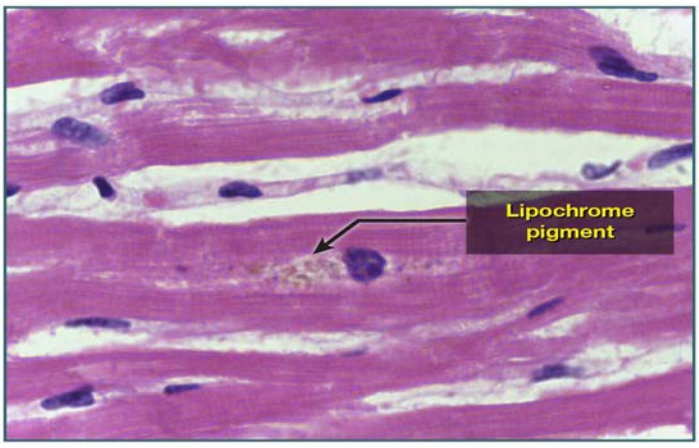
Hemosiderin pigment



Melanin pigment



Lipochrome accumulation in cardiac myocyte



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Solution to Question 7:

Atheromatous plaques are associated with dystrophic calcification. This is seen in the presence of normal calcium levels in the serum.

The deposition of calcium in dead or dying tissues is called dystrophic calcification. Although it occurs in the presence of normal serum calcium, it can be worsened by hypercalcemia.

Dystrophic calcification is seen in areas of necrosis of any type. Some examples include atheromas of advanced atherosclerosis and areas of caseous necrosis in tuberculosis.

Solution to Question 8:

Tuberculosis is associated with dystrophic calcification in the areas of caseous necrosis, not metastatic calcification.

Metastatic calcification occurs in normal tissues in the presence of hypercalcemia. Causes of hypercalcemia include Paget's disease, malignancy, and sarcoidosis.

Metastatic calcification can occur throughout the body, but it mainly affects:

• Interstitial tissues of the vasculature

• Kidneys

• Lungs

• Gastric mucosa

The calcium deposits morphologically resemble those described in dystrophic calcification. Although they generally do not cause clinical dysfunction, extensive calcifications in the lungs may be evident on radiographs and may produce respiratory distress. Massive deposits in the kidney (nephrocalcinosis) can lead to renal damage.

Solution to Question 9:

The Congo red stain is used for staining amyloid bodies, not calcium.

The following staining techniques are used for calcium:

• Hematoxylin and eosin (H&E) -

• Calcium forms a blue-black lake with hematoxylin

• Azan stain -

• Used to distinguish osteoid from the mineralized bone

• Alizarin red S stain -

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• Forms an orange-red lake with calcium

• Works best with small amounts of calcium

• An example is Michaelis–Gutmann (MG) bodies, seen in malakoplakia

• Von Kossa method -

• Useful for tissues containing large amounts of phosphates and carbonates, such as bone

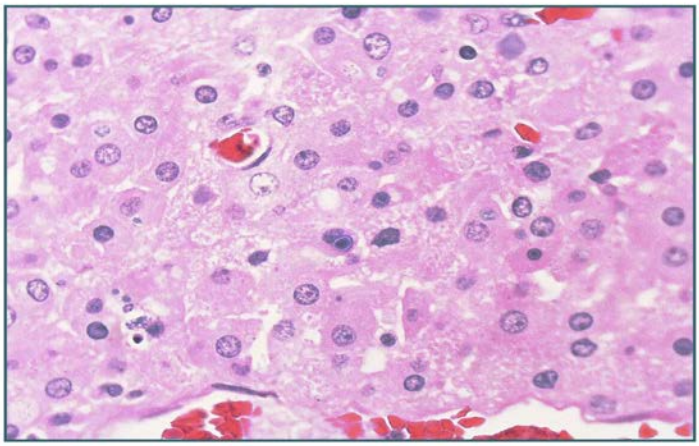
• Silver ions react with phosphate in the presence of acidic material

• Silver phosphate gets degraded to silver in presence of light, giving black color

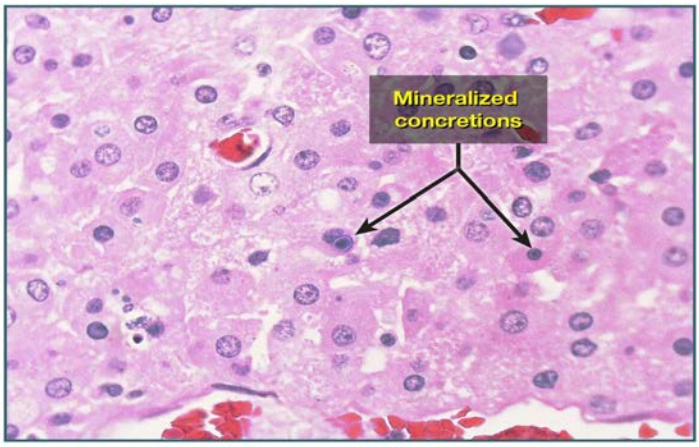
• MG bodies also stain with von kossa stain.

The image given below demonstrates MG bodies which are seen in malakoplakia using the Von Kossa stain.

Michaelis-Gutmann bodies - Malakoplakia



Michaelis-Gutmann bodies - Malakoplakia



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Solution to Question 10:

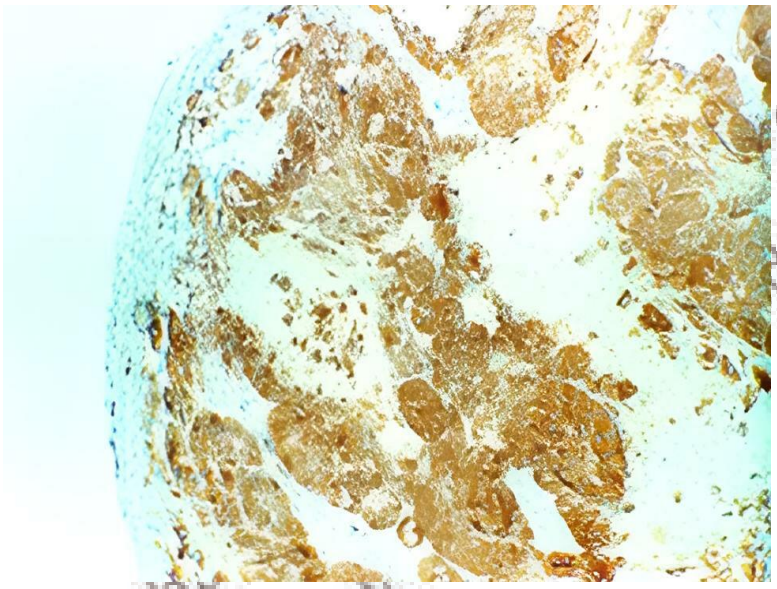
Masson–Fontana stain is used to stain melanin, a brown-black endogenous pigment.

The following different staining techniques are used for melanin:

• Dihydroxyphenylalanine (DOPA)-oxidase method -

• Most specific method

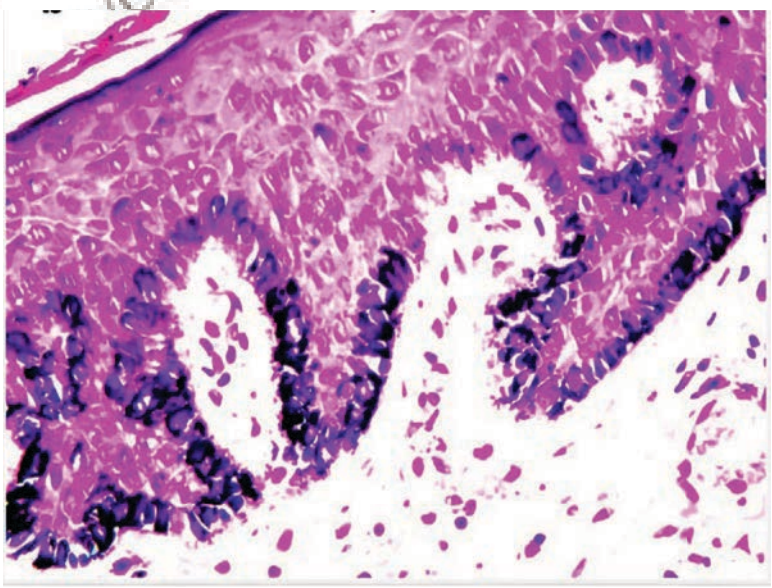
• DOPA-oxidase acts on DOPA in the melanin-producing cells to produce a brownish-black deposit as shown below



• Masson Fontana stain -

• Used to stain melanin and argentaffin granules in neuroendocrine cells (e.g. carcinoid syndrome)

• It stains melanin black, as shown below



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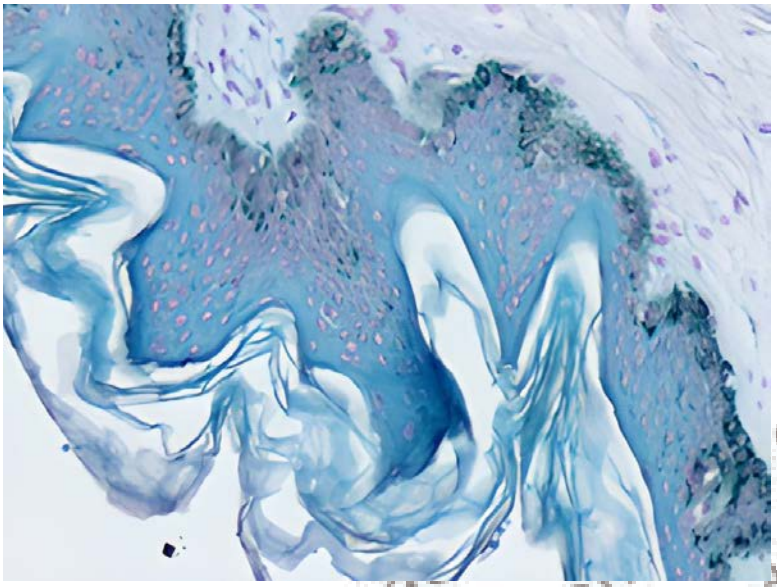
• Schmorl's method - stains melanin blue-green, as shown below



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Solution to Question 11:

Increased incidence of cancer in old age is due to telomerase reactivation.

Normally, with every cell division, there is some shortening of telomeres at the ends of chromosomes. Once the telomeres are shortened beyond a certain point, it may cause cell-cycle arrest or apoptosis. This is called replicative senescence.

Telomerase is the enzyme that prevents the shortening of telomeres. This enzyme is usually present in germ cells but is absent in most somatic cells.

Abnormal reactivation of telomerase in somatic cells leads to evasion of senescence and apoptosis. It enables the cells to divide several times than normal.

Solution to Question 12:

Sirtuins are responsible for an increase in insulin sensitivity. Hence, it can play an important role in the treatment of diabetes.

Sirtuins are a class of proteins that possess either mono-ADP-ribosyltransferase or deacylase activity. They have been shown to slow down the aging process. Calorie restriction and intake of red wine are associated with an increase in sirtuin levels.

Sirtuins act by the following mechanisms:

• Inhibition of the metabolic activity

• Reduction in apoptosis

• Stimulation of protein folding

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• Inhibition of free radical damage

• Increased insulin sensitivity and glucose metabolism

• Ensure that damaged DNA is not propagated, preventing the accumulation of mutations

• Promotes replicative senescence under chronic stress

Solution to Question 13:

A frozen section is done for the fixation of fats. This ensures that the tissue need not go through routine processing, which can remove lipids.

When the tissue sample goes through rapid freezing, it becomes firmer. The ice acts as an embedding media allowing the tissue to be sectioned.

The temperature range in the cryostat machine usually ranges from o■C to -35■C. The majority of the tissue can be appropriately sectioned between -15■C to -25■C. Tissue samples that contain water can be sectioned at a higher temperature. The tissues that contain more fat will need to be cut at a lower temperature.

The stain used for fat is the oil red O stain. It can identify neutral lipids and fatty acids in smears and tissues. It is used in the following conditions:

• Fat emboli in lung tissue

• Renal cell carcinoma

• Sebaceous gland tumors of the skin

• Lipid-rich carcinomas

Fixatives containing alcohols, or routine processing with clearing, will remove lipids. Fixation can be achieved by the following methods:

• Physical methods - heating, microwaving, cryopreservation

• Chemical methods - immersion of specimen in fixative, perfusing vascular system with a fixative

Given below are a few fixatives with their uses:

The most commonly used fixative is 10% neutral buffered formalin.

Technique/Tissue	Fixative
Electron microscopy	Glutaraldehyde
Trephine biopsy-bone marrow	Zenker's fluid (AZF fixative)
GI biopsies	Bouin's fixative
Brain	Formalin ammonium chloride
Adrenal biopsy	Orth's fluid
Pap smear	Ethanol

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Solution to Question 14:

The given clinical scenario is suggestive of hemochromatosis in which there is iron overload. The excess iron gets deposited in tissues as hemosiderin which can be detected using Perl's Prussian blue stain.

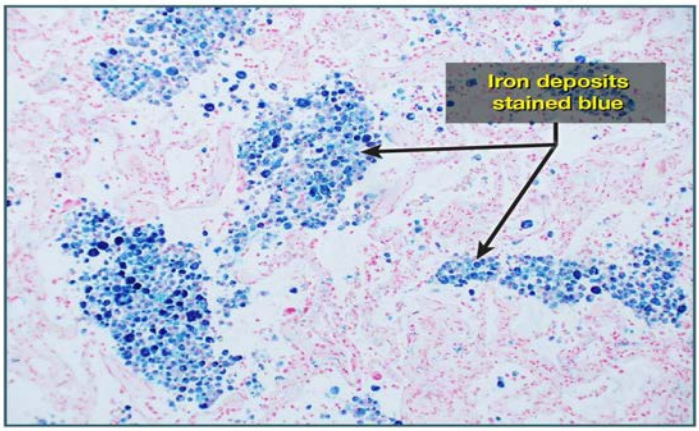
It is based on the principle of the formation of ferric ferrocyanide, which is blue in color.

Hemosiderin is a hemoglobin-derived granular pigment that is golden yellow to brown. It accumulates in the tissues when there is a local or systemic excess of iron.

Iron is normally stored within cells in association with the protein apoferritin, forming ferritin micelles. Large aggregates of these micelles are hemosiderin deposits seen both in light and electron microscopy.

Hemosiderin pigment - Hematoxylin and eosin stain

Hemosiderin pigment - Perls' Prussian blue stain



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Solution to Question 15:

The given clinical features are suggestive of Werner syndrome, a premature aging disorder. The mutated gene encodes a DNA helicase.

Werner syndrome is an autosomal recessive disease caused by mutations in the WRN gene. This gene encodes a protein with multiple DNA-dependent enzymatic functions including:

- ATPase
- Helicase
- Exonuclease

DNA helicase is involved in DNA replication and repair. A defect in this enzyme causes rapid accumulation of damaged chromosomes that may mimic the injury that normally accumulates during cellular aging. Affected persons show various manifestations of premature aging including:

- Atherosclerosis
- Senile cataract
- Skin atrophy
- Alopecia
- Osteoporosis

They are also at risk for the development of a variety of cancers. Patients typically die in the 5th decade from either cancer or cardiovascular disease.

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Acute Inflammation

Question 1:

Who listed the four cardinal signs of inflammation?

a) Joseph Lister

b) Claudius Galen

c) Aulus Celsus

d) Rudolph Virchow

Question 2:

Which of the following stimuli can trigger an inflammatory response?

a) 1, 2, 3, 5

b) 1, 4

c) 2, 3, 5

d) 1, 2, 3, 4, 5

Question 3:

Which of the following are cytosolic pattern-recognition receptors?

a) 2, 4, 5

b) 1, 3, 4

c) 1, 3, 5

d) 2, 4

Question 4:

Which of the following is false about the acute inflammatory process?

a) It is a mechanism of innate immunity

b) Monocytes and macrophages are mainly involved

c) Tissue injury is usually mild and self-limited

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d) Local and systemic signs are prominent

Question 5:

What is the most common mechanism of vascular leakage in acute inflammation?

a) Contraction of endothelial cells

b) Direct endothelial injury

c) Complement mediated endothelial injury

d) Leukocyte-dependent endothelial injury

Question 6:

A man is brought to the casualty with swelling after sustaining a bee sting over his face. Which of the following vascular changes is not observed in this condition?

a) Increased hydrostatic pressure

b) Stasis of blood

c) Transcytosis

d) Increased oncotic pressure

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Question 7:

During normal blood flow in venules, which cells occupy the central axial column?

a) RBCs

b) Neutrophils

c) Platelets

d) Lymphocytes

Question 8:

Which of the following is not true with regard to selectins?

a) Involved in initial rolling interactions

b) There are L, E and P types of selectins

c) P-selectins are expressed on the endothelium

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d) Selectins mediate high-affinity interactions

Question 9:

Which of the following is not an integrin molecule?

a) LFA-1

b) MAC-1

c) VLA-4

d) CD31

Question 10:

Which of the following is not a ligand for integrins?

a) CD 54

b) CD 102

c) CD 106

d) CD 34

Question 11:

Sialyl-Lewis X is linked to which of the following?

a) Selectin

b) ICAM

c) CD31

d) LFA-1

Question 12:

Which molecule plays a major role in the following phenomenon seen in leukocytes?

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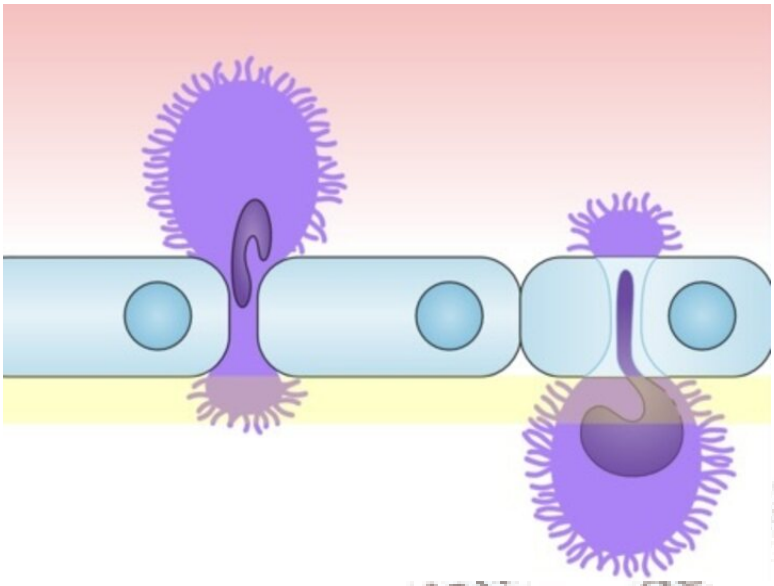

a) CD31

b) CD62

c) CD102

d) CD54

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Question 13:

In patients with acute respiratory distress syndrome, which of the following cells are the major cause of tissue injury?

a) Neutrophils

b) Eosinophils

c) Macrophages

d) Plasma cells

Question 14:

Infection with which of the following organisms would produce an inflammatory infiltrate with neutrophilic predominance beyond 48 hours?

a) Pseudomonas

b) Staphylococci

c) Fungi

d) Virus

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Question 15:

Which of the following is involved in inducing the migration of leukocytes to sites of injury?

a) C5a

b) C3b

c) C3a

d) C5b

Question 16:

Which of the following is an opsonin?

a) C3a

b) C3b

c) C5a

d) C6

Question 17:

Which of the following does not have antioxidant action?

a) Myeloperoxidase

b) Ceruloplasmin

c) Catalase

d) Glutathione peroxidase

Question 18:

Oxygen-dependent killing is done through which of the following?

a) NADPH oxidase

b) Carotenoids

c) Transferrin

d) Glutathione peroxidise

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Question 19:

A 7-month-old male infant was brought with a 2-day history of fever and abscess over the neck. The mother reveals that the child has had similar recurrent infections in the past. The result of the nitroblue tetrazolium dye reduction test was found to be abnormal. What is the most likely diagnosis?

a) Leukocyte adhesion deficiency

b) Chronic granulomatous disease

c) Severe combined Immunodeficiency

d) Chediak Higashi syndrome

Question 20:

A nitroblue tetrazolium test is performed in a child with recurrent infections. Functions of which of the following are assessed by this test?

a) Phagocytes

b) Complement

c) T-cells

d) Neutrophils

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Question 21:

Patients with which of the following conditions have defective phagolysosome formation?

a) Chronic granulomatous disease

b) Chediak–Higashi syndrome

c) Mannose-binding lectin deficiency

d) Glanzmann-Rinicker syndrome

Question 22:

What is frustrated phagocytosis?

a) Release of lysosomal contents due to damaged membrane

b) Engulfment of infectious pathogens and degradation by phagolysosome

c) Release of lysosomal enzymes when phagocytes cannot engulf targets

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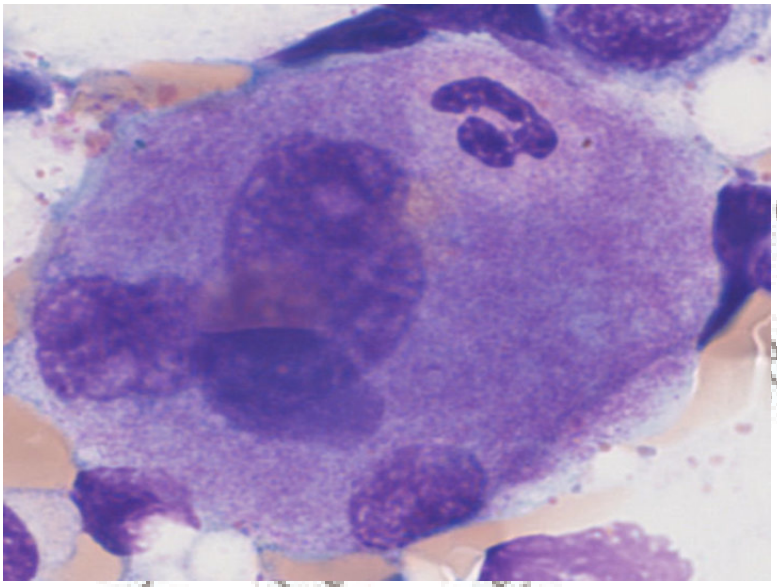
d) Defective phagolysosome formation

Question 23:

What does the following image show?



a) Autophagy

b) Emperipolesis

c) Phagocytosis

d) Amoebic autophagy

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Question 24:

Which of the following is not present in the primary granules of neutrophils?

a) Myeloperoxidase

b) Defensin

c) Acid hydrolases

d) Lactoferrin

Question 25:

In which of the following is major basic protein seen?

a) Neutrophils

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b) Eosinophils

c) Basophils

d) Macrophage

Question 26:

Which of the following statements is incorrect regarding neutrophil extracellular traps (NETs)?

a) They prevent the spread of the microbes by trapping them in the fibrils

b) Nuclear chromatin in the NETs are the source of nuclear antigens in SLE

c) In sepsis, platelet activation is involved in NET formation

d) NETs play a major role in phagocytosis

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Answer Key

Question No.	Correct Option
1	c
2	a
3	d
4	b
5	a
6	d
7	a
8	d
9	d
10	d
11	a
12	a
13	a
14	a
15	a
16	b
17	a
18	a

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19	b
20	a
21	b
22	c
23	b
24	d
25	b
26	d

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Detailed Explanations

Solution to Question 1:

The four cardinal signs of inflammation were first listed by Aulus Celsus. He was a Roman medical writer of the first century AD. These are:

• Rubor - redness

• Tumour - swelling

• Calor - heat

• Dolor - pain

These signs are the hallmarks of acute inflammation.

Rudolf Virchow added the fifth clinical sign of inflammation, loss of function, functio laesa.

Solution to Question 2:

The complement system does not trigger an inflammatory response. It reacts against microbes and results in the production of mediators of inflammation.

The major triggers of inflammation include:

• Infections - bacteria, viruses, fungi, parasites, toxins

• Tissue necrosis - due to ischemia, trauma, physical or chemical injuries

• Foreign bodies -

• Endogenous - DNA breakdown products (uric acid), cholesterol crystals, lipids

• Exogenous - splinters, dirt, sutures, etc

• Trauma

• Immune reactions - against microbes, self-antigens, or environmental substances

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Solution to Question 3:

NOD-like receptors and RIG-like receptors are cytosolic pattern-recognition receptors.

Pattern-recognition receptors are the cellular receptors that recognize microbes and damaged cells.

Types of pattern-recognition receptors:

• Cellular receptors for microbes -

• Toll-like receptors on the plasma membrane and endosomal vesicles

• C-type lectin receptors on the plasma membrane of macrophages and dendritic cells

• Cytosolic receptors -

• NOD-like receptors detect bacterial peptidoglycan

• RIG-like receptors detect viral RNA

• Circulating proteins: Mannose-binding lectin and collectins

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Solution to Question 4:

The prominent cells in acute inflammation are neutrophils.

The initial, rapid response to infections agents and tissue damage is called acute inflammation. It is a mechanism of innate immunity that occurs in response to mild and self-limited tissue injury. It is associated with prominent local and systemic signs.

The major components of acute inflammation are:

• Vasodilation and increased permeability of small blood vessels

• Changes in the leukocytes -

• Migration from the microcirculation

• Accumulation at the site of inflammation

• Activation to eliminate the offending agent

Chronic inflammation is a mechanism of adaptive immunity and is of longer duration. It is associated with

• Presence of lymphocytes and macrophages

• Proliferation of blood vessels

• Deposition of connective tissue

Solution to Question 5:

The most common mechanism of vascular leakage in acute inflammation is the contraction of endothelial cells.

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This is an immediate, transient response mediated by histamine, bradykinin, and leukotrienes. The contraction of the endothelial cells results in an increase in the interendothelial spaces.

Other mechanisms of vascular leakage include:

• Endothelial injury - results in endothelial cell necrosis and detachment

• Transcytosis - increased transport of fluids and proteins

Solution to Question 6:

Bee stings result in acute inflammation at the site of the sting. In this condition, there is decreased oncotic pressure due to protein leakage.

There is a release of inflammatory mediators like histamine which result in the following vascular changes:

• Vasodilation - results in erythema and stasis of blood flow

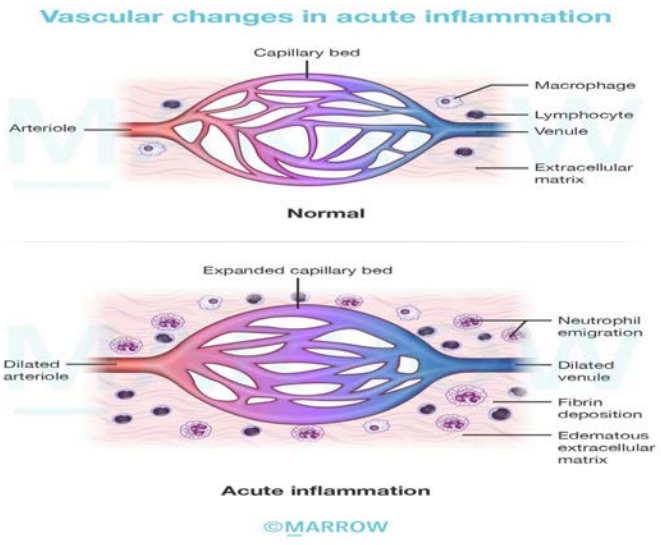
• Increased vascular permeability -

• Due to mediators like histamine, kinins, or endothelial injury (direct or leukocyte-induced), or transcytosis

• Results in leakage of proteins (reduced vascular oncotic pressure) and leukocyte migration

• Increased hydrostatic pressure - results in fluid leakage from blood vessels resulting in edema

The image below shows the changes seen during acute inflammation.



Solution to Question 7:

Blood flows in blood vessels as central axial/laminar column and peripheral chaotic columns. During normal blood flow in venules, the central axial column is occupied by the red blood cells

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(RBCs).

These RBCs displace the leukocytes toward the wall of the vessel (chaotic column).
During inflammation, stasis leads to slow blood flow and reduced wall shear stress. This further pushes the WBCs towards a peripheral position along the endothelial surface. This is called margination.

Subsequently, leukocytes adhere to the endothelium, then detach and bind again. This is referred to as rolling on the vessel wall. The cells finally come to rest and adhere firmly to the endothelial wall.

Solution to Question 8:

Selectins are a group of molecules that mediate low-affinity interactions between the leukocytes and the endothelium.

Due to the low-affinity nature of these interactions, they are easily disrupted by the flowing blood. They play a major role in the initial rolling interactions of leukocytes with the vascular endothelium. The expression of selectins and their ligands is regulated by cytokines produced in response to infection and injury.

There are 3 types of selectins:

• L-selectin - expressed on leukocytes

• E-selectin - expressed on endothelium

• P-selectin - expressed on activated platelets and endothelium

Solution to Question 9:

CD 31 or platelet endothelial cell-adhesion molecule 1 (PECAM-1) is a member of the immunoglobulin superfamily. It is not an integrin molecule.

The various endothelial and leukocyte adhesion molecules include:

• Selectin family - mediates initial rolling interactions between leukocytes and endothelium

• Integrin family -

• Involved in migration and firm adhesion of leukocytes to the endothelium

• Includes LFA-1, MAC-1, and VLA-4

• Immunoglobulin family -

• PECAM (CD31) - most important adhesion molecule for diapedesis

• ICAM-1 - binds to ° 2 integrins on leukocytes

Solution to Question 10:

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The ligands for integrins include:

• ICAM-1 (CD54)

• ICAM-2 (CD102)

• VCAM-1 (CD106)

Solution to Question 11:

Sialyl-Lewis X refers to sialylated oligosaccharides bound to mucin-like glycoprotein. These molecules function as ligands for selectins.

The expression of selectins and their ligands is regulated by cytokines produced in response to infection and injury.

Solution to Question 12:

The image shows diapedesis by leukocytes. CD31 or platelet endothelial cell adhesion molecule (PECAM-1) plays a major role in diapedesis.

Diapedesis or transmigration refers to the migration of the leukocytes through the endothelium. It mainly occurs in postcapillary venules.

Solution to Question 13:

In acute respiratory distress syndrome (ARDS), acute tissue injury is caused mainly by neutrophils.

ARDS is a clinical syndrome manifested as a result of severe lung injury. The initiating event is alveolar epithelial cell damage. It is characterized by acute inflammation, causing increased pulmonary vascular permeability and edema.

Neutrophils adhere to the activated endothelium and migrate into the interstitium and the alveoli. Here, they degranulate and release inflammatory mediators. These include:

• Proteases

• Reactive oxygen species

• Cytokines

Macrophages are involved in the stage of resolution.

Solution to Question 14:

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In Pseudomonas infection, the inflammatory infiltrate has a neutrophilic predominance for several days.

Normally, in acute inflammation, neutrophils predominate the inflammatory infiltrate during the first 6 to 24 hours. However, they are short-lived, and disappear within 24 to 48 hours, following which they are replaced by monocytes.

Monocytes survive longer and also proliferate in the tissues. Thus, they become the dominant population in prolonged inflammatory reactions.

The exceptions to this pattern include:

• Pseudomonas infections - neutrophilic dominance in the infiltrate for several days

• Viral infections - lymphocytes are the initial cells

• Allergic reactions - eosinophils are the main cell type

• Some types of hypersensitivity - dominated by activated lymphocytes, macrophages, and plasma cells

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Solution to Question 15:

C5a induces the migration of leukocytes to the site of injury. It functions as an endogenous chemoattractant.

Both exogenous and endogenous substances can act as chemoattractants. The most common exogenous agents include bacterial products like peptides with N-formylmethionine terminal amino acids and certain lipids.

Endogenous chemoattractants include several chemical mediators:

• Cytokines - particularly those of the chemokine family (IL-8)

• Complement system components - particularly C5a

• Arachidonic acid metabolites - mainly leukotriene B4

Solution to Question 16:

C3b functions as an opsonin.

Opsonization is the process of coating a foreign particle and preparing it for phagocytosis. The substances involved in this process are called opsonins and include:

• Mannose-binding lectin

• C3b, C4b, C5b

• IgM and Fc receptor of IgG

• CRP

• Fibrinogen

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Elie Metchnikoff was the first person to describe the process of phagocytosis, and is hence known as the Father of Innate Immunity.

Solution to Question 17:

Myeloperoxidase is an oxidative enzyme, not an antioxidant.

Antioxidants provide protection against potentially harmful oxygen-derived radicals. Serum, tissue fluids, and host cells possess antioxidant mechanisms. These include:

- Catalase
- Superoxide dismutase
- Glutathione peroxidase
- Iron-free fraction of transferrin
- Carotenoids
- Ceruloplasmin

Myeloperoxidase is an oxidative enzyme with antimicrobial activity. It is seen in azurophil (primary) granules of neutrophils. It is involved in the production of hypochlorous acid and destroys microbes by means of halogenation and lipid peroxidation.

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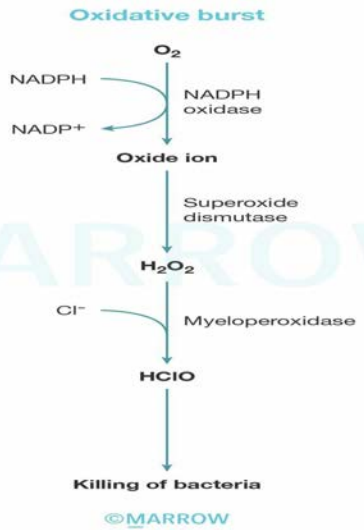
Solution to Question 18:

NADPH oxidase is involved in the oxygen-dependent killing of microbes. It results in generation of reactive oxygen intermediates.

This process is called the oxidative burst. It involves the generation of H_2O_2, and eventually hypochlorous acid. This H_2O_2-MPO-halide system is the most efficient bactericidal system of neutrophils.



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Carotenoids, glutathione peroxidase, and the iron-free fraction of transferrin are antioxidants or free radical scavengers that prevent oxygen-mediated injury.

Solution to Question 19:

The given clinical scenario and abnormal nitroblue tetrazolium dye reduction test are suggestive of chronic granulomatous disease (CGD).

CGD is a rare primary immunodeficiency of phagocytes. It is an X-linked recessive disorder due to the deficiency in the NADPH oxidase enzyme. This is important in the respiratory or oxidative burst.

It usually manifests in the first year of life with recurrent pyogenic infections with catalase-positive organisms, including:

• Staphylococcus aureus

• Escherichia coli

• Aspergillus species

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Solution to Question 20:

Nitroblue tetrazolium test (NBT) is done to assess the function of phagocytes.

The principle is based on the color change of the colorless nitroblue tetrazolium compound to a deep blue when exposed to reactive oxygen species (ROS). The higher the nitroblue test score, the better the cell is at producing ROS.

In chronic granulomatous disease, there is an NADPH oxidase defect. Hence, the phagocyte is unable to produce reactive oxygen species or radicals required for bacterial killing, which results in recurrent infections. Hence, there is a reduced color change with the NBT test.

Solution to Question 21:

Defective phagolysosome formation is seen in patients with Chediak–Higashi syndrome (CHS). It is a rare autosomal recessive defect.

There is an abnormal fusion of azurophilic lysosomes of neutrophils and cytoplasmic granules of monocytes and lymphocytes, which leads to the presence of giant lysosomal granules. Hence, there is abnormal post-phagocytic phagolysosomal fusion, degranulation, and impaired microbicidal activity. There is rapid neutrophil turnover leading to low counts.

Clinical features include:

• Recurrent infections -

• Commonly affect the skin, upper and lower respiratory tract

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• Common organisms - Staphylococcus aureus, Haemophilus influenzae, Group A Streptococcus, Gram-negative enteric (Klebsiella, Proteus, Shigella, Pseudomonas)

• Accelerated phase in some patients -

• Hemophagocytic syndrome and aggressive lymphoma

• These patients require bone marrow transplantation

• Albinism with neurological defects

Solution to Question 22:

The term frustrated phagocytosis refers to the release of large amounts of lysosomal contents into the external environment due the inability of the phagocytes to engulf.

When immune complexes are deposited on relatively flat immovable surfaces, the phagocytes are unable to surround and ingest them. In this case, the activation signals lead to an uncontrolled release of the lysosomal contents, despite lack of phagocytosis. This is known as frustrated phagocytosis.

Other processes may lead to the release of lysosomal contents into the external environment:

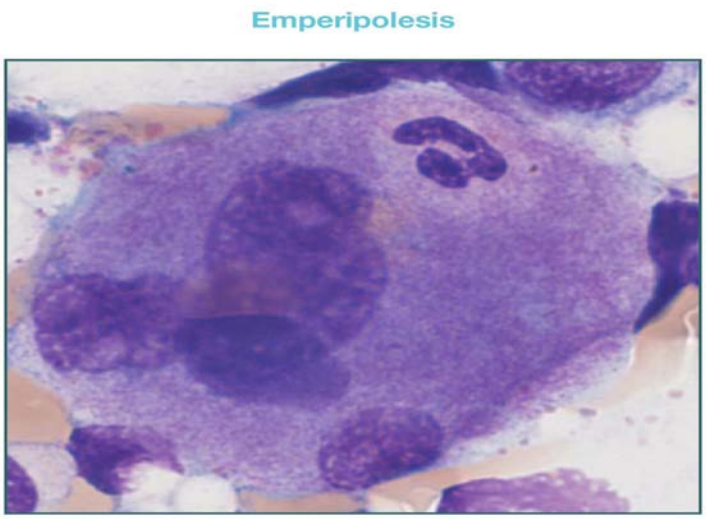
• Controlled secretion of granule contents - normal response of activated leukocytes

• Damage to the phagolysosome membrane by certain phagocytosed substances like urate crystals

Solution to Question 23:

The image shows the phenomenon of emperipolesis. Here, intact hematopoietic cells are seen within the cytoplasm of the host cell without any damage.

The cells frequently involved are neutrophils, lymphocytes, and plasma cells. Both the cells are viable and there are no physiological and morphological consequences to either of them.



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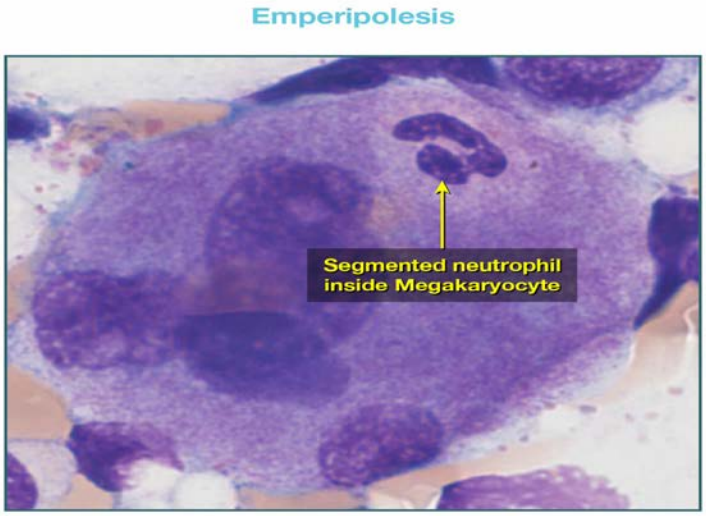

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Solution to Question 24:

Lactoferrin is present in the secondary granules of neutrophils, not primary.

The types of granules present in neutrophils are:

Primary and secondary granules can fuse with phagocytic vacuoles containing engulfed material. Otherwise, the granule contents can be released into the extracellular space.

Azurophil (Primary) granules	Specific (Secondary) granules	Small storage granules
Antimicrobial molecules		
LysozymeMyeloperoxidase,defensins, BPI	LysozymeLactoferrin	---
Neutral proteinases		
ElastaseCathepsin GProteinase 3	Collagenase complement activator	GelatinasePlasminogen activator
Acid hydrolases		
Cathepsins B, D°-D-Glucuronidaseα-MannosidasePhospholipase A2	Phospholipase A2	Cathepsins B, D°-D-Glucuronidaseα-Mannosidase
Cytoplasmic membrane receptors		
---	CR3, CR4FMLP receptorsLaminin receptors	---
Other molecules		

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Azurophil (Primary) granules	Specific (Secondary) granules	Small storage granules
Chondroitin-4-sulfate	Cytochrome B558Monocyte-chemotactic factorHistaminaseVitamin B12-binding protein	Cytochrome B558
BPI: bactericidal permeability-increasing proteinFMLP: N-formyl methionyl-leucyl-phenylalanine		

Solution to Question 25:

The major basic protein is the predominant constituent of the crystalline core of the eosinophil granule.

It is also called proteoglycan-2 and is encoded by the PRG2 gene. This protein is involved in:

• Antiparasitic defense mechanisms - functions as a cytotoxin and helminthotoxin

• Immune hypersensitivity reactions

• Lysis of epithelial cells

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Solution to Question 26:

Neutrophil extracellular traps (NETs) are not involved in phagocytosis. This is because the nuclei of the neutrophils are lost during NET formation, leading to their death. Hence, they cannot phagocytose pathogens.

NETs are networks of extracellular fibers that consist of a viscous meshwork of nuclear chromatin. They trap microbes at sites of infection, preventing their further spread. They also contain a high concentration of antimicrobial proteins like neutrophil elastase, cathepsin G, and histones that have a high affinity for DNA.

They are produced by neutrophils in response to the following triggers:

• Pathogens - Mainly bacteria and fungi

• Inflammatory mediators -

• Chemokines

• Cytokines (mainly interferons)

• Complement proteins

• Reactive oxygen species

NETs have also been detected in the blood during sepsis. In this condition, platelet activation is involved in NET formation

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The nuclear chromatin in the NETs is a source of nuclear antigens (histones and associated DNA) in systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE). This triggers autoantibody production and further clinical manifestations.

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Inflammatory Mediators and Granulomatous Inflammation

Question 1:

Which among the following is the first mediator to be released during inflammation?

a) Serotonin

b) Interleukins

c) Prostaglandins

d) Bradykinin

Question 2:

Which of the following may serve as a source of histamine production?

a) 1, 3, 4

b) 2, 3, 4

c) 1, 4, 5

d) 1, 2, 5

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Question 3:

The release of arachidonic acid from the membrane phospholipids is mainly mediated by which of the following?

a) Phospholipase A1 and C

b) Phospholipase A2 and C

c) Phospholipase B and C

d) Phospholipase A1 and B

Question 4:

Which of the following statements about prostaglandins is false?

a) TxA2 is the major product in platelets

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b) Prostacyclin is a vasodilator and inhibits platelet aggregation

c) PGD2 is the major prostaglandin produced by mast cells

d) Vascular endothelium lacks prostacyclin synthase

Question 5:

Which of the following statements is incorrect regarding leukotrienes?

a) They are produced by leukocytes and mast cells by action of lipoxygenase

b) 5-lipoxygenase is the predominant enzyme in neutrophils

c) LTB4 is a potent chemotactic agent and activator of neutrophils

d) Leukotrienes are less potent mediators of bronchospasm

Question 6:

What is the principal action of leukotrienes C4, D4, and E4?

a) Chemotaxis

b) Vasodilation

c) Leukocyte adhesion

d) Increased vascular permeability

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Question 7:

Which of the following is an anti-inflammatory cytokine?

a) IL-1

b) IL-4

c) TNF

d) IFNγ

Question 8:

Which of the following is a CXC chemokine?

a) IL-8

b) RANTES

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c) Lymphotactin

d) Fractalkine

Question 9:

Fractalkine belongs to which chemokine family?

a) C

b) CX3C

c) CXC

d) CC

Question 10:

What type of chemokine is MCP-1?

a) C

b) CX3C

c) CXC

d) CC

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Question 11:

Serum concentrations of which of the following decrease during inflammation?

a) Albumin

b) Serum amyloid A (SAA)

c) C-reactive protein (CRP)

d) Fibrinogen

Question 12:

A 39-year-old woman is being evaluated for anemia. She is a known case of rheumatoid arthritis. Increased levels of which of the following is responsible for her anemia?

a) Fibrinogen

b) CRP

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c) SAA

d) Hepcidin

Question 13:

Which of the following statements is not true for platelet-activating factor?

a) It is secreted by mast cells

b) It does not cause vasoconstriction

c) It increases vascular permeability

d) It is involved in leukocyte adhesion

Question 14:

The critical step in complement activation involves the proteolysis of the which component?

a) C1

b) C3

c) C5

d) C2

Question 15:

Patients with an inherited deficiency of C1 inhibitor will have which of the following?

a) Paroxysmal nocturnal hemoglobinuria

b) Hereditary angioedema

c) Neisseria infection

d) Glomerulonephritis

Question 16:

Which of the following is not caused by bradykinin?

a) Increased vascular permeability

b) Smooth muscle contraction

c) Pain at the site of injection

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d) Generalised vasospasm

Question 17:

During an inflammatory response, which of the following does not increase vascular permeability?

a) IL-4

b) C3a

c) Serotonin

d) Leukotriene C4

Question 18:

Fever occurs during inflammation due to all except:

a) IL 1

b) Prostaglandins

c) TNF

d) Histamine

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Question 19:

Which of the following is true about fever?

a) Aspirin increases fever by inhibiting prostaglandin synthesis

b) PGD2 is responsible for resetting the temperature to a higher level

c) IL-1 is an endogenous pyrogen

d) Fever occurs during inflammation due to release of histamine

Question 20:

IL-1 is activated by :

a) Caspase - 1

b) Caspase - 3

c) Caspase - 9

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d) Caspase - 8

Question 21:

Which of the following is not secreted by T-helper type 2 cells?

a) IL-4

b) IL-5

c) IL-13

d) IFN gamma

Question 22:

In patients with which of the following conditions would you observe tertiary lymphoid organs?

a) 1, 3 and 5

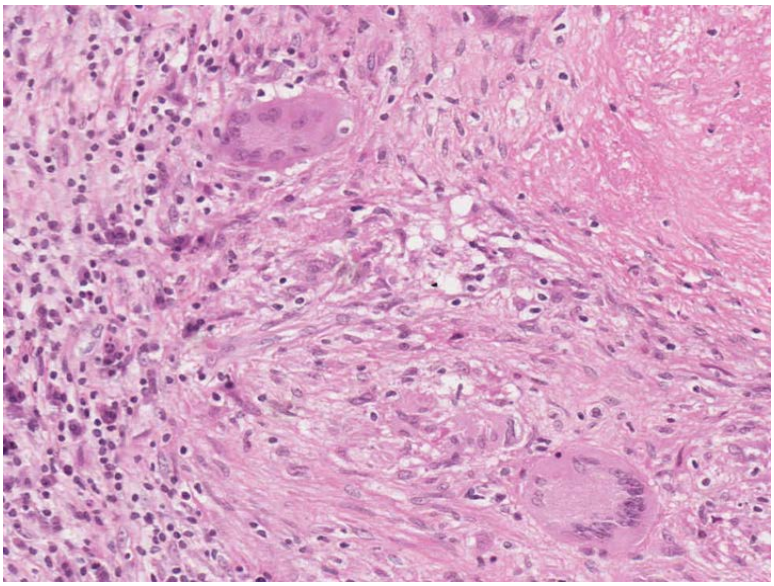
b) 3 and 5

c) 1, 2 and 4

d) 2, 4 and 5

Question 23:

Lymph node biopsy of a patient with tuberculosis demonstrated the following findings. From which of the following are these cells derived?



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a) CD8 T-lymphocytes

b) Neutrophils

c) CD4 T-lymphocytes

d) Macrophages

Question 24:

Epithelioid granulomas are not seen in which of the following diseases?

a) Sarcoidosis

b) Syphilis

c) Toxoplasmosis

d) Kikuchi's lymphadenitis

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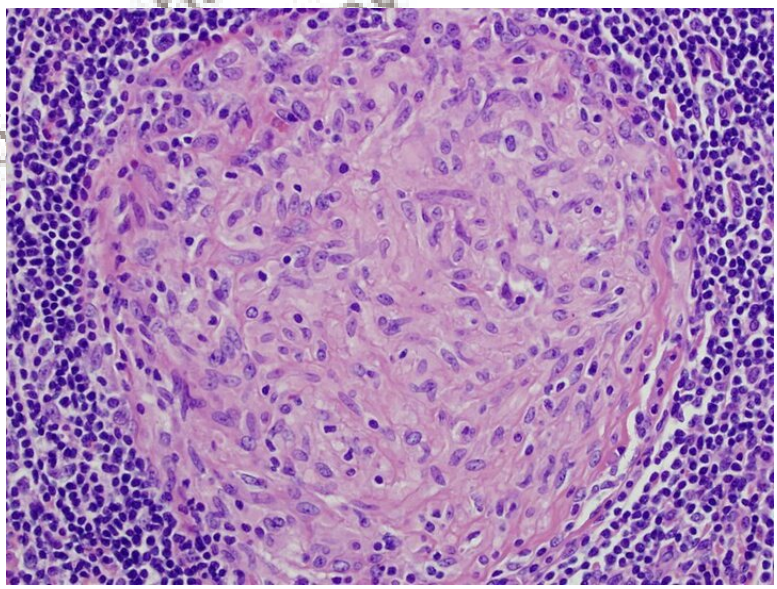
Question 25:

A pathologist observes the given findings during the examination of a lymph node sample. Which of the following is the least likely cause?



a) Leprosy

b) Crohn's disease

c) Sarcoidosis

d) Tuberculosis

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Question 26:

Stellate granuloma is seen in :

a) Sarcoidosis

b) Cat-scratch disease

c) Cryptococcosis

d) Histoplasmosis

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Answer Key

Question No.	Correct Option
1	a
2	d
3	b
4	d
5	d
6	d
7	b
8	a
9	b
10	d
11	a
12	d
13	b
14	b
15	b
16	d
17	a
18	d
19	c
20	a
21	d
22	c

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23	d
24	d
25	d
26	b

Detailed Explanations

Solution to Question 1:

Serotonin and histamine are among the first mediators to be released during inflammation. They are stored as preformed molecules in cells.

Serotonin (5-hydroxytryptamine) is a preformed vasoactive mediator that is present in platelets and certain neuroendocrine cells, such as in the gastrointestinal tract. Its functions include vasoconstriction and neurotransmitter action in the gastrointestinal tract.

Solution to Question 2:

The sources of histamine include platelets, basophils, and mast cells (major source).

Preformed histamine is stored in the granules of mast cells and other cells. It is released by degranulation in response to a variety of stimuli, including:

• Physical injuries - trauma, cold, or heat

• Binding of antibodies to mast cells

• Products of complement called anaphylatoxins (C3a and C5a)

Its vasoactive effects are mediated mainly via binding to H1 receptors on microvascular endothelial cells.

The functions of histamine include:

• Vasodilation

• Increased vascular permeability

• Endothelial activation

Solution to Question 3:

The release of arachidonic acid (AA) from the membrane phospholipids is mainly mediated by phospholipase A2 and C.

AA is a polyunsaturated fatty acid that may be derived from the following sources:

• Dietary sources

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• From the conversion of the essential fatty acid linoleic acid

• From membrane phospholipids via phospholipase A2 and C (in response to mechanical, chemical, or physical stimuli)

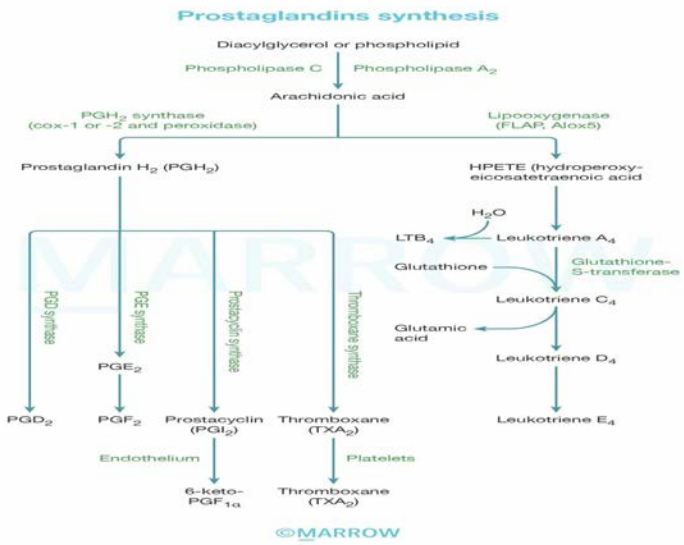
• From diacylglycerol by the action of diacylglycerol lipase

AA-derived mediators are also called eicosanoids (20-carbon fatty acids). They are synthesized by two major classes of enzymes:

• Cyclooxygenases - produces prostaglandins

• Lipoxygenases - produces leukotrienes and lipoxins

These mediators bind to G protein-coupled receptors (GPCRs) on many cell types. They stimulate vascular and cellular reactions in acute inflammation.



Solution to Question 4:

Prostacyclin synthase is present in the vascular endothelium.

It is responsible for the formation of prostacyclin (PGI2) and PGF1a (its stable end product). Prostacyclin is a vasodilator and a potent inhibitor of platelet aggregation.

Thromboxane synthase is present in platelets, and hence, TxA2 is the major product in these cells.

PGD2 is the major prostaglandin produced by mast cells and is a chemoattractant for neutrophils.

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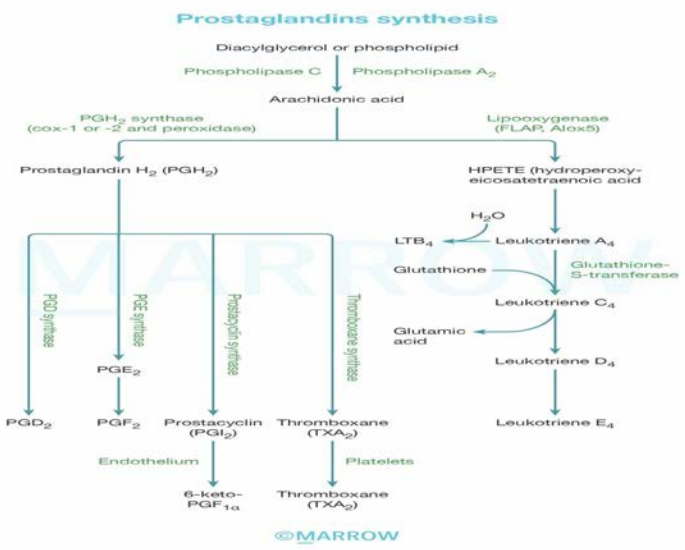

Solution to Question 5:

Leukotrienes are more potent than histamine in increasing vascular permeability and causing bronchospasm.

They are produced by leukocytes and mast cells from arachidonic acid by the action of lipoxygenase. They are involved in vascular and smooth muscle reactions. There are three different lipoxygenases (5, 12, 15). 5-lipoxygenase is predominant in neutrophils.

The principal actions of various arachidonic acid metabolites in inflammation are as follows:

Eicosanoid	Action
PGI2(prostacyclin)PGE1,PGE 2,PGD2	Vasodilation
Thromboxane A2	Vasoconstriction
LeukotrienesC4,D4,E4	Increased vascular permeabil ityIntense vasoconstrictionBr onchospasm
LeukotrienesB4	Chemotaxis,neutrophilactivat ionLeukocyte adhesionGener ation of reactive oxygen speci esRelease of lysosomal enzy mes

Solution to Question 6:

The principal action of leukotrienes C4, D4, and E4 is increased vascular permeability.

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Eicosanoid	Action
PGI2(prostacyclin)PGE1,PGE 2,PGD2	Vasodilation
Thromboxane A2	Vasoconstriction
LeukotrienesC4,D4,E4	Increasedvascularpermeabilit yIntensevasoconstrictionBro nchospasm
LeukotrienesB4	Chemotaxis,neutrophilactivat ionLeukocyte adhesionGener ation of reactive oxygen speci esRelease of lysosomal enzy mes

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Solution to Question 7:

IL-4 is an anti-inflammatory cytokine.

It induces alternatively activated macrophages. This results in tissue repair and the resolution of inflammation.

The following are anti-inflammatory cytokines:

• IL-4

• IL-10

• IL-13

• TGF-°

• Lipoxins

Lipoxins suppress inflammation by inhibiting leukocyte recruitment. They inhibit neutrophil chemotaxis and adhesion to endothelium.

Solution to Question 8:

IL-8 is a typical example of a CXC chemokine.

Chemokines are a family of small (8 to 10 kD) proteins. They act primarily as chemoattractants for specific types of leukocytes.

They are classified into 4 groups, according to the arrangement of cysteine (C) residues in the proteins. This is given in the image and the table below.

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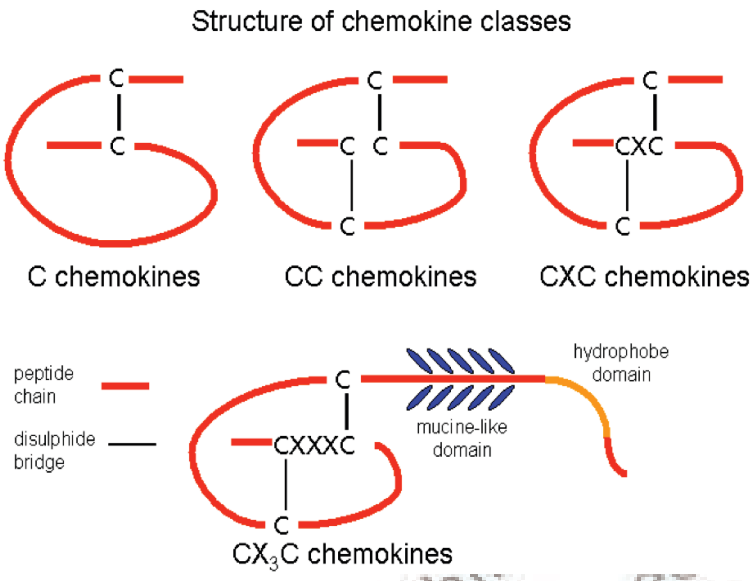

Type of chemokine	Structure	Action and example
C-X-C	1 amino acid residue separating the first 2 of the 4 conserved cysteine residues	Involved inneutrophil activationandchemotaxisExample-IL-8
C-C	The first 2 conserved cysteine residues remain adjacent	Attract monocytes, eosinophils, basophils, lymphocytesExamples:Monocyte chemoattractant protein (MCP-1)Eotaxin Macrophage inflammatory protein- 1α (MIP-1α)Regulated and normal T--cell expressed and secreted (RANTES)
C chemokines	Lack the 1st and 3rd of the 4 conserved cysteines	Specific forlymphocytesExample- lymphotactin
CX3C	Contain 3 amino acids between the 2 cysteines	The only known member of this class is calledfractalkine.

Solution to Question 9:

Fractalkine is the only known member of the CX3C chemokine group.

CX3C chemokines contain 3 amino acids between the 2 cysteines.

This chemokine exists in two forms:

• Cell surface-bound protein -

• Induced on endothelial cells by inflammatory cytokines

• Promotes the strong adhesion of monocytes and T cells

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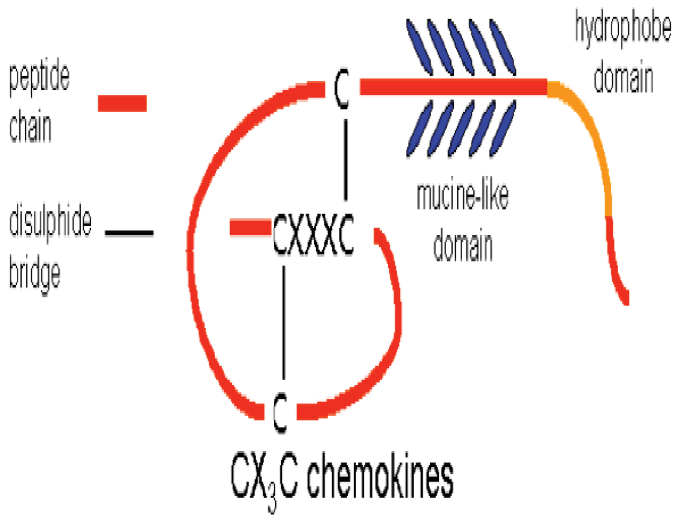
• Soluble form -

• Derived by proteolysis of the membrane-bound protein

• Potent chemoattractant activity for the same cell.

The image below shows the structure of CX3C chemokine.



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Solution to Question 10:

MCP-1 belongs to the CC type of chemokine. Here, the first two conserved cysteine residues remain adjacent to each other.

The CC chemokines include:

• Monocyte chemoattractant protein (MCP1)

• Eotaxin

• Macrophage inflammatory protein1α (MIP1α)

• Regulated and normal T-cell expressed and secreted (RANTES)

The image below shows the structure of C-C chemokine:

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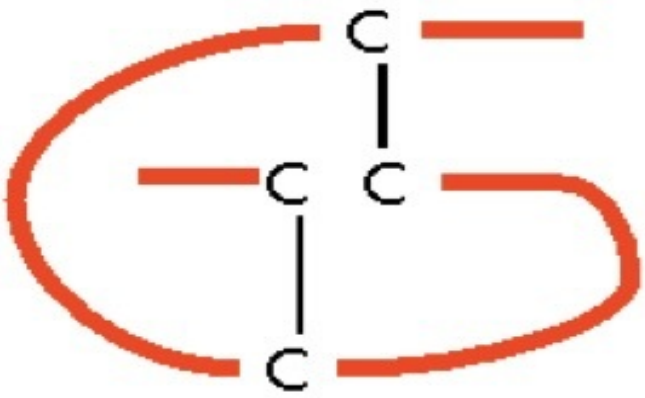

CC chemokines

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Solution to Question 11:

During inflammation, there are reduced levels of albumin.

This occurs in order to allow an increase in the liver's capacity to synthesize acute phase reactants. Hence, albumin is called a negative phase reactant.

Negative acute-phase proteins concentration decreases during inflammation. These are:

- Albumin
- Transferrin
- Retinol-binding protein
- Antithrombin
- Transcortin
- Alpha 2-HS glycoprotein
- Alpha-fetoprotein
- Thyroxin-binding protein
- Insulin-like growth factor 1
- Factor 12

Acute-phase proteins are plasma proteins synthesized by the liver in response to inflammation. These include C-reactive protein (CRP), fibrinogen, and serum amyloid A (SAA) protein. The synthesis of these molecules in hepatocytes is stimulated by cytokines. IL-6 stimulates the synthesis of CRP and fibrinogen and IL-1 or TNF for SAA.

Solution to Question 12:

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In this scenario, the woman has a chronic illness, rheumatoid arthritis. In chronic disease states, elevated plasma concentrations of hepcidin cause anemia. Increased hepcidin reduces the availability of iron.

Fibrinogen binds to red cells and causes rouleaux formation. They sediment more rapidly at unit gravity than do individual red cells. This is the basis for measuring the erythrocyte sedimentation rate in inflammation.

C-reactive protein (CRP) and serum amyloid A (SAA) bind to microbial cell walls. They act as opsonins and fix complement. They also bind chromatin.

Solution to Question 13:

Platelet-activating factor (PAF) primarily causes vasoconstriction.

PAF is a phospholipid-derived mediator known to have multiple inflammatory effects. It may be secreted by the following:

• Platelets

• Basophils

• Mast cells

• Neutrophils

• Macrophages

• Endothelial cells.

Its functions include:

• Platelet aggregation

• Vasoconstriction

• Bronchoconstriction

• Leukocyte adhesion

• Vascular permeability and vasodilation at low doses

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Solution to Question 14:

The critical step in complement activation is the proteolysis of the third (and most abundant) component, C3.

The complement system can be activated by one of three pathways:

• Classical pathway - antibody-mediated and triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen

• Alternative pathway - triggered by microbial surface molecules in the absence of antibody

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• Lectin pathway - plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1.

All three pathways of complement activation lead to the formation of an active enzyme called the C3 convertase. It splits C3 into two functionally distinct fragments, C3a and C3b.

Solution to Question 15:

The deficiency of C1 INH causes hereditary angioedema.

C1-inhibitor (C1 INH)is the largest member of the serpin superfamily of proteins. It normally inhibits the following:

• Complement system

• Kallikrein system

• Factor XII or Hageman factor

Deficiency of C1 INH is associated with hereditary angioedema (hereditary angioneurotic edema). It leads to decreased C4 and C2 levels and bradykinin accumulation. There is swelling due to leakage of fluid from blood vessels into connective tissue. It is an autosomal dominant disorder.

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Solution to Question 16:

Bradykinin results in vasodilation.

Kinins are vasoactive peptides derived from plasma proteins called kininogens, by the action of specific proteases called kallikreins. The enzyme kallikrein cleaves high molecular weight kininogen, to produce bradykinin.

Actions of bradykinin:

• Increases vascular permeability

• Potent vasodilator

• Contraction of smooth muscle

• Dilation of blood vessels

• Pain when injected into the skin

Solution to Question 17:

IL-4 is an anti-inflammatory cytokine and does not have any effect on vascular permeability.

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Inflammatory change	Principal Mediators
Vasodilation	HistaminеProstaglandins
Increased vascular permeability	HistamineandserotoninC3aandC5a(by the release of vasoactive amines from mast cells, other cells)LeukotrienesC4,D4, E4,
Chemotaxis, leukocyte recruitment, activation	TNF, IL-1ChemokinesC3aand C5aLeukotriene B4
Fever	IL-1, TNFProstaglandins
Pain	ProstaglandinsBradykinin
Tissue damage	Lysosomal enzymes of leukocytesReactive oxygen species

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Solution to Question 18:

Histamine is involved in the mediation of vascular events of inflammation, not fever.

Fever is characterized by an elevation of body temperature, usually by 1° to 4°C. It is one of the most prominent manifestations of the acute-phase response, especially if associated with infection.

Substances that induce fever are called pyrogens. They may be exogenous or endogenous.

• Endogenous pyrogens - IL-1, TNF, prostaglandins

• Exogenous pyrogens -

• Lipopolysaccharides of bacterial walls

• They stimulate leukocytes to release endogenous pyrogens (IL-1 and TNF)

Cytokines result in an increase in cyclooxygenases that convert arachidonic acid into prostaglandins. These prostaglandins are produced in the vascular and perivascular cells of the hypothalamus. In the hypothalamus, they stimulate the production of neurotransmitters that reset the temperature setpoint to a higher level. This is especially by PGE2.

Solution to Question 19:

IL-1 is an endogenous pyrogen

Substances that induce fever are called pyrogens. They may be exogenous or endogenous.

• Endogenous pyrogens - IL-1, TNF, prostaglandins

• Exogenous pyrogens -

• Lipopolysaccharides of bacterial walls

• They stimulate leukocytes to release endogenous pyrogens (IL-1 and TNF)

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In the hypothalamus, prostaglandins such as PGE2 stimulate the production of neurotransmitters that reset the temperature setpoint at a higher level. Aspirin decreases fever by inhibiting prostaglandin synthesis.

Solution to Question 20:

Caspase- 1 activates the biologically active form of IL-1.

IL-1 is involved in pyroptosis, a form of programmed cell death that is different from apoptosis and necrosis. It is involved in the clearance of necrotic and microbe-infected cells. It occurs in the following sequence:

• Activation of the inflammasome complex

• Activation of caspase-1

• Generation of IL-1 - results in fever, inflammation, leukocyte recruitment

Solution to Question 21:

TH2 cells secrete IL4, IL5, and IL13.

Three subsets of CD4+ T cells secrete different types of cytokines and elicit different types of inflammation.

Solution to Question 22:

Tertiary lymphoid organs are seen in autoimmune conditions such as:

• Hashimoto thyroiditis - in the thyroid

• Rheumatoid arthritis - in the synovium

• SLE (systemic lupus erythematosus) - in the kidneys

Tertiary lymphoid organs are a feature of chronic inflammatory conditions. Here, the accumulated lymphocytes, antigen-presenting cells, and plasma cells cluster together to form lymphoid tissues resembling lymph nodes.

Solution to Question 23:

The given histopathological findings in a patient with tuberculosis are suggestive of granulomatous inflammation, with epithelioid and multinucleated giant cells. These cells are derived from the monocyte-macrophage lineage.

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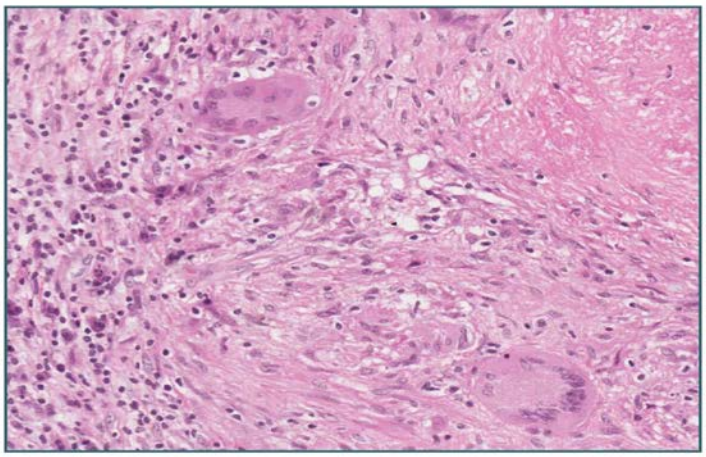
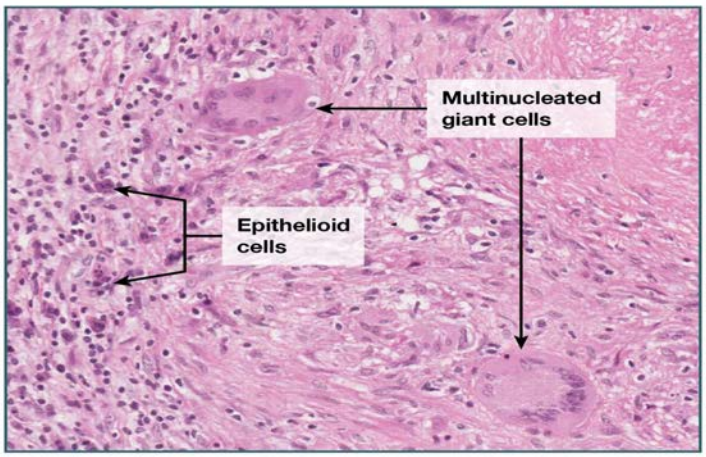
Tuberculoid granuloma



Tuberculoid granuloma



Macrophages activated by IFN-γ develop into cells with abundant cytoplasm. They resemble epithelial cells and are thus called epithelioid cells. Some activated macrophages may fuse, forming multinucleated giant cells. Collections of activated macrophages, often with T lymphocytes are seen in granulomatous inflammation. Sometimes it is associated with central caseating necrosis.

Granulomas may be formed in response to various stimuli:

• Immune granulomas - due to T-cell mediated response; macrophages activate T cells to produce cytokines, such as IL-2 and IFN-γ

• Foreign body granulomas - due to inert foreign bodies in the absence of a T-cell mediated response

Solution to Question 24:

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Kikuchi's lymphadenitis is associated with histiocytic necrotizing lymphadenitis. It does not show epithelioid granulomatous lesions.

Common conditions characterized by epithelioid granuloma formation:

• Tuberculosis

• Sarcoidosis (non-caseating granuloma)

• Brucellosis

• Cat scratch disease (stellate shaped or round granuloma)

• Syphilis (gumma)

• Lymphogranuloma inguinale

• Leprosy

• Inflammatory bowel disease

• Toxoplasmosis

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Solution to Question 25:

The given histopathological image of a lymph node shows a non-caseating granuloma. Tuberculosis is least likely as it is commonly associated with caseating granulomas.

Non-caseating granulomas can be seen in the following conditions:

• Leprosy

• Cat-scratch disease

• Sarcoidosis

• Berylliosis

• Crohn's disease

• Hypersenitive pneumonitis

• Foreign body granuloma

• Q fever

• Granulomatosis with polyangiitis (Wegener's).

• Hodgkin's lymphoma

Solution to Question 26:

Stellate granuloma is seen in cat-scratch disease. It is also known as subacute regional lymphadenitis.

It is a bacterial infection caused by Bartonella henselae. It is acquired following contact with infected animals (commonly cats).

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Regional lymph nodes demonstrate:

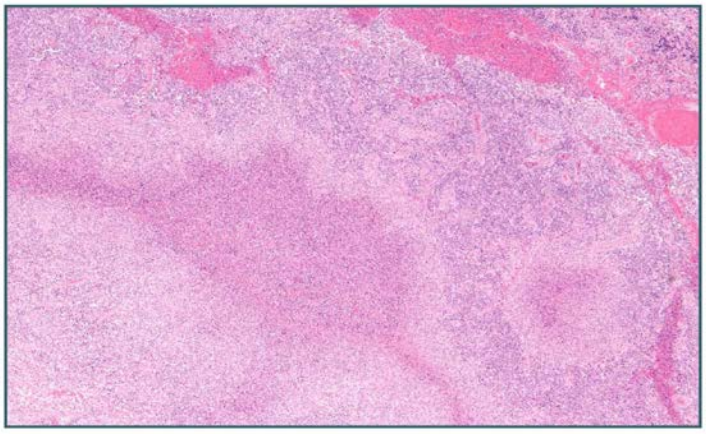
• Follicular hyperplasia with circumscribed central stellate necrosis with neutrophils

• Surrounded by palisading histiocytes (suppurative granulomas)

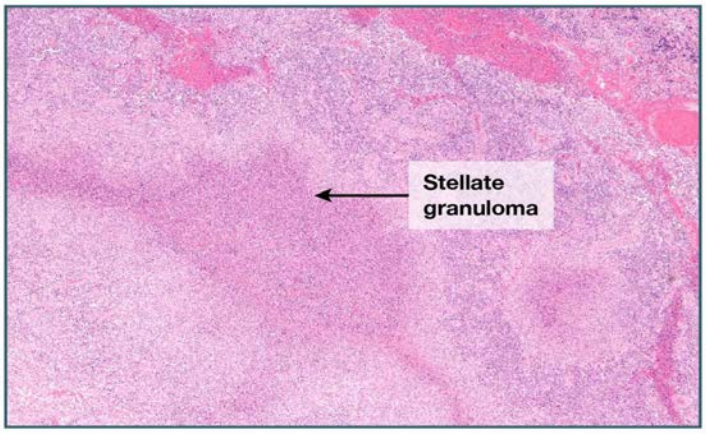
• Sinuses packed with monocytoid B cells

• Usually, there are no perifollicular and intrafollicular epithelioid cells

Cat Scratch Disease



Cat Scratch Disease



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Tissue Repair

Question 1:

Which of the following structures lack labile cells?

a) Vagina

b) Salivary gland

c) Uterus

d) Liver

Question 2:

Which of the following tissues does not consist of stable cells?

a) Liver

b) Pancreas

c) Smooth muscle

d) Cardiac muscle

Question 3:

Which of the following does not contain permanent cells?

a) Neurons

b) Cardiac cells

c) Skeletal muscle

d) Smooth muscle

Question 4:

Oval cells are seen in which of the following?

a) Ovary

b) Liver

c) Lung

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d) Eyes

Question 5:

Which of the following is a false statement regarding TGF-°?

a) It increases the synthesis of collagen

b) It increases the degradation of the extracellular matrix

c) It is involved in the development of fibrosis in solid organs

d) It is an anti-inflammatory cytokine

Question 6:

All of the following delay healing except:

a) Glucocorticoid deficiency

b) Local pressure

c) Location of injury

d) Vitamin C deficiency

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Question 7:

In healing by primary intention, by when do macrophages replace neutrophils at the site of injury?

a) Day 2

b) Day 3

c) Day 5

d) Day 4

Question 8:

A 38-year-old man underwent excision of a lipoma. The swelling had been excised with a clear linear incision and was sutured cleanly. In this wound, when would you expect peak neovascularization?

a) Day 4

b) Day 3

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c) Day 5

d) Day 7

Question 9:

A patient presented with an abscess on his back. Septic precautions were taken and the abscess was drained. On follow up, a healthy scar was visible. What is the type of collagen seen in the provisional matrix in this type of healing?

a) Type I

b) Type II

c) Type III

d) Type IV

Question 10:

The accumulation of excessive amounts of collagen during repair may give rise to which of the following?

a) Adherence of scar

b) Dehisence of scar

c) Contracture of scar

d) Hypertrophy of scar

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Question 11:

A 24-year-old man comes with the following findings. He says that he cut himself while shaving 3 months back. What is the diagnosis?

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a) Exuberant granulation

b) Hypertrophic scar

c) Keloid

d) Pyogenic granuloma

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Question 12:

A patient presented to the OPD with the following finding on her finger. She says that she cut her finger while chopping vegetables 2 weeks ago. What is the likely diagnosis?

a) Keloid

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b) Hypertrophic scar

c) Exuberant granulation

d) Pyogenic granuloma

Question 13:

In postoperative patients, what is the strength of the incision site in comparison with normal skin following suture removal at the end of 1 week?

a) 10

b) 30

c) 50

d) 70

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Answer Key

Question No.	Correct Option
1	d
2	d
3	d
4	b
5	b
6	a
7	b
8	c
9	c
10	d
11	c
12	c
13	a

Detailed Explanations

Solution to Question 1:

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The liver contains stable cells, not labile cells.

Based on the regenerative capacity of cells, tissues are classified into 3 types:

• Labile tissues

• Stable tissues

• Permanent tissues

Labile cells refer to continuously proliferating cells that are lost and replaced by the maturation of stem cells and the proliferation of these mature cells. Tissues containing these cells can readily regenerate after an injury as long as the pool of stem cells is preserved.

Some examples of labile cells include:

• Hematopoietic cells in the bone marrow

• Majority of surface epithelia -

• Stratified squamous epithelia of the skin, oral cavity, vagina, and cervix

• Cuboidal epithelia of the ducts draining exocrine organs (salivary glands, biliary tract)

• Columnar epithelium of the GIT, uterus, and fallopian tubes

• Transitional epithelium of the urinary tract

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Solution to Question 2:

Cardiac muscle does not contain stable cells. It contains permanent cells which are terminally differentiated and non-proliferative.

Based on the regenerative capacity of cells, tissues are classified into 3 types:

• Labile tissues

• Stable tissues

• Permanent tissues

Stable cells are quiescent (in the G0 stage of the cell cycle) and have only minimal proliferative activity in their normal state. However, they can divide in response to injury or loss of tissue mass.

They include the following:

• Parenchyma of solid tissues (liver, kidney, and pancreas)

• Endothelial cells

• Fibroblasts

• Smooth muscle cells

Solution to Question 3:

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Smooth muscle does not contain permanent cells. It consists of stable cells that are capable of dividing in response to injury or loss of tissue mass.

Based on the regenerative capacity of cells, tissues are classified into 3 types:

• Labile tissues

• Stable tissues

• Permanent tissues

Permanent cells are those which are considered to be terminally differentiated and non-proliferative in postnatal life. In permanent tissues, the repair is typically dominated by scar formation. These cells include:

• Neurons

• Cardiac muscle

• Skeletal muscle - contains satellite cells attached to the endomysial sheath which have some regenerative capacity

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Solution to Question 4:

Oval cells refer to stem cells in the liver. They are located in the canals of Hering.

Regeneration of the liver occurs by two major mechanisms:

• Proliferation of remaining hepatocytes - occurs following partial hepatectomy (resection of up to 90% of the liver can be corrected by this mechanism)

• Repopulation from progenitor cells (oval cells) - occurs following chronic liver injury or inflammation

Solution to Question 5:

TGF-° (transforming growth factor-°) decreases the degradation of the extracellular matrix by inhibiting metalloproteinases.

It is produced by most cells in granulation tissue, including alternatively activated macrophages.

The functions of TGF-° include:

• Stimulates fibroblast migration and proliferation

• Increases synthesis of collagen and fibronectin (connective tissue proteins)

• Decreased degradation of ECM by inhibiting metalloproteinases

• Involved in scar formation after injury

• Development of fibrosis in lung, liver, and kidneys following chronic inflammation

• Anti-inflammatory action by inhibiting lymphocyte proliferation and activity

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Solution to Question 6:

Glucocorticoid excess results in delayed healing, not glucocorticoid deficiency.

Various factors affect wound healing including mechanical factors (pressure and torsion and site of injury) and location and extent of the injury.

Vitamin C helps in the activation of prolyl and lysyl hydroxylases which help in the hydroxylation of procollagen. As inadequately hydroxylated procollagen is vulnerable to enzymatic degradation, vitamin C plays an essential role in wound healing.

Solution to Question 7:

By day 3 of healing by primary intention, macrophages replace the neutrophils at the site of injury.

The sequence of events in wound healing is as follows:

Time after injury	Events
Within 24 hours	Neutrophils:Migratefrom the incision margin towards the f ibrin clotReleaseproteolytic e nzymesthat begin to clear the debrisBasal cells:Located at t he cut edge of the epidermisS howincreased mitotic activity
24 to 48 hours	Epithelial cells:Migrate andpr oliferatefrom the wound edge s towards the centerDeposit basement membrane compo nentsForm acontinuousepith elial layerthat closes the wou nd
Day 3	Macrophagesbecome predom inant, with very few neutroph ilsGranulation tissueprogress ively invades the incision spa ceCollagen fibersat the incisi on marginsIncreased thickne ss of the epithelial layer thro ugh continuedepithelialprolif eration
Day 5	Neovascularizationreaches its peakas granulation tissue fills the incisional spaceAs new v essels areleaky, new granulati on tissue is oftenedematous
2nd week	Continued collagen accumula tionFibroblast proliferation.

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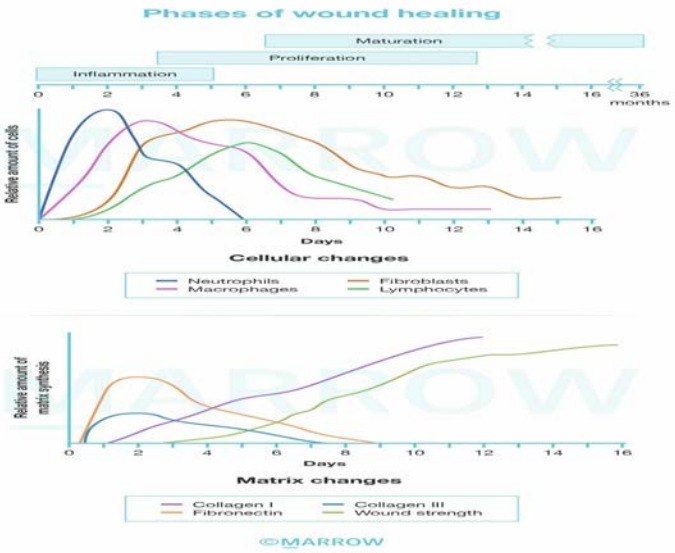
Time after injury	Events
End of the 1stmon th	Scar contains cellular connec tive tissueLargely devoid of i nflammatory cellsCovered by an essentiallynormal epider mis



Solution to Question 8:

The given clinical scenario of a clean surgical incision that is sutured is an example of healing by primary intention. In this type of healing, neovascularization reaches its peak by day 5, as granulation tissue fills the incisional space.

These new vessels are leaky, allowing the passage of plasma proteins and fluid into the extravascular space. Hence, new granulation tissue is often edematous.

Solution to Question 9:

The given scenario is an example of wound healing by secondary intention. The initial provisional matrix in this type of healing is composed of type III collagen, fibrin, and plasma fibronectin.

It is later replaced by a matrix composed primarily of type I collagen.

This type of healing occurs when cell or tissue loss is more extensive, such as in large wounds, abscesses, ulceration, and ischemic necrosis in parenchymal organs. The repair process involves a combination of regeneration and scarring.

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Solution to Question 10:

Accumulation of excessive amounts of collagen during repair leads to the formation of hypertrophic scar. When this scar tissue grows beyond the boundaries of the original wound, it is known as a keloid.

Collagen plays a role in the normal adherence of tissue edges at the site of injury. Contraction in the size of a wound is an important part of the normal healing process. An exaggeration of this process gives rise to contractures. They are particularly prone to develop on the palms, soles, anterior thorax and are commonly seen after serious burns.

Inadequate formation of granulation tissue or formation of a scar leads to wound dehiscence and ulceration.

The following image shows a hypertrophic scar.

Solution to Question 11:

The history of a shaving cut and the image showing a large area of scar tissue are suggestive of a keloid.

A keloid refers to excess accumulation of collagen at the scar site with growth of the scar tissue beyond the boundaries of the original wound. It does not regress.

Option A: Exuberant granulation or proud flesh refers to the protrusion of excessive amounts of granulation tissue above the level of the surrounding skin. This blocks re-epithelialization.

Option B: The accumulation of excessive amounts of collagen may give rise to a raised scar known as a hypertrophic scar. However, it remains within the boundaries of the original scar.

Option D: Pyogenic granuloma is a benign, vascular tumor.

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Solution to Question 12:

The given scenario and clinical findings are suggestive of exuberant granulation.

It is a deviation in wound healing where excessive amounts of granulation tissue protrude above the level of the surrounding skin and blocks re-epithelialization. It is also known as proud flesh.

Solution to Question 13:

When sutures are removed, usually at 1 week, the wound strength is approximately 10% of that of normal skin.

This increases rapidly over the next 4 weeks. Wound strength reaches approximately 70 to 80% of normal by 3 months. Beyond this, there is not much improvement.

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Disorders of Hemodynamics and Hemostasis

Question 1:

A patient presented with the following finding. Which of the following can cause this condition?

a) 1 and 3

b) 2 and 3

c) 1 and 4

d) 2 and 4

Question 2:

Which of the following statements is false about transudate?

a) It is a non-inflammatory edema or effusion

b) It is a protein-poor and cell-poor fluid

c) It has a specific gravity of less than 1.012

d) It is caused by increased vascular permeability

Question 3:

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In which of the following conditions does edema result from decreased colloidal osmotic pressure?

a) Congestive heart failure

b) Deep venous thrombosis

c) Nephrotic syndrome

d) Renal artery stenosis

Question 4:

Which of the following is not true?

a) Periorbital edema is seen in severe renal disease

b) Pitting edema occurs due to edema in subcutaneous tissues

c) Exudative effusions are typically protein-rich and cloudy

d) Chylous peritoneal effusion is an example of an exudate

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Question 5:

Which of the following statements is false?

a) Hyperemia is an active process

b) Congestion is a passive process

c) Arteriolar dilation is seen in hyperemia.

d) Congestion is seen in inflammation

Question 6:

An 82-year-old man presents to the ER with fever and tachycardia since last night. On examination, he is drowsy, his BP is 92/54 mmHg and his temperature is 103 °F. His wife tells you he had been diagnosed with a urinary tract infection 5 days ago for which he had been prescribed antibiotics. He is a known case of colon cancer and also has a history of myocardial infarction 6 months ago. What type of shock is he likely suffering from?

a) Anaphylactic shock

b) Cardiogenic shock

c) Hypovolemic shock

d) Septic shock

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Question 7:

What is the first step of hemostasis?

a) Platelet plug formation

b) Arteriolar vasoconstriction

c) Tissue factor release

d) Binding of platelets to exposed vWF

Question 8:

Which of the following coagulation factors is bound and activated by tissue factor?

a) VIII

b) XII

c) X

d) VII

Question 9:

Which of the following is not found in α-granules of platelets?

a) Fibrinogen

b) vWF

c) Factor V

d) Serotonin

Question 10:

A patient with prolonged bleeding is found to have vitamin K deficiency. The function of which of the following clotting factors would be unaffected in this condition?

a) II

b) V

c) IX

d) X

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Question 11:

The function of which of the following factors is not screened by the partial thromboplastin time assay?

a) II

b) V

c) XII

d) VII

Question 12:

What is the function of thrombomodulin?

a) Anticoagulant

b) Procoagulant

c) Fibrinolytic

d) Thrombin activator

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Question 13:

Leiden mutation is of factor:

a) V

b) VIII

c) I

d) X

Question 14:

Which of the following is not a part of Virchow's triad?

a) Endothelial injury

b) Turbulent blood flow

c) Hyperviscosity

d) Hypercoagulability

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Question 15:

In which of the following structures are lines of Zahn seen?

a) Thrombi

b) Artery

c) Vein

d) Muscle

Question 16:

Which of the following do chicken fat clots refer to?

a) Post-mortem clots

b) Antemortem venous thrombi

c) Antemortem mural thrombi

d) Antemortem arterial thrombi

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Question 17:

Saddle embolus is seen in which of the following vessels?

a) Pulmonary artery

b) Pulmonary vein

c) Ascending aorta

d) Descending aorta

Question 18:

Following autopsy, an H&E stained specimen of the lung was obtained which is given below. What could be the likely cause of death?

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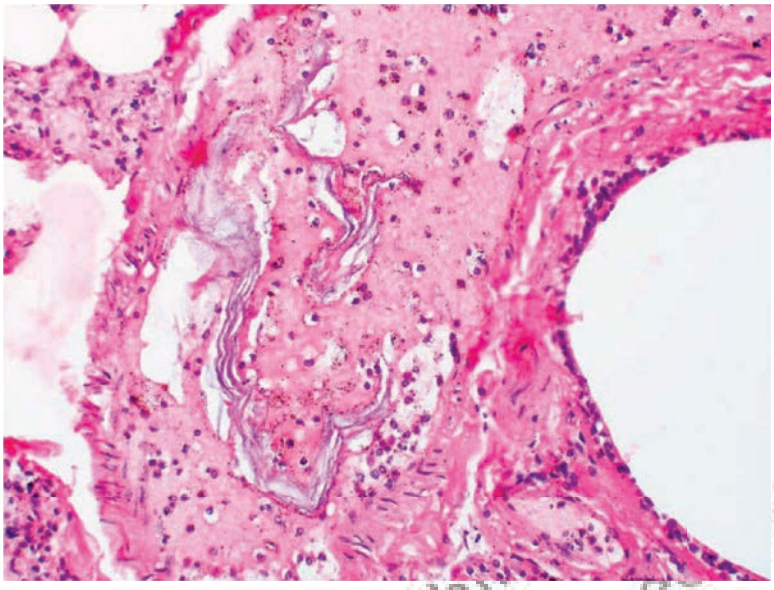

a) Pulmonary embolism

b) Marrow embolism

c) Air embolism

d) Amniotic fluid embolism

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Question 19:

Which of the following is not seen in patients with DIC?

a) Decreased fibrinogen

b) Increased activated partial thromboplastin time

c) Decreased prothrombin time

d) Increased fibrin degradation products

Question 20:

Red infarcts do not occur in which of the following organs?

a) Testes

b) Lung

c) Small intestine

d) Spleen

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Question 21:

A bridge construction worker presents with generalized bone pain. He is found to have ischemic necrosis of bilateral femoral heads, left tibia, and right humerus. Caisson disease is suspected. What is this condition related to?

a) Change in pressure

b) Change in viscosity

c) Change in blood flow

d) Change in coagulability

Question 22:

Chest X-ray of a 60-year-old woman with dyspnoea at rest revealed right-sided pleural effusion. A pleural fluid analysis was done. Which of the following findings would rule out a transudative cause?

a) High plasma protein content

b) Little or no cellular material

c) Low specific gravity

d) Low fibrin content

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Answer Key

Question No.	Correct Option
1	c
2	d
3	c
4	d
5	d
6	d
7	b
8	d
9	d
10	b
11	d

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12	a
13	a
14	c
15	a
16	a
17	a
18	d
19	c
20	d
21	a
22	a

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Detailed Explanations

Solution to Question 1:

The finding seen in the given image is pitting edema. Edema can be caused by elevated hydrostatic pressure and reduced colloid osmotic pressure.

Under normal circumstances, there is little net movement of fluid out of vessels due to the balance of:

• Vascular hydrostatic pressure which has the tendency to push water and salts out of capillaries into the interstitial space

• Plasma osmotic pressure or colloid oncotic pressure which has a tendency to pull water and salts back into vessels.

The pressure dynamics seen inside a capillary is given below.

Atarterial end	Atvenous end
Capillary hydrostatic pressur e = 30-35 mmHg	Capillary hydrostatic pressur e = 15-20 mmHg
Osmotic Pressure = 25 mmH g	Osmotic Pressure = 25 mmH g
Hydrostatic Pressure > Osmo tic Pressure →Fluid moves o utof the capillary	Hydrostatic Pressure < Osmo tic Pressure →Fluid moves in to the capillary

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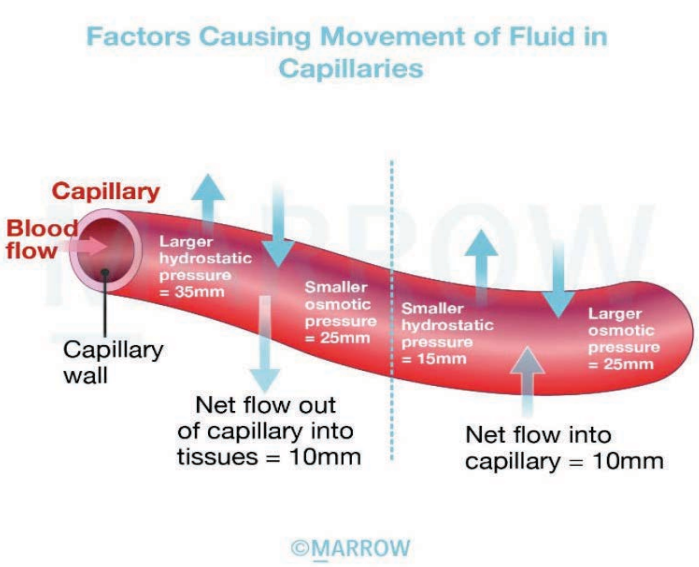

Many pathologic disorders are associated with an increase in capillary hydrostatic pressure or a decrease in plasma osmotic pressure, which lead to edema.

Solution to Question 2:

Transudate results from increased fluid pressures or diminished oncotic forces in the plasma and is not due to increased vascular permeability.

There are 2 types of extravascular fluid - transudate and exudate

These differences are depicted in the image below.

Transudate	Exudate
Non-inflammatory edema	Inflammatory edema
Ultrafiltrate of plasma	Increasedvascular permeabilitycaused by inflammatory mediators
Low protein content (<3g/dl), mainly albumin	High (>3g/dl) protein content
No tendency to coagulate	Coagulates readily due to high content of fibrinogen
Low specific gravity (<1.012)	High specific gravity (>1.018)
Low LDH levels	High LDH levels
Low cell count (< 500-1000/µL)	High cell count
Eg. Edema in congestive cardiac failure	Eg. Pus

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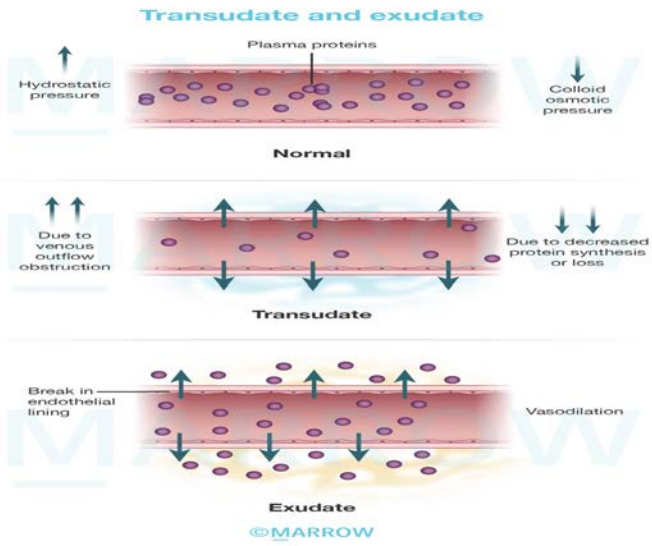

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Solution to Question 3:

In nephrotic syndrome, edema occurs due to massive proteinuria that leads to a decrease in plasma colloid osmotic pressure.

The common causes of reduced plasma osmotic pressure are conditions that cause inadequate synthesis or increased loss of albumin (mainly) and other plasma proteins from circulation. These conditions include:

- Protein-losing glomerulopathies (nephrotic syndrome)
- Liver cirrhosis (ascites)
- Malnutrition
- Protein-losing gastroenteropathy

Edema can also occur due to increased hydrostatic pressure as a result of impaired venous return. This is seen in conditions like:

- Congestive heart failure
- Deep venous thrombosis
- Renal artery stenosis

Solution to Question 4:

Chylous peritoneal effusion caused by the lymphatic blockage is an example of a transudate.

Transudative effusions are typically protein-poor, translucent, and straw-colored. However, there may be certain exceptions like chylous peritoneal effusions which may be milky due to the presence of lipids absorbed from the gut.

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Exudative effusions are protein-rich and often cloudy due to the presence of WBCs.

Subcutaneous edema has the following features:

• Dependent edema - dependent areas (towards gravity) have high hydrostatic pressures i.e., in the legs when standing and the sacrum when recumbent

• Pitting edema - finger pressure over markedly edematous subcutaneous tissue displaces the interstitial fluid and leaves a depression.

Edema resulting from renal dysfunction often appears initially in parts of the body containing loose connective tissue, such as the eyelids. Thus, periorbital edema is a characteristic finding in severe renal disease.

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Solution to Question 5:

Hyperemia is seen in inflammation, not congestion.

The differences between hyperemia and congestion are summarised below:

Hyperemia	Congestion
Active process due to arteriolar dilation	Passive process due to impaired venous outflow
Edema is absent	Edema is present
Red color of the tissues	Blue-red color of the tissue (due to deoxyhemoglobin)
Seen in inflammation	Seen in right heart failure and portal venous obstruction in cirrhosis

Solution to Question 6:

This clinical scenario is suggestive of septic shock as a result of gram-negative sepsis originating from a urinary tract infection.

Gram-negative organisms contain lipopolysaccharide in the outer membrane, which triggers the release of cytokines, such as tumor necrosis factor (TNF). These cytokines cause a cascade of events culminating in increased capillary permeability and redistribution of circulatory volume into the interstitium. It is also known as warm shock, due to fever and increased perfusion.

Other types of shock are:

• Anaphylactic shock - sudden circulatory collapse due to type I hypersensitivity reaction

• Cardiogenic shock - ventricular failure, often following myocardial infarction; is a form of cold shock

• Hypovolemic shock - due to blood or fluid loss

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Solution to Question 7:

The first step of hemostasis is arteriolar vasoconstriction.

The normal process of hemostasis is as follows:

• Arteriolar vasoconstriction - After vascular injury, local neurohumoral factors induce transient vasoconstriction.

• Primary hemostasis - The various steps involved in this process are:

• Platelets bind via glycoprotein Ib (GpIb) receptors to von Willebrand factor (vWF) on exposed extracellular matrix (ECM)

• Activation of platelets which undergo a change in shape and release their granules

• Released adenosine diphosphate (ADP) and thromboxane A2 (TxA2) induce additional platelet aggregation through platelet GpIIb-IIIa receptor binding to fibrinogen

• Formation of the primary platelet plug

• Secondary hemostasis - Local activation of the coagulation cascade involving tissue factor and platelet phospholipids results in fibrin polymerization, cementing the platelets into a definitive secondary hemostatic plug.

• Clot stabilization and resorption - Counter-regulatory mechanisms, mediated by tissue plasminogen activator (tPA, a fibrinolytic product) and thrombomodulin, confine the hemostatic process to the site of injury.

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Solution to Question 8:

The tissue factor binds and activates factor VII.

Tissue factor is produced by the subendothelial cells in the vessel wall such as vascular smooth muscle cells and fibroblasts. It is a membrane-bound procoagulant glycoprotein.

Secondary hemostasis involves a sequence of events, which results in the polymerization of fibrin. This is achieved by cross-linking fibrin monomers into insoluble strands that serve to stabilize the loose platelet clot formed in primary hemostasis.

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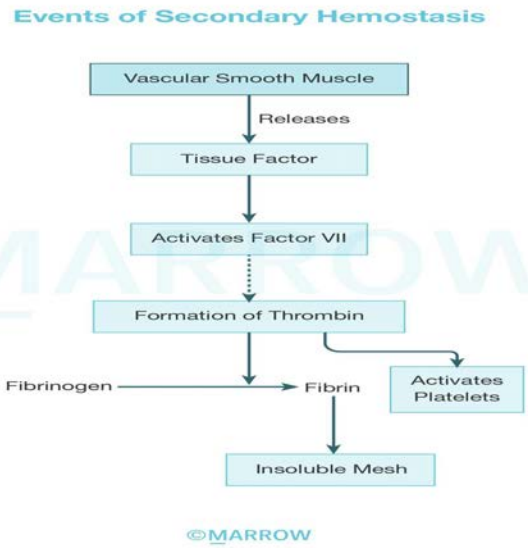

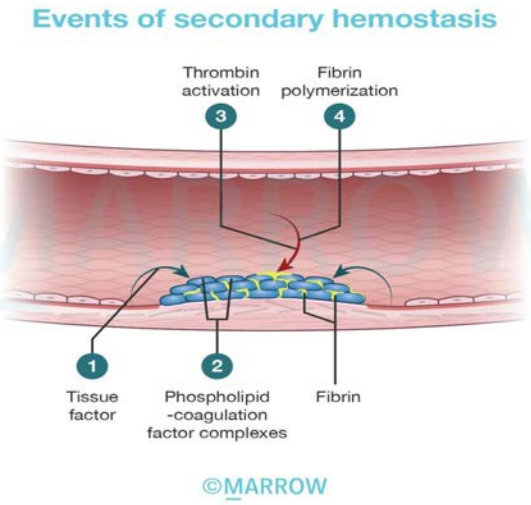

Solution to Question 9:

Serotonin is present in the dense or delta(δ) granules of the platelets, not alpha(α) granules.

Platelets are disc-shaped, anucleate cell fragments that are released from the megakaryocytes in the bone marrow into the bloodstream. The functions of these platelets depend on their glycoprotein receptors, contractile cytoskeleton, and cytoplasmic granules.

There are two types of cytoplasmic granules present in platelets:

• Alpha granules

• Dense or delta granules

α-granules contain:

• Adhesion molecule P-selectin on their membranes

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• Proteins involved in coagulation like -

• Fibrinogen

• Coagulation factor V

• vWF

• Protein factors involved in wound healing like -

• Fibronectin

• Platelet factor 4 (a heparin-binding chemokine)

• Platelet-derived growth factor (PDGF)

• Transforming growth factor ° (TGF °)

δ-granules contain:

• Adenosine diphosphate (ADP) and adenosine triphosphate (ATP)

• Ionized calcium

• Serotonin

• Epinephrine

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Solution to Question 10:

A deficiency of vitamin K does not alter the function of factor V.

Vitamin K is required as a cofactor for the γ-carboxylation of factors II, VII, IX, and X. Calcium binds to γ-carboxylated glutamic acid residues that are present in these factors during clotting.

This action of vitamin K is antagonized by drugs such as warfarin, which is widely used as an anticoagulant.

Solution to Question 11:

The partial thromboplastin time (PTT) assay screens the function of the proteins in the intrinsic pathway. As factor VII is only a part of the extrinsic pathway, it cannot be assessed by this test.

The factors assessed by the PTT assay are XII, XI, IX, VIII, X, V, and II and fibrinogen.

In this assay, clotting of plasma is initiated by the addition of negatively charged particles (e.g., ground glass) that activate factor XII (Hageman factor) together with phospholipids and calcium, and the time to fibrin clot formation is recorded.

Solution to Question 12:

Thrombomodulin is an anticoagulant.

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It is produced by all endothelial cells except those in cerebral microcirculation. It binds to thrombin on the endothelial cell surface. When bound in this complex, thrombin loses its ability to activate coagulation factors and platelets, and instead cleaves and activates protein C. Activated protein C/protein S complex is a potent inhibitor of coagulation factors Va and VIIIa. This action results in an anticoagulant effect.

The effect of recombinant thrombomodulin administration in sepsis-induced coagulopathy and DIC is being studied currently.

Other important anticoagulant substances are:

• Antithrombin III - It inhibits the activity of thrombin and other factors like XIIa, XIa, Xa, and IXa. It is activated by binding to heparin-like molecules.

• Proteins C and S - These proteins are vitamin K–dependent proteins that inactivate factors Va and VIIIa.

• Endothelial prostacyclin (PGI2) and nitric oxide (NO) - These are potent vasodilators and inhibitors of platelet aggregation.

• Tissue factor pathway inhibitor - This is derived from the endothelium and inhibits tissue factor VIIa and Xa molecules.

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Solution to Question 13:

Leiden mutation is a single nucleotide mutation that occurs in factor V. This is named after the city in The Netherlands where it was discovered.

Of the inherited causes of hypercoagulability, point mutations in the factor V gene and prothrombin gene are the most common.

Solution to Question 14:

Hyperviscosity is not part of Virchow's triad. However, hyperviscosity states as in polycythemia vera may, in turn, cause small vessel stasis that may cause thrombosis.

Virchow's triad in thrombosis:

• Injury to endothelial cells can alter local blood flow and affect coagulability.

• Abnormal blood flow (stasis or turbulence), in turn, can cause endothelial injury.

• Hypercoagulability of blood

These factors may promote thrombosis independently or in combination.

Solution to Question 15:

Thrombi often have grossly and microscopically apparent laminations called lines of Zahn. These are formed by pale platelet and fibrin deposits alternating with darker red cell-rich layers.

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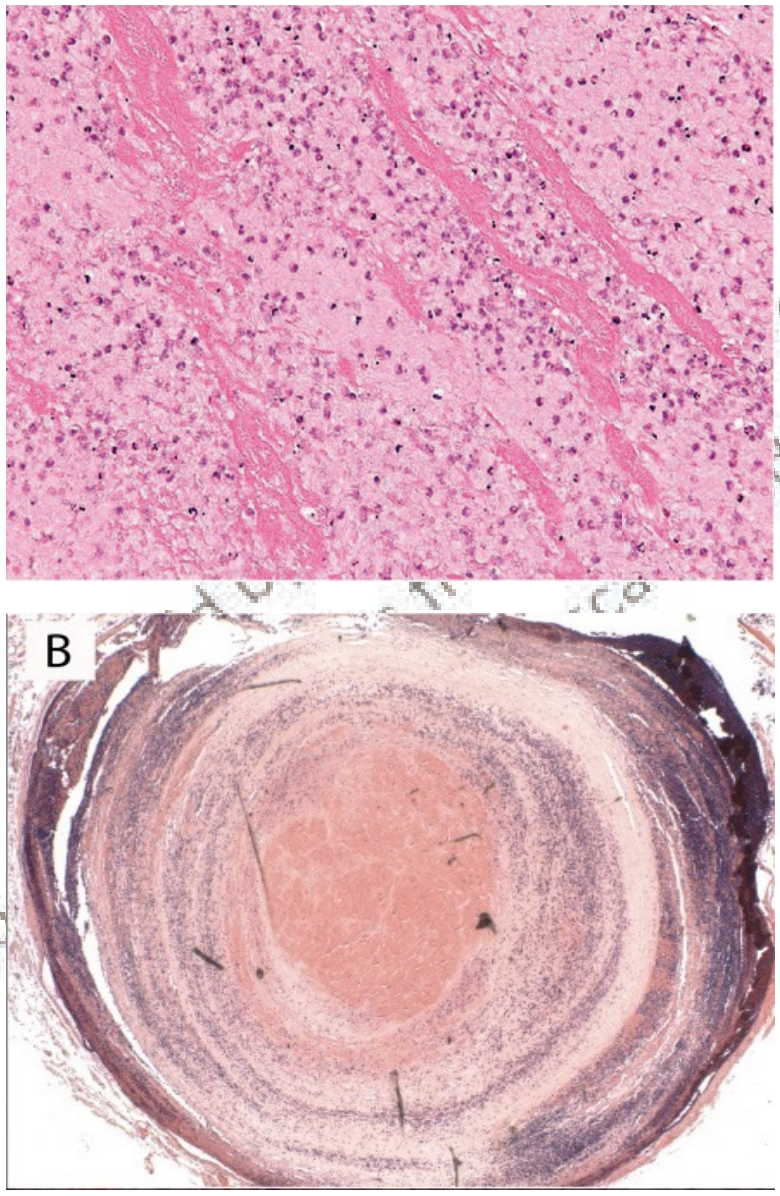
They signify that a thrombus has formed in flowing blood. Their presence can therefore distinguish antemortem clots from the nonlaminated postmortem clots.

The below histopathological image of a thrombus shows these alternating bands called lines of Zahn.



Solution to Question 16:

Chicken fat clots refer to post-mortem clots i.e., clots that are formed after death.

Postmortem clots are gelatinous and have a dark red (currant jelly) dependent portion where red cells have settled by gravity and a yellow (chicken fat) upper portion due to coagulation of plasma.

Antemortem clots can be differentiated from postmortem clots by:

• Presence of lines of Zahn

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• Attachment to the underlying vessel wall

Solution to Question 17:

An embolus in the bifurcation of the main pulmonary artery is referred to as a saddle embolus.

Pulmonary emboli (PE) originate from deep venous thromboses and are the most common form of thromboembolic disease. In more than 95% of cases, PE originates from leg deep vein thrombi (DVTs).

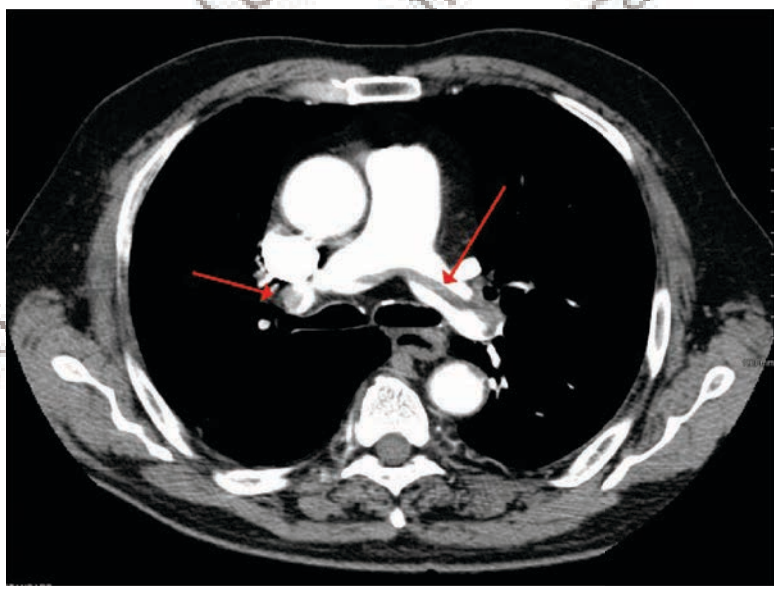
Fragmented thrombi from DVTs are carried through progressively larger veins and the right side of the heart, before slamming into the pulmonary arterial vasculature. Depending on the size of the embolus, it can have 3 fates:

• It can occlude the main pulmonary artery

• It can straddle the pulmonary artery bifurcation (saddle embolus)

• It can pass out into the smaller, branching arteries

The CT image given below shows a saddle embolus lodged in the main pulmonary artery extending into both its limbs as indicated by the red arrows.



Solution to Question 18:

The given image shows the presence of laminated swirls of squamous cells in the pulmonary arteriole which is characteristically seen in amniotic fluid embolism(AFE).

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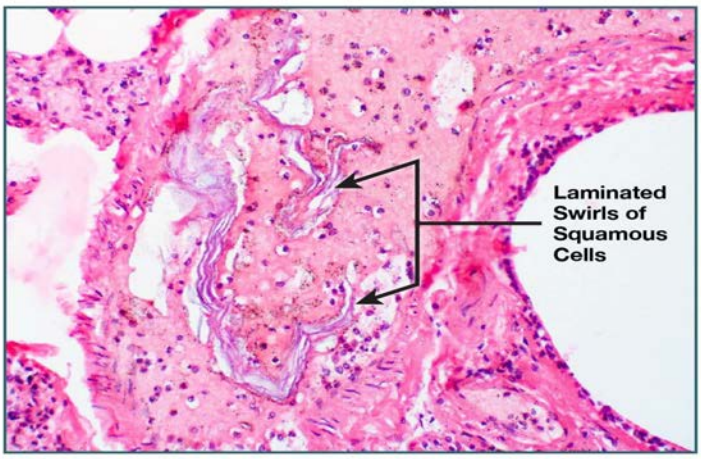
Amniotic Fluid Embolism



AFE is a life-threatening obstetric emergency characterized by sudden cardiorespiratory collapse and disseminated intravascular coagulation (DIC). The underlying cause is the infusion of amniotic fluid or fetal tissue into the maternal circulation via a tear in the placental membranes or rupture of uterine veins.

Findings at autopsy include:

• Presence in the maternal pulmonary micro-vasculature of-

• Squamous cells shed from fetal skin

• Lanugo hair

• Fat from vernix caseosa

• Mucin derived from the fetal respiratory or gastrointestinal tract

• Marked pulmonary edema

• Diffuse alveolar damage

• Presence of fibrin thrombi in many vascular beds due to DIC

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Solution to Question 19:

Increased prothrombin time (PT) is a feature of disseminated intravascular coagulation (DIC).

Disseminated intravascular coagulation (DIC) is an acute, subacute, or chronic thrombohemorrhagic disorder occurring as a secondary complication in a variety of diseases.

It is characterized by the activation of the coagulation sequence, which leads to the formation of microthrombi throughout the microcirculation of the body. As a consequence of the thrombotic diathesis, there is a consumption of platelets, fibrin, and coagulation factors and, secondarily, activation of fibrinolytic mechanisms.

Laboratory investigations in DIC reveal the following:

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• Thrombocytopenia

• Prolonged prothrombin time (PT)/thrombin time (TT)

• Decreased fibrinogen level

• Elevated levels of fibrin-split products (D-dimers)

Solution to Question 20:

White infarcts occur in the spleen, not red infarcts.

Red infarcts occur in the following conditions:

• Venous occlusions (e.g., testicular torsion)

• Loose, spongy tissues (e.g., lung), where blood can collect in the infarcted zone

• Tissues with dual circulations (e.g., lung and small intestine), which allows blood to flow from an unobstructed parallel supply into a necrotic zone

• Tissues previously congested by sluggish venous outflow

• When flow is re-established at a site of previous arterial occlusion and necrosis (e.g., following angioplasty of an arterial obstruction)

The below image shows a hemorrhagic, roughly wedge-shaped pulmonary red infarct.

White infarcts occur with arterial occlusions in solid organs with end-arterial circulation (e.g., heart, spleen, and kidney), and where tissue density limits the seepage of blood from adjoining capillary beds into the necrotic area.

The below image shows a sharply demarcated white infarct in the spleen.

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Septic infarctions occur when infected cardiac valve vegetations embolize or when microbes seed necrotic tissue. In these cases, the infarct is converted into an abscess, with a correspondingly greater inflammatory response.

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Solution to Question 21:

Caisson disease is a chronic form of decompression sickness which occurs when individuals experience a sudden decrease in atmospheric pressure.

It is named after the pressurized vessels that are used in bridge construction as workers in these vessels are known to suffer from both acute and chronic forms of decompression sickness.

When air is breathed at high pressure, increased amounts of gas, particularly nitrogen, are dissolved in the blood and tissues. If there is a sudden fall in pressure, the nitrogen comes out of the solution in the tissues and the blood and forms gas emboli. In Caisson disease, the persistence of gas emboli in the skeletal system leads to the development of multiple foci of ischemic necrosis. The more common sites are the femoral heads, tibia, and humeri.

Solution to Question 22:

High plasma protein content in the pleural fluid would rule out a transudative cause. In a transudative effusion, the fluid has low protein content, little or no cellular material, and low specific gravity.

It is essentially an ultrafiltrate of the blood plasma. It is produced as a result of osmotic or hydrostatic imbalance across the vessel wall. There is no increase in vascular permeability.

The table below gives the differences between transudative and exudative effusion.

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Features	Transudate	Exudate
Process	Passive (increased pressure)	Active (inflammation)
Vascular permeability	Normal	Increased
Plasma protein leak	Absent	Present
Protein content of fluid	Low S.G<1.012Low protein	High S.G>1.020High prot ein
Fibrin	Absent	Present
Inflammatory cells	Absent	Present

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Modes of Inheritance

Question 1:

Which of the following are caused by single-gene mutations?

a) Complex multigenic disorders

b) Mendelian disorders

c) Structural chromosomal disorders

d) Numerical chromosomal disorders

Question 2:

Which of the following diseases is associated with non-sense mutation?

a) ° o thalassemia

b) Alpha-thalassemia

c) Sickle-cell anemia

d) Hereditary spherocytosis

Question 3:

Which of the following traits are examples of co-dominance inheritance?

a) 2, 3 and 4 only

b) 1, 2 and 4 only

c) 1 and 5 only

d) 3, 4 and 5 only

Question 4:

What is the term for the phenomenon where a single mutant gene leads to many end-effects?

a) Pleiotropism

b) Variable expressivity

c) Polymorphism

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d) Genetic heterogeneity

Question 5:

Which of the following is autosomal dominant?

a) Cystic fibrosis

b) Duchene muscular dystrophy

c) Sickle cell anemia

d) Achondroplasia

Question 6:

A 46-year-old woman presents with sudden onset chorea and behavioral changes. Genetic investigation reveals CAG repeats. What is the mode of inheritance of this disease?

a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

Question 7:

A 28-year-old man is being evaluated for weakness and atrophy of distal limb musculature. Physical examination showing characteristic facies is given below. What is the mode of inheritance of this disease?

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a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

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Question 8:

After evaluation, a patient with the given finding is diagnosed with Bourneville disease. What is the mode of inheritance of this condition?

a) Autosomal dominant

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b) Autosomal recessive

c) X linked dominant

d) X linked recessive

Question 9:

Which of the following diseases have autosomal recessive inheritance?

a) Albinism

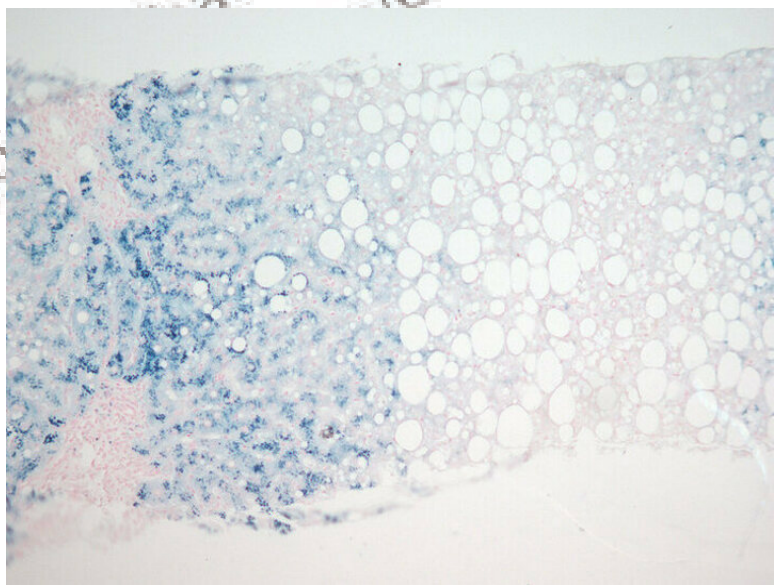
b) G6PD deficiency

c) Marfan's syndrome

d) Lesch-Nyhan syndrome

Question 10:

A 55-year-old man presents with a dark tan despite avoiding sun exposure. He was recently diagnosed with diabetes mellitus. Physical examination reveals hepatomegaly. His liver microscopy on Prussian blue staining is given below. What is the mode of inheritance of his disease?



a) Autosomal dominant

b) Autosomal recessive

c) X-linked recessive

d) X-linked dominant

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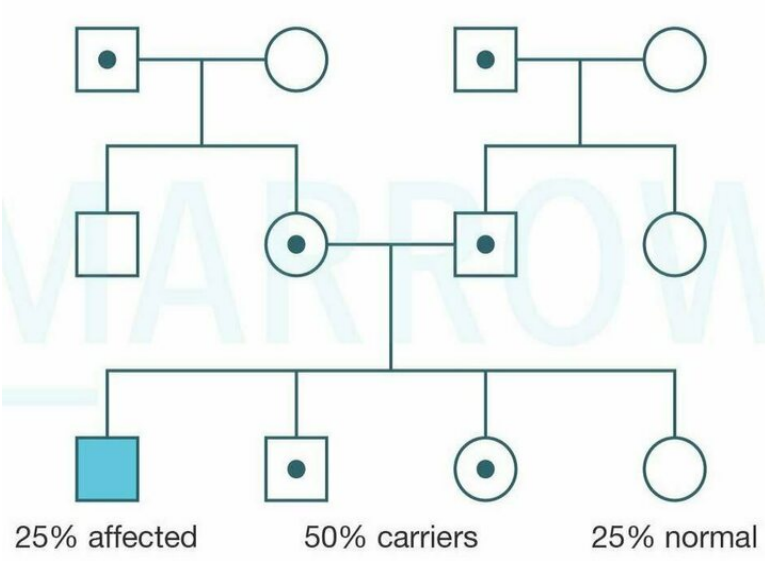
Question 11:

Which of the following patients has a disease showing the given mode of inheritance?



a) A 16-year-old boy with hundreds of adenomatous polyps throughout the colon

b) A 15-year-old boy with ataxia, cardiomegaly, scoliosis, and pes cavus

c) A 2-year-old-boy with vitamin D–resistant rickets

d) A 1-year-old boy with micro-thrombocytopenia, eczema and recurrent infections

Question 12:

A newborn on routine head-to-toe examination was found to have ambiguous genitalia. Further investigations confirmed a deficiency of the 21-hydroxylase enzyme. What is the mode of inheritance of the given condition?

a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

Question 13:

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A baby is brought to the OPD with a history of vomiting and poor feeding. Examination reveals a musty odor in the baby's sweat and urine. Guthrie's test is found to be positive. Which of the following is false about this condition?

a) The mode of inheritance is autosomal recessive

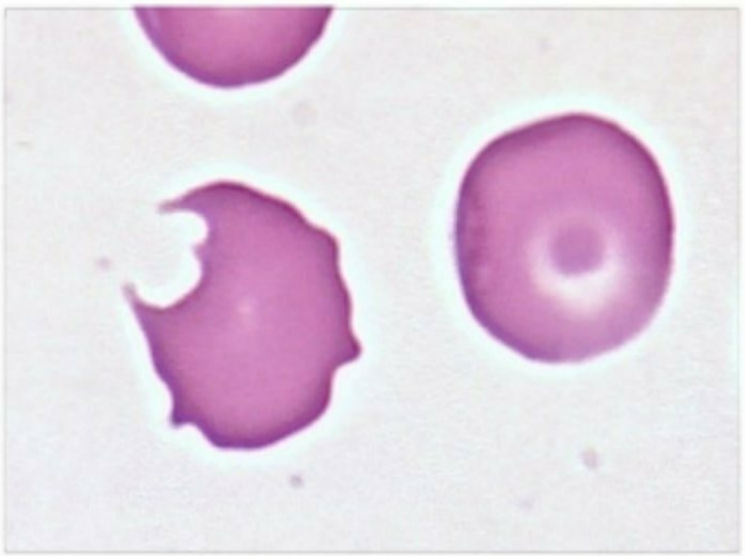
b) It is due to mutations in the PKU gene

c) It is an inborn error of amino acid metabolism

d) Enzyme deficient is phenylalanine hydroxylase

Question 14:

A 28-year old man presents to the clinic with complaints of lower back pain and passing dark red-colored urine. He was diagnosed with malaria and is on antimalarials for the past 3 days. The peripheral smear of the patient is shown below. What is the mode of inheritance of this condition?



a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

Question 15:

A 4-year-old boy is brought to the pediatrician with delayed developmental milestones. On examination, multiple lip lacerations and the given nail findings are noted. Laboratory

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reports reveal hyperuricemia. What is the mode of inheritance in this condition?

a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

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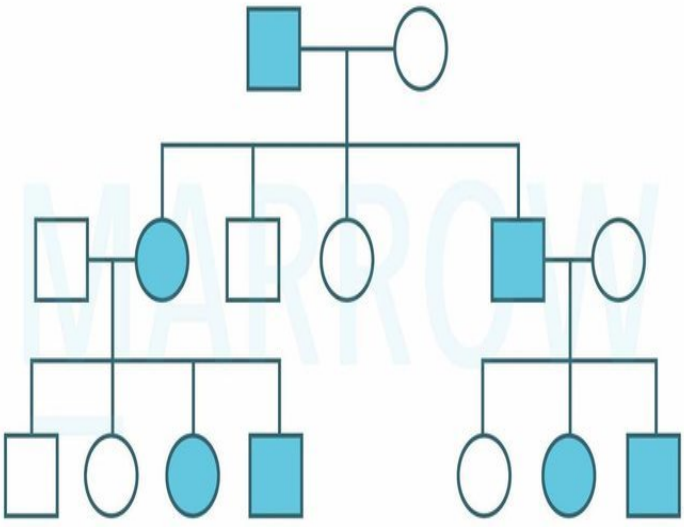
Question 16:

A 6-foot-5-inch man undergoing a routine physical examination was found to have an early diastolic murmur. His family pedigree chart is given below. Identify the mode of inheritance of this condition.



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a) Autosomal dominant

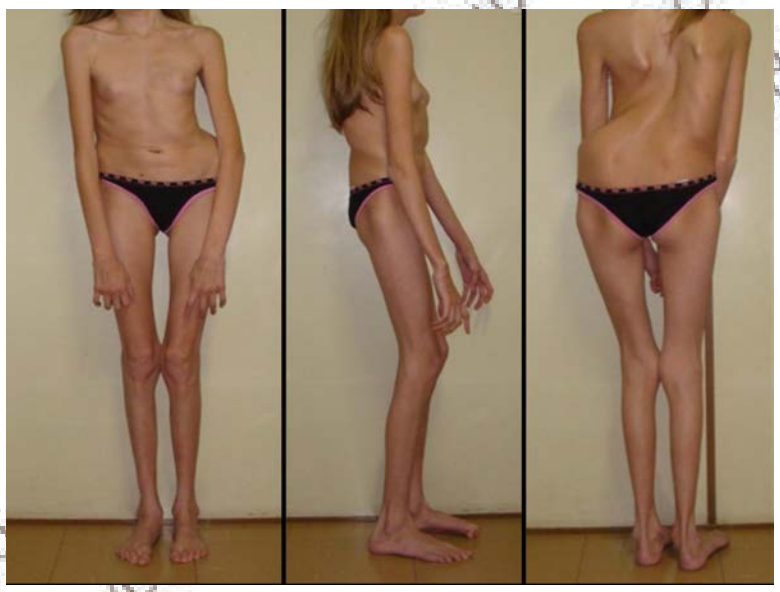
b) Autosomal recessive

c) X-linked

d) Mitochondrial

Question 17:

A 16-year-old girl with the given physical findings develops mitral regurgitation due to mitral valve prolapse. Eye examination reveals bilateral dislocation of the lens. This condition most commonly results from an inherited defect in which of the following proteins?



a) Fibrillin 1

b) Fibrillin 2

c) Collagen 2

d) Collagen 4

Question 18:

The most striking abnormalities of the Marfan syndrome are seen in which of the following systems?

a) Skeletal system

b) Muscular system

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c) Ocular system

d) Cardiovascular system

Question 19:

What is the most common cause of death in Marfan syndrome?

a) Cardiac arrhythmias

b) Mitral valve prolapse

c) Cardiac failure

d) Rupture of aortic dissection

Question 20:

Which of the following mode of inheritances is seen in Ehler–Danlos syndrome?

a) 1 and 4

b) 1 only

c) 1 and 2

d) 3 and 5

Question 21:

A 20-year-old woman presents with back pain and weakness. On examination, she is found to have lax skin. X-ray findings are shown below. Lab reports show a deficiency of lysyl hydroxylase. What is the most likely diagnosis?

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a) Ehlers-Danlos type III

b) Ehlers-Danlos type VI

c) Ehlers-Danlos type V

d) Ehlers-Danlos type IV

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Question 22:

What type of collagen is involved in the classic Ehlers-Danlos syndrome?

a) Type 1

b) Type 3

c) Type 5

d) Type 4

Question 23:

The dermatosparaxis type of Ehlers-Danlos syndrome is classified as:

a) EDS type VII a

b) EDS type VII b

c) EDS type VII c

d) EDS type IV

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Question 24:

Which of the following pair is incorrectly matched?

a) Wilson's disease - Autosomal recessive

b) Vitamin D–resistant rickets - X-linked dominant

c) Spinal muscular atrophy - Autosomal dominant

d) Wiskott–Aldrich syndrome - X-linked recessive

Question 25:

A 1-month-old infant diagnosed with primary adrenal insufficiency presented with failure to thrive, recurrent emesis, and hepatosplenomegaly. Bilateral adrenal calcification was noted radiologically. Which of the following enzyme is deficient in this condition?

a) Sphingomyelinase

b) Lysosomal acid phosphatase

c) Lysosomal glucosidase

d) Lysosomal acid lipase

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Answer Key

Question No.	Correct Option
1	b
2	a
3	c
4	a
5	d
6	a
7	a
8	a
9	a
10	b
11	b
12	b
13	b

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14	d
15	d
16	a
17	a
18	a
19	d
20	c
21	b
22	c
23	c
24	c
25	d

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Detailed Explanations

Solution to Question 1:

Mendelian disorders are caused by single-gene mutations.

A mutation is defined as a permanent change in the genetic material that can result in altered protein function and phenotypic changes.

Mutations that affect germ cells are transmitted to the progeny and can give rise to inherited diseases.

Human genetic disorders can be broadly classified into three categories:

• Single-gene mutations - these diseases usually follow the classic Mendelian pattern of inheritance.

• Chromosomal disorders - These arise from the structural or numerical alteration in the autosomes and sex chromosomes. Like a monogenic disease, they are uncommon but associated with high penetrance.

• Complex multigenic disorders - They are more common and are caused by interactions between multiple variant forms of genes and environmental factors. Such variations in genes are common within the population and are also called polymorphisms.

Solution to Question 2:

A non-sense mutation is seen in °o thalassemia.

A point mutation is a change in which a single base is substituted with a different base. The point mutations within the coding sequences of the DNA are of two types:

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• Missense mutations: These involve alteration of a single base in a triplet of bases. It leads to the replacement of one amino acid by another in the gene product. These mutations alter the meaning of the sequence of the encoded protein. Based on the substituted amino acid coded, the missense mutations are again of two types:

• Conservative missense mutation: The substituted amino acid is biochemically similar to the original. It typically causes little change in the function of the protein.

• Non-conservative missense mutation: This type of mutation replaces the normal amino acid with a biochemically different one.

• Nonsense mutations: It is a point mutation in a sequence of DNA that results in a premature stop codon.

For example, a point mutation affecting the codon for glutamine (CAG) creates a stop codon (UAG) if U is substituted for C. This change leads to premature termination of ° -globin gene translation, and the short peptide that is produced is rapidly degraded. The resulting deficiency of ° -globin chains can give rise to a severe form of anemia called ° o thalassemia.

Option B: α-thalassemias are caused by inherited deletions that result in the reduced or absent synthesis of α-globin chains.

Option C: Sickle-cell anemia is an example of non-conservative missense mutation. It occurs due to the replacement of the 6th glutamic acid by valine in the beta-globin gene on chromosome 11.

Option D: Hereditary spherocytosis (HS) is an inherited disorder caused by intrinsic defects in the red cell membrane skeleton that render red cells spheroid less deformable and vulnerable to splenic sequestration and destruction.

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Solution to Question 3:

ABO blood group and HLA are both examples of codominant inheritance.

In a codominant phenotype, alleles of a gene pair in a heterozygote are fully expressed. Thereby resulting in an offspring with a phenotype that is neither dominant nor recessive and both the alleles of a gene pair contributes to the phenotype.

Mendelian traits are usually described as dominant or recessive:

• A dominant allele produces a dominant phenotype in individuals who have one copy of the allele, which can come from just one parent.

• A recessive allele produces a recessive phenotype, in individuals who have two copies of the allele, one from each parent.

The illustration below shows the codominant inheritance pattern of the blood group.

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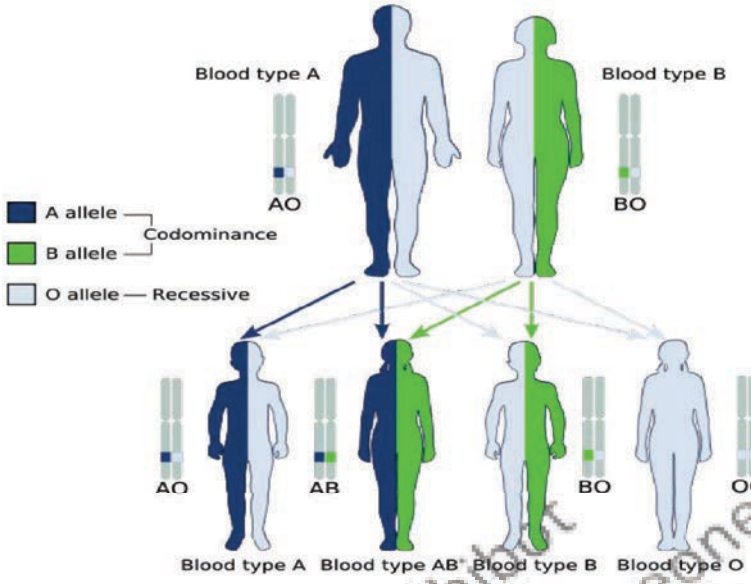

Hair colour, height, and skin color are polygenic traits.

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Solution to Question 4:

Pleiotropism is characterized by a single mutant gene, which may lead to many end effects.

For example, in sickle-cell anemia, the point mutation in the gene not only predisposes the red blood cells to hemolysis but can also block the vessels. This leads to splenic fibrosis, organ infarcts, and bone changes. The numerous differing end-organ derangements are all related to the primary defect in hemoglobin synthesis.

Option B: In variable expressivity, a trait is seen in all individuals carrying the mutant gene but is expressed differently among them.

Option C: Polymorphisms are caused by interactions between multiple variant forms of genes and environmental factors.

Option D: Genetic heterogeneity refers to mutations at several genetic loci that may produce the same trait. An example of this is profound childhood deafness - an apparently homogeneous clinical entity that results from many different types of autosomal recessive mutations.

Solution to Question 5:

Achondroplasia is an autosomal dominant disorder.

It is caused by a mutation of the fibroblast growth factor receptor-3 (FGFR-3) gene.

The primary defect is abnormal chondrocyte proliferation at the growth plate that causes development of short and thick bones.

Clinical features:

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• Short limbs

• Normal trunk

• Large head

• Saddle nose

• Exaggerated lumbar lordosis

• Severe spinal deformity may lead to cord compression

Solution to Question 6:

The given clinical scenario is suggestive of Huntington's disease. It is an autosomal-dominant inherited disorder.

Huntington disease (HD) also known as Huntington chorea is associated with CAG repeats and anticipation. It has an adult-onset and cell loss within a specific subset of neurons in the basal ganglia and cortex is seen. The characteristic features of HD include involuntary movements, dementia, and behavioral changes.

Solution to Question 7:

The given scenario and image showing the characteristic hatchet facies are suggestive of myotonic dystrophy (dystonia myotrophica). It is an autosomal dominant genetic disorder affecting muscle function.

There are mainly two types:

• DM1 - In this type, the affected gene is DMPK, which codes for myotonic dystrophy protein kinase, a protein expressed predominantly in skeletal muscle. The gene is located on the long arm of chromosome 19.

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• DM2 - It is caused by a defect of the CNBP gene on chromosome 3.

Solution to Question 8:

Tuberous sclerosis complex (TSC)/ Bourneville disease is an autosomal-dominant genetic disorder.

TSC affects the differentiation, proliferation, and migration of cells early in development. This results in a variety of hamartomatous lesions that may affect virtually every organ system of the body. Two distinct genetic loci have been identified which are on chromosome 9 (TSC1) and on chromosome 16 (TSC2).

The most common cutaneous manifestation of TSC is hypomelanotic macules (ash-leaf macules) and is observed in most children with tuberous sclerosis. It presents at birth or appears within the first few years of life and may fade or disappear in adulthood.

The following image shows an ash-leaf macule.

Solution to Question 9:

Albinism is inherited in an autosomal recessive pattern.

Solution to Question 10:

The given scenario is suggestive of hereditary hemochromatosis. It is an autosomal recessive genetic disorder that involves the HFE gene.

Hemochromatosis is characterized by excessive iron accumulation that results in tissue damage. It consists of a triad of:

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• Micronodular cirrhosis

• Bronzing of the skin

• Diabetes mellitus

Diagnosis is by elevated levels of serum ferritin, serum iron, transferrin saturation, and confirmation by a gene assay.

Note: Autosomal recessive disorders include almost all inborn errors of metabolism.

Solution to Question 11:

The given pedigree chart is pointing towards an autosomal recessive mode of inheritance. A boy with cardiomegaly, scoliosis, and pes cavus is suggestive of Friedreich's ataxia. This is an autosomal recessive inherited disease, resulting from a mutation of a gene locus on chromosome 9.

The condition causes nervous system damage and movement problems. It usually begins in childhood and leads to impaired muscle coordination (ataxia) that worsens over time. Scoliosis, cardiomegaly, and foot problems may also develop.

Option A: Hundreds of adenomatous polyps throughout the colon are suggestive of familial adenomatous polyposis(FAP) which is an autosomal-dominant inherited disorder.

Option C: Vitamin D–resistant rickets is an X-linked dominant inherited disorder.

Option D: A child with a triad of micro-thrombocytopenia, eczema, and recurrent infections points towards Wiskott–Aldrich syndrome. It is an X-linked recessive inherited disorder.

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Solution to Question 12:

The given clinical scenario is suggestive of congenital adrenal hyperplasia. It includes a group of autosomal recessive disorders, each of which involves a deficiency of an enzyme involved in the synthesis of cortisol, aldosterone, or both.

The most common form is known to occur due to the deficiency of 21-hydroxylase, resulting from mutations or deletion of CYP21A.

Solution to Question 13:

The given clinical scenario is suggestive of phenylketonuria (PKU). It is caused by mutations in the PAH gene which encodes for phenylalanine hydroxylase.

Phenylketonuria is the most common inborn error of amino acid metabolism. It is less commonly known as phenylalanine hydroxylase (PAH) deficiency. The mode of inheritance is autosomal recessive.

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Solution to Question 14:

The given scenario is suggestive of glucose-6-phosphate dehydrogenase (G6PD) deficiency. It is the most common enzyme deficiency in humans, inherited as an X-linked recessive disorder. The gene that codes for G6PD is located in the distal long arm of the X chromosome at the Xq28 locus.

The inheritance pattern is similar to that of hemophilia and color blindness, where males usually manifest the abnormality and females are carriers. Females may be symptomatic if they are homozygous or if inactivation of their normal X chromosome occurs.

Solution to Question 15:

The given scenario is suggestive of Lesch–Nyhan syndrome. It is an X-linked recessive inherited disorder characterized by the deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HGPRT).

Lesch–Nyhan syndrome and its variants are caused by mutations in the HPRT gene on the X chromosome.

The disorder is associated with 3 major clinical elements:

• Overproduction of uric acid (hyperuricemia)

• Neurologic disability - intellectual disability and delayed milestones

• Behavioral problems - self-mutilation (excessive biting of lips and nails)

Solution to Question 16:

The patient's height and the presence of early diastolic murmur in the given clinical scenario are suggestive of Marfan syndrome. It is inherited in an autosomal dominant disorder. The family pedigree confirms the mode of inheritance.

The following flow chart helps in making out the pattern of inheritance from a given pedigree chart.

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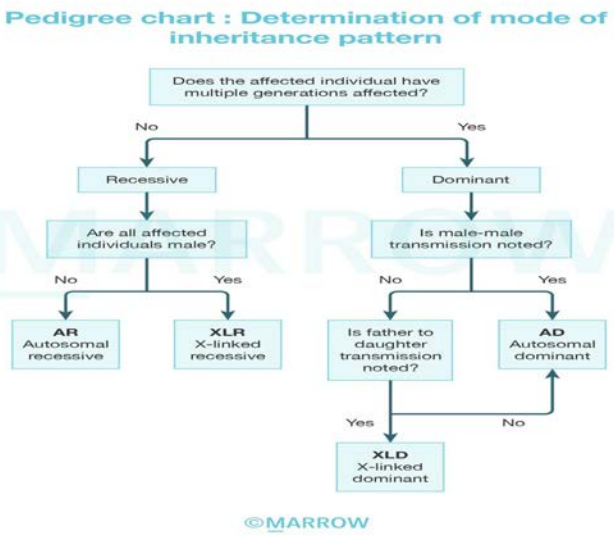

Patients with Marfan syndrome have pleiotropic manifestations:

• Skeletal systems - Tall and decreased upper to lower segment ratio with long arms, hands, and fingers

• Deformities of the chest wall, vertebral column, and foot arches

• Cardiovascular abnormalities - mitral valve prolapse leading to mitral regurgitation and dilatation of aortic root leading to aortic regurgitation, aortic dissection, and rupture.

• Ocular - superio-temporal lens dislocation

Solution to Question 17:

The given clinical scenario is suggestive of Marfan's syndrome. It is due to the inherited defect of the protein fibrillin 1.

Fibrillin is a major building block of microfibrils. This constitutes the structural components of the suspensory ligament of the ocular lens and serves as substrates for elastin in the aorta and other connective tissues.

It occurs in two homologous forms:

• Fibrillin-1: encoded by FBN1, mapped on chromosomes 15q21.1. Mutations cause Marfan's syndrome.

• Fibrillin-2: encoded by FBN2, mapped on chromosomes 5q23.31. Mutations cause congenital contractural arachnodactyly.

Solution to Question 18:

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Skeletal abnormalities are the most striking feature of Marfan syndrome.

Skeletal abnormalities include:

• Unusually tall, with exceptionally long extremities and long, tapering fingers and toes

• The joint ligaments in the hands and feet are lax, suggesting that the patient is double-jointed. Typically, the thumb can be hyper-extended back to the wrist

• The head is commonly dolichocephalic (long-headed) with bossing of the frontal eminences and prominent supraorbital ridges

Spinal deformities include:

• Kyphosis

• Scoliosis

• Rotation/slipping of the dorsal or lumbar vertebrae

• Pectus excavatum (deeply depressed sternum)

• Pigeon-breast deformity

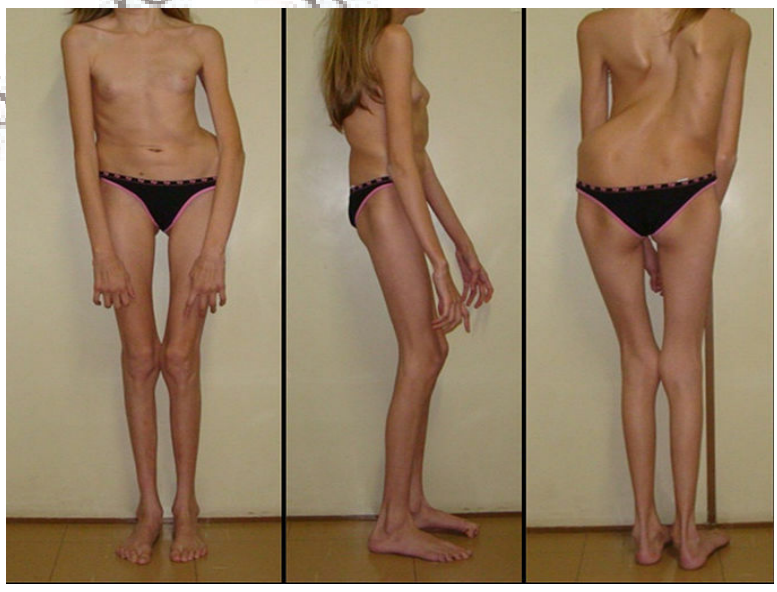
Ocular changes include bilateral subluxation or dislocation (outward and upward) of the lens, referred to as ectopia lentis.

Cardiovascular lesions are the most life-threatening features of this disorder. The two most common lesions are:

• Mitral valve prolapse

• Dilation of the ascending aorta due to cystic medionecrosis

The images given below show features seen in patients with Marfan's syndrome.



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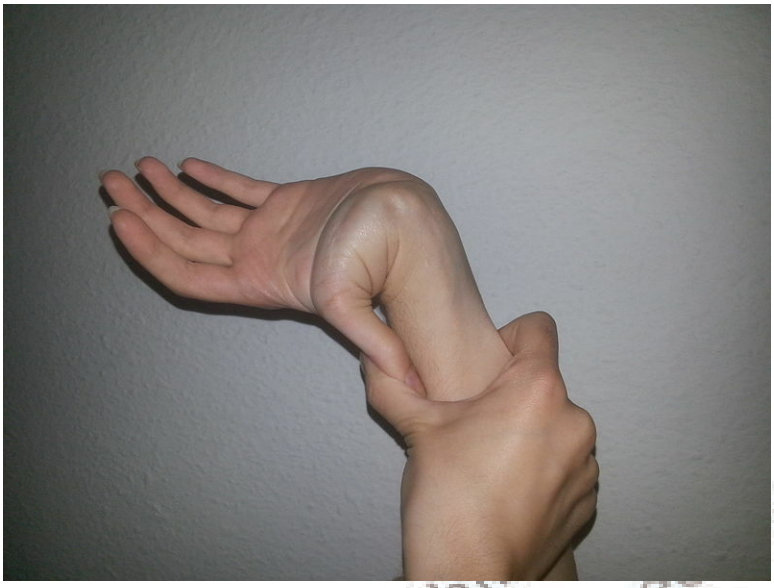

Solution to Question 19:

Cardiovascular lesions, like rupture of aortic dissections, are the most life-threatening features of the Marfan syndrome.

The weakening of the media predisposes the aorta to an intimal tear. It may initiate an intramural hematoma that cleaves the layers of the media to produce aortic dissection.

After causing the cleavage of the aortic layers for a considerable length, sometimes extending to the root of the aorta or down to the iliac arteries, the hemorrhage often ruptures through the aortic wall.

Although mitral valve lesions are more frequent, they are clinically less important than aortic lesions. Loss of connective tissue support in the mitral valve leaflets makes them soft and billowy, creating a so-called floppy valve.

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Valvular lesions, along with the lengthening of the chordae tendineae, frequently give rise to mitral regurgitation. Similar changes may affect the tricuspid and, rarely, the aortic valves.

Solution to Question 20:

The mode of inheritance of Ehler–Danlos syndrome (EDS) encompasses two Mendelian patterns, namely:

• Autosomal dominant

• Autosomal recessive

The biosynthesis of collagen can be disturbed by genetic errors that may affect any one of the numerous structural collagen genes or enzymes necessary for posttranscriptional modifications of collagen. Such molecular heterogeneity results in the expression of EDS as a clinically variable disorder, with varied patterns of inheritance.

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Solution to Question 21:

The given scenario is suggestive of the kyphoscoliotic form of Ehlers-Danlos syndrome (EDS). This was previously known as Type VI EDS.

The kyphoscoliotic form of EDS is caused by the deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1, or lysyl hydroxylase 1).

It is a generalized connective tissue disorder characterized by:

• Friable hyperextensible skin

• Thin scars

• Easy bruising

• Generalized joint laxity

• Severe muscular hypotonia at birth

• Progressive scoliosis may be present at birth or may develop within the first year of life

Solution to Question 22:

Classic Ehlers-Danlos syndromes (EDS) type involves type V collagen (defects in genes COL5A1 and COL5A2).

Types I and II of EDS are termed as classic forms. Type I is severe, while type II is milder.

It has an autosomal-dominant type of inheritance. Clinically, this type is characterized by skin and joint hypermobility, atrophic scars, and easy bruising.

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Solution to Question 23:

Dermatosparaxis type of Ehlers-Danlos syndrome (EDS) is type VIIc.

Solution to Question 24:

Spinal muscular atrophy has an autosomal recessive inheritance, not autosomal dominant.

Solution to Question 25:

The given scenario is suggestive of Wolman disease. It is due to a deficiency of the lysosomal acid lipase enzyme. It is an autosomal recessive disease.

It leads to the accumulation of cholesterol esters and triglycerides. It presents in the first few weeks of life with:

- Failure to thrive
- Vomiting
- Abdominal distention
- Steatorrhea
- Hepatosplenomegaly
- Hyperlipidemia
- Extensive bilateral calcifications of the adrenal glands

No specific therapy is available and death usually occurs within 6 months of life.

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Lysosomal and Glycogen Storage Diseases

Question 1:

Which of these is not a form of sphingolipidoses?

a) Hurler disease

b) Tay–Sachs disease

c) Fabry disease

d) Gaucher disease

Question 2:

What is the most common lysosomal storage disorder?

a) Tay–Sachs disease

b) Niemann–Pick disease

c) Gaucher disease

d) Sandhoff's disease

Question 3:

An 8-month-old child presents with mental retardation, blindness, and muscle weakness. On evaluation, deficiency of hexosaminidase α-subunit is found. What is the most likely diagnosis?

a) Tay–Sachs disease

b) Sandhoff disease

c) Krabbe disease

d) Gaucher disease

Question 4:

Which of the following statements is false about Tay–Sachs Disease?

a) Affected infants are normal at birth

b) Neurons in the CNS, ANS, and retina are affected

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c) Accumulations stain positive for oil red O and Sudan black B

d) Whorled configurations within mitochondria are seen

Question 5:

Patients with metachromatic leukodystrophy will have which of the following enzyme deficiency?

a) Aryl sulfatase A

b) Alpha galactosidase

c) Galactosylceramidase

d) °-galactosidase

Question 6:

Which of the following enzyme is deficient in patients with Krabbe disease?

a) Galactosylceramidase

b) α-Galactosidase A

c) Glucocerebrosidase

d) Beta glucosidase

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Question 7:

Patients with which of the following diseases will have ceramide trihexoside accumulation?

a) Fabry disease

b) Gaucher disease

c) Tay-Sachs disease

d) Krabbe disease

Question 8:

Which of the following statements is false about Niemann–Pick disease?

a) Inherited deficiency of aryl sulfatase is present

b) Type A has bad prognosis

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c) Type B has associated organomegaly

d) Chromosome 11 is involved

Question 9:

Given below is an electron microscopy picture of lysosomes. What is the most likely diagnosis?

a) Tay–Sachs disease

b) Niemann–Pick disease

c) Gaucher disease

d) Krabbe disease

Question 10:

Which of the following statements is false regarding I-cell disease?

a) It is characterised by defective phosphorylating enzymes

b) It is a glycogen storage disorder

c) It is associated with gingival hyperplasia

d) High levels of hydrolytic enzymes in plasma are seen

Question 11:

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Which of the following is false about mucopolysaccharidosis?

a) Hunter syndrome is due to a deficiency of iduronate 2-sulphatase

b) Hurler syndrome is due to a deficiency of α-L-iduronidase

c) They are inherited as autosomal recessive traits, except Hunter syndrome

d) Hunter syndrome is inherited as an autosomal dominant disease

Question 12:

Which glycogen storage disorder is a lysosomal storage disease?

a) Type 1

b) Type 2

c) Type 3

d) Type 4

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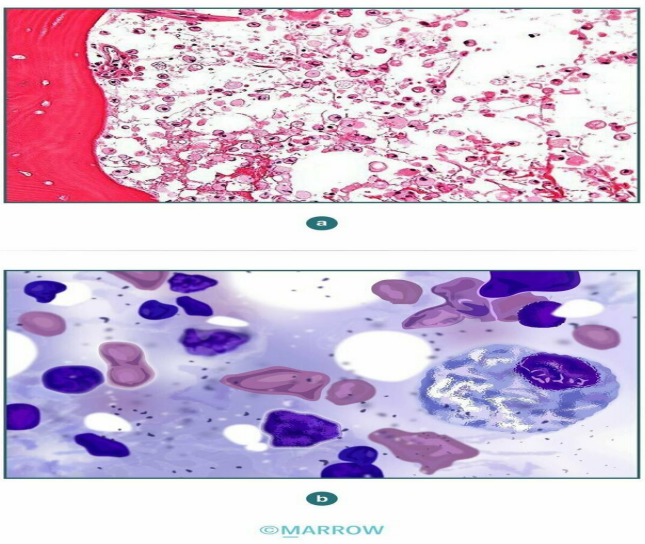
Question 13:

A 4-year-old boy presented with severe pain in his left leg which worsened over the last few months. On examination, hepatosplenomegaly and developmental delays were noticed. Labs revealed the following findings on light and oil immersion respectively of the bone marrow aspiration. Which of the following is deficient in this condition?



a) Hexosaminidase A

b) Sphingomyelinase

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c) Glucocerebrosidase

d) Galactocerebrosidase

Question 14:

Which of the following statements is incorrect about Gaucher's disease?

a) Type 1 spares the brain

b) Type 1 has splenic and skeletal involvement

c) Type 1 has no detectable enzyme activity

d) Type 2 has acute cerebral disease

Question 15:

A 1-year-old child presents with growth retardation and abdominal distension. On examination, the child has characteristic doll-like facies with thin extremities. Blood investigations reveal hypoglycemia, lactic acidosis, hyperlipidemia, and hyperuricemia. USG abdomen shows hepatomegaly and renomegaly. What deficiency causes the given clinical condition?

a) Glucose phosphorylase

b) Enolase

c) Branching enzyme

d) Glucose 6 phosphatase

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Question 16:

Which enzyme is deficient in McArdle's syndrome?

a) Hepatic hexokinase

b) Muscle phosphorylase

c) Muscle hexokinase

d) Muscle phosphofructokinase

Answer Key

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Question No.	Correct Option
1	a
2	c
3	a
4	d
5	a
6	a
7	a
8	a
9	b
10	b
11	d
12	b
13	c
14	c
15	d
16	b

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Detailed Explanations

Solution to Question 1:

Hurler disease is a mucopolysaccharidosis.

Sphingolipidoses are a group of lysosomal storage disorders characterized by the accumulation of sphingolipids. It includes:

- Niemann–Pick disease
- Fabry disease
- Krabbe disease
- Gaucher disease
- Tay–Sachs disease
- Metachromatic leukodystrophy

Solution to Question 2:

Gaucher disease is the most common lysosomal storage disorder.

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It is an autosomal recessive disorder resulting from mutations in the gene encoding glucocerebrosidase.

Solution to Question 3:

The given scenario and hexosaminidase α-subunit deficiency are seen in Tay–Sachs disease.

Sphingolipidoses with their deficient enzyme:

• GM1 Gangliosidoses - GM1 Ganglioside °- galactosidase deficiency

• Type 1- infantile, generalizsed

• Type 2- juvenile

• GM2 Gangliosidosis:

• Tay–Sachs disease - Hexosaminidase α-subunit

• Sandhoff disease - Hexosaminidase °-subunit

• GM2 Gangliosidosis variant AB - Ganglioside activator protein

Note: Tay–Sachs disease is the most common form of GM2 gangliosidosis.

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Solution to Question 4:

In Tay–Sachs disease, an electron microscope shows whorled configurations within lysosomes composed of onion-skin layers of membranes.

Affected infants appear normal at birth but begin to manifest signs and symptoms at about 6 months of age. The involvement of neurons in the central and autonomic nervous systems and retina dominates the clinical picture.

There is a severe motor and mental deterioration, beginning with motor incoordination and mental obtundation. This leads to muscular flaccidity, blindness, and increasing dementia. Over the span of 1 or 2 years, a completely vegetative state is reached, followed by death at age 2 to 3 years

On histologic examination, the neurons are ballooned with cytoplasmic vacuoles, each representing a markedly distended lysosome filled with gangliosides.

A cherry-red spot appears in the macula, representing the accentuation of the normal color of the macular choroid. This is in contrast with the pallor produced by the swollen ganglion cells in the remainder of the retina. This finding is characteristic of Tay-Sachs disease and other storage disorders affecting the neurons.

The image given below shows a cherry-red spot on retina.

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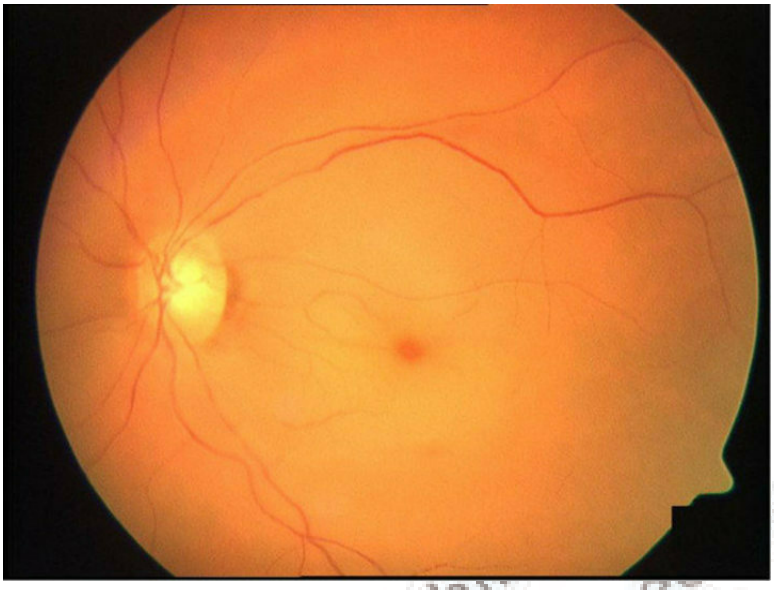

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Solution to Question 5:

Metachromatic leukodystrophy is an autosomal recessive condition caused by the deficiency of arylsulfatase A.

The deficiency of this enzyme leads to the accumulation of cerebroside sulfate. These sulfatides can contribute to white matter injury, demyelination, and gliosis.

Macrophages with vacuolated cytoplasm are scattered throughout the white matter. They contain metachromatic material, which can be detected in the urine and peripheral nerves when stained with toluidine blue.

Solution to Question 6:

Krabbe disease is due to the deficiency of galactosylceramidase.

The onset of symptoms is between 3 and 6 months of age, dominated by motor signs such as stiffness and weakness. They often don't survive beyond the age of 2 years. The brain shows loss of myelin and oligodendrocytes with a similar process affecting the peripheral nerves.

The aggregation of engorged macrophages called globoid cells in the brain parenchyma and around blood vessels is the characteristic and diagnostic feature of Krabbe disease.

Solution to Question 7:

Ceramide trihexoside (also known as globotriaosylceramide) is accumulated in Fabry disease.

The enzyme defect seen in this disease is α-galactosidase A.

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Clinical features:

- Painful acroparaesthesia
- Hypohidrosis
- Abdominal cramping
- Diarrhea
- Small petechiae around the umbilicus
- Lenticular opacities
- Corneal dystrophy

Solution to Question 8:

Niemann–Pick disease types A and B are two related disorders that are characterized by lysosomal accumulation of sphingomyelin due to an inherited deficiency of sphingomyelinase.

The disease is typically inherited as an autosomal recessive condition on chromosome 11.

Type A is a severe infantile form with extensive neurologic involvement, marked visceral accumulations of sphingomyelin, progressive wasting, and early death within the first 3 years of life.

Type B disease patients have organomegaly, but generally no central nervous system involvement. They usually survive into adulthood.

Solution to Question 9:

Electron microscopy showing zebra bodies is suggestive of Niemann–Pick disease.

Zebra bodies are engorged secondary lysosomes that contain membranous cytoplasmic bodies resembling concentric lamellated myelin figures. Similar zebra bodies can also be seen in mucopolysaccharidoses.

Solution to Question 10:

Inclusion-cell (I-cell) disease, also referred to as mucolipidosis II, is a part of the lysosomal storage disease family.

It is characterized by the deficiency of phosphorylating enzymes essential for the formation of the mannose-6-phosphate recognition marker.

Acid hydrolases lacking the recognition marker cannot be targeted to the lysosomes but are secreted extracellularly.

It is characterized by:

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• Coarse facial features

• Gingival hyperplasia

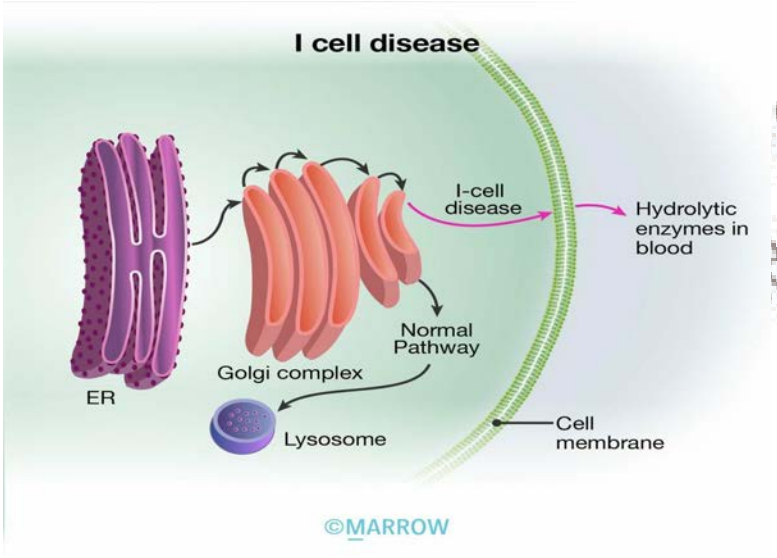
• Clouded corneas

• Restricted joint movements

• Claw hand deformities

• Kyphoscoliosis

• High plasma levels of lysosomal enzymes



Solution to Question 11:

All the mucopolysaccharidoses are inherited as autosomal-recessive traits except Hunter syndrome. It is inherited as an X-linked recessive disease.

The mucopolysaccharidoses (MPSs) are a group of closely related syndromes that result from genetically determined deficiencies of enzymes involved in the degradation of mucopolysaccharides (glycosaminoglycans).

Mucopolysaccharides are abundant in the ground substance of connective tissues. In the absence of enzymes involved in their degradation, they accumulate within lysosomes in various tissues and organs of the body. Two among these are:

• Hurler syndrome - deficiency of α-L-iduronidase

• Hunter syndrome - deficiency of iduronate 2-sulphatase

Solution to Question 12:

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Glycogen storage disorder type II, also called Pompe disease, is the only glycogen storage disease with a defect in lysosomal metabolism.

It is an autosomal-recessive metabolic disorder. It is caused by the accumulation of glycogen in the lysosome due to deficiency of the lysosomal acid alpha-glucosidase enzyme.

Solution to Question 13:

The given scenario and bone marrow aspiration images showing necrotic bone with lack of osteocytes in the lacunae (Image A) and Gaucher cells (Image B)are suggestive of Gaucher's disease. This condition has a deficiency of glucocerebrosidase.

Gaucher cells are plump macrophages that characteristically have a crumpled tissue paper appearance (Image B) of the cytoplasm. It is due to the accumulation of glucocerebrosides.

They can be seen in Virchow–Robin spaces (perivascular fluid-filled cavities that surround perforating arteries and veins in the brain parenchyma) in patients with cerebral involvement.

Solution to Question 14:

In type 1, enzyme activity is reduced but detectable.

Gaucher disease is of two types:

Type 1:Chronicnon-neuropathic form	Type 2:Acute neuronopathic form
Most common	Less common
Spleen and skeletal system are mainly involved	Hepatosplenomegaly is seen
Spares the central nervous system	The central nervous system is involved
Enzyme activity is reduced but detectable	No detectable enzyme activity
Principally in Jews of European stock	Has no predilection for Jews
Longevity is shortened	Death at an early age

Solution to Question 15:

The given clinical scenario is suggestive of von Gierke disease. It is due to the deficiency of glucose 6 phosphatase enzyme.

The condition usually manifests as:

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• Failure to thrive

• Stunted growth

• Hepatomegaly

• Renomegaly

Hypoglycemia is due to the failure of glucose mobilization which often leads to convulsions. Lactic acidosis, hyperlipidemia, and hyperuricemia result from deranged glucose metabolism. Many patients also develop gout, skin xanthomas, and bleeding tendency (due to platelet dysfunction).

With treatment, most patients survive and develop late complications (e.g., hepatic adenomas).

Solution to Question 16:

McArdle's syndrome is caused due to the deficiency of muscle phosphorylase.

In the skeletal muscles, as opposed to the liver, glycogen is used predominantly as a source of energy during physical activity. If enzymes hydrolyzing glucose are deficient, there will be an accumulation of glycogen in the muscles. This will cause muscle weakness due to impaired energy production.

Enzyme deficiencies leading to muscle glycogen storage include:

• McArdle disease/type V glycogenosis - deficiency of muscle phosphorylase

• Type VII glycogen storage disease - deficiency of muscle phosphofructokinase

Typically, individuals with myopathic forms present with muscle cramps after exercise. This is because lactate levels in the blood fail to rise after exercise due to a block in glycolysis.

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Chromosomal Disorders and Other Genetic Disorders

Question 1:

At what stage of mitosis is standard karyotyping performed?

a) Anaphase

b) Metaphase

c) Prophase

d) Telophase

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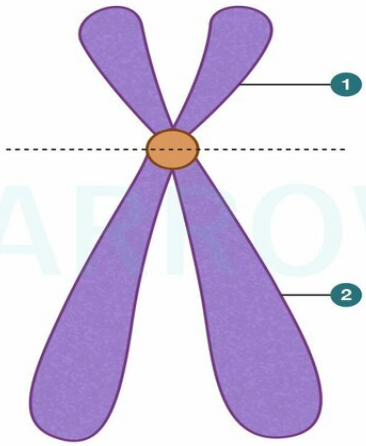
Question 2:

In cytogenetic terminology, how are the following marked structures designated?



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a) 1-q, 2-s

b) 1-p, 2-r

c) 1-q, 2-p

d) 1- p, 2- q

Question 3:

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What aberration occurs when a break occurs at both ends of a chromosome with the fusion of the damaged ends?

a) Translocation

b) Ring chromosome

c) Inversion

d) Iso-chromosome formation

Question 4:

Which of the following is not associated with the change in genetic material?

a) Inversion

b) Insertion

c) Deletion

d) Transversion

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Question 5:

Which of the following is incorrect about Down's syndrome?

a) Leukemia is the major cause of death in early childhood

b) It is the most common chromosomal disorder

c) Robertsonian translocations of chromosome 21 are less common

d) These children are prone to develop autoimmune diseases

Question 6:

A 1-year-old child was brought by the mother with complaints of delay in reaching motor milestones. Examination revealed oblique palpebral fissures, epicanthal folds, and the following finding. Auscultation revealed a pan-systolic murmur in the left sternal border. This child is at risk of developing which of the following?

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a) Acute monoblastic leukemia

b) Acute promyelocytic leukemia

c) Acute myelomonocytic leukemia

d) Acute megakaryoblastic leukemia

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Question 7:

A 7-month-old infant is being evaluated for failure to thrive. Examination reveals low-set ears, a short neck, and the following findings. Auscultation reveals a holosystolic murmur over the pulmonic area. Which of the following statements about this condition is false?

a) Incidence is 1 in 8000 births

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b) Karyotype of this child is 47, XY + 18

c) It may be associated with horseshoe kidney

d) There is increased risk of leukemia

Question 8:

Which of the following is not seen in children with Patau syndrome?

a) Cleft palate

b) Umbilical hernia

c) Rocker-bottom feet

d) High-set ears

Question 9:

What hypothesis states that one X chromosome, maternal or paternal, is randomly inactivated during development?

a) Lyon

b) Hardy

c) Maxwell

d) Barr

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Question 10:

A 25-year-old man was referred for infertility evaluation. On examination, he was tall with a lack of body hair. Gynecomastia and micropenis were also noted. Karyotyping analysis revealed an XXY karyotype. Which of the following statements is not true about the condition?

a) Levels of follicle-stimulating hormone are reduced

b) Testosterone levels are reduced

c) Plasma estradiol levels are elevated

d) Risk of SLE is increased

Question 11:

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A 16-year-old girl is referred for evaluation of primary amenorrhea and short stature. Examination shows a webbed neck, widely spaced nipples, and absent secondary sexual characteristics. USG abdomen shows a small uterus and streak ovaries. What is the most common karyotypic abnormality seen in individuals with this condition?

a) Missing entire X chromosome

b) Isochromosome of the long arm of X chromosome

c) Deletion of portions of long arm of X chromosome

d) Deletion of ends of long and short arm of X chromosome

Question 12:

Which of the following conditions is not caused by trinucleotide-repeat mutations involving non-coding regions?

a) Huntington disease

b) Fragile X syndrome

c) Myotonic dystrophy

d) Friedreich ataxia

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Question 13:

All of the following are features of fragile X syndrome except:

a) Trinucleotide mutation in FMR-1 gene

b) Mental retardation

c) Micro-orchidism

d) Large everted ears

Question 14:

70 CGG premutations in the FMR1 gene are characteristic of which of the following?

a) Fragile X syndrome

b) Prader Willi syndrome

c) Fragile X ataxia

d) Friedreich ataxia

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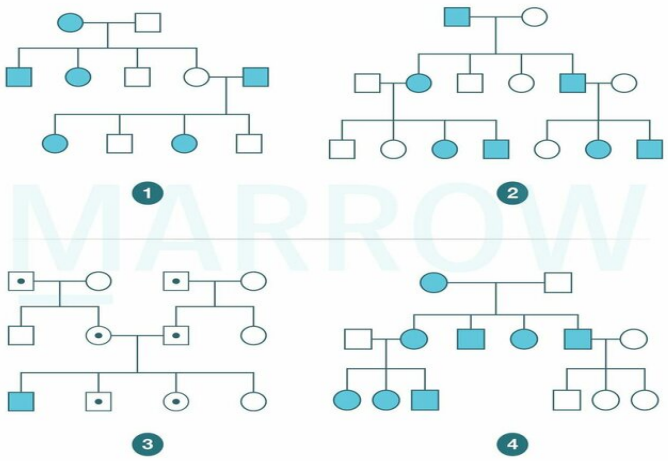
Question 15:

What is the mode of inheritance of Leber hereditary optic neuropathy?



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a) 1

b) 2

c) 3

d) 4

Question 16:

Which chromosome is involved in myotonic dystrophy?

a) Chromosome 19

b) Chromosome 20

c) Chromosome 21

d) Chromosome 22

Question 17:

Maltese cross crystals in the urine are seen in which of the following diseases other than nephrotic syndrome?

a) Friedrich's ataxia

b) Felty syndrome

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c) Fanconi anemia

d) Fabry's disease

Question 18:

A young male patient as shown below presents with complaints of infertility. On examination, he lacked pubic and facial hair. The genital examination was consistent for a micropenis. Further investigations reveal elevated LH and FSH levels. What is the most common cardiac lesion associated with this condition?

a) Mitral valve prolapse

b) Ventricular septal defect

c) Mitral regurgitation

d) Patent ductus arteriosus

Question 19:

Which of the following is the correct statement regarding Huntington's chorea?

a) It is a trinucleotide repeat disorder

b) There is loss of function type of mutation

c) There are abnormal repeats of CUG

d) Abnormality is seen due to mutation in chromosome 6

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Question 20:

Which amongst the following is true about Turner's syndrome?

a) Webbing of hands and toes are associated with risk of visceral anomalies

b) Noonan syndrome is more associated with cardiac defects

c) Absence of neck webbing is associated with higher risk of co-arctation of aorta

d) Webbing of neck is associated with higher risk of cardiac anomalies

Question 21:

A 5-year-old girl is brought for evaluation of intellectual disability. She also has difficulty in walking and balancing, and her speech is delayed for her age. The parents also say that she frequently has sudden bouts of laughter. She is a known case of seizure disorder since the age of 3. This condition is associated with which of the following chromosomal abnormalities?

a) 2, 3

b) 2, 4

c) 1, 3

d) 1, 4

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Answer Key

Question No.	Correct Option
1	b
2	d
3	b
4	a
5	a
6	d
7	d
8	d
9	a
10	a
11	a
12	a

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13	c
14	c
15	d
16	a
17	d
18	a
19	a
20	d
21	a

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Detailed Explanations

Solution to Question 1:

Standard karyotyping refers to an arrangement of chromosomes from a cell that is undergoing mitosis at metaphase.

At other mitotic stages, the chromosomes are not sufficiently condensed or are too dispersed to allow for the counting and comparison of pairs under the microscope. In a metaphase spread, the individual chromosomes take the form of two chromatids connected to the centromere.

A variety of staining methods are available to identify the individual chromosomes on the basis of a distinctive and reliable pattern of alternating light and dark bands. The most common method used involves a Giemsa stain and is hence called G-banding. Standard G-banding can detect approximately 400 to 800 bands per haploid set.

The image below shows G-banding (karyogram of human male using Giemsa staining):

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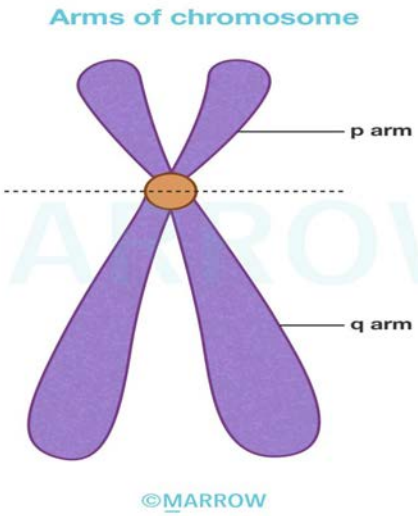
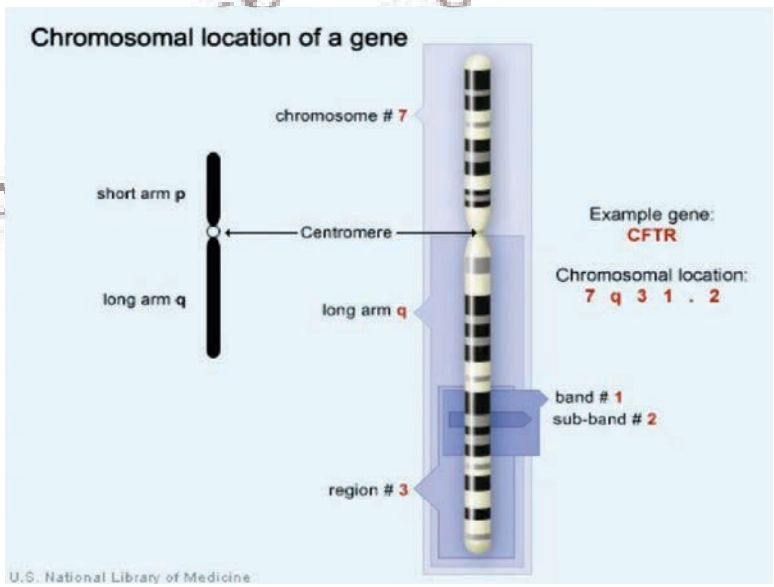
Solution to Question 2:

The short arm of a chromosome (marked as 1) is designated p (for petite), and the long arm (marked as 2) is referred to as q (the next alphabet).



In a banded karyotype, each arm of the chromosome is divided into two or more regions bordered by prominent bands. The regions are numbered (e.g., 1, 2, 3) from the centromere outward. Each region is further subdivided into bands and sub-bands, and these are ordered numerically as well.



Solution to Question 3:

A ring chromosome is an aberrant chromosome whose broken ends fuse together to form a ring.

Ring chromosomes behave abnormally in meiosis or mitosis and usually result in serious consequences. In rare cases, the telomeres at the ends of a chromosome fuse without any loss of

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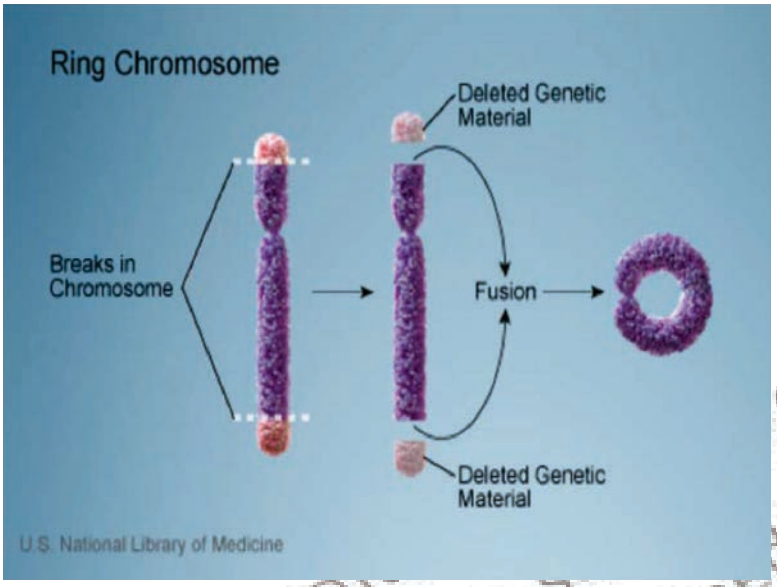
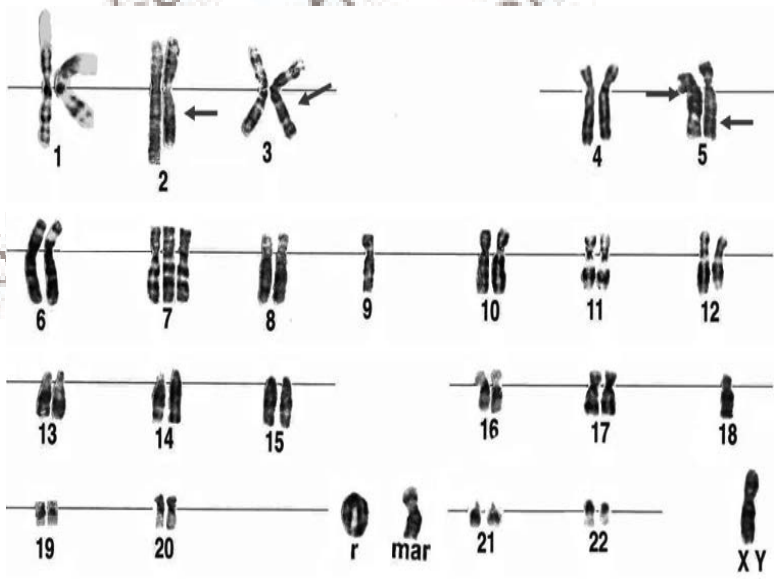
genetic material, which results in a normal phenotype. A ring chromosome is denoted by the symbol r in human genetics.



The following image shows a representative karyotype from a well-differentiated transitional cell carcinoma of the bladder. The chromosome indicated by 'r' represents a ring chromosome. Also evident are monosomy 9, 18, and X and trisomy 7.



Option A: In a translocation, a segment of one chromosome is transferred to another.

Option C: Inversion refers to a rearrangement that involves two breaks within a single chromosome, with reincorporation of the inverted, intervening segment.

Option D: Isochromosome formation results when one arm of a chromosome is lost and the remaining arm is duplicated. It results in a chromosome consisting of two short arms only or of two long arms.

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Solution to Question 4:

Inversion involves only a rearrangement of the genetic material. There is no change in the genetic material.

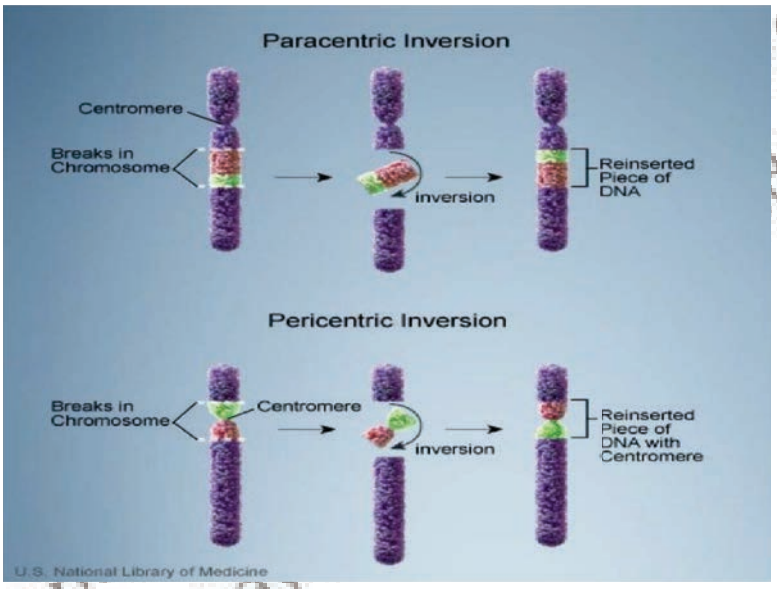
It occurs as a result of two breaks within a single chromosome. The intervening segment between the breaks gets inverted and reincorporated. It is of two types:

• Paracentric - inversion involving only one arm of the chromosome

• Pericentric - inversion involving opposite sides of the centromere

Inversions are often fully compatible with normal development.

Transversions are mutations where a purine base pair is replaced by a pyrimidine or vice versa.



Solution to Question 5:

In Down's syndrome, the major cause of death in infancy and early childhood is cardiac disease, not leukemia.

Down's syndrome is the most common chromosomal disorder and is a major cause of mental retardation. Maternal age is a strong risk factor. This condition can occur by the following mechanisms:

• Majority of cases - meiotic nondisjunction of chromosome 21 in the ovum

• Rarely - Robertsonian translocation of the long arm of chromosome 21 to another acrocentric chromosome (e.g., 22 or 14)

The clinical features of Down's syndrome include:

• Mental retardation

• Facial dysmorphism - flat facial profile, oblique palpebral fissures, and epicanthic folds

• Congenital heart disease - endocardial cushion defects (ASD, VSD, AV valve malformations)

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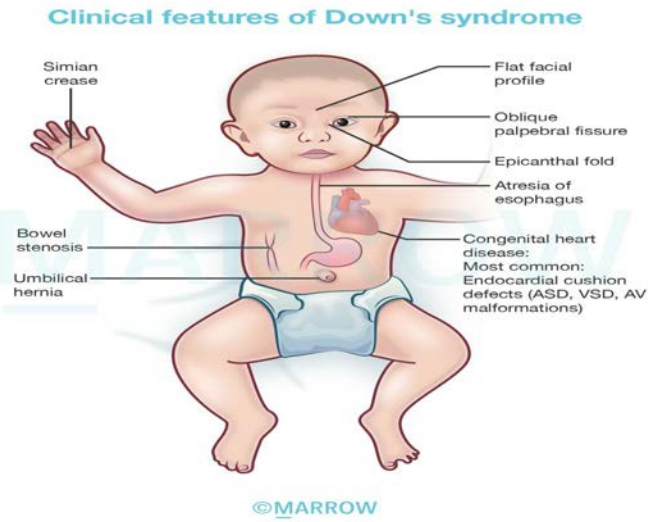
• Atresias of the esophagus and small bowel

• Neuropathologic changes characteristic of Alzheimer's disease - in patients > 40 years

• Increased risk of developing acute megakaryoblastic leukemia (AML-M7)

• Predisposition to autoimmune diseases and serious lung infections



Solution to Question 6:

This clinical scenario and image showing a single palmar crease (simian crease) are suggestive of Down's syndrome. It is associated with an increased risk of acute megakaryoblastic leukemia (AML-M7) in affected children < 2 years old.

Children with trisomy 21 have a 10 to 20-fold increased risk of developing acute leukemia.

• In children < 2 years of age - acute megakaryoblastic leukemia(AML-M7) is the most common

• In children > 3 years of age - acute lymphoblastic leukemia (ALL) is the most predominant

Solution to Question 7:

The images show the index finger overlapping other fingers and rocker bottom feet. This along with the clinical features is suggestive of Edward's syndrome. Leukemia is not a feature of this condition.

It is due to the inheritance of a complete extra copy of chromosome 18 as a result of meiotic nondisjunction (47, XY+18). The incidence is 1 in 8000 births.

The clinical features of Edward's syndrome include:

• Low-set ears

• Short neck

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• Overlapping fingers
• Congenital heart defects
• Renal malformations
• Limited hip abduction
• Rocker-bottom feet
• Prominent occiput
• Mental retardation
• Micrognathia

Note: Although, rocker bottom feet are seen in both Edward's syndrome and Patau's syndrome, overlapping of fingers is characteristic of Edward's syndrome.

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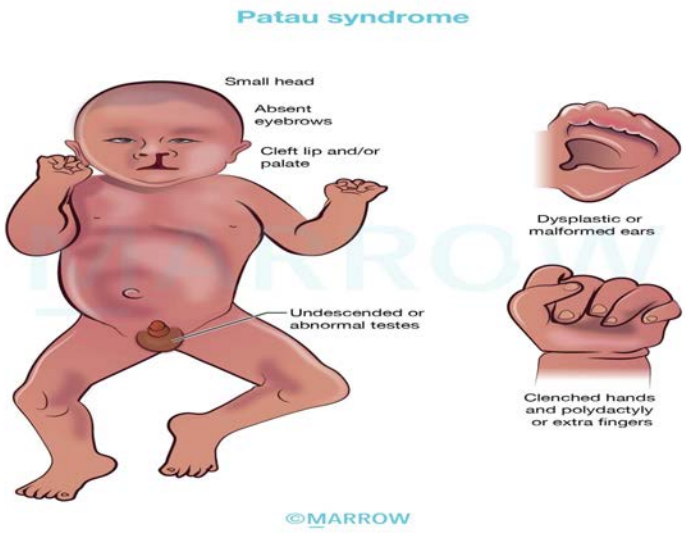
Solution to Question 8:

Low set ears are a feature of Patau syndrome, not high set ears.

Patau syndrome occurs due to trisomy 13 and is characterized by:

• Microphthalmia
• Polydactyly
• Microcephaly and mental retardation
• Cleft lip and palate
• Cardiac defects
• Umbilical hernia
• Renal defects
• Rocker-bottom feet (commonly seen in Edwards syndrome also)



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Solution to Question 9:

Lyon's hypothesis states the idea of the inactivation of the X chromosome.

It states the following:

• Only one of the X chromosomes is genetically active

• The other X undergoes heteropyknosis and is rendered inactive (known as Barr body)

• Inactivation of either the maternal or paternal X occurs at random among all the cells of the blastocyst on or about day 5.5 of embryonic life

• Inactivation of the same X chromosome persists in all the cells derived from each precursor cell.

The molecular basis of X inactivation involves the XIST gene.

Solution to Question 10:

The given clinical scenario is suggestive of Klinefelter's syndrome. In this condition, the follicle-stimulating hormone (FSH) levels are elevated.

The clinical features include:

• Eunuchoid body habitus - elongated body and long legs (increased length between the soles and the pubic bone)

• Absence of secondary sexual characteristics - lack of body and facial hair, deep voice

• Small atrophic testes

• Micropenis

• Gynecomastia

• Lower IQ, but no mental retardation

The following hormonal variations are seen in these patients:

• Elevated FSH

• Elevated estradiol

• Low testosterone

• Insulin resistance - increased incidence of type 2 diabetes

Patients with Klinefelter syndrome are at a higher risk for:

• Male breast cancer (20x more common than in normal males)

• Extragonadal germ cell tumors

• Autoimmune diseases - systemic lupus erythematosus

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Solution to Question 11:

The given clinical scenario is highly suggestive of Turner's syndrome. In this condition, the most common karyotypic abnormality seen is a missing entire X chromosome, seen in more than half the cases.

Less commonly, structural abnormalities of the X chromosome and mosaicism can also occur. The common feature of the structural abnormalities is to produce partial monosomy of the X chromosome.

In order of frequency, the structural abnormalities of the X chromosome include the following:

• An isochromosome of the long arm, 46,X,i(X)(q10), resulting in the loss of the short arm

• Deletion of portions of both long and short arms, resulting in the formation of a ring chromosome - 46, X,r(X)

• Deletion of portions of the short or long arm - 46X,del(Xq) or 46X,del(Xp).

The mosaic patients have a 45,XO cell population along with one or more karyotypically normal or abnormal cell types.

Few patients with this condition also have Y-chromosome sequences, either as a complete Y chromosome or as fragments of Y chromosomes translocated on other chromosomes. These patients are at a higher risk for the development of a gonadal tumor (gonadoblastoma).

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Solution to Question 12:

Huntington's disease is due to CAG (trinucleotide) repeat mutation in the coding region of the gene, not the non-coding region.

Expansion of trinucleotide repeats is an important genetic cause of human disease, particularly neurodegenerative disorders. The causative mutations are associated with the expansion of a stretch of trinucleotides that usually share the nucleotides G and C. In all cases, the DNA is unstable, and an expansion of the repeats above a certain threshold impairs gene function.

Expansions affecting noncoding regions will cause a loss of function mutation. They include:

• Fragile X syndrome

• Myotonic dystrophy

• Friedreich ataxia

Expansions affecting coding regions cause a gain of function mutation. They include:

• Spinobulbar muscular atrophy (Kennedy disease)

• Huntington disease

• Dentatorubral-pallidoluysian atrophy (Haw–River syndrome)

• Spinocerebellar ataxia types 1, 2, 3, 6, 7

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Solution to Question 13:

Macro-orchidism (large testicles) are seen in fragile X syndrome, not micro-orchidism.

Fragile X syndrome is the second most common genetic cause of mental retardation (Down syndrome being the most common). It is caused by a trinucleotide mutation, characterised by multiple tandem repeats of the CGG sequence in the familial mental retardation-1 (FMR1) gene. It is associated with the phenomenon of anticipation, where the disease phenotype worsens over generations within a family.

The affected males are mentally retarded, with an IQ in the range of 20 to 60.

The characteristic phenotypic features include the following:

• Long face with a large mandible

• Large everted ears

• Macro-orchidism

• Hyperextensible joints

• High arched palate

• Mitral valve prolapse

The given image shows a child suffering from fragile X syndrome.

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Solution to Question 14:

CGG premutations in the FMR1 gene are characteristic of fragile X ataxia. It is also known as fragile X tremor and fragile X-associated primary ovarian failure.

Normally, the FMR1 gene is methylated and silenced, and the number of CGG repeats remains < 55.

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However, abnormalities in this gene lead to the accumulation of CGG-containing FMR1 mRNAs, which are toxic to the cell. Depending on the type of mutation, there are 2 distinct syndromes:

• Fragile X ataxia syndrome (FXTAS): 55-200 repeats (premutation) which causes gain of function

• Fragile X syndrome (FXs): 200- 4000 repeats (full mutation) leading to loss of function

More than half the individuals with FXTAS develop a progressive neurodegenerative syndrome starting in their 6th decade. It is characterized by intention tremors and cerebellar ataxia and may progress to Parkinsonism.

Option B: Prader-Willi syndrome is associated with deletion of paternal chromosome 15q12 and the silencing of the maternal allele.

Option D: Friedreich ataxia is due to GAA repeat sequences in the noncoding regions.

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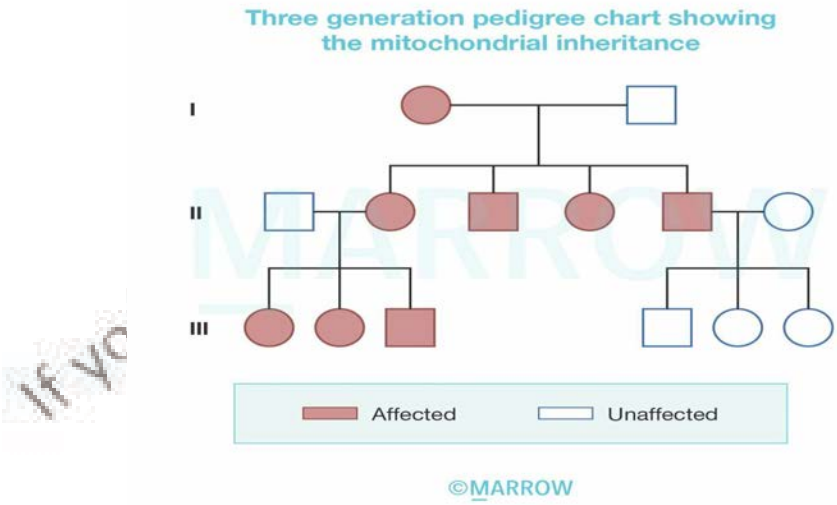
Solution to Question 15:

Leber hereditary optic neuropathy (LHON) is an example of mitochondrial inheritance. It is inherited along the maternal line, as shown in image 4.



In diseases following the mitochondrial pattern of inheritance, all children of an affected mother and normal father develop the disease. However, children born to an affected father and a normal mother do not inherit the disease. Hence, only the daughters of the affected mother will transmit the disease.

This is because this condition is due to a mutation in the mitochondrial DNA (mtDNA), which is derived from the maternal mitochondria. The ovum contains several mitochondria, while the spermatozoa have very few mitochondria if present. Hence, the mitochondrial DNA of the zygote is entirely derived from the ovum.

LHON is a neurodegenerative disease that manifests as progressive bilateral loss of central vision. Visual impairment starts between ages 15 and 35, leading eventually to blindness. Other features include cardiac conduction defects and minor neurologic manifestations.

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Solution to Question 16:

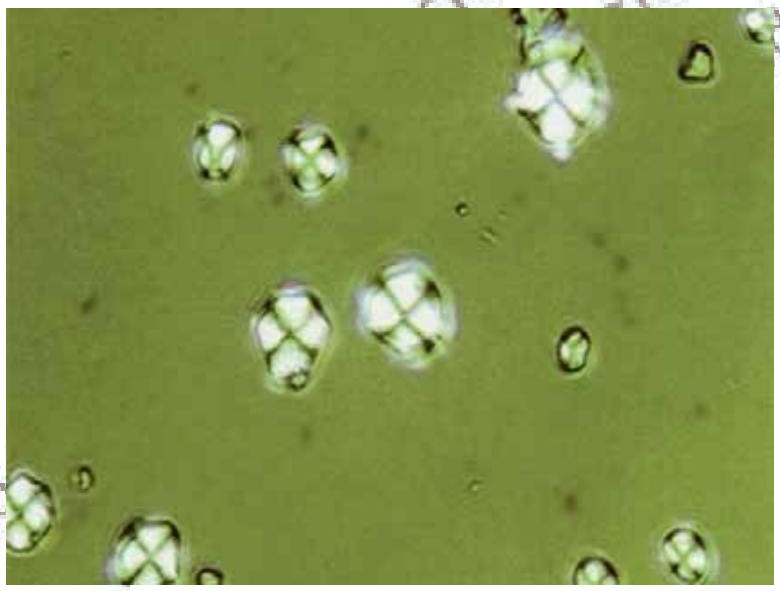
Chromosome 19 is involved in myotonic dystrophy.

Solution to Question 17:

Maltese cross crystals in the urine are seen in Fabry's disease.

Urine analysis in Fabry's disease may reveal oval fat bodies and birefringent glycolipid globules under polarized light showing a Maltese cross appearance. It can also be seen in nephrotic syndrome.

The following image shows Maltese cross casts:



Note: Maltese cross appearance is also seen in short-range shotgun wounds and babesiosis.

Solution to Question 18:

The given clinical picture most likely suggests Klinefelter's syndrome. The most common cardiac lesion in this condition is mitral valve prolapse which is seen in nearly half the adults.

Systemic manifestations associated with Klinefelter's syndrome:

- Gynecomastia
- Type 2 diabetes and metabolic syndrome
- Mitral valve prolapse
- Osteoporosis and fractures

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• Male infertility

• Higher risk for breast cancer, extragonadal germ-cell tumors

• Systemic lupus erythematosus

Solution to Question 19:

Huntington's chorea is a trinucleotide repeat disorder.

It is an autosomal dominant neurodegenerative disorder. It is caused by CAG trinucleotide repeats (>40). It occurs due to a gain-of-function (expansion) mutation in the huntingtin gene on chromosome 4p.

The disease shows genetic anticipation and has an early-onset (2-3 decades) if inherited from the father.

Cognitive impairment is an early feature. Pathologically, atrophy of caudate and putamen with ex vacuo ventriculomegaly is seen. Decreased acetylcholine leads to dementia and decreased GABA and increased dopamine lead to chorea.

Treatment consists of haloperidol and tetrabenazine.

Trinucleotide repeat disorders:

Disease	Repeats	Clinical features
Fragile X- syndrome	CGG	Mental retardation, large ears, and jaws, macroorchidism in males
Myotonic Dystrophy(chromosome 19)	CTG	Muscle loss, cardiac arrhythmia,cataracts, frontal balding
Huntington's disease	CAG	Affective disorder
Spinocerebellar ataxia type 1	CAG	Progressive ataxia, dysarthria, dysmetria.
Friedreich's ataxia	GAA	Progressive ataxia,dysarthria, hypertrophiccardiomyopathy.

Solution to Question 20:

In Turner's syndrome, webbing of the neck is associated with a higher risk of cardiac anomalies.

The image below summarises the clinical features of Turner's syndrome.

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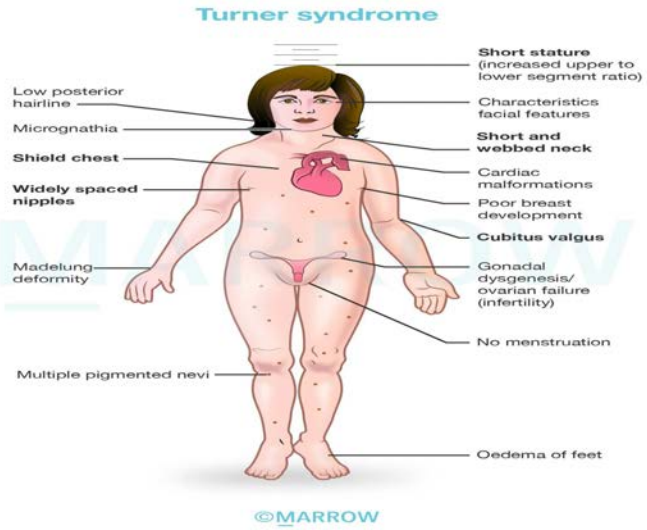

The image given below shows the webbing of neck.

Noonan syndrome is characterised by mutations in the RAS-MAPK pathway. The most common of these is the PTPN11 which encodes a protein tyrosine phosphatase on chromosome 12.

Clinical features include:

• Short stature

• Short webbed neck

• Cystic hygroma

• Tall forehead

• Low posterior hairline

• Dental malocclusion

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Although it shares many clinical features with Turner's syndrome, Noonan syndrome affects both sexes. It follows an autosomal dominant pattern and it also has a different pattern of congenital heart disease, typically involving right-sided lesions.

Solution to Question 21:

The given clinical scenario is suggestive of Angelman syndrome. It can occur due to one of the following genetic abnormalities:

• Deletion (most common) - band q12 on the long arm of maternal chromosome 15

• Paternal uniparental disomy - inheritance of both chromosomes of a pair from the paternal pair of chromosomes

• Defective imprinting - defect in the resetting/maintaining of imprints during gametogenesis or after fertilization

Chromosome 15 diseases (mnemonic - MAP):

• M: Marfan syndrome

• A: Angelman syndrome

• P: Prader Willi syndrome

The following images show children suffering from Prader-Willi syndrome.

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	Prader-Willi syndrome	AngelMan syndrome
Deletion(most common)	Paternal chromosome 15	Maternal chromosome 15
Uniparental disomy(less common)	Maternal disomy(duplication)	Paternal disomy(duplication)
Clinical features	Elevated ghrelin levels - hyperphagiaTruncal obesitySevere hypotoniaShort statureSmall hands and feet with hypotoniaHypogonadotropic hypogonadismCognitive impairment	Short statureSeveremental retardationwith lack of speechStiff arm movementsSpastic, uncoordinated walk (ataxia)SeizuresInappropriate outbursts of laughter (happy puppets)

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The following image shows a child suffering from Angelman syndrome.

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Characteristics of Neoplasms and Epidemiology

Question 1:

Which of the following is not a hallmark of malignancy?

a) Self-sufficiency in growth signals

b) Sensitivity to growth-inhibitory signals

c) Sustained angiogenesis

d) Evasion of apoptosis

Question 2:

Which of the following is incorrect regarding the Warburg effect?

a) Cancer cells are characterized by high levels of glucose uptake

b) Cancer cells convert glucose to lactic acid even in the presence of ample oxygen

c) Conversion of glucose to lactic acid is done via the HMP pathway

d) Aerobic glycolysis provides cancer cells with metabolic intermediates

Question 3:

Which of the following statements is false about adenomas?

a) They are benign tumors

b) Pleomorphic adenoma is an example

c) They can form non-glandular structures

d) They can be of non-glandular origin

Question 4:

All are small round blue cell tumors except:

a) Hemangioblastoma

b) Ewing's sarcoma

c) Retinoblastoma

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d) Neuroblastoma

Question 5:

Which of the following is a disorganized but benign mass composed of cells indigenous to the involved site?

a) Choristoma

b) Hamartoma

c) Papilloma

d) Teratoma

Question 6:

While examining an excision biopsy sample, the pathologist notices anaplastic cells. Which of the following tumors will show this characteristic finding?

a) Papilloma

b) Sarcoma

c) Chondroma

d) Adenoma

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Question 7:

What is the normal nuclear to cytoplasmic ratio?

a) 1:1

b) 1:2

c) 1:4

d) 1:8

Question 8:

A 50-year-old woman is diagnosed with metastatic breast cancer. Which of the following features is least likely to be seen in the microscopic examination of the resected tumor?

a) Retention of polarity

b) Lack of differentiation

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c) Atypical mitoses

d) Pleomorphism

Question 9:

A 45-year-old woman presents with complaints of post-coital bleeding. On per speculum examination, a friable mass is seen and a punch biopsy is done. The presence of which of the following features in microscopic examination of biopsy specimen differentiates invasive carcinoma from carcinoma in situ?

a) Nuclear hyperchromasia

b) Typical mitoses

c) Pleomorphism

d) Breachment of basement membrane

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Question 10:

Choose the correct statement(s):

a) Both A and R are true, and R is the correct explanation of A

b) Both A and R are true, but R is not the correct explanation of A

c) A is true; R is false

d) A is false; R is true

Question 11:

A 40-year-old patient is diagnosed with a breast lump. On clinical examination, nodes are not palpable. Mammography is suggestive of a malignant tumor. Which of the following nodes is often biopsied to assess the presence of metastasis microscopically?

a) Largest lymph node in the region of the primary tumor

b) Smallest lymph node in the region of the primary tumor

c) First lymph node that receives lymph flow from the primary tumor

d) Last lymph node that receives lymph flow from the primary tumor

Question 12:

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Which of the following is not an angiogenesis promoter in tumor cells?

a) Thrombospondin

b) Interleukin-8

c) Epidermal growth factor

d) Angiogenin

Question 13:

Which of the following malignancies is least likely to occur in those with only alcohol abuse and without any additional risk factors?

a) Carcinoma of the oropharynx

b) Carcinoma of the larynx

c) Carcinoma of the oesophagus

d) Carcinoma of the colon

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Question 14:

A textile factory worker who is repeatedly exposed to benzene is at increased risk of developing which of the following tumors?

a) Bladder carcinoma

b) Lung carcinoma

c) Acute myeloid leukemia

d) Prostate carcinoma

Question 15:

A 60-year-old patient employed in plastic industry for 30 years is diagnosed with a tumor in the liver. On resection, the gross specimen shows greyish white lesions with multiple reddish-brown hemorrhagic foci and several blood-filled spaces shown by arrows in the image given below. Which of the following is not a risk factor for the development of this tumor?

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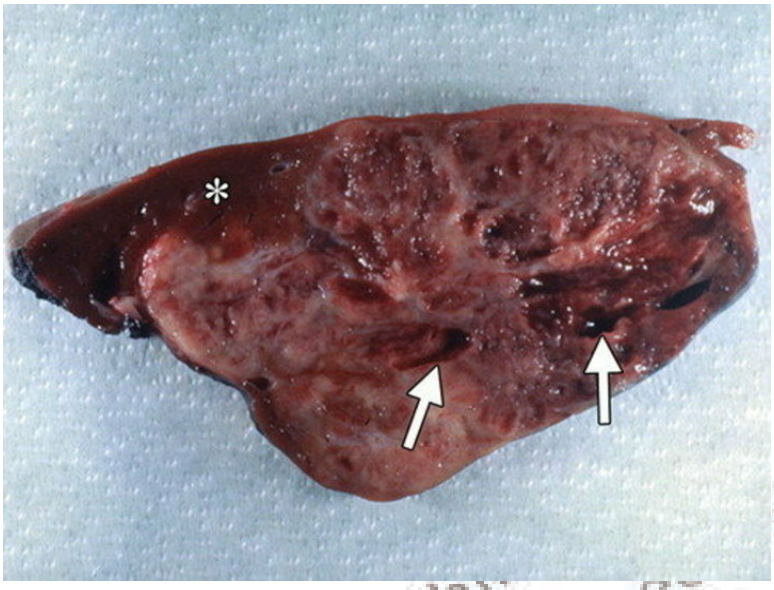

a) Arsenic

b) Thorotrast

c) Vinyl chloride

d) Beryllium

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Question 16:

A 50-year-old patient is diagnosed with lung carcinoma. Which of the following is implicated in the causation of this tumor?

a) Radon

b) Cadmium

c) Barium

d) Thallium

Question 17:

A 50-year-old patient who is a known case of cholangiocarcinoma presents with intermittent fever and jaundice. Which of the following organisms is commonly implicated in the pathogenesis of this tumor?

a) Opisthorchis viverrini

b) Paragonimus westermani

c) Echinococcus granulosus

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d) Diphyllobothrium latum

Question 18:

Which of the following is the least radiosensitive cell in blood?

a) RBC

b) Neutrophil

c) Lymphocyte

d) Platelets

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Answer Key

Question No.	Correct Option
1	b
2	c
3	b
4	a
5	b
6	b
7	c
8	a
9	d
10	d
11	c
12	a
13	d
14	c
15	d
16	a
17	a
18	d

Detailed Explanations

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Solution to Question 1:

Cancer cells are insensitive to growth-inhibitory signals.

All cancer cells are known to show around 8 fundamental physiological changes in the cell, which are considered as the hallmarks of cancer. These changes include the following:

• Self-sufficiency in growth signals - once activated, tumors can proliferate without external stimuli

• Insensitivity to growth-inhibitory signals - tumors do not respond to inhibitors of cell growth. This is attributed to the inactivation of the tumor-suppressor genes in cancer cells

• Altered cellular metabolism - tumor cells switch to aerobic glycolysis, called the Warburg effect

• Evasion of apoptosis

• Limitless replicative potential

• Sustained angiogenesis

• Ability to invade and metastasis

• Ability to evade the host immune response

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Solution to Question 2:

Increased conversion of glucose to lactic acid is done via the glycolytic pathway (not HMP).

Even in the presence of ample oxygen, cancer cells demonstrate a distinctive form of cellular metabolism. This is characterized by high levels of glucose uptake and increased conversion of glucose to lactic acid via the glycolytic pathway. This phenomenon is called the Warburg effect.

Aerobic glycolysis provides rapidly dividing tumor cells with metabolic intermediates that are required for the synthesis of cellular components, whereas mitochondrial oxidative phosphor-ylation□ does not.

Solution to Question 3:

Pleomorphic adenoma is an example of a mixed tumor consisting of epithelial and myoepithelial cells with or without stromal components.

Adenomas are benign epithelial tumors. They can arise from:

• Glandular cells and form glandular structures - for example, follicular adenomas of the thyroid, which arise from the thyroid gland and forms glandular structures

• Glandular cells but form non-glandular structures - for example, heterogeneous mass of adrenal cortical cells growing as a solid sheet

• Non-glandular cells and form glandular structures - for example, benign epithelial neoplasm that arises from renal tubular cells growing in the form of numerous tightly clustered small glands

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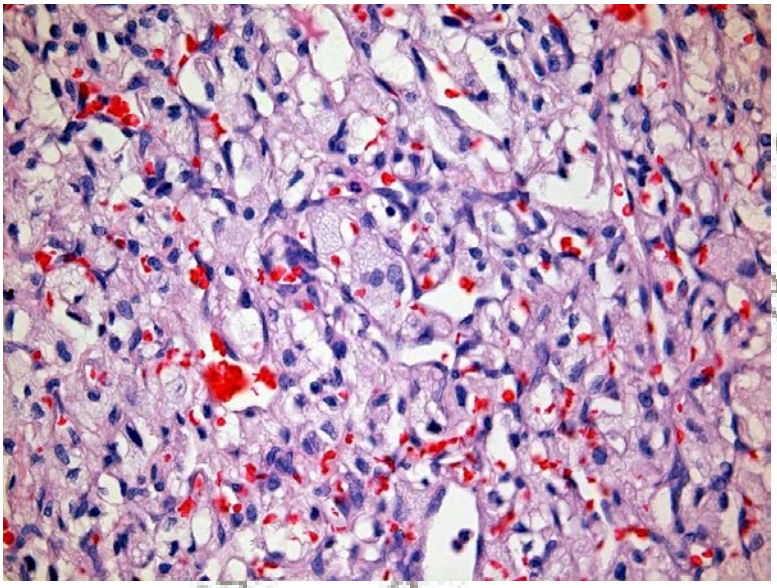
Solution to Question 4:

Hemangioblastoma is not a small round blue cell tumor.

Hemangioblastomas are tumors of central nervous system that originate from vascular tissues. They demonstrate the proliferation of capillaries with variable sized, closely packed, and thin walled vessels as seen in the image below.



Small round blue cell tumors consist of small round cells that stain blue on routine H&E staining sections. They include:

- Neuroblastoma
- Retinoblastoma
- Ewing's sarcoma
- Wilms tumor
- Rhabdomyosarcomas
- Acute leukemia

The following is the image of neuroblastoma showing Homer-Wright pseudorosettes.

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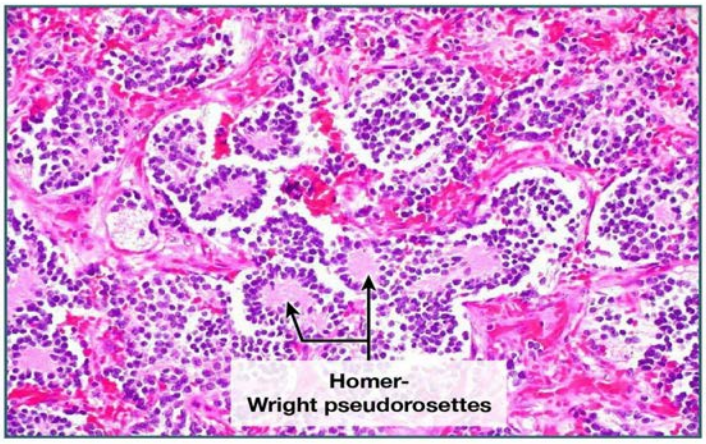
Neuroblastoma



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Solution to Question 5:

Hamartomas are disorganized but benign, masses composed of cells indigenous to the involved site.

Examples of hamartoma include:

- Mammary hamartoma
- Pulmonary chondromatous hamartoma
- Splenic hamartoma
- Neurocristic hamartoma
- Fibrous hamartoma of infancy

Option A: Choristomas are heterotopic rests of cells.

Option D: Teratomas arise from totipotent germ cells. They contain recognizable mature or immature cells or tissues belonging to more than one germ cell layer, and sometimes all three germ layers.

Option C: Papillomas are benign epithelial neoplasms. They are characterized by microscopically or macroscopically visible finger-like or warty projections from epithelial surfaces.

Solution to Question 6:

Anaplasia or lack of differentiation is a characteristic feature of malignant neoplasm like sarcoma.

Differentiation refers to the extent to which neoplastic parenchymal cells resemble the corresponding normal parenchymal cells, both morphologically and functionally.

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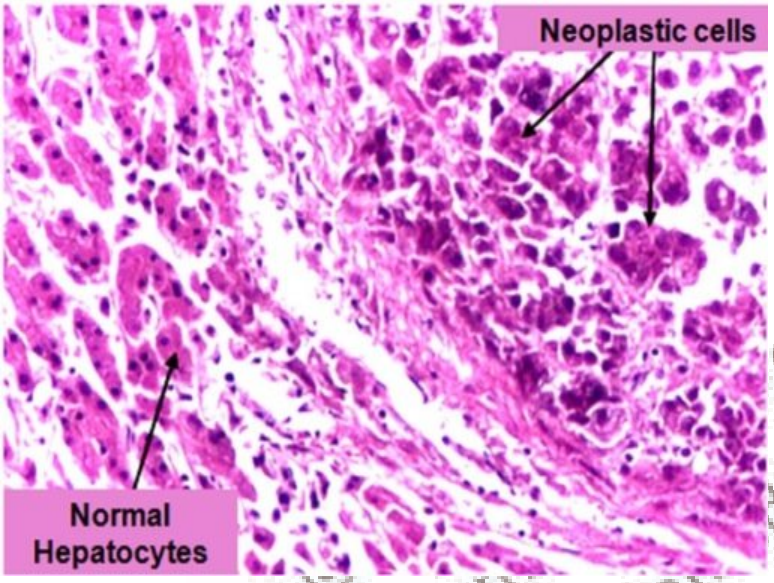
The image below shows a hepatocellular carcinoma characterized by large anaplastic carcinoma cells with eosinophilic cytoplasm, large hyperchromatic nuclei, and prominent nucleoli. The normal trabecular structure of the liver is distorted.



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Solution to Question 7:

The normal nuclear to cytoplasmic ratio is 1:4 to 1:6.

Normal nuclear to cytoplasmic ratio implies that the volume occupied by the cytoplasm is 4 to 6 times greater than the volume occupied by the nucleus.

Abnormal nuclear morphologies that are seen in malignant cells:

- Nuclei disproportionately large for the cell
- Nuclear shape is variable and often irregular
- Chromatin
- Coarsely clumped
- Hyperchromatic
- Nucleoli are abnormally large

Solution to Question 8:

Loss of polarity is a microscopic finding in malignant neoplasm, like metastatic breast cancer.

In malignancy, the orientation of cells is markedly disturbed, and polarity is lost. Sheets or large masses of tumor cells grow in an anarchic, disorganized fashion.

Morphological changes in cancer cells:

- Anaplasia

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• Pleomorphism

• Nuclear changes

• Nuclei disproportionately large for the cell

• Nuclear shape is variable and often irregular

• Chromatin - coarsely clumped and hyperchromatic

• Nucleoli are abnormally large

• Atypical mitosis

• Loss of polarity

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Solution to Question 9:

Once the tumor cells breach the basement membrane, the tumor is said to be invasive.

Progression of cancer occurs in the following stages: dysplasia→carcinoma in situ→invasive carcinoma

In situ carcinoma is when dysplastic changes are marked and involve the full thickness of the epithelium, but the lesion does not penetrate the basement membrane. It is a pre-invasive neoplasm.

The tumor is said to be invasive when the basement membrane is breached by the tumor cells.

Solution to Question 10:

All tumors with invasive property (malignant tumors) may not necessarily metastasize.

Examples of tumors with invasive properties but do not metastasize are:

• Gliomas

• Basal cell carcinomas of the skin

Both of these cancers invade early in their course, but rarely metastasize. Thus, it is evident then that the properties of invasion and metastasis are separable.

Solution to Question 11:

The sentinel lymph node, which is the first node in a regional lymphatic basin that receives lymph flow from the primary tumor, is often used to assess the presence or absence of metastatic lesions in the lymph nodes microscopically.

Sentinel node mapping can be done by the injection of radiolabeled tracers or colored dyes. Examination of frozen sections of the sentinel lymph node is often performed during surgery. It can guide the surgeon to the appropriate therapy.

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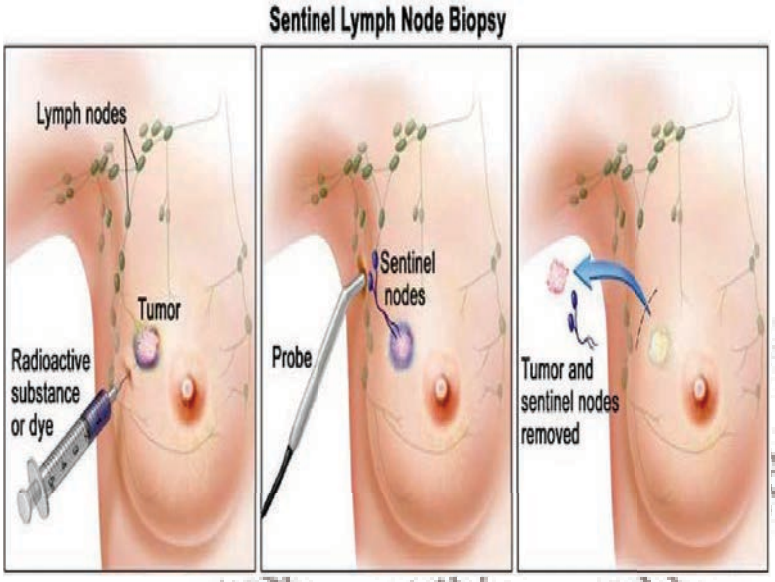
Sentinel node examination has also been used for detecting the spread of:

• Melanomas

• Colon cancers



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Solution to Question 12:

Thrombospondin is an anti-angiogenic factor.

Angiogenic and antiangiogenic factors are produced by tumor and stromal cells and are essential for the vascularization of tumors.

Angiogenic activators include:

• Angiogenin

• Interleukin-8

• Growth factors:

• Vascular endothelial growth factor (VEGF)

• Basic fibroblast growth factor (bFGF)

• Transforming growth factor (TGF)-α and °

• Tumor necrosis factor (TNF)-α

• Platelet-derived endothelial growth factor

• Granulocyte colony-stimulating factor

• Placental growth factor

• Hepatocyte growth factor

• Epidermal growth factor

Anti-angiogenic factors include:

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- Angiostatin
- Endostatin
- Interferon
- Platelet factor 4
- Thrombospondin
- Prolactin 16 KD fragment
- Tissue inhibitor of metalloproteinase-1, 2, and 3

Solution to Question 13:

Alcohol abuse alone increases the risk of carcinomas of the oropharynx (excluding lip), larynx, and esophagus.

Alcohol and tobacco together synergistically increase the risk of cancers in the upper airway and digestive tract.

Solution to Question 14:

Repeated exposure to benzene is associated with increased risk of acute myeloid leukemia (AML)

Malignancies associated with repeated exposure to benzene:

- Acute myeloid leukemia (AML)
- Acute lymphocytic leukemia (ALL).
- Chronic lymphocytic leukemia (CLL).
- Multiple myeloma.

Note: While studies have shown that benzene has a propensity to cause bladder carcinoma , it is most commonly associated with AMLs.

Solution to Question 15:

The given clinical history and findings of the gross specimen are suggestive of angiosarcoma of the liver and beryllium is not a risk factor for the development of this tumor.

Angiosarcoma of the liver is associated with exposure to:

- Vinyl chloride
- Androgenic steroids
- Arsenic
- Thorotrast

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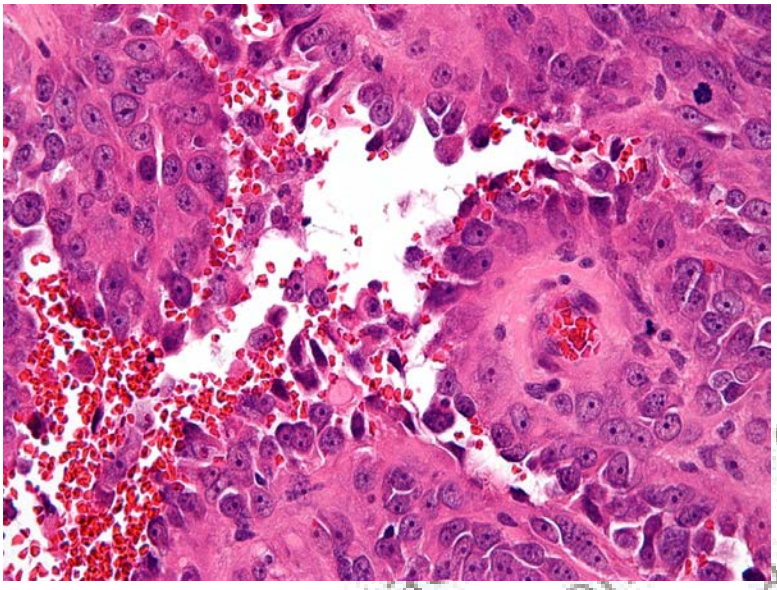
Histological specimen of angiosarcoma of the liver is given below.



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Solution to Question 16:

Radon is implicated in the causation of lung carcinoma.

Carcinogens implicated in lung carcinoma are:

- Asbestos
- Arsenic
- Beryllium
- Chromium
- Nickel
- Radon.

Solution to Question 17:

Opisthorchis viverrini (liver fluke) is implicated in the pathogenesis of cholangiocarcinoma.

Apart from Opisthorchis viverrini, Clonorchis sinensis is also known to cause cholangiocarcinoma.

Solution to Question 18:

The least radiosensitive cell in the blood is the platelet.

The most radiosensitive cell in the blood is the lymphocyte.

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The most radiosensitive phase of the cell cycle is G2M.

The least radiosensitive is the S phase.

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Molecular Basis of Cancer and Tumor Immunity

Question 1:

Which of the following is overexpressed in patients diagnosed with glioma?

a) PDGF-°

b) ERB-1

c) RET

d) NGF

Question 2:

Which of the following is associated with loss of function mutation in RET proto-oncogene?

a) Medullary carcinoma of the thyroid

b) Pheochromocytoma

c) Hirschsprung disease

d) Pituitary adenoma

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Question 3:

Which of the following tumors is associated with mutation of the ALK receptor?

a) Colon carcinoma

b) Pancreatic carcinoma

c) Glioma

d) Neuroblastoma

Question 4:

A 60-year-old man presents with a painless loss of vision. Fundus examination reveals the lesion shown in the image. Which of the following GTP-binding proteins show point mutations in this condition?

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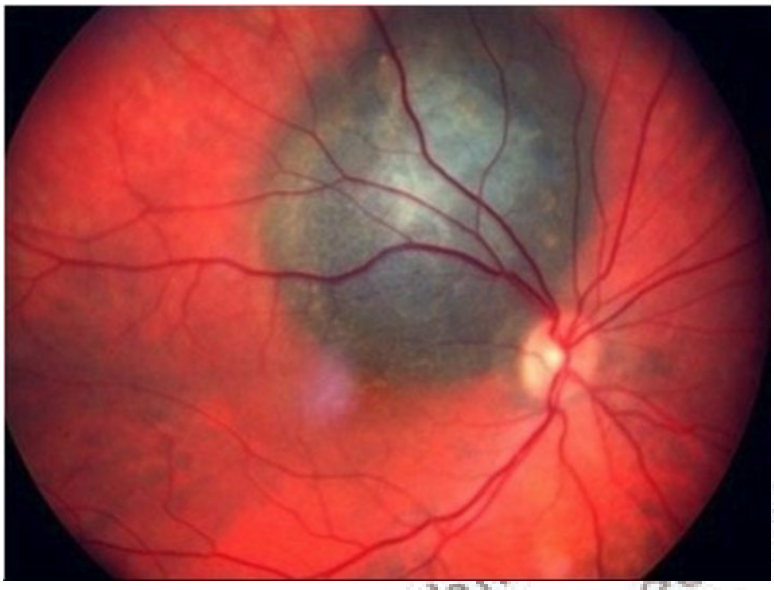

a) NRAS

b) KRAS

c) GNAQ

d) GNAS

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Question 5:

Which of the following are coded by the MYC genes?

a) Cell cycle regulators

b) Nuclear regulatory proteins

c) Signal transduction proteins

d) Growth factor receptors

Question 6:

Which of the following is associated with the translocation of cyclin D1?

a) Chronic myeloid leukemia

b) Non-Hodgkin's lymphoma

c) Acute lymphoblastic leukemia

d) Mantle cell lymphoma

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Question 7:

Which of the following is false about Knudson's two-hit hypothesis theory on retinoblastoma?

a) Familial type is inherited as an autosomal recessive trait

b) It involves both alleles of RB at chromosome locus 13q14

c) In sporadic cases, both normal RB alleles must undergo somatic mutation in the same retinoblast

d) In familial cases, children inherit one defective copy of the RB gene and the other copy is normal

Question 8:

If the RB gene is hypophosphorylated, which of the following will happen?

a) Cell cycle will stop at G2

b) Cell cycle will stop at G1

c) There will be no effect on cell cycle as RB gene phosphorylation is not needed

d) The cell cycle progresses and cell divides

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Question 9:

Which of the following statements is false about p53?

a) It regulates cellular senescence

b) P53 inactivation causes cell cycle arrest at G2-M

c) Cancers demonstrate biallelic loss of function mutations in TP53

d) p53 can be inactivated by E6 protein of HPV

Question 10:

Which of the following is essential for the differentiation of stratified squamous epithelia?

a) p53

b) p63

c) p53 and p63

d) p63 and p73

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Question 11:

A 22-year-old man was found to have multiple GI polyps. He was operated on for thyroid cancer 2 years back. His family history is significant for breast cancer in his mother and endometrial cancer in his aunt. Germline loss-of-function mutations of which gene is associated with this condition?

a) CDKN2A

b) SMAD2

c) APC

d) PTEN

Question 12:

A 24-year-old woman presented with hearing loss and tinnitus. MRI was done and showed the presence of bilateral acoustic schwannomas. Which protein involved in cytoskeletal stability is mutated in this condition?

a) Neurofibromin

b) Merlin

c) PATCHED

d) RB protein

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Question 13:

Germline loss-of-function mutation of which gene causes Gorlin syndrome?

a) STK11

b) SDHB

c) WT1

d) PTCH1

Question 14:

A 25-year-old man patient presents with anemia and abdominal pain. On examination, he has pigmented macules over the palms, soles, and oral mucosa. Further investigations reveal loss-of-function mutations of the STK11 gene. What is the most probable diagnosis?

a) HNPCC

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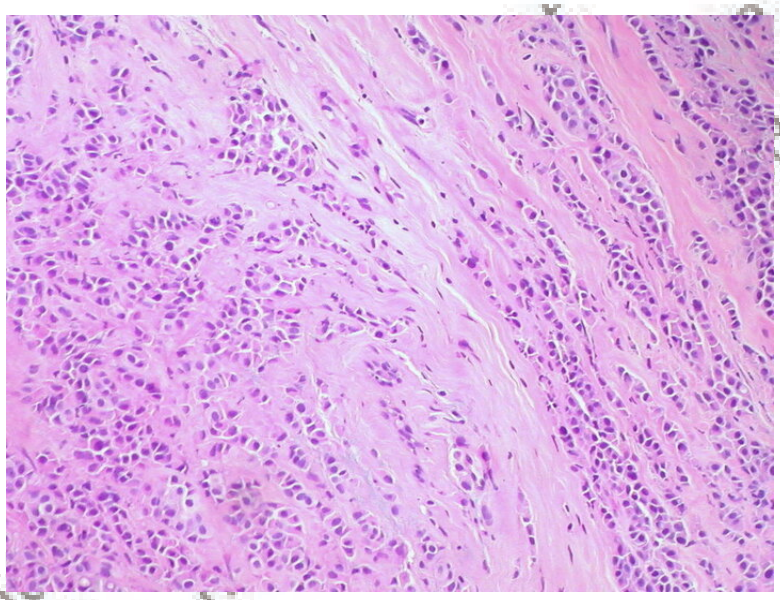
b) Gorlin syndrome

c) von Hipple-Lindau syndrome

d) Peutz-Jeghers syndrome

Question 15:

A 38-year-old woman presents with complaints of a palpable mass in both breasts. Histopathology examination shows the following finding. Immunohistochemistry showed estrogen receptor positivity. Which protein that maintains cell adhesion, and thereby inhibits cell motility, is mutated in this condition?



a) p63

b) p53

c) E Cadherin

d) Integrin

Question 16:

Which of the following is incorrect regarding the BRCA genes?

a) BRCA1 is located on the long arm of chromosome 17

b) BRCA1 mutation causes well-differentiated cancer

c) BRCA2 carcinomas are ER/PR- positive

d) BRCA 2 mutation is associated with male breast carcinoma

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Question 17:

Which of the following is incorrect regarding apoptosis?

a) p53 induces apoptosis in cells with DNA damage

b) Extrinsic apoptotic pathway is more frequently disabled in cancer cells

c) Chemoradiation induces apoptosis in cancer cells

d) BCL2 is over-expressed in follicular lymphomas

Question 18:

Which of the following genes promote epithelial-mesenchymal transition in epithelial tumors?

a) 1, 2 and 3 only

b) 2, 3, and 5 only

c) 4 and 5 only

d) 2 and 3 only

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Question 19:

Which of the following is a non-receptor tyrosine kinase?

a) ABL

b) RET

c) KIT

d) ALK

Question 20:

The mutations/changes that convert proto-oncogene to oncogene include all except:

a) Promoter insertion

b) Enhancer deletion

c) Gene amplification

d) Point mutation

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Question 21:

Mutation in which of the following oncogenes can serve as a tumor antigen?

a) EBNA

b) MUC-1

c) p53

d) RAS

Question 22:

Which of the following mechanisms does not lead to immune evasion by the tumor cells?

a) Inhibition of PD-1 receptor on T-cells

b) Upregulation of expression of PD-L1

c) Induction of galactin

d) Induction of regulatory T-cells

Question 23:

An 8-year-old girl is referred with recurrent blistering rashes over the face and upper limbs which worsened following exposure to sunlight. There is a history of similar skin lesions in her family and 2 of her uncles were diagnosed with skin cancers at young ages. Examination reveals the presence of multiple lentigos and xerosis. What is the likely pathological mechanism of this condition?

a) Defective base excision repair

b) Defective DNA nucleotide excision repair

c) Defective mismatch repair

d) Defective non-homologous end joining repair

Question 24:

Which of the following disorders is not associated with defective homologous recombination DNA repair mechanism?

a) Familial breast cancer

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b) Fanconi anemia

c) Fanconi syndrome

d) Ataxia-telengeictasia

Question 25:

A 30-year-old patient presents with right iliac fossa pain. Imaging shows the presence of an ileocaecal mass. Biopsy of the mass shows a starry sky pattern. What is the translocation involved in this tumor?

a) t(8;14)

b) t(15;17)

c) t(9;22)

d) t(11;14)

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Question 26:

Which epigenomic regulatory gene is mutated in most of the follicular lymphomas?

a) MLL1

b) MLL2

c) ARID1A

d) SNF5

Question 27:

The loss of which of the following micro RNAs leads to upregulation of BCL-2?

a) miR-200

b) miR-15

c) miR-155

d) miR-25

Question 28:

Identify the correct statement regarding immune surveillance.

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a) Anti CTLA 4 Ab is a new modality in the treatment of advanced cancers

b) Mutation of tumor supressor genes decreases antigen toxicity

c) PD1/ PDL1 activation leading to tumor supression

d) Binding of CD28 leads to immune tolerance

Answer Key

Question No.	Correct Option
1	a
2	c
3	d
4	c
5	b
6	d
7	a
8	b
9	b
10	b
11	d
12	b
13	d
14	d
15	c
16	b
17	b
18	d
19	a
20	b
21	d
22	a
23	b
24	c
25	a
26	b
27	b

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28	a

Detailed Explanations

Solution to Question 1:

Gliomas show overexpression of PDGF-° and TGF-α.

Isocitrate dehydrogenase (IDH) wild-type glioblastomas are associated with epidermal growth factor receptor (EGFR) amplification and homozygous CDKN2A deletion.

Solution to Question 2:

Loss of function mutation in RET proto-oncogene is associated with Hirschsprung's disease.

Hirschsprung's disease is caused by mutations in other genes encoding proteins involved in enteric neurodevelopment. These include:

• RET ligand glial-derived neurotrophic factor

• Endothelin

• Endothelin receptor

Note: Medullary thyroid carcinoma and multiple endocrine neoplasias, types 2A and 2B are usually due to gain of function mutations in RET proto-oncogene.

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Solution to Question 3:

Anaplastic lymphoma kinase (ALK) is a membrane-bound receptor tyrosine kinase. When aberrantly expressed, it is associated with neuroblastoma pathogenesis. It serves as a therapeutic target.

Neuroblastoma is one of the most common solid cancers among children.

Solution to Question 4:

The given scenario and fundus examination are suggestive of uveal melanoma which is associated with a point mutation of GNAQ protein or GNA11 genes.

Uveal melanomas (UM) originate from melanocytes in the interior wall of the eye. This includes the iris, ciliary body, and the choroid with marked differences in light exposure (from dark anterior to illuminated posterior).

GNAS mutation causes pituitary adenoma and other endocrine tumors.

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The 3 RAS genes in humans (H-RAS, K-RAS, and N-RAS) are the most common oncogenes in human cancer. They code for a family of proteins called GTP-binding (G) proteins, which are involved in transmitting signals within cells (cellular signal transduction). When RAS is 'switched on' by incoming signals, it subsequently switches on other proteins, which ultimately results in cell growth, differentiation, and survival.

Mutations in RAS genes can lead to the production of permanently activated RAS proteins. As a result, this can cause unintended and overactive signaling inside the cell, even in the absence of incoming signals. Because these signals result in cell growth and division, overactive RAS signaling can ultimately lead to cancer.

Solution to Question 5:

MYC oncogene codes for nuclear regulatory proteins. It is the most commonly involved transcription factor in tumors.

The MYC proto-oncogene MYC activates the expression of many genes that are involved in cell growth. It upregulates the expression of telomerase and reprograms somatic cells into pluripotent stem cells.

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Solution to Question 6:

Translocation of cyclin D1 is seen in mantle cell lymphoma.

Mantle cell lymphoma is an uncommon lymphoid neoplasm that is characterized by overexpression of cyclin D1. It is a type of non Hodgkins lymphoma that involves (11;14) translocation i.e. between IgH locus on chromosome 14 and the cyclin D1 locus on chromosome 11.

Solution to Question 7:

Retinoblastoma is inherited as an autosomal dominant trait.

Knudson's hypothesis, also known as the two-hit hypothesis or multiple-hit hypothesis states that cancer is the result of accumulated mutations in a cell's DNA. Two mutations (hits), involving both alleles of RB at chromosome locus 13q14, are required to produce retinoblastoma.

In familial cases, children inherit one defective copy of the RB gene in the germline (the first hit), and the other copy is normal. Retinoblastoma develops when the normal RB allele is mutated in retinoblasts as a result of a spontaneous somatic mutation (the second hit). Most individuals inheriting a germline defect in one RB allele develop unilateral or bilateral retinoblastoma as it is an autosomal dominant disease.

Sporadic cases are comparitively rare. In sporadic cases, both normal RB alleles must undergo somatic mutation in the same retinoblast (two hits).

The image given below shows the Knudson's two-hit hypothesis.

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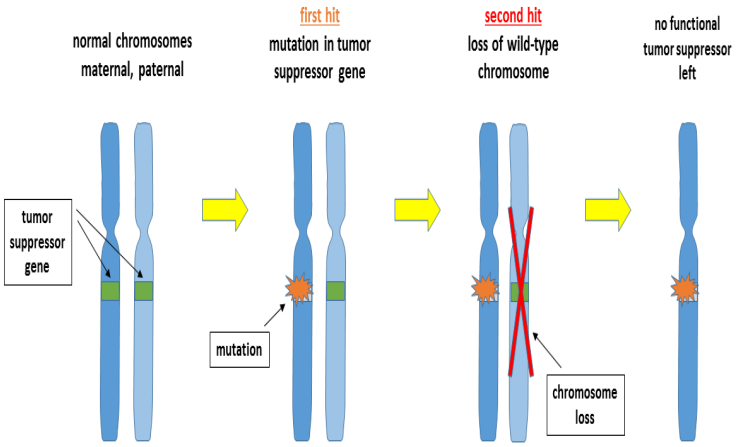

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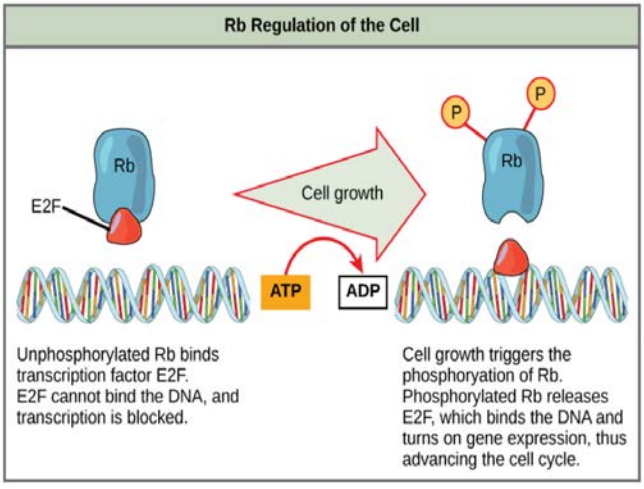
Solution to Question 8:

If the retinoblastoma (RB) gene is hypophosphorylated, it is active and the cell cycle will stop at G1.

RB is a cell-cycle regulator because it binds to and inactivates a transcription factor (E2F). This is necessary for the transcription of certain genes necessary for the progression from the G1 to S phase. The phosphorylation of RB results in the release of E2F. This activates gene transcription and cell-cycle progression occurs.

The image given below shows the cell cycle regulation by RB gene.



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Solution to Question 9:

P53 is the tumor suppressor gene and activation (not inactivation) causes cell cycle arrest at the G1-S and G2-M phase of the cell cycle.

P53 regulates:

• Cell cycle progression

• DNA repair

• Cellular senescence

• Apoptosis

It is activated by:

• Anoxia

• Inappropriate signaling by mutated oncoproteins

• DNA damage

It is the most frequently mutated gene in cancers. It upregulates the expression of proteins such as the cyclin-dependent kinase inhibitor p21, thereby causing cell-cycle arrest at the G1-S. It also transactivates and transrepresses target gene to induce G2/M arrest. Mutation in the p53 gene causes resistance in tumors to radiation and chemotherapy.

The E6 protein of human papillomavirus (HPV) binds to and helps in the degradation of p53 and stimulates the expression of telomerase reverse transcriptase (TERT), which is the catalytic subunit of telomerase, thereby helping in the longevity of the cells. E6 from high-risk HPV types has a higher affinity for p53 than E6 from low-risk types.

Li-Fraumeni syndrome is an autosomal dominant disorder due to a defect in the tumor suppressor gene P53 located on chromosome 17.

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Solution to Question 10:

p63 is essential for the differentiation of stratified squamous epithelia.

p53 is ubiquitously expressed, while p63 and p73 show more tissue specificity.

p73 has strong pro-apoptotic effects after DNA damage induced by chemotherapeutic agents.

Solution to Question 11:

The given scenario is suggestive of Cowden syndrome. This condition is caused due to germline loss of function mutation in PTEN (phosphatase and tensin homolog) gene.

PTEN is a membrane-associated phosphatase encoded by a gene on chromosome 10q23 that is mutated.

Cowden syndrome is characterized by skin appendage tumors and an increased incidence of epithelial cancers, particularly of the breast, endometrium, and thyroid.

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Solution to Question 12:

The given scenario and MRI findings are suggestive of neurofibromatosis type 2 (NF-2). Merlin protein is mutated in NF-2, sporadic schwannomas, and meningiomas.

Cells lacking Merlin do not establish stable cell-to-cell junctions. They are insensitive to normal growth arrest signals generated by cell-to-cell contact.

Solution to Question 13:

Germline loss-of-function mutations of the PTCH1 gene cause Gorlin syndrome.

Gorlin syndrome is an autosomal-dominant disorder. Clinical features include:

- Multiple basal cell carcinomas
- Highly characteristic facies - large forehead
- Bifid or misshapen ribs
- Vertebral and other skeletal anomalies
- Pits of the skin of the palms and soles
- Dysgenesis of the corpus callosum
- Calcification of the falx cerebri - at an earlier age than is seen in non■affected individuals
- Macrocephaly

Acquired biallelic loss-of-function mutations of PTCH1 cause sporadic basal cell carcinomas and medulloblastoma.

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Solution to Question 14:

The given scenario is suggestive of Peutz–Jeghers syndrome.

Loss-of-function mutations of STK11 cause the Peutz–Jeghers syndrome. The STK22 gene, also known as LKB1, encodes a serine/threonine kinase that is an important regulator of cellular metabolism.

Peutz-Jeghers syndrome is an autosomal-dominant disorder. It is associated with arborizing polyps of the gastrointestinal tract (small intestine > colon > stomach). It increases the risk of multiple epithelial cancers, particularly of colon, breast, lung, pancreas, and thyroid.

Solution to Question 15:

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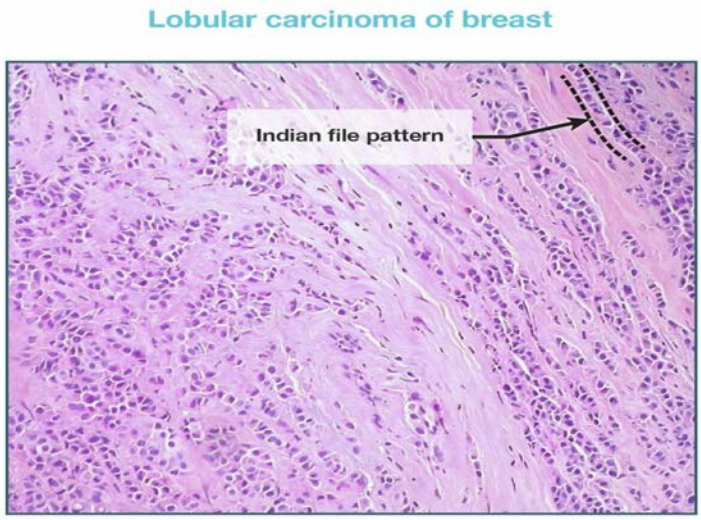
The given scenario is suggestive of lobular carcinoma of the breast which involves mutated E-cadherin protein. In this condition, the histopathological examination shows infiltrating small monomorphic discohesive tumor cells arranged in an Indian-file or single-file pattern.

The image below shows the single file pattern seen in lobular carcinoma of the breast.



Reduced cell surface expression of E-cadherin is seen in carcinomas of:

- Breast
- Esophagus
- Colon
- Ovary
- Prostate

E-cadherin is a cell-surface protein that maintains intercellular adhesiveness. Loss of E-cadherin causes disaggregation of cells, which can then invade locally or metastasize.

Germline loss-of-function mutations of the E-cadherin gene lead to familial gastric carcinoma. Sporadic gastric carcinomas are also associated with the loss of E-cadherin expression.

Solution to Question 16:

BRCA2 (not BRCA 1) mutation causes well-differentiated cancer.

Solution to Question 17:

The intrinsic apoptotic pathway is most frequently disabled in cancer cells to evade cell death.

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p53 is an important pro-apoptotic protein that induces apoptosis in cells that are unable to repair DNA damage.

Chemotherapy and radiation therapy kills cancer cells mainly by inducing apoptosis via the intrinsic pathway.

In greater than 85% of follicular B-cell lymphomas, the anti-apoptotic gene BCL2 is overexpressed due to a (14;18) translocation.

Solution to Question 18:

SNAIL and TWIST, which encode transcription factors, promote epithelial-to-mesenchymal transition (EMT).

In EMT, carcinoma cells downregulate certain epithelial markers (e.g., E-cadherin) and upregulate certain mesenchymal markers (e.g. vimentin and smooth muscle actin). This favors the development of a promigratory phenotype that is essential for metastasis. EMT has been documented mainly in breast carcinoma.

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Solution to Question 19:

ABL is a non-receptor tyrosine kinase.

Tyrosine kinases may be receptors and non-receptors.

Nonreceptor tyrosine kinases normally localize to the cytoplasm or the nucleus. These are:

• ABL - translocation causes CML and point mutation causes ALL

• JAK mutation - seen in polycythemia vera, essential thrombocythemia, and myelofibrosis as well as other myeloproliferative disorders

Receptor tyrosine kinases:

• VEGFR

• PDGFR

• EGFR

In chronic myelogenous leukemia (CML) and some acute lymphoblastic leukemia (ALL), the ABL gene is translocated from its normal abode on chromosome 9 to chromosome 22 where it fuses with the BCR gene forming the Philadelphia chromosome. The resultant chimeric gene encodes a constitutively active, oncogenic BCR-ABL tyrosine kinase.

Solution to Question 20:

Enhancer deletion does not convert a proto-oncogene to an oncogene.

Mechanisms of activating oncogenes:

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Mechanism	Activation of oncogenes
Mutation	Mutation activates the gene. A classic example is the point mutation of the RAS oncogene.
Promoter insertion	Insertion of a viral promoter region near a gene activates it.
Enhancer insertion	Insertion of a viral enhancer region near a gene activates it.
Chromosomal translocation	One chromosome is split off and joined to another. An example is the Philadelphia chromosome.
Gene amplification	Abnormal multiplication of a gene resulting in many copies. This can occur with oncogenes and genes involved in tumor drug resistance.

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Solution to Question 21:

RAS is an oncogene that undergoes mutation and serves as a tumor antigen.

Tumor cells express antigenic molecules on their surface that elicit an immune response. These are called tumor antigens. Some tumor cells evade immune response which results in growth of the tumor.

Solution to Question 22:

Inhibition of PD-1 receptor (programmed death -1 receptor) on T cells causes activation of immunity against the tumor cells, not evasion.

PD-1 receptors present on T cells inhibit T-cell activation. This allows tumors to evade the host immunity by the upregulation of the expression of factors like PD-L1 and PD-L2, which act on PD-1 receptors.

Solution to Question 23:

The given clinical scenario is suggestive of xeroderma pigmentosum. It is caused by a defect in the DNA nucleotide excision repair pathway resulting in inability to repair pyrimidine dimers.

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Clinical features of xeroderma pigmentosum:

• Actinic keratosis

• Hyperkeratotic lesions

• Multiple lentigos

• Xerosis

• Corneal scarring

The image of a child with xeroderma pigmentosum is given below.

Solution to Question 24:

Fanconi syndrome is not associated with defective homologous recombination DNA repair mechanism. It is a rare disorder of kidney tubule function.

Diseases with defects in DNA repair by homologous recombination:

• Bloom syndrome and ataxia–telangiectasia triggered by DNA-damaging agents such as ionizing radiation

• Fanconi anemia is an autosomal recessive disease caused by mutations in multiple genes responsible for coding for proteins that participate in DNA repair pathways and are triggered by DNA-crosslinking agents like chemotherapeutic drugs.

• Familial breast cancer is due to inherited gene defects in BRCA1 and BRCA 2 genes

Solution to Question 25:

The given clinical history and biopsy findings are suggestive of Burkitt lymphoma and the translocation involved is t(8;14).

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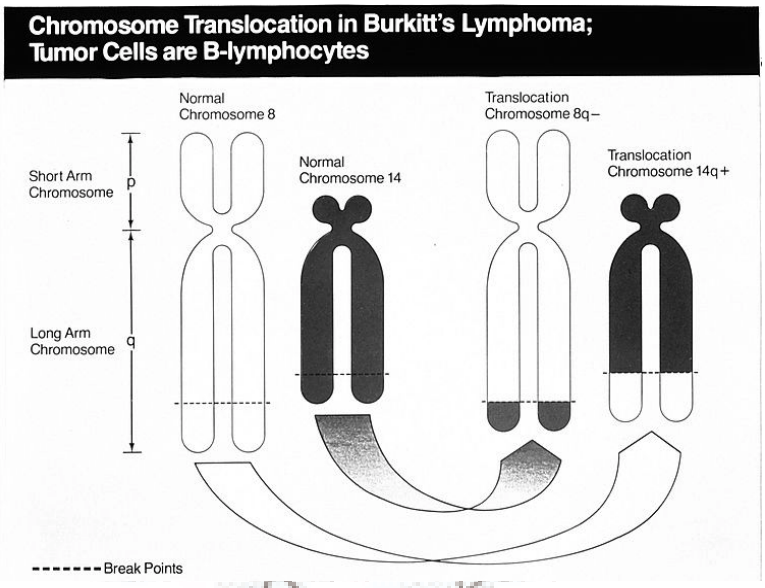
Burkitt lymphoma, also known as small non-cleaved-cell lymphoma, is a highly aggressive B-cell non-Hodgkin lymphoma. It is characterized by the translocation and deregulation of the c-myc gene on chromosome 8.

The classic t(8;14)(q24;q32) reciprocal translocation results in the transposition of the c-myc proto-oncogene on chromosome 8 with one of the immunoglobulin heavy chain (IGH) genes on chromosome 14. This results in activation of the c-myc gene and is considered responsible for tumor proliferation.



Solution to Question 26:

MLL2 is an epigenomic regulatory gene that is mutated in most follicular lymphomas. It results in histone methylation.

Epigenetics refers to factors other than the sequence of DNA that regulate gene expression. These factors involved in epigenetics are:

- Histone modifications
- DNA methylation
- Nucleosome positioning/ chromatin remodeling

Solution to Question 27:

The loss of miR-15 leads to upregulation of the anti-apoptotic protein BCL-2.

miR-15 and miR-16 are tumor-suppressive miRNAs involved in chronic lymphocytic leukemia (CLL).

Onco-miRNAs include:

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• miR200 - promotes epithelial-mesenchymal transitions that promote tumor invasion and metastasis

• miR155 - involved in human B-cell lymphomas

Solution to Question 28:

Anti-CTLA-4 antibody ipilimumab was the first drug to achieve a significant improvement in survival of advanced-stage melanoma. Cytotoxic T lymphocyte antigen 4 (CTLA-4) plays an important inhibitory role in the control of T-cell activation.

Ipilimumab is a fully-humanized IgG1 monoclonal antibody that inhibits cytotoxic T lymphocyte antigen-4 (CTLA-4).

It has been postulated that anti-CTLA-4 antibodies act by blocking inhibitory signals from effector T-cells, allowing costimulatory signaling and generation of antitumor T-cell responses. In vitro studies demonstrated also that the antitumor activity of CTLA-4 blockade is mediated by Fc gamma receptor-expressing macrophage and hypothesized a possible role of regulatory T-cell depletion in the tumor microenvironment.

Option B - Mutation of tumor supressor genes is associated with increased risk of cancer. Antigen toxicity is when the immune response to an antigen is excessive or misdirected, causing damage to tissues or organs.

Option C - PD1/PDL1 is an immune checkpoint whose activation inhibits T-cell function and helps with immune tolerance. Blocking PD-1/PD-L1 interaction using immune checkpoint inhibitors reactivates T cells and enhances immune responses against tumors.

Option D - CD28 is primarily involved in providing the second signal required for T cell activation. The first signal comes from the interaction between the T cell receptor (TCR) and the antigen presented by the major histocompatibility complex (MHC) on antigen-presenting cells (APCs). Without CD28-mediated costimulation, T cells that only receive the TCR signal (without the second signal) can become anergic.

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Carcinogenesis, Paraneoplastic Syndromes and Tumor Markers

Question 1:

Which of the following tumors is best suited to study the mechanism of multi-step carcinogenesis?

a) Colon carcinoma

b) Melanoma

c) Thyroid carcinoma

d) Breast carcinoma

Question 2:

Which of the following procarcinogens does not require metabolic activation?

a) Cyclophosphamide

b) Benzidene

c) 3-Methylcholanthrene

d) Dimethylaminoazobenzene

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Question 3:

A 45-year-old man presents with a hyperpigmented lesion on his face. He is a farmer by occupation and works for long hours with sun exposure. He is at increased risk for all of the following except:

a) Squamous cell carcinoma

b) Basal cell carcinoma

c) Seborrheic keratosis

d) Actinic keratosis

Question 4:

Which form of radiation is responsible for cutaneous cancer?

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a) Only UVA

b) Only UVB

c) Both UVB and UVC

d) Both UVA and UVC

Question 5:

Individuals with repeated exposure to ionizing radiation are at increased risk of which of the following malignancies?

a) Hodgkin lymphoma

b) Myeloid leukemia

c) Malignant melanoma

d) Squamous cell carcinoma

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Question 6:

Which of the following tumors is not caused by microbes?

a) Burkitt lymphoma

b) Castleman's disease

c) Adenocarcinoma lung

d) Primary effusion lymphoma

Question 7:

Which of the following malignancies is caused by HTLV-1?

a) Adult T-cell leukemia/ lymphoma

b) Enteropathy associated T-cell lymphoma

c) Diffuse large B cell lymphoma

d) B cell lymphomas

Question 8:

Which of the following pairs of HPV oncoproteins and target genes are correctly matched?

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a) E6-RB, E7-p53

b) E6-p53, E7-RB

c) E5-RB, E6-p53

d) E5-p53, E6-RB

Question 9:

A 13-year-old child presents to the OPD with fever, pharyngitis, and cervical lymphadenopathy. Peripheral smear showed a predominance of lymphocytes. The heterophile agglutination test is positive. The causative organism of this condition is not implicated in which of the following tumors?

a) Burkitt lymphoma

b) Hodgkin's lymphoma

c) Nasopharyngeal carcinoma

d) Follicular lymphoma

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Question 10:

Which of the following statements about Epstein-Barr virus is incorrect?

a) EBV infection always results in Burkitt lymphoma

b) It uses the complement receptor CD21 to attach and infect B cells

c) It is implicated in B-cell lymphomas in immunosuppressed people

d) It is a potent inducer of B-cell growth and transformation

Question 11:

Which of the following pathogens is implicated in the causation of primary effusion lymphoma and Castleman disease?

a) JC virus

b) Polyoma BK virus

c) EBV

d) HHV 8

Question 12:

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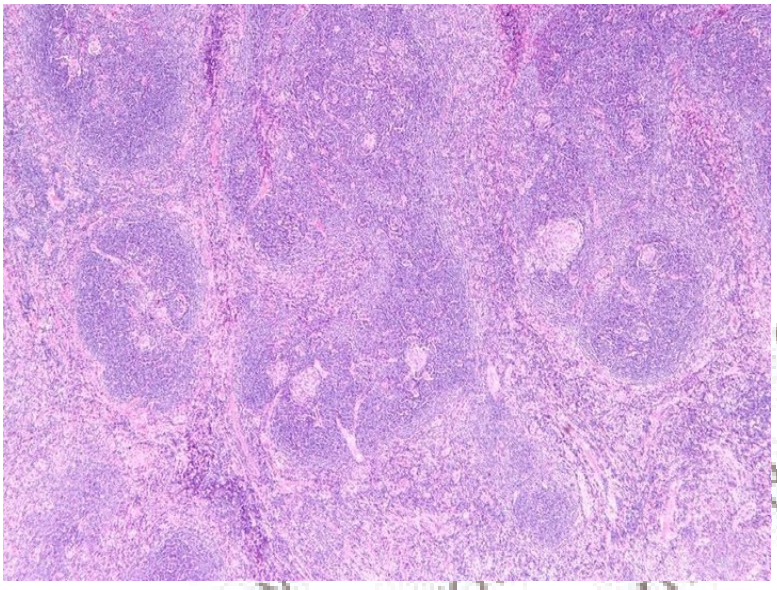
A patient presents with abdominal distension and intermittent fever. Peripheral smear findings are normal. A tumor is resected and the histopathology image of the resected lymph node is shown below. What is the most probable diagnosis?



a) Angiolymphoma

b) Hodgkin's lymphoma

c) IgG4-related disease

d) Castleman disease

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Question 13:

Which of the following is an EBV oncogene behaving like a constitutively active CD40 receptor?

a) LMP-1

b) EBNA-2

c) EBNA-1

d) LMP-2

Question 14:

Helicobacter pylori increases the risk of development of which of the following conditions?

a) 1, 3, 5

b) 2, 4, 5

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c) 1, 2, 4

d) 1, 3, 4

Question 15:

Which of the following is the most common endocrinopathy caused by tumors?

a) Cushing syndrome

b) Osteomalacia

c) SIADH

d) Hypercalcemia

Question 16:

Patients with which of the following tumors present with pure red cell aplasia as a paraneoplastic manifestation?

a) Pancreatic carcinoma

b) Renal carcinoma

c) Thymoma

d) Acute myeloid leukemia

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Question 17:

Which subtype of acute myeloid leukemia presents with disseminated intravascular coagulation as a paraneoplastic manifestation?

a) AML minimally differentiated

b) Acute promyelocytic leukemia

c) Acute myelomonocytic leukemia

d) Acute megakaryoblastic leukemia

Question 18:

A 60-year-old patient presents with loss of weight and appetite. On clinical examination, grade IV clubbing is evident. Imaging shows periosteal new bone formation and synovial effusion. Which of the following tumors is associated with this condition?

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a) Bronchogenic carcinoma

b) Carcinoma of the pancreas

c) Esophageal carcinoma

d) Acute myeloid leukaemia

Question 19:

A 55-year-old patient presents with generalized tiredness, malaise, muscle weakness, and bone pain. Laboratory investigations reveal serum calcium to be 13 mg/dL. Which of the following is lung cancers is implicated in this patient?

a) Squamous cell carcinoma of lung

b) Adenosquamous carcinoma of lung

c) Small cell carcinoma of lung

d) Large cell carcinoma of lung

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Question 20:

Which of the following paraneoplastic manifestations is likely to occur in a patient with a phosphaturic mesenchymal tumor?

a) Cushing syndrome

b) Osteomalacia

c) SIADH

d) Polycythemia

Question 21:

A 48-year-old obese female presents with skin changes in her axilla and neck as shown in the image. Which of the following tumors is not associated with this condition?

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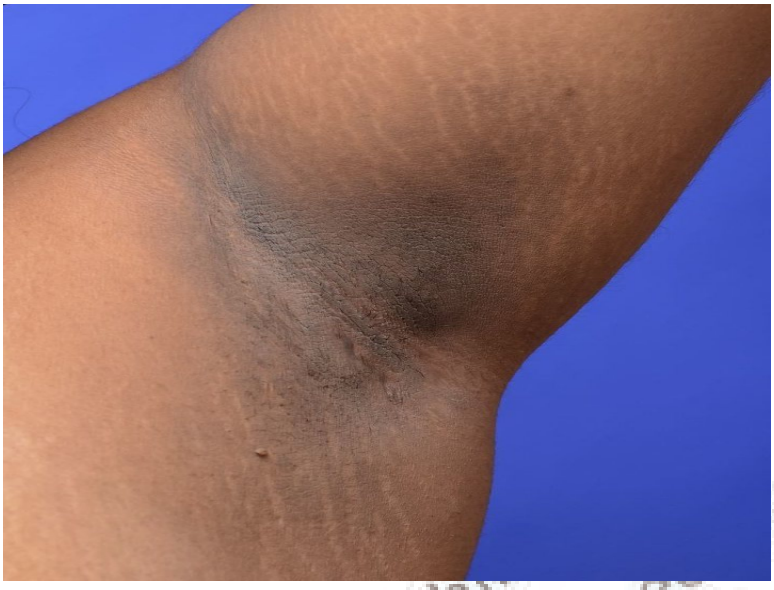

a) Gastric carcinoma

b) Bladder carcinoma

c) Uterine carcinoma

d) Thymoma

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Question 22:

A 45-year-old patient presents with headache, vertigo, tinnitus, and visual disturbance. On further evaluation, blood hemoglobin and hematocrit levels are found to be 18 g/dL and 62% respectively. Which of the following tumors does not present with these paraneoplastic manifestations?

a) Melanoma

b) Renal cell carcinoma

c) Cerebellar hemangioma

d) Hepatocellular carcinoma

Question 23:

Which of these paraneoplastic syndromes is associated with small-cell carcinoma lung?

a) Osteomalacia

b) SIADH

c) Polycythemia

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d) Hypercalcemia

Question 24:

A 60-year-old patient notices spontaneously appearing and disappearing painful, linearly arranged nodules in different parts of the body. Which of the following malignancies is not associated with this clinical presentation?

a) Uterine carcinoma

b) Pancreatic carcinoma

c) Bronchogenic carcinoma

d) Bladder carcinoma

Question 25:

A 24-year-old patient with paroxysmal hypertension is suspected to have malignant pheochromocytoma. Which of the following tumor markers will help you confirm your diagnosis?

a) Calcitonin

b) Catecholamine

c) α-fetoprotein

d) Carcinoembryonic antigen

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Question 26:

Which of the following are oncofetal antigens?

a) 1 and 3

b) 1, 3 and 4

c) 3, 4 and 5

d) 1 and 2

Question 27:

A 42-year-old patient is diagnosed with breast cancer. Which of the following glycoproteins is expected to be elevated in this patient?

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a) CA-125

b) CA-19-9

c) CA-15-3

d) CA-5-13

Question 28:

A 51-year-old male patient who is a chronic smoker presents with dry persistent cough and progressive dyspnea. You are suspecting small cell carcinoma of lung. Which of the following tumor markers is likely to be elevated in this condition?

a) Lactate dehydrogenase

b) Acid phosphatase

c) Neuron-specific enolase

d) Thymidine kinase

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Question 29:

Which of the following is not a marker for gastrointestinal stromal tumors?

a) KIT

b) SDH

c) PDGFRA

d) NRG-1

Answer Key

Question No.	Correct Option
1	a
2	a
3	c
4	b
5	b
6	c
7	a

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8	b
9	d
10	a
11	d
12	d
13	a
14	d
15	a
16	c
17	b
18	a
19	a
20	b
21	d
22	a
23	b
24	d
25	b
26	d
27	c
28	c
29	d

Detailed Explanations

Solution to Question 1:

Multi-step carcinogenesis is best studied in colon carcinoma.

The molecular model for the evolution of colorectal cancers is described as Fearon-Vogelstein adenoma-carcinoma sequence.

Solution to Question 2:

Cyclophosphamide is a directly-acting carcinogen that does not require metabolic activation.

Carcinogens can be direct-acting or indirect-acting based on their activation.

Direct-acting carcinogens require no metabolic conversion to become carcinogenic. Most are weak carcinogens, but some are important because they are cancer chemotherapeutic drugs (e.g.,

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alkylating agents). The direct-acting carcinogens include:

• Alkylating Agents:

• °-Propiolactone

• Dimethyl sulfate

• Diepoxybutane

• Anticancer drugs (cyclophosphamide, chlorambucil, nitrosoureas, and others)

• Acylating Agents:

• 1-Acetyl-imidazole

• Dimethylcarbamyl chloride

Indirect-acting carcinogens (procarcinogens) are chemicals that require metabolic conversion to become active carcinogens. The carcinogenic product of metabolism is called an ultimate carcinogen. The indirect-acting carcinogens include:

• Polycyclic and heterocyclic aromatic hydrocarbons:

• Benz[a]anthracene

• Benzo[a]pyrene

• Dibenz[a,h]anthracene

• 3-Methylcholanthrene

• 7,12-Dimethylbenz[a]anthracene

• Aromatic amines, amides, azo dyes:

• 2-Naphthylamine (°-naphthylamine)

• Benzidine

• 2-Acetylaminofluorene

• Dimethylaminoazobenzene (butter yellow)

• Natural plant and microbial products:

• Aflatoxin B1

• Griseofulvin

• Cycasin

• Safrole

• Betel nuts

• Others

• Nitrosamine and amides

• Vinyl chloride, nickel, chromium

• Insecticides, fungicides

• Polychlorinated biphenyls

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Solution to Question 3:

Seborrheic keratosis is not associated with exposure to ultraviolet (UV) rays from sun exposure.

UV rays derived from sun exposure are associated with the increased incidence of:

• Squamous cell carcinoma

• Basal cell carcinoma

• Melanoma of the skin

Actinic keratosis is a precancerous skin condition that can cause squamous cell cancer if untreated.

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Solution to Question 4:

UVB (ultraviolet B) causes cutaneous cancers due to the formation of pyrimidine dimers in DNA.

When DNA absorbs energy from UVB, there is a covalent crosslinking of pyrimidine bases and distortion of the DNA helix. This prevents proper pairing of the dimer with bases in the opposite DNA strand.

Normally, these defects are repaired by nucleotide excision repair pathway. Defects in nucleotide excision repair pathway result in xeroderma pigmentosum.

UV portion of the solar spectrum is divided into three wavelength ranges:

Note: UVC is the most potent mutagen but is not considered significant as it is filtered out by the ozone layer.

Spectrum	Wavelength
UVA	320-400 nm
UVB	280-320 nm
UVC	200-280 nm

Solution to Question 5:

Individuals with repeated exposure to ionizing radiation are at increased risk of myeloid leukemia.

Carcinogenic radiations include:

• Electromagnetic radiation -

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• X-rays

• γ rays

• Particulate radiation -

• α particles

• ° particles

• Protons

• Neutrons

Cancers due to ionizing radiation:

• Most frequent - myeloid leukemia and thyroid cancer

• Intermediate frequency - cancers of breast, lungs, and salivary glands

• Relatively resistant cancers - cancers of skin, bone, and gastrointestinal tract

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Solution to Question 6:

Adenocarcinoma carcinoma of the lung is not associated with microbial etiopathogenesis. It is associated with smoking and genetic predispositions.

Solution to Question 7:

Human T-cell leukemia-lymphoma virus (HTLV-1) causes adult T-cell leukemia/lymphoma (ATLL).

HTLV-1 encodes the viral protein Tax, which leads to polyclonal expansion of T cells. It exhibits tropism for CD4+ T cells.

Human infection requires transmission of infected T cells through sexual intercourse, blood products or breast feeding. Leukemia develops only in 3-5% of infected individuals, typically after a long latent period of 40-60 years.

Solution to Question 8:

The target genes for viral oncoproteins of human papilloma virus (HPV) are as follows:

• E6 - p53

• E7 - RB

The image given below shows the functions of the E6 and E7 oncoproteins of HPV.

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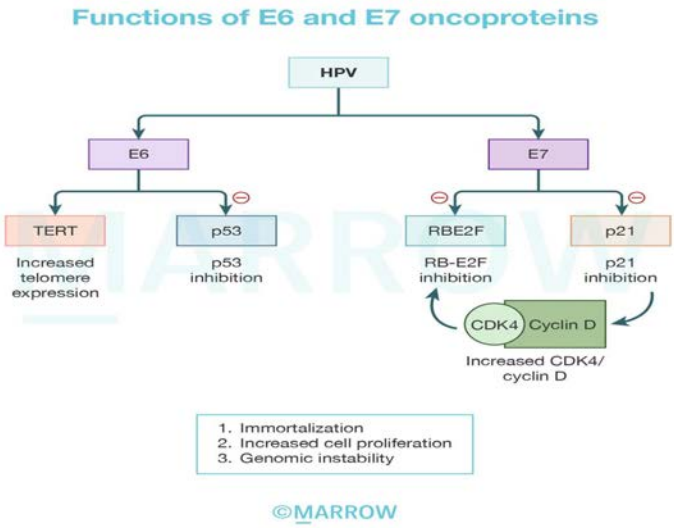

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Solution to Question 9:

The clinical scenario is suggestive of infectious mononucleosis caused by Epstein-Barr virus. This virus is not implicated in follicular lymphoma.

Epstein–Barr virus (EBV), a member of the herpesvirus family, has been implicated in:

- African form of Burkitt lymphoma
- B-cell lymphomas in immunosuppressed
- A subset of Hodgkin lymphoma
- Nasopharyngeal carcinoma
- Gastric carcinoma - most common EBV associated malignancy
- T-cell lymphoma and natural killer (NK) cell lymphoma

Solution to Question 10:

Epstein-Barr virus (EBV) infection does not always result in Burkitt lymphoma.

EBV infection is highly prevalent even in areas where Burkitt lymphoma is not found. It commonly causes infectious mononucleosis.

EBV uses the complement receptor CD21 to attach to and infect B cells. EBV genome triggers B-cell signaling pathways inducing B-cell growth and transformation.

The infection of B cells is latent as there is no viral replication and the cells are not killed. However, B cells latently infected with EBV express viral proteins that result in the ability to propagate indefinitely in vitro. In the absence of T-cell immunity, EBV-infected B cells can rapidly grow out as aggressive B-cell tumors.

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Solution to Question 11:

Human herpesvirus 8 (HHV8) is a gamma-herpesvirus associated with Kaposi sarcoma, multicentric Castleman disease, and primary effusion lymphoma.

They are lymphoproliferative diseases that are most commonly observed in immunocompromised individuals. The viral genome expresses genes responsible for inhibition of apoptosis, cell cycle entry, and angiogenesis.

Solution to Question 12:

The given clinical scenario and histopathological image showing follicular hyperplasia of lymph nodes are suggestive of Castleman disease.

Castleman disease (angiofollicular lymph node hyperplasia) is a lymphoproliferative disorder that can be associated with HHV-8 (multicentric Castleman disease or MCD) or idiopathic (unicentric Castleman disease or UCD)

There are 3 major histological subtypes:

• Hypervascular (UCD) -

• Lollipop appearance - atrophic germinal centers with radially penetrating blood vessels

• Onion skin appearance of mantle zone around germinal centers

• Plasma cell subtype (UCD or MCD) - hypertrophic germinal centers, increased vascularity

• Mixed variant (MCD) - mix of hypervascular and plasma cell subtype features in the same lymph node

The clinical features include:

• Multiple enlarged lymph nodes

• Night sweats

• Weight loss

• Weakness and fatigue

• Hepatosplenomegaly

As this condition is associated with elevated levels of IL-6, the treatment involves IL-6 inhibitors like siltuximab and tocilizumab.

Note: Hodgkin's lymphoma has characteristic Reed-Sternberg cells in the histopathological section of lymph nodes.

Solution to Question 13:

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LMP-1 is an EBV oncogene that behaves like a constitutively active CD40 receptor.

The CD40 receptor-like activity stimulates B-cell growth. LMP-1 activates the NF-κB and JAK / STAT signaling pathways and promotes B-cell survival. It also prevents apoptosis by activating BCL2.

Solution to Question 14:

Helicobacter pylori is implicated in the following conditions:

• Peptic ulcer

• Gastric adenocarcinoma - preceded by chronic gastritis, gastric atrophy, intestinal metaplasia, and dysplasia

• MALT lymphoma of the stomach - through polyclonal B cell proliferation

Helicobacter pylori is protective for:

• Barrett's esophagus

• Adenocarcinoma of esophagus

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Solution to Question 15:

Cushing syndrome is the most common endocrinopathy caused by tumors.

Endocrinopathy refers to ectopic hormone production by non-endocrine tumors. Approximately, 50% of the individuals with Cushing syndrome as endocrinopathy have carcinoma of the lung, chiefly the small-cell type.

Hypercalcemia is the most common paraneoplastic syndrome. Cancer-associated hypercalcemia occurs due to:

• Osteolysis induced by cancer - due to primary or secondary involvement of the skeleton by tumor

• Production of calcemic humoral substances by extraosseous neoplasms - for example, parathyroid hormone-related protein. Only this mechanism is considered to be paraneoplastic.

Solution to Question 16:

Thymoma often presents with pure red cell aplasia as a paraneoplastic manifestation.

Thymomas are unusual neoplasms of thymic epithelial tissue, ranging from small indolent tumors to aggressive thymic carcinomas.

Pure red cell aplasia is a rare cause of anemia, caused by the absence of RBC precursors in the bone marrow. Causes of pure red cell aplasia include:

• Neoplasms - thymomas and large granular lymphocytic leukemia

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• Drug exposure - phenytoin, azathioprine, and isoniazid

• Auto-immune disorders - neutralizing antibodies against erythropoietin

• Parvovirus infection

• Hereditary - Diamond Blackfan syndrome

Solution to Question 17:

Disseminated intravascular coagulation (DIC) as a paraneoplastic syndrome is most commonly associated with acute promyelocytic leukemia (APL) and prostatic adenocarcinoma.

Major determinants of coagulopathy in APL are endogenous factors of the malignant leukemic cells and their interaction with host defense mechanisms.

Factors that cause coagulopathy include:

• Increased expression of procoagulant activity (PCA)

• Expression of fibrinolytic and proteolytic properties

• Secretion of pro-inflammatory cytokines - interleukin-1b (IL-1b) and tumor necrosis factor (TNF)

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Solution to Question 18:

The given clinical history is suggestive of hypertrophic osteoarthropathy. It is commonly associated with bronchiogenic carcinoma.

Hypertrophic osteoarthropathy is characterised by the following:

• Periosteal new bone formation, primarily at the distal ends of long bones, metatarsals, metacarpals, and proximal phalanges

• Arthritis of the adjacent joints

• Clubbing of the digits

Solution to Question 19:

The given clinical history and laboratory investigations are suggestive of hypercalcemia. It is associated with squamous cell carcinoma of the lung.

Tumors associated with paraneoplastic hypercalcemia:

• Breast carcinoma

• Lung carcinoma

• Renal cell carcinoma

• Ovarian carcinoma

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Solution to Question 20:

Phosphaturic mesenchymal tumor presents with osteomalacia as a paraneoplastic manifestation.

Phosphaturic mesenchymal tumor is caused due to mutation of the FGF-23 gene.

Solution to Question 21:

The given clinical picture is suggestive of acanthosis nigricans. It is not associated with thymoma.

Acanthosis nigricans is a disorder characterized by gray-black patches of thickened, hyperkeratotic skin with a velvety appearance. The causal mechanism is immunologic due to secretion of epidermal growth factor.

Acanthosis nigricans is commonly associated with:

- Gastric carcinoma
- Lung carcinoma
- Gynecological cancers
- Breast carcinoma
- Bladder carcinoma
- Gallbladder and bile-duct carcinoma
- Acromegaly and gigantism
- Dermatomyositis
- Diabetes
- Hashimoto thyroiditis
- Lupus erythematosus
- Phenylketonuria
- Polycystic ovary syndrome
- Systemic sclerosis
- Wilson syndrome

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Solution to Question 22:

The given clinical history and laboratory investigations are suggestive of polycythemia which is not seen in melanoma as a paraneoplastic manifestation.

Polycythemia, as a paraneoplastic syndrome, is mediated by erythropoietin (EPO). EPO is a glycoprotein that induces differentiation of erythrocyte colony-forming units in the bone marrow

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to promote red blood cell production.

Under normal physiological conditions, EPO is produced by peritubular renal interstitial cells in response to local tissue hypoxia. However, in tumors, EPO production occurs in the neoplastic cells themselves.

Solution to Question 23:

Syndrome of inappropriate antidiuretic hormone (SIADH) is associated with small cell carcinoma of lung.

Solution to Question 24:

The given clinical presentation is suggestive of migratory thrombophlebitis (Trousseau syndrome) and it is not associated with bladder carcinoma.

Trousseau syndrome may be encountered in association with deep-seated cancers, most often carcinomas of the pancreas or lung. It is caused by hypercoagulability leading to multiple repeated venous thromboembolism.

Malignant brain tumors, hematological malignancies, and adenocarcinomas of the pancreas, stomach, ovary, uterus, lungs, and kidneys are at the highest risk of venous thromboembolism (VTE) development.

Advanced, metastatic cancer has been shown to be associated with an increased risk of VTE compared with localized tumors.

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Solution to Question 25:

The serum levels of catecholamines are elevated in malignant pheochromocytoma. Extra-adrenal location is the only criteria for malignancy in pheochromocytoma.

Pheochromocytoma is a rare catecholamine-secreting tumor that may precipitate life-threatening hypertension. It is classically associated with three syndromes:

• von Hippel-Lindau (VHL) syndrome

• Multiple endocrine neoplasia type 2 (MEN 2)

• Neurofibromatosis type 1 (NF1)

Catecholamines produced by pheochromocytomas are metabolized within chromaffin cells. Norepinephrine is metabolized to normetanephrine, and epinephrine is metabolized to metanephrine. Because this process occurs within the tumor, independent of catecholamine release, pheochromocytomas are best diagnosed by the measurement of these metabolites, rather than by measurement of the parent catecholamines.

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Solution to Question 26:

Alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) are oncofetal antigens.

Alpha-fetoprotein is a valuable clinical aid in diagnosis, prognosis, and monitoring of the following tumors:

- Primary hepatocellular carcinoma
- Hepatoblastoma
- Non-seminomatous testicular germ cell tumors
- Embryonal carcinoma
- Teratomas
- Choriocarcinoma
- Yolk sac carcinoma
- Germ cell tumors of the ovary and extragonadal germ cell tumors

Regenerated hepatic tissue following liver damage due to viral hepatitis, chemically induced necrosis, and liver surgery are associated with moderately raised serum AFP levels.

Carcinoembryonic antigen is normally detected in glycocalyx of fetal epithelial cells. It is useful in detection, assessing recurrence, and prognosis of the following tumors:

- Adenocarcinoma of lung
- Colorectal carcinoma

CEA levels >5 ng/dL are noted in ascites fluid associated with malignancy. Canalicular pattern for polyclonal CEA more sensitive for hepatocellular carcinoma, metastases in pancreatic adenocarcinoma and not sensitive for metastasis in bile duct adenoma.

Elevated levels are also present in the following non-neoplastic conditions:

- Cirrhosis
- Biliary obstruction
- Hepatitis
- Inflammatory bowel disease
- Smokers
- Post-surgical bowel sequestration
- Mucocele
- Benign cysts may be positive for carcinoembryonic antigen

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Solution to Question 27:

The level of cancer antigen 15-3 (CA 15-3) is elevated in patients with breast cancer.

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The reference range of serum CA 15-3 is less than 30 U/mL. It is used to monitor response to breast cancer treatment and disease recurrence.

Solution to Question 28:

The given clinical scenario is suggestive of small cell carcinoma of the lung (SCLC) in which levels of neuron-specific enolase (NSE) are elevated.

NSE is also called gamma enolase or enolase 2 (ENO2) and is encoded by ENO2 gene. It is a phosphopyruvate hydratase that is produced by small-cell lung carcinomas, which are neuroendocrine in origin. Their levels have been implicated as a prognostic factor for patients with small-cell lung cancer.

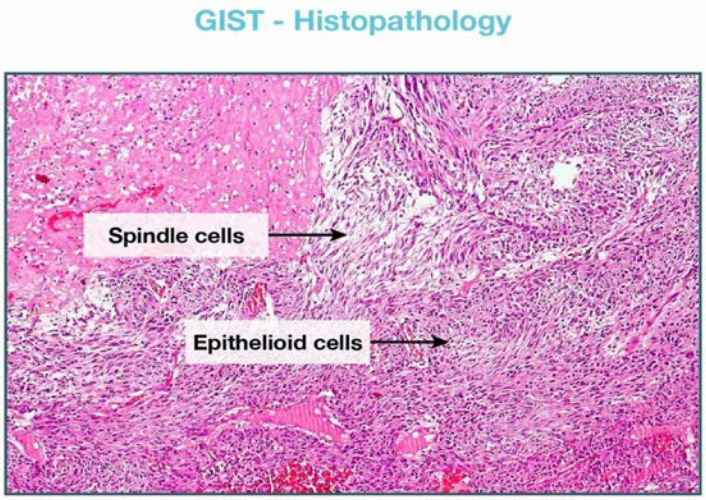
Solution to Question 29:

NRG-1 (Neuregulin-1) is not a marker for gastrointestinal stromal tumors (GISTs).

GIST are the most common mesenchymal tumor of the abdomen, the stomach being the most common site. They arise from the interstitial cells of Cajal, the pacemaker cells of the GIT. GIST is seen in the 5th to 6th decade of life and has an equal preponderance among males and females. Most patients present with haematemesis, melena, or vague abdominal pain. The most common indications for surgery include bleeding and obstruction.

The GIST may occur in a sporadic form or as part of familial syndromes. In sporadic GIST, the most common mutations seen are gain-of-function mutation in KIT (75-80%) and PDGFRA mutation (8%). Microscopically, GIST has elongated spindle cells or plumper epithelioid cells, or a mixed pattern.

The below image shows the microscopy of GIST composed of bundles, or fascicles, of spindle-shaped tumor cells.



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Succinate dehydrogenase (SDH)-deficient GIST is a subset of wild-type GIST seen with Carney triad or Carney-Stratakis syndrome.

Imatinib can be used to treat GIST with mutations in KIT or PDGFRA. Succinate dehydrogenase (SDH) - deficient GIST is imatinib-resistant, so sunitinib, sorafenib, or regorafenib can be used instead.

During surgical resection of GIST, care must be taken to prevent capsule rupture, which causes seeding of nearby tissues leading to relapse in 100% of the cases. If capsule rupture occurs, adjuvant therapy with imatinib is indicated regardless of tumor extent.

Other options:

Option A: KIT (CD117): This is the most well-known marker for GISTs. About 85% of GISTs show mutations in the KIT gene, leading to the expression of the KIT protein on the cell surface. KIT is a receptor tyrosine kinase, and its activation is a key driver in the pathogenesis of GISTs.

Option B: SDH (Succinate Dehydrogenase): SDH mutations are associated with a subset of GISTs, particularly those that are KIT and PDGFRA wild-type. Loss of SDH function is characteristic of this subgroup, and SDH deficiency can be demonstrated through immunohistochemistry.

Option C: PDGFRA (Platelet-Derived Growth Factor Receptor Alpha): Mutations in the PDGFRA gene account for approximately 5-10% of GISTs. Similar to KIT, PDGFRA is a receptor tyrosine kinase, and mutations in this gene can lead to the development of GISTs.

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Components of Immune System

Question 1:

Which of the following is not a component of innate immunity?

a) Neutrophils

b) Natural killer cells

c) C-reactive protein

d) B cells

Question 2:

What is the mechanism by which toll-like receptors stimulate immune response against bacterial products?

a) Perforin and granzyme-mediated apoptosis

b) FADD ligand apoptosis

c) NFκB mediated transcription of nuclear factor

d) RIPK3 mediated necroptosis

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Question 3:

Antibody-dependent cellular cytotoxicity (ADCC) is seen with:

a) Natural killer (NK) cells only

b) Macrophages only

c) NK cells, neutrophils and eosinophils

d) Neutrophils and eosinophils only

Question 4:

Which of the following occurs due to gain-of-function mutations in NOD-Like receptors?

a) Granulomatous diseases

b) Autoinflammatory syndromes

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c) Autoimmune conditions

d) Malignancy

Question 5:

What is the normal CD4+: CD8+ T lymphocyte ratio?

a) 2:1

b) 1:2

c) 4:1

d) 1:4

Question 6:

Which of the following is not expressed in the B-cell receptor complex?

a) CD86

b) CD79a

c) CD21

d) CD40

Question 7:

Which of the following are the most important antigen-presenting cells?

a) Dendritic cells

b) Neutrophils

c) B cells

d) T cells

Question 8:

Which of the following statements is false about macrophages?

a) It acts as an antigen presenting cell

b) It plays a role in humoral immunity

c) It plays a role in cell-mediated immunity

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d) It is a component of innate immunity only

Question 9:

Which of the following is false about natural killer cells?

a) CD16 and CD56 are the surface molecules

b) They are involved in antibody-dependant cytotoxic killing

c) IL-12 stimulates the proliferation of NK cells

d) They activate macrophages by secreting IFN-γ

Question 10:

Which of these is common to both cytotoxic T-cells and NK cells?

a) They are MHC l restricted cells

b) Require antibodies to be present for action

c) Effective against virus-infected cells

d) Their action is antigen specific

Question 11:

Which of the following markers on antigen-presenting cells function as costimulatory molecules for T cells?

a) CD28 and CD86

b) Only CD80

c) CD28 and CD80

d) CD80 and CD86

Question 12:

Which of the following cytokines induces T-helper type 2 cells?

a) TGF-°

b) IL-4

c) IL-6

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d) IL-2

Question 13:

B-cells are induced to produce IgE by which of the following:

a) IL-2

b) IL-4

c) IL-1

d) IL-6

Question 14:

Production of which of the following antibodies is induced by polysaccharides and lipids?

a) IgG

b) IgM

c) IgA

d) IgD

Question 15:

When papain acts on a molecule of immunoglobulin, which of the following are the end products?

a) 2 FC and 1 FAB fragments

b) 1 Variable chain and 1 constant chain

c) 1 Fc and 2 Fab fragments

d) 2 Fc and 2Fab fragments

Question 16:

In which of the following cells is recirculation seen?

a) Plasma cells

b) T lymphocytes

c) Both plasma cells and T lymphocytes

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d) Both B lymphocytes and plasma cells

Question 17:

Which of the following about γ■ T-cells is incorrect:

a) Kills extracellular bacteria by granulysin and perforin

b) Need antigen processing and presentation for it recognition

c) Direct killing of infected macrophages

d) Provide protection against mycobacteria

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Question 18:

Basophils are activated by:

a) IL-5

b) INF-gamma

c) TNF-alpha

d) IL-2

Question 19:

Among the following, which cells have MHC class II?

a) NK cells

b) All nucleated cells

c) B cells, dendritic cells, mononuclear phagocytes

d) Platelets

Question 20:

Which of the following is not encoded by MHC class III genes?

a) Complement component C2

b) Tumor necrosis factor

c) Heat-shock proteins

d) °2 microglobulin associated molecules

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Answer Key

Question No.	Correct Option
1	d
2	c
3	c
4	b
5	a
6	a
7	a
8	d
9	c
10	c
11	d
12	b
13	b
14	b
15	c
16	b
17	b
18	a
19	c
20	d

Detailed Explanations

Solution to Question 1:

B cell is not a component of innate immunity. It is a component of adaptive immunity.

Innate immunity refers to the body's natural immunity. It is a built-in defence system that is present since birth. It differs from adaptive immunity in that it does not require any prior sensitization to an antigen.

The major components of innate immunity are as follows:

• Epithelial barriers that block the entry of microbes

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• Phagocytic cells (neutrophils and macrophages)

• Natural killer (NK) cells

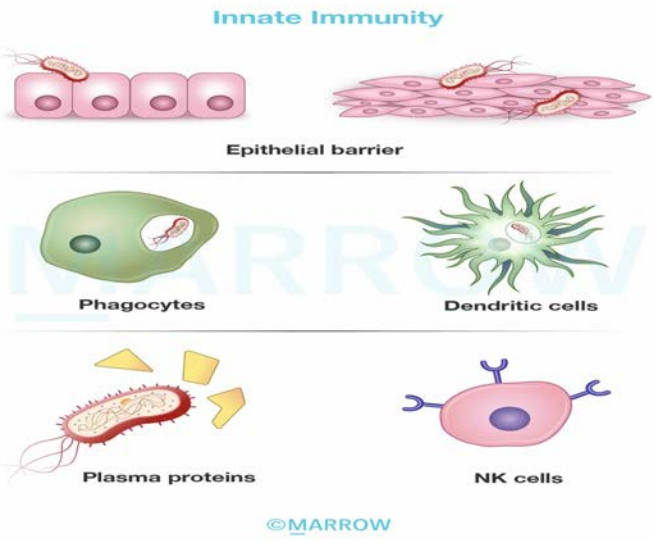
• Dendritic cell

• Cells that can sense and react to microbes - mast cells, epithelial and endothelial cells

• Plasma proteins - complement system factors, mannose-binding lectin, and C-reactive protein

• Innate lymphoid cells

• Lung surfactant



Solution to Question 2:

Toll-like receptors (TLRs) stimulate immune response by NFκB mediated transcription of nuclear factors.

TLRs are pattern recognition receptors which activate two sets of transcription factors:

• NF-κB - stimulates the synthesis and secretion of cytokines and the expression of adhesion molecules. Both are critical for the recruitment and activation of leukocytes

• Interferon regulatory factors - stimulate the production of the antiviral cytokines like type I interferons

The image given below shows a toll-like receptor.

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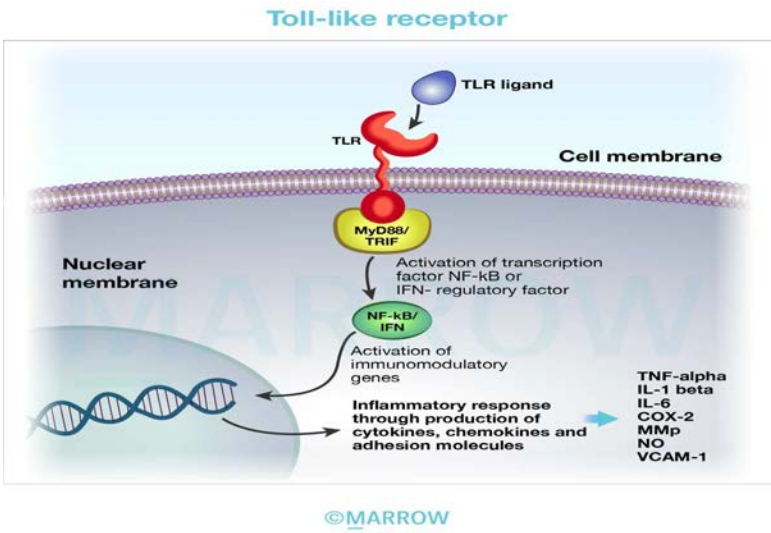

The various classes of innate immune receptors are as follows:

Mannose receptor is a soluble pattern-recognition receptor. All the others are surface pattern-recognition receptors.

Receptors	Location	Function
Toll-likereceptors	Plasma membrane and endosomal vesicles	Important TLRs and molecules recognised:TLR2 -peptidoglycanof gram + bacteria, lipopolysaccharide ofLeptospira TLR3 - dsRNA virusesTLR4Q -Chlamydiaandlipopolysaccharide
NOD-like receptors	Cytosol of immune cells and epithelial cells	Recognise substances from necrotic cells and microbial productsSignals via inflammasome which activates caspase and IL-1
C-type lectin receptors	Plasma membrane of macrophages and dendritic cells	Detectfungal glycansand elicit inflammatory reactions to fungi
RIG-like receptors	Cytosol of most cell types	Detectnucleic acids of viruses that replicate in the cytoplasm of infected cellsStimulate the production of antiviral cytokinesRecognize short bacterial peptides containingN-formyl methionyl residues and stimulate chemotaxis
Mannose receptors	Plasma membrane of macrophages, immature dendritic cells, and liver sinusoidal endothelial cells	Detectmicrobial sugars(which often contain terminal mannose residues) and induce phagocytosis of the microbes

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Solution to Question 3:

Antibody-dependent cellular cytotoxicity (ADCC) is mediated by NK cells, neutrophils and eosinophils (killing certain parasitic worms like helminths via IgE antibodies).

In ADCC, cells/ antigens are coated with IgG antibodies. These are killed by effector cells like NK cells and macrophages. These effector cells bind to the target by their receptors for the Fc fragment of IgG and cell lysis proceeds without phagocytosis.

Solution to Question 4:

The gain of function mutations in NOD-Like receptors (NLRs) result in periodic fever syndromes called autoinflammatory syndromes.

They are a group of clinical conditions characterised by recurrent inflammatory episodes. This disorder is marked by abnormally increased inflammation, mediated predominantly by cells and molecules of the innate immune system, with a significant host predisposition.

NOD-like receptors are cytosolic receptors that signal via a cytosolic multiprotein complex called the inflammasome. This activates caspase-1 that generates biologically active form of interleukin-1 (IL-1). IL-1 is a mediator of inflammation that recruits leukocytes and induces fever. The autoinflammatory syndromes respond very well to treatment with IL-1 antagonists.

Note: Autoimmune diseases result from T and B-lymphocyte reactions against self-antigens.

Solution to Question 5:

Normal CD4+: CD8+ T lymphocyte ratio is 2:1. Approximately 60% of mature T cells are CD4+ and about 30% are CD8+.

T-lymphocytes (thymus-derived cells) constitute 60–70% of peripheral blood lymphocytes. T-cell progenitors are derived from the bone marrow, but travel to the thymus, where they mature. T cells can be divided into three main subtypes:

They are located in the paracortical areas of lymph nodes and the periarteriolar sheaths of the spleen. They have an antigen-specific T-cell receptors (TCR) which have alpha/beta polypeptide chains components. Demonstration of TCR gene rearrangement by southern blot is a molecular marker of T-cell lineage.

The CD molecules present on T cells are CD1, CD2, CD3, CD4, CD5, CD7, CD8 and CD28. CD3 is involved in signal transduction and is also called a pan T-cell marker. CD40 ligand on the surface is required for B-cell activation and induction of immunoglobulin.

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Type of T cell	Function
Helper T cell (CD4+)	Helps B lymphocytes to make antibodies and activate other leukocytes to destroy microbes
Cytotoxic T lymphocytes (CTLs or CD8+)	Kill infected cells
Regulatory T cells	Limit immune responses and prevent reactions against self-antigens.

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Solution to Question 6:

CD86 is a protein expressed on antigen-presenting cells, and not B-cell receptor complex. This protein provides costimulatory signals necessary for T-cell activation and survival.

B-cell receptor complex expresses the following:

• CD79a and CD79b - essential for signal transduction through the antigen receptor

• CD21 or CR2 - complement receptor (recognize complement products during innate immune response) and Epstein–Barr virus (EBV) receptor

• CD40 - receives signals from helper T cells

Other B cell-associated markers are CD10 (CALLA), CD19, CD20, CD22, CD23.

Solution to Question 7:

Dendritic cells or interdigitating dendritic cells are the most important antigen-presenting cells. They initiate T-cell responses against protein antigens.

They are located in the epithelium and interstitium. They express many receptors for capturing and responding to microbes (and other antigens), including toll-like receptors (TLRs) and lectins. They also express high levels of major histocompatibility complex (MHC) for presenting antigens to and activating T cells.

In response to microbes, dendritic cells are recruited to the T-cell zones of lymphoid organs. Here, they present antigens to T cells with help of MHC.

Similar cells with dendritic morphology in the germinal centers of lymphoid follicles in the spleen and lymph nodes are follicular dendritic cells. They bear Fc receptors for IgG and receptors for C3b. Immature dendritic cells within the epidermis are called Langerhans cells.

Note:

• Aggretope - part of the antigen associated with the MHC molecule on the antigen-presenting cell

• Epitope - antigenic part of contact with the T-cell receptor

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Solution to Question 8:

Macrophages are components of both innate and acquired immunity.

They phagocytose microbes and protein antigens. They process the antigens and present the peptide fragments to T cells. Thus, macrophages function as antigen-presenting cells in T-cell activation.

They also participate in the effector phase of humoral immunity. Macrophages efficiently phagocytose and destroy microbes that are opsonized (coated) with IgG or C3b.

They are key effector cells in certain forms of cell-mediated immunity to eliminate intracellular microbes. In this type of response, T cells activate macrophages and enhance their ability to kill ingested microbes.

Solution to Question 9:

IL-2 and IL-15 stimulate the proliferation of NK cells. On the other hand, IL-12 activates the killing of target cells and secretion of IFN-γ.

NK cells are large granular lymphocytes, which constitutes 5% to 10% of peripheral blood lymphocytes. CD16 and CD56 are the surface molecules.

Functions of NK cells:

• Killing of a variety of virus-infected cells and tumor cells, without prior exposure to or activation by these microbes or tumors

• Secretion of interferon-γ (IFN-γ), which activates macrophages to destroy ingested microbes

• Antibody-dependent cell-mediated cytotoxicity (ADCC) - NK cells express CD16 which is a receptor for IgG Fc tails. Hence, these cells have the ability to lyse IgG-coated target cells.

ADCC is also seen in immune responses involving neutrophils, eosinophils, macrophages, etc.

The image given below shows activating and inhibitory receptors of natural killer (NK) cells.

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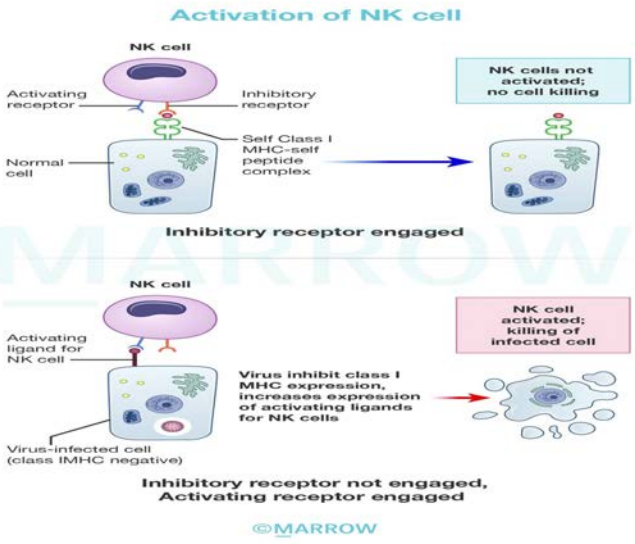

Note: A new group of T cells has been discovered called NK-T cells. These are T cells that contain markers of NK cells. These are important defence mechanisms against microorganisms like Listeria monocytogenes and Mycobacterium tuberculosis.

Solution to Question 10:

Both cytotoxic T-cells and NK cells are effective against virus-infected cells.

The NK cells have different mechanisms of action while killing target cells.

NK cells can lyse IgG-coated target cells by binding to the Fc tail of IgG, through the CD16 receptor expressed on NK cells. This phenomenon is known as antibody-dependent cellular cytotoxicity (ADCC).

NK cells secrete various cytokines such as interferon-γ (IFN-γ), which activate macrophages to destroy ingested microbes.

Target cell destruction by NK cells is also mediated through two others receptors - activating receptors and inhibitory receptors.

The activating receptors enable NK cells to recognize infected and stressed cells. The inhibitory receptors recognize self class-I MHC molecules, that are expressed on all healthy cells thereby preventing NK cells from killing normal cells. Virus infection / neoplastic transformation overexpresses the activating receptors and simultaneously reduces the expression of class-I MHC molecules. As a result, NK cells are activated and the infected cells are killed.

CD8+ cytotoxic T lymphocytes directly kill damaged cells.

The differences between NK cells and cytotoxic T-cells are:

Natural killer (NK) cell	Cytotoxic T-cells
Does not requirepriming -rap id response in hours	requirepriming -takes days to respond

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Natural killer (NK) cell	Cytotoxic T-cells
MHC unrestricted	MHC restricted
Antibody-mediated and non-antibody-mediated killing	Non-antibody mediated killing / direct cytotoxicity
Kills virus-infected and neoplastic cells by apoptosis	Kills virus-infected, neoplastic, and donor graft cells by apoptosis
Antigen non-specific	Antigen-specific
Memory is absent	Memory is present

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Solution to Question 11:

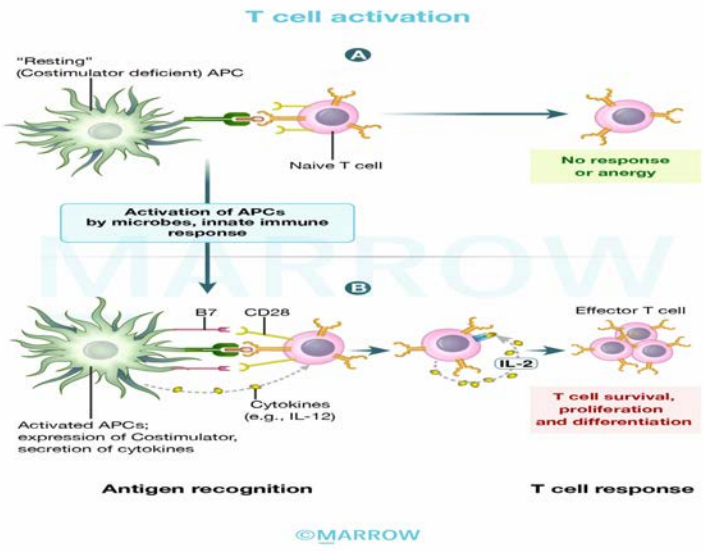
CD80 (B7-1) and CD86 (B7-2) are the costimulatory molecules present on antigen-presenting cells (APCs). They bind to CD28 protein present on T cells. This promotes the expansion of antigen-stimulated T cells and their differentiation into effector and memory cells.

T-cell activation requires two signals that are delivered by APCs. They include:

• Antigens displayed by APCs in the form of peptides bound to MHC molecules, that are recognised by T-cell receptors

• Costimulatory signal (as it stimulates T cells in conjunction with antigen) provided by molecules on APCs that engage particular costimulatory receptors on T cells

In the absence of costimulation, T cells that recognize antigen either fail to respond and die or enter a state of unresponsiveness known as anergy. Thus, costimulation is a key determinant of the outcome of a T-cell encounter with an antigen.



Solution to Question 12:

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IL-4 induces T helper 2 cells.

Mechanism of cell-mediated immunity:

• Antigen-presenting cells → recognized by naive CD4+ T cells → IL-2 secretion → T-cell proliferation and differentiation → activated CD4+ T helper cells

• Activated CD4+ T cells further differentiate into effector cells that secrete different sets of cytokines and perform different functions

Solution to Question 13:

IL-4 stimulates B-cells to differentiate into IgE secreting plasma cells.

Solution to Question 14:

Polysaccharides and lipids stimulate the secretion of mainly IgM antibodies.

B lymphocytes use their antigen receptors to recognize various types of antigens:

• Proteins (through CD40L and cytokine-mediated helper T-cell actions) - induce production of IgG, IgA, IgE

• Polysaccharides and lipids - induce production of IgM mainly

Helper T cells also help in antibodies by the mechanisms:

• Stimulate formation of germinal centers which consist of proliferating B cells

• Induce isotype switching through cytokines IFN-γ and IL-4

• Affinity maturation - stimulate the production of antigen-specific antibodies

Isotype switching and affinity maturation occur mainly in germinal centers.

Solution to Question 15:

When papain acts on a molecule of immunoglobulin, the end products are 1 Fc and 2 Fab fragments.

If an antibody molecule is digested with papain, cleavage occurs above the disulfide bonds that hold the heavy chains together. This generates 3 separate fragments, two of which are called Fab (fragment antigen binding), and one of which is called Fc (fragment crystallizable).

The image given below shows the cleavage of immunoglobulin by papain.

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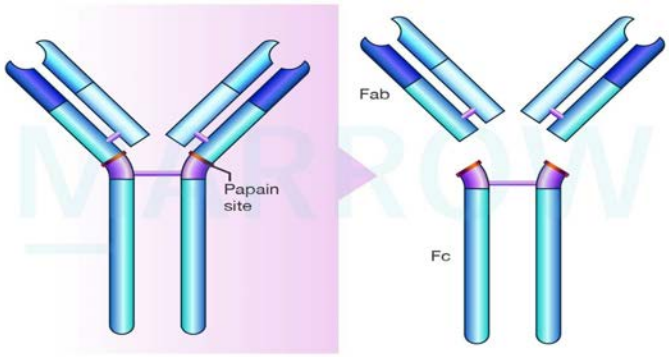
Action of papain on immunoglobulin



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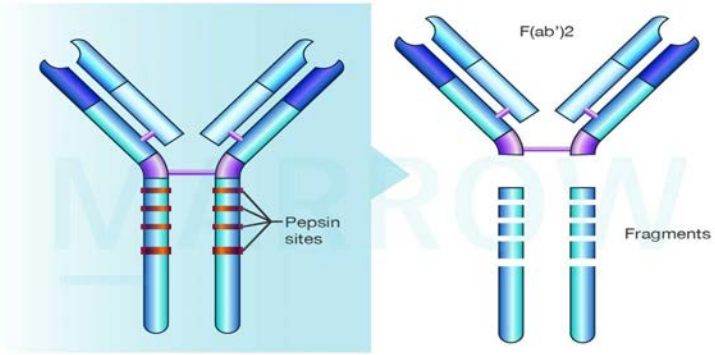
Cleavage of the antibody molecule with pepsin generates one large fragment called F(ab´)2 and a digested Fc fragment.

The image given below shows the cleavage of immunoglobulin by pepsin.

Action of pepsin on immunoglobulin



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Solution to Question 16:

Lymphocyte recirculation is seen in T lymphocytes.

Migration of the lymphocytes between blood and lymphoid organs is called recirculation. Naive lymphocytes traverse the peripheral lymphoid organs, where immune responses are initiated. When antigen-presenting cells activate them, the effector lymphocytes migrate to sites of infection and inflammation.

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In contrast, plasma cells remain in lymphoid organs and the bone marrow. They do not need to migrate to sites of infection because they secrete antibodies that are carried to distant tissues.

Solution to Question 17:

γ■ T-cells do not need antigen processing and presentation for its recognition.

There are two types of T cells: γ■ T-cells and αβ T-cells.

The functions of γ■ T-cells:

• Provide protection against mycobacteria by direct killing of infected macrophages

• Kills extracellular bacteria by granulysin and perforin

• Plays a role in maintaining self-tolerance

• Capable of recognising and lysing diverse cancers in an MHC-unrestricted manner

αβ T-cells have MHC restricted action.

Solution to Question 18:

Basophils are activated by IL-5 and IL-3.

Note: IL-5 primarily activates eosinophils.

Solution to Question 19:

Class II major histocompatibility complex (MHC) molecules are mainly expressed on macrophages, B lymphocytes, and dendritic cells. These cells present ingested antigens to T-cells.

The function of MHC molecules is to display peptide fragments of protein antigens for recognition by antigen-specific T cells. In humans, the MHC molecules are called human leukocyte antigens (HLA) because they were initially detected on leukocytes by the binding of antibodies. The combination of HLA alleles in each individual is called the HLA haplotype.

The genes encoding HLA molecules are clustered on the short arm of chromosome 6.

Uses of MHC/ HLA typing include:

• Anthropology

• Transfusion

• Paternity testing

• Forensic science

• Transplantation

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• Disease correlation

Solution to Question 20:

° 2 microglobulin associated cell surface molecules are encoded by MHC class I and not class III.

Class III MHC molecules include:

• Complement proteins (such as C2, C4, and B factor)

• Cytokines (such as TNF-α, LTA, and LTB)

• Properdin factor BQ of alternate pathway

• Enzyme tyrosine hydroxylase

• Heat-shock proteins

Class III molecules are encoded by genes located between those that encode class I and class II molecules.

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Hypersensitivity and Autoimmunity

Question 1:

A child, upon disturbing a beehive, had several stings. After a few minutes, he developed shock, respiratory failure, and vascular collapse. What is the pathogenesis of this condition?

a) NK cell-mediated cytotoxicity

b) IgE-mediated reaction

c) Type 4 hypersensitivity reaction

d) IgA-mediated hypersensitivity reaction

Question 2:

Arthus reaction is caused by which of the following process?

a) Localized immune-complex-mediated

b) Systemic immune-complex-mediated

c) Complement-mediated

d) Antibody-mediated

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Question 3:

A 42-year-old female patient presents with ptosis, diplopia, and progressive muscular weakness towards the end of the day. She has improvements in symptoms after administering edrophonium. The given clinical condition is an example of which of the following?

a) Type 1 hypersensitivity reaction

b) Type 2 hypersensitivity reaction

c) Type 3 hypersensitivity reaction

d) Type 4 hypersensitivity reaction

Question 4:

A 6-year-old child abruptly develops malaise, fever, nausea, oliguria, and smoky, cola-colored urine 2 weeks after recovery from a sore throat. He is found to have periorbital edema and

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mild hypertension. Urine examination shows dysmorphic red cells and red cell casts in the urine with mild proteinuria. Which type of hypersensitivity is responsible for this condition?

a) Type I hypersensitivity

b) Type II hypersensitivity

c) Type III hypersensitivity

d) Type IV hypersensitivity

Question 5:

A 25-year-old man with a fever and chronic cough is administered 0.1 mL of purified protein derivative intradermally over the forearm. After a few hours, the injection site appears as follows. Which of the following does this represent?

a) Type I hypersensitivity

b) Immune-complex-mediated hypersensitivity

c) Antibody-mediated hypersensitivity

d) Cell-mediated hypersensitivity

Question 6:

True about anaphylactoid reaction are all except:

a) Involves degranulation of mast cells

b) IgE mediated

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c) Can occur on first exposure

d) Most commonly caused by NSAIDs

Question 7:

Which of the following autoimmune diseases are not mediated by antibodies?

a) Pemphigus vulgaris

b) Pernicious anemia

c) Rheumatoid arthritis

d) Goodpasture syndrome

Question 8:

Which gene is most frequently implicated in autoimmunity?

a) FOXP3

b) PTPN22

c) NOD2

d) AIRE

Question 9:

During development, thymic cells recognizing self-antigens are removed to prevent autoimmunity. Which gene among the following is involved in the process?

a) NOTCH1

b) RB gene

c) CPK gene

d) AIRE

Question 10:

Which of the following is responsible for autoimmunity in Epstein-Barr virus infection?

a) Molecular mimicry

b) Polyclonal B-cell activation

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c) Upregulation of co-stimulatory molecules

d) Antigenic cross-reactivity

Question 11:

Homogeneous or diffuse nuclear staining pattern may reflect antibodies to all the following except:

a) RNA

b) Double stranded DNA

c) Chromatin

d) Histones

Question 12:

What type of cell is the lupus erythematosus cell?

a) Lymphocyte

b) Endothelial cell

c) Eosinophil

d) Neutrophil

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Question 13:

A 32-year-old lady presents with the following finding. On further investigations, anti-ds DNA and anti-Smith antibodies are found to be positive. Which of the following is not seen in the given clinical condition?

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a) Hematoxylin bodies in lymph nodes

b) Onion-skin lesions in the spleen

c) Vasculitis with fibrinoid necrosis

d) Lymphocytic infiltration in salivary gland

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Question 14:

Which of the following is not a part of the IgG4 spectrum?

a) Mikulicz syndrome

b) Riedel thyroiditis

c) Idiopathic retroperitoneal fibrosis

d) Celiac disease

Answer Key

Question No.	Correct Option
1	b
2	a
3	b
4	c
5	d

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6	b
7	c
8	b
9	d
10	b
11	a
12	d
13	d
14	d

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Detailed Explanations

Solution to Question 1:

The given clinical scenario is suggestive of anaphylaxis following a bee sting. This is an example of IgE-mediated reaction or type 1 hypersensitivity.

Injurious immune reactions are called hypersensitivity reactions. There are four types of hypersensitivity reactions.

Immediate (Type 1) hypersensitivity is also called allergic reactions. They are induced by environmental antigens (allergens) that stimulate strong TH2 responses and IgE production in genetically susceptible individuals.

IgE coats mast cells by binding to Fcεg receptors. Reexposure to the allergen leads to cross-linking of the IgE and FcεRI, activation of mast cells, and release of mediators. The principal mediators are histamine, proteases, and other granule contents like prostaglandins and leukotrienes and cytokines.

It occurs in two phases: immediate phase and late phase. The mediators are responsible for the immediate vascular and smooth muscle reactions and the late-phase reaction (inflammation). The clinical manifestations may be local or systemic and range from mildly annoying rhinitis to fatal anaphylaxis.

The image given below shows the sequence of events in immediate hypersensitivity.

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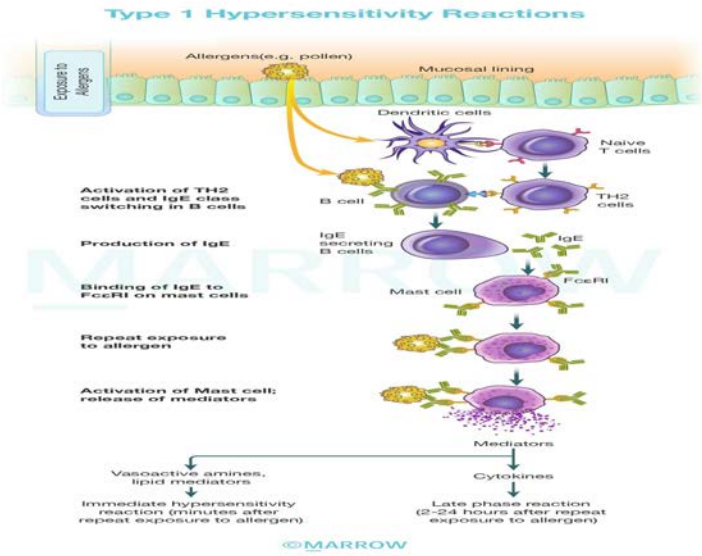

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Solution to Question 2:

Arthus reaction is characterized by a localized area of tissue necrosis due to immune-complex-mediated (type III hypersensitivity reaction) vasculitis in the skin.

This reaction can be produced experimentally by intracutaneous injection of antigen in a previously immunised animal that contains circulating antibodies against the antigen. As the antigen diffuses into the vessel wall, it binds with the preformed antibody, and immune complexes are formed locally. These complexes precipitate in the vessel walls and cause fibrinoid necrosis.

Solution to Question 3:

The given clinical condition is highly suggestive of myasthenia gravis. It is an example of a type II hypersensitivity reaction.

Myasthenia gravis is an autoimmune disease that is usually associated with autoantibodies directed against acetylcholine receptors. In Type II hypersensitivity, antibodies react with antigens present on cell surfaces or in the extracellular matrix cause. These antibodies destroy cells, trigger inflammation, or interfering with normal functions.

Solution to Question 4:

The given clinical scenario is suggestive of nephritic syndrome due to post-streptococcal glomerulonephritis. This is an example of a type III hypersensitivity reaction.

In type III hypersensitivity, immune complexes may deposit in tissues or blood vessels, and elicit an acute inflammatory reaction by activating complement. The pathogenesis of systemic immune

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complex disease can be divided into three phases:

• Formation of immune complexes

• Deposition of immune complexes

• Inflammation and tissue injury

This results in various manifestations like vasculitis, glomerulonephritis and arthritis.

Examples of type III hypersensitivity reactions:

• Post-streptococcal glomerulonephritis

• Systemic lupus erythematosus

• Reactive arthritis

• Polyarteritis nodosa

• Serum sickness

• Arthus reaction

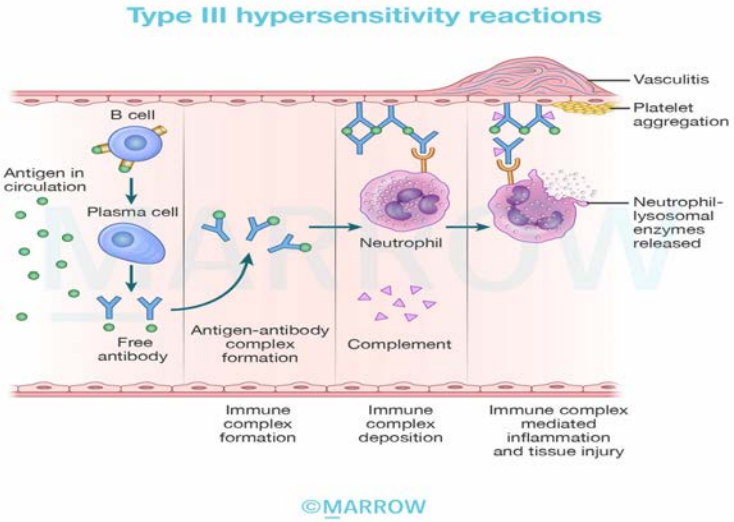
• Farmer's lung

• Hypersensitivity pneumonitis

• Type II lepra reaction

• Henoch–Schonlein purpura

The image given below shows the mechanism of type III hypersensitivity reactions.



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Solution to Question 5:

The given clinical scenario shows a positive tuberculin test. It is a classical example of type IV or delayed or cell-mediated hypersensitivity reaction.

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Tuberculin test involves intradermal injection of purified protein derivative (PPD, also called tuberculin), a protein-containing antigen of the tubercle bacillus. In a previously sensitized individual, reddening and induration of the site appear in 8 to 12 hours, reach a peak in 24 to 72 hours, and thereafter slowly subside.

Morphologically, delayed-type hypersensitivity is characterized by the accumulation of mononuclear cells, mainly CD4+ T cells and macrophages, around venules. The cell-mediated type of hypersensitivity is caused by inflammation resulting from cytokines produced by CD4+ T cells and cell killing by CD8+ T cells.

Solution to Question 6:

Anaphylactoid reactions are those reactions that are similar to the anaphylactic reactions but are not IgE mediated. These reactions are caused by direct degranulation of the mast cells or basophils, which causes the release of mediators.

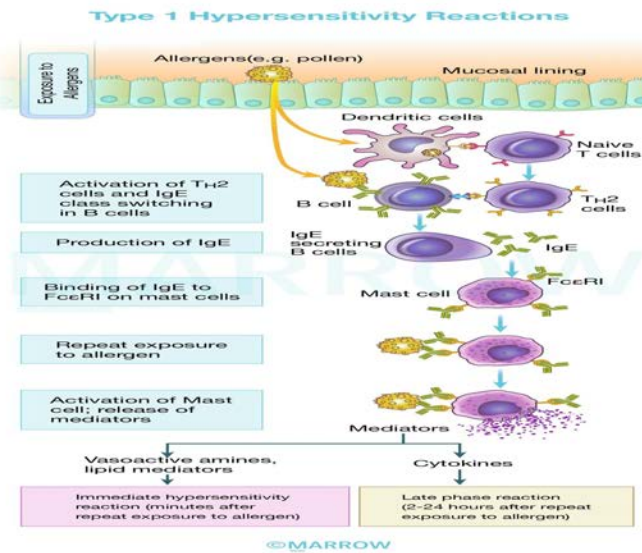
Unlike the classic anaphylaxis which occurs on re-exposure to the allergen, the anaphylactoid reaction can occur even on the first exposure. The most common agents that can cause an anaphylactoid reaction include NSAIDs and radiocontrast media.

In 2014, World Allergy Organisation has introduced two new terms:

• Immunologic anaphylaxis - It includes anaphylactic reactions mediated by IgE, IgG (in animals), and immune complex/ complement-mediated reactions.

• Non-immunologic anaphylaxis (previously called anaphylactoid reaction) - It includes reactions caused by agents which cause massive degranulation of mast cells or basophils in the absence of immunoglobulin.

The image given below shows the sequence of events in type 1 hypersensitivity reaction.



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Solution to Question 7:

Rheumatoid arthritis is mediated by T cells, not antibodies.

Antibody-mediated diseases:

• Autoimmune hemolytic anemia

• Autoimmune thrombocytopenic purpura

• Pemphigus vulgaris

• Vasculitis caused by ANCA

• Goodpasture syndrome

• Myasthenia gravis

• Acute rheumatic fever

• Graves disease

• Pernicious anemia

• Insulin resistant diabetes

T cell-mediated diseases:

• Rheumatoid arthritis

• Multiple sclerosis

• Psoriasis

• Type 1 diabetes mellitus

• Inflammatory bowel disease

• Contact sensitivity

Note: In T cell mediated diseases, although the role of T cells have been demonstrated, antibodies may also be involved in tissue injury.

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Solution to Question 8:

PTPN22 gene is most frequently implicated in autoimmunity.

PTPN22, which encodes the protein tyrosine phosphatase, is associated with the following conditions:

• Rheumatoid arthritis

• Inflammatory bowel disease (IBD)

• Type 1 diabetes

Because these disorders have a fairly high prevalence, PTPN22 is said to be the gene that is most frequently implicated in autoimmunity.

Option A: Mutations in FOXP3 cause a systemic autoimmune disease called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked).

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Option C: Polymorphisms in the gene encoding for NOD2 are associated with Crohn's disease.

Option D: AIRE mutation is associated with the autoimmune polyendocrinopathy syndrome type 1 (APS-1).

Solution to Question 9:

The above process is called central tolerance and the AIRE (AutoImmune REgulator) protein is necessary for this process.

Immature self-reactive T and B lymphocyte clones recognize self-antigens during their maturation in the central lymphoid organs (thymus for T cells, bone marrow for B cells). They are killed or rendered harmless.

The removal of self reacting T lymphocytes in the thymus is called negative selection/ deletion. For this process, AIRE protein is needed. Mutations in the AIRE gene results in autoimmune disorders (autoimmune polyendocrinopathy).

B cells undergo a process called receptor editing. When developing B cells encounter an antigen, it formulates a change in the receptor that makes the antigen unrecognizable. Self-reacting B cells can also undergo apoptosis.

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Solution to Question 10:

Autoimmunity in Epstein–Barr virus (EBV) infection is the result of polyclonal B cell activation.

Microbes may induce other abnormalities that promote autoimmune reactions. Some viruses, such as EBV and HIV, cause polyclonal B-cell activation, which may result in the production of autoantibodies.

The role of infections in autoimmunity is exemplified by the following:

• Molecular mimicry of antigenic cross-reactivity: The structural similarity of the microbial antigens and self-antigens. Rheumatic heart disease is an example in which streptococcal proteins cross-react with myocardial proteins causing myocarditis.

• Upregulation of co-stimulatory molecules by infectious organisms.

• Polyclonal B cell activation: Caused by EBV and HIV, resulting in the production of autoantibodies.

• Alteration of tissue antigens: Infections may alter tissue self-antigens so that they activate T cells and lose the property of self-tolerance.

Solution to Question 11:

Homogeneous or diffuse nuclear staining does not reflect antibodies to RNA. The nucleolar pattern of staining represents antibodies to RNA.

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Antinuclear antibodies (ANAs) are directed against antibodies to:

- DNA
- Histones
- Nonhistone proteins bound to RNA
- Nucleolar antigens

The most widely used method for detecting ANAs is indirect immunofluorescence. The pattern of nuclear fluorescence suggests the type of antibody present in the patient's serum.

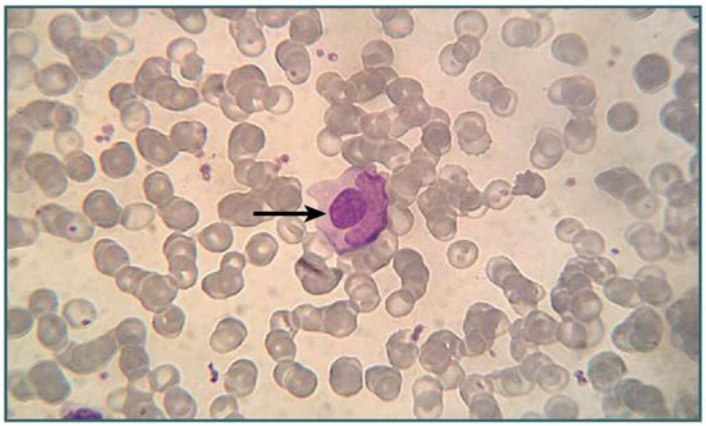
Solution to Question 12:

The lupus erythematosus (LE) cell is a phagocytic neutrophil or macrophage.

Nuclei of damaged cells react with ANAs, lose their chromatin pattern, and become homogeneous to produce LE bodies or hematoxylin bodies. Phagocytic neutrophils or macrophages engulf the denatured nucleus of an injured cell. Demonstration of LE cells in vitro was used in the past for the diagnosis of SLE.

The image below shows a lupus erythematosus (LE) cell.

LE cell or hematoxylin bodies



Solution to Question 13:

The given clinical picture is highly suggestive of systemic lupus erythematosus (SLE). In this condition, lymphocytic infiltration in the salivary gland is not seen. However, this finding is seen in Sjogren's syndrome.

If cell nuclei are exposed to anti-nuclear antibodies (ANAs), they can bind to them. The nuclei of damaged cells react with ANAs, lose their chromatin pattern, and become homogeneous. They are called lupus erythematosus (LE) bodies or hematoxylin bodies.

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An acute necrotizing vasculitis involving capillaries, small arteries, and arterioles with fibrinoid necrosis is seen in SLE. Central penicilliary arteries in the spleen may show concentric intimal and smooth muscle cell hyperplasia, producing so-called onion-skin lesions.

Solution to Question 14:

Celiac disease is not an IgG4-Related disease.

IgG4-related disease (IgG4-RD) is a newly recognized constellation of disorders characterized by tissue infiltrates dominated by IgG4 antibody-producing plasma cells and lymphocytes, particularly T cells, storiform fibrosis, obliterative phlebitis, and usually increased serum IgG4.

IgG4-RD spectrum includes:

- Mikulicz syndrome - enlargement and fibrosis of salivary and lacrimal glands
- Riedel thyroiditis
- Idiopathic retroperitoneal fibrosis
- Autoimmune pancreatitis
- Inflammatory pseudotumors of the orbit, lungs, and kidney

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Immunodeficiency Syndromes

Question 1:

Leukocyte-adhesion deficiency type 2 is due to the absence of which of the following?

a) Selectin

b) LFA-1

c) TLR-3

d) Sialyl-Lewis X

Question 2:

Which of the following statements is false about Chédiak-Higashi syndrome?

a) There is aberrant phagolysosome fusion

b) It has an autosomal recessive inheritance

c) Investigations show neutropenia

d) Granules are absent in white blood cells

Question 3:

A 2-month-old baby was brought with complaints of fever and fast breathing for 5 days, and was diagnosed with pneumonia. Further history revealed baby had recurrent infections. Blood culture revealed infection from Nocardia spp. Nitroblue tetrazolium test turned out to be negative. Which of the following statement is false regarding this condition?

a) It has autosomal recessive inheritance

b) It is due to oxidase deficiency

c) Defective superoxide production by granulocytes

d) Due to lymphocytic inflammatory reaction

Question 4:

Match the following complement deficiencies with the disorders.

a) 1-d, 2-c, 3-a, 4-b

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b) 1-b, 2-d, 3-a, 4-c

c) 1-c, 2-d, 3-b, 4-a

d) 1-d, 2-a, 3-b, 4-c

Question 5:

A patient presents with recurrent swelling of the face and lips as shown with vomiting and diarrhea when emotionally stressed. What is the most likely deficiency?

a) C1 inhibitor

b) C2

c) C3

d) C1, C2, C4

Question 6:

A 4-month-old baby was brought with severe diaper rash. The parents gave a history of recurrent infections in the past 4 months which required frequent hospitalization. On examination white patches were present in oral mucosa which could be scraped easily. The biopsy of the thymus showed remnants of Hassall's corpuscles. Which of the following statements is false about this condition?

a) It has autosomal inheritance pattern

b) Adenosine deaminase enzyme is deficient

c) It is due to defect only in cell mediated immune response

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d) B cell count can be normal

Question 7:

Which gene is not involved in SCID?

a) BTK

b) JAK-3

c) RAG1

d) IL-7Rα

Question 8:

A 9-month-old baby was brought with a cough and difficulty in breathing. The baby was admitted with similar complaints in the past. On auscultation, coarse crepitations were heard. Quantitative serum immunoglobulin analysis was done and serum IgG, IgA, and IgM levels were low. His cellular immunity was found to be normal. Which of the following is false about his condition?

a) X-linked inheritence

b) Germinal centres of lymph nodes are underdeveloped

c) Manifestation is seen usually after 6 months of age

d) Not associated with autoimmune disease

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Question 9:

A 2-year-old boy was brought to the OPD with delayed development. On examination, he had the following appearance. Further workup revealed hypocalcemia and an atrial septal defect. Chromosomal studies showed deletion of 22q11. All are true about this syndrome except:

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a) It is associated with T cell deficiency

b) Thymic aplasia is a prominent feature

c) Parathyroid gland is defective

d) Failure of development of 3rd and 4th pharyngeal arches

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Question 10:

Which of the following is least likely to be a feature in a patient with Hyper-IgM syndrome?

a) It has X-linked mode of inheritance

b) They have normal serum IgG levels

c) Autoimmune hemolytic anemia can be seen

d) They have normal B-cell and T-cell numbers

Question 11:

A 3-year-old boy presents with recurrent bacterial infections and Pneumocystis jiroveci pneumonia. The flow cytometry analysis of the boy (Boxes 3& 4) is shown below (Boxes 1 & 2 are normal). What is the most likely diagnosis?

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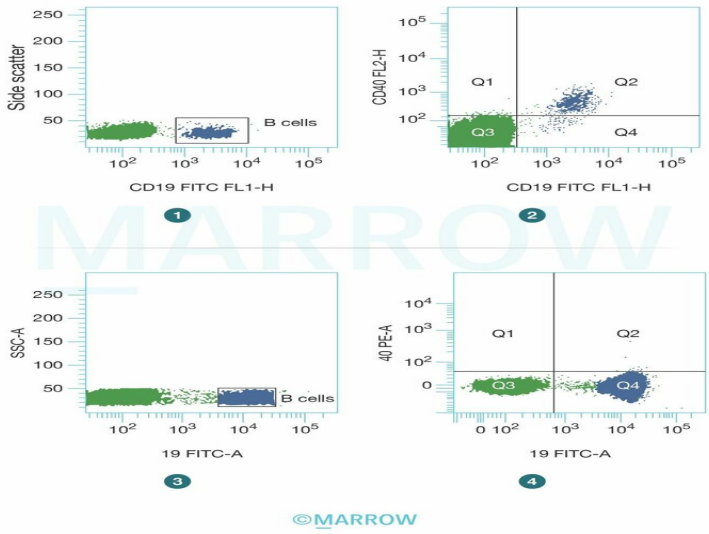

a) Bare lymphocytes

b) Chronic granulocyte deficiency

c) Hyper IgM syndrome

d) DiGeorge syndrome

Question 12:

Patients with isolated Ig A deficiency would have associated deficiency of which of the following IgG subtypes?

a) IgG1, IgG3

b) IgG1, IgG4

c) IgG2, IgG4

d) IgG2, IgG3

Question 13:

Which of the following are mutated in X-linked lymphoproliferative syndrome?

a) SLAM-associated protein

b) LYST

c) BTK

d) TBX1

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Question 14:

Which of the following lymphoid tissue findings is seen most commonly in patients with common variable hypogammaglobulinemia?

a) Decreased B-cell count

b) Increased B-cell count

c) Normal B-cell count

d) Absent B-cells

Question 15:

A 3-year-old boy is brought with complaints of red rashes over his skin. His mother says that the child will be constantly scratching the rashes. On asking any previous history she says the child keeps getting recurrent infections which mostly require hospitalization. Blood investigations showed a low platelet count. Which of the following is false regarding this syndrome?

a) IgG normal

b) IgA elevated

c) IgE elevated

d) IgM normal

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Question 16:

A 5-year-old girl was brought to the OPD with complaints of repeated falls while walking for the past 1 year. She had difficulty in eating, gripping, or holding things. On examination, hand mouth incoordination and slurring of speech were noted. On ocular examination, the following finding was seen. All are true about this condition except:

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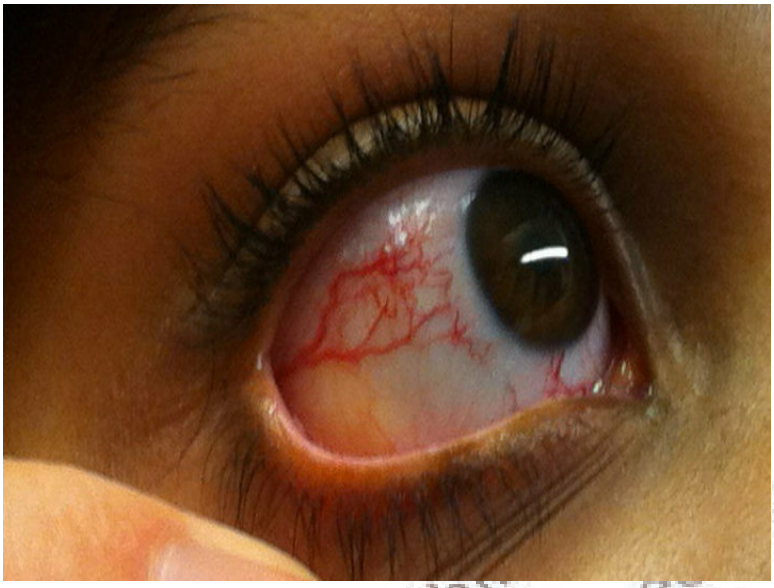

a) There is defective production of IgA and IgG2

b) Affected gene is located on chromosome 11

c) Autosomal-dominant inheritance is seen

d) There is increased risk of malignancy

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Question 17:

Human immunodeficiency virus affects CD4 cells due to their interaction with which protein?

a) gp 120

b) gp 41

c) CCR5

d) CXCR4

Question 18:

Which of the following cell types is not a target for the initiation and maintenance of HIV infection?

a) CD4 T cell

b) Macrophage

c) Dendritic cell

d) Neutrophil

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Question 19:

Which is the most common CNS neoplasm in HIV patients?

a) Meduloblastoma

b) Astrocytoma

c) Primary CNS lymphoma

d) Glioblastoma

Question 20:

A 25-year-old man, who is HIV-positive, presents with generalized lymphadenopathy. Which of the histopathological features is least likely to be seen on lymph node biopsy?

a) Florid reactive hyperplasia

b) Follicle lysis

c) Hematoxylin bodies

d) Collection of monocytoid B Cells in sinuses

Question 21:

A 50-year-old HIV-seropositive man presents with raised violaceous plaques over the legs. Microscopy shows a lesion in the dermis with dilated, jagged vascular channels lined and surrounded by plump spindle cells. It contains red cells with marked hemorrhage, hemosiderin pigment, and mononuclear inflammation. Mitotic figures are also seen. Which organism is associated with this tumor?

a) Human herpes virus 8

b) Epstein barr virus

c) Bartonella henselae

d) Human papillomavirus

Question 22:

A 45 -year-old HIV-positive patient has patchy pneumonia. Smears of induced sputum and sedimented cells from lavage fluid stained with methenamine silver are as seen below. Which is the most likely organism implicated?

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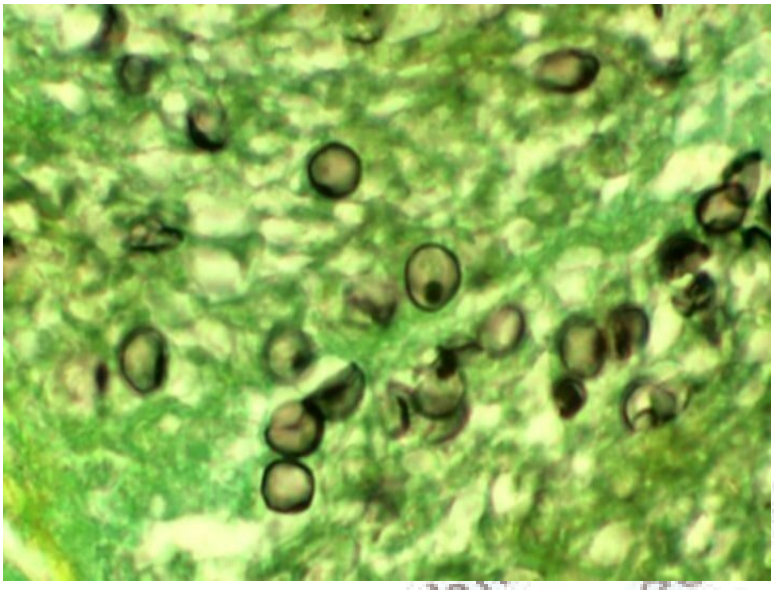

a) Mycobacterium tuberculosis

b) Nocardia asteroides

c) Histoplasma capsulatum

d) Pneumocystis jirovecii

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Answer Key

Question No.	Correct Option
1	d
2	d
3	d
4	b
5	a
6	c
7	a
8	d
9	d
10	b
11	c
12	c
13	a
14	c

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15	d
16	c
17	a
18	d
19	c
20	c
21	a
22	d

Detailed Explanations

Solution to Question 1:

Leukocyte-adhesion deficiency (LAD) type 2 is due to the absence of Sialyl-Lewis X.

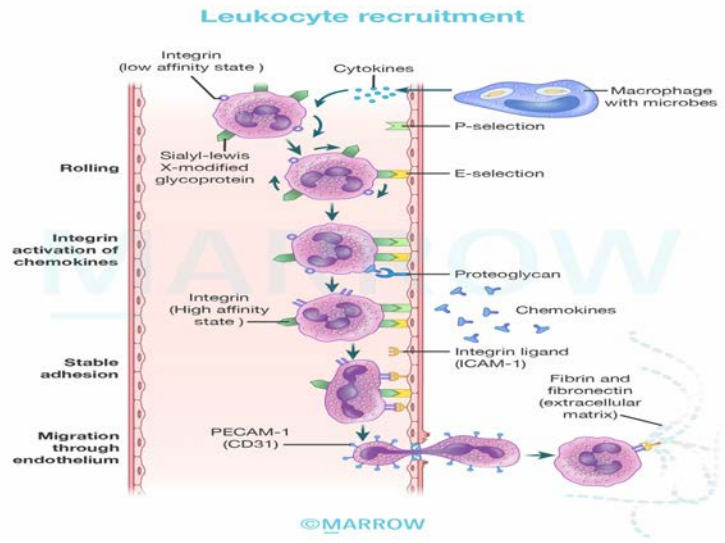
Physiologically Sialyl-Lewis X has the necessary ligand for the selectins which bind to leukocytes.

Inherited defects in leukocyte adhesion:

• Type 1 - defect in the biosynthesis of the °2 chain shared by the LFA-1 and Mac-1 integrins

• Type 2 - absence of sialyl-Lewis X, the fucose containing ligand for E- and P-selectins. It is due to a defect in the fucosyltransferase, the enzyme that attaches fucose moieties to protein backbones.

The major clinical problem in both conditions is recurrent bacterial infections due to inadequate granulocyte function.



Solution to Question 2:

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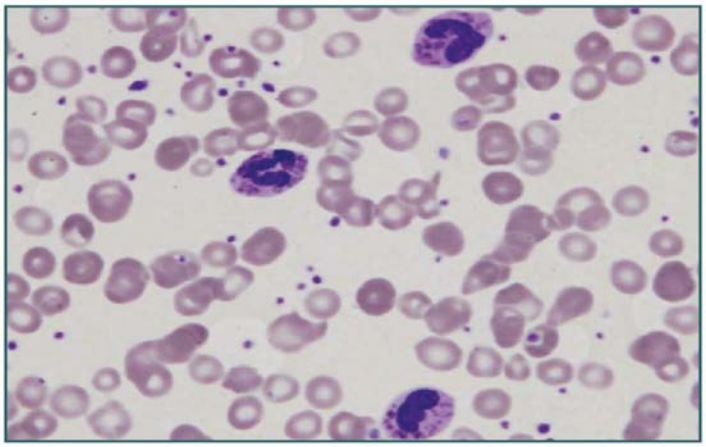
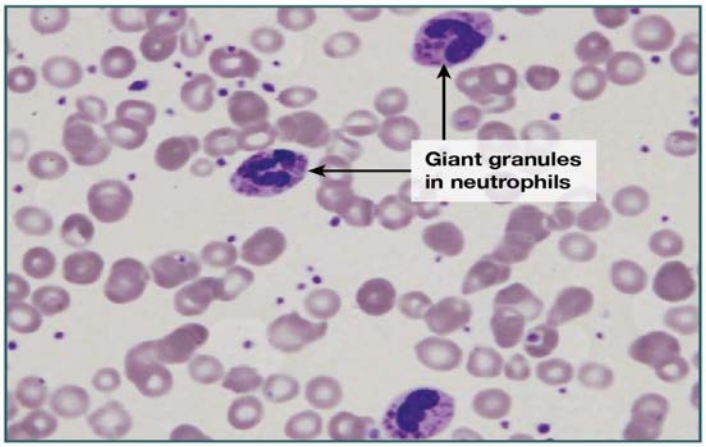
Leukocytes contain giant granules in Chédiak–Higashi syndrome as seen in peripheral blood smears. They are due to aberrant phagolysosome fusion.

The image shows giant granules in a neutrophil in Chédiak–Higashi syndrome.

Chédiak–Higashi syndrome



Chédiak–Higashi syndrome



Chédiak–Higashi syndrome is an autosomal recessive condition. The defective fusion of phagosomes and lysosomes results in defective phagocytes function and susceptibility to infections.

The abnormalities are neutropenia, defective degranulation, and delayed microbial killing, causing:

- Albinism - melanocytes
- Nerve defects - nervous system cells
- Bleeding disorders - platelets

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The gene associated with this disorder encodes a large cytosolic protein called LYST, which is believed to regulate lysosomal trafficking.

Solution to Question 3:

The given clinical scenario suggests chronic granulomatous disease. It is due to a macrophage-rich chronic inflammatory reaction, not lymphocytic.

Chronic granulomatous disease is a defect in bacterial killing and renders patients susceptible to recurrent bacterial infections. The name of this disease comes from the macrophage-rich chronic inflammatory reaction that tries to control the infection when the initial neutrophil defense is inadequate. This often leads to collections of activated macrophages that wall off the microbes, forming granulomas.

Solution to Question 4:

The disorders caused due to complement deficiency are:

The deficiency of C2 is the most common complement protein deficiency.

Complement	Disease/syndrome
C1 esterase inhibitor	Hereditary angioneurotic ede ma
C1, C2, C4	Pyogenic infections, systemic lupus erythematosus (SLE)
C1q, C1r, C1s	Pyogenic infections, SLE
C3	Pyogenic infections,Glomerul onephritis, SLE
Factor H	Hemolytic uremic syndrome(HUS), Pyogenic infections, Gl omerulonephritis, SLE
C5 to C8	Recurrent infections withNei sseriaspp.
Properdin	Meningococcal meningitis
Factor D	Meningitis, sepsis -Neisseria
Factors H and I	Recurrent pyogenic infection s
DAFF and CD59	Paroxysmal nocturnal hemog lobinuria (PNH)
Mannan-binding lect in	Respiratory tract infections
MASP-2	Respiratory tract infections

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Solution to Question 5:

The given clinical scenario is suggestive of hereditary angioneurotic edema. It is due to the deficiency of C1 inhibitors.

Hereditary angioneurotic edema is an autosomal dominant disorder, which is more common than complement deficiency states.

Targets of C1 inhibitors are proteases, specifically C1r and C1s of the complement cascade, factor XII of the coagulation pathway, and the kallikrein system. Deficiency of C1 inhibitor leads to unregulated activation of kallikrein. This increases the production of vasoactive peptides such as bradykinin.

It causes episodes of edema affecting the skin and mucosal surfaces such as the larynx and the gastrointestinal tract. This may result in life-threatening asphyxia or nausea, vomiting, and diarrhea after minor trauma or emotional stress.

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Solution to Question 6:

The given clinical scenario is suggestive of severe combined immunodeficiency (SCID). The biopsy of the thymus showing remnants of Hassall's corpuscles indicates it is due to adenosine deaminase (ADA) deficiency. SCID is a defect in both humoral and cell-mediated immune responses. Usually the defect lies in the T-cell compartment with secondary impairment in humoral immunity.

Affected infants present with prominent thrush (oral candidiasis), extensive diaper rash, and failure to thrive. Some patients develop a morbilliform rash shortly after birth because maternal T cells are transferred across the placenta and attack the fetus, causing graft-versus-host disease (GVHD).

Persons with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including:

- Candida albicans
- Pneumocystis jiroveci
- Pseudomonas
- Cytomegalovirus
- Varicella

There are 2 types of SCID based on inheritance:

1. X-linked SCID is the most common form and hence it is more common in boys than in girls. The genetic defect is the mutation in the common γ-chain (γc) subunit of cytokine receptors. T-cell numbers are greatly reduced, and although B cells may be normal in number, antibody synthesis is impaired because of the lack of T-cell help. The thymus contains lobules of undifferentiated epithelial cells resembling fetal thymus.

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2. Autosomal recessive is most commonly caused due to deficiency of the enzyme adenosine deaminase (ADA). The deficiency of ADA leads to the accumulation of deoxyadenosine and its derivatives (e.g., deoxy-ATP). They are toxic to rapidly dividing immature lymphocytes, especially those of the T-cell lineage. Hence, there may be a greater reduction in the number of T lymphocytes.

In the two most common forms (γc mutation and ADA deficiency), the thymus is small and devoid of lymphoid cells. In SCID caused by ADA deficiency, remnants of Hassall's corpuscles can be found.

Note: X-linked SCID is the first human disease in which gene therapy has been successful.

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Solution to Question 7:

BTK mutation causes X-linked agammaglobulinemia and not SCID (severe combined immunodeficiency).

Severe combined immunodeficiency is a defect in both humoral and cell-mediated immune responses. In this condition, the following genes are involved:

- JAK3
- RAG1
- IL-7R

Persons with SCID are extremely susceptible to recurrent, severe infections by a wide range of pathogens, including:

- Candida albicans
- Pneumocystis jiroveci
- Pseudomonas
- Cytomegalovirus
- Varicella

Solution to Question 8:

The given clinical scenario is suggestive of Bruton agammaglobulinemia/ X-linked agammaglobulinemia (XLA). Even though it is an immunodeficiency disease, it is paradoxically associated with autoimmune diseases such as arthritis and dermatomyositis in 35% of individuals.

The classic form of this disease has the following characteristics:

- B cells are absent or markedly decreased and the serum levels of all classes of immunoglobulins are decreased
- T-cell mediated reactions are normal
- Germinal centers of lymph nodes, Peyer's patches, the appendix, and tonsils are underdeveloped

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• Plasma cells are absent throughout the body

XLA is characterized by the failure of B-cell precursors (pro-B cells and pre-B cells) to develop into mature B cells. It is associated with mutations in a cytoplasmic tyrosine kinase called Bruton tyrosine kinase (Btk).

The related gene is located on the long arm of the X chromosome. This X-linked disease is seen almost entirely in males. The disease usually does not become apparent until about 6 months of age, when maternal immunoglobulins are depleted.

Affected individuals are susceptible to infections with:

• Bacteria that are normally opsonized by antibodies and cleared by phagocytosis

• Haemophilus influenzae

• Streptococcus pneumonia

• Staphylococcus aureus

• Giardia lamblia - intestinal protozoan that is normally resisted by secreted IgA, causes persistent infections

• Enteroviruses

• Echovirus

• Poliovirus

• Coxsackievirus

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Solution to Question 9:

The given clinical scenario with the image suggests DiGeorge syndrome. It results from the failure of the development of the 3rd and 4th pharyngeal pouches. They give rise to the thymus, the parathyroids, some of the C cells of the thyroid, and the ultimobranchial body.

The absence of cell-mediated immunity causes poor defense against certain fungal and viral infections. The T-cell zones of lymphoid organs, i.e. paracortical areas of the lymph nodes and the periarteriolar sheaths of the spleen, are depleted. Ig levels may be normal or reduced, depending on the severity of the T-cell deficiency.

Solution to Question 10:

The serum of patients with Hyper-IgM syndrome contains extremely low levels of IgG.

In Hyper-IgM syndrome production of IgM antibodies is normal but the ability to produce IgG, IgA, and IgE antibodies is deficient. There are normal or elevated levels of IgM, no IgA or IgE, and extremely low levels of IgG. It affects the ability of helper T cells to deliver activating signals to B cells and macrophages. However, B cells and T cells counts are normal.

It is mostly an X-linked disease, that has mutations in the gene encoding CD40L located on Xq26. If the disease is inherited in an autosomal recessive pattern, then there are loss-of-function

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mutations involving either CD40 or the enzyme called activation-induced cytidine deaminase (AID).

Those with CD40L mutations are also susceptible to pneumonia caused by the intracellular organism Pneumocystis jiroveci. This is due to CD40L-mediated macrophage activation, a key reaction of cell-mediated immunity being defective. Recurrent pyogenic infection occurs because the level of opsonizing IgG antibodies is low.

Occasionally, the IgM antibodies react with blood cells, giving rise to autoimmune hemolytic anemia, thrombocytopenia, and neutropenia. In older patients, the proliferation of IgM-producing plasma cells that infiltrate the mucosa of the gastrointestinal tract is seen.

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Solution to Question 11:

The deficiency of the CD40 and its absence in B cells interferes with class switching and the production of memory cells. The B-cell response to antigens, is unaffected, accounting for the presence of increased IgM antibodies. Hence, the condition is known as Hyper IgM syndrome.

The given clinical scenario and the flow cytometry is suggestive of Hyper IgM syndrome. The flow cytometry shows the following findings:

• In comparison of image 3 to 1, where side scatter is plotted against CD 19: B-cell gating is present.

Gating of B cells means selecting a cell during a flow cytometry experiment for further analysis or data presentation.CD 19 is widely expressed on B cells. Hence the graph shows B cell gating. Side scatter measurement provides information about the granularity of a cell.

• In comparison of image 4 to 2, where CD 40 is plotted against CD 19: B cells are present only in quadrant 4, which means that there is CD 40 deficiency.

The deficiency of the CD40 and its absence in B cells interferes with class switching and the production of memory cells. The B-cell response to antigens is unaffected, accounting for the presence of increased IgM antibodies. Hence, the condition is known as Hyper IgM syndrome.

Given below is the explanation of how to interpret flow cytometry results:

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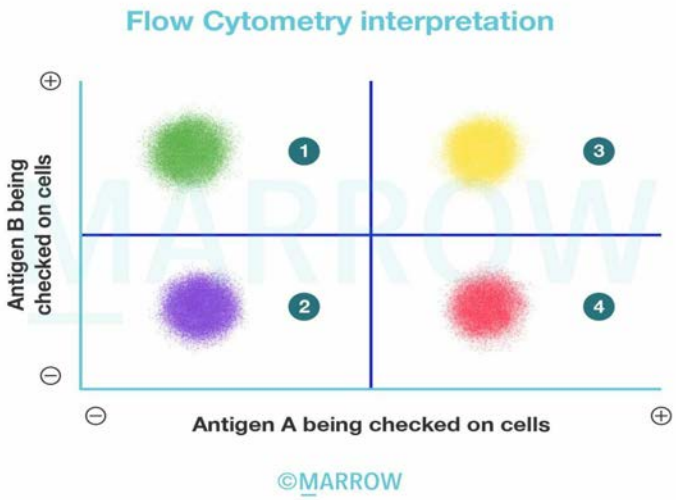

Interpretation of results:

Quadrant 1- Cells marked in green: -VE for A antigen, +VE for B antigen

Quadrant 2- Cells marked in purple: -VE for both the antigens.

Quadrant 3- Cells marked in yellow: +VE for both the antigens

Quadrant 4- Cells marked in red: +VE for A antigen, -VE for B antigen

Solution to Question 12:

Isolated IgA deficiency is associated with deficiency of IgG subtypes IgG2 and IgG4.

IgA deficiency-affected individuals have extremely low levels of both serum and secretory IgA. It may be familial or acquired in association with toxoplasmosis, measles, or some other viral infection.

Because IgA is the major antibody in external secretions, mucosal defenses are weakened, and infections occur in the respiratory, gastrointestinal, and urogenital tracts. Symptomatic patients commonly have recurrent sinopulmonary infections and diarrhea.

IgA-deficient patients have a high frequency of respiratory tract allergy and a variety of autoimmune diseases, particularly systemic lupus erythematosus (SLE) and rheumatoid arthritis.

Solution to Question 13:

The X-linked lymphoproliferative syndrome is due to mutations in the gene encoding an adaptor molecule called SLAM-associated protein (SAP).

It is characterized by an inability to eliminate Epstein-Barr virus (EBV), eventually leading to fulminant infectious mononucleosis and the development of B-cell tumors.

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In about 80% of cases, the disease is due to mutations in the gene encoding the adaptor molecule SAP. Defects in SAP contribute to attenuated NK cell and T-cell activation, resulting in increased susceptibility to viral infections.

Option B: LYST gene is associated with Chediak-Higashi syndrome.

Option C: BTK gene is associated with Isolated growth hormone deficiency type III.

Option D: TBX1 gene is associated with 22q11.2 deletion syndrome.

Solution to Question 14:

Normal B-cell count is most commonly seen in lymphoid tissues of individuals with the common variable hypogammaglobulinemia.

It is a heterogeneous group of disorders in which the common feature is hypogammaglobulinemia, generally affecting all the antibody classes, but sometimes only IgG.

In contrast to X-linked agammaglobulinemia, most individuals with common variable immunodeficiency have normal or near-normal numbers of B-cells in the blood and lymphoid tissues. These B cells, however, are not able to differentiate into plasma cells.

FDA approved XEMBIFY in 2019, 20% immunoglobulin solution for subcutaneous injection. It is indicated for the use of primary humoral immunodeficiency disorders in patients 2years of age and older.

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Solution to Question 15:

The given history with eczema, recurrent infections, and thrombocytopenia points towards Wiskott–Aldrich syndrome. In this condition, IgM levels in the serum are low.

Wiskott–Aldrich syndrome is caused by mutations in the gene encoding the Wiskott–Aldrich syndrome protein (WASP), which is located on Xp11.23. The X-linked disease is characterized by thrombocytopenia, eczema, and a marked vulnerability to recurrent infection, resulting in early death.

Platelets are small in size. The thymus is morphologically normal, at least early in the course of the disease, but there is the progressive loss of T lymphocytes in the peripheral blood and in the T-cell zones (paracortical areas) of the lymph nodes, with variable defects in cellular immunity.

Patients do not make antibodies to polysaccharide antigens, and the response to protein antigens is poor. IgM levels are low, IgG is usually normal, while the levels of IgA and IgE are often elevated. Patients are prone to developing B-cell lymphomas.

Solution to Question 16:

The above clinical scenario and image showing telangiectasia are diagnostic of ataxia-telangiectasia. It is an autosomal-recessive disorder, not autosomal dominant.

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The most prominent humoral immune abnormalities are defective production of IgA and IgG2. The gene responsible for this disorder is located on chromosome 11 and encodes a protein called ATM. The ATM protein is a sensor of DNA damage (double-strand breaks), and it activates p53 by phosphorylation.

Ataxia-telangiectasia is characterized by abnormal gait (ataxia), vascular malformations (telangiectases), neurologic deficits, increased incidence of tumors, and immunodeficiency. It may affect both B and T cells.

There is a high incidence of lymphomas and leukemias.

Solution to Question 17:

The CD4 cells are affected by HIV due to their interaction with gp120.

HIV-1 virion is spherical and contains an electron-dense, cone-shaped core surrounded by a lipid envelope derived from the host cell membrane. Target cells of HIV include CD4+ helper T cells (worst affected), monocyte-macrophages, and dendritic cells.

The virus core contains:

• Major capsid protein p24

• Nucleocapsid protein p7/p9

• Two copies of viral genomic RNA

• The three viral enzymes (protease, reverse transcriptase, and integrase)

The viral core is surrounded by a matrix protein called p17, which lies underneath the virion envelope. The viral envelope is studded by two viral glycoproteins, gp120 and gp41, which are critical for HIV infection of cells.

Viral glycoprotein gp120 binds to CD4+ cells in the host. CXCR4 and CCR5 function as coreceptors for HIV-1 entry into CD4+ cells. This binding leads to a conformational change in gp41 causing exposure of a hydrophobic region called the fusion peptide at the tip of gp41. This peptide inserts into the cell membrane of the target cells (e.g., T cells or macrophages), leading to the fusion of the virus with the host cell.

The image below shows the pathogenesis of HIV infection.

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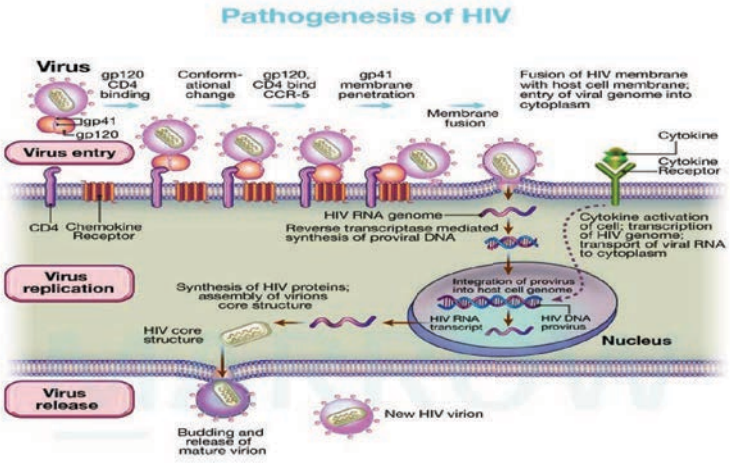

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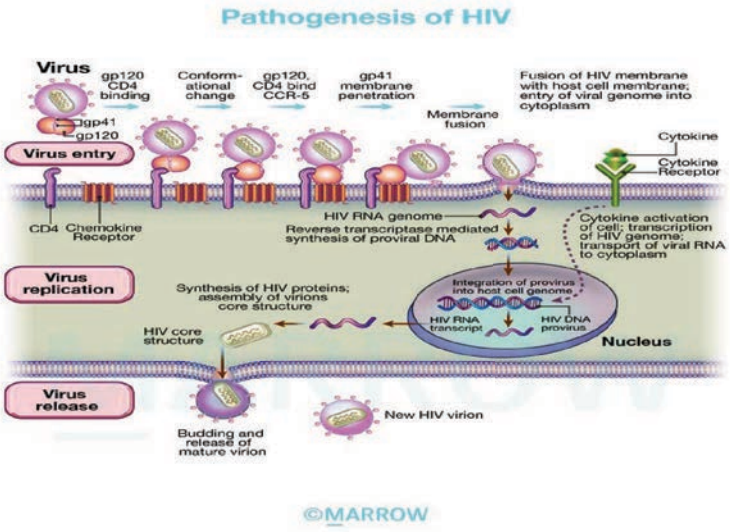
Solution to Question 18:

The neutrophil is not a target for the initiation and maintenance of human immunodeficiency virus (HIV) infection.

HIV enters the body and affects T cells, dendritic cells, and macrophages. Particularly, memory and activated T cells are infected, but it is inefficient at productively infecting naive (unactivated) T cells.

Completion of the viral life cycle in latently infected cells occurs only after cell activation, and in the case of most $CD4^+$ T cells, virus activation results in cell lysis.

The image below shows the pathogenesis of HIV infection.



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Solution to Question 19:

The most common central nervous system (CNS) neoplasm in patients with HIV infection is primary CNS lymphoma.

Lymphomas are the most common CNS neoplasm in immunosuppressed individuals, including those with acquired immunodeficiency syndrome (AIDS) and immunosuppression after transplantation. They are associated with latent infection with Epstein–Barr virus (EBV). The vast majority of primary brain lymphomas are of B-cell origin.

At least two mechanisms appear to underlie the increased risk of B-cell tumors in HIV-infected individuals. They are:

• The unchecked proliferation of B cells infected with oncogenic herpes viruses in the setting of profound T-cell depletion (AIDS).

• Germinal center B-cell hyperplasia in the setting of early HIV infection.

The most common site for lymphoma in patients with acquired immunodeficiency syndrome (AIDS) is the central nervous system (CNS).

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Solution to Question 20:

Hematoxylin bodies are seen in lymph nodes in systemic lupus erythematosus (SLE).

Features of AIDS-related lymphadenopathy:

Early stages of HIV infection:

• Florid hyperplasia of B cell follicles

• Follicle lysis

• Monocytoid B cells in sinuses

• Neutrophils and dermatopathic lymphadenopathy

• The interfollicular zone shows vascular proliferation, which may progress to Kaposi sarcoma

Late stages of HIV infection:

• Severe lymphoid involution

• Possible hyalinization of the germinal centers

• Burnt-out lymph nodes, which become atrophic and may harbor numerous opportunistic pathogens, often within macrophages

Solution to Question 21:

The most likely diagnosis is Kaposi sarcoma, caused by human herpesvirus 8 (HHV8).

Kaposi sarcoma is a vascular neoplasm, that is highly associated with acquired immunodeficiency syndrome (AIDS). It is the most common cancer seen in patients having AIDS. Though the

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incidence of Kaposi carcinoma reduced, it still occurs in 2-3% of HIV-infected individuals.

The pathogenesis of Kaposi sarcoma that is caused by HHV8 includes:

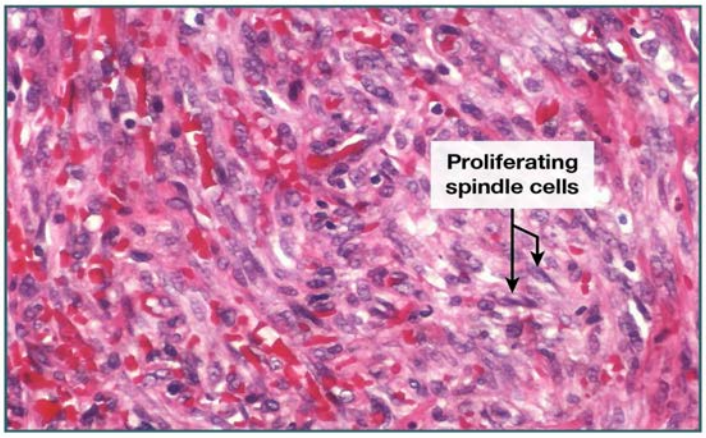
• A virally encoded G protein that induces VEGF production, stimulating endothelial growth

• The lytic infection caused by HHV8 increases the pro-inflammatory cytokines

• HHV8 encoded proteins inhibit the p53 induced apoptosis

The given images show coalescent red-purple macules and plaques of the skin and the histologic appearance of Kaposi sarcoma, demonstrating sheets of proliferating spindle cells:

Kaposi sarcoma



Solution to Question 22:

The smears stained with methenamine silver show black-colored stained cysts resembling the crushed ping pong balls of Pneumocystis jirovecii.

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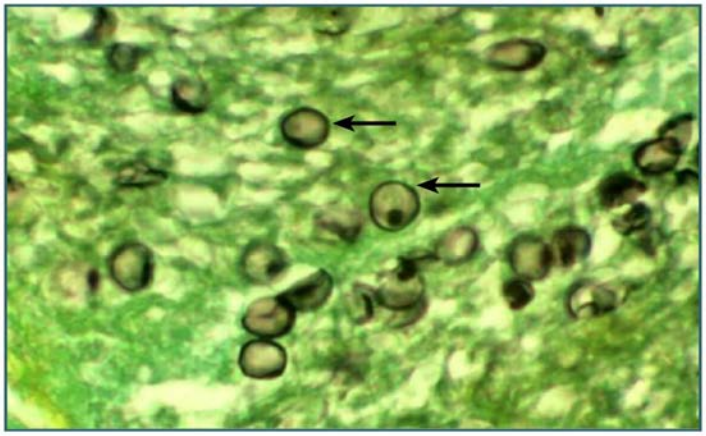
Approximately 15% to 30% of untreated HIV-infected people develop pneumonia during the course of the disease. It is mainly caused by the fungus P. jirovecii (reactivation of prior latent infection).

Pneumocystis jirovecii



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Amyloidosis and Graft Rejection

Question 1:

Which among the following best describes an amyloid?

a) Colloid

b) Lipoprotein

c) Proteoglycan

d) Intermediate filament

Question 2:

In a patient with reactive systemic amyloidosis, which of the following proteins are likely to get deposited in the tissues?

a) A°

b) AL

c) AA

d) APrP

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Question 3:

What is the most common cause of reactive amyloidosis worldwide?

a) Rheumatoid arthritis

b) Multiple myeloma

c) Crohn's disease

d) Diabetes mellitus

Question 4:

An elderly woman is brought with worsening memory for the past 3 years. Recently, she has been unable to carry out her daily chores and frequently gets lost in the neighborhood. There is no history of personality changes, rigidity, or gait disturbances. MRI brain shows temporal lobe atrophy. Which of the following deposits is likely to be seen in this patient?

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a) A° 2m amyloid

b) A° amyloid

c) ATTR amyloid

d) AIAPP amyloid

Question 5:

A diabetic patient with chronic kidney disease has been undergoing hemodialysis for the past 4 years. Deposition of which of the following is likely in this condition?

a) α1 microglobulin

b) ° 2 microglobulin

c) α2 macroglobulin

d) γ globulin

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Question 6:

Which type of amyloidosis is caused by the mutation of the transthyretin protein?

a) Familial Mediterranean fever

b) Familial amyloidotic polyneuropathy

c) Systemic senile amyloidosis

d) Reactive systemic amyloidosis

Question 7:

Who among the following patients is at increased risk for developing amyloidosis?

a) A patient with maturity-onset diabetes of the young

b) A 15-year-old diabetic boy who is on insulin therapy

c) A 50-year-old diabetic patient with insulin resistance

d) A patient with autosomal dominant non-insulin dependent form of diabetes

Question 8:

A middle-aged woman presents with thyroid swelling. The histological examination of the swelling is shown below. What type of amyloid deposits are seen in this condition?

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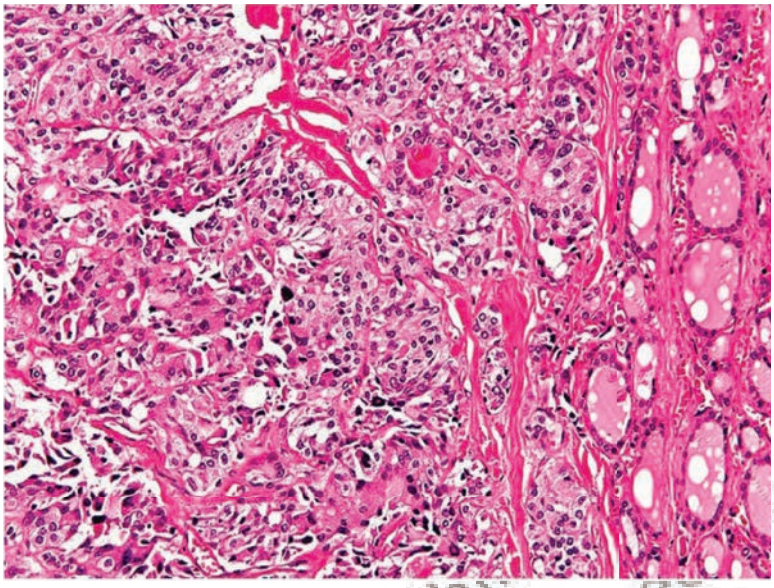

a) A Cal

b) A° 2m

c) AL

d) A°

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Question 9:

Which of the following is the most common organ involved in AL amyloidosis?

a) Cardiac tissue

b) Renal tissue

c) Splenic tissue

d) Hepatic tissue

Question 10:

A bone marrow examination is being planned for a patient with AL amyloidosis. Which of the following is likely to be seen?

a) Plasmacytosis

b) Dry tap

c) Fibrosis

d) Granulomatous reaction

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Question 11:

In lardaceous spleen, deposition of amyloid occurs in which of the following sites?

a) Sinusoids of red pulp

b) White pulp

c) Splenic follicles

d) Splenic capsule

Question 12:

Match the following.

a) 1-b, 2-c, 3-a, 4-d

b) 1-a, 2-d, 3-b, 4-c

c) 1-c, 2-a, 3-d, 4-b

d) 1-d, 2-b, 3-c, 4-a

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Question 13:

In a patient with suspected systemic amyloidosis, which of the following is the initial investigation of choice?

a) Kidney biopsy

b) Abdominal fat staining

c) Bone marrow aspiration

d) Rectal biopsy

Question 14:

A kidney biopsy sample is obtained from a patient with high suspicion of amyloidosis. All of the following can be used to stain this sample, except:

a) Thioflavin

b) Crystal violet

c) Iodine

d) Sudan black

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Question 15:

A pathologist is examining a sample from a patient with amyloidosis. Which of the following is false about the specimen's appearance?

a) Pink-red color on Congo-red staining

b) Rose pink appearance under crystal violet stain

c) Apple-green birefringence under light microscopy

d) Mahogany brown color on iodine staining

Question 16:

Which of the following is not directly involved in graft rejection?

a) T-Cells

b) Antibodies

c) Macrophages

d) NK cells

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Question 17:

A man is receiving a matched blood group kidney allograft. While closing the abdomen, the surgeon notices a sudden color change to pale-white in the transplanted kidney. He decides to remove it. Which of the following is responsible for graft rejection in this patient?

a) Preformed antibodies in the recipient

b) Cytotoxic T lymphocyte–mediated injury

c) Tubulointerstitial inflammation due to antibodies

d) Donor antibodies causing endotheliitis

Question 18:

A patient underwent kidney transplantation due to severe diabetic nephropathy. A few months later, he presented with fever, malaise, and flank pain. During evaluation, oliguria and an acute rise in creatinine levels were observed. A biopsy of the kidney showed endotheliitis. What is the likely diagnosis?

a) Acute cell-mediated graft rejection

b) Acute antibody mediated graft rejection

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c) Chronic graft rejection

d) Graft vs host disease

Question 19:

In patients with acute graft-versus-host disease, which of the following organs is least likely to be involved?

a) Skin

b) GIT

c) Liver

d) Lung

Question 20:

Graft from identical twin is called:

a) Allograft

b) Autograft

c) Isograft

d) Xenograft

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Answer Key

Question No.	Correct Option
1	c
2	c
3	a
4	b
5	b
6	b
7	c
8	a
9	b
10	a

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11	a
12	c
13	b
14	d
15	c
16	c
17	a
18	a
19	d
20	c

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Detailed Explanations

Solution to Question 1:

Amyloid can be best described as a proteoglycan.

Amyloidosis refers to the extracellular deposition of fibrillar proteins.

Abnormal fibrils are produced by the aggregation of misfolded proteins. The fibrillar deposits bind a wide variety of proteoglycans and glycosaminoglycans (heparan sulfate and dermatan sulfate), and plasma proteins (serum amyloid P component).

The abundant charged sugar groups in these adsorbed proteins give the deposits staining characteristics that resemble starch (amylose). Therefore, these deposits are called amyloid.

Amyloid appears as an amorphous, eosinophilic, hyaline, extracellular substance.

Solution to Question 2:

There is the deposition of AA proteins in reactive systemic amyloidosis (secondary amyloidosis).

In inflammatory states, there is a release of IL-1 and IL-6, which act on the liver cells. The liver increases the production of SAA (serum amyloid-associated) proteins which circulate bound to high-density lipoproteins. This gives rise to AA proteins, which get deposited in tissues causing reactive systemic amyloidosis or secondary amyloidosis.

The most common sites are the kidney and heart.

It is usually seen secondary to:

• Rheumatoid arthritis (most common)

• Tuberculosis

• Bronchiectasis

• Chronic osteomyelitis

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• Inflammatory bowel disease

• Ankylosing spondylitis

• Malignancies - renal cell cancer, Hodgkin's lymphoma

Solution to Question 3:

The most common cause of reactive amyloidosis worldwide is rheumatoid arthritis.

Amyloidosis is reported to occur in 3% of patients with rheumatoid arthritis and is clinically significant in one-half of those affected.

Conditions associated with reactive systemic (secondary) amyloidosis:

• Rheumatoid arthritis (most common)

• Ankylosing spondylitis

• Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

• Tuberculosis

• Bronchiectasis

• Chronic osteomyelitis

• Malignancies - renal cell cancer, Hodgkin's lymphoma

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Solution to Question 4:

The given clinical scenario is suggestive of Alzheimer's disease. A° amyloid deposition is seen in this condition.

A° constitutes the core of cerebral plaques found in Alzheimer's disease. It also gets deposited in the walls of cerebral blood vessels. The A° protein is derived by proteolysis from a much larger transmembrane glycoprotein, called amyloid precursor protein (APP).

Solution to Question 5:

Patients on long-term hemodialysis for renal failure can develop amyloidosis as a result of the deposition of ° 2-microglobulin.

This protein is present in high concentrations in the serum of persons with renal disease. The protein is retained in the circulation because it cannot be filtered through the dialysis membranes.

It gets deposited in the synovium, joints, and tendon sheaths. When this deposition takes place in the carpal ligament of the wrist, it leads to the development of carpal tunnel syndrome.

With new dialysis filters, the incidence of this complication has decreased substantially.

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Solution to Question 6:

Familial amyloidotic polyneuropathy (FAP) is associated with the deposition of mutant transthyretin protein (TTR).

FAP is an autosomal dominant condition. The deposition occurs as amyloid fibrils in peripheral and autonomic nerves. Mutated TTR is prone to misfolding and aggregation, and shows resistance to proteolysis.

Systemic senile amyloidosis (amyloid of aging) refers to the systemic deposition of normal TTR amyloid in elderly patients. Symptomatic patients present with restrictive cardiomyopathy and arrhythmias. Another rare form affecting predominantly the heart results from the deposition of a mutant form of TTR.

Familial Mediterranean fever (FMF) is an autosomal-recessive condition seen in individuals of Mediterranean descent (Armenian, Sephardic Jewish, and Arabic). The affected gene encodes a protein called pyrin, which is involved in cytokine production. The amyloid fibril proteins in this condition are made up of AA proteins. It presents with attacks of fever and serositis.

Isolated atrial amyloidosis is associated with AANP (atrial natriuretic peptide) amyloid deposition

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Solution to Question 7:

Older individuals with insulin resistance are likely to have type 2 diabetes mellitus. These patients are at increased risk of developing amyloidosis.

Microscopic deposits of localized amyloid may be found in certain conditions such as:

- Medullary carcinoma of the thyroid gland
- Islet tumors of the pancreas
- Pheochromocytomas
- Undifferentiated carcinomas of the stomach
- Islets of Langerhans in individuals with type 2 diabetes mellitus

Solution to Question 8:

The slide is showing the presence of amyloid-rich stroma (pinkish material) and nests of polygonal cells, suggestive of medullary carcinoma thyroid. The major fibril protein that gets deposited is A Cal, which is derived from calcitonin.

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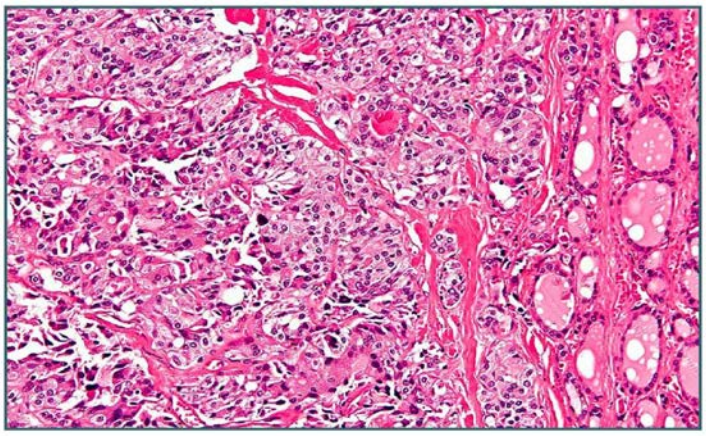
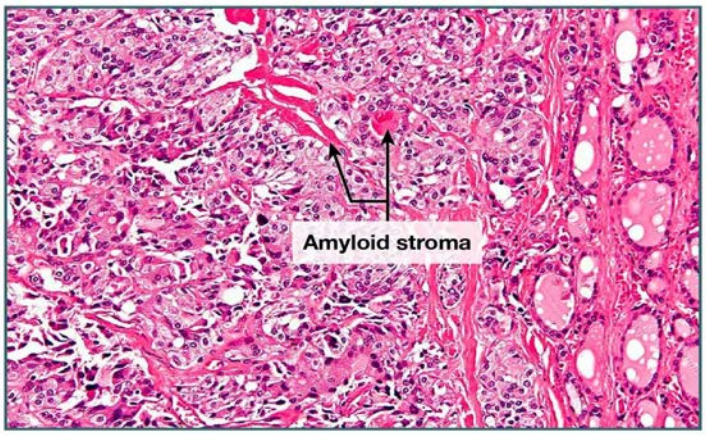
Medullary Carcinoma of Thyroid



Medullary Carcinoma of Thyroid



Microscopic deposits of localized amyloid may be found in certain conditions such as:

- Medullary carcinoma of the thyroid gland
- Islet tumors of the pancreas
- Pheochromocytomas
- Undifferentiated carcinomas of the stomach
- Islets of Langerhans in individuals with type 2 diabetes mellitus

Solution to Question 9:

The most common organ involved in AL amyloidosis is renal tissue (Kidneys). They are affected in 70–80% of patients with amyloidosis.

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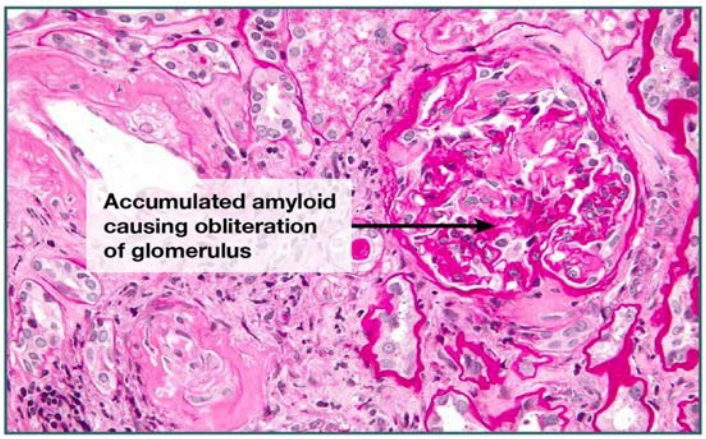
Heart is the second most commonly affected organ (50–60%), and cardiac involvement is the leading cause of death from AL amyloidosis.

Renal amyloidosis usually manifests as proteinuria, often in the nephrotic range, and is associated with hypoalbuminemia, secondary hypercholesterolemia, hypertriglyceridemia, and edema or anasarca.

Amyloid deposition in kidney



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Solution to Question 10:

Bone marrow examination in AL amyloidosis shows plasmacytosis.

The AL type of amyloid or primary amyloidosis is associated with immunocyte dyscrasias like multiple myeloma or other B cell neoplasms. The tumor cells in multiple myeloma secrete light chains of the immunoglobulins of either the lambda or kappa type, which get deposited in the tissues as amyloid.

The chemical nature of the amyloid is AL (A for amyloid and L for light chain).

Solution to Question 11:

Lardaceous spleen is due to the deposition of amyloid in sinusoids of the red pulp.

Sago spleen is due to the deposition of amyloid in splenic follicles (white pulp).

Solution to Question 12:

The correct match is:

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Condition	Amyloid protein
Familial Mediterranean fever	AA
Alzheimer's disease	A°
Systemic senile amyloidosis	ATTR
Hemodialysis-associated amyloidosis	A° 2m

Solution to Question 13:

In suspected systemic amyloidosis, the initial investigation of choice is abdominal fat aspirate staining.

Diagnosis of amyloidosis involves the following:

• Localized amyloidosis - biopsy the organ involved. e.g., kidney

• Systemic amyloidosis - deposits can be found in any tissue of the body

• Initial test - non-invasive test on easily accessible tissue (eg: abdominal fat) which is positive in >80% of cases

• If this is negative - more invasive biopsies of the kidney, heart, lung or GI tract (rectal biopsy)

• Suspected AL amyloidosis - serum and urine electrophoresis and immunoelectrophoresis

The histological examination of the biopsy material is the commonest confirmatory method for the diagnosis in a suspected case of amyloidosis. The next best step is to determine the type of precursor protein by immunohistochemistry, immunoelectron microscopy, or extraction and biochemical analysis employing mass spectrometry.

Scintigraphy with radiolabeled serum amyloid P component is a rapid and specific test, which gives the extent of the disease. It can be used to follow up on patients undergoing treatment.

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Solution to Question 14:

Sudan Black is used for staining lipids, not amyloid.

Staining for amyloid:

• Congo red - most widely used and specific

• Iodine staining -

• Used for unfixed specimens or histological sections

• Amyloid stains mahogany brown and turns violet on adding sulfuric acid

• Thioflavin T and S -

• Secondary immunofluorescence with ultraviolet light

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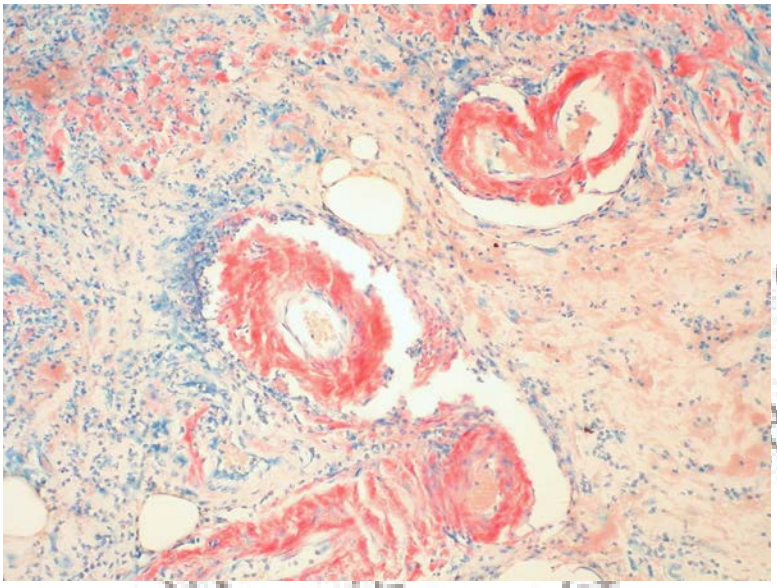
• Thioflavin T is useful for demonstrating the juxtaglomerular apparatus of the kidney

• Metachromatic stains (crystal violet and methyl violet) - rose-pink appearance.

• Periodic-acid Schiff (PAS) positive

The image given below shows the amyloid appearance on congo red under plain microscopy.



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Solution to Question 15:

Amyloid shows apple-green birefringence under polarised microscopy, after staining with Congo red.

The appearance of amyloid:

• Light microscopy - amorphous, eosinophilic, hyaline, extracellular substance

• Congo red stain - the characteristic appearance using this stain is due to the cross-° -pleated sheet conformation

• Under ordinary light, it appears pink or red color (as shown below)

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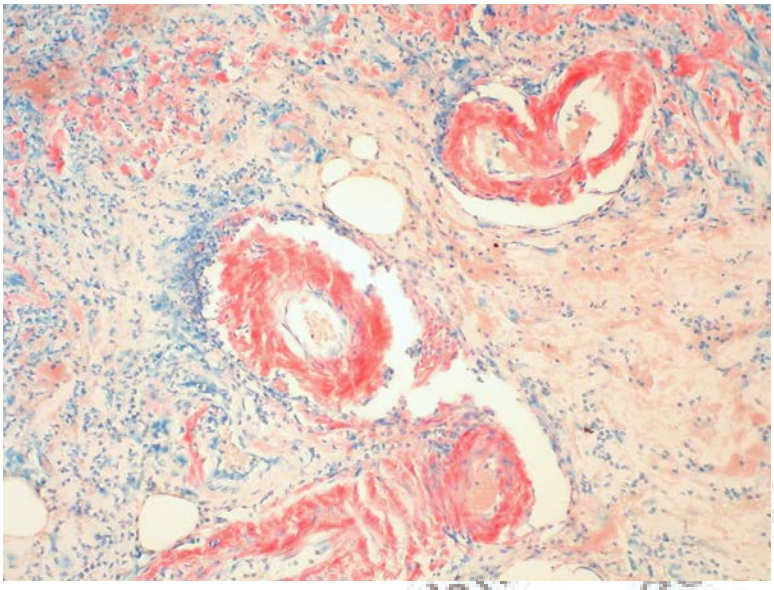
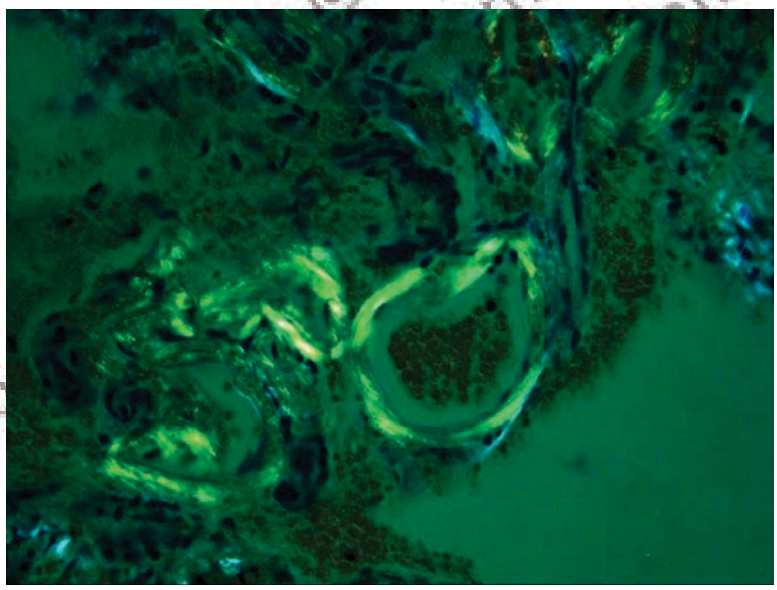


- Under the polarizing microscope - imparts apple-green birefringence to amyloid deposits (as shown in the image below)



• Electron microscopy - continuous, nonbranching fibrils with a diameter of approximately 7.5 to 10 nm

• X-ray crystallography and infrared spectroscopy - Characteristic cross-° -pleated sheet conformation.

It appears mahogany brown on iodine staining and rose-pink on staining with crystal violet.

Solution to Question 16:

Macrophages present foreign graft antigens to the T-cells but are not directly involved in graft rejection.

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Graft rejection is both humoral and cell-mediated in nature. It is a process in which T-cells and antibodies produced against graft antigens react against tissue grafts and destroy it.

The major antigenic differences that result in the rejection of transplants are differences in HLA alleles. The recipient T-cells are involved in the recognition of the donor MHC molecules and mount an immune response. Depending on the antigen-presenting cells (APCs) that are involved in T-cell activation, there are 2 pathways:

• Direct pathway of allorecognition - MHC antigens are presented by the APCs in the graft

• Indirect pathway of allorecognition - MHC antigens are presented by the recipient's own APCs (e.g., macrophages)

The early activation of NK cells kill allogeneic target cells directly or via antibody-dependent cellular cytotoxicity and release various chemokines and immunomodulatory cytokines.

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Solution to Question 17:

The given clinical scenario within minutes of transplant is suggestive of hyperacute rejection and is due to preformed antibodies from the recipient.

Solution to Question 18:

The given clinical history and the biopsy findings of endotheliitis suggest a diagnosis of acute cell-mediated graft rejection.

In acute cell-mediated graft rejection, CD8+ CTLs directly destroy graft cells or CD4+ cells secrete cytokines that damage the graft.

On histopathology, it produces two different patterns of injury in the graft:

• Tubulointerstitial pattern (type I): extensive interstitial and tubular inflammation associated with focal tubular injury

• Vascular pattern - Inflammation (type II) and necrosis (type III), endotheliitis (swollen endothelial cells with lymphocytes between endothelium and vessel wall)

Immunosuppressive therapy aims to prevent and reduce acute rejection by blocking the activation of alloreactive T cells. In the absence of humoral rejection, patients respond well to immunosuppressive therapy.

Solution to Question 19:

The lung is least likely to get affected in acute graft-versus-host disease (GVHD).

GVHD occurs when immunologically competent cells or their precursors are transplanted into immunologically crippled recipients. The transferred cells recognize alloantigens in the host and attack host tissues.

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It is seen most commonly in the setting of hematopoietic stem cell (HSC) transplantation. Rarely, it may occur following transplantation of solid organs rich in lymphoid cells (e.g., the liver) or transfusion of unirradiated blood.

It is of two types, acute and chronic.

Acute GVHD develops within days to weeks. There is the involvement of the immune system and epithelium of the skin, liver, and intestines. It presents with:

• Generalized rash

• Jaundice

• Bloody diarrhea due to mucosal ulceration

• Non-infectious pulmonary infiltrates (rarely), the outcome is generally poor

Chronic GVHD may follow the acute syndrome or occur insidiously. It presents with:

• Skin - extensive cutaneous injury, with the destruction of skin appendages and dermal fibrosis (may resemble systemic sclerosis)

• Liver - chronic liver disease, manifested as cholestatic jaundice

• GIT - esophageal strictures

• Immune system involvement - involution of the thymus and depletion of lymphocytes

GVHD is mediated by T lymphocytes contained in the transplanted donor cells. Therefore, depletion of donor T cells before transfusion virtually eliminates the disease.

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Solution to Question 20:

A graft from an identical twin is called an isograft.

Isograft is defined as an organ or tissue that is taken from a donor and is transplanted to a recipient who has the same genetic constitution as the donor. For example, graft between identical twins.

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Microcytic Anemia

Question 1:

Which is the most common type of anemia worldwide?

a) Aplastic anemia

b) Megaloblastic anemia

c) Iron deficiency anemia

d) Anemia of chronic diseases

Question 2:

What is the most common hematologic manifestation seen in patients with HIV infection?

a) Thrombocytopenia

b) Neutropenia

c) Lymphocytosis

d) Anemia

Question 3:

Which of the following anemia is not due to diminished erythropoiesis?

a) Iron deficiency anemia

b) Hereditary spherocytosis

c) Megaloblastic anemia

d) Aplastic anemia

Question 4:

In a patient with MCV of 109 fl, which of the following is least likely?

a) Hypothyroidism

b) Thiamine deficiency

c) Orotic aciduria

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d) Anemia of chronic disease

Question 5:

A 30-year-old woman with iron deficiency anaemia is prescribed oral iron supplements. Foods containing which of the following can she take to increase its absorption?

a) Phosphate

b) Oxalate

c) Carbonate

d) Ascorbate

Question 6:

Which of the following contains most of the functional iron in the body?

a) Hemoglobin

b) Myoglobin

c) Transferrin

d) Ferritin

Question 7:

Which transporter is required for the transport of iron into the enterocyte?

a) Ferroportin

b) Divalent metal transporter 1

c) Divalent metal transporter 2

d) Haptocorrin

Question 8:

Which of the following is involved in iron metabolism?

a) Haptocorrin

b) Cubulin

c) Selenoprotein

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d) Ceruloplasmin

Question 9:

Hepcidin inhibits iron transfer from the enterocyte to the plasma by binding to _____

a) Transferrin

b) Ferroportin

c) Ferritin

d) Divalent metal transporter 1

Question 10:

What is the main site of iron absorption?

a) Duodenum

b) Stomach

c) Jejunum

d) Ileum

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Question 11:

Which of the following is true regarding the internal iron homeostasis in iron-deficiency anaemia?

a) Ferritin mRNA concentration iron-responsive element increases and ferritin synthesis decreases

b) Transferrin receptor 1 iron-responsive elements increases transferrin receptor mRNA concentration and synthesis

c) Transferrin receptor 1 iron responsive elements decreases transferrin receptor mRNA concentration and synthesis

d) Ferritin mRNA concentration iron responsive element decreases and ferritin synthesis increases

Question 12:

Peripheral smear of a patient with koilonychia is given below. Which of the following lab findings is consistent with her likely diagnosis?

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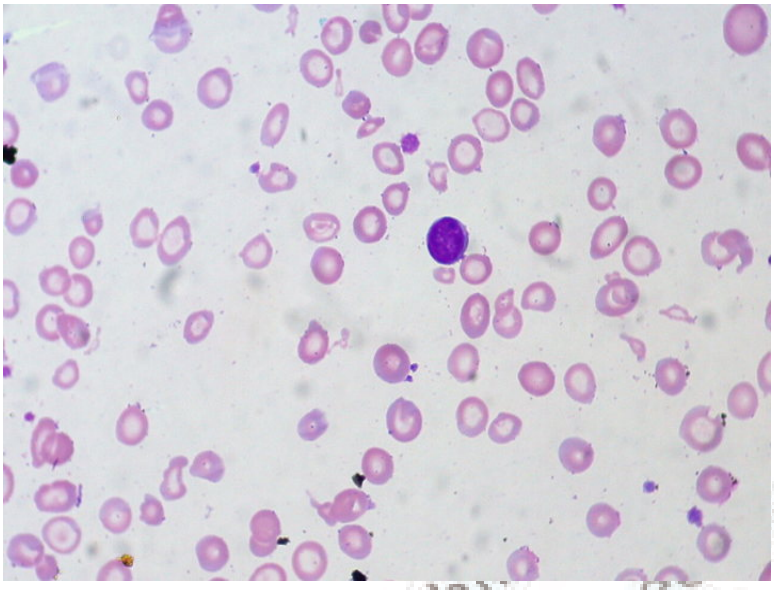

a) Option 1

b) Option 2

c) Option 3

d) Option 4

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Question 13:

You would expect iron-deficiency anaemia in all of the following patients except:

a) A 5-year-old boy with hookworm infestation

b) A 60-year-old man with carcinoma cecum

c) A 54-year-old woman after Billroth II operation

d) A 25-year-old woman with maize-rich diet

Question 14:

Which of the following laboratory findings is seen in a patient with sideroblastic anaemia?

a) Increased total iron binding capacity

b) Increased transferrin saturation

c) Decreased serum ferritin

d) Low serum iron

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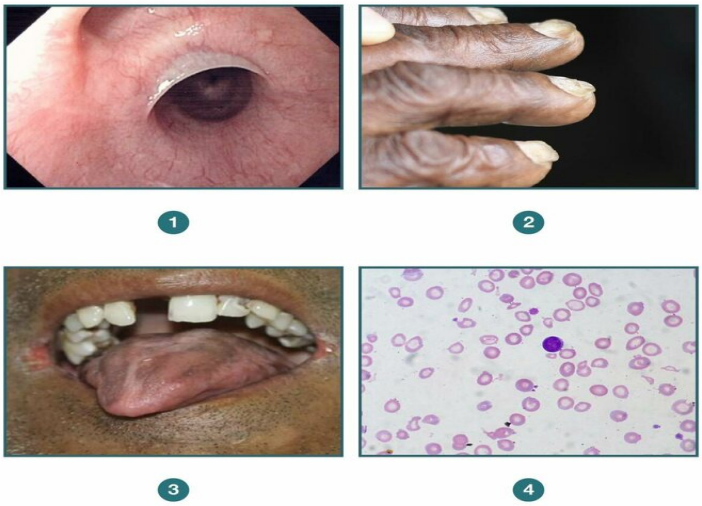
Question 15:

Which of the following is not included in the triad of the Plummer-Vinson syndrome?



a) 1

b) 2

c) 3

d) 4

Question 16:

A 34-year-old woman with severe anaemia was started on parenteral iron. Which of the following would occur first in this patient as a response to therapy?

a) Increase in serum iron level

b) Increase in serum ferritin level

c) Increase in MCV

d) Increase in reticulocyte count

Answer Key

Question No.	Correct Option
1	c

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2	d
3	b
4	d
5	d
6	a
7	b
8	d
9	b
10	a
11	b
12	c
13	d
14	b
15	b
16	a

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Detailed Explanations

Solution to Question 1:

The most common type of anaemia worldwide is iron deficiency anemia. It is also the most common type of nutritional anemia in India.

WHO recommendations for diagnosing anemia (g/dl) are:

Population	Normal	Mild Anemia	Moderate Anemia	Severe Anemia
Men ≥15 years	≥13	11 - 12.9	8 - 10.9	<8
Non-pregnant women	≥12	11 - 11.9	8 - 10.9	<8
Pregnant women	≥11	10 - 10.9	7 - 9.9	<7

Solution to Question 2:

Anaemia is the most common hematologic abnormality associated with HIV infection. It affects 60–80% of patients during the late stage.

In most cases, the cause of anaemia in HIV-infected patients is multifactorial. It is often associated with infection, inflammation, malignancy, malnutrition, and polypharmacy.

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Note: Prior to the use of potent antiretroviral therapy (ART), thrombocytopenia was a common finding in individuals infected with HIV. With use of potent ART, the incidence of thrombocytopenia is far lower.

Solution to Question 3:

Hereditary spherocytosis is not due to diminished erythropoiesis. It is a type of hemolytic anemia.

Classification of anemia according to underlying mechanism:

• Anemias of diminished erythropoiesis - decreased red cell production

• Hemolytic anemias - increased red cell destruction

• Anemia due to blood loss

Anemias due to diminished erythropoiesis:

• Iron deficiency anemia

• Megaloblastic anemia

• Anemia of chronic diseases

• Aplastic anemia

• Myelophthisic anemia

• Fanconi's anemia

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Solution to Question 4:

MCV >100 fl indicates macrocytic anaemia which is not seen in anaemia of chronic disease. RBCs in anemia of chronic disease are initially normocytic and normochromic, becoming microcytic and hypochromic over time.

Vitamin B12 deficiency, thiamine deficiency, and orotic aciduria cause macrocytic anaemia.

Solution to Question 5:

Absorption of iron is increased by ascorbic acid. It is decreased by phosphates, oxalates, and carbonates.

Solution to Question 6:

Most of the functional iron (80%) in the body is found in hemoglobin.

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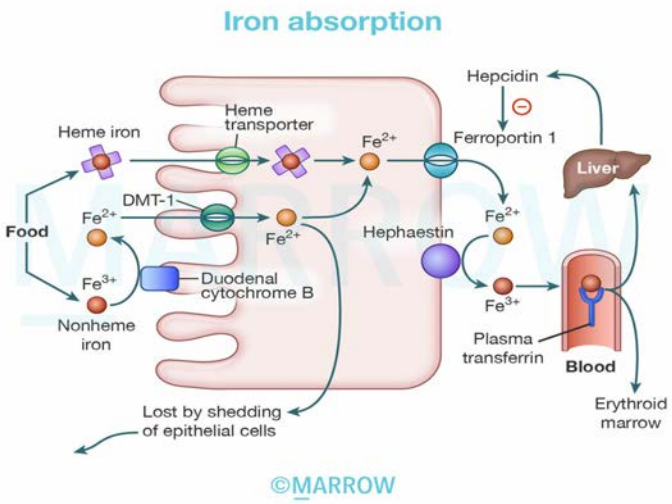
The storage pool represented by hemosiderin, and ferritin contains about 15% to 20% of total body iron. Myoglobin and iron-containing enzymes such as catalase and the cytochromes contain the rest.

Solution to Question 7:

DMT1 (divalent metal transporter 1) is required for the transport of iron into the enterocyte.

Dietary iron is mostly in Fe3+ (ferric state) and must be reduced to Fe2+ (ferrous state) by ferrireductases. Fe2+ iron destined for circulation is transported from the cytoplasm across the basolateral enterocyte membrane by ferroportin 1.

Hephaestin is an iron oxidase that converts Fe2+ to Fe3+



Solution to Question 8:

Ceruloplasmin is involved in iron metabolism.

Ferritin is the storage form of iron in the body. Ceruloplasmin and hephaestin help in oxidation of Fe2+ to Fe3+ at the basolateral border of enterocytes. This is coupled with transport through ferroportin. In plasma, iron is transported by transferrin.

Haptocorrin and cubulin are involved in vitamin B12 absorption. Selenoprotein is involved in selenium metabolism.

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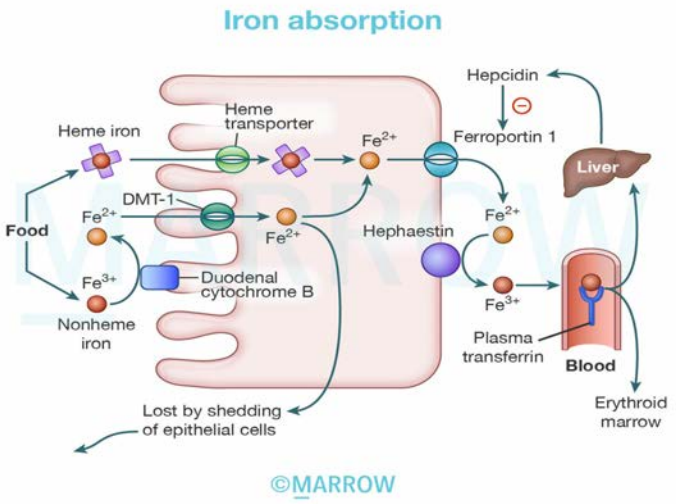

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Solution to Question 9:

Hepcidin inhibits iron transfer from the enterocytes into the plasma by binding to ferroportin, which is an iron efflux channel in the enterocyte.

Iron metabolism is regulated by hepcidin, a protein and acute phase reactant produced by the liver. It binds to ferroportin and degrades it. This inhibits the transfer of iron from the enterocyte to the plasma via ferroportin. As a result, iron becomes trapped within the duodenal cells (enterocytes) in the form of mucosal ferritin and is lost in feces when these cells are shed off.

Transcription of hepcidin is increased by the following factors:

• Increased levels of iron

• Inflammatory cytokines

Transcription of hepcidin is decreased by the following factors:

• Iron deficiency

• Hypoxia

• Ineffective erythropoiesis

Hepcidin is encoded by the HAMP gene and its mutations are associated with hereditary hemochromatosis.

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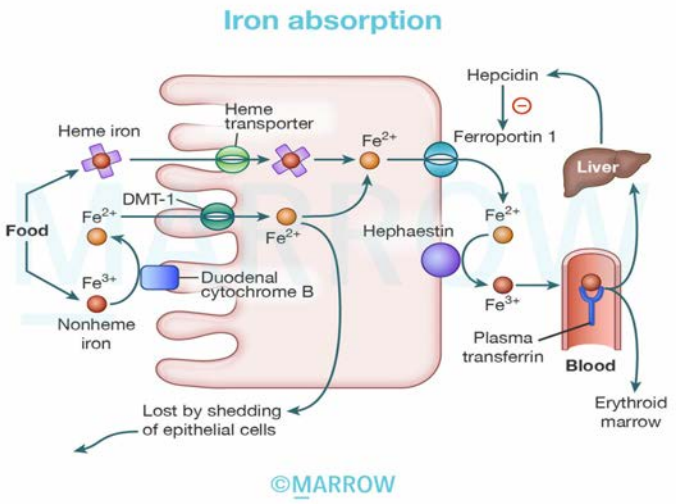

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Solution to Question 10:

Absorption of iron mainly occurs in the proximal duodenum.

Solution to Question 11:

In iron deficiency anaemia, there is an increase in transferrin receptor mRNA concentration and synthesis.

Iron absorbed through diet or which is released from circulation is bound to transferrin (iron transfer protein). When erythropoiesis is stimulated, iron-transferrin complexes act as transferrin receptors on the surface of bone marrow erythroid cells. Through receptor-mediated endocytosis, this complex is internalised.

This iron is then made available for heme synthesis while the transferrin-receptor complex is recycled to the surface of the cell, from where the transferrin is released back into circulation and the transferrin receptor re-anchors into the cell membrane. The excess iron after hemoglobin synthesis binds to apoferritin (storage protein), forming ferritin.

Senescent RBCs undergo phagocytosis in the cells of the reticuloendothelial system. The hemoglobin is broken down, the globin and other proteins are returned to the amino acid pool, and the iron is shuttled back to the surface of the reticuloendothelial cell, where it is taken up by transferrin via ferroportin (iron export channel).

There is no regulated excretory pathway for iron, and the only mechanisms by which iron is lost are blood loss (via gastrointestinal bleeding, menstruation, or other forms of bleeding) and the loss of epithelial cells from the skin, gut, and genitourinary tract. The normal daily iron loss from the body is 1-2 mg.

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Variables	Iron-deficient state	Iron-excess state
Iron uptake	↑	↓
Transferrin receptor synthesis	↑	↓
Transferrin receptor mRNA concentration	↑	↓
Iron storage	↓	↑
Ferritin synthesis	↓	↑
Ferritin mRNA concentration	No change	No change

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Solution to Question 12:

The given peripheral smear showing microcytic and hypochromic picture with pencil cells is suggestive of iron-deficiency anaemia. In this condition, TIBC is increased, transferrin saturation is decreased, and ferritin is decreased.

Solution to Question 13:

Maize rich diet is not one of the causes of iron deficiency anaemia. It can cause pellagra.

Iron deficiency anaemia can be caused by hookworm infestation, carcinoma of the cecum and in Billroth II operation.

Solution to Question 14:

In sideroblastic anemia, the transferrin saturation is increased.

Serum iron and serum ferritin are also elevated.

Solution to Question 15:

The triad of the Plummer-Vinson syndrome does not include koilonychia (marked as 2).

Triad of Plummer–Vinson syndrome:

- Esophageal webs
- Microcytic hypochromic anaemia
- Atrophic glossitis

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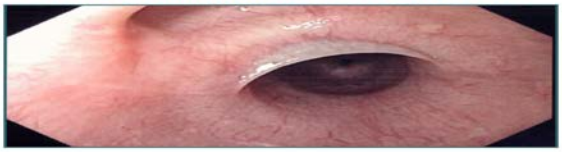
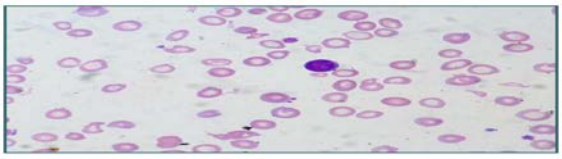
Triad of Plummer Vinson Syndrome



Esophageal web

Glossitis



Microcytic hypochromic anaemia

Koilonychia is a symptom of iron deficiency anaemia. It may or may not be present in Plummer Vinson syndrome. Hence, it is not a part of the triad.

Koilonychia

Solution to Question 16:

One of the earliest responses to the correction of iron deficiency anaemia is increase in serum iron.

Responses after initiation of treatment:

• 12 to 24 hours - Replenishment of intracellular iron enzymes; decreased irritability; increased appetite; increase in serum iron.

• 36 to 48 hours - Erythroid hyperplasia in bone marrow

• 48 to 72 hours - Reticulocytosis, peaking at 5-7 days

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• 4 to 30 days - Increase in hemoglobin level, increase in ferritin, increase in MCV

• 1 to 3 months - Repletion of stores

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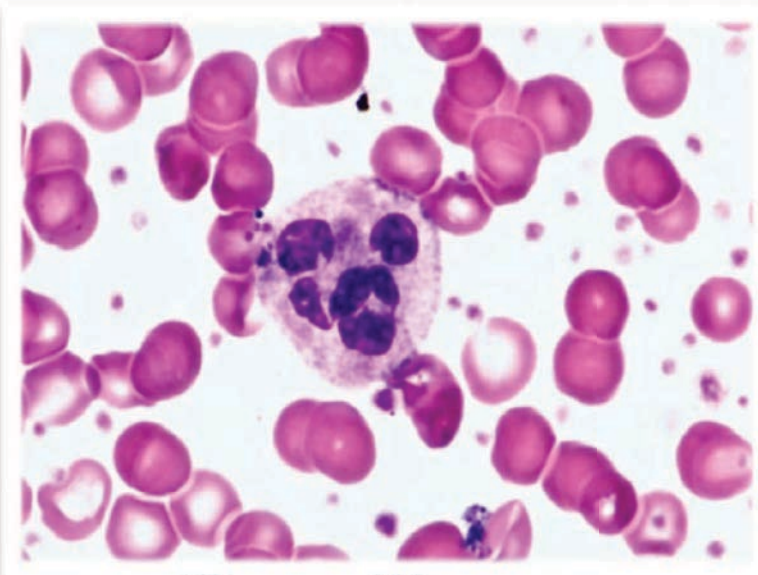
Normocytic And Macrocytic Anemia

Question 1:

A 30-year-old woman who is taking OCPs presents with weakness and fatigue. Her laboratory investigations and peripheral smear are given below. What is the most likely diagnosis?



a) Megaloblastic anemia

b) Aplastic anemia

c) Paroxysmal nocturnal hemoglobinuria

d) Iron deficiency anaemia

Question 2:

A 40-year-old man with a history of bowel resection for Crohn's disease develops megaloblastic anaemia. Which component of the vitamin B12 metabolism is likely to be affected in this patient?

a) Cubilin

b) Haptocorrin

c) Transcobalamin

d) Intrinsic factor

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Question 3:

In which of the following patients would you not suspect megaloblastic anaemia caused by vitamin B12 deficiency?

a) A 5-year-old child with fish tapeworm infestation

b) A 45-year-old man who underwent gastrectomy

c) A 38-year-old man with ileitis

d) A 23-year-old woman on phenytoin therapy

Question 4:

A 20-year-old female with easy fatiguability and pallor presented to the OPD. The image of her hand is as given below. What is the most likely diagnosis?

a) Aplastic anemia

b) Vitamin B12 deficiency

c) Iron deficiency anemia

d) Hypoalbuminemia

Question 5:

What is your diagnosis with respect to the findings shown in the peripheral smear given below?

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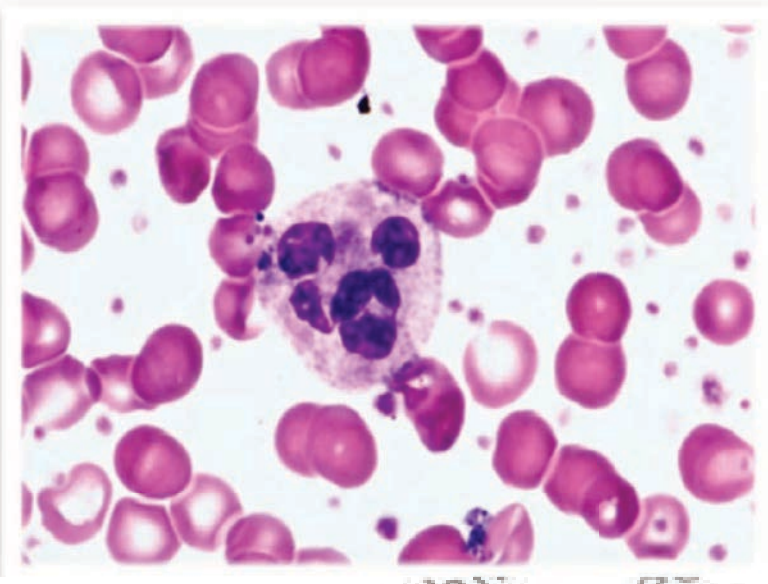

a) Iron deficiency anemia

b) B12 deficiency

c) Hereditary spherocytosis

d) Acute myeloid leukemia

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Question 6:

Which of the following findings would you not expect to see in patients with megaloblastic anaemia?

a) Increased reticulocyte count

b) Raised bilirubin

c) Mild splenomegaly

d) Nucleated RBC progenitors

Question 7:

A patient is suspected to have megaloblastic anaemia. Which of the following will not be helpful in differentiating vitamin B12 deficiency from folate deficiency?

a) Increased serum homocysteine levels

b) Increased methylmalonate levels

c) Neurological changes

d) Increased LDH levels

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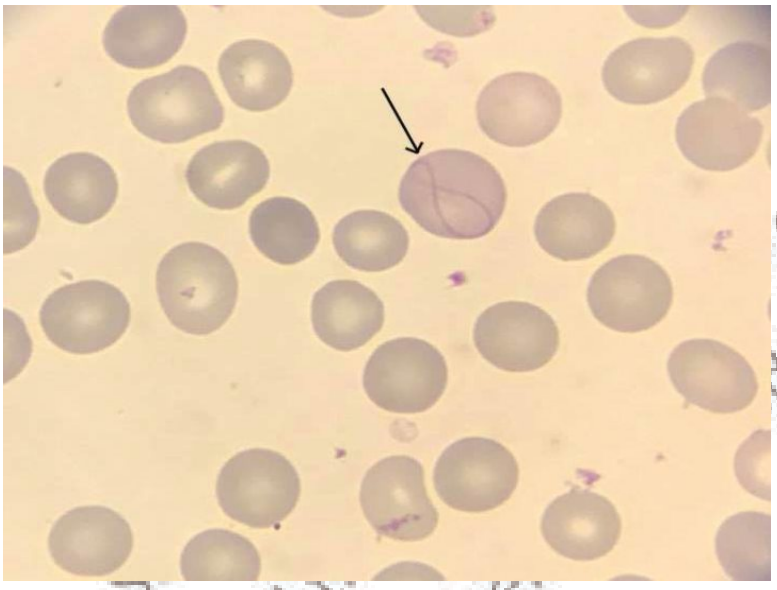
Question 8:

You are examining the peripheral smear of a patient with anaemia and see the following finding. Name the finding and its pathogenesis.



a) Heinz body - oxidative damage

b) Basophilic stippling - ribosomal precipitation

c) Cabot's rings - ineffective erythropoiesis

d) Howell Jolly body - ineffective RBC enucleation

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Question 9:

Schilling's test can be used for all the following except _____

a) To differentiate between vitamin B12 and folate deficiency

b) To identify the cause of vitamin B12 deficiency

c) To identify the extent of megaloblastic anaemia

d) To rule out pernicious anaemia

Question 10:

Which of the following statements is false regarding the antibodies of pernicious anaemia?

a) Type I antibodies are found in both plasma and gastric juice

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b) Type I antibody blocks the binding of vitamin B12 to intrinsic factor

c) Type II antibodies prevent the binding of the IF-B12 complex to ileal receptors

d) Type III antibodies are against haptocorrin

Question 11:

A 53-year-old woman presents with complaints of light-headedness every time she stands up. She is a known case of rheumatoid arthritis on methotrexate. On examination, she has pallor and brittle nails. Which of the following statements is true regarding her condition?

a) Serum iron and tissue iron levels are normal

b) Anemia can be normocytic and normochromic

c) Hepcidin levels are low

d) Total iron-binding capacity is high

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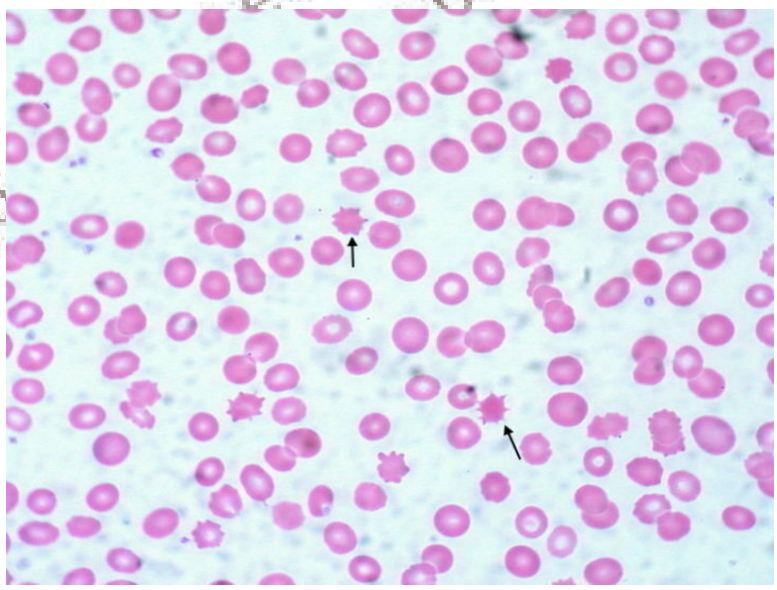
Question 12:

Identify the cell in the given peripheral blood smear and the likely diagnosis.



a) Acanthocyte in anemia of renal disease

b) Acanthocyte in anemia of liver disease

c) Echinocyte in anemia of renal disease

d) Echinocyte in anemia of liver disease

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Question 13:

Which of the following is the most common cause of aplastic anemia?

a) Drugs

b) Autoimmune

c) Infection

d) Radiation

Question 14:

A 35-year-old woman presents with progressive weakness and fatigue. Her hemogram is given below. What is the best investigation to arrive at the diagnosis?

a) Bone marrow aspiration

b) Bone marrow biopsy

c) Hb electrophoresis

d) Flow cytometry

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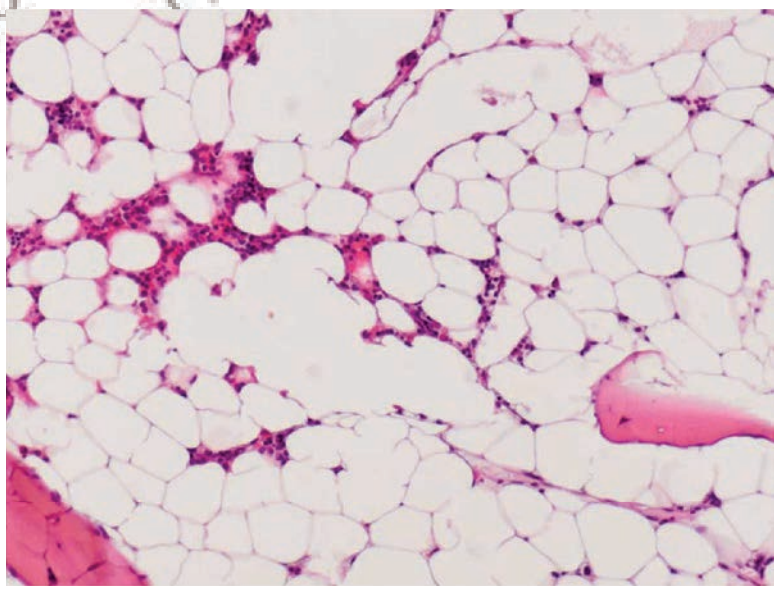
Question 15:

Bone marrow biopsy of a patient with pancytopenia is given below. What is the most common infectious cause of this condition?



a) Parvovirus B19

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b) Cytomegalovirus

c) Epstein-Barr virus

d) Hepatitis virus

Question 16:

Which of the following is likely to develop in a patient with aplastic anaemia?

a) 2, 3, 4

b) 1, 2

c) 1, 5

d) 1, 3, 5

Question 17:

Which of the following causes pure red cell aplasia?

a) 1, 2

b) 2, 3, 5

c) 1, 4

d) 1, 2, 4

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Question 18:

What is the most common cause of myelophthisic anaemia?

a) Granulomatous diseases

b) Metastatic cancer

c) Myeloproliferative neoplasms

d) Radiation

Question 19:

A 70-year-old man presents with progressive weakness and chronic fatigue. Physical examination reveals a hard nodule of about 1cm in the prostate. His lab reports reveal low Hb and elevated PSA. Peripheral blood smear shows a normocytic normochromic picture. There are some occasional myelocytes, a few tear-drop cells and 2 nucleated RBCs per 100 white

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cells. What is the most likely diagnosis?

a) Myelodysplastic syndrome

b) Myelophthisic anemia

c) Myelofibrosis

d) Myeloproliferative disorder

Question 20:

A 52-year-old male patient comes with complaints of abdominal pain, nausea, and vomiting. A peripheral blood smear reveals macrocytes and hypersegmented neutrophils and an endoscopy reveals atrophic gastritis. Which of the following conditions is likely to be seen this patient?

a) Vitamin B12 deficiency

b) Folate deficiency

c) Pyridoxine deficiency

d) Niacin deficiency

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Answer Key

Question No.	Correct Option
1	a
2	a
3	d
4	b
5	b
6	a
7	a
8	c
9	c
10	d
11	b
12	b
13	a
14	b

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15	d
16	c
17	d
18	b
19	b
20	a

Detailed Explanations

Solution to Question 1:

The given clinical scenario is suggestive of megaloblastic anaemia due to the following reasons:

- History of OCP use
- Hemogram shows decreased hemoglobin and increased MCV
- Peripheral smear shows anisopoikilocytosis, macroovalocytes, and hypersegmented neutrophils

Solution to Question 2:

Ileal resection for Crohn's disease can cause megaloblastic anaemia due to the decrease in cubilin receptors. They are the vitamin B12 receptors on the ileum.

Absorption of vitamin B12 involves the following steps:

- Pepsin in the stomach releases vitamin B12 from the binding proteins in the food
- Released B12 binds to haptocorrin, which is a salivary protein
- In the duodenum, pancreatic proteases release B12 from haptocorrin
- B12 binds to intrinsic factor to form IF-B12 complex
- In the ileum, ileal enterocytes that contain cubulin receptors (IF receptor) endocytose the complex
- In the ileal cells, B12 is associated with transcobalamin II, which is a carrier protein
- B12 is delivered to the liver, bone marrow and GIT

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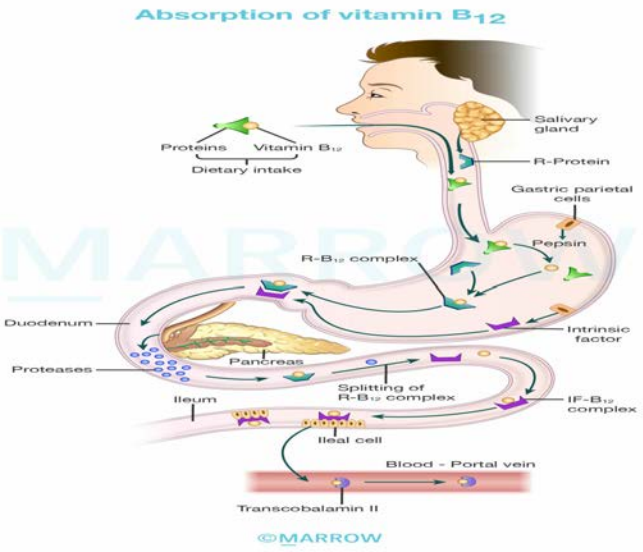

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Solution to Question 3:

Phenytoin therapy causes folate deficiency leading to megaloblastic anaemia. It does not cause vitamin B12 deficiency.

Dietary folate is in polyglutamate form, which is then converted into monoglutamates by the intestinal conjugase. Phenytoin acts by inhibiting this enzyme, thereby causing folate deficiency, and thus megaloblastic anaemia.

Options A, B and C: They cause megaloblastic anemia due to vitamin B12 deficiciency.

Solution to Question 4:

Skin hyperpigmentation especially on the dorsum of hands involving the knuckles is seen in cyanocobalamin or vitamin B12 deficiency which is a causative factor of megaloblastic anaemia.

In megaloblastic anaemia, there is impairment of DNA synthesis that leads to ineffective hematopoiesis. It also causes distinctive morphologic changes, including abnormally large erythroid precursors and red cells.

Clinical features of megaloblastic anaemia (cyanocobalamin and folate deficiency) include:

Peripheral smear findings:

• Macro-ovalocytes

• Most macrocytes lack the central pallor of normal red cells and even appear hyperchromic, but the MCHC is not elevated.

• Reticulocyte count is low

• Nucleated red cell progenitors occasionally appear in the circulating blood when anaemia is severe

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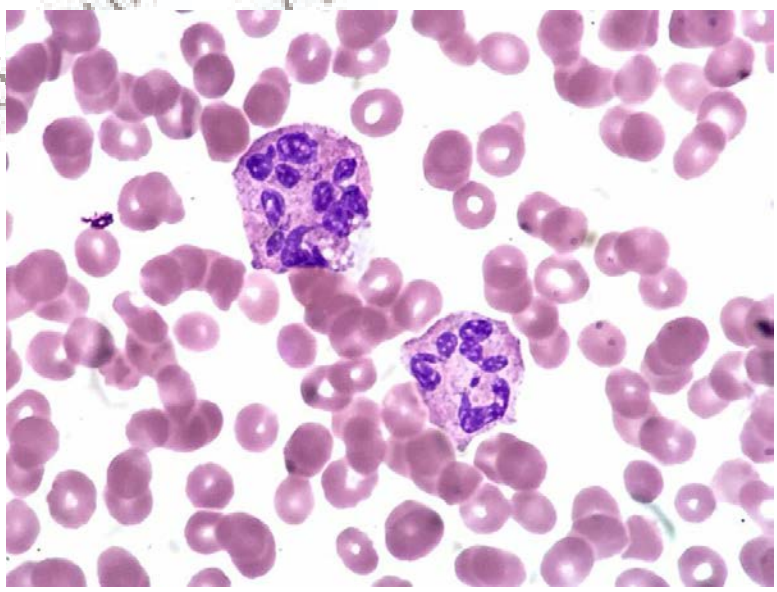
• Neutrophils are also larger than normal (macro polymorphonuclear) and show nuclear hypersegmentation, having five or more nuclear lobules

The image given below shows hypersegmented neutrophils seen in megaloblastic anaemia.

System	Clinical features
Oral	GlossitisAngular cheilosis
Gastrointestinal	AnorexiaWeight lossDiarrhea Constipation
Skin	Hyperpigmentation(reversible)
Hematological	ThrombocytopeniaLeucopeniaIneffective erythropoiesis and unconjugatedjaundice
Cardiovascular	Atherosclerosis leading to PVD, CAD (due to elevated homocysteine)
Neurological (only B12)	Peripheral neuropathySubacute combined degeneration (degeneration of the posterior and pyramidal tracts of the spinal cord)
Pregnancy (only folate)	Recurrent fetal lossNeural tube defects
Others	Mildfeverin severe casesPsychiatric disturbances



Bone marrow findings:

• Markedly hypercellular as a result of increased hematopoietic precursors.

• Sieve-like pattern of chromatin of immature precursors (Megaloblasts)

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• Granulocytic precursors also display dysmaturation in the form of giant metamyelocytes and band forms

• Megakaryocytes can be abnormally large and have bizarre, multilobate nuclei

• The derangement in DNA synthesis causes most precursors to undergo apoptosis in the marrow (ineffective hematopoiesis) and leads to pancytopenia

Solution to Question 5:

The peripheral smear showing macro-ovalocytes and a hypersegmented neutrophil are suggestive of megaloblastic anaemia. Vitamin B12 deficiency is a cause of megaloblastic anaemia.

Peripheral smear findings in megaloblastic anaemia:

• Macro-ovalocytes

• Most macrocytes lack the central pallor of normal red cells and even appear hyperchromic, but the MCHC is not elevated.

• Reticulocyte count is low

• Nucleated red cell progenitors occasionally appear in the circulating blood when anaemia is severe

• Neutrophils are also larger than normal (macro polymorphonuclear) and show nuclear hypersegmentation, having five or more nuclear lobules

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Solution to Question 6:

The reticulocyte count is decreased in megaloblastic anaemia.

The reticulocyte count is indicative of bone marrow function and its ability to produce healthy erythrocytes. In megaloblastic anemia, there is intramedullary hemolysis leading to raised indirect bilirubin and impaired erythroid maturation leading to a low reticulocyte count.

Solution to Question 7:

Increased serum homocysteine levels are common to both vitamin B12 deficiency and folate deficiency. Hence, it cannot be used to differentiate between them.

Solution to Question 8:

The marked structure in this peripheral smear showing figure of 8 appearance is a Cabot ring. They are RBC inclusion bodies seen in conditions due to ineffective erythropoiesis. It is considered a remnant of microtubules during cell division.

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Cabot rings can be seen in the following conditions:

• Megaloblastic anaemia

• Post-splenectomy patients

• Lead poisoning

• Hemolytic anemias

Option A: Heinz bodies are due to oxidative damage, seen in G6PD deficiency.

Option B: Basophilic stippling is due to ribosomal precipitation, seen in heavy metal poisoning, thalassemia and sickle cell disease.

Option D: Howell Jolly bodies are due to ineffective RBC enucleation, characteristic of asplenia.

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Solution to Question 9:

Schilling test cannot identify the extent of megaloblastic anaemia.

Solution to Question 10:

Type III antibodies are not against haptocorrin. They recognize the α and ° subunits of the gastric proton pumps.

Pernicious anaemia is a specific form of megaloblastic anaemia caused by autoimmune gastritis. It impairs the production of intrinsic factor, which is required for vitamin B12 uptake from the gut.

Types of antibodies in pernicious anaemia are:

• Type I antibodies - block the binding of vitamin B12 to intrinsic factor. They are found in both plasma and gastric juice

• Type II antibodies - prevent binding of the intrinsic factor-vitamin B12 (IF-B12) complex to its ileal receptor

• Type III antibodies - recognize the α and ° subunits of the gastric proton pump of parietal cells

Solution to Question 11:

The given clinical scenario is suggestive of anaemia of chronic diseases (ACD). In this condition, the anaemia initially can be normocytic normochromic.

ACD occurs in the setting of persistent systemic inflammation. It is associated with

• Low serum iron

• Reduced total iron-binding capacity

• Abundant stored iron in tissue macrophages

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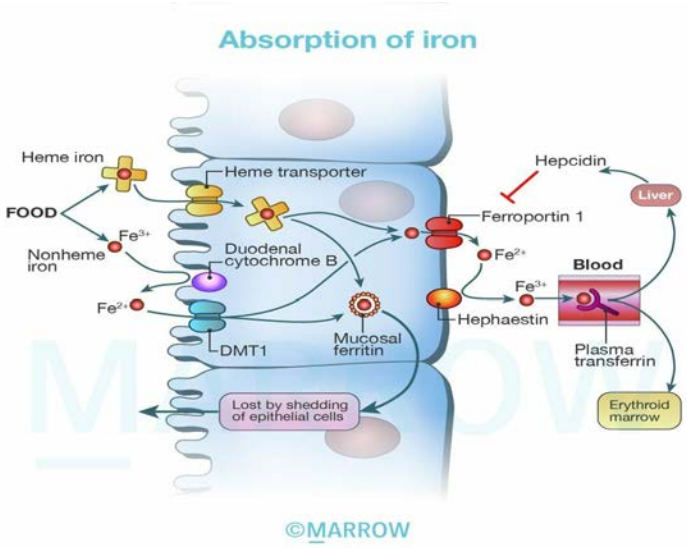
Inflammatory mediators like IL-6 stimulate an increase in the production of hepcidin. This inhibits ferroportin function in the macrophages and reduces the transfer of iron from the storage pool to developing erythroid precursors in the marrow. As a result, erythroid precursors are starved for iron despite the availability of plenty of iron in tissue macrophages.



Solution to Question 12:

Acanthocyte or spur cells are seen in anaemia of liver disease. These cells are characterized by only a few spicules of varying sizes that project from the cell surface at irregular intervals.

Conditions where acanthocytes can be seen include:

- Severe liver disease
- Abetalipoproteinemia
- Post splenectomy
- Hyposplenism

The image given below shows a peripheral smear with acanthoctye.

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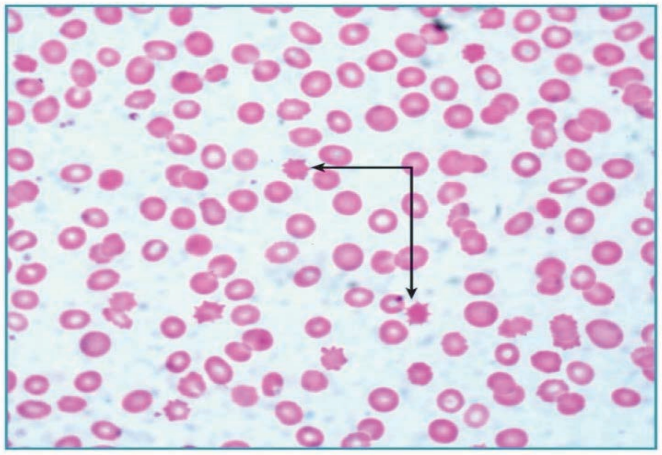
Acanthocytes



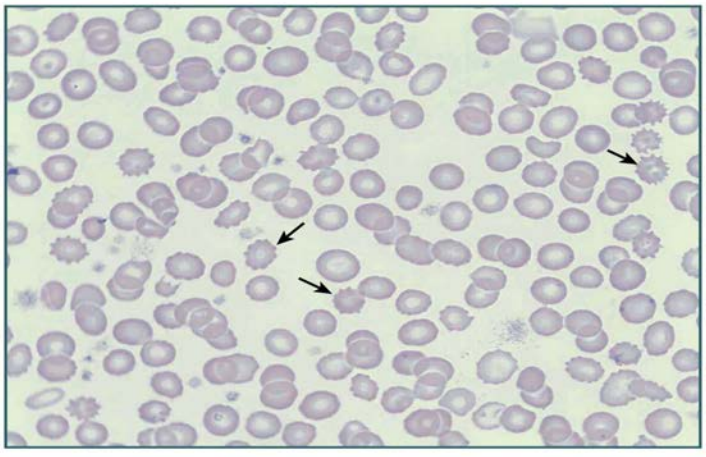
Echinocytes or burr cells are seen in anaemia of renal disease. These cells are characterized by smaller, regularly spaced projections, smoothly rounded crenulations which are uniform in shape and distribution compared to acanthocytes.

Conditions where echinocytes can be seen include:

- Anaemia of renal disease (uremia)
- In premature infants, after exchange transfusion
- Storage artefact

The image given below shows a peripheral smear with echinocytes.

Echinocyte



Solution to Question 13:

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From the given options, the most common cause of aplastic anemia is drugs.

Causes of aplastic anemia:

Acquired

• Idiopathic - most common cause (about 65% of the cases)

• Acquired stem-cell defects

• Immune-mediated

Chemical agents

• Dose-related

• Alkylating agents

• Antimetabolites

• Benzene

• Chloramphenicol

• Inorganic arsenals

• Idiosyncratic

• Chloramphenicol

• Phenylbutazone

• Organic arsenicals

• Carbamazepine

• Penicillamine

• Gold salts

Physical agents

• Whole-body irradiation

• Viral infections - Hepatitis, CMV, EBV, VZ

Inherited

• Fanconi anemia

• Telomerase defects

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Solution to Question 14:

The given hemogram is suggestive of pancytopenia. Cause of pancytopenia can be aplastic anaemia (hypocellular bone marrow) or myeloid neoplasms (hypercellular bone marrow). Hence, the best investigation is bone marrow biopsy to differentiate between them.

Findings in bone marrow biopsy in aplastic anaemia:

• Markedly hypocellular bone marrow largely devoid of hematopoietic cells

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• Abundant fat cells

• Fibrous stroma, scattered lymphocytes, and plasma cells

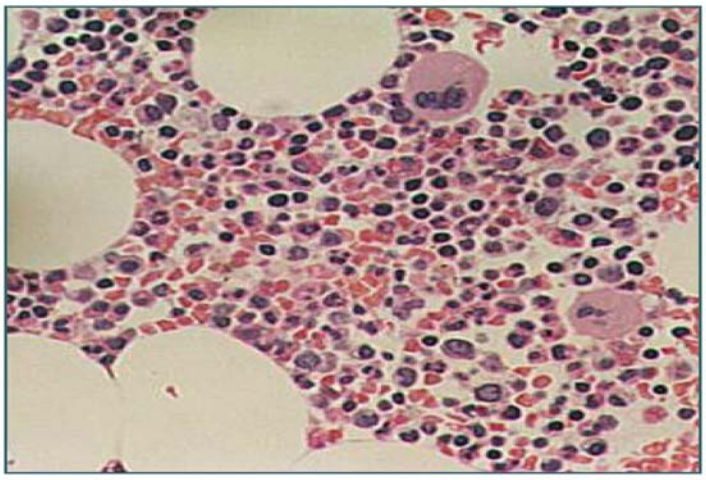
Bone marrow aspiration often yields a dry tap, so biopsy is preferred.

Solution to Question 15:

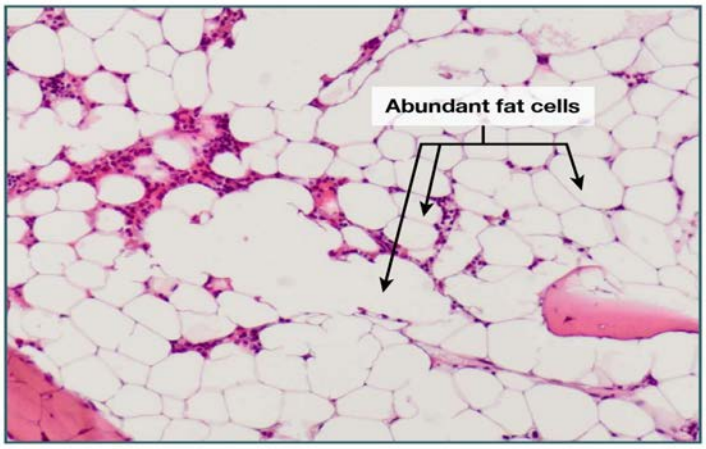
The given bone marrow biopsy shows a hypocellular bone marrow with abundant fat cells which is suggestive of aplastic anaemia. In this condition, the most common infectious cause is viral hepatitis of the non-A, Non-B, Non-C, and Non-G type.

The images given below show the normal and hypocellular bone marrow.

Normal Bone Marrow



Hypocellular Bone Marrow



Note- Viral hepatitis, parvovirus B19, human immunodeficiency virus (HIV), cytomegalovirus and Epstein-Barr virus can cause aplastic anemia. Viral hepatitis is however the most common cause.

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Solution to Question 16:

Aplastic anaemia can transform into both acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Solution to Question 17:

Causes of pure red cell aplasia include:

- Neoplasms - thymomas and large granular lymphocytic leukemia
- Drug exposure - phenytoin, azathioprine and isoniazid
- Auto-immune disorders - neutralizing antibodies against erythropoietin
- Parvovirus infection
- Hereditary - Diamond Blackfan syndrome

Solution to Question 18:

The most common cause of myelophthisic anaemia is metastatic cancer from the breast, lung, and prostate.

Myelophthisic anaemia describes a form of marrow failure in which space-occupying lesions replace normal marrow elements. Causes include:

- Metastatic cancer
- Granulomatous diseases
- Myeloproliferative neoplasms.

This leads to the release of nucleated erythroid precursors and immature granulocytic forms into peripheral blood (leukoerythroblastosis) and tear-drop shaped red cells.

The image given below shows a peripheral smear with teardrop cells.

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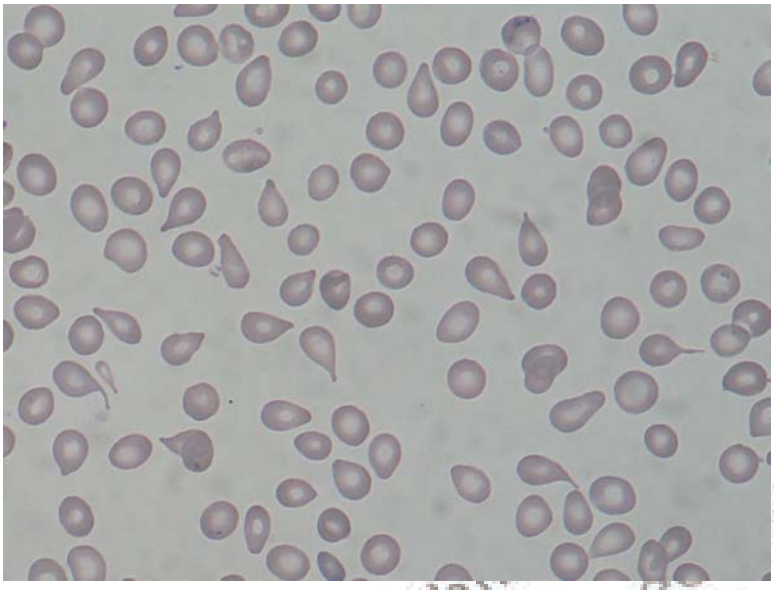

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Solution to Question 19:

The given clinical scenario is suggestive of myelophthisic anaemia. Prostatic mass with elevated PSA and age suggestive of prostatic carcinoma, which could be the likely cause in this case.

It is a form of marrow failure in which space-occupying lesions replace normal marrow elements. The most common cause is metastatic cancer from the breast, lung, and prostate.

Lab findings of myelophthisic anaemia include:

- Myelocytes + nucleated RBCs = leukoerythroblastic image
- Presence of tear-drop cells

Solution to Question 20:

The given findings are suggestive of pernicious anemia, which is associated with atrophic gastritis and vitamin B12 deficiency.

Anemic patient with a peripheral smear showing macrocytic RBCs and hypersegmented neutrophils are important characteristic features of megaloblastic anemia. Vitamin B12 and folic acid deficiency are the main causes of megaloblastic anemia.

Pernicious anemia is an autoimmune disease characterized by the presence of autoantibodies which impairs the production or activity of the intrinsic factor (IF). This is required for the uptake of vitamin B12. There are three types of autoantibodies namely, type I, II, and III. The action of each of these include:

- Autoantibody type I prevents the binding of vitamin B12 to the intinsic factor (IF).
- Autoantibody type II prevents the binding of vitamin B12-IF complex to the ileal receptors.

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• Autoantibody type III acts against the α and ° subunits of the gastric proton pump, which impairs the production of intrinsic factor.

These patients also develop chronic atrophic gastritis, characterized by loss of parietal cells, infiltration of lymphocytes and plasma cells and megaloblastic changes in mucosal cells.

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Basics of Hemolysis and Intravascular Hemolysis

Question 1:

Match the types of hemoglobin with their globin chains.

a) 1-B, 2-A, 3-C

b) 1-C, 2-A, 3-B

c) 1-C, 2-B, 3-A

d) 1-A, 2-B, 3-C

Question 2:

Enzyme deficiency in which of the following pathways can cause hemolysis?

a) Orotic acid pathway

b) Glycolysis

c) Fatty acid synthesis

d) Polyol pathway

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Question 3:

What is the normal reticulocyte count?

a) 0.5–1.5%

b) 2.5–5%

c) 5–10%

d) 1.5–2.5%

Question 4:

Which of the following statements is false about reticulocytes?

a) They are nucleated

b) They contain ribosomal RNA

c) They are larger in size than red cell

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d) Their normal count is 0.5-1.5%

Question 5:

A 25-year-old woman had severe blood loss during delivery 2-days ago. Her current hemoglobin is 5 gm/dL and reticulocyte count is 9%. What is her corrected reticulocyte count?

a) 6

b) 4.5

c) 3

d) 0.5

Question 6:

In a patient with microcytic hypochromic anaemia, red cell distribution width was measured. What is this parameter used to identify?

a) Anisocytosis

b) Poikilocytosis

c) Anisochromia

d) Biconcavity

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Question 7:

Which of the following is not increased in intravascular hemolysis?

a) Lactate dehydrogenase

b) Free hemoglobin

c) Methemoglobin

d) Haptoglobin

Question 8:

Which of the following does not cause intravascular hemolysis?

a) Paroxysmal nocturnal hemoglobinuria

b) Thrombotic thrombocytopenic purpura

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c) Infection

d) Thalassemia

Question 9:

Which of the following pairs of mutation and involved genes describes paroxysmal nocturnal hemoglobinuria?

a) AD inheritance - UMOD

b) Acquired genetic mutation - PIGA

c) AR inheritance - MUC1

d) Acquired genetic mutation - GPI

Question 10:

Which of the following cells are involved in paroxysmal nocturnal hemoglobinuria?

a) RBCs

b) RBCs and WBCs

c) WBCs and platelets

d) RBCs, WBCs and platelets

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Question 11:

A 23-year-old man with pancytopenia is suspected to have PNH. Which of the following findings is inconsistent with this condition?

a) Increased LAP score

b) Thrombosis

c) Thrombocytopenia

d) Increased methemoglobin

Question 12:

Which of the following is most likely the cause of death in a patient with paroxysmal nocturnal hemoglobinuria?

a) Sepsis

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b) Budd-Chiari syndrome

c) Renal failure

d) Hemorrhage

Question 13:

Flow cytometric analysis in a patient with pancytopenia shows a deficiency of GPI-linked proteins on blood cells. Which of the following is not a complication of this condition?

a) Deep vein thrombosis

b) Cryoglobulinemia

c) Acute myeloid leukemia

d) Myelodysplastic syndrome

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Question 14:

What is the gold standard for the diagnosis of paroxysmal nocturnal hemoglobinuria?

a) Ham test

b) Bone marrow biopsy

c) HPLC

d) Flow cytometry

Question 15:

A 37-year-old man presents with a history of dark coloured urine in the morning for 2 months. His lab investigations and flow cytometry are given below. What is the curative therapy for this condition?

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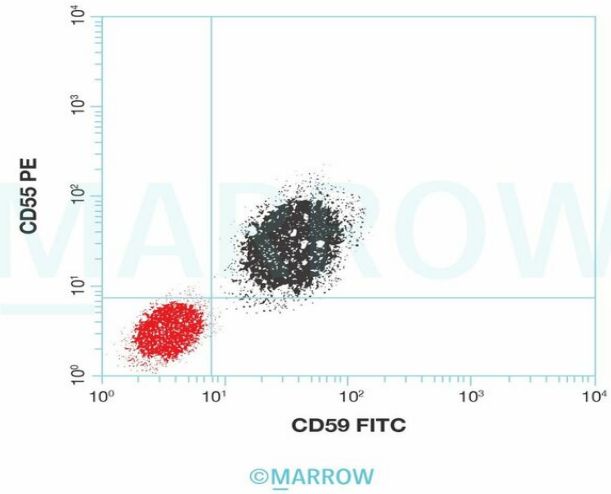

a) Eculizumab

b) Immunosuppressants

c) Blood transfusion

d) Hematopoietic stem cell transplant

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Answer Key

Question No.	Correct Option
1	b
2	b
3	a
4	a
5	c
6	a
7	d
8	d
9	b
10	d
11	a
12	b
13	b
14	d

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15	d

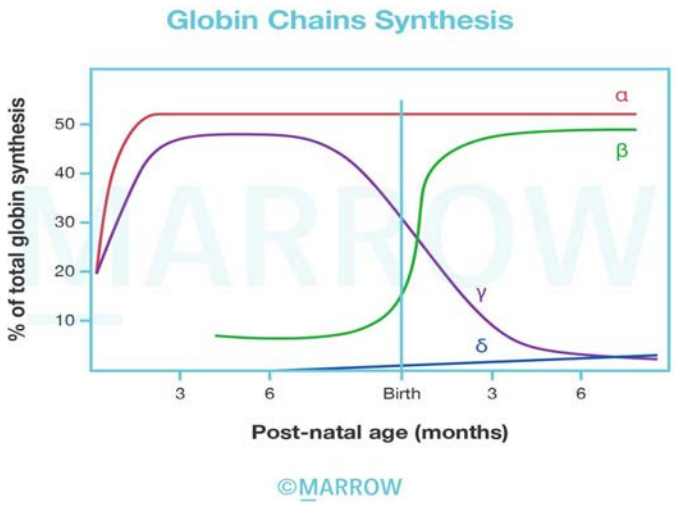
Detailed Explanations

Solution to Question 1:

The types of hemoglobin along with their globin chains are:

The image given below shows the graphical representation of the globin chain synthesis.

Hemoglobin	Components
HbF	$\alpha_2\gamma_2$
HbA	$\alpha_2^\circ 2$
HbA2	$\alpha_2\delta_2$



Solution to Question 2:

Enzyme deficiency in the glycolytic pathway can cause hemolysis.

The following enzyme deficiencies can cause hemolysis:

In the glycolytic pathway:

• Pyruvate kinase deficiency

• Hexokinase deficiency

In the HMP shunt pathway:

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• G6PD deficiency

• Glutathione synthetase deficiency

Note: Orotic aciduria causes megaloblastic anaemia.

Solution to Question 3:

Normal reticulocyte count is 0.5–1.5% of total red cells.

Causes of increased reticulocyte count:

• Hemolytic anaemia

• Acute and chronic blood loss

Causes of decreased reticulocyte count:

• Iron deficiency anaemia

• Megaloblastic anaemia

• Aplastic anaemia

• Anaemia of chronic diseases

• Myelodysplastic syndromes

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Solution to Question 4:

Reticulocytes are red cell precursors, which are non-nucleated.

They have blue-red polychromatophilic cytoplasm due to the presence of a reticular (mesh-like) network of ribosomal RNA. They can be visualized using supravital stains like methylene blue and brilliant cresyl blue, which stain the ribosomal RNA.

Reticulocytosis (increased reticulocytes) indicates effective erythropoiesis i.e. good bone marrow response to anaemia. It is seen in:

• Hemolytic anaemias

• Acute blood loss

Reticulocytopenia (decreased reticulocytes) indicates ineffective erythropoiesis i.e. poor bone marrow response to anaemia. It is seen in:

• Chemotherapy

• Aplastic anaemia

• Bone marrow malignancy

• Anaemia of chronic disease

• Iron-deficiency anaemia

• Vitamin B12 and folate deficiency

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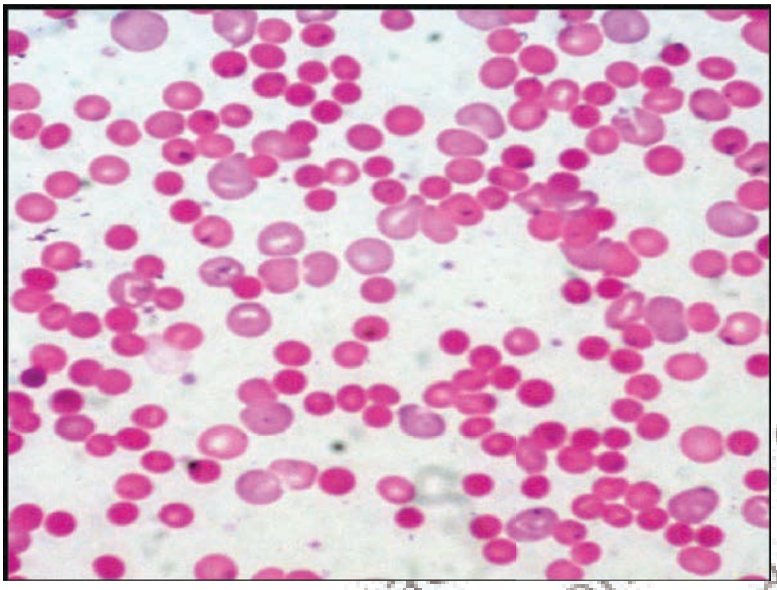
The peripheral smear shows reticulocytosis and spherocytosis seen in non-Hodgkin lymphoma.



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Solution to Question 5:

In the given scenario, the corrected reticulocyte count is 3.

It is given by the following formula:

Corrected reticulocyte count = Reticulocyte count × (patient's hemoglobin or hematocrit / standard hemoglobin or hematocrit)

So, in this case, the corrected reticulocyte count = 9×5/15 = 9/3 = 3

This formula corrects for hemoglobin. It will show you if the patient is making enough reticulocytes for the degree of anemia present. As the hemoglobin drops, reticulocytes increase from the normal range of 0.5–2.0%.

The standard reference range of hemoglobin concentration in females is 12-15 g/dl. Accordingly, in this scenario, corrected reticulocyte count would range between 3-3.75%. So, the best answer to this question remains option C.

Absolute reticulocyte count is the percentage of red cells that are reticulocytes (normal is about 0.5 – 2.0%). However, it does not reflect the fact that as the hemoglobin drops, there should be more reticulocytes, percentage-wise (for example, at a hemoglobin of 5, you should have a much higher percentage of reticulocytes than you should at a hemoglobin of 10). To take this into account, we use corrected reticulocyte count.

Reticulocyte Index = Corrected reticulocyte count / maturation factor

This corrects for the longer life span of prematurely released reticulocytes in the blood which is a phenomenon of increased red blood cell production.

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Hematocrit	Maturation factor
≥ 35%	1.0
35% > Hct ≥ 25%	1.5
25% > Hct ≥ 20%	2.0
< 20%	2.5

Solution to Question 6:

Red cell distribution width (RDW) deals with anisocytosis of RBCs. It refers to the unequal size of the RBCs.

Normal values are:

• RDW-SD (Standard deviation) - 39-46 fL

• RDW-CV (Coefficient of variation) - 11.6-14.6%

RDW is of great use in two clinical situations. They are:

• To differentiate between thalassemia and iron deficiency anaemia (IDA)

• Thalassemia - the RBCs are small (low MCV) and of uniform size (normal RDW)

• IDA - the RBCs are small (low MCV) but vary greatly in size (high RDW).

• To diagnose dimorphic anaemia (anaemia due to both iron and vitamin B12 deficiency)

• High RDW

• Normal MCV

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Solution to Question 7:

Haptoglobin is decreased in intravascular hemolysis.

Types of hemolysis based on location:

• Intravascular hemolysis - hemolysis that occurs mainly within the blood vessels

• Extravascular hemolysis - hemolysis that occurs via macrophages of the reticuloendothelial system in the spleen, liver, bone marrow, and lymph nodes

Features of intravascular hemolysis are:

• Decreased haptoglobin

• Increased lactate dehydrogenase

• Hemoglobinemia

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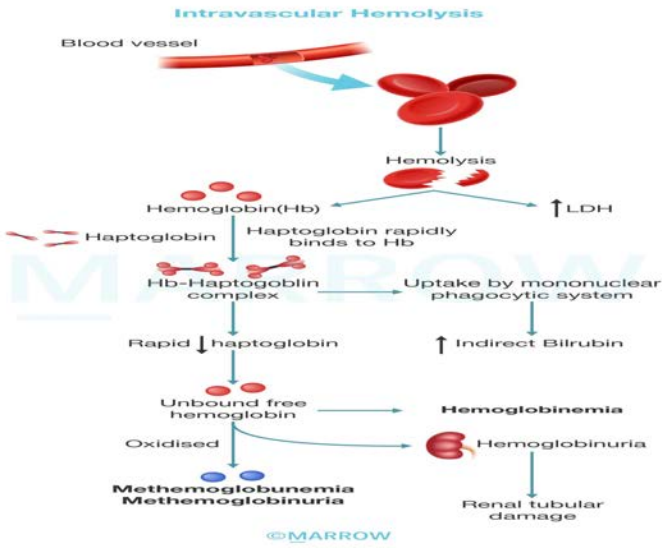
• Hemoglobinuria

• Hemosiderinuria

• Methemoglobinemia

• Methemoglobinuria

• Indirect hyperbilirubinemia



Solution to Question 8:

Thalassemia causes extravascular hemolysis.

Causes of intravascular hemolysis:

• Mechanical injury

• Trauma caused by cardiac valves

• Microangiopathic hemolytic anaemias (hemolytic uremic syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura)

• Repetitive physical trauma

• Complement fixation (antibody-mediated destruction)

• Hemolytic disease of the newborn

• Transfusion reaction

• Drug-induced

• Infections of red blood cells

• Malaria

• Babesiosis

• Exogenous toxic factors - Clostridial sepsis

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Causes of extravascular hemolysis:

• Hereditary spherocytosis

• Thalassemia

• Sickle cell anaemia

Causes of both intravascular and extravascular:

• G6PD deficiency

• Autoimmune hemolytic anaemia

Solution to Question 9:

Paroxysmal nocturnal hemoglobinuria (PNH) is a disease that results from acquired mutations in the phosphatidylinositol glycan complementation group A gene (PIGA).

This gene codes for an enzyme that is essential for the synthesis of certain membrane-associated complement regulatory proteins. It is the only hemolytic anaemia caused by an acquired genetic defect.

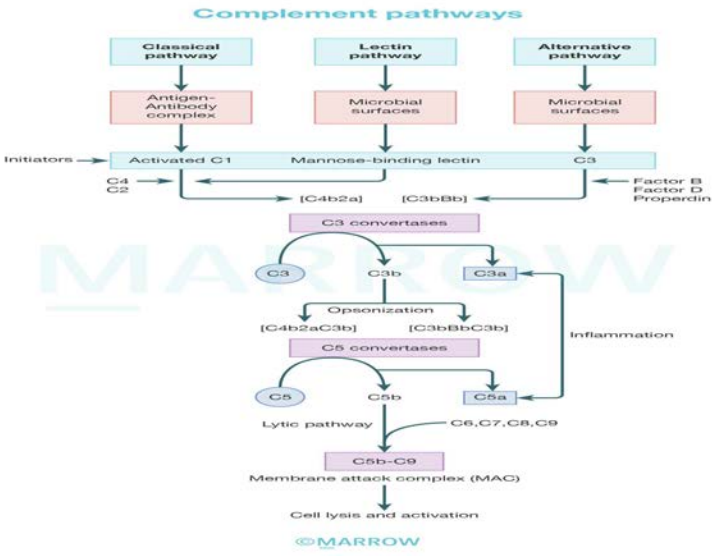
PNH blood cells are deficient in 3 GPI-linked proteins that regulate complement activity:

• Decay Accelerating Factor or CD55

• Membrane Inhibitor of Reactive Lysis or CD59

• C8-binding protein

CD59, a potent inhibitor of C3 convertase, prevents the spontaneous activation of the alternative complement pathway. Red cells deficient in these GPI-linked factors are abnormally susceptible to lysis or injury by C5b-C9 membrane attack complex of the complement system.



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Solution to Question 10:

All three cell lines, RBCs, WBCs, and platelets are affected in paroxysmal nocturnal hemoglobinuria (PNH).

PNH occurs from acquired mutations in the gene PIGA which affect GPI-linked proteins. These causative mutations occur in a hematopoietic stem cell. Hence, all of its clonal progeny, i.e., red cells, white cells, and platelets, are deficient in GPI-linked proteins.

Clinical features of PNH include:

• Intravascular hemoglobinuria - cola-colored urine

• Pancytopenia + hypercellular bone marrow

• Thrombosis (if hepatic vein involved → Budd–Chiari syndrome)

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Solution to Question 11:

In PNH, the leukocyte alkaline phosphatase (LAP) score is decreased.

Alkaline phosphatase activity is found predominantly in mature segmented neutrophils. LAP score is obtained by assessing the staining intensity in 100 consecutive neutrophils, with each neutrophil scored on a scale of 1–4. Conditions that result in an increase in leukocytes in all stages of maturity will reflect a corresponding increase in LAP.

Increased LAP	Decreased LAP
Leukemoid reactionPregnancyPolycythemia veraHodgkin's disease	CMLPNHSickle cell anemia

Solution to Question 12:

Among the following, Budd-Chiari Syndrome is the most likely the cause of death in a patient with paroxysmal nocturnal hemoglobinuria (PNH).

Thrombosis (particularly venous thrombosis) is the leading cause of disease-related death in patients with PNH. 40% of PNH patients suffer from venous thrombosis, which commonly affects the hepatic, portal, or cerebral veins.

The pathophysiology of thrombosis in PNH is not completely understood, but two main mechanisms may be responsible:

• Nitric oxide (NO) is absorbed by free hemoglobin (which is released during hemolysis).

• Endothelial damage caused by the C5-9 membrane attack complex (due to deficiency of CD59).

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Solution to Question 13:

The deficiency of GPI linked proteins on blood cells is seen in paroxysmal nocturnal hemoglobinuria (PNH). Cryoglobulinemia is not a complication of this condition.

Thrombosis is the leading cause of disease-related death in individuals with paroxysmal nocturnal hemoglobinuria (PNH). About 5% to 10% of patients eventually develop acute myeloid leukemia (AML) or myelodysplastic syndrome.

Solution to Question 14:

The gold standard for the diagnosis of PNH is flow cytometry. It provides a sensitive means for detecting red cells that are deficient in GPI-linked proteins such as CD59.

Investigations in PNH include:

• Flow cytometry (gold standard) - deficiency of CD59 and CD55

• Ham test (acidified serum lysis) - lysis of RBCs in a mildly acidic pH due to complement fixation

• Bone marrow biopsy -

• Hypercellularity with erythroid hyperplasia is seen in classical presentations

• Patients who develop pancytopenia will have hypocellular bone marrow

• Imaging - to evaluate venous thrombosis

Solution to Question 15:

The given clinical scenario is suggestive of PNH (paroxysmal nocturnal hemoglobinuria). The curative therapy for this condition is a hematopoietic stem cell transplant.

Pancytopenia is seen in this condition. Flow cytometry shows 2 populations of red cells:

• Marked red in the left lower quadrant - deficient in both CD55 and CD59, characteristic of PNH.

• Marked black in the right upper quadrant - CD55+ and CD59+ cells from the residual normal hematopoietic cells

Eculizumab is a monoclonal antibody that can be used in PNH. It prevents the conversion of C5 to C5a and reduces hemolysis.

Immunosuppressive drugs are sometimes beneficial for those with evidence of marrow aplasia.

Note: FDA has approved the following drugs for treatment of adults with PNH:

• Ravulizumab injection, a long-acting C-5 complement inhibitor

• Pegcetacoplan, which acts by binding to complement protein C3 and increasing hemoglobin concentration

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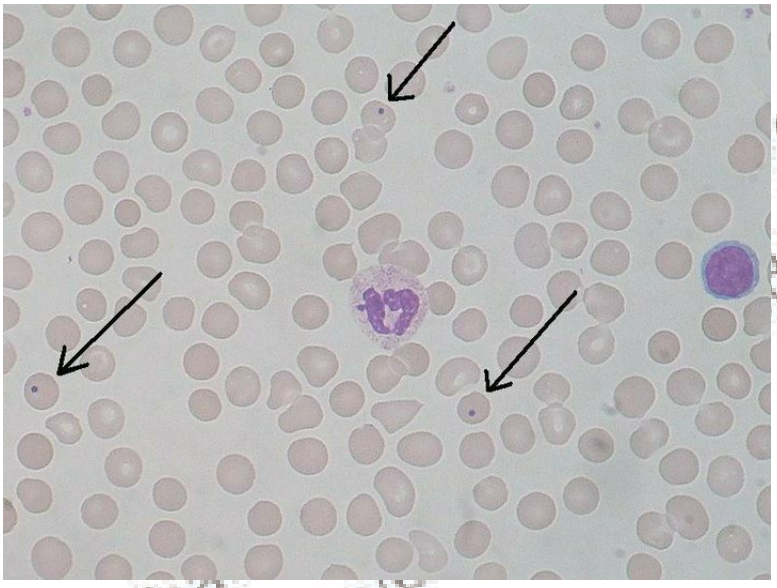
Extravascular Hemolysis

Question 1:

The peripheral smear of a patient with chronic fatigue is shown below. This marked finding is seen in all of the conditions except



a) Sickle cell anemia

b) Hereditary spherocytosis

c) Paroxysmal nocturnal hemoglobinuria

d) Thalassemia

Question 2:

Match the types of thalassemia with their most common mutations.

a) 1-C, 2-A, 3-B

b) 1-C, 2-B, 3-A

c) 1-A, 2-B, 3-C

d) 1-B, 2-A, 3-C

Question 3:

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Which chromosome is affected in alpha-thalassemia?

a) 16

b) 11

c) 6

d) 12

Question 4:

Which of the following statements is false regarding α-thalassemia?

a) Free ° and γ chains are more soluble than free α chains

b) ° tetramer is known as HbH

c) α chains are coded by a pair of genes

d) Hb Barts is the most severe form

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Question 5:

A woman with an obstetric score of G3P2A0L0, in a consanguinous marriage, delivered a hydropic stillborn at 32 weeks of gestation. Further evaluation revealed the presence of Hb Barts in the fetal blood. Which of the following globin chains tetramer is found in this condition?

a) α4

b) °4

c) γ4

d) δ4

Question 6:

A 26-year-old Chinese translator presents with fever, jaundice and splenomegaly. His Hb is 6 g% and peripheral smear with brilliant cresyl blue is given below. Which of the following globin chains would you expect to see in this patient?

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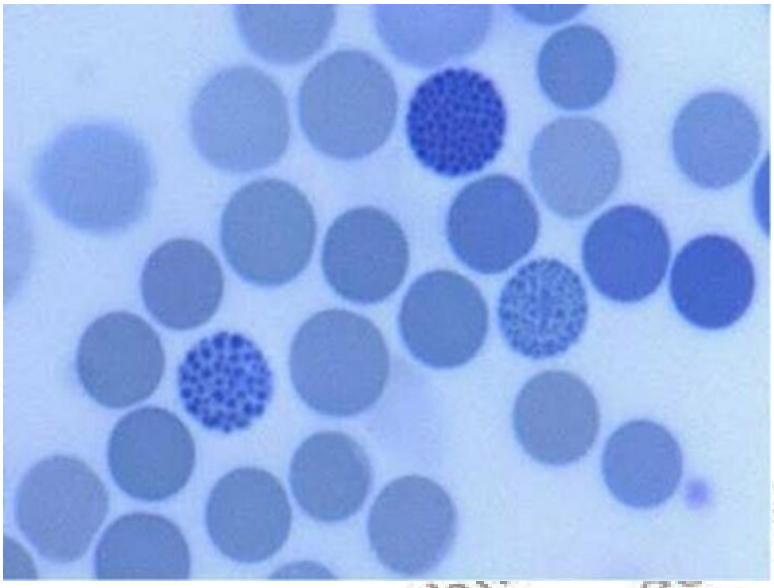

a) α4

b) °4

c) γ4

d) δ4

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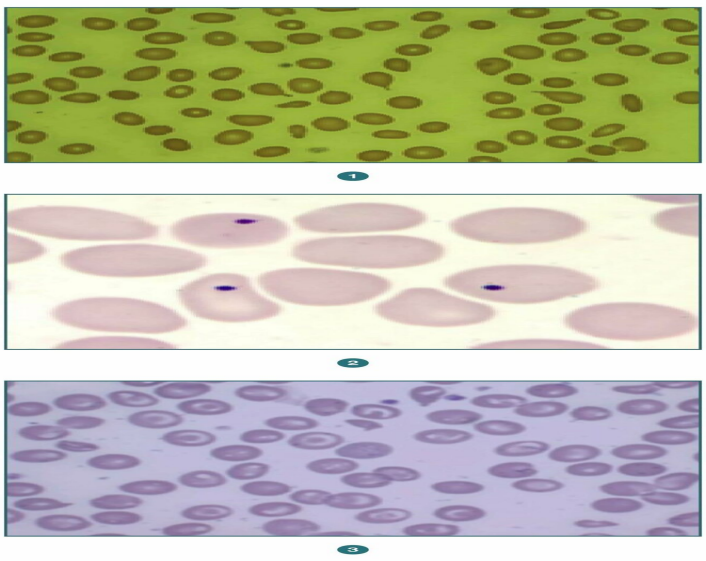
Question 7:

A patient has a HbA2 of 3% and HbF of 97%. A peripheral blood smear is taken. Which of the following blood pictures will be seen in this patient?



a) 1, 2 and 3

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b) 1 and 2

c) 2 and 3

d) 1 and 3

Question 8:

Given below is the hemogram of a patient. Calculate the Mentzer index.

a) 10

b) 12

c) 30

d) 6

Question 9:

The following test was performed with blood sample from a patient with anaemia. What is this test used for?

a) Detection of sickle cell trait

b) Screening of thalassemia

c) Confirmatory test for hereditary spherocytosis

d) Bedside diagnostic test for PNH

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Question 10:

A couple with a family history of thalassemia comes for genetic counselling. Their HPLC reports are given below. What is the risk of their offspring having thalassemia major?

a) 0

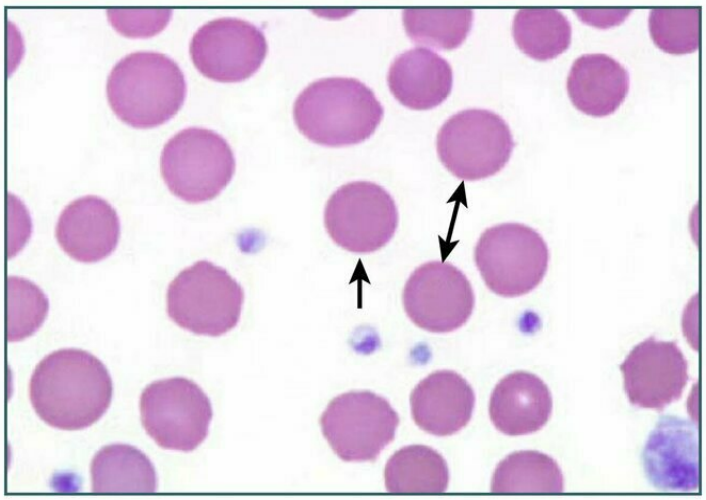
b) 25

c) 50

d) 75

Question 11:

A 25-year old man presents with chronic anemia and gall stones. His family history is significant for a similar illness. His peripheral blood smear is given below. What is the mode of the inheritance of the given clinical condition?



a) Autosomal dominant

b) Autosomal recessive

c) X-linked dominant

d) X-linked recessive

Question 12:

What is the most common protein deficiency associated with hereditary spherocytosis?

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a) Spectrin

b) Ankyrin

c) Actin

d) Glycophorin

Question 13:

The peripheral smear of a patient with anaemia, jaundice and splenomegaly shows pincer cells. Which protein deficiency is responsible for this finding?

a) α spectrin

b) Ankyrin

c) Band 3

d) Band 4.1

Question 14:

Which of the following features would you least expect to see in a patient with hereditary spherocytosis?

a) Pallor

b) Gallstones

c) Splenomegaly

d) Hemoglobinuria

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Question 15:

What is the life span of affected red cells in patients with hereditary spherocytosis?

a) 10–20 days

b) 20–30 days

c) 30–60 days

d) 60–90 days

Question 16:

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In a patient with hereditary spherocytosis, MCHC of 38 g/dL was noted. What could be the probable reason for this finding?

a) Dehydration

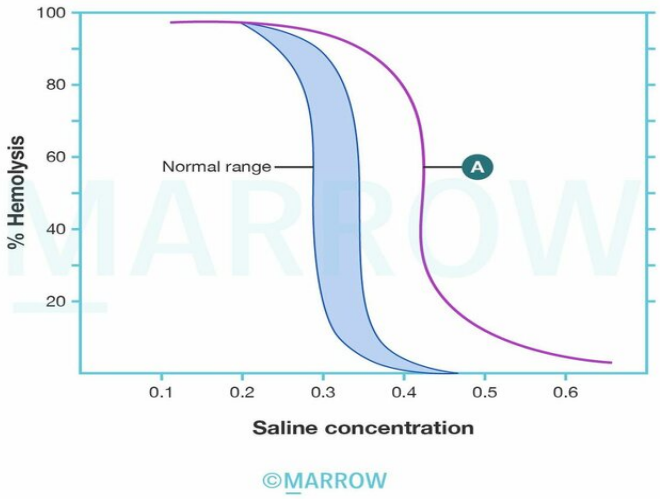
b) Increased in Hb content

c) Compensatory erythropoiesis

d) Change in shape

Question 17:

In the following osmotic fragility curve, A occurs in _____.



a) Beta thalassemia

b) Sickle-cell anaemia

c) Hereditary spherocytosis

d) Iron deficiency anaemia

Question 18:

A 7-year-old girl presents with fever and jaundice for 5 days. On examination, splenomegaly is noted. Her lab reports are given below. What is the likely trigger to have caused this condition?

a) Parvovirus

b) EBV

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c) Plasmodium

d) Meningococcus

Question 19:

Which amino acid lies at the sixth position of the beta chain of hemoglobin?

a) Valine

b) Glutamine

c) Glutamate

d) Lysine

Question 20:

A blood sample is taken from a suspected case of sickle cell anaemia. Which of the following properties can be used to differentiate HbS from HbA?

a) Function

b) Stability

c) Affinity

d) Solubility

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Question 21:

A 35-year-old man was diagnosed to have heterozygous sickle cell trait. What will be the approximate percentage of HbS in this patient?

a) 40%

b) 60%

c) 50%

d) 30%

Question 22:

Patients with which of the following combinations of beta-globin chains tend to have a more severe sickle cell disease?

a) HbA and HbS

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b) HbA2 and HbS

c) HbS and HbC

d) HbS and HbF

Question 23:

In patients with sickle cell anaemia, which of the following factors promote sickling of RBC?

a) Decreased MCHC

b) HbF type

c) HbC type

d) High pH

Question 24:

Which of the following reagents is used for sickling test?

a) Sodium thiocyanate

b) Sodium chloride

c) Sodium metabisulfite

d) Hydrochloric acid

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Question 25:

A 12-year-old girl presents with fever and severe pain in her hands and feet. There is no history of trauma. Her lab reports reveal Hb to be 8.2 g/dL and peripheral smear as shown below. Which of the following parasitic infections is this condition protective against?

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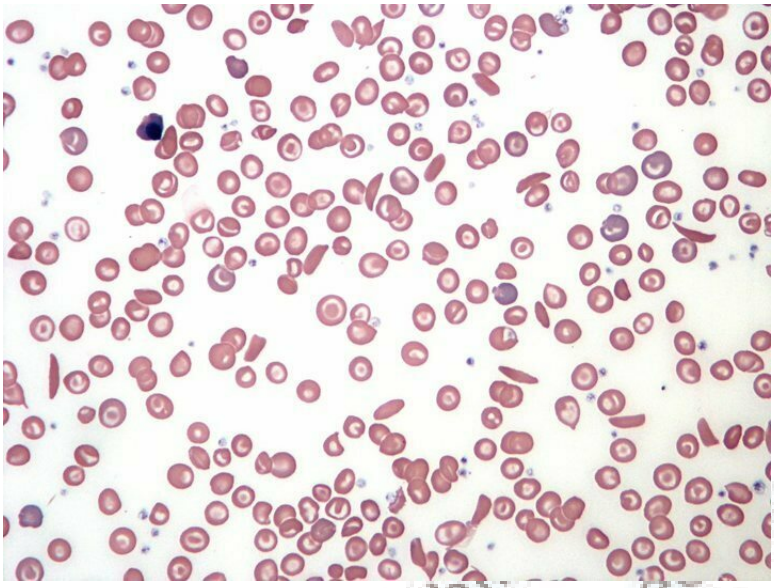

a) P. falciparum

b) P. vivax

c) P. ovale

d) Babesia

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Question 26:

What happens to the severity of hemolytic anaemia in concurrent sickle cell anaemia and α-thalassemia?

a) Increases

b) Decreases

c) No change

d) Both cannot co-exist

Question 27:

A 23-year-old patient with sickle cell anaemia presents with fever and malaise. IgM ELISA confirms a parvovirus B19 infection. Which of the following crises will you expect to see in this patient?

a) Aplastic

b) Sequestration

c) Vaso occlusion

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d) Acute chest syndrome

Question 28:

During USG examination in a patient with hemolytic anemia, the spleen was not visualized. There is no past history of trauma or surgery. What is the most probable diagnosis?

a) Sickle cell anaemia

b) G6PD deficiency

c) Beta-thalassemia

d) Hereditary spherocytosis

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Answer Key

Question No.	Correct Option
1	c
2	a
3	a
4	c
5	c
6	b
7	d
8	a
9	b
10	a
11	a
12	b
13	c
14	d
15	a
16	a
17	c
18	a
19	c
20	d

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21	a
22	c
23	c
24	c
25	a
26	b
27	a
28	a

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Detailed Explanations

Solution to Question 1:

The given peripheral smear shows Howell–Jolly bodies. They are not seen in paroxysmal nocturnal hemoglobinuria.

They are small nuclear remnants seen as inclusions in red cells and are characteristic of asplenia. They are seen in the following conditions:

- Sickle cell anaemia - due to auto splenectomy
- Hereditary spherocytosis
- Thalassemia post-splenectomy

The images given below show Howell–Jolly bodies in peripheral blood smear.

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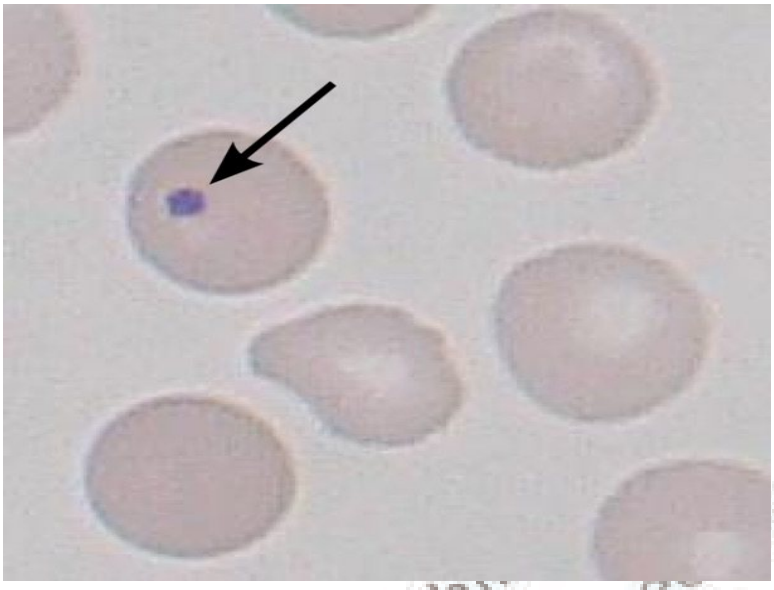

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Solution to Question 2:

The most common types of mutations causing thalassemia are:

The different splicing mutations are:

• Mutations that destroy the normal RNA splice junctions - completely prevent the production of normal °-globin mRNA resulting in °0-thalassemia

• Mutations that create an ectopic splice site within an intron with normal splice regions - some normal °-globin mRNA is made resulting in °+ thalassemia

There are two subtypes of chain terminator mutations:

• New stop codon within an exon

• Small insertions or deletions that shift the mRNA reading frames

Thalassemia	Most common mutation
°+ thalassemia	Splicing mutation
°0thalassemia	Terminator mutation
α thalassemia	Gene deletion

Solution to Question 3:

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Chromosome 16 contains an identical pair of α-globin genes which is affected in alpha-thalassemia. This condition is due to decreased synthesis of alpha chains.

The two ° chains are encoded by a single °-globin gene on chromosome 11.

Solution to Question 4:

α chains are coded by 4 genes i.e. two pairs of genes located on chromosome 16.

Free ° and γ chains are more soluble than free α chains. They also form more stable homotetramers. Hence, hemolysis and dyserythropoiesis in α thalassemia are less severe when compared to ° thalassemia.

In HbH disease, excess °-globin chains form °4 tetramers. They are seen in older children with α-thalassemia.

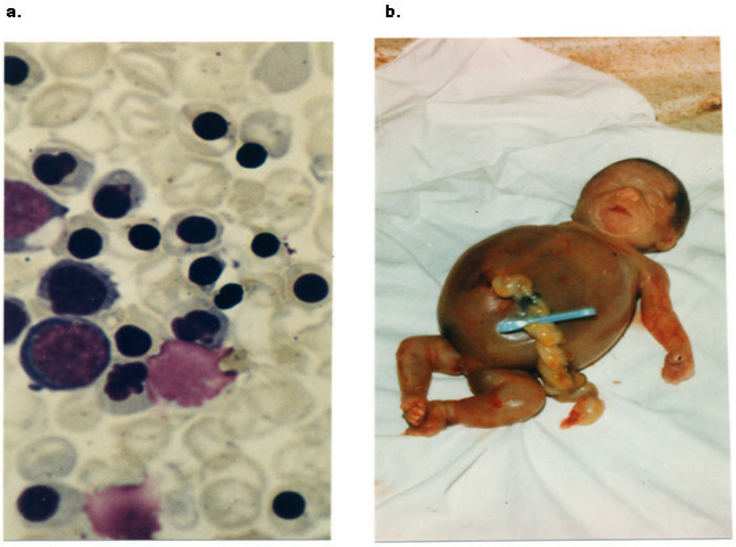
Hydrops fetalis is the most severe form of α-thalassemia. It is caused by the deletion of all four α-globin genes. This leads to excess γ-globin chains forming γ-globin tetramers (hemoglobin Barts).

Solution to Question 5:

Hb Barts is a tetramer of γ-globin chains (γ4). This type of hemoglobin is seen in newborns with the most severe form of α-thalassemia and results in hemoglobin Barts hydrops fetalis. There is no production of α chains.

Hb Barts has a higher affinity for oxygen. This leads to intrauterine hypoxia, eventually leading to stillbirth.

The image given below shows (a) immature red cell precursors in peripheral smear and (b) stillborn hydropic infant in Hb Barts hydrops syndrome.



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In HbH disease, excess °-globin chains form °4 tetramers. They are seen in older children with α-thalassemia.

Solution to Question 6:

The given clinical scenario of extravascular hemolysis (jaundice and splenomegaly) and peripheral smear showing golf ball cells is suggestive of HBH disease. It is a type of α thalassemia where the HbH is composed of tetramers of ° chains (°4).

Hb-H disease is one type of alpha-thalassaemia with inactivation of 3 of the 4 alleles. It is more common in the Asian population. It usually manifests in the 1st year of life. It causes acute episodes of hemolysis when triggered by infections or oxidant drugs.

The decreased α chain production leads to a relative excess of ° chains. This leads to the formation of HbH which has a high affinity for oxygen. Such RBCs are more prone to oxidation which causes precipitation of HbH to form golf ball inclusion bodies. This leads to increased sequestration and phagocytosis in the spleen.

Solution to Question 7:

The presence of HbA2 3% and HbF 97% indicates that it is a case of thalassemia major. In thalassemia major, hematological findings in image 1 showing poikilocytes and image 3 showing target cells are seen. Image 2 showing Howell Jolly bodies are seen in post-splenectomy thalassemia patients and not in this case.

Hematological findings in thalassemia major include the following:

- Anisopoikilocytosis
- Target cells (codocytes)
- Nucleated RBC's
- Dacrocytes
- Basophilic stippling
- Polychromatophilic cells

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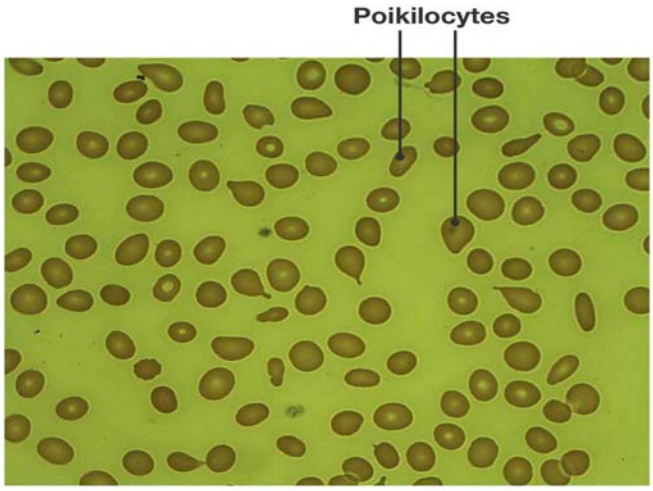

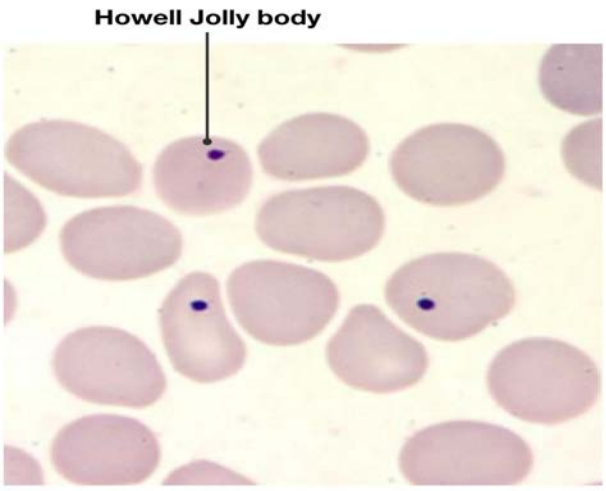

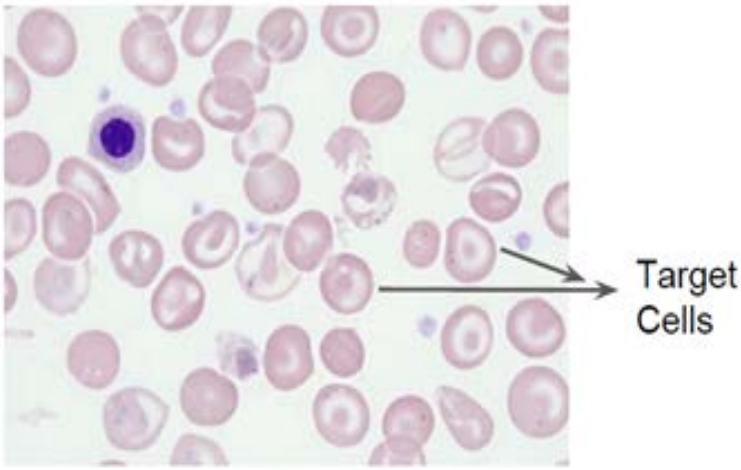

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Solution to Question 8:

From the given hemogram, the Mentzer index is 10.

The formula for Mentzer index is MCV (fL) / TRBC (millions/mm3) i.e. 60/6 = 10

This index is used to differentiate between iron-deficiency anemia and beta-thalassemia trait. If the index is <13, it is most likely to be a thalassemia trait.

Differences between iron deficiency anemia and beta-thalassemia minor (beta-thalassemia trait) are given below.

Feature	Iron-deficiencyanemia	Beta-thalassemia minor
Peripheral blood smear	Microcytic hypochromic	Microcytic hypochromic
Retic count	Low	Low
RDW	Wide	Narrow
TRBC	Low	High
Mentzer index	>14	<12
Serum ferritin	Low	Normal
Serum iron	Low	Normal
TIBC	High	Normal
HbA2	2-3%(normal)	>3.5%

Solution to Question 9:

The given image shows NESTROFT i.e. Naked Eye Single Tube Red cell Osmotic Fragility test. It is a very useful screening tool for thalassemia, particularly in poor resource settings.

The principle is based on the decreased osmotic fragility of red cells in thalassemia. It is performed as follows:

• Mix EDTA blood and 0.36% buffered saline solution.

• Shake the tube and leave it at room temperature for 30 minutes.

• Shake the tube again and immediately hold the tube in front of a piece of paper with text or lines.

The image given below shows the NESTROFT.

NESTROFT	Inference	Reason
Lines visible (negative)	Normal	Hemolysis has occurred

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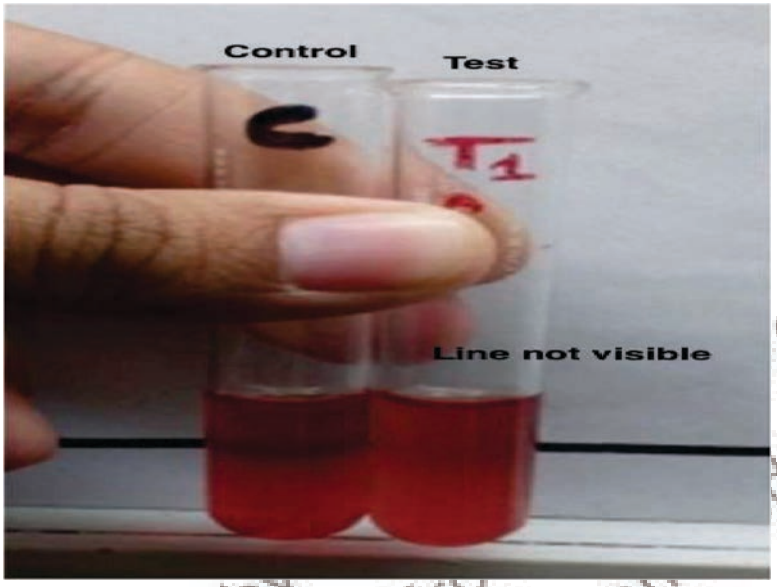
NESTROFT	Inference	Reason
Lines not seen (positive)	Thalassemia	Stable RBC, unable to lyse



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Solution to Question 10:

In the given clinical scenario, the risk of their offspring having thalassemia major is 0%.

From the given HPLC reports, the husband is normal (normal value of HbA2 is 2.5%±0.3%) and the wife has ° thalassemia minor (HbA2 level 4.9%). This disease is transmitted with an autosomal recessive inheritance. Hence, the chance of their offspring having full blown thalassemia is zero.

In ° thalassemia minor, the Hb A2 levels are increased to 4–8%. This is due to an elevated ratio of δ chain to ° chain synthesis. Hb F levels are generally normal or slightly increased.

Note: Increased HbF (diagnostic) and normal HbA2 levels are features of thalassemia major.

Solution to Question 11:

The given peripheral smear showing spherocytes, along with the history, is suggestive of hereditary spherocytosis. Inheritance of this condition is mainly autosomal dominant.

Hereditary spherocytosis is a structural RBC disorder making the RBCs more spheroid. The RBCs are less deformable and more vulnerable to splenic sequestration and destruction. This decreases the lifespan of RBCs.

Solution to Question 12:

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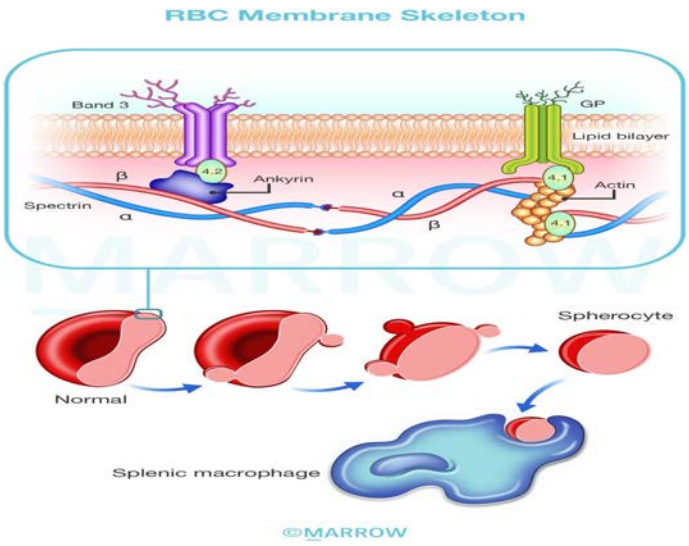
Ankyrin is the most common protein deficiency associated with hereditary spherocytosis (HS).

The chief protein component of the RBC membrane skeleton is spectrin. It consists of two polypeptide chains, alpha and beta. These dimers associate with actin oligomers. The spectrin–actin skeleton is then connected to the cell membrane by two distinct interactions.

• Ankyrin and band 4.2 binds spectrin to the transmembrane ion transporter, band 3

• Protein 4.1 binds the tail of spectrin to the transmembrane protein glycophorin A

Defect in any of the components of the red cell membrane skeleton results in hereditary spherocytosis. The image given below shows the pathogenesis of this condition.



Note: Few one-liners on membrane skeleton -

• Most abundant integral proteins - glycophorin, band 3

• Responsible for biconcave shape of RBC - spectrin

• Most severe deficiency - spectrin

• Hereditary elliptocytosis is due to deficiency of alpha spectrin

• Mushroom cells appearance due to deficiency of band 3

• Never involved in HS - glycophorin

Solution to Question 13:

Pincer cell or mushroom cell is seen in hereditary spherocytosis associated with deficiency of cytoskeletal protein band 3.

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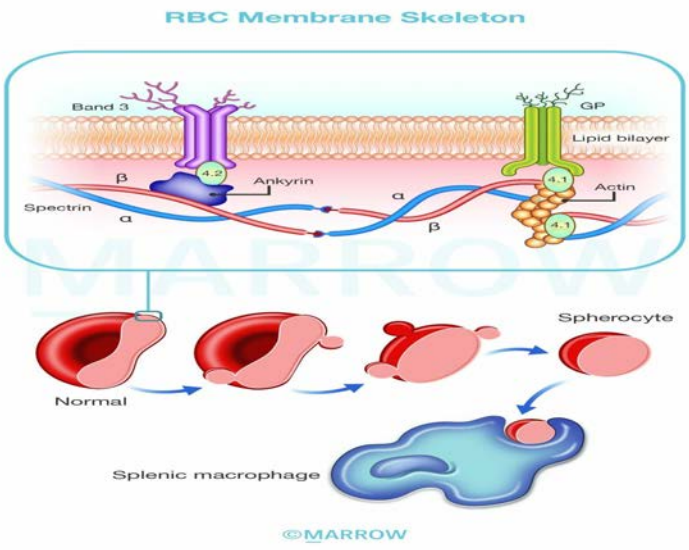

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Solution to Question 14:

Hemoglobinuria is not seen in hereditary spherocytosis where extravascular hemolysis occurs. It is a feature of intravascular hemolysis. Pigment gallstones, pallor and splenomegaly can be seen in this condition.

Cinical features of extravascular hemolysis include:

• Anaemia

• Jaundice

• Splenomegaly

Causes of extravascular hemolysis:

• Hereditary spherocytosis

• Thalassemia

• Sickle cell anaemia

Note: G6PD deficiency and autoimmune hemolytic anaemia can cause both intravascular and extravascular hemolysis.

Solution to Question 15:

The life span of affected red cells in hereditary spherocytosis is 10 to 20 days. The normal life span of RBC is 120 days.

Solution to Question 16:

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Increased MCHC in hereditary spherocytosis is due to dehydration caused by the loss of K+ and H_2O.

MCHC (mean corpuscular hemoglobin concentration) is given by the formula hemoglobin / PCV (g/dL). It indicates the amount of hemoglobin per unit volume.

Note:

• MCV (mean corpuscular volume) is given by the formula PCV / RBC (fL). It denotes the size of the RBCs.

• MCH (mean corpuscular hemoglobin) is given by the formula hemoglobin / RBC (pg). It quantifies the hemoglobin in the RBCs.

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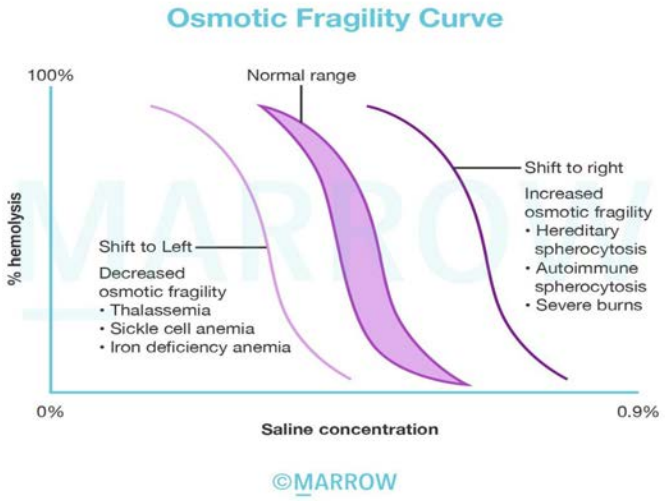
Solution to Question 17:

Osmotic fragility curve shifts to the right in hereditary spherocytosis.

In hereditary spherocytosis, the cells are spherocytic in normal plasma (0.9% NaCl) and hemolyse readily at higher concentrations than normal discoid red cells do, hence shifting the curve to the right.

Osmotic fragility is the susceptibility of the RBC to rupture under osmotic stress.
In hypotonic solutions, RBCs swell to become spherical and eventually hemolyse. In the graph, the x-axis represents the saline concentration while the y-axis represents the percentage of red cells that have undergone hemolysis. When osmotic fragility is normal, red cells begin to hemolyse at 0.5% saline, with 50% of hemolysis occuring at 0.40-0.42% saline and complete hemolysis occuring at 0.35% saline as represented in the curve.

In thalassemia and sickle cell anemia on the other hand, the cells are resistant to hemolysis and don't hemolyse unless the concentration of saline is very low, shifting the graph to the left.



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Solution to Question 18:

The given hemogram showing pancytopenia and spherocytes in peripheral smear is suggestive of aplastic crisis in hereditary spherocytosis. It is usually triggered by parvovirus infection.

Parvovirus infects and kills the red cell precursors. This creates a transient arrest of erythropoiesis i.e. aplastic crisis as the life span of RBCs are shortened. The immune response clears the virus in 1-2 weeks.

Blood transfusions may be necessary during acute phases of the infection. This crisis can also occur in other hemolytic anaemias.

Solution to Question 19:

Glutamate lies at the 6th position of the beta chain of hemoglobin.

Sickle-cell disease is caused by a point mutation in the sixth codon of ° -globin. This leads to the replacement of a glutamate residue with a valine residue.

Solution to Question 20:

Solubility can be used to differentiate as HbS is less soluble than HbA. The function, stability and affinity of HbS are similar to that of HbA.

In HbS, glutamic acid, which is a polar amino acid, is replaced by a non-polar amino acid valine at the 6th position. HbS molecules have the tendency to stack into polymers when deoxygenated. This process converts the red cell cytosol from a free-flowing liquid into a viscous gel. This causes a change in the solubility of the hemoglobin.

The major pathologic manifestations of decreased solubility and polymerisation of HbS are chronic hemolysis, microvascular occlusions, and tissue damage.

Solution to Question 21:

In heterozygotes with sickle-cell trait, about 40% of the hemoglobin is HbS. The rest of hemoglobin (60%) is HbA.

Sickle cell trait is a largely asymptomatic condition characterised by heterozygosity seen for HbS (sickle hemoglobin). As only a fraction of the Hb are HbS, polymerization leading to sickling only occurs in severe and prolonged hypoxia. Offsprings of 2 heterozygotes have a 1 in 4 chance of having sickle cell disease.

In HbSC heterozygotes, HbS is 50% and HbC is 50%.

Solution to Question 22:

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Among the given options, the heterozygous combination of HbS and HbC causes a more severe form of the disease. Overall severity is more in homozygous HbS.

Severity sequence is HbSS > HbSC > HbSA > HbSF.

In HbC, lysine is substituted for glutamate in the sixth amino acid residue of °-globin. The percentage of HbS is 50% in HbSC red cells and 40% in HbAS cells. Moreover, HbSC cells tend to lose salt and water and become dehydrated, which increases the intracellular concentration of HbS. Both of these factors increase the tendency for HbS to polymerize. As a result, individuals who are compound heterozygotes for HbS and HbC, have symptomatic sickling disorder (termed HbSC disease). However, it is milder than sickle cell disease (HbSS).

HbF inhibits the polymerization of HbS even more than HbA. Hence, infants do not become symptomatic until they reach 5 or 6 months of age when the level of HbF normally falls.

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Solution to Question 23:

HbC promotes the sickling of RBC, whereas HbF opposes it.

Factors that promote sickling are:

• Increased MCHC

• Hb C

• Acidic pH

• Hypoxia

HbF has a high affinity for oxygen than other hemoglobins. Hence, high oxygen content prevents sickling. HbF inhibits the polymerization of HbS. So the infants do not become symptomatic until they reach 5 or 6 months of age when the level of HbF normally falls.

Solution to Question 24:

The reagent used for the sickling test is sodium metabisulfite. It is an oxygen-consuming reagent, which induces the sickling of red cells in the presence of HbS.

Sickling test with sodium metabisulfite is used as a screening test for sickle cell anaemia.

Solution to Question 25:

The given clinical scenario is suggestive of sickle cell anaemia. HbS gives protection against Plasmodium falciparum malaria.

Hand-foot syndrome or dactylitis of bones of hands and feet is a severe acute inflammatory response seen in sickle cell anaemia. It is caused by vaso-occlusive episodes leading to ischemia and finally infarction of the distal portions of the extremities.

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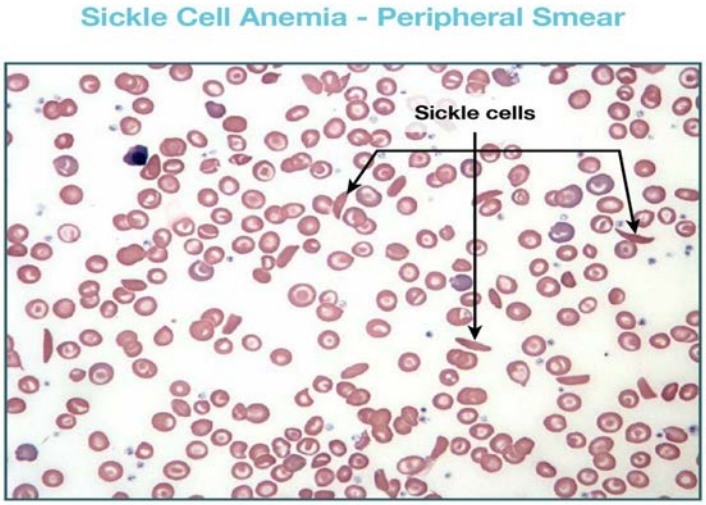
Sickle cells impair the formation of membrane knobs containing a protein made by P. falciparum called PfEMP-1. This decreases the adherence of infected red cells to the endothelium.

Individuals with sickle cell trait are significantly less likely to have severe disease or to die from malaria. It is because of the increased phagocytosis of sickled cells in the spleen, which keeps the parasite load down.

The image given below shows sickle cells seen on peripheral smear in sickle cell anemia.



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Solution to Question 26:

The concurrence of sickle cell anaemia and α-thalassemia results in less severe hemolytic anaemia.

Sickle cell anaemia is caused by point mutations in ° globin synthesis leading to defective HbS synthesis. When these RBCs release oxygen, the HbS polymerises leading to membrane distortion

Thalassemia is due to germline mutations causing decreased globin chain synthesis (α or °). Since these diseases have a different pathogenesis, they can occur concurrently.

In alpha-thalassemia, the concentration of hemoglobin is decreased. Therefore the concentration of HbS in sickle cell anaemia is also decreased. Since HbS molecules should be close to each other for polymerization to occur. Since there is a decreased concentration of HbS in alpha-thalassemia, the HbS molecules are far apart. So there is a decreased polymerization of HbS and therefore less severity of the disease.

Solution to Question 27:

Aplastic crisis in sickle cell anaemia is caused by parvovirus B19. It is a transient arrest of erythropoiesis, usually triggered by an acute parvovirus infection. Parvovirus infects and kills red cell precursors. It occurs in sickle cell disease and other hemolytic anaemias.

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Vaso-occlusive crises (pain crises) are episodes of hypoxic injury and infarction that cause severe pain in the affected region. The most commonly involved sites are the bones, lungs, liver, brain, spleen, and penis. Acute chest syndrome is a type of vaso-occlusive crisis involving the lungs. It typically presents with fever, cough, chest pain, and pulmonary infiltrates. Pulmonary inflammation may cause blood flow to become sluggish and "spleenlike," leading to sickling and vaso-occlusion.

Sequestration crises occur in children with intact spleens. Massive entrapment of sickle red cells leads to rapid splenic enlargement, hypovolemia, and sometimes shock. Both sequestration crises and acute chest syndrome may be fatal and sometimes require prompt treatment with exchange transfusions.

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Solution to Question 28:

Non-visualisation of the spleen on routine USG is suggestive of autosplenectomy, which is seen in sickle cell anemia. Splenomegaly is seen in thalassemia and hereditary spherocytosis.

In children with sickle cell anaemia, there is moderate splenomegaly. This is due to red pulp congestion caused by the entrapment of sickled red cells. As age advances, chronic erythrostasis produces hypoxic damage and infarcts. By adulthood, the spleen is reduced to a band of fibrous tissue. This process is called autosplenectomy.

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G6PD deficiency and Autoimmune Hemolytic Anemias

Question 1:

A 29-year-old African American man receives primaquine chemoprophylaxis before traveling for a business trip. Four days later, he presents with jaundice and dark urine. Laboratory investigations show anemia, reticulocytosis, and unconjugated hyperbilirubinemia. The peripheral blood smear shows the presence of Heinz bodies. What is the most likely mode of inheritance of the given clinical condition?

a) Autosomal dominant

b) Autosomal recessive

c) Mitochondrial

d) X-Linked recessive

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Question 2:

Which of the following is the most common trigger for hemolysis in patients with G6PD deficiency?

a) Infection

b) Drugs

c) Fava beans

d) Dehydration

Question 3:

Peripheral smear of a patient with viral hepatitis is given below. Which of the following statements is false about this finding?

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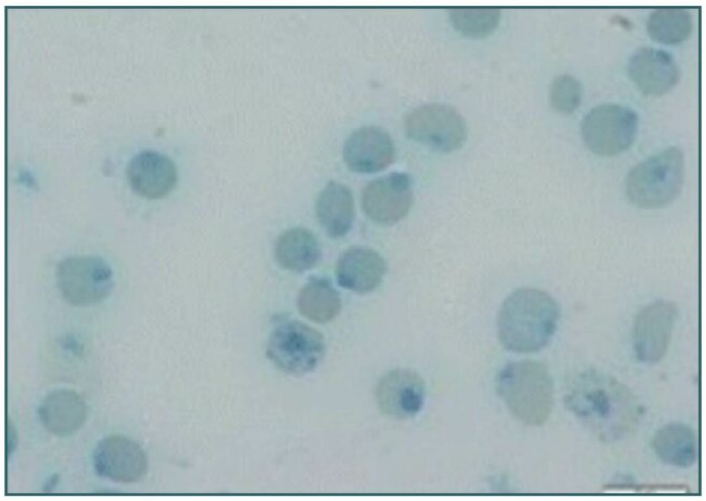

a) These are seen in G6PD deficiency

b) They are due to denaturation of globin chains

c) They are plucked out by macrophages in the spleen

d) They do not cause intravascular hemolysis

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Question 4:

A patient with G6PD deficiency was suspected to have acute hemolytic episode. Which of the following features would you expect to see in this patient?

a) 1, 3, 5

b) 1, 4, 5

c) 1, 2, 3

d) 2, 4, 5

Question 5:

A 23-year-old food blogger presents with complaints of icterus and abdominal fullness. She returned yesterday from a vacation in Egypt where she tried fava beans. Her peripheral smear is given below. This condition is protective against which of the following malarial parasites?

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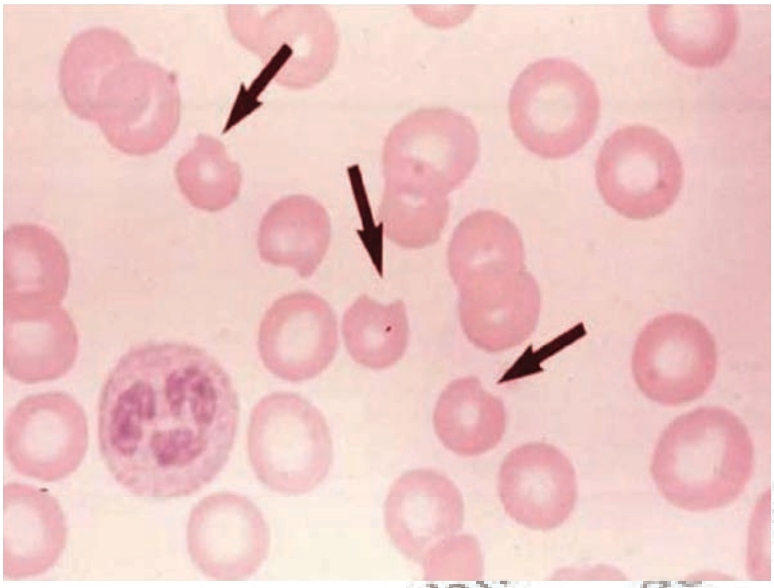

a) Falciparum

b) Vivax

c) Ovale

d) Malariae

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Question 6:

Which of the following statements is not true about G6PD-deficiency anemia?

a) Hemolytic episodes occur both intravascularly and extravascularly

b) G6PD Mediterranean deficiency is the most severe form.

c) Older RBCs are more prone to hemolysis than younger ones

d) Hemolysis continues as long as there is exposure to oxidant drugs

Question 7:

What class of antibodies are involved in the most common form of immunohemolytic anaemia?

a) Ig G

b) Ig A

c) Ig M

d) Ig G and Ig M

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Question 8:

Match the immunohemolytic anaemia with the type of hemolysis.

a) 1-B, 2-A, 3-C

b) 1-C, 2-A, 3-B

c) 1-C, 2-B, 3-A

d) 1-B, 2-C, 3-A

Question 9:

A 30-year-old woman was brought to the casualty with loss of consciousness. On examination, pallor, icterus and splenomegaly were noted. Her past history was significant for meningitis 2 weeks ago which was treated with iv antibiotics. Lab investigations showed anemia and increased osmotic fragility. Which of the following statements is false regarding the probable diagnosis?

a) Rh blood group complex are involved in the pathogenesis

b) LDH levels are always normal

c) Direct Coombs agglutination test is diagnostic

d) Peripheral smear shows spherocytes

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Question 10:

Which of the following statements is false about paroxysmal cold hemoglobinuria?

a) IgG class of antibodies are involved

b) Antibodies are directed against Rh antigen

c) Complement-mediated lysis occurs at 37°C

d) It mostly occurs in children following a viral infection

Question 11:

In which of the following conditions is microangiopathic hemolytic anaemia most commonly seen?

a) Disseminated intravascular coagulation

b) Thrombotic thrombocytopenic purpura

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c) Hemolytic uremic syndrome

d) Cardiac valve prosthesis

Answer Key

Question No.	Correct Option
1	d
2	a
3	d
4	a
5	a
6	d
7	a
8	c
9	b
10	b
11	a

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Detailed Explanations

Solution to Question 1:

The given clinical history suggestive of hemolysis after the antimalarial (primaquine) and Heinz bodies on PBF, points to a diagnosis of G6PD deficiency (Glucose-6-phosphate dehydrogenase deficiency). It is inherited as an X-linked recessive trait.

G6PD is an enzyme belonging to the hexose monophosphate shunt (HMP) pathway. Deficiency of enzymes of this pathway causes hemolysis as the protective ability of RBCs from oxidative stress is impaired.

The image given below shows the Heinz bodies seen on peripheral smear.

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Solution to Question 2:

The most common trigger for hemolysis in G6PD deficiency is infection. Viral hepatitis, pneumonia, and typhoid are the common infections that trigger hemolysis.

Episodic hemolysis (both intravascular and extravascular) is seen in G6PD deficiency. It is due to exposures that cause oxidative stress. The triggers include:

- Infections - oxygen-derived free radicals produced by activated leukocytes
- Drugs
- Antimalarials - primaquine and chloroquine
- Sulfonamides
- Nitrofurantoin
- Diet - fava bean

Solution to Question 3:

The given peripheral smear shows Heinz bodies which are dark stained inclusion bodies in red cells. They can cause intravascular as well as extravascular hemolysis.

In G6PD-deficiency, the RBCs are exposed to high levels of oxidants. This causes cross-linking of reactive sulfhydryl groups on globin chains. The globin chains become denatured and form membrane-bound precipitates known as Heinz bodies. These can be detected by supravital staining.

Heinz bodies can damage the membrane sufficiently to cause intravascular hemolysis.

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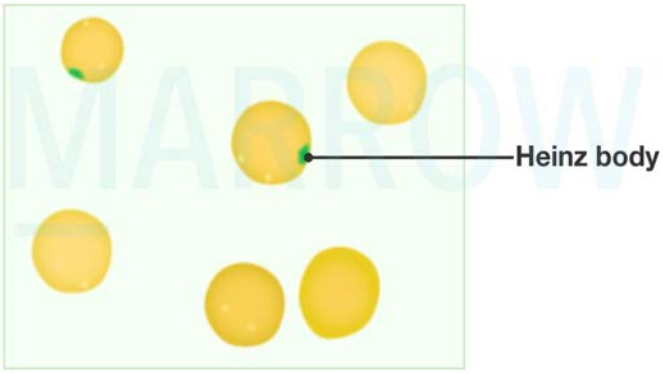
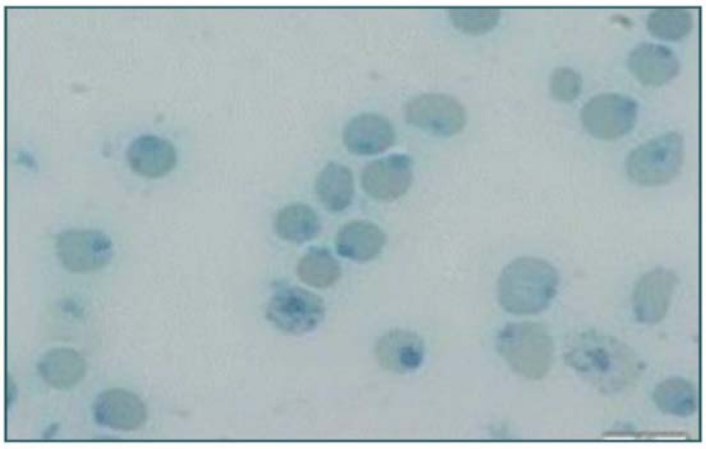
As RBCs with Heinz bodies pass through the spleen, the macrophages pluck out the Heinz bodies. As a result, some of these partially devoured cells retain an abnormal shape i.e. as if a bite was taken out of them. Such cells are called bite cells. Bite cells are trapped in splenic cords and removed by phagocytes leading to extravascular hemolysis.

The images given below show Heinz bodies and bite cells seen in G6PD deficiency.



Heinz bodies



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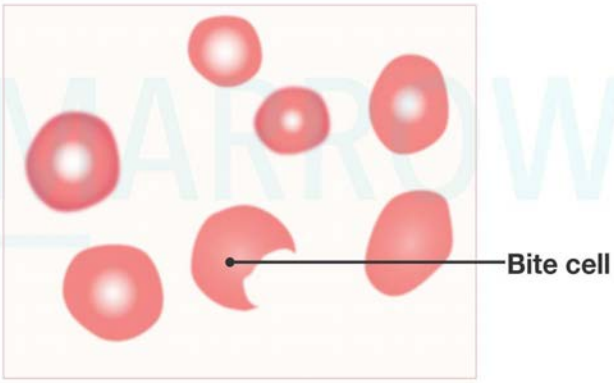

Bite cells

Solution to Question 4:

Acute hemolysis in G6PD deficiency is intravascular. This is marked by anaemia, hemoglobinemia, and hemoglobinuria.

These episodes are self-limited and intermittent. Reticulocytosis occurs during the recovery phase. Hence, features related to chronic hemolysis (e.g., splenomegaly, cholelithiasis) are absent.

Solution to Question 5:

The peripheral smear shows RBCs with anisopoikilocytosis with polychromasia and many bite cells (arrows) suggestive of G6PD deficiency. This condition is protective against Plasmodium

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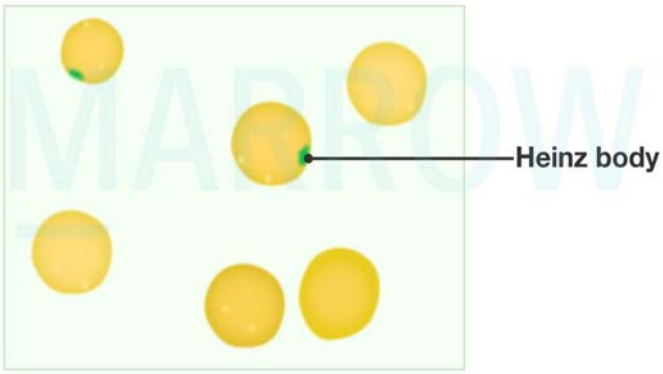
falciparum malaria.

Malarial parasites preferentially invade RBCs which are rich in G6PD. G6PD deficiency causes oxidative stress and hemolysis, preferably in the older RBCs. Reticulocytes and young erythrocytes have much higher G6PD activities and are less susceptible to oxidant damage.

P. falciparum can invade erythrocytes of all ages. P. vivax, and P. ovale invade reticulocytes (immature erythrocytes) preferentially. Hence, a low G6PD level in older RBC is protective against P. falciparum malaria.

Episodic hemolysis in this condition can be triggered by fava beans which is a staple in Egyptian cuisine.

The images given below show Heinz bodies and bite cells seen in G6PD deficiency.



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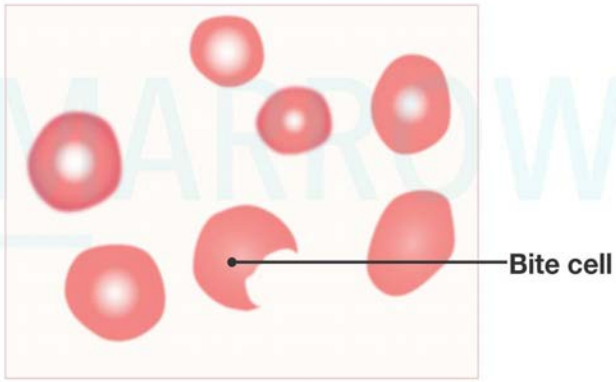

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Solution to Question 6:

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Hemolysis in G6PD-deficiency anemia does not continue for the entire period that the patient takes the offending drug. It stops after a few days.

Two variants of G6PD, designated as G6PD– and G6PD Mediterranean, cause most of the clinically significant hemolytic anemias. The half-life of G6PD- is moderately reduced, whereas that of G6PD Mediterranean is markedly reduced; hence, the severity of deficiency is greater with the Mediterranean variant. The most common normal variant is G6PD B.

The hemolysis in G6PD deficiency is both extravascular and intravascular hemolysis. The damaged red cells are sequestered in the spleen and killed
by macrophages, causing extravascular hemolysis. The oxidative stresses can denature hemoglobin, resulting in intravascular hemolysis.

In individuals with G6PD deficiency, acute intravascular hemolysis begins 2 to 3 days after exposure to oxidants. Only older RBCs are at risk for lysis. The hemolytic episode is self-limited because hemolysis stops when only younger G6PD-replete red cells remain, even if the patient continues to take the offending drug.

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Solution to Question 7:

Warm antibody type is the most common form of immunohemolytic anaemia. Most of the causative antibodies in this condition belong to the IgG class.

Immunohemolytic anaemia is caused by antibodies that cause premature destruction of the red cells. Based on the temperature at which the different types of antibodies bind to the RBCs stably, they are classified as:

- Warm antibody type - most common
- Cold agglutinin type
- Cold hemolysin type

Solution to Question 8:

The type of hemolysis seen in the different immunohemolytic anemia are:

Autoimmune hemolytic anemias (AIHA) cause both extravascular and intravascular hemolysis.

In warm antibody type, hemolysis is extravascular. IgG-coated red cells are phagocytosed and destroyed in the spleen.

In cold agglutinin type, hemolysis is extravascular and intravascular. In the peripheral vascular bed (low temperature), IgM binds to the red cells. This causes agglutination and complement-fixing. They are unbound when they reach the general circulation. However, the IgM interaction causes deposition of sublytic quantities of C3b. It is an excellent opsonin, which leads to the removal of RBCs by phagocytes in the spleen, liver, and bone marrow.

Cold hemolysin type is a rare subtype of AIHA. Hemolysis is intravascular. IgG binds to the P blood group antigen on the red cells, which leads to complement-mediated lysis.

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Type	Hemolysis
Warm antibody	Extravascular
Cold agglutinin	Extravascular and intravascular
Cold hemolysin	Intravascular

Solution to Question 9:

The given clinical scenario is suggestive of drug-induced warm antibody type of immunohemolytic anemia. In this condition, primarily extravascular hemolysis is present. LDH may be increased when there is hemolysis.

Two different mechanisms for drug-induced immune hemolytic anemias are:

Antigenic drugs:

• Anemia occurs 1-2 weeks after initiation of large IV dose of the offending drug

• These drugs bind to red cell membrane and are recognised by anti-drug antibodies

• They can cause both extravascular and intravascular hemolysis

• E.g. penicillin, cephalosporins, quinidine

Tolerance-breaking drugs:

• Antibodies are produced against red cell antigens, particularly Rh antigens

• E.g. alpha-methyl dopa

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Solution to Question 10:

In paroxysmal cold hemoglobinuria (PCH), antibodies are directed against the P blood group antigen.

PCH is a cold hemolysin type of hemolysis caused by IgG autoantibodies classically. They are also called Donath Landsteiner antibodies and are produced often in response to a viral infection. This antibody is a biphasic hemolysin. i.e., the antibody binds to RBC at colder temperature but hemolysis occurs at core temperature 37°C.

This can cause substantial, sometimes fatal, intravascular hemolysis, and hemoglobinuria. Most cases are seen in children following viral infections and usually recover within 1 month.

Immuno-hemolytic anaemias are of 3 types:

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	Antibody type	Antigen on the RBC surface	Temperature for hemolysis
Warm agglutinin	IgG	Rh antigen	37°C or higher
Cold agglutinin	IgM	I antigen (adults)i antigen (infants)	30°C, usually 0-10°C
Cold hemolysin	IgG	P antigen	Biphasic hemolysis (37°C)

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Solution to Question 11:

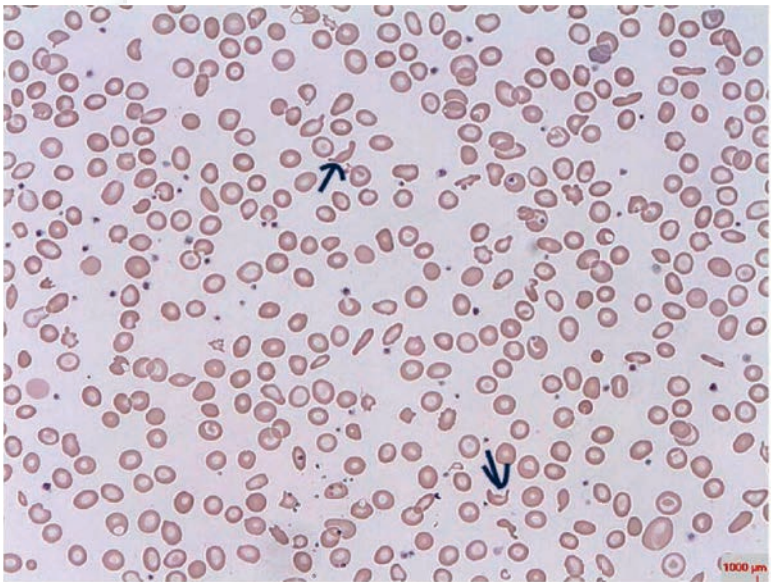
Microangiopathic hemolytic anaemia is most commonly seen with disseminated intravascular coagulation.

It occurs in the following conditions:

- Disseminated intravascular coagulation (DIC)
- Thrombotic thrombocytopenic purpura (TTP)
- Hemolytic-uremic syndrome (HUS)
- Malignant hypertension
- Systemic lupus erythematosus
- Disseminated cancer

A common pathogenic feature in these disorders is a microvascular lesion. Deposition of fibrin and platelets result in luminal narrowing. These vascular changes produce shear stresses. These changes mechanically injure the passing red cells producing schistocytes or helmet cells on the peripheral smear.

The image given below shows schistocytes or helmet cells.



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Platelet Disorders

Question 1:

Which of the following is the most potent vasoconstrictor?

a) Endothelin

b) Urotensin

c) Angiotensin

d) Vasopressin

Question 2:

Which of the following is a component of δ granules of platelets?

a) Platelet-derived growth factor

b) Epinephrine

c) Fibrinogen

d) Platelet factor 4

Question 3:

Rees and Ecker diluting fluid is used in _____

a) Wintrobe tube

b) WBC Pipette

c) RBC Pipette

d) Hemoglobin pipette

Question 4:

A 12-year-old girl with dengue hemorrhagic fever is being monitored by measuring platelet count. Spontaneous bleeding is associated with platelet values below _____ /μL.

a) 30,000

b) 50,000

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c) 20,000

d) 10,000

Question 5:

Which of the following statements is true regarding functional platelet disorders?

a) Normal platelet count and normal bleeding time

b) Normal platelet count and increased bleeding time

c) Decreased platelet count and increased bleeding time

d) Decreased platelet count and decreased bleeding time

Question 6:

Which of the following statements is false about vonWillebrand factor?

a) It is synthesized by hepatocytes

b) Its deficiency can also cause factor VIII defect

c) Its deficiency may cause defective platelet adhesion

d) It serves as a carrier for factor VIII

Question 7:

A 24-year-old woman is found to have uncontrolled bleeding after a minor cut injury. Her lab investigations are given below. Which of the following statements are false about her condition?

a) Type 1 is most common

b) Type 2 is a qualitative defect

c) Type 3 is inherited as autosomal dominant

d) Type 3 is the severe form

Question 8:

Which of the following occurs due to a defect in δ granules of the platelets?

a) Quebec platelet syndrome

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b) Grey platelet syndrome

c) Wiskott–Aldrich syndrome

d) Hermansky–Pudlak syndrome

Question 9:

A patient with large platelets on peripheral smear is diagnosed to have Bernard-Soulier disease. Deficiency of which of the following causes this condition?

a) Gp IIb/ IIIa

b) Gp Ib/ IX

c) von Willebrand factor

d) Factor VIII

Question 10:

Which of the following statements is false about Bernard-Soulier syndrome?

a) There is defective adhesion of platelets to sub-endothelial matrix

b) Deficiency of the platelet membrane glycoprotein complex Ib-IX is seen

c) Platelet aggregation by ristocetin is normal

d) It has an autosomal recessive inheritance

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Question 11:

A 4-year-old girl with a history of easy bruising was referred for further evaluation. Her previous lab reports showed that platelet count and morphology were normal. Platelet aggregations tests are given below. What is the likely diagnosis?

a) Bernard-Soulier syndrome

b) Grey platelet syndrome

c) von Willebrand Disease

d) Glanzmann thrombasthenia

Question 12:

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A 1-year-old boy is brought with a history of recurrent impetigo. Physical examination findings are given below. Platelet counts are low and peripheral smear shows abnormally small-sized platelets. What is the most likely diagnosis?

a) Idiopathic thrombocytopenia purpura

b) Bernard-Soulier syndrome

c) Disseminated intravascular coagulation

d) Wiskott-Aldrich syndrome

Question 13:

A 28-year-old woman presents with epistaxis, easy bruising and menorrhagia. There is no history of drug intake. Physical examination shows scattered petechiae and a normal-sized spleen. Her lab investigations are given below. Antibodies against which of the following can lead to this condition?

a) vWF

b) Glycoprotein IIb/IIIa

c) ADAMTS13

d) Thromboxane A2

Question 14:

Which class of antiplatelet antibodies are seen in patients with chronic immune thrombocytopenic purpura?

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a) Ig G

b) Ig A

c) Ig M

d) Ig E

Question 15:

A 27-year-old woman is diagnosed to have idiopathic ITP. Which of the following features is least likely to be seen in her?

a) Megathrombocytes

b) Petechiae and ecchymosis

c) Lymphadenopathy

d) Normal PT and PTT

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Question 16:

Patients with which of the following predisposing conditions are likely to develop chronic immune thrombocytopenic purpura?

a) 1, 2, 3

b) 2, 3, 4, 5

c) 1, 4, 5

d) 1, 2, 3, 5

Question 17:

A 63-year-old man with moderate COVID pneumonia developed DVT. Therapeutic anticoagulation with heparin was started. His lab investigations are given below. Which of the following is false about this condition?

a) Antibodies recognise heparin-platelet factor 4 complex

b) Lesser incidence with use of LMWH

c) Pulmonary thromboembolism is a complication

d) It is a self-resolving condition

Question 18:

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All of the following commonly cause drug-induced thrombocytopenia except _____

a) Vancomycin

b) Quinine

c) Rifampin

d) Terlipressin

Question 19:

A post-operative patient was started on prophylactic unfractionated heparin for DVT. Which of the following is false regarding this drug?

a) It is an indirect thrombin-factor Xa inhibitor

b) It is safe in patients with renal impairment

c) It requires monitoring with aPTT

d) On development of HIT, LMWH can be started alternately

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Question 20:

Patients with which of the following conditions is associated with ADAMTS13 deficiency?

a) Immune thrombocytopenic purpura

b) Hemolytic uremic syndrome

c) Thrombotic thrombocytopenic purpura

d) Von Willebrand disease

Question 21:

A 7-year-old girl is brought with complaints of hematuria and melena for 10 days. Laboratory investigations reveal mild thrombocytopenia and normal coagulation tests. Peripheral smear is given below. Which organism is most frequently involved in this condition?

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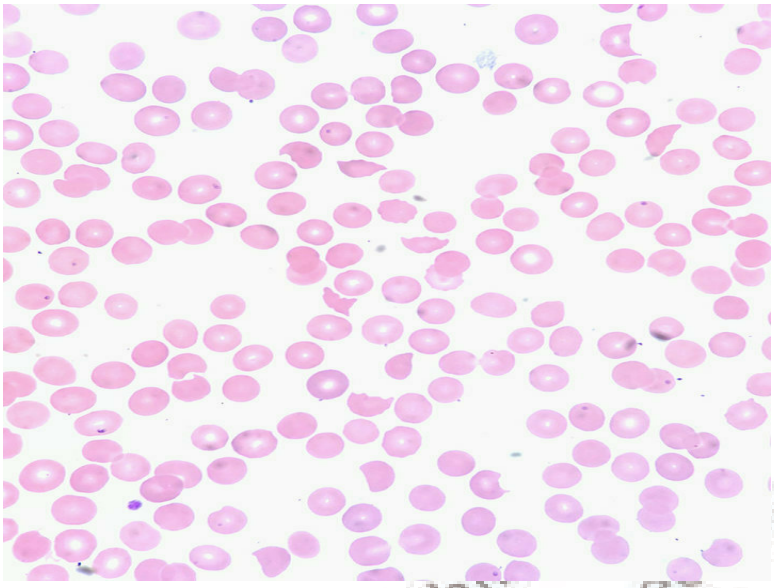

a) E.coli O157:H7

b) Shigella

c) Enteroinvasive E.coli

d) Salmonella

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Question 22:

Deficiency of which of the following complement components is not associated with atypical hemolytic uremic syndrome?

a) Factor H

b) CD46

c) Factor I

d) CD59

Question 23:

Coombs test is found to be positive in a patient with thrombocytopenia. Which of the following conditions could be a likely cause?

a) Thrombotic thrombocytopenic purpura

b) Hemolytic uremic syndrome

c) Immune thrombocytopenic purpura

d) Disseminated intravascular coagulation

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Question 24:

Which of the following is affected in patients with Weber-Osler-Rendu syndrome?

a) Collagen

b) Platelets

c) Clotting factors

d) Blood vessels

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Answer Key

Question No.	Correct Option
1	b
2	b
3	c
4	c
5	b
6	a
7	c
8	d
9	b
10	c
11	d
12	d
13	b
14	a
15	c
16	d
17	d
18	d
19	d
20	c
21	a
22	d

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23	c
24	d

Detailed Explanations

Solution to Question 1:

The most potent vasoconstrictor is urotensin2 followed by endothelin and angiotensin.

Solution to Question 2:

Epinephrine is a component of δ granules of platelets.

The different components of platelet granules are:

- α granules
- Fibrinogen
- Fibronectin
- PF4
- Factor V, VIII
- PDGF
- TGF
- δ granules
- ADP
- Calcium
- Serotonin
- Histamine
- Epinephrine

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Solution to Question 3:

Rees and Ecker's solution is used as a diluting fluid in the RBC pipette for performing platelet counts. Its composition is:

The steps involved in platelet count are:

I - Filling the pipette

- Diluting fluid is drawn to mark 1 of the RBC pipette and expelled

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• Blood is aspirated to 0.5 mark of the RBCs diluting pipette

• Diluting fluid is aspirated to 101 mark

• Blood and diluting fluid are mixed mechanically for 5 min

II - Filling the counting chamber

• Allow the counting chamber to stand for 20-30 minutes to allow the platelets to settle.

• To prevent drying out of the preparation, it should be kept in a moist atmosphere, this is most easily arranged by placing the filled counting chamber in the bottom of a clean Petri dish, alongside which arrange a small piece of cotton wool which has been soaked in water and squeezed out. Petri dish lid is additionally put over the dish.

• After 20-30minutes, the counting chamber can be removed and carefully transferred to the microscope stage.

III - Counting the number of platelets

• Focus on the surface of the hemocytometer chamber with a high power dry objective. Dim the light to make the thrombocytes visible, and count all of the thrombocytes in the entire center 1 mm^2 (erythrocyte counting area) of both sides of the hemocytometer. This gives the number of thrombocytes in 0.2 l of 1: 200 dilution of blood.

• The number of thrombocytes counted X 1000 = number of thrombocytes/l of undiluted blood.

Components	Value
Sodium citrate	3.8 g
Formaldehyde (40 %)	0.2 ml
Brilliant cresyl blue	0.1 g
Distilled water	100 ml

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Solution to Question 4:

Spontaneous bleeding (non-traumatic) is associated with platelet values below 20,000 platelets/µL.

It most often involves small vessels. The common sites for such hemorrhages are:

• Skin

• Mucosa of gastrointestinal and genitourinary tracts

• Intracranial bleeding - most feared site of bleeding

The production of the platelets is regulated by the hormone thrombopoietin produced in the liver. The platelet synthesis is also specifically increased by interleukin 6. The average lifespan of the platelets is 7–10 days. The normal platelet count is 1,50,000 - 4,00,000 /µL.

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Solution to Question 5:

Functional platelet disorders have normal platelet count and increased bleeding time.

Classification of platelet functional disorders:

• Defect in platelet-vessel wall interaction (disorders of adhesion)

• Von Willebrand disease - deficiency or defect in plasma vWF

• Bernard–Soulier syndrome - deficiency or defect in GP Ib IX

• Defects in platelet-platelet interaction (disorders of aggregation)

• Congenital afibrinogenemia - deficiency of plasma fibrinogen

• Glanzmann thrombasthenia - deficiency or defect in GPIIb-IIIa

• Disorders of platelet secretion and signal transduction

• Storage pool deficiency - α-Granule deficiency and gamma-Granule deficiency

• Quebec platelet disorder

• Chediak–Higashi syndrome

• Gray platelet syndrome

• Wiskott–Aldrich syndrome

• Disorders of platelet coagulation-protein interaction

• Scott syndrome - defect in factor Va-Xa interaction on platelets

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Solution to Question 6:

Von Willebrand factor (vWF) is not synthesized by hepatocytes. They are produced by endothelial cells of liver and megakaryocytes. It is also found in:

• Platelet granules - lesser compared to endothelial cells

• Endothelial cells within cytoplasmic vesicles called Weibel-Palade bodies

• Subendothelium - binds to collagen

It mediates the adhesion of platelets to sites of vascular injury (subendothelium). It links the exposed collagen to platelets. It facilitates platelet to platelet interaction and also stabilizes the hemostatic plug against shear forces.

It is a carrier protein for factor VIII and also protects it from proteolytic degradation and stabilizes it. The half-life of factor VIII is about 2.4 hours when free and 12 hours when bound to vWF in the circulation.

Since vWF stabilizes factor VIII, a deficiency of vWF gives rise to a secondary decrease in factor VIII levels. This may be reflected by a prolongation of the partial thromboplastin time (PTT) in von Willebrand disease types 1 and 3.

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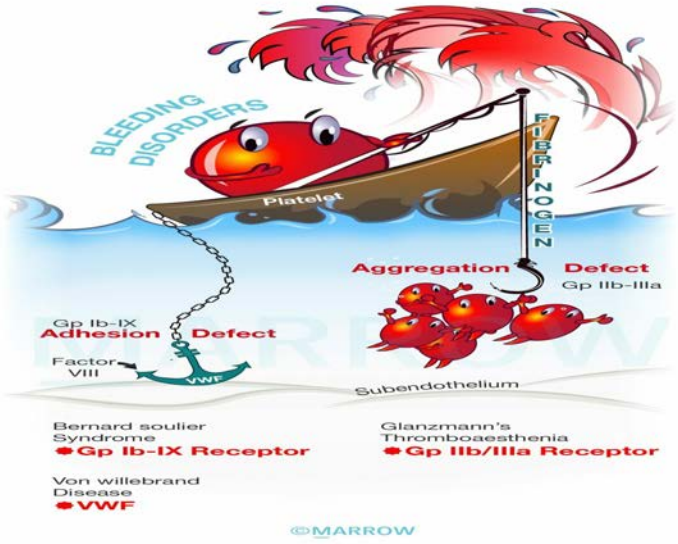

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Solution to Question 7:

The given clinical scenario is suggestive of von Willebrand disease (vWD). Type 3 vWD is inherited as an autosomal recessive disease.

The characteristics of different subtypes of vWD are:

Type 1 is the most common subtype of vWD. In Type 2, vWF is expressed in normal amounts, but missense mutations are present that lead to defective multimer assembly. This type has several subtypes, of which type 2A is the most common.

Laboratory findings in vWD:

• Prolonged bleeding time

• Normal platelet count

• Hess test - positive tourniquet test due to defective platelet adhesion

• Ristocetin-induced aggregation - defective and diagnostic of this disease

• Platelet aggregation with ADP, collagen, and thrombin - normal

• Increased aPTT

Though the synthesis of factor VIII remains normal, the half-life of VIII in plasma decreases due to reduced vWF (carrier) levels. This leads to secondary VIIIC deficiency in plasma. So, the intrinsic pathway of coagulation is affected. Hence, aPTT is increased in these patients.

Subtype	Description	Inheritance	Lab findings
Type 1	Quantitative deficiency of vWF	Autosomal dominant	Reduced vWF antigen, activity and Factor VIII

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Subtype	Description	Inheritance	Lab findings
Type 2	Qualitative defect in vWF	Autosomal dominant	Reduced vWF activity to antigen ration<0.6
Type 3	Near-complete (quantitative) deficiency of Factor VIII	Autosomal recessive	Marked reduction or absence in Factor VIII levels

Solution to Question 8:

Hermansky–Pudlak syndrome occurs due to a defect in platelet δ granules.

Platelet granules disorders include:

• Gray platelet syndrome - involves α granules and characterized by thrombocytopenia with large platelets that appear pale on the peripheral smear (due to deficiency of the α granules)

• Quebec platelet syndrome - defect in α granules

• Hermansky–Pudlak syndrome - defect in δ granules and characterized by hypopigmentation and bleeding manifestation

• Wiskott–Aldrich syndrome - mutations in the WASp gene expressed in the X chromosome and characterized by microthrombocytopenia, eczema, recurrent infections

Solution to Question 9:

Bernard–Soulier disease is due to deficiency of Gp Ib/ IX.

Bernard–Soulier syndrome is characterized by large platelets. Ristocetin aggregation is abnormal.

Factor VIII deficiency causes hemophilia.

Deficiency	Defect	Disease
Gp Ib/IX	Adhesion of platelets	Bernard–Soulier syndrome
Gp IIb/IIIa	Aggregation of platelets	Glanzmann thrombasthenia
von Willebrand factor	Adhesion>Aggregation	Von Willebrand disease

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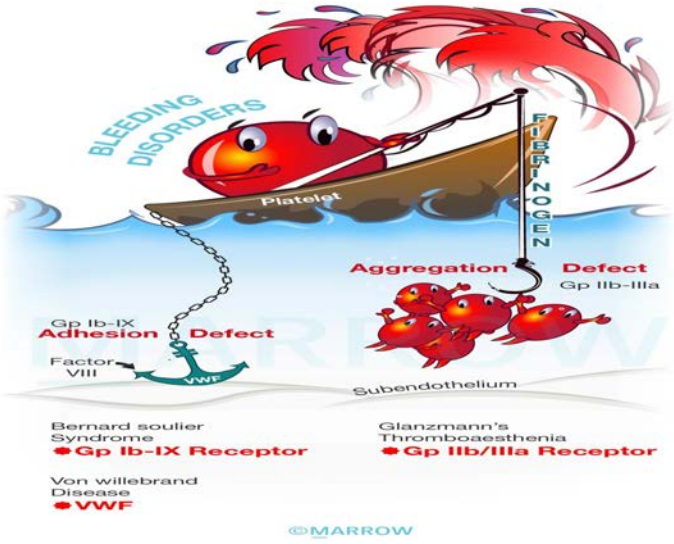

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Solution to Question 10:

In Bernard–Soulier syndrome, platelet aggregation by ristocetin is abnormal.

The receptor for vWF i.e. Ib-IX is essential for normal platelet adhesion to the subendothelial extracellular matrix. In this condition, there is deficiency of Gp Ib/ IX. Clinical manifestations include epistaxis, ecchymoses, menorrhagia, gingival bleeding, and gastrointestinal bleeding.

Laboratory findings seen in Bernard-Soulier syndrome:

• Prolonged bleeding time

• Moderate thrombocytopenia

• Platelet aggregation by ristocetin is deficient (but ADP, arachidonic acid, epinephrine, collagen - normal).

• Clot retraction - normal

• Abnormally large platelets

The image given below shows the abnormally large platelets on peripheral smear seen in Bernard-Soulier syndrome.

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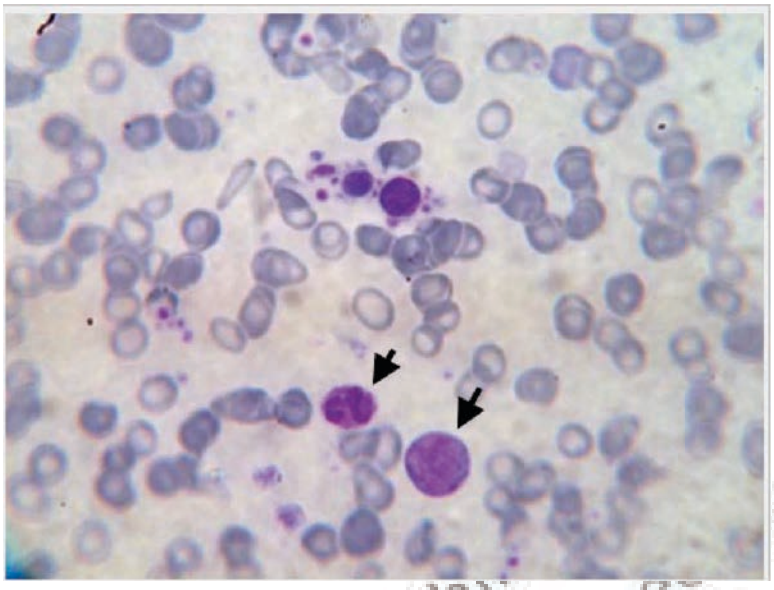

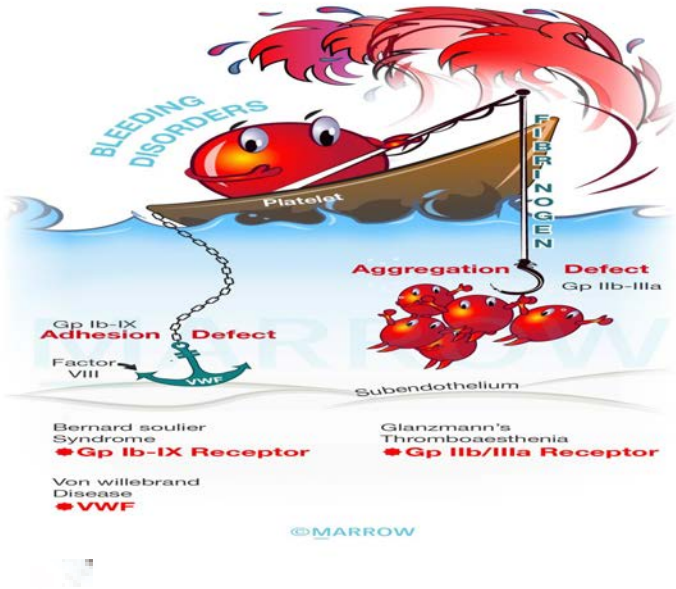

Solution to Question 11:

The given clinical scenario is suggestive of Glanzmann thrombasthenia.

It is an abnormality of platelet GPIIb-IIIa (fibrinogen receptor). Platelets are unable to adhere to each other and to the underlying tissue of the damaged blood vessels. It is inherited in an autosomal recessive manner. The symptoms include mucocutaneous bleeding in the neonatal period, menorrhagia, ecchymoses, epistaxis, and gingival hemorrhage.

Types of Glanzmann thrombasthenia include:

• Type 1: Absence of GPIIb-IIIa

• Type 2: Reduced surface expression of GPIIb-IIIa/ Essentialis athrombia - clot retraction is normal

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• Type 3: Dysfunction of GPIIb-IIIa

Laboratory features of Glanzmann thrombasthenia:

• Normal platelet count and morphology

• Platelet aggregation occurs in response to ristocetin, but not to other agonists (such as ADP, thrombin, collagen or epinephrine)

• Clot retraction is absent

Solution to Question 12:

The given clinical scenario is suggestive of Wiskott–Aldrich syndrome (WAS). The given image shows (A) multiple petechiae over face and hematoma under the right eye and (B) eczema of the foot.

This syndrome is an X-linked recessive, primary immunodeficiency disorder involving the WAS gene. It is characterised by the triad of:

• Severe eczema

• Thrombocytopenia

• Recurrent infections

Small platelets are seen in:

• Wiskott–Aldrich syndrome

• X-linked thrombocytopenia

Large platelets are seen in:

• Bernard-Soulier syndrome

• Myeloproliferative syndrome

• Myelodysplastic syndrome

• May–Hegglin anomaly

• Gray platelet syndrome

Solution to Question 13:

The given clinical scenario is suggestive of chronic immune thrombocytopenic purpura (ITP). Autoantibodies seen in ITP are most often directed against platelet membrane glycoproteins IIb-IIIa or Ib-IX. It is a diagnosis of exclusion due to the following findings:

• Bleeding tendency - petechiae

• Low platelet count, elevated bleeding time

• Presence of megathrombocytes in the peripheral smear - a sign of accelerated thrombopoiesis

• Female preponderance

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• Absence of splenomegaly

Note: Prothrombin time (PT) is normal in ITP.

Solution to Question 14:

Antiplatelet antibodies in chronic immune thrombocytopenic purpura (ITP) are mainly IgG class.

Autoantibodies most often directed against platelet membrane glycoproteins are IIb-IIIa or Ib-IX. It can be demonstrated in the plasma and bound to the platelet surface in about 80% of patients.

Solution to Question 15:

Lymphadenopathy and splenomegaly are uncommon in idiopathic (primary) ITP. They are seen in secondary ITP.

Chronic ITP occurs most commonly in adult women younger than 40 years of age. The female-to-male ratio is 3: 1. It is a type II hypersensitivity reaction. It is of 2 types:

• Primary or idiopathic - without any risk factors

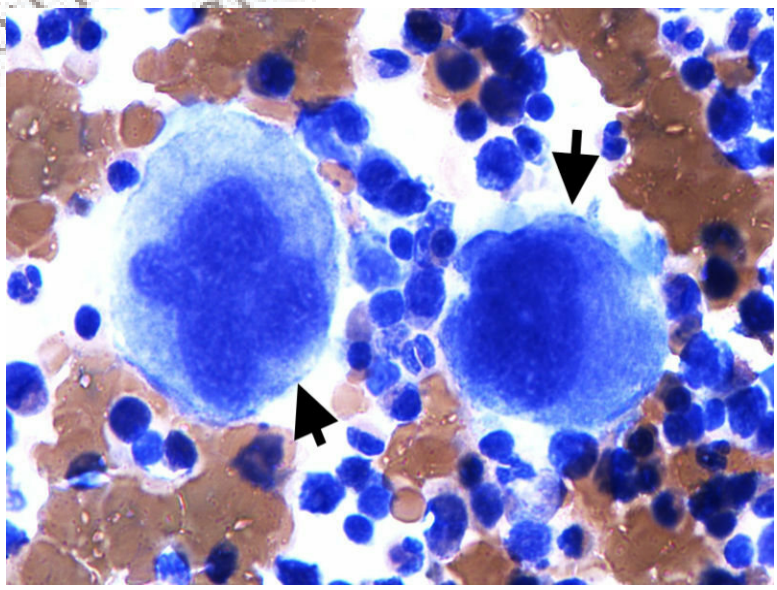
• Secondary - presence of predisposing conditions like SLE, HIV, CLL

Signs of accelerated thrombopoiesis that are seen in this condition are:

• Megakaryocytes in bone marrow

• Megathrombocytes (abnormally large platelets) in peripheral blood

The image given below shows 2 megakaryocytes seen in bone marrow aspirate (Wrights stain).



Acute ITP is mainly a disease of childhood. It occurs with equal frequency in both sexes, mostly after a viral illness. It is self-limited condition, resolves within 6 months.

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Solution to Question 16:

Systemic lupus erythematosus, HIV infection, chronic lymphocytic leukemia, antiphospholipid antibody syndrome can predispose to the development of secondary immune thrombocytopenic purpura (ITP).

The predisposing conditions of secondary chronic ITP include:

- Autoimmune conditions
- Systemic lupus erythematosus (SLE)
- Antiphospholipid antibody syndrome (APS)
- Immune thyroid disease
- Evans syndrome
- Lymphoproliferative diseases
- Chronic lymphocytic leukemia
- Large granular T-lymphocyte lymphocytic leukemia
- Chronic infection
- Helicobacter pylori
- Human immunodeficiency virus (HIV)
- Hepatitis C virus (HCV)

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Solution to Question 17:

The given clinical scenario is suggestive of type II heparin-induced thrombocytopenia (HIT). It is not self-resolving.

Thrombocytopenia occurs in about 5% of persons receiving heparin and is of two types:

Feature	Type I	Type II
Incidence	More common	Less common
Occurrence	Rapidly after onset of therapy	5 to 14 days after therapy
Pathogenesis	Direct platelet-aggregating effect of heparin	Antibodies against heparin-platelet factor 4 complexes
Severity	Less severe	Often leads to life-threatening venous and arterial thrombosis
Treatment	Self-resolving	Immediate discontinuation of heparinAlternate non-heparin anticoagulant to be used

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Solution to Question 18:

Terlipressin does not cause drug-induced thrombocytopenia.

Drug-induced thrombocytopenia can be caused by:

• Vancomycin

• Quinine

• Rifampin

They cause thrombocytopenia through direct effects on platelets or secondary to immunologically mediated platelet destructions. Quinine, quinidine, and vancomycin bind to platelet glycoprotein and create antigenic determinants that are recognized by antibodies.

Solution to Question 19:

The risk of severe heparin-induced thrombocytopenia is lowered with LMWH but not eliminated. Hence, once severe HIT develops even LMWH exacerbates the thrombotic tendency and must be avoided.

Management of HIT includes the immediate withdrawal of heparin therapy and instituting an alternative non-heparin anticoagulant.

Solution to Question 20:

ADAMTS13 deficiency is associated with thrombotic thrombocytopenic purpura (TTP).

ADAMTS13 is also called vWF metalloprotease which degrades very high-molecular-weight multimers of von Willebrand factor (vWF). Its deficiency causes accumulation of these multimers in the plasma and promotes platelet activation and aggregation.

TTP is a part of a spectrum of clinical syndromes called thrombotic microangiopathy. They are caused by insults that lead to excessive activation of platelets, which deposit as thrombi in small blood vessels.

Features of TTP include:

• Fever

• Thrombocytopenia

• Microangiopathic hemolytic anaemia

• Transient neurologic deficits

• Renal failure

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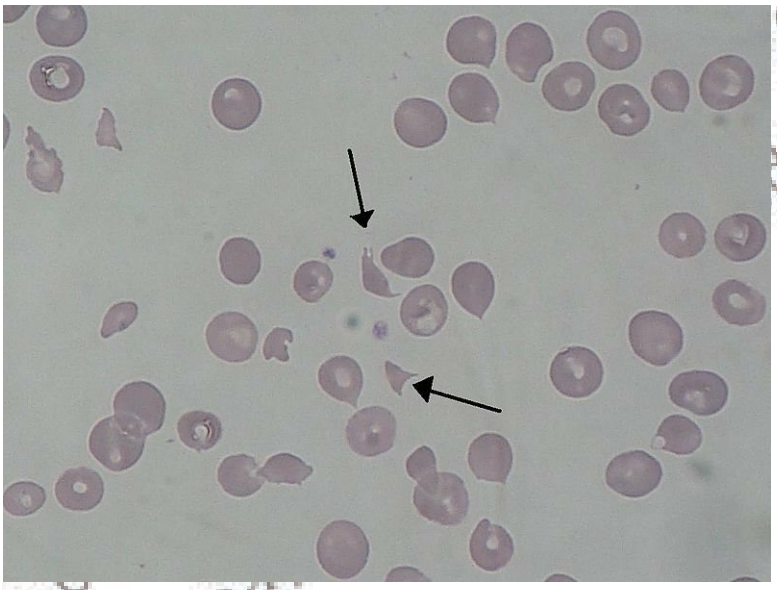
Solution to Question 21:

The given clinical scenario and peripheral smear showing helmet cells or schistocytes are suggestive of hemolytic uremic syndrome (HUS). This condition is most commonly associated with enterohemorrhagic Escherichia coli strain O157: H7 worldwide.

This strain releases Shiga-like toxin. This toxin is absorbed from the inflamed gastrointestinal mucosa into the circulation and causes endothelial dysfunction. It leads to platelet activation and aggregation. Children and older adults are at the highest risk.

The image given below shows schistocytes or helmet cells seen in HUS.



Solution to Question 22:

Atypical hemolytic uremic syndrome is not associated with deficiency of CD59.

It is associated with deficiency of the following components:

• Complement factor H

• Membrane cofactor protein (CD46)

• Complement factor I

These three proteins prevent excessive activation of the alternative complement pathway.

Deficiencies of these proteins can be caused by inherited defects or acquired inhibitory autoantibodies. The disease may be associated with a remitting, relapsing course.

Solution to Question 23:

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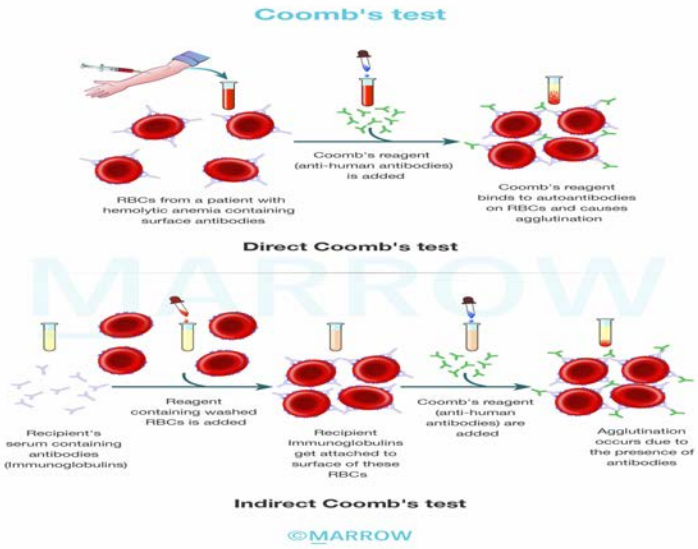
Coombs test is positive in immune thrombocytopenic purpura (ITP) as it is an immunogenic cause of thrombocytopenia.

Thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) and disseminated intravascular coagulation (DIC) are nonimmunogenic causes. Hence, Coombs test is negative in these conditions.



Solution to Question 24:

Weber–Osler–Rendu syndrome is a disorder of the blood vessels.

It is an autosomal-dominant disorder caused by mutations that modulate TGF-° signalling. It is also known as hereditary hemorrhagic telangiectasia.

This condition is characterized by dilated, tortuous blood vessels with thin walls that bleed readily. Bleeding is most common in the mucous membranes of the nose (epistaxis), tongue, mouth, and eyes, and throughout the gastrointestinal tract.

Platelet count, prothrombin time (PT), and activated partial thromboplastin time (aPTT) are normal.

Clinical conditions in which abnormalities of vessel wall cause bleeding include:

• Infections - meningococcemia, infective endocarditis, rickettsioses

• Collagen defects - Ehlers–Danlos syndrome, scurvy, and Cushing's syndrome

• Perivascular amyloidosis - most common with amyloid light-chain (AL) amyloidosis

• Henoch–Schönlein purpura

• Drug reactions

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Coagulation Pathway Disorders

Question 1:

What is the most common hereditary disease associated with life-threatening bleeding?

a) Hemophilia A

b) Immune thrombocytopenic purpura

c) Thrombotic thrombocytopenic purpura

d) von Willebrand disease

Question 2:

A 12-year-old boy presents with the following finding after a trivial fall. His lab investigations are given below. What is the most likely diagnosis?

a) Immune thrombocytopenic purpura

b) Bernard Soulier syndrome

c) Hemophilia

d) Vitamin K deficiency

Question 3:

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A 7-year-old boy was found to have excessive bleeding following tooth extraction. Lab investigations revealed prolonged aPTT, decreased serum factor VIII levels and normal VwF activity. What is the mode of inheritance of this condition?

a) X-linked recessive

b) X-linked dominant

c) Autosomal dominant

d) Autosomal recessive

Question 4:

Which of the following statements is false about hemophilia?

a) Hemophilia B never affects females

b) Hemophilia C can affect females

c) Hemophilia A in female may indicate unfavourable lyonization

d) Hemophilia A can occur without any family history

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Question 5:

A 10-year-old child with easy bruising was diagnosed to have moderate hemophilia A. What will be the percentage of normal factor VIII in her?

a) 5-15%

b) 2-5%

c) 15-30%

d) 40-60%

Question 6:

Which of the following lab findings are seen in patients with hemophilia A?

a) Option 1

b) Option 2

c) Option 3

d) Option 4

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Question 7:

A newborn baby develops severe umbilical cord bleeding soon after birth. Lab investigations are given below. What is the most likely diagnosis?

a) Vitamin K deficiency

b) von Willebrand disease

c) Hemorrhagic disease of newborn

d) Factor XIII deficiency

Question 8:

A Hemogram of a 23-year-old patient with a bleeding disorder is given below. Which of the following would you use to differentiate between heparin-induced thrombocytopenia and afibrinogenemia in this patient?

a) Reptilase

b) Ristocetin

c) Russel viper venom

d) Hyperosmolar urea

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Question 9:

A 1-year-old child was diagnosed to have Kasabach-Merritt syndrome. What is this condition associated with?

a) Thrombotic thrombocytopenic purpura

b) Disseminated intravascular coagulation

c) Immune thrombocytopenic purpura

d) Hemolytic uremic syndrome

Question 10:

Which of the following clotting factor deficiency will not affect clotting in vivo?

a) Factor VII

b) Factor V

c) Factor XII

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d) Factor IX

Question 11:

Which test evaluates the extrinsic pathway?

a) APTT

b) PT

c) TT

d) Bleeding time

Question 12:

You are collecting a blood sample to send for prothrombin time in a patient in the ward. Which of the following is true about this investigation?

a) Sample must be immediately refrigerated

b) Sample must contain platelet-rich plasma

c) Test must be done within 2 hours of sample collection

d) Sample is activated with kaolin

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Question 13:

At what temperature should you store the sample for antiphospholipid antibody factor assays?

a) Room temperature

b) 4 to 8 degrees

c) <4 degree

d) -8 degree

Question 14:

A 50-year-old male patient presents to the casualty with severe bleeding following a road traffic accident. He is a known cardiac disease patient on anticoagulant therapy. As an intern, you were asked to collect blood for coagulation studies. Which colour vacutainer will you pick?

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a) Lavender

b) Green

c) Red

d) Blue

Question 15:

Which of the following is the color of vacutainer containing sodium fluoride as a content?

a) Red

b) Grey

c) Blue

d) Yellow

Question 16:

A child was brought to the emergency department with a big lesion on his forearm. As a surgery resident you decide to excise the lesion in the emergency operation theatre. Which of the following investigations will test the entire coagulation pathway?

a) Activated partial thromboplastin time

b) Prothrombin time

c) Thromboelastography

d) Bleeding time

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Answer Key

Question No.	Correct Option
1	a
2	c
3	a
4	a
5	b
6	a
7	d

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8	a
9	b
10	c
11	b
12	c
13	c
14	d
15	b
16	c

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Detailed Explanations

Solution to Question 1:

The most common hereditary disease associated with life-threatening bleeding is hemophilia A. It is caused by mutations in factor VIII, an essential cofactor for factor IX in the coagulation cascade.

Note: von Willebrand disease is the most common inherited bleeding disorder.

Solution to Question 2:

The given clinical scenario showing hemarthrosis and elevated aPTT is suggestive of hemophilia.

Specific tests for measuring levels of factor VIII and factor IX can determine whether it is hemophilia A or hemophilia B respectively.

Clinical features of hemophilia:

• Hemarthroses - joint hemorrhages, later causing progressive deformities

• Recurrent bleeding

• Pseudotumour syndrome - fascial hemorrhages that occur as blood-filled cysts with calcification and proliferation of fibroblasts, giving the appearance of the tumor

It is associated with elevated aPTT and normal platelet count, bleeding time, and PT.

Option A: In ITP, the platelet count is low and bleeding time is prolonged.

Option B: In functional platelet disorders, like Bernard Soulier syndrome, the platelet count is normal and bleeding time is prolonged.

Option D: In vitamin K deficiency, both PT and aPTT are prolonged. PT is relatively more prolonged than is the aPTT.

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Solution to Question 3:

The given clinical scenario is suggestive of Hemophilia A (factor VIII deficiency). It is inherited as an X-linked recessive trait. Hence, it affects mainly males and homozygous females.

Hemophilia B is also inherited as X-linked recessive trait.

Hemophilia C is inherited as an autosomal-recessive trait.

Solution to Question 4:

Hemophilia A and B mostly affect males, but rarely can affect females also.

Hemophilia A is an X-linked recessive disorder, affecting mainly males and homozygous females. Rarely, excessive bleeding occurs in heterozygous females. It is due to the inactivation of the X chromosome bearing the normal factor VIII allele by chance in most cells (unfavourable lyonization). About 30% of patients have no family history and the disorder is caused due to new mutations.

Hemophilia B is inherited as X-linked recessive trait. There is a deficiency of factor IX.

Hemophilia C is an autosomal-recessive condition and hence can occur in females. There is a deficiency of factor XI.

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Solution to Question 5:

Patients with moderate hemophilia A have 2% - 5% of normal levels of factor VIII.

The clinical manifestations of Hemophilia A vary in severity, corresponding to the level of factor VIII present. They can be classified as:

Severity	Levels of factor VIII
Mild	6-50%
Moderate	2-5%
Severe	<1%

Solution to Question 6:

Patients with hemophilia A have:

• Prolonged partial thromboplastin time (aPTT) - intrinsic pathway abnormality

• Normal prothrombin time (PT)

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• Normal bleeding time

• Normal platelet count

Solution to Question 7:

The given scenario is suggestive of factor XIII deficiency. A positive urea lysis test confirms the diagnosis.

Factor XIII is also known as clot-stabilizing factor that converts unstable fibrin clot into a stable clot. Its deficiency typically presents as excessive umbilical cord bleeding in the newborn.

Laboratory findings in this condition are:

• Normal levels of bleeding time (BT), platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT)

• Positive urea lysis test - confirmatory test which demonstrates lysis of clot by hyperosmolar urea in affected individuals

The parameters for the given diseases:

Condition	PT	aPTT	BT	TT	Platelet count	Urea lysis test
Vitamin K deficiency	increased	increased	increased	normal/increased	normal/decreased	negative
Von Willebrand disease	normal	normal/increased	increased	normal	normal	negative
Hemorrhagic disease of newborn	increased	increased	increased	normal/increased	normal/decreased	negative
Factor XIII deficiency	normal	normal	normal	normal	normal	positive

Solution to Question 8:

Reptilase is a thrombin agonist which is used to differentiate heparin-induced thrombocytopenia (HIT) and afibrinogenemia. It is resistant to the action of heparin.

The differential diagnosis for normal platelet count with elevated PT, aPTT and TT are HIT and afibrinogenemia. After adding reptilase, if the TT is corrected, it points to HIT.
In afibrinogenemia, since there is an absence of fibrin, there is no change in the TT.

Solution to Question 9:

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Kasabach–Merritt syndrome is associated with DIC (disseminated intravascular coagulation). This syndrome is characterised by the following features:

• Rapidly growing vascular tumour

• Thrombocytopenia

• Microangiopathic haemolytic anaemia

• Consumptive coagulopathy

An unusual form of DIC occurs in association with giant hemangiomas. In this type, stasis and recurrent trauma to the fragile blood vessels cause thrombi to form within the neoplasm.

The image given below shows a reddish-blue lesion covering the lower part of the abdomen. It is a caverno-capillary haemangioma seen in Kasabach–Merritt syndrome.

Solution to Question 10:

Factor XII deficiency will not affect the clotting in vivo.

Unlike the clotting cascade in the lab (in vitro), the cascade in the body (in vivo) differs slightly - as tissue factor (TF) is the major initiator of the cascade. The TF/VIIa complex is the most important activator of factor IX and factor IXa/factor VIIIa complex is the most important activator of factor X. Factor V is involved in both the pathways as shown in the image below.

The coagulation cascade in the laboratory:

• Extrinsic pathway sequence (in a test tube): Tissue factor → Factor VII → Factor X.

• Intrinsic pathway sequence (in a test tube): Factor XII → Factor XI → Factor IX → Factor X

Laboratory methods to initiate clotting include:

• Intrinsic pathway - adding phospholipids, calcium, and either a negatively charged substance such as glass beads

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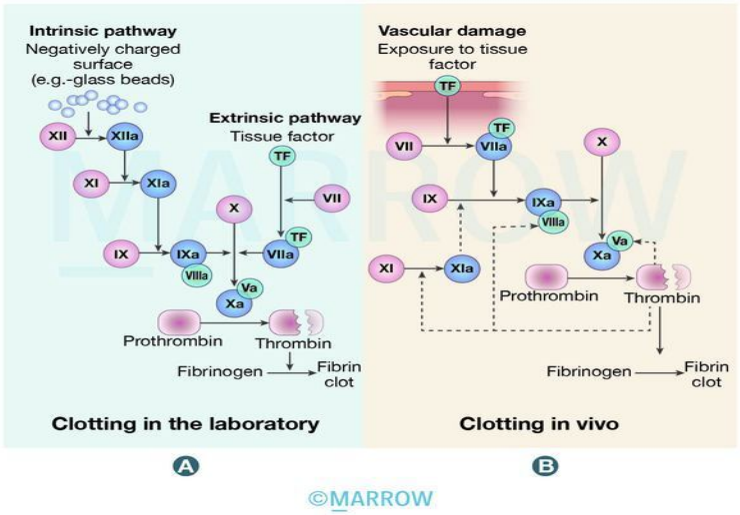
• Extrinsic pathway - a source of tissue factor



Solution to Question 11:

Prothrombin time (PT) evaluates the extrinsic pathway of coagulation.

PT measures the clotting time of plasma in the presence of an optimal concentration of tissue extract (thromboplastin). This indicates the overall efficiency of the extrinsic clotting system.

Causes of prolonged PT:

• Administration of oral anticoagulant drugs - vitamin K antagonists

• Liver disease - obstructive jaundice

• Vitamin K deficiency

• Disseminated intravascular coagulation

• Previously undiagnosed factor VII, X, V or prothrombin deficiency or defect (rare)

Activated partial thromboplastin time (APTT) measures the clotting time of plasma after the activation of contact factors and the addition of phospholipid and $CaCl_2$, but without added tissue thromboplastin. It indicates the overall efficiency of the intrinsic pathway.

Causes of prolonged APTT:

• Disseminated intravascular coagulation

• Liver disease

• Massive transfusion with plasma-depleted red blood cells

• Administration of or contamination with heparin or other anticoagulants

• A circulating anticoagulant (inhibitor)

• Deficiency of a coagulation factor other than factor VII

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• Intake of oral anticoagulant drugs

• Vitamin K deficiency

Solution to Question 12:

The test for prothrombin time is done within 2 hours.

The differences between PT and aPTT are:

Feature	PT	aPTT
Coagulation pathway tested	Extrinsic and common	Intrinsic and common
Normal value	11-13 seconds	25-35 seconds
Sample	Platelet-poor plasma	Platelet-poor plasma
Activating agent	Thomboplastin	KaolinSilicaEllagic acid

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Solution to Question 13:

The sample for antiphospholipid antibody assay must be stored at <4°.

Samples for coagulation studies should be stored always at room temperature (20 to 25 degrees).

Solution to Question 14:

The most commonly used vacutainer for coagulation studies is a blue vacutainer containing trisodium citrate.

The benefits of trisodium citrate are that the calcium ion is neutralized more rapidly in citrate.

Other anticoagulants are unacceptable for coagulation studies. The labile factors (factors V and VIII) are unstable in oxalate (grey), whereas heparin (green) and EDTA (lavender) directly inhibit the coagulation process and interfere with end-point determinations. Also, activated partial thromboplastin time (aPTT) tests are more sensitive to the presence of heparin (green).

The image given below shows colour coding of vacutainers with the anticoagulant used and their practical uses.

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Color coding of vacutainers

Cap colour	Additive	Use
	EDTA	CBC
	Sodium citrate	Coagulation studies ESR by Westergren method
	Potassium oxalate or Sodium fluoride	Blood glucose or alcohol
	No additive	Collection of serum
	Acid citrate dextrose	Preservation of RBCs for blood banking and HLA typing
	Heparin	Osmotic fragility ABG Leukocyte function test Immunophenotyping

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Note: Heparin is used for blood sample collection for electrolyte estimation.

Solution to Question 15:

Sodium fluoride is present in the grey coloured tube.

Sodium fluoride inhibits glycolysis. Hence, is used for the estimation of blood glucose and alcohol.

Solution to Question 16:

Thromboelastography (TEG) tests the entire coagulation pathway. It measures coagulation cascade, platelet function, and fibrinolysis.

It is a test that quantitatively measures the ability of whole blood to form a clot. The advantages are:

-

Global assessment of blood coagulability, including coagulation cascade, platelet function, and fibrinolysis

-

Rapid real-time bedside test with a simple methodology (point-of-care testing)

-

Diagnosis of coagulopathic bleeding

-

Guide transfusion therapy and decrease the use of blood products

-

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Detect dynamic changes in blood coagulation during resuscitation

•

Predict the clinical efficacy of therapeutic agents affecting blood coagulability

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Blood Products and Transfusion Reactions

Question 1:

Choose the correct option regarding the storage temperatures of blood components.

a) RBC 20-22°C, Platelet 2-6°C, FFP -30°C

b) RBC 2-6°C, Platelet 20-22°C, FFP -30°C

c) RBC -30°C, FFP 2-6 °C, Platelet 20-22°C

d) RBC 20-22°C, FFP below -30°C, Platelet 2-6 °C

Question 2:

Which of the following can be used to store blood for up to 35 days?

a) Acid Citrate dextrose

b) Citrate phosphate dextrose

c) Citrate phosphate 2 dextrose

d) Citrate phosphate dextrose adenine - 1

Question 3:

What is correct regarding transfusion of the blood received from blood bank?

a) It should be started within 4 hours of receiving it from the blood bank.

b) It should be completed within 4 hours of receiving from the blood bank.

c) No such time restraint and can be done anytime.

d) It should be completed within 6 hours of receiving from the blood bank.

Question 4:

Which of the following patients receiving blood transfusions are more prone to develop bacterial sepsis?

a) A young women with severe anaemia

b) A patient with severe thrombocytopenia

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c) A child with hemophilia A

d) A patient with vonWillebrand disease

Question 5:

A patient has been brought with severe bleeding to your ER. His blood group is unknown. Fresh frozen plasma from which of the following blood groups can be given?

a) O

b) AB

c) B

d) A

Question 6:

What is the most common reaction occurring in patients undergoing blood transfusions?

a) Febrile hemolytic

b) Febrile non-hemolytic

c) Non-febrile hemolytic

d) Acute hemolytic

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Question 7:

Blood transfusion was started in a patient with severe anaemia. Within a few minutes she developed generalised pruritis, swelling of the tongue and stridor. Which antibody deficiency in the recipient most commonly causes this condition?

a) Ig E

b) Ig A

c) Ig M

d) Ig G

Question 8:

Following blood transfusion in a post-operative patient, the following finding was noted. Which of the following is responsible for this reaction?

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a) Ig E antibodies of donor

b) Ig E antibodies of recipient

c) Ig A antibodies of donor

d) Ig A antibodies of recipient

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Question 9:

A patient with thalassemia developed pallor and dizziness 1 week following blood transfusion. His lab reports are given below. Which of the following is seen in this condition?

a) Direct coombs test negative, IgG mediated

b) Direct Coombs test positive, IgG mediated

c) Direct coombs test negative, IgM mediated

d) Direct coombs test positive, IgM mediated

Question 10:

A patient who was admitted for blood transfusion developed transfusion-related acute lung injury. Which of the following statements is false about this condition?

a) Pre-existing lung diseases are a risk factor

b) Incidence with platelet transfusion is more than that with whole blood

c) Symptoms develop after 2 days of transfusion

d) Subsequent transfusions from the same donor increases the incidence

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Question 11:

A 33-year-old man is receiving massive blood transfusion following a fall from height. 4 hours after transfusion, he becomes breathless and oxygen saturation decreases. Chest X-ray shows diffuse bilateral lung infiltrates. Which of the following statements is false regarding this condition?

a) Antibodies against MHC are associated

b) Treatment involves discontinuation of blood transfusion

c) Mortality rate is 5-10%

d) It is mediated by macrophages in lung vasculature

Question 12:

A CKD patient had to undergo dialysis and his Hb was 5.2gm/dL. So two blood transfusions were to be given. The first bag was completed in 2 hours. The second was started and in the midway, he developed shortness of breath and hypertension. Vitals were BP - 180/120 mmHg and pulse rate - 110/min. What is the cause?

a) Allergic

b) Transfusion related circulatory overload

c) Transfusion-related acute lung injury

d) Febrile non-hemolytic transfusion reaction

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Question 13:

A patient who receives recurrent transfusions for thalassemia develops fever and chills during this time. There is no evidence of hemolysis. Which of the following measures can decrease the rate of transfusion reactions?

a) Leukoreduced RBCs

b) Antibiotics

c) Irradiation

d) Washed RBCs

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Answer Key

Question No.	Correct Option
1	b
2	d
3	b
4	b
5	b
6	b
7	b
8	b
9	b
10	c
11	d
12	b
13	a

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Detailed Explanations

Solution to Question 1:

The recommended storage temperatures of different blood components is as follows:

Blood component	Storage temperature
Whole blood and red blood cells	2–6°C
Fresh frozen plasma	-30°C or lower
Cryoprecipitate	Below -30°C
AlbuminFreeze-dried factor VIII	2–8°C
Platelet	20–24°C

Solution to Question 2:

Citrate dextrose phosphate adenine-1 (CDPA-1) can be used to store blood for up to 35 days. It helps in improving ATP synthesis during storage. Hence, it increases the shelf life.

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The disadvantage of using CDPA-1 is that it increases uric acid stone formation.

The shelf life of storage with other components are:

• Acid Citrate dextrose – 21 days

• Citrate-phosphate dextrose – 21 days

Solution to Question 3:

Blood received from blood bank should be completely transfused within 4 hours of receiving.

Principles of blood administration:

• All blood products should be given through an appropriate blood administration set containing a filter.

• A careful aseptic technique should be practised at all times.

• Vital signs should be documented before and after transfusion and as clinically required. For the first 15 minutes after the infusion has begun, the patient should be kept under close observation to detect any signs of a serious transfusion reaction. If none is observed, the infusion rate may be increased.

• One unit of red cells is often given in 1 to 4 hours, depending on the amount to be transfused and on the patient's cardiovascular status. Infusion of a unit for longer than 4 hours is not recommended, as there is a risk of bacterial proliferation because the opened unit is at room temperature.

• No other solution and no medication should be added to or infused through the same tubing as a blood product.

• Ringer's lactate or other solutions containing calcium must never be added to a blood product because the calcium present leads to coagulation.

• After the transfusion has been completed, the transfusion tag or record should become part of the patient's chart.

Solution to Question 4:

Patients with thrombocytopenia receiving blood transfusions (platelets) are more prone to develop bacterial sepsis.

Sepsis is mostly due to significant bacterial contamination of the blood products. Platelets have the maximum risk of causing this condition when compared to red cell preparations. Since patients with thrombocytopenia receive platelet transfusion, they are at an increased risk of infections.

Platelets (unlike red cells) must be stored at room temperature. This is a condition that is favourable for bacterial proliferation. Broad-spectrum antibiotics must be started while waiting for the culture reports.

The blood components that are preferred for the other conditions are:

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- Anaemia - RBCs
- Hemophilia - FFP
- vonWillebrand disease - cryoprecipitate

Solution to Question 5:

Fresh Frozen Plasma (FFP) from AB blood group can be given to this patient as it is the universal plasma donor. AB plasma does not contain antibodies against antigens on RBCs of AB blood group.

O Rh-negative blood is the universal blood donor. It is used during emergency packed cell blood transfusion with an unknown blood group. It is preferred because it lacks the A and B and Rh antigens. Hence, it cannot be hemolyzed by anti-A, anti-B or anti-D antibodies in the recipient's blood.

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Solution to Question 6:

The most common blood transfusion reaction is the febrile nonhemolytic reaction.

Solution to Question 7:

The given clinical scenario is suggestive of severe, potentially fatal, allergic reactions. These are most likely to occur in patients with IgA deficiency.

Such reactions may occur when blood products containing certain antigens are given to previously sensitized recipients. It is triggered by recipient IgG antibodies that recognize IgA in the infused blood product.

Solution to Question 8:

The given image, showing a raised and erythematous lesion, is suggestive of urticaria. Such reactions may be triggered by the presence of an allergen in the donated blood product that is recognized by IgE antibodies in the recipient.

These are mild reactions occurring more commonly in 1% to 3% of transfusions.

Solution to Question 9:

The given clinical scenario is suggestive of delayed hemolytic reaction following blood transfusion. It is IgG mediated and gives a positive result in direct Coombs test.

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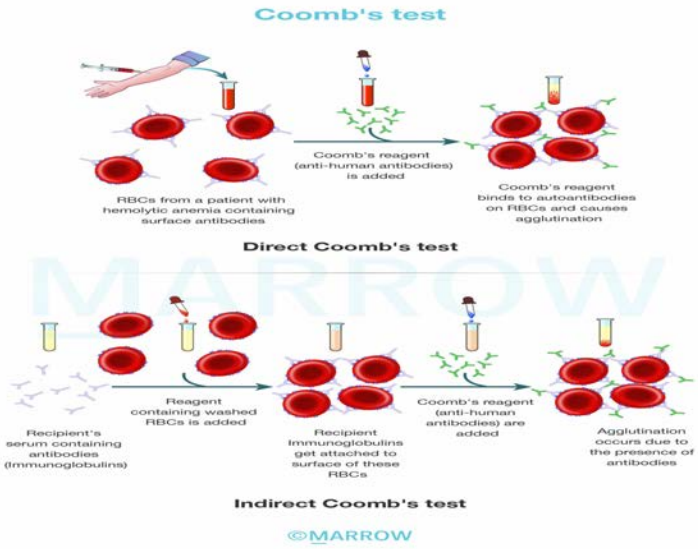
These antibodies recognize foreign protein red cell antigens in a previously sensitized recipient (through a prior blood transfusion). They present with laboratory features of hemolysis like low haptoglobin level and elevated LDH.

Acute hemolytic reactions are usually caused by preformed IgM antibodies against donor red cells that fix complement. The direct Coombs test is usually positive.



Solution to Question 10:

Transfusion-related acute lung injury (TRALI) is sudden-onset respiratory failure that occurs during or soon after the transfusion. It occurs within 6 hours, and not after 2 days following transfusion.

TRALI is a severe fatal complication of blood transfusion. The incidence of TRALI is low (1 per 10,000 transfusions). However, it may occur more frequently in patients with preexisting lung disease.

The pathogenesis involves a two-hit hypothesis:

• Priming event - increased sequestration and sensitization of neutrophils in the microvasculature of the lung

• Second hit - the factor (most commonly MHC class I antigens) present in the transfused blood product activates the primed neutrophils

TRALI can occur in transfusions with all plasma-containing blood products. However, it is more likely to occur following the transfusion of fresh frozen plasma and platelets. This is because these products contain high levels of donor antibodies.

Note: TRALI is important to recognize because donor products that induce complications in one patient are much more likely to do so in a second. Indeed, recent measures to exclude multiparous women from plasma donation have resulted in reduced incidence of TRALI.

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Solution to Question 11:

The given clinical scenario is suggestive of TRALI (transfusion-related acute lung injury). It is mediated by neutrophils entrapped in the lung vasculature.

Features of TRALI are:

• Fever

• Hypotension

• Hypoxemia

• Bilateral pulmonary infiltrates - not responsive to diuretics

Treatment is mainly supportive and blood transfusions are discontinued. The mortality rate in this condition is 5-10%.

Solution to Question 12:

The given clinical scenario is suggestive of transfusion-associated circulatory overload (TACO).

TACO is caused by rapid or excess transfusion of red cell preparations or plasma products. This condition is characterized by:

• Dyspnea with O2% <90 at room air

• Bilateral infiltrates on chest X-ray

• Systolic hypertension

• Elevation of brain natriuretic peptide, 1.5 times that of pre-transfusion levels

It can be prevented by administering the transfusion slowly, at the rate of 1 to 2 ml of blood/kg of body weight per hour. Diuretics are also used if necessary.

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Solution to Question 13:

The given scenario is suggestive of febrile non-hemolytic transfusion reaction (FNHTR). Such reactions can be prevented by using leukoreduced RBCs.

Removal of leukocytes from the blood is called leukoreduction. It is done before storage to prevent cytokine formation.

FNHTR may occur due to the following:

• Sensitization to the WBC antigens by previous blood transfusions or pregnancy

• Cytokines produced by the donor leukocytes during storage

• Bacterial contamination

Note: Luspatercept is an erythroid maturation agent, a receptor fusion protein consisting of a modified extracellular domain of human activin receptor type-2B linked to the human Ig-G1 Fc domain. The drug was recently approved by the FDA for the treatment of transfusion-dependent

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Acute Lymphocytic Leukemia (ALL)

Question 1:

Which of these is not a pre-leukemic condition?

a) Paroxysmal nocturnal hemoglobinuria

b) Aplastic anemia

c) Myelodysplastic syndrome

d) Paroxysmal cold hemoglobinuria

Question 2:

Which of the following is true about the pathogenesis of acute leukemia?

a) Arrest in differentiation and increased apoptosis

b) Enhanced differentiation and decreased apoptosis

c) Enhanced differentiation and increased apoptosis

d) Arrest in differentiation and decreased apoptosis

Question 3:

As per WHO classification, what percentage of blast cells in bone marrow biopsy is required to diagnose a patient with acute leukemia?

a) 15

b) 20

c) 25

d) 30

Question 4:

Which of the following conditions does not increase the risk of acute lymphoblastic leukemia?

a) Bloom syndrome

b) Li-Fraumeni syndrome

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c) Fanconi anemia

d) Polycythemia vera

Question 5:

Which of the following is the most common type of acute lymphoblastic leukemia?

a) Pre B cell

b) B cell

c) T cell

d) Pre T cell

Question 6:

Which of the following is not a primary T-cell marker?

a) CD1

b) CD5

c) CD8

d) CD10

Question 7:

Block-like positivity for PAS on immunohistochemistry of a bone marrow sample is seen. Which of the following cells show this finding?

a) Lymphoblast

b) Myeloblast

c) Monoblast

d) Erythroblast

Question 8:

Which of the following cells does not stain positively with Sudan black?

a) Lymphocytes

b) Myeloblasts

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c) Eosinophils

d) Promyelocytes

Question 9:

What is the most commonly affected gene in patients with T-cell acute lymphoblastic leukemia?

a) NOTCH1

b) PAX5

c) ETV6

d) RUNX1

Question 10:

A patient with acute lymphoblastic leukemia is found to have t(9;22). What will be the size of BCR-ABL fusion protein produced?

a) 210 kDa

b) 190 kDa

c) 230 kDa

d) 170 kDa

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Question 11:

On immunophenotyping of a patient with early pre-B acute leukemia, which of the following marker will be negative?

a) TdT

b) DR

c) CD19

d) Cytoplasmic immunoglobulin

Question 12:

Which of the following is not usually involved in the immunohistochemistry of acute lymphoblastic leukemia?

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a) Tdt

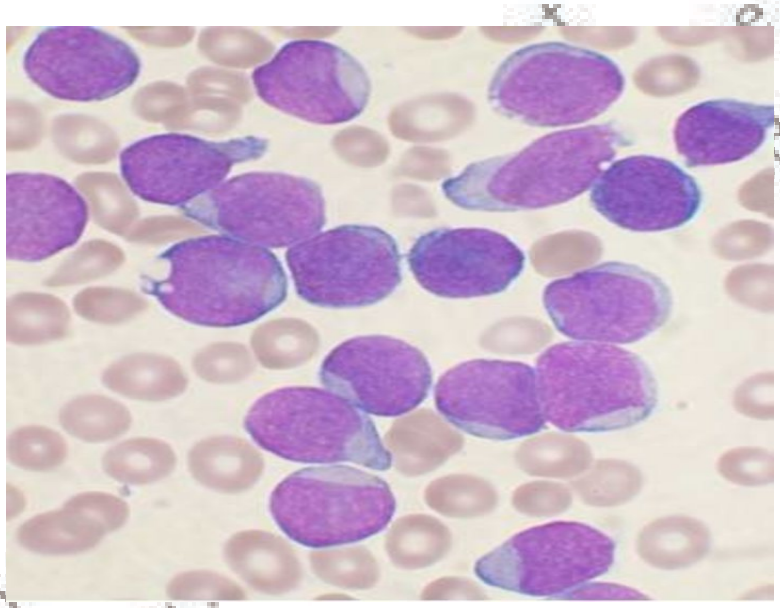
b) CD1a

c) CD3

d) Cytokeratin

Question 13:

A 10-year-old boy with fever, weight loss came to the hospital. On examination, he was pale and had significant lymphadenopathy. The bone marrow histology of the person is as given below. Your diagnosis is?



a) Acute monocytic leukemia

b) Acute myelomonocytic leukemia

c) Acute lymphoblastic leukemia

d) Juvenile myelomonocytic leukemia

Question 14:

An adolescent male patient presents with fatigue. His total leucocyte count is 138 x 10^9 / L with 80% blasts on the peripheral smear. Chest X-ray shows a large mediastinal mass. The bone marrow aspirate is as shown below. What would the immunophenotyping of this patient's blasts most likely demonstrate?

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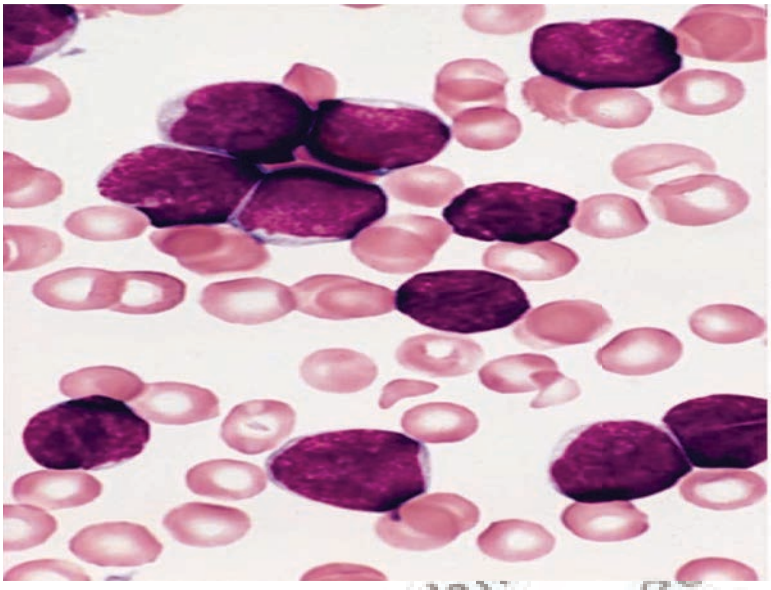

a) Pre B-cell phenotype

b) Immature T-cell phenotype

c) Myeloid phenotype

d) Mature B-cell phenotype

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Question 15:

In a patient with acute leukemia, the immunophenotype pattern of the blasts is positive for CD10, CD13, CD19, and CD33. What is the most probable diagnosis?

a) Acute lymphoblastic leukemia

b) Biphenotypic leukemia

c) Acute myeloid leukemia - M1

d) Acute myeloid leukemia - M3

Question 16:

A patient with weight loss and fever is diagnosed with acute lymphoblastic leukemia. Which of the following is a good prognostic indicator of this condition?

a) MLL gene translocation

b) t (12;21)

c) t (9;22)

d) Hypodiploidy

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Question 17:

Bone marrow biopsy of a patient shows > 20% immature blasts with scanty cytoplasm, no granules, and inconspicuous nucleoli. They also stain positive with PAS. Which of the following are good prognostic markers of this condition?

a) 2, 3, and 5

b) 1, 3, and 4

c) 2, 4, and 5

d) 1, 2, and 5

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Answer Key

Question No.	Correct Option
1	d
2	d
3	b
4	d
5	a
6	d
7	a
8	a
9	a
10	b
11	d
12	d
13	c
14	b
15	a
16	b
17	d

Detailed Explanations

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Solution to Question 1:

Paroxysmal cold hemoglobinuria is not a preleukemic condition.

It is an autoimmune hemolytic anemia due to IgG autoantibodies that bind to the P blood group antigen and cause intravascular hemolysis and hemoglobinuria. Most cases are seen in children and show recovery within a month.

Option A: Few patients with paroxysmal nocturnal hemoglobinuria (PNH) develop acute non-lymphocytic leukemia. This is thought to arise from the injured marrow as a secondary hematopoietic disorder.

Option B: Bone marrow aplasia preceding acute lymphoblastic leukemia (ALL) is a rare condition that usually affects children. It generally follows the recovery of normal blood counts and most commonly occurs within 6 months of the onset of aplasia.

Option C: Acute myeloid leukemia (AML) occurs in 10% to 40% of individuals with myelodysplastic syndromes (MDS). It is usually accompanied by the appearance of additional cytogenetic abnormalities.

Solution to Question 2:

In acute leukemia, there is an arrest in differentiation and decreased apoptosis.

Genomic aberrations create oncoproteins. They arrest normal maturation, turn on pro-growth signaling pathways, or protect cells from apoptotic death.

Solution to Question 3:

As per WHO classification, 20% of blast cells must be present in the bone marrow and / peripheral smear for the diagnosis of acute leukemia.

In FAB criteria, the cut-off is more than 30%.

Solution to Question 4:

Polycythemia vera increases the risk of developing AML, not ALL.

Inherited diseases that are associated with a higher risk of developing leukemias are:

- Bloom syndrome
- Fanconi anemia
- Ataxia–telangiectasia
- Down syndrome
- Type-1 neurofibromatosis

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Other germline risk factors for the development of ALL:

• Li-Fraumeni syndrome

• Familial ALL syndrome

Note: AML has a higher incidence during the neonatal period than ALL among children with Fanconi anemia, Bloom syndrome, and Down syndrome.

Solution to Question 5:

Precursor B-cell or pre B cell (previously classified as L1) type is the most common subtype of acute lymphoblastic leukemia (ALL).

Solution to Question 6:

CD10 is not a primary marker of T cells. It is a marker of pre-B cells and germinal-center B cells.

Note: Although CD10/ Common ALL antigen (CALLA) can be found in B-ALL and T-ALL, it is primarily expressed by pre-B cells and germinal centre B cells. Lymphoblasts of both B and T cell lineages, express CD10 that is lost upon progression to a mature phenotype. It is variably expressed by a few mature B cell tumours. However, the expression of CD10 by mature T cells has not been well established.

Solution to Question 7:

Lymphoblasts in acute lymphocytic leukemia (ALL) show block-like or dot-like PAS positivity.

Erythroblasts in acute myeloid leukemia-M6 (AML-M6) show diffuse periodic acid-Schiff (PAS) positivity.

The image given below shows dot-like positivity for periodic acid-Schiff (PAS) in lymphoblasts.

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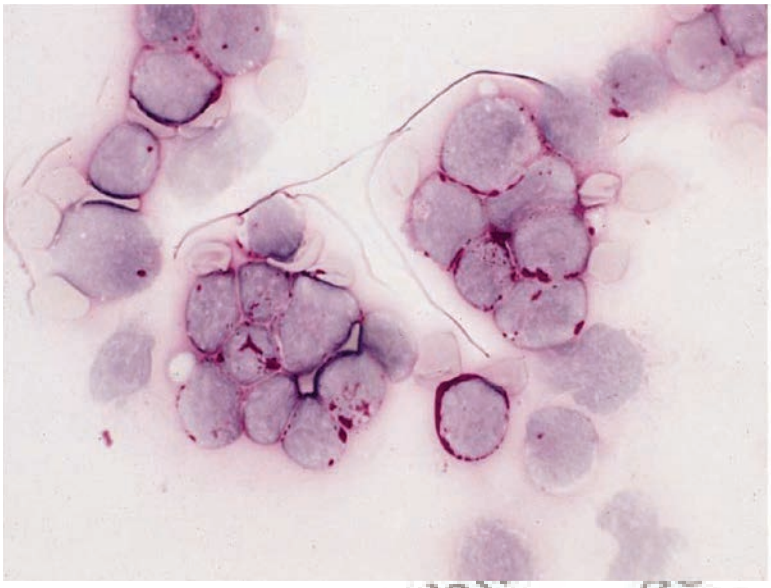

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Solution to Question 8:

Lymphocytes do not stain positively with Sudan black dye. Although some positivity may be seen in azurophilic granules of lymphoblasts.

Sudan Black B (SBB) is a lipophilic dye that binds irreversibly to an undefined granule component in granulocytes, eosinophils, and some monocytes.

Solution to Question 9:

The most commonly affected gene in T-cell acute lymphoblastic leukemia (T-ALL) is NOTCH1.

B-cell acute lymphoblastic leukemia is associated with mutations of genes such as PAX5, E2A, and EBF. It may be associated with balanced t(12;21) involving the genes ETV6 and RUNX1.

Solution to Question 10:

The size of BCR-ABL protein in t(9;22) associated with acute lymphoblastic leukemia (ALL) is 190 kDa.

BCR-ABL fusion transcript protein with t(9;22):

• Major BCR (M-BCR) 210 kDa size in chronic myeloid leukemia (CML) with weaker tyrosine kinase activity

• Minor BCR (m-BCR) 190 kDa size in acute lymphoblastic leukemia (ALL) with stronger tyrosine kinase activity

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• Micro BCR (μ-BCR) 230 kDa size in myeloproliferative neoplasm (MPN) with exuberant neutrophilia

Solution to Question 11:

Cytoplasmic immunoglobulins and CD10 are negative in early pre-B acute leukemia but become positive in pre-B ALL.

Solution to Question 12:

Cytokeratin is not a marker of acute lymphoblastic leukemia (ALL). It is an epithelial cell marker for thymoma.

Tdt, CD1a, and CD3 are markers of ALL.

Solution to Question 13:

The given scenario with bone marrow histology showing lymphoblasts (condensed nuclear chromatin, small nucleoli, scanty agranular cytoplasm) is suggestive of acute lymphoblastic leukemia.

ALL is more common in childhood. Clinical features of ALL include:

• Bone marrow failure - anemia, fever, infections, bleeding

• Mass effects due to neoplastic infiltration - bone pain, generalized lymphadenopathy, splenomegaly, hepatomegaly, and testicular enlargement

• CNS manifestations - headache, vomiting, and nerve palsies

• B-ALL - Pancytopenia due to marrow involvement

• T-ALL - Mediastinal mass, compression of large vessels and airways in the mediastinum, lymphadenopathy, splenomegaly

Solution to Question 14:

The given clinical scenario and bone marrow aspirate are suggestive of T-cell acute lymphoblastic leukemia. Thus, immunophenotyping of the blasts would demonstrate an immature T-cell phenotype (Tdt/CD34/CD7 positive).

The bone marrow aspirate shows lymphoblast with condensed nuclear chromatin, small inconspicuous nucleoli, and scanty cytoplasm lacking granules.

ALL is usually seen in adolescent boys with thymic involvement in 50% to 70%. It has an abrupt stormy onset, within days to a few weeks of the first symptoms.

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Clinical features of ALL include:

• Bone marrow failure - anemia, fever, infections, bleeding

• Mass effects due to neoplastic infiltration - bone pain, generalized lymphadenopathy, splenomegaly, hepatomegaly, and testicular enlargement

• CNS manifestations - headache, vomiting, and nerve palsies

• B-ALL - Pancytopenia due to marrow involvement

• T-ALL - Mediastinal mass, compression of large vessels and airways in the mediastinum, lymphadenopathy, splenomegaly

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Solution to Question 15:

The given clinical scenario points to the diagnosis of acute lymphoblastic leukemia (ALL) based on immunophenotyping.

CD10 and CD19 are markers for B-cell lineage and this patient most probably have B-ALL. Although CD13 and CD33 are myeloid antigens, their expression does not exclude the diagnosis of B- ALL.

Option B: The diagnosis of mixed phenotypic acute leukemia (MPAL)/ acute leukemia of ambiguous lineage (ALAL) (previously known as biphenotypic leukemia) requires a demonstration of multiple lineages in blast cells. According to WHO's latest update (2022), the requirements for assigning more than one lineage to blast cells are :

In the absence of MPO or evidence of monocytic differentiation, expression of CD13 and CD33 is not sufficient for a diagnosis of MPAL. Hence, biphenotypic leukemia is not the answer here.

B cell lineage	CD19 strong:≥1 expressed CD 10, CD22, CD79aCD 19 weak: ≥ 2 or more strongly expresse d CD10, CD22, CD79a
T cell lineage	CD3 positive
Myeloid linea ge	Myeloperoxidase (MPO)ORM onocyte differentiation (non-specific esterase, CD11c, CD1 4, CD64, lysozyme)

Solution to Question 16:

The presence of t (12;21) indicates a good prognosis in acute lymphoblastic leukemia (ALL). It involves genes ETV6 and RUNX1.

Conversely, a translocation involving the MLL gene, t(9;22), and hypodiploidy are associated with a bad prognosis.

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Solution to Question 17:

The given bone marrow biopsy report is suggestive of acute lymphoblastic leukemia (ALL). The good prognostic markers of ALL include trisomy 7, hyperdiploidy, and age of 5 years.

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Acute Myeloid Leukemia (AML)

Question 1:

Which of the following is not a myeloid marker?

a) CD64

b) CD3

c) CD11b

d) CD117

Question 2:

Which of the following is the most common type of acute myeloid leukemia?

a) AML M1

b) AML M2

c) AML M3

d) AML M7

Question 3:

What is the most common subtype of acute myeloid leukemia seen in patients with Down's syndrome?

a) AML M3

b) AML M4

c) AML M6

d) AML M7

Question 4:

A 35-year-man presents with nosebleeds, bleeding gums, and multiple ecchymoses. Lab investigations show the following findings. The blasts are positive for CD33. What is the most likely diagnosis?

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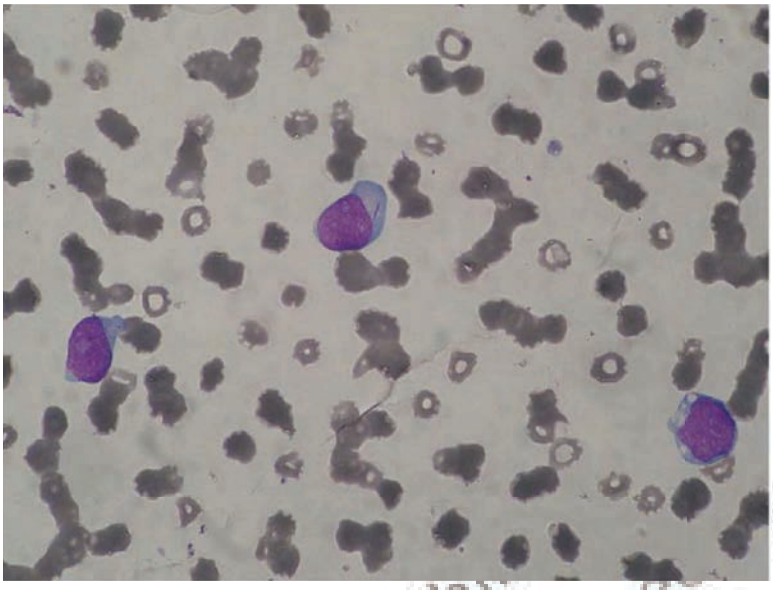

a) Acute myeloid leukemia

b) Acute lymphoblastic leukemia

c) Small Lymphocytic lymphoma

d) Myelodysplastic syndrome

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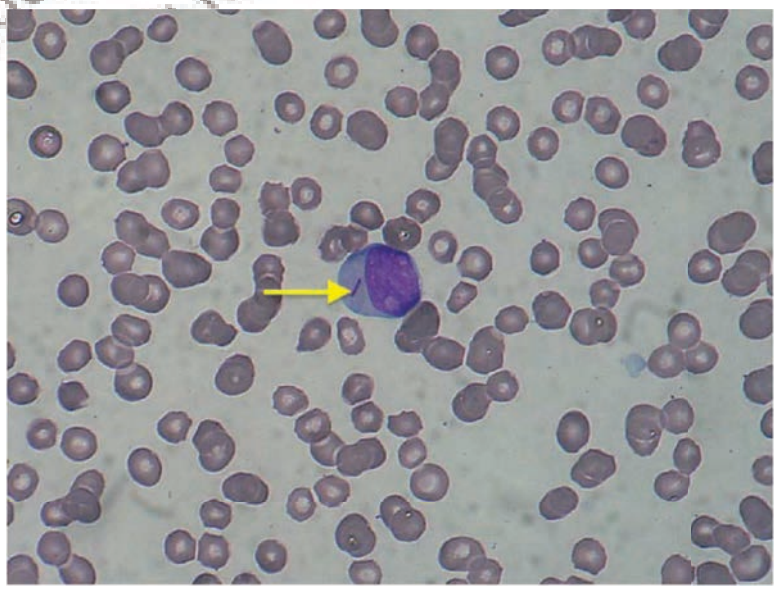
Question 5:

Peripheral smear of a patient with acute promyelocytic leukemia shows myeloblasts with the following finding. What are these made of?



a) Lysosomes

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b) Golgi apparatus

c) Endoplasmic reticulum

d) Ribosomes

Question 6:

In which of the following conditions are Auer rods seen?

a) 1 and 2 only

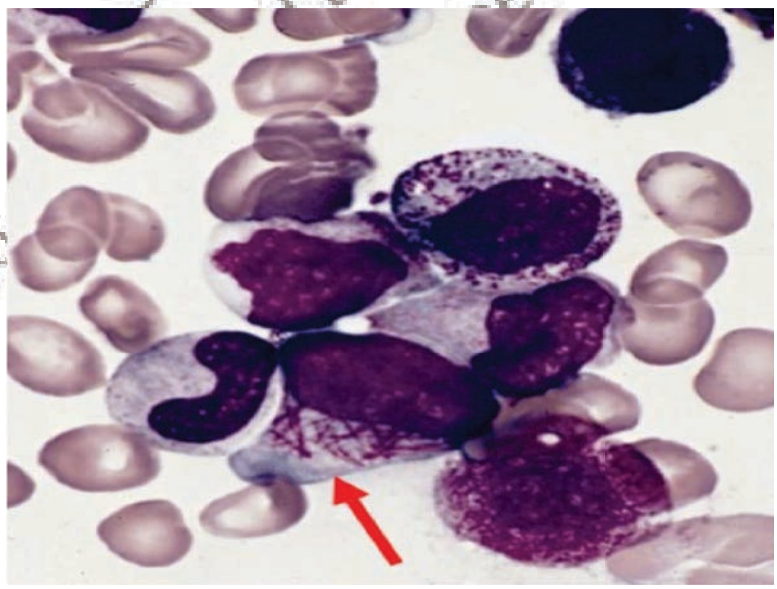
b) 3, 4, and 5

c) 1, 2, 3, 4, and 5

d) 1, 3, and 4

Question 7:

A 20-year-old male patient is diagnosed with acute myeloid leukemia. The peripheral blood smear picture is given in the image. The cell indicated by the arrow is best described as:



a) Auer rod

b) Flaming promyelocyte

c) Faggot cell

d) Dusky promyelocyte

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Question 8:

Increased levels of serum muramidase are seen in patients with which of the following conditions?

a) Acute myeloid leukemia - M4

b) Acute myeloid leukemia - M2

c) Acute myeloid leukemia - M6

d) Acute myeloid leukemia - M3

Question 9:

Which type of AML is known as Di Guglielmo disease?

a) Acute myeloid leukemia - M2

b) Acute myeloid leukemia - M5

c) Acute myeloid leukemia - M6

d) Acute myeloid leukemia - M7

Question 10:

In patients with which of the following conditions, a dry tap may be seen on bone marrow aspiration?

a) Burkitt lymphoma

b) Acute myeloid leukemia - M6

c) Acute myeloid leukemia - M7

d) Undifferentiated leukemia

Question 11:

Bone marrow aspirate of a patient diagnosed with acute myeloid leukemia shows the presence of faggot cells. What is the most likely subtype of acute myeloid leukemia, the patient is suffering from?

a) Acute myeloid leukemia - M5

b) Acute myeloid leukemia - M4

c) Acute myeloid leukemia - M3

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d) Acute myeloid leukemia - M2

Question 12:

A patient diagnosed with acute myeloid leukemia presents with a one-day history of bleeding gums, subconjunctival bleed, and purpuric rash. Investigations done are given below. Which of the following genetic abnormalities is most likely to be detected?

a) Inversion 16

b) t(8;21)

c) Inversion 3

d) t(15;17)

Question 13:

Which type of acute myeloid leukemia is myeloperoxidase negative?

a) Acute myeloid leukemia - M0

b) Acute myeloid leukemia - M1

c) Acute myeloid leukemia - M2

d) Acute myeloid leukemia - M4

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Question 14:

A patient with fatigue and recurrent infections undergoes bone marrow evaluation. It shows > 20% myeloblasts, which stain positive for CD61. What is the likely diagnosis?

a) Acute promyelocytic leukemia

b) Acute megakaryocytic leukemia

c) Acute myelomonocytic leukemia

d) Acute monocytic leukemia

Question 15:

A patient who developed the following lesions over the body was diagnosed with acute myeloid leukemia. Which subtype of AML does this patient most likely have?

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a) Acute myeloid leukemia - M5

b) Acute myeloid leukemia - M3

c) Acute myeloid leukemia - M6

d) Acute myeloid leukemia - M2

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Question 16:

A 38-year-old man presents with bleeding gums for 20 days. He has gingival hyperplasia, hepatosplenomegaly, and lymphadenopathy. Investigations done are given below. Bone marrow biopsy shows 100% cellularity with many blasts cells that are peroxidase negative and non-specific esterase positive. What is the most likely diagnosis?

a) Acute myeloid leukemia - M2

b) Acute myeloid leukemia - M0

c) Acute myeloid leukemia - M5

d) Acute myeloid leukemia - M7

Question 17:

A child presents with bilateral proptosis. After evaluation, he is diagnosed with chloroma. Which of the following is not a marker for this condition?

a) Lysozyme

b) CD43

c) CD45

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d) CD61

Question 18:

In which of the following conditions are Arbiskov cells seen?

a) Leukemia cutis

b) Myeloblastoma

c) Di Guglielmo disease

d) Richter's syndrome

Question 19:

All-trans retinoic acid is used in the treatment of tumor that is associated with which of the following genetic aberrations?

a) PML-RARA

b) BCR ABL

c) cMYC

d) RUNX1 ETO

Question 20:

Which of the following cytogenetic changes suggest a favorable prognosis in patients with acute myeloid leukemia?

a) t (11q23;v) with diverse MLL fusion genes

b) Normal karyotyping with mutated NPM

c) Activating mutations in FLT3

d) Inversion (3)

Question 21:

Which among the following patients with acute myeloid leukemia has a good prognosis?

a) A 56-year-old patient who developed post-chemotherapy AML

b) An infant with AML having complex karyotype

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c) A 60-year-old patient diagnosed with AML-M0 type

d) A patient with AML having Inversion 16

Answer Key

Question No.	Correct Option
1	b
2	b
3	d
4	a
5	a
6	d
7	c
8	a
9	c
10	c
11	c
12	d
13	a
14	b
15	a
16	c
17	d
18	b
19	a
20	b
21	d

Detailed Explanations

Solution to Question 1:

CD3 is not a myeloid marker. It is a T-cell lymphoid marker.

Cell markers:

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• B-cell: CD10, CD19, CD20, CD22, CD23, CD24, CD79b, CD103, Pax-5, kappa, lambda, CD200, cytoplasmic kappa, cytoplasmic lambda

• T- cell: CD1, CD2, CD3, CD4, CD5, CD6,CD7, CD8, TCR apha-beta, TCR gamma-delta, cytoplasmic CD3

• Myeloid: CD11b, CD13, CD14, CD15, CD33, CD64, CD 117, myeloperoxidase

Solution to Question 2:

The most common type of acute myeloid leukemia (AML) is AML - M2 or AML with maturation.

The least common type of AML is AML M7 or megakaryocytic.

Solution to Question 3:

The most common subtype of AML seen in Down's syndrome is acute myeloid leukemia-M7 (AML - M7) or acute megakaryocytic leukemia.

Myeloid proliferations of Down's syndrome are usually megakaryoblastic. It includes:

• Transient abnormal myelopoiesis (TAM) - occurs at birth or within days of birth and resolves in 1 to 2 months

• Myeloid leukemia associated with Down syndrome - occurs later, but usually in the first 3 years of life.

Both are characterized by GATA1 mutations and mutations of the JAK-STAT pathway.

Solution to Question 4:

The given clinical scenario is suggestive of acute myeloid leukemia (AML).

AML is a tumor of hematopoietic progenitors caused by acquired oncogenic mutations that impede differentiation, leading to the accumulation of immature myeloid blasts in the marrow. It occurs at all ages, but the incidence rises throughout life, peaking after 60 years of age.

The peripheral smear shows blasts with abundant cytoplasm, fine azurophilic granules, Auer rods, and delicate nuclear chromatin with 1-4 prominent nucleoli. The blasts are positive for CD33. Occasionally, blasts are entirely absent from the blood (aleukemic leukemia). Bone marrow examination is essential to exclude acute leukemia in pancytopenic patients.

Solution to Question 5:

The image shows Auer rods in myeloblasts. These are needle-shaped azurophilic intracytoplasmic inclusion bodies formed by the fusion of lysosomes.

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Auer rods contain peroxidase and lysosomal enzymes. Myeloblasts with bundles of Auer rods are called faggot cells and are seen in acute promyelocytic leukemia.

Solution to Question 6:

Auer rods are seen in:

• Acute promyelocytic leukemia

• Myelodysplastic syndromes

• Chronic myelomonocytic leukemia

These are not seen in acute monocytic leukemia and acute lymphoblastic leukemia.

Solution to Question 7:

The given cell shows multiple Auer rods clustered together within a single cell resembling a bundle of sticks. Such cells have been termed as faggot cells (faggot in French means bundle of sticks).

Since the question specifically asks about the cell, the best answer is faggot cell (not Auer rods).

Option A: Auer rods are distinctive needle-like azurophilic granules present in many cases but particularly numerous in AML with the t(15;17) aberration (acute promyelocytic leukemia).

Option B: The term flaming promyelocyte refers to cells that appear to be breaking apart, taking on a vibrant reddish-purple hue with the apparent liberation of granules into the surrounding cellular matrix.

Option C: Promyelocytes containing fine granules appear dusky or hazy and are referred to as dusky promyelocytes.

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Solution to Question 8:

Serum muramidase or lysozyme levels are seen to be increased in patients with acute myelomonocytic leukemia (AML - M4).

It is also increased in chronic myelomonocytic leukemia and chronic myeloid leukemia (CML).

Solution to Question 9:

Acute myeloid leukemia-M6 (AML-M6) or acute erythroid leukemia is known as Di Guglielmo disease.

AML-M6 accounts for 1% of AML cases. It has two subtypes:

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• Erythroid/myeloid leukemia (M6a, more common) - Dyserythropoiesis is prominent

• Pure erythroid leukemia/ erythemic myelosis/ Di Guglielmo disease (M6b, rare) - >80% erythroid precursors. Clinical findings include anemia, thrombocytopenia, and variable neutropenia.

Positive stains for erythroid cells are glycophorin A, hemoglobin A, CD36, CD71, CD117, and PAS.

Solution to Question 10:

Acute megakaryocytic leukemia (AML M7) may yield a dry tap on marrow aspiration.

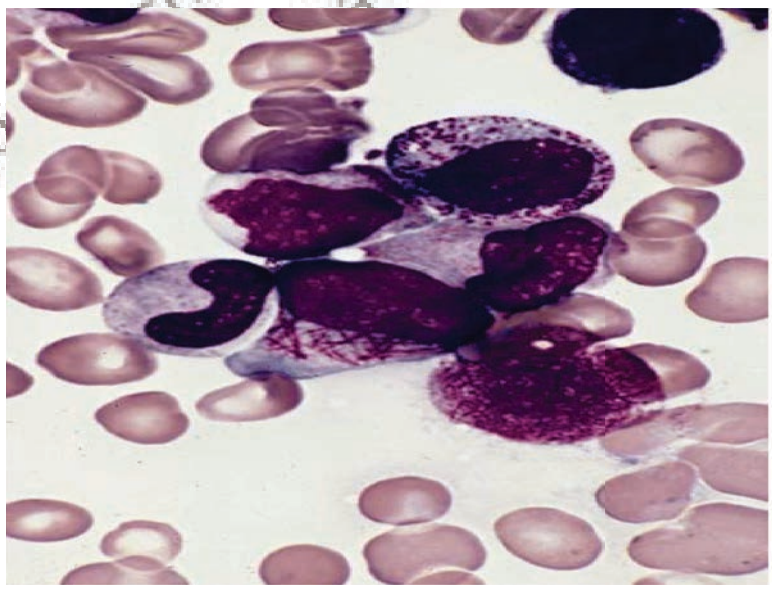
It may be associated with extensive bone marrow fibrosis as a result of the stimulation of the normal fibroblasts by the local secretion of platelet-derived growth factor (PDGF) by the leukemic cells.

Solution to Question 11:

The presence of faggot cells is highly suggestive of acute myeloid leukemia - M3 (AML - M3) or acute promyelocytic leukemia.

A cluster of Auer rods is known as a faggot cell. It is characteristic of acute myeloid leukemia (AML) M3.

The image given below shows AML M3 with a cluster of Auer rods (faggot cell).



Solution to Question 12:

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The patient shows features of disseminated intravascular coagulation (DIC). It is most likely to be associated with acute myeloid leukemia - M3 or acute promyelocytic leukemia. The pathogenesis behind this is t(15,17) or PML-RARA fusion gene.

Option A: Inversion 16 is seen in acute myelomonocytic leukemia or AML - M4.

Option B: t(8;21) is seen in AML with differentiation or AML - M2.

Option C: Inversion 3 is seen in AML - M7 (megakaryoblastic) which shows normal or increased platelet count. It has a poor prognosis.

Solution to Question 13:

AML M0 is negative for myeloperoxidase (MPO). AML-M5 (monocytic), AML-M6 (erythroid), and AML-M7 (megakaryocytic) are also negative for MPO.

Myeloperoxidase (MPO) is located in the primary granules of neutrophils and their precursors, in eosinophil granules, and in the azurophilic granules of monocytes.

The most primitive myeloblasts are negative, with granular positivity appearing progressively as they mature toward the promyelocyte stage. Promyelocytes and myelocytes are the most strongly staining cells in the granulocyte series. Monoblasts and monocytes may be negative or positive.

AML-M4 shows both myelocytic and monocytic differentiation. Hence, it shows both MPO and non-specific esterase (marker for monocytes) positivity.

Solution to Question 14:

The given clinical scenario with myeloblasts that stain positive for CD61 is suggestive of acute megakaryocytic leukemia (AML-M7).

AML M7 is the least common type of AML. Blasts of megakaryocytic lineage predominate and are associated with marrow fibrosis. There is also frequent budding of cytoplasmic margins.

They are CD41+ and CD61+. They stain negatively with Sudan black B (SBB) and myeloperoxidase (MPO). Blasts are reactive with PAS and acid phosphatase.

The prognosis for this type of acute leukemia is poor.

Solution to Question 15:

The given image shows leukemia cutis. It is seen in acute myeloid leukemia - M4 and acute myeloid leukemia - M5. It refers to leukemic cells infiltrating the skin.

Signs and symptoms related to the involvement of tissues other than the marrow are usually less striking in AML than in acute lymphocytic leukemia (ALL). But tumors with monocytic differentiation (AML M4, M5) often infiltrate the skin (leukemia cutis) and the gingiva. This probably reflects the normal tendency of monocytes to extravasate into tissues.

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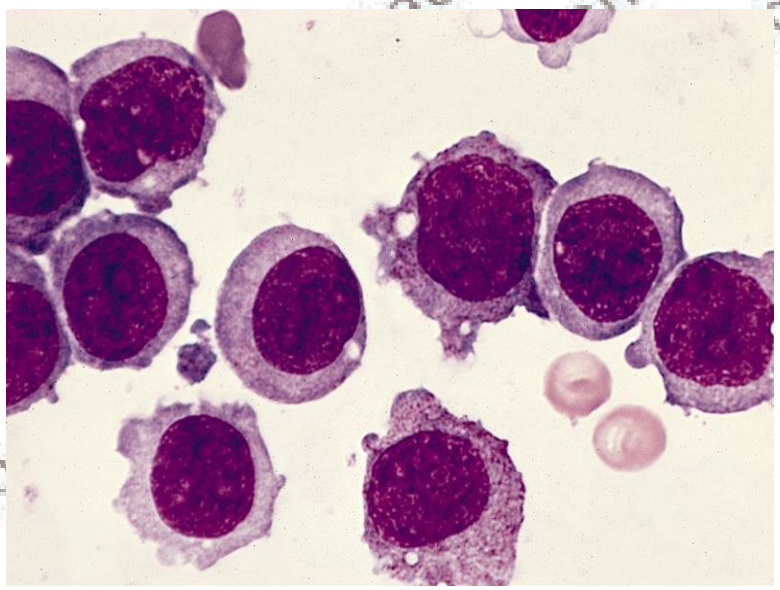
Solution to Question 16:

The given clinical scenario is suggestive of acute myeloid leukemia-M5 (AML-M5) or acute monocytic leukemia.

The patients with AML - M5 develop organomegaly, lymphadenopathy, gingival hyperplasia, CNS involvement, and other tissue infiltration. The bone marrow aspirate shows 20% or more blasts. Monoblasts have folded or lobulated nuclei, lack Auer rods, and are nonspecific esterase positive.

Myeloperoxidase is present in the azurophilic granules of neutrophils and their precursors. It is positive in AML M1, M2, M3, M4 and negative in AML M0. Monoblasts and monocytes may be negative or positive. When positive, the granules are smaller than in neutrophils and diffusely scattered throughout the cytoplasm.

The image given below shows bone marrow aspirate in AML - M5.



Solution to Question 17:

CD61 is a marker of acute megakaryoblastic leukemia, not chloroma. Lysozyme, CD43, CD45, CD117, and MPO are positive markers of chloroma.

Chloroma, also called myeloid sarcoma, granulocytic sarcoma, or myeloblastoma is an extramedullary tumor that occurs in 2% to 14% of patients with AML. Frequent sites of involvement are:

- Skin
- Lymph nodes
- Gastrointestinal tract

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• Bone

• Soft tissue, testis

• Peritoneum

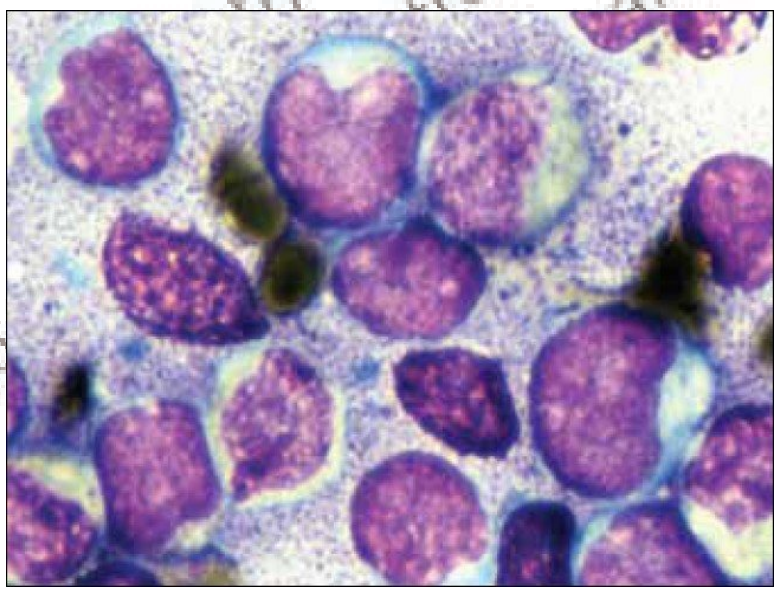
Orbital involvement of myeloid sarcoma is rare without any evidence of systemic involvement. Proptosis is the most common presentation. Other symptoms include lacrimal swelling, conjunctival mass lesion, retinal hemorrhages, ptosis, dystopia. Decreased visual acuity and ocular movement restriction have also been reported.

Solution to Question 18:

Arbiskov cells are monocytes seen in myeloblastoma or chloroma.

Chloroma, also known as granulocytic sarcoma, is a hematopoietic stem cell tumor, where myeloblasts are located at extramedullary sites. Orbit is one of the most common sites of occurrences in pediatric population. It is seen in AML - M2 most commonly. Other conditions associated are myelodysplastic and myeloproliferative syndromes.

The image given below shows Arbiskov cells in chloroma.



Solution to Question 19:

All-trans retinoic acid (ATRA) is used in the treatment of acute promyelocytic leukemia (APML), which is associated with PML-RARA fusion gene.

Acute promyelocytic leukemia (APML) is associated with a reciprocal translocation between chromosomes 15 and 17 producing a PML-RARA fusion gene. This fusion gene encodes for a chimeric protein, which consists of a part of the PML protein and a part of the retinoic acid receptor-α (RARα).

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The normal RARα binds to the DNA and activates the transcription in the presence of retinoids. However, the chimeric protein produced by PML-RARA has reduced affinity for retinoids. This causes inhibition of transcription, thereby preventing gene expression for cellular differentiation. This leads to the accumulation of myeloid progenitor cells.

The condition is treated with all-trans retinoic acid. It binds to the PML-RARA chimeric protein. This causes conformational change such that the protein regains its normal function and activates DNA transcription.

Solution to Question 20:

Normal karyotyping with mutated NPM indicates a favorable prognosis in acute myeloid leukemia (AML).

Solution to Question 21:

Inversion 16 is associated with a good prognosis in acute myeloid leukemia (AML).

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Hodgkin's Lymphoma

Question 1:

Which is the most common subtype of Hodgkin's lymphoma?

a) Nodular sclerosis

b) Mixed cellularity

c) Lymphocyte predominant

d) Lymphocyte rich

Question 2:

A lymph node biopsy specimen of a patient shows giant cells with an owl-eyed appearance. Which of the following statements is incorrect with respect to the diagnosis in this case?

a) Single axial group of lymph nodes is affected

b) Spleen is the first extranodal tissue to be involved

c) Mesenteric nodes are frequently involved

d) Extranodal involvement is uncommon

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Question 3:

Activation of which of the following is a common event in classical Hodgkin's lymphoma?

a) TNF alpha

b) TGF °

c) NF- κB

d) TNFAIP3

Question 4:

Copy-number gains of which proto-oncogene on chromosome 2p are common in Hodgkin lymphoma?

a) REL

b) RET

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c) MYC

d) RAS

Question 5:

In which of the following lesions can we see the Reed-Sternberg-like cells?

a) 1 and 3

b) 1 and 2

c) 3 and 4

d) 2 and 3

Question 6:

Which of the following is not a variant of the Reed-Sternberg cell?

a) Popcorn

b) Classic

c) Mononuclear

d) Monomorphic

Question 7:

A patient with generalized lymphadenopathy and Pel-Ebstein fever is diagnosed with Hodgkin's lymphoma. Which of the following is a characteristic finding seen in this condition?

a) Pain in nodes relieved by alcohol

b) Pain in nodes aggravated by alcohol

c) Fever relieved by alcohol

d) Fever increased by alcohol

Question 8:

A lymph node biopsy sample of a patient showed Reed-Sternberg cells that were CD15 & CD30 negative. Which of the variants of Hodgkin lymphoma is the patient most likely to have?

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a) Mixed cellularity

b) Lymphocyte rich

c) Lymphocyte depleted

d) Lymphocyte predominant

Question 9:

Which subtype of Hodgkin's lymphoma has an incidence as shown in the graph given below?

a) Mixed cellularity

b) Lymphocyte predominant

c) Lymphocyte depleted

d) Nodular sclerosis

Question 10:

Which subtype of Hodgkin's lymphoma is associated with older age, systemic symptoms, and advanced tumor stage?

a) Mixed cellularity

b) Lymphocyte predominant

c) Lymphocyte rich

d) Nodular sclerosis

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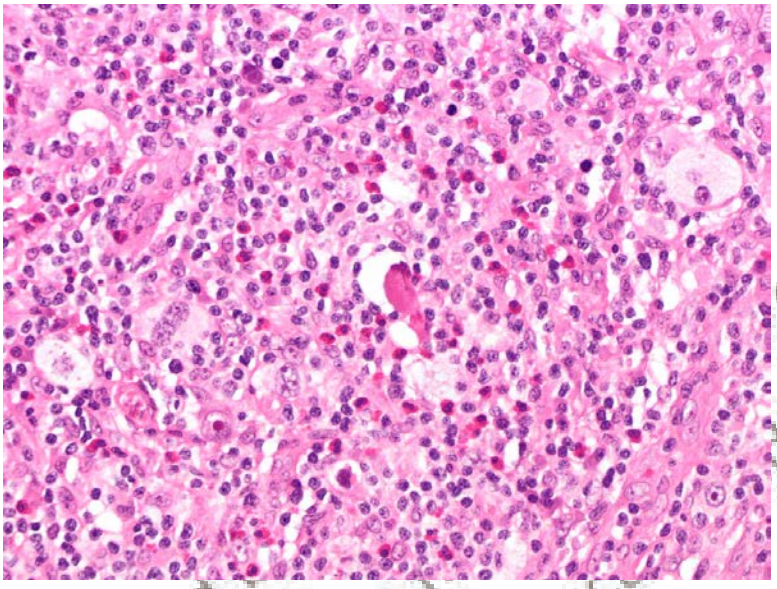
Question 11:

The given histological findings were noted on a lymph node biopsy of a patient with lymphadenopathy. What is the likely diagnosis?



a) Mixed cellularity Hodgkin's lymphoma

b) Lymphocyte depletion Hodgkin's lymphoma

c) Nodular sclerosis Hodgkin's lymphoma

d) Lymphocyte predominant Hodgkin's lymphoma

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Question 12:

Which of the following statements is false regarding the nodular sclerosis variant of Hodgkin lymphoma?

a) Reed-Sternberg cells are positive for PAX 5

b) It is uncommonly associated with Epstein Barr Virus

c) Prognosis is excellent

d) Reed-Sternberg cells are positive for CD45

Question 13:

Lymph node biopsy of which of the following variants of Hodgkin lymphoma will show the maximum area of necrosis?

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a) Mixed cellularity

b) Lymphocyte predominant

c) Lymphocyte depleted

d) Nodular sclerosis

Question 14:

Which subtype of Hodgkin's lymphoma is most commonly associated with HIV?

a) Nodular sclerosis

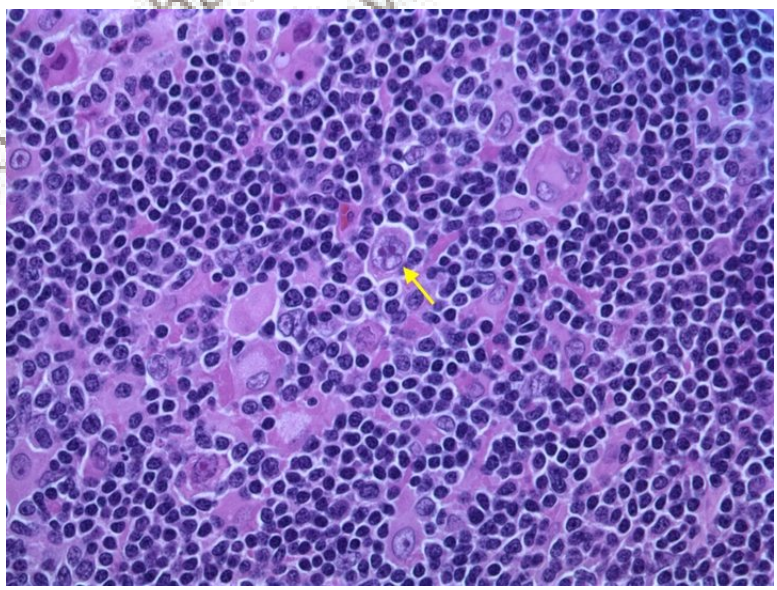
b) Lymphocyte depletion

c) Mixed cellularity

d) Lymphocyte rich

Question 15:

A 15-year-old male patient came to the OPD with cervical lymph node enlargement. The biopsy was examined, which showed a variant of the Reed-Sternberg cell given in the image. Which of the following types of Hodgkin's lymphoma frequently has this cell in its histology?



a) Mixed cellularity

b) Lymphocyte predominant

c) Lymphocyte rich

d) Nodular sclerosis

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Question 16:

A young male presented with cervical lymphadenopathy. The biopsy of the lymph node showed RS cells with vague nodule formation and a background of reactive T-lymphocytes. The cells were positive for CD20, LCA, EMA and negative for CD 15 and CD30. What is the diagnosis?

a) Nodular Sclerosis - Hodgkin Lymphoma

b) CLL

c) T cell rich B cell lymphoma

d) Nodular Lymphocyte predominant Hodgkin Lymphoma (NLPHL)

Question 17:

In a patient with lymphocyte-predominant Hodgkin lymphoma, cells are found to be positive for which of the following marker?

a) Bcl- 6

b) Bcl- 2

c) Bcl- 5

d) Bcl- 4

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Question 18:

Which of the following is incorrect about lymphocyte-predominant Hodgkin's lymphoma?

a) It can progress to a tumor resembling DLBCL

b) The prognosis is excellent

c) The bone marrow involvement is rare

d) A strong association with EBV is seen

Question 19:

A 23-year-old man is diagnosed to have Stage II (A) Hodgkin's lymphoma. What staging system was most likely used to classify the tumor of this patient?

a) TNM

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b) Masaoka

c) Durie-Salmon

d) Ann-Arbor

Question 20:

Who among the following patients is likely to have the best prognosis?

a) A patient with mononuclear variant of Reed-Sternberg cells on lymph node biopsy

b) A patient whose lymph node biopsy showed lacunar Reed-Sternberg cells

c) A patient with predominant reticular variant of Reed- Sternberg cells

d) A patient with Reed-Sternberg cells amid mixed variety of background cells

Question 21:

Which among the following is incorrect about Hodgkin's lymphoma?

a) Histologic type is the most important prognostic variable.

b) The cure rate of patients with stages I and IIA is close to 90%.

c) Long-term survivors treated with radiotherapy had a much higher incidence of secondary malignancies.

d) It most commonly presents as painless lymphadenopathy.

Question 22:

Which of these parameters would be considered a poor prognostic factor in patients with Hodgkin's lymphoma?

a) Serum albumin level <5g/dL

b) WBC count < 15000 cells/cumm

c) Absolute lymphocyte count <600 cells/cumm

d) Age <45 years

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Answer Key

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Question No.	Correct Option
1	a
2	c
3	c
4	a
5	d
6	d
7	b
8	d
9	a
10	a
11	c
12	d
13	c
14	c
15	b
16	d
17	a
18	d
19	d
20	b
21	a
22	c

Detailed Explanations

Solution to Question 1:

Nodular sclerosis is the most common type of Hodgkin's lymphoma, while mixed cellularity is most common in India.

The incidence of nodular sclerosis is equal in men and women. It commonly involves the lower cervical, supraclavicular, and mediastinal lymph nodes. It commonly affects adolescents and young adults. It has an excellent prognosis.

Mixed-cellularity Hodgkin lymphoma is seen in patients older than 50 years of age. There is a male predominance.

The image given below shows the histology of nodular sclerosis showing a lacunar variant of Reed–Sternberg cells

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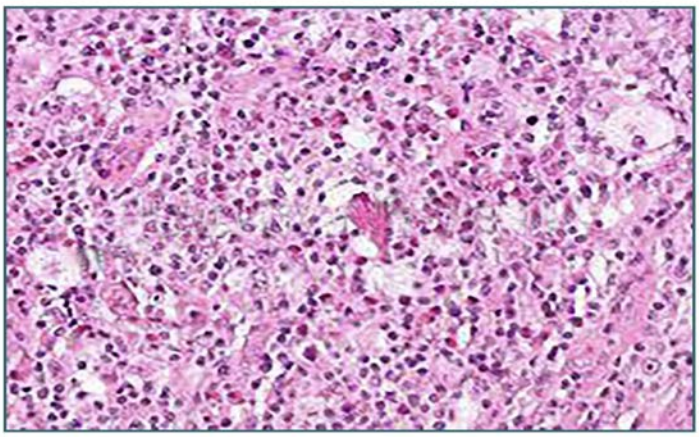
Nodular Sclerosis variant of Hodgkin Lymphoma



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Solution to Question 2:

An owl-eyed appearance of giant cells in lymph nodes is characteristic of Hodgkin's lymphoma (HL). Mesenteric lymph nodes are infrequently involved in HL.

Hodgkin's lymphoma is a group of lymphoid neoplasms arising in a single group of lymph nodes. Extranodal involvement is uncommon. However, if it spreads from the nodes, the first organ to be involved is the spleen, then the liver, and finally the bone marrow. This pattern of spread is known as the contiguous spread.

This predictable route of spread is important clinically as it aids in staging and prognosis as well as treatment of HL.

Solution to Question 3:

Activation of the transcription factor NF-κB is a common event in classical Hodgkin's lymphoma (HL).

NF-κB may be activated by Epstein–Barr virus (EBV) infection. EBV+ tumor cells express latent membrane protein-1 (LMP-1) which upregulates NF-κB. Activation of NF-κB may occur in EBV tumors as a result of the acquired loss-of-function mutations in TNF alpha-induced protein 3 (TNFAIP3).

Activation of NF-κB by EBV rescues crippled germinal center B cells that cannot express Igs from apoptosis, eventually leading to the formation of Reed–Sternberg cells.

Solution to Question 4:

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Copy-number gains in the REL proto-oncogene on chromosome 2p are particularly common in Hodgkin's lymphoma. It may also contribute to increased NF-Kβ activity.

Reed-Sternberg cells are aneuploid and possess diverse clonal chromosomal aberrations.

Note: the MYC gene, commonly associated with Burkitt lymphoma is present on chromosome 8.

Solution to Question 5:

Reed–Sternberg-like cells (RSLC) can be seen in the following:

• Infectious mononucleosis

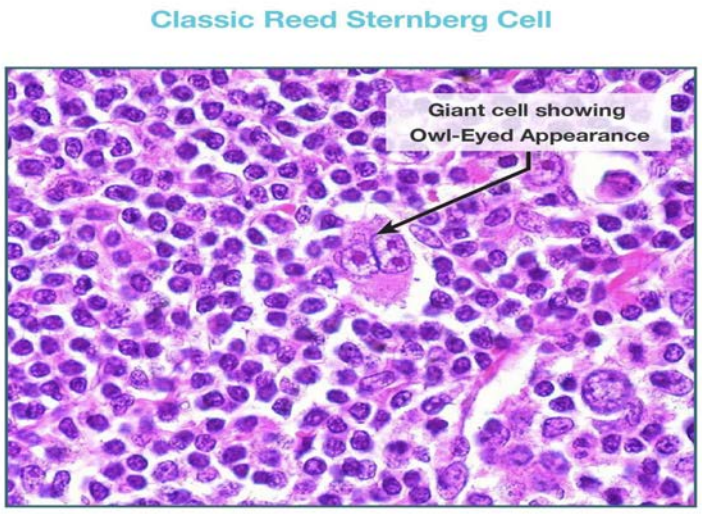
• Large-cell non-Hodgkin lymphomas (most common in immunoblastic NHL)

• Solid tissue cancers

While Reed-Sternberg cells (RS cells) are seen in Hodgkin's lymphoma, there can be presence of Reed-Sternberg like cells which that may have morphologic features resembling RS cells.

Diagnostic Reed–Sternberg cells are large cells with multiple nuclei or a single nucleus with multiple nuclear lobes, each with a large inclusion-like nucleolus, about the size of a small lymphocyte with abundant cytoplasm (owl-eye appearance).

The image given below shows the classic Reed Sternberg cells.



Solution to Question 6:

Monomorphic is not a variant of RS cell.

Reed–Sternberg cell (RS cell) is the characteristic tumor giant cell of Hodgkin Lymphoma. It is derived from the germinal center B cell. It has a classic owl-eyed appearance due to the presence of a symmetric or mirror-image bilobed nucleus, with prominent nucleoli surrounded by a clear

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space. It has the following variants:

• Lacunar

• Classic

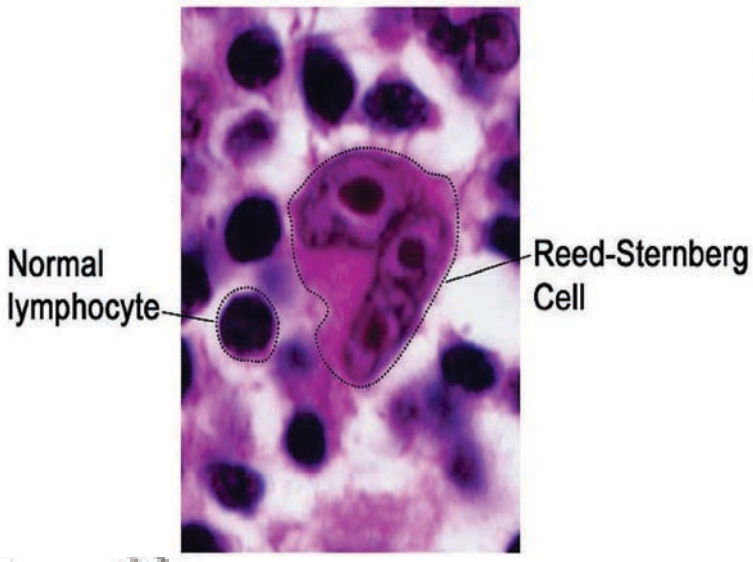
• L&H Popcorn cells

• Pleomorphic

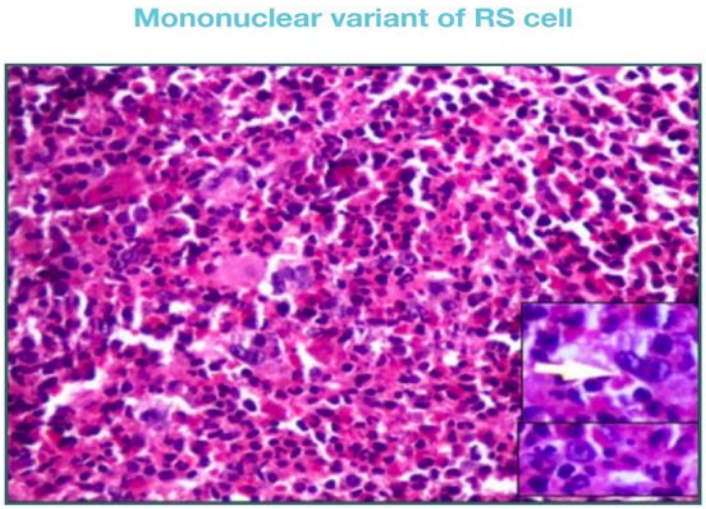
• Mononuclear

RS cells should be present in a background of non-neoplastic inflammatory cells like lymphocytes, plasma cells, and eosinophils, to make a diagnosis of Hodgkin's lymphoma.

The image given below shows the diagnostic Reed-Sternberg cell, with two nuclear lobes, large inclusion-like nucleoli, and abundant cytoplasm, surrounded by lymphocytes, macrophages, and an eosinophil.



The image below shows Reed-Sternberg cell, mononuclear variant.



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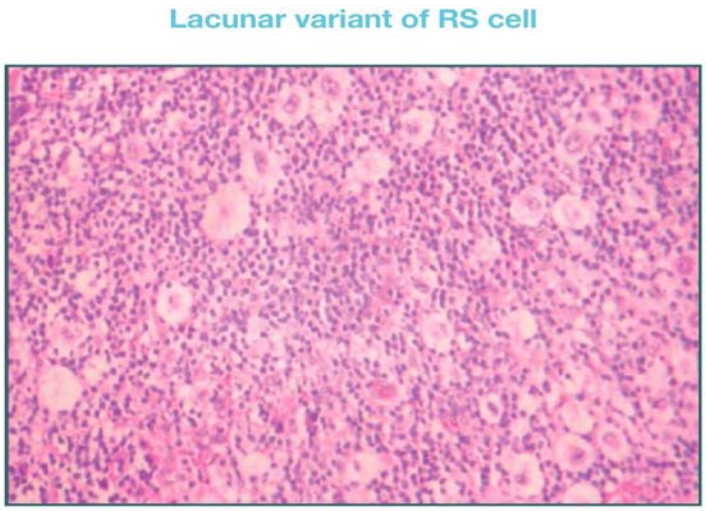
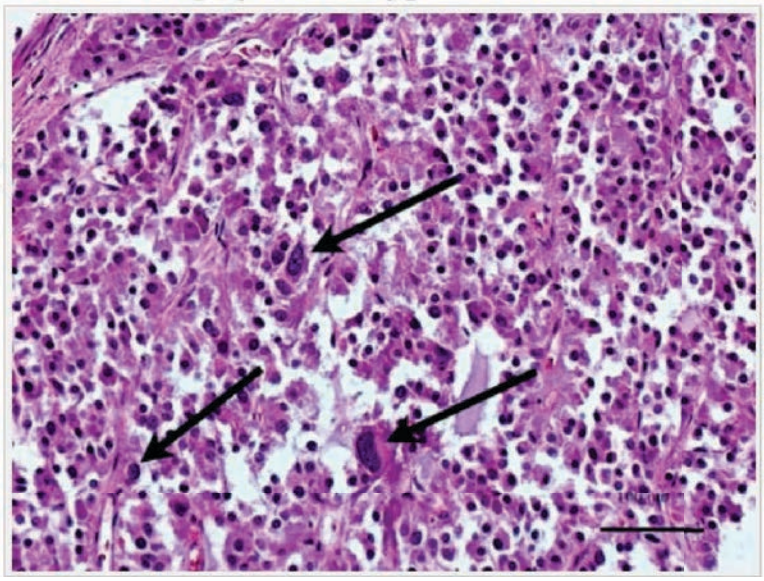
The image below shows Reed-Sternberg cell, lacunar variant. This variant has a folded or multilobated nucleus and lies within an open space, which is an artefact created by disruption of the cytoplasm during tissue sectioning.



The image below shows the Reed-Sternberg cell, lymphohistiocytic variant. Several such variants with multiple infolded nuclear membranes, small nucleoli, fine chromatin, and abundant pale cytoplasm are present.



Solution to Question 7:

In the case of Hodgkin's Lymphoma, the pain in the lymph nodes aggravates following the intake of alcohol.

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Clinical features of HL:

• Painless enlargement of lymph nodes is the most common presenting symptom.

• Cyclical fever (Pel–Ebstein fever) - cyclical increase, which then decreases over an average period of one or two weeks and night sweats in disseminated disease. This cyclical fever may be due to the release of cytokines.

A unique paraneoplastic syndrome associated with Hodgkin's lymphoma is the occurrence of pain in the affected lymph nodes during alcohol consumption. This has been attributed to the enlargement of the affected lymph nodes following alcohol consumption, which stretches the capsule of the lymph node and produces pain.

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Solution to Question 8:

The given clinical scenario with biopsy findings of CD15 and CD30 negative Reed–Sternberg cell is suggestive of nodular lymphocyte-predominant Hodgkin lymphoma.

The Reed–Sternberg cells are positive for CD15 and CD30 for most subtypes, except in lymphocyte-predominant HL, in which the neoplastic cells stains for CD20 and BCL-6.

Solution to Question 9:

The given graph shows a disease with a biphasic incidence which is characteristically seen in mixed cellularity type of Hodgkin lymphoma.

It has a male predominance, biphasic incidence, peaking in young adults and again in adults older than 55 years. It has more systemic symptoms like night sweats and weight loss. There is diffuse involvement of the entire lymph node. It consists of a mixture of cells composed of T cells, eosinophils, plasma cells, and benign macrophages mixed with Reed–Sternberg cells. The mononuclear variant and diagnostic Reed–Sternberg cells are seen in this type.

Reed–Sternberg cell is infected with Epstein–Barr virus in 70% of cases. It has very good prognosis.

Image given below shows mononuclear variant of RS cell.

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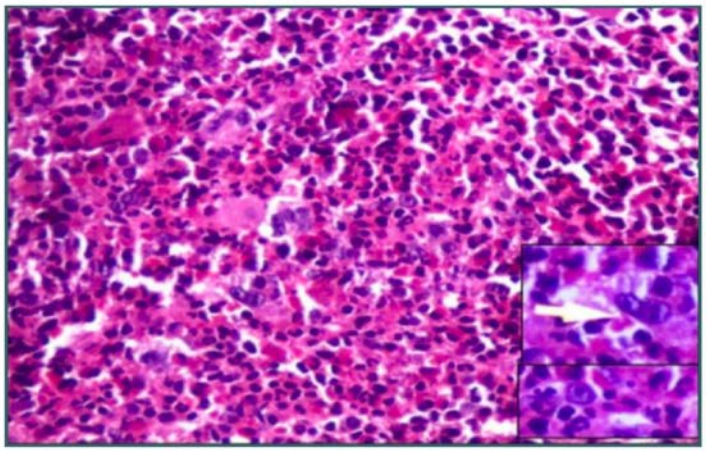
Mononuclear variant of RS cell



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Solution to Question 10:

Mixed-cellularity Hodgkin's lymphoma is associated with older age, systemic symptoms like night sweats and weight loss, and advanced tumor stage.

It has a biphasic incidence peaking in young adults and again in adults more than 55 years of age. It also has a strong association with HIV. It is more common in males than females.

Nonetheless, the overall prognosis is very good.

Solution to Question 11:

The given image shows a lacunar variant of Reed–Sternberg cell. These are common in the nodular sclerosis subtype of Hodgkin lymphoma.

Subtypes of Hodgkin's lymphoma along with their characteristic types of RS cells is given below:

Hodgkin lymphoma (subtypes)	Diagnostic cells in histology	Immunophenotype
Nodular sclerosis	Lacunar variant	CD 15+, CD 30 +
Mixed cellularity	Mononuclear and Diagnostic RS cells (70% EBV +)	CD 15+, CD 30 +
Lymphocyte Rich	Mononuclear and Diagnostic RS cells (40% EBV +)	CD 15+, CD 30 +
Lymphocyte Depletion	Reticular variant; (most EBV +)	CD 15+, CD 30 +
Lymphocyte predominance	Lymphocytic and histiocytic variant, popcorn cells (EBV -)	CD 20+, BCL6+CD 15 -, CD 30 -

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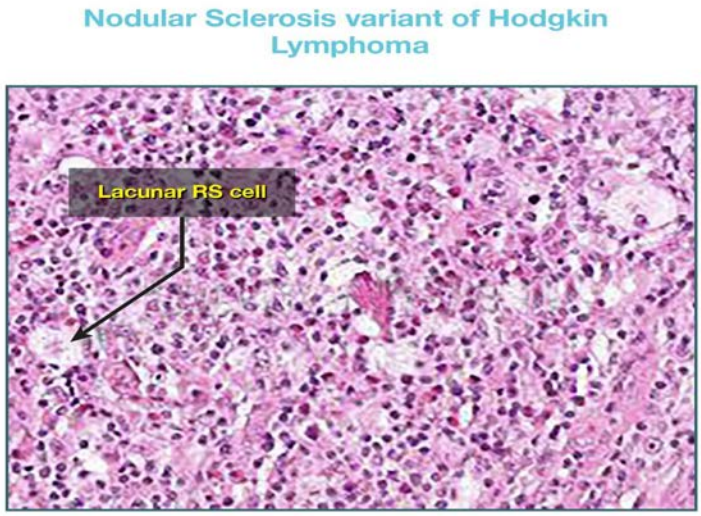
The image given below shows nodular sclerosis type of HL with lacunar cells.



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Solution to Question 12:

Reed–Sternberg cells in nodular sclerosis variant of Hodgkin lymphoma (HL) are negative for CD45. It is the most common variant.

These are characterized by the presence of lacunar variant Reed–Sternberg cells and the deposition of collagen bands. These bands divide involved lymph nodes into circumscribed nodules.

The Reed-Sternberg cells are found in a polymorphous background of T cells, eosinophils, plasma cells, and macrophages. Diagnostic Reed-Sternberg cells are often uncommon.

The Reed–Sternberg cells are positive for PAX5 (a B-cell transcription factor), CD15, and CD30, and negative for other B-cell markers, T-cell markers, and CD45 (leukocyte common antigen). This subtype is uncommonly associated with Epstein–Barr virus (EBV).

Involvement of the spleen, liver, bone marrow and other organs and tissues can occur later in the disease.

The prognosis is excellent.

Solution to Question 13:

The lymphocyte-depleted subtype of Hodgkin lymphoma is associated with maximum necrosis of the lymph nodes.

Lymphocyte-depleted is the least common type (<5%). It is seen in older and HIV-infected individuals and can present with systemic symptoms. There is a paucity of lymphocytes and a

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relative abundance of Reed–Sternberg (RS) cells or their pleomorphic variants. RS cells are CD15+ and CD30+ RS cells are infected with Epstein–Barr virus (EBV) in 90% of the cases. It has a poor prognosis.

Solution to Question 14:

The Mixed cellularity subtype of Hodgkin's lymphoma (HL) is most commonly associated with HIV.

Note: Although both mixed cellularity and lymphocyte depletion are seen in patients with HIV, mixed cellularity is more commonly associated with HIV.

Solution to Question 15:

The given image shows the lymphohistiocytic variant (L&H) of Reed–Sternberg (RS) cell. It is seen frequently in lymphocyte-predominant Hodgkin's lymphoma.

The cell has the following features:

• Polypoid nuclei

• Inconspicuous nucleoli

• Moderately abundant cytoplasm

As it resembles popcorn in its morphology it is also termed popcorn cell.

Note: A unique paraneoplastic syndrome associated with Hodgkin's lymphoma is the occurrence of pain in the affected lymph nodes during alcohol consumption. This has been attributed to the enlargement of the affected lymph nodes following alcohol consumption, which stretches the capsule of the lymph node and produces pain.

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Solution to Question 16:

The given clinical scenario is suggestive of nodular lymphocyte-predominant Hodgkin's lymphoma (NLPHL).

Axial group (cervical) lymphadenopathy and along with the L&H variant of Reed-Sternberg cells is characteristic.

RS cells are neoplastic giant cells. In NLPHL, the cells have vague nodular formation. Immunophenotyping is positive for CD20 (B cell-associated), LCA (CD45), EMA (epithelial marker), and negative for CD15 (monocyte or macrophage-associated) and CD30 (activation marker).

The image given below shows the L&H variant of RS cells seen in NLPHL.

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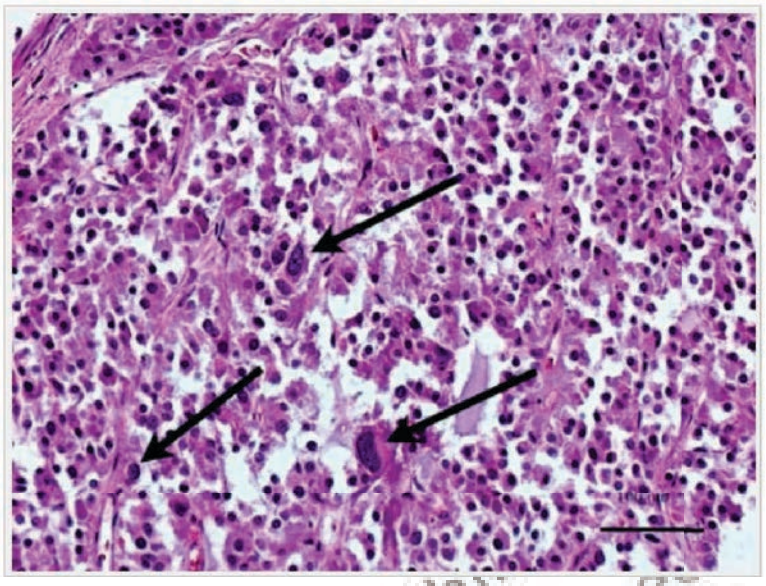

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Solution to Question 17:

Nodular-lymphocyte predominant Hodgkin Lymphomas have Reed Sternberg cells(aka L&H CELL) that are BCL-6 positive & CD 20 positive and CD 15 & CD 30 negative.

Note:

• CD30 is the most sensitive marker of Reed–Sternberg cell.

• PAX5 is the most specific marker of Reed–Sternberg cell.

Solution to Question 18:

Lymphocyte-predominant Hodgkin's lymphoma (HL) is not associated with Epstein–Barr virus (EBV) infection.

In 3% to 5% of cases, this type transforms into a tumor resembling diffuse large B-cell lymphoma.

A majority of patients are males, usually younger than 35 years of age, who typically present with cervical or axillary lymphadenopathy. Mediastinal and bone marrow involvement is rare.

This form of HL is more likely to recur than the classical subtypes, but the prognosis is excellent.

Solution to Question 19:

Clinical staging of both Hodgkin and Non-Hodgkin lymphoma is done by Ann-Arbor classification.

Option B: Masaoka staging is used for thymoma.

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Option C: Modified Durie–Salmon staging is used for multiple myeloma.

Solution to Question 20:

The prognosis of the nodular sclerosis (a subtype of classical Hodgkin lymphoma) is excellent compared to the other subtypes mentioned in the options. Lacunar Reed-Sternberg cells are seen in this condition.

The nodular sclerosis type occurs with equal frequency in males and females. It has a propensity to involve the lower cervical, supraclavicular, and mediastinal lymph nodes of adolescents or young adults.

Subtypes of Hodgkin's lymphoma along with their characteristic types of RS cells is given below:

Nodular lymphocyte-predominant non-classical Hodgkin lymphoma also has an excellent prognosis.

Hodgkin lymphoma (subtypes)	Diagnostic cells in histology	Immunophenotype
Nodular sclerosis	Lacunar variant	CD 15+, CD 30 +
Mixed cellularity	Mononuclear and Diagnostic RS cells (70% EBV +)	CD 15+, CD 30 +
Lymphocyte Rich	Mononuclear and Diagnostic RS cells (40% EBV -)	CD 15+, CD 30 +
Lymphocyte Depletion	Reticular variant; (most EBV +)	CD 15+, CD 30 +
Lymphocyte predominance	Lymphocytic and histiocytic variant, popcorn cells (EBV -)	CD 20+, BCL6+CD 15 -, CD 30 -

Solution to Question 21:

With current treatment protocols, the tumor stage is the most important prognostic variable, not histologic type.

Hodgkin's Lymphoma most commonly presents as painless lymphadenopathy.

The cure rate of patients with stages I and IIA are close to 90%.

Long-term survivors treated with radiotherapy had a much higher incidence of certain malignancies, such as lung cancer, melanoma, and breast cancer.

Solution to Question 22:

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Absolute lymphocyte count <600 cells/cumm is a poor prognostic factor for Hodgkin lymphoma.

Poor prognostic factors for Hodgkin's lymphoma:

- Age >45 years
- Male gender
- Haemoglobin <10.5 g/dl
- Total WBC count >15000 cells/mm3
- Lymphocytopenia: absolute count <600/mm3 or lymphocytes <8% of leukocytes
- Serum albumin level: <4g/dl
- Stage IV

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Non Hodgkin Lymphomas: General Considerations

Question 1:

Which of the areas in the histology of lymph nodes show small-unchallenged B cells surrounding pale-staining germinal centres?

a) Germinal center

b) Marginal zone

c) Mantle zone

d) Paracortical area

Question 2:

Which of the following is not a B lymphocyte marker?

a) CD10

b) CD20

c) CD23

d) CD13

Question 3:

Which of the following statements is false regarding Non-Hodgkin lymphoma?

a) It involves multiple peripheral lymph nodes

b) Mesenteric nodes and Waldeyer ring are rarely involved

c) Extra-nodal involvement is common

d) Noncontiguous spread occurs

Question 4:

Which is the most common non-Hodgkin lymphoma in adults?

a) Burkitt's lymphoma

b) Diffuse large B-cell lymphoma

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c) MALT lymphoma

d) Follicular lymphoma

Question 5:

Which of the following is not a B-cell neoplasm?

a) Follicular lymphoma

b) Burkitt lymphoma

c) Anaplastic large-cell Lymphoma

d) Mantle cell lymphoma

Question 6:

Which of the following is the most common site for primary extranodal lymphoma?

a) Spleen

b) Stomach

c) Intestine

d) Brain

Question 7:

Which lymphoid neoplasm is associated with the human herpesvirus 8?

a) Burkitt lymphoma

b) Mantle zone lymphoma

c) Anaplastic large-cell lymphoma

d) Primary effusion lymphoma

Question 8:

Which of the following is correctly matched with its associated etiological factor?

a) 1-b, 2-c, 3-e, 4-a, 5-d

b) 1-d, 2-e, 3-c, 4-d, 5-b

c) 1-e, 2-a, 3-d, 4-b, 5-c

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d) 1-c, 2-d, 3-b, 4-e, 5-a

Answer Key

Question No.	Correct Option
1	c
2	d
3	b
4	b
5	c
6	b
7	d
8	d

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Detailed Explanations

Solution to Question 1:

The mantle zone of the lymph nodes shows small, unchallenged B cells surrounding pale-staining germinal centres.

Structures in a follicle:

• Germinal centre - round/oval zone containing pale-staining cells surrounded by darker cells.

• Mantle zone - small, unchallenged B cells surrounding pale-staining germinal centres.

• Marginal zone - Light zone surrounding follicles; contains post-follicular memory B cells derived after stimulation of recirculating cells from T-cell-dependent antigen.

Solution to Question 2:

CD13 is an antigen of monocyte/macrophage and not B-cell.

Solution to Question 3:

Mesenteric nodes and Waldeyer ring are commonly involved in non-Hodgkin lymphoma (NHL).

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Solution to Question 4:

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL) in adults and children over the age of 15 years, worldwide and in India.

Burkitt's lymphoma is the most common NHL in children under the age of 15 years.

Solution to Question 5:

Anaplastic large cell lymphoma is a T-cell lymphoma.

Solution to Question 6:

The most common site for primary extranodal lymphoma is the stomach.

The term primary extranodal non-Hodgkin's lymphoma (PE-NHL) refers to lymphomas that present with the disease at any organ or tissue other than lymph nodes or spleen.

Gastrointestinal lymphoma is the most common form of primary extranodal lymphoma, accounting for 30%–40% of cases. The most common site involved is the stomach (60%–75% of cases), followed by the small bowel, ileum, cecum, colon, and rectum.

Note: The most common site for extranodal non-Hodgkin lymphoma (NHL) in AIDS is Primary CNS lymphoma.

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Solution to Question 7:

Primary effusion lymphoma is associated with human herpesvirus 8 (HHV-8).

It is a rare type of diffuse large B cell lymphoma with lymphomatous effusions in pleural, pericardial, and abdominal cavities, but no tumor mass.

Only one body cavity is typically involved. It is strongly associated with HHV8 and advanced HIV and usually EBV. It can also occurs in non-immunosuppressed patients, often the elderly.

Solution to Question 8:

The correctly matched neoplasms with their associated etiological factor:

- Extranodal marginal cell lymphoma - H.pylori infection (c)
- Intestinal T-cell lymphomas - Gluten-sensitive enteropathy (d)
- Anaplastic large cell lymphoma - Breast implants (b)

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• Lymphoplasmacytic lymphoma - Hepatitis C infection (e)

• Diffuse large B-cell lymphoma - HIV infection (a)

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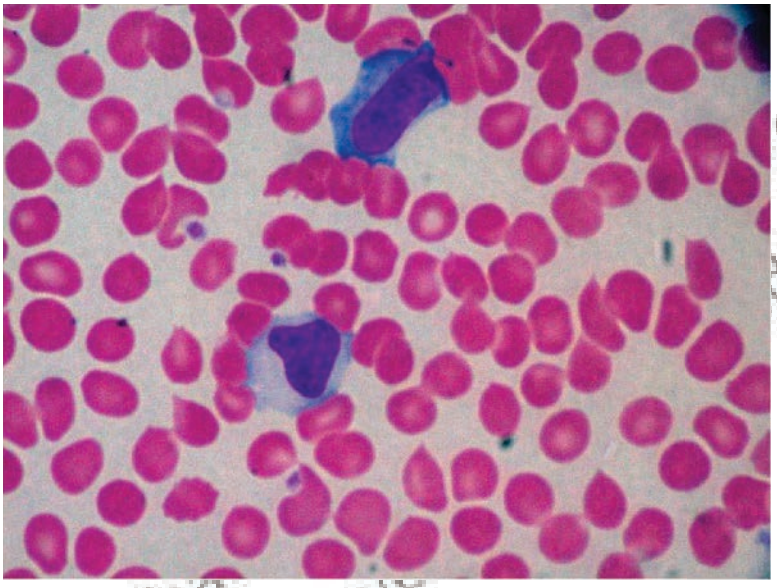
Non Hodgkin Lymphomas: Low Grade

Question 1:

The peripheral smear finding of a patient with fever and lymphadenopathy is shown below. What is the most likely diagnosis?



a) Infectious mononucleosis

b) Follicular lymphoma

c) Chronic lymphocytic leukemia

d) Hairy-cell leukemia

Question 2:

Bruton tyrosine kinase is involved in which type of B-cell lymphoma?

a) Mantle-cell lymphoma

b) Diffuse large B-cell lymphoma

c) Chronic lymphocytic lymphoma

d) Burkitt lymphoma

Question 3:

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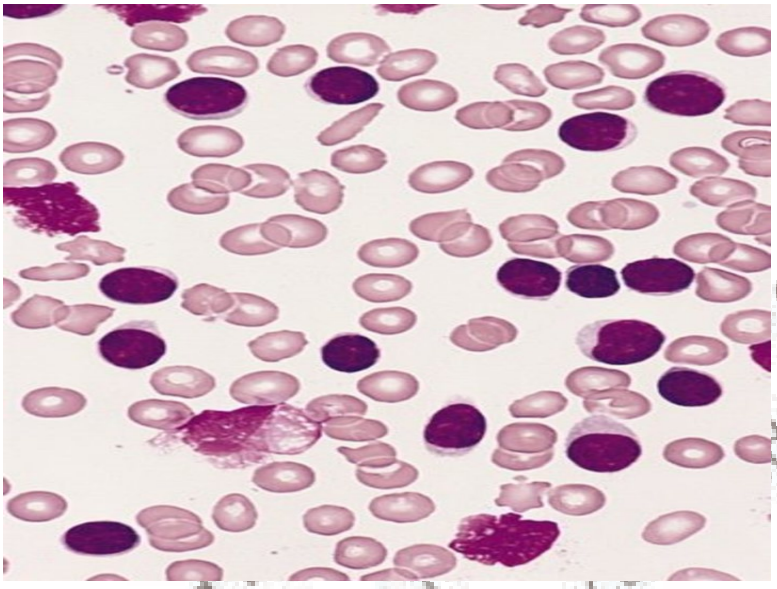
A 65-year-old man presents with easy fatigability, weight loss, and anorexia. On examination, he is found to have generalized lymphadenopathy and hepatosplenomegaly. Investigations show a total WBC count of 1 lakh per microliter, with 80% lymphocytes. Peripheral smear is as shown below. What is the most likely diagnosis?



a) Chronic myeloid leukemia

b) Chronic lymphocytic leukemia

c) Hodgkin lymphoma

d) Hairy cell leukemia

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Question 4:

The neoplastic cells in chronic lymphocytic leukemia/ small lymphocytic lymphoma originate from which of the following?

a) Pre B cell

b) Germinal center B cell

c) Mantle zone cell

d) Post-germinal-center memory B cell

Question 5:

Which of the following is not a genetic anomaly seen in patients with chronic lymphocytic lymphoma/ small lymphocytic lymphoma?

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a) Deletion of 11q

b) Trisomy 17p

c) Trisomy 12q

d) Deletion of 13q

Question 6:

A 70-year-old man presents with weakness and generalized lymphadenopathy. Lymph node biopsy shows difuse effacement with small lymphocytes and proliferation centers. What is the likely diagnosis?

a) Follicular lymphoma

b) Chronic lymphocytic leukemia/small lymphocytic lymphoma

c) Mantle-cell lymphoma

d) Diffuse large B-cell lymphoma

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Question 7:

A 58-year-old man with cervical lymphadenopathy is suspected to have chronic lymphocytic leukemia. What should be the absolute lymphocyte count/mm3 to diagnose this condition?

a) >2000

b) >5000

c) >10000

d) >100000

Question 8:

Flow cytometric analysis of four patients is given below. Who among the following is most likely suffering from chronic lymphocytic leukemia?

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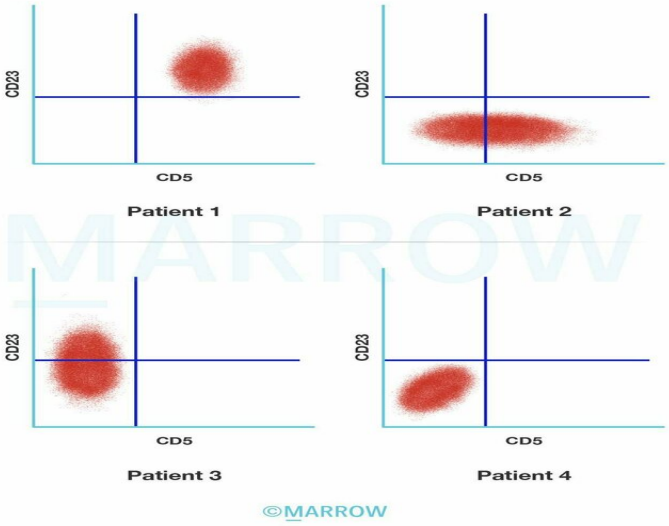


a) Patient 1

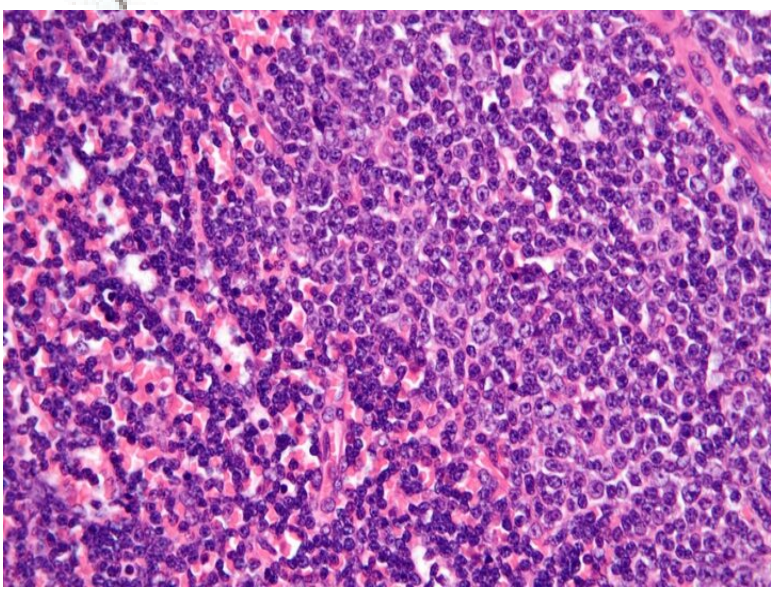
b) Patient 2

c) Patient 3

d) Patient 4

Question 9:

A 73-year-old man came with complaints of malaise and low-grade fever. He had generalized lymphadenopathy. The histopathological examination of the lymph node is as shown below. These cells showed positivity for CD5, CD19, CD20, and CD23. Which of the following does not indicate a poor prognosis in this condition?



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a) Deletions of 11q and 17p

b) Lack of somatic hypermutation

c) Expression of ZAP-70

d) Absence of of NOTCH1 mutations

Question 10:

A middle-aged woman presented with chronic fatigue and generalized lymphadenopathy. Investigations revealed overexpression of BCL2. What is the likely diagnosis?

a) Burkitt lymphoma

b) Follicular lymphoma

c) Diffuse large-cell lymphoma

d) Mantle cell lymhoma

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Question 11:

Which of the following chromosomal abnormality is likely to be seen in patients with follicular lymphoma?

a) t(11;14)

b) t(14;18)

c) t(8;14)

d) t(9;14)

Question 12:

A 45-year-old man presents with painless generalized lymphadenopathy and weakness. Lymph node biopsy shows the following picture. Which of the following is not true for this condition?

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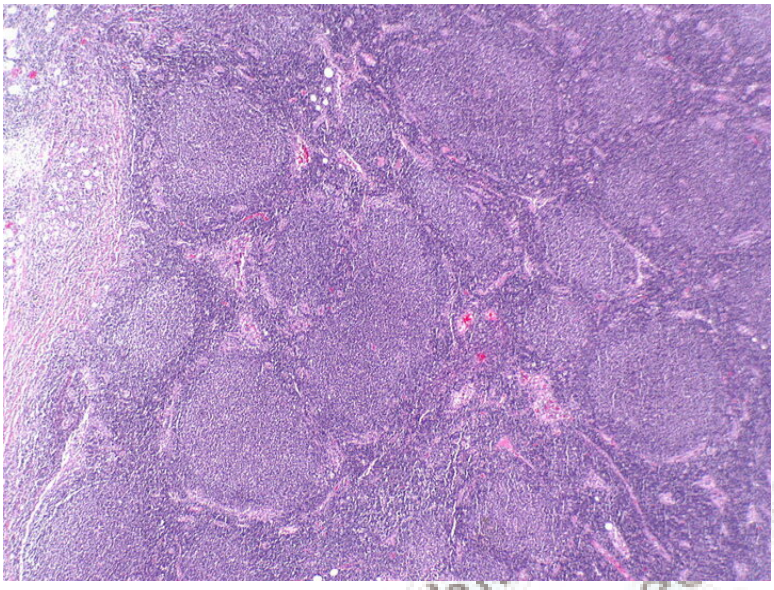

a) BCL2 positivity

b) BCL6 positivity

c) Aggressive course

d) Possible transformation into diffuse large B-cell lymphoma

Question 13:

A patient with longstanding cervical lymphadenopathy was diagnosed with mantle cell lymphoma. What is the cell of origin for this condition?

a) Pro B cells

b) Naive B cells

c) Mature B cells

d) Memory B cells

Question 14:

Which of the following statements about mantle cell lymphoma is false?

a) Centroblasts are absent

b) Most common presentation is painless lymphadenopathy

c) Associated with overexpression of cyclin D1

d) Tumor cells are CD5 + and CD23 +

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Question 15:

A 53-year-old man was evaluated for painless lymphadenopathy. Biopsy showed a homogenous population of small lymphocytes with cleaved nuclear contours. Which translocation is seen in this condition?

a) t(18:14)

b) t(8:14)

c) t(11:18)

d) t(11:14)

Question 16:

A patient with cervical lymphadenopathy has t(11;14) positive. Which of the following markers should be done to confirm the diagnosis?

a) 1, 2, 5

b) 2, 4

c) 1, 3, 5

d) 3, 4

Question 17:

What is the immunohistochemistry marker for cyclinD1 negative mantle cell lymphoma?

a) SOX11

b) MYD88

c) ITRA 1

d) ANNEXIN V

Question 18:

Which of the following statements about marginal zone lymphoma is false?

a) They arise within tissues involved by chronic inflammatory disorders

b) They spread rapidly to other sites

c) They may regress if the inciting agent is eradicated

d) Transformation to diffuse large B-cell lymphoma may occur

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Question 19:

A patient with long-standing Hashimoto's thyroiditis was noted to have a swelling in the thyroid region. After evaluation, it was diagnosed as a marginal zone lymphoma. What is the cell of origin of this lymphoma?

a) Naive B cell

b) Germinal-center B cell

c) Memory B cell

d) Pre-B cell

Question 20:

A patient presents to you with rapidly growing swelling on her right cheek. Past history is significant for Sjögren syndrome. You suspect a lymphoid neoplasm in her. What is the most probable diagnosis?

a) Anaplastic large cell lymphoma

b) Marginal-zone lymphoma

c) Mantle cell lymphoma

d) Burkitt's lymphoma

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Question 21:

Which of the following translocations is seen in extra-nodal marginal-zone lymphoma?

a) t(4;18)

b) t(8;14)

c) t(2;14)

d) t(11;18)

Question 22:

A 34-year-old woman came with complaints of chronic lethargy and weakness. Complete blood counts revealed pancytopenia. The peripheral smear showed the following picture. Which of the following statements is false about this condition?

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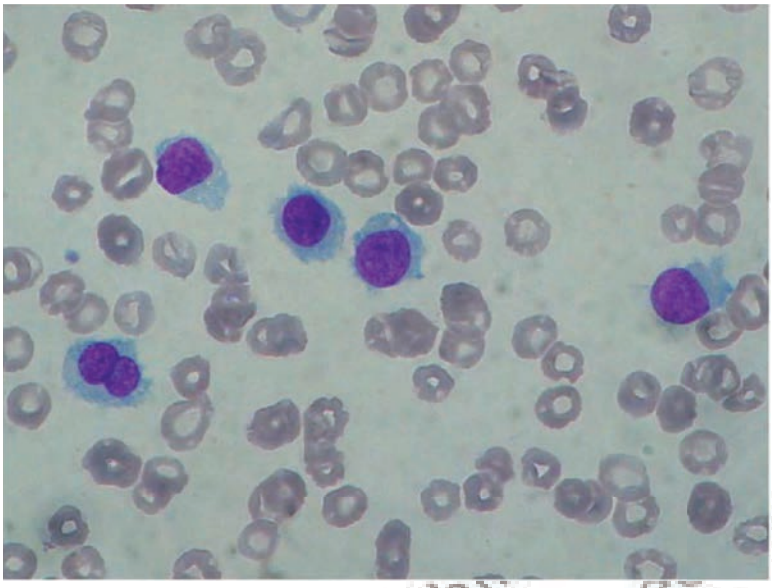

a) Neoplastic T lymphocytes are seen

b) Cells are positive for annexin

c) Cell stain positive for TRAP

d) Massive splenomegaly occurs

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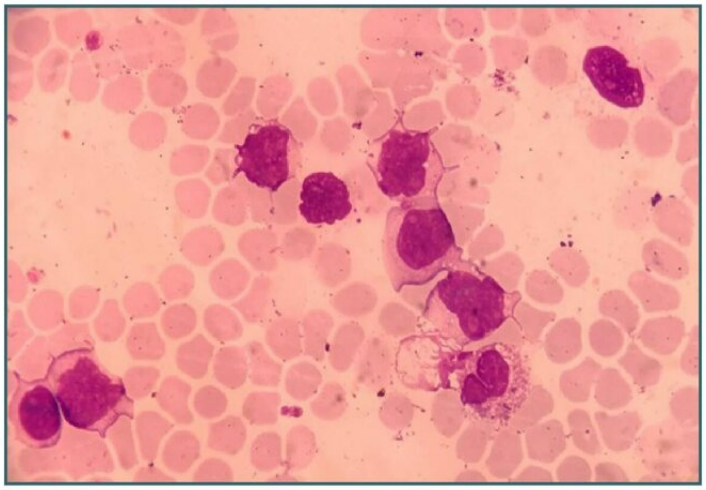
Question 23:

A 65-year-old man with a dragging sensation in his abdomen is found to have massive splenomegaly. The peripheral blood smear findings are as follows. Which of the following markers would you test to confirm the diagnosis?



a) CD65

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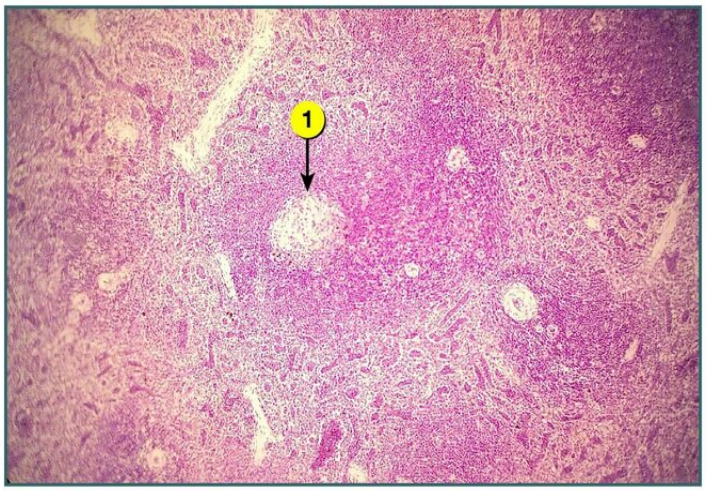
b) CD207

c) CD1a

d) CD103

Question 24:

A histological specimen of the spleen is shown below. Which non-Hodgkin's lymphoma does not arise from the area marked as 1?



a) Hairy-cell leukemia

b) Burkitt's lymphoma

c) Follicular lymphoma

d) Mantle cell lymphoma

Question 25:

A 60-year-old woman presented with generalized itching and mild hypoaesthesia of the skin. On examination, maculopapular patches were seen on her back. Biopsy revealed the presence of atypical lymphocytes with cerebriform nuclei infiltrating the dermis and epidermis. What is the most likely diagnosis?

a) Anaplastic large cell lymphoma

b) Mycosis fungoides

c) Peripheral T-cell lymphoma

d) Adult T-cell leukemia/lymphoma

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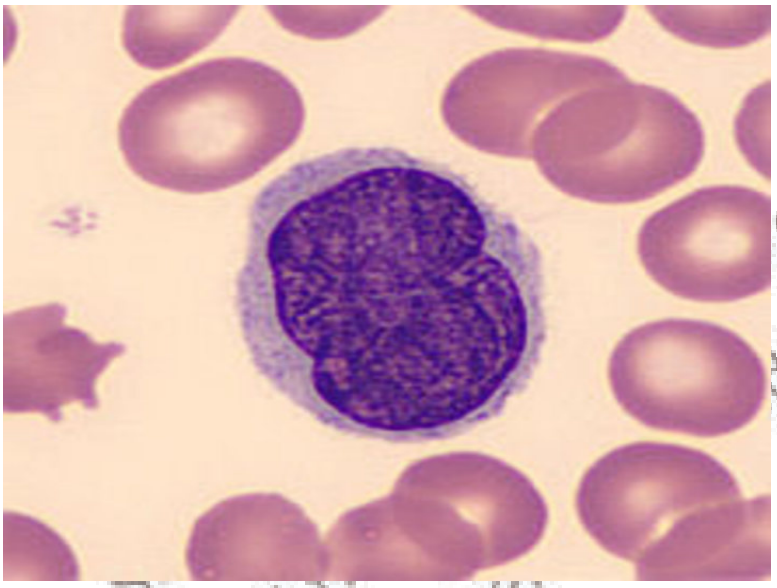
Question 26:

A patient presents with generalized exfoliative erythroderma. The peripheral blood smear shows the following cell. What is the likely diagnosis?



a) Mycosis fungoides

b) Sezary syndrome

c) Adult T cell leukemia

d) Peripheral NK cell leukemia

Question 27:

You suspect a lymphoid neoplasm in a patient who is a known case of rheumatoid arthritis. On workup, she has splenomegaly and her blood count showed neutropenia and lymphocytosis. Which of the following is the most likely diagnosis?

a) Marginal zone lymphoma

b) Follicular lymphoma

c) Burkitt lymphoma

d) Large granular lymphocytic leukemia

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Answer Key

Question No.	Correct Option
1	a
2	c
3	b
4	d
5	b
6	b
7	b
8	a
9	d
10	b
11	b
12	c
13	b
14	d
15	d
16	d
17	a
18	b
19	c
20	b
21	d
22	a
23	d
24	a
25	b
26	b
27	d

Detailed Explanations

Solution to Question 1:

The peripheral smear finding shows Downey cells or ballerina skirt cells. These are typically seen in infectious mononucleosis caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

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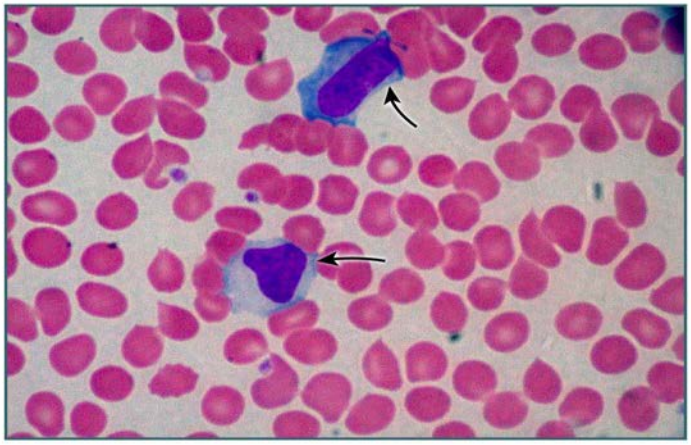
They are atypical lymphocytes with abundant basophilic cytoplasm containing clear vacuolations and prominent nucleoli. They become large as a result of antigen stimulation.

Downey cell



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Solution to Question 2:

Bruton tyrosine kinase (BTK) is associated with B-cell chronic lymphocytic lymphoma/ small lymphocytic lymphoma (CLL/SLL).

Tumour cells in CLL rely on signals generated by the B-cell receptor for growth and survival. These signals are transduced by a cascade of kinases that include BTK.

Note: BTK is also defective in patients with congenital X-linked agammaglobulinemia.

Solution to Question 3:

The clinical presentation and peripheral smear findings point toward a diagnosis of chronic lymphocytic leukemia.

The peripheral smear shows smudge cells and increased lymphocytes with scant cytoplasm, round to slightly irregular nuclei containing clumped chromatin. This large number of monotonous, uniform-looking, mature lymphocytes is often described as a "convent-girl" appearance.

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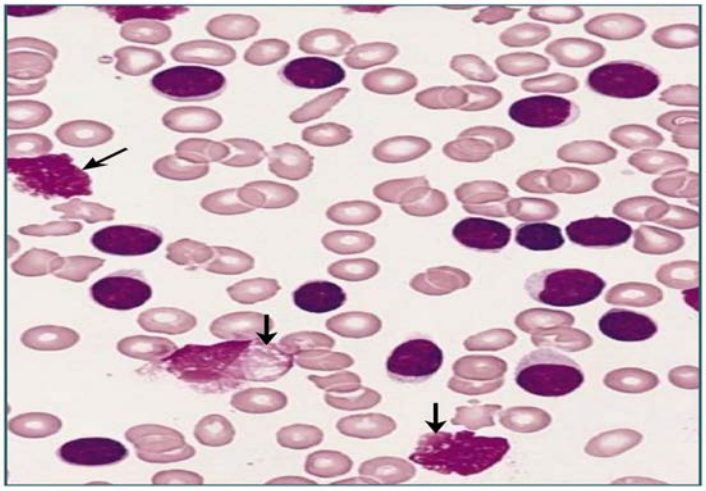
Peripheral smear of chronic lymphocytic leukemia showing smudge cells



Chronic Lymphocytic Leukemia (CLL) / Small lymphocytic lymphoma(SLL) is the most common leukemia among adults in the western world.

The differentiating point between CLL and SLL is that in CLL the absolute lymphocyte count is >5000 per mm³ and in SLL:<5000 per mm³.

It is usually asymptomatic at diagnosis but can present with easy fatigability, weight loss, and anorexia. Generalized lymphadenopathy and hepatosplenomegaly are usually seen.

• Total blood count:

• Total leukocyte count is highly variable; leukopenia is seen when the marrow is involved.

• Hypogammaglobulinemia is common and contributes to increased susceptibility to infections.

• 10% to 15% of patients develop hemolytic anemia or thrombocytopenia due to autoantibodies made by nonneoplastic B cells.

• Peripheral smear:

• Predominantly shows small lymphocytes with scant cytoplasm

• Smudge cells or basket cells or parachute cells - artifacts of the lymphocytes which are disrupted during the process of making smears.

• Contains a large number of monotonous, uniform-looking, mature lymphocytes, which is often described as a convent-girl appearance.

• Spherocytes (due to coexisting autoimmune hemolytic anemia) and nucleated RBCs (due to premature release of progenitors in face of severe anemia, marrow infiltration by the tumor, or both)

• Lymph node biopsy:

• Diffuse effacement composed of small lymphocytes admixed with variable numbers of larger activated lymphocytes that often gather in loose aggregates

• Referred to as proliferation centers, which contain mitotically active cells. Proliferation centers are pathognomonic for CLL / SLL.

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The chromosomal defects:

• Deletion of 13q (commonest and has a good prognosis)

• Deletion of 11q

• Trisomy 12q

• Deletion of 17p (poor prognosis).

Solution to Question 4:

The cell of origin for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is either a post-germinal center memory B cell or a naive B cell.

The cells of CLL show both unmutated Ig segments (those of naive B-cell origin) and somatic hypermutated Ig segments (those of post-germinal center memory B cell).

Tumours with unmutated Ig segments (those of naive B-cell origin) pursue a more aggressive course.

Solution to Question 5:

Deletion of 17p is a genetic anomaly seen in chronic lymphocytic lymphoma (CLL)/ small lymphocytic lymphoma (SLL), not trisomy 17p.

The genetic anomalies seen in CLL/SLL are:

• Trisomy 12q

• Deletion of 13q

• Deletion of 17p (bad prognosis)

• Deletion of 11q (bad prognosis)

Solution to Question 6:

The given clinical scenario is suggestive of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

Lymph node biopsy in CLL/SLL shows effacement of normal nodal architecture by sheets of predominantly small lymphocytes. They have round to slightly irregular nuclei, condensed chromatin, and scant cytoplasm.

Admixed are a variable number of larger activated lymphocytes that often gather in loose aggregates referred to as proliferation centers. These contain mitotically active cells. When present, proliferation centers are pathognomic for CLL/SLL (also known as a pseudofollicular pattern).

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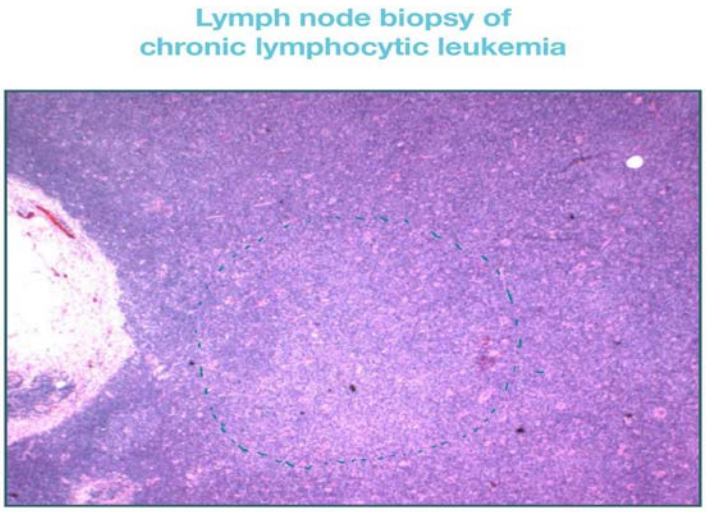
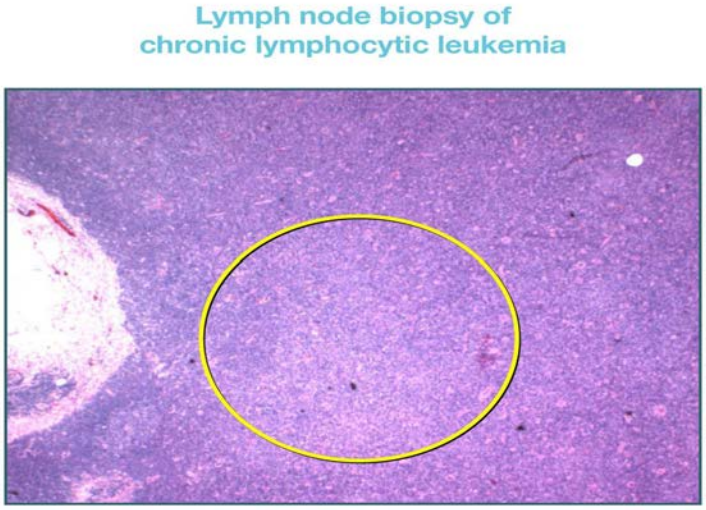
The image given below shows a lymph node biopsy of CLL in a low-power view. It shows loss of normal architecture and a large, pale-staining area in the center of the node (a proliferation center)





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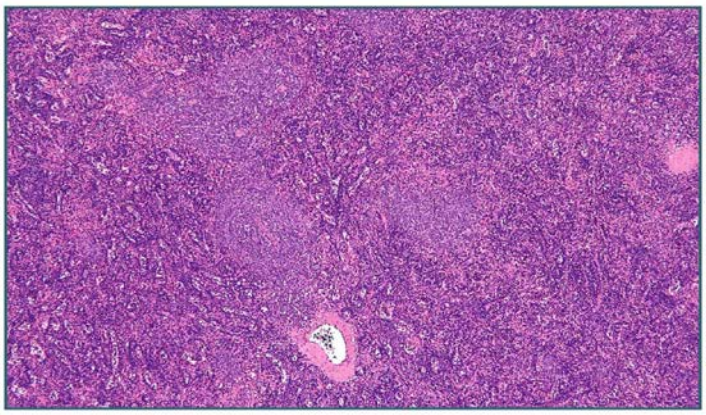
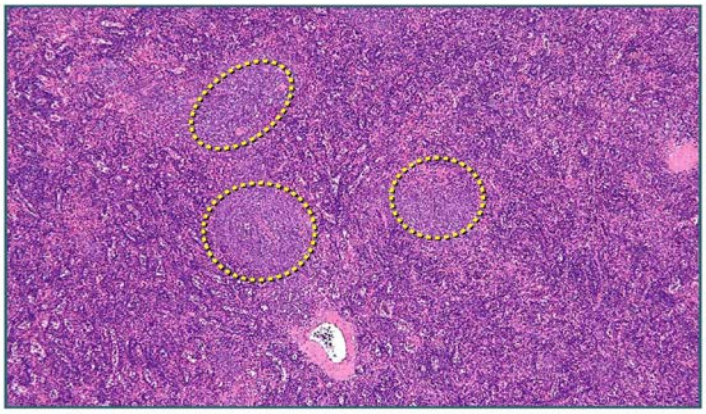
Lymph node biopsy
showing pseudofollicles in CLL



Lymph node biopsy
showing pseudofollicles in CLL



Solution to Question 7:

The diagnostic requirement for chronic lymphocytic leukemia (CLL) is absolute lymphocyte count >5000 per cubic millimetre.

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) differ only in the degree of peripheral blood lymphocytosis:

• CLL - 5000/mm3

• SLL - <5000 cells/mm3

Note: CLL is the most common leukemia of adults in the western world.

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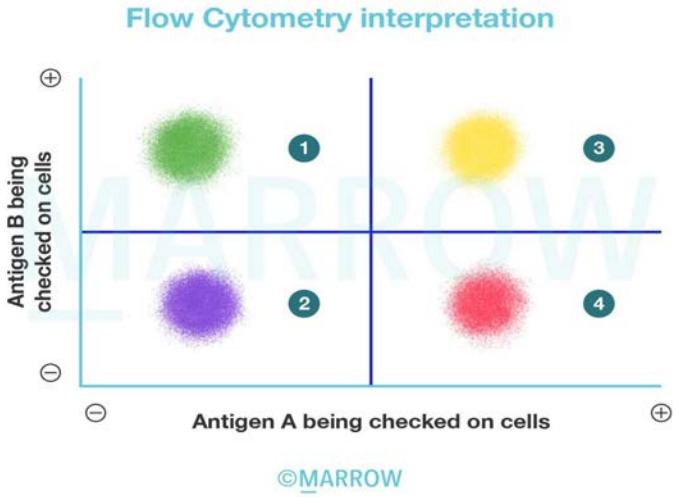
Solution to Question 8:

Small lymphocytes of chronic lymphocytic leukemia (CLL)/ small lymphocytic leukemia (SLL) are CD23 and CD5 positive. Hence, the flow cytometry of patient 1 (CD23 and CD5 positive) correctly represents the phenotype of CLL.

The tumour cells also express the pan B-cell markers CD19 and CD20

Low-level expression of surface Ig (usually IgM or IgM and IgD) is also typical.

Given below is the explanation of how to interpret flow cytometry results:



Interpretation of results:

Quadrant 1- Cells marked in green: -VE for A antigen, +VE for B antigen

Quadrant 2- Cells marked in purple: -VE for both the antigens.

Quadrant 3- Cells marked in yellow: +VE for both the antigens

Quadrant 4- Cells marked in red: +VE for A antigen, -VE for B antigen

Solution to Question 9:

The given scenario and histopathological findings are suggestive of chronic lymphocytic leukemia (CLL). The presence of NOTCH1 mutation is associated with a poor prognosis in chronic lymphocytic leukaemia (CLL).

The histopathological image shows small, darker staining lymphocytes with prominent nucleoli which are typically seen in chronic lymphocytic leukaemia (CLL).

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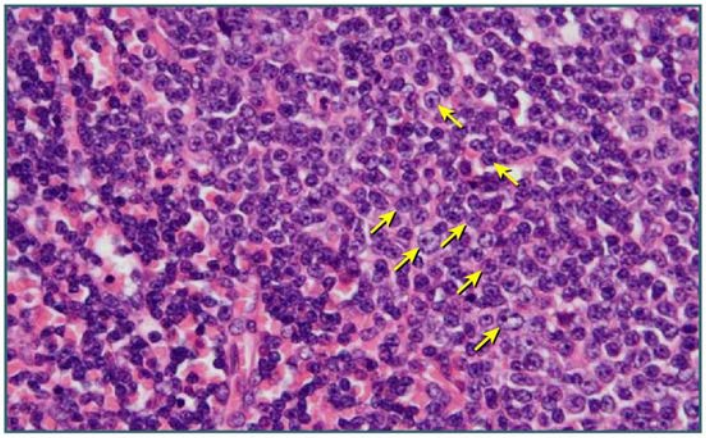
Lymph node biopsy of CLL



Variables that correlate with a worse outcome include:

- The presence of deletions of 11q and 17p
- Lack of somatic hypermutation
- Expression of ZAP-70
- Presence of NOTCH 1 mutations

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Solution to Question 10:

The given clinical scenario is suggestive of follicular lymphoma. This condition is associated with overexpression of BCL2.

It usually presents in middle age as painless generalized lymphadenopathy. The involvement of extranodal sites is relatively uncommon. It has an indolent waxing and waning course.

In almost 50% of patients, this cancer gets transformed to diffuse large B-cell lymphoma. The median survival rate is for 7-9 years.

The cell of origin for follicular lymphoma is germinal centre B cells. It shows (14;18) translocation.

Lymph node biopsy shows closely packed follicles. Centrocytes (small cells with the cleaved nucleus and scant cytoplasm) and centroblasts (large cells with open nuclear chromatin and multiple nucleoli) are seen.

Bone marrow is involved in 85% of the cases and shows para-trabecular lymphoid aggregates.

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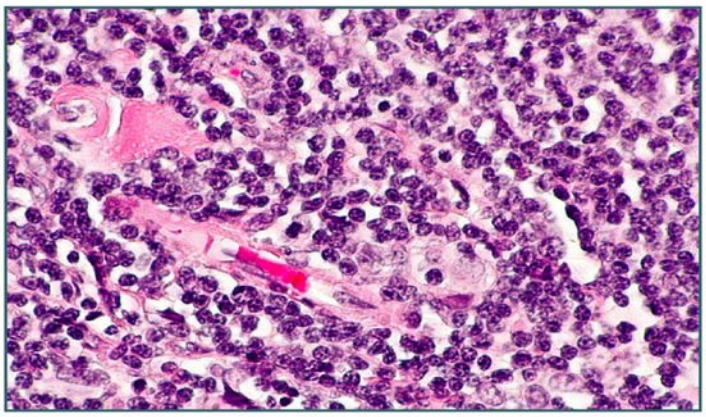
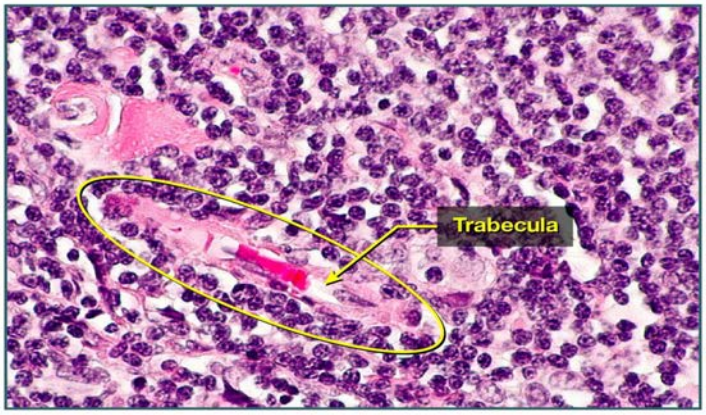
Bone marrow involvement in follicular lymphoma



Bone marrow involvement in follicular lymphoma



Solution to Question 11:

Follicular lymphoma shows t(14;18).

Its hallmark is a translocation that juxtaposes the IgH locus on chromosome 14 and the BCL2 locus on chromosome 18. It is seen in up to 90% of follicular lymphomas and leads to overexpression of BCL2.

BCL2 inhibits apoptosis and promotes the survival of follicular lymphoma cells.

Solution to Question 12:

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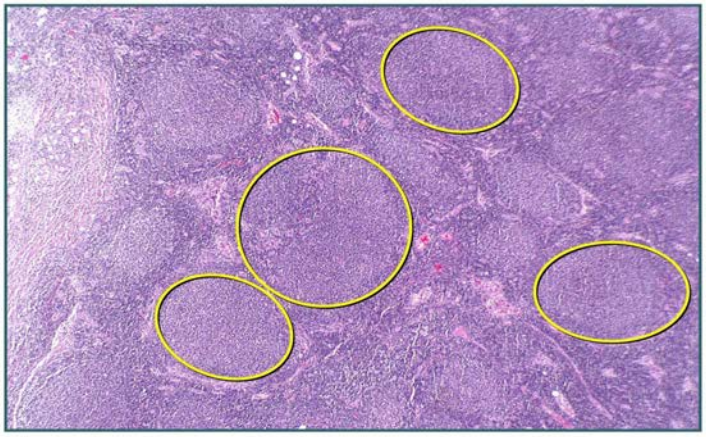
The lymph biopsy shows closely packed back-to-back follicles of variable areas and very less inter-follicular area. It is suggestive of follicular lymphoma.

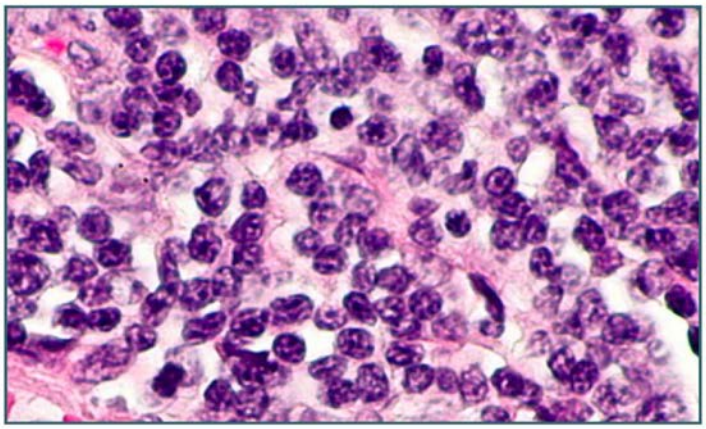
Lymph node biopsy of follicular lymphoma



Follicular lymphoma usually follows an indolent waxing and waning course, not an aggressive course.

Lymph node (LN) biopsy shows a nodular pattern with centrocytes and centroblasts as shown below.

Lymph node biopsy of follicular lymphoma



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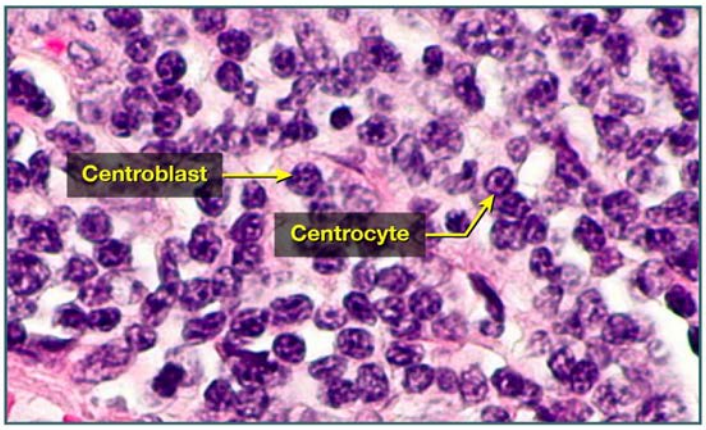
Lymph node biopsy of follicular lymphoma



Immunophenotyping:

• The cell of origin is germinal-center B cell, so it is positive for CD19, CD20, CD10, BCL6, and surface Ig.

• BCL2 expression is positive in over 90% of cases.

Histologic transformation to diffuse large B-cell lymphoma (DLBCL) occurs in 30 to 50% of cases.

Note: In contrast to follicular lymphoma, DLBCL has an aggressive course, shows a diffuse pattern of growth in lymph node biopsy and shows BCL-6 positivity.

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Solution to Question 13:

Mantle-cell lymphoma arises from the mantle-zone B cells which are naive B cells as they lack somatic hypermutation IgH gene.

Mantle-cell lymphomas have an (11;14) translocation involving the IgH locus on chromosome 14 and overexpression of cyclin D1.

It is CD5 positive and CD23 negative.

Comparison between mantle-cell lymphoma and chronic lymphocytic leukemia/ small lymphocytic lymphoma (CLL/ SLL):

	Mantle cell lymphoma	CLL/SLL
CD5	Positive	Positive
CD23	Negative	Positive
CyclinD1	Positive	Negative

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	Mantle cell lymphoma	CLL/SLL
FMC7	Positive	Negative
CD10, BCL6	Negative	Negative

Solution to Question 14:

The neoplastic cells in mantle cell lymphoma are CD5 positive and CD23 negative.

Mantle cell lymphoma usually presents as painless lymphadenopathy. Centroblasts and proliferation centers are absent, differentiating it from chronic lymphocytic lymphoma.

Immunophenotyping reveals the cells expressing cyclin D1, CD5, CD19, CD20, surface Ig. CD23 is negative in these cells.

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Solution to Question 15:

The given clinical picture and pathological findings point toward the diagnosis of mantle cell lymphoma.

The lymph node biopsy typically shows proliferation consisting of a homogenous population of small lymphocytes. The nuclei of these cells have irregular or deeply cleaved contours.

Mantle cell lymphoma has(11;14) translocation involving the IgH locus on chromosome 14 and the cyclin D1 locus on chromosome 11 that leads to overexpression of cyclin D1.

Option A: Follicular lymphoma has t(14:18), not t(18:14). Hence, it is not the answer.

Solution to Question 16:

Translocation (11;14) is characteristic of mantle cell lymphoma. The markers to be done to confirm the diagnosis, are Sox11 and Cyclin D1.

Mantle cell lymphoma is seen in the fifth and sixth decades of life and has a male predominance. It is characterised by painless lymphadenopathy and splenomegaly.

In some cases, there is multifocal mucosal involvement of the small bowel and colon known as lymphomatoid polyposis.

It has (11;14) translocation.

Lymph node biopsy shows nodal tumour cells may surround reactive germinal centres.
A homogeneous population of small lymphocytes with irregular to occasionally deeply cleft (cleaved) nuclear contours is typically seen.

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Large cells resembling centroblasts and proliferation centres are absent, distinguishing mantle cell lymphoma from follicular lymphoma and CLL/SLL, respectively.

Immunophenotyping is positive for cyclin D and SOX-11. SOX11 variant that often presents with circulating disease with splenomegaly but without significant lymphadenopathy and with a low Ki67 index (<10%).

Other markers include:

• CD 5, CD19 and CD20 +ve

• CD 23 -ve

• Moderately high levels of surface Ig (usually IgM and IgD with κ or λ light chain)

The IgH genes lack somatic hypermutation, supporting an origin from a naive B cell.

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Solution to Question 17:

SOX11 is the marker used for cyclinD1 negative mantle cell lymphoma.

Note: MYD88 is a marker for Waldenstorm macroglobulinemia.

Solution to Question 18:

Marginal zone lymphoma does not spread rapidly to other sites. It remains localised for prolonged periods and spread systematically in the later course of the disease.

They are B-cell tumours that arise within lymph nodes, spleen, or extranodal tissues. It is the most common primary extranodal lymphoma.

They arise within tissues involved by chronic inflammatory disorders of autoimmune or infectious aetiology:

• Salivary gland in Sjögren disease

• Thyroid gland in Hashimoto thyroiditis

• Stomach in Helicobacter gastritis

They may regress if the inciting agent is eradicated. Antibiotic therapy directed against Helicobacter pylori leads to tumour regression.

Translocations are associated with MALToma are t(11;18),t(14;18) and t(1;14). These translocations then upregulate BCL-10/MALT1, a protein that activates NF-kB and promotes the growth and survival of B-cells.

They may invade epithelial structures to form lymphoepithelial lesions. Transformation to diffuse large B-cell lymphoma may occur.

Solution to Question 19:

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Marginal zone lymphomas are considered to be of memory B cell origin. In most cases, they show evidence of somatic hypermutation.

The category of marginal zone lymphoma encompasses a heterogeneous group of B cell tumours that arise within lymph nodes, spleen, or extranodal tissues. They are often referred to as MALTomas.

Solution to Question 20:

Lymphomas arising in the setting of Sjögren syndrome in the salivary gland is marginal-zone lymphomas.

They often arise in tissues involved by chronic inflammatory disorders of autoimmune or infectious aetiology such as:

- Salivary gland in Sjögren syndrome
- Thyroid gland in Hashimoto thyroiditis
- Stomach in Helicobacter gastritis.

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Solution to Question 21:

The translocation seen in marginal-zone lymphoma is t(11;18). Other translocations include t(14;18), t(1;14).

Marginal-zone lymphoma begins as a polyclonal immune reaction. Signals from the antigen-stimulated T helper cells, drive the growth and survival of the clonal B-cells. At this stage, it is reversible, as in gastric MALToma after antibiotics against Helicobacter pylori.

With time tumour cells may acquire mutations that render their growth and survival antigen-independent. Translocations such as t(11;18), t(14;18), or t(1;14) up-regulate the expression and function of BCL10 or MALT1 and promote the growth and survival of B cells.

These translocations are relatively specific for extranodal marginal-zone lymphomas.

Solution to Question 22:

The given clinical scenario is suggestive of hairy cell leukemia. It is a B-cell neoplasm and not a T-cell lymphoma.

The peripheral smear shows leukemic cells with fine circumferential cytoplasmic hairy projections as shown below.

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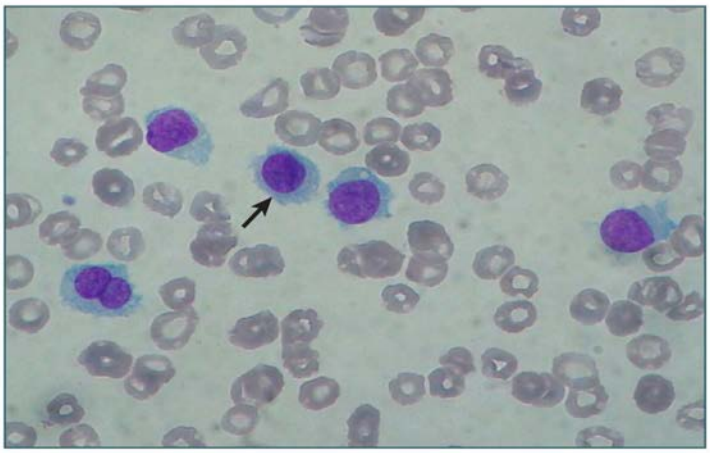
Peripheral smear of hairy cell leukemia



Patients present with massive splenomegaly and pancytopenia. There is an increased incidence of atypical mycobacterial infections, possibly related to frequent unexplained monocytopenia.

Activating point mutations in the serine/threonine kinase BRAF is seen in 90% of cases.

Peripheral smear shows fine circumferential cytoplasmic hairy projections which are best recognized under the phase-contrast microscope. The bone marrow aspirate produces a dry tap.

A trephine biopsy reveals infiltration by the cancer cells often in the pattern of a honeycomb appearance. Leukemic cells have nuclei surrounded by a cytoplasmic halo (fried egg appearance).

The neoplastic cells stain positive for tartrate-resistant acid phosphatase (TRAP).

Markers for hairy cell leukemia include:

- pan-B-cell markers- CD 19, CD20
- CD11c
- CD25
- CD103
- annexin A1

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Solution to Question 23:

The clinical features and peripheral smear showing fine circumferential cytoplasmic hairy projections point towards the diagnosis of hairy cell leukaemia.

It's a rare but distinctive neoplasm of the B cells where splenomegaly is often the only abnormal finding. Pancytopenia from marrow involvement and sequestration of cells in the enlarged spleen is seen in half the cases and infections are seen in one-third of the affected patients.

CD103 must be tested among the markers to confirm hairy cell leukaemia.

Hairy-cell leukaemias typically express the following markers:

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• Pan B-cell markers CD19, CD20, surface Ig (usually IgG)

• CD11c

• CD25

• CD103

• Annexin A1.

Annexin A1 is the most specific and sensitive marker.

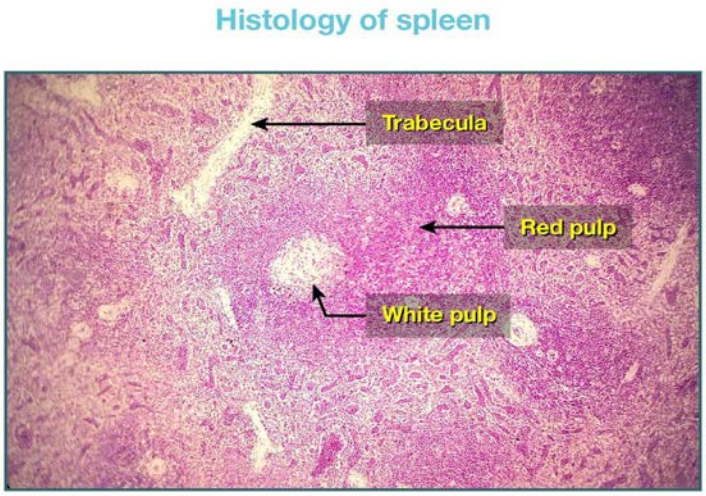
Solution to Question 24:

The area marked '1' in the image is the white pulp of the spleen. Hairy-cell leukemia does not arise from the white pulp, it involves only the red pulp of the spleen. The other condition involving the red pulp is hepato-splenic lymphoma.

All the other non-Hodgkin lymphomas (NHLs) involve white pulp.

Splenomegaly is the most common and often the only abnormal physical finding in hairy-cell leukemia. The spleen in this condition is described as a beefy red spleen.

The image given below shows the normal histology of the spleen.



Solution to Question 25:

The given pathological feature is characteristic of a Pautrier's microabscess. These are seen in mycosis fungoides.

It is a mature, cutaneous, CD4+ T-cell non-Hodgkin lymphoma. Skin lesions include truncal scaling, red-brown patches, plaques, and fungating nodules. Lesions may evolve into a systemic lymphoma, with visceral and nodal spread.

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Sezary syndrome is a variant of mycosis fungoides. It is the leukemic seeding of blood by malignant T cells from the skin (CD4+). It presents with diffuse erythroderma and scaling.

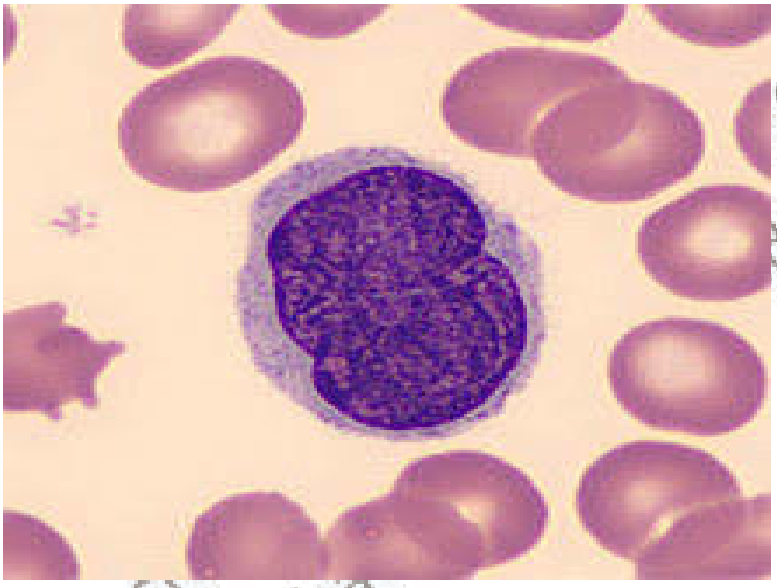
Histological hallmark includes:

• Sézary-Lutzner cells - cells with cerebriform nuclei (infolded/hyper-convoluted nuclear membrane).

• Pautrier's microabscesses - tumor cells invade the epidermis as single cells and small clusters.

• Epidermotropism - invasion of the tumor cells into the epidermis.

The image shows sezary cells with cerebriform nuclei in the peripheral smear.



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Solution to Question 26:

The image shows a classical Sezary cell with cerebriform nuclei which points towards a diagnosis of Sezary syndrome. These are neoplastic T cells.

Sezary syndrome and mycosis fungoides are different manifestations of tumors of CD4+ helper T cells that are home to the skin.

Sezary syndrome is a variant presenting as generalized exfoliative erythroderma. It rarely goes into tumefaction and there is associated leukemia of Sezary cells.

In Mycosis fungoides, only the epidermis and upper dermis are infiltrated by neoplastic T cells with the characteristic cerebriform appearance. In the later stages of the disease, progression occurs to lymph nodes and bone marrow. Tumour cells are not seen in blood. The disease progresses through the premycotic phase, plaque phase, and tumour phase.

Solution to Question 27:

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A triad of rheumatoid arthritis, splenomegaly, and neutropenia is known as Felty's syndrome. Some patients with Felty's syndrome have large granular lymphocytic leukemia as an underlying cause.

Large granular lymphocytic leukemia is a T-cell (CD3+) and NK-cell (CD56+) variant leukemia. They are associated with mutations in the transcription factor, STAT3.

Patients usually presents with mild to moderate lymphocytosis and splenomegaly. Neutropenia and anemia are also present. Lymphadenopathy and hepatomegaly are usually absent.

There is an increased incidence of rheumatological disorders associated with this condition.

The peripheral smear picture shows large lymphocytes with abundant blue cytoplasm and few azurophilic granules.

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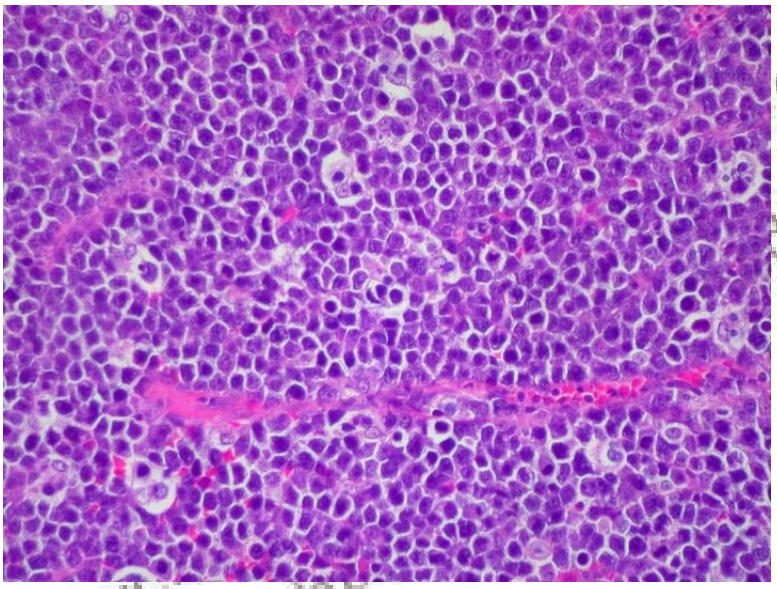
Non Hodgkin Lymphomas: High Grade

Question 1:

A 5-year-old boy presents with weight loss, fever, and a painless swelling in the area of his jaw. CBC reveals anaemia and lymphocytosis. Biopsy findings from the swelling are shown in the image below. Which of the following is not true about this patient's condition?



a) All forms of this tumour are associated with translocations of the MYC gene

b) Endemic forms are latently infected with EBV

c) Tumor exhibits a high mitotic index

d) Neoplastic cells are usually BCL2 positive

Question 2:

A 7-year-old boy who presented with the following finding was diagnosed with Burkitt's lymphoma. Which of the following translocations is most likely to be seen in this condition?

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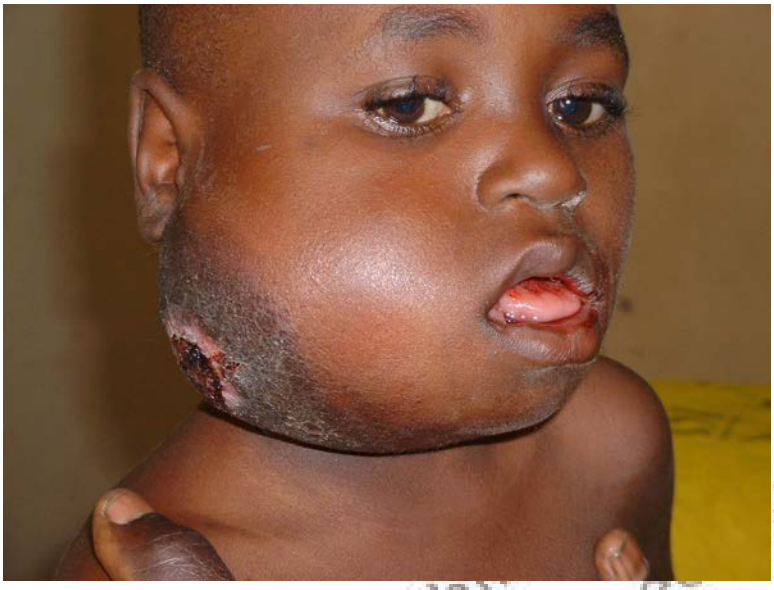

a) t(8;14)

b) t(11;18)

c) t(14;18)

d) t(11;14)

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Question 3:

Translocations of which of the following proto-oncogenes is most likely present in patients with Burkitt lymphoma?

a) ABL

b) BRAF

c) RAS

d) MYC

Question 4:

What is the most common site for sporadic Burkitt's lymphoma?

a) Jaw

b) Ileocecum

c) CNS

d) Liver

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Question 5:

Which lymphoma has ki67 index near 100%?

a) Mantle-cell lymphoma

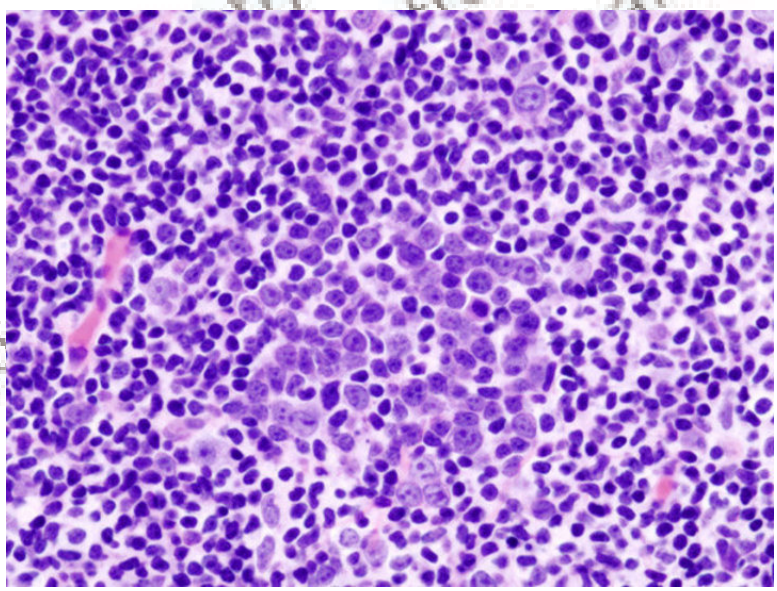
b) Diffuse large B-cell lymphoma

c) Burkitt's lymphoma

d) Extranodal NK cell lymphoma

Question 6:

A 35-year-old presented with fever and ulcerated tonsils. His peripheral smear showed lymphocytosis. The Monospot test was negative. Tonsillectomy was done, and the biopsy showed the following picture. The larger cells were positive for CD20, EBVLMP1, MUM1, and CD79a and negative for CD15. Background cells were positive for CD3. What is the most probable diagnosis?



a) Infectious mononucleosis

b) Hodgkin lymphoma

c) EBV-positive DLBCL

d) EBV-positive mucocutaneous ulcer

Question 7:

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A lymph node biopsy of a patient suffering from follicular lymphoma shows the presence of large cells with prominent multilobulated nuclei and abundant basophilic cytoplasm. Which of the following will test positive in this condition?

a) 1,3

b) 2, 4, 5

c) 3, 4

d) 1, 2, 5

Question 8:

You have been asked to use the International prognostic index for lymphomas to predict the prognosis of a patient suffering from DLBCL. Which of the following is not the component of this index?

a) Stage of the disease

b) Number of extra lymphatic sites involved

c) Lactate dehydrogenase levels

d) Hemoglobin levels

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Question 9:

A 55-year-old woman, on treatment for chronic lymphocytic leukemia, notices rapidly growing swellings in her neck and axilla. She also complains of fever and weight loss. The physician suspects a transformation to diffuse large B-cell lymphoma. What is this condition called?

a) Richter syndrome

b) Chédiak–Higashi syndrome

c) Sezary syndrome

d) Kostmann's syndrome

Question 10:

A 58-year-old woman came with complaints of swelling in her hard palate. Biopsy from the swelling showed the following picture. What is the most probable diagnosis?

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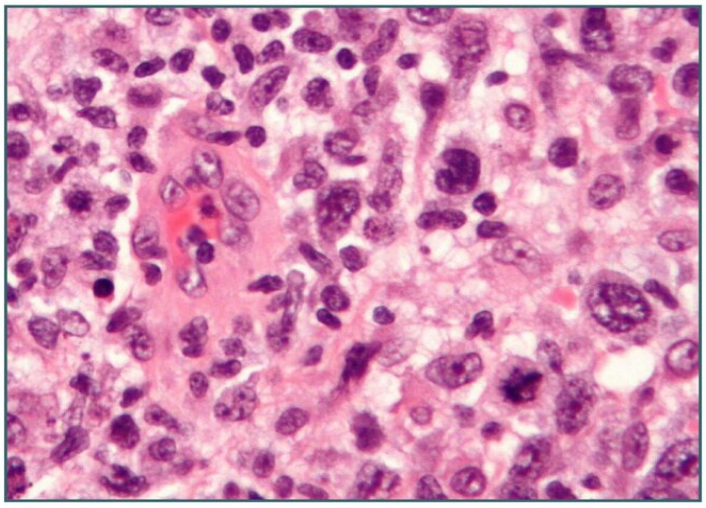

a) Hodgkin lymphoma

b) Hairy cell leukemia

c) Large granular lymphocytic leukemia

d) Anaplastic large cell lymphoma

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Question 11:

Which is an aggressive lymphoid neoplasm that classically occurs in the oral cavity of immunosuppressed patients?

a) Plasmablastic lymphoma

b) Hairy-cell leukemia

c) Anaplastic large-cell lymphoma

d) Extranodal NK/T-Cell Lymphoma

Question 12:

A 44-year-old man with nasal obstruction, nasal secretion, and facial erythema was diagnosed with facial cellulitis. When his condition did not improve on antibiotics, a CT scan was performed. It showed a destructive mass in the right nasal cavity extending into the nasopharynx. Which of the following is most likely to present this way?

a) Anaplastic large cell lymphoma

b) Extranodal NK/T-cell Lymphoma

c) Adult T-cell lymphoma

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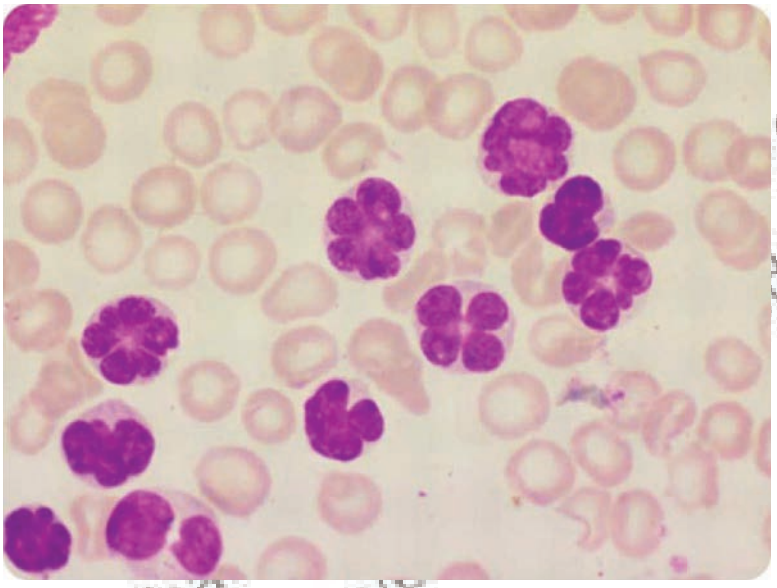
d) Mycosis fungoides

Question 13:

A 63-year-old man presented with severe pallor and giddiness. Clinical examination revealed bilateral cervical lymphadenopathy. Peripheral blood examination showed lymphocytosis and the following findings. What is the most likely diagnosis?



a) Large granular lymphocytic leukemia

b) Peripheral T-cell lymphoma

c) Anaplastic large-cell lymphoma

d) Adult T-cell leukemia/lymphoma

Question 14:

A 35-year-old man presents with weight loss and abdominal pain. He is a known case of celiac disease on a strict gluten-free diet. CT of the abdomen revealed a thickened loop of small bowel with stricture and associated lymphadenopathy. A lymphoid neoplasm is suspected. What is the most probable diagnosis?

a) Marginal zone lymphoma

b) Peripheral T-cell lymphoma

c) High-grade B-cell lymphoma

d) Enteropathy-associated T-cell lymphoma

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Question 15:

A 56-year-old woman came with complaints of pain and swelling in the left side of the abdomen. Investigations revealed multiple polyps in the rectum and sigmoid colon. A preliminary biopsy report was suggestive of a lymphoid neoplasm. Which of the following is the most probable diagnosis?

a) Mantle cell lymphoma

b) Marginal zone lymphoma

c) Burkitt lymphoma

d) Follicular lymphoma

Question 16:

BRAF V600E mutation is not seen in which of the following condition?

a) Hairy cell leukaemia

b) Malignant melanoma

c) Langerhans cell histiocytosis

d) Glioblastoma multiforme

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Answer Key

Question No.	Correct Option
1	d
2	a
3	d
4	b
5	c
6	c
7	d
8	d
9	a
10	d
11	a
12	b

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13	d
14	d
15	a
16	d

Detailed Explanations

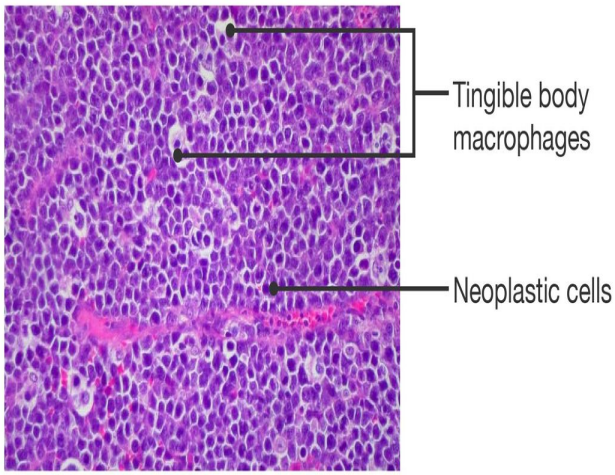
Solution to Question 1:

The clinical presentation and biopsy findings point to a diagnosis of Burkitt's lymphoma. Neoplastic cells in Burkitt's lymphoma are usually BCL2 negative.

The biopsy image shows the classical finding of Burkitt's lymphoma called the starry sky appearance.

Tumour cells show multiple small nucleoli, minimal cytoplasm and a high mitotic index. They are closely apposed to each other forming a dark blue background (sky).

The macrophages get stuffed in between along with cellular debris. They are called tingible body macrophages. Upon fixation, the cytoplasm of these phagocytes washes away leaving behind white spaces filled with debris (the stars).



Burkitt lymphoma is the most common NHL in children <15 years.

Three distinct clinical forms of Burkitt's lymphoma are:

• Endemic- affects children in Africa, affects jaw, maxilla, and is EBV-associated.

• Sporadic- in adults in western countries.

• Immunodeficiency associated- is associated with HIV infection.

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It is the most rapidly proliferating human tumor, Ki-67 stains for 100% of cells (DLBCL- 40% staining with Ki-67). Histology shows the characteristic starry sky pattern.

Immunophenotypic markers include:

• Surface IgM type and immunoglobulin light chains (kappa > lambda)

• B cell-associated antigens -CD19, CD20, CD22, CD79a

• Germinal centre-associated markers- CD10 & BCL-6

• HLA-DR and CD43

• Expression of CD21 -the Epstein-Barr virus (EBV)/C3d receptor, is dependent on the EBV status of the tumors

• Endemic BL: EBV (+), express CD21

• Non-endemic BL: EBV (--) and lack CD21 expression

Treatment must begin within 48h of diagnosis in both children and adults with an intensive combination of chemotherapy regimens with high doses of cyclophosphamide and CNS prophylaxis.

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Solution to Question 2:

The translocation seen in Burkitt's lymphoma is t(8;14) causing translocation of the MYC gene. It is the most common translocation and is seen in 70% of the cases.

Other translocations that may be present include t(2;8) and t(8;22).

Solution to Question 3:

All forms of Burkitt lymphoma are highly associated with translocations of the MYC gene on chromosome 8 that lead to increased MYC protein levels.

In addition to the MYC translocations in Burkitt lymphoma and a subset of other B and T cell tumours, MYC is amplified in some breast, colon, lung, and many other carcinomas.

The functionally identical NMYC and LMYC genes are also amplified in neuroblastomas and small-cell cancers of the lung, respectively.

Solution to Question 4:

Sporadic Burkitt's lymphoma most often presents as a mass involving the ileocecum and peritoneum. About 15 to 20% of these are associated with Epstein–Barr virus (EBV).

Endemic Burkitt's lymphoma, in contrast, presents as a mass involving the mandible. It shows an unusual predilection for the involvement of abdominal viscera, particularly kidneys, ovaries and adrenal glands. Involvement of the bone marrow and peripheral blood is uncommon.

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Immunodeficiency-associated Burkitt's lymphoma commonly involves the gastrointestinal tract (GIT) and central nervous system (CNS).

Solution to Question 5:

Burkitt's lymphoma is a very aggressive tumour, having a very high mitotic index and a ki67 of about 100%.

ki67 is a proliferation marker used to assess the mitotic index of the tumour. It is high in high-grade tumours and low in low-grade tumours.

Both mantle-cell lymphoma and DLBCL also have a high ki67, but it is not as high as that seen in Burkitt's. Follicular lymphoma is a low-grade tumour, and hence, it has a low ki67 index.

The following are the images of Burkitt's lymphoma.

• Image a - sheets of medium-sized cells with numerous tingible body macrophages showing the classic starry-sky pattern.

• Image b - BCL 6 stain positivity in lymphoma cells.

• Image c - the Ki-67 proliferation rate of virtually 100%.

• Image d - EBER (Ebstein-Barr encoding region) in situ hybridization with numerous positive cells.

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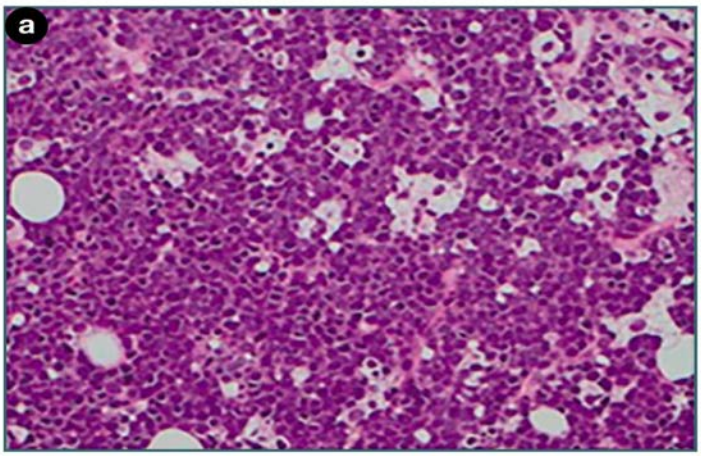
Lymph node biopsy of Burkitt's lymphoma



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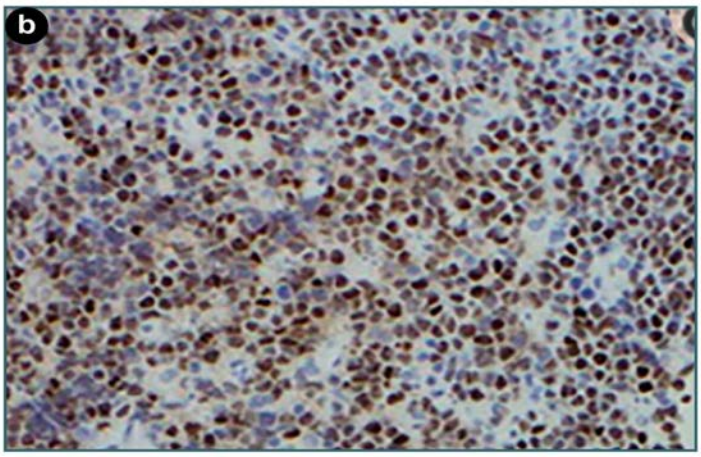
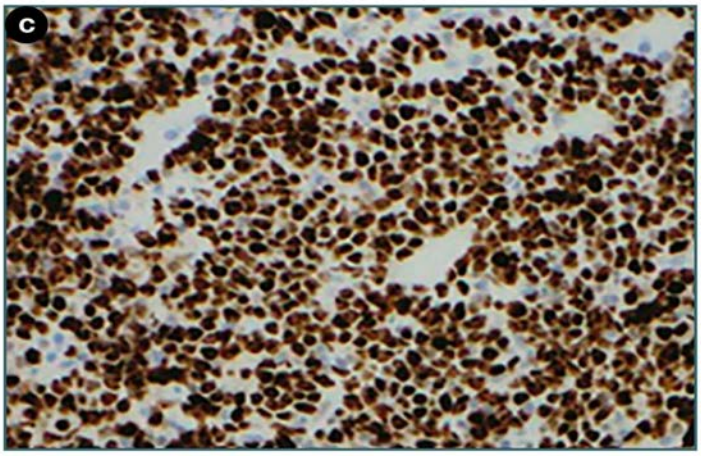
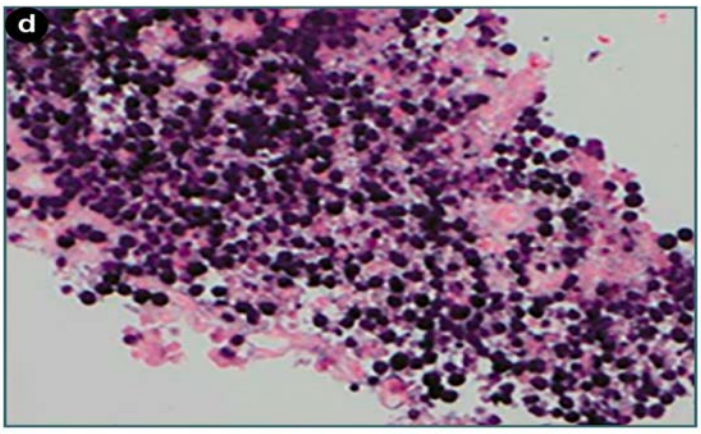
Bcl-6 positivity in Burkitt's lymphoma



Ki-67 index of Burkitt's lymphoma



EBER in-situ hybridisation in Burkitt's lymphoma



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Solution to Question 6:

The given clinical scenario is suggestive of Epstein-Barr virus (EBV) positive diffuse large-cell lymphoma (DLBCL).

The histopathological findings show large cells with multilobed irregular nuclei. These cells are positive for CD20, CD79a, IRF4/MUM1, EBVLMP1. The smaller cells in the background are CD3+ which is a T-cell marker.

It is seen in the elderly (>50 years) and without immunodeficiency or prior lymphoma. 70% of the cases are extranodal and mainly affect skin, lung, tonsil, and stomach with or without LN involvement. 30% of the cases have LN disease alone.

Option A: This is not infectious mononucleosis as the monospot test is negative.

Option B: It is not Hodgkin lymphoma because it is positive for CD20 and CD79a and negative for CD15.

Option D: It is not EBV positive mucocutaneous ulcer as the patient is immunocompetent and it is strongly positive for CD20.

Note: EBV positive mucocutaneous ulcer occurs in immunocompromised patients and reverts to treating the immunocompromised state. It shows polymorphous infiltrate and atypical large B cells with RS cell-like morphology admixed abundant T cells.

There is a uniform expression of CD30, MUM1, PAX5, OCT2. There is variable expression of CD20,CD45, CD15, CD79a, BCL6.

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Solution to Question 7:

The given history and histopathological examination point towards the diagnosis of diffuse large B-cell lymphoma (DLBCL).

It is molecularly heterogeneous and can show the given abnormalities:

• BCL6 (transcription factor) overexpression is most common

• 10 to 20% cases have t(14;18) leading to overexpression of BCL2 (a proto-oncogene)

• 5% are associated with MYC translocations (like Burkitt's lymphoma)

• Mutations in gene encoding histone acetyltransferases

DLBCL and follicular lymphoma, both are positive for CD19, CD20, CD10, and BCL6 (germinal-center B-cell origin). While BCL2 is positive in >90% of the cases of follicular lymphoma, it can also be positive in DLBCL.

To differentiate DLBCL from follicular lymphoma, the ki67 index is used. If ki67 >40% (high) it suggests DLBCL.

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Solution to Question 8:

Hemoglobin levels are not a part of the International prognostic index (IPI) score.

IPI is based on the presence or absence of five adverse prognostic factors:

• Age >60 years

• Raised serum lactate dehydrogenase (LDH)

• Performance status >2 (ECOG) or <70 (Karnfosky)

• >1 site of extranodal (extra lymphatic) involvement

• Ann Arbor stage III or IV

Solution to Question 9:

The transformation of chronic lymphocytic leukemia (CLL)/ small lymphocytic leukemia (SLL) to diffuse large B-cell lymphoma is called Richter syndrome. It is seen in approximately 5% to 10% of the cases.

Option B: Chédiak–Higashi syndrome is an autosomal-recessive disorder that arises from a mutation of a lysosomal trafficking regulator protein. It leads to a decrease in phagocytosis, recurrent pyogenic infections, albinism, and peripheral neuropathy.

Sézary syndrome (SS) is a triad of erythroderma, generalized lymphadenopathy, and the presence of clonally related neoplastic T cells. These cells have cerebriform nuclei (Sézary cells) and are seen in the skin, lymph nodes, and peripheral blood.

Kostmann's syndrome is an autosomal recessive disorder characterized by severe neutropenia. It is associated with mutations in G-CSF.

Solution to Question 10:

The given scenario and histopathological image point towards a diagnosis of anaplastic large cell lymphoma.

The biopsy shows characteristic large anaplastic cells, some containing horseshoe-shaped nuclei and voluminous cytoplasm called hallmark cells.

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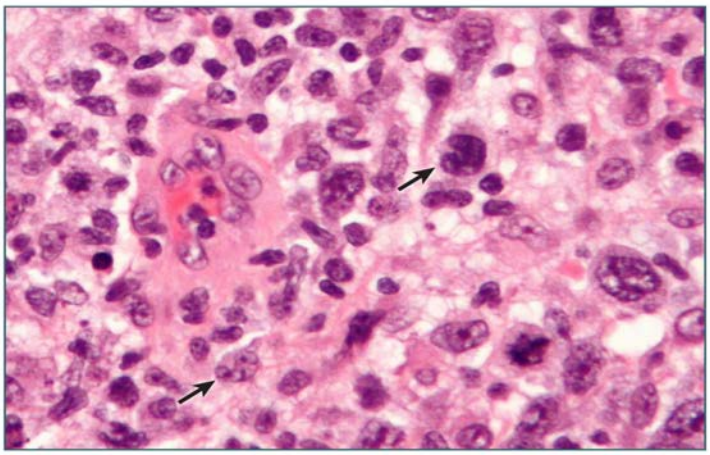
Biopsy of anaplastic large cell lymphoma



It is a type of T-cell lymphoma that consists of large lymphoid cells.

This occurs due to rearrangements in the ALK gene and usually affects children and young adults. It frequently involves soft tissue and carries a good prognosis. T-cell lymphomas with similar morphology without ALK positivity occur in older adults and have a bad prognosis.

CD markers: T cell markers (CD3, CD4, CD8 etc) +, CD30+.

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Solution to Question 11:

Plasmablastic lymphoma is an aggressive lymphoid neoplasm that classically occurs in the oral cavity in immunosuppressed patients.

Plasmablastic lymphoma usually occurs in HIV+ patients (73%), immunosuppressed or elderly patients without known immunodeficiency, and EBV+ patients.

Lymphomas more specific to HIV+ patients:

- Primary effusion lymphoma
- Plasmablastic lymphoma
- Primary CNS lymphoma

Solution to Question 12:

Extranodal NK/T-Cell Lymphoma is most likely to present as a destructive nasopharyngeal mass. Less common sites of presentation include the testis and the skin.

It accounts for 3% of all non-Hodgkin lymphomas (NHLs) in Asia. Extranodal NK/T-cell lymphoma is highly associated with EBV.

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The tumor cells typically surround and invade the small vessels leading to extensive ischemic necrosis. In touch preparations, large azurophilic granules are seen in the cytoplasm of the tumor cells.

They express NK-cell markers (CD16, CD56) supporting an NK-cell origin.

Most extranodal NK/T-cell lymphomas are highly aggressive neoplasms that respond well to radiation therapy but are resistant to chemotherapy.

Solution to Question 13:

The given clinical scenario and peripheral smear findings showing cloverleaf cells, point towards a diagnosis of adult T-cell leukemia/ lymphoma.

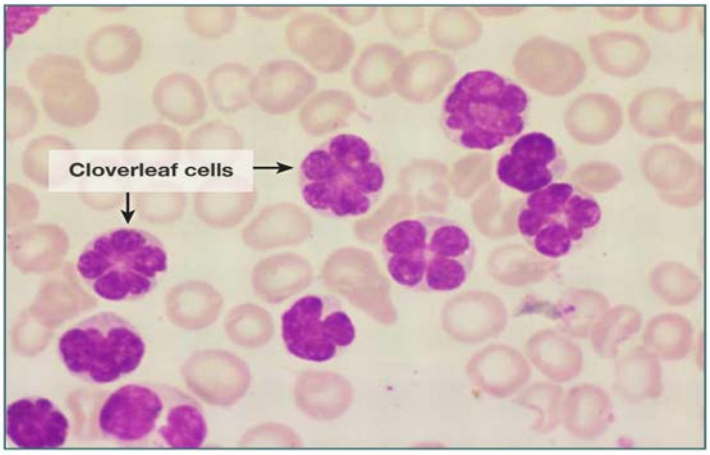
Adult T-cell leukemia/ lymphoma occurs in adults infected by human T-cell leukemia retrovirus type 1 (HTLV-1). Common findings include skin lesions, generalized lymphadenopathy, hepatosplenomegaly and hypercalcemia.

Peripheral smear blood shows characteristic cloverleaf cells or flower cells which are tumour cells with multilobulated nuclei. Lymphocytosis is also observed.

It is a rapidly progressive disease that is fatal within months to 1 year.

The image given below shows peripheral blood smear findings in adult T-cell leukemia/lymphoma.

Peripheral smear of Adult T-cell leukemia



Note: Apart from adult T-cell leukemia, HTLV-1 may also give rise to progressive demyelinating disease of the CNS and spinal cord.

Solution to Question 14:

The most probable diagnosis in this patient is enteropathy-associated T-cell lymphoma.

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Individuals with celiac disease have a higher than normal rate of malignancy. The most common cancer associated with celiac disease is enteropathy-associated T-cell lymphoma. It is an aggressive lymphoma of intraepithelial T lymphocytes.

When the symptoms in a celiac disease patient deteriorate, even being on a strict gluten-free diet, cancer must be considered.

Note: Small intestinal adenocarcinoma is also more frequent in individuals with celiac disease.

Solution to Question 15:

The given scenario points towards the diagnosis of lymphomatoid polyposis. The most common among the non-Hodgkin's lymphoma to present like this is mantle cell lymphoma.

Lymphomatoid polyposis is characterized by multifocal mucosal involvement of the proliferating lymphocytes. It has aggressive behavior and a relatively poor prognosis. It must be treated accordingly as a high-grade lymphoma with systemic chemotherapy.

Solution to Question 16:

BRAF V600E (valine to glutamate substitution at residue 600) mutation is not seen in glioblastoma multiforme.

BRAF is a serine/threonine kinase positioned immediately downstream of RAS in the MAPK signalling cascade.

It is seen in the following conditions:

- Hairy cell leukaemia
- Malignant melanoma
- Langerhans cell histiocytosis
- Papillary carcinoma thyroid
- Pilocytic astrocytoma
- Erdheim–Chester disease

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Multiple Myeloma and Plasma Cell Disorders

Question 1:

What is the normal ratio between kappa and lambda light chains?

a) 70:30

b) 60:40

c) 40:60

d) 30:70

Question 2:

Patients with which of the following can be classified under smoldering multiple myeloma?

a) Lack of symptoms and a high plasma M component with bone marrow plasma cells >10%

b) Plasma cells >10% in the bone marrow, no paraprotein in blood and presence of lytic bone lesions

c) Plasma cells >10% in bone marrow, abnormal serum free light chain ratio and hypercalcemia

d) Presence of symptoms and a low plasma M component with plasma cells <10%

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Question 3:

A 76-year-old man presents for a routine health check-up and is found to be mildly anemic. Physical examination reveals no abnormalities. Serum protein electrophoresis with immunofixation demonstrates an IgG-kappa monoclonal protein with markedly reduced IgM and IgA levels. Bone marrow biopsy shows 12% plasma cells. A skeletal survey reveals osteopenia and several punched-out lytic lesions, but no fractures. What is the most likely diagnosis?

a) Plasma cell leukemia

b) Multiple myeloma

c) Plasmacytoma

d) MGUS

Question 4:

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What is the most common cytogenetic abnormality in multiple myeloma?

a) Translocation 14q

b) Deletion of 13q

c) Translocation 11q

d) Deletion of 17p

Question 5:

Which cytokine is an important growth factor for plasma cells in multiple myeloma?

a) IL-2

b) IL-6

c) Interferon γ

d) IL-1

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Question 6:

Which of the following is the most common monoclonal immunoglobulin seen in patients with myeloma?

a) IgM

b) IgA

c) IgE

d) IgG

Question 7:

In patients with multiple myeloma, lytic lesions are most commonly seen in which bone?

a) Skull

b) Ribs

c) Pelvis

d) Vertebrae

Question 8:

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Which substance is responsible for the marked increase in bone resorption and hypercalcemia in patients with multiple myeloma?

a) IL 6

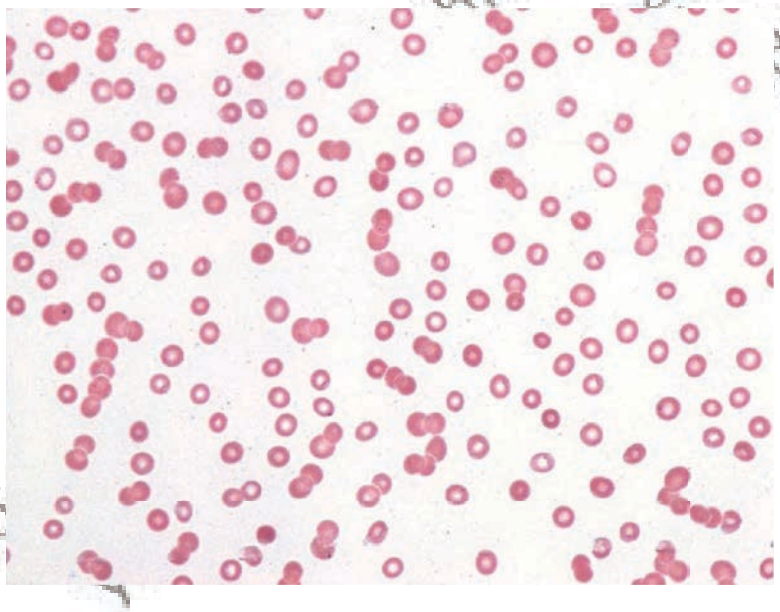
b) MIP 1α

c) NF- κB

d) ALP

Question 9:

A pathologist observed the following finding in a peripheral blood smear. In patients with which of the following conditions is this seen?



a) 1 and 4 only

b) 2, 3, and 5

c) 1, 2, and 5

d) 3 and 4 only

Question 10:

Which of the following is least likely to be seen in patients with multiple myeloma?

a) Dutcher bodies

b) Russell bodies

c) Mooser bodies

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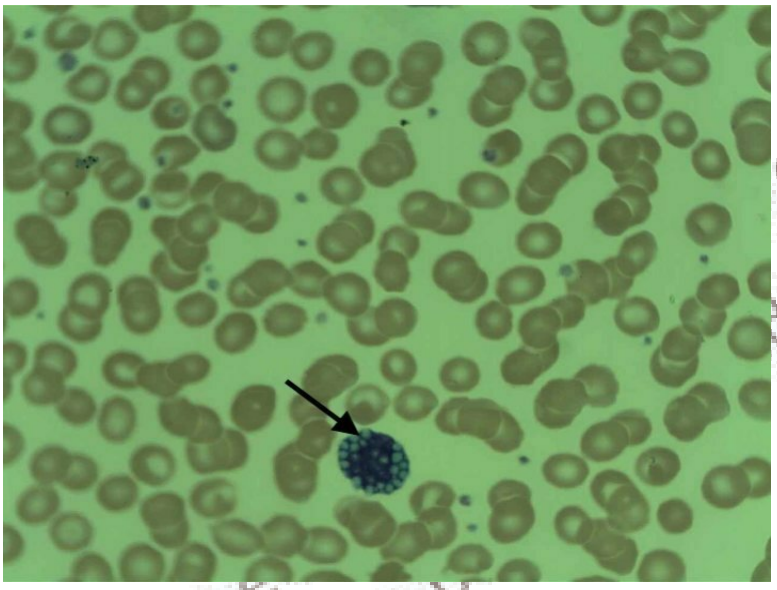
d) Mott cells

Question 11:

The peripheral smear of a patient diagnosed with multiple myeloma is shown below. What does the marked structure contain?



a) Immunoglobulin

b) Golgi bodies

c) Rough endoplasmic reticulum

d) Apoptotic bodies

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Question 12:

The marked finding in plasma cells is due to:

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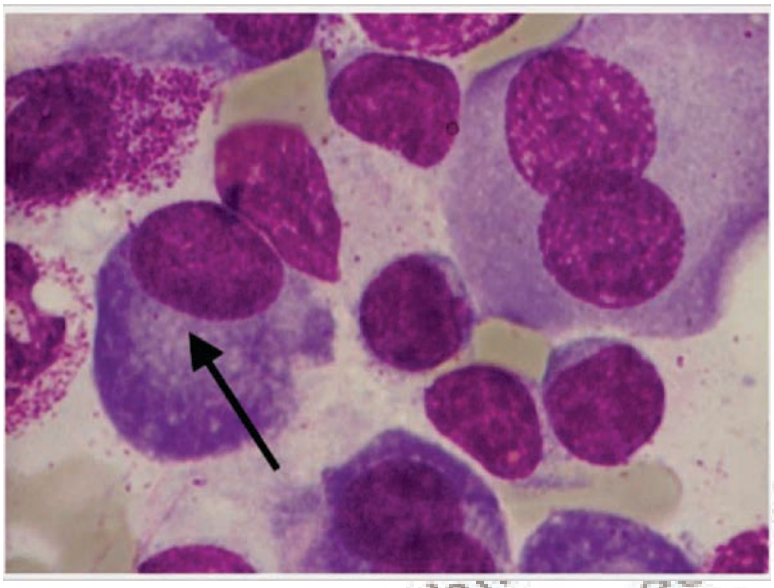

a) Lysosomes

b) Golgi apparatus

c) Ig deposits

d) Cytoplasmic vacuole

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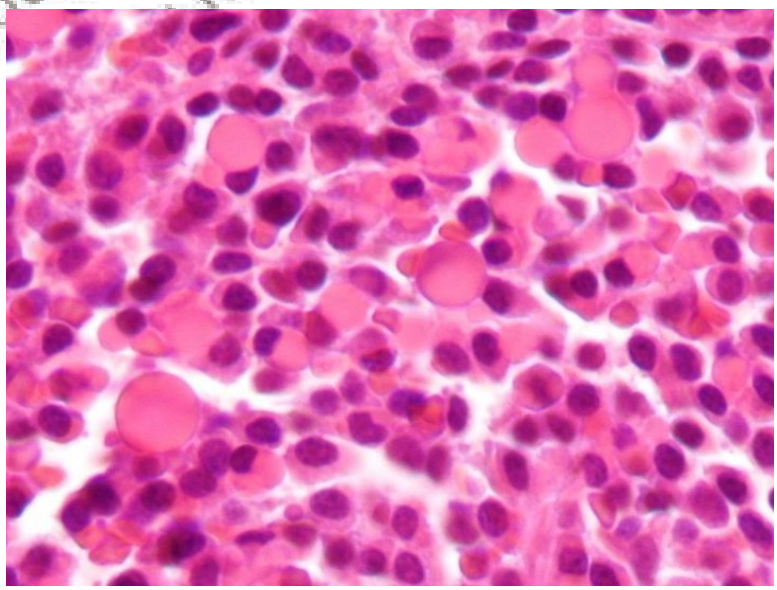
Question 13:

A 60-year-old male presented with a history of intractable diarrhea. Based on the histological image shown below which of the following is the most appropriate diagnosis:



a) Lymphoma

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b) Leishmaniasis

c) Urate nephropathy

d) Multiple myeloma

Question 14:

A patient with pallor and pathological fracture is diagnosed with multiple myeloma. Which of the following is not a kidney finding of such patients?

a) Tubular casts

b) Nephrocalcinosis

c) Wire-loop lesions

d) Renal tubular necrosis

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Question 15:

What do Bence Jones proteins in the urine of multiple myeloma patients represent?

a) Light chains

b) Heavy chains

c) Intact antibodies

d) Part of heavy chains

Question 16:

Hyperviscosity symptoms in patients with multiple myeloma occur due to which of the following types of M protein?

a) IgG1

b) IgG2

c) IgG3

d) IgG4

Question 17:

Multiple myeloma patients associated with which type of M protein has the highest risk of renal insufficiency?

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a) IgM

b) IgG

c) IgA

d) IgD

Question 18:

Which of the following tumor markers is least likely to be positive in a patient with multiple myeloma?

a) CD 56

b) syndecan-1

c) CD 138

d) CD 21

Question 19:

Which of the following is not considered as a myeloma-defining event, according to the revised criteria for the diagnosis of multiple myeloma?

a) More than one focal lesionon MRI of 5 mm or more

b) 60% or more clonal plasma cells on bone marrow examination

c) Biopsy proven plasmacytoma

d) Serum involved/uninvolved free light-chain ratio of 100 or greater

Question 20:

A 60-year-old lady presents with complaints of pallor, recurrent UTI, and bone pain in lower limbs. Peripheral smear shows rouleaux formation. X-ray done is given below. Which is the best immunohistochemical marker for this condition?

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a) Annexin A1

b) CD20

c) Cyclin D1

d) Hep-par 1

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Question 21:

A patient diagnosed with multiple myeloma develops features of restrictive cardiomyopathy and macroglossia. Which of the following amyloid is responsible for this?

a) AL

b) AA

c) A° 2m

d) A Cal

Question 22:

What is the most common cause of death in patients with myeloma?

a) Renal failure

b) Infections

c) Cardiac failure

d) Hypercalcemic crisis

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Question 23:

A 60-year-old man presents with complaints of fatigue, pain over the ribs, and confusion. Lab investigations reveal anemia, hypercalcemia, and increased serum creatinine. X-ray shows lytic lesions on the bones. Which of the following is the most powerful prognostic indicator of this condition at the time of diagnosis?

a) Number of myeloma cells in the marrow

b) ° 2 microglobulin

c) Serum C-reactive protein

d) Serum creatinine

Question 24:

Which of the following is not associated with poor prognosis in a patient with multiple myeloma?

a) t(4;14)

b) High serum beta-2 microglobulin

c) Low serum albumin

d) t(11;14)

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Question 25:

A 70-year-old man presents with chronic low back pain. On examination, he has pallor and bony tenderness. A skeletal radiographic survey reveals several punched-out lytic lesions. Serum protein electrophoresis shows an M band in the gamma globulin region. Which of the following is not associated with a poor prognosis in this condition?

a) Translocation involving cyclin D1

b) t(14;16)

c) Deletions of 17p

d) t(14;20)

Question 26:

Which among these is not diagnostic of monoclonal gammopathy of undetermined significance?

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a) Serum M protein level < 3 g/dL

b) Bence-Jones proteins in urine

c) Bone marrow plasma cells <10%

d) Absence of lytic bone lesions

Question 27:

A patient with complaints of blurred vision, bleeding gums, and tingling sensation over the extremities is diagnosed with lymphoplasmacytic lymphoma. Which of the following immunoglobulins is this condition associated with?

a) IgG

b) IgA

c) IgE

d) IgM

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Question 28:

A 40-year-old man is diagnosed with lymphoplasmacytic lymphoma. Which of the following genes is mutated in this condition?

a) MYC

b) MYD88

c) SOX

d) RUNX1

Question 29:

Which of the following is not seen in patients with Waldenstrom macroglobulinemia?

a) M spike in serum protein electrophoresis

b) Increased serum calcium

c) Features due to organ infiltration

d) Absence of lytic lesions on imaging

Question 30:

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Which of the following is the most common site for extramedullary plasmacytoma?

a) Gastrointestinal system

b) Upper respiratory tract

c) Genitourinary system

d) Central nervous system

Question 31:

What is Seligmann's disease?

a) α- heavy chain disease

b) γ- heavy chain disease

c) μ- heavy chain disease

d) ° - heavy chain disease

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Question 32:

A 60-year-old man presents with a history of bone pain, weakness, and loss of weight for 3 years. On examination, enlarged lymph nodes and organomegaly are noted. Peripheral smear shows 22% plasma cells, which are λ-chain restricted. Serum IgE level is elevated. X-ray image of the lumbar vertebra shows lytic punched-out lesions. What is the diagnosis?

a) Multiple myeloma

b) Plasmacytoma

c) Lymphoplasmacytic lymphoma

d) Plasma cell leukemia

Answer Key

Question No.	Correct Option
1	b
2	a
3	b
4	a

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5	b
6	d
7	d
8	b
9	c
10	c
11	a
12	b
13	d
14	c
15	a
16	c
17	d
18	d
19	c
20	c
21	a
22	b
23	b
24	d
25	a
26	b
27	d
28	b
29	b
30	b
31	a
32	d

Detailed Explanations

Solution to Question 1:

The normal ratio of kappa to lambda light chains is 60:40.

In multiple myeloma, usually this ratio is skewed, i.e., favorable secretion of one type of light chain occurs at the expense of the other. Serum-free light chain assay is a recommended part of the initial diagnostic workup for multiple myeloma.

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Solution to Question 2:

Smoldering multiple myeloma refers to an uncommon variant defined by a lack of symptoms and a high plasma M component.

The difference between MGUS, smouldering multiple myeloma, and multiple myeloma is given below:

MGUS	Smouldering multiple Myelo ma	Multiple Myeloma
Asymptomatic	Asymptomatic	Symptomatic
M protein in serum <3g/dL	M-protein in serum:IgG ≥3 g/ dL,IgA >1 g/dL	M protein in serum and urin e
Bone Marrow (BM) plasma c ells <10%	BM plasma cells 10-60%	BM plasma cells ≥60%
No other organ or tissue imp airment	No other organ or tissue imp airment	Related impairment is seen.(CRAB)

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Solution to Question 3:

The given clinical scenario is suggestive of multiple myeloma.

Plasma cell dyscrasias are B-cell proliferations that contain neoplastic plasma cells that secrete a monoclonal Ig or Ig fragment. Multiple myeloma is a malignant neoplasm of plasma cells characterized by the presence of monoclonal immunoglobulin or light chains in the serum and urine. It is a disease of older adults, with a peak age of incidence of 65 to 70 years.

Signs and symptoms include:

• Hypercalcemia

• Pathologic fractures/ lytic bone lesions

• Renal failure

• Anemia

Investigations reveal:

• Radiography - Punched-out lytic lesions on X-ray

• Electrophoresis - Monoclonal elevation of one immunoglobulin

• Urinalysis - Free kappa and lambda light chains (Bence Jones proteins)

• Bone marrow biopsy - 10 to 20%plasma cells (normal is < 5%)

• Peripheral smear - Rouleaux formation. A high level of M proteins in myeloma causes red cells in the peripheral blood smears to stick to one another in linear arrays, a finding referred to as rouleaux formation.

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Plasma cell tumors are positive for CD138.

Solution to Question 4:

The most common cytogenetic abnormality in multiple myeloma is translocation 14q.

Cytogenetic abnormalities in multiple myeloma include:

• Translocations involving IGH on chromosome 14q - most frequent

• Monosomy or partial deletion of chromosome 13 (13q14) - Found by FISH (nearly half the cases)

• Translocation of the IgH occurs frequently with cyclin D1 on chromosome 11q and cyclin D3 on chromosome 6p

• Deletions of chromosome 17p involving TP53 tumor-suppressor locus

Translocations with cyclin D1 are associated with a good outcome, whereas deletion of 17p and t(4;14) portend an aggressive course.

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Solution to Question 5:

The proliferation and survival of plasma cells are dependent on several cytokines, most notably IL-6.

It is an important growth factor for plasma cells. It is produced by the tumor cells themselves and by resident marrow stromal cells. IL6, along with other cytokines, promotes osteoclastic activity and lytic bone lesions. High serum levels of IL-6 are seen in patients with active disease and are associated with a poor prognosis.

Solution to Question 6:

The most common monoclonal Ig (M protein) in myeloma is IgG (approximately 55% of patients), followed by IgA (approximately 25% of cases).

The immunosecretory disorders are a diverse group of diseases associated with the proliferation of an abnormal clone of immunoglobulin-synthesizing, terminally differentiated B cells. These disorders include:

• Multiple myeloma (MM) and its variants

• Plasmacytoma

• Waldenstrom macroglobulinemia

• Monoclonal gammopathy of undetermined significance

• Monoclonal Ig deposition diseases - Includes primary amyloidosis and nonamyloidotic types.

The immunoglobulin can be complete or can be composed of either heavy or light chains and is termed M-(monoclonal) protein. Most myelomas are associated with more than 3 gm/dL of serum

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immunoglobulin. Myelomas expressing IgM, IgD, or IgE occur, but they are rare.

Solution to Question 7:

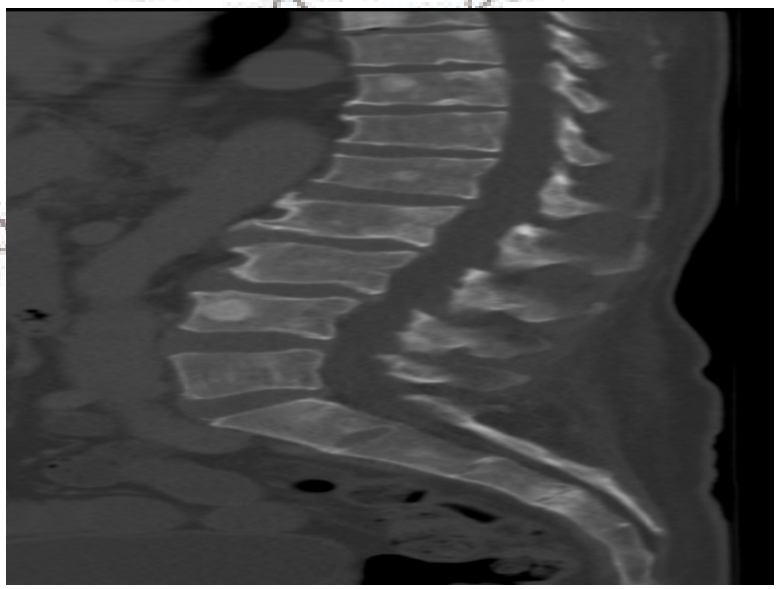
Lytic bony lesions in myeloma patients are most commonly seen in the vertebrae.

Multiple myeloma usually presents as destructive plasma cell tumors involving the axial skeleton. The bones most commonly affected (in descending order of frequency) are:

- Vertebral column
- Ribs
- Skull
- Pelvis
- Femur
- Clavicle
- Scapula

Pathologic fractures are common in this condition. The bone lesions appear radiographically as punched-out defects, usually 1 to 4 cm in diameter.

The image given below shows osteoblastic lesions of vertebra in multiple myeloma.



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Solution to Question 8:

MIP1α secreted by myeloma cells is responsible for the marked increase in bone resorption and hypercalcemia.

Factors produced by neoplastic plasma cells mediate bone destruction, the major pathologic feature of multiple myeloma. Of particular importance, myeloma-derived macrophage

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inflammatory protein 1α (MIP1α) upregulates the expression of the receptor activator of NF-κB ligand (RANKL) by bone marrow stromal cells, which in turn activates osteoclasts.

Other factors released from tumor cells, such as modulators of the Wnt pathway, are potent inhibitors of osteoblast function.

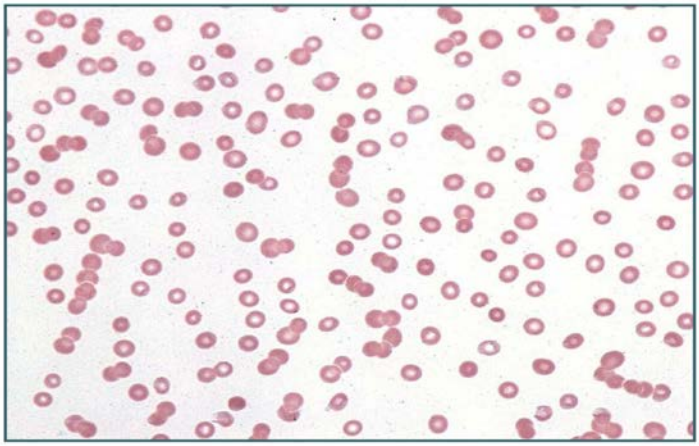
The net effect is a marked increase in bone resorption, which leads to hypercalcemia and pathological fractures.

Serum alkaline phosphate levels are normal in multiple myeloma.

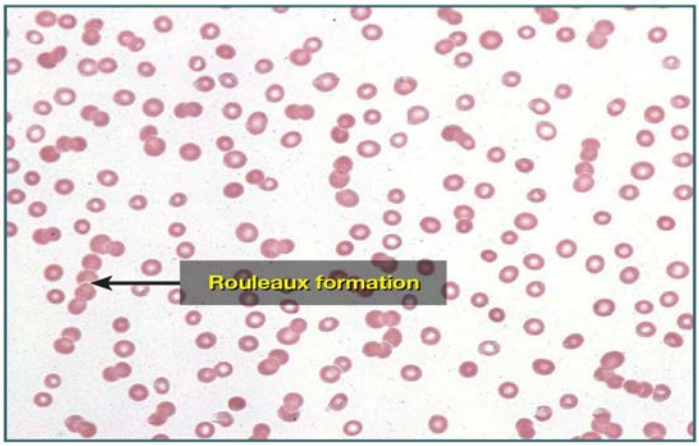
Solution to Question 9:

The given peripheral smear shows rouleaux formation. It is seen in patients with early HIV, SLE, and multiple myeloma.

Rouleaux formation in peripheral smear



Rouleaux formation in peripheral smear



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Conditions that cause rouleaux formation are:

• Multiple myeloma

• Connective tissue disorders like SLE

• Early HIV

• Infections

Rouleaux formation is retarded by albumin.

Solution to Question 10:

Mooser bodies are seen in Typhus fever, not in multiple myeloma.

Histopathological findings seen in multiple myeloma:

• Dutcher bodies - pale-staining intranuclear inclusions within plasma cells containing Ig, which are more common in IgA myeloma (Image below).

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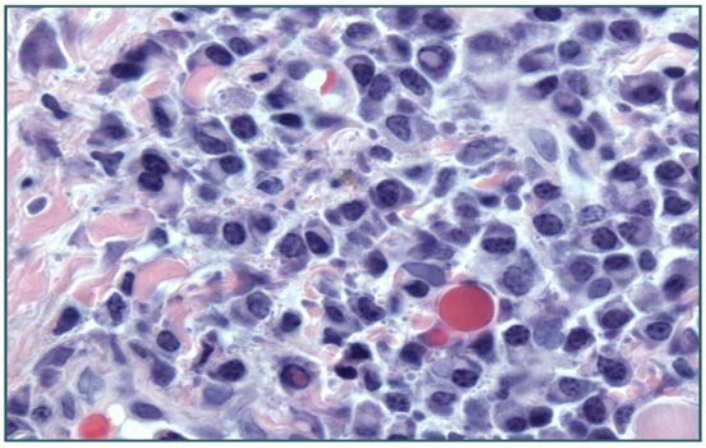
Multiple myeloma - Dutcher bodies



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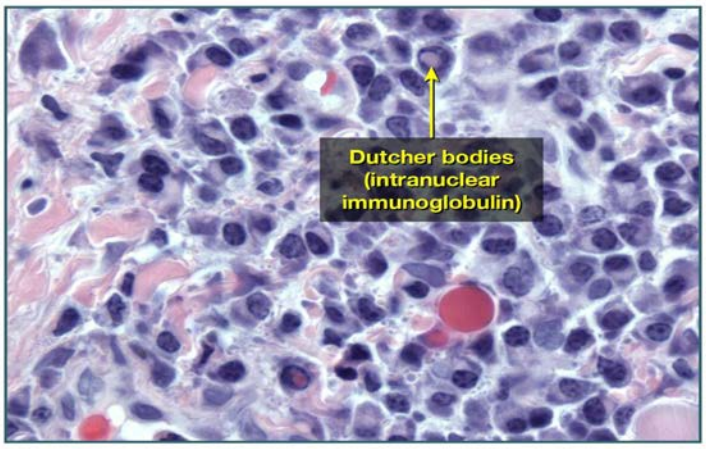
Multiple myeloma - Dutcher bodies



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• Russell bodies - Hyaline intracytoplasmic inclusions containing Ig

• Mott cells/ morula cells - Plasma cells containing multiple grape-like cytoplasmic inclusions comprised of Ig

• Flame cells - Vermillion-staining, glycogen-rich IgA in cytoplasmic projections

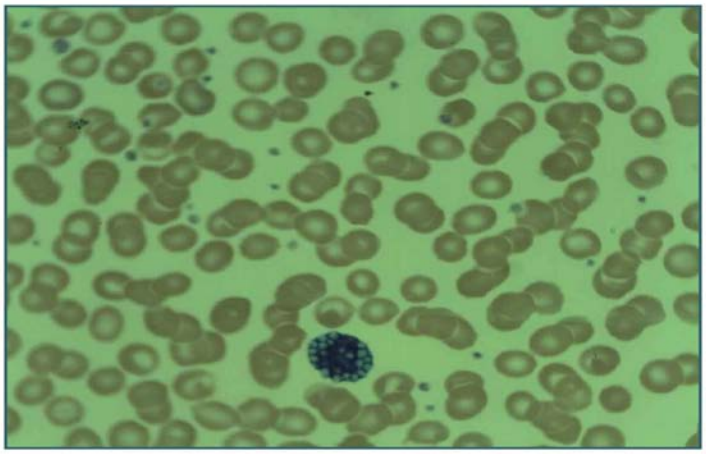
• Thesaurocytes - Dilated endoplasmic reticulum cisternae

Solution to Question 11:

The given image shows a Mott cell which is a plasma cell with globular cytoplasmic inclusions containing immunoglobulins called Russell bodies.

Inclusions containing Ig are frequently seen in the cytoplasm (Russell bodies) or the nucleus (Dutcher bodies) of some of the plasma cells in myeloma.

Multiple myeloma - Mott cell



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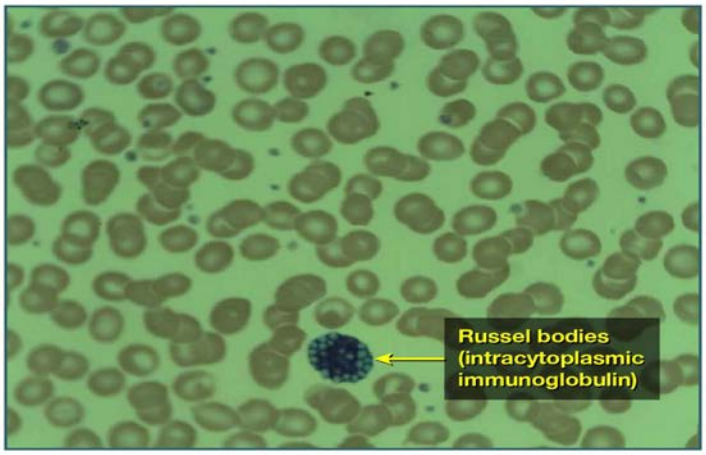
Multiple myeloma - Mott cell



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Solution to Question 12:

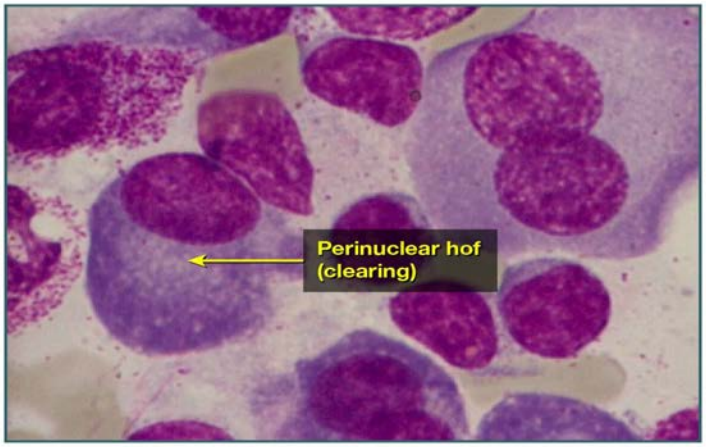
The marked finding is perinuclear hof (perinuclear clearing) in plasma cells. It occurs due to a prominent Golgi apparatus.

Plasma cell characteristics include:

- Eccentric nuclei
- Moderate to abundant basophilic cytoplasm
- Pale perinuclear hof, representing the Golgi zone

The image given below shows plasma cells with perinuclear hof.

Plasma cells



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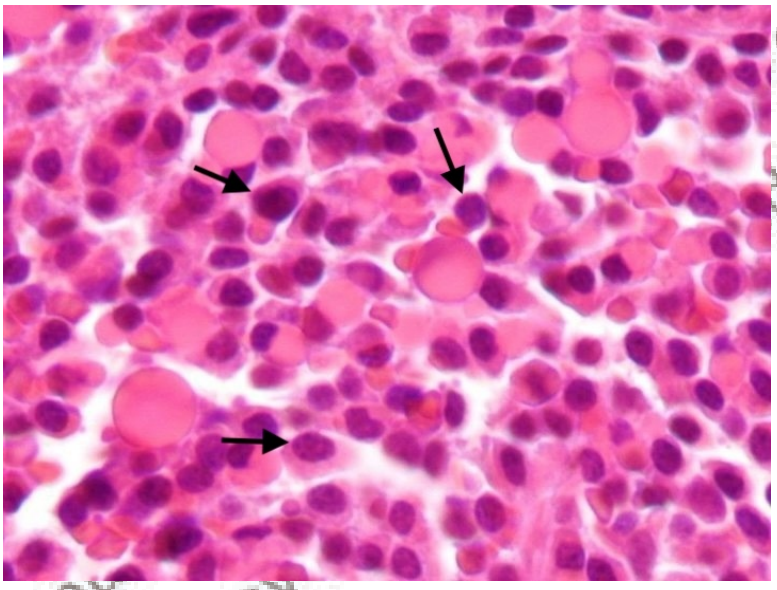
Solution to Question 13:

The given clinical scenario points to the diagnosis of multiple myeloma.

The image shows Russell bodies which are eosinophilic, large, homogeneous immunoglobulin-containing inclusions usually found in a plasma cell undergoing excessive synthesis of immunoglobulins. Russell bodies are distended endoplasmic reticulum.

Globular inclusions are Russell bodies (if cytoplasmic) and Dutcher bodies (if nuclear).

The below image shows Russell bodies:



Solution to Question 14:

Wire-loop lesions are seen in systemic lupus erythematosus and not in multiple myeloma.

Renal insufficiency occurs in half the patients with multiple myeloma and several factors are responsible for it. They develop acute kidney injury with ologuria and chronic kidney disease. Tubular casts, amyloidosis, and renal tubular necrosis are all described in the myeloma kidneys.

Features of myeloma kidney:

• Bence–Jones proteinuria and cast nephropathy - The main cause of renal dysfunction is related to Bence–Jones (light-chain) proteinuria. Ig light chains are directly toxic to epithelial cells. Bence-Jones proteins form large, histologically distinct tubular casts that obstruct the tubular lumens and induce a characteristic inflammatory reaction (light-chain cast nephropathy).

• Amyloidosis of AL type, formed from free light chains (usually of λ type)

• Light-chain deposition disease - light chains (usually of κ type) deposit in the glomerular basement membrane and mesangium causing a glomerulopathy and in tubular basement membranes, which may cause tubulointerstitial nephritis.

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• Hypercalcemia - Nephrocalcinosis

Solution to Question 15:

Bence Jones proteins are immunoglobulin light chains (paraproteins) produced by neoplastic plasma cells.

They can be kappa (most of the time) or lambda. The light chains can be immunoglobulin fragments or single homogeneous immunoglobulins. In patients with plasma cell tumors, the level of free light chains is usually elevated. One of the light chains is elevated with a reduction in the other. Free light chains are excreted in the urine because they are small in size, where they are referred to as Bence Jones proteins. Tests for Bence Jones protein are:

• Heat test

• Urine protein electrophoresis

• Immunofixation

Solution to Question 16:

Symptoms related to hyperviscosity in multiple myeloma occurs due to excessive production of M proteins, usually of IgG3 or IgA subtype.

Waldenstrom macroglobulinemia (IgM myeloma) is the most common cause for hyperviscosity syndrome due to excess IgM paraprotein. Less commonly, it also occurs in multiple myeloma (with myeloma proteins IgA and IgG3 types) and connective tissue diseases.

Normal relative serum viscosity ranges from 1.4 to 1.8 units. Symptoms are not seen at <4, and hyperviscosity syndrome typically requires a viscosity of >5 units.

Clinical features include:

• Visual impairment

• Neurologic problems

• Bleeding

• Cryoglobulinemia

Solution to Question 17:

IgD type of multiple myeloma has the highest risk of renal insufficiency.

IgG is most commonly involved in multiple myeloma. The higher the level of IgG, the more is the risk of renal failure in patients with multiple myeloma overall. But the rarer IgD predominant multiple myeloma has the highest risk of renal insufficiency when compared to other types.

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IgD type multiple myeloma is a rare type of multiple myeloma. In this condition, there is monoclonal IgD in serum. On serum electrophoresis, there is no or absent M spike. There is a higher incidence of extramedullary involvement, amyloidosis, proteinuria, and renal insufficiency in comparison to IgG or IgA type multiple myeloma. It has a poor prognosis.

Solution to Question 18:

Plasma-cell tumors are least likely to show positivity for CD 21.

They are positive for CD138, an adhesion molecule also known as syndecan-1, CD 38, and often express CD56.

Solution to Question 19:

Biopsy-proven plasmacytoma is not considered as a myeloma-defining event (MDE).

Revised International Myeloma Working Group criteria for the diagnosis of multiple myeloma:

Clonal bone marrow plasma cells ≥10% (or) Biopsy-proven bony or extramedullary plasmacytoma.

AND

Myeloma defining events (one or more): Evidence of end-organ damage attributable to the underlying plasma cell proliferative disorder, specifically-

• HyperCalcemia: Serum calcium level >1 mg/dL higher than the upper limit of normal or >11 mg/dL

• Renal insufficiency: Creatinine clearance <40 mL/min or serum creatinine >2 mg/dL

• Anemia: Hemoglobin level of >20 g/L (2gm/dl) below the lowest limit of normal, or Hb <10 g/dL

• Bone lesions: One or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)/CT.

• Any one or more biomarkers of malignancy: Clonal bone marrow plasma cells ≥60%; Serum involved/uninvolved free light-chain ratio ≥ 100; >1 focal lesion on magnetic resonance imaging (MRI) that is ≥ 5 mm in size.

Solution to Question 20:

The given clinical scenario and X-ray showing lytic lesions on the bone are suggestive of multiple myeloma. The best immunohistochemical (IHC) marker for this condition is cyclin D1.

Multiple myeloma is associated with diverse translocations involving the IgH locus; overexpression of D cyclins—cyclin D1 and D3. Plasma cell tumors are positive for CD138 and often express CD56.

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Solution to Question 21:

The given clinical scenario is suggestive of amyloidosis. The amyloid of the AL type is produced from free Ig light chains secreted by a monoclonal population of plasma cells and its deposition is associated with multiple myeloma.

Solution to Question 22:

Infections are the most common cause of death in patients with myeloma.

Complications of multiple myeloma include:

- Infections
- Renal failure
- Cardiac failure
- Hypercalcemia
- Anemia

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Solution to Question 23:

The given clinical scenario is suggestive of multiple myeloma. The most powerful prognostic indicator of this condition at the time of diagnosis is serum °2 microglobulin.

Beta-2 microglobulin is a low-molecular-weight protein found on the surface of all nucleated cells. It is the light chain of the HLA histocompatibility complex.

Solution to Question 24:

t(11;14) is associated with a good prognosis in patients with myeloma.

t(4;14), high serum beta-2 microglobulin, and low serum albumin are all poor prognostic factors in myeloma.

Solution to Question 25:

The given clinical scenario is highly suggestive of multiple myeloma. Translocations involving cyclin D1 are associated with a good outcome in this condition.

t(14;16), deletions of 17p, and t(14;20) are associated with a more aggressive course.

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Solution to Question 26:

Bence–Jones proteinuria is not diagnostic of monoclonal gammopathy of undetermined significance (MGUS) because it is seen in multiple myeloma also.

MGUS is the most common monoclonal gammopathy.

Diagnostic criteria of MGUS according to International Myeloma Working Group guidelines (2014):

• Serum monoclonal protein <3g/dL

• Clonal bone marrow plasma cells < 10%

• Absence of end-organ damage such as hypercalcemia, renal failure, anemia and bone lesions (CRAB)

• No amyloidosis

The three distinct clinical types of MGUS are:

• Non-IgM MGUS:

• Most common subtype of MGUS

• Approximately 1% of patients with MGUS develop a symptomatic plasma cell neoplasm, usually multiple myeloma, per year

• IgM MGUS:

• IgM MGUS accounts for approximately 15% of MGUS cases

• It can progress to Waldenström macroglobulinemia, but progression to multiple myeloma is rare

• Bence–Jones proteinuria has been reported in approximately 20% of these cases

• Light chain MGUS (LC-MGUS):

• LC-MGUS is a unique subtype of MGUS in which there is no immunoglobulin heavy-chain component

• Urinary M protein <500 mg/24 hour

• LC-MGUS may progress to light-chain smoldering multiple myeloma (idiopathic Bence–Jones proteinuria) and to light-chain multiple myeloma

Solution to Question 27:

High levels of IgM are seen in lymphoplasmacytic lymphoma.

In lymphoplasmacytic lymphoma, high levels of IgM lead to symptoms related to hyperviscosity of the blood. This is known as Waldenstrom's macroglobulinemia. 'M' or monoclonal spike is seen in this condition. Here, it is caused by IgM; in multiple myeloma, it is caused by IgG. It is characterized by the absence of lytic lesions and normal serum calcium levels.

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IgM greatly increases the viscosity of the blood, giving rise to a hyperviscosity syndrome characterized by the following:

• Visual impairment

• Neurologic problems

• Bleeding

• Cryoglobulinemia

The normal relative viscosity of the serum is 1.8.

Hyperviscosity is seen in:

• Multiple myeloma

• Waldenstrom's macroglobulinemia

• Cryoglobulinemia

• Myeloproliferative disorders

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Solution to Question 28:

Virtually all cases of lymphoplasmacytic lymphoma are associated with acquired mutations in MYD88.

The most common cytogenetic abnormality associated with lymphoplasmacytic lymphoma is deletion of 6q.

Solution to Question 29:

Serum calcium levels remain normal in Waldenström macroglobulinemia.

Waldenström macroglobulinemia is a syndrome characterised by the following:

• Hyperviscosity syndrome due to high levels of IgM

• Most commonly occurs in association with lymphoplasmacytic lymphoma

• 'M' or monoclonal spike

• Absence of lytic lesions

• Normal serum calcium levels

• Diffuse marrow infiltration by plasma cells, plasmacytoid lymphocytes, and lymphocytes (all from the same clone)

• Cells do not form tumor masses or produce lytic lesions

• Lymphocytes commonly contain Dutcher bodies (intranuclear inclusions)

• Bence–Jones proteins in 20–30%

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Solution to Question 30:

Extramedullary plasmacytomas are seen in the upper respiratory tract. Most of them are seen in the nasopharynx, oropharynx, sinuses, and larynx.

Plasmacytoma is a tumor of plasma cells of bony or soft tissue. It can occur anywhere in the body without evidence of systemic disease.

Solution to Question 31:

α- heavy chain disease (HCD) is known as Seligmann's disease.

There are three heavy chain diseases:

• α- heavy chain disease - Seligmann's disease

• γ- heavy chain disease - Franklin's disease

• μ- heavy chain disease - Associated with light-chain secretion (Bence–Jones proteinuria) in a few cases

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Solution to Question 32:

The given clinical scenario points to the diagnosis of plasma cell leukemia. In this case, the peripheral blood smear shows 22% of plasma cells and presents with organomegaly.

Plasma cell leukemia is defined by the observation in blood of more than 20% clonal plasma cells by differential count of the leucocytes or by counting more than 2 × 109 per liter circulating clonal plasma cells. Plasma cell leukemia (PCL) is a rare and aggressive form of leukemia and plasma cell dyscrasia. PCL can be divided into primary PCL (PCL) and secondary PCL (sPCL) following previously diagnosed multiple myeloma (MM); the latter typically occurring at a late and advanced stage of MM.

Patients with plasma cell leukemia are more likely to have extramedullary involvement of liver and spleen, causing organomegaly than in multiple myeloma. (Option A)

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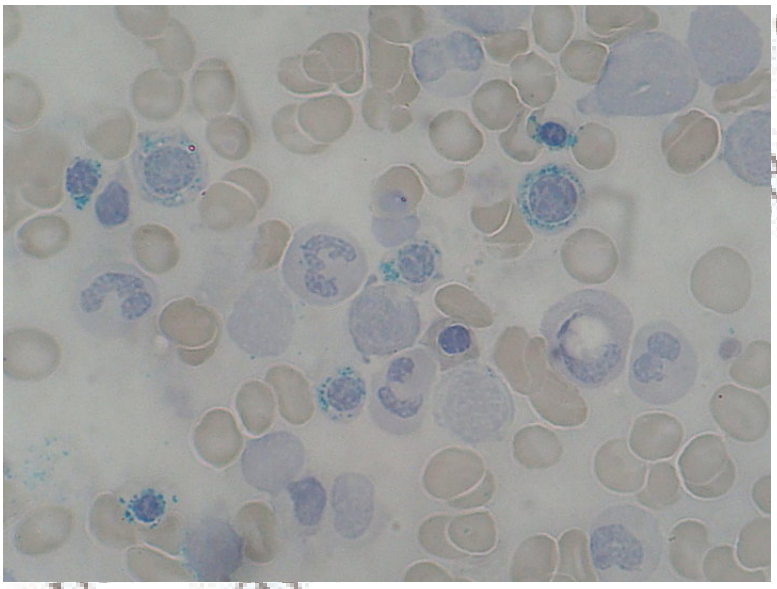
Myelodysplastic Syndrome, Myeloproliferative Syndromes and Histiocytosis

Question 1:

A 73-year-old woman presents with chronic fatigue and easy bruising. She has had surgery for ovarian cancer 7 years ago along with chemoradiation. Her lab reports reveal pancytopenia and bone marrow biopsy shows the following finding. What is the most probable diagnosis?



a) Aplastic anemia

b) Myelodysplastic syndrome

c) Acute lymphoblastic leukemia

d) Myelophthisic anemia

Question 2:

What is the most common cytogenetic change in children with myelodysplastic syndrome?

a) 5q deletion

b) Monosomy 5

c) 7q deletion

d) Monosomy 7

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Question 3:

Which of these histopathological findings would you not expect to see in patients with myelodysplastic syndrome?

a) Ringed sideroblast

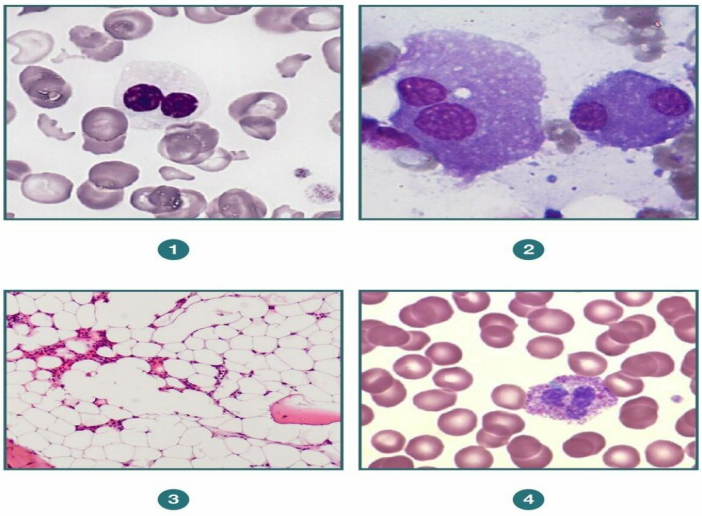
b) Pawn-ball megakaryocyte

c) Dohle bodies

d) Pelger-Huet cells

Question 4:

Which of the following bone marrow and peripheral blood findings is not seen in patients with myelodysplastic syndrome?



a) Image 1

b) Image 2

c) Image 3

d) Image 4

Question 5:

A 60-year-old man presents with complaints of fatigue, weight loss, and heaviness in the left hypochondrium for 6 months. His hemogram and peripheral smear are given below. What is the most likely diagnosis?

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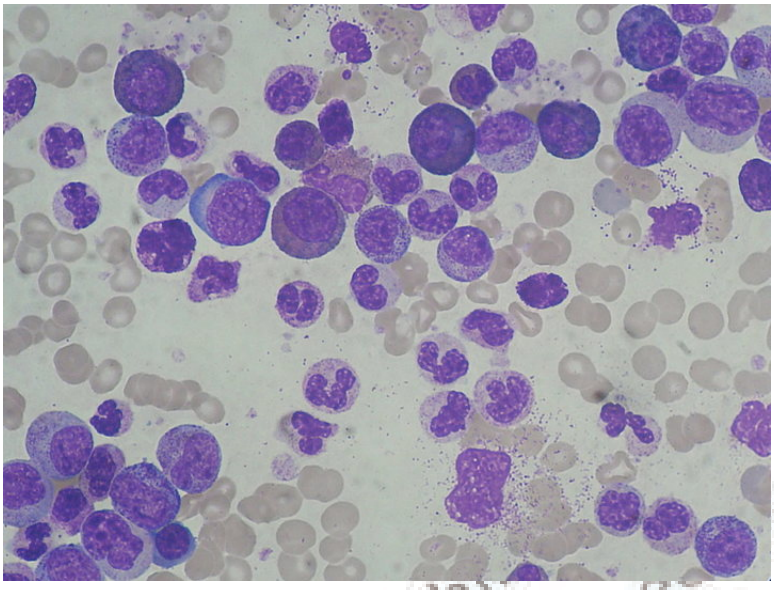

a) Chronic lymphocytic leukemia

b) Chronic myeloid leukemia

c) Acute lymphoblastic leukemia

d) Acute myeloid leukemia

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Question 6:

What mutation results in Philadelphia chromosome?

a) t(9;22)(q11;q34)

b) t(22;9)(q11;q34)

c) t(22;9)(q34;q11)

d) t(9;22)(q34;q11)

Question 7:

Bone marrow biopsy in a patient shows pseudo-Gaucher cells. What is the most probable diagnosis?

a) Primary myelofibrosis

b) Chronic myeloid leukemia

c) Essential thrombocythemia

d) Chronic Lymphocytic leukemia

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Question 8:

A 60-year-old woman with fever and splenomegaly was diagnosed to have chronic myeloid leukemia. She was started on imatinib therapy. After a few months of therapy, she had persistent progressive splenomegaly and fatigue. Which of the following will not be seen in this phase?

a) >20% blasts in blood or marrow

b) > 20% basophils in blood

c) Platelet count of <100 × 10^9/L

d) WBC count >10 × 10^9/L

Question 9:

What is the percentage of blast cells in the blast phase of CML?

a) <10%

b) 10-15%

c) >20%

d) 15-20%

Question 10:

Which of the following is not seen in a patient with Myelodysplastic/Myeloproliferative syndrome (MDS/MPN) with neutrophilia?

a) Philadelphia chromosome negative

b) Basophilia >10%

c) Blasts <20%

d) Neutrophil precursors >10%

Question 11:

Which of the following patients will have a decreased leukocyte alkaline phosphatase score?

a) A 65-year-old-man with garden party appearance on peripheral smear

b) A 50-year-old man with Reed Sternberg cells on LN biopsy

c) A 35-year-old woman with Hb level of 23 g/dL

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d) A 43-year-old woman with smudge cells on peripheral smear

Question 12:

Which of the following does not cause relative polycythemia?

a) Dehydration

b) Dengue hemorrhagic fever

c) Gaisbock syndrome

d) High altitude

Question 13:

A young boy from high altitude came with fever and weakness and had the following reports - Hemoglobin 17 g%, TLC is 21,000 with neutrophils 25, lymphocytes 30, eosinophils 5, myelocytes and metamyelocytes 40 in peripheral smear. Next step in the investigation should be:

a) Philadelphia chromosome

b) JAK mutation

c) Erythropoietin levels

d) Bone Marrow biopsy with reticulin stain

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Question 14:

A 24-year-old woman who presented with aquagenic pruritis had a Hb level of 20 g/dL. Her lab investigations are given below. Which of the following is not seen in this condition?

a) Acute meyloid leukemia

b) Budd-Chiari syndrome

c) Myelofibrosis

d) Hepatic failure

Question 15:

A 63-year-old woman complains about throbbing pain over both palms. Her examination findings and lab reports are given below. What is the most likely diagnosis?

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a) Polycythemia vera

b) Essential thrombocythemia

c) Myelofibrosis

d) Leukemoid reaction

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Question 16:

Patients with which of the following conditions do not have a leukoerythroblastic picture on peripheral smear?

a) Myelofibrosis

b) Myelophthisic anemia

c) Thalassemia

d) Gaucher disease

Question 17:

Which of the following is not included under MDS/MPN overlap syndromes?

a) MDS/MPN with neutrophilia

b) Chronic myelomonocytic leukemia

c) MDS/MPN with SF31B mutation and thrombocytosis

d) MDS with excess blasts

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Question 18:

Which of the following is not compatible with a diagnosis of chronic myelomonocytic leukemia?

a) Peripheral blood monocytosis more than 1×10^9/L

b) Absence of Philadelphia chromosome

c) More than 20% blasts in blood or bone marrow

d) Absent or minimal dysplasia in myeloid lineages

Question 19:

A 2-year-old boy with Noonan syndrome presents with hepatosplenomegaly and lymphadenopathy. You are suspecting juvenile myelomonocytic leukemia. Which of the following is not seen in this condition?

a) GM-CSF hypersensitivity

b) Absence of Philadelphia chromosome

c) Poor prognosis

d) Increased Hb A2 level

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Question 20:

JAK2 mutation is most commonly associated with _____

a) Polycythemia vera

b) Essential thrombocytosis

c) CML

d) PMF

Question 21:

Which of the following patients is least likely to have leukemoid reaction?

a) A patient with severe meningitis

b) A child with Down syndrome

c) A patient with hemorrhagic shock

d) A patient with acute myocardial infarction

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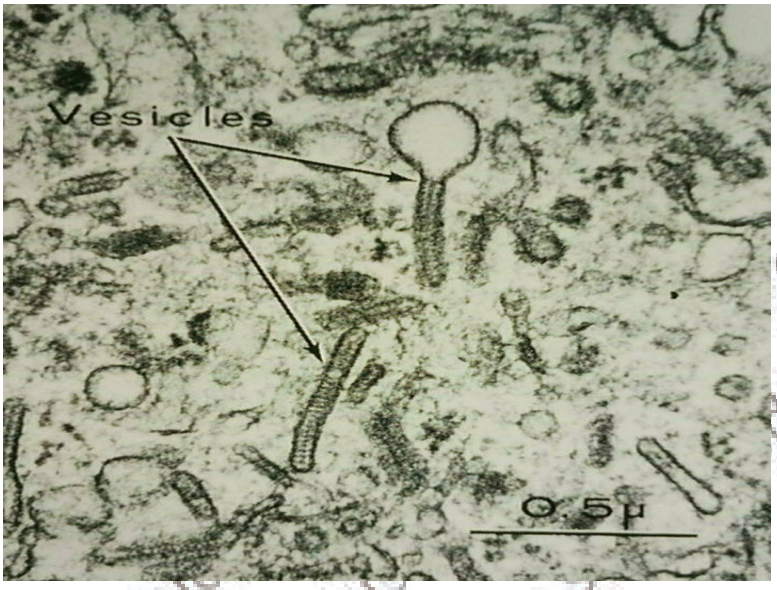
Question 22:

Electron microscopic picture of which of the following conditions is shown below?



a) Bernard–Soulier syndrome

b) Mycosis fungoides

c) Glanzmann thrombasthenia

d) Langerhans cell histiocytosis

Question 23:

Which of the following is not a histiocytic neoplasm?

a) Langerhans cell histiocytosis

b) Rosai-Dorfman disease

c) Erdheim-Chester disease

d) Disseminated juvenile xanthogranuloma

Question 24:

You are suspecting Langerhans cell histiocytosis in a child with an enlarging scalp lesion. Which of the following markers will you test to confirm your diagnosis?

a) CD11a

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b) HLA-DQ

c) CD107

d) S-100

Question 25:

A 5-year-old girl is brought to you by her father, who states that the girl is drinking a lot of water lately. Physical examination reveals exophthalmos. Further workup shows the presence of multiple lytic bone lesions involving her calvarium and the base of her skull. What is the most likely diagnosis?

a) Letterer-Siwe disease

b) Hand- Schuller- Christian disease

c) Eosionophilic granuloma

d) Unifocal Langerhans cell histiocytosis

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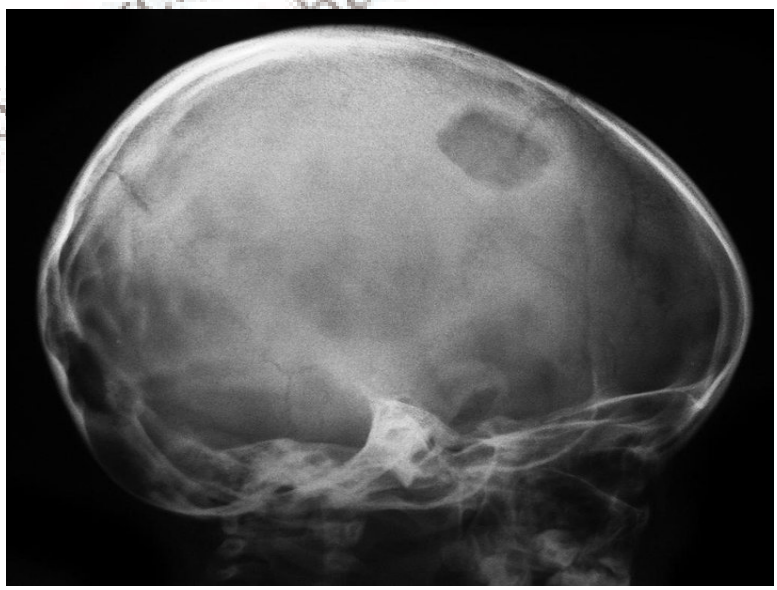
Question 26:

The X-ray of a 65-year-old man is given below. Clinical examination, and hematological and urinary tests were normal. Which of the following is the probable diagnosis?



a) Multiple myeloma

b) Langerhans cell histiocytosis

c) Metastasis

d) Hyperparathyroidism

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Question 27:

Which of the following is not true regarding the procedure done using the instrument given in the image below?

a) Contraindicated if platelet count <40,000

b) Breath holding is required

c) Procedure can be done in both lateral & prone position

d) Diagnosing an infiltrative or granulomatous disease

Question 28:

Blood examination shows pancytopenia, which can be correct?

a) B, D

b) A, B, C

c) B, C, D

d) A, B, D

Question 29:

Which of the following conditions will have the least chances of a dry tap on bone marrow aspiration?

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a) Hairy cell leukemia

b) Follicular lymphoma

c) AML M7

d) Myelodysplastic syndrome

Answer Key

Question No.	Correct Option
1	b
2	d
3	d
4	c
5	b
6	d
7	b
8	a
9	c
10	b
11	a
12	d
13	c
14	d
15	b
16	c
17	d
18	c
19	d
20	a
21	d
22	d
23	b
24	d
25	b
26	b
27	a

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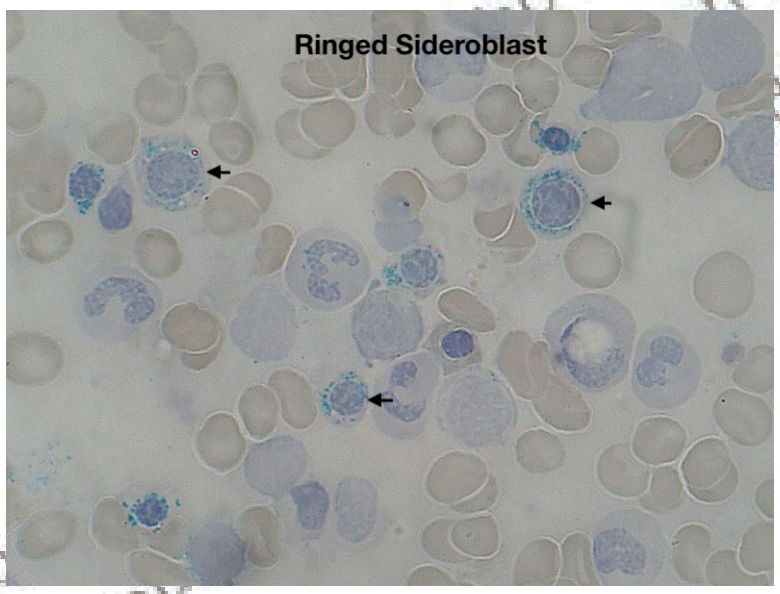
28	b
29	b

Detailed Explanations

Solution to Question 1:

The given clinical scenario is suggestive of therapy-related myelodysplastic syndrome (t-MDS).

The bone marrow biopsy stained with Perl's Prussian blue shows ringed sideroblasts. They are erythroblasts with iron-laden mitochondria visible as perinuclear granules as shown in the image below.



Myelodysplastic syndrome is a group of clonal stem cell disorders characterized by maturation defects, associated with ineffective hematopoiesis.

It is of two types:

• Primary MDS - develops slowly, usually after 50 years of age.

• Secondary or therapy-related MDS (t-MDS) - develops 2 to 8 years after toxic drug or radiation exposure with poor prognosis

Patients usually present with weakness, infections and hemorrhages due to pancytopenia. Both types of MDS have a high risk of transformation to acute myeloid leukemia (AML). However, most frequent and rapid transformation occurs in therapy-related MDS (t-MDS).

Solution to Question 2:

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Monosomy 7 is the most common cytogenetic change seen in myelodysplastic syndrome (MDS) in children.

5q deletion is the most common cytogenetic change seen in MDS in adults.

The del(5q) abnormality is the dominant clone in most cases of MDS. This involves the stem-cell compartment and hence occurs as an early or initiating event in disease pathogenesis.

Solution to Question 3:

Pseudo–Pelger–Huet cells are seen in myelodysplastic syndrome (MDS) and not Pelger–Huet cells.

Pelger–Huet cells are seen in Pelger–Huet syndrome, which is due to mutations in the lamin B-receptor gene. It is a neutrophil differentiation disorder with leukocyte appearance as:

• Dumbbell-shaped bilobed nuclei

• Reduced number of nuclear segments

• Coarse clumping of the nuclear chromatin

In MDS, pseudo-Pelger Huet cells are seen due to abnormal nuclear budding i.e. neutrophils with only 2 nuclear lobes.

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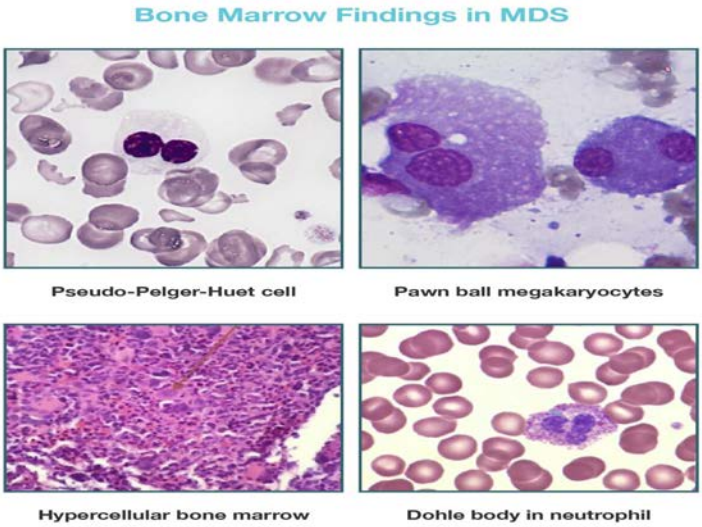
Solution to Question 4:

Image 3 showing hypocellular bone marrow is not seen in myelodysplastic syndrome (MDS.) In this condition, bone marrow is hypercellular. However, pancytopenia results from ineffective hematopoiesis.

The image given below shows the histopathological findings seen in MDS.



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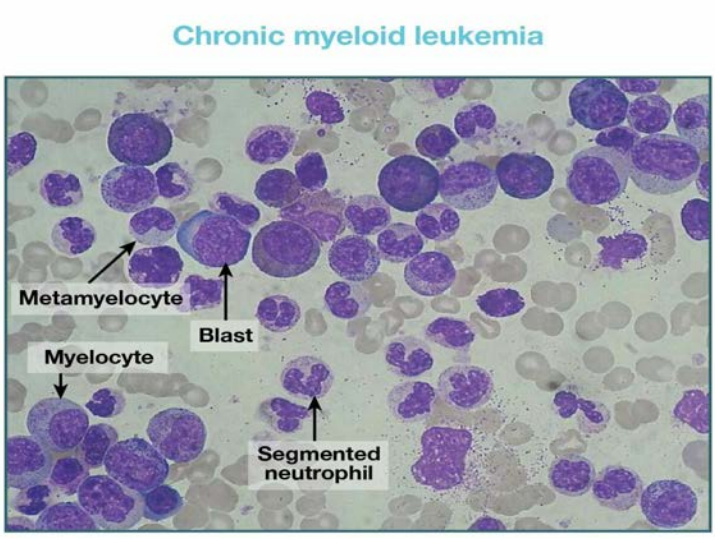
Solution to Question 5:

The given clinical scenario is suggestive of chronic myelogenous leukemia (CML).

In this condition, the peripheral smear contains neutrophils and their precursors of various sizes and configurations like band cells, myelocytes, metamyelocytes, and blasts. Hence, the histological picture is described to have garden party or college girl appearance.

The image given below shows the peripheral smear in CML showing garden party or college girl appearance.



CML is a myeloproliferative disorder with peak incidence in the 5th to 6th decades of life. It occurs due to the chimeric BCR-ABL gene.

Clinical features of CML:

- Hypermetabolism
- Fatigability
- Weakness
- Weight loss and anorexia
- Extensive extramedullary hematopoiesis causing -
- Splenomegaly
- Mild hepatomegaly
- Lymphadenopathy

Hematological findings include:

- Mild-to-moderate anemia
- Leukocytosis

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• Platelets - usually increased

• DLC shows predominantly neutrophils, band forms, metamyelocytes, myelocytes, eosinophils, and basophils and blasts (>10%)

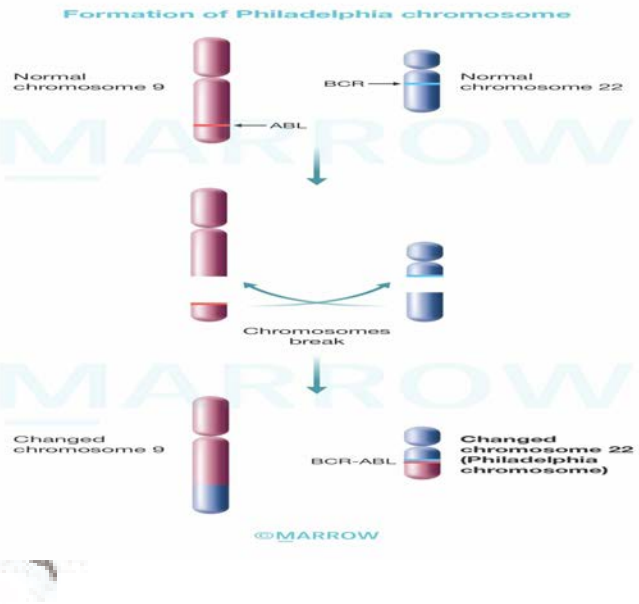
Note: Convent girl appearance is seen in CLL.

Solution to Question 6:

Philadelphia chromosome results from t(9;22)(q34;q11). It is most commonly seen in chronic myeloid leukemia (CML).

CML is due to the formation of a chimeric BCR-ABL gene or Philadelphia chromosome. This gene is derived from a reciprocal translocation (9;22)(q34;q11).

The image given below shows the formation of the Philadelphia chromosome.



This translocation can be identified on fluorescence in situ hybridisation (FISH).

The image given below shows (9;22) translocation as seen on FISH.

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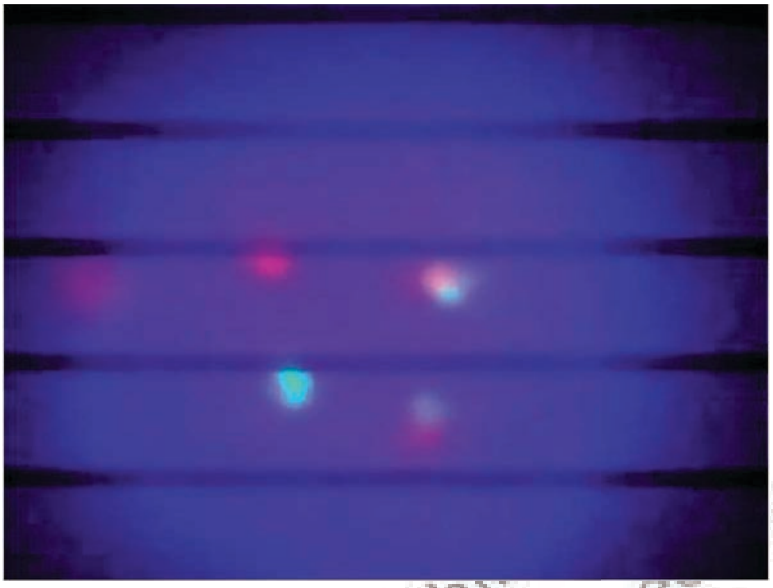

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Solution to Question 7:

Psuedo-Gaucher cells are characteristic of chronic myeloid leukemia (CML). These cells are scattered macrophages with abundant wrinkled, green-blue cytoplasm. Their presence indicates a good prognosis.

Bone marrow findings in CML:

- Markedly hypercellular marrow - increased maturing granulocytic precursors
- Elevated eosinophils and basophils
- Increased megakaryocytes - include small, dysplastic forms
- Erythroid progenitors - normal or mildly decreased
- Increased reticulin deposition
- Overt marrow fibrosis - rare early in the course
- Pseudo-Gaucher cells
- Sea blue histiocytes

The image given below shows pseudo-Gaucher cells in chronic myeloid leukemia (CML).

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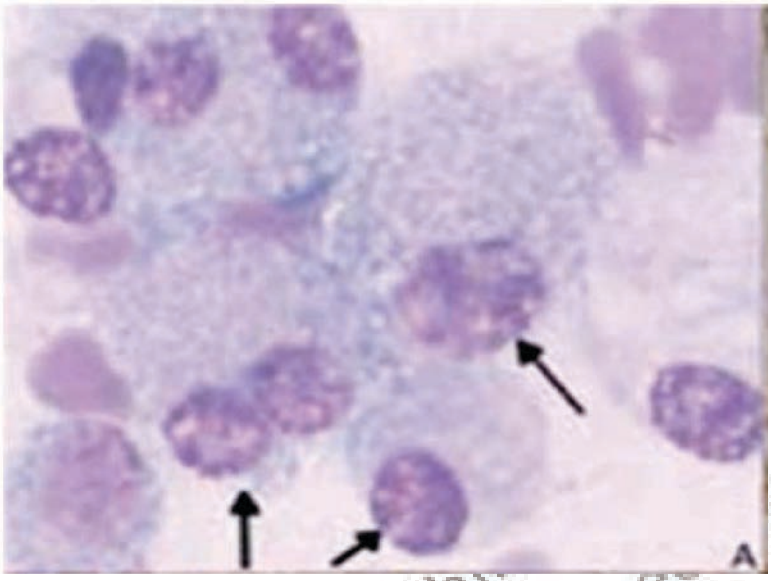

Solution to Question 8:

In a patient with chronic myeloid leukemia (CML), progressive splenomegaly, not responsive to therapy is suggestive of an accelerated phase. In this phase, blasts are <20% in blood or marrow.

Diagnosis of an accelerated phase of CML requires one of the following criteria:

• Persistent or increasing WBC (>10 × 109/L), unresponsive to therapy

• Persistent or increasing splenomegaly, unresponsive to therapy

• Persistent thrombocytosis (>1000 × 109/L), unresponsive to therapy

• Persistent thrombocytopenia (<100 × 109/L) unrelated to therapy

• 20% or more basophils in the peripheral blood

• 10%-19% blasts in the peripheral blood or bone marrow

• Additional clonal chromosomal abnormalities in Ph+ cells at diagnosis that include “major route” abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, or abnormalities of 3q26.2

• Any new clonal chromosomal abnormality in Ph+ cells that occurs during therapy

Solution to Question 9:

In the blast phase of chronic myeloid leukemia, there are >20% blasts in the bone marrow.

The 3 phases of CML are:

• Chronic phase is the most common presentation. It is characterized by:

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• Leukocytosis - bimodal distribution with higher proportions of mature segmented neutrophils and myelocytes

• Blast cells <10%

• Increased basophils and eosinophils

• Monocytosis <3%

• Accelerated phase occurs in 50% of the patients who present with increasing anemia, thrombocytopenia and splenomegaly. It is characterized by:

• Blast count 10-19%

• Basophilia >20%

• Blast phase in CML occurs in an average of 3 years after the diagnosis. It is characterized by:

• Large foci or clusters of blasts on the bone marrow biopsy >20%.

• Presence of extramedullary blastic infiltrates (e.g., myeloid sarcoma or chloroma)

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Solution to Question 10:

Myelodysplastic/Myeloproliferative syndrome (MDS/MPN) with neutrophilia (previously named as atypical chronic myeloid leukemia) shows minimal absolute basophilia, i.e., <2% of total WBCs.

Myelodysplastic/Myeloproliferative syndrome (MDS/MPN) with neutrophilia is a leukemic disorder having features of both myelodysplastic and myeloproliferative features at the time of diagnosis. It is classified under the WHO 5th edition (2022) MDS/MPN category.

Characteristics of myelodysplastic/myeloproliferative syndrome (MDS/MPN) with neutrophilia:

• Peripheral blood leukocytosis with an increased number of mature and immature neutrophils

• Prominent dysgranulopoiesis

• Philadelphia chromosome-negative

• Neutrophil precursors (promyelocytes, myelocytes, metamyelocytes) >10% of WBCs

• Minimal absolute basophilia <2% of WBCs

• Absolute monocytosis <10% of WBCs

• Hypercellular bone marrow

• <20% blasts in blood and bone marrow

• Thrombocytopenia

Differences between CML and myelodysplastic/myeloproliferative syndrome (MDS/MPN) with neutrophilia:

Feature	CML	Myelodysplastic/Myeloproliferative syndrome (MDS/MPN) with neutrophilia
BCR-ABL gene	Present	Absent

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Feature	CML	Myelodysplastic/Myeloproliferative syndrome (MDS/MPN) with neutrophilia
Basophilia	Present	<2%
Myeloblasts in peripheral blood Myeloblasts in bone marrow	<2% <5%	<20% <20%
Granulocytic dysplasia	Minimal/ absent	Prominent

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Solution to Question 11:

Leukocyte alkaline phosphatase (LAP) score is decreased in chronic myeloid leukemia (CML) i.e. garden party appearance on peripheral smear.

Solution to Question 12:

High altitude produces absolute polycythemia and not relative polycythemia.

Polycythemia denotes an abnormally high red cell count, usually with a corresponding increase in the hemoglobin level (> 16 ±2 g/dL). It is 2 types:

• Relative - hemoconcentration due to decreased plasma volume

• Absolute - increase in the total red cell mass

Causes of relative polycythemia include:

• Dehydration - deprivation of water, prolonged vomiting or diarrhea, excessive use of diuretics

• Gaisböck syndrome - stress polycythemia where affected individuals are usually hypertensive, obese, and anxious

Causes of absolute polycythemia include:

• Primary - intrinsic abnormality of hematopoietic precursors

• Polycythemia vera

• Inherited erythropoietin receptor mutations

• Secondary - red cell progenitors responding to increased levels of erythropoietin

• Compensatory due to cyanotic heart and lung disease, high altitude

• Paraneoplastic erythropoietin secreting tumours

Note: In dengue hemorrhagic fever, increased vascular permeability causes plasma leakage and volume loss. Hence, relative polycythemia is seen.

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Solution to Question 13:

The given clinical scenario is suggestive of polycythemia (Hb>16 g/dL). Hence, erythropoietin levels (EPO) are estimated next, to differentiate between primary or secondary polycythemia. Based on EPO levels:

• Primary polycythemia - normal/ decreased

• Secondary polycythemia - increased

Options A and B: JAK 2 mutation and Philadelphia chromosome analysis is only done as a last resort.

Option D: Bone marrow estimation with reticulin is done for myelofibrosis which can be seen in the spent/ late stage of the disease. However, peripheral smear findings are not suggestive of primary myelofibrosis. Leukoerythroblastic reaction with dacrocytes is seen in myelofibrosis.

Solution to Question 14:

The given clinical scenario is suggestive of polycythemia vera. Hepatic failure is not seen in this condition.

Polycythemia vera is strongly associated with activating point mutations in the tyrosine kinase JAK2. In this condition, clonal erythrocytosis occurs autonomously i.e. independent of erythropoietin.

Clinical features of polycythemia vera:

• Headache

• Hypertension

• Dizziness

• Intense pruritis, aquagenic pruritis

• Peptic ulcer

• Venous thrombosis - Budd-Chiari syndrome (hepatic vein thrombosis), bowel infarction, stroke, myocardial infarction

• Minor hemorrhages - epistaxis, gum bleeding

Laboratory findings in polycythemia vera:

• Panmyelosis - increased marrow production of red cells, granulocytes, and platelets

• Low erythropoietin

• Elevated hematocrit

• Hyperuricemia

Complications of polycythemia vera:

• Myelofibrosis and extensive extramedullary hematopoiesis - spent /late phase

• Acute myeloid leukemia

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Solution to Question 15:

The given clinical scenario is suggestive of essential thrombocythemia (ET). The image showing erythematous hands is suggestive of erythromelalgia.

Essential thrombocythemia (essential thrombocytosis) is a myeloproliferative neoplasm. It is associated with mutations that increase JAK-STAT signaling.

WHO criteria for diagnosis of essential thrombocythemia:

• Major criteria -

• Platelet count ≥450 × 109/L

• Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei

• Not meeting WHO criteria for BCR-ABL1 chronic myeloid leukemia, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms

• Presence of JAK2, CALR, or MPL mutation

• Minor criteria - the presence of a clonal marker or absence of evidence for reactive thrombocytosis

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion

Option A: Polycythemia vera can also present with erythromelalgia. However, it also presents with increased Hb levels.

Option C: Fibrosis (not reticulin fibrils) is seen in bone marrow biopsy of primary myelofibrosis.

Option D: WBC counts are increased in leukemoid reactions.

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Solution to Question 16:

Leukoerythroblastic picture is not seen in patients with thalassemia as it is a hemoglobinopathy and does not involve myeloid precursors.

Abnormal presence of immature precursors of blood in the peripheral blood smear is called leukoerythroblastosis. Findings include:

• Nucleated red cells

• Dacryocytes (or teardrop RBC) - formed due to damage to red cell membrane caused by fibrous tissue in the marrow

• Immature cells of granulocytic series

It occurs due to conditions causing marrow replacement like:

• Primary myelofibrosis - fibrosis of bone marrow

• Myelophthisic anemia - space occupying lesions of bone marrow

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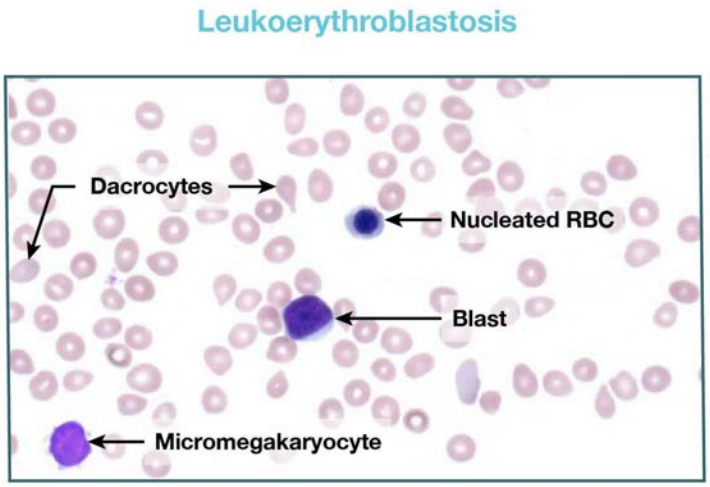
• Gauchers disease

• Spent phase of polycythemia vera

The image given below shows a leukoerythroblastic blood picture with nucleated RBCs, tear-drop cells, and immature myeloid cells.



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Solution to Question 17:

Myelodysplastic syndrome/ myeloproliferative neoplasm (MDS/MPN) overlap syndromes are a group of chronic clonal myeloid malignancies in which there are features of both MDS and MPN at the time of presentation. According to the 5th edition WHO classification (2022), it includes:

• Chronic myelomonocytic leukemia

• MDS/MPN with neutrophilia (previously atypical chronic myeloid leukemia)

• MDS/MPN with SF31B mutation and thrombocytosis

• MDS/MPN not otherwise specified

Solution to Question 18:

More than 20% of blasts in the blood or bone marrow are not compatible with a diagnosis of chronic myelomonocytic leukemia (CMML). In this condition, blasts are less than 20%.

WHO 5th edition diagnostic criteria (2022_for chronic myelomonocytic leukemia (CMML) include:

Prerequisite criteria:

• 1. Persistent absolute (≥0.5 × 109/ L) and relative (≥10%) peripheral blood monocytosis.

• 2. Blasts constitute <20% of the cells in the peripheral blood and bone marrow.

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• 3. Not meeting diagnostic criteria of chronic myeloid leukemia or other myeloproliferative neoplasms (MPN).b

• 4. Not meeting diagnostic criteria of myeloid/lymphoid neoplasms with tyrosine kinase fusions.c

Supporting criteria:

• 1. Dysplasia involving ≥1 myeloid lineage.d

• 2. Acquired clonal cytogenetic or molecular abnormality.

• 3. Abnormal partitioning of peripheral blood monocyte subsets.e

Pre-requisite criteria must be present in all cases:

• If monocytosis is ≥ 1 × 109/ L: one or more supporting criteria must be met.

• If monocytosis is ≥0.5 and <1 × 109/ L: supporting criteria 1 and 2 must be met.

Subtype criteria:

• Myelodysplastic CMML (MD-CMML): WBC < 13 × 109/L

• Myeloproliferative CMML (MP-CMML): WBC ≥ 13 × 109/L

a. Blasts and blast equivalents include myeloblasts, monoblasts, and promonocytes.

b. MPN with monocytosis can mimic CMML. In these instances, a documented history of MPN excludes CMML. The presence of MPN features in the bone marrow and/or a high burden of MPN-associated mutations (JAK2, CALR, or MPL) tends to support MPN with monocytosis rather than CMML.

c. Criteria for myeloid/lymphoid neoplasms with tyrosine kinase fusions should be specifically excluded in cases with eosinophilia.

d. Morphologic dysplasia should be present in ≥10% of cells of a hematopoietic lineage in the bone marrow.

e. Based on the detection of increased classical monocytes (>94%) in the absence of known active autoimmune diseases and/or systemic inflammatory syndromes.

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Solution to Question 19:

HbF levels are increased in juvenile myelomonocytic leukemia (JMML), not Hb A2.

JMML is a hematopoietic stem cell-derived myeloproliferative neoplasm of early childhood. It is one of the myeloproliferative neoplasms. It is associated with mutations in the RAS pathway. Neurofibromatosis 1, Noonan syndrome, and trisomy 8 mosaicism can predispose to this condition. Aggressive types include PTPN11 mutation and neurofibromatosis type 1.

WHO diagnostic guidelines of JMML:

*Germline mutation (indicating Noonan syndrome) needs to be excluded.

It is associated with a poor prognosis and only a few patients undergo spontaneous regression.

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Category I (Mandatory):Clinical and hematologic features	Category II:Genetic (only 1 required)	Category III: Category I + these findings:
SplenomegalyPeripheral blood monocyte count ≥1 × 109/L Blast percentage in peripheral blood and bone marrow <20%No Philadelphia chromosome (BCR/ABL1 rearrangement)Exclusion of KMT2A mutation	Somatic mutation inPTPN11 * orKRAS* orNRAS*Clinical diagnosis of Neurofibromatosis type 1 or NF1 mutationGermline CBL mutation	Hemoglobin F increased for ageMyeloid or erythroid precursors on the peripheral blood smearHypersensitivity to GM-CSF by colony assay and STAT5 hyperphosphorylationThrombocytopenia with hypercellular bone marrow

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Solution to Question 20:

Polycythemia vera is strongly associated with activating point mutations in the tyrosine kinase JAK2.

A mutation in JAK2, a key member of the cytokine intracellular signaling pathway, can be found in 90–95% of patients with polycythemia vera.

It is characterized by :

• Increased marrow production of red cells, granulocytes, and platelets (panmyelosis)

• Low erythropoietin levels and elevated hematocrit

• Blood viscosity and sludging lead to both thrombosis and bleeding.

• Headache, dizziness, hypertension, dizziness, venous thrombosis (Budd Chiari syndrome due to hepatic vein thrombosis), bowel infarction, and stroke.

• Intense pruritus especially aquagenic pruritus

• Peptic ulceration, hyperuricemia

• 15% to 20% of patients after an average period of 10 years ->Myelofibrosis and extensive extramedullary hematopoiesis,

• PCV transforms into AML in 2% of patients.

Primary myelofibrosis

• Marrow fibrosis associated with extramedullary hemopoiesis in the spleen.

• Activating mutation in JAK2 (more commonly) or MPL.

• Presence of neoplastic megakaryocytes, which are responsible for the release of fibrogenic factors like PDGF (platelet-derived growth factor) and TGF-° .

• Bone marrow aspiration yields dry tap due to fibrosis of the bone marrow.

• So, bone marrow biopsy is the investigation of choice, which shows the presence of hypocellularity with increased deposition of reticulin inside the marrow, abnormal megakaryocytes and the characteristic finding of dilated marrow sinusoids.

• Blood shows mild leukocytosis, decreased Hb and hematocrit levels, and elevated LAP scores.

• Acute myeloid leukemia (AML) occurs in 5% to 20% of cases.

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Essential thrombocytosis (ET) may also be associated with JAK2, MPL, or CALR mutations.

• Essential thrombocytosis (ET) is often associated with activating point mutations in JAK2 (50% of cases) or MPL (5% to 10% of cases), a receptor tyrosine kinase that is normally activated by thrombopoietin.

• In addition, recent DNA sequencing studies have revealed that most of the remaining cases have mutations in calreticulin (CALR), a protein with several functions in the endoplasmic reticulum and the cytoplasm. Since JAK2 and calreticulin mutations are mutually exclusive, it is hypothesized that the calreticulin mutations also increase JAK-STAT signaling through mechanisms that are currently unknown.

CML is the consequence of the balanced translocation between chromosomes 9 and 22 (t[9;22]).

PV, PMF, and ET are characterized by driver mutations that directly or indirectly constitutively activate JAK2, a tyrosine kinase essential for the function of the erythropoietin andthrombopoietin receptors and also utilized by granulocyte colony stimulating factor receptor.

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Solution to Question 21:

Myocardial infarction does not cause leukemoid reaction.

Leukemoid reaction is defined as persistent leukocytosis above 50000 cells /mm3, where the cause is other than leukemia.

Causes of leukemoid reaction include:

• Severe infections

• Malignancy

• Severe hemorrhage

• Acute hemolysis

• Trisomy 21 (Down syndrome)

• Asplenia

• Diabetic ketoacidosis

Solution to Question 22:

The given electron microscopy image shows tennis racket shaped Birbeck granules. These granules are characteristic of Langerhans cell histiocytosis.

These granules are pentalaminar tubules with dilated terminal ends. This gives a characteristic tennis racket appearance on electron microscopy. They contain the protein langerin (CD207).

The image given below shows the Birbeck granules as seen on electron microscopy.

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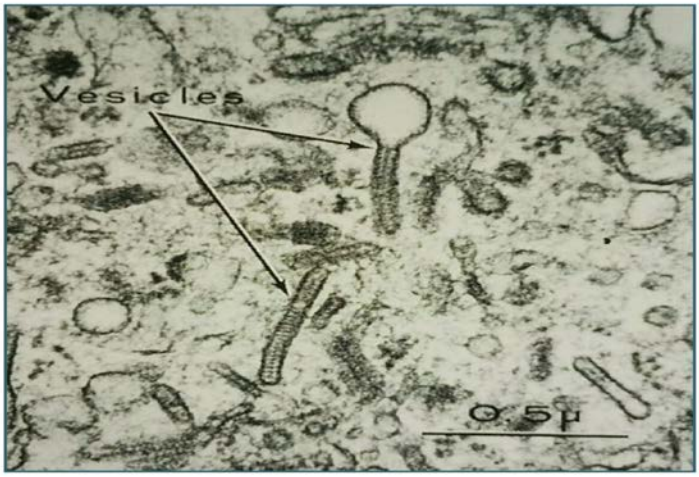
Birbeck Granules - Langerhans Cell Histiocytosis



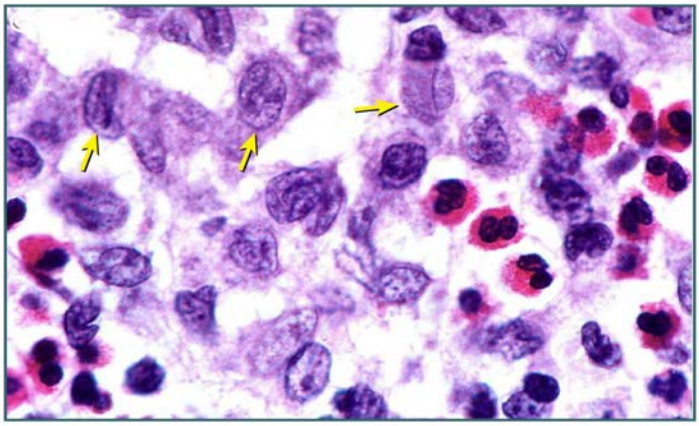
On peripheral smear, the proliferating Langerhans cells are characterised by:

• Abundant vacuolated cytoplasm

• Vesicular nuclei containing linear grooves or folds - coffee bean nuclei

The image given below shows Langerhans cells with coffee bean nuclei and moderately abundant pale cytoplasm mixed with a few eosinophils.

Coffee Bean Nuclei - Langerhans Cell Histiocytosis



Note: Tennis racket cells in light microscopy seen in sarcoma botryoides.

Solution to Question 23:

Rosai–Dorfman disease is not a histiocytic neoplasm. It is sinus histiocytosis with massive lymphadenopathy.

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WHO classification of histiocytic/ hematolymphoid neoplasm 2016 includes the following:

• Histiocytic sarcoma

• Langerhans cell histiocytosis

• Langerhans cell sarcoma

• Indeterminate dendritic cell tumour

• lnterdigitating dendritic cell sarcoma

• Follicular dendritic cell sarcoma

• Fibroblastic reticular cell tumour

• Disseminated juvenile xanthogranuloma

• Erdheim–Chester disease

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Solution to Question 24:

S-100 is a marker for Langerhans cell histiocytosis.

Tumour cells in this condition typically express the following:

• HLA-DR

• S-100

• CD1a

Solution to Question 25:

The given clinical scenario is suggestive of Hand–Schüller–Christian disease.

Langerhans cell histiocytosis presents as multiple clinicopathological entities:

1. Hand–Schüller–Christian disease is a multifocal unisystem Langerhans cell histiocytosis. It usually affects young children. It is characterized by the triad of:

• Diabetes insipidus (excessive thirst) - involvement of the posterior pituitary stalk of the hypothalamus

• Exophthalmos

• Multiple lytic bone lesions

It usually undergoes spontaneous regression. It is treated with local excision or irradiation.

2. Letterer–Siwe disease is a multifocal multisystem Langerhans cell histiocytosis. It occurs most frequently before 2 years of age, but occasionally affects adults.

It is characterized by the following features:

• Cutaneous lesions, resembling a seborrheic eruption - caused by infiltrates of Langerhans cells over the front and back of the trunk and on the scalp

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• Hepatosplenomegaly

• Lymphadenopathy

• Pulmonary lesions

• Destructive osteolytic bone lesions

• Due to marrow infiltration - anemia, thrombocytopenia, predisposition to recurrent infections (otitis media and mastoiditis)

Treatment involves intensive chemotherapy. This condition is fatal if left untreated.

3. Eosinophilic granuloma is a unifocal unisystem Langerhans cell histiocytosis. It is characterized by the proliferation of Langerhans cells admixed with variable numbers of eosinophils, lymphocytes, plasma cells, and neutrophils.

These lesions occur in the following sites:

• Medullary cavities of bones - most commonly the calvarium, ribs, and femur

• Skin

• Lungs

• Stomach

Bone lesions can manifest as:

• Asymptomatic

• Pain

• Tenderness

• Pathologic fractures.

Treatment is by local excision or irradiation.

4. Pulmonary Langerhans cell histiocytosis is most often seen in adult smokers. It regresses spontaneously upon cessation of smoking.

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Solution to Question 26:

The given image showing a solitary punched-out lytic lesion without a sclerotic rim with a beveled edge appearance, along with the age of the patient with history of normal hematological and urinary tests is suggestive of Langerhans cell histiocytosis.

Langerhans cell histiocytosis occurs due to the proliferation of a special type of immature dendritic cells, called Langerhans cells. Their normal function is to present antigens.

It is characterized by single or multiple osteolytic bone lesions. It can also infiltrate the skin (of the scalp), lungs, liver, spleen, bone marrow, or the central nervous system.

Solution to Question 27:

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The image shows a bone marrow biopsy needle. Thrombocytopenia is not in itself a contraindication for bone marrow biopsy. However, a platelet count >20,000 is ensured for safety purposes.

Indications of bone marrow biopsy:

• Evaluation of unexplained anemia, leukopenia, thrombocytopenia, pancytopenia

• Evaluation of polycythemia, thrombocytosis, leukocytosis

• Diagnosis and staging of lymphoma or solid tumors

• Diagnosis and evaluation of plasma cell disorders and leukemias

• Evaluation of suspected infiltrative and storage diseases

• Evaluation of fever of unknown origin, suspected mycobacterial, fungal, or parasitic infections, or granulomatous diseases

Contraindications of bone marrow biopsy:

• Severe hemophilia

• Severe disseminated intravascular coagulopathy

• Severe bleeding disorders

Procedure for bone marrow biopsy:

Prone or lateral position is chosen for the procedure. Posterior superior iliac spine is identified. After disinfection and local anaesthesia, the patient is asked to inhale slowly through the nose and exhale slowly through the mouth to relieve anxiety .The needle is inserted and rotated on its axis.

On reaching the desired depth, the stylet is removed and needle is advanced. The needle is rotated in the opposite direction to loosen the specimen. It is then withdrawn using the same rotational movement.

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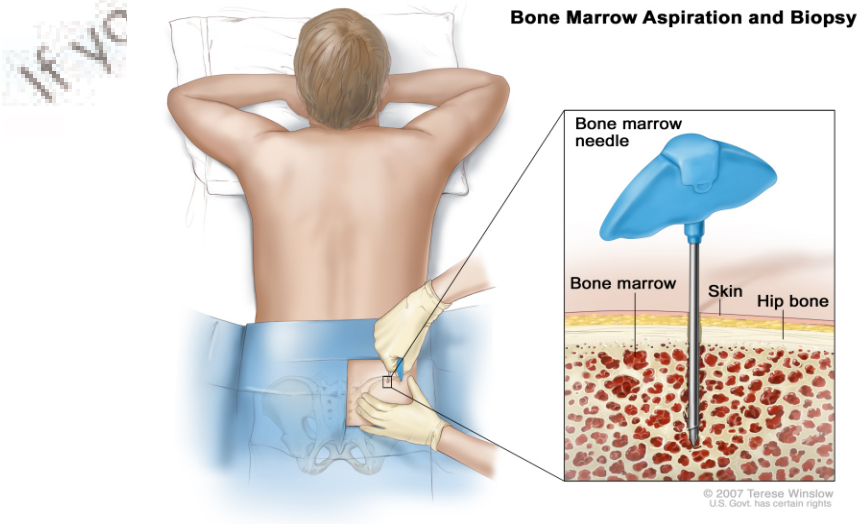

Solution to Question 28:

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Megaloblastic anemia (hypocellular phase), hairy cell leukemia, and hypocellular MDS can show pancytopenia. Acute promyelocytic leukemia is not associated with pancytopenia.

Causes of pancytopenia with hypocellular bone marrow:

• Acquired aplastic anemia

• Hypocellular myelodysplastic syndrome

• Rare aleukemic leukemia

• Some acute lymphoid leukemia

• Rare lymphomas of bone marrow

• Copper deficiency

Causes of pancytopenia with cellular bone marrow:

• Myelodysplastic syndromes

• Systemic lupus erythematosus

• Paroxysmal nocturnal hemoglobinuria (PNH)

• Hypersplenism

• B12, folate deficiency, Copper deficiency

• Myelofibrosis

• Aleukemic leukemia

• HIV, Brucellosis, Leishmaniasis, Tuberculosis Sepsis

• Myelophthisis

• Bone marrow lymphoma

• Sarcoidosis

• Hairy cell leukemia

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Solution to Question 29:

Follicular lymphoma is the least likely cause of a dry tap on bone marrow aspiration.

Causes of dry tap are:

• Metastatic carcinoma infiltration

• Chronic myeloid leukemia

• Myelofibrosis

• Hairy cell leukemia

• Acute leukemia

• Hodgkin's lymphoma

• AML- M7

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Causes of pancytopenia with cellular marrow are:

Primary disease of marrow-

- Myelodysplastic syndrome
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Myelofibrosis
- Aleukemic leukemia
- Myelophthisis
- Bone marrow lymphoma
- Hairy cell leukemia

Secondary to systemic disease-

- SLE, sarcoidosis
- B12, folate deficiency
- Copper deficiency
- Hypersplenism
- Alcohol
- HIV infection, TB
- Brucellosis, leishmaniasis

Note: Although marrow is hypercellular in CML, MDS etc., extensive marrow fibrosis (rare) has been proposed to account for a dry tap on bone marrow biopsy.

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Leukopenia, Leukocytosis and Lymphadenitis

Question 1:

From which period of embryogenesis does the liver become the chief site of hematopoiesis?

a) 3rd week

b) 3rd month

c) 4th month

d) 1st month

Question 2:

Which cells in the bone marrow are referred to as nurse cells?

a) Megakaryocytes

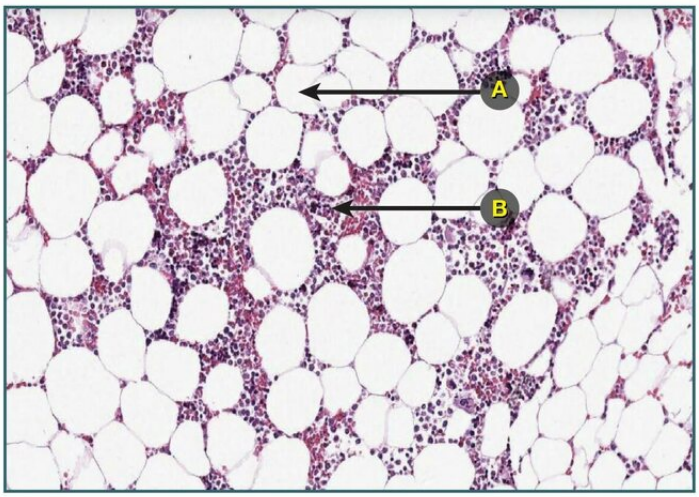
b) Macrophages

c) Parasite-infected progenitors

d) Fat cells

Question 3:

Bone marrow biopsy of a normal adult is given below. What is the ratio of structures marked A and B?



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a) 2:1

b) 1:1

c) 1:2

d) 1:3

Question 4:

Which of the following is a marker for pluripotent hematopoietic stem cells?

a) CD1

b) CD34

c) CD79

d) CD45

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Question 5:

Which of the following is called leukocyte common antigen?

a) CD10

b) CD45

c) CD3

d) CD1

Question 6:

Which of the following is a characteristic feature of Kostmann syndrome?

a) Neutrophilia

b) Neutropenia

c) Thrombocytopenia

d) Lymphopenia

Question 7:

What is the most common cause of agranulocytosis?

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a) Marrow infiltration

b) Autoimmune

c) Drug toxicity

d) Radiation exposure

Question 8:

A patient who was started on chemotherapy 2 weeks ago is found to have a neutrophil count of 2000/mm3. Below what neutrophil count is he at risk of developing serious infections?

a) 1500/mm3

b) 1000/mm3

c) 500/mm3

d) 100/mm3

Question 9:

A 5-year-old boy is brought with complaints of episodes of severe, violent coughs, followed by a high-pitch intake of breath that sounds like a whoop. These coughing episodes are usually followed by vomiting. He and his family are refugees and his prior vaccination records are not available. Lab investigations of this child will likely reveal which of the following?

a) Neutrophilia

b) Eosinophilia

c) Monocytosis

d) Lymphocytosis

Question 10:

A 50-year-old man admitted to ICU develops sepsis 3 days after insertion of a central venous catheter. A peripheral blood smear reveals the following. What does the structure marked by the arrow indicate?

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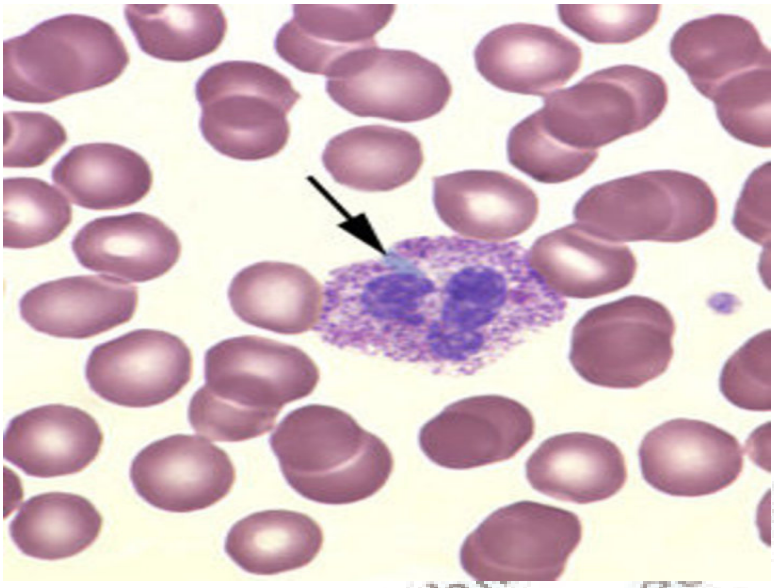

a) Toxic granule

b) Döhle body

c) Creola body

d) Toxic vacuolation

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Question 11:

Which of the following does not cause follicular hyperplasia of the lymph nodes?

a) Rheumatoid arthritis

b) Toxoplasmosis

c) Early stage of HIV infection

d) B cell lymphoma

Question 12:

Which of the following is not a feature of reactive lymphoid hyperplasia?

a) Recognizable light and dark zones

b) Presence of frequent mitotic figures

c) No variation in shape and size of the follicles

d) Preservation of lymph node architecture

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Question 13:

In which of the following organs are tingible body macrophages found?

a) Bone marrow

b) Spleen

c) Lymph node

d) Thymus

Question 14:

A 16-year-old boy presented with complaints of fever, sore throat, and enlarged lymph nodes. Paul Bunnell's test was done and found to be positive. What type of lymphoid hyperplasia is seen in this condition?

a) Follicular hyperplasia

b) Paracortical hyperplasia

c) Reticular hyperplasia

d) Sinus histiocytosis

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Question 15:

In patients with breast cancer with lymph node metastases, which of the following changes is seen in affected lymph nodes?

a) Follicular hyperplasia

b) Para cortical hyperplasia

c) Reticular hyperplasia

d) Cortical hyperplasia

Question 16:

Which of the following statements about hemophagocytic lymphohistiocytosis is false?

a) There is systemic activation of macrophages and CD8+ T cells

b) The most common trigger is infection with Epstein-Barr virus

c) It presents as an acute febrile illness with hepatosplenomegaly

d) Hemophagocytosis seen in bone marrow is sufficient for diagnosis

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Question 17:

Which of the following is not a feature in patients with hemophagocytic lymphohistiocytosis?

a) Disseminated intravascular coagulation

b) High serum triglycerides

c) Low serum ferritin

d) High plasma IL2 receptor

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Answer Key

Question No.	Correct Option
1	b
2	b
3	b
4	b
5	b
6	b
7	c
8	c
9	d
10	b
11	d
12	c
13	c
14	b
15	c
16	d
17	c

Detailed Explanations

Solution to Question 1:

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From the 3rd month of embryogenesis, the liver becomes the chief site of hematopoiesis.

Development of hematopoietic tissues:

• Yolk sac - blood cell progenitors first appear during the 3rd week

• Liver - hematopoietic stem cells migrate to the liver during the 3rd month of embryogenesis

• Bone marrow - hematopoiesis starts in bone marrow during the 4th month of intrauterine life and becomes the predominant site after birth

Solution to Question 2:

Nurse cells are specialized macrophages in the bone marrow that assist in the development of red blood cells (RBCs).

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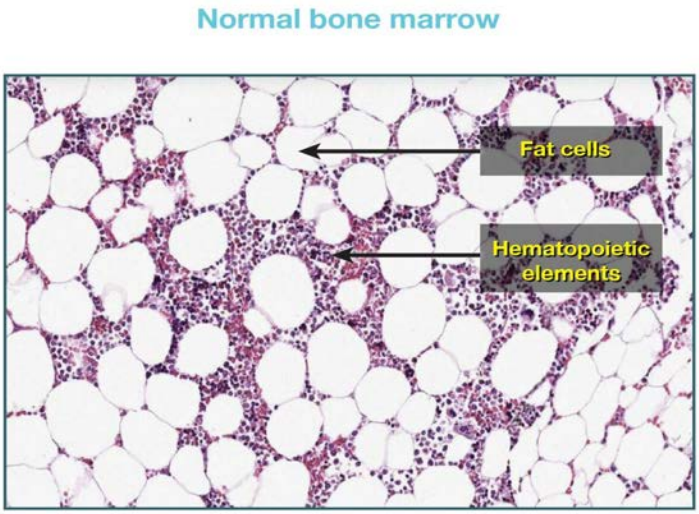
Solution to Question 3:

The structures marked A are fat cells and B are hematopoietic elements. The normal ratio of fat cells to hematopoietic elements in a normal adult is 1:1.



In hypoplastic states (like aplastic anemia), the proportion of fat cells is greatly increased (increased fat to cell ratio).

Conversely, fat cells often disappear in conditions like hematopoietic tumors and in diseases with compensatory hyperplasias (like hemolytic anemias) and neoplastic proliferations such as leukemias (decreased fat-to-cell ratio).

Solution to Question 4:

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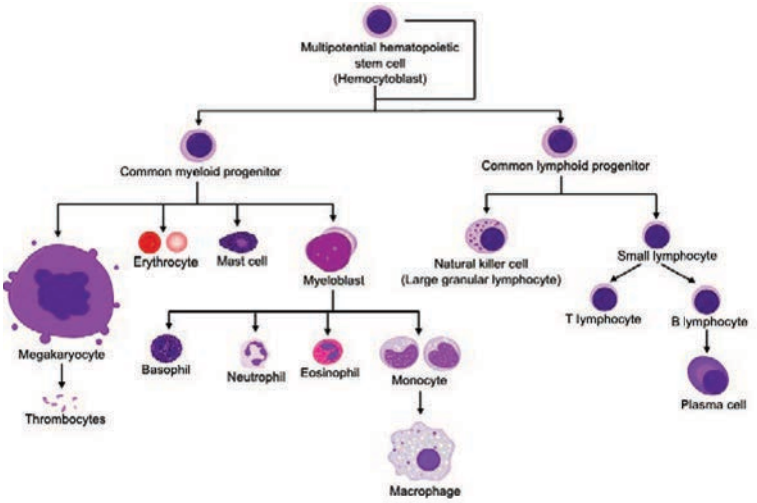
CD34 is an antigen of pluripotent hematopoietic stem cells and progenitor cells of many lineages.



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Solution to Question 5:

CD45 is called leukocyte common antigen because it is found in all leukocytes.

Solution to Question 6:

Kostmann syndrome is characterized by neutropenia.

It is a rare congenital condition in which inherited defects in specific genes impair granulocytic differentiation. This results in severe congenital neutropenia.

It presents in young children as recurrent bacterial infections (such as otitis media, cellulitis) and oral ulcers. It is associated with an increased risk of acute myeloid leukemia (AML).

Solution to Question 7:

The most common cause of agranulocytosis is drug toxicity.

Causes of agranulocytosis include:

• Inadequate or ineffective granulopoiesis -

• Suppression of hematopoietic stem cells - aplastic anemia, infiltrative marrow disorders

• Suppression of committed granulocytic precursors

• Ineffective hematopoiesis - megaloblastic anemia, myelodysplastic syndromes

• Congenital conditions - Kostmann syndrome

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• Increased destruction or sequestration of neutrophils -

• Immunological injury to neutrophils - idiopathic, systemic lupus erythematosus, drug exposure

• Increased peripheral utilization - bacterial, fungal, or rickettsial infections

• Splenomegaly

Solution to Question 8:

Serious infections are most likely when the neutrophil count falls below 500/mm3.

Solution to Question 9:

The given clinical scenario is suggestive of whooping cough or pertussis. It is due to Bordetella pertussis infection and results in lymphocytosis.

Causes of lymphocytosis include:

• Pertussis

• Tuberculosis

• Brucellosis

• Hepatitis A

• Cytomegalovirus

• Epstein-Barr virus

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Solution to Question 10:

The given peripheral smear, prepared from an individual with bacterial sepsis, shows reactive changes in neutrophils. The arrow-marked structure is a Döhle body.

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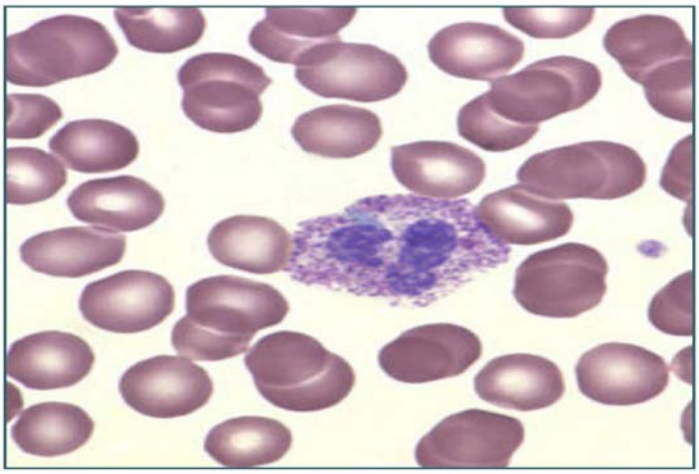
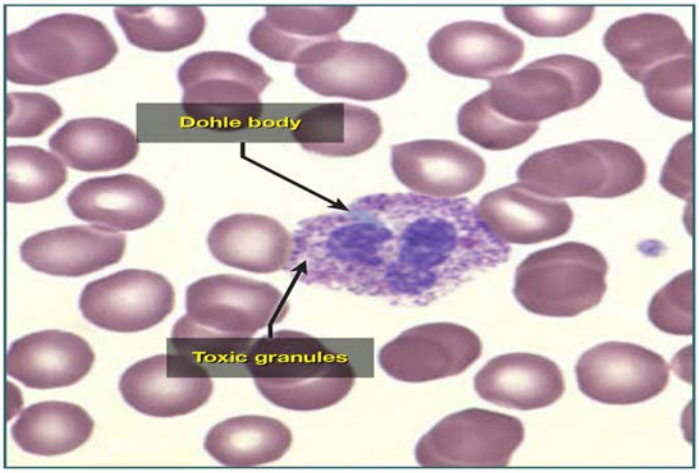
Reactive changes in neutrophils



Reactive changes in neutrophils



Reactive changes in neutrophils associated with leukocytosis in severe inflammatory disorders are:

• Toxic granules, which are coarser and darker than the normal neutrophilic granules, represent abnormal azurophilic (primary) granules

• Döhle bodies are patches of the dilated endoplasmic reticulum that appear as sky-blue cytoplasmic puddles

• Toxic cytoplasmic vacuoles

The image given below shows a neutrophil with cytoplasmic vacuoles.

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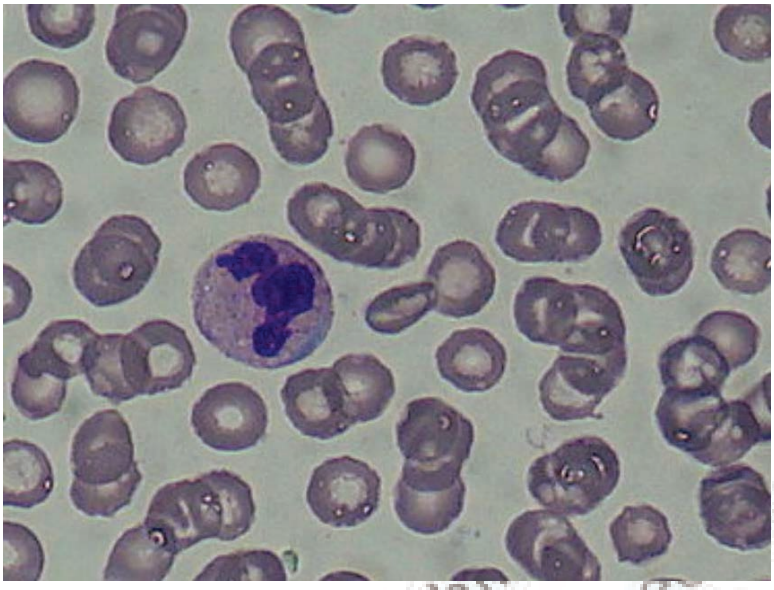

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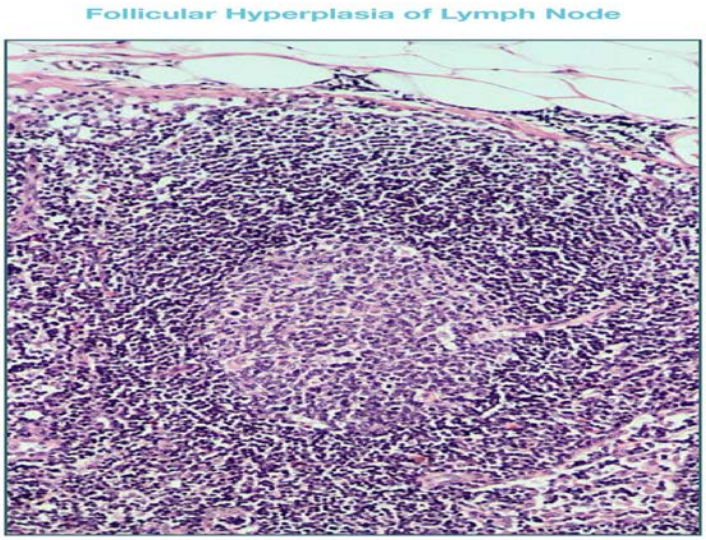
Solution to Question 11:

B-cell lymphoma results in malignant proliferation within the lymph node, not follicular hyperplasia.

Follicular hyperplasia is a benign condition caused by stimuli that activate humoral immune responses. It may occur in:

- Rheumatoid arthritis
- Toxoplasmosis
- Early stages of HIV infection

It is defined by the presence of large oblong germinal centres (secondary follicles), which are surrounded by a collar of small, resting naive B cells (mantle zone).



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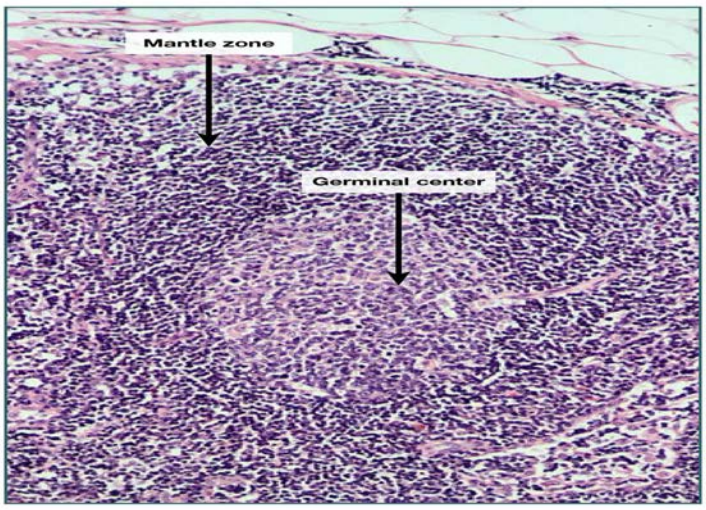
Follicular Hyperplasia of Lymph Node



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Solution to Question 12:

In reactive lymphoid hyperplasia, there is marked variation in the shape and size of follicles.

Features favoring reactive lymphoid hyperplasia, which are absent in neoplastic follicles are:

• Preservation of the lymph node architecture, including the interfollicular T-cell zones and the sinusoids

• Marked variation in the shape and size of the follicles

• Presence of frequent mitotic figures and phagocytic macrophages

• Recognizable light and dark zones

Solution to Question 13:

Tingible-body macrophages are found in lymph nodes.

A tingible-body macrophage is a type of macrophage predominantly found in germinal centers containing many phagocytosed apoptotic cell debris. This debris is referred to as tingible bodies (tingible meaning stainable). The presence of these macrophages suggests non-neoplastic reactive hyperplasia of the lymph node, or can be seen as the stars in the starry sky appearance of Burkitt lymphoma.

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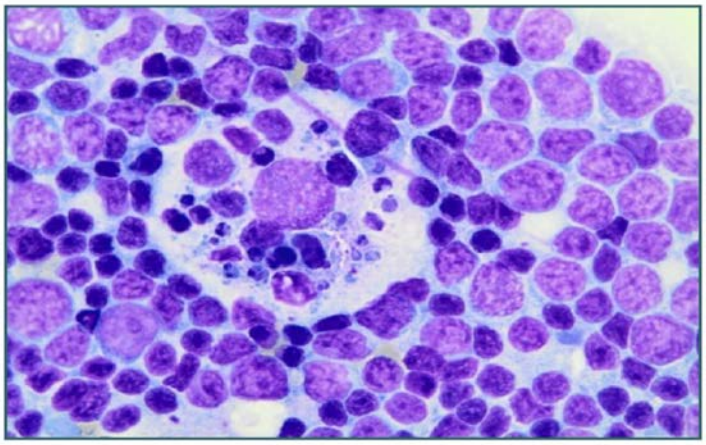
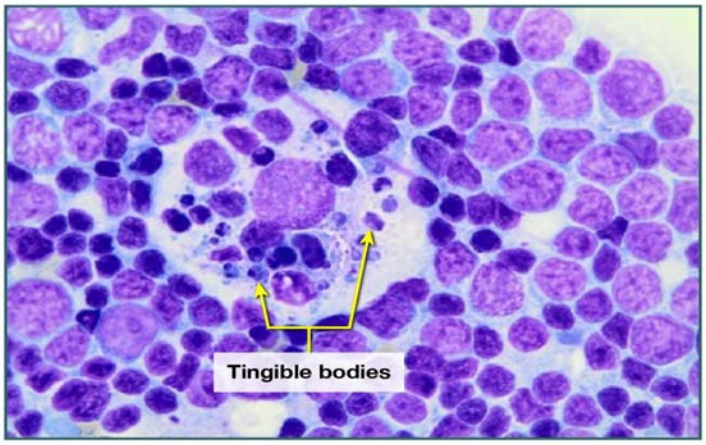
Tingible Body Macrophage



Tingible Body Macrophage



Solution to Question 14:

The given clinical scenario is suggestive of infectious mononucleosis. Acute viral infections, like infectious mononucleosis, produce paracortical hyperplasia.

There are three types of lymph node hyperplasia. They are:

• Follicular hyperplasia

• Paracortical hyperplasia

• Sinus histiocytosis (reticular hyperplasia)

Paracortical hyperplasia is seen in the T-cell-containing paracortical region of the lymph node. It is caused by stimuli that trigger T-cell–mediated immune responses. The involved regions typically contain:

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• Immunoblasts

• Activated T-cells 3-4 times the size of resting lymphocytes t

• Round nuclei

• Open chromatin

• Several prominent nucleoli

• Moderate amounts of pale cytoplasm

• Hypertrophy of sinusoidal and vascular endothelial cells, with infiltrating macrophages and eosinophils

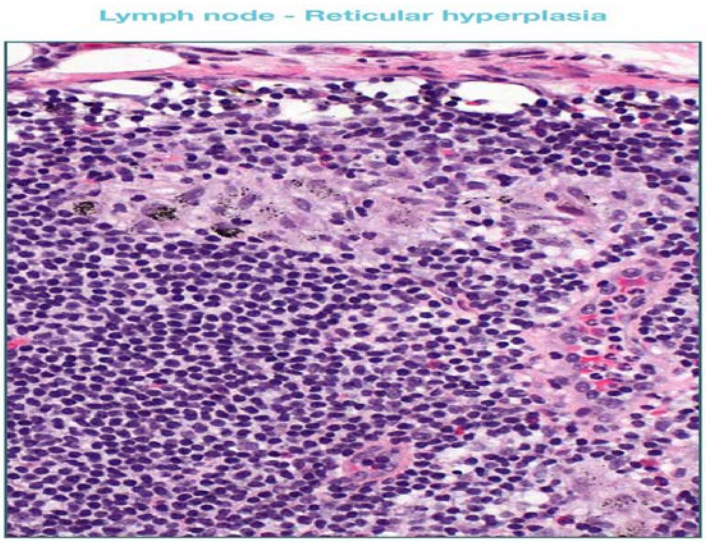
Solution to Question 15:

In the case of lymph node metastases, there is prominent reticular hyperplasia.

Reticular hyperplasia or sinus histiocytosis refers to an increase in the number and size of the cells that line lymphatic sinusoids. Although nonspecific, this form of hyperplasia may be particularly prominent in lymph nodes draining cancers such as carcinoma of the breast.

The lining lymphatic endothelial cells are markedly hypertrophied and macrophages are greatly increased in numbers, resulting in the expansion and distension of the sinuses.

The image given below shows reticular hyperplasia in the lymph node.



Solution to Question 16:

Hemophagocytosis is usually seen on bone marrow examination, but it is neither sufficient nor required to make the diagnosis of hemophagocytic lymphohistiocytosis (HLH).

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HLH is a reactive condition also known as macrophage-activation syndrome. The common feature of all forms of HLH is the systemic activation of macrophages and CD8+ T-cells.

The most common trigger for HLH is an infection, particularly with EBV (Epstein-Barr virus). It is characterized by acute febrile illness associated with splenomegaly, hepatomegaly, and cytopenias.

Solution to Question 17:

Hemophagocytic lymphohistiocytosis (HLH) is associated with very high serum ferritin levels.

Laboratory findings in HLH include:

- Anemia
- Thrombocytopenia
- High serum ferritin
- High plasma IL2 receptor levels
- Elevated liver enzyme levels
- High triglyceride levels
- Features of disseminated intravascular coagulation (DIC)

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Hypertensive Vascular Disease and Atherosclerosis

Question 1:

Vascular injury causes intimal thickening by which of the following mechanisms?

a) Endothelial cell hyperplasia

b) Smooth muscle proliferation

c) Thickening of basement membrane

d) Deposition of hyaline material

Question 2:

Endothelial dysfunction is implicated in all of the following except:

a) Aneurysm formation

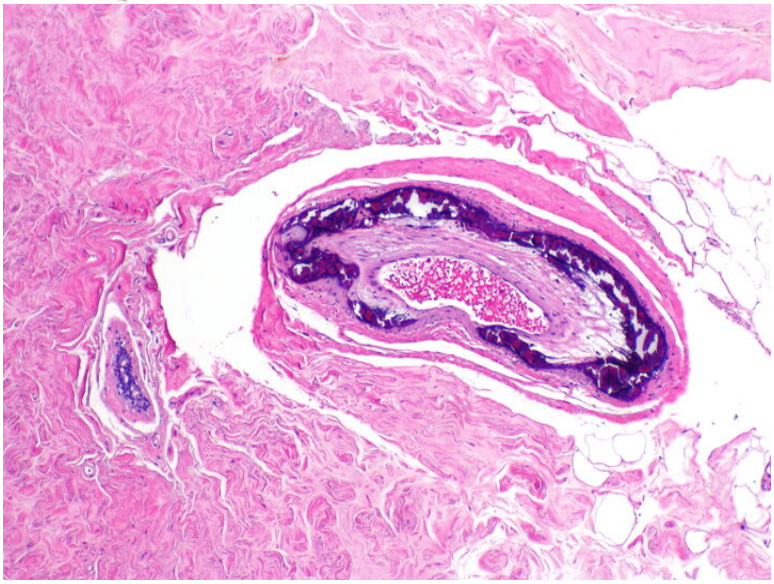
b) Atherosclerotic plaque

c) Hypertensive vascular disease

d) Diabetic microangiopathy

Question 3:

Identify the condition:



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a) Monckeberg's medial sclerosis

b) Hyaline arteriosclerosis

c) Hyperplastic arteriosclerosis

d) Atherosclerosis

Question 4:

The following incidental finding is seen on a radiograph of a 60-year-old man. Which of the following is true regarding this condition?

a) It involves the internal elastic lamina

b) It involves the external elastic lamina

c) It is associated with diabetes

d) It is associated with hypertension

Question 5:

Which of the following pathological changes occurs in the small vessels of patients suffering from hypertension?

a) Aneurysm formation

b) Hyaline arteriosclerosis

c) Atherosclerosis

d) Cerebrovascular hemorrhage

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Question 6:

Which of the following is responsible for arteriolar wall thickening in hyaline arteriosclerosis?

a) Plasma protein deposition

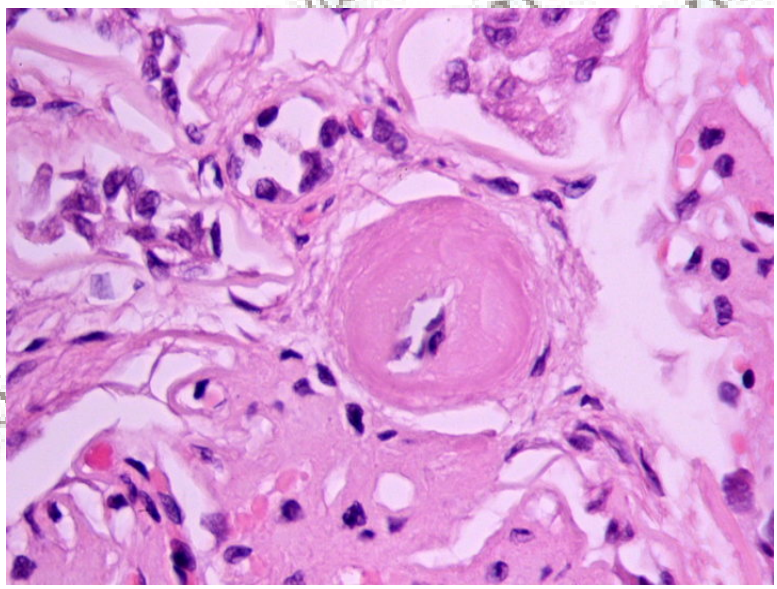
b) Immune complex deposition

c) Amyloid deposition

d) Smooth muscle proliferation

Question 7:

A pathology resident is studying a vascular biopsy sample. This vascular lesion is less likely seen in which of the following conditions



a) Diabetes mellitus

b) Severe hypertension

c) Benign hypertension

d) Age-related degeneration

Question 8:

The renal biopsy of a 50-year-old chronic hypertensive patient is given below. What is the likely diagnosis?

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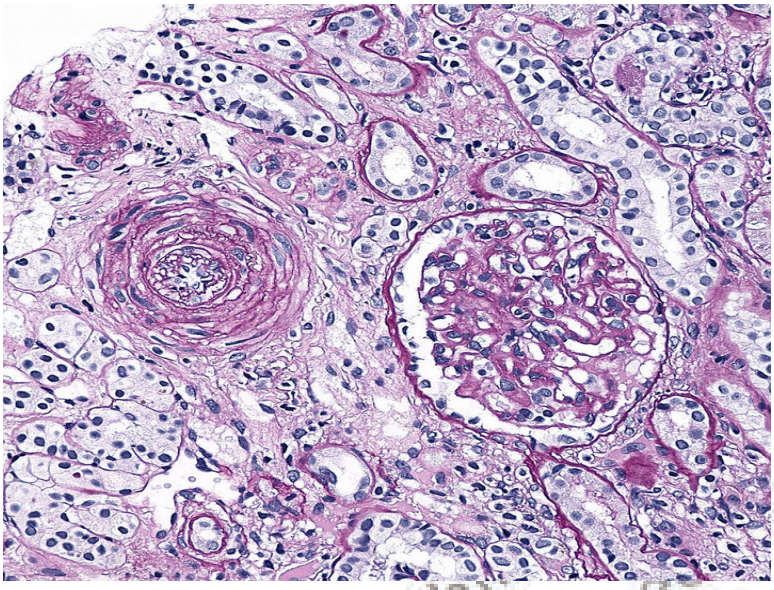

a) Benign nephrosclerosis

b) Malignant nephrosclerosis

c) Renal artery stenosis

d) Nodular glomerulosclerosis

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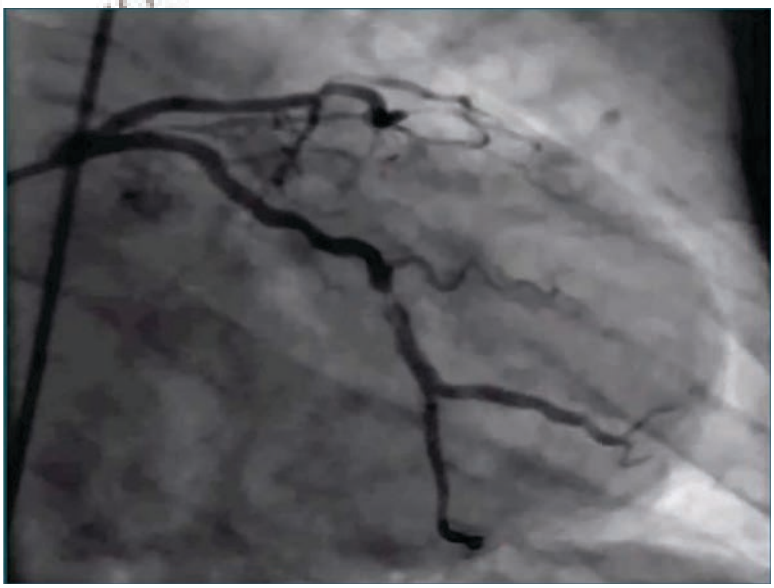
Question 9:

A 65-year-old man presented with chest pain. Past history is significant for dyslipidemia and an ischemic stroke 2 years ago. Coronary angiography was performed and showed the following. What is the correct sequence of events leading to this condition?



a) 1,2,3,4

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b) 2,3,1,4

c) 3,2,4,1

d) 3,4,2,1

Question 10:

What is the most important independent risk factor for atherosclerosis?

a) Age

b) Hypertension

c) Family history

d) Lack of exercise

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Question 11:

Which of the following is the most common site of atherosclerosis?

a) Lower abdominal aorta

b) Femoral artery

c) Internal carotid artery

d) Popliteal artery

Question 12:

The autopsy of a 14-year-old boy who died in a motor vehicle accident showed the following lesions on the inner surface of the aorta. What do these lesions indicate?

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a) Atherosclerosis

b) Fibrinoid necrosis

c) Foamy macrophages

d) Calcification

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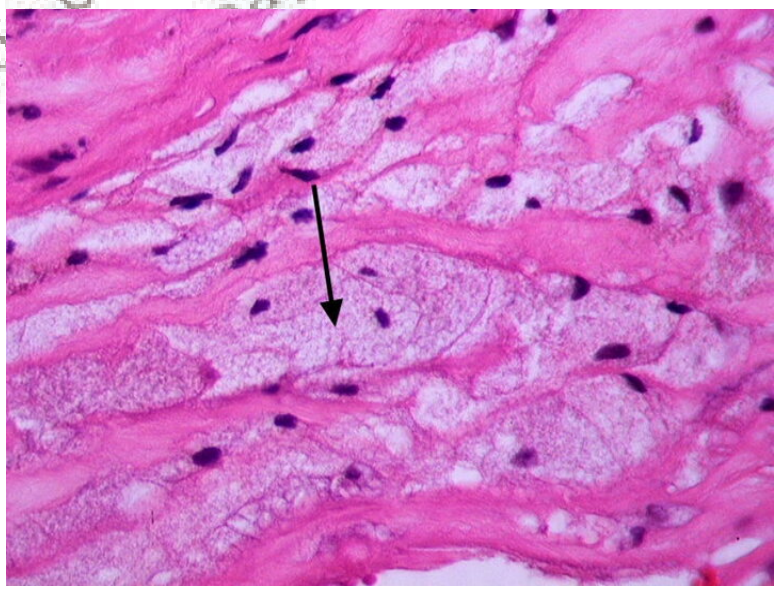
Question 13:

Where are the following cells in an atheromatous plaque derived from?



a) T-lymphocytes

b) Monocytes

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c) Fibroblasts

d) Endothelial cells

Question 14:

In which part of the atheromatous plaque are the T-cells and macrophages in abundance?

a) Fibrous cap

b) Core

c) Periphery

d) Shoulder

Question 15:

Which of the following is true regarding a stable atherosclerotic plaque?

a) Abundant smooth muscle cells

b) Abundant T-cells

c) Abundant foam cells

d) Abundant extracellular lipid

Question 16:

In a 50-year-old normotensive patient with a 10-year history of dyslipidemia, which of the following complications is he at the least risk of developing?

a) Infarction

b) Claudication

c) Aneurysm

d) Dissection

Question 17:

A patient with anginal chest pain is planned for coronary angiography. What level of stenosis would you expect to see in the affected artery?

a) > 55%

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b) > 65%

c) > 70%

d) > 60%

Question 18:

Elevated levels of which of the following is not a predictor for stroke?

a) C-reactive protein

b) Homocysteine

c) Plasminogen

d) Plasminogen activator Inhibitor-1

Question 19:

A patient presented with symptoms of heart failure. He had undergone a coronary bypass procedure with a small-diameter graft 3 weeks ago. What is the likely cause for his presentation?

a) Atherosclerotic plaque

b) Neointimal hyperplasia

c) Thrombosis

d) Aneurysm

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Question 20:

Which of the following is false regarding the KLF-2 transcription factor?

a) Activates atheroprotective genes

b) Turns on inflammatory gene transcription

c) Production is induced by laminar blood flow

d) Responsible for the atheroprotective role of statins

Answer Key

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Question No.	Correct Option
1	b
2	a
3	a
4	a
5	b
6	a
7	b
8	b
9	c
10	c
11	a
12	c
13	b
14	d
15	a
16	d
17	c
18	c
19	c
20	b

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Detailed Explanations

Solution to Question 1:

Vascular injury results in intimal thickening due to smooth muscle proliferation.

Vascular injury stimulates the migration of smooth muscle cells of the tunica media to the tunica intima. These smooth muscle cells proliferate and also synthesize extracellular matrix leading to intimal thickening. This is the stereotypical response of the vessel wall to an injury regardless of the cause of injury.

The image below shows intimal thickening occurring in response to vascular injury.

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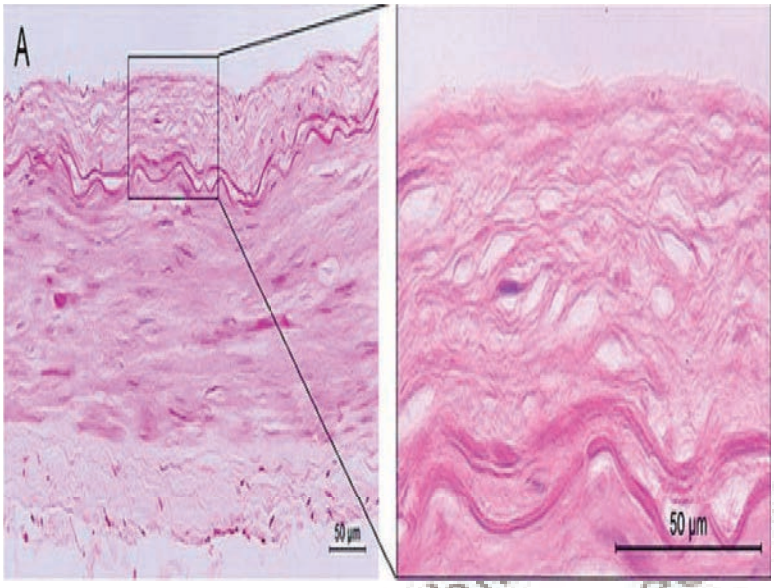

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Solution to Question 2:

Endothelial dysfunction is not implicated in aneurysm formation. An aneurysm occurs due to the pathology of connective tissue within the vascular wall.

Endothelial dysfunction is the pathological alteration of the endothelium such that it becomes pro-inflammatory and prothrombogenic. It is caused by various injuries to endothelial cells:

- Hemodynamic stresses - responsible for vascular pathology in hypertension
- Lipid products - leading to the pathogenesis of atherosclerosis
- Advanced glycation end-products (AGE) - responsible for diabetic microangiopathy
- Viruses, bacterial products, cytokines, and complement components

Solution to Question 3:

The given image shows arteriosclerosis and calcification in the tunica media, that does not encroach on the vessel lumen. This is suggestive of Monckeberg's medial sclerosis.

Monckeberg's medial sclerosis affects medium-sized muscular arteries and is characterized by calcification of the medial walls of the affected arteries. Adults aged over 50 years are usually affected.

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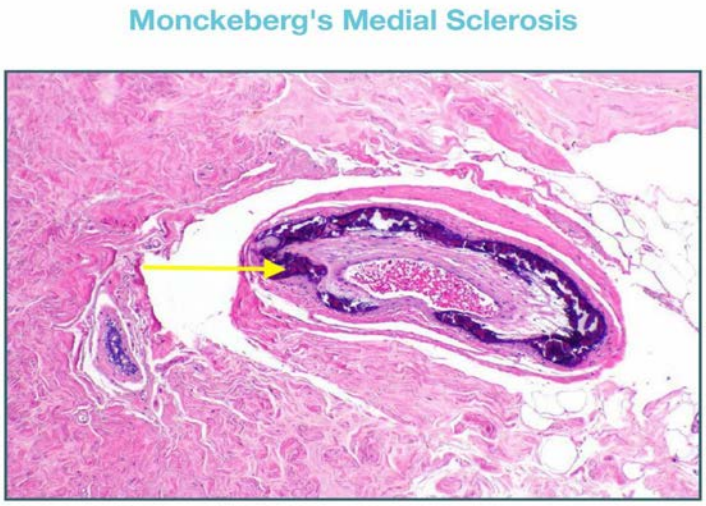

Arteriosclerosis refers to the thickening of the arterial wall and loss of elasticity. There are four patterns of arteriosclerosis:

• Small vessel arteriosclerosis - involves small arteries and arterioles

• It has two variants - hyaline arteriosclerosis, and hyperplastic arteriosclerosis

• Monckeberg medial sclerosis - involves calcification of the walls of muscular arteries

• Fibromuscular intimal hyperplasia- usually a healing response to inflammation (eg: arteritis) or mechanical injury (eg: stent insertion)

• Atherosclerosis - mainly involves elastic and muscular arteries

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Solution to Question 4:

The given radiograph shows extensive calcification of the femoral arteries which is suggestive of Monckeberg medial sclerosis. It is characterized by the calcification of the walls of muscular arteries, typically starting along the internal elastic lamina and involves the media of the arteries.

It occurs in people aged 50 years and above as a part of senile degeneration. It is not associated with hypertension or diabetes. It is usually an incidental finding.

Solution to Question 5:

Hypertension results in hyaline arteriosclerosis of the small vessels.

Hypertension leads to a variety of vascular pathologies. In small blood vessels, hypertension may lead to arteriosclerosis which is the thickening of the vessel wall. It has two variants which are hyaline arteriosclerosis and hyperplastic arteriosclerosis.

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In large and medium-sized arteries, hypertension leads to degenerative changes in the vessel walls, leading to:

- Dissection
- Aneurysm formation
- Cerebrovascular hemorrhage
- Acceleration of atherosclerosis

Solution to Question 6:

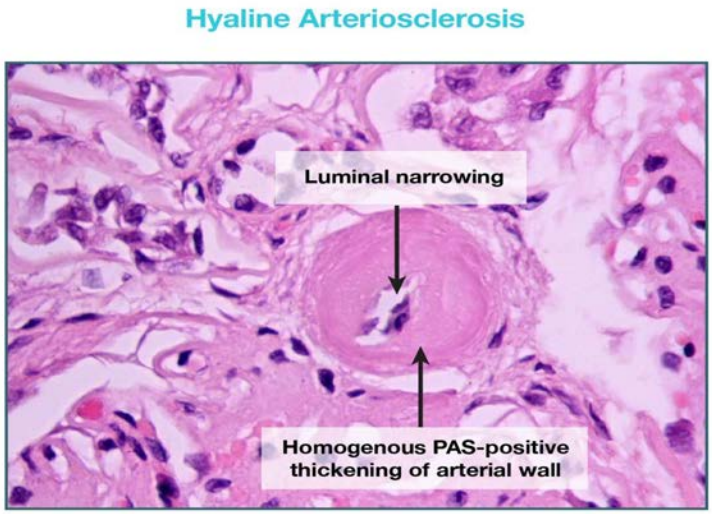
The arteriolar wall thickening in hyaline arteriosclerosis occurs as a result of plasma protein deposition.

Hyaline arteriosclerosis occurs due to injury to the endothelial cells. This allows plasma protein leakage into the arteriolar wall. The endothelial injury also stimulates increased matrix synthesis by the smooth muscle cells. These lead to the deposition of homogenous pink hyaline material causing the thickening of arteriolar walls.

Solution to Question 7:

The given image shows hyaline arteriosclerosis. It occurs in the following conditions:

- Elderly patients who are normotensive
- Benign hypertension: due to chronic hemodynamic stresses
- Diabetes mellitus: due to hyperglycemia-induced endothelial dysfunction



Severe hypertension causes hyperplastic arteriosclerosis with the characteristic onion skin appearance as seen below:

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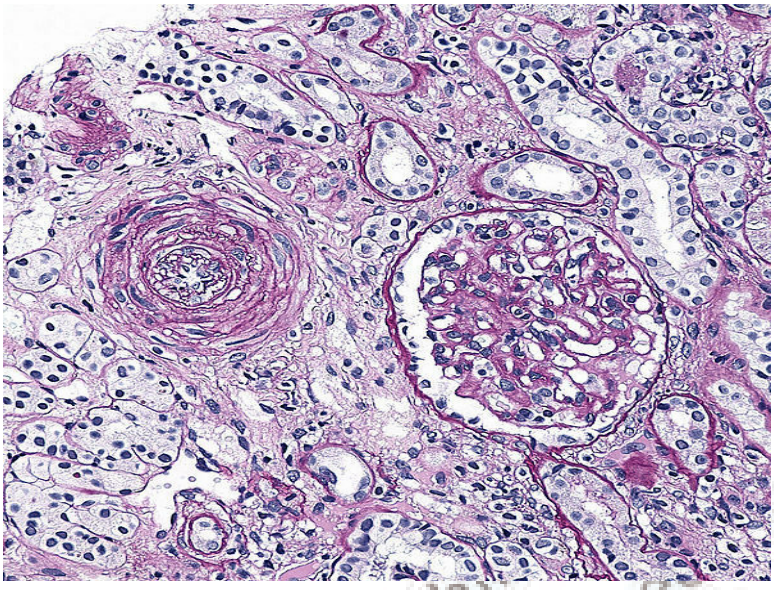

Solution to Question 8:

The given image shows hyperplastic arteriosclerosis, as noted by the onion-skin appearance of the arteriole. This is seen in malignant nephrosclerosis.

Nephrosclerosis is caused by sclerosis of the small arteries and the arterioles of the kidney leading to diffuse impairment of renal blood supply. It is of 2 types:

Benignnephrosclerosis	Malignantnephrosclerosis
Seen in benign hypertension	Seen in malignant hypertensi on
Causeshyaline arteriosclerosi s	Causeshyperplastic arterioscl erosisandfibrinoid necrosisof the arterioles.

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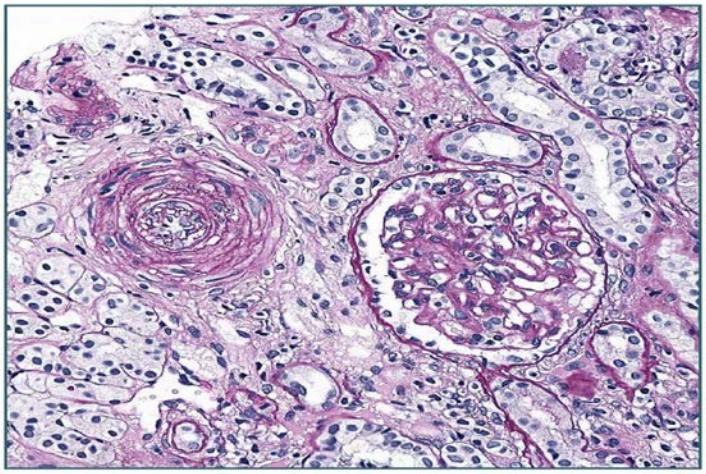
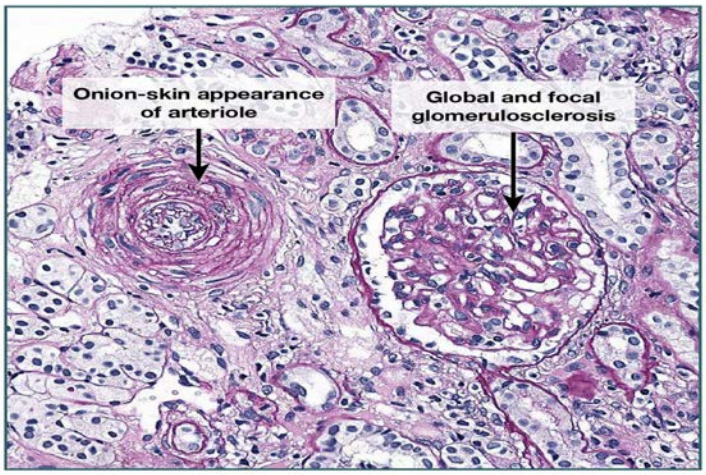
Malignant Nephrosclerosis



Malignant Nephrosclerosis



The characteristic flea-bitten appearance of the kidney is seen in malignant nephrosclerosis (shown below). This is due to small petechial hemorrhages resulting from the rupture of arterioles.

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Solution to Question 9:

This clinical scenario and image showing occlusion of the left circumflex coronary artery are suggestive of atherosclerosis. It progresses in the following sequence:

- Endothelial injury and dysfunction
- Accumulation of lipoproteins in the vessel wall
- Monocyte adhesion to the endothelium
- Platelet adhesion
- Factor release from activated platelets, macrophages, and vascular wall cells
- Smooth muscle cell proliferation, extracellular matrix production, and recruitment of T cells
- Lipid accumulation both extracellularly and within cells
- Calcification of ECM and necrotic debris late in the pathogenesis

Hence, atherosclerosis is a chronic inflammatory and healing response of the arterial wall to endothelial injury. The two most important causes of endothelial injury leading to atherosclerosis are hemodynamic disturbances and hypercholesterolemia.

The image below shows partial occlusion of the left circumflex coronary artery.

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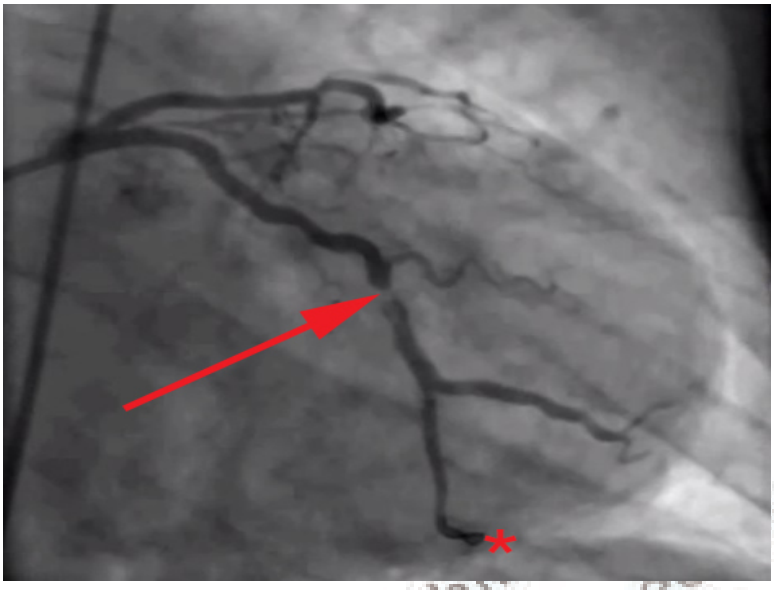

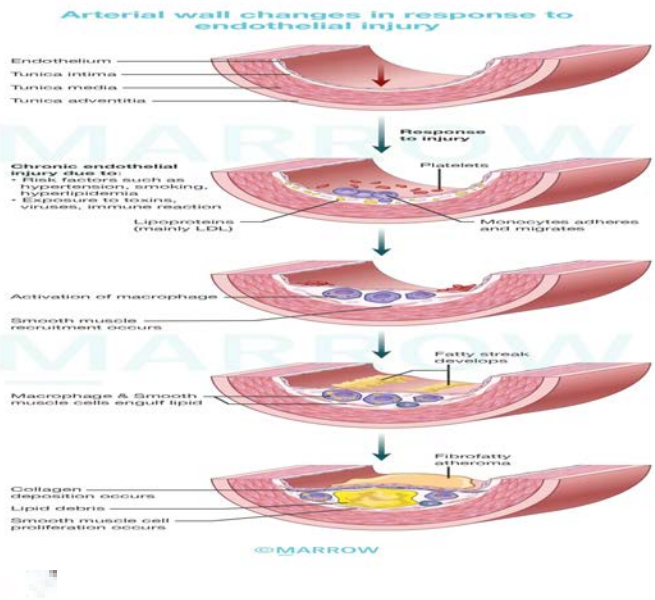

Solution to Question 10:

The most important independent risk factor for atherosclerosis is family history.

The familial predisposition to atherosclerosis is usually polygenic. It is related to the familial clustering of other established risk factors, such as hypertension or diabetes. It may also be due to inherited variations in pathophysiologic processes such as inflammation.

Hyperlipidemia (specifically hypercholesterolemia) is a major risk factor for atherosclerosis. Even in the absence of other risk factors, hypercholesterolemia is sufficient to initiate lesion development.

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Solution to Question 11:

The most common site of atherosclerosis is the lower abdominal aorta.

In descending order, the most extensively involved vessels in atherosclerosis are:

• Lower abdominal aorta

• Coronary arteries

• Popliteal arteries

• Internal carotid arteries

• Arteries of the circle of Willis

Solution to Question 12:

The above image shows yellow spots on the inner surface of the aorta, which represent fatty streaks. They indicate a collection of foamy macrophages in the intima of the vessel wall.

Fatty streaks may be present in the aorta of infants, virtually all adolescents, and even individuals without known risk factors. These lesions are not indicative of atherosclerosis, but some of them may evolve into atheromatous plaques later in life by smooth muscle proliferation and extracellular matrix deposition.

Solution to Question 13:

The cells marked in the image above are the foam cells in atheromatous plaques. They refer to lipid-laden monocytes/ macrophages or smooth muscle cells within the plaques.

These cells ingest lipoproteins accumulated within the intima of the vessel wall. Since these lipoproteins are modified due to the action of inflammatory mediators, they cannot be degraded further within these cells. This leads to the accumulation of modified lipids within these cells converting them to foam cells.

Solution to Question 14:

T-cells and macrophages are in abundance in the shoulder of an atheromatous plaque.

Structure of an atherosclerotic plaque:

• Superficial fibrous cap - made up of smooth muscle cells and connective tissue, especially collagen. It also contains macrophages, foam cells, and lymphocytes. It determines the stability of plaque.

• Necrotic core - contains lipid (cholesterol and cholesterol esters), debris from dead cells, calcium, and foam cells.

• Shoulder - a more cellular area containing macrophages, T-cells, and smooth muscle cells.

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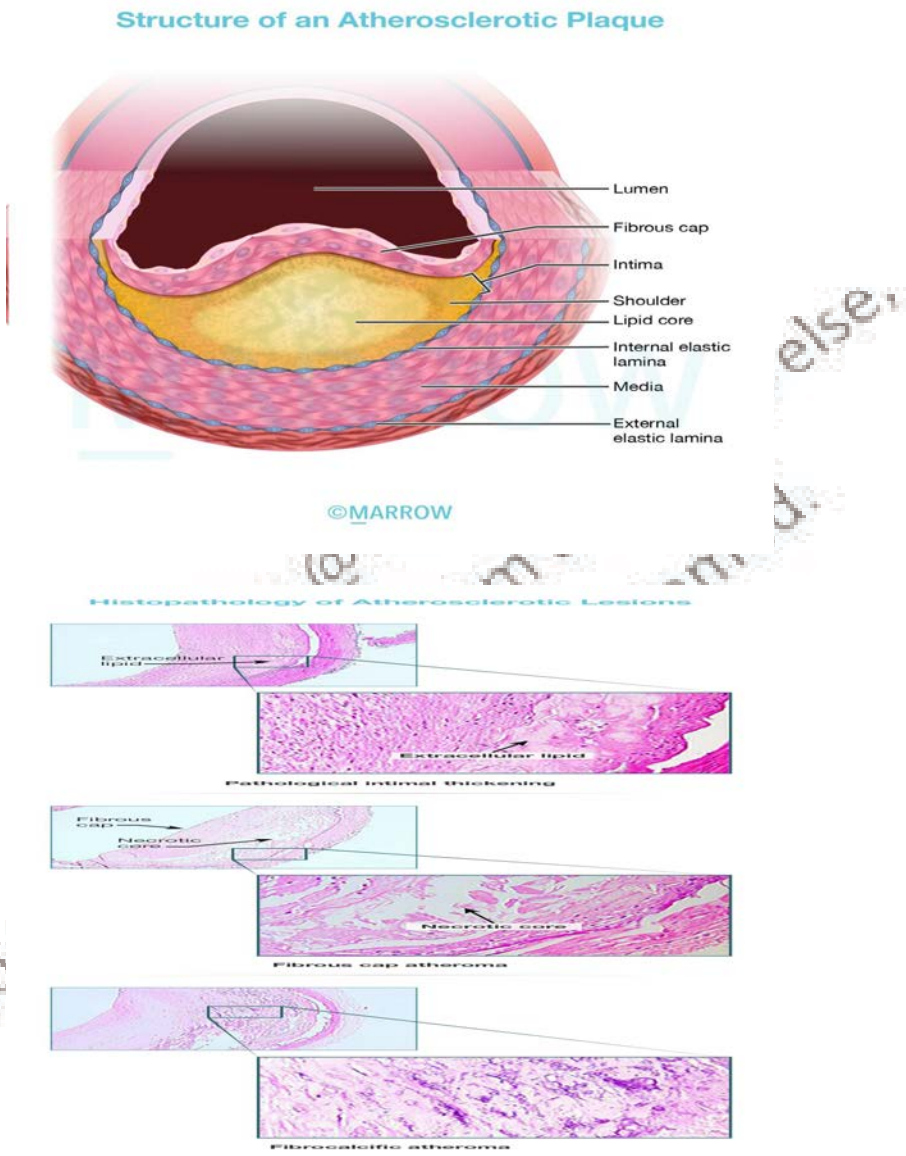
• Periphery - shows neovascularization/proliferation of small blood vessels.

The image below shows the structure of an atherosclerotic plaque.



Solution to Question 15:

A stable atherosclerotic plaque has abundant smooth muscle cells.

These cells synthesize collagen which stabilizes the plaque. Both these features contribute to a thick fibrous cap that prevents the easy rupture of a plaque.

Stable plaque	Vulnerable plaque
Dense collagen	Less collagen
Thick fibrous cap	Thin fibrous cap

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Stable plaque	Vulnerable plaque
Minimal inflammation	Increased inflammation
Less extracellular lipid	Abundant extracellular lipid
Abundant smooth muscle ce lls	Few smooth muscle cells
Few foam cells	Abundant foam cells

Solution to Question 16:

A 50-year-old patient suffering from dyslipidemia for the past 10 years is likely to have atherosclerosis. Dissection is associated with hypertension, not atherosclerosis.

An atherosclerotic plaque may undergo pathological changes such as:

• Thrombus formation - due to rupture, ulceration, erosion

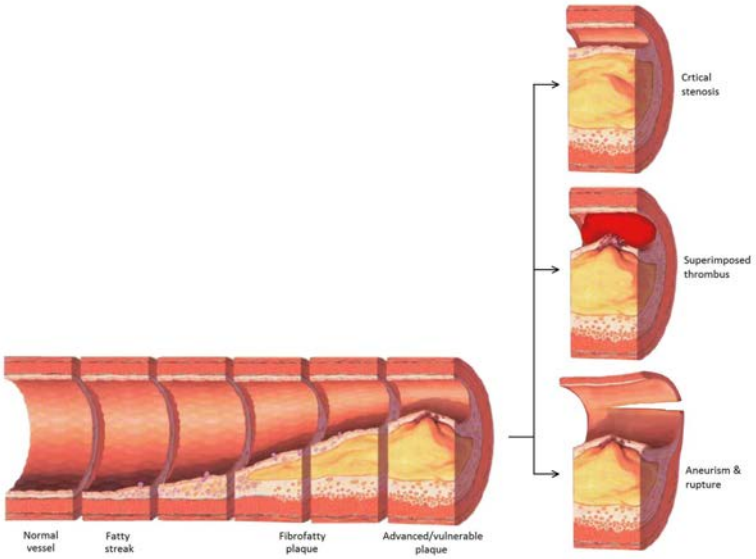
• Increase in plaque size - due to hemorrhage into the plaque

These consequences occlude the lumen of the vessel and impair the blood supply. Impaired blood supply may lead to claudication, ischemic heart disease, myocardial infarction, cerebral infarction, or even gangrene.

The thrombus may dislodge and cause an embolism. Atherosclerotic debris released due to plaque rupture may produce microemboli, known as atheroembolism.

Atherosclerotic plaques also cause ischemic atrophy of the underlying media. This causes weakness of the vessel wall leading to aneurysm formation.

The image below depicts the late complications of atherosclerosis.



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Solution to Question 17:

This symptomatic patient likely has >70% occlusion of his coronary arteries. This is known as critical stenosis.

It refers to the stage at which the occlusion is sufficiently severe to produce tissue ischemia. This leads to clinical manifestations of ischemia such as:

• Stable angina

• Bowel ischemia

• Intermittent claudication

Solution to Question 18:

Elevated plasminogen levels are not associated with stroke. Elevated levels of the following are predictors for stroke:

• C-reactive protein - also indicates risk for MI, PAD and used to monitor effectiveness of risk reduction measures like exercise, weight loss

• Homocysteine - also correlates with MI, PAD, venous thrombosis, and premature vascular disease

• Plasminogen activator inhibitor-1 - marker of hemostatic and/or fibrinolytic function and also predicts risk of MI

Solution to Question 19:

The above scenario is suggestive of an early failure of a small diameter venous graft (≤8 mm). The likely mechanism for graft failure within the 1st month is acute thrombosis.

Late vein graft failure (after months to years) is due to:

• Neointimal hyperplasia (1 month to 1 year)

• Atherosclerotic plaque (> 1 year)

• Aneurysm

Based on the diameter of the synthetic or autologous vascular graft, it can be:

• Large diameter graft (12-18mm) -

• Used in high-flow locations such as the aorta

• Small diameter graft (≤8 mm) -

• Includes saphenous vein or left internal mammary artery

• Used in coronary bypass surgeries

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Solution to Question 20:

Kruppel like factor-2 (KLF-2) is responsible for turning off the inflammatory gene transcription.

KLF-2 production is induced by laminar blood flow which is seen in normal endothelium. This transcription factor activates the atheroprotective genes and turns off inflammatory gene transcription. Statins up-regulate KLF-2 expression in endothelial cells, and this activity is associated with an anti-inflammatory phenotype.

Up-regulation of KLF-2 gene expression may be a novel strategy for the prevention and treatment of atherosclerosis.

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Aneurysm and Dissection

Question 1:

Pulsating hematoma is associated with which of the following conditions?

a) False aneurysm

b) Saccular aneurysm

c) Dissection

d) Fusiform aneurysm

Question 2:

A patient presented with a severe headache and transient loss of consciousness. On examination, neck rigidity was present and blood pressure was 160/110 mmHg. A CT brain was done as shown below. Which type of aneurysm could have been involved in causing this condition?

a) Saccular aneurysms

b) Fusiform aneurysms

c) False aneurysms

d) Dissecting aneurysms

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Question 3:

A patient who is a known case of hypertension was diagnosed with an abdominal aortic aneurysm. What is the likely underlying pathophysiology causing this condition?

a) Obliterative endarteritis of vasa vasorum

b) Increased matrix metalloproteinase expression

c) Decreased matrix metalloproteinase expression

d) Medial hypertrophy of vasa vasorum

Question 4:

Arterial aneurysms due to underlying cystic medial degeneration are seen in patients with which of the following conditions?

a) Marfan syndrome

b) Friedrich ataxia

c) Down syndrome

d) Kawasaki syndrome

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Question 5:

Which of the following causes aneurysm formation due to defective elastin?

a) Ehler-Danlos syndrome

b) Loeys-Dietz syndrome

c) Marfan syndrome

d) Scurvy

Question 6:

What is the most common site of syphilitic aneurysms?

a) Ascending aorta

b) Circle of Willis

c) Iliac arteries

d) Abdominal aorta

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Question 7:

A 55-year-old normotensive patient with dyslipidemia is undergoing a regular check-up. He is at an increased risk of developing all of the following except:

a) Ischemic heart disease

b) Stroke

c) Iliac artery aneurysm

d) Deep vein thrombosis

Question 8:

Which of the following myocardial infarcts cause aneurysm as a post-MI complication?

a) Subendocardial

b) Anterior transmural

c) Posterior transmural

d) Inferior wall

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Question 9:

A patient was diagnosed with an asymptomatic abdominal aortic aneurysm of a diameter of 3.6cm. On a follow-up visit 1 year later, the diameter was noted to be 3.8cm. What is the risk of rupture of the aneurysm in this patient at present?

a) Nil

b) 1%

c) 11%

d) 25%

Question 10:

A 55-year-old man presents with sudden onset chest pain radiating to the back between the scapulae. The CT of this patient is given below. What is the major risk factor for developing this condition?

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a) Hypertension

b) Atherosclerosis

c) Congenital weakness

d) Trauma

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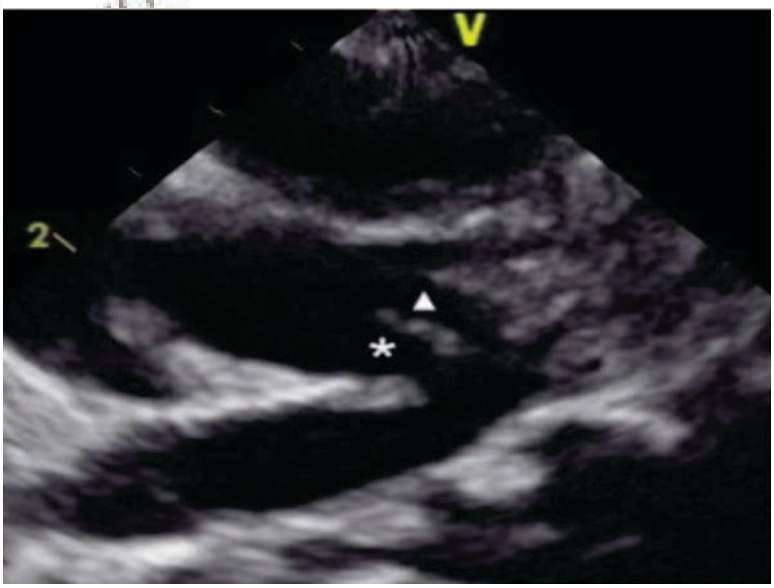
Question 11:

A 2D echocardiography of a patient who presented with chest pain showed the following appearance of the aorta on suprasternal parasagittal view. Which of the following is incorrect regarding this condition?



a) It has two intimal tears

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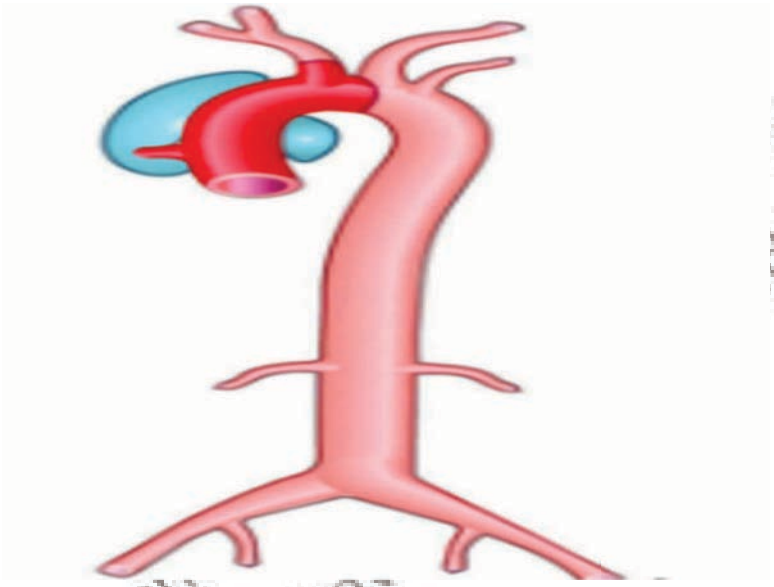
b) It is a severe type of dissection

c) It leads to chronic dissection

d) It has false vascular channel

Question 12:

How would you classify the following according to the DeBakey classification?



a) Type II

b) Type III

c) Type I

d) Type IIb

Answer Key

Question No.	Correct Option
1	a
2	a
3	b
4	a
5	b
6	a

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7	d
8	b
9	a
10	a
11	b
12	a

Detailed Explanations

Solution to Question 1:

Pulsating hematoma is associated with a false aneurysm.

An aneurysm is a localized abnormal dilation of a blood vessel or the heart. There are 2 types:

• True aneurysm

• Due to weakened and thinned, but intact arterial wall

• False aneurysm

• Due to a defect in the vascular wall

• Results in an extravascular hematoma that communicates with intravascular space

• Causes transmission of arterial pulsations to the hematoma (pulsating hematoma)

Dissection occurs when blood enters a defect in the arterial wall and tunnels/dissects between its layers.

The image below shows a pseudo/false aneurysm of the left ventricle.

False aneurysm	Dissection
Defect across all the layers of the vessel wall	Defect is usually an intimal t ear
Hematoma is extravascular (outside the vessel wall)	Hematoma is within the laye rs of the vessel wall
Hematoma is lined by extrav ascular connective tissue	Hematoma is lined by the lay ers of the vessel wall

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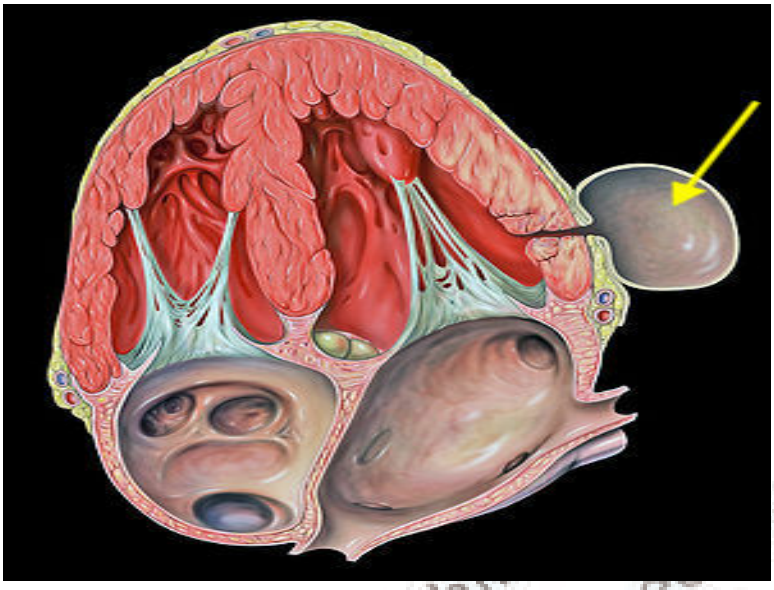

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Solution to Question 2:

The given clinical scenario is suggestive of subarachnoid hemorrhage (SAH) in a hypertensive patient. It may occur due to the rupture of Berry aneurysms, which are saccular aneurysms.

Aneurysms are classified as:

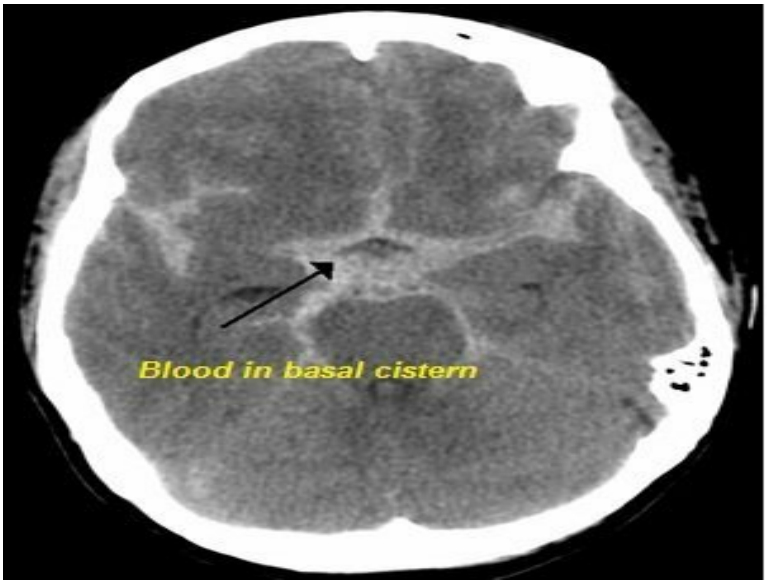
• Saccular aneurysms are spherical outpouchings involving only a portion of the vessel wall.

• Fusiform aneurysms are diffuse, circumferential dilations involving long vascular segments.

• Both saccular and fusiform aneurysms are true aneurysms because they have an intact vessel wall.

• Dissecting aneurysm is produced when a dissection leads to an aneurysm.

The image below shows the CT appearance of a SAH.



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Solution to Question 3:

The likely underlying pathophysiology causing this condition is increased metalloproteinase expression that degrades extracellular matrix and weakens the vessel wall.

The two most important causes of aortic aneurysms are atherosclerosis and hypertension. Aneurysms occuring as a consequence of atherosclerosis occurs most commonly in the abdominal aorta and common iliac arteries.

Option A: Obliterative end-arteritis of vasa-vasorum occurs in late stage syphilis and can contribute to aneurysms

Option D: Medial hypertrophy of vasa-vasorum occurs in hypertension, which is associated most commonly with ascending aortic aneurysms.

Solution to Question 4:

Cystic medial degeneration leading to aneurysms is a feature of Marfan syndrome.

Cystic medial degeneration refers to the degenerative changes in the media of the vessel wall that lead to aneurysm formation. These include:

• Loss of smooth muscle cells

• Loss of elastic fibers

• Inadequate extracellular matrix synthesis

• Increased production of glycosaminoglycan

It can be caused due to:

• Medial ischemia - atherosclerosis, hypertension

• Defective connective tissue - Marfan syndrome, scurvy

The image below (Movat stain) shows a cross-section of the aortic media from a patient with Marfan's syndrome showing elastin fragmentation (stained black) and loss of smooth muscle cells (cells stained red and nuclei stained violet).

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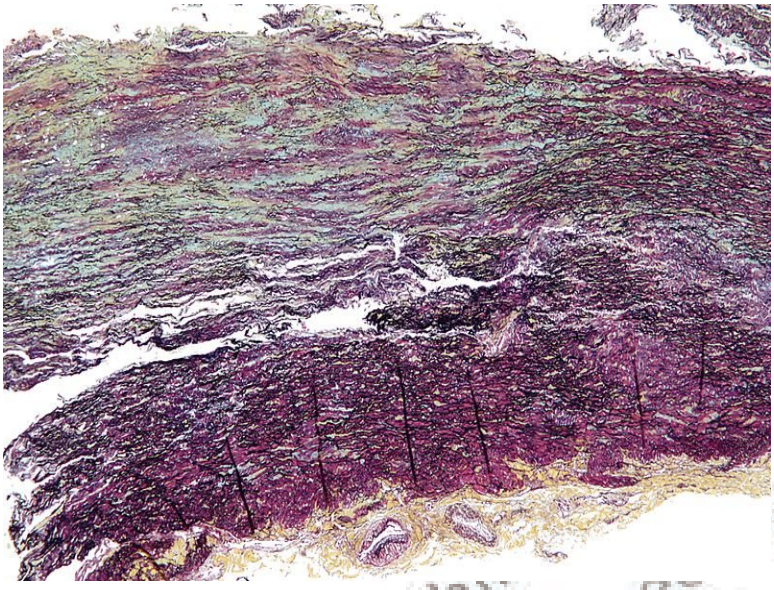

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Solution to Question 5:

Loeys–Dietz syndrome leads to aneurysm formation due to defective elastin (due to a defect in TGF-° signalling pathway).

Aneurysms are caused due to structural or functional defects in the connective tissue of the vascular wall. The following conditions cause intrinsic defects in connective tissue leading to aneurysm formation:

Syndrome	Defect in
Loeys–Dietzsyndrome	Synthesis ofelastinandcollagens IandIII
Ehlers–Danlossyndrome	Synthesis oftype III collagenin some subtypes
Marfansyndrome	Synthesis of the proteinfibrillincausing weakening of elastic tissue
Scurvy(vitamin C deficiency)	Collagencross-linking

Solution to Question 6:

Syphilitic aneurysms most commonly involves the ascending aorta.

Late-stage syphilis causes obliterative endarteritis of vasa vasorum of the aorta. This leads to ischemic injury of the aortic media resulting in aneurysmal dilation.

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Solution to Question 7:

Dyslipidemia is not a direct risk factor for deep vein thrombosis.

Dyslipidemia is a risk factor for atherosclerosis and its complications, including abdominal aortic aneurysms (AAA). AAA can also be associated with smaller aneurysms of the iliac arteries. Patients with AAA are also likely to have atherosclerotic lesions in other vascular beds that may lead to ischemic heart disease or stroke.

Solution to Question 8:

Anterior transmural infarcts are involved in causing aneurysm as a post-MI complication.

Posterior transmural infarcts are more likely to be complicated by conduction blocks, right ventricular involvement, or both.

Solution to Question 9:

Abdominal aortic aneurysms (AAA) of size ≤ 4 cm with slow growth have no risk of rupture.

The risk of rupture for AAA is directly related to the size of the aneurysm:

• ≤4 cm - nil

• 4–5 cm - 1% per year

• 5–6 cm - 11% per year

• >6 cm - 25% per year

Most aneurysms expand at a rate of 0.2 to 0.3 cm/year. The risk of rupture increases when there is a growth of > 0.5 cm/6 months as well as in active smokers.

Solution to Question 10:

The given clinical scenario with the CT finding of a second column of blood after an intimal tear is the classic presentation of an aortic dissection. The major risk factor for aortic dissection is hypertension.

Dissection occurs when blood enters into the media to form a blood-filled channel between the laminar planes of the media. It usually occurs due to a tear in the intima which allows blood in the lumen to flow into the media. It may also occur due to the rupture of vasa vasorum.

It occurs due to:

• Hypertension

• Connective tissue defects like Marfan syndrome

• Iatrogenic trauma during coronary catheterization or cardiopulmonary bypass

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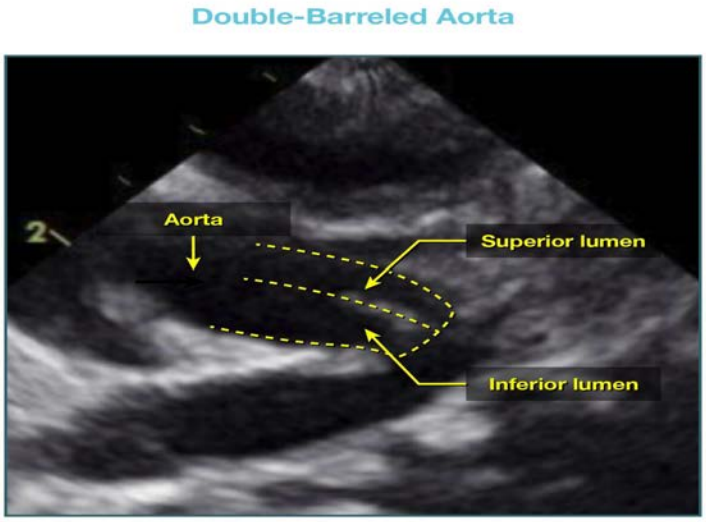
Solution to Question 11:

The above image shows a double-barreled aorta with a superior and inferior lumen. It is a less severe type of dissection because it is less likely to cause hemorrhage.



A double-barreled aorta is seen there are two intimal tears. Hence, the hematoma enters the media through an intimal tear but re-enters back into the lumen through another intimal tear present distally. As the blood enters the lumen back, this type of dissection does not progress, thus averting hemorrhage.

This creates a false vascular channel in the blood vessel which, over time, can be endothelialized to become chronic dissections.

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Solution to Question 12:

The above image shows proximal dissection of only the ascending aorta. This is classified as type II as per DeBakey's classification.

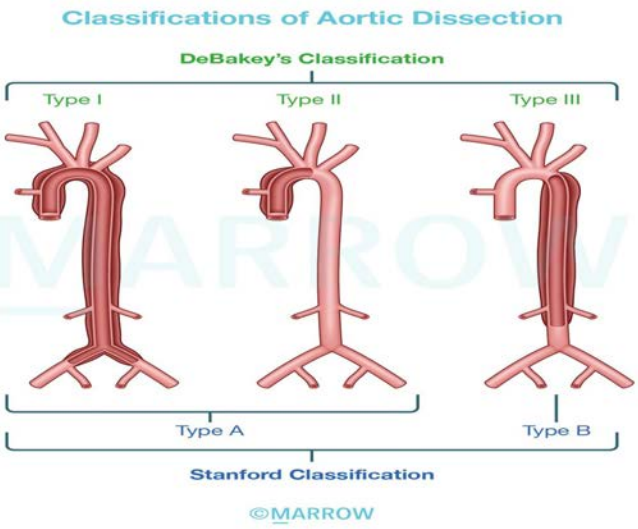
Classification of aortic dissection:

• Stanford Type A - proximal lesions. These are more common and dangerous. It may involve:

• Both the ascending and descending aorta - DeBakey type I

• Only the ascending aorta - DeBakey type II

• Stanford Type B or DeBakey type III - distal lesions not involving the ascending part and usually beginning distal to the subclavian artery



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Vasculitis

Question 1:

Which of the following is a large vessel vasculitis?

a) Giant cell arteritis

b) Behcet's syndrome

c) Cogan's syndrome

d) Cryoglobulinemia

Question 2:

All of the following vasculitides involves veins except?

a) Thrombangiitis obliterans

b) Behcet disease

c) Leucocytoclastic vasculitis

d) Giant cell arteritis

Question 3:

A 60-year-old man presents with sudden onset blindness. He gives a history of frequent headaches along the sides of his scalp. What is the most probable diagnosis?

a) Thromboangiitis obliterans

b) Granulomatosis with polyangiitis

c) Takayasu arteritis

d) Giant cell arteritis

Question 4:

An elderly patient presented with temporal headache and jaw claudication. She was diagnosed to be a case of Giant cell arteritis. Which of the following statements about giant cell arteritis is incorrect?

a) Inflammatory lesions are focally distributed

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b) A negative biopsy excludes the diagnosis

c) The classic lesions are medial granulomas

d) Fragmentation is seen in internal elastic lamina

Question 5:

A 30-year-old lady presents with weakness of the left upper limb. On examination, the blood pressure recorded on the left upper limb was found to be lower than that of the right upper limb. Her aortic arch angiogram showed narrowing of the arch of the aorta and subclavian artery. What is the likely diagnosis?

a) Giant-cell arteritis

b) Takayasu arteritis

c) Thrombangiitis obliterans

d) Behcet's Disease

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Question 6:

A young girl with bilaterally unequal pulses is diagnosed with Takayasu Arteritis. Which of the following is the most commonly involved site in Takayasu arteritis?

a) Pulmonary artery

b) Coronary arteries

c) Abdominal aorta

d) Subclavian artery

Question 7:

A young male presents to the emergency room with severe abdominal pain. The small bowel is found to have a small infarcted area which is surgically removed. Histopathological examination of the biopsy specimen is given below. Which of the following is the most likely cause of the small bowel infarction?

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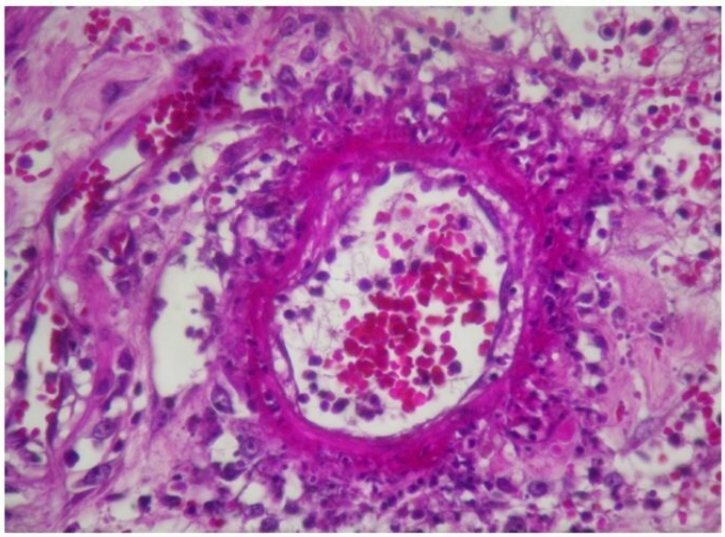

a) Hyperplastic arteriosclerosis

b) Cystic medial degeneration

c) Mönckeberg's arteriosclerosis

d) Polyarteritis nodosa

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Question 8:

Which of the following is characteristically spared in polyarteritis nodosa?

a) Coronary circulation

b) Gastro-intestinal circulation

c) Renal circulation

d) Pulmonary circulation

Question 9:

A 3-year-old child was brought to the hospital with complaints of fever, rash and swelling of her hands and feet since past 5 days. There is desquamative skin rash, oedema of hands and feet, erythema of palms and soles, oral erythema, and cervical lymphadenopathy. What is the likely condition?

a) Kawasaki disease

b) Measles

c) Scarlet fever

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d) Henoch Schonlein Purpura

Question 10:

Which of the following antibodies is associated with vasculitis seen in patients with Kawasaki disease?

a) Immune complex deposition

b) Antineutrophil cytoplasmic antibodies

c) Antiendothelial cell antibodies

d) Autoreactive T cells

Question 11:

Which of the following is known as mucocutaneous lymph node syndrome?

a) Behcet disease

b) Kawasaki disease

c) Espundia

d) Tubercular lymphadenitis

Question 12:

A 27-yr-old woman, presented to OPD with complaints of joint pain and photosensitivity. On examination, you see a butterfly rash on the face and petechial hemorrhages on the lower limbs. On serology ANA, turns out to be positive. Which of the following is the most likely cause of vasculitis in this patient?

a) Autoreactive T cells

b) Antiendothelial cell antibodies

c) Antineutrophil cytoplasmic antibodies

d) Immune complex deposition

Question 13:

A 43 year-old-male patient came to the clinic with complaints of occasional hematuria and recurrent upper respiratory tract infections. Examination revealed tiny petechial

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hemorrhages over his lower limbs. The patient tests positive for the anti-proteinase-3 antibody. Which of the following is true about this major antibody?

a) It is also known as p-ANCA

b) It is induced by propylthiouracil

c) It is triggered by infections

d) It shows perinuclear staining on immunofluorescence

Question 14:

Which of the following is a pauci-immune rapidly progressive glomerulonephritis?

a) Lupus nephritis

b) Microscopic polyangiitis

c) IgA nephropathy

d) Goodpasture syndrome

Question 15:

Which of the following statements about microscopic polyangiitis is not true?

a) It affects capillaries, small arterioles, and venules

b) MPO-ANCA positivity is seen

c) It is also known as leukocytoclastic vasculitis

d) Lesions of different stages of activity coexist in the same vessel

Question 16:

A 21-year-old boy, who is a known case of asthma, presents with wheezing and rhinitis. Laboratory results show peripheral eosinophilia and antibodies against neutrophil myeloperoxidase. What is the most likely diagnosis?

a) Churg-Strauss syndrome

b) Granulotomatosis with polyangiitis

c) Good pasteur syndrome

d) Wegener granulomatosis

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Question 17:

A 45-year-old man presents with hematuria, intermittent hemoptysis and chronic sinusitis. His chest radiograph shows multiple opacities and cavities. Renal biopsy suggests focal necrotizing glomerulonephritis. Which of the following is not seen in this condition?

a) Necrotizing granulomas of the upper respiratory tract

b) Small to medium-sized vessel vasculitis

c) Associated predominantly with MPO- ANCA

d) Cresentic glomerulonephritis

Question 18:

A 15-year old boy comes to the clinic complaining about recurrent painful oral ulcers. He also experiences repeated episodes of eye redness and pain which subside with medication. On examination, ulcers are seen on his genitals. Which of the following features would you not expect to see in this patient?

a) Dural sinus thrombosis

b) Pulmonary aneurysms

c) Nailfold capillary abnormalities

d) Uveitis

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Question 19:

A 5-year-old child presents with colicky abdominal pain and purpuric skin lesions on the extensor surfaces of the arms and legs. Urine analysis reveals hematuria and mild proteinuria. The most probable diagnosis is:

a) Henoch-Schönlein Purpura

b) Wegener's granulomatosis

c) Kawasaki's disease

d) Good pasteur syndrome

Question 20:

Which of the following structures are involved in Buerger's disease?

a) Arteries only

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b) Veins only

c) Arteries and veins

d) Arteries, nerves and veins

Question 21:

A 32-year-old male smoker presents with intermittent claudication and gangrene of the lower extremities. Biopsy of the blood vessels supplying this area shows acute and chronic inflammation, with luminal thrombosis containing small neutrophilic microabscesses. Granulomatous inflammation appears to extend into the contiguous veins and nerves. What is the most likely diagnosis?

a) Thrombangiitis obliterans

b) Churg-Strauss syndrome

c) Wegener's granulomatosis

d) Berger disease

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Question 22:

Which of the following histologic findings would be most suggestive of Buerger's disease in a patient?

a) Mononuclear infiltrates with perivascular cuffing of the vasavasorum

b) Fragmentation of neutrophils

c) Thrombosis with microabscesses

d) Fibrinoid necrosis

Answer Key

Question No.	Correct Option
1	a
2	d
3	d
4	b
5	b

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6	d
7	d
8	d
9	a
10	c
11	b
12	d
13	c
14	b
15	d
16	a
17	c
18	c
19	a
20	d
21	a
22	c

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Detailed Explanations

Solution to Question 1:

Giant cell arteritis is a large vessel vasculitis.

Solution to Question 2:

Giant cell arteritis does not involve the veins.

Vasculitides affecting the veins are as follows:

- Leukocytoclastic vasculitis
- Behcet disease
- Buerger disease (Thrombangiitis obliterans)

Solution to Question 3:

The given clinical scenario is suggestive of giant cell arteritis.

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Giant cell / temporal arteritis is a chronic inflammatory disorder of large to small-sized arteries that especially affects the temporal arteries. It is seen in people over 50 years of age. It usually presents with facial pain or headache along the course of the superficial temporal artery.

It can also affect:

• Ophthalmic arteries- leading to sudden onset diplopia or blindness

• Aorta- leading to giant-cell aortitis

• Vertebral arteries

A biopsy is needed to confirm the diagnosis.

Giant cell arteritis needs to be promptly diagnosed and treated with steroids to prevent permanent blindness.

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Solution to Question 4:

A negative biopsy cannot exclude the diagnosis of giant cell arteritis. It is because the lesions are focally distributed. A biopsy sample may be taken from the normal part of the artery leading to a false-negative report. An adequate biopsy requires at least a 1-cm segment.

Biopsy findings:

• Giant cell arteritis is primarily medial granulomatous inflammation.

• These lesions involve the internal elastic lamina leading to elastic lamina fragmentation.

• There is intimal thickening that reduces the luminal diameter.

Granulomas with multinucleated giant cells, infiltrate of T cells (CD4+ >CD8+), and macrophages.

Note : According to the 21st edition of Harrison's Medicine, as involvement of the vessel may be segmental, getting a biopsy segment of 3–5 cm together with serial sectioning of biopsy specimens would help to increase a positive yield. And Robbin's 10th edition mentions that an adequate biopsy requires at least a 1-cm segment.

Image: Giant-cell arteritis with intimal thickening and internal elastic lamina fragmentation

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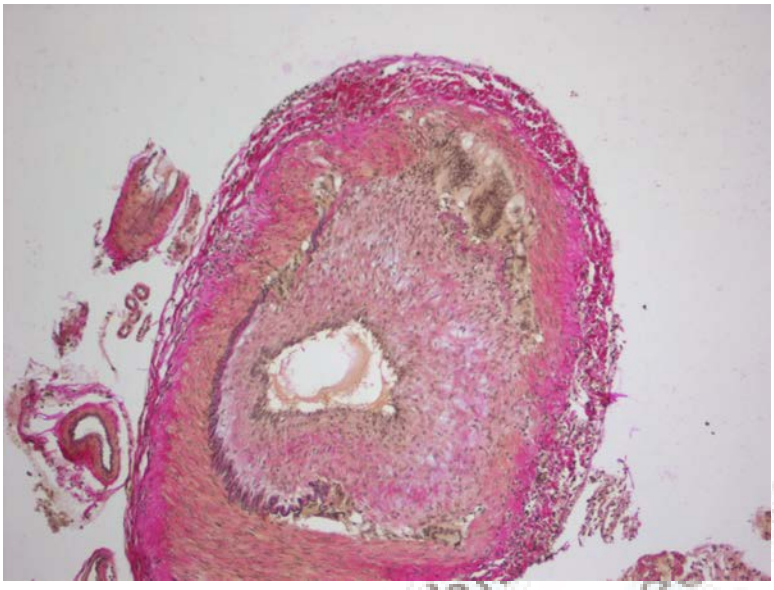

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Solution to Question 5:

The given clinical scenario and radiological findings are suggestive of Takayasu arteritis.

Takayasu's arteritis is a granulomatous vasculitis affecting medium and large-sized arteries, in this case, the aortic arch and its branches. Clinical manifestations include vision disturbances and profound weakening of the pulses, especially in the upper extremities.

Histopathology:

• Irregular thickening of the vessel wall is seen with associated intimal hyperplasia.

• Characteristic granulomatous inflammation, with the presence of giant cells and patchy medial necrosis.

• Disease progression is associated with collagenous scarring and chronic inflammatory infiltrates across all layers of the vessel wall.

Other options-

Option A: Giant cell arteritis (GCA), also known as temporal arteritis, is an inflammation of medium and large-sized vessels. It is more common in women and people aged >50 years.

The clinical features include headache associated with scalp pain and jaw claudication, fever, fatigue, malaise, and weight loss. Half of the patients have temporal artery abnormalities such as enlargement, tenderness, nodular swelling, and loss of pulse of the temporal artery, either unilateral or bilateral. Gentle pressure on the scalp may elicit focal or generalized tenderness.

Though the arch of the aorta may also be involved in giant cell arteritis (known as giant cell aortitis), it is seen in people more than 50 years of age. Whereas, Takayasu arteritis is seen more commonly in adolescents and young women.

Option C: Thromboangitis obliterans, also known as Buerger's disease, is an inflammatory occlusive vascular disorder involving medium- and small-sized vessels in the distal extremities. It is most frequently seen in male smokers less than 40 years of age.

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Option D: Behcet's disease is a neutrophilic vasculitis affecting small- to medium-sized vessels that classically presents as a clinical triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis. There can also be gastrointestinal and pulmonary manifestations, with disease mortality related to severe neurologic involvement or rupture of vascular aneurysms.

Solution to Question 6:

The most commonly involved blood vessel in Takayasu arteritis is sublclavian artery.

Takayasu arteritis is an inflammatory and stenotic disease of medium and large-sized arteries characterized by a strong predilection for the aortic arch and its branches. It is also known as aortic arch syndrome.

The order of arteries affected in Takayasu arteritis is subclavian artery > common carotid artery > abdominal aorta > renal artery > aortic arch = vertebral > coeliac axis > iliac > pulmonary > coronary artery.

Takayasu arteritis causes irregular thickening of the vessel wall with intimal hyperplasia leading to narrowing of the lumen and organ ischemia.

It may have various clinical presentations depending on the vessel involved:

• Arch of aorta and its branches:

• Subclavian artery- leads to weak pulses in the upper extremities. Hence it is also known as pulseless disease

• Carotid arteries- leads to weak pulses, blindness, neurological deficits

• Distal aorta- leads to claudication of the legs

• Pulmonary artery- leads to pulmonary hypertension

• Coronary arteries- leads to myocardial infarction

• Renal arteries- leads to systemic hypertension

Solution to Question 7:

The given clinical scenario and the histopathological findings are suggestive of polyarteritis nodosa (PAN).

PAN affects small or medium-sized muscular arteries. It typically affects young adults. The patient may present with rapidly accelerating hypertension due to renal artery involvement (most common) or abdominal pain and bloody stools caused by involvement of gastrointestinal vessels.

Option A: Hyperplastic arteriosclerosis is a vascular pathology seen in severe hypertension.

Option B: Cystic medial degeneration leads to dissecting aortic aneurysm.

Option C: Mönckeberg's arteriosclerosis does not cause infarction.

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Solution to Question 8:

Polyarteritis nodosa (PAN) characteristically spares the pulmonary circulation.

PAN is a systemic vasculitis of small or medium-sized muscular arteries. It typically involves the renal (most commonly involved) and visceral vessels. It has no association with ANCA, but about 30% of patients have chronic hepatitis-B.

Solution to Question 9:

The given clinical scenario is suggestive of Kawasaki disease or mucocutaneous lymph node syndrome.

Kawasaki disease is an acute febrile illness associated with arteritis of medium to large-sized vessels. It is commonly seen in infants and children <4 years of age.

Clinical features include:

• Fever

• Conjunctival and oral erythema

• Blistering, edema of hands and feet

• Erythema of palms and soles

• Desquamative rash

• Cervical lymphadenopathy

The disease is usually self-limiting. In some cases, the disease may involve coronary artery leading to thrombosis and acute myocardial infarction. Intravenous immunoglobulin and aspirin may be given to reduce the risk of coronary artery disease.

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Solution to Question 10:

Antibodies to endothelial cells are associated with vasculitis in Kawasaki disease.

Option A: Immune complex deposition is characteristic of vasculitis due to systemic immunologic disorders such as SLE.

Option B: ANCA-associated vasculitis is seen in microscopic polyangiitis, Churg–Strauss syndrome, and granulomatosis with polyangiitis.

Option D: Autoreactive T cells are seen in giant cell arteritis.

Reports have been described in children with a multisystem inflammatory condition (MIS-C) linked to COVID-19 infection with some features similar to Kawasaki disease and toxic shock syndrome. Although shock is rarely associated with Kawasaki disease, many children with the inflammatory syndrome related to COVID show signs of shock.

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Solution to Question 11:

Kawasaki disease is also known as mucocutaneous lymph node syndrome.

Kawasaki disease is an acute febrile illness occurring in children aged 4 years or younger. It is usually self- limiting. This vasculitis affects large to medium-sized vessels and even small vessels.

It is also known as mucocutaneous lymph node syndrome because it can present with non-purulent conjunctivitis, oral erythema, edema of the hands and feet, desquamative rash, and cervical lymph node enlargement.

It has a predilection for coronary artery involvement and is the leading cause of acquired heart disease in children. Untreated patients may develop coronary artery ectasia or aneurysms, leading to rupture or thrombosis, myocardial infarction, and sudden death.

Espundia is the muco-cutaneous variant of Leishmaniasis

Solution to Question 12:

The given clinical scenario is suggestive of systemic lupus erythematosus. The vasculitis occurring in a patient with systemic lupus erythematosus is due to immune complex deposition.

Vasculitis is the inflammation of the vessel wall. The various mechanisms that cause vasculitis are:

• Immune-mediated inflammation- Vasculitis caused by immune-mediated inflammation may occur due to the following factors:

• Immune complex deposition: Seen in systemic immunological disorders like systemic lupus erythematosus (SLE)

• Antineutrophil cytoplasmic antibodies (ANCA): Seen in Wegener's granulomatosis, Churg–Strauss disease, etc

• Anti endothelial cell antibodies: Implicated in Kawasaki disease

• Autoreactive T cells

• Infectious pathogens- by direct invasion, generating immune complexes or triggering cross-reactivity.

• Physical or chemical injury- from irradiation, trauma, toxins, etc.

Solution to Question 13:

Anti-proteinase-3/PR3-ANCA / c-ANCA is triggered by certain infections as proteinase 3 shares similarities with many microbial peptides. This is the major antibody responsible for Granulomatosis with Polyangiitis (GPA).

Antineutrophil cytoplasmic antibodies (ANCA) are a heterogeneous group of autoantibodies directed against the constituents of neutrophils or monocytes. Many patients with vasculitis have circulating antibodies that react with neutrophil cytoplasmic antigens.

The two most important ANCAs related to vasculitis are:

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• Anti-proteinase-3/PR3-ANCA/c-ANCA - Directed against PR3 which is a neutrophil azurophilic granule constituent.

• Anti-myeloperoxidase/MPO-ANCA/p-ANCA - Directed against MPO which is a lysosomal granule constituent involved in oxygen free-radical generation. MPO-ANCAs are induced by several therapeutic agents, particularly propylthiouracil.

Solution to Question 14:

Type III or pauci-immune-type of rapidly progressive glomerulonephritis (RPGN) may be a component of systemic vasculitis such as Wegener granulomatosis or microscopic polyangiitis.

Solution to Question 15:

All lesions of microscopic polyangiitis tend to be of the same age in any given patient, unlike polyarteritis nodosa where all stages of activity from early to late may coexist in different vessels or even within the same vessel.

Microscopic polyangiitis is a necrotizing vasculitis that affects capillaries, small arterioles, and venules. It is associated with MPO-ANCA. It is also called leukocytoclastic vasculitis because of apoptotic neutrophils.

It may involve the skin, mucous membranes, lungs, brain, heart, gastrointestinal tract, kidneys, and muscle. Therefore, the patient may present with hemoptysis, hematuria, proteinuria, bowel pain or bleeding, muscle pain or weakness, and palpable cutaneous purpura. Necrotizing glomerulonephritis (90% of patients) and pulmonary capillaritis are particularly common.

Solution to Question 16:

The given clinical scenario and the lab findings are suggestive of Churg–Strauss syndrome.

Churg-Strauss Syndrome / Allergic granulomatosis and angiitis is a small-vessel necrotizing vasculitis classically associated with:

• asthma

• allergic rhinitis

• asymmetric mono neuritis multiplex

• lung infiltrates

• peripheral hypereosinophilia

• extravascular necrotizing granulomata.

It is a multisystem disease with cutaneous involvement (palpable purpura), gastrointestinal tract bleeding, and renal disease. Eosinophilic infiltrates may also be seen in the myocardium giving rise to cardiomyopathy.

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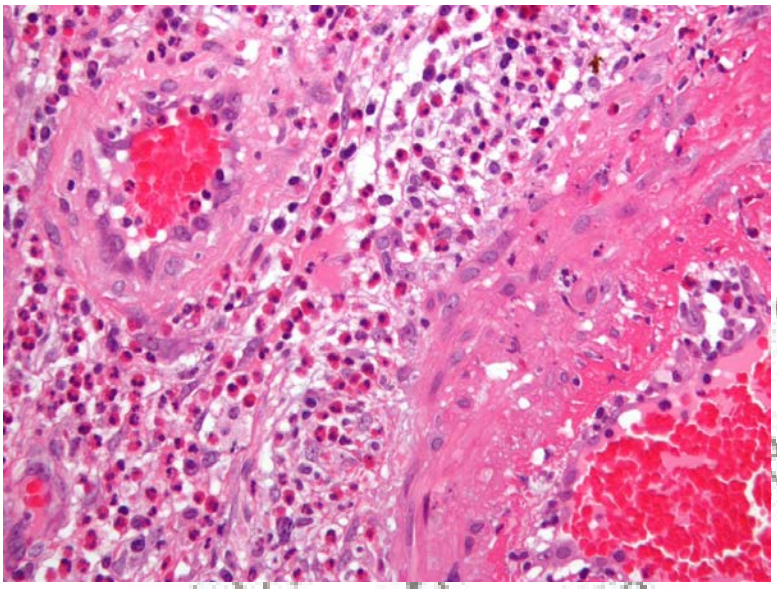
p- ANCA (MPO-ANCA) is positive in about 50% of cases. Histological features are similar to those observed in polyarteritis nodosa (PAN) or microscopic polyangiitis but characteristically accompanied by granulomas and eosinophils.

Eosinophilic vasculitis seen in Churg-Strauss syndrome:



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Solution to Question 17:

The given clinical scenario suggests a diagnosis of Wegener's granulomatosis. It is associated with PR3- ANCA (and not MPO- ANCA) in about 95% of cases.

Granulomatosis with Polyangiitis/Wegener granulomatosis is a necrotizing vasculitis characterized by a triad of necrotizing inflammation:

• Necrotizing granulomas of the upper respiratory tract or the lung

• Necrotizing or granulomatous vasculitis affecting small to medium-sized vessels, most prominently in the lungs

• Focal necrotizing crescentic glomerulonephritis

Males are affected more often than females. The most common clinical features include persistent pneumonitis with bilateral nodular and cavitary infiltrates, chronic sinusitis, mucosal ulcerations of the nasopharynx, and evidence of renal disease.

Image: Chest radiograph showing pulmonary granulomatosis

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Solution to Question 18:

The given clinical scenario is suggestive of Behçet disease. Nail fold capillary abnormalities are typically seen in systemic sclerosis.

Behcet disease is a neutrophilic vasculitis affecting small- to medium-sized vessels that classically presents as a clinical triad of recurrent oral aphthous ulcers, genital ulcers, and uveitis. Other skin findings include erythema nodosa (red tender nodules on legs) and positive pathergy test (pustular reaction 24-48 hrs after sterile needle puncture or normal saline injection).

There can also be gastrointestinal and pulmonary manifestations, with disease mortality related to severe neurologic involvement or rupture of vascular aneurysms. Dural sinus thrombosis is the most common CNS manifestation in children. Pulmonary aneurysms are the most severe feature of pediatric BD.

It is associated with HLA subtype B51. T helper 17 (Th17) cells play an important contribution in the recruitment of neutrophils, which will later infiltrate into the vessel wall.

Solution to Question 19:

The clinical features and the investigations are suggestive of Henoch-Schonlein purpura.

Henoch-Schönlein purpura is a systemic immune disorder, commonly seen in the age group of 3-8 years. The patient may present with the following clinical features:

• Skin lesions- characteristically involve the extensor surfaces of arms and legs, and also the buttocks

• Abdominal manifestations- include pain, vomiting, and intestinal bleeding.

• Renal manifestations- include gross or microscopic hematuria, nephritic or nephrotic syndrome. Renal manifestations are more severe in the adults

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It is strongly associated with atopy in a few patients, and the onset often follows an upper respiratory infection. IgA is deposited in the glomerular mesangium in a distribution similar to that of IgA nephropathy.

Solution to Question 20:

Arteries, veins and nerves can be involved in thrombangiitis obliterans (Buerger's disease). It is a vasculitis of small and medium-sized arteries and secondarily extends into contiguous veins and nerves. With time, all three structures can be encased in fibrous tissue.

Solution to Question 21:

The most likely diagnosis is thromboangiitis obliterans / Buerger disease.

It is the segmental, thrombosing, acute and chronic inflammation of medium-sized and small arteries. It principally involves the tibial and radial arteries.

It is seen in heavy cigarette smokers, usually before the age of 35 years. HLA-A-9 and HLA-B-5 associated with a high risk of TAO.

The patients present with intermittent claudication, chronic ulcerations of the extremity, and later progress to frank gangrene. The microscopy findings include luminal thrombosis (thrombangiitis), that is, thrombus containing microabscesses that occlude the lumen (obliterans). They contain small microabscesses composed of neutrophils.

Berger disease refers to IgA nephropathy. It is seen within 3-5 days of sore throat. It is associated with purpuric rash in the lower limbs.

Solution to Question 22:

Luminal thrombosis containing small microabscesses composed of neutrophils is seen in thromboangiitis obliterans or Buerger disease.

Option A: Adventitial mononuclear infiltrates with perivascular cuffing of the vasa vasorum has been described in Takayasu arteritis.

Option B: Fragmented neutrophils undergoing apoptosis infiltrating blood vessels termed leukocytoclastic vasculitis are seen in small vessel vasculitis.

Option D: Fibrinoid necrosis is seen in immune reactions involving blood vessels seen in immunologically mediated vasculitis syndromes.

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Vascular Tumors

Question 1:

Which of the following best describes angiosarcoma?

a) Congenital malformation

b) Reactive proliferation

c) Epithelial tumor

d) Malignant neoplasm

Question 2:

Which of the following vascular tumors are not derived from endothelial cells?

a) Hemangioma

b) Hemangiopericytoma

c) Lymphangioma

d) Angiosarcoma

Question 3:

Which of the following is a true neoplasm?

a) Nevus flammeus

b) Port wine stain

c) Cystic hygroma

d) Bacillary angiomatosis

Question 4:

Which of the following is the most common form of vascular ectasia?

a) Nevus flammeus

b) Spider telangiectasia

c) Port-wine stain

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d) Hereditary hemorrhagic telangiectasia

Question 5:

A young girl presents with recurrent seizures, mental retardation and a skin lesion as shown in the image below. Which of the following is the most likely diagnosis?

a) Sturge Weber syndrome

b) Von Hippel Lindau syndrome

c) Osler Weber Rendu syndrome

d) Ataxia telengiectasia

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Question 6:

Which of the following statements about hemangioma is true?

a) Capillary hemangioma is the most common type of hemangioma

b) Cavernous hemangioma usually regresses completely by 7 years of age

c) Juvenile hemangioma is infiltrative and does not regress spontaneously

d) Pyogenic granuloma is most commonly caused by Staphylococcus aureus

Question 7:

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A child is brought by her parents to the OPD with complaints of a swelling on the right thigh. Further evaluation led to the diagnosis of capillary hemangioma in this patient. What is the most appropriate next best step?

a) Explain about the risk of malignant transformation of the tumor

b) Test the child for retrovirus infection

c) Enquire about history of exposure to polyvinyl chloride

d) Assure the parents about spontaneous regression of the tumor

Question 8:

A patient with bilateral pheochromocytoma is diagnosed with von Hippel-Lindau disease. This condition is associated with which of the following?

a) Capillary hemangioma

b) Cavernous hemangioma

c) Strawberry hemangioma

d) Hemangioendothelioma

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Question 9:

Which of the following vascular lesions are commonly seen in patients with Turner syndrome?

a) Pyogenic granuloma

b) Capillary lymphangioma

c) Capillary hemangioma

d) Cavernous lymphangioma

Question 10:

A middle aged male patient presents with a swelling on his left thumb as shown in the image below. Which of the following statements about this swelling is false?

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a) It is caused by a bacterial infection

b) Lesions bleed easily

c) It is a benign tumor

d) It is a type of capillary hemangioma

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Question 11:

Granuloma gravidarum is a type of _____.

a) Juvenile hemangioma

b) Cavernous hemangioma

c) Pyogenic granuloma

d) Capillary hemangioma

Question 12:

Which of the following vascular tumors arising from arteriovenous structures is involved in thermoregulation?

a) Hemangioendothelioma

b) Capillary hemangioma

c) Hemangiopericytoma

d) Glomus tumour

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Question 13:

What is the most common site of glomus tumors?

a) Retroperitoneum

b) Oral cavity

c) Middle ear cavity

d) Distal portion of digits

Question 14:

A 46-year-old HIV-positive female patient presents with fever, weight loss, and cutaneous lesions as shown in the image. Microscopic examination reveals capillary proliferation and neutrophilic infiltration. Which of the following is the causative organism?

a) Bartonella henselae

b) Human Herpes Virus - 6

c) Bartonella bacilliformis

d) Human Herpes Virus - 8

Question 15:

A 50-year-old HIV seropositive male presents with skin lesions over the distal portion of the lower limbs as shown in the image below. Biopsy shows a lesion composed of proliferating spindle cells along with small vessels and spaces containing red cells. Which of the following

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is the most likely diagnosis?

a) Cavernous hemangioma

b) Kaposi sarcoma

c) Bacillary angiomatosis

d) Angiosarcoma

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Question 16:

Which type of Kaposi sarcoma is most commonly seen in patients with HIV infection?

a) Classical

b) Endemic

c) Epidemic

d) African

Question 17:

A patient with vague upper abdominal pain is diagnosed with hemangioendothelioma of the liver. What is this classified as?

a) Benign neoplasm

b) Intermediate-grade neoplasm

c) Malignant neoplasm

d) Reactive hyperplasia

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Question 18:

An elderly male working in a factory manufacturing PVC pipes is at risk of developing which of the following cancers?

a) Hemangioendothelioma

b) Angiosarcoma

c) Cavernous hemangioma

d) Hemangiopericytoma

Question 19:

Which of the following is the most common causative agent for lymphangitis?

a) Filaria

b) Streptococci

c) Staphylococci

d) Pseudomonas

Question 20:

Which of the following best describes Milroy disease?

a) Simple congenital primary lymphedema

b) Heredofamilial congenital primary lymphedema

c) Secondary lymphoedema

d) Obstructive lymphedema

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Answer Key

Question No.	Correct Option
1	d
2	b
3	c

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4	a
5	a
6	a
7	d
8	b
9	d
10	a
11	c
12	d
13	d
14	a
15	b
16	c
17	b
18	b
19	b
20	b

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Detailed Explanations

Solution to Question 1:

Angiosarcoma is a malignant neoplasm. It is a vascular tumor arising from the endothelial cells.

Benign vascular tumors are characterized by well-formed vascular channels lined by normal endothelial cells. Whereas, malignant vascular tumors are characterized by poorly formed vessels with cellular atypia.

Solution to Question 2:

Hemangiopericytoma is not derived from endothelial cells. It is a malignant vascular tumor derived from supporting cells of the blood vessels.

Vascular tumors derived from endothelial cells are:

• Hemangioma

• Lymphangioma

• Angiosarcoma

The endothelial origin of vascular neoplasms can be confirmed using endothelial cell-specific markers such as CD31 or von Willebrand factor.

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Solution to Question 3:

Cystic hygroma / cavernous lymphangioma is a true neoplasm. It is a benign vascular tumor arising from endothelial cells.

Options A and B: Nevus flammeus and port wine stain are vascular ectasias which are not true neoplasms. They are congenital or acquired malformations.

Option D: Bacillary angiomatosis is non-neoplastic reactive vascular proliferation in response to opportunistic bacilli.

Solution to Question 4:

The most common form of vascular ectasia is nevus flammeus.

Vascular ectasias are the conditions involving the dilatation of blood vessels. They can be congenital or acquired malformations or hamartomas. Telangiectasia is the permanent dilation of small blood vessels. They lead to red lesions in the skin or mucous membranes.

Various types of vascular ectasias are as follows:

• Nevus flammeus (birthmark): Pink/purple flat lesions on the head or neck. They regress spontaneously.

Image showing nevus flammeus in a newborn:

• Port-wine stain: A special form of nevus flammeus. It thickens the skin surface. It grows during childhood and does not fade with time.

Image showing port-wine stain in a child:

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• Spider telangiectasias: They are pulsatile and blanch with pressure. These commonly occur on the face, neck, or upper chest. They are associated with hyperestrogenic states, such as pregnancy or liver cirrhosis.

• Hereditary hemorrhagic telangiectasia (Osler–Weber–Rendu disease) is caused by mutations in genes related to the TGF-° signaling pathway. It is characterized by dilated blood vessels with thin walls that bleed easily. There can be bleeding from the mucous membranes of the nose (epistaxis), tongue, mouth, eyes, and the gastrointestinal tract.

The image below shows multiple flat non pulsating telengiectasias in a patient with Osler-Weber-Rendu disease:

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Solution to Question 5:

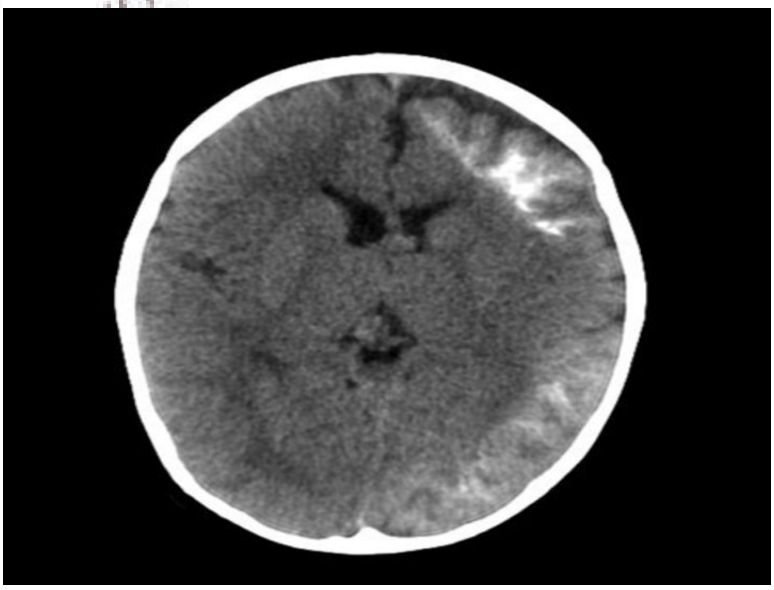
The given clinical scenario and the facial port-wine stain as seen in the image is characteristic of Sturge-Weber syndrome.

This is characterized by a triad of:

• Facial port wine nevus - usually found in the distribution of the ophthalmic division (V1) of the trigeminal nerve

• Glaucoma

• Ipsilateral leptomeningeal angiomatosis (LAM) - can lead to seizures, mental retardation or hemiplegia and are seen as intracranial tram-track calcifications on CT as given below.



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Solution to Question 6:

The most common type of hemangioma is capillary hemangioma.

Hemangiomas are benign vascular tumors of infancy and childhood. They are of the following types:

• Capillary hemangiomas are the most common type. They occur in the skin, subcutaneous tissues, and mucous membranes of the oral cavities and lips.

• Cavernous hemangiomas are composed of large, dilated vascular channels. They are more infiltrative and frequently involve deep structures. They do not spontaneously regress.

• Juvenile hemangiomas/strawberry type hemangiomas of the newborn are extremely common. They arise in the skin and grow rapidly for a few months, and usually regress completely by the age of 7 years.

• Pyogenic granulomas are capillary hemangiomas that present as rapidly growing red pedunculated lesions on the skin, gingival, or oral mucosa. They bleed easily and are often ulcerated. It is not caused by bacterial infection.

Solution to Question 7:

Capillary hemangiomas are present from birth and initially increase in size, but many eventually regress spontaneously. They are generally benign.

Images show the gross and microscopic pictures of capillary hemangioma:

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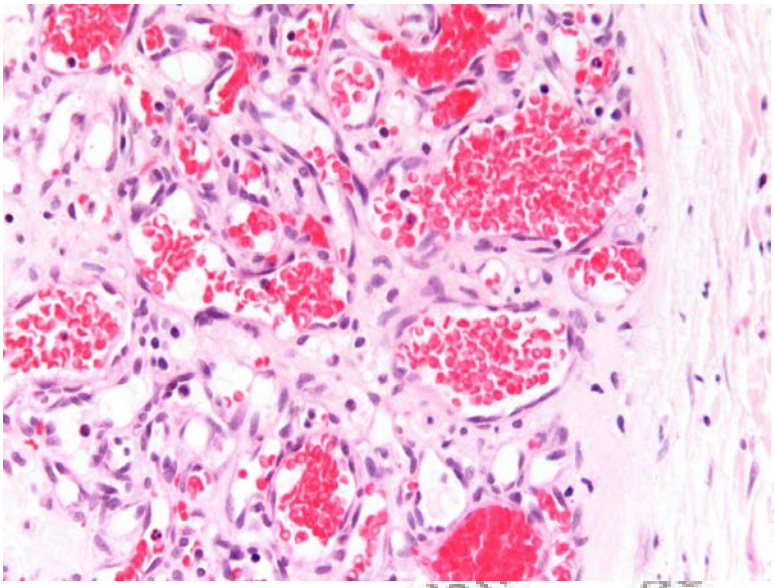

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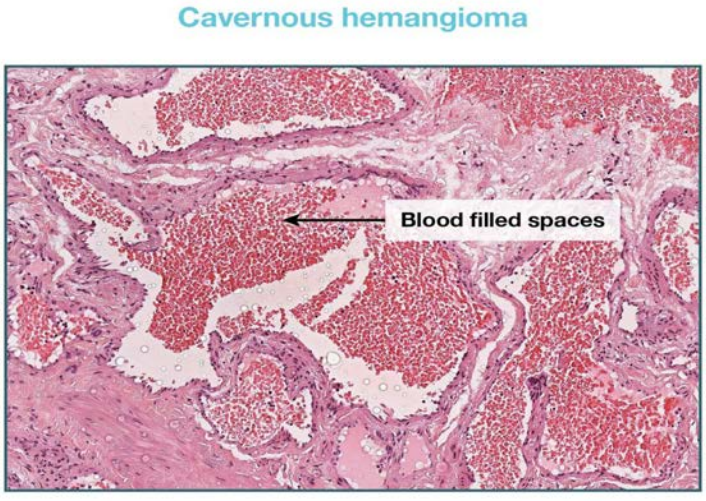
Solution to Question 8:

von Hippel–Lindau disease is associated with cavernous hemangiomas. These vascular lesions are commonly found in the cerebellum, brain stem, retina, pancreas, and liver.

Cavernous hemangiomas are large, cavernous blood-filled vascular spaces separated by connective tissue stroma. They are infiltrative and involve deep structures. They do not regress spontaneously.

The given image shows the microscopic appearance of cavernous hemangioma:



Solution to Question 9:

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The vascular lesions commonly seen in Turner syndrome are cavernous lymphangiomas of the neck.

Cavernous lymphangiomas (cystic hygromas) are massively dilated lymphatic spaces lined by endothelial cells and separated by connective tissue stroma. They are typically found in the neck or axilla of children and rarely in the retroperitoneum. They can be enormous causing gross deformities around the neck.

Image shows cavernous lymphangioma of the neck associated with a girl having Turner syndrome:

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Solution to Question 10:

The given image shows a pyogenic granuloma. It is not caused by bacterial infection. The term pyogenic granuloma is a misnomer as it neither contains pus nor is it a granulomatous lesion.

These are capillary hemangiomas that appear as red pedunculated lesions on the skin, gingival, or oral mucosa. They are most commonly benign. They tend to grow rapidly, bleed easily and are often ulcerated.

Histologic image of pyogenic granuloma:

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Solution to Question 11:

Pregnancy tumor or granuloma gravidarum is a type of pyogenic granuloma that occurs infrequently in gingiva of pregnant women.

These lesions may spontaneously regress, especially after pregnancy, or they may undergo fibrosis. Occasionally, they require surgical excision.

Solution to Question 12:

The vascular tumor arising from arteriovenous structures involved in thermoregulation is glomus tumor.

These tumors arise from modified smooth muscle cells of the glomus bodies which are specialized arteriovenous structures involved in thermoregulation. They are benign but extremely painful due to abundant nerve fibers.

Histopathology shows branching vascular channels separated by stroma containing glomus cells in nests:

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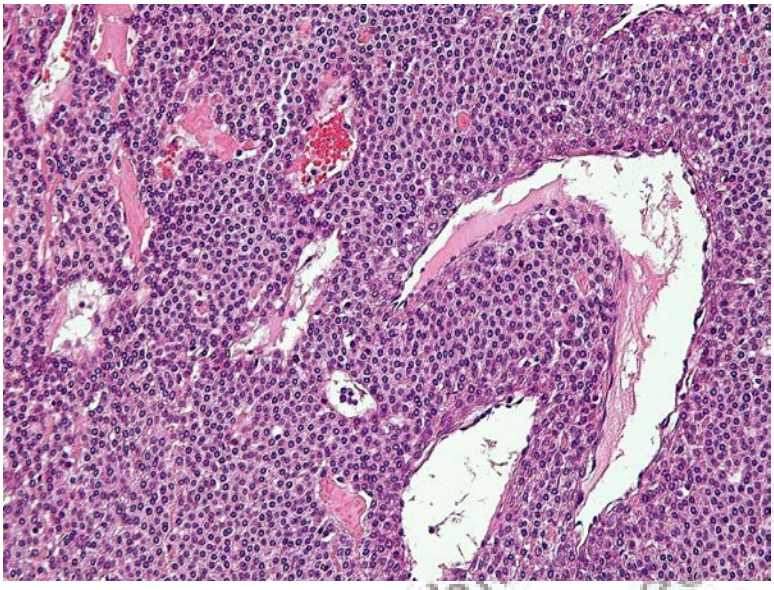

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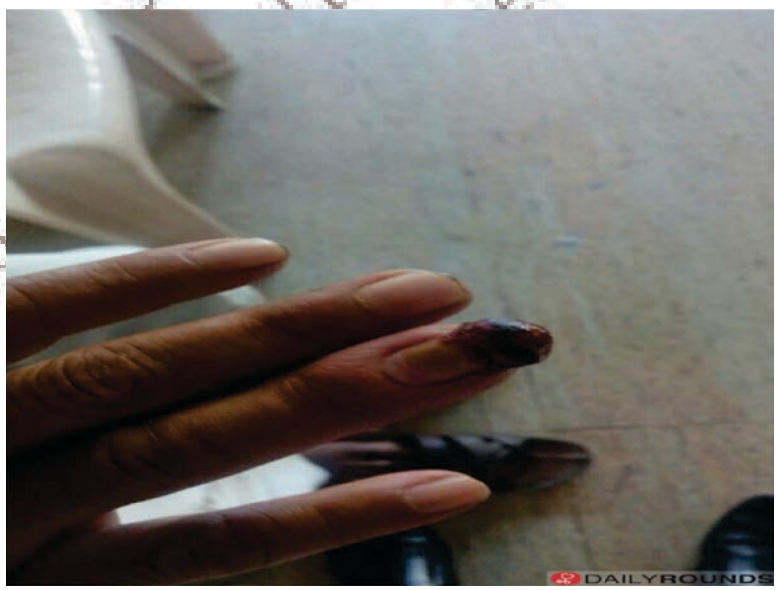
Solution to Question 13:

Glomus tumors are most commonly found in the distal portion of the digits, especially under the fingernails.



Solution to Question 14:

The clinical vignette and the microscopic findings suggest the diagnosis of bacillary angiomatosis caused by Bartonella henselae.

Bacillary angiomatosis is a vascular proliferation in immunocompromised hosts caused by opportunistic gram-negative bacilli of the Bartonella family like Bartonella henselae

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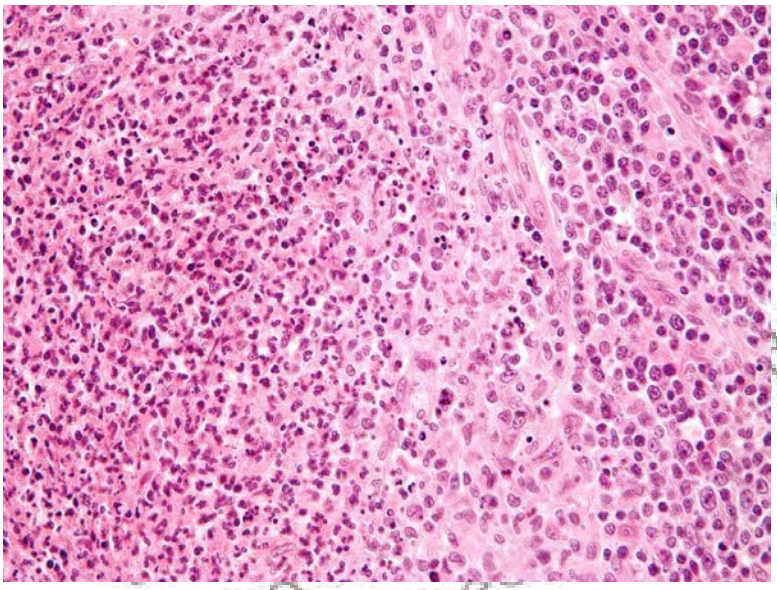
and Bartonella quintana.

These lesions can involve the skin, bone, brain, and other organs. They contain stromal neutrophils, nuclear dust, and causal bacteria. Histology shows capillary proliferation with endothelial cells exhibiting nuclear atypia and mitosis.

Modified silver (Warthin-Starry) stain is used for demonstrating clusters of tangled bacilli.

The given image shows histologic appearance of bacillary angiomatosis:



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Solution to Question 15:

The given clinical scenario and the histopathological findings are most suggestive of Kaposi sarcoma.

Kaposi sarcoma is a vascular neoplasm caused by human herpesvirus 8 (HHV8) and is highly associated with AIDS (acquired immunodeficiency syndrome). Classic Kaposi sarcoma occurs in older men of Eastern European and Mediterranean descent. It has the following three clinical stages:

• Patches- red-purple macules on the distal lower extremities

• Plaques- patches progress to large violaceous raised plaques. Lesions spread proximally.

• Nodules- Lesions become nodular with more neoplastic features. This stage also progresses to involve nodes and viscera.

Diseases caused by HHV-8 infection primarily in patients with HIV infection include:

• Kaposi sarcoma

• Multicentric Castleman disease (MCD)

• Primary effusion lymphoma (PEL)

The given image shows sheets of proliferating spindle cells:

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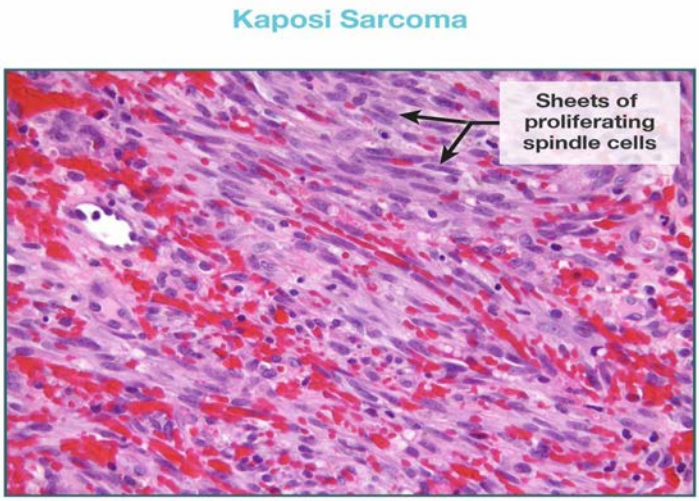

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Solution to Question 16:

AIDS-associated or epidemic Kaposi sarcoma (KS) is an AIDS-defining illness, and worldwide, it represents the most common HIV-related malignancy.

Four forms of KS are recognized, based on population demographics and risks:

Type	Classic	Endemic African	Transplant-associated	AIDS- associated epi demic KS
Epidemiolo gy	Older men of eastern European and Meditt eranean descentNot a ssociated with HIV	HIV seronegative indi viduals	Solid organ transplan t recipients	HIV-infected individ uals
Clinical feat ures	Skin plaques and nod ules	Lymph node and visc eral involvement	Cutaneous, mucosal a nd visceral lesions	Lymph nodes involve d

Solution to Question 17:

Hemangioendothelioma is classified as intermediate-grade neoplasm. It encompasses a spectrum of vascular neoplasms with clinical behavior intermediate between benign well-differentiated hemangiomas and anaplastic angiosarcomas.

Solution to Question 18:

Hepatic angiosarcoma is associated with carcinogenic exposures to polyvinyl chloride.

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Angiosarcoma is a malignant endothelial neoplasm that primarily affects older adults. The tumor often involves the skin, soft tissue, breast, and liver. Angiosarcomas are locally invasive and can readily metastasize.

Solution to Question 19:

Group A beta-hemolytic streptococci are the most common agents responsible for lymphangitis.

Lymphangitis represents acute inflammation elicited by the spread of bacterial infections into lymphatics. It is manifested by red, painful subcutaneous streaks (the inflamed lymphatics) and painful enlargement of the draining lymph nodes (lymphadenitis).

Filariasis causes obstructive lymphedema and chronic lymphadenitis.

Solution to Question 20:

Milroy disease refers to heredofamilial congenital lymphedema.

Causes of lymphedema:

Primary lymphedema:

• Simple congenital lymphedema

• Heredofamilial congenital lymphedema (Milroy disease)

Secondary or obstructive lymphedema:

• Malignant tumors obstructing lymphatic channels

• Surgical removal of regional groups of lymph nodes, e.g., radical mastectomy

• Postirradiation fibrosis

• Filariasis

• Post-inflammatory thrombosis and scarring

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Heart Failure and Ischemic Disease

Question 1:

Which of the following layers is not present in the cardiac valve?

a) Atrialis

b) Ventricularis

c) Spongiosa

d) Adventitia

Question 2:

You are conducting an autopsy of an elderly patient who was found dead in his home. Which of the following changes in the heart will not be suggestive of normal aging?

a) Increased subepicardial fat

b) Basophilic degeneration of myocardium

c) Increased left ventricular cavity size

d) Elastic fragmentation of aorta

Question 3:

What type of cells are heart failure cells?

a) Stem cells

b) Macrophages

c) Type II pneumocytes

d) Type I pneumocytes

Question 4:

What is the most common cause of left-sided diastolic heart failure?

a) Mitral stenosis

b) Hypertension

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c) Atherosclerosis

d) Aortic stenosis

Question 5:

Which of the following does not cause isolated right-sided heart failure?

a) Parenchymal lung disease

b) Primary pulmonary hypertension

c) Pulmonary thrmboembolism

d) Left-sided heart failure

Question 6:

A massive pulmonary embolism occurs in a patient with acute cor-pulmonale. What pathological changes do you expect in the heart of this patient?

a) Right ventricular hypertrophy with dilation

b) Right ventricular dilation without hypertrophy

c) Right ventricular hypertrophy without dilation

d) Right ventricular dilation with hypertrophy

Question 7:

The liver specimen obtained after the autopsy of a patient is given below. What could be the likely cause of this finding?

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a) Liver cirrhosis

b) Haemochromatosis

c) Heart failure

d) Non-cirrhotic portal fibrosis

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Question 8:

Which hormone reduces the risk of myocardial infarction in women of reproductive age?

a) Progesterone

b) Estrogen

c) Human chorionic gonadotropin

d) Human placental lactogen

Question 9:

A 65-year-old man presented to the casualty with severe, sudden-onset chest pain radiating to the left arm. ECG showed ST-segment elevation in precordial leads. The person succumbed after 3 hours. On autopsy, the patient's heart was immersed in triphenyl tetrazolium chloride solution. What colour would be imparted to the heart?

a) Entire myocardium appears pale

b) Viable myocardium appears brick red and infarct appears pale

c) Viable myocardium appears red and infarct appears dark blue

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d) Viable myocardium appears unstained and the infarct appears dark red

Question 10:

What is the approximate time of onset of microvascular injury in ischemic cardiac myocytes?

a) 10 minutes

b) Few seconds

c) 40 minutes

d) More than one hour

Question 11:

What is the earliest detectable ultrastructural feature of myocardial infarction?

a) Myocyte hypereosinophilia

b) Relaxation of myofibrils

c) Neutrophilic infiltrate

d) Sarcolemmal disruption

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Question 12:

You are conducting the autopsy of a patient who passed away following myocardial infarction. What would be the earliest light microscopic change that can be observed in the heart of this patient?

a) Waviness of the fiber

b) Neutrophilic infiltration

c) Contraction band necrosis

d) Pyknosis of nuclei

Question 13:

Following myocardial infarction, coagulative necrosis begins at?

a) 1/2 - 4 hours

b) 4 - 12 hours

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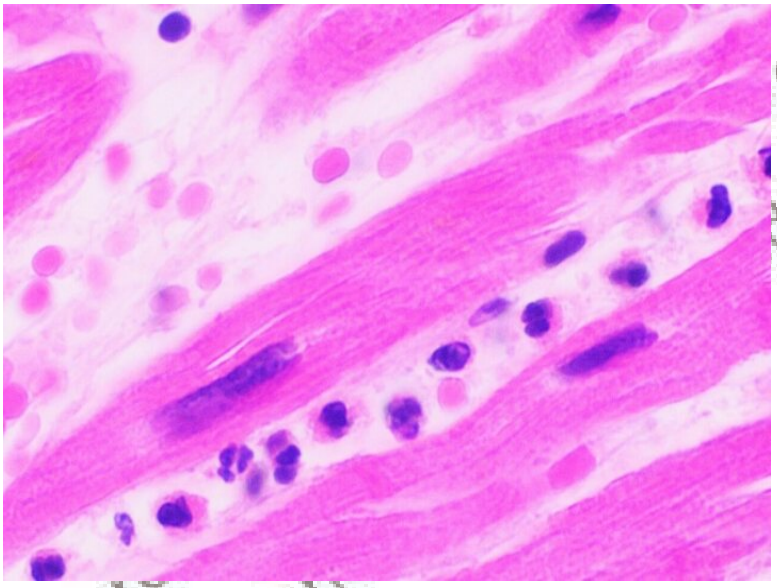
c) 12 - 24 hours

d) 1 - 3 days

Question 14:

The heart of a patient who had suffered a myocardial infarction is subjected to a histopathological examination. The microscopic image is given below. What time following infarction would you observe this?



a) 30 minutes to 4 hours

b) 4-12 hours

c) 12-24 hours

d) 3-7 days

Question 15:

A patient was admitted four days back following acute myocardial infarction. What type of cells would you expect to see in the infarcted area in this patient?

a) Neutrophils

b) Lymphocytes

c) Macrophage

d) Basophils

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Question 16:

Match the following:

a) 1-d, 2-e, 3-b, 4-d, 5-c

b) 1-c, 2- d, 3-a, 4-e, 5-a

c) 1-e, 2-d, 3-b, 4-e, 5-b

d) 1-c, 2-e, 3-a, 4-d, 5-b

Question 17:

A 67-year-old woman is found dead in her home. On autopsy, hemopericardium secondary to ventricular wall rupture is seen. How long before her death did she probably have a myocardial infarction?

a) 1 day

b) 3 -7 days

c) 12 - 14 days

d) >2 weeks

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Question 18:

What causes tigered myocardium?

a) Rheumatic fever

b) Fatty change

c) Myocarditis

d) Hyaline change

Question 19:

Which of the following causes the maximum damage in reperfusion injury?

a) Neutrophil aggregation

b) Monocytes activation

c) Calcium overload

d) Free radicals

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Question 20:

What creatine kinase isoenzymes do the heart muscle contain?

a) MM

b) MB

c) MM and MB

d) MM, MB and BB

Question 21:

A patient comes to the hospital after 3 hours of the onset of chest pain. ECG reveals ST-segment elevation in the precordial leads. Which of the following enzymes would be elevated in this patient?

a) CK-MB

b) LDH

c) SGOT

d) SGPT

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Question 22:

A 56-year-old man presented to the emergency department with progressive dyspnoea. His wife reports that he had chest pain 7 days back which had lasted for 2 days. You suspect that the patient's chest pain was due to myocardial infarction. If so, blood levels of which of the following enzymes would be elevated now?

a) CPK

b) SGOT

c) Troponin

d) Myoglobin

Question 23:

The blood levels of various cardiac biomarkers are measured in a patient following myocardial infarction. This is represented in the given graph. Which biomarker does the yellow curve depict?

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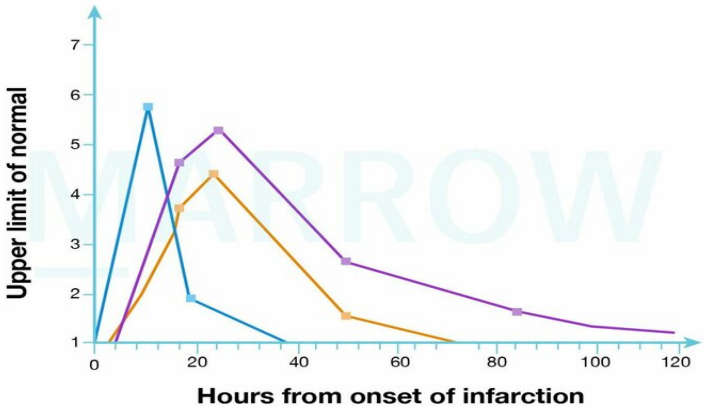

a) Myoglobin

b) Troponin I

c) CK-MB

d) LDH

Question 24:

Loss-of-function mutation in potassium channel gene KCNQ1 results in which of the following?

a) Long QT syndrome

b) Short QT syndrome

c) Brugada syndrome

d) Familial atrial fibrillation

Question 25:

What is the most common mechanism behind sudden cardiac death?

a) Infarction

b) Arrythmia

c) Thrombosis

d) Myocardial rupture

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Question 26:

Patients with which of the following conditions have an increased susceptibility to coronary artery disease?

a) Vitamin D deficiency

b) von Willebrand's disease

c) Hyperlipidemia

d) Amyloidosis

Question 27:

What is lipoprotein a [Lp (a)] composed of?

a) apo B100 + apo A

b) apo B48 + apo A

c) apo B48 + apo B100

d) apo E + apo A

Question 28:

Histology of reperfused myocardium:

a) Wavy fibres

b) Neutrophils in cardiac muscle

c) Swelling of cells

d) Eosinophilc contraction band

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Answer Key

Question No.	Correct Option
1	d
2	c
3	b
4	b
5	d

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6	b
7	c
8	b
9	b
10	d
11	b
12	a
13	b
14	c
15	c
16	d
17	b
18	b
19	d
20	c
21	a
22	c
23	c
24	a
25	b
26	c
27	a
28	d

If yo... you... else, ...d.

Detailed Explanations

Solution to Question 1:

Adventitia is not a layer of the cardiac valves. It is the outermost layer of a blood vessel. It contains connective tissue, a few cells, macrophages, mast cells, fibroblasts, and the nerves and vessels that supply the vascular wall.

Cardiac valves are lined by endothelium and share a tri-layered architecture:

- Fibrosa is a dense collagenous core at the outflow surface. It is connected to the valvular supporting structures.
- Spongiosa is a central core of loose connective tissue
- Ventricularis or atrialis is a layer rich in elastin on the inflow surface.

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Solution to Question 2:

In the given scenario, an increase in the size of the left ventricle is not normally seen in the heart of an elderly person. The size of the left ventricular cavity is decreased in the aged heart, particularly in the base-to-apex dimension. This change is exacerbated by systemic hypertension.

Changes in the aging heart:

• Chambers:

• Increased left atrial cavity size

• Decreased left ventricular cavity size

• Valves:

• Fibrous thickening of valve leaflets

• Aortic and mitral valve calcific deposits

• Epicardial coronary arteries:

• Diminished compliance

• Calcific deposits

• Atherosclerotic plaques

• Myocardium:

• Increased subepicardial fat

• Brown atrophy

• Lipofuscin deposition

• Basophilic degeneration

• Amyloid deposits

• Aorta:

• Dilated with a rightward shift

• Elastic fragmentation and collagen accumulation

• Atherosclerotic plaque

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Solution to Question 3:

Heart failure cells are hemosiderin-laden macrophages. They are telltale signs of previous episodes of pulmonary edema.

In cardiac failure, red cells and plasma proteins extravasate into the edema fluid within the alveolar spaces. These are then phagocytosed and digested by macrophages. The iron recovered from haemoglobin is stored in the form of hemosiderin.

The image given below shows heart failure cells within alveolar spaces.

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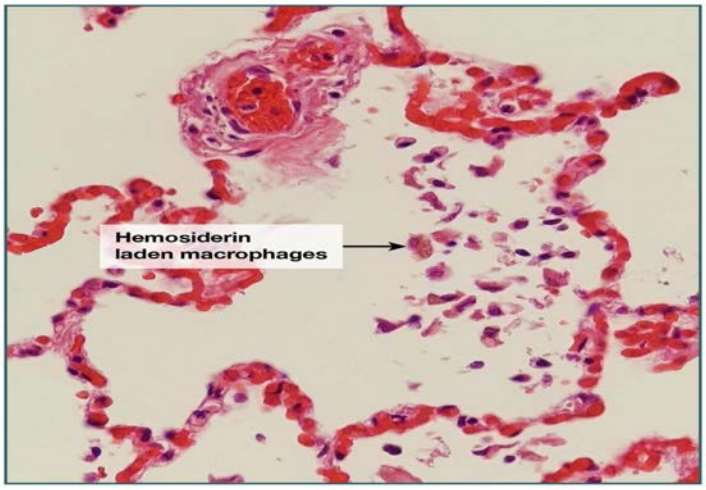
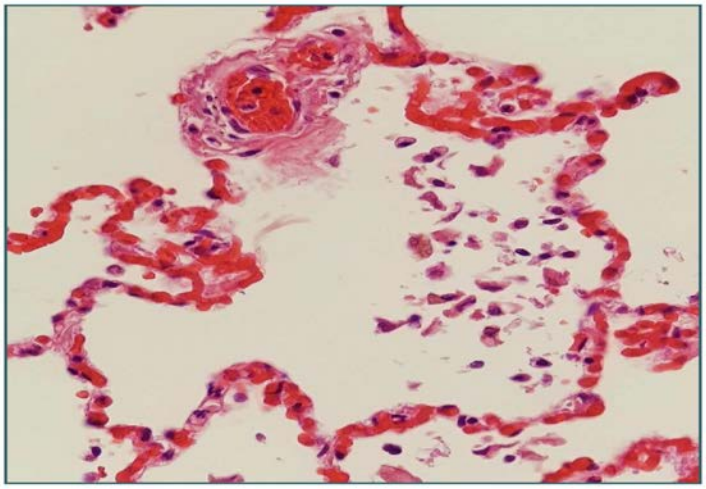
Heart failure cells



Heart failure cells



Solution to Question 4:

Hypertension is the most common cause of left-sided diastolic heart failure.

Left-sided heart failure can be divided into systolic and diastolic failure. Diastolic failure predominantly occurs in patients older than age 65 years. Here, the left ventricle is abnormally stiff and cannot relax during diastole.

Causes of diastolic heart failure:

- Hypertension: most common
- Diabetes mellitus
- Obesity
- Bilateral renal artery stenosis

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Systolic failure is due to insufficient ejection fraction, i.e., pump failure. It occurs when the contractile function of the left ventricle is deranged.

Solution to Question 5:

Isolated right-sided heart failure is not caused by left-sided heart failure.

Isolated right-sided heart failure is not common and usually occurs in patients with disorders affecting the lungs. Therefore, it is often referred to as cor pulmonale. It is caused by disorders of the lung parenchyma and pulmonary vasculature. It is also caused by conditions causing pulmonary vasoconstriction like obstructive sleep apnea and altitude sickness.

Pulmonary hypertension is the common feature of these disorders, which leads to hypertrophy and dilation of the right side of the heart.

Right-sided heart failure is most commonly caused by left-sided heart failure. This is because an increase in pressure in the pulmonary circulation from left-sided failure burdens the right side of the heart.

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Solution to Question 6:

In the given scenario, the patient has acute cor pulmonale. This causes right ventricular dilation without hypertrophy. On cross-section, the normal crescent shape of the right ventricle is transformed to a dilated ovoid.

In chronic cor pulmonale, the right ventricular wall thickens. The hypertrophied right ventricle may compress the left ventricular chamber. It can also cause regurgitation and fibrous thickening of the tricuspid valve.

Solution to Question 7:

In the image, the liver specimen shows a nutmeg liver appearance, which occurs in congestive hepatomegaly. This is secondary to passive congestion due to right heart failure.

In right heart failure, there is congestion of hepatic and portal vessels, greatest around the central veins. This leads to increased liver size and weight. The pericentral zones become congested and red-brown. The periportal regions are normal coloured and tan. This leads to a nutmeg liver appearance. With longstanding failure, the central areas can become fibrotic, eventually culminating in cardiac cirrhosis.

Pathological changes are also seen in the spleen and the gastrointestinal tract. Portal venous hypertension also causes the enlargement of the spleen, with platelet sequestration. This is known as congestive splenomegaly. This can also contribute to chronic congestion and oedema of the bowel.

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Solution to Question 8:

Estrogen reduces the risk of myocardial infarction in women in the reproductive age group.

Accelerated coronary artery disease is associated with the postmenopausal decline in estrogen production. However, postmenopausal hormonal replacement therapy (HRT) has not been shown to be beneficial.

The most common cause of death in older women is ischemic heart disease.

Through middle age, males have a relatively increased risk of myocardial infarction.

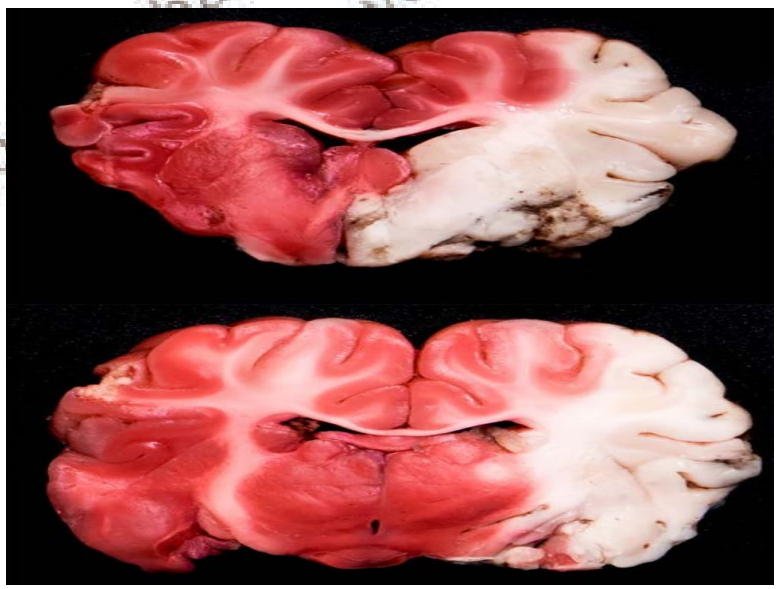
Solution to Question 9:

Triphenyl tetrazolium chloride solution imparts a brick red colour to the viable non-infarcted myocardium. The infarct appears unstained and pale.

Myocardial infarcts < 12 hours old are usually not apparent on gross examination. However, if the infarct preceded death by 2 to 3 hours, it is possible to identify the area of necrosis. This is done by immersing the tissue slices in triphenyl tetrazolium chloride solution.

The histochemical stain imparts a brick-red colour to intact, noninfarcted myocardium.
Here, lactate dehydrogenase, LDH, activity is preserved. LDH leaks out through the damaged membranes of dead cells, so an infarct appears as an unstained pale zone.

The image given below shows an ischemic brain after immersion in triphenyl tetrazolium chloride solution. The pale unstained region is the infarcted zone.



Solution to Question 10:

Microvascular injury begins >1 hour after the onset of ischemia.

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Solution to Question 11:

Relaxation of myofibrils is the earliest detectable ultrastructural feature of myocardial infarction.

Myofibril relaxation, mitochondrial swelling and glycogen loss can be detected by electron microscopy within half an hour of myocardial infarction.

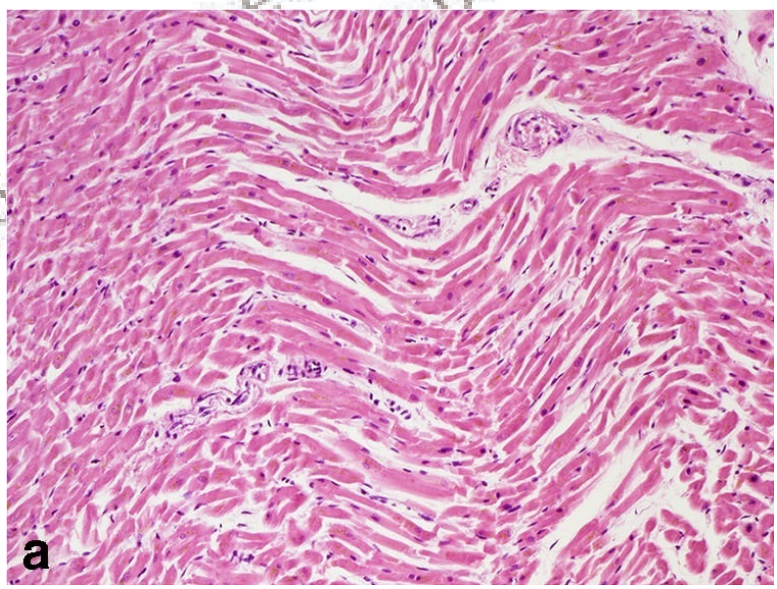
Solution to Question 12:

The earliest light microscopic change that can be observed in the heart of this patient is the waviness of myocardial fibres. This is seen within ½-4 hours at the border of the infarct.

These changes are a result of the forceful contractions of viable fibres. The contractions cause stretching and buckling of immediately adjacent, noncontractile dead fibres.

Myocyte vacuolization or myocytolysis may also be seen in the infarct margins. It is due to the accumulation of salt and water in the sarcoplasmic reticulum. Such myocytes are viable but poorly contractile.

The image below shows microscopic features of myocardial infarction showing wavy myocardial fibres. There are wavy fibres that are elongated and narrow, as compared with normal fibres. The widened spaces between the dead fibres contain edema fluid and scattered neutrophils.



Solution to Question 13:

Early coagulative necrosis begins in myocardial infarction by 4–12 hours.

However, it is prominent between 1 to 3 days after myocardial infarction.

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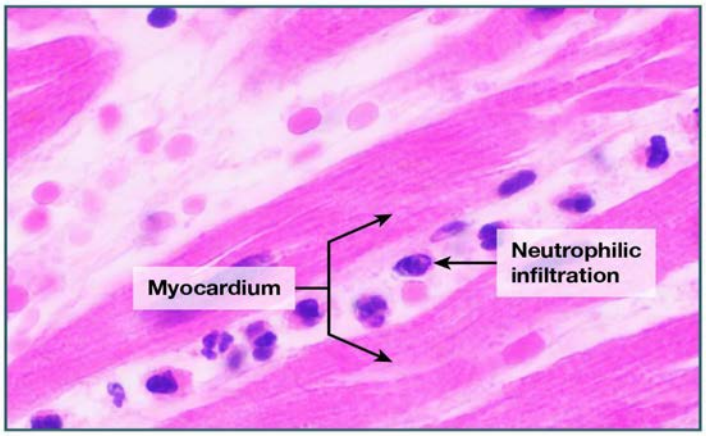
Solution to Question 14:

The given image shows neutrophilic infiltration into the myocardium. Early neutrophil infiltration starts by 12–24 hours following the infarction. It can be visualised by examination with a light microscope.

The necrotic myocardium elicits acute inflammation most prominent between 1 and 3 days. During this time, there is a brisk interstitial infiltrate of neutrophils.

The image given below shows neutrophilic infiltration into the myocardium following MI.

Neutrophilic infiltration in myocardium



Solution to Question 15:

In the given scenario, 4 days after MI, macrophages are seen in the infarcted area.

They phagocytose dead myocytes at the border of the infarct earliest by 72 hours. Removal of the necrotic myocytes is most noticeable by 3 to 7 days.

The image below shows a macrophagic infiltrate in the infarcted area.

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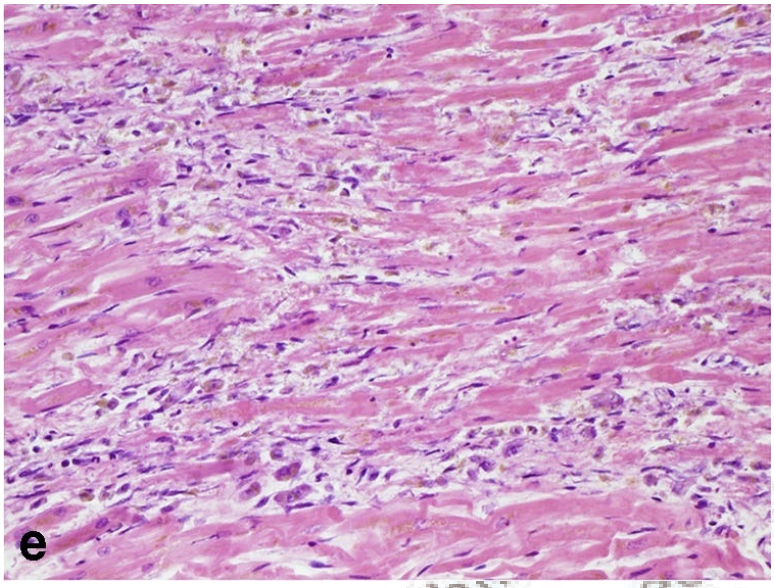

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Solution to Question 16:

The correct match is:

• Well established granulation - 10 - 14 days

• Complete scarring - > 2 months

• Myocyte hypereosinophilia - 12 - 24 hours

• Grey white scar - 2-8 weeks

• Loss of nuclei and striations - 1 - 3 days

Solution to Question 17:

The given autopsy finding of hemopericardium secondary to ventricular wall rupture occurs most frequently 3-7 days after myocardial infarction (MI). During this time, the lysis of the necrotic myocardium is maximum. Thus most of the infarct has been converted to friable granulation tissue.

The risk factors for free-wall rupture are:

• Age > 60 years

• Female gender

• First MI

• Large, transmural and anterior MI

• Absence of left ventricular hypertrophy

• Preexisting hypertension

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It is less frequent in patients with prior MI because associated fibrotic scarring inhibits myocardial tearing.

Complications of MI:

• Heart failure -

• This is due to ventricular dysfunction caused by the infarct and ventricular remodeling

• Usually occurs within a day

• Cardiogenic shock -

• This is usually seen in severe multivessel coronary artery disease due to extensive involvement of myocardium

• Usually occurs within a day

• Arrhythmias - most common complication, occurring usually 2 days after infarction

• Most common arrhythmia within one hour of MI - ventricular fibrillation

• Most common arrhythmia after one hour of MI - supraventricular tachycardia

• Myocardial rupture - occurs when there is transmural necrosis of a ventricle. It includes the following -

• Left ventricular free wall rupture (most common) - leads to cardiac tamponade

• Interventricular septal rupture - leads acute ventricular septal defect (VSD)

• Papillary muscle rupture - leads to severe mitral regurgitation

• Mitral regurgitation (MR) - this can occur due to -

• Transient papillary muscle dysfunction - mid-systolic or late-systolic murmur

• Rupture of papillary muscle - pansystolic murmur

• Dressler syndrome (post-MI syndrome) -

• This is an immune-mediated reaction and presents as pericarditis, pleurisy, and fever

• It can occur even 48 hrs after MI but usually occurs 1–6 weeks after MI and often subside after a few days

• Ventricular aneurysm

• Infarct expansion associated with mural thrombus

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Solution to Question 18:

Tigered myocardium appearance occurs as a result of prolonged moderate hypoxia due to fatty change. It is the gross appearance of the heart with bands of yellow myocardium alternating with normal myocardium.

Solution to Question 19:

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In reperfusion injury, the maximum damage is caused by free radicals.

Reperfusion is the restoration of blood flow to the ischemic myocardium threatened by infarction. Reperfused infarcts are usually hemorrhagic because the vasculature is injured during ischemia. Once the flow is restored, there is bleeding.

On microscopic examination, the irreversibly injured myocytes exhibit contraction bands that are intensely eosinophilic intracellular stripes. These contraction bands are composed of closely packed sarcomeres.

Reperfusion injury may be mediated by:

• Oxidative stress

• Calcium overload

• Inflammatory cells recruited after tissue reperfusion

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Solution to Question 20:

Heart muscle contains MM and MB isoenzymes of creatine kinase.

Creatine kinase (CK) has three isoenzymes:

• CK-1 (BB) - brain, nerve tissue, prostate (small amounts), intestine, lung, bladder, kidney, uterus, thyroid

• CK-2 (MB) - heart and skeletal muscle

• CK-3 (MM) - skeletal and heart muscle

Elevation of the CK-MB isoforms is seen in MI. CK-MB is less sensitive and less specific, therefore, troponins are preferred for the diagnosis of MI. CK-MB begins to rise within 3-12 hours of the onset of MI. It peaks at about 24 hours and returns to normal within approximately 48-72 hours.

Solution to Question 21:

The given scenario is suggestive of acute myocardial infarction (MI). Enzymes elevated after 4 to 8 hours of MI are CK-MB (creatine kinase MB) and troponins.

When cardiac troponin is available, CK-MB should not be used for the initial diagnosis of acute MI. If it is the only assay available, it can be used, but it is far less sensitive and less specific.

Solution to Question 22:

In the given scenario, on post-MI day 7, troponin and LDH will be raised. Troponins are highly specific for MI and remain elevated for 7 to 10 days.

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Troponins are proteins that regulate calcium-mediated contraction of the cardiac and skeletal muscles. It is the single biomarker preferred for diagnosing MI, late diagnosis of MI, and diagnosis of reinfarction. Troponin I is more important than troponin T.

Cardiac troponin increases rapidly in patients with reinfarction. Sometimes, the cardiac troponin concentration is elevated, but stable or decreasing at the time of suspected reinfarction. Then the diagnosis of reinfarction requires a 20% or greater increase in the cTn measurement.

Myoglobin is the earliest enzyme to increase after MI. It is a protein that is found in the skeletal and cardiac muscles, which binds oxygen. It is a very sensitive indicator of muscle injury. But it is not specific to cardiac muscle and can be elevated to any form of injury to skeletal muscle. Myoglobin and SGOT levels come to baseline before day 1.

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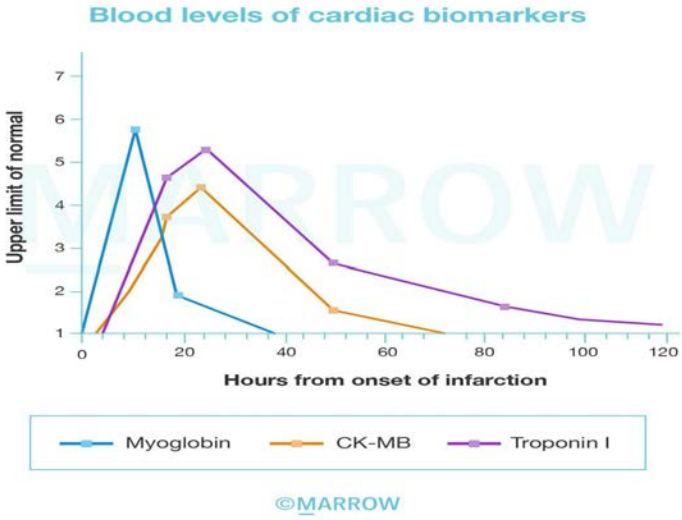
Solution to Question 23:

The yellow curve here shows the levels of CK-MB which starts rising around 4 to 8 hrs post-MI, peaks at 24 hours and becomes normal at 48 to 72 hrs.

The post-myocardial infarction blood levels of the different cardiac biomarkers are shown in the image given below.



Solution to Question 24:

Loss of function mutation in K+ channel genes KCNQ1 and KCNH2 produces the long QT syndrome. The gain-of-function mutation produces the short QT syndrome.

Long QT syndrome manifests as arrhythmias associated with excessive prolongation of cardiac repolarization. Stress-induced syncope or sudden cardiac death (SCD), are common presentations.

Short QT syndrome presents with arrhythmias associated with abbreviated repolarization intervals. They also present with palpitations, syncope, and SCD.

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Brugada syndrome manifests as ECG abnormalities like ST-segment elevations and right bundle-branch block. This occurs in the absence of structural heart disease. Here, patients classically present with syncope or SCD during rest or sleep or after large meals.

Familial atrial fibrillation is caused by a gain of function mutation in genes coding potassium channels.

Solution to Question 25:

The mechanism behind sudden cardiac death (SCD) is most often a lethal arrhythmia, e.g., asystole or ventricular fibrillation.

Coronary artery disease is the leading cause of SCD, responsible for 80% to 90% of cases. But, the mechanism of SCD is most often a lethal arrhythmia. Infarction need not occur. Most of the patients who have SCD but are successfully resuscitated do not show any enzymatic or ECG evidence of myocardial necrosis.

Ischemic injury can directly affect the major components of the conduction system. But, most cases of fatal arrhythmia are triggered by electrical irritability of the myocardium.

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Solution to Question 26:

Patients with hyperlipidemia have an increased susceptibility to coronary artery disease (CAD).

Hyperlipidemia is considered the second most common risk factor for CAD worldwide after hypertension. Hypercholesterolemia was implicated in 55% of cases with combined hyperlipidemia in 41% cases.

Solution to Question 27:

Lipoprotein a [Lp(a)] contains the apolipoprotein B-100 portion of LDL linked to apolipoprotein A (apo A). It is an altered form of low-density lipoprotein (LDL).

Increased Lp(a) levels are associated with coronary and cerebrovascular disease risk. It is independent of total cholesterol or LDL levels.

Solution to Question 28:

Reperfused myocardium shows eosinophilic contraction bands on light microscopy. They occur in irreversibly injured myocytes with damaged membranes, when blood supply is restored 12-24 hours after MI.

During ischemia, the intracellular levels of calcium are increased due to impaired calcium cycling and sarcolemmal damage. This leads to augmented and uncontrolled contraction of myofibrils

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after reperfusion.

On microscopic examination, the irreversibly injured myocytes exhibit contraction bands that are intensely eosinophilic intracellular stripes. These contraction bands are composed of closely packed sarcomeres.

Reperfused infarcts are usually hemorrhagic because the vasculature is injured during ischemia. This leads to bleeding after the flow is restored.

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Myocardial and Pericardial Diseases and Cardiac Tumors

Question 1:

What is the most common type of cardiomyopathy?

a) Dilated cardiomyopathy

b) Arrhythmogenic right ventricular cardiomyopathy

c) Hypertrophic cardiomyopathy

d) Restrictive cardiomyopathy

Question 2:

Alcohol abuse is strongly associated with the development of:

a) Pericarditis

b) Hypertrophic cardiomyopathy

c) Dilated cardiomyopathy

d) Myocarditis

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Question 3:

Which of the following is the largest protein expressed in humans?

a) Myosin

b) Collagen

c) Titin

d) Dystrophin

Question 4:

Two brothers were arguing over a property dispute when the elder of the two complained of chest pain and collapsed. He was taken to the hospital but was declared brought dead. The condition responsible for the death of the patient is grouped under which of the following?

a) Dilated cardiomyopathy

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b) Constrictive cardiomyopathy

c) Restrictive cardiomyopathy

d) Arrhythmogenic cardiomyopathy

Question 5:

A patient is admitted to the hospital with heart failure due to dilated cardiomyopathy. Toxicity by which of the following does not cause this?

a) Lead

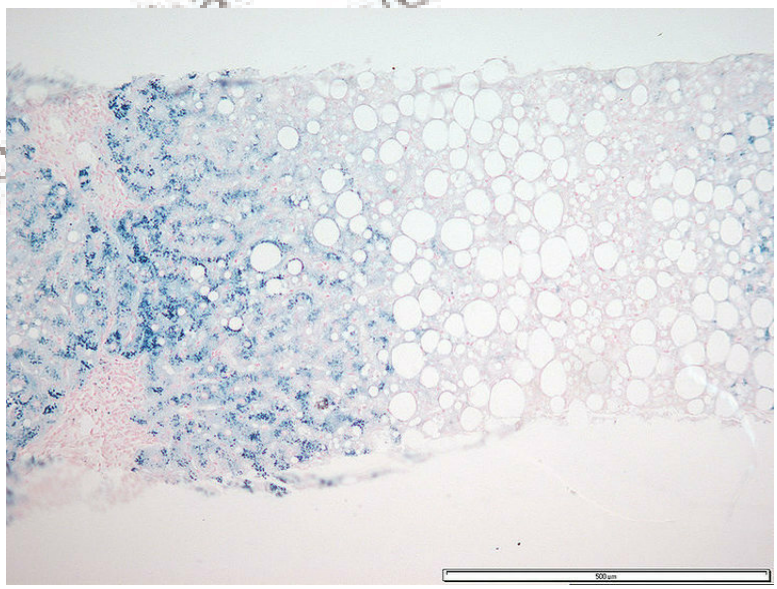
b) Mercury

c) Selenium

d) Cobalt

Question 6:

A 55 yr old man is found to have hepatomegaly on physical examination. He also complains of dark tan despite avoiding sun exposure. His liver microscopy is given on the slide below. Which type of cardiomyopathy is usually seen in this condition?



a) Dilated cardiomyopathy

b) Hypertrophic cardiomyopathy

c) Restrictive cardiomyopathy

d) Left ventricular non-compaction cardiomyopathy

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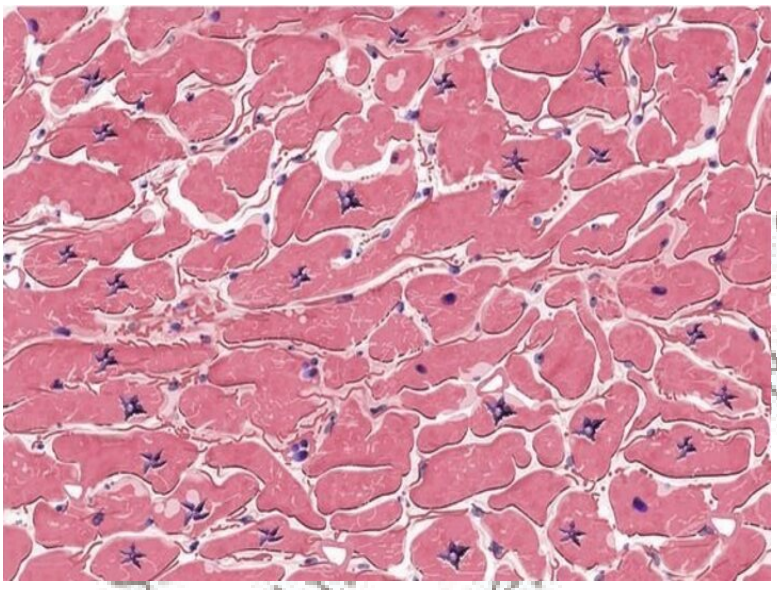
Question 7:

The histological examination of the heart of a patient who died due to heart failure is given below. What underlying condition did the patient most likely have?



a) Hypertrophic cardiomyopathy

b) Restrictive cardiomyopathy

c) Arrhythmogenic cardiomyopathy

d) Dilated cardiomyopathy

Question 8:

A 14-year-old boy who collapsed while playing basketball was brought to the emergency room and was resuscitated. On evaluation, he was found to have sustained ventricular tachycardia secondary to arrhythmogenic right ventricular cardiomyopathy. Which syndrome is associated with this?

a) Naxos syndrome

b) Nelson syndrome

c) Carvajal syndrome

d) Takotsubo syndrome

Question 9:

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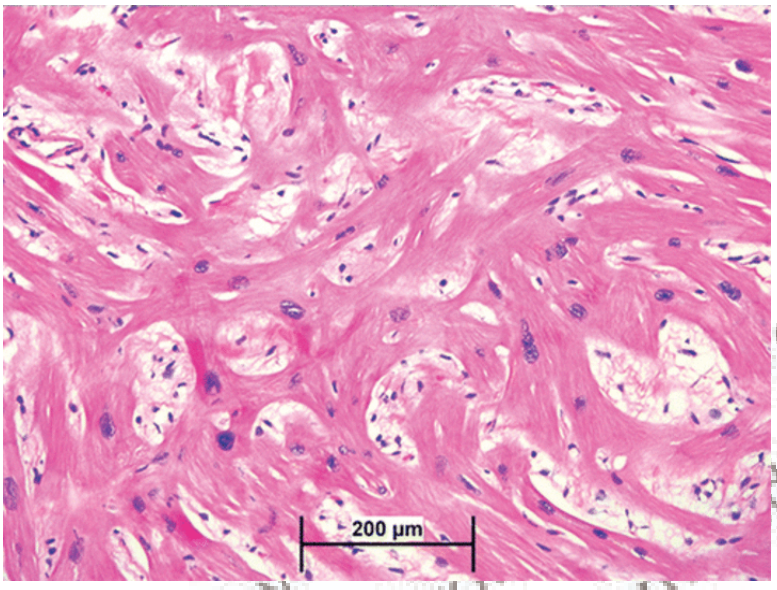
An autopsy was done for a young patient who had a sudden cardiac death. It revealed massive myocardial hypertrophy without ventricular dilation. The image obtained on microscopy is given below. What is the most likely diagnosis?



a) Ischemic cardiomyopathy

b) Arrhythmogenic right ventricular dysplasia

c) Hypertrophic cardiomyopathy

d) Takotsubo cardiomyopathy

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Question 10:

Mutations causing hypertrophic cardiomyopathy are most commonly seen in the gene encoding which of the following?

a) Titin

b) °-myosin heavy chain

c) α-tropomyosin

d) Cardiac Troponin I

Question 11:

Which of the following can cause restrictive cardiomyopathy?

a) 1 and 4

b) 2, 3 and 5

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c) 1, 2 and 3

d) 1, 2, 4 and 5

Question 12:

A 35-year-old female presents with progressive dyspnoea on exertion for one week along with a diffuse rash. Blood investigations are significant for an absolute eosinophil count of 4600 / mm^3. Which of the following is caused by the patient's condition?

a) Hypertrophic cardiomyopathy

b) Dilated cardiomyopathy

c) Both hypertrophic and dilated cardiomyopathy

d) Restrictive cardiomyopathy

Question 13:

A 2-year-old girl was brought to the outpatient department with complaints of difficulty in breathing and fatigue. The child had a history of intrauterine exposure to mumps. The cardiac evaluation showed a decrease in ventricular compliance. Which of the following would be the cause of the child's symptoms?

a) Endomyocardial fibrosis

b) Loeffler endomyocarditis

c) Endocardial fibroelastosis

d) Arrhytmogenic right ventricular cardiomyopathy

Question 14:

Myocarditis is most commonly caused by which of the following viral infections?

a) Influenza virus

b) Cytomegalovirus

c) Coxsackie virus

d) Epstein-Barr virus

Question 15:

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Which serum protein is the major component of senile cardiac amyloid deposits?

a) Haptoglobin

b) Transthyretin

c) Fibronectin

d) Amylin

Question 16:

One week following a diagnosis of myocardial infarction, a patient experiences precordial pain and develops a fever of 101.5°F. Physical examination is remarkable for a loud friction rub. Which of the following is the most likely diagnosis?

a) Caseous pericarditis

b) Fibrinous pericarditis

c) Hemorrhagic pericarditis

d) Purulent pericarditis

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Question 17:

A 52-year-old man with a history of myocardial infarction 4 weeks back, develops fever, pericardial chest pain and pericardial effusion. What is the aetiology behind the patient's present condition?

a) Viral

b) Bacterial

c) Free radical

d) Autoimmune

Question 18:

The autopsy of a patient who died due to heart failure revealed concretio cordis. Which of the following is this condition associated with?

a) Blunt trauma to the heart

b) Penetrating trauma to the heart

c) Constrictive pericarditis

d) Acute fibrinous pericarditis

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Question 19:

Which of the following is the most common primary tumour of the adult heart?

a) Hemangioma

b) Myxoma

c) Rhadomyoma

d) Fibroma

Question 20:

Which of the following conditions is commonly seen in patients with null mutations of the PRKAR1A gene?

a) Gastrointestinal stromal tumor

b) Paraganglioma

c) Cardiac myxoma

d) Rhabdomyoma

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Question 21:

What is the most common site of a cardiac myxoma?

a) Left atrium

b) Right atrium

c) Left ventricle

d) Interventricular septum

Question 22:

The histopathologic findings seen in a resected heart mass is given below. What is the diagnosis?

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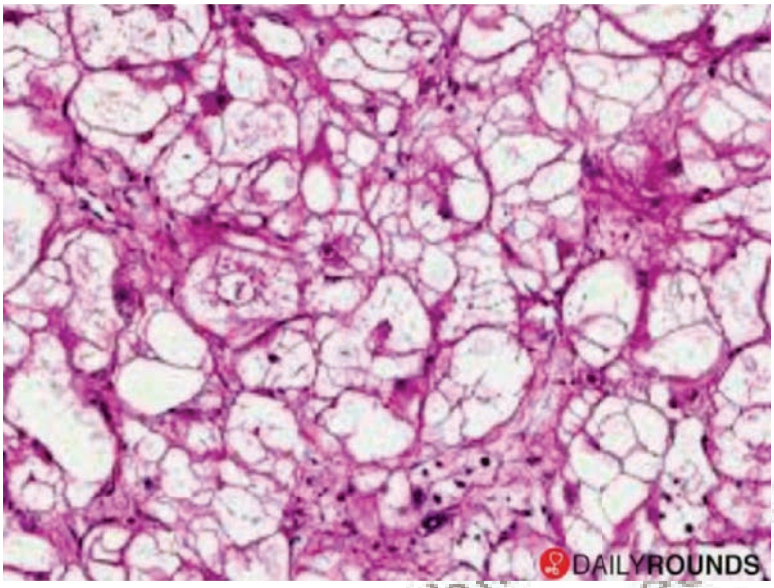

a) Cardiac Myxomas

b) Papillary fibroelastoma

c) Cardiac Rhabdomyoma

d) Cardiac Rhabdomyosarcoma

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Question 23:

The single most important long-term limitation of cardiac transplantation is _____

a) Allograft rejection

b) Allograft arteriopathy

c) Infection

d) Malignancy

Question 24:

What is the most common cause of the condition shown in the given image?

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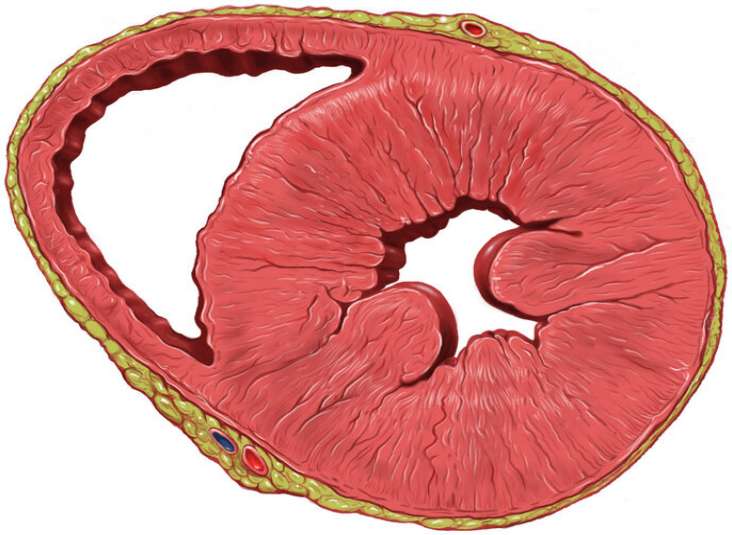

a) Malignant hypertension

b) Chronic hypertension

c) Amyloidosis

d) Hypertrophic obstructive cardiomyopathy

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Question 25:

Which of the following patients with cardiac hypertrophy will have an associated increase in capillary density?

a) A patient with systemic hypertension

b) A patient with an echo finding of an aortic valvular area of 0.6cm²

c) A patient with a high pitched holosystolic murmur best heard at the apex

d) A patient who is a marathon runner who came for a pre-run evaluation

Answer Key

Question No.	Correct Option
1	a
2	c
3	c
4	a

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5	c
6	a
7	d
8	a
9	c
10	b
11	d
12	d
13	c
14	c
15	b
16	b
17	d
18	c
19	b
20	c
21	a
22	c
23	b
24	b
25	d

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Detailed Explanations

Solution to Question 1:

The most common type of cardiomyopathy is dilated cardiomyopathy. Restrictive cardiomyopathy is the least frequent.

Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction. They usually exhibit inappropriate ventricular hypertrophy or dilatation. The causes are frequently genetic.

Cardiomyopathies maybe primary predominantly involving the heart or secondary to a systemic or multiorgan disorder. They occur in the absence of any coronary artery disease, valvular heart disease, congenital heart disease, or systemic arterial hypertension.

Types of cardiomyopathy:

• Dilated cardiomyopathy

• Hypertrophic cardiomyopathy

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• Restrictive cardiomyopathy

• Arrhythmogenic right ventricular cardiomyopathy

• Left ventricular non-compaction cardiomyopathy

Solution to Question 2:

Alcohol abuse is strongly associated with the development of dilated cardiomyopathy.

Alcohol and its metabolites, especially acetaldehyde have a direct toxic effect on the myocardium which leads to the development of dilated cardiomyopathy.

Causes of dilated cardiomyopathy:

• Acquired causes :

• Infectious and non-infectious myocarditis: most common cause globally

• Alcohol is the most common cause in India

• Pregnancy:

• Pregnancy-associated cardiomyopathy (PACM)

• Peripartum cardiomyopathy (PPCM)

• Stress-induced: Takotsubo cardiomyopathy

• Drug-induced:

• Doxorubicin (anthracycline)

• Trastuzumab

• Cyclophosphamide

• Nutritional deficiency:

• Beriberi (thiamine),

• Keshan disease (selenium),

• Carnitine deficiency

• Endocrine: Hypo and hyperthyroidism, acromegaly, diabetes mellitus

• Others:

• Cobalt toxicity,

• Heavy metals (lead, mercury, arsenic, lithium)

• Familial causes (50%):

• Mutation in the cardiac myocyte titin gene

• Haemochromatosis

• Syndromes: Duchenne muscular dystrophy, Becker's muscular dystrophy

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Solution to Question 3:

Titin is the largest protein expressed in humans.

Titin is the third myofilament of cardiac muscle. It has a single giant polypeptide spanning from Z-disk to the M-band region of the sarcomere.

Mutation in TTN, the gene encoding titin, is responsible for 20% of all cases of dilated cardiomyopathy.

Solution to Question 4:

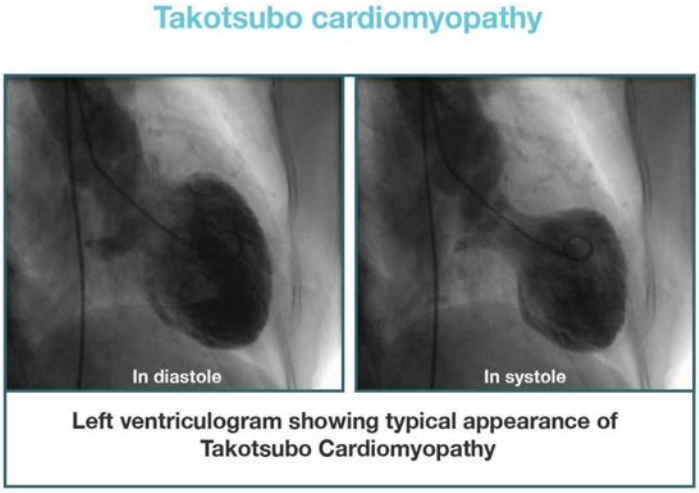
The given clinical scenario of sudden cardiac death in a previously healthy man, under a stressful situation, is suggestive of takotsubo cardiomyopathy. It is a type of dilated cardiomyopathy.

Takotsubo cardiomyopathy is also called broken heart syndrome, apical ballooning syndrome, or stress-induced cardiomyopathy. During extreme psychological stress, there is a catecholamine surge. This causes microcirculation spasms which lead to a transient myocardial stunning. It is usually seen in middle-aged women.

It leads to left ventricular contractile dysfunction. The left ventricular apex is most often affected which leads to apical ballooning. This resembles a "takotsubo," which is Japanese for "fishing pot for trapping octopus".

Histologically, acute cases may show microscopic areas of necrosis characterized by myocyte hyper contraction known as contraction band necrosis. Chronic cases may exhibit microscopic foci of granulation tissue.

The first image below shows a ventriculogram showing takotsubo cardiomyopathy. The second image shows a 'takotsubo,' or octopus fishing pot.



Left ventriculogram showing typical appearance of Takotsubo Cardiomyopathy

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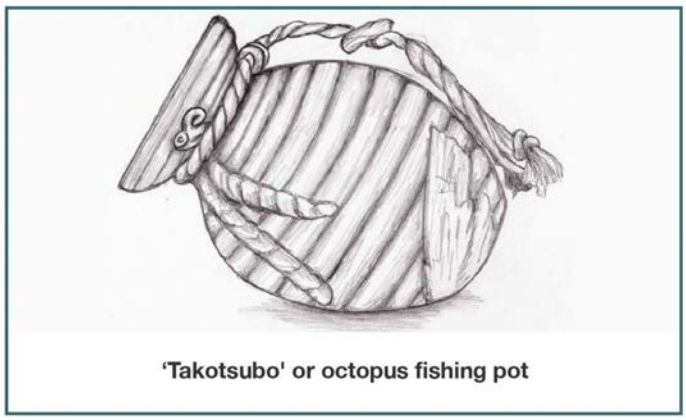
Takotsubo cardiomyopathy



'Takotsubo' or octopus fishing pot

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Solution to Question 5:

Selenium deficiency (Keshan's disease) is known to produce dilated cardiomyopathy and not its toxicity.

Causes of dilated cardiomyopathy:

Acquired causes:

- Infectious and non-infectious myocarditis is the most common cause globally
- Alcohol is the most common cause in India
- Pregnancy:
- Pregnancy-associated cardiomyopathy (PACM)
- Peripartum cardiomyopathy (PPCM)
- Stress-induced: Takotsubo cardiomyopathy
- Drug-induced:
- Doxorubicin: anthracyclines
- Trastuzumab
- Cyclophosphamide
- Nutritional deficiency:
- Beriberi (thiamine),
- Keshan disease (selenium)
- Carnitine deficiency
- Endocrine: Hypo and hyperthyroidism, acromegaly, diabetes mellitus
- Others:

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• Cobalt toxicity

• Heavy metals (lead, mercury, arsenic, lithium)

Familial causes (50%):

• Mutation in the cardiac myocyte titin gene

• Haemochromatosis

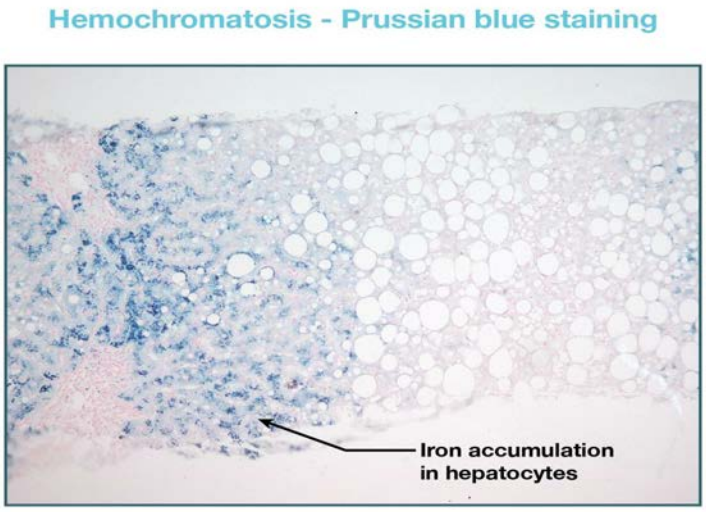
• Syndromes: Duchenne muscular dystrophy, Becker's muscular dystrophy

Solution to Question 6:

In the given scenario, liver microscopy shows hepatocellular iron, stained blue with Perl's Prussian blue stain. The patient most likely suffers from hemochromatosis. Dilated cardiomyopathy (DCM) is the predominant type of cardiomyopathy seen in hemochromatosis.

Hemochromatosis can also produce restrictive cardiomyopathy, but it is less common than DCM.

The image below shows hemochromatosis. There is hepatocellular iron, stained with Perl's Prussian blue.



Solution to Question 7:

In the given scenario, the histology image shows ninja-star like nuclei in myocytes. This is suggestive of dilated cardiomyopathy (DCM).

These are non-specific findings but the presence of ≥ 5% myocytes with ninja star-like nuclei are suggestive of DCM. Here, DCM is due to titin-truncating mutations. Truncating mutations are those which shorten the coding sequence of the genes.

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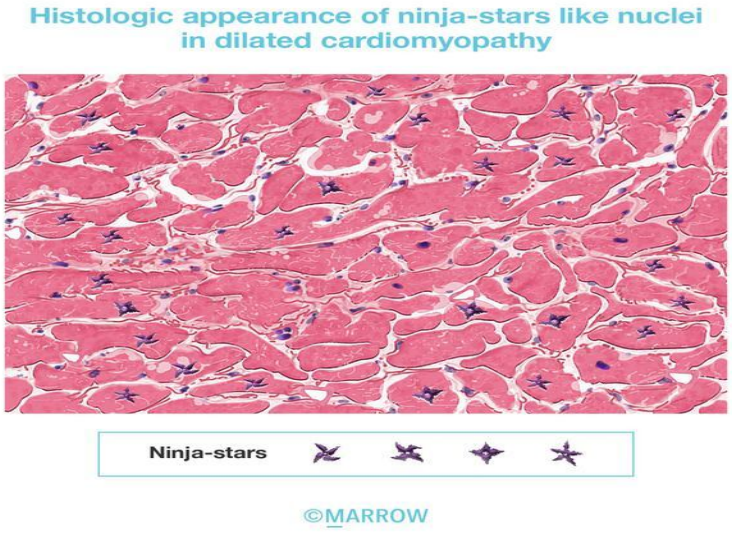
Histologically they appear as variable myocyte hypertrophy and interstitial fibrosis. The nuclei are enlarged, bizarre and hyperchromatic exhibiting a ninja-star like appearance.

The image given below explains the ninja star-like nuclei in the myocytes.



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Solution to Question 8:

In the given scenario, the patient suffered from sustained ventricular tachycardia secondary to arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is associated with Naxos syndrome.

ARVC is autosomal dominant cardiomyopathy characterized by fibrofatty replacement in the myocardium of the ventricles. It most commonly affects the right ventricle. It is due to mutations in the gene encoding desmosome-associated protein plakophilin 2. This leads to defective cell-adhesion proteins in the desmosomes that link adjacent cardiac myocytes.

As shown in the image below, Naxos syndrome is characterized by woolly hair and palmoplantar hyperkeratosis.

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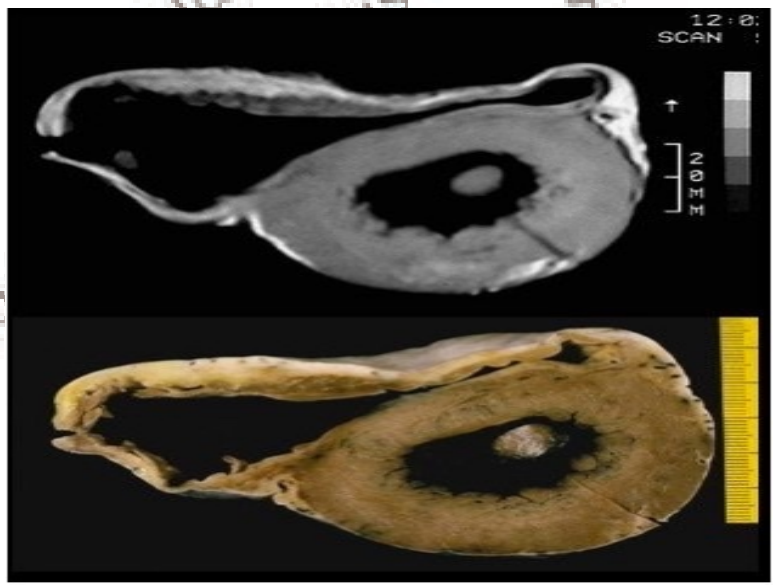
Morphology shows severe thinning of the right ventricular wall due to loss of myocytes, accompanied by extensive fatty infiltration and fibrosis.

The image given below is a gross photograph of the heart showing dilated right ventricle and near transmural replacement of its free wall with fat and fibrosis.



Carvajal syndrome is a variant of Naxos disease but is associated with dilated cardiomyopathy.

Solution to Question 9:

The given clinical scenario and autopsy findings are suggestive of hypertrophic cardiomyopathy (HCM). The image given is a histologic section of cardiac muscle showing myocyte disarray and extreme hypertrophy as seen in HCM.

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HCM is the leading cause of sudden cardiac death in young adults. It is defined as left ventricular hypertrophy of >15mm on ECHO. The left ventricular myocardium is poorly compliant. This leads to abnormal diastolic filling and intermittent ventricular outflow obstruction, i.e., primarily diastolic dysfunction.

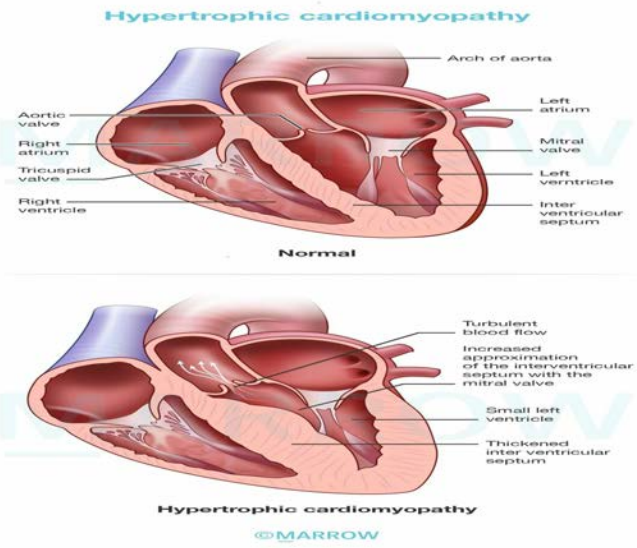
The gross features of HCM are:

• Massive myocardial hypertrophy usually without ventricular dilation

• Asymmetric septal hypertrophy- disproportionate thickening of the ventricular septum relative to the left ventricle free wall

• Banana-shaped left ventricle- due to bulging of the ventricular septum into the lumen

The image given below shows changes in hypertrophic cardiomyopathy compared to a normal heart. HCM shows asymmetric septal hypertrophy and thickened left ventricle wall.



Histologic features of the HCM are:

• Massive myocyte hypertrophy- with transverse myocyte diameters frequently greater than 40 µm, normal is approximately 15 µm.

• Myofiber disarray- haphazard disarray of bundles of myocytes, individual myocytes, and contractile elements in sarcomeres within cells

• Interstitial fibrosis and replacement fibrosis

The image given below is a histologic section of cardiac muscle showing myocyte disarray and extreme hypertrophy seen in an abnormal HCM septum.

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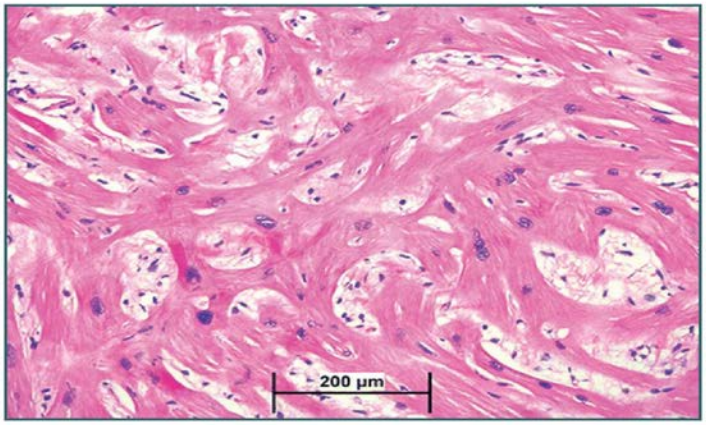
Hypertrophic cardiomyopathy -
Myocyte hypertrophy and disarray



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Solution to Question 10:

Mutations causing hypertrophic cardiomyopathy are most commonly seen in the genes encoding °-myosin heavy chain (°-MHC).

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease. In the majority of cases it is due to missense mutations in the following two sarcolemmal protein genes:

• Myosin binding protein C (MYBC)

• Beta myosin heavy chain (MYH7)

Solution to Question 11:

Restrictive cardiomyopathy is caused by hemochromatosis, ergotamine, amyloidosis and carcinoid syndrome. Trastuzumab causes dilated cardiomyopathy.

Restrictive cardiomyopathy (RCM) is characterized by increased ventricular stiffness causing impaired diastolic filling of the ventricles. The stiffness is secondary to an underlying disease causing accumulation of intra and intercellular substances in the myocardium.

Causes of RCM:

• Infiltration disorders

• Amyloidosis (most common)

• Sarcoidosis

• Storage disorders

• Fabry's disease

• Glycogen storage disease (type II>> III)

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• Hemochromatosis (DCM>RCM)

• Fibrotic disorders

• Scleroderma

• Endomyocardial fibrosis

• R-Radiation

• E-Ergotamine

• S-Serotonin

• T-Tropical Endomyocardial fibrosis

• C-Carcinoid syndrome

• Miscellaneous: post open heart surgery, diabetes.

Morphology of RCM:

• Ventricles are of almost normal size or slightly enlarged

• The myocardium is non-compliant

• Biatrial dilation is commonly observed

• Patchy or diffuse interstitial fibrosis

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Solution to Question 12:

In the given scenario, the patient has progressive dyspnoea along with hypereosinophilia. This is suggestive of Loeffler's endocarditis. It leads to restrictive cardiomyopathy.

There is peripheral eosinophilia and eosinophilic infiltrates in multiple organs, including the heart. Major basic protein (MBP) is a toxic product released from eosinophils. This initiates endomyocardial necrosis followed by scarring. It leads to endomyocardial fibrosis, typically with large mural thrombi.

Many patients with Loeffler's endocarditis have a myeloproliferative disorder. This is associated with chromosomal rearrangements involving platelet-derived growth factor receptor (PDGF)-α or -° genes.

Solution to Question 13:

In this scenario, the decrease in ventricular compliance indicates restrictive cardiomyopathy. Endocardial fibroelastosis is an uncommon restrictive heart condition characterized by fibroelastic thickening that typically involves the left ventricular endocardium.

It is most common in the first 2 years of life. It results from several different insults including viral infections (e.g., intrauterine exposure to mumps) or mutations in the gene for tafazzin. These mutations affect mitochondrial inner membrane integrity.

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Endomyocardial fibrosis is a disease of children and young adults in Africa and other tropical areas. It is characterized by fibrosis of the ventricular endocardium and subendocardium that extends from the apex upward. The aetiology is unknown.

Loeffler endomyocarditis results in endomyocardial fibrosis, typically with large mural thrombi. The overall morphology is similar to the tropical disease. In addition to the cardiac changes, there is often peripheral eosinophilia and eosinophilic infiltrates in multiple organs, including the heart.

Solution to Question 14:

Viral infections are the most common cause of myocarditis. Coxsackie viruses A and B and other enteroviruses account for most of the cases.

Myocarditis is a diverse group of pathologic entities in which infectious microorganisms and/or a primary inflammatory process cause myocardial injury.

Solution to Question 15:

Transthyretin is the major component of senile cardiac amyloid deposits. It is a normal serum protein synthesized in the liver that transports thyroxine and retinol-binding protein.

Amyloidosis of the heart can develop as a consequence of systemic amyloidosis or it may be localized. This is particularly seen in the elderly (senile cardiac amyloidosis). It has a far better prognosis than systemic amyloidosis.

Presentation of cardiac amyloidosis:

• Restrictive cardiomyopathy- most common

• Asymptomatic

• Dilation

• Arrhythmias

• Ischemic disease

• Valvular disease.

The chambers are usually of normal size, but can be dilated and have thickened walls. Small, semitranslucent nodules resembling drips of wax may be seen on the atrial endocardial surface, particularly on the left.

Histologically, hyaline eosinophilic deposits of amyloid are found in:

• Interstitium

• Conduction tissue

• Valves, endocardium

• Pericardium

• Small intramural coronary arteries.

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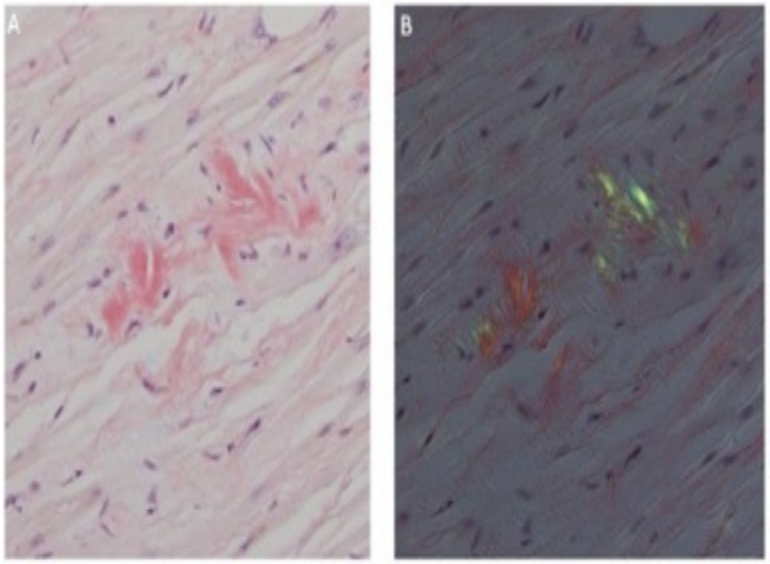
The image given shows an endomyocardial biopsy of a patient with cardiac amyloidosis stained as follows: A) Congo red only, B) Apple-green birefringence under polarized light



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Solution to Question 16:

The given clinical scenario suggests post-myocardial infarction fibrinous pericarditis. It is the most common type of pericarditis.

Clinically, there is a loud pericardial friction rub. There is a rubbery fibrin mass loosely glueing the parietal and visceral pericardium together (bread and butter). It may resolve or become organized to produce adhesive pericarditis.

It is usually seen following:

• Myocardial infarction

• Rheumatic fever

• Trauma

• Uremia

• Radiation

• Systemic lupus erythematosus (SLE)

• Severe pneumonia

Types of acute pericarditis:

Serous pericarditis: There is a mild inflammation of epicardial and pericardial surfaces. Both acute and chronic inflammatory cells are present. There is exudative serous fluid, usually 50–200 mL. Thus, it develops slowly and rarely alters cardiac function.

It is caused by:

• Rheumatic fever

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• SLE

• Systemic scleroderma

• Tumours

• Uremia

• Viral infection

• Tuberculosis

Suppurative /purulent pericarditis: It may be due to bacterial, mycotic, or parasitic invasion. The inflammation may extend into the surrounding mediastinum. It usually, results in organization and, therefore, constrictive pericarditis with clinical sequelae. The entry of the pathogen into the pericardium may be by:

• direct extension

• seeding from blood

• lymphatic spread

• seeding by instrumentation

Hemorrhagic pericarditis: It can be due to tuberculosis or a malignant neoplasm (from lung or breast). It can also be seen following cardiac surgery. Caseous pericarditis is almost always tubercular in origin.

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Solution to Question 17:

In the given scenario, fever, pericardial pain and effusion 4 weeks after MI, is suggestive of Dressler's syndrome. The aetiology of Dressler's syndrome is autoimmune.

It is also known as post-myocardial infarction (post-MI) cardiac injury syndrome. It occurs one week to as long as two to three months after MI.

A fibrinous or fibrinohemorrhagic pericarditis usually develops around the second or third day following a transmural infarct. It is a result of the underlying myocardial inflammation.

Dressler's syndrome is believed to have an autoimmune aetiology. There is an inflammatory reaction to myocardial neo-antigens formed as a result of MI.

Solution to Question 18:

Concretio cordis occurs in advanced cases of constrictive pericarditis.

In constrictive pericarditis, a thick,0.5 - 1cm, fibrous scar tissue is formed. This can obliterate the pericardial space and sometimes calcify. In extreme cases, it can resemble a plaster mold and is known as concretio cordis.

Constrictive pericarditis may be idiopathic or can occur following:

• Pericarditis- serous or caseous

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• Cardiac surgery

• Heavy irradiation

Adhesive mediastinopericarditis occurs when adhesion and fibrosis extends from the parietal pericardium into the mediastinum

Soldier's plaque is a focal pearly thickened epicardial plaque. It indicative of healed pericarditis

Solution to Question 19:

Myxomas are the most common primary tumours of the heart in adults.

90% of myxomas are located in the atria. The left-to-right ratio of the myxoma is approximately 4:1. The region of the fossa ovalis in the atrial septum is the favoured site of origin.

Histopathological examination shows stellate or globular myxoma, "lepidic," cells. Peculiar vessel-like or gland-like structures are characteristic. Major clinical manifestations are fever and malaise (due to IL-6). Valvular "ball-valve" obstruction or embolization can occur.

Important points on cardiac tumors:

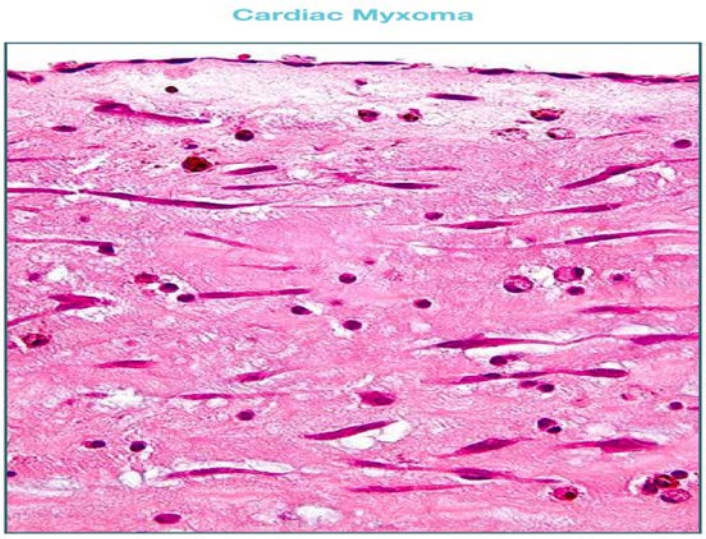
• Most common cardiac tumour: metastasis

• Most common benign cardiac tumour: atrial myxoma

• Most common primary cardiac tumour in adults: atrial myxoma

• Most common primary cardiac tumour in children: rhabdomyoma

The image given below shows an abundant amorphous extracellular matrix. It contains scattered multinucleate myxoma cells in various groupings, including abnormal vessel-like formations.



Solution to Question 20:

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Null mutations in the PRKAR1A gene is seen in Carney's complex. Cardiac myxomas are present in 30–40% of Carney complex patients.

Familial syndromes associated with myxomas have activating mutations in the GNAS1 gene or null mutations in PRKAR1A. Mutations in GNAS1 is associated with McCune-Albright syndrome. PRKAR1A gene encodes a regulatory subunit of a cyclic-AMP-dependent protein kinase (Carney complex).

Skin lesions are the most common manifestation of the Carney complex. The most common type of endocrine tumour in the Carney complex is the primary pigmented nodular adrenocortical disease (PPNAD). It is a form of bilateral adrenal hyperplasia that leads to adrenocorticotropic hormone (ACTH)-independent Cushing syndrome.

NAME syndrome and LAMB syndrome are subsets of the Carney complex. The LAMB acronym refers to lentigines, atrial myxoma, and blue nevi. NAME refers to nevi, atrial myxoma, myxoid neurofibromas, and ephelids.

Components of Carney Complex:

• Skin pigmented lesions (lentigines, blue nevi, other)

• Myxomas (cutaneous, mucosal, cardiac, other)

• PPNAD (Cushing Syndrome)

• GH-PRL-producing adenomas (acromegaly)

• Leydig or Sertoli cell tumors

• Ovarian cystadenoma or carcinoma

• Thyroid adenoma or cancer

• Psammomatous melanotic schwannoma

• Breast ductal adenoma

• Osteochondromyxoma

• Cancers (liver, pancreas, adrenal)

Carney triad:

• Extra-adrenal paraganglioma

• Gastrointestinal stromal tumor

• Pulmonary chondroma

Carney–Stratakis Syndrome: Familial paraganglioma and gastrointestinal stromal tumour (GIST)

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Solution to Question 21:

Atrial myxomas most commonly occur in the left atrium.

Myxoma is usually single, but can rarely be multiple. The region of the fossa ovalis in the atrial septum is the favoured site of origin. Mobile tumours exert a “wrecking-ball” effect, causing damage to the valve leaflets.

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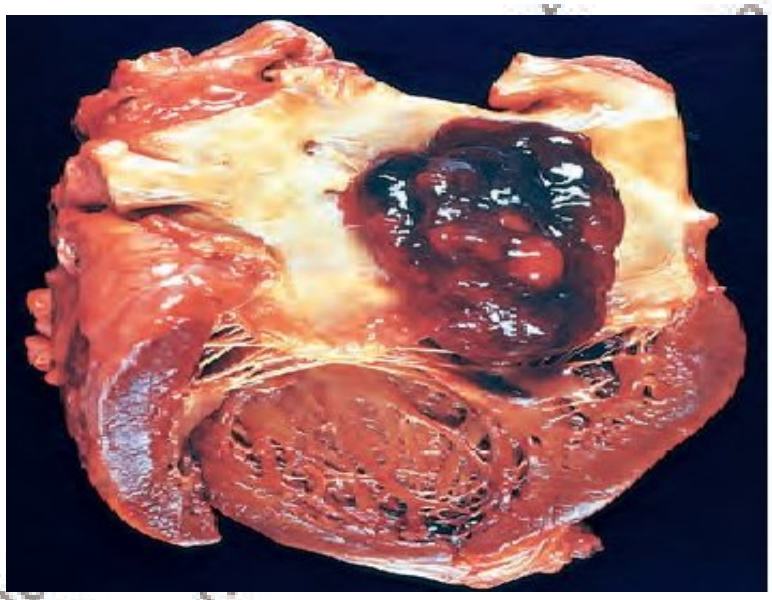
They can be sporadic or familial.

The image given below shows a gross picture of an atrial cardiac myxoma arising from the region of the fossa ovalis and extending to mitral valve orifice:

Sporadic Type Myxoma	Familial Type Myxoma
Single	Multiple
Postoperative recurrance NIL	Present
Younger age	
Left atria - Most common site	



Solution to Question 22:

The given histological slide shows abundant spider cells. They are seen in rhabdomyoma.

Microscopically, they are composed of bizarre, markedly enlarged myocytes. Routine histologic processing often artifactually reduces the abundant cytoplasm to thin strands that stretch from the nucleus to the surface membrane. This appearance is referred to as “spider” cells.

Rhabdomyoma is the most frequent primary tumour of the pediatric heart. 50% of cases are associated with tuberous sclerosis, with mutations in the tumour-suppressor genes TSC1 and TSC2. They are usually multiple and occur in ventricles preferentially. They often regress spontaneously and may, therefore, be considered as hamartomas.

Image given shows spider cell in rhabdomyoma:

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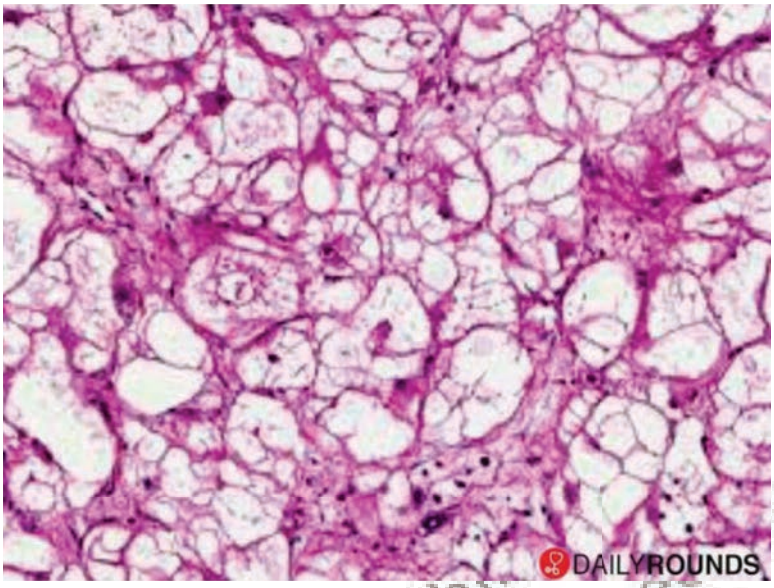

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Solution to Question 23:

The single most important long-term limitation of cardiac transplantation is allograft arteriopathy.

Complications following cardiac transplantation:

Allograft rejection: It is the primary concern that requires close surveillance. Both classic cellular rejection and antibody-mediated rejection is recognized. Cellular rejection is characterized by interstitial lymphocytic inflammation, with associated myocyte damage.

Allograft arteriopathy: It is the single most important long-term limitation for cardiac transplantation. It is a late, progressive, diffusely stenosing intimal proliferation in the coronary arteries, leading to ischemic injury. It can lead to silent myocardial infarction since transplant patients have denervated hearts and do not experience angina. Progressive congestive heart failure and sudden cardiac death can also occur.

Other postoperative problems include infection and malignancies, especially Epstein–Barr virus-associated B-cell lymphomas.

The image given below shows allograft arteriopathy. There is severe diffuse concentric intimal thickening producing critical stenosis. The internal elastic lamina and media are intact (Movat pentachrome stain, elastin black)

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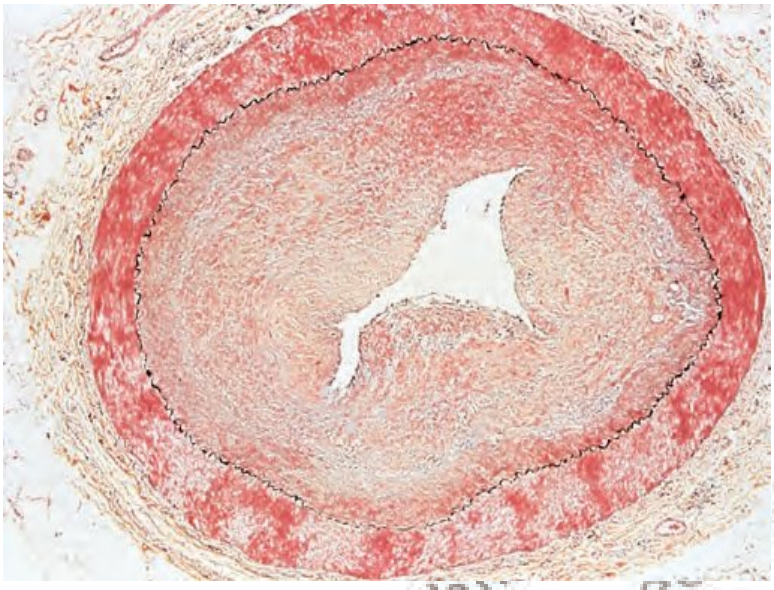

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Solution to Question 24:

The image shows a heart with left ventricular hypertrophy. The most common cause of left ventricular hypertrophy is chronic hypertension.

Solution to Question 25:

In the given scenario, a marathon runner will have cardiac hypertrophy with increased capillary density. Aerobic exercise, e.g., long-distance running, is associated with volume-load hypertrophy accompanied by an increase in capillary density. This is not seen in other forms of hypertrophy. This decreases resting heart rate and blood pressure.

In hypertrophy due to pressure or volume overload, there is a sustained increase in mechanical work. This cause myocytes to increase in size thus increasing the size and weight of the heart. The hypertrophied heart has an increased oxygen consumption but decreased supply. This is because hypertrophy is not accompanied by a proportional increase in capillary numbers. This leads to ischemia-related decompensation, which can evolve to cardiac failure and eventually lead to death.

The causes and consequences of hypertrophy are summarized in the below image.

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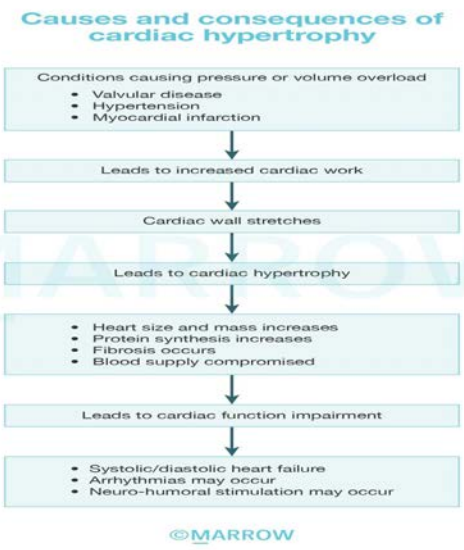

Heart weight, rather than wall thickness, is the best measure of hypertrophy in dilated hearts.

A patient with systemic hypertension has pressure-overload hypertrophy.

A patient with an echo finding of an aortic valvular area of 0.6cm^2 is suggestive of aortic stenosis. There is pressure-overload hypertrophy.

A patient with a high pitched holosystolic murmur best heard at the apex is suggestive of mitral regurgitation. There is volume-overload hypertrophy.

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Congenital and Valvular Heart Disease

Question 1:

Most congenital heart diseases arise between what weeks of embryogenesis?

a) 1 to 4

b) 3 to 8

c) 8 to 12

d) 10 to 14

Question 2:

What congenital heart defect is associated with Char syndrome?

a) Patent ductus arteriosus (PDA)

b) Atrial septal defect (ASD)

c) Ventricular septal defect (VSD)

d) Tetralogy of Fallot (TOF)

Question 3:

Which of the following cardiac defects is not associated with Down's syndrome?

a) Coarctation of aorta

b) Ventricular septal defect

c) Patent ductus arteriosus

d) Atrial septal defect

Question 4:

What is the most common type of atrial septal defect?

a) Primum anomalies

b) Secundum ASD

c) Sinus venosus defect

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d) Membranous type

Question 5:

Which of the following is not a feature of tetralogy of Fallot?

a) Left ventricular hypertrophy

b) Subpulmonary stenosis

c) Overriding aorta

d) Ventricular Septal Defect

Question 6:

A 5-year-old child was brought to the OPD for evaluation of cognitive impairment. Parents report that the child is overly-friendly with strangers. On examination, elfin facies and hypotonia are noted. Investigations reveal hypercalcemia. Which of the following cardiac defects is associated with this syndrome?

a) Ventricular septal defect

b) Atrial septal defect

c) Aortic stenosis

d) Hypoplastic ventricles

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Question 7:

Which of the following is the most common cause of mitral stenosis?

a) Rheumatic heart disease

b) Calcification

c) Atherosclerotic damage

d) Infective endocarditis

Question 8:

A 42-year-old man presented with chest pain and exertional dyspnea for the past 2 months. He has no history of cardiac disease. Examination revealed an ejection systolic murmur. Transesophageal echocardiography was done, which revealed an aortic valve with 2

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functional cusps and a valve area of 0.8 sq. cm. Which of the following is false regarding this condition?

a) Chromosomes 18q, 5q, and 13q are linked

b) Loss-of-function mutations in NOTCH1

c) It is due to abnormal fusion of valve commissures

d) Midline of larger cusp is major site of calcification

Question 9:

A 45-year-old woman who came for a routine check-up was incidentally found to have a late systolic murmur with a mid-systolic click. Echocardiography revealed thickening and redundancy of mitral leaflets with bulging into the left atrium. Which of the following is not a feature of this condition?

a) Annular dilation

b) Myxomatous degeneration

c) Degenerative calcified deposits

d) Thickening of mural endocardium

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Question 10:

A 48-year-old man presented with dull aching abdominal pain and diarrhea for the past 2 months. On examination, his face and chest appeared flushed. In a 24-hour urine sample, 5HIAA levels were elevated. CT scan of the abdomen revealed a mass in the terminal ileum. Cardiac involvement in this syndrome is characterized by all of the following except:

a) Endocardial fibrosis

b) Tricuspid insufficiency

c) Pulmonary stenosis

d) Mitral stenosis

Question 11:

Which is the most commonly involved valve in carcinoid heart disease?

a) Mitral

b) Tricuspid

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c) Aortic

d) Pulmonary

Answer Key

Question No.	Correct Option
1	b
2	a
3	a
4	b
5	a
6	c
7	a
8	c
9	c
10	d
11	b

If you purcha... you may have... else, ...d.

Detailed Explanations

Solution to Question 1:

Most congenital heart diseases arise from faulty embryogenesis during gestational weeks 3 to 8 when major cardiovascular structures form and begin to function.

The most common congenital heart disease is ventricular septal defect (VSD), whereas the 2nd most common is atrial septal defect (ASD).

Solution to Question 2:

Char syndrome is associated with patent ductus arteriosus (PDA).

The clinical presentation of this syndrome includes PDA with facial dysmorphism and abnormal fifth digits.

The following images show the facial dysmorphism associated with Char syndrome.

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Solution to Question 3:

Coarctation of the aorta is a feature of Turner's syndrome, not Down's syndrome.

Down's syndrome (trisomy 21) is the most common cause of congenital heart disease (CHD). Cardiac defects in Down's syndrome are due to endocardial cushion defects.

Cardiac defects in various chromosomal anomalies are as follows:

Syndrome	Cardiac defects
Down's syndrome (Trisomy 21)	Ventricular septal defectPatent ductus arteriosusAtrial septal defect
Patau syndrome (Trisomy 13)	Ventricular septal defectPatent ductus arteriosusAtrial septal defect
Edward's syndrome (Trisomy 18)	Ventricular septal defectPatent ductus arteriosusAtrial septal defectDextroposition
Turner syndrome (Monosomy X)	Bicuspid aortic valveCoarctation of the aortaDilated ascending aorta

Solution to Question 4:

Secundum atrial septal defect (ASD) is the most common type of ASD.

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ASDs are abnormal, fixed openings in the atrial septum caused by incomplete tissue formation that allows communication of blood between the left and right atria.

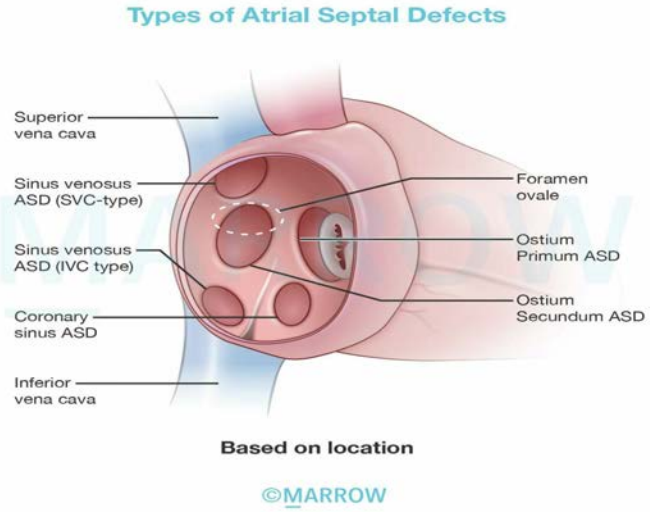
It results in a left-to-right shunt. Excess blood flow through the ASD and/or the pulmonary valve results in a murmur. They are generally well-tolerated and usually do not become symptomatic before the age of 30 years.

ASDs are classified according to their location:

• Secundum ASD (90%) - usually isolated defects, can be of any size, multiple or fenestrated

• Primum anomalies (5%) - occur adjacent to the AV valves, often associated with AV valve defects and/or VSD

• Sinus venosus defects (5%) - located near SVC entrance and can be associated with anomalous pulmonary venous return to the right atrium



Solution to Question 5:

Right ventricular hypertrophy (RVH) is a feature of the tetralogy of Fallot (TOF), not left ventricular hypertrophy.

The four cardinal features of tetralogy of Fallot are as follows:

• Ventricular septal defect (VSD)

• Obstruction of the right ventricular outflow tract (subpulmonary stenosis)

• An aorta that overrides the VSD

• Right ventricular hypertrophy

It is the most common type of cyanotic congenital heart disease (CHD). The heart is typically enlarged and is classically boot-shaped due to marked right ventricular hypertrophy.

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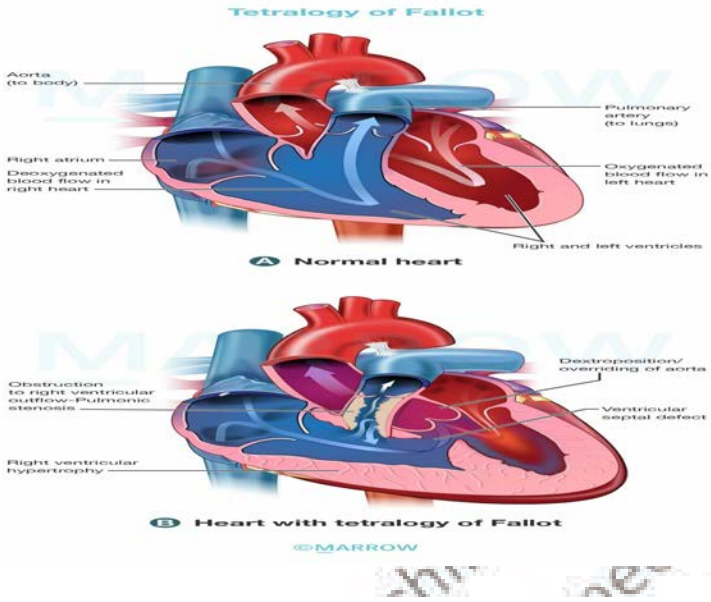
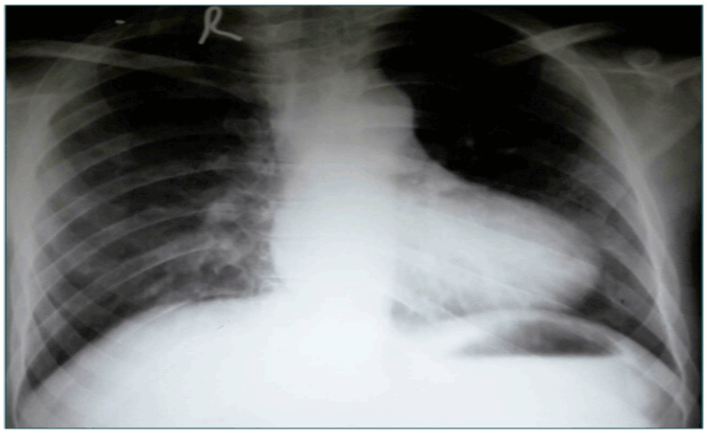


Boot-shaped heart



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Solution to Question 6:

The given features are suggestive of Williams (Williams–Beuren) syndrome. It is associated with supravalvular aortic stenosis.

This condition is due to deletions on chromosome 7 which includes the gene for elastin. These mutations may cause supravalvular stenosis by disrupting elastin–smooth muscle cell interactions during aortic morphogenesis. There is thickening of ascending aortic wall and consequent luminal constriction.

Other features of the syndrome include:

• Elfin facies - wide mouth, chubby cheeks, long philtrum, small nose, and delicate chin (as shown in the image)

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• Cognitive abnormalities

• Intellectual disability (usually mild)

• Personality changes - over-friendliness to strangers

• Hypotonia

• Connective tissue abnormalities

• Endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, early puberty)

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Solution to Question 7:

The most common cause of mitral stenosis is rheumatic heart disease. Mitral stenosis is the most common lesion in rheumatic heart disease.

In rheumatic mitral stenosis, calcification and fibrous bridging across the valvular commissures create fish mouth or buttonhole stenosis. Rheumatic mitral stenosis is associated with loud S1.

The most common causes of various valvular diseases are:

• Aortic stenosis (AS) - calcification due to normal aging or congenitally bicuspid aortic valves

• Aortic regurgitation (AR) - dilatation of the ascending aorta, often secondary to hypertension and/or aging

• Mitral regurgitation (MR) - myxomatous degeneration (mitral valve prolapse)

Solution to Question 8:

The clinical scenario and echo findings are suggestive of calcific aortic stenosis secondary to bicuspid aortic valve (2 functional cusps). It is due to incomplete separation of valve commissures during development, not abnormal fusion.

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In a congenitally bicuspid aortic valve, the 2 functional cusps are usually of unequal size. The larger cusp has a midline raphe that results from incomplete commissural separation during development. The raphe is frequently a major site of calcific deposits.

This condition is associated with mutations in the following areas:

• Chromosomes 18q, 5q, and 13q

• Chromosome 9q - loss-of-function mutations in NOTCH1 gene

Late complications include:

• Aortic stenosis or regurgitation

• Infective endocarditis

• Aortic dilation and/or dissection.

• Predisposed to progressive calcification - Approximately 50% of cases of aortic stenosis in adults.

Note: Acquired bicuspid valves result from abnormal fusion of valve commissures because of an acquired deformity (rheumatic valve disease). It produces a conjoined cusp that is generally twice the size of the nonconjoined cusp.

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Solution to Question 9:

The clinical features and echocardiography findings are suggestive of mitral valve prolapse (MVP) or Barlow syndrome. It is not associated with degenerative calcified deposits (seen in calcific valvular degeneration, not MVP).

Barlow syndrome is more common in females. It may be an isolated condition or less commonly can be associated with connective tissue disorders like Marfan's syndrome.

In this condition, there is mitral annular dilatation with floppy mitral valve leaflets. They prolapse or balloon back into the left atrium during systole. The following pathological changes are seen:

• Interchordal ballooning (hooding) of the mitral leaflets

• Thick, rubbery, redundant leaflets

• Thickened mural endocardium

The main histologic change is marked thickening of the spongiosa layer with deposition of mucoid called myxomatous degeneration.

Most individuals diagnosed with MVP are asymptomatic. On auscultation, a mid-systolic click, sometimes followed by a mid to late systolic murmur is heard. Chest pain mimicking angina and dyspnea occur rarely.

The complications include:

• Infective endocarditis

• Mitral insufficiency

• Stroke or other systemic infarcts

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• Arrhythmias

• Sudden cardiac death (rarely)

Solution to Question 10:

The clinical scenario is suggestive of carcinoid syndrome. Mitral stenosis is not a feature of cardiac involvement in this condition.

Carcinoid heart disease refers to the cardiac manifestations caused by the bioactive compounds released by carcinoid tumors. Classically, the endocardium and valves of the right heart are primarily affected.

Findings in carcinoid heart syndrome:

• Endocardial plaque-like thickening and fibrosis

• Tricuspid insufficiency

• Pulmonary stenosis

• No valve destruction

• Myocardium not involved

The left side of the heart is less commonly affected because the pulmonary vascular bed degrades the mediators. However, left heart carcinoid lesions can occur in the setting of ASD or VSD, or in the case of primary pulmonary carcinoid tumors.

Solution to Question 11:

Carcinoid heart disease most commonly affects the tricuspid valve.

It usually affects right heart structures. The most common features are tricuspid regurgitation and pulmonary stenosis.

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Rheumatic Fever and Endocarditis

Question 1:

A 12-year-old boy is admitted with fever and polyarthritis. He had a bout of streptococcal sore throat infection two weeks back. His ESR on admission was 80mm/hr and fever 39°C. What is the mechanism of tissue injury in this condition?

a) Type II hypersensitivity

b) Type III hypersensitivity

c) Type II and type III hypersensitivity

d) Type II and type IV hypersensitivity

Question 2:

Which is the least commonly affected heart valve in acute rheumatic fever?

a) Mitral

b) Aortic

c) Tricuspid

d) Pulmonary

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Question 3:

A 45-year-old woman died due to cardiac failure. On autopsy, on the mitral valve, small warty vegetations were present along the lines of closure. There were also irregular thickenings in the left atrium. What is the likely diagnosis?

a) Rheumatic heart disease

b) Rhabdomyoma

c) Infective endocarditis

d) Libman-Sacks endocarditis

Question 4:

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In a town where the prevalence of all-age rheumatic heart disease is 5 per 1000 per year, all of the following are included as major Jones criteria except:

a) Pancarditis

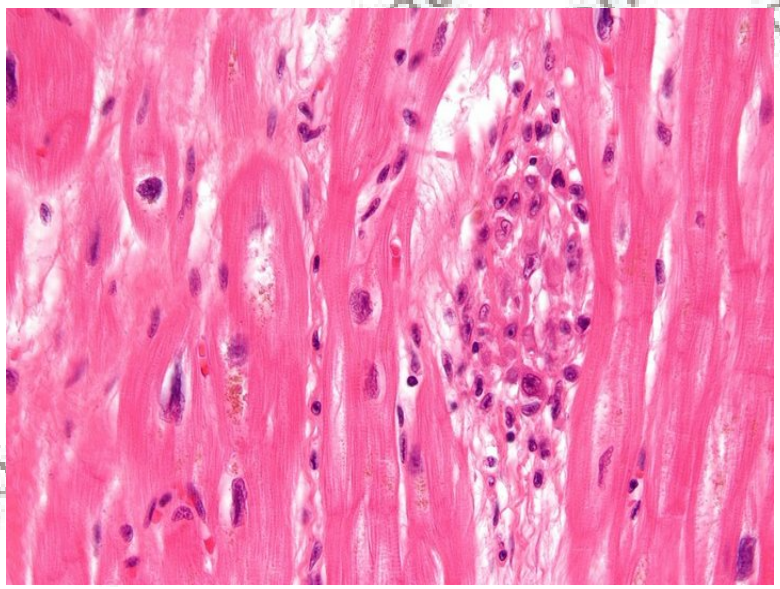
b) Monoarthritis

c) Subcutaneous nodules

d) Monoarthralgia

Question 5:

A 30-year-old male patient presents with severe dyspnoea. Mitral stenosis with left atrial hypertrophy is seen. Vegetations present on the mitral valve were excised. What is the most likely diagnosis based on the given HPE image?



a) Rheumatic valvular disease

b) Infective endocarditis

c) Myxoma

d) Sarcoidosis

Question 6:

The following finding was observed in a post-mortem specimen taken from a patient with acute rheumatic carditis. All of the following features are present except:

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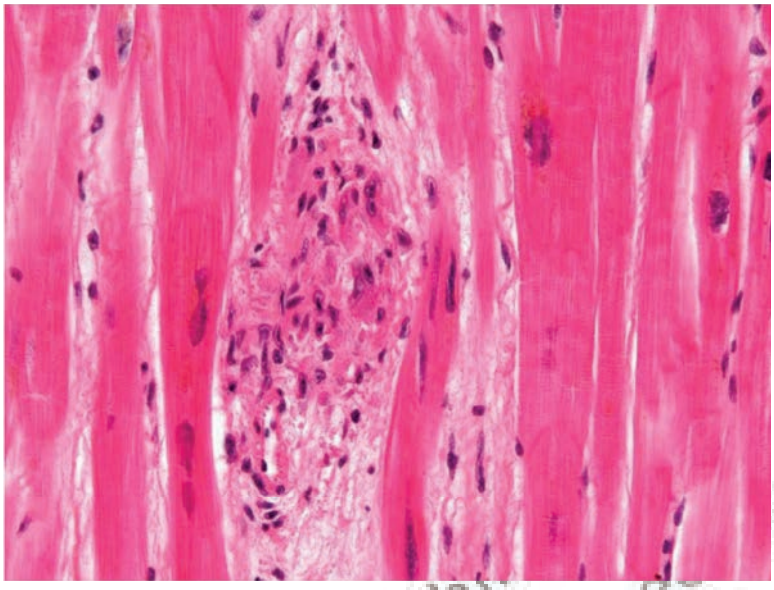

a) Anitschkow cells

b) Fibrinoid necrosis

c) Giant cells

d) Bacterial colonies

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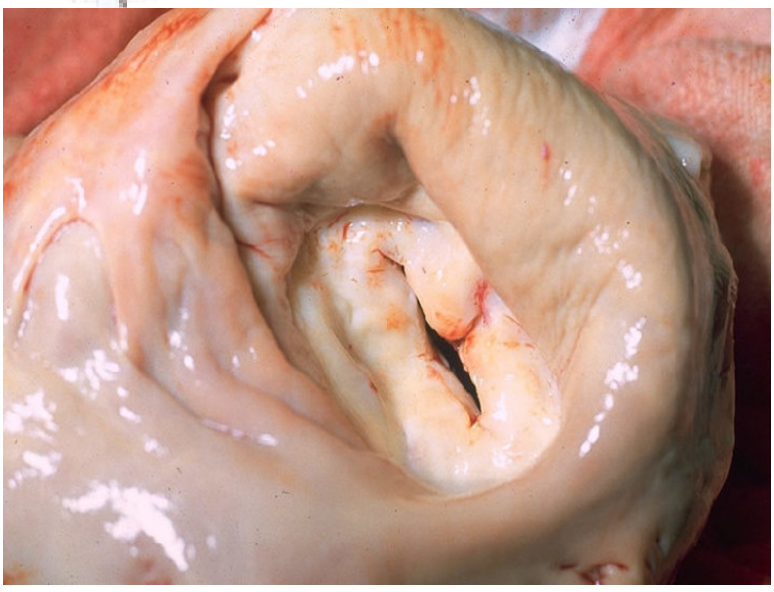
Question 7:

A 47-year-old female patient with a long-standing history of rheumatic heart disease was admitted to hospital due to severe breathlessness. She died on the 3rd day following admission. The mitral valve shows the following findings on autopsy. What is the cause of these findings?



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a) Rupture of valve

b) Calcification and fibrosis

c) Hypertrophy of ventricular wall

d) Hypertrophy of the atrial wall

Question 8:

Which of the following is implicated in acute infective endocarditis?

a) Staphylococcus aureus

b) Streptococcus viridans

c) Staphylococcus epidermidis

d) Streptococcus pyogenes

Question 9:

A 50-year-old man with severe rheumatic mitral stenosis underwent prosthetic mitral valve insertion. In the first 2 months following surgery, he is at the highest risk of infection with which of the following organisms?

a) S. viridans and S. gallolyticus

b) S. aureus and S. viridans

c) S. aureus and S. epidermidis

d) S. aureus and E. faecalis

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Question 10:

A 30-year-old man presented with a high-grade fever, chills, and breathlessness for 4 days. He has no other known medical conditions but has a history of IV drug abuse. On examination, the following painful lesions were noted and a regurgitant murmur was heard on auscultation. All of the following are minor criteria for diagnosis of this condition except:

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a) Predisposing heart lesion

b) Fever

c) Janeway lesions

d) Echo showing a valve-related mass

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Question 11:

Which of the following statements is true regarding the modified Duke's criteria?

a) Single positive blood culture for HACEK group is a major criterion

b) Single positive blood culture for Coxiella Burnetti is a major criterion

c) Complete dehiscence of prosthetic valve

d) Documentation of four minor criterion allows a clinical diagnosis

Question 12:

A 40-year-old woman presented with chest pain and breathlessness for 1 month. Examination revealed a regurgitant murmur. Transesophageal echocardiography revealed vegetations on both sides of mitral valve leaflets. What is the likely diagnosis?

a) Systemic lupus erythematosus

b) Systemic sclerosis

c) Sjogren's syndrome

d) Sarcoidosis

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Question 13:

Large, friable, irregular vegetations on heart valves are seen in which condition?

a) Infective endocarditis

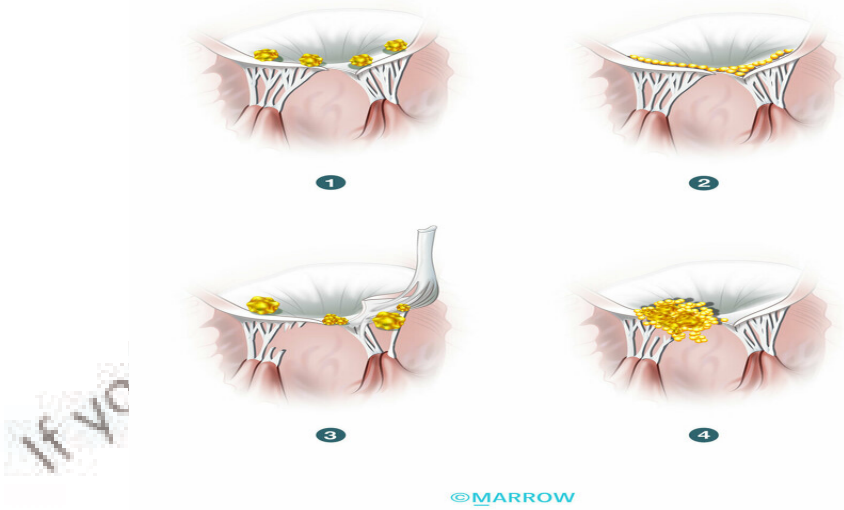
b) Rheumatic heart disease

c) Libman-Sacks endocarditis

d) Non-bacterial thrombotic carditis

Question 14:

Match the following morphology of vegetations with the conditions in which they are found.



a) 1-C, 2-A, 3-D, 4-B

b) 1-A, 2-C, 3-D, 4-B

c) 1-D, 2-A, 3-C, 4-B

d) 1-C, 2-B, 3-D, 4-A

Question 15:

Which of the following is not true about non-bacterial thrombotic endocarditis?

a) It causes emboli

b) Vegetations > 5 mm size are seen

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c) Sterile vegetations are seen

d) It is locally nondestructive

Answer Key

Question No.	Correct Option
1	a
2	d
3	a
4	d
5	a
6	d
7	b
8	a
9	c
10	d
11	b
12	a
13	a
14	a
15	b

Detailed Explanations

Solution to Question 1:

The given clinical scenario with polyarthritis (1 major) along with fever and ESR elevated (2 minor) is suggestive of acute rheumatic fever. It is an example of type II hypersensitivity.

This condition classically occurs a few weeks after an episode of group A streptococcal pharyngitis or, less commonly, skin infections. The antibodies to streptococcal cell-wall antigen cross-react with myocardial antigen resulting in macrophage activation and inflammation.

Acute rheumatic carditis is a common manifestation of active RF and may progress over time to chronic rheumatic heart disease (RHD), mainly manifesting as valvular abnormalities. Damage to heart tissue may be caused by a combination of antibody and T-cell-mediated reactions.

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Solution to Question 2:

The least commonly affected valve in acute rheumatic fever is the pulmonary valve.

The most commonly affected valve is the mitral valve.

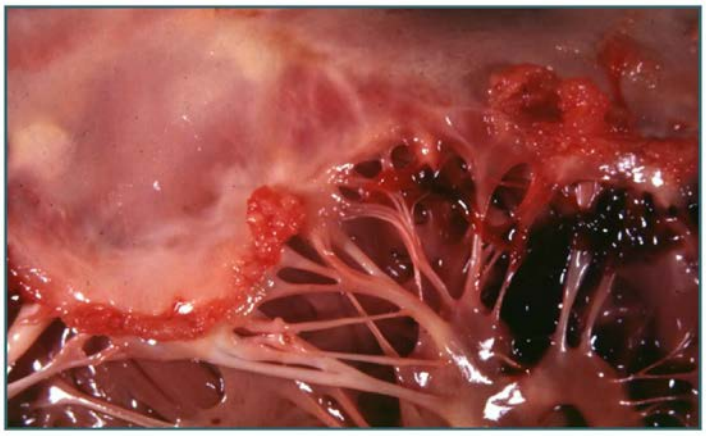
Solution to Question 3:

The clinical scenario and the gross findings seen are diagnostic of rheumatic heart disease.

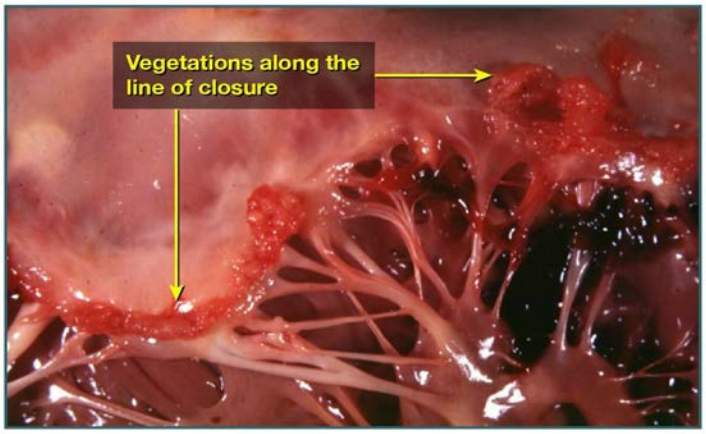
Inflammation of the endocardium and the left-sided valves results in fibrinoid necrosis within the cusps or tendinous cords. Overlying these necrotic foci and along the lines of closure are small (1 to 2 mm) warty vegetations.

Subendocardial lesions, exacerbated by regurgitant jets, can induce irregular thickenings called MacCallum plaques, usually in the left atrium.

Warty vegetations - Rheumatic Heart Disease



Warty vegetations - Rheumatic Heart Disease



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Solution to Question 4:

Monoarthralgia is a minor Jones criterion in moderate-high risk population (all-age rheumatic heart disease prevalence of >1 per 1000 population per year).

Major criteria for acute rheumatic fever include the following:

Criteria	Characteristics
Carditis	Most commonly affected valve - Mitral valveAcute RHD - MRChronic RHD - MSLeast common - Pulmonary valvePancarditis, bread and butter pericarditis
Migratory Polyarthritis	Most common manifestation Affects large joints,involves one joint after the otherNon-erosive arthritisNo residual deformityImproves rapidly with aspirin
Subcutaneous nodules	Painless nodulesOn extensor surfaces of elbows, shin, and occiput
Erythema marginatum	Red macular rash that spares the faceNo residual scarring
Sydenham's chorea	Late manifestationInvoluntary purposeless movementsAssociated with emotional lability and depression

Solution to Question 5:

The given image depicts Aschoff's body, which is suggestive of rheumatic valvular disease.

Aschoff's bodies have the following components:

• Anitschkow cells or plump macrophages

• Abundant cytoplasm

• Caterpillar cells - refer to centrally condensed chromatin into slender, wavy ribbons

• Foci of fibrinoid necrosis

• Aschoff's giant cells - multinucleated larger macrophages

• T-cells

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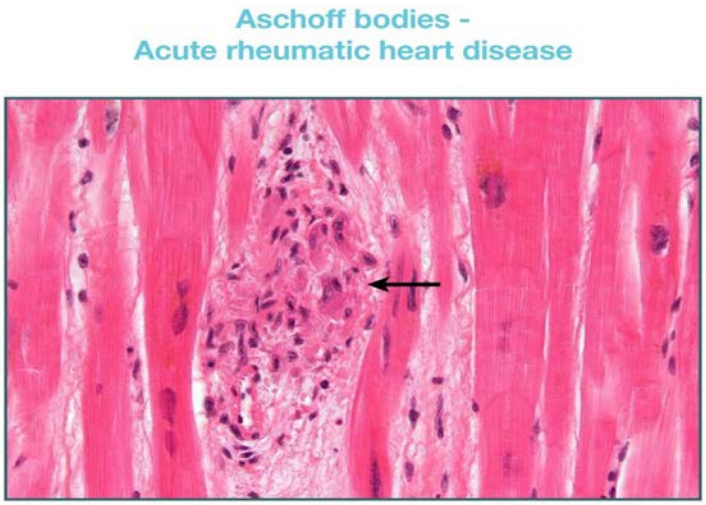
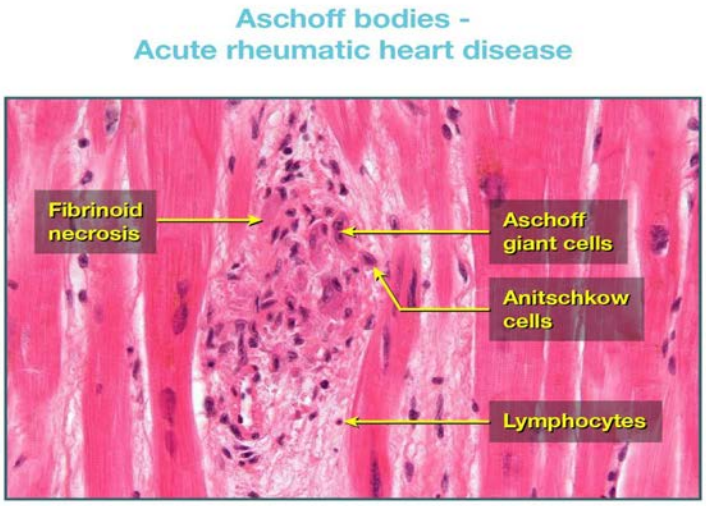
• Plasma cells





Solution to Question 6:

The given image shows Aschoff's bodies. Bacterial colonies are not a component.

Aschoff's bodies have the following components:

• Anitschkow cells or plump macrophages

• Abundant cytoplasm

• Caterpillar cells - refer to centrally condensed chromatin into slender, wavy ribbons

• Foci of fibrinoid necrosis

• Aschoff's giant cells - multinucleated larger macrophages

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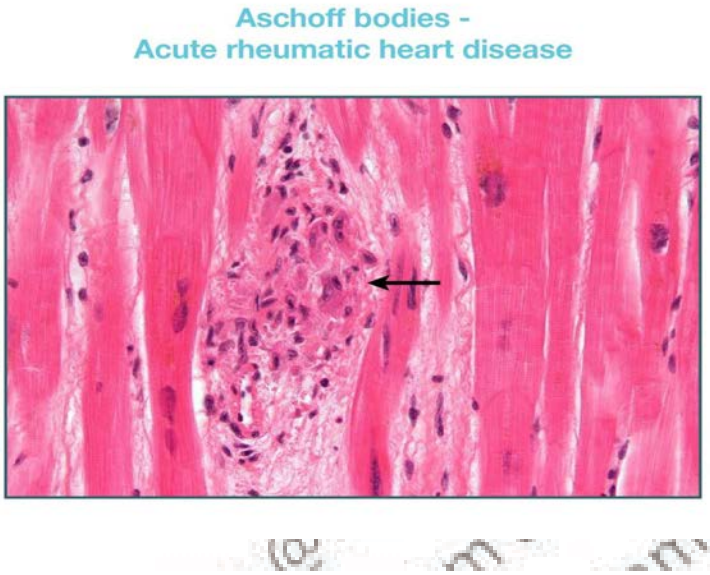
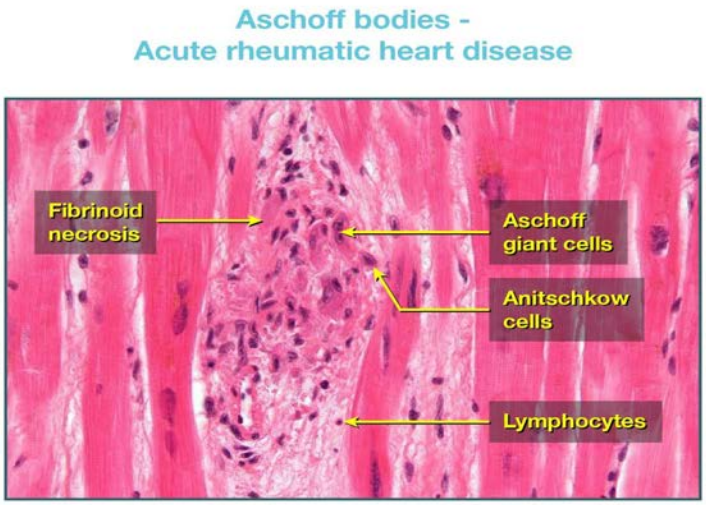
• T-cells

• Plasma cells





Solution to Question 7:

The given image is of mitral stenosis showing fish mouth or buttonhole appearance in rheumatic heart disease. It is due to calcification and fibrosis.

Rheumatic heart disease is also associated with subendocardial irregular thickenings known as McCallum plaques, as shown below.

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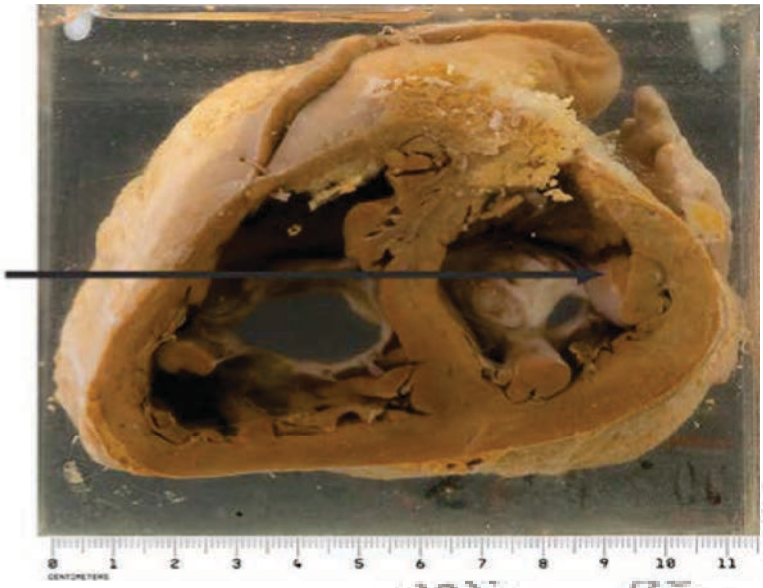

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Solution to Question 8:

Acute infective endocarditis is due to infection by highly virulent organisms like Staphylococcus aureus. It results in rapidly necrotizing and destructive lesions.

Infective endocarditis is classified into acute and subacute forms.

• Acute - infection of a previously normal heart valve by a highly virulent organism

• Subacute - infection in previously deformed valves by organisms of lower virulence (S.viridans, S. epidermidis, HACEK)

Solution to Question 9:

Staphylococcus aureus and coagulase-negative Staphylococci (like S. epidermidis).

The following organisms are implicated in infective endocarditis following prosthetic valve surgery:

• Early (< 2 months) - Staphylococcus aureus, Staphylococcus epidermidis

• Intermediate (2-12 months) and late (> 12 months):

• Streptococci and Staphylococcus aureus - more common

• Enterococci and Staphylococcus epidermidis

Solution to Question 10:

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The given features and the image showing painful Osler nodes are suggestive of infective endocarditis. Echo showing a valve-related mass is a major criterion according to Duke's criteria.

Infective endocarditis (IE) is a microbial infection of the heart valves or the mural endocardium. The aorta, aneurysms, other blood vessels, and prosthetic devices can also become infected. Most infections are bacterial.

Vegetations on heart valves are the classic hallmark of IE. They are friable, bulky, potentially destructive lesions. They contain fibrin, inflammatory cells, bacteria, or other organisms. The mitral valve is most commonly involved.

Complications of infective endocarditis:

• Cardiac complications - valvular insufficiency or stenosis, myocardial ring abscess, suppurative pericarditis

• Embolic complications - left-sided (brain, spleen, kidney) or right-sided lesion (lung infarct and abscess)

• Renal complications - embolic infarcts, focal (more common) or diffuse glomerulonephritis (less common)

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Solution to Question 11:

Single positive blood culture for Coxiella burnetti is considered as one of the major criteria to establish the diagnosis of infective endocarditis.

Solution to Question 12:

The given clinical scenario with vegetations on both sides of valve leaflets is suggestive of Libman–Sacks endocarditis. It is a feature of systemic lupus erythematosus.

The vegetations in this condition have the following features:

• Small - 1 to 4 mm in diameter

• Single or multiple

• Sterile, pinkish vegetations

• May be located on both sides valve leaflets

• Associated with intense valvulitis - characterized by fibrinoid necrosis

Mitral valve is more frequently involved and regurgitation is the usual functional abnormality.

Solution to Question 13:

Large, friable, irregular vegetations on heart valves are seen in infective endocarditis.

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Infective endocarditis is characterized by the presence of large, friable, irregular vegetations on heart valves. Aortic and mitral valves are the most commonly affected, however, in some cases, the right heart valves may be involved.

Vegetations may be single or multiple and may involve one or more valves. Embolization often occurs and may lead to septic infarcts or mycotic aneurysms at the site of lodgement due to the presence of virulent organisms in the emboli.

Solution to Question 14:

The rightly matched vegetations with the conditions that they are seen are as follows: 1-C, 2-A, 3-D, 4-B

Rheumatic heart disease often presents with rheumatic fever phase where small, warty 1- 2 mm vegetations, also called veruccae, extend along the lines of closure of the valve leaflets. The cardinal anatomical changes of the mitral valve in chronic RHD are:

• Leaflet thickening

• Commissural fusion and shortening

• Thickening and fusion of the tendinous chords

Infective endocarditis has large, irregular, friable masses on the valve cusps that can extend onto the chordae. These vegetations can be single or multiple and may involve one or more valves. They are potentially destructive lesions and contain fibrin, inflammatory cells, bacteria or other organisms. They can erode into the underlying myocardium and produce a ring abscess. They are prone to embolisations, resulting in abscess formation wherever they lodge due to the presence of virulent organisms. Thus, it may lead to sequelae like septic infarcts or mycotic aneurysms.

Subacute infective endocarditis contains less destructive vegetations. They contain granulation tissue at their bases indicative of healing. Fibrosis, calcification and a chronic inflammatory infiltrate can develop over the time.

Nonbacterial thrombotic endocarditis is characterised by one or more small, 1-5 mm, sterile vegetations which are usually attached at the line of closure. They are seen associated with hypercoagulable states like chronic DIC or malignancy. They are loosely attached to the underlying valve and are non-destructive in nature. They do not cause any inflammatory reaction but they can be a source of systemic embolisation.

Libman-Sack's endocarditis has small- or medium-sized, 1- 4 mm, sterile vegetations associated with systemic lupus erythematosus. They may be present on one or both the sides of the leaflets, on the valve surface, chordae or anywhere on the endocardium. These vegetations develop due to immune complex deposition and complement activation. They cause intense valvulitis resulting in fibrinoid necrosis of the valve substance. Persistent injury to the valves can result in scarring and leaflet fusion.

Solution to Question 15:

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Vegetations in non-bacterial thrombotic endocarditis (NBTE) are of 1 to 5 mm size.

NBTE is seen in patients with debilitating conditions such as cancer and sepsis or systemic hypercoagulable states. Hence it is also called marantic endocarditis.

There is the deposition of small sterile thrombi loosely attached to the leaflets of cardiac valves. They form single or multiple vegetations along the lines of closure of the leaflets or cusps. They are non-invasive and do not elicit an inflammatory reaction. It can be a source of systemic emboli.

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Glomerular Diseases

Question 1:

What is the minimum amount of proteinuria required to diagnose a patient with nephrotic syndrome?

a) > 2.5 g/day

b) > 3 g/day

c) > 3.5 g/day

d) > 2.8 g/day

Question 2:

A 7-year-old girl is brought with complaints of generalized swelling of the body and frothy urine. Urinary examination revealed grade 3 proteinuria and the presence of hyaline and fatty casts. There were no red blood cells in the urine. Which of the following statements about her condition is true?

a) IgA nephropathy is the likely diagnosis.

b) It is associated with low C3 levels.

c) No IgG or C3 deposition is seen on renal biopsy.

d) Alport syndrome is the likely diagnosis.

Question 3:

A 10-year-old boy is brought for a follow-up visit. He was diagnosed with nephrotic syndrome 3 months ago and had been started on a course of oral prednisolone. During the current visit, no improvement is noted with regards to facial puffiness and urine analysis reveals grade 3 proteinuria. Mutations in all of the following are associated with this condition except:

a) Nephrin

b) Megalin

c) Alpha-actinin 4

d) Podocin

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Question 4:

A 67-year-old man presents with sudden onset flank pain and hematuria. Ultrasound reveals enlargement of both kidneys. He is a known case of membranous nephropathy. What is the likely pathophysiology for his current presentation?

a) Loss of antithrombin III

b) Increased fibrinogen

c) Factor 5 Leiden mutation

d) Increase in protein C

Question 5:

In a patient with nephrotic syndrome, all of the following are decreased except:

a) Thyroid-binding globulin

b) Transferrin

c) Fibrinogen

d) Ferritin

Question 6:

A patient with radiologically confirmed reflux nephropathy develops nephrotic-range proteinuria. What is the most likely cause?

a) Membranous glomerulopathy

b) Focal segmental glomerulosclerosis

c) Nodular glomerulosclerosis

d) Proliferative glomerulonephritis with crescents

Question 7:

Patients diagnosed with which variant of focal segmental glomerulosclerosis are likely to have the worst prognosis?

a) Tip variant

b) Collapsing variant

c) Cellular variant

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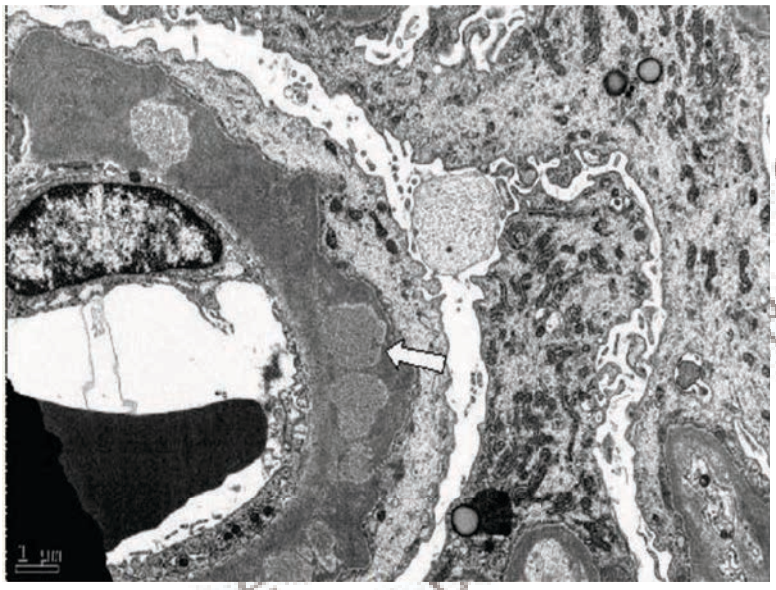
d) Perihilar variant

Question 8:

Given below is an electron microscopy image showing deposits in the kidney. What could be the diagnosis?



a) Goodpasture syndrome

b) Membranoproliferative glomerulonephritis

c) Membranous nephropathy

d) Minimal change disease

Question 9:

A 40-year-old man presents with complaints of facial puffiness and frothy urine. Given below is his renal biopsy findings. What is the likely diagnosis?

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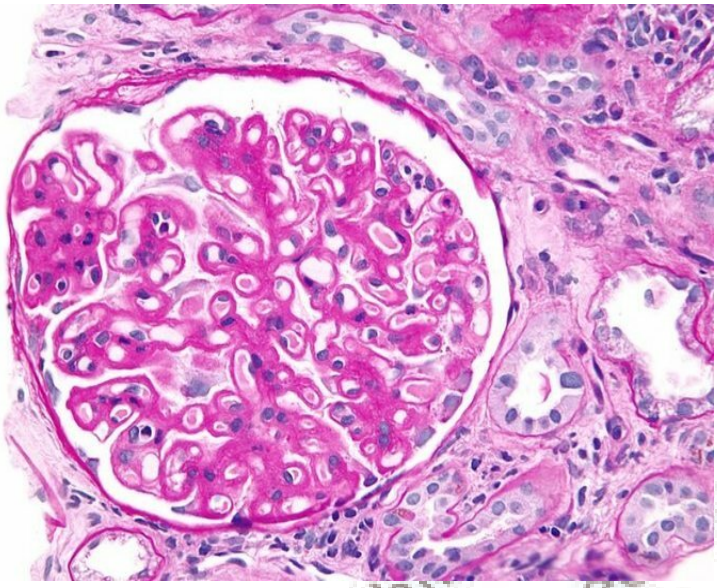

a) Membranous nephropathy

b) Focal segmental glomerulosclerosis

c) Membranoproliferative nephritis

d) Dense deposit disease

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Question 10:

Mesangial deposits are seen in which of the following conditions?

a) 1, 2, 5

b) 3, 4, 5

c) 2, 3, 4

d) 1, 2, 4

Question 11:

A 29-year-old man presented with complaints of blood in his urine. Urine analysis was positive for proteins and red cell casts. A renal biopsy was done as shown below. Immunofluorescence microscopy revealed granular deposits of C3 on either side of the glomerular basement membrane but was negative for IgG, C1q, and C4. What is the likely diagnosis?

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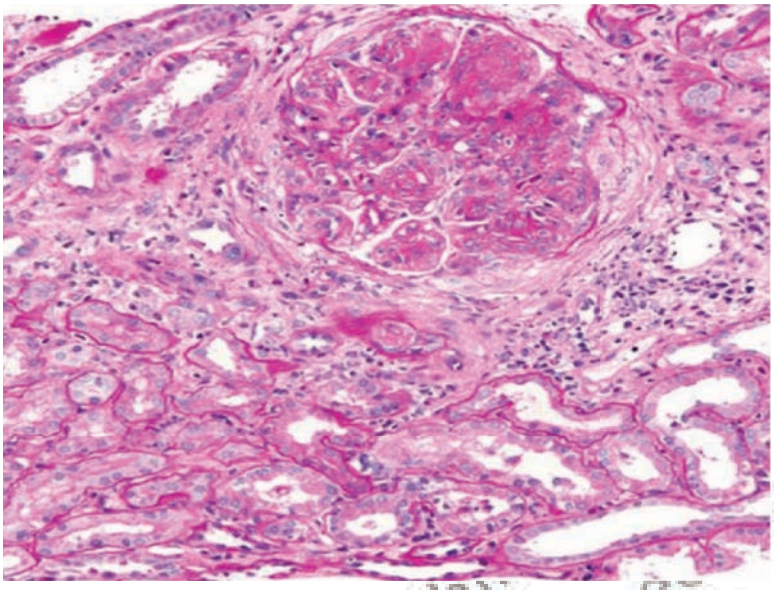


a) Membranoproliferative glomerulonephritis type 1

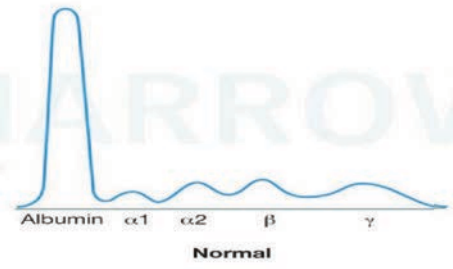
b) Membranoproliferative glomerulonephritis type 2

c) Fibrillary glomerulonephritis

d) Rapidly progressive glomerulonephritis

Question 12:

What is the most likely diagnosis based on the given serum electrophoresis image?



a) Multiple myeloma

b) Tuberculosis

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c) Hepatic cirrhosis

d) Nephrotic syndrome

Question 13:

What is the most common cause of primary nephritic syndrome?

a) Post-streptococcal glomerulonephritis

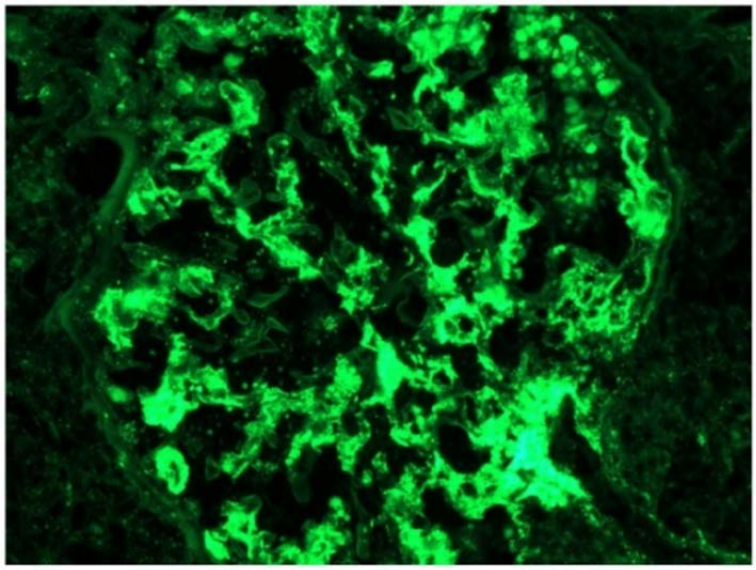
b) Diabetic nephropathy

c) IgA nephropathy

d) Membranoproliferative glomerulonephritis

Question 14:

A 28-year-old man is being evaluated for hematuria after UTI. Histopathology showed mesangial widening and endocapillary proliferation. The following finding is seen on immunofluorescence, which was positive for C3 and negative for IgG. What is the likely diagnosis?



a) Goodpasture syndrome

b) IgA nephropathy

c) MPGN type I

d) MPGN type 2

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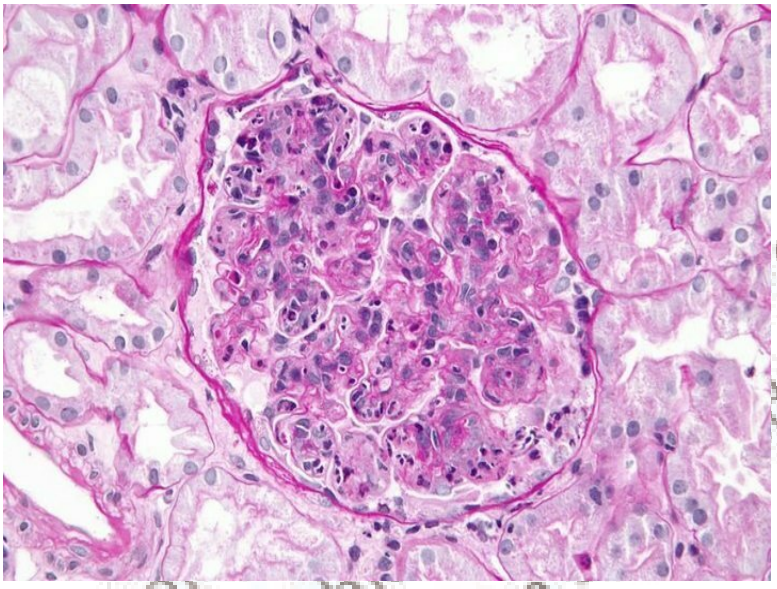
Question 15:

A 6-year-old child abruptly develops fever, oliguria, periorbital edema and smoky cola-colored urine 2-weeks after recovery from sore throat. His renal biopsy image is given below. Which of the following statements is false about the given condition?



a) A rapidly progressive form with oliguria develops in 50% of children

b) It is a form of proliferative glomerulonephritis

c) Granular IgG and C3 deposits are seen on immunofluorescence

d) Dome-shaped subepithelial humps are seen on electron microscopy

Question 16:

A pathologist is examining the following renal biopsy specimen. What does it show?

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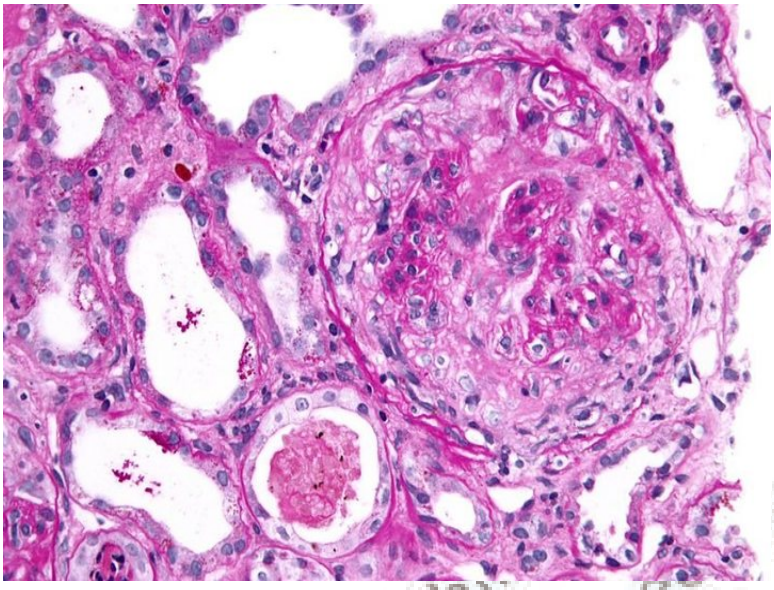

a) Proliferating parietal and visceral epithelial cells and WBCs in Bowman space

b) Diffuse thickening of the glomerular capillary wall

c) Proliferating mesangial cells and increased matrix deposition in the mesangium

d) Proliferation of capillaries with fibrin deposition

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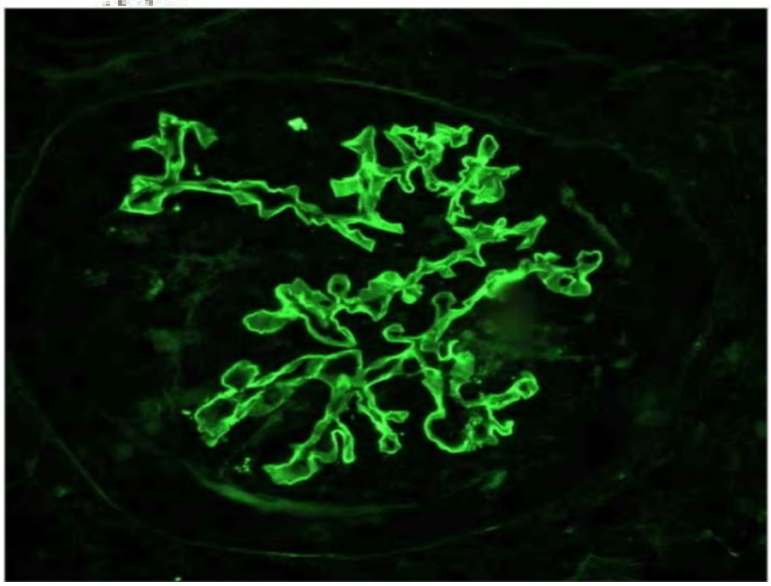
Question 17:

A patient with recurrent hemoptysis and renal failure underwent renal biopsy. It revealed the presence of crescents in most of the glomeruli. Immunofluorescence finding is shown in the image below. What is the diagnosis?



a) Acute post-infectious glomerulonephritis

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b) Membranous nephropathy

c) Goodpasture's syndrome

d) Wegeners granulomatosis

Question 18:

An 18-year-old otherwise healthy boy presents with complaints of hematuria. His father has also had similar complaints since childhood. Light microscopy of the renal biopsy specimen showed no abnormalities. Diffuse thinning of the glomerular basement membrane was seen on electron microscopy. What is the most likely diagnosis?

a) Benign familial hematuria

b) Goodpasture syndrome

c) Alport syndrome

d) Berger's disease

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Question 19:

What is the most common manifestation of Alport's syndrome?

a) Hematuria

b) Oliguria

c) Deafness

d) Proteinuria

Question 20:

A middle-aged male patient has proteinuria. Looking at the immunofluorescence image below, what is the diagnosis?

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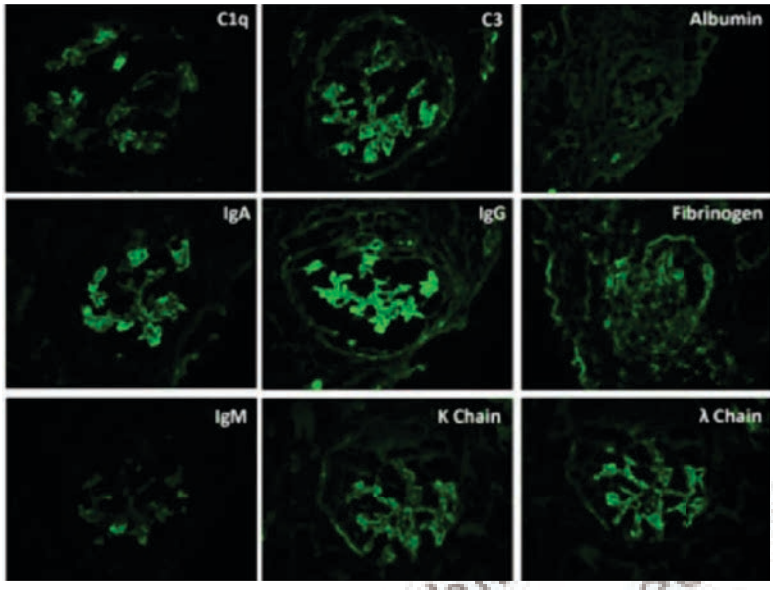

a) Focal segmental glomerulosclerosis (FSGS)

b) Post-streptococcal glomerulonephritis (PSGN)

c) Good pasture syndrome

d) Lupus nephritis

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Question 21:

Urinary albumin excretion of how much is considered as microalbuminuria?

a) 100-150 mg/24 hours

b) 151-200 mg/24 hours

c) 30-300 mg/24 hours

d) 3-30 mg/24 hours

Question 22:

A 50-year-old man presented with the blurring of vision. Urine examination showed proteinuria. Fundus examination showed dot and blot hemorrhages, microaneurysms, and cotton wool spots. Histopathology of the kidney was as shown below. What is your diagnosis?

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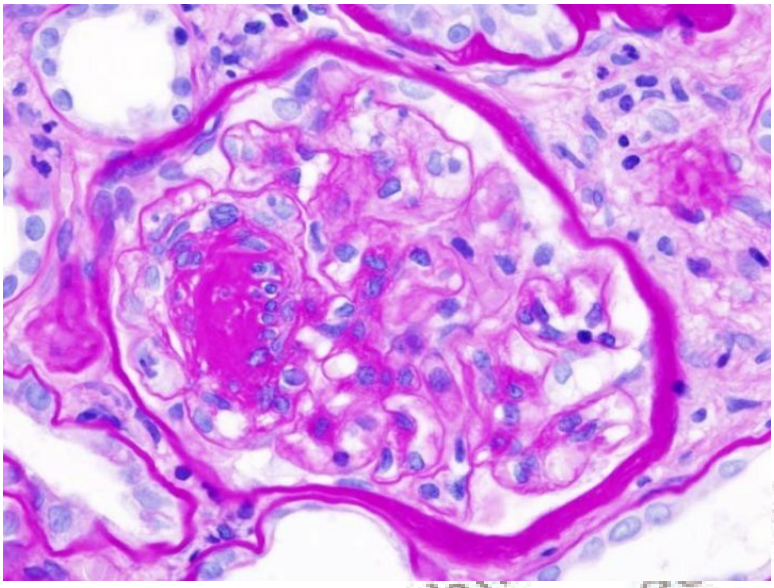

a) Renal amyloidosis

b) Focal segmental glomerulosclerosis

c) Kimmelstiel-Wilson disease

d) Lupus nephritis

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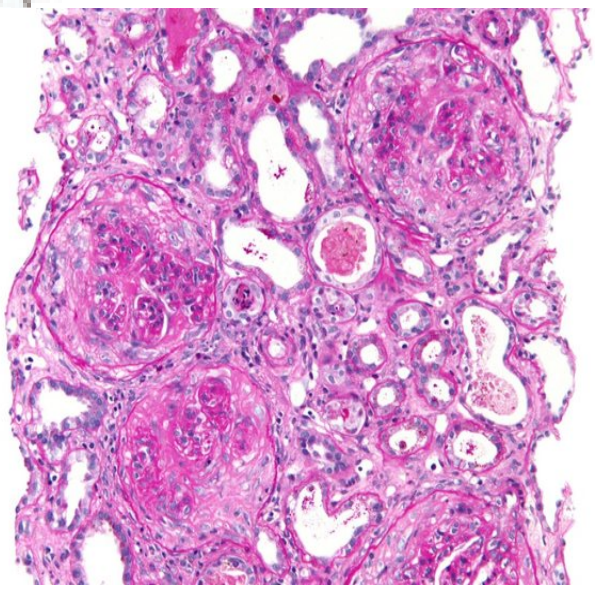
Question 23:

A 51-year-old male patient came with complaints of hematuria to the clinic. On examination, he was normotensive and had pedal edema. Investigations revealed the patient had no glycosuria and had a creatinine of 9. His renal biopsy is shown below. Which of the following investigations should be done to identify the disease?



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a) ANA

b) Anti GBM antibodies

c) HIV RNA

d) Urine immunoelectrophoresis

Question 24:

Membranoproliferative glomerulonephritis is seen in:

a) 1, 2, 3

b) 1, 2, 3, 4

c) 2, 3, 4

d) 1, 2

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Answer Key

Question No.	Correct Option
1	c
2	c
3	b
4	a
5	c
6	b
7	b
8	c
9	a
10	d
11	b
12	d
13	c
14	b
15	a
16	a
17	c
18	a

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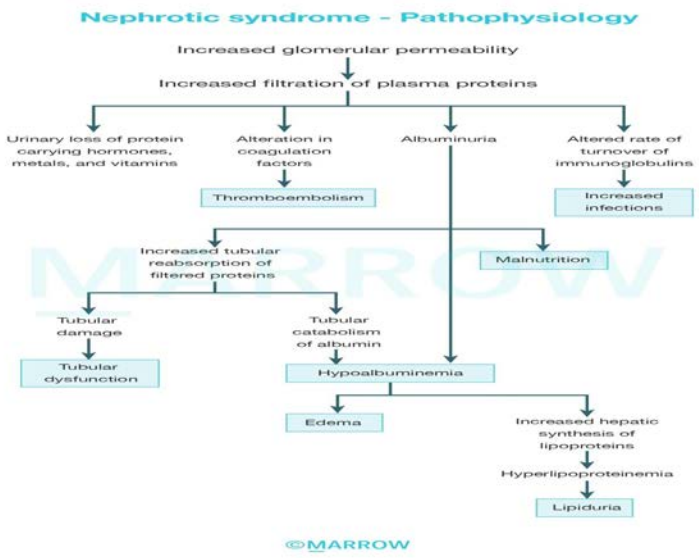
19	a
20	d
21	c
22	c
23	b
24	b

Detailed Explanations

Solution to Question 1:

The minimum amount of proteinuria required to diagnose a patient with nephrotic syndrome is 3.5 g/day.



Solution to Question 2:

The given clinical scenario in this child is strongly suggestive of nephrotic syndrome due to minimal change disease (MCD). It is characterized by the absence of immune deposits on biopsy and histopathological examination.

It is the most common cause of nephrotic syndrome in children (peaks between 2–6 years).

Biopsy findings of MCD are as follows:

• Light microscopy - glomeruli appear normal (hence called 'minimal change')

• Immunofluorescence studies - no Ig or complement deposits

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• Electron microscopy - diffuse effacement of foot processes of visceral epithelial cells (podocytopathy)

Solution to Question 3:

The given clinical scenario is suggestive of steroid-resistant nephrotic syndrome. It can be caused due to mutations in the following components of the glomerular filtration barrier:

• Nephrin, podocin - are molecular components of the slit diaphragm complex

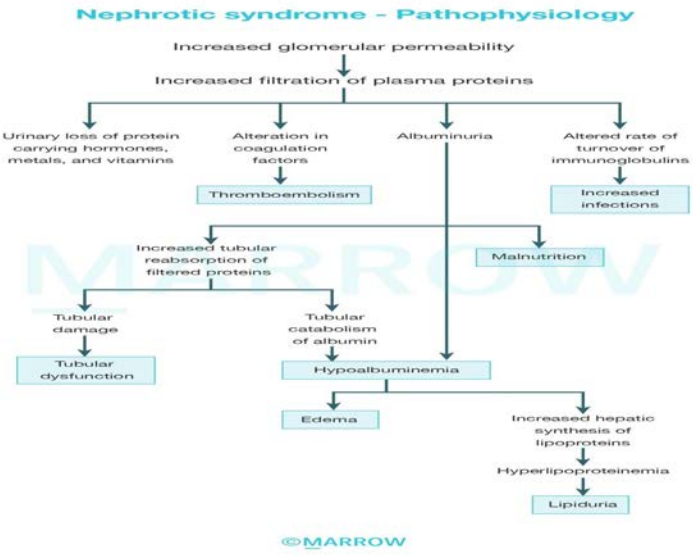
• Alpha-actinin 4 - is a component of the foot process cytoskeleton

Megalin is not a component of the glomerular filtration barrier. It is present in proximal convoluted tubular cells. Mutations in megalin may lead to some proteinuria but not nephrotic syndrome because glomerular filtration of proteins is not affected.

Solution to Question 4:

The given clinical scenario in a patient suffering from membranous nephropathy, which is a type of nephrotic syndrome, is suggestive of renal vein thrombosis. It is due to the loss of antithrombin III (an endogenous anticoagulant) in urine.

Renal vein thrombosis is most often a consequence of a hypercoagulable state. In adults, it is most commonly seen in patients with membranous nephropathy.



Solution to Question 5:

In nephrotic syndrome, there is an increase in fibrinogen levels.

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The following proteins are increased in nephrotic syndrome:

• Fibrinogen

• Lipoproteins - due to increased synthesis

The following proteins are decreased in nephrotic syndrome as a consequence of selective proteinuria:

• Albumin - the largest proportion of protein lost in nephrotic syndrome.

• Transferrin

• Cholecalciferol-binding protein

• Thyroxine-binding globulin (TBG)

• Ferritin

• Coagulation factors

• Antithrombin III

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Solution to Question 6:

The given clinical scenario is suggestive of nephrotic syndrome due to a secondary cause (reflux nephropathy). Secondary nephrotic syndrome in adults is most likely due to focal segmental glomerulosclerosis (FSGS).

FSGS is the most common cause of nephrotic syndrome in adults. It is a podocytopathy, with degeneration and focal disruption of visceral epithelial cells and effacement of foot processes. Glomerular hyalinosis and sclerosis are seen due to the entrapment of plasma proteins and increased extracellular matrix deposition.

FSGS is classified as follows:

• Primary

• Idiopathic FSGS

• Secondary

• HIV associated

• Heroin addiction

• Sickle cell disease

• Obesity

• Hypertensive nephropathy

• Renal conditions

• Focal glomerulonephritis (e.g. IgA nephropathy)

• Renal ablation

• Unilateral renal agenesis or renal dysplasia

• Reflux nephropathy

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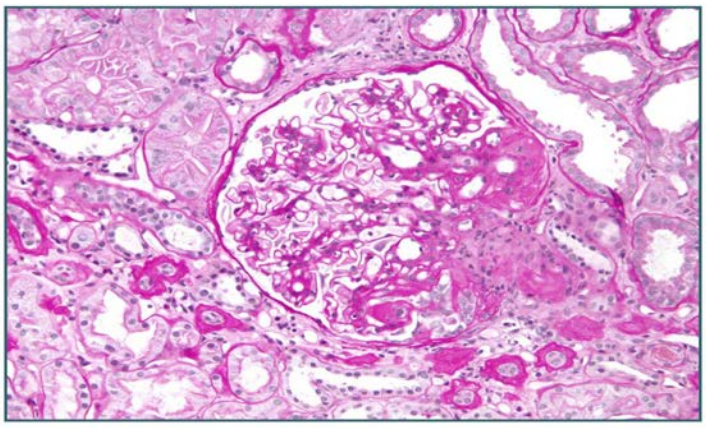
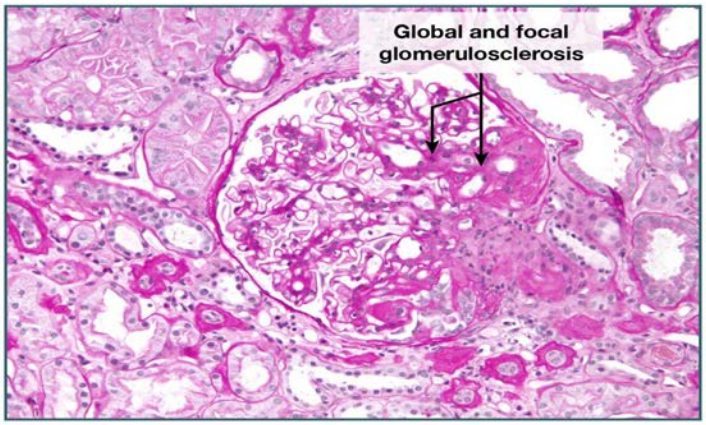
• Inherited

• Mutated proteins of the slit diaphragm - podocin, alpha-actinin 4, TRPC6

Focal segmental glomerulosclerosis -
Light microscopy



Focal segmental glomerulosclerosis -
Light microscopy



Electron microscopy of FSGS shows:

• Diffuse effacement of the podocyte foot processes

• Focal detachment and degeneration of the epithelial cells

• Absence of electron-dense deposits

Solution to Question 7:

The collapsing variant of focal segmental glomerulosclerosis (FSGS) is associated with the worst prognosis.

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There are 5 variants of FSGS:

• Collapsing variant - poor prognosis

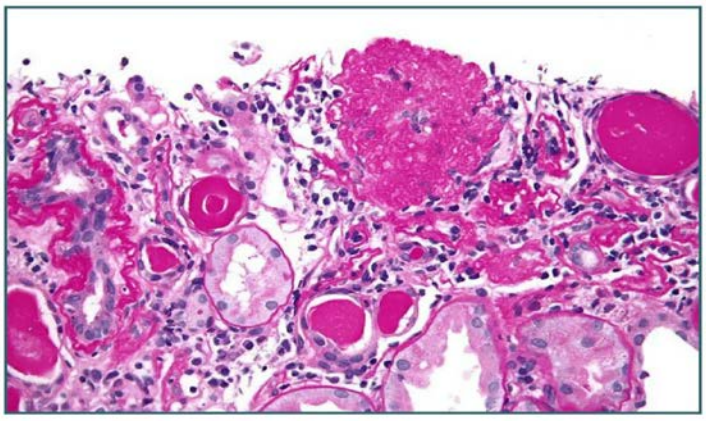
• Glomerular tip variant - good prognosis

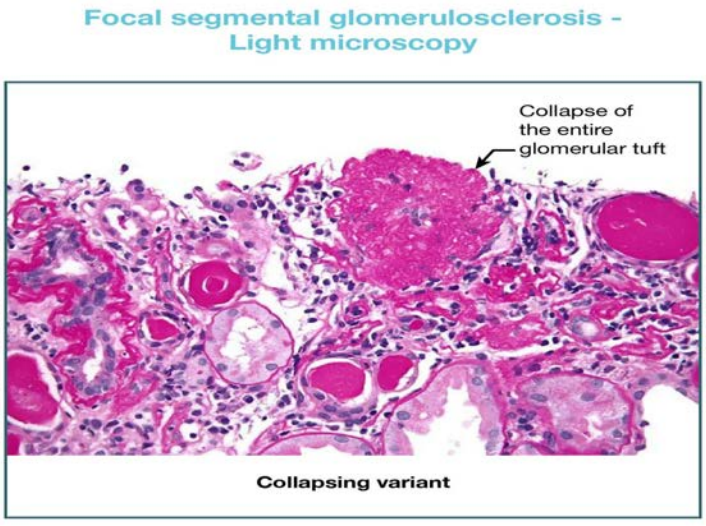
• Cellular variant

• Perihilar variant

• Not otherwise specified - most common

Given below is a histological image of collapsing glomerulopathy showing the involvement of the entire glomerular tuft and proliferation of visceral epithelial cells.





Solution to Question 8:

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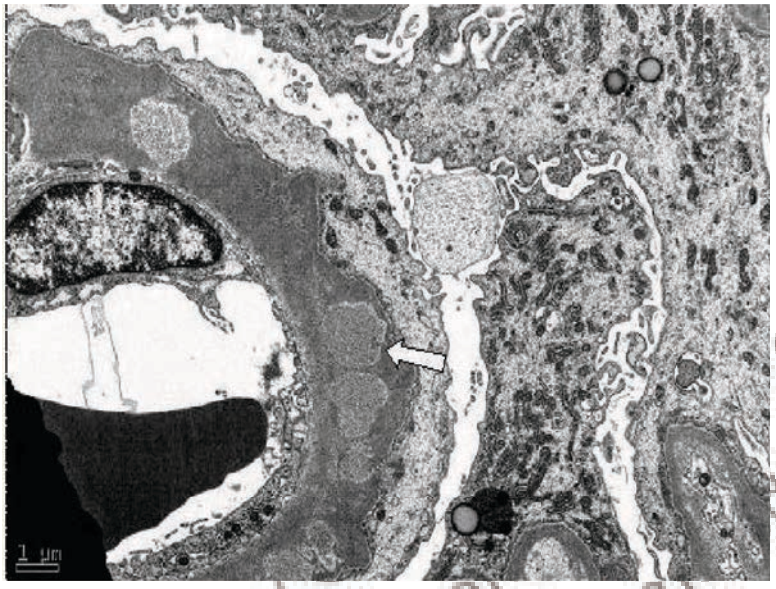
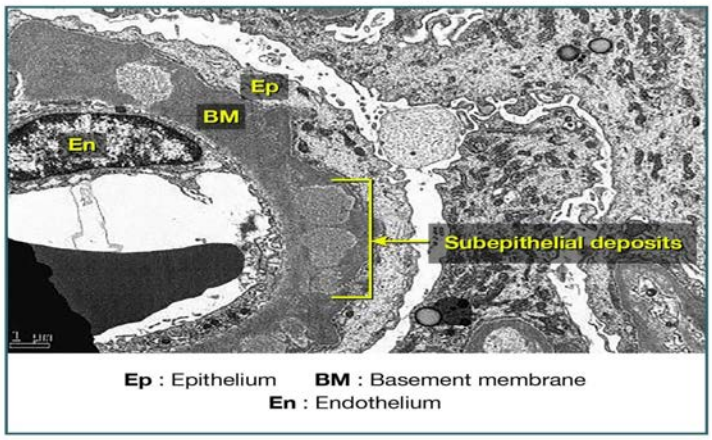
The given electron microscopy image shows subepithelial deposits in the kidney which is suggestive of membranous nephropathy.

The following electron microscopy image shows subepithelial deposits in the kidney.



Membranous nephropathy - Electron microscopy



Membranous nephropathy is characterized by the diffuse thickening of the glomerular capillary wall. It is due to the accumulation of deposits containing Ig along the subepithelial side of the basement membrane.

Solution to Question 9:

This clinical scenario and the histopathological image showing uniform, diffuse thickening of the glomerular capillary wall are suggestive of membranous nephropathy.

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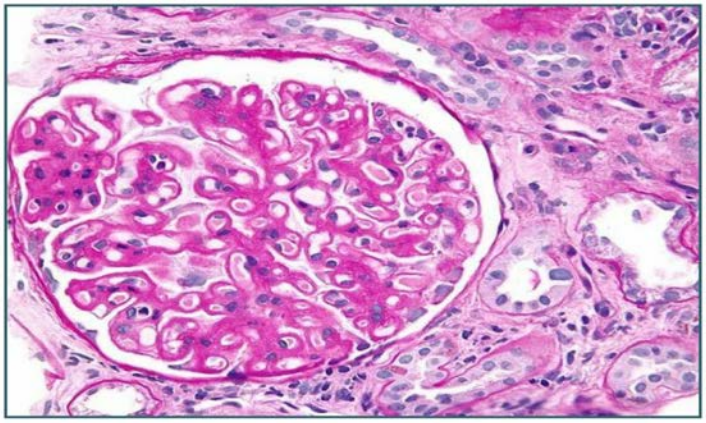
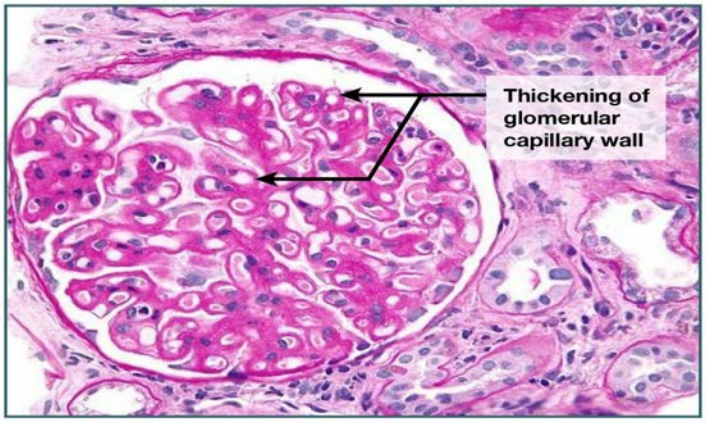
Membranous nephropathy -
Light microscopy



Membranous nephropathy -
Light microscopy



Membranous nephropathy is one of the most common causes of nephrotic syndrome in the adults/elderly. It is a chronic immune-complex-mediated disease.

The following image of the glomerulus shows the characteristic spikes. The spikes are formed due to the presence of basement membrane material (have affinity to silver stain) in between the immune complex deposits (lack affinity to silver stain).

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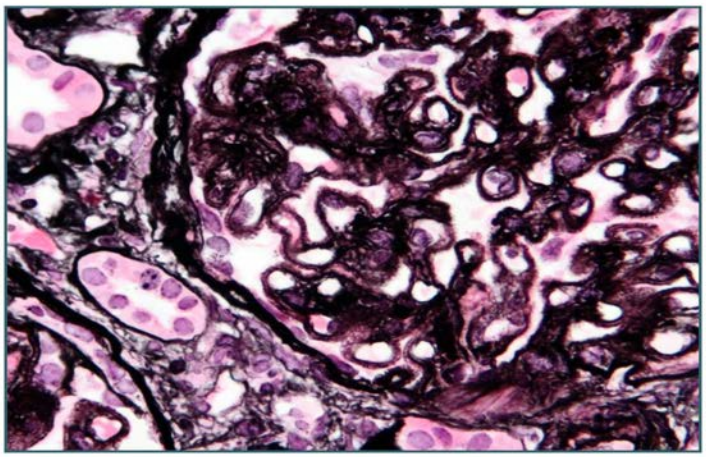
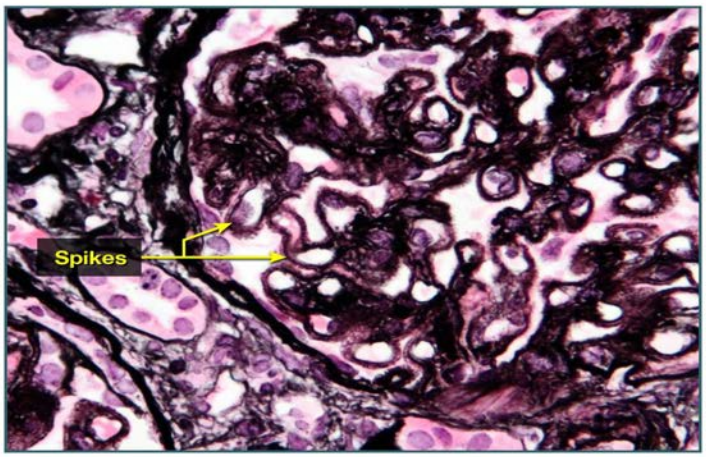
Membranous nephropathy - Silver staining



Membranous nephropathy - Silver staining



Solution to Question 10:

Mesangial deposits are seen in the following conditions:

- IgA nephropathy (Berger disease)
- Henoch–Schonlein purpura
- Rapidly progressive glomerulonephritis
- Lupus nephritis classes I and II
- Resolving postinfectious glomerulonephritis

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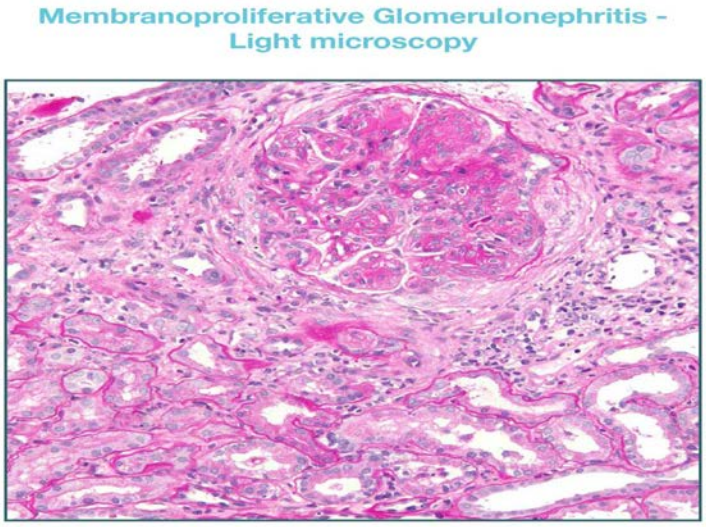
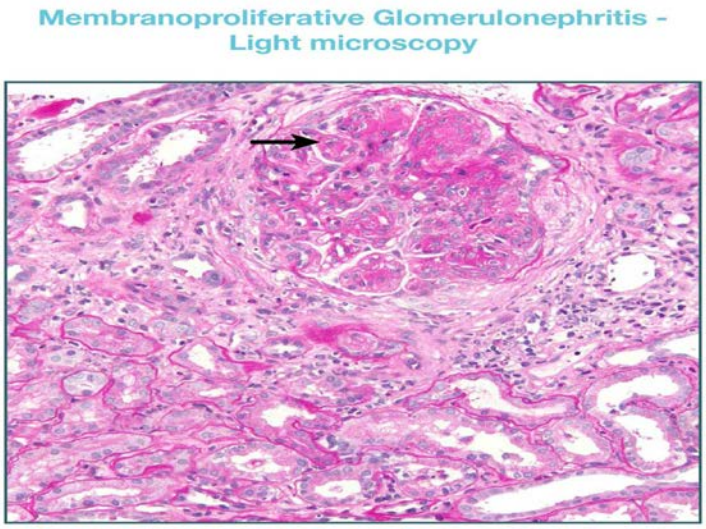
Solution to Question 11:

The given clinical scenario, immunofluorescence findings, and the image showing proliferating mesangial cells and capillary endothelial cells are suggestive of membranoproliferative glomerulonephritis type 2 (MPGN type 2) or dense-deposit disease.





The following image shows bright deposits scattered along capillary walls and in the mesangium by immunofluorescence microscopy with antibodies to C3.

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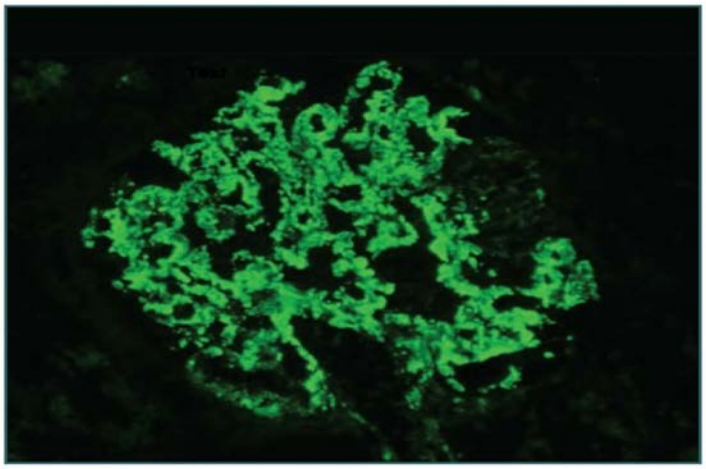
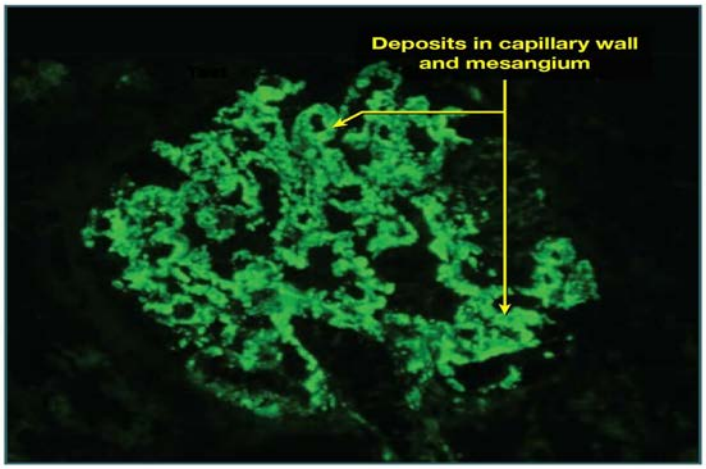
Dense-deposit disease -Immunofluorescence



Dense-deposit disease -Immunofluorescence



This condition belongs to a group of disorders called C3 glomerulopathies and primarily affects children and young adults. It is associated with a dysregulation in the alternative complement pathway. It is clinically and morphologically similar to MPGN type 1 but pathogenetically distinct from it.

In this condition, a circulating autoantibody called C3 nephritic factor is present, which stabilizes the C3 convertase enzyme. The stabilized C3 convertase enhances C3 activation and consumption causing hypocomplementemia. Patients will have consistently decreased serum C3 levels, but normal C1 and C4 levels.

The prognosis is poor, with about half of these patients progressing to end-stage renal disease (ESRD).

Solution to Question 12:

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The given electrophoresis shows hypoalbuminemia and increased alpha-2 globulin, which is classically seen in nephrotic syndrome.

Solution to Question 13:

IgA nephropathy (Berger disease) is the most common cause of primary nephritic syndrome in the world.

Nephritic syndrome is characterized by:

- Acute onset of hematuria
- Urinalysis - red cell casts
- Diminished glomerular filtration rate (GFR) (oliguria)
- Mild to moderate proteinuria
- Hypertension
- Azotemia

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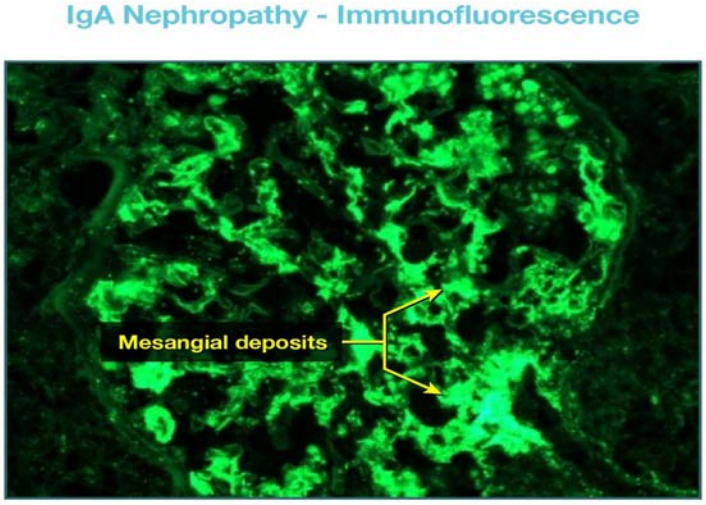
Solution to Question 14:

The given clinical scenario, histopathology findings of mesangial widening and endocapillary proliferation, as well as immunofluorescence showing mesangial deposits are suggestive of IgA nephropathy (Berger's disease).

It is the most common type of glomerulonephritis worldwide. It is characterized by recurrent hematuria/ nephritic syndrome and the presence of prominent IgA deposits in the mesangium. Patients generally present with gross hematuria after respiratory, gastrointestinal or urinary tract infection.



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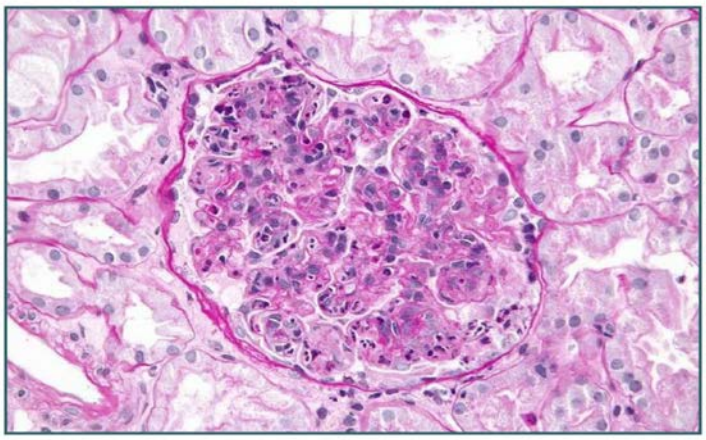
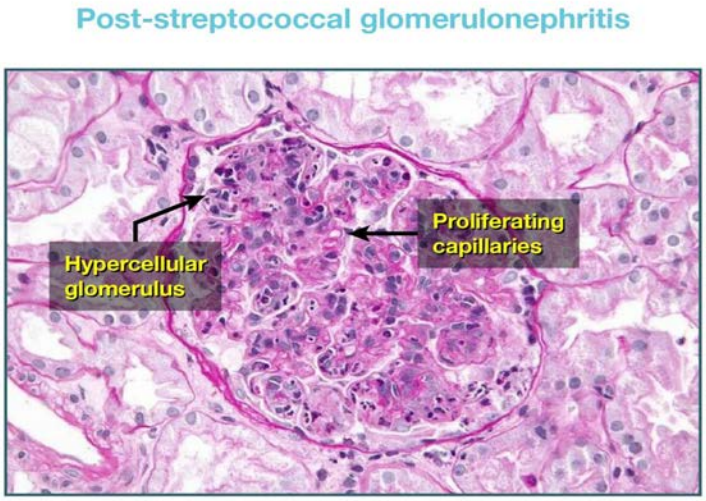
The systemic variant of IgA nephropathy is called Henoch–Schönlein purpura. It is a disorder of children which presents with similar renal manifestations with characteristic IgA deposits in the mesangium in about one-third of the patients.

Solution to Question 15:

The given clinical scenario and histopathology image showing hypercellular glomeruli are suggestive of post-streptococcal glomerulonephritis (PSGN). Rapidly progressive disease with oliguria is very rare (< 1% of patients).





Post-streptococcal glomerulonephritis is a type of diffuse proliferative glomerulonephritis. It is usually preceded by an acute streptococcal sore throat or impetigo around 1-4 weeks prior.

It usually presents with features of nephritic syndrome including:

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• Hematuria

• Red cell casts in the urine

• Azotemia, oliguria

• Hypertension

• Mild to moderate proteinuria

• Edema

On microscopy, the following findings are seen:

• Light microscopy - enlarged, hypercellular glomeruli with influx of leucocytes (endocapillary proliferation)

• Electron microscopy - subepithelial humps

• Immunofluorescence - granular IgG and C3 deposits on glomerular basement membrane and mesangium

Majority (> 95%) of affected children eventually recover renal function with conservative therapy.

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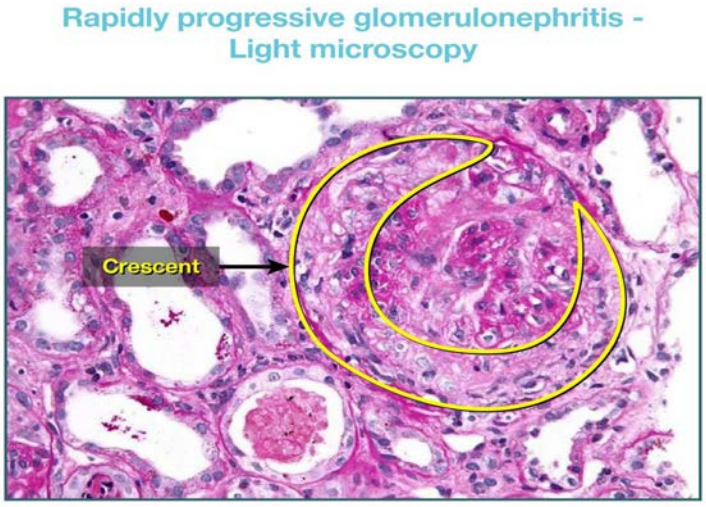
Solution to Question 16:

The given image shows a crescent-shaped mass of proliferating parietal and visceral epithelial cells and leukocytes within the Bowman capsule. It is a characteristic feature of rapidly progressive glomerulonephritis (RPGN) or crescentic glomerulonephritis.



RPGN is a type of nephritic syndrome associated with severe glomerular injury with necrosis and formation of crescents. It is usually immune-mediated and may be associated with circulating anti-neutrophil cytoplasmic antibodies (ANCAs), anti-GBM antibodies, and antinuclear antibodies (ANA).

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Injury to the glomerular capillary wall leads to the escape of procoagulant factors and cytokines in the Bowman space. This triggers:

• Proliferation of glomerular epithelial cells - mostly parietal, but also some visceral cells

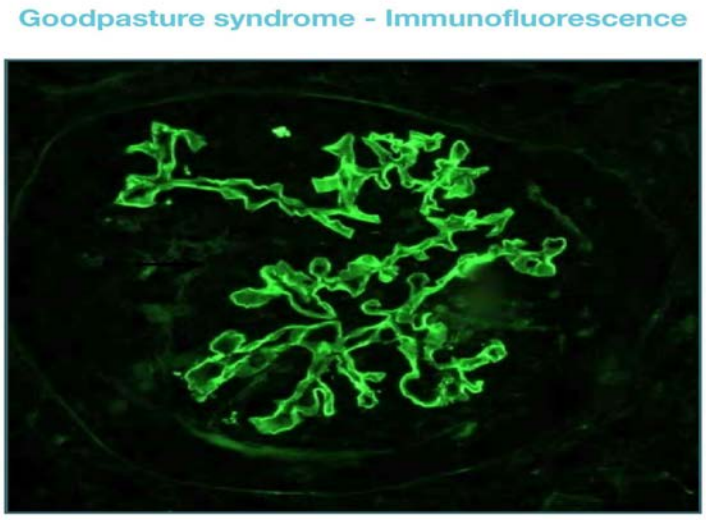
• Recruitment of leukocytes and fibroblasts

• Pathognomonic crescents - due to the circumferential accumulation of these cells and fibrin

The crescents progressively compress the capillary tuft. This results in a rapid decline of glomerular filtration rate (GFR) and, consequently, acute kidney injury (AKI). Thus, the degree of crescent formation correlates with the severity and the prognosis of the disease.

Solution to Question 17:

The given clinical scenario, histopathology findings, and immunofluorescence showing linear, dense, and smooth deposits are suggestive of Goodpasture's syndrome.



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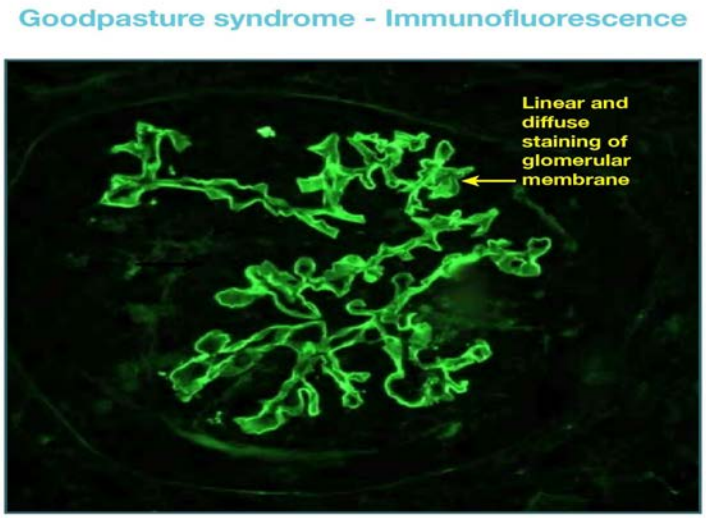

Goodpasture's syndrome is an anti-GBM (glomerular basement membrane) antibody-mediated disease. The antibodies are directed against the non-collagenous portion of the α3 chain of collagen type IV. As it is present in both the alveoli and GBM, it usually presents with pulmonary hemorrhage and renal failure. It makes up about 1/5 of cases of rapidly progressive glomerulonephritis.

Crescents with linear deposits of IgG and C3 in the glomerular basement membrane are seen on histopathology.

Note: Wegener's granulomatosis (granulomatosis with polyangiitis) causes the pauci-immune type of rapidly progressive glomerulonephritis. There is an absence of immune complex deposition on immunofluorescence.

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Solution to Question 18:

The given clinical scenario with normal findings on light microscopy and diffuse thinning of the glomerular basement membrane on electron microscopy are highly suggestive of benign familial hematuria (thin basement membrane disease).

It is a type of hereditary nephritis manifested clinically by familial asymptomatic hematuria.

The following are the differences between Alport's syndrome and benign familial hematuria.

Features	Alport's syndrome	Benign familial hematuria
Inheritance	X-linked (most common)Aut osomal inheritance	Autosomal inheritance
Affected protein	α5 chain of type IV collagen (Most commonly)	α3 or α4 chains of type IV co llagen.
Hearing Loss	Present	Absent
Ocular abnormalities	Present	Absent

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Features	Alport's syndrome	Benign familial hematuria
Progress to end-stage renal d isease	Yes	No
Electron microscopy	Irregularthickeningandthinni ngof basement membraneSpl itting and lamination of lami na densa -basket-weaveappea rance	Diffuse thinningof the glomer ular basement membrane
Prognosis	Poor	Good

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Solution to Question 19:

The most common manifestation of Alport syndrome is gross or microscopic hematuria, frequently accompanied by red cell casts.

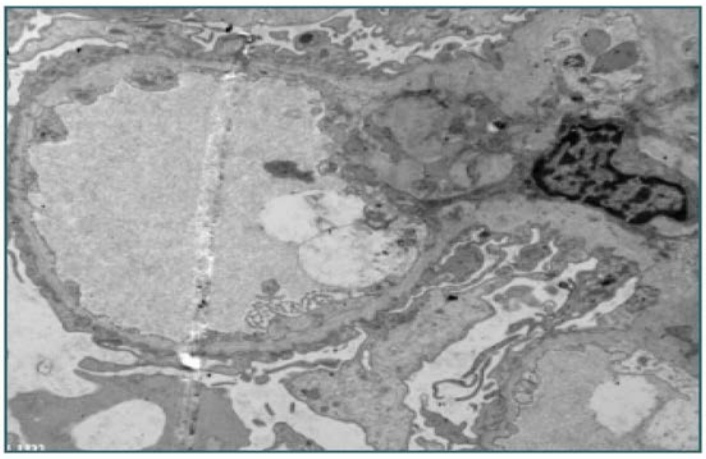
Proteinuria and oliguria may develop later in the disease, and rarely, nephrotic syndrome develops. The deafness may be subtle requiring sensitive testing.

There are no significant light microscopy changes in Alport syndrome. On electron microscopy, the glomerular basement membrane shows:

• Irregular foci of thickening, alternating with attenuation (thinning)

• Pronounced splitting and lamination of the lamina densa - basket-weave appearance

Electron Microscopy - Alport Syndrome



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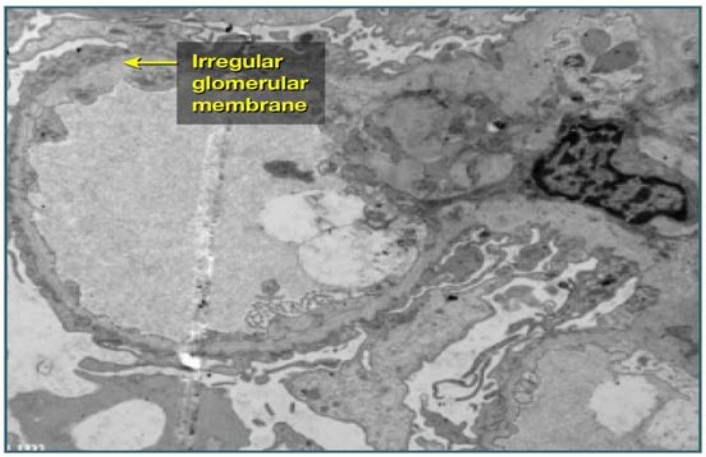
Electron Microscopy - Alport Syndrome



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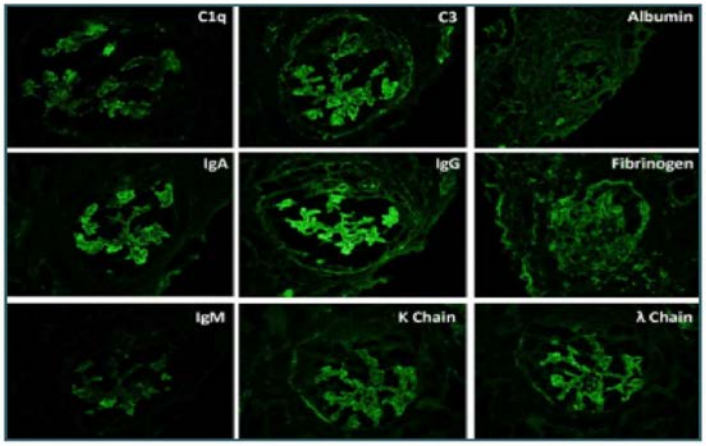
Solution to Question 20:

The given immunofluorescence staining of the kidney biopsy specimen shows positive staining for fibrinogen, IgG, IgA, IgM, C1q, C3, λ chain, and k light chain. This is known as full-house effect. It is seen in lupus nephritis.

Lupus nephritis - Immunofluorescence



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Solution to Question 21:

Urinary albumin excretion in the range of 30–300 mg/24 hours is called microalbuminuria. It is the hallmark of early diabetic nephropathy.

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The terms microalbuminuria and macroalbuminuria are no longer used now. Proteinuria is currently classified as:

Type of Proteinuria	Total proteinuria (mg/day)	Albuminuria(mg/day)
Normal-range	<150Mainly Tamm-Horsfall protein (70-75 mg/day)	< 30
Moderately increased	150-500	30-300
Severely increased	> 500	> 300

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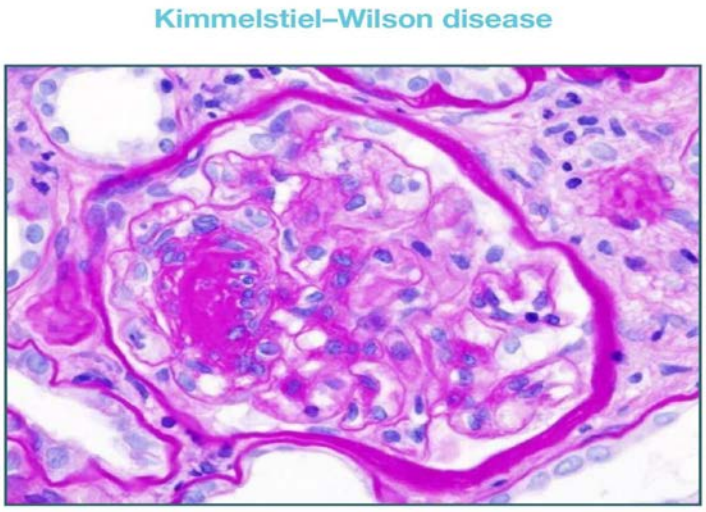
Solution to Question 22:

The given clinical scenario and histopathology image showing acellular periodic acid Schiff (PAS)-positive nodules are suggestive of Kimmelstiel–Wilson disease. It occurs in patients with diabetic nephropathy.



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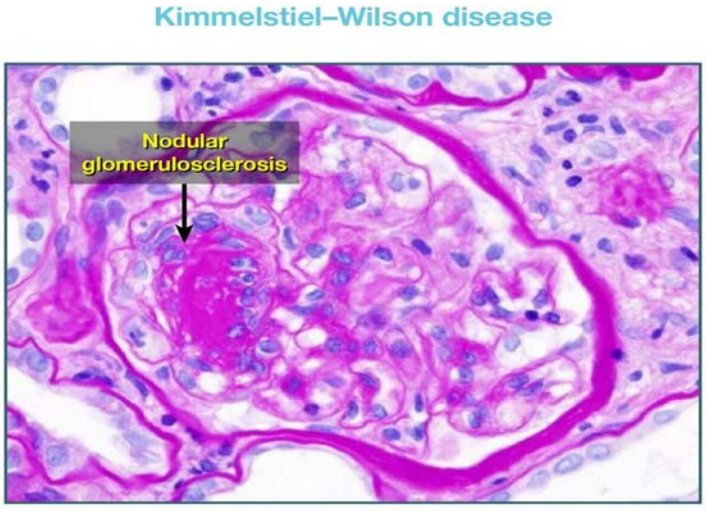

The following renal lesions are encountered in diabetic nephropathy:

• Glomerular lesions -

• Capillary basement membrane thickening

• Diffuse mesangial sclerosis

• Nodular glomerulosclerosis/ Kimmelstiel–Wilson disease

• Intercapillary glomerulosclerosis

• Renal vascular lesions - hyaline arteriolosclerosis

• Pyelonephritis - necrotizing papillitis

Option A: In amyloidosis, glomerular deposits appear as thickenings of the mesangial matrix, forming interlacing broad ribbons of amyloid.

Option B: In focal segmental glomerulosclerosis, there is focal and segmental hyalinosis and sclerosis of the capillary wall with lipid droplets in the sclerosed area.

Option D: In lupus nephritis, immune complex deposits are seen in the mesangium or along the entire basement membrane (wire loop lesions), with mesangial cell proliferation.

Solution to Question 23:

Based on the given clinical history and microscopy showing crescents, rapidly progressive glomerulonephritis (RPGN) is suspected. Among the given options, anti- GBM antibody testing should be done, since it is a part of the work-up of RPGN.

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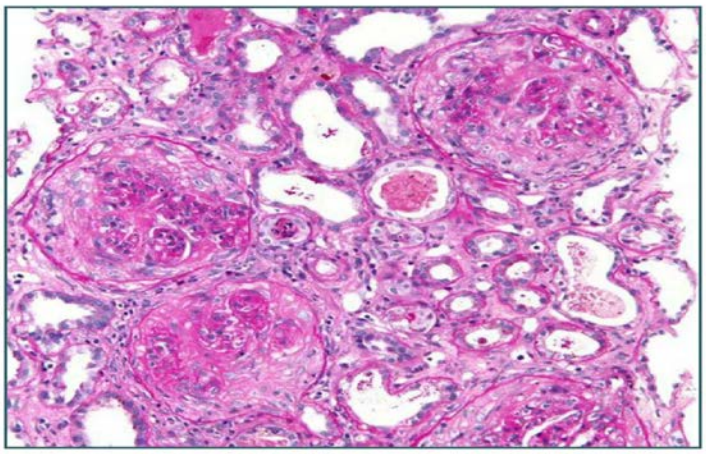
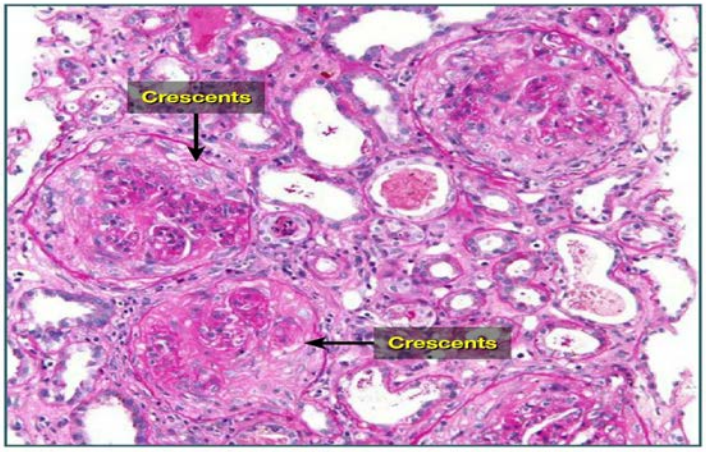
Rapidly Progressive Glomerulonephritis - Light microscopy



Rapidly Progressive Glomerulonephritis - Light microscopy



Type 1 RPGN includes renal limited disease and Goodpasture's disease. In this condition, antibodies are produced against the non-collagenous domain of the α3 chain of collagen IV of the GBM.

Microscopy findings of Goodpasture's disease are:

• Immunofluorescence - linear deposits of Ig and complement along the glomerular basement membrane

• Electron microscopy - wrinkling of the glomerular basement membrane with focal disruptions without any immune complex deposition.

A variant of Goodpasture's disease with pulmonary involvement is known as Goodpasture's syndrome.

Option A: ANA testing is done if SLE is suspected. Electron microscopy will show immune complex deposits.

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Option C: HIV RNA testing is done in immunodeficiency syndrome associated with weight loss. Electron microscopy will show diffuse podocyte injury with complete foot process effacement. Tubuloreticular inclusions will be seen in endothelial cells.

Option D: Urine electrophoresis is done if nephrotic syndrome is suspected.

Solution to Question 24:

Membranoproliferative glomerulonephritis (MPGN) is seen in HIV, SLE, CLL, and Hepatitis B.

MPGN is caused due to immune-mediated injury. It often presents with a nephritic-nephrotic picture.

The causes of MPGN are as follows:

• Primary MPGN (Idiopathic)

• Secondary MPGN

• System lupus erythematosus (SLE)

• α1-antitrypsin deficiency

• Infections - hepatitis B, hepatitis C, HIV, schistosomiasis, endocarditis, infected ventriculoatrial shunts, chronic visceral abscesses

• Malignancies - chronic lymphocytic leukemia (CLL)

MPGN is characterized by the proliferation of cells predominantly in the mesangium and the capillary loops. Hence it is also called mesangiocapillary glomerulonephritis. There are 2 types of MPGN:

• Type I - It is characterized by the deposition of immune complexes and mesangiocapillary proliferation.

• Type II - It is now known as dense-deposit disease. It belongs to a group of disorders called C3 glomerulopathies.

Light microscopy findings of MPGN are as follows:

• Lobular glomeruli with proliferating mesangial cells, capillary endothelium, and infiltrating leukocytes (endocapillary proliferation)

• Duplication of the basement membrane gives a double contour or tram-track appearance. It is especially evident in silver or PAS stains.

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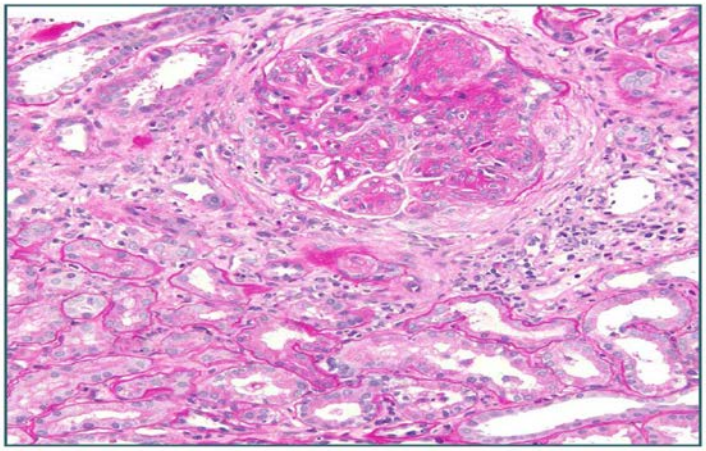
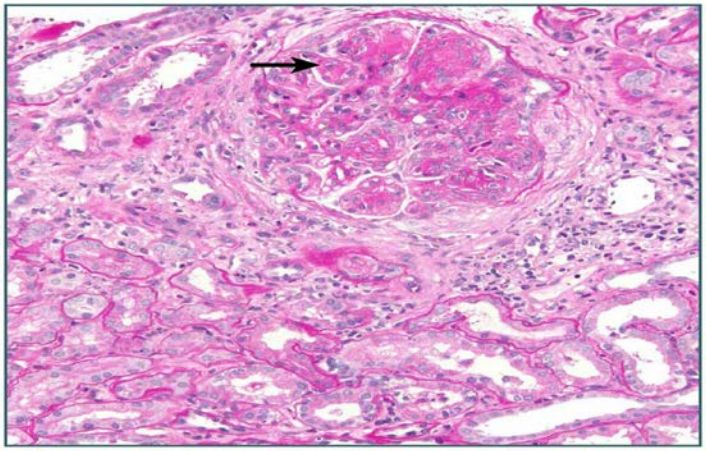
Membranoproliferative Glomerulonephritis - Light microscopy



Membranoproliferative Glomerulonephritis - Light microscopy



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Tubulointerstitial, Vascular and Cystic Diseases

Question 1:

A 45-year-old man was brought to the ER by his friends after they found him lying unconscious next to an empty antifreeze bottle. Investigations were significant for the following findings. This condition predominantly affects which part of the kidney?

a) Proximal convoluted tubule

b) Distal convoluted tubule

c) Collecting duct

d) Loop of Henle

Question 2:

A 27-year-old woman presents with urinary frequency, urgency, and burning during urination of two days duration. Presence of which of the following additional findings would make you suspect pyelonephritis in this patient?

a) Fever

b) Bacteriuria

c) White blood cell casts

d) Sterile pyuria

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Question 3:

What is the most common organism causing acute pyelonephritis?

a) Klebsiella

b) Escherichia coli

c) Beta-hemolytic streptococci

d) Proteus species

Question 4:

Periglomerular fibrosis is considered typical of which of the following conditions?

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a) Chronic pyelonephritis

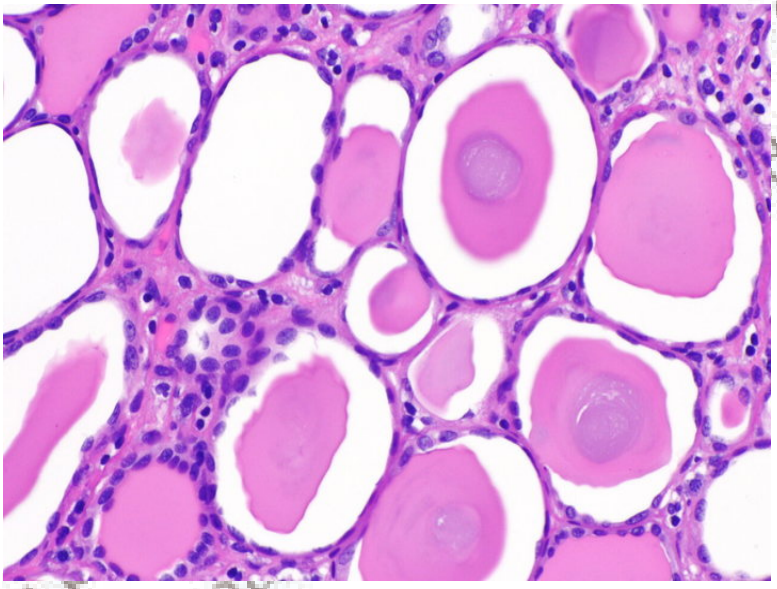
b) Chronic glomerulonephritis

c) Arterionephrosclerosis

d) Malignant hypertension

Question 5:

A pathologist noted the following microscopic finding while examining a slide of a kidney. What is the likely cause?



a) Acute tubular necrosis

b) Chronic pyelonephritis

c) Acute interstitial nephritis

d) Systemic lupus erythematosus

Question 6:

All of the following patients are at risk of developing renal papillary necrosis except:

a) A 14-year-old girl being treated for thalassemia major

b) A 60-year-old man with longstanding diabetes mellitus

c) A 46-year-old man with a history of analgesic abuse

d) A 24-year-old woman identified to have sickle cell trait

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Question 7:

A 48-year-old woman presented with recurrent episodes of flank pain and fever with chills. CECT abdomen showed dilated and enlarged left renal pelvis with the multiloculated calyces and resection of the kidney was done. The gross specimen showed large yellowish-orange nodules. Histological examination revealed foamy macrophages. Which of the following is associated with this condition?

a) Pseudomonas infection

b) Proteus infection

c) Staphylococcus infection

d) Tuberculosis

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Question 8:

Which of the following do not result in granular contracted kidneys?

a) 1, 2 only

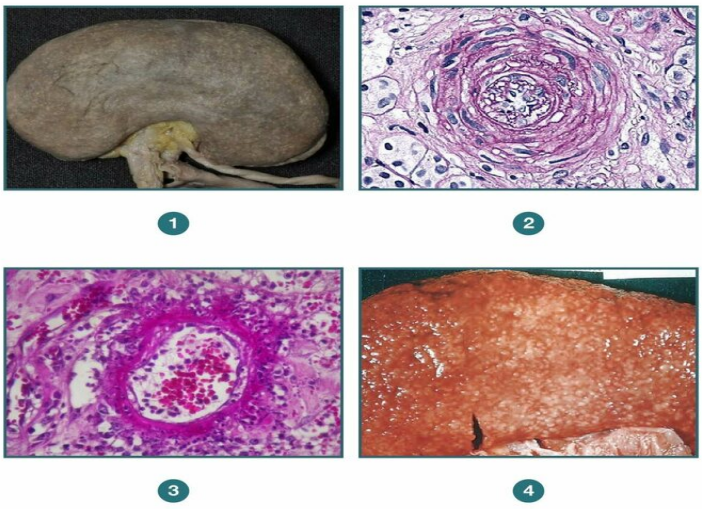
b) 1, 4 only

c) 2, 4 only

d) 2, 3, 5

Question 9:

Which of the following findings is not associated with malignant hypertension?



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a) Image 1

b) Image 2

c) Image 3

d) Image 4

Question 10:

Atypical hemolytic uremic syndrome can be caused by all except:

a) Antiphospholipid antibodies

b) Oral contraceptives

c) Scleroderma

d) Deficiency of ADAMTS13

Question 11:

An 8-year-old boy is brought with blood in the urine. His mother says he had bloody diarrhea, fever, and vomiting 10 days ago. His BP is 130/90 mm Hg, and he is jaundiced. Investigations reveal a platelet count of 50,000 cells/cu mm, BUN of 35mg/dl, and creatinine of 3.5mg/dl. Which of the following cells would you expect to see in the peripheral smear?

a) Spherocytes

b) Schistocyte

c) Target cells

d) Heinz bodies

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Question 12:

Cholemic nephrosis is associated with which of the following casts?

a) Bile

b) Cholesterol

c) Lipids

d) Hyaline

Question 13:

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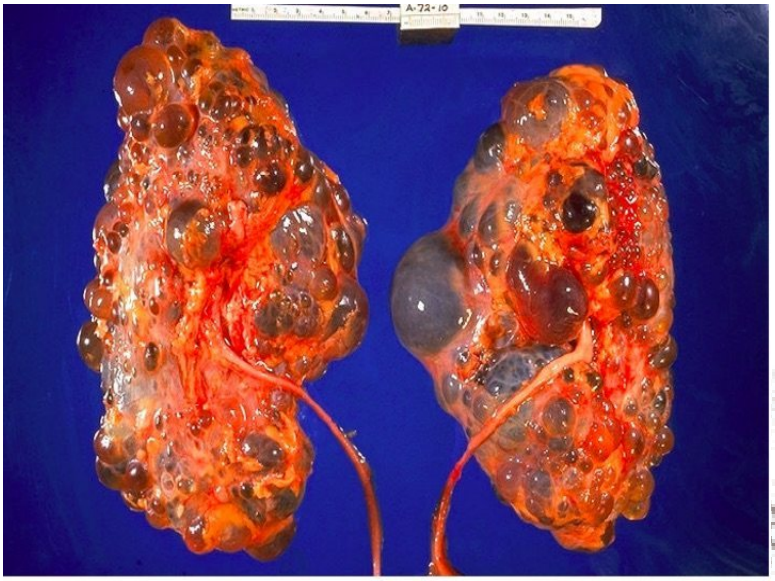
A 35-year-old man died in a road traffic accident. On autopsy, the following appearance of the kidney was noted. Which of the following is not associated with this condition?



a) Cysts in liver, pancreas, and spleen

b) Berry aneurysms

c) Mitral valve prolapse

d) Hepatic fibrosis

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Question 14:

Which of the following is false about the polycystin gene?

a) Polycystin-1 is most commonly involved in ADPKD

b) Polycystin-2 is a calcium ion channel

c) Mutation in polycystin-2 causes more severe form of ADPKD

d) Polycystin-1 is involved in cell interactions

Question 15:

What is the most common extrarenal site of cysts in autosomal dominant polycystic kidney disease?

a) Liver

b) Lung

c) Pancreas

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d) Spleen

Question 16:

In patients with ADPKD, the mutated genes are located on which chromosomes?

a) 16, 4

b) 11, 4

c) 11, 16

d) 16, 6

Question 17:

Mutations in fibrocystin are seen in which condition?

a) Autosomal dominant polycystic kidney disease

b) Medullary sponge kidney

c) Multicystic renal dysplasia

d) Autosomal recessive polycystic kidney disease

Question 18:

Hepatic fibrosis is a feature of which of the following conditions?

a) Childhood polycystic kidney disease

b) Medullary sponge Kidney

c) Acquired renal cystic disease

d) Autosomal-dominant polycystic kidney disease

Question 19:

A routine urine examination of a 46-year-old woman shows thorn-apple crystals. Past history is significant for constipation and longstanding use of laxatives. What is the likely composition of these crystals?

a) Calcium oxalate

b) Triple phosphate

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c) Uric acid

d) Ammonium biurate

Question 20:

In patients with chronic kidney disease, what type of casts are seen?

a) Broad casts

b) WBC casts

c) Epithelial casts

d) Granular casts

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Answer Key

Question No.	Correct Option
1	a
2	c
3	b
4	a
5	b
6	a
7	b
8	b
9	d
10	d
11	b
12	a
13	d
14	c
15	a
16	a
17	d
18	a
19	d
20	a

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Detailed Explanations

Solution to Question 1:

The clinical scenario is suggestive of acute tubular necrosis (ATN) due to ingestion of ethylene glycol. Toxins usually result in ATN by causing damage to the proximal convoluted tubules (PCTs).

Ethylene glycol poisoning produces marked ballooning and hydropic or vacuolar degeneration of PCT. Calcium oxalate crystals are often also found in tubular lumens.

Direct toxic injury to the tubules in ATI can be caused by:

- Endogenous agents: Myoglobin, hemoglobin, monoclonal light chains, bile/bilirubin
- Exogenous agents: Drugs, radiocontrast dyes, heavy metals, and organic solvents

Solution to Question 2:

White blood cell casts are specific features of pyelonephritis. Neutrophil-rich casts (pus casts) indicate renal involvement because casts are formed only in tubules.

The urine contains many leukocytes (pyuria) derived from the inflammatory infiltrate. It is found in both upper and lower UTIs and cannot differentiate between them. Fever is also a non-specific finding.

Ascending infection is the most common cause of clinical pyelonephritis.

Note: Sterile pyuria is defined as white cells in the urine in the absence of significant bacterial growth. It is seen in renal TB.

Solution to Question 3:

The most common organism causing acute pyelonephritis is Escherichia coli.

The organisms that cause acute pyelonephritis include:

- E. coli
- Proteus
- Klebsiella
- Enterobacter species
- Mycobacteria - caseating granulomatous inflammation
- Fungi - non-caseating granulomatous inflammation
- Viruses (CMV and adenovirus) - immunocompromised people

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Solution to Question 4:

Periglomerular fibrosis is considered typical of chronic pyelonephritis.

Histopathological features of chronic pyelonephritis are:

• Dilated tubules with flattened epithelium may be filled with casts resembling thyroid colloid (thyroidization)

• Chronic interstitial inflammation and fibrosis in the cortex and medulla

• Periglomerular fibrosis

• Secondary focal segmental glomerulosclerosis (FSGS), usually several years after the scarring has occurred and often in the absence of continued infection or persistent vesicoureteral reflux

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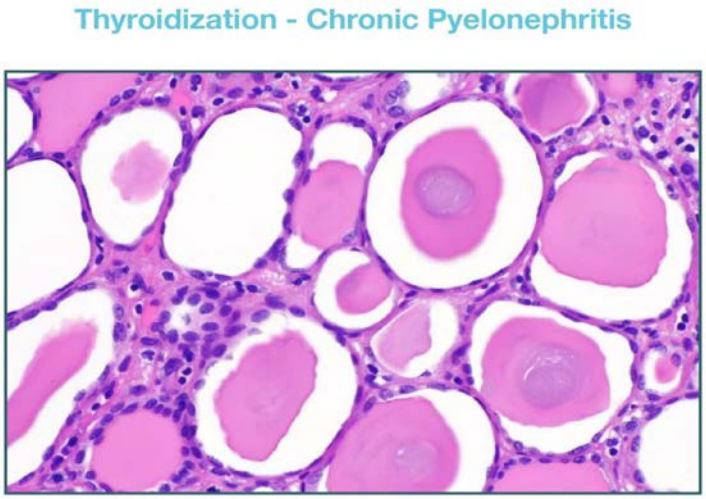
Solution to Question 5:

The given image shows dilated tubules with flattened epithelium, filled with casts, resembling thyroid colloid (thyroidization). This is seen in chronic pyelonephritis.



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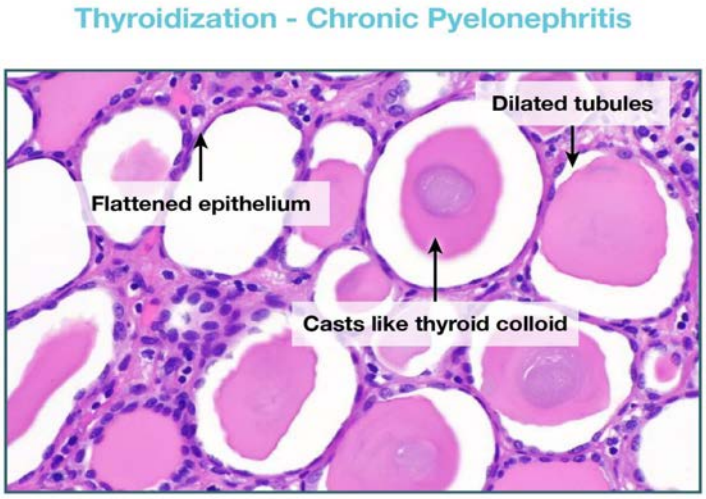

Option A: In acute tubular necrosis, there is focal tubular epithelial necrosis, tubulorrhexis.

Option C: In acute interstitial nephritis, there is patchy edema and mononuclear cell infiltrates.

Option D: In systemic lupus erythematosus (SLE), wire-loop lesions are seen.

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Solution to Question 6:

Necrotizing papillitis or acute papillary necrosis is not associated with thalassemia.

Major causes of acute papillary necrosis include

- Diabetes mellitus
- Sickle cell disease or trait
- Analgesic abuse nephropathy
- Obstruction by calculi
- Focally in renal tuberculosis

Solution to Question 7:

The clinical features and histological findings are suggestive of xanthogranulomatous pyelonephritis. It is associated with Proteus infection and obstructive uropathy.

Xanthogranulomatous pyelonephritis is a relatively rare form of chronic pyelonephritis characterized by the accumulation of foamy macrophages intermingled with plasma cells, lymphocytes, polymorphonuclear leukocytes, and occasional giant cells.

The lesions sometimes produce large, yellowish-orange nodules that may be grossly confused with renal cell carcinoma. CECT abdomen shows dilated and enlarged renal pelvis and calyces showing a multiloculated appearance referred to as the bear paw sign.

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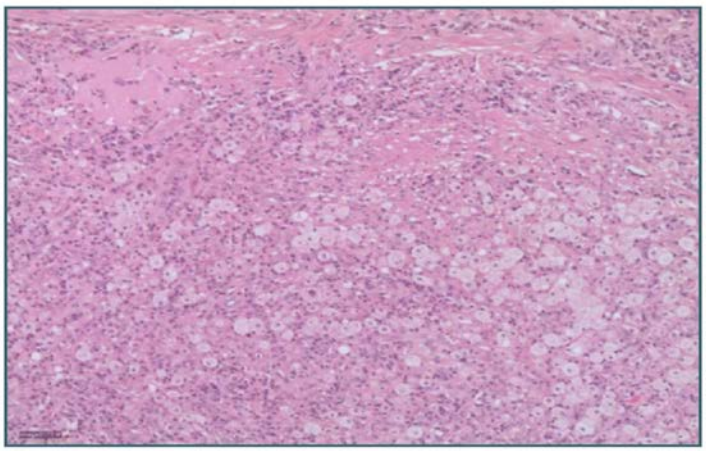
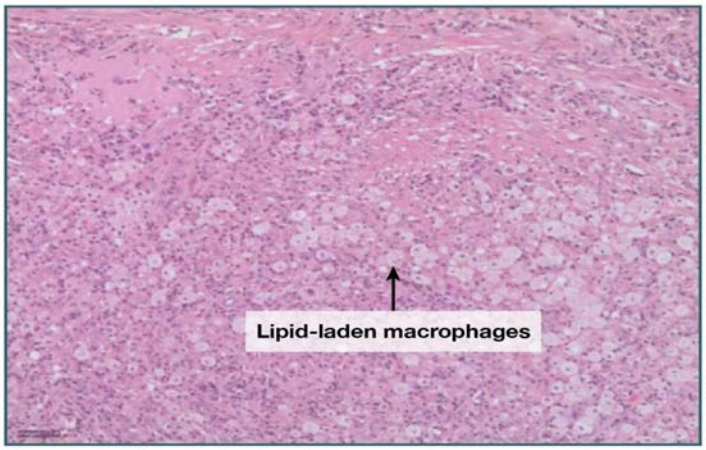
Xanthogranulomatous Pyelonephritis



Xanthogranulomatous Pyelonephritis



Solution to Question 8:

Rapidly progressive glomerulonephritis and amyloidosis cause enlarged kidneys.

Causes of contracted kidneys:

• Symmetric

• Chronic glomerulonephritis

• Benign nephrosclerosis

• Asymmetric

• Chronic pyelonephritis

Causes of enlarged kidneys:

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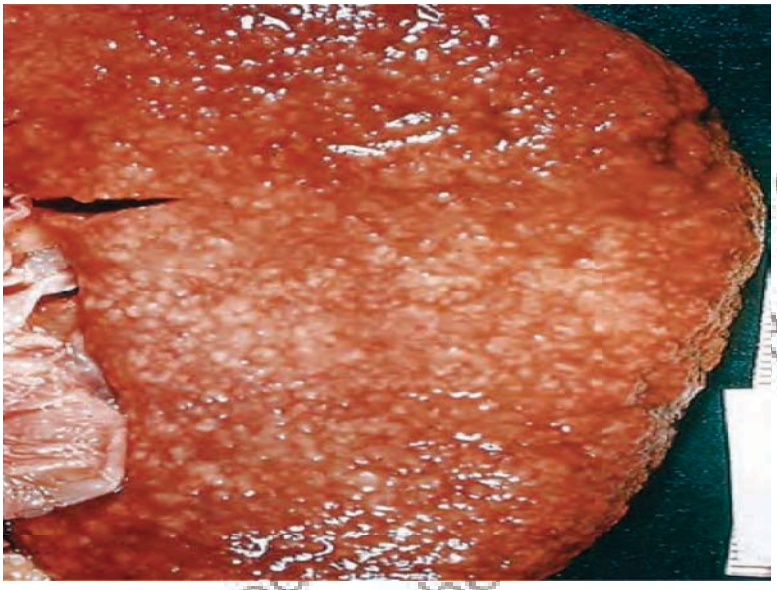
• Rapidly progressive glomerulonephritis

• Amyloidosis

• Polycystic kidney disease

• Hydronephrosis (bilateral obstruction)

The following image shows the gross appearance in benign nephrosclerosis illustrating the fine, leathery granularity of the surface.



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Solution to Question 9:

Image 4 shows a leather-grain appearance, which is seen in benign nephrosclerosis.

Features of malignant hypertension:

• Flea bitten kidney - small petechial hemorrhages on the cortical surface, leading to a mottled appearance

• Fibrinoid necrosis of arterioles - cytologic detail is lost and the vessel wall takes on a smudgy eosinophilic appearance due to fibrin deposition

• Onion-skinning (hyperplastic arterioles) - intimal thickening with the fine concentric layering of collagen & smooth muscles

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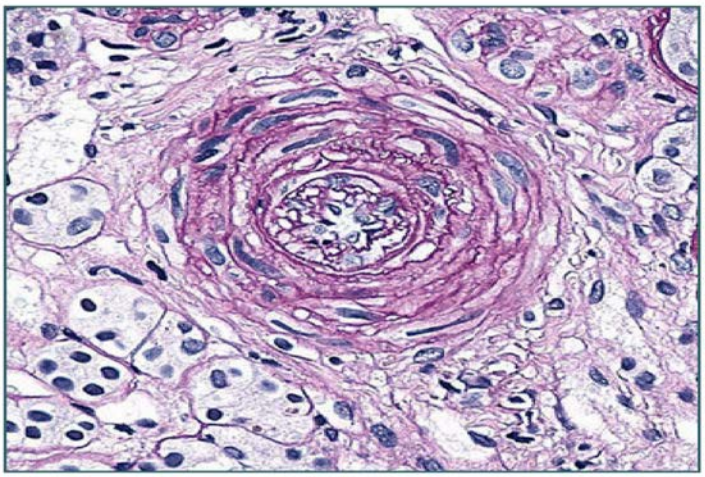
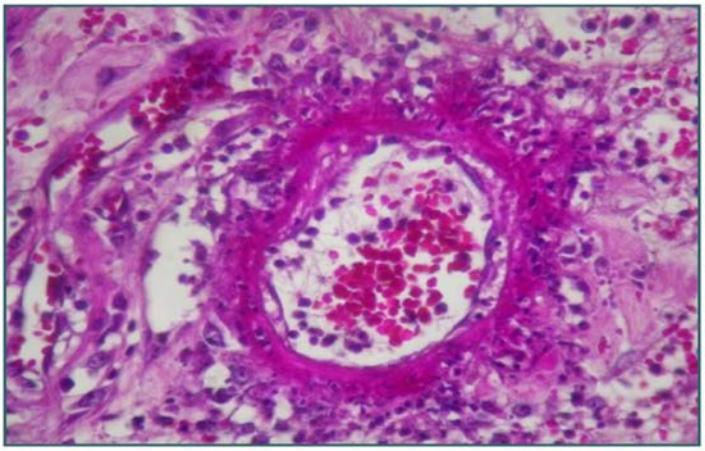
Flea bitten kidney

Onion skinning appearance



Fibrinoid necrosis



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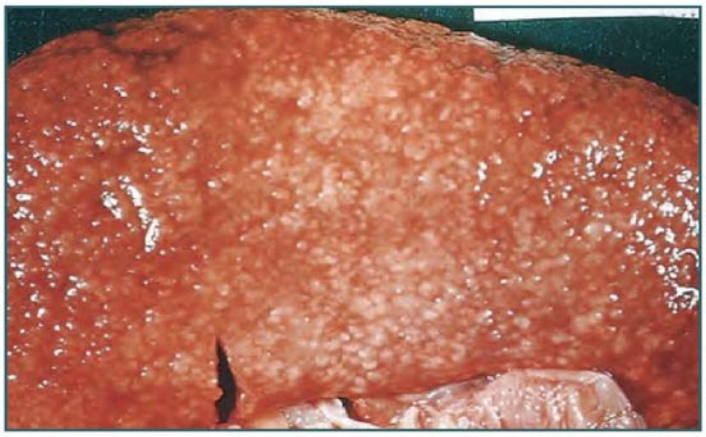
Leather grain appearance of Kidney



The differential diagnosis for flea-bitten kidney includes:

- Polyarteritis nodosa
- Subacute bacterial endocarditis (SABE)
- Malignant hypertension

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Solution to Question 10:

Deficiency of ADAMTS13 leads to thrombotic thrombocytopenic purpura (TTP).

Two common pathogenetic triggers of thrombotic microangiopathies are:

- Endothelial injury - HUS
- Excessive platelet activation and aggregation - TTP

Typical HUS	Atypical HUS
5-10 days afterdiarrhealillnes sE.coliO157:H7orShigella dys enteriaetype I	Mutation in genes encoding c omplement regulatory protei n
Shiga-liketoxinsproduced cau seendothelialdamage.This lea ds to platelet activation and t hrombi.	Uncontrolledactivationof the complementsystem due to:An tiphospholipid antibodiesPre gnancy complicationsOCPsSc leroderma

Solution to Question 11:

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The clinical scenario is suggestive of hemolytic uremic syndrome (HUS). It is characterized by the presence of schistocytes in peripheral smear. It indicates microangiopathic hemolytic anemia.

Solution to Question 12:

Cholemic nephrosis is associated with casts of bile.

In patients with acute or chronic liver disease with advanced liver failure, renal function may be impaired. This is called hepatorenal syndrome. This can be associated with highly elevated bilirubin levels with bile cast formation (also known as cholemic nephrosis) in distal nephron segments.

Solution to Question 13:

The gross image suggests that the patient had autosomal-dominant polycystic kidney disease (ADPKD). This condition is not associated with hepatic fibrosis. However, patients with autosomal recessive (childhood) polycystic kidney disease (ARPKD) have congenital hepatic fibrosis.

ADPKD is associated with mutations in PKD1, encoding polycystin 1, and PKD2, encoding polycystin 2. The multiple expanding cysts of both kidneys ultimately destroy the renal parenchyma and cause renal failure. Cysts arise from the tubules throughout the nephron and, therefore, have variable lining epithelia.

The common extrarenal manifestations of ADPKD include:

• Hepatic cysts - most common

• Seminal vesicle cysts - can result in infertility

• Arachnoid membrane cysts - usually asymptomatic, may increase the risk of subdural hematoma

• Pancreatic cysts

• Splenic cysts

• Intracranial berry aneurysms

• Subarachnoid hemorrhages

• Mitral valve prolapse

There are very few case reports with lung cysts in ADPKD patients, but the association between ADPKD and lung cysts has not been proved. However, there is a three-fold increase in the incidence of bronchiectasis in ADPKD patients.

Solution to Question 14:

The polycystin-2 mutation is less commonly involved and less severe.

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Polycystin-1 is encoded by the PKD1 gene located on chromosome 16p13.3. It is expressed in tubular epithelial cells, particularly those of the distal nephron. It contains domains that are usually involved in cell-cell and cell-matrix interactions. Mutations in PKD1 account for about 85% of cases of ADPKD (autosomal dominant polycystic kidney disease) and it causes a more severe form of the disease.

Polycystin-2 is an integral membrane protein that is expressed in all segments of the renal tubules and in many extrarenal tissues. It functions as a Ca2+ cation channel. Overall, it causes a less severe form of ADPKD disease.

Solution to Question 15:

The most common extrarenal site of cysts in autosomal dominant polycystic kidney disease (ADPKD) is the liver.

40% of individuals with autosomal-dominant polycystic kidney disease (ADPKD) have one to several cysts in the liver (polycystic liver disease) that are usually asymptomatic. The cysts are derived from the biliary epithelium.

Cysts occur much less frequently in the spleen, pancreas, and lungs. There are very few case reports with lung cysts in ADPKD patients, but the association between ADPKD and lung cysts has not been proved.

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Solution to Question 16:

The genes mutated in autosomal dominant polycystic kidney disease (ADPKD) are located on chromosomes 16 and 4.

This condition occurs due to mutations of the PKD1 gene (chromosome 16) and PKD2 gene (on chromosome 4). These genes encode for polycystin 1 and 2 proteins respectively.

Solution to Question 17:

Autosomal recessive polycystic kidney disease (ARPKD) is caused by mutations in the PKHD1 gene on chromosome 6p21-p23 which encodes fibrocystin.

The gene is highly expressed in adult and fetal kidneys and also in the liver and pancreas. Fibrocystin has been localized to the primary cilium of tubular cells.

The serious manifestations of ARPKD are usually present at birth, and may cause death by renal failure. The following gross findings are seen:

• Enlarged kidneys with smooth external appearance

• Spongelike appearance due to numerous small cysts in the cortex and medulla

• Dilated elongated channels at right angles to the cortical surface, completely replacing the medulla and cortex

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On microscopic examination, there is cylindrical or, less commonly, saccular dilation of all collecting tubules with linning of cuboidal cells. In almost all cases, the liver has cysts associated with portal fibrosis and proliferation of the portal bile ducts, termed congenital hepatic fibrosis.

Solution to Question 18:

Hepatic fibrosis is a feature of childhood (autosomal recessive) polycystic kidney disease.

Solution to Question 19:

Ammonium biurate crystals appear as spheres with radial or concentric striations and irregular projections or thorns, referred to as thorn apples. They are seen in laxative abuse.

Solution to Question 20:

Broad casts are seen in patients with chronic kidney disease (CKD). They are also known as renal failure casts.

Broad casts are defined as those with a diameter 2-6 times that of normal casts. They indicate chronically damaged tubules or collecting ducts. They indicate a poor prognosis.

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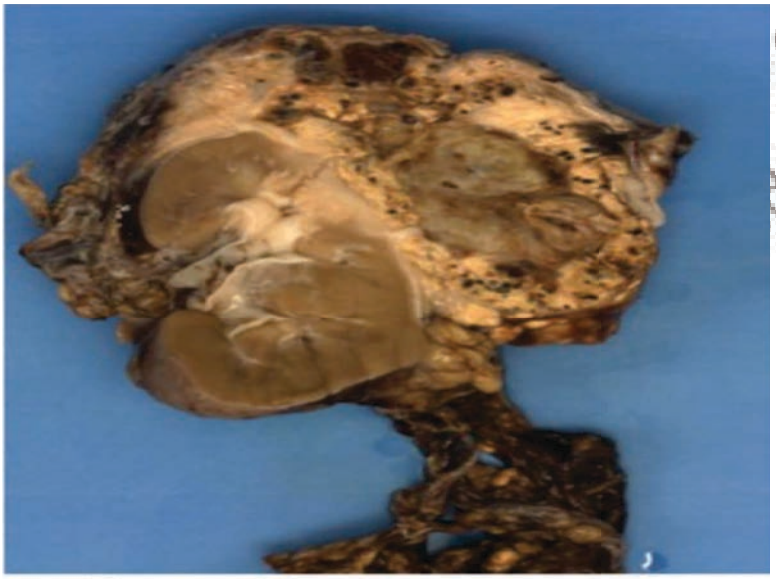
Renal Tumors

Question 1:

An 18-month-old child is brought to OPD with complaints of blood in his urine. Examination reveals a non-tender mass in the left flank that does not cross the midline. Blood pressure is also found to be elevated. Imaging reveals a left renal tumor and surgical resection is planned. The gross appearance of the mass is shown below. What is the likely diagnosis?



a) Renal cell carcinoma

b) Nephroblastoma

c) Neuroblastoma

d) Angiomyolipoma

Question 2:

Which of the following statements is true regarding Wilms tumor?

a) It is inherited as an autosomal recessive disorder

b) It is associated with MIC-2 gene expression

c) It is associated with the deletion of chromosome 11p13

d) The most common presentation is hematuria

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Question 3:

In patients with Wilms tumors, which of the following microscopic features are indicative of resistance to chemotherapy?

a) Presence of nephrogenic cell rests

b) Presence of monophasic morphology

c) Presence of anaplasia

d) Presence of capsular infiltration

Question 4:

Which of the following is the most important prognostic factor in Wilms' tumor?

a) Anaplastic histology

b) Tumor size

c) Age of the patient

d) Chromosome 11q deletion

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Question 5:

Which of the following is not associated with Wilms tumor?

a) Hemihypertrophy

b) Aniridia

c) Omphalocele

d) Bilateral polycystic kidneys

Question 6:

A 16-year-old girl is being evaluated for a history of recurrent seizures and abdominal discomfort. Examination reveals the following nail findings. Which of the following should she be screened for?

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a) Renal cell carcinoma

b) Angiomyolipoma

c) Oncocytoma

d) Wilms tumour

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Question 7:

A 50-year-old diabetic patient is being evaluated for chronic abdominal discomfort. CECT of the abdomen and pelvis shows a heterogeneously enhancing renal mass with a central stellate scar. On resection, the tumor appears mahogany brown. What is the site of origin of this tumor?

a) Proximal tubule

b) Distal tubule

c) Loop of henle

d) Collecting duct

Question 8:

Which of the following is the most important determinant of malignant potential in the papillary type of renal tumor?

a) Immnunohistology

b) Size

c) Cytogenetics

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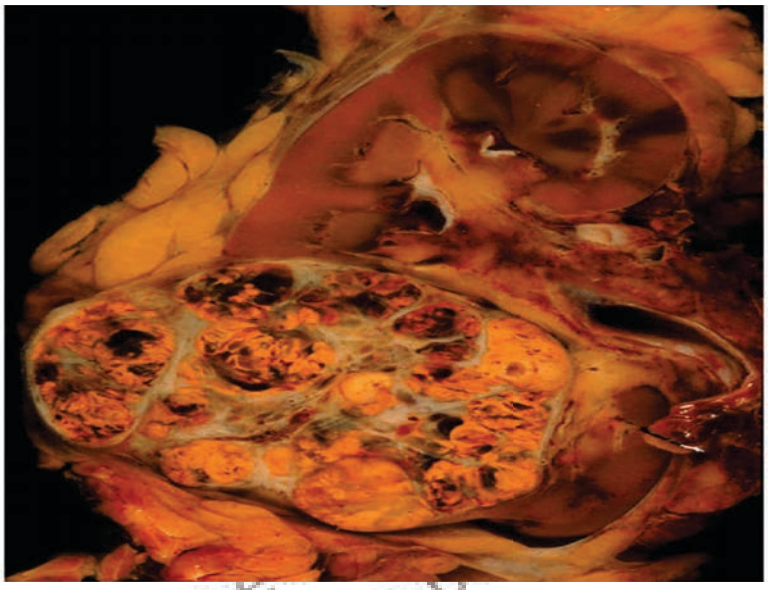
d) Part of kidney involved

Question 9:

The following image shows a nephrectomy specimen of a patient diagnosed with renal cell carcinoma. What is the likely histopathological finding in this tumor?



a) Clear cells

b) Signet cells

c) Small cells with high N/C ratio

d) Malignant squamous cells

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Question 10:

The nephrectomy specimen of a tumor of a 40-year-old man shows the following histological presentation. Which of the following familial cancer syndromes is this condition associated with?

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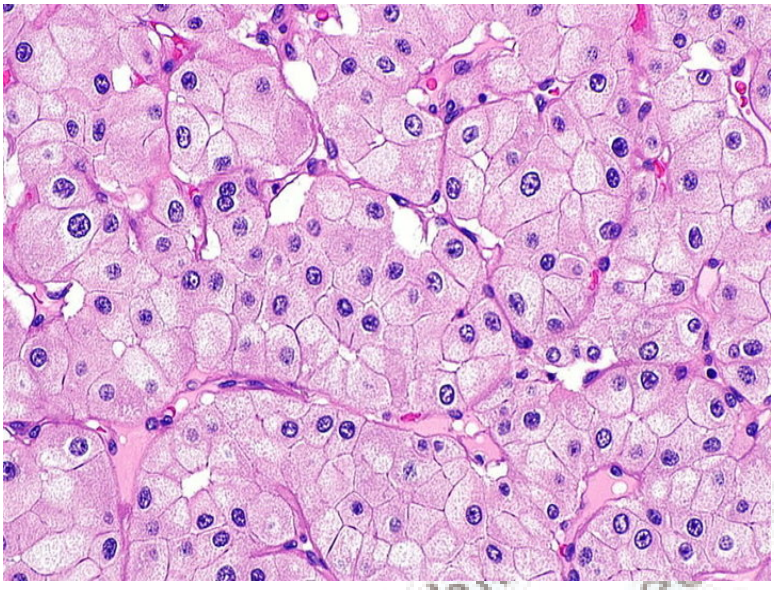

a) Von Hippel-Lindau syndrome

b) Hereditary leiomyomatosis and renal cell cancer syndrome

c) Birt-Hogg-Dube syndrome

d) Tuberous sclerosis

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Question 11:

Which of the following subtypes of renal cell carcinoma is matched incorrectly with its respective cytogenetic patterns?

a) Hereditary clear-cell RCC - 3p deletion

b) Sporadic clear-cell RCC - 3p deletion

c) Hereditary papillary RCC - loss of Y

d) Sporadic papillary RCC - loss of Y

Question 12:

Which of the following is the most common histological subtype of renal cell carcinoma?

a) Clear cell

b) Chromophobe

c) Papillary

d) Collecting duct

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Question 13:

Which of the following tumors does not have papillary architecture on histopathology?

a) Hereditary leiomyomatosis renal cell carcinoma

b) Succinate dehydrogenase-deficient renal cell carcinoma

c) Xp11 translocation renal cell carcinoma

d) Collecting duct renal cell carcinoma

Question 14:

Which of the following subtypes of renal cell carcinoma shows large cells having a plant-cell-like appearance with a perinuclear halo on histological examination?

a) Clear cell

b) Papillary

c) Chromophobe

d) Collecting duct

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Question 15:

A patient with Birt-Hogg-Dube syndrome is found to have a renal tumor and malignancy is suspected. Which of the following statements is incorrect regarding the renal tumor associated with this condition?

a) It constitutes 5% of all renal tumors

b) Cytogenetic testing of the tumor shows multiple chromosomal losses

c) It has the worst prognosis

d) It arises from the intercalated cells of the collecting duct

Question 16:

Which of the following tumors characteristically shows a hobnail pattern on microscopy?

a) Clear cell

b) Chromophobe

c) Papillary

d) Collecting duct

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Question 17:

Individuals with the sickle cell trait are at a higher risk of developing which of the following?

a) Clear cell renal cell carcinoma

b) Medullary renal cell carcinoma

c) Papillary renal cell carcinoma

d) Collecting duct renal cell carcinoma

Question 18:

A pathologist is studying the histopathological slide from a nephrectomy specimen from a patient with renal carcinoma. He observes neoplastic cells with clear cytoplasm and papillary architecture. Which of the following subtypes of renal carcinoma is this likely to be?

a) Papillary carcinoma

b) Bellini duct carcinoma

c) Xp11 translocation carcinoma

d) Succinate dehydrogenase deficient RCC

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Question 19:

Which of the following statements is incorrect regarding renal cell carcinoma?

a) It can invade the renal vein

b) It can present with hypercalcemia

c) It may arise from the proximal convoluted tubule

d) It occurs commonly in females

Question 20:

Which of the following is the most common site of metastasis of renal cell carcinoma?

a) Lung

b) Liver

c) Bones

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d) Adrenals

Question 21:

Which of the following types of renal cell carcinoma has the worst prognosis?

a) Clear cell

b) Papilllary

c) Medullary

d) Collecting duct

Question 22:

Which of the following genes is not mutated in familial renal cell carcinoma syndromes?

a) C-met gene

b) Fumarate hydratase gene

c) BHD gene

d) WT gene

Question 23:

Which of the following pairs correctly describes the immunohistochemical property of renal cell carcinoma in a cancer of unknown origin?

a) CK7 positive, CK20 positive

b) CK7 negative, CK20 positive

c) CK7 positive, CK20 negative

d) CK7 negative, CK20 negative

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Answer Key

Question No.	Correct Option
1	b
2	c

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3	c
4	a
5	d
6	b
7	d
8	b
9	a
10	c
11	c
12	a
13	b
14	c
15	c
16	d
17	b
18	c
19	d
20	a
21	d
22	d
23	d

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Detailed Explanations

Solution to Question 1:

This clinical scenario and image showing a well-circumscribed tumor with multiple necrotic, hemorrhagic, and cystic changes in the upper pole of the kidney are suggestive of a nephroblastoma or Wilms' tumor.

It is the most common primary renal tumor of childhood (2-5 years of age). Around 10% of cases are associated with genetic syndromes and gonadal dysgenesis may be seen.

Clinical manifestations of Wilms' tumor include:

• Large abdominal mass - usually unilateral and does not cross the midline

• Abdominal pain

• Hematuria

• Hypertension

• Intestinal obstruction (in some cases)

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Nephrogenic rests are the precursor lesions of Wilms' tumor and suggest an increased risk of developing a contralateral Wilms' tumor.

Solution to Question 2:

Wilms' tumor is associated with the deletion of chromosome 11p13.

It is an autosomal-dominant disorder. The most common clinical presentation is an abdominal mass.

Note: MIC-2 gene expression is seen in neuroblastoma.

Solution to Question 3:

In Wilms' tumor, the presence of anaplasia is indicative of resistance to chemotherapy.

This correlates with the presence of TP53 mutations and, hence, is associated with a poor prognosis.

Solution to Question 4:

Anaplastic histology is the most important prognostic factor in Wilms' tumor.

It is seen in about 5% of cases and is characterized by the presence of cells with large, hyperchromatic, pleomorphic nuclei, and abnormal mitoses. It is associated with TP53 mutations and resistance to chemotherapy.

Anaplasia is uncommon in children < 2 years. Hence, tumors presenting at an young age have a significantly better prognosis than those presenting in older children.

Prognostic factors in Wilms' tumor include:

	Favorable prognosis	Adverse prognosis
Histologic type	Classic triphasic componen t	Anaplastic histology
Tumor stage	Low	High
Molecular alteration s	----	11q deletion16q deletionGain of chromosome 1q
Age of onset	<2 years	>2 years

Solution to Question 5:

Bilateral polycystic kidneys are not associated with Wilms tumor.

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Wilms' tumor can be associated with:

• Aniridia - WAGR syndrome

• Gonadal dysgenesis - Denys–Drash syndrome

• Hemihypertrophy and omphalocele - Beckwith–Wiedemann syndrome

Solution to Question 6:

This clinical scenario and image showing periungual fibromas are strongly suggestive of tuberous sclerosis. This condition is associated with renal angiomyolipomas (present in 25–50% of cases).

Tuberous sclerosis is a multisystem disorder that has an autosomal dominant mode of inheritance. The mutations are involved in the TSC1 gene that encodes hamartin on chromosome 9 and the TSC2 gene that encodes a protein tuberin on chromosome 16.

The clinical features of tuberous sclerosis include:

• Skin lesions -

• Hypomelanotic ash leaf–type macules

• Periungual fibromas or Koenen tumors (small fibromas or nodules of skin around fingernails or toenails)

• Shagreen patch- roughened, raised lesion with an orange-peel consistency, primarily in the lumbosacral region

• Facial angiofibromas

• Confetti skin lesions

• Neurological features -

• Epilepsy and intellectual disability (due to cortical tubers)

• Autism spectrum disorder

• Subependymal giant cell astrocytomas

• Other tumors -

• Cardiac rhabdomyoma

• Renal angiomyolipomas, renal cysts

• Pulmonary lymphangioleiomyomatosis

Angiomyolipoma is a benign renal neoplasm (hamartoma) originating from perivascular epithelioid cells (PEComa). It consists of vessels, smooth muscle, and fat in variable proportions. They are highly susceptibility to spontaneous hemorrhage.

The histological image of renal angiomyolipoma is given below:

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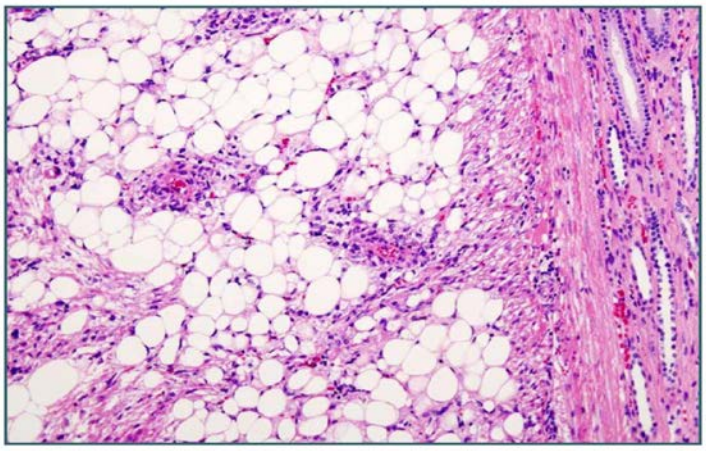
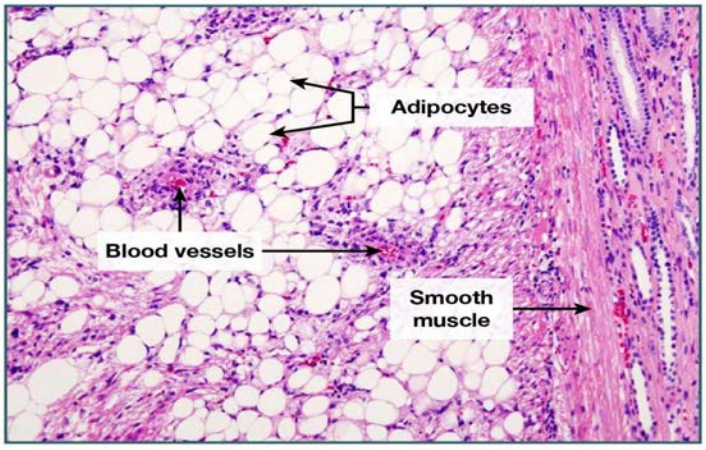
Renal Angiomyolipoma



Renal Angiomyolipoma



Solution to Question 7:

The given clinical history is suggestive of renal oncocytoma. It arises from the intercalated cells of the collecting ducts.

It is a benign epithelial neoplasm. Grossly, these tumors appear tan or mahogany brown and relatively homogeneous. They are usually well encapsulated with a central scar in one-third of cases.

Microscopically, they are composed of large eosinophilic cells having small, round, benign-appearing nuclei that have large nucleoli. Ultrastructurally, these eosinophilic cells have numerous mitochondria.

The gross and histological appearances of renal oncocytoma are shown in the images given below:

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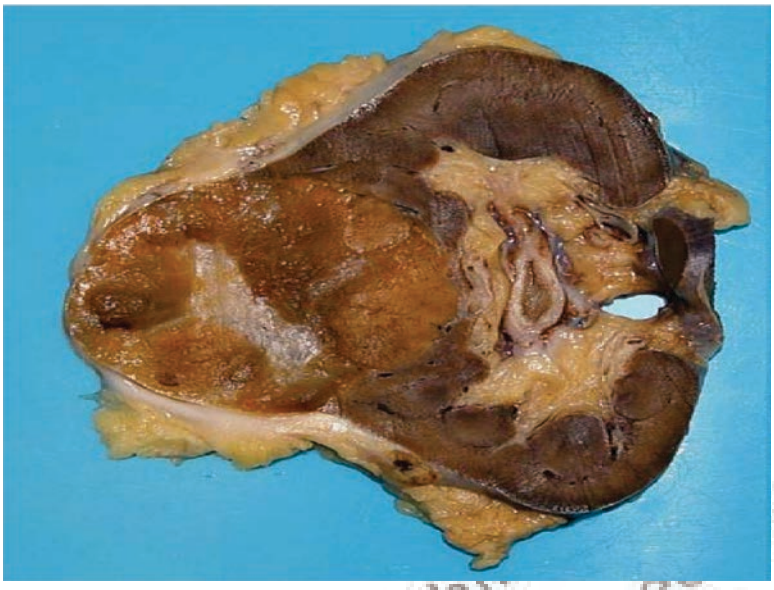
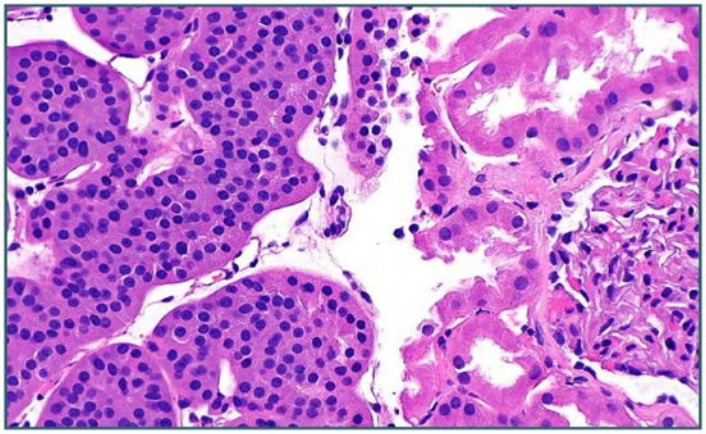
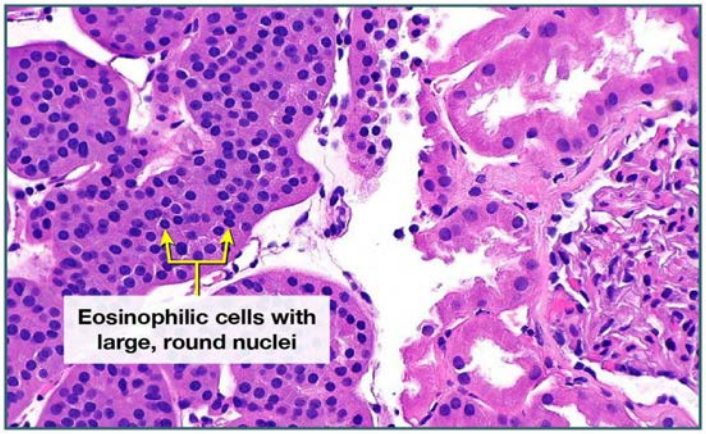


Renal Oncocytoma



Renal Oncocytoma



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Oncocytes refer to epithelial cells with abundant eosinophilic granular cytoplasm (due to the accumulation of mitochondria). They can arise in various tissues and are referred to as:

• Hurthle cells/Ashkenazy cells in the thyroid gland

• Oxyphilic cells in the parotid gland

• Apocrine metaplasia in the breast

Solution to Question 8:

The most important determinant of malignant potential in the papillary type of renal tumor is the size of the tumor.

The papillary type of renal tumors includes:

• Renal papillary adenoma (≤ 1.5 cm)

• Papillary type of renal cell carcinoma (RCC) - > 1.5 cm

Small renal papillary growths are fairly common and incidentally found. Ruling out of malignancy is one of the processes carried out during the evaluation of donor transplant kidneys.

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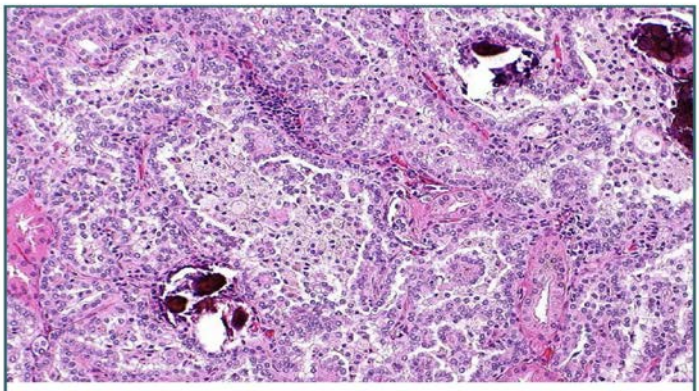
Renal Papillary Adenoma



Papillary architecture (Nipple-like projections)

Papillary renal cell carcinoma (RCC) is the second most common type of renal cell carcinoma and it arises from proximal tubules. It can be multifocal or bilateral. It is typically hemorrhagic and cystic, especially when large.

It is often a circumscribed tumor composed of papillae formed by delicate fibrovascular cores that often contain foamy macrophages and Psammoma bodies.

It has two histological types:

• Type 1 papillary RCC - single layer of cells on the basement membrane and low-grade nuclear features

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• Type 2 papillary RCC - pseudostratification of cells and usually has high-grade nuclear features

Solution to Question 9:

The given image shows a bright yellow variegated mass distorting the renal outline at the lower pole. This is suggestive of the clear cell type of renal cell carcinoma (RCC). The yellow color is due to prominent lipid accumulation.

Gross findings of various types of renal tumors:

	Clear-cell RCC	Papillary RCC	Chromophobe RCC	Oncocytoma	Angiomyolipoma
Site of origin	Proximal tubular epithelium	Proximal tubule	Intercalated cells of collecting ducts	Intercalated cells of collecting ducts	Perivascular epithelioid cells (PEComa)
Number	Solitary, globular, unilateral	Multifocal and bilateral	Solitary, unilateral	Usually solitary	Mostly solitary, can be multifocal
Color	Golden yellow, due to the high lipid content of their cells	Grey tan to dark brown,depending on the degree of intratumoral hemorrhage	Light tan to brown	Mahogany brown	Yellow to pinkish-tan,depending on the relative proportions of the various components
Capsule	Pseudocapsule+	Pseudocapsule+	Circumscribed but unencapsulated	Well encapsulated	Circumscribed but unencapsulated
Appearance	Variegated with cysts, necrosis, hemorrhagic foci	Variegated, friable	Homogenous	Homogenous	Variable

Solution to Question 10:

The given image shows eosinophilic cells with prominent cell membranes and perinuclear halo, which is suggestive of chromophobe cell renal cell carcinoma (RCC). It is associated with Birt–Hogg–Dubé syndrome.

Other familial cancer syndromes and the common malignancies associated with them are:

• Hereditary leiomyomatosis and renal cell cancer syndrome - papillary RCC

• Large cells with abundant eosinophilic cytoplasm, large nuclei, and prominent inclusion-like eosinophilic nucleoli.

• Tuberous sclerosis - clear-cell RCC

• Von Hippel–Lindau syndrome (VHL) - clear-cell RCC

The image given below shows the histology of chromophobe cell RCC.

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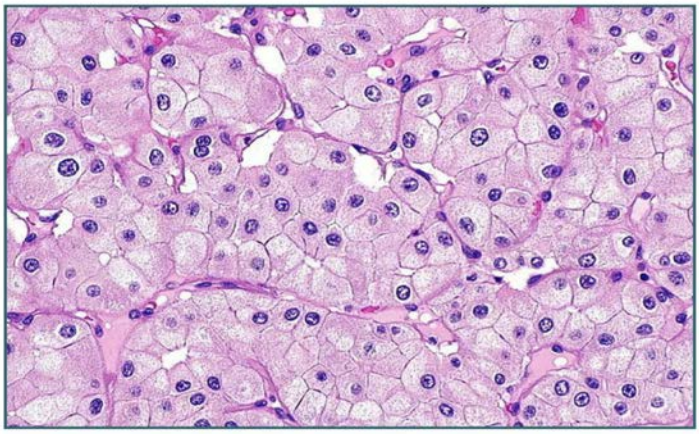
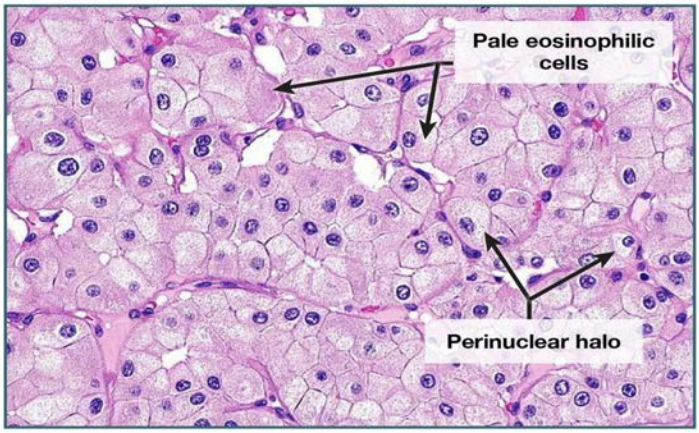
Chromophobe Cell Renal Cell Carcinoma



Chromophobe Cell Renal Cell Carcinoma



Solution to Question 11:

Loss of Y chromosome is a feature of sporadic papillary carcinoma, not hereditary papillary RCC.

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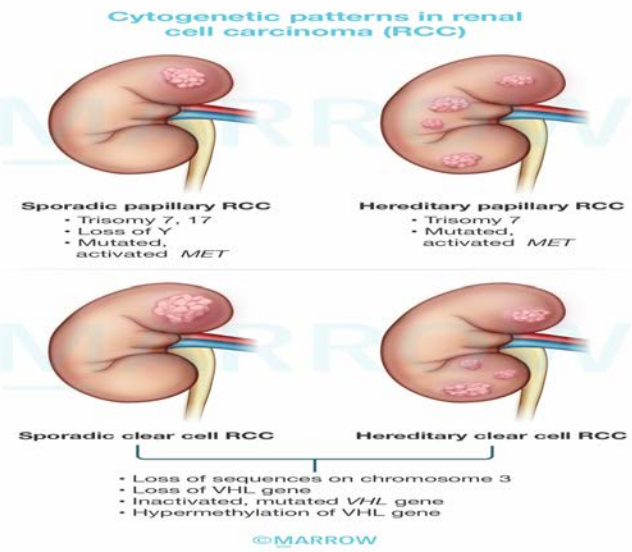

Various types of renal carcinoma and their cytogenetic abnormalities are given below:

• Papillary renal cell carcinoma -

• Sporadic type - trisomies 7 and 17, loss of Y chromosome

• Familial type - trisomy 7 (mapped to MET gene)

• Clear-cell renal-cell carcinoma (whether familial, sporadic, or associated with VHL syndrome)

• Loss of sequences on the short arm of chromosome 3, which harbors the VHL gene

Solution to Question 12:

Clear-cell renal cell carcinoma is the most common histological subtype of renal cell carcinoma, accounting for 70% to 80% of renal cell cancers.

It is most likely to arise from the proximal tubular epithelium as solitary lesions. It has a characteristic tendency to invade the renal vein. The histological features are:

• Rounded or polygonal tumor cells

• Abundant clear or granular cytoplasm, which contains glycogen and lipids

• Arranged in a solid to trabecular (cordlike) or tubular pattern

The histological appearance of clear-cell renal cell carcinoma is shown in the image given below:

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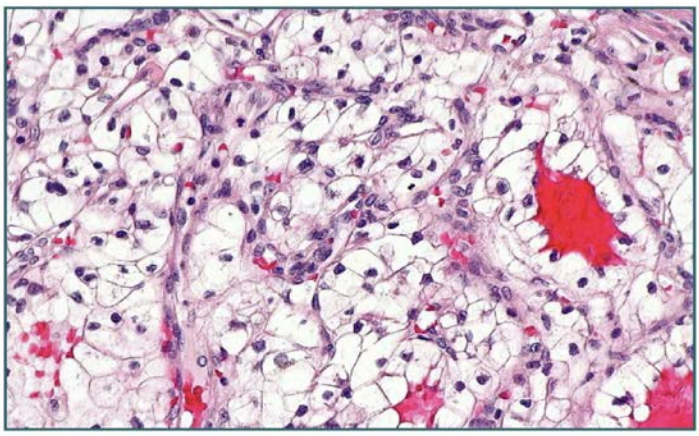
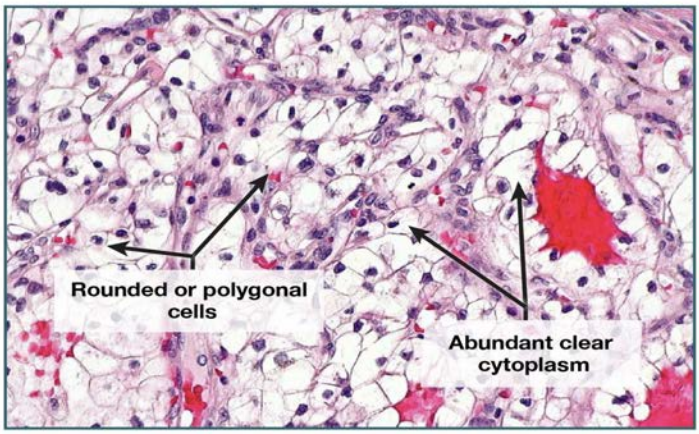
Clear Cell Carcinoma (RCC)



Clear Cell Carcinoma (RCC)



Note: The Furhman nuclear grading system was previously used for histological grading of RCC (except chromophobe RCC). It is now replaced by the WHO/International Society of Urologic Pathology (ISUP) grading system.

Solution to Question 13:

Succinate dehydrogenase (SDH)-deficient renal cell carcinoma does not show papillary architecture. It is associated with a bubbly appearance of histopathology.

It is a malignant epithelial tumor associated with germline mutations in the SDH gene. It is composed of vacuolated, eosinophilic-clear cells arranged in a solid, nested, or tubular pattern. The presence of the vacuoles imparts the characteristic bubbly appearance, as shown below.

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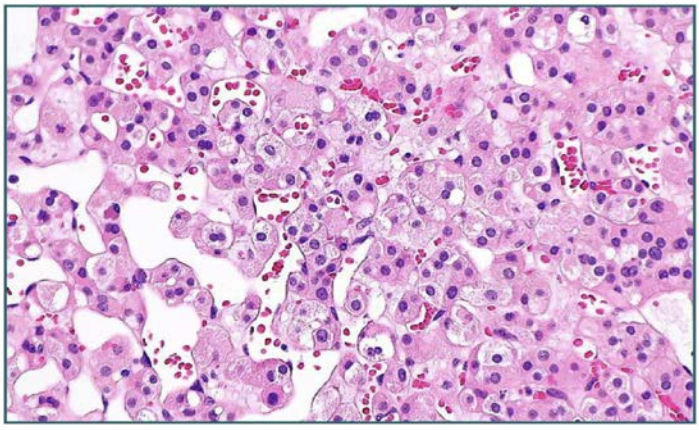
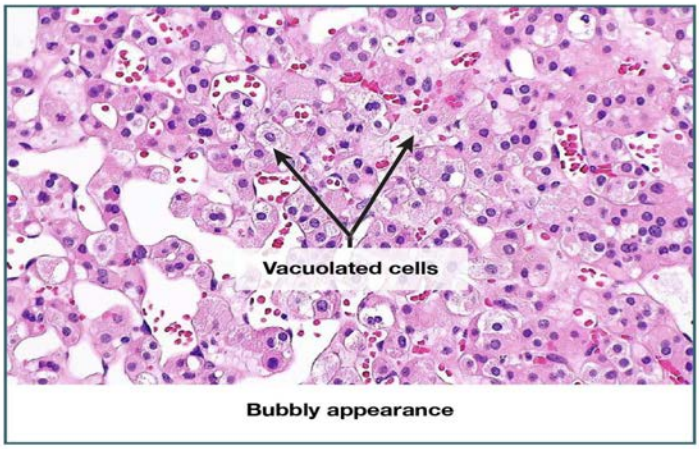
SDH-Deficient Renal Cell Carcinoma



SDH-Deficient Renal Cell Carcinoma



Renal cell carcinoma subtypes with papillary architecture in histology:

- Papillary renal cell carcinoma
- Hereditary leiomyomatosis renal cell carcinoma
- Xp11 translocation renal cell carcinoma
- Collecting duct renal cell carcinoma

Solution to Question 14:

Chromophobe renal cell carcinoma shows large cells having plant-cell-like appearance with a perinuclear halo.

They are arranged in solid sheets with a concentration of the largest cells around blood vessels.

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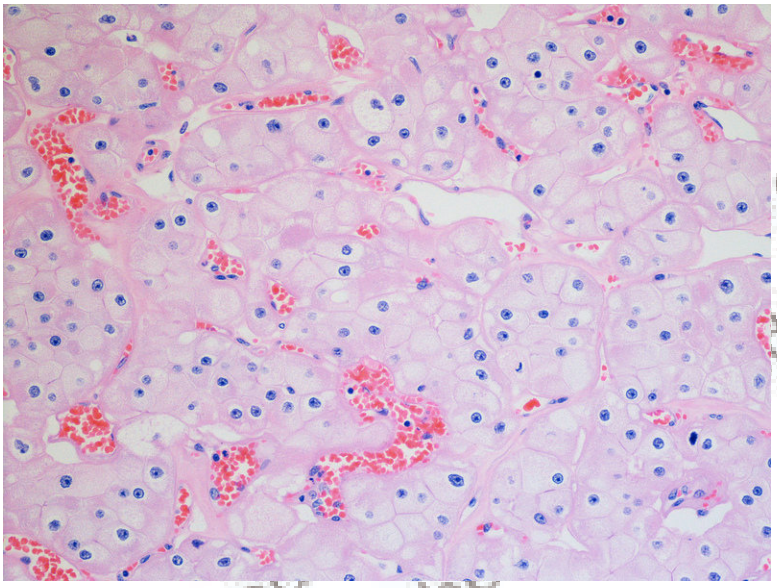
Chromophobe renal cell carcinoma can differentiated from oncocytoma and clear cell RCC as follows:

• Oncocytoma does not show perinuclear halo whereas chromophobe RCC shows perinuclear halo

• CK7 is diffusely positive in chromophobe RCC but it is negative in clear-cell RCC.

Chromophobe RCC cannot be histologically graded because of its innate nuclear atypia.

The histological image of chromophobe renal cell carcinoma is given below:



Solution to Question 15:

The renal tumor commonly associated with Birt-Hogg-Dube syndrome is chromophobe renal cell carcinoma (RCC). It has an excellent prognosis.

It constitutes 5% of all renal carcinomas. It arises from the intercalated cells of the collecting duct. Cytogenetic testing of the tumor shows multiple chromosomal losses and extreme hypodiploidy.

The histological image of chromophobe RCC is given below:

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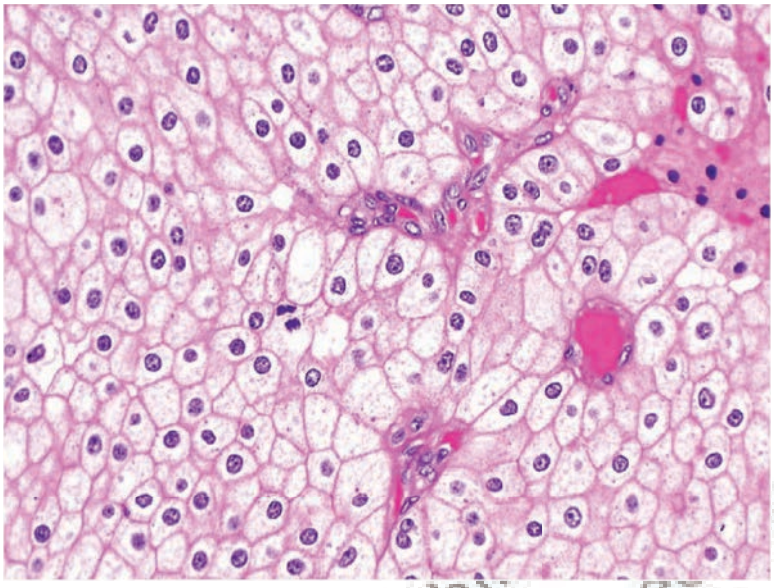

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Solution to Question 16:

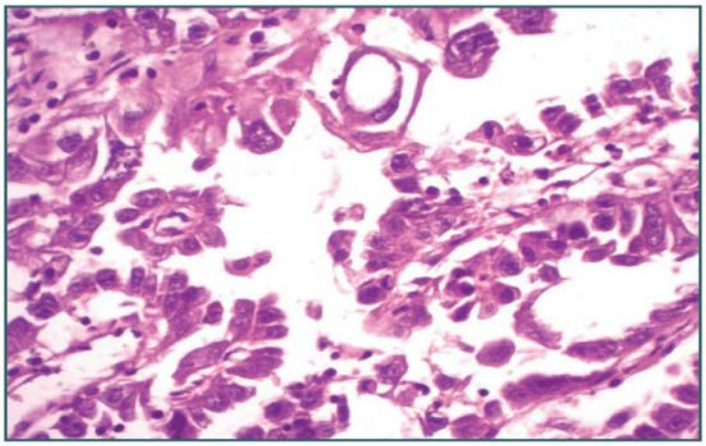
Collecting duct carcinoma or Bellini duct carcinoma shows a characteristic hobnail pattern and prominent desmoplastic stroma on microscopy.

The hobnail pattern refers to the bulbous nuclear projections of epithelial cells that protrude into the lumen as little bumps. It is associated with tubular, tubulopapillary, or tubulocystic pattern.

Collecting duct carcinoma arises from the principal cells of the renal collecting ducts of Bellini. The majority of these tumors are associated with poor outcome, due to their highly aggressive clinical course.

The histological section showing collecting duct carcinoma with the characteristic hobnail pattern is given below:

Renal Collecting Duct / Bellini Duct Carcinoma



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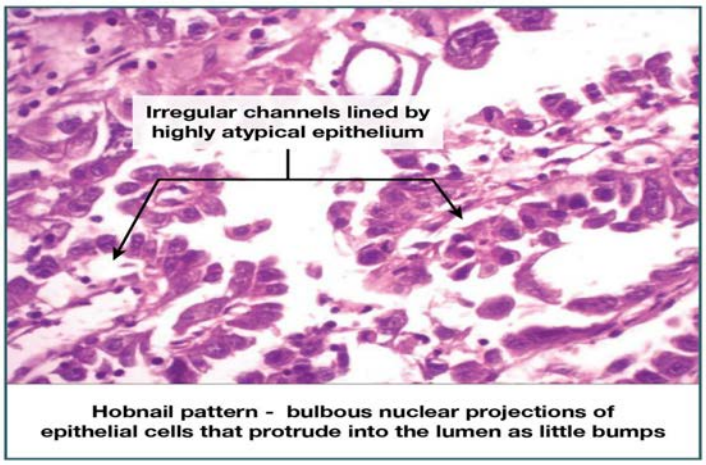
Renal Collecting Duct / Bellini Duct Carcinoma



Note: The hobnail pattern is also seen in clear cell carcinoma of the ovary.

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Solution to Question 17:

Individuals with the sickle cell trait are at a higher risk of developing medullary renal cell carcinoma.

It is a rare, highly aggressive neoplasm and is morphologically similar to collecting duct carcinoma.

The hypoxic microenvironment in the renal medulla created by hyperosmolarity, low pH, and stasis enhances red blood sickling and ischemic damage. This leads to chronic regenerative proliferation of medullary epithelium and activation of hypoxia-induced signaling pathways, which in turn promote neoplastic change.

The histological section of renal medullary carcinoma showing prominent cytological atypia is shown below:

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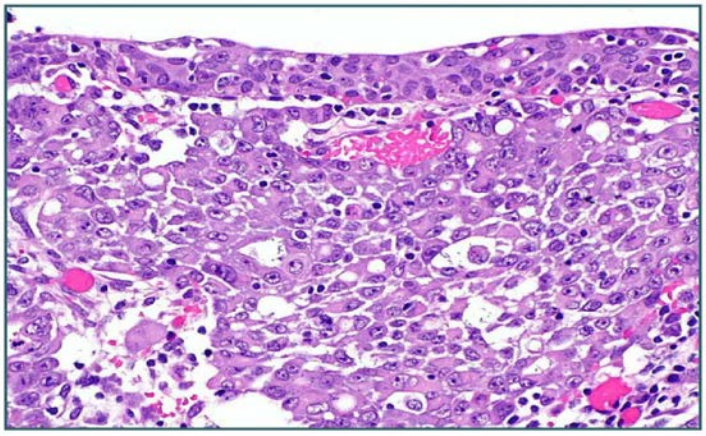
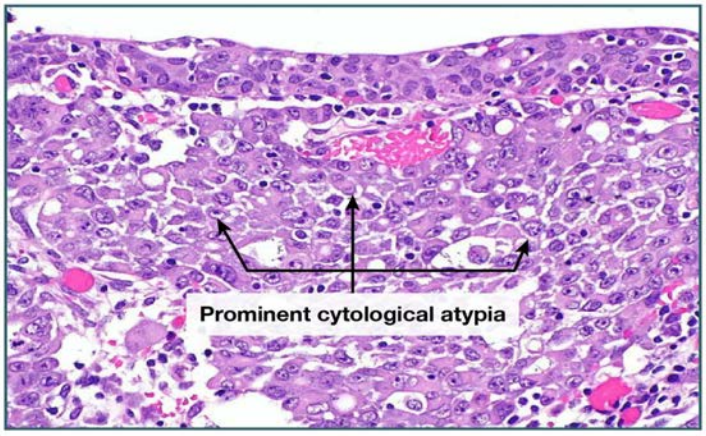
Renal Medullary Carcinoma



Renal Medullary Carcinoma



Solution to Question 18:

Xp11 translocation carcinoma contains neoplastic cells with clear cytoplasm with a papillary architecture on histopathology. It is also associated with Psammoma bodies.

This condition is caused by translocations of the TFE3 gene located on Xp11.2, which results in overexpression of the TFE3 transcription factor. It often occurs in young patients and is associated with a poor prognosis.

The histological section of Xp11 translocation carcinoma is given below:

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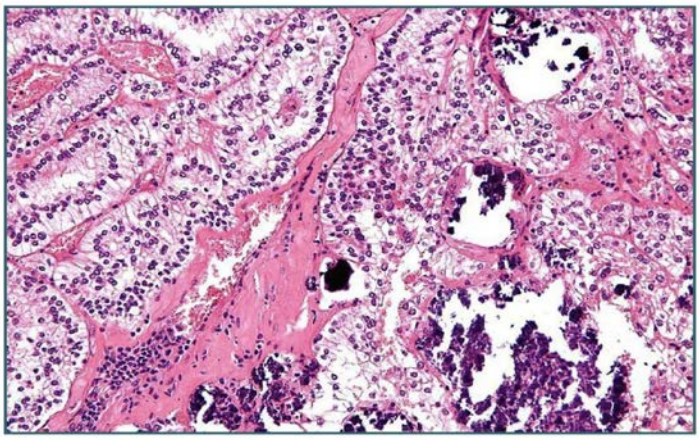
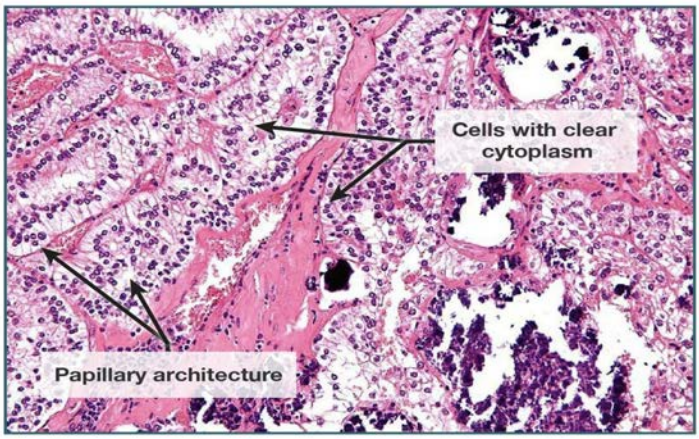
Xp11 Translocation Carcinoma



Xp11 Translocation Carcinoma



Solution to Question 19:

Renal cell carcinoma (RCC) is more common among males, with a male to female ratio of 2:1.

Renal cell carcinoma may arise from the proximal convoluted tubules (PCT). The classical clinical features of renal cell carcinoma are costovertebral pain, palpable mass, and painless hematuria. It characteristically invades the renal vein and has a high tendency for distant metastasis.

Paraneoplastic manifestations of renal cell carcinoma include:

- Polycythemia
- Hypercalcemia
- Hypertension
- Hepatic dysfunction

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- Feminization or masculinization
- Cushing syndrome
- Eosinophilia
- Leukemoid reactions
- Amyloidosis

Solution to Question 20:

The most common site of metastasis in renal cell carcinoma (RCC) is the lung (more than 50%).

Common sites of metastasis of renal cell carcinoma in descending order are:

- Lungs
- Bones - osteolytic lesions
- Regional lymph nodes
- Liver
- Adrenals
- Brain

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Solution to Question 21:

Collecting duct renal cell carcinoma has the worst prognosis of all renal cell carcinoma subtypes.

The renal cell carcinoma subtypes with poor prognosis in descending order are

- Collecting duct renal cell carcinoma
- Medullary renal cell carcinoma
- Clear cell renal cell carcinoma

Chromophobe renal cell carcinoma has the best prognosis.

Solution to Question 22:

WT gene is mutated in Wilms' tumor, not renal cell carcinoma.

The following gene mutations are associated with familial renal cell carcinoma syndromes:

- C-met proto-oncogene
- Fumarate hydratase gene
- BHD gene
- VHL gene

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- TSC1 gene
- PTEN gene

Solution to Question 23:

Renal cell carcinoma is CK7 negative and CK20 negative.

The most common subtype of renal cell carcinoma is clear-cell renal cell carcinoma, which is CK7 negative. Therefore, in determining the origin of cancer of unknown primary, immunohistochemistry (IHC) expression of renal cell carcinoma will generally be CK7 negative and CK20 negative. Chromophobe renal cell carcinoma and papillary renal cell carcinoma are positive for CK7.

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Lower Urinary Tract

Question 1:

A 36-year-old woman presented with intermittent suprapubic pain, increased urinary frequency, and dysuria for 2 months. A cystoscopy revealed the presence of Hunner ulcers. What is the likely diagnosis?

a) Malakoplakia

b) Transitional cell carcinoma of bladder

c) Follicular cystitis

d) Interstitial cystitis

Question 2:

A 31-year-old man presented with a history of recurrent UTIs and hematuria. Urine culture showed growth of E. coli. Flexible cystoscopy revealed yellow-brown soft plaques with a central umbilication. Microscopy of the plaque showed Michaelis-Gutmann bodies. What is the likely diagnosis?

a) Xanthogranulomatous cystitis

b) Malakoplakia

c) Follicular cystitis

d) Polypoid cystitis

Question 3:

What is the most common cause of polypoid cystitis?

a) Cyclophosphamide use

b) Systemic allergic disorders

c) Indwelling catheters

d) Adenovirus infection

Question 4:

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A pathologist observed a metaplastic lesion in a biopsy sample taken from the bladder mucosa of a patient. Which of the following is not a differential diagnosis?

a) Malakoplakia

b) Nephrogenic adenoma

c) Cystitis glandularis

d) Cystitis cystica

Question 5:

What is the most common tumor of the urinary bladder?

a) Squamous cell carcinoma

b) Adenocarcinoma

c) Transitional carcinoma

d) Small cell carcinoma

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Question 6:

A 57-year-old man presented with chronic hematuria and dysuria. Microscopic examination of urine showed the following parasitic eggs. What type of bladder carcinoma is commonly associated with this condition?

a) Squamous cell carcinoma

b) Transitional cell carcinoma

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c) Adenocarcinoma

d) Small cell carcinoma

Question 7:

Which of the following is not a carcinogen for bladder cancer?

a) Benzidine

b) Isopropyl alcohol

c) Aryl amines

d) Phenacetin

Question 8:

Which of the following genetic changes is not associated with bladder carcinoma?

a) Gain-of-function mutations in FGFR3

b) Activating mutations in the NRAS

c) Loss-of-function mutations in the TP53

d) 9p chromosome deletions

Question 9:

The most consistent and persistent feature of bladder carcinoma is:

a) Painless hematuria

b) Painful hematuria

c) Dysuria

d) Suprapubic mass

Question 10:

Which of the following is not included in the latest International Society of Urological Pathology grading of urothelial tumors?

a) Urothelial papilloma

b) Urothelial neoplasm of low malignant potential

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c) Papillary urothelial carcinoma, low grade

d) Papillary urothelial carcinoma, grade 3

Question 11:

A 67-year-old chronic smoker with gross painless hematuria was diagnosed with infiltrating urothelial carcinoma. What is the most important prognostic factor for his condition?

a) Size

b) Grade

c) Stage

d) Histological type

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Answer Key

Question No.	Correct Option
1	d
2	b
3	c
4	a
5	c
6	a
7	b
8	b
9	a
10	d
11	c

Detailed Explanations

Solution to Question 1:

Hunner ulcers are chronic mucosal ulcers that are characteristic of interstitial cystitis or chronic pelvic pain syndrome.

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It is a rare idiopathic condition that occurs most frequently in women. It presents with intermittent severe suprapubic pain, urinary frequency, urgency, hematuria, and dysuria.

The following cystoscopic findings are seen in the bladder mucosa:

• Fissures

• Punctate hemorrhages (glomerulations)

The microscopic findings include:

• Mucosal ulceration covered by fibrin and necrotic material

• Increased numbers of mucosal mast cells

• Submucosal edema

In later stages, transmural fibrosis may occur, leading to a contracted bladder. Biopsy must be done to rule out carcinoma in situ, which may clinically mimic interstitial cystitis.

The following image shows a Hunner's ulcer in a patient with interstitial cystitis.

Solution to Question 2:

This clinical scenario with the presence of Michaelis-Gutmann bodies is suggestive of malakoplakia.

Malakoplakia is a chronic inflammatory reaction resulting from acquired defects in phagocyte function, commonly affecting the urinary bladder. It can also be seen in other organ systems like the gastrointestinal tract, female genital tract, and central nervous system.

It is seen in chronic bacterial infection, mostly by Escherichia coli or occasionally Proteus species.

Grossly, it presents as soft, yellow-brown, slightly raised mucosal plaques. Microscopically, the following findings are seen:

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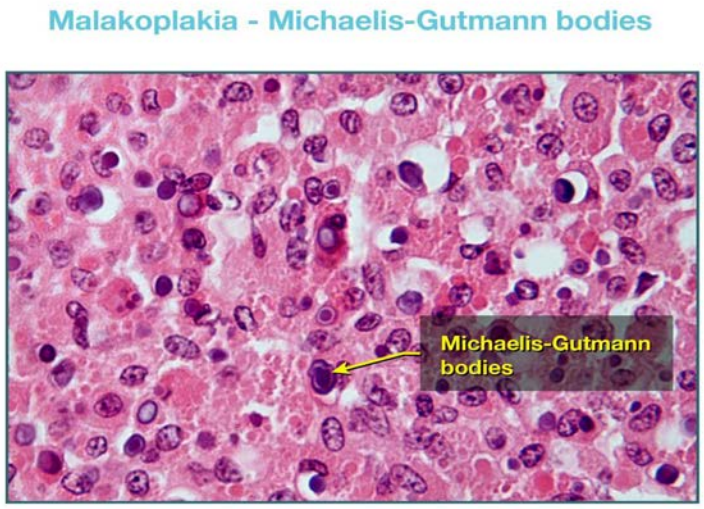
• Large, foamy macrophages containing -

• Abundant granular cytoplasm due to undigested bacterial products

• Michaelis-Gutmann bodies - PAS-positive basophilic concretions due to iron and calcium deposits in lysosomes

• Occasional multinucleated giant cells and lymphocytes



Note: Xanthogranulomatous cystitis is morphologically and probably pathogenetically similar to malakoplakia, but it lacks Michaelis–Gutmann bodies.

Solution to Question 3:

The most common cause of polypoid cystitis is indwelling catheters.

Polypoid cystitis is an inflammatory lesion resulting from mucosal irritation. It may also be associated with radiation therapy and malignant tumors. It usually involves the posterior wall of the bladder.

Grossly, it may show bulbous or papillary appearance and may be confused with papillary urothelial carcinoma. Microscopically, the papillary projections are broad-based, non-branching, and without atypia. Stroma is edematous with minimal inflammation.

Options A and D: Adenovirus infection and the use of anti-cancer drugs like cyclophosphamide cause hemorrhagic cystitis.

Option B: Systemic allergic disorders cause eosinophilic cystitis.

Solution to Question 4:

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Malakoplakia is not a metaplastic lesion of the bladder. It is a type of chronic granulomatous cystitis due to defective phagocytic function that may mimic malignancy.

Metaplastic lesions of the bladder include the following:

• Nests of urothelium (Brunn nests) may grow downward into the lamina propria resulting in the following lesions -

• Cystitis glandularis - epithelial cells in the center of the nest undergo metaplasia and take on a cuboidal or columnar appearance

• Cystitis cystica - epithelial cells retract to produce cystic spaces lined by flattened urothelium

• Squamous metaplasia - in response to injury, urothelium is replaced by stratified squamous epithelium.

• Nephrogenic adenoma - due to implantation of shed renal tubular cells at sites of injured urothelium, resulting in replacement of urothelium by cuboidal epithelium with a papillary growth pattern

Solution to Question 5:

The most common tumor of the urinary bladder is transitional cell carcinoma or urothelial carcinoma.

Other epithelial tumors like squamous cell carcinoma, adenocarcinoma, and small cell carcinoma may also occur.

Sarcomas are distinctly uncommon in the bladder. However, the most common sarcoma in infancy or childhood is embryonal rhabdomyosarcoma, and the most common sarcoma in the bladder in adults is leiomyosarcoma.

Solution to Question 6:

The image shows oval-shaped eggs with the terminal spine which is characteristic of Schistosoma haematobium. It is most commonly associated with squamous cell carcinoma of the bladder.

The ova are deposited in the bladder wall and incite a brisk chronic inflammatory response. This induces progressive mucosal squamous metaplasia and dysplasia and, in some instances, neoplasia.

Schistosomal infection can less frequently result in adenocarcinoma or transitional cell carcinoma.

Solution to Question 7:

Isopropyl alcohol is not implicated in the causation of bladder cancer.

Benzidine, arylamines, and phenacetin are well-established risk factors for bladder cancer.

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Solution to Question 8:

Activating mutation in HRAS (not NRAS) is responsible for bladder carcinoma.

Genetic changes associated with carcinoma bladder:

• Noninvasive low-grade papillary urothelial carcinoma is associated with:

• Gain-of-function mutations of FGFR3 and HRAS genes

• Chromosome 9p and 9q deletions

• High-grade invasive urothelial carcinoma (either papillary or flat) is associated with:

• Loss-of-function mutations of TP53 and RB genes

Note: Erdafitinib (kinase inhibitor) is the first targeted drug therapy approved by the FDA for the treatment of metastatic urothelial carcinoma especially in patients with mutations of FGFR3 or FGFR2.

Solution to Question 9:

The most consistent and persistent feature of carcinoma bladder is painless hematuria.

Bladder tumors produce a wide range of clinical features including:

• Painless hematuria - classical feature and may be the only clinical manifestation

• Irritative urinary symptoms (frequency, urgency, dysuria) - diffuse tumors or tumors at the bladder neck

• Pyelonephritis or hydronephrosis - when the ureteral orifice is involved

• Obstructive symptoms, palpable suprapubic mass, or lower extremity edema - late presentation with a large tumor mass

• Weight loss and/or localized bone pain - metastatic disease

Solution to Question 10:

International Society of Urological Pathology (ISUP) grading system classifies papillary urothelial carcinoma into 2 grades - low grade and high grade. The classification of papillary urothelial carcinoma into grades 1, 2, 3 was was part of the earlier WHO classification.

Grading of urothelial (transitional cell) tumors:

WHO/ISUP grades:

• Urothelial papilloma

• Urothelial neoplasm of low malignant potential

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• Papillary urothelial carcinoma, low grade

• Papillary urothelial carcinoma, high grade

WHO grades (old classification):

• Urothelial papilloma

• Urothelial neoplasm of low malignant potential

• Papillary urothelial carcinoma, grade 1

• Papillary urothelial carcinoma, grade 2

• Papillary urothelial carcinoma, grade 3

Solution to Question 11:

The staging (extent of spread) at the time of initial diagnosis is the most important prognostic factor in infiltrating urothelial carcinoma.

The prognosis of bladder carcinoma depends on the histologic grade and the stage at diagnosis. As most infiltrating urothelial carcinomas are high-grade, staging becomes the major factor to determine the prognosis.

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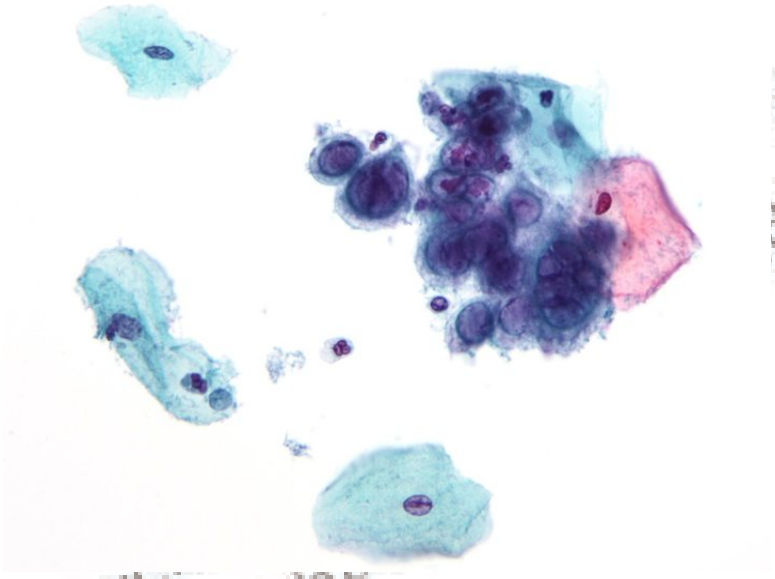
Female Genital Tract

Question 1:

A 30-year-old woman presented with purulent vaginal discharge associated with fever, malaise, and inguinal pain. A Pap smear revealed the following findings. What is the causative agent?



a) Molluscum contagiosum

b) Gardnerella vaginalis

c) Trichomonas vaginalis

d) Herpes simplex

Question 2:

What are the cystic remnants of mesonephric ducts in the cervix and vagina called?

a) Gartner duct cysts

b) Bartholin cysts

c) Paroophoron

d) Epoophoron

Question 3:

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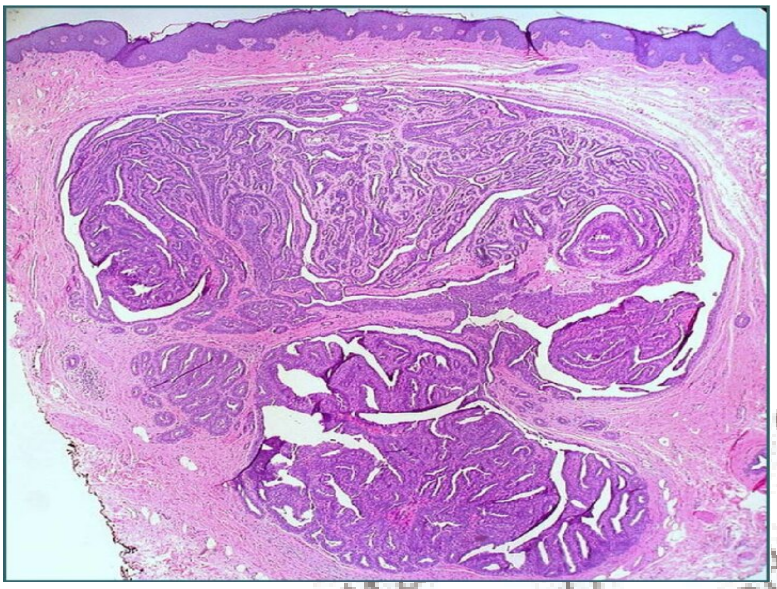
The following histological image depicts a pathology in which of the following sites?



a) Vagina

b) Cervix

c) Fallopian tube

d) Vulva

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Question 4:

A 3-year-old girl presents with a mass protruding from the anterior vaginal wall that appears like grape clusters. Histopathological examination reveals tadpole cells. What is the most likely diagnosis?

a) Embryonal rhabdomyosarcoma

b) Adenocarcinoma cervix

c) Extra-mammary Paget's disease

d) Papillary hidradenoma

Question 5:

Which of the following is false regarding precursor squamous epithelial lesions of the cervix?

a) LSIL progress directly to invasive carcinoma

b) LSILs are 10 times more common than HSILs

c) HPV-16 is the most common HPV type in both LSIL and HSIL

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d) They progress to invasive carcinoma over many years

Question 6:

What is the most common type of human papilloma virus causing cervical carcinoma?

a) HPV 31

b) HPV 18

c) HPV 6

d) HPV 16

Question 7:

A young woman comes to the gynecology OPD for cervical cancer screening. What is the staining technique used for this?

a) Supravital staining

b) PAS staining

c) Papanicolaou staining

d) Wright's staining

Question 8:

Which of the following is incorrect about type I endometrial carcinoma?

a) It is associated with obesity and diabetes

b) It shows endometrioid morphology

c) Smoking is a high risk factor

d) It is caused by unopposed estrogen stimulation

Question 9:

Which of the following is not a criterion to distinguish leiomyosarcoma from leiomyoma?

a) Mitoses

b) Necrosis

c) Atypia

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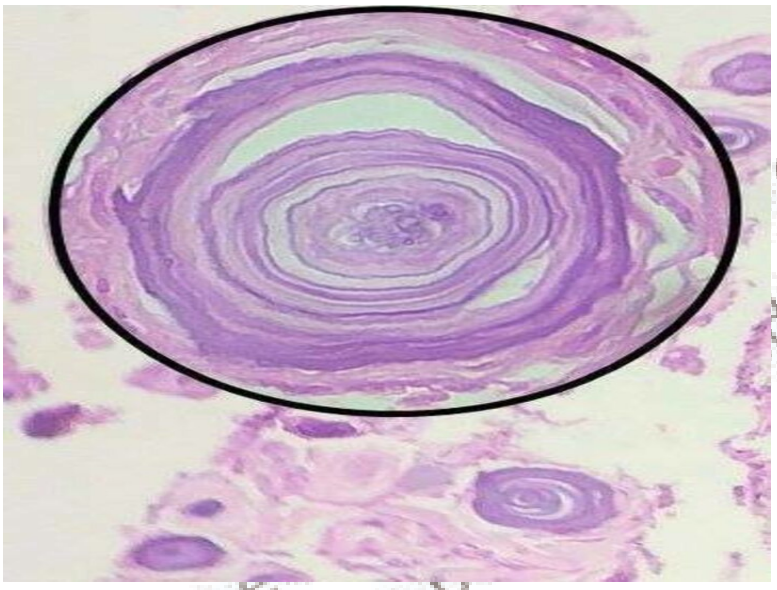
d) Size

Question 10:

Histopathological examination of an ovarian mass sent to the pathology department revealed the following. Which of the following is false regarding this condition?



a) It is more common in women with low parity

b) The pathogenesis is related to family history and heritable mutations

c) High-grade tumors are associated with TP53 mutations

d) It is most commonly unilateral

Question 11:

Which of the following is false regarding mucinous tumors of the ovary?

a) Vast majority are malignant tumors

b) It is rarely bilateral.

c) It occurs principally in middle adult life

d) Mutation of the KRAS proto-oncogene is seen

Question 12:

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A 30-year-old woman underwent an evaluation for an abdominal mass. A laparotomy was decided upon for the removal of the mass. The gross appearance of the mass is as follows. Histopathological examination revealed no malignant change. What is the most likely diagnosis?

a) Mature teratoma

b) Immature teratoma

c) Mucinous adenoma

d) Serous adenoma

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d.

Question 13:

A 45-year-old woman presented to the gynecology OPD with a history of abdominal pain and distension of abdomen. Ultrasound imaging revealed tumor in the right ovary. Serum level of inhibin was raised. The histopathology of the tumor is given below. What is the most likely diagnosis?

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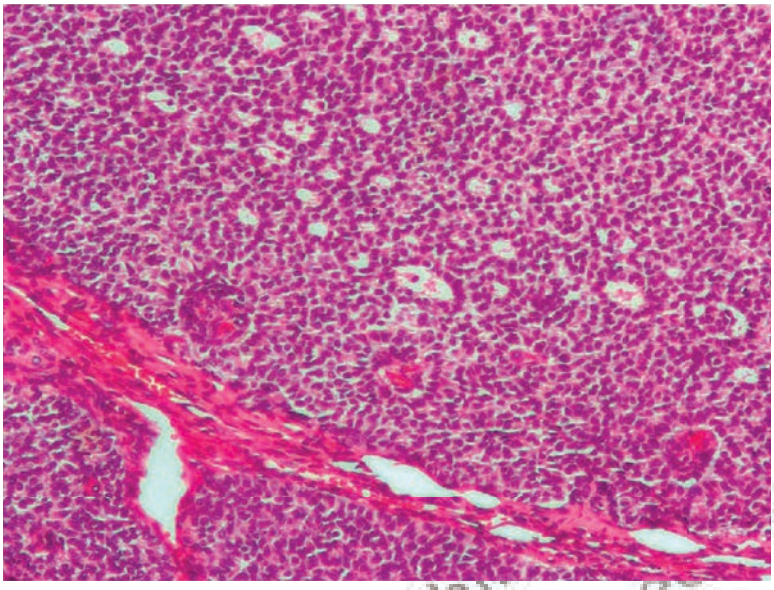

a) Granulosa cell tumor

b) Sertoli cell tumor

c) Brenner's tumor

d) Embryonal carcinoma

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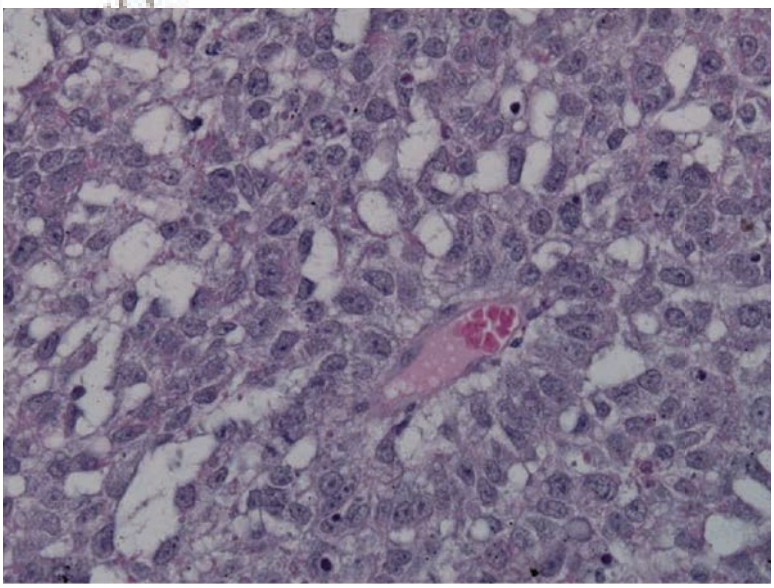
Question 14:

A 12-year-old girl, who is yet to attain her menarche, presents with an ovarian mass. Her serum biomarkers are normal except for elevated AFP. Staging laparotomy was performed and the histopathological image is given below. What is your diagnosis?



a) Dysgerminoma

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b) Endodermal sinus tumor

c) Brenner tumor

d) Granulosa cell tumor

Question 15:

Which of the following are sex cord-stromal tumors?

a) 2, 3, 4

b) 1, 3, 5

c) 3, 4, 5

d) 1, 4, 5

Question 16:

A 40-year-old woman presented with bilateral adnexal masses. Histopathological examination of the resected specimen showed sheets of mucin-producing signet-ring cells. What is the most likely diagnosis?

a) Serous papillary carcinoma

b) Struma ovarii

c) Krukenberg tumour

d) Malignant teratoma

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Question 17:

A 32-year-old woman was diagnosed with molar pregnancy and underwent suction and evacuation. The resected specimen is shown below. Histopathological examination revealed thin-walled, cystic structures consisting of hydropic villi with extensive trophoblastic proliferation along its entire circumference. Immunohistochemistry was negative for p57. Which of the following is false about this condition?

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a) The genetic material is completely maternally derived

b) Embryo dies very early in development and therefore is usually not identified

c) It is associated with a 2.5% risk of subsequent choriocarcinoma

d) The possible karyotypes are 46XX or 46XY

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Question 18:

A 26-year-old woman with a positive pregnancy test presented with vaginal bleeding in the first trimester. On examination, grape-like vesicles were noted in the vagina. A transvaginal ultrasound revealed the presence of fetal tissues. A suction evacuation was performed. What is the most likely karyotype of the evacuated material?

a) 69 XXY

b) 46 XX

c) 46 XY

d) 47 XO

Question 19:

What is the most common site of metastasis in gestational choriocarcinoma?

a) Lungs

b) Breast

c) Vagina

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d) Liver

Question 20:

The genetic profile of malignant mixed Müllerian tumors resembles that of:

a) Cervical cancer

b) Uterine sarcoma

c) Endometrial carcinoma

d) Ovarian tumor

Question 21:

Which of the following are the components of Meig's syndrome?

a) 1, 4, 5

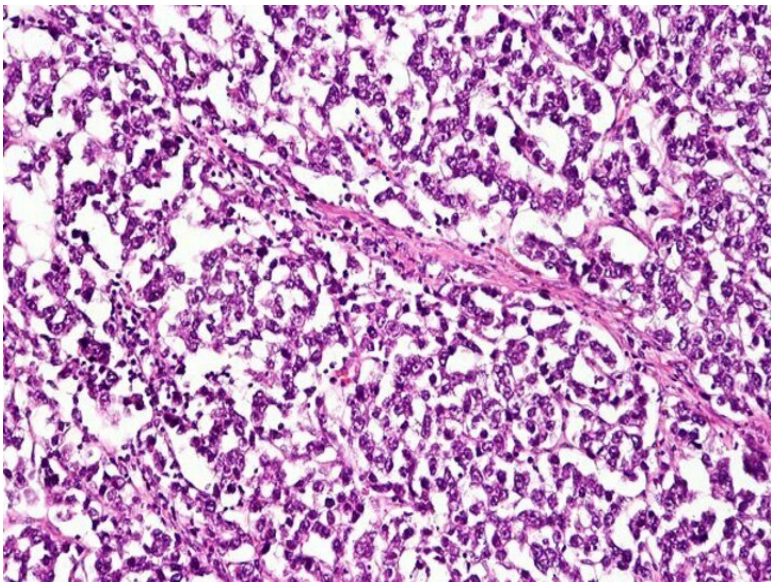
b) 2, 3, 5

c) 1, 2, 3

d) 1, 3, 4

Question 22:

A 35-year-old woman was operated for an ovarian mass and the sample was sent for histopathological examination. The findings are given below. Which of the following is false about the given condition?



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a) It is a malignant tumor

b) It expresses OCT-3, OCT4, and NANOG

c) It is unresponsive to radiotherapy

d) It occurs in patients with gonadal dysgenesis

Answer Key

Question No.	Correct Option
1	d
2	a
3	d
4	a
5	a
6	d
7	c
8	c
9	d
10	d
11	a
12	a
13	a
14	b
15	a
16	c
17	a
18	a
19	a
20	c
21	d
22	c

Detailed Explanations

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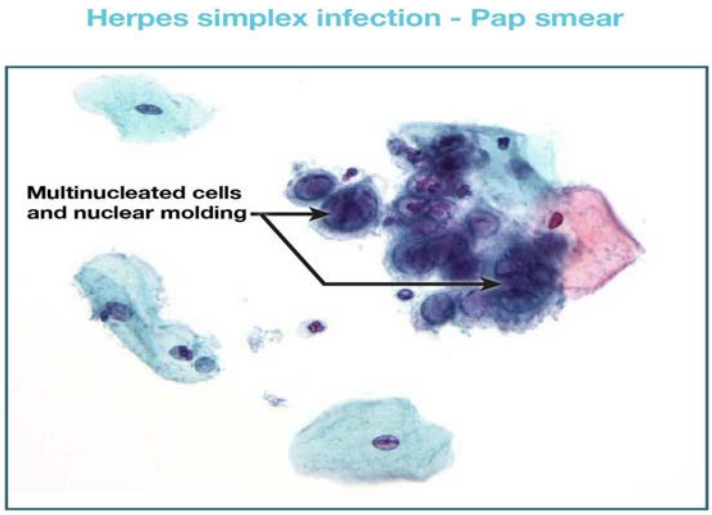
Solution to Question 1:

The given image of Pap smear shows cells with ground glass nuclei, viral inclusions, multinucleation, and margination of chromatin. These findings are characteristic of herpes simplex infection.



Some infections of the female genital tract and their diagnostic features are given below:

Infections	Diagnostic features
Herpes simplex	Ground glass nuclei with3M's: MultinucleationMargination of chromatinMolding of nuclei
Molluscum contagiosum	Pearly dome-shaped papule containing cells withcytoplasmic viral inclusions
Trichomonas vaginalis	Strawberry cervix; pear-shaped flagellated organism.
Gardnerella vaginalis	Clue cells -squamous cells covered with a shaggy coating coccobacilli
Candida	Pseudospores and filamentous fungal hyphae

Solution to Question 2:

Cystic remnants of mesonephric ducts in the cervix and vagina are termed Gartner duct cysts.

The mesonephric (Wolffian) ducts normally regress in females. Its remnants may persist into adult life as epithelial inclusions adjacent to the ovaries, tubes, and uterus. In the cervix and

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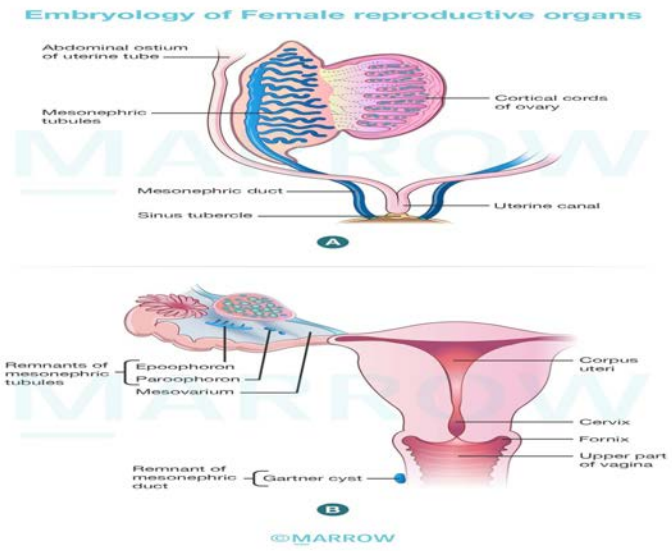
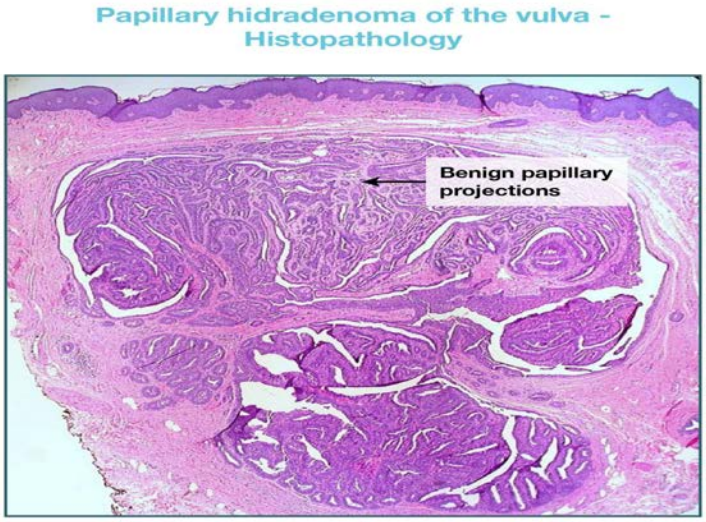
vagina, these ducts may be cystic and are termed Gartner duct cysts.

The following images show the embryological development of the mesonephric duct and its persistence into adult life.



Solution to Question 3:

The given histopathological image shows benign papillary projections covered with columnar secretory epithelium and underlying myoepithelial cells. These are commonly seen in papillary hidradenoma of the vulva.



It presents as a sharply circumscribed nodule, most commonly on the labia majora or interlabial folds. Like the breast, the vulva also contains modified apocrine sweat glands. Its histologic appearance is identical to that of intraductal papilloma of the breast.

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Solution to Question 4:

The most likely diagnosis is embryonal rhabdomyosarcoma (sarcoma botryoides).

It is an uncommon vaginal tumor composed of malignant embryonal rhabdomyoblasts. It is most frequently found in infants and in children < 5 years of age. They are locally invasive tumors that cause death by penetration into the peritoneal cavity or by obstruction of the urinary tract.

Grossly, polypoid, rounded, bulky masses that appear like grape clusters can be seen. On microscopy, small tumor cells with oval nuclei, and small protrusions of cytoplasm from one end resembling a tennis racket (tadpole cells) can be seen. Beneath the vaginal epithelium, the tumor cells are crowded in a cambium layer, in the dermis.

Solution to Question 5:

Low-grade squamous intraepithelial lesion (LSIL) does not progress directly to invasive carcinoma. They initially progress to a high-grade squamous intraepithelial lesion (HSIL), then invasive carcinoma.

The WHO currently recommends a 2-tier system of classification for cervical lesions - low and high-grade intraepithelial lesions (LSIL and HSIL). HPV-16 is the most common HPV type associated with both LSIL and HSIL.

LSILs are 10 times more common than HSILs. Most of these lesions regress spontaneously. Progression to invasive carcinoma is unpredictable and can take place over years.

Solution to Question 6:

Human papillomavirus (HPV)-16 is the most common type of HPV causing cervical carcinoma. It accounts for almost 60% of cervical cancer cases.

The ability of HPV to act as a carcinogen depends on the viral proteins E6 and E7. These proteins interfere with the activity of tumor-suppressor proteins that regulate cell growth and survival.

• E6 - binds with p53 gene and promote its degradation

• E7 - binds with RB gene and promotes its degradation

Solution to Question 7:

Cervical cancer screening test, commonly known as Pap smear, is stained using the Papanicolaou method.

The time for initiating Pap smear screening is 21 years, regardless of the age of first sexual intercourse.

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The sample is collected using Ayre's spatula and endocervical brush. 2 samples are taken:

• 1st slide - prepared from a sample taken from portio vaginalis of the cervix

• 2nd slide - prepared from the sample taken from the endocervix (transformation zone)

95% ethanol is used as a fixative.

It is a highly specific test. Colposcopic examination and biopsy are recommended in case of abnormal Pap smear results.

Solution to Question 8:

Smoking is strongly associated with mucinous cystadenocarcinoma of the ovary, but not endometrial carcinoma.

Endometrial carcinoma is the most common invasive cancer of the female genital tract. Type 1 endometrial carcinoma shows endometrioid morphology and is associated with:

• Unopposed estrogen exposure (endometrial hyperplasia)

• Obesity

• Diabetes mellitus

• Hypertension

PTEN tumor-suppressor gene is mutated in approximately 20% of endometrial hyperplasias.

Genomic sequencing of endometrial carcinoma has revealed 4 major molecular subtypes of endometrioid and serous carcinomas:

• Ultramutated/ POLE tumors - mutations in DNA polymerase ε (POLE)

• Hypermutated/ MSI (microsatellite instability) tumors - mutations involving mismatch repair genes

• Copy number low/ MSS (microsatellite stable) tumors - mutations involving the PI3K/AKT pathway

• Copy number high/ serous-like tumors - TP53 mutations and numerous genomic copy number variants

Solution to Question 9:

The size of the tumor is not a criterion to distinguish between leiomyosarcoma and leiomyoma.

The following features are seen in leiomyosarcomas:

• Mitotic index - ≥10 mitoses / 10 hpf

• Nuclear atypia - in the presence of nuclear atypia, 5 mitoses / 10 hpf

• Tumor cell necrosis -

• Characterized by an abrupt transition from viable to non-viable areas

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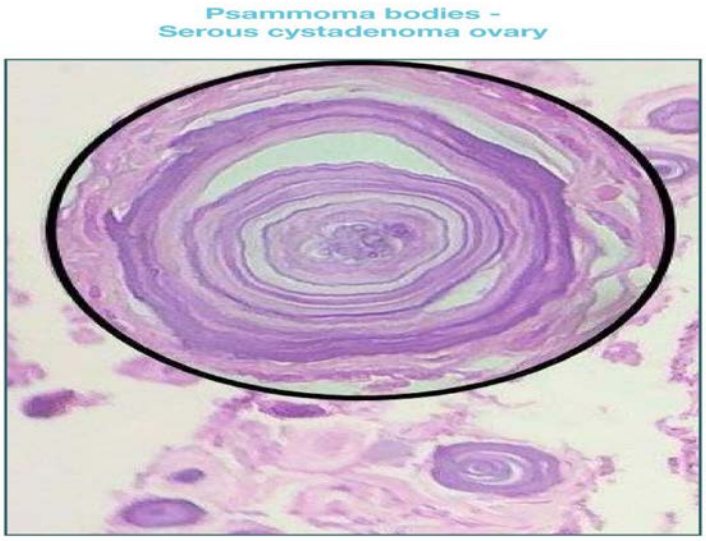
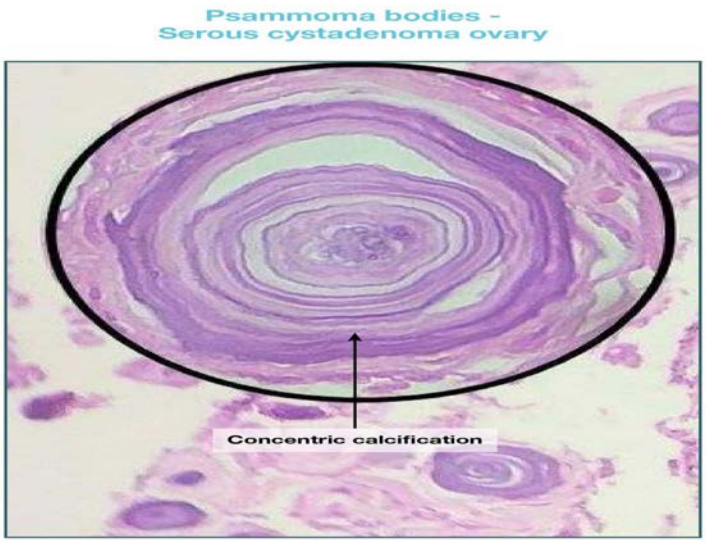
• Within the necrotic zones, atypical cells can be seen

Solution to Question 10:

The given image denotes Psammoma bodies which are a histopathological finding seen in ovarian papillary serous cystadenoma and cystadenocarcinoma. These tumors are most commonly bilateral.





The majority of serous tumors of the ovary are benign or borderline. But the serous carcinomas of the ovary include the most common malignant tumors of the ovary.

Nulliparity, family history, and heritable mutations play a role in the development of these tumors. Mutations in the oncogenes KRAS, BRAF, or ERBB2 result in low-grade tumors, and mutation in TP53 is associated with high-grade tumors.

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There is a higher frequency of carcinoma in women with low parity. Women on oral contraceptive pills or those who have undergone tubal ligation are at a lower risk. The marker for ovarian tumors is CA-125.

Solution to Question 11:

The vast majority of mucinous tumors of the ovary are benign or borderline tumors (not malignant).

It occurs principally in middle adult life and is rare before puberty and after menopause. The surface of the ovary is rarely involved, they are rarely bilateral. It is associated with the mutation of KRAS proto-oncogene.

Grossly it is multiloculated and filled with sticky, gelatinous fluid (rich in glycoproteins).

Solution to Question 12:

The given scenario and image showing unilocular cystic space containing hair and sebaceous material are suggestive of mature teratoma.

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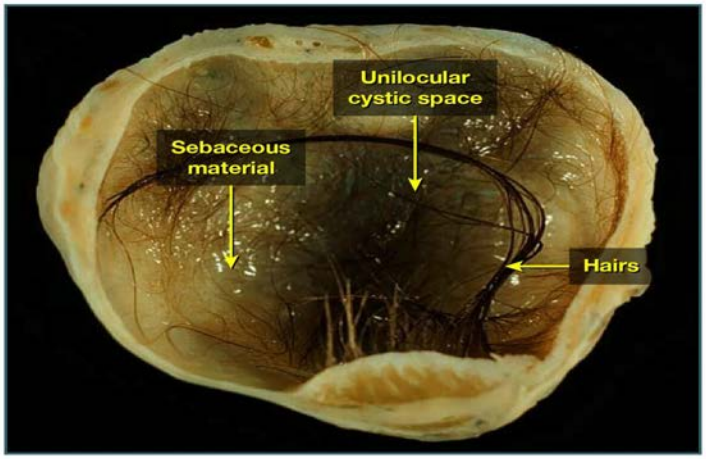
Mature Teratoma - Gross specimen

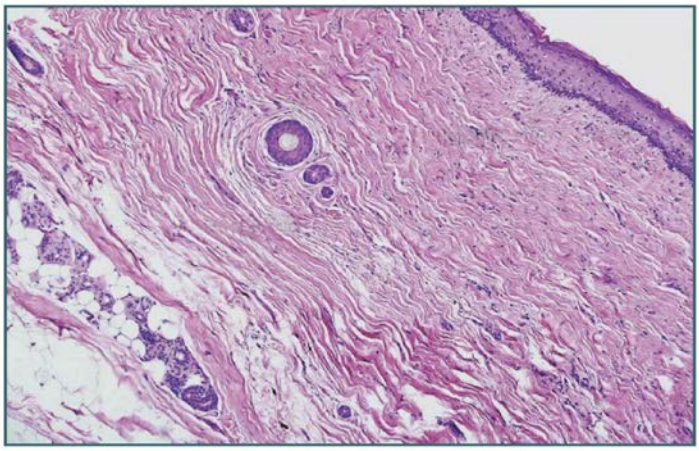


Dermoid cysts or mature teratomas are benign tumors, usually found in young women during the active reproductive years. It is bilateral in 10% to 15% of cases.

Microscopically, the cyst wall is composed of tissues from all 3 germ layers. This includes stratified squamous epithelium, with underlying sebaceous glands, hair shafts, and other skin adnexal structures. Sometimes cartilage, bone, thyroid, and neural tissue can be seen.

About 1% of the dermoids undergo malignant transformation, most commonly to squamous cell carcinoma. It can also transform into other cancers (e.g., thyroid carcinoma, melanoma).

Dermoid cyst - Histopathology



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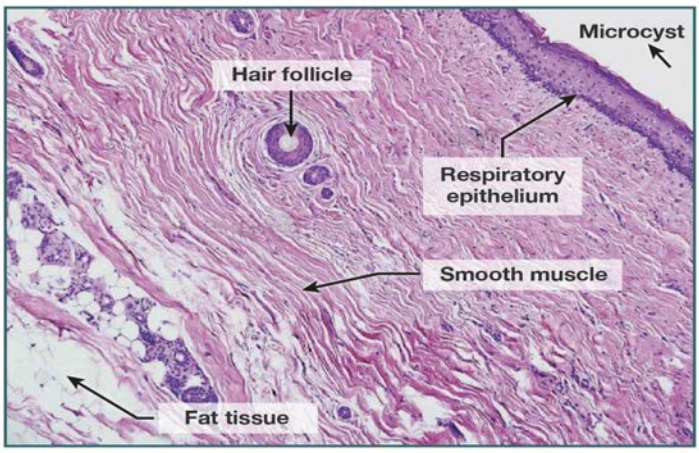
Dermoid cyst - Histopathology



The component tissue of immature malignant teratomas resembles embryonal and immature fetal tissue. It often consists of primitive neuroepithelial cells. The tumor is found chiefly in prepubertal adolescents and young women, the mean age being 18 years.

Monodermal or specialized teratomas:

• Struma ovarii - composed entirely of mature thyroid tissue, which may be functional and cause hyperthyroidism.

• Ovarian carcinoid - arises from intestinal tissue, may be functional causing carcinoid syndrome in the absence of hepatic metastasis

Solution to Question 13:

The given clinical scenario and histopathology showing Call-Exner bodies are suggestive of granulosa cell tumor.

Call-Exner bodies are small, distinctive, glandlike structures filled with an acidophilic material resembling immature follicles. Additionally, small, cuboidal to polygonal cells are seen which may grow in anastomosing cords, sheets, or strands.

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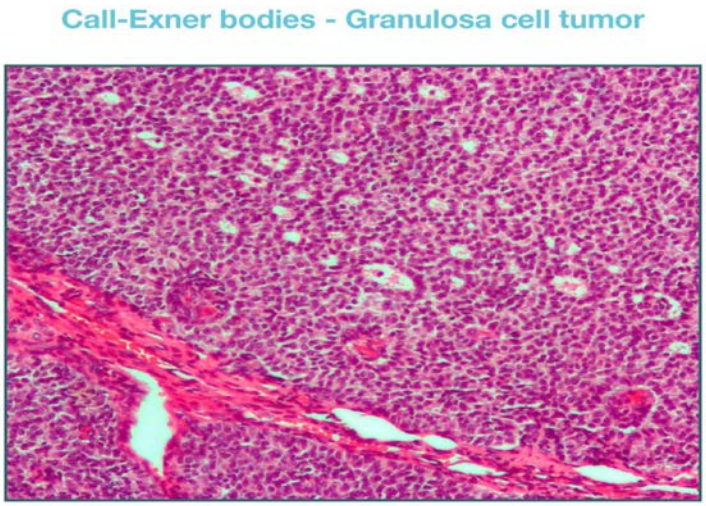

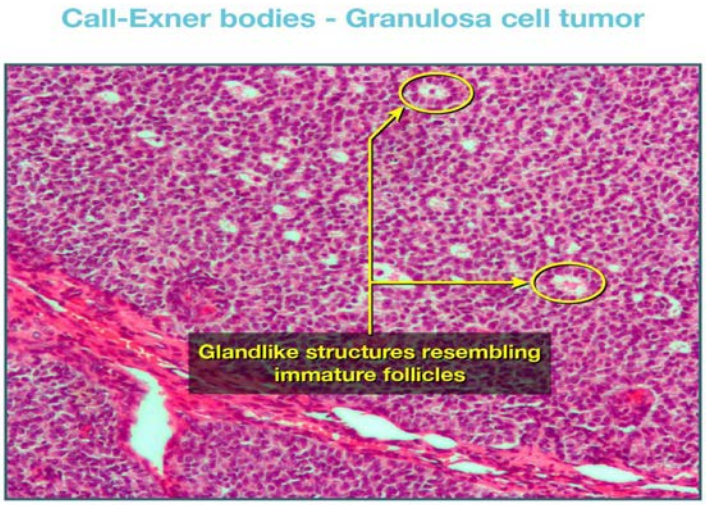

Granulosa cell tumors are composed of cells that resemble granulosa cells of a developing ovarian follicle. It can be of adult and juvenile types. Elevated tissue and serum levels of inhibin, a product of granulosa cells, are associated with this tumor.

Mutations of the FOXL2 gene are seen in most adult granulosa cell tumors.

Solution to Question 14:

The given clinical features and the histopathological image showing Schiller Duval bodies are suggestive of endodermal sinus tumors. It is also known as yolk sac tumor.

The Schiller-Duval body is a glomerulus-like structure composed of a central blood vessel enveloped by tumor cells within a space that is also lined by tumor cells.

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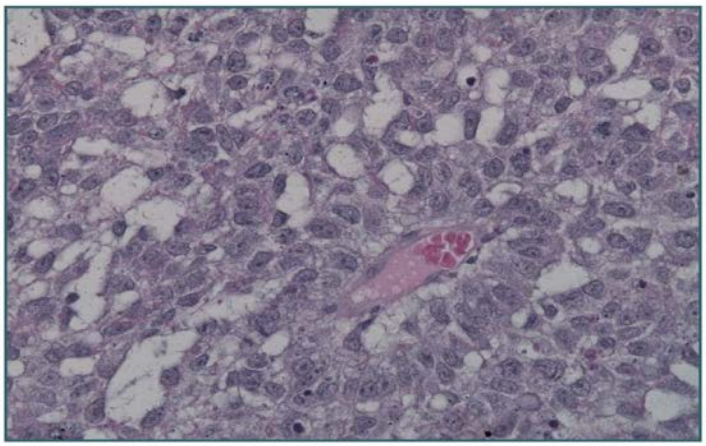
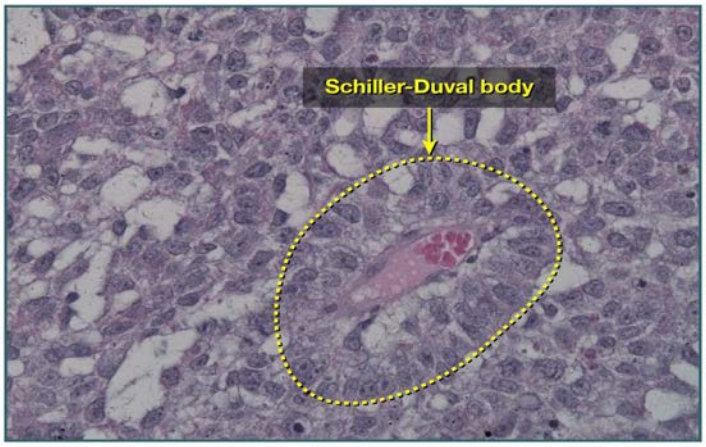
It is the second most common malignant tumor of germ cell origin. It is a unilateral tumor usually affecting children or young women.

Yolk sac tumor - Histopathology



Yolk sac tumor - Histopathology



Solution to Question 15:

Sex cord-stromal tumors include the following:

- Granulosa cell tumor
- Sertoli cell tumor
- Fibroma

Brenner tumor is an epithelial tumor and dysgerminoma is a germ cell tumor.

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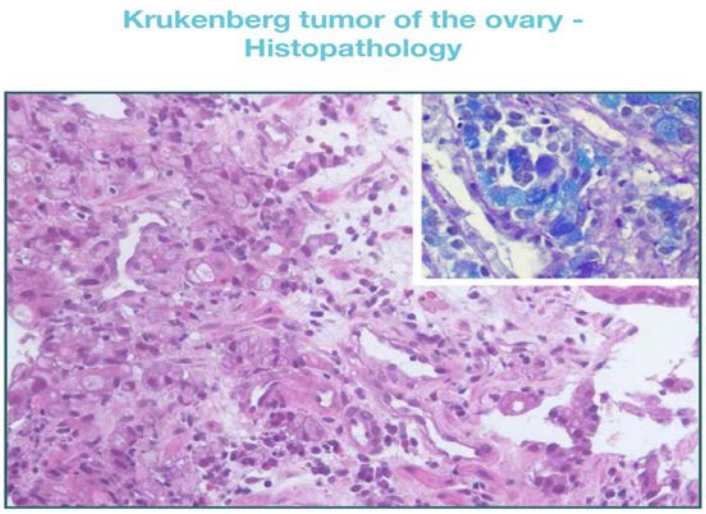
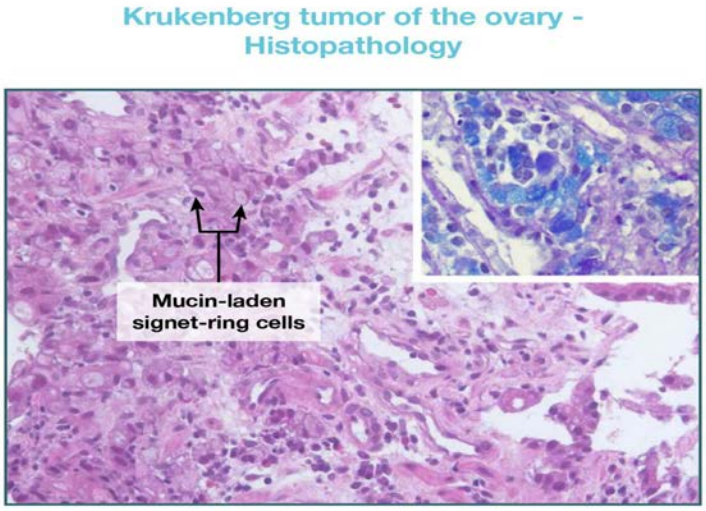
Solution to Question 16:

The given clinical scenario and histopathology findings are suggestive of metastatic carcinoma of the ovary or Krukenberg tumor.

It can arise from primary carcinomas of the stomach (most common), colon, appendix, and breast (invasive lobular carcinoma). It is often bilateral and on microscopy shows mucin-laden signet-ring cells with eccentric hyperchromatic nuclei.





Metastatic tumors of the ovary include:

• Tumors of Müllerian origin (most common) - the uterus, fallopian tube, contralateral ovary, or pelvic peritoneum

• Tumors of extra-Müllerian tumors - breast and gastrointestinal tract carcinomas

• Pseudomyxoma peritonei - derived from appendiceal tumors

• Krukenberg tumor

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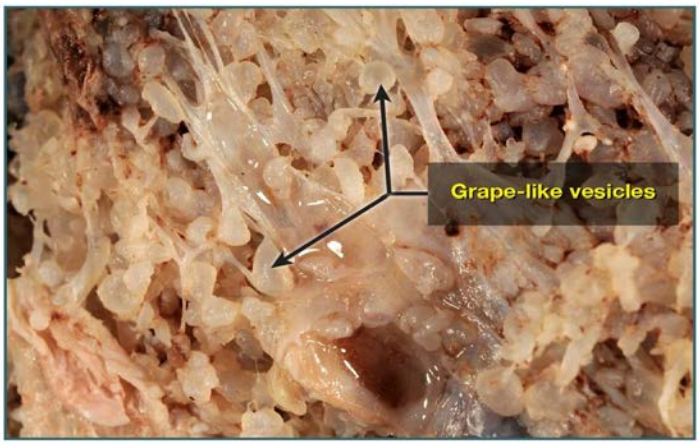
Solution to Question 17:

The given clinical scenario and image showing grapelike vesicles are suggestive of a complete mole. It results from the fertilization of an egg that has lost its female chromosomes, and as a result, the genetic material is completely paternally derived.

Hydatidiform mole - Gross appearance

Hydatidiform mole - Gross appearance



The pathogenesis of complete mole is as follows:

• Androgenesis (most common) - 46XX karyotype stemming from the duplication of the genetic material of 1 sperm

• Dispermy - 46XX or 46XY karyotype due to fertilization of an empty egg by 2 sperms

Microscopically, thin-walled, cystic, grapelike structures consisting of hydropic villi are seen. Trophoblastic proliferation involving the entire circumference of the villi is seen.

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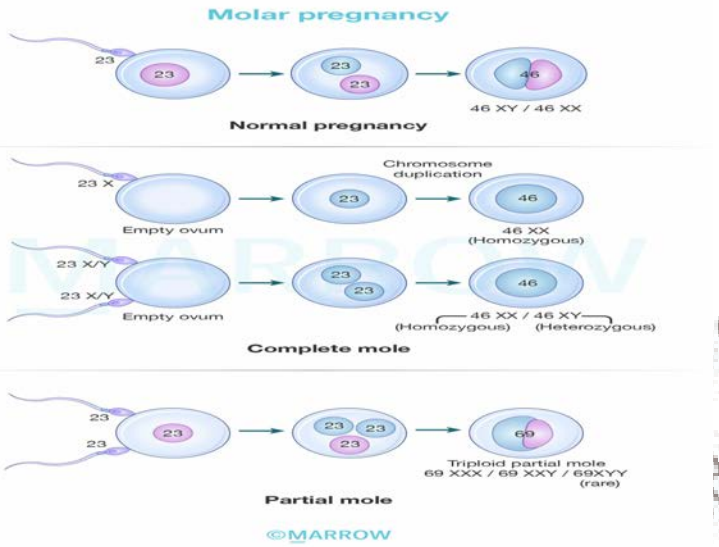
The embryo dies very early in development and, therefore, is usually not identified. Patients have a 2.5% risk of subsequent choriocarcinoma and a 15% risk of the persistent or invasive mole.

The following image shows the pathogenesis of molar pregnancy.

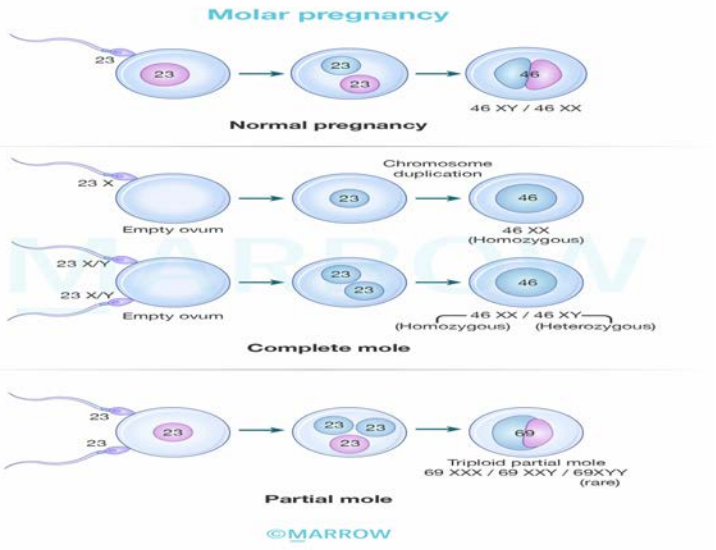


Solution to Question 18:

The given clinical scenario with grape-like vesicles in the vagina and the presence of fetal tissues on transvaginal ultrasound are suggestive of partial mole. The karyotype in a partial mole is triploid (e.g., 69XXY) or occasionally tetraploid (92XXXY).

It results from the fertilization of an egg with 2 sperms. There is an increased risk of persistent molar disease but it is not associated with choriocarcinoma.

Given below is an image showing the karyotype of molar pregnancy.



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Solution to Question 19:

Lungs are the most common site of metastasis in gestational choriocarcinoma.

It is followed by the vagina, brain, liver, bone, and kidney in descending order of frequency.

Gestational choriocarcinomas are malignant neoplasm of trophoblastic cells derived from a previously normal or abnormal pregnancy, such as an extrauterine ectopic pregnancy. The hCG levels are elevated to levels above those encountered in hydatidiform moles. It shows hematogenous spread. It is rapidly invasive and metastasizes widely.

Gestational choriocarcinomas are chemosensitive whereas non-gestational choriocarcinomas are chemoresistant.

Solution to Question 20:

Malignant mixed Müllerian tumors (MMMTs) are carcinosarcomas whose genetic profile closely resembles endometrial carcinomas.

They involve mutations in the same genes - PTEN, TP53, and PIK3CA. The usual genetic alterations found in sarcomas are absent in MMMTs.

MMMTs are endometrial adenocarcinomas with malignant mesenchymal components. The mesenchymal component may resemble uterine mesenchymal elements (stromal sarcoma, leiomyosarcoma) or contain heterologous malignant cell types (striated muscle, cartilage, adipose tissue, and bone).

It occurs in postmenopausal women and presents with bleeding. It is associated with a poor outcome.

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Solution to Question 21:

Meigs' syndrome triad includes the following:

• Solid benign ovarian tumor (fibroma)

• Right-sided hydrothorax

• Ascites - disappears after the removal of the tumor

Pseudo-Meigs' syndrome is characterized by the following:

• Non-malignant ascites

• Pleural effusion

• Pelvic tumors - other than solid benign ovarian tumors

Note: Ovarian fibroma is also associated with nevoid basal cell carcinoma. This association is known as Gorlin syndrome.

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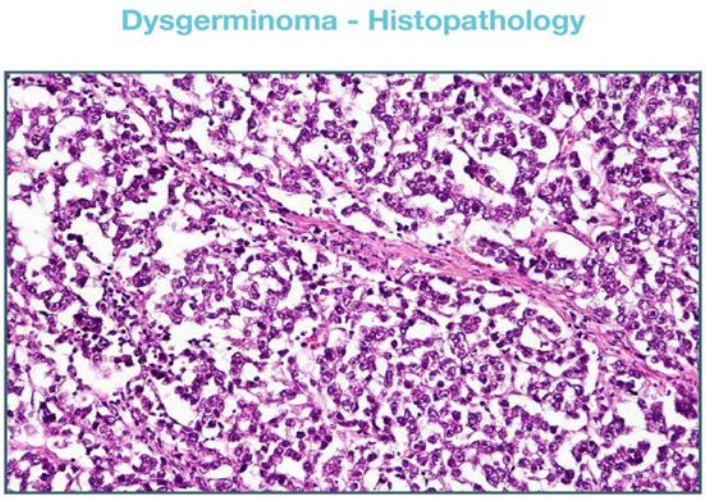
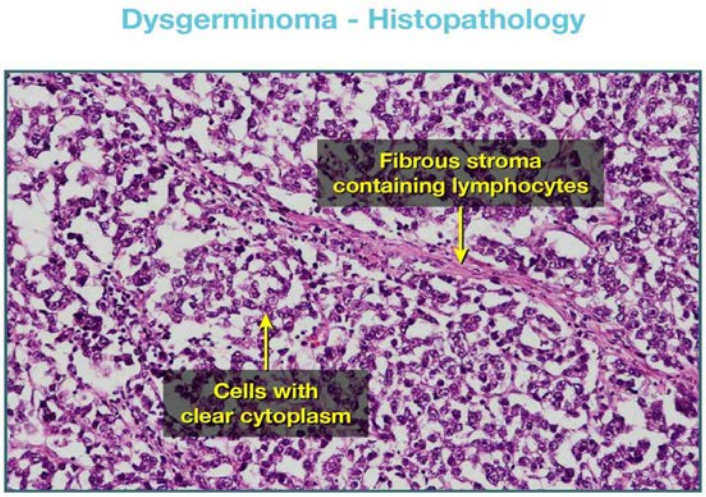
Solution to Question 22:

The given histopathological image shows large cells with clear cytoplasm (fried egg appearance), tumor cells arranged in sheets, and cords of fibrous stroma infiltrated by lymphocytes. These findings are suggestive of dysgerminoma. It is highly responsive to radiotherapy.





Dysgerminomas are the ovarian counterparts of testicular seminoma. They may occur in childhood, but most commonly occur in the 2-3rd decades. It may occur in patients with gonadal dysgenesis, including pseudohermaphroditism. The majority of these tumors are unilateral. They express OCT-3, OCT4, and NANOG.

All dysgerminomas are malignant, but the degree of histologic atypia is variable. Only about one-third of these lesions are aggressive. These neoplasms are responsive to chemoradiation, and overall survival exceeds 80%.

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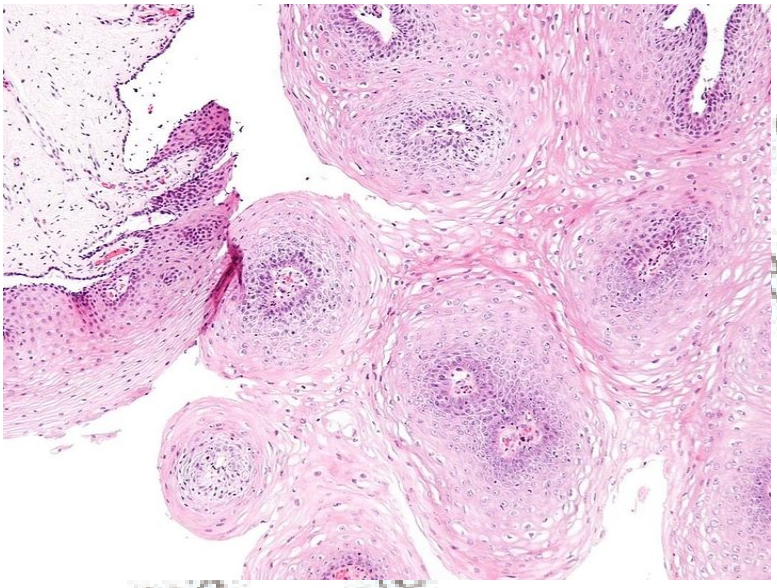
Male Genital Tract

Question 1:

A young sexually active man presented with multiple polypoid growths over his penis. Histopathological image of an excised lesion is as shown below. What is the diagnosis?



a) Condyloma lata

b) Bowen's disease

c) Condyloma acuminata

d) Verrucous carcinoma

Question 2:

All of the following are true regarding Bowen's disease except:

a) Strong association with HPV 16 infection

b) Marked dysplasia and hyperproliferative epidermis are seen

c) Intact basement membrane

d) Virtually never develops into an invasive carcinoma

Question 3:

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The biopsy of a resected inguinal mass from a patient shows marked fibrotic changes with prominent Leydig cells and hypoplastic Sertoli cells. What is the most likely diagnosis?

a) Peyronie disease

b) Cryptorchidism

c) Bowen disease

d) Torsion testis

Question 4:

Testicular atrophy is not seen in which of the following conditions?

a) A 25-year-old man with karyotype XXY

b) A 45-year-old man with liver cirrhosis

c) a 28-year-old man with painful orchitis

d) a 30-year-old man with torsion testis

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Question 5:

A 30-year-old man undergoes testicular biopsy as part of infertility work-up. Sperm count shows oligospermia. Microscopy shows only Sertoli cells in the seminiferous tubules. What is the most likely finding seen in the condition?

a) Increased FSH levels

b) Increased LH levels

c) Increased inhibin levels

d) Decreased testosterone levels

Question 6:

An 18-year-old boy presents with acute onset of testicular pain. On examination, the left testis is enlarged, tender and positioned higher than the right at an unusual angle. Pain is not relieved on elevation of the scrotum. What histopathological changes can be seen in this condition?

a) Marked fibrosis with prominent Leydig cells and hypoplastic Sertoli cells

b) Dysplastic cells with hyperchromatic nuclei, koilocytic atypia

c) Inflammatory cells and necrotic debris

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d) Intense congestion, hemorrhage, and areas of infarction

Question 7:

Which of the following infections primarily affects the testis?

a) Syphilis and tuberculosis

b) Tuberculosis and gonorrhoea

c) Syphilis and mumps

d) Mumps and gonorrhoea

Question 8:

Which of the following testicular tumors is derived from germ-cell neoplasia in situ?

a) Prepubertal yolk sac tumor

b) Prepubertal teratoma

c) Spermatocytic tumor

d) Seminoma

Question 9:

All of the following are true about tumors of the testis except:

a) Postpubertal teratoma are invariably malignant

b) Pure choriocarcinoma has an excellent prognosis

c) Seminomas only rarely occur in infants

d) Non-seminomatous germ-cell tumour metastasize using hematogenous route

Question 10:

What is the most common testicular tumor in infants?

a) Testicular lymphoma

b) Prepubertal yolk sac tumor

c) Prepubertal teratoma

d) Embryonal carcinoma

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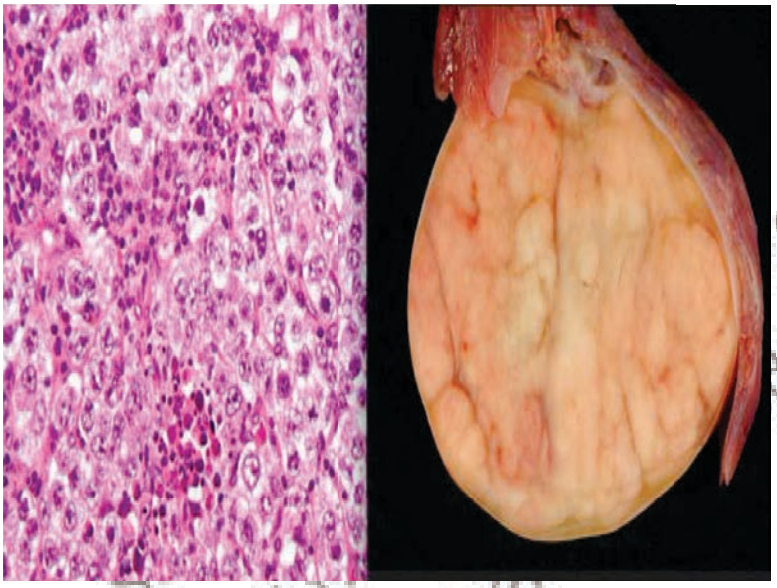
Question 11:

A 30-year-old man presented with a painless testicular mass. Inguinal orchidectomy was done and the gross and histological image is given below. What is the likely diagnosis?



a) Seminoma

b) Yolk sac tumour

c) Teratoma

d) Testicular lymphoma

Question 12:

A 30-year-old man presented with a testicular mass. Microscopic examination of the orchidectomy specimen was done. It showed highly anaplastic cells with hyperchromatic nuclei with prominent nucleoli growing in alveolar and tubular patterns. They stained positive for PLAP, cytokeratin, and CD30 and negative for KIT. What is the likely diagnosis?

a) Seminoma

b) Embryonal carcinoma

c) Teratoma

d) Yolk sac tumour

Question 13:

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A young man presented with a testicular mass and increased AFP levels. What is the likely diagnosis?

a) Choriocarcinoma

b) Teratoma

c) Yolk sac tumor

d) Seminoma

Question 14:

Which of the following is true about teratomas?

a) In post-pubertal males, all teratomas are considered benign.

b) All teratomas are benign even if they show immature elements.

c) All teratomas are considered malignant in post-pubertal males.

d) Orchidectomy is curative for testicular teratomas.

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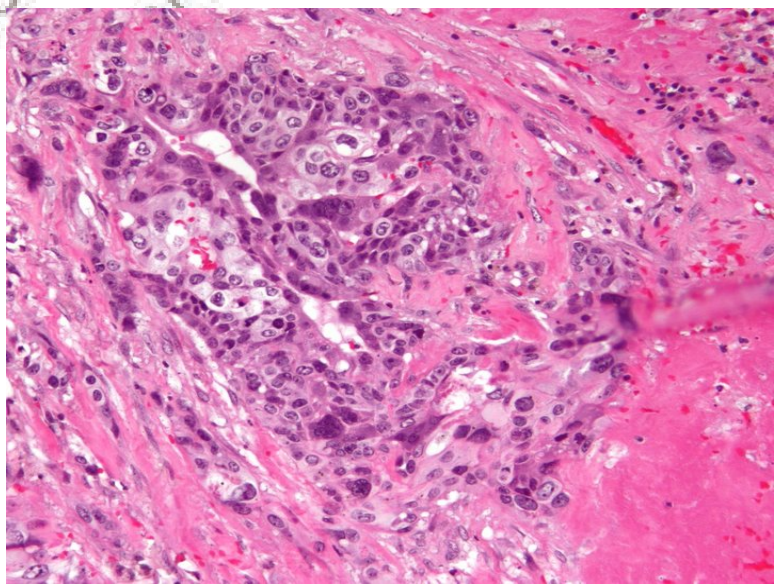
Question 15:

A 35-year-old man presents with hemoptysis and loss of weight. Chest radiograph shows multiple canon-ball metastases. Physical examination revealed no palpable mass. The serum HCG level is raised, but no change in AFP and CEA levels. Biopsy from the lung lesion reveals the following finding. What is the most likely primary tumor?



a) Seminoma

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b) Choriocarcinoma

c) Endodermal sinus tumor

d) Embryonal carcinoma

Question 16:

All of the following are true for spermatocytic tumors except:

a) It affects individuals generally younger than 35 years.

b) It does not have any extra-testicular sites of origin.

c) It is a slow-growing tumor that does not produce metastases.

d) It has an excellent prognosis.

Question 17:

A 40-year-old man presents with gynecomastia. Ultrasonography reveals a 1 cm solid mass within the body of the testis. His serum testosterone is 600 ng/dL and estradiol is 35 pg/mL. What is the most likely diagnosis?

a) Spermatocytic tumour

b) Sertoli cell tumour

c) Granulosa cell tumour

d) Leydig cell tumour

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Question 18:

What is the most common testicular neoplasms in men older than 60 years?

a) Lymphoma

b) Seminoma

c) Spermatocytic tumour

d) Leydig cell tumour

Question 19:

In patients with testicular tumors, what lymph nodes are primarily involved?

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a) Retroperitoneal paraortic

b) Inguinal

c) External iliac

d) Pre-aortic

Question 20:

Laboratory testing of a 30-year-old man diagnosed with a testicular mass showed increased levels of alpha-fetoprotein. All of the following can be included in the differential, except:

a) Choriocarcinoma

b) Teratocarcinoma

c) Yolk sac tumor

d) Embryonal carcinoma

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Question 21:

Which tumor responds best to radiation therapy?

a) Choriocarcinoma

b) Embryonal carcinoma

c) Teratoma

d) Seminoma

Question 22:

What is the most common malignant paratesticular tumor in children?

a) Liposarcoma

b) Rhabdomyosarcoma

c) Adenomatoid tumour

d) Lymphoma

Question 23:

Which of the following is not used as a tumor marker for germ cell testicular tumors?

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a) AFP

b) LDH

c) hCG

d) CEA

Question 24:

A 61-year-old male patient with benign prostatic hyperplasia is planned for transurethral resection of the prostate. Which of the following is removed during the procedure?

a) Central zone

b) Peripheral zone

c) Transitional zone

d) Can arise from any zone

Question 25:

An elderly man presenting with the features of urinary retention was thoroughly investigated and diagnosed with prostate carcinoma. All of the following statements about the Gleason system used for prognosis/survival of the patient are true except:

a) Grade group 1 represents the most well-differentiated tumors.

b) Tumors with Gleason scores 8 to 10 tend to be advanced cancers.

c) Gleason system correlates with pathologic stage and prognosis.

d) Gleason Score is reported from 1 to 10.

Question 26:

A 68-year-old man presented with hesitancy, incomplete voiding, and pelvic pain. On a digital rectal examination, an irregularly enlarged prostate with a nodular surface was felt. Transrectal biopsy revealed poorly formed glands arranged in a cribriform pattern. According to the modified Gleason score, how would you classify the pattern seen in this patient?

a) Pattern 2

b) Pattern 3

c) Pattern 4

d) Pattern 5

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Question 27:

What is the normal upper limit of prostate-specific antigen value for a 75-year-old man?

a) 2.5 ng/mL

b) 4.5 ng/mL

c) 5.5 ng/mL

d) 6.5 ng/mL

Question 28:

A 68-year-old patient was diagnosed with prostate cancer. Hematogenous spread of this cancer would occur predominantly to which of the following?

a) Bones

b) Lungs

c) Liver

d) Bladder

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Answer Key

Question No.	Correct Option
1	c
2	d
3	b
4	d
5	a
6	d
7	c
8	d
9	b
10	b
11	a
12	b
13	c
14	c

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15	b
16	a
17	d
18	a
19	a
20	a
21	d
22	b
23	d
24	c
25	d
26	c
27	d
28	a

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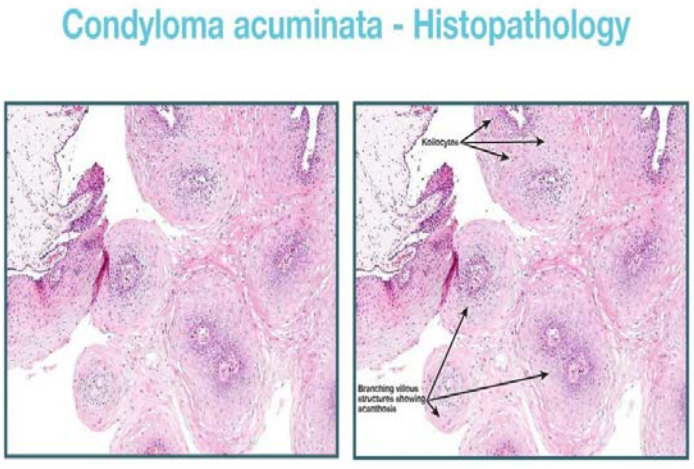
Detailed Explanations

Solution to Question 1:

The given histopathological image showing papillary (villous) architecture with acanthosis, hyperkeratosis and koilocytosis of squamous epithelium, are characteristic findings of condyloma acuminatum.

Koilocytes have a prominent cell membrane, hyperchromatic resinoid nucleus, and perinuclear halo.



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Grossly, they consist of single or multiple sessile or pedunculated, red papillary excrescences on the coronal sulcus, and the inner surface of the prepuce.

Option A: Condyloma lata is a maculopapular/nodular lesion seen in secondary syphilis.

Option B: Bowen's disease is carcinoma in situ of the penis characterized by the hyperproliferative epidermis and dysplastic epithelium.

Option D: Verrucous carcinoma / very well-differentiated squamous cell carcinoma, shows hyperkeratosis, acanthosis, and keratin pearls.

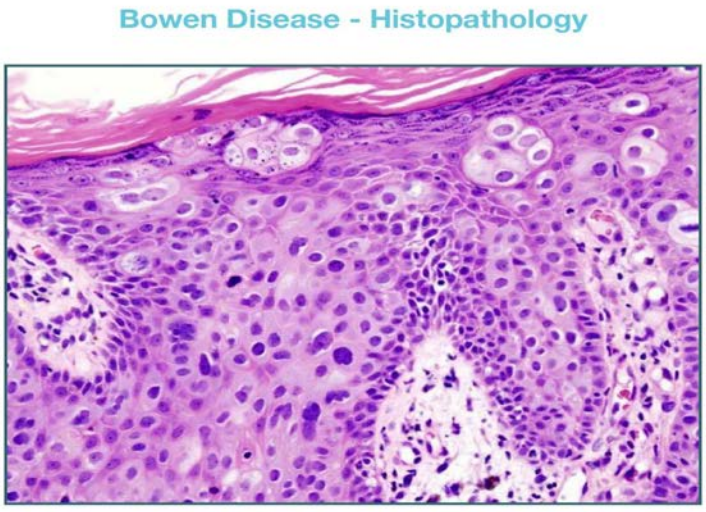
Solution to Question 2:

Bowen's disease starts as a premalignant lesion and transforms into infiltrating squamous cell carcinoma in approximately 10% of patients, usually over a span of many years.

Bowen's disease occurs in the genital region of both men and women, usually in those older than age 35 years. These lesions have a strong association with infection by high-risk human papillomavirus (HPV), most commonly type 16.

Grossly, it appears as a solitary, thickened, gray-white, and opaque plaque.

The below histological image of Bowen's disease shows dysplastic cells with large hyperchromatic nuclei, koilocytic atypia and an intact basement membrane.



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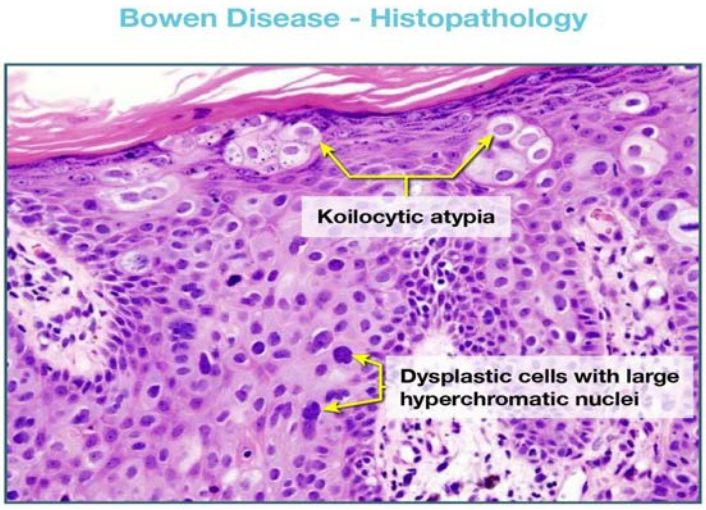

Premalignant lesions of invasive penile SCC:

• Erythroplasia of Queyrat

• Condyloma acuminatum

• Bowen's disease

Bowenoid papulosis occurs in young, sexually active adults. It presents as multiple reddish-brown papular lesions and it is histologically indistinguishable from Bowen's disease, but virtually never develops into invasive carcinoma.

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Solution to Question 3:

The given histopathological features are strongly suggestive of cryptorchidism.

Cryptorchidism is histopathologically characterized by the following:

• Testicular atrophy: thickening of the basement membrane, arrested germ cell development, marked hyalinization

• Tubules showing Sertoli cells but no spermatogenesis

• Increase in the interstitial Leydig cells.

Cryptorchidism is the failure of the descent of the intra-abdominal testes into the scrotal sac. It is the most common congenital abnormality of the genitourinary tract. The testes can arrest anywhere during descent, and the most common site is the inguinal region.

Phases of testicular descent:

• Transabdominal phase: Testes come to lie in the lower abdomen or pelvis. This phase of descent is regulated by Mullerian-inhibiting substances.

• Inguinoscrotal phase: Testes descend along the inguinal canal and reach the scrotal sac. This phase of the descent is regulated by androgen-induced calcitonin gene-related peptide from the

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genitofemoral nerve.

The exact pathogenesis remains unknown, however, deficiency in gonadotropins and Mullerian-inhibiting substance (MIS) and increased expression of estradiol in the placenta are thought to play a role. It is associated with testicular atrophy and dysfunction, which result in sterility. Cryptorchid testes carry a 3–5-fold higher risk for testicular cancer (usually seminoma).

Solution to Question 4:

Torsion testis does not cause testicular atrophy. It may cause intense congestion to widespread hemorrhage to testicular infarction.

Causes of testicular atrophy:

• Progressive atherosclerotic narrowing of the blood supply in old age

• End-stage of an inflammatory orchitis

• Cryptorchidism - associated with progressive tubular atrophy and sterility

• Hypopituitarism

• Generalized malnutrition or cachexia

• Irradiation

• Prolonged administration of antiandrogens (treatment for advanced carcinoma of the prostate)

• Liver cirrhosis - may cause testicular atrophy as a result of increased levels of circulating endogenous estrogens not metabolized by the diseased liver

• Exhaustion atrophy, which may follow persistent stimulation by high levels of the follicle-stimulating pituitary hormone

• Occasionally occurs as a primary failure of genetic origins, such as in Klinefelter (XXY) syndrome

The histological image below of testicular atrophy shows small tubules with few or no germ cells, thickening of the basement membrane of the spermatic tubules, and prominent Leydig cells. The near-normal seminiferous tubules are seen side-by-side with atrophic seminiferous tubules.

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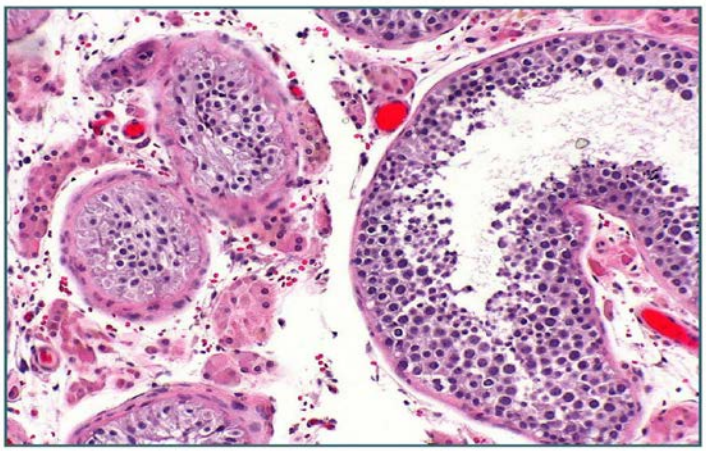
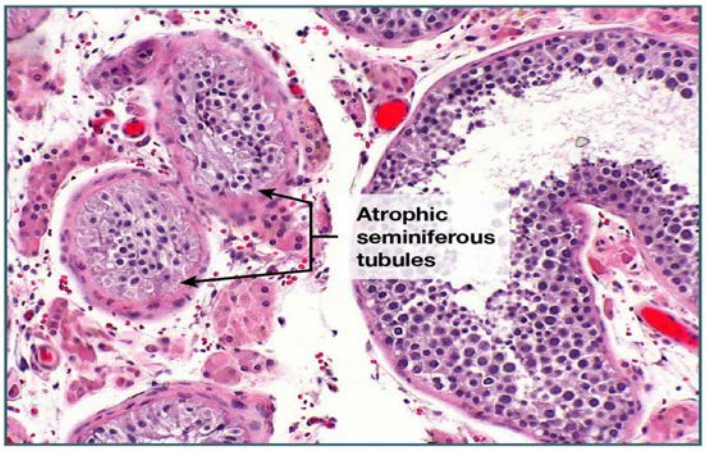
Testicular Atrophy - Histopathology



Testicular Atrophy - Histopathology



Solution to Question 5:

The above clinical scenario depicts that the patient is having Sertoli cell-only syndrome, and patients with this syndrome will have increased levels of follicle-stimulating hormone (FSH).

The below image shows normal histology of testis:

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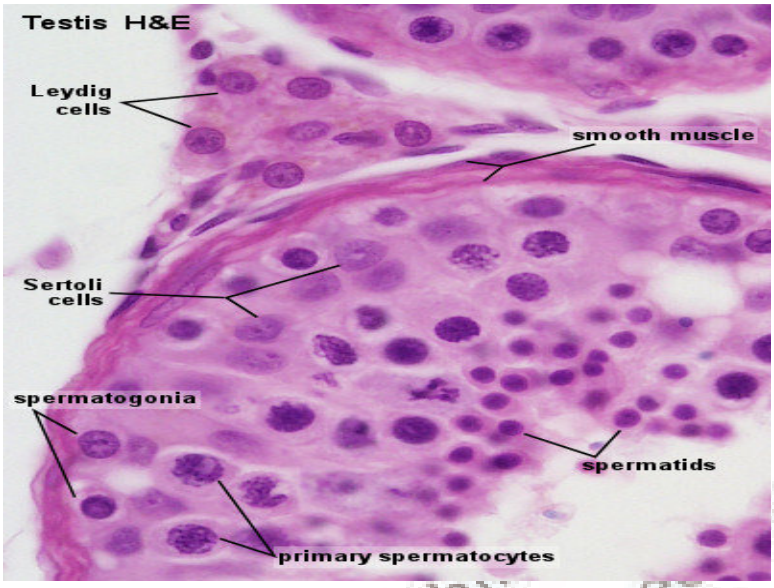

In normal males, as spermatogenesis and testosterone production increase, the Sertoli cells produce inhibin, which inhibits the release of FSH. The Sertoli cells are supporting cells that are under the action of FSH. Leydig cells, which are present in the interstitial spaces, are under the action of luteinizing hormone(LH) and produce testosterone. Testosterone has a feedback inhibition on LH.

In Sertoli cell-only syndrome, within the seminiferous tubules, only Sertoli cells are seen and no germ cells. Hence, there are no spermatozoa and there is no feedback inhibition, which results in increased FSH levels. So, testosterone levels, and LH levels remain unaffected since Leydig cells are not affected. Hence, the patient will have male secondary sexual characters.

The most important indication of testicular biopsy is infertility workup.

Solution to Question 6:

The most likely diagnosis is testicular torsion. The pathological changes range from intense congestion to widespread hemorrhage to testicular infarction. In advanced stages, the testis is markedly enlarged and consists entirely of soft, necrotic, hemorrhagic tissue.

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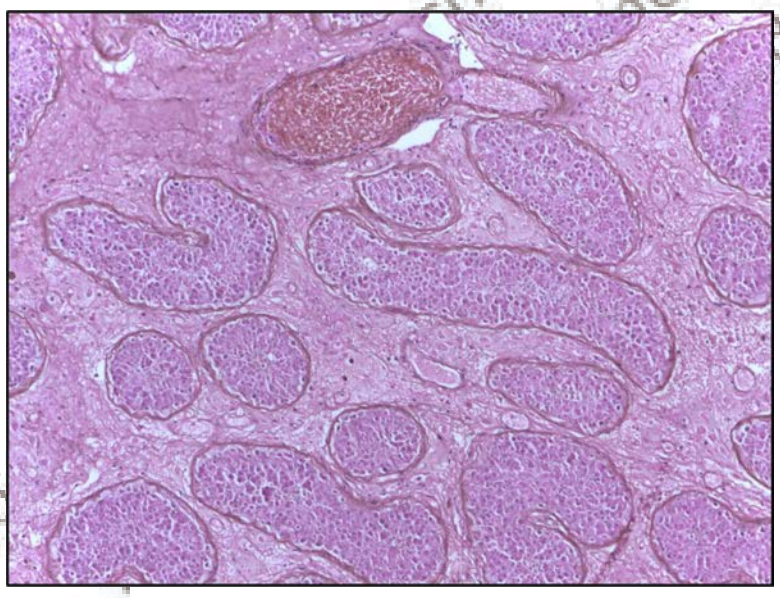

Adult torsion is typically seen in adolescence and presents with the sudden onset of testicular pain. Neonatal torsion can occur either in utero or shortly after birth and the cause is unknown.

It results from a bilateral anatomic defect that leads to increased mobility of the testes (bell-clapper□ abnormality). Twisting of the spermatic cord typically cuts off the venous drainage of the testis. But, thick-walled arteries remain patent, producing intense vascular engorgement, followed by hemorrhagic infarction. If the testis is manually untwisted within approximately 6 hours of the onset of torsion, there is a good chance that the testis will remain viable.

Solution to Question 7:

Syphilis and mumps affect the testis primarily and later spread to surrounding structures.

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Syphilis can affect both the testis and epididymis, but invariably, the testis is involved first as gummas and diffuse interstitial inflammation.

Mumps most commonly affects school-aged children, but testicular involvement is uncommon in this age. Mumps infection in postpubertal males can lead to acute interstitial orchitis in 20 to 30% of cases.

Gonorrhea and tuberculosis affect the epididymis first, which can later spread to the testis.

Solution to Question 8:

Germ-cell neoplasia in situ (GCNIS) is a common precursor lesion of seminoma.

Most testicular germ-cell tumors originate from a precursor lesion called GCNIS. It is believed to arise in utero and stay dormant until puberty, after which it may progress to seminoma or non-seminomatous tumors.

The exceptions to this rule are:

• Prepubertal yolk-sac tumors

• Teratomas

• Adult spermatocyte tumors

The lesion consists of atypical primordial germ cells, which have large nuclei and a clear cytoplasm and fail to develop into spermatogonia. This is because these cells retain the expression of the transcription factors OCT3/4 and NANOG, which maintain the pluripotency of germ cells and prevent their maturation.

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Solution to Question 9:

Pure choriocarcinoma is a rare, but aggressive, tumor and has a poor prognosis.

It generally does not cause any testicular enlargement. It spreads rapidly via the bloodstream. This results in the frequent involvement of the lung and liver. However, pure germ-cell tumors (GCTs) are rare and about 60% of testicular GCTs are mixed tumors.

Teratomas in children usually follow a benign course. But, in the postpubertal male, all teratomas are regarded as malignant because they are capable of metastatic behavior.

Solution to Question 10:

Yolk sac tumor is the most common testicular tumor in infants and children up to 3 years of age.

Prepubertal teratoma is the second most common testicular tumor in infants and children.

In adults, pure yolk sac tumor is rare. The yolk sac elements frequently occur in combination with embryonal carcinoma (as a mixed tumor).

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Solution to Question 11:

The gross specimen showing a homogeneous, grey-white, lobulated cut surface that bulges around the surrounding parenchyma is characteristic of a seminomatous germ-cell tumor or seminoma.

The histological image shows sheets of uniform cells with clear cytoplasm and central nucleus, with a prominent nucleolus (fried-egg appearance), delicate fibrous septa containing a lymphocytic infiltrate.

Seminoma is the most common type of GCT. The peak incidence is the 3rd decade and almost never occurs in infants. It is the testicular equivalent of an ovarian dysgerminoma. Immunohistochemistry is positive for KIT, (regardless of KIT mutational status), OCT3/4, and placental alkaline phosphatase (PLAP).

Option B: Yolk sac tumor is non-encapsulated with mucinous appearance. Schiller–Duval bodies are characteristic. It is seen in children less than 3 years.

Option C: Teratoma shows derivatives of more than one germ layer like cartilage, hair, sebaceous glands.

Option D: Testicular lymphoma is a rare extranodal presentation of non-Hodgkin lymphoma

Testicular biopsy is contraindicated in case of a suspicious testicular mass because it is associated with a risk of tumor cell spillage. High inguinal orchidectomy followed by histopathological evaluation is the preferred standard management. Fixative used for testicular biopsy is Bouin's fluid.

Solution to Question 12:

The above clinical scenario of the germ-cell tumor is suggestive of embryonal carcinoma.

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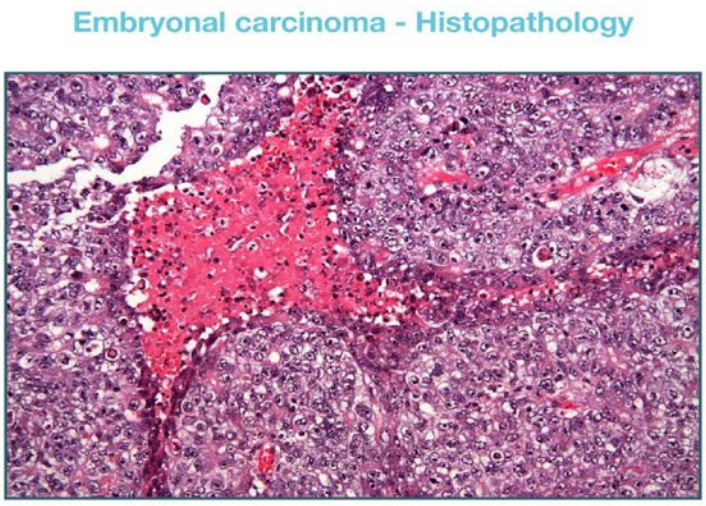
It is a non-seminomatous germ cell tumor (NSGCTs) that occurs mostly in the 20 to 30 year age group. These tumors are more aggressive than seminomas. Embryonal carcinomas share some markers with seminomas such as OCT 3/4 and PLAP but differ by being positive for cytokeratin and CD30 and negative for KIT.

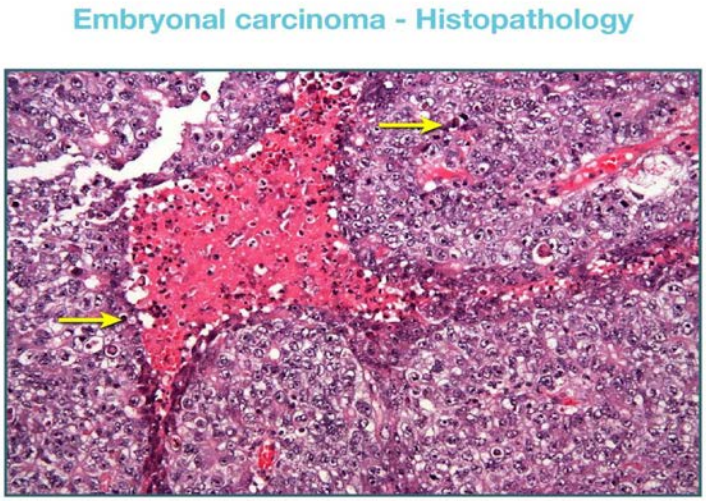
Most patients present with a testicular mass, which can be painful due to rapid growth and may be mistaken for torsion.

Grossly, the tumor is often variegated, poorly demarcated at the margins, and punctuated by foci of hemorrhage or necrosis.

Histologically, the cells grow in alveolar or tubular patterns, sometimes with papillary convolutions; the neoplastic cells have an epithelial appearance, are large and anaplastic, and exhibit hyperchromatic nuclei with prominent nucleoli.

The below image is the histology of embryonal carcinoma showing anaplastic cells with large hyperchromatic nuclei.





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Option A: Seminoma will have sheets of uniform cells with poor, demarcated lobules divided by delicate fibrous septa infiltrated by lymphocytes. Seminomas are positive PLAP and KIT, but negative for cytokeratin and CD30.

Option C: Teratoma will show derivatives of more than one germ layer like cartilage, hairs, sebaceous glands in the histology.

Option D: Yolk sac tumor affects children up to 3 yrs of age, will have elevated alpha-fetoprotein (AFP), and exhibit Schiller–Duval bodies on histology.

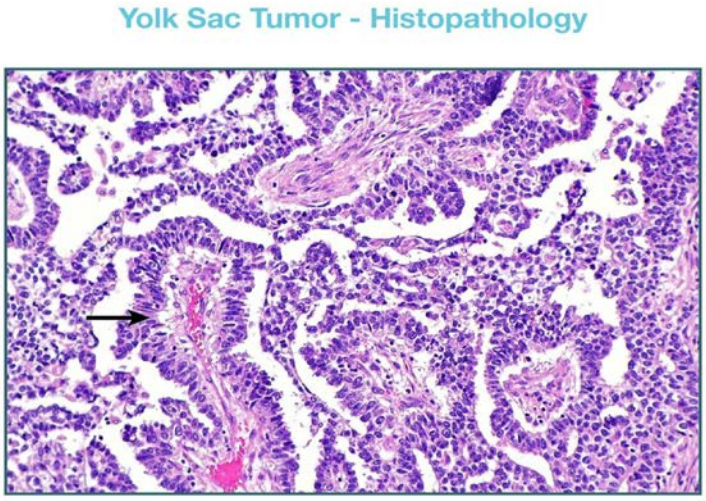
Solution to Question 13:

Marked elevation of serum alpha-fetoprotein (AFP) levels is produced by the yolk sac tumor / endodermal sinus tumor.

It is the most common testicular tumor in infants and children up to 3 years of age (prepubertal yolk sac tumor). Postpubertal yolk sac tumors are associated with germ-cell neoplasia in situ and almost always occur in mixed forms.

Grossly, pure yolk sac tumors have a homogenous, mucinous appearance.

The below image is of a yolk sac tumor showing lace-like architecture and Schiller–Duval bodies (Arrow) (a hallmark of YST), and hyaline-like globules. These structures consist of a mesodermal core with central capillary as well as a visceral and parietal layer of cells (glomeruloid pattern)



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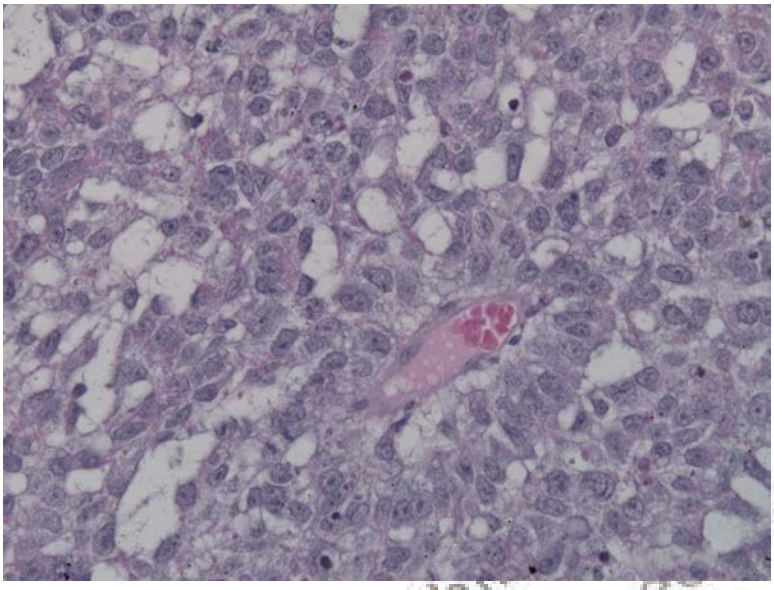

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Solution to Question 14:

In post-pubertal males, teratomas are considered malignant, regardless of the presence of immature elements.

Teratomas are non-seminomatous germ cell tumors (NSGCTs), which are characteristically composed of more than one germ layer derivative (ectoderm, mesoderm, endoderm).

Teratomas have complex histopathology and 2 variants may be seen:

• Mature: Adult-type, well-differentiated cells or organoid structures

• Immature: Embryonal-type, undifferentiated cells or primitive neural elements

In ovarian teratomas, immature elememts are needed to consider it malignant. However, the degree of immaturity is clinically insignificant in testicular teratomas. In prepubertal children, testicular teratomas have a benign course. However, in postpubertal males, teratomas are considered malignant.

The below image shows the histology of teratoma of the testis.

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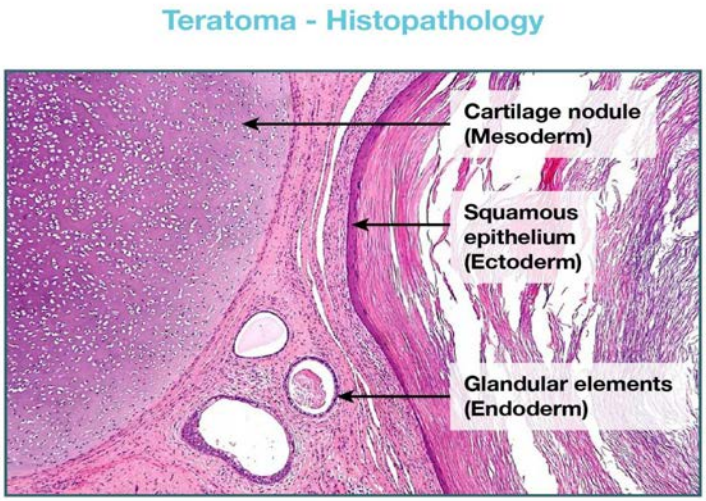

Solution to Question 15:

From the given clinical scenario and image showing cytotrophoblasts and multinucleated syncytiotrophoblasts in a hemorrhagic background, the most likely primary tumor appears to be choriocarcinoma.

The syncytiotrophoblasts secrete °-hCG, at levels that serve as important serological markers.

Pure choriocarcinoma, although rare, is the most aggressive non-seminomatous germ cell tumor (NSGCT). It often does not cause any testicular enlargement; instead, it spreads rapidly via the bloodstream. This results in the frequent involvement of the lung(cannon-ball metastases) and liver and a poor prognosis.

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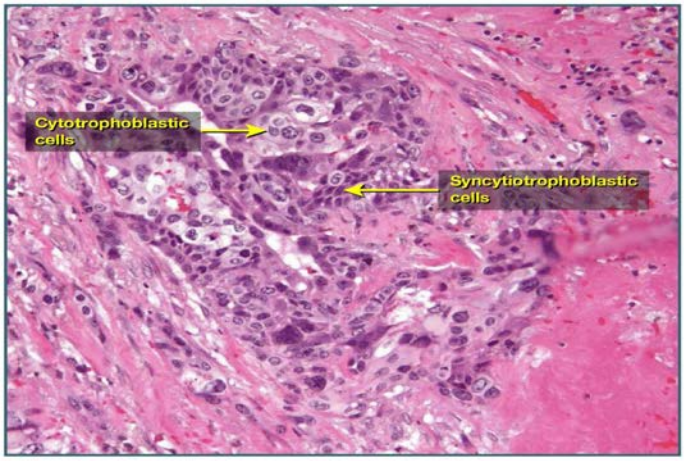
Choriocarcinoma



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Solution to Question 16:

With a spermatocytic tumor, affected individuals are generally older than 65 years.

A spermatocyte tumor (previously called spermatocytic seminoma) is a rare, slow-growing germ cell tumor that is distinct from classical seminoma, both clinically and histologically.

GCNIS: Germ-cell neoplasia in situ

PLAP: Placental alkaline phosphatase

The below image is the histology of spermatocytic tumor showing a population of small, medium-sized, and large cells and mucoid lakes

Characteristics	Seminoma	Spermatocytic tumor
Age	20–40 yrs	>65 yrs
Association with GCNIS, othe r GCT, cryptorchidism	Present	Absent
Histology	Uniform looking cellsLymph ocytes and granuloma Presen t	Small, medium and large cell sLymphocytes and granulom a Absent
Intracytoplasmic glycogen	Present	Absent
PLAP reactivity	Present	Absent
Extra testicular origin, metas tasis	Present	Absent

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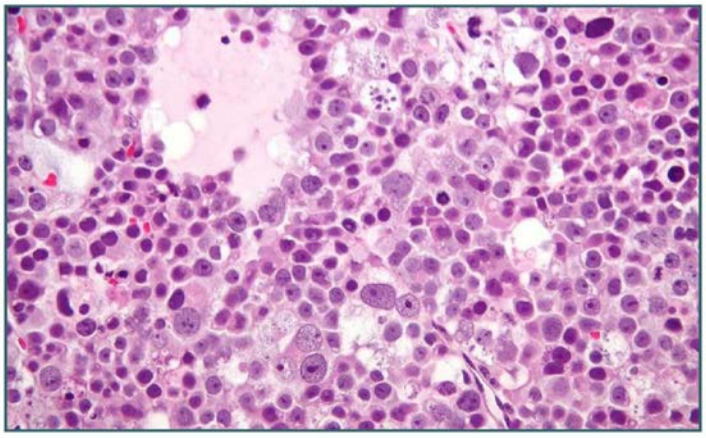
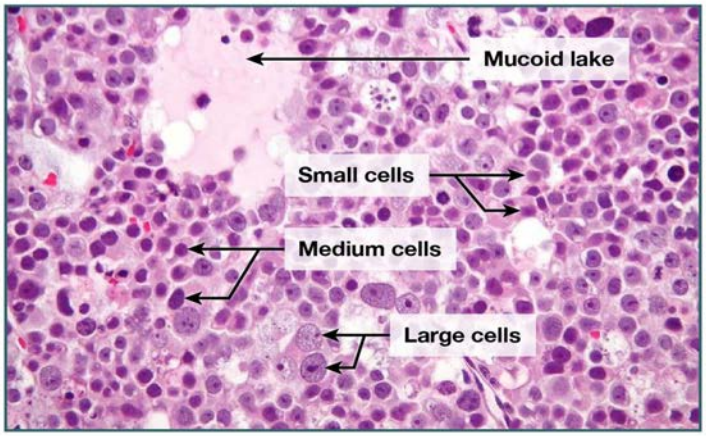
Spermatocytic Tumor - Histopathology



Spermatocytic Tumor - Histopathology



Solution to Question 17:

The given scenario is suggestive of Leydig cell tumor of the testis.

It is the most common sex-cord stromal type of testicular neoplasm. It is mostly benign and invariably unilateral. Most cases occur between 20 and 60 years of age. However, they can present at any age.

The most common presenting feature is testicular swelling or gynecomastia (~15% of cases). In children, hormonal effects manifested primarily as sexual precocity, are the dominant features. Tumors of Leydig cells may secrete androgens and estrogens, and even corticosteroids.

Grossly it shows golden brown, homogeneous circumscribed nodules <5 cm in diameter.

Histologically:

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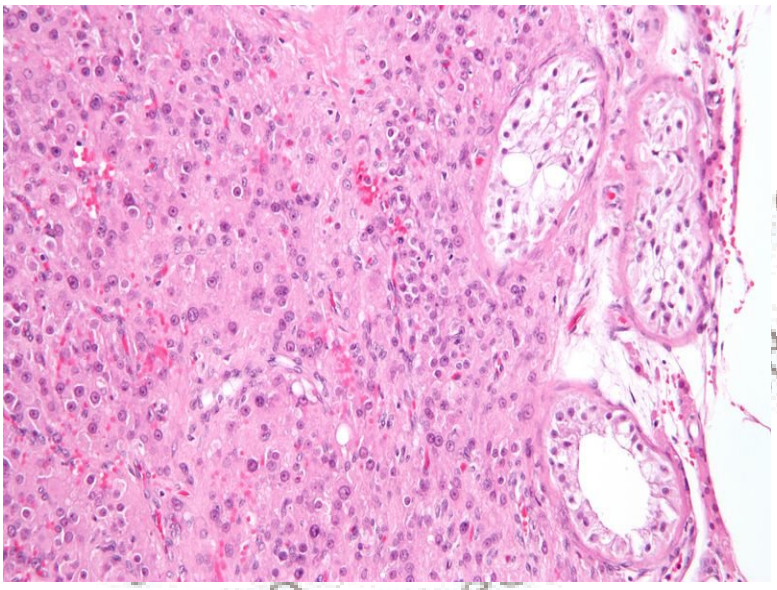
• large, round, or polygonal cells

• round central nucleus and prominent nucleoli

• abundant granular eosinophilic cytoplasm containing lipid droplets, vacuoles, or lipofuscin pigment

• crystalloids of Reinke, rod-shaped eosinophilic cytoplasmic bodies are seen in about 25% of the tumors



Option A: Spermatocytic tumor mainly occurs in older adults as a slow-growing testicular mass. They are usually hormonally silent

Option B: Sertoli cell tumor mostly presents as a painless testicular mass. They are usually hormonally silent. Hence, gynecomastia and precocious puberty are very rare.

Option C: Granulosa cell tumor usually presents as a slow-growing and non-functioning testicular mass. Gynecomastia is rare. They usualy secrete estrogen.

Solution to Question 18:

Non-Hodgkin lymphoma is the most common testicular neoplasm in men older than 60 years.

The most common types of testicular lymphomas in decreasing order of frequecy:

• Diffuse large B-cell lymphoma

• Burkitt lymphoma

• Epstein–Barr virus - positive extranodal NK/T cell lymphoma.

Testicular lymphomas are aggressive tumors with a poor prognosis. They have a higher propensity for CNS involvement.

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Solution to Question 19:

Retroperitoneal para-aortic nodes are the first to be involved in the lymphatic spread of testicular tumors.

Testicular tumors have a characteristic mode of spread:

• Lymphatic spread is common to all forms of testicular tumors. Initially, it spreads to retroperitoneal para-aortic nodes, then spreads to the mediastinal and supraclavicular nodes.

• Hematogenous spread is primarily to the lungs, but the liver, brain, and bones may also be involved.

Solution to Question 20:

Serum alpha-fetoprotein (AFP) level is raised in all the above conditions except pure choriocarcinoma and pure seminoma.

Choriocarcinomas have elevated levels of HCG, which can be readily demonstrated in the cytoplasm of syncytiotrophoblastic cells.

AFP is a marker of hepatocellular cancer and non-seminomatous germ cell tumors of testes, mainly yolk sac tumors.

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Solution to Question 21:

Seminomas are extremely radiosensitive tumors.

The counterpart of seminoma, which arises in the ovary, is dysgerminoma.

Solution to Question 22:

The most common malignant paratesticular tumor in children is rhabdomyosarcoma.

The paratesticular region is an extratesticular anatomical area, which includes the contents:

• Spermatic cord,

• Testicular tunics,

• Epididymis

• Vestigial remnants, such as the appendices epididymis and testis.

The most common malignant paratesticular tumor in adults is liposarcoma.

The most common benign paratesticular tumor is an adenomatoid tumor.

The most common paratesticular mesenchymal tumor is a lipoma.

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Solution to Question 23:

Carcinoembryonic antigen (CEA) is not used as a tumor marker for germ-cell testicular tumors. It is an oncofetal antigen used as a tumor marker in adenocarcinoma of the colon, pancreas, lung, breast, and ovary.

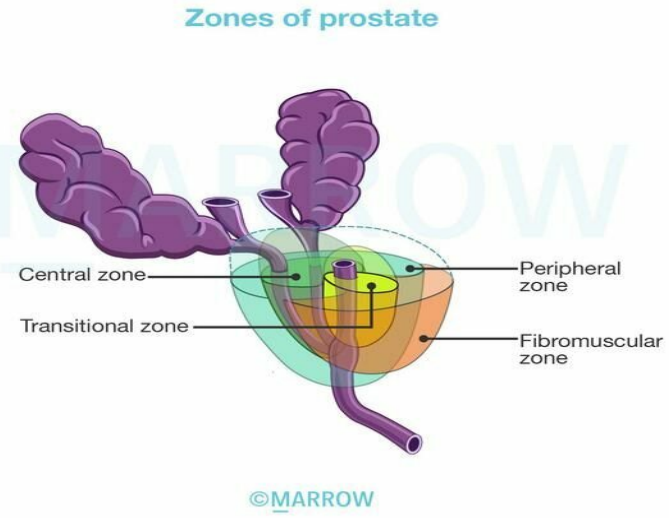
Markers of germ cell testicular tumors include alpha-fetoprotein (AFP), human chorionic gonadotropin, placental alkaline phosphatase, placental lactogen, and lactate dehydrogenase (LDH).

Solution to Question 24:

Benign prostatic hyperplasia originates almost exclusively in the transitional zone, hence it is surgically removed.

Nodular hyperplasia or benign prostatic hyperplasia (BPH) is the most common benign prostatic disease in men above 50 years. It arises from the inner aspect of the prostate gland, i.e., the transitional zone. It is characterized by benign, hyperplastic proliferation of prostatic stroma and epithelial elements, which is driven by dihydrotestosterone. This growth progressively compresses the urethra resulting in urinary obstructive symptoms.

The normal prostate contains several distinct regions, including a central zone (CZ), peripheral zone (PZ), transitional zone (TZ), and periurethral zone, as shown in the image below.



Note: Most carcinomas arise from the peripheral zone and maybe palpable during the digital examination of the rectum.

Solution to Question 25:

The Gleason score is currently reported from 6-10.

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WHO/ISUP modified Gleason score is the histopathological grading system, which corresponds with the clinical behavior of prostate cancer. It is one of the key methods used in confirmation of the diagnosis, prognostication, and staging of prostate cancer (adenocarcinoma).

The Gleason grading system is primarily based on analyzing the architecture of the tumor cells in the biopsy specimens obtained. The architecture, i.e., the Gleason Patterns are classified as:

• Pattern 3: Well-formed glands

• Pattern 4: Poorly formed/Fused/Cribriform glands/Glomeruloid glands

• Pattern 5: Sheets of the tumor, individual cells, cords, and solid nests of cells, Comedo necrosis

• Pattern 1 and 2 are no longer defined

Most tumor specimens contain more than one pattern. Therefore, a numeric grade is assigned to both the primary pattern and the next most frequent secondary pattern. The sum of the numeric grades provides the Gleason score.

• Scores 2–5 are no longer assigned.

• Scores of 6 - 7 are potentially treatable cancers.

• Scores 8 - 10 are advanced cancers that are less likely to be cured.

Based on the gleason score, they are classified into the following grade groups:

• Grade group 1: score<=6

• Grade group 2: 3+4=7

• Grade group 3: 4+3=7

• Grade group 4: score 8

• Grade group 5: scores 9-10

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Solution to Question 26:

The given scenario is suggestive of prostate cancer and all cribriform patterns are now defined as Gleason pattern 4 according to the 2014 WHO/ISUP grading consensus conference.

The below image of prostate cancer with Gleason pattern 4 shows cribriform pattern

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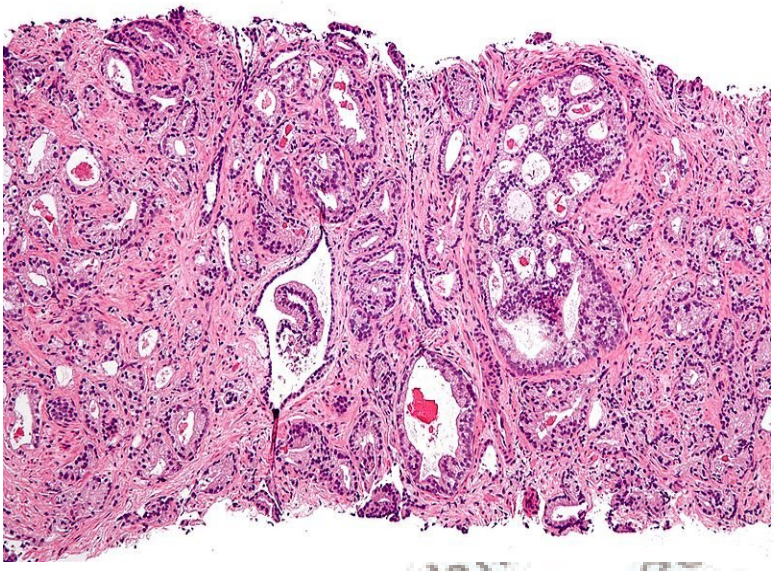

Highlights of 2014 WHO/ISUP modified Gleason score:

1) Gleason Pattern:

• Pattern 3- Well formed glands

• Pattern 4- Poorly formed/Fused/Cribriform glands/Glomeruloid glands

• Pattern 5- Sheets of the tumor, individual cells, cords and solid nests of cells, Comedo necrosis

• Pattern 1 and 2 are no longer defined

2) Gleason Score:

The current Gleason score ranges from 6–10. Scores 2–5 are no longer assigned.

3) Grade group:

• Grade group 1: score ≤6

• Grade group 2: 3+4=7

• Grade group 3: 4+3=7

• Grade group 4: score 8

• Grade group 5: scores 9–10

Solution to Question 27:

The upper-age-specific reference value of serum prostate-specific antigen (PSA) in men of age 70–79 is 6.5 ng/mL.

PSA is a product of prostatic epithelium secreted in the semen. Measurement of serum PSA levels is widely used to assist the diagnosis, prognosis, and management of prostate cancer. Older men have a higher serum PSA level than younger men, so the normal range varies with age.

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The serum PSA levels as a screening test for prostatic cancer has poor sensitivity and specificity. This is because various other factors such as trauma, infections, BPH, instrumentation/digital exam of the prostate, and ejaculation can increase serum PSA levels. A value of ≥4 ng/mL usually warrants serial testing or further evaluation.

In an effort to improve the sensitivity and specificity of serum PSA levels, many novel indices are used:

• Age-specific PSA reference ranges

• PSA velocity: Rate of change of PSA values with time. It is considered that PSA velocity of 0.75 ng/mL per year measured at least 3 times over a period of 1.5 to 2 yrs is significant to diagnose Prostate cancer.

• PSA density: Serum PSA/volume of the prostate gland

• The ratio of free to bound serum PSA

Age	Upper age-specific PSA(ng/mL)
40–49 yrs	2.5
50–59 yrs	3.5
60–69 yrs	4.5
70–79 yrs	6.5

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Solution to Question 28:

Hematogenous spread of carcinoma prostrate occurs predominantly to the bones and are typically osteoblastic.

The commonly involved bones in decreasing order of frequency:

• Lumbar spine

• Proximal femur

• Pelvis

• Thoracic spine

• Ribs

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Alcoholic and Infectious Liver Disease

Question 1:

A 50-year-old man who developed myocardial infarction 3 days ago now presents with jaundice. Lab investigations done are given below. Which region of the liver lobule is most likely affected here?

a) Zone 1

b) Zone 2

c) Zone 3

d) Both zone 1 and 2

Question 2:

Patients with which of the following conditions are least likely to develop centrilobular necrosis of liver?

a) Myocardial infarction

b) Acetaminophen toxicity

c) Yellow fever

d) Cardiac failure

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Question 3:

A chronic alcoholic developed cirrhosis of the liver. Which is the principal cell type involved in scar deposition in this condition?

a) Hepatocytes

b) Hepatic stellate cells

c) Sinusoidal endothelial cells

d) Kupffer cells

Question 4:

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Histopathological examination of liver biopsy reveals steatosis. Which of the following conditions is least likely to cause this change?

a) Hepatitis B infection

b) Hepatitis C infection

c) Wilson's disease

d) Protein malnutrition

Question 5:

Which of the following conditions causes macrovesicular steatosis of liver?

a) Reye syndrome

b) Obesity

c) Fatty liver of pregnancy

d) Valproate hepatotoxicity

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Question 6:

A 4-year-old girl, with a history of URTI, now presents with severe vomiting, lethargy, and altered mental status. You are suspecting Reye's syndrome. Which of the following liver biopsy findings will confirm your diagnosis?

a) Centrizonal haemorrhagic necrosis

b) Marked microvesicular steatosis

c) Portal tract edema and perisinusoidal fibrosis

d) Cirrhosis and periportal eosinophilic inclusion bodies

Question 7:

Histopathological examination of liver biopsy in a patient with jaundice shows the following finding. Which of the following conditions is least likely in this patient?

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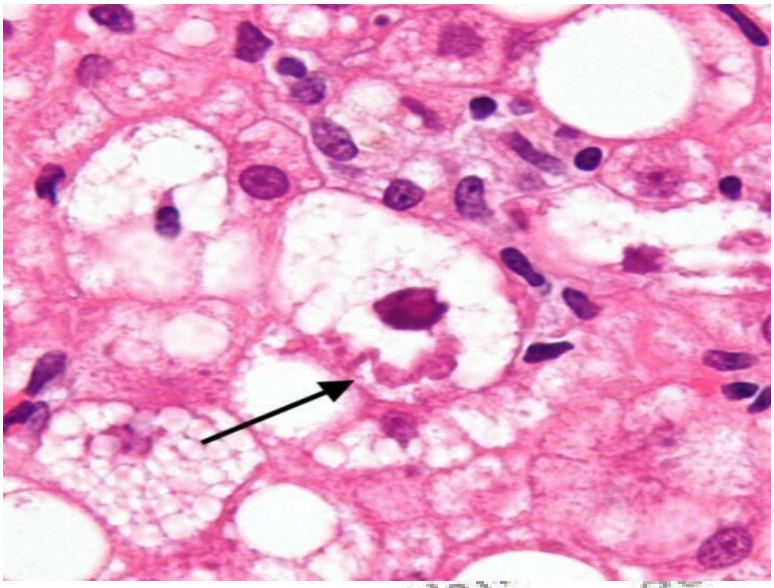

a) Wilson's disease

b) Primary biliary cholangitis

c) Primary sclerosing cholangitis

d) Indian childhood cirrhosis

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Question 8:

Which of the following causes Laennec cirrhosis?

a) Alcohol

b) Hepatitis B

c) Hemochromatosis

d) Hepatitis C

Question 9:

Which of the following histopathological findings will be seen in patients with chronic alcoholism?

a) Chicken-wire fence fibrosis

b) Rosette formation

c) Feathery degeneration of hepatocytes

d) Ground glass hepatocytes

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Question 10:

Which of the following conditions does not result in micronodular cirrhosis?

a) Alcoholic cirrhosis

b) Viral hepatitis

c) Budd-Chiari syndrome

d) Hemochromatosis

Question 11:

In patients with non-alcoholic steatohepatitis, which of the following features is not seen on liver biopsy?

a) Hepatocyte ballooning

b) Portal fibrosis

c) Lymphoid follicles

d) Perisinusoidal inflammation

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Question 12:

What is the most common hepatotoxin causing acute liver failure?

a) Methotrexate

b) Aflatoxin

c) Alcohol

d) Acetaminophen

Question 13:

Which of the following does not cause chronic infection?

a) Hepatitis D

b) Hepatitis C

c) Hepatitis E

d) Hepatitis A

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Question 14:

There is an outbreak of hepatitis A infection in a college hostel. Which of the following is false about this infection?

a) It does not cause hepatocellular carcinoma

b) The incubation period is 2-6 weeks

c) Liver failure is not a complication

d) Case fatality rate is 0.1%

Question 15:

Which among the following is the most common cause of sporadic acute hepatitis in India?

a) HAV

b) HBV

c) HCV

d) HEV

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Question 16:

A 53-year-old man who has a history of chronic hepatitis B is diagnosed to have hepatocellular carcinoma. Which of the following is involved in the pathogenesis of this condition?

a) HBs Ag

b) HBe Ag

c) HBV DNA polymerase

d) HBx protein

Question 17:

Which of the following serological markers can be used to diagnose hepatitis B infection during the window period?

a) HBs Ag

b) Anti-HBs Ab IgM

c) Anti-HBc Ab IgM

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d) HBe Ag

Question 18:

In a patient who is both HBsAg and HBeAg positive, what does declining IgM anti-HBc and rising total anti-HBc indicate?

a) Chronic non-infective hepatitis

b) Chronic infective hepatitis

c) Acute non-infective hepatitis

d) Acute fulminant hepatitis

Question 19:

A patient with a history of unprotected sexual intercourse turns out to be HBsAg positive. Which of the following is the best predictor for development of chronic disease?

a) Age

b) Viral load

c) Immune status

d) Pre-existing liver diseases

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Question 20:

An IV drug abuser has been found to be seropositive for HBsAg, HBeAg, and anti-HBc IgM. Which of the following is least likely to be seen in the liver biopsy of such patients?

a) Ballooning degeneration

b) Ground glass hepatocytes

c) Focal or spotty necrosis

d) Confluent necrosis of hepatocytes

Question 21:

A man with a history of intranasal cocaine abuse is at most risk for which of the following infections?

a) Hepatitis E

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b) Hepatitis B

c) Hepatitis C

d) Hepatitis A

Question 22:

Which of the following is the most common clinical course in patients diagnosed with hepatitis C infection?

a) Chronic carrier state

b) Cirrhosis

c) Hepatic decompensation

d) Hepatocellular carcinoma

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Question 23:

Which genotype of hepatitis C virus is associated with metabolic syndrome?

a) 4

b) 2

c) 3

d) 5

Question 24:

A 40-year-old male patient with chronic hepatitis B infection comes for a follow-up visit. Which of the following is not a histopathological feature of the liver in such cases?

a) Bridging necrosis and fibrosis

b) Ground-glass hepatocytes

c) Ballooning degeneration

d) Piecemeal necrosis

Question 25:

In patients with liver failure, which of the following tests is not used to evaluate the synthetic function of hepatocytes?

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a) Serum ammonia

b) APTT

c) Serum albumin

d) Serum alkaline phosphatase

Question 26:

Which of the following is not seen in the histopathological examination of the liver in patients with malaria?

a) Mononuclear portal infiltrate

b) Macronodular cirrhosis

c) Hemozoin pigment deposition

d) Fatty change and periportal inflammation

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Question 27:

Identify the incorrect match.

a) Mallory-Denk bodies—Alcoholic liver disease

b) Councilman bodies—Chronic hepatitis

c) Ground glass hepatocytes—Hepatitis B

d) Onion skin fibrosis—Primary sclerosing cholangitis

Question 28:

A patient with ascites, melena, and splenomegaly is diagnosed with portal hypertension. Which of the following is not an intrahepatic cause of this condition?

a) Non-alcoholic fatty liver disease

b) Amyloidosis

c) Schistosomiasis

d) Obstructive thrombosis of portal vein

Question 29:

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Which of the following is not a feature of liver histology in patients with non-cirrhotic portal fibrosis?

a) Sinusoidal dilatation

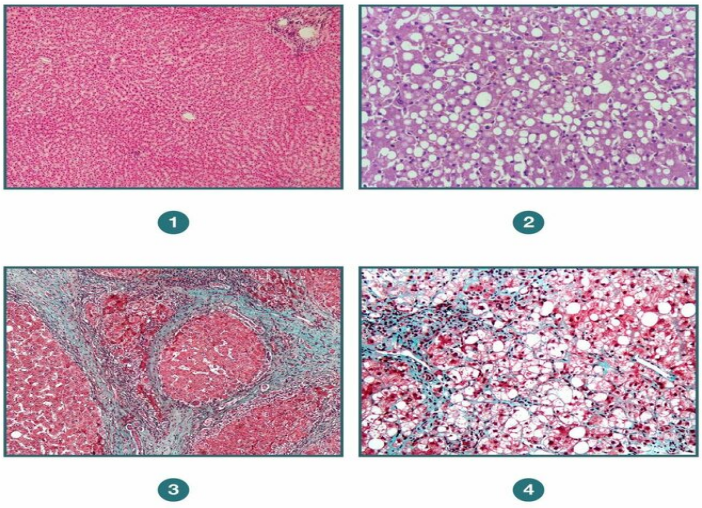
b) Thrombosis of the medium and small portal vein branches

c) Micronodular transformation

d) Bridging fibrosis

Question 30:

Match the histopathological sections of liver and the different conditions.



a) 1-Alcoholic steatosis, 2-Alcoholic hepatitis, 3-micronodular cirrhosis, 4-Portal fibrosis

b) 1-Macronodular cirrhosis, 2-Micronodular cirrhosis, 3-Alcoholic steatosis, 4-Alcoholic hepatitis

c) 1-Normal liver, 2-Alcoholic steatosis, 3- Micronodular cirrhosis, 4-Alcoholic hepatitis

d) 1-Normal liver, 2-Alcoholic hepatitis, 3-Macronodular cirrhosis, 4-Alcoholic steatosis

Question 31:

Match the following:

a) 1-C, 2-D, 3-A, 4-B

b) 1-B, 2-D, 3-A, 4-C

c) 1-D, 2-A, 3-B, 4-C

d) 1-B, 2-A, 3-D, 4-C

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Answer Key

Question No.	Correct Option
1	c
2	c
3	b
4	a
5	b
6	b
7	c
8	a
9	a
10	b
11	c
12	d
13	d
14	c
15	d
16	d
17	c
18	b
19	a
20	b
21	c
22	a
23	c
24	c
25	d
26	b
27	b
28	d
29	d
30	c
31	b

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d.

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Detailed Explanations

Solution to Question 1:

The given clinical scenario is suggestive of acute hepatocellular injury due to ischemia. Zone 3 (centrilobular zone) of the liver is most susceptible for ischemia because this zone is the farthest from the blood supply.

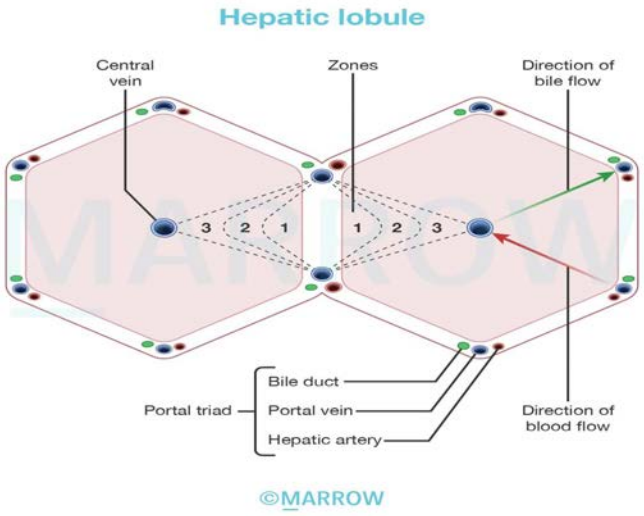
On the basis of blood flow, liver parenchyma can be divided into three zones. Zone 1 is closest to the blood supply and zone 3 is the farthest. They are:

• Zone 1 - Periportal (around portal triad)

• Zone 2 - Midzonal parenchyma

• Zone 3 - Centrilobular (around hepatic vein)

A schematic diagram showing the hepatic lobule indicating the direction of blood flow and the zones of decreasing oxygenation is given below.



Note: Zone most susceptible to toxin damage is zone 1.

Solution to Question 2:

Centrilobular necrosis is not seen in yellow fever. In yellow fever, swelling and necrosis of hepatocytes are seen in the midzone of the liver lobule.

Conditions causing tissue injury in the different zones of liver:

• Centrilobular (Zone 3)

• Chronic venous congestion (cardiac failure)

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• Acetaminophen toxicity

• Budd Chiari syndrome

• Ischemia

• Alcoholic hepatitis

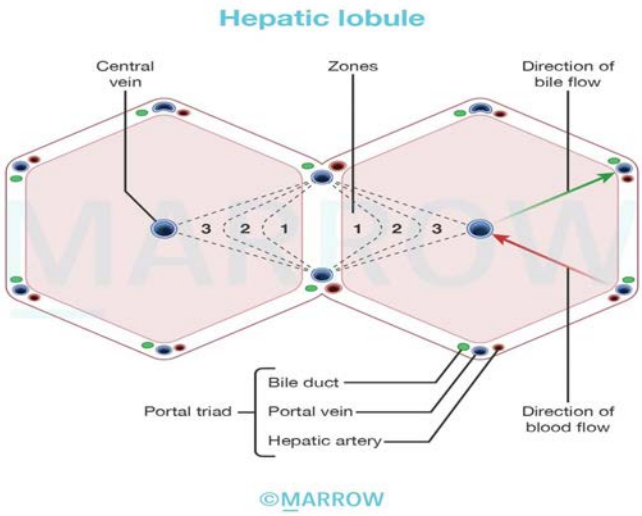
• Midzonal (Zone 2)

• Yellow fever

• Periportal (Zone 1)

• Viral hepatitis

A schematic diagram showing the hepatic lobule indicating the direction of blood flow and the zones of decreasing oxygenation is given below.



Solution to Question 3:

The principal cell type involved in scar deposition in cirrhosis of the liver is the hepatic stellate cell or Ito cell.

Hepatic stellate cells deposit primarily type I and type III collagen in the lobule and cause fibrosis. In their quiescent form, these cells store lipids and vitamin A.

Solution to Question 4:

Steatosis or fatty change of liver is not seen in hepatitis B infections.

Steatosis is the abnormal accumulation of triglycerides within a cell due to impaired lipid metabolism. In the liver, pathological steatosis is defined as fatty change involving >5% of hepatocytes. In the histologic sections, they appear as empty vacuoles within the hepatocyte

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cytoplasm.

Hepatitis C genotype 3 is reported to cause periportal steatosis. It is due to its association with metabolic syndrome and non-alcoholic fatty liver disease (NAFLD).

In Wilson's disease, there is focal hepatocyte necrosis and steatosis due to toxic injury by the excess copper.

In protein malnutrition, fatty liver results from the reduced synthesis of the carrier protein component of lipoproteins.

Solution to Question 5:

Macrovesicular fatty liver (steatosis) is seen in obesity.

Macrovesicular steatosis is characterized by a single, large vacuole of fat that fills up the hepatocyte and displaces the nucleus to the periphery. Causes include:

• Late alcoholic liver disease

• Obesity

• Protein-energy malnutrition

• Non-alcohlic steatohepatitis (NASH)

• Chronic hepatitis C

Microvesicular steatosis is characterized by small intracytoplasmic fat vacuoles, which accumulate in the cell. Causes include:

• Acute fatty liver of pregnancy

• Reye syndrome

• Early alcoholic liver disease

• Drugs and toxins

The image given below shows macrovesicular and microvesicular steatosis of liver:

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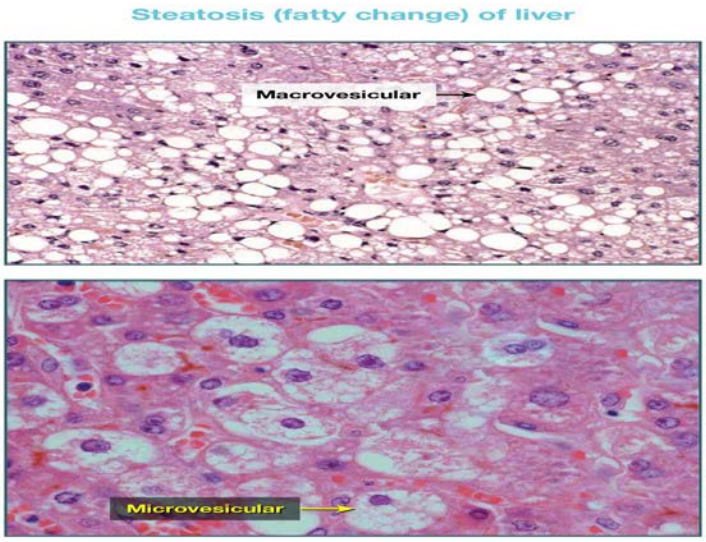

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Solution to Question 6:

The liver biopsy in Reye's syndrome will show marked microvesicular steatosis.

Reye's syndrome is an acute illness, encountered exclusively in children <15 years. Its onset usually follows upper respiratory tract infections. The actual cause is unknown, although viral agents and salicylates (aspirin) have been implicated.

Pathogenesis behind this condition is generalized mitochondrial dysfunction with structural and functional alterations of mitochondria in the liver, brain, and muscle. Liver is enlarged but jaundice is absent or minimum. It is characterized by clinical features such as:

• Vomiting

• Signs of progressive CNS damage

• Signs of hepatic injury

• Hypoglycemia

Extensive accumulation of fat droplets within hepatocytes (microvesicular steatosis) can be seen in histopathology. Extra-hepatic changes include fatty changes of renal tubular cells, cerebral edema, and neuronal degeneration of the brain.

The image given below shows microvesicular steatosis of liver.

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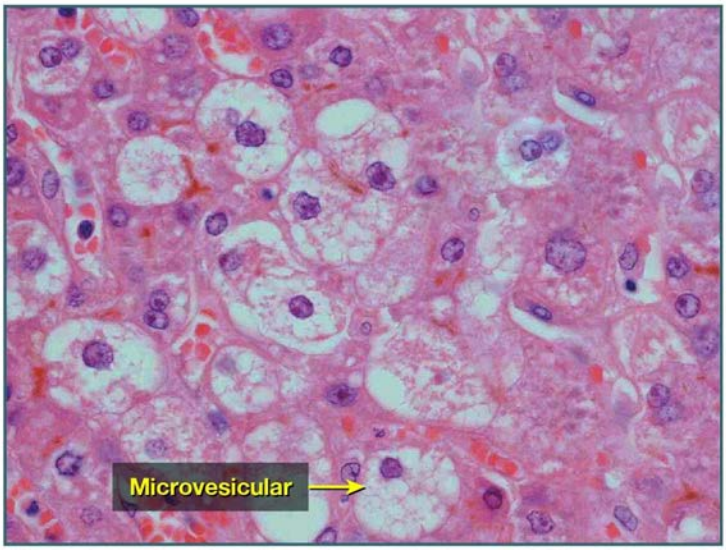

Note: Aspirin is generally contraindicated in children, except in the treatment of Kawasaki disease and juvenile idiopathic arthritis.

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Solution to Question 7:

The marked structure in the image is Mallory hyaline body which is not seen in primary sclerosing cholangitis. In this condition, onion skin fibrosis is seen.

Mallory hyaline bodies (Mallory–Denk bodies) are usually present as clumped, amorphous, eosinophilic material in ballooned hepatocytes. They are made up of cytokeratin 8 and cytokeratin 18. They have a twisted rope-like appearance. On trichrome stain, they appear green/dark brown. They are seen in:

- Alcoholic liver disease
- Non-alcoholic fatty liver disease
- Wilson's disease
- Hepatocellular carcinoma
- Alpha-1 antitrypsin deficiency
- Primary biliary cholangitis (formerly called primary biliary cirrhosis)
- Indian childhood cirrhosis

The image given below shows Mallory hyaline bodies.

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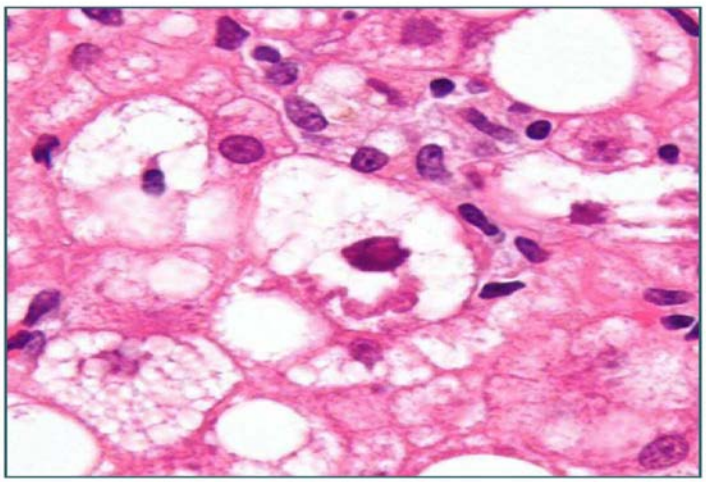
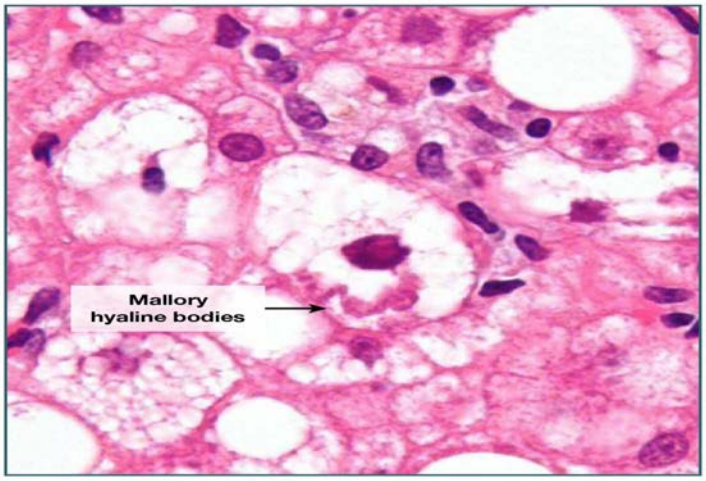
Mallory hyaline bodies



Mallory hyaline bodies



Solution to Question 8:

Laennec cirrhosis is the classic micronodular cirrhosis seen in end-stage alcoholic liver disease.

There are three distinctive, overlapping forms of alcoholic liver injury:

- Hepatic steatosis (fatty liver)
- Fatty change - completely reversible if there is abstention from further intake of alcohol
- Starts in centrilobular area
- Alcoholic (steato) hepatitis
- Ballooning degeneration and necrosis
- Mallory–Denk bodies

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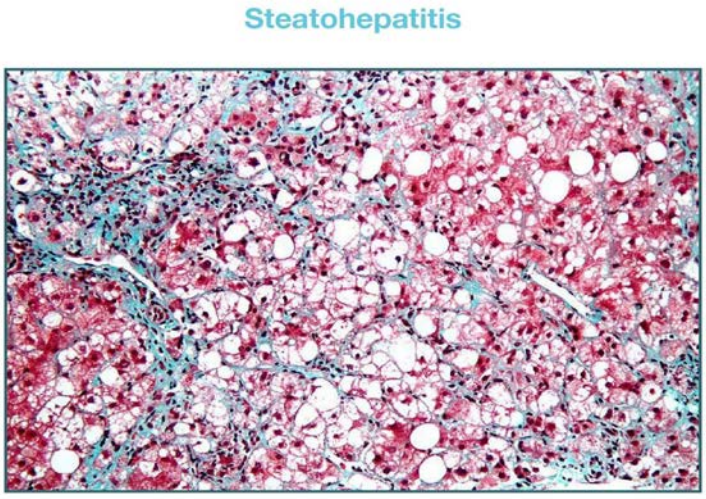
- Neutrophilic reaction
- Alcoholic steatofibrosis
- Perisinusoidal fibrosis and sclerosis of the central vein
- Diffuse nodularity of liver surface
- Micronodular/ Laennec cirrhosis
- Irreversible

Solution to Question 9:

Chicken-wire fence pattern of fibrosis is seen in the liver biopsy of patients with alcoholic steatohepatitis. This pattern is due to perisinusoidal fibrosis encircling small clusters of hepatocytes.

Trichrome staining of liver biopsy specimen showing perisinusoidal fibrosis (stained blue) in characteristic chicken-wire fence pattern is given below.



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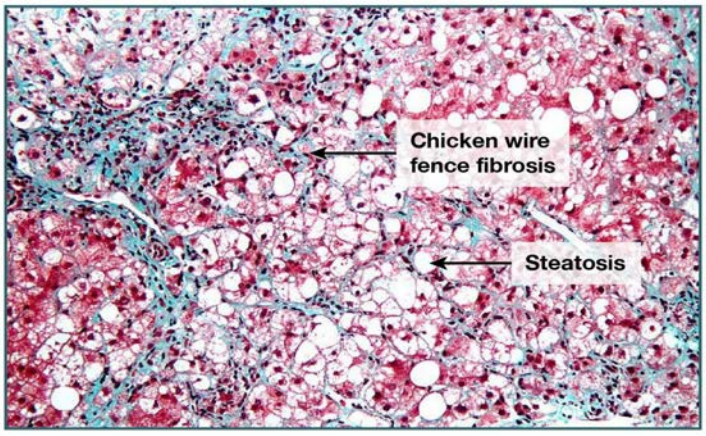
Steatohepatitis



Note: Other conditions with chicken-wire pattern in histopathology:

• Chicken wire calcification - chondroblastoma

• Chicken wire vasculature - oligodendroglioma and myxoid liposarcoma

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Solution to Question 10:

Viral hepatitis is associated with macronodular cirrhosis.

Cirrhosis is comprised of regenerating parenchymal nodules surrounded by dense bands of the scar and variable degrees of vascular shunting. It is of two types:

The images given below show gross and histopathological micronodular alcoholic cirrhosis.

Macronodular cirrhosis	Micronodular cirrhosis
Irregularnodules with variation insize>3 mm	Uniformnodules of size<3 mm
Causes:Chronicviral hepatitis Wilsons diseaseα1-antitrypsin deficiencyDrugs and toxins Hereditary hemorrhagic telangiectasiaCryptogenic cirrhosis	Causes:Alcoholic cirrhosisPrimary biliary cirrhosisHepatic vein obstructionLarge bile duct obstructionHemochromatosisIntestinal bypassCystic fibrosisIndian childhood cirrhosis

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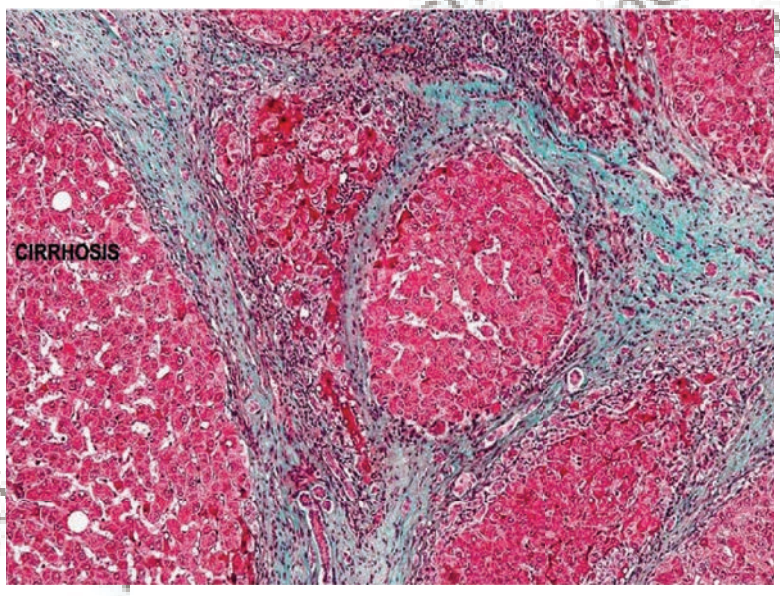

Solution to Question 11:

The presence of lymphoid follicles is not a feature on liver biopsy in patients with non-alcoholic steatohepatitis (NASH). It is a feature of chronic hepatitis C infection.

The histopathological features of NASH include:

- Ballooning degeneration of hepatocytes
- Steatosis
- Perisinusoidal inflammation and fibrosis
- Portal fibrosis
- Mallory-Denk bodies

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• Mononuclear infiltrate

NASH and alcoholic liver disease (ALD) have almost similar histopathological features. They can be differentiated as follows:

Features	ALD	NASH
Mallory-Denk bodies	More prominent	Less prominent
Fibrosis	Perivenular and perisinusoidal>portal	Portal fibrosis is more prominent
Inflammation	More pronounced	Less pronounced
Inflammatory cells	Neutrophils>macrophages	Macrophages>neutrophils

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Solution to Question 12:

The most common hepatotoxin causing acute liver failure is acetaminophen.

Acetaminophen itself is not toxic. The toxic metabolite produced by the cytochrome P-450 system in zone 3 hepatocytes causes hepatocellular necrosis.

The most common hepatotoxin causing chronic liver failure is alcohol.

Solution to Question 13:

Hepatitis A does not cause chronic infection. It is usually a benign, self-limited disease.

Hepatitis B, C, and D can cause chronic infection. Hepatitis E causes chronic infection only in immunocompromised individuals, not in immunocompetent.

Solution to Question 14:

Hepatitis A virus (HAV) can cause acute hepatic failure in a few patients. However, it does not cause chronic hepatitis or a carrier state.

HAV is a usually benign, self-limited disease, with an incubation period of 15- 50 days (2 - 6 weeks).

HAV is spread by feco-oral route and is shed in the stool for 2 to 3 weeks before and 1 week after the onset of jaundice. It can also spread by sexual route. Diagnosis is by the detection of serum IgM anti HAV.

Since it does not progress to chronic infection, it does not cause hepatocellular carcinoma. The fatality rate associated with HAV is only about 0.1-0.3%.

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Solution to Question 15:

Hepatitis E virus (HEV) infection accounts for most of the cases of sporadic acute hepatitis in India. It exceeds the frequency of hepatitis A virus infection.

A feature of HEV infection is the high mortality rate among pregnant women, approaching 20%.

Solution to Question 16:

HBx protein has been implicated in the pathogenesis of hepatocellular carcinoma in hepatitis B virus (HBV) infection. HBx protein is involved in the intracellular regulation of virus replication, transcription, and signal transduction.

Option A: HBsAg (surface antigen) indicates current hepatitis B infection.

Option B: HBeAg (precore antigen) is an indicator of active viral replication. It is a qualitative marker of infectivity.

Option C: HBV DNA polymerase is an indicator of active viral replication. It is a quantitative marker of infectivity.

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Solution to Question 17:

During the window period of hepatitis B, the serologic diagnosis can be made by the detection of IgM anti-HBc antibody.

The window period of hepatitis B refers to the time between the disappearance of the HBsAg antigen and appearance of Anti-HBs antibody.

The window period for a test designed to detect a specific disease is the time between the first infection and when the test can reliably detect that infection.

Solution to Question 18:

In patients who are both HBsAg and HBeAg positive, declining IgM anti-HBc and rising total anti-HBc are indicative of chronic infective hepatitis.

Anti-HBc IgM antibody signifies acute infection/window period, whereas, the presence of IgG anti-HBc indicates chronic infection. However, there is no test available to directly detect the IgG anti-HBC. Over a period of months, the IgM anti-HBc antibodies are replaced by the IgG anti-HBc antibodies. Thus a decline of IgM antibodies in the presence of rising total anti-HBC indicates that the IgM is being converted to IgG and thus the infection is chronic.

HBeAg, HBV-DNA, and DNA polymerase appear in serum soon after HBsAg, and all signify active viral replication.

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Occasionally, mutated strains of HBV emerge that do not produce HBeAg but are replication-competent and express HBcAg.

Solution to Question 19:

The age at the time of infection is the best predictor of chronicity. Younger the age at the time of hepatitis B virus (HBV) infection, higher the probability of chronicity.

Other predictors in the development of chronic disease:

• comorbid conditions (including exposure to other infectious agents)

• host immunity

Presentations of hepatitis B infection:

• Asymptomatic - 65%

• Non-specific symptoms - 25%

• Chronic disease - 5-10%

• Acute fulminant liver disease - 0.1-0.5%

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Solution to Question 20:

The given clinical scenario is suggestive of acute hepatitis B infection. Ground-glass hepatocytes are not seen in the liver biopsy of such patients.

Histopathological findings in acute hepatits are:

• Ballooning degeneration - due to inflammation

• Portal or lobular inflammatory infiltration - lymphocytes, plasma cells, and eosinophils

• Necrosis

• Confluent necrosis - group of hepatocytes

• Panlobular or panacinar necrosis - entire lobule

• Bridging necrosis (in severe cases) - connecting vascular structures

Ground-glass appearance of hepatocytes is due to the endoplasmic reticulum which is swollen with HBsAg accumulation. It is a diagnostic hallmark of chronic hepatitis B infection.

The image given below shows ground glass hepatocytes in the liver biopsy.

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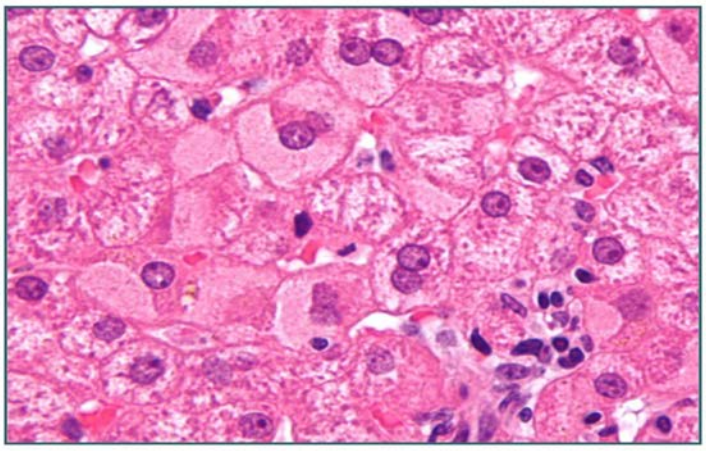
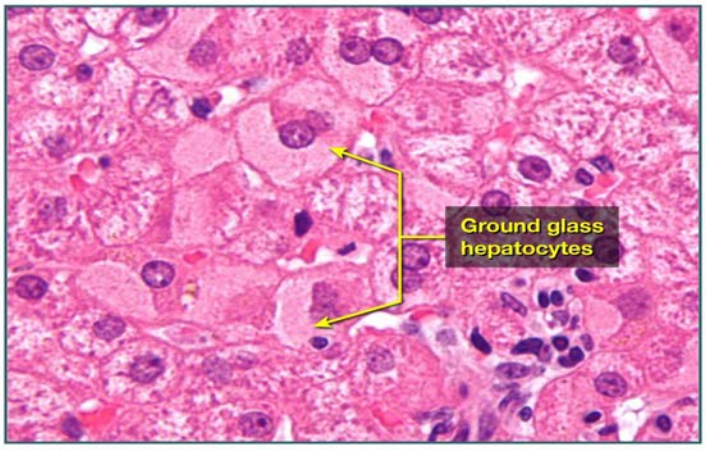
Chronic hepatitis B infection



Chronic hepatitis B infection



Solution to Question 21:

Intranasal cocaine abuse is a risk factor for hepatitis C.

Contaminated implements (like straws used to inhale cocaine) inserted into the nasal cavity might come into contact with hepatitis C virus (HCV)-infected mucus or blood. This might then be transmitted to a susceptible individual while sharing the same implements.

Transmission of hepatitis C infection:

• Intravenous drug abuse (54%) - Most common

• Multiple sex partners

• Needle-stick injury

• Multiple contacts with a person with hepatitis C virus infection

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• Employment in medical or dental fields

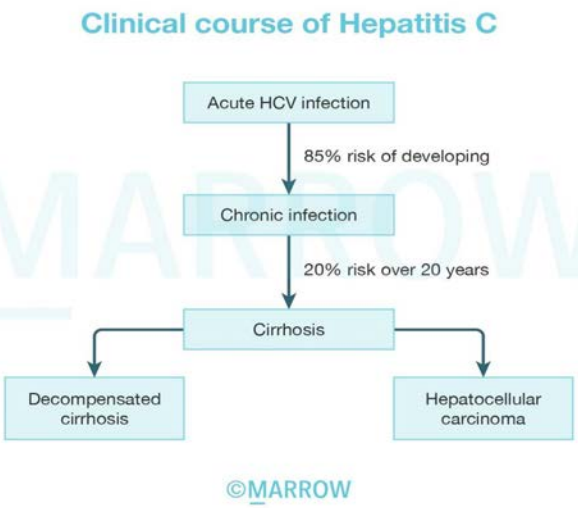
• Blood transfusion

• Perinatal - major route of infection in children

Solution to Question 22:

The most common clinical course seen in hepatitis C infection is chronic carrier state.

Acute clinical illness is often asymptomatic/mild with a high rate of conversion to chronic hepatitis (~85%).



Solution to Question 23:

Hepatitis C virus (HCV) genotype 3 is associated with metabolic syndrome.

HCV can give rise to insulin resistance and non-alcoholic fatty liver disease (NAFLD).

Solution to Question 24:

Ballooning degeneration is not associated with chronic hepatitis. It is seen in acute hepatitis.

Histopathological findings in chronic viral hepatitis are:

• Portal lymphocytic/ lymphoplasmacytic inflammation

• Interface activity - inflammatory cells cross the limiting plate and cause periportal hepatocyte injury

• Portal, periportal, and portoportal bridging fibrosis

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Specific findings in viral hepatitis:

- Hepatitis B - ground glass hepatocytes
- Hepatitis C - lymphoid aggregates and steatosis

Solution to Question 25:

Serum alkaline phosphatase is used to evaluate biliary excretory function. It is not used to evaluate the synthetic function of hepatocytes.

Serum ammonia, activated partial thromboplastin time (aPTT), and serum albumin are used to evaluate hepatic synthetic function.

Prothrombin time (PT), aPTT and serum ammonia levels are increased in liver failure, whereas serum albumin level is decreased.

Solution to Question 26:

Macronodular cirrhosis is not seen in the histopathological examination of patients with malaria.

Histopathological changes in the liver in cases of malaria include the following:

- Kupffer cell hyperplasia
- Hemozoin pigment deposition within Kupffer cells and macrophages
- Focal necrosis
- Mild mononuclear portal infiltrate
- Fatty change and periportal inflammation

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Solution to Question 27:

Councilman bodies are apoptotic hepatocytes seen in acute hepatitis and yellow fever.

Option A: Mallory–Denk bodies are eosinophilic materials made of keratin intermediate filaments. They are seen in alcoholic liver disease, non-alcoholic fatty liver disease, Wilson's disease, and chronic biliary tract diseases.

Option C: Ground-glass hepatocytes are liver cells that have eosinophilic granular, glassy cytoplasm seen on light microscopy. The appearance is due to the swelling of the endoplasmic reticulum by HBsAg and is a diagnostic hallmark of chronic hepatitis B.

Option D: Circumferential onion skin fibrosis around a degenerating bile-duct lumen is seen in primary sclerosing cholangitis.

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Solution to Question 28:

Obstructive portal vein thrombosis is the prehepatic cause of portal hypertension.

Non-alcoholic fatty liver disease, cirrhosis, and schistosomiasis are intrahepatic causes of portal hypertension. The most dominant cause is cirrhosis.

Solution to Question 29:

Bridging fibrosis is not seen in non-cirrhotic portal fibrosis. In this condition, there is periportal and perisinusoidal fibrosis. The fibrous septa end blindly in the lobule and do not bridge with other portal tracts, unlike those seen in cirrhosis.

Idiopathic non-cirrhotic portal hypertension (INCPH) is a rare disease characterized by intrahepatic portal hypertension in the absence of cirrhosis or other causes of liver disease and splanchnic venous thrombosis.

A liver biopsy is essential in making a diagnosis of INCPH. The features observed are as follows:

• Luminal narrowing or obliteration of portal vein branches

• Micronodular transformation

• Sinusoidal dilatation with formation of mega sinusoids

• Periportal and perisinusoidal fibrosis

Solution to Question 30:

In the given image, images marked 1 is normal liver, 2 is alcoholic steatosis, 3 is micronodular cirrhosis and 4 is alcoholic hepatitis.

Histopathological findings in the following conditions are:

• Alcoholic steatosis:

• A mix of small and large fat droplets

• Ethanol inhibits fatty acid metabolism, leading to lipolysis and increased triglyceride. These triglycerides accumulate and cause steatosis. Liver enzymes are normal at this stage.

• Micronodular cirrhosis:

• The average nodule size is 3 mm in this close-up view, which is typical of the micronodular cirrhosis of alcoholic liver disease

• Alcoholic hepatitis:

• Mallory-Denk bodies - clumped, amorphous, eosinophilic material in ballooned hepatocytes. These inclusions are characteristic, but not a specific feature of alcoholic liver disease.

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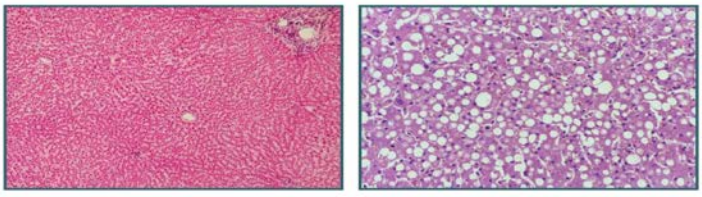
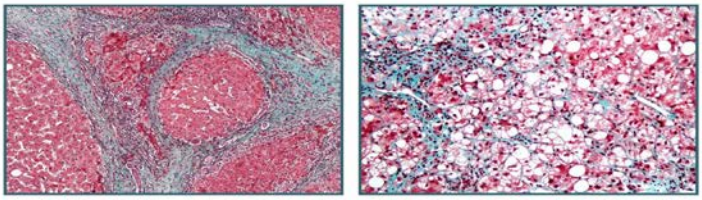


Normal liver | Alcoholic Steatosis



Micronodular Cirrhosis | Alcoholic Hepatitis

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Solution to Question 31:

The liver findings seen in the hepatotoxic drugs are:

Drugs	Liver findings
Valproate	Microvesicular steatosis
Allopurinol	Fibrin ring granuloma
Amiodarone	Mallory-Denk bodies
Isoniazid	Noncaseating epitheloid granulomas

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Autoimmune and Metabolic Liver Disease

Question 1:

Mutation in which of the following genes causes Wilson's disease?

a) ADP 7B

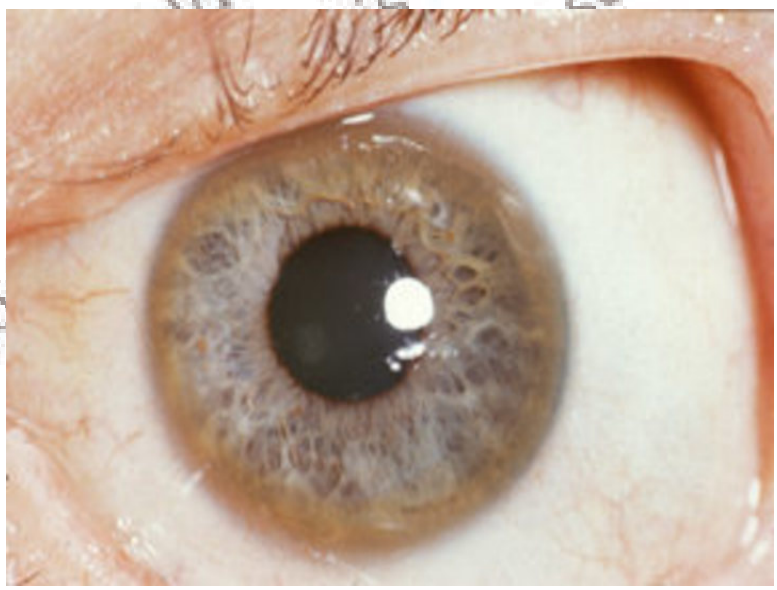
b) ADP 7A

c) ATP 7A

d) ATP 7B

Question 2:

A 35-year-old man with tremors and chronic hepatitis is found to have the following ophthalmic finding. This patient is also likely to have which of the following?



a) Pulmonary hypoplasia

b) Islet cell atrophy

c) Cerebellar atrophy

d) Basal ganglia atrophy

Question 3:

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Which of the following would you use to screen an asymptomatic sibling of a patient with Wilson's disease?

a) Serum ceruloplasmin levels

b) Genetic testing for ATP7B gene

c) Hepatic tissue copper

d) 24-hour urinary excretion of copper

Question 4:

A 30-year-old male patient presented with personality changes and jaundice. Slit-lamp examination confirmed the diagnosis of Wilson's disease. Which of the following statements is true regarding the condition?

a) Ceruloplasmin in blood increases and urinary copper excretion decreases

b) Ceruloplasmin in blood decreases and urinary copper excretion decreases

c) Ceruloplasmin in blood increases and urinary copper excretion increases

d) Ceruloplasmin in blood decreases and urinary copper excretion increases

Question 5:

Which of the following stains can be used to demonstrate excess copper deposition in Wilson's disease?

a) Prussian blue stain

b) Orcein stain

c) Rhodanine stain

d) Periodic acid Schiff stain

Question 6:

A 55 yr old man is found to have hepatomegaly on physical examination. He also complains of dark tan despite avoiding sun exposure. His liver microscopy is given on the slide below. This patient most likely suffers from _____

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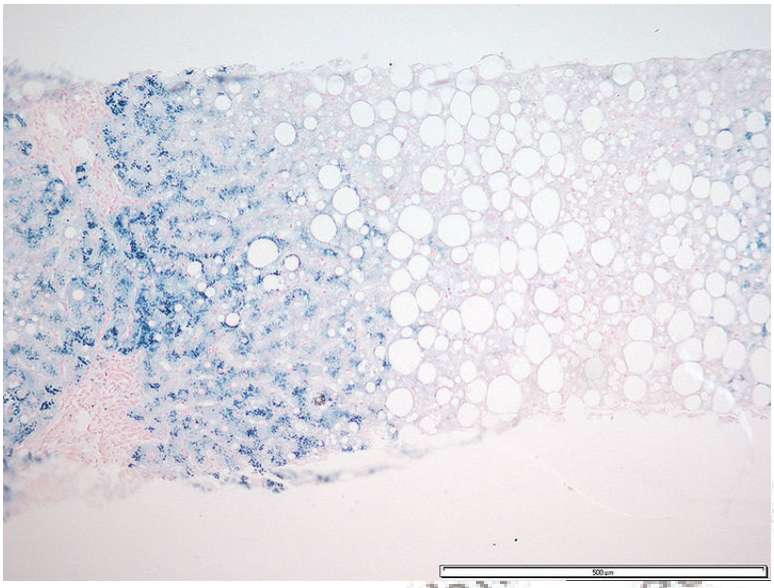

a) Wilson's disease

b) Autoimmune hepatitis

c) Alpha-1 antitrypsin deficiency

d) Hemochromatosis

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Question 7:

A patient with hereditary hemochromatosis is found to have a mutation in the HFE gene. On which chromosome is it located?

a) Chromosome 6

b) Chromosome 10

c) Chromosome 13

d) Chromosome 7

Question 8:

A 34-year-old man evaluated for chronic abdominal pain is found to have hepatomegaly and serum ferritin level of 1800 micro g/l. Which of the following complications is he at the greatest risk of developing?

a) Fat malabsorption and osteoporosis

b) Basal ganglia atrophy

c) Hepatocellular carcinoma

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d) Hepatic decompensation

Question 9:

Which of the following is true regarding hemochromatosis?

a) 2, 3 and 5

b) 3, 4 and 5

c) 1, 3 and 4

d) 1, 2 and 4

Question 10:

Which of the following organs does not show hemosiderin deposits in hemochromatosis?

a) Testis

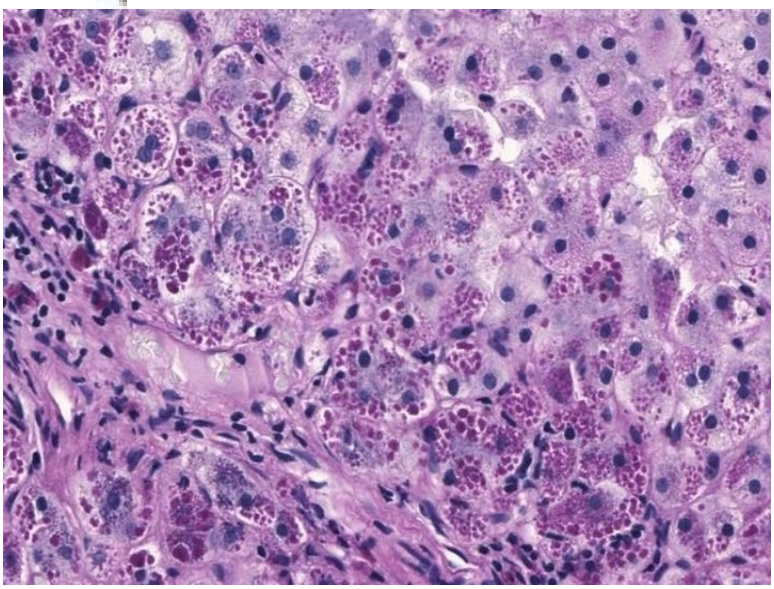
b) Pituitary

c) Heart

d) Skin

Question 11:

A 35-year-old male patient with emphysema was found to have elevated liver transaminases. His liver biopsy image is given below. What is the most likely diagnosis?



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a) Primary biliary cirrhosis

b) Hemochromatosis

c) Alpha-1 antitrypsin deficiency

d) Primary sclerosing cholangitis

Question 12:

On which chromosome is the gene for alpha-1 antitrypsin present?

a) 6

b) 14

c) 21

d) 7

Question 13:

What is the most common clinically significant mutation causing alpha-1 antitrypsin deficiency?

a) PiMM

b) PiZ

c) Pi-null

d) PiS

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Question 14:

An 11-year-old girl with persistently elevated serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) has been diagnosed with autoimmune hepatitis. Which of the following pathological features would you not expect in this patient?

a) Interface hepatitis

b) Rosette formation

c) Emperipolesis

d) Bile duct injury and granulomas

Question 15:

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Which of the following statements is false with regard to autoimmune hepatitis?

a) Type 2 autoimmune hepatitis shows antinuclear antibodies (ANA).

b) It is associated with HLA-DR.

c) It can progress to liver failure.

d) Inflammatory infiltrate is predominantly composed of plasma cells.

Question 16:

Which of the following antibodies would you not expect to see in a patient with autoimmune hepatitis?

a) Anti-TIF1γ antibodies

b) ANA

c) ASMA

d) Anti-LKM

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Question 17:

Identify the incorrect match.

a) LKM 1-Autoimmune hepatitis

b) LKM 2-Drug-induced hepatitis

c) LKM 1-Chronic hepatitis C

d) LKM 2-Chronic hepatitis D

Question 18:

The histopathological findings obtained after a liver biopsy is given below. What would be the most probable diagnosis?

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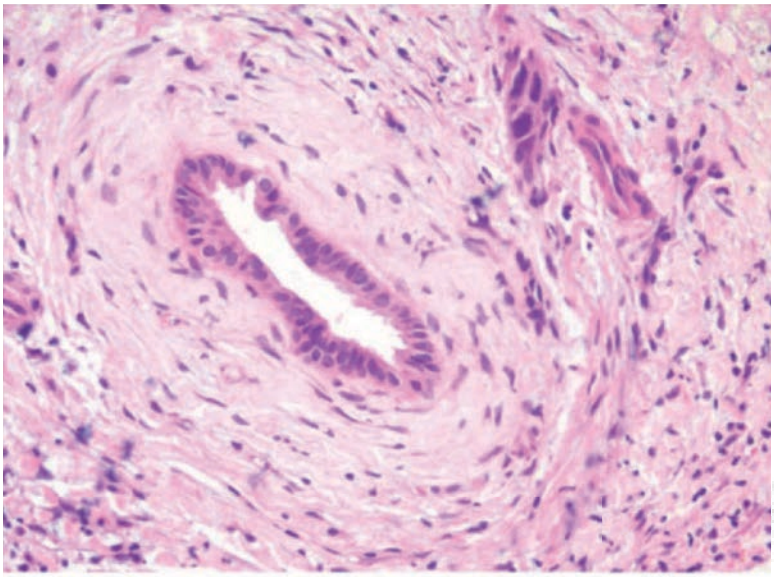

a) Mirizzi syndrome

b) Primary sclerosing cholangitis

c) Primary billiary cholangitis

d) Post radiation therapy

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Question 19:

Which of the following is not a feature of primary sclerosing cholangitis?

a) Affects males > females

b) Shows ANCA positivity

c) Shows beading on radiology

d) Only affects extra-hepatic ducts

Question 20:

Primary biliary cholangitis is most commonly associated with which of the following conditions?

a) Sjogren syndrome

b) Ulcerative colitis

c) Scleroderma

d) Crohn's disease

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Answer Key

Question No.	Correct Option
1	d
2	d
3	b
4	d
5	c
6	d
7	a
8	c
9	d
10	a
11	c
12	b
13	b
14	d
15	a
16	a
17	d
18	b
19	d
20	a

Detailed Explanations

Solution to Question 1:

Wilson's disease is caused due to a loss-of-function mutation in the ATP7B gene. It an autosomal recessive condition.

The ATP7B gene is located on chromosome 13q. The gene encodes a copper transporting ATPase (ATP7B) which has 2 functions:

• Maintains copper in bound form by binding copper to apoceruloplasmin

• Helps excrete free copper in bile.

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The resulting ATP7B deficiency leads to reduced bound copper and impaired free copper excretion. This causes excess deposition of free copper in the tissues, particularly in the liver, brain and eye.

Menkes disease is an X-linked recessive condition leading to impaired absorption of copper and subsequent copper deficiency. Here, the mutation is in the ATP7A gene.

Solution to Question 2:

The given image shows the Kayser-Fleischer ring. This,along with the background of hepatitis and neuropsychiatric features is characteristic of Wilson's disease. The patient is thus likely to have basal ganglia atrophy.

In the majority of cases, neuropsychiatric manifestations follow hepatic manifestations. It is due to the deposition of free copper in the basal ganglia and cortex. Free copper deposition in the basal ganglia leads to bilateral degeneration and atrophy.

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Solution to Question 3:

Genetic testing for the ATP7B gene is used to screen asymptomatic 1st and 2nd-degree relatives of patients with Wilson's disease. This helps to differentiate the heterozygous from the homozygous individuals. This can be useful in the early initiation of treatment before the onset of symptoms.

Low serum ceruloplasmin, raised 24 hr urinary copper and Kayser-Fleischer rings are diagnostically helpful.

Estimation of hepatic tissue copper is the gold standard for diagnosis. It is measured using neutron activation analysis / atomic absorption spectrometry.

Solution to Question 4:

The ceruloplasmin level in the blood decreases, and the copper content in urine increases in Wilson's disease.

Lab markers	Change in Wilson's disease	Reason
Serum ceruloplasmin	↓↓	ATP7B deficiency results in reduced bound copper
24h urinary copper	↑↑	Excess free copper excreted in urine

Solution to Question 5:

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Excess copper deposition in Wilson's disease is demonstrated by rhodanine stain.

Microscopic findings in Wilson's disease include:

• Fatty infiltration (macrovesicular)

• Glycogen deposition in periportal hepatocytes

• Macronodular cirrhosis in decompensated stages.

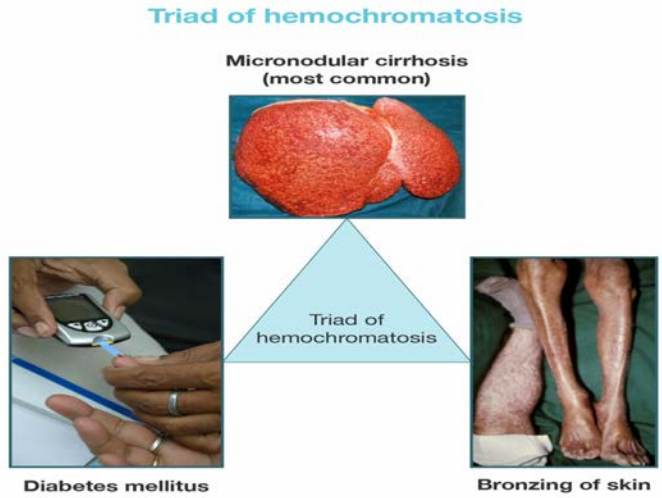
Orcein stain is used to stain copper-associated proteins (eg: ceruloplasmin).

Solution to Question 6:

The patient most likely suffers from hemochromatosis. In the given scenario, the liver microscopy image shows hepatocellular iron, which is stained blue with Perl's Prussian blue stain.

Hemochromatosis is an inherited or acquired metabolic disorder caused by excessive iron absorption. Iron overload leads to the accumulation of iron in parenchymal organs such as the liver and pancreas followed by the heart, joints, and endocrine organs.

The image below shows the triad of haemochromatosis.



The image below is the liver microscopy image showing hepatocellular iron, stained with Perl's Prussian blue.

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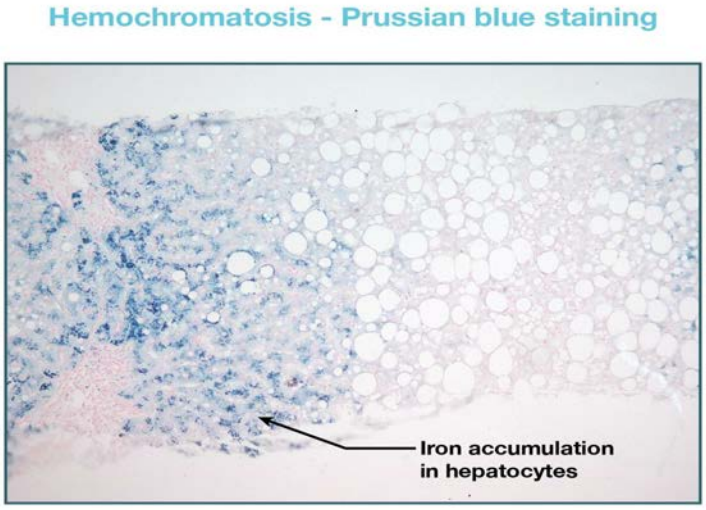

The total body iron pool ranges from 2 to 6 gm in normal adults. In hemochromatosis, total iron accumulation may exceed 50 gm, more than one-third of which accumulates in the liver.

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Solution to Question 7:

HFE gene is located on the short arm of chromosome 6 (6p). It is the most commonly mutated gene in patients with hereditary hemochromatosis.

HFE encodes an HLA class I–like molecule that regulates the synthesis of hepcidin in hepatocytes. The most common HFE mutation is a cysteine-to-tyrosine substitution at amino acid 282 (C282Y).

Solution to Question 8:

The given clinical scenario is suggestive of hemochromatosis. A patient with hemochromatosis is at risk of developing hepatocellular carcinoma.

Hepatocellular carcinoma is a significant cause of death in hemochromatosis. The risk is much greater than in the general population.

The disease progression of hemochromatosis is as shown below:

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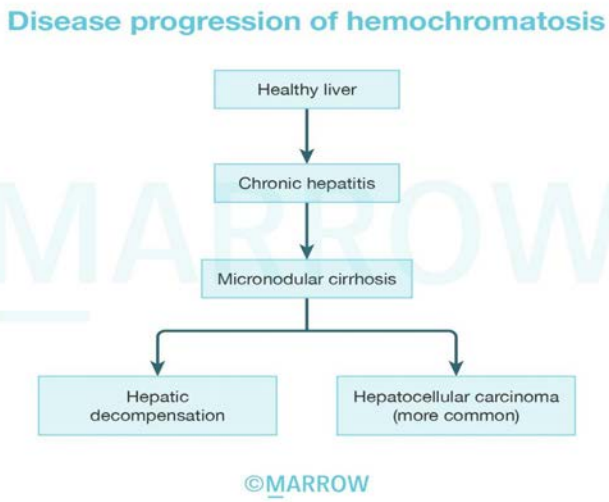

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Solution to Question 9:

Neonatal hemochromatosis is not an inherited disease. It is a disease of unknown origin manifested by severe liver disease and extrahepatic hemosiderin deposition. It might be related to maternal alloimmune injury to the fetal liver.

Adult hemochromatosis is generally a milder disease than the juvenile form. With treatment, life expectancy is normal.

Bantu siderosis or African iron overload is due to dietary iron overload. Consumption of beer prepared in iron pots or drums is the cause of dietary iron overload.

Skin pigmentation in hemochromatosis mostly results from increased melanin synthesis. This is due to iron deposition and not hemosiderin deposition.

In severe hemochromatosis, total iron accumulation may exceed 50 gm. More than one-third of this accumulates in the liver. In normal adults, it is in the range of 2 to 6 gms.

Solution to Question 10:

The testes do not show hemosiderin deposits in hemochromatosis.

Hypogonadism in hemochromatosis is not due to the deposition of iron in the testis. It is due to a derangement in the hypothalamic-pituitary axis. This results in decreased gonadotrophins and testosterone levels. The testis will appear small and atrophic.

Deposition of hemosiderin is seen in the following organs in the decreasing order of severity:

- Liver
- Pancreas
- Myocardium

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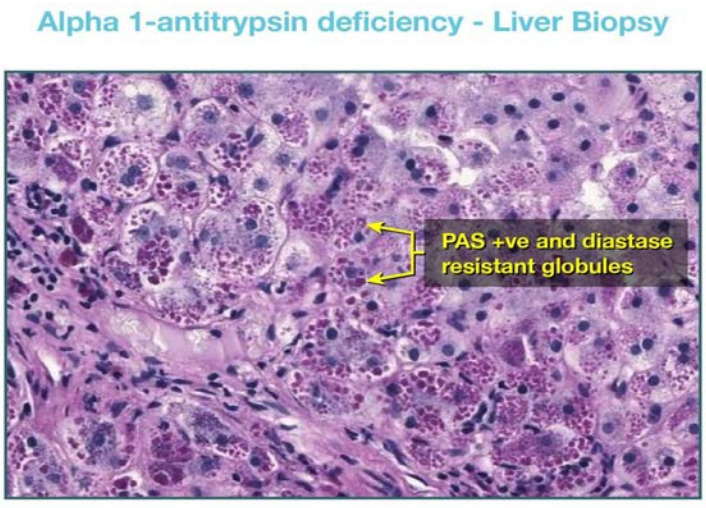
- Pituitary gland
- Adrenal gland
- Thyroid
- Parathyroid gland
- Joints
- Skin

Solution to Question 11:

In the given clinical scenario, the most likely diagnosis is alpha-1 antitrypsin deficiency. The liver biopsy image shows periodic acid–Schiff (PAS)-positive and diastase-resistant round-to-oval cytoplasmic globular inclusions in hepatocytes. These are characteristic of alpha-1 antitrypsin deficiency.

It is an autosomal-recessive disorder of protein misfolding that results in impaired secretion of α1 antitrypsin into the serum. α1AT deficiency results in excessive degradation of alveoli by neutrophil elastase causing panacinar emphysema. It also causes liver disease as a consequence of an abnormal accumulation of the misfolded protein within hepatocytes. Cutaneous necrotizing panniculitis also occurs in a minor subset of patients. Hepatocellular carcinoma develops in 2% to 3% of cases.

The image given is a photomicrograph of a liver biopsy from a patient with alpha-1 antitrypsin deficiency. The PAS with diastase stain shows the diastase-resistant pink globules that are characteristic of this disease.



Solution to Question 12:

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The gene for alpha-1 antitrypsin is located on the long arm of chromosome 14. Alpha-1 antitrypsin is a plasma glycoprotein synthesized predominantly by hepatocytes.

For α1-antitrypsin genes, the general notation is “Pi” for “protease inhibitor." An alphabetic letter is given for the position on the isoelectric gel.

This gene has different alleles that produce different amounts of alpha-1 antitrypsin (AAT).

• M allele - normal levels of the AAT protein

• S allele - moderately low levels

• Z allele - very low levels

The alleles are expressed in a codominant manner.

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Solution to Question 13:

The most common clinically significant mutation causing α1-antitrypsin deficiency is PiZ. Homozygous individuals, with PiZZ, have only 10% of normal circulating α1-antitrypsin. So, they are at high risk of developing clinical disease.

PiMM is the most common genotype seen in normal individuals, present in about 90% of individuals.

PiS variant is clinically asymptomatic.

Pi-null is a rare variant with no detectable serum alpha-1 antitrypsin.

Solution to Question 14:

Bile duct injury and granulomas are uncommon in autoimmune hepatitis except in case of overlap with primary biliary cirrhosis.

Autoimmune hepatitis (AIH) is characterised by extensive inflammation, fibrosis and ultimately cirrhosis. The pathologic features include:

• Emperipolesis - Lymphocytes and plasma cells within the cytoplasm of hepatocytes.

• Interface hepatitis or piecemeal necrosis.

• Rosette formation due to necrosis of groups of hepatocytes and resultant regeneration.

The image given below shows autoimmune hepatitis with lymphoplasmacytic interface hepatitis.

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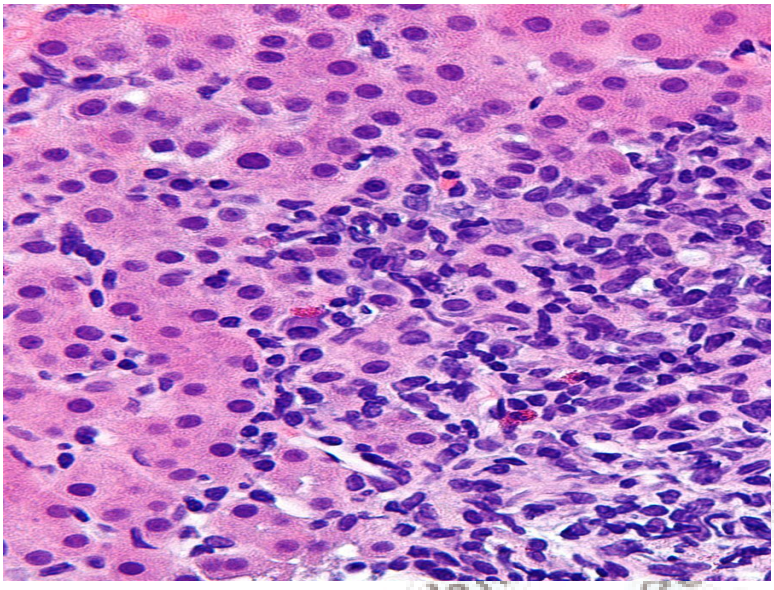
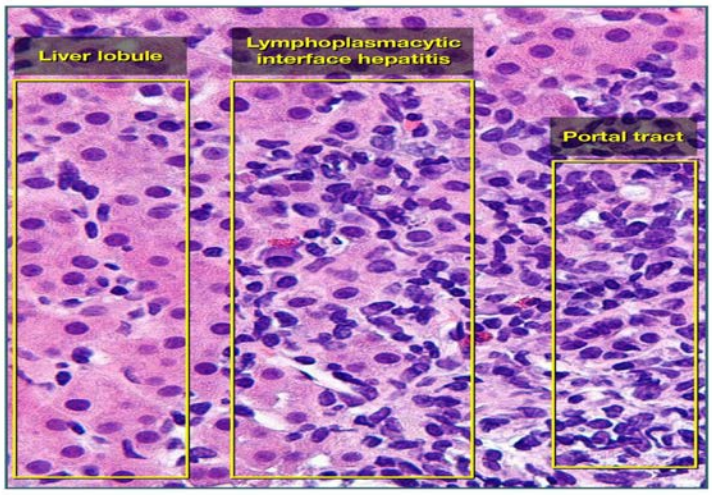


Autoimmune hepatitis



Solution to Question 15:

Type 2 autoimmune hepatitis shows anti-liver kidney microsomal autoantibodies (anti-LKM1) and anti–liver cytosol-1 (ACL-1) antibodies not ANA.

Type 1 autoimmune hepatitis shows anti-nuclear (ANA), anti-smooth muscle antibodies (ASMA) and anti–soluble liver antigen / liver pancreas antigen (anti-SLA/LP) antibodies. It less commonly shows anti-mitochondrial (AMA) antibodies.

Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular necrosis and inflammation. It can progress to cirrhosis and liver failure.

Histocompatibility haplotypes such as HLA-B1, HLA-B8, HLA-DR3, and HLA-DR4 are common in patients with autoimmune hepatitis.

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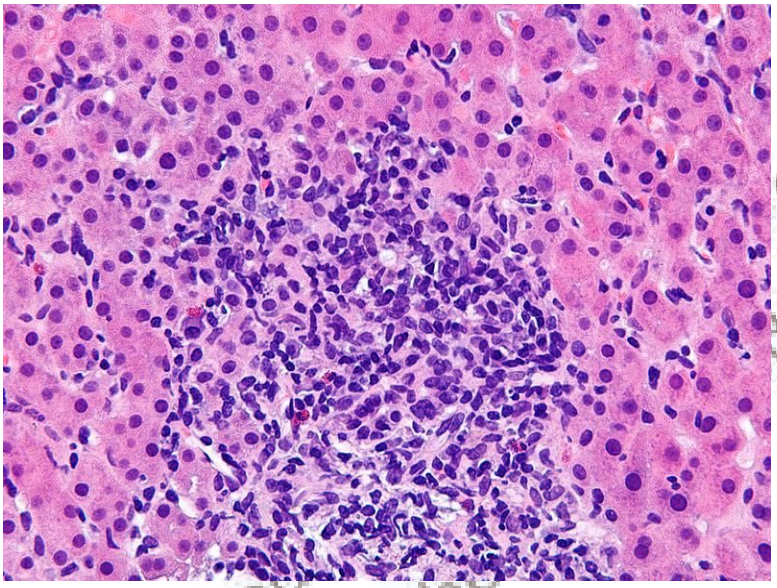
Histopathological features include:

• Plasma cell predominance in inflammatory infiltrates

• Extensive interface hepatitis (piecemeal necrosis)

• Hepatocyte rosettes

The image given below shows autoimmune hepatitis showing characteristic lymphoplasmacytic infiltrate and interface hepatitis.



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Solution to Question 16:

Anti-TIF1γ antibodies are not associated with autoimmune hepatitis. Anti-TIF1γ antibodies are found in patients with dermatomyositis.

Solution to Question 17:

Chronic hepatitis D is associated with anti-LKM 3 antibodies.

Solution to Question 18:

Onion-skin fibrosis is seen in primary sclerosing cholangitis.

The smaller ducts in primary sclerosing cholangitis show a striking circumferential “onion skin” fibrosis around an increasingly atrophic duct lumen. This eventually leads to the obliteration by a “tombstone” scar.

The image shows primary sclerosing cholangitis. There is a degenerating bile duct that is entrapped in the dense concentric onion-skin fibrosis.

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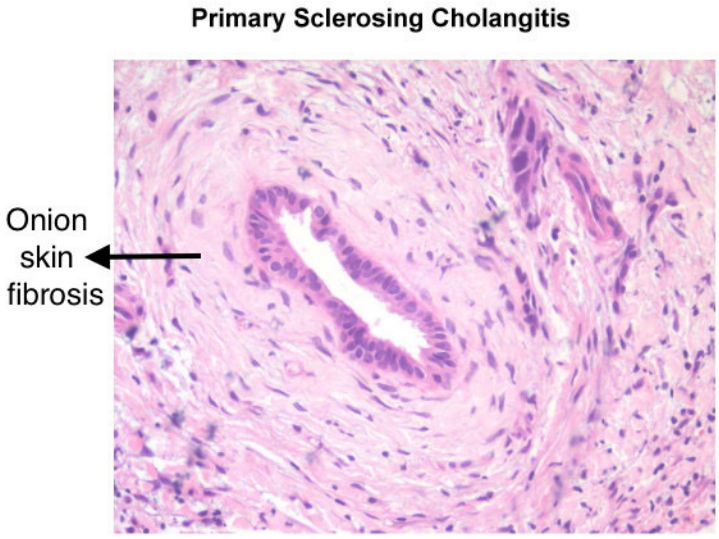

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Solution to Question 19:

Primary sclerosing cholangitis is characterized by inflammation and obliterative fibrosis of intrahepatic and extrahepatic bile ducts. There is dilation of preserved segments.

On histopathologic examination, large ducts show acute neutrophilic inflammation of the epithelium. The inflamed areas develop strictures. Small ducts show onion-skin fibrosis around the atrophic duct lumen. There is an obliteration of ducts by a tombstone scar.

Solution to Question 20:

Primary biliary cholangitis is most commonly associated with Sjogren's syndrome. Other associated conditions are:

- Thyroiditis
- Scleroderma
- Rheumatoid arthritis
- Raynaud phenomenon
- Celiac disease

PBC is an autoimmune disease. It is characterized by nonsuppurative, inflammatory destruction of small and medium-sized intrahepatic bile ducts. Large intrahepatic ducts and the extrahepatic biliary tree are not involved. It is a disease of middle-aged women, with a female predominance of 9:1. Antimitochondrial antibodies are the most characteristic laboratory finding in PBC.

Histopathologic examination shows diagnostic florid duct lesions. These are lymphoplasmacytic infiltrates with or without granulomas centred around the bile duct. They also show Mallory–Denk bodies.

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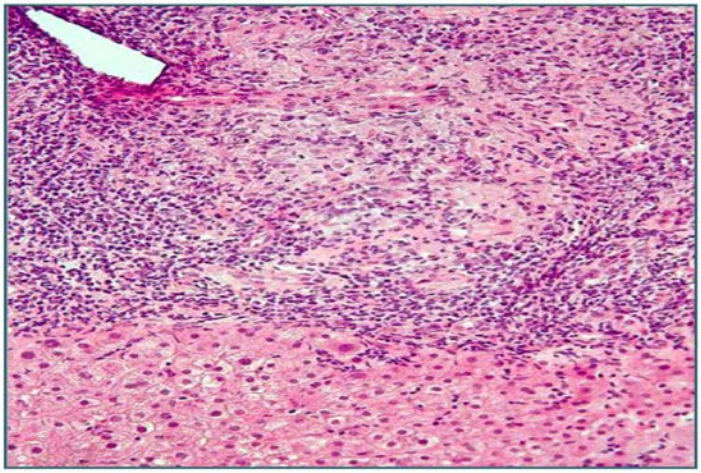
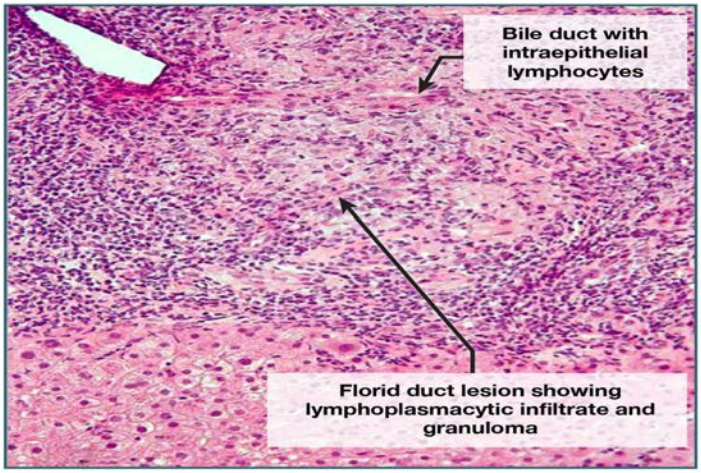
The image given below shows primary biliary cholangitis.

Primary biliary cholangitis



Primary biliary cholangitis



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Neoplasms of Liver and Biliary tract

Question 1:

Which of the following is the most common benign tumor of the liver?

a) Liver cell adenoma

b) Focal nodular hyperplasia

c) Cavernous hemangioma

d) Hepatoma

Question 2:

A 30-year-old woman presents with a history of abdominal pain. She has been taking oral contraceptives for the past 7 years. CECT reveals an isodense lesion in the liver with homogenous enhancement in the arterial phase and washout in the portal venous phase. Which of the following statements is incorrect regarding this condition?

a) It may rupture spontaneously

b) It can be associated with MODY-3

c) Serum amyloid A may be upregulated

d) °-catenin-activated adenoma has no risk of malignant transformation

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Question 3:

Patients with cirrhosis of the liver are at a higher risk of developing which of the following?

a) Focal nodular hyperplasia

b) Hepatocellular adenoma

c) Dysplastic nodule

d) Fibrolamellar carcinoma

Question 4:

A 2-year-old boy is brought with abdominal swelling. On examination, a mass is palpable in the right upper quadrant. Laboratory evaluation shows serum alpha-fetoprotein level of

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1,50,000 ng/mL. What is the likely diagnosis?

a) Hepatocellular Carcinoma

b) Hepatoblastoma

c) Wilms tumour

d) Extragonadal germ cell tumor

Question 5:

Patients with all of the following are at a higher risk of developing hepatoblastoma except:

a) A 6-year-old child diagnosed with new-onset hypertension

b) A premature infant with low birth weight

c) A 5-year-old child diagnosed with Beckwith-Wiedemann syndrome

d) A 9-year-old child with a family history of familial adenatomatous polyposis

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Question 6:

Which of the following parameters indicates a good prognosis in hepatoblastoma?

a) Low alpha-fetoprotein levels

b) Small-cell undifferentiated histology

c) Low birth weight

d) Pure fetal histology

Question 7:

Which one of the following syndromes is associated with a higher incidence of hepatoblastoma?

a) Hereditary tyrosinemia

b) Gardner syndrome

c) Familial hemochromatosis

d) Alpha-1 antitrypsin deficiency

Question 8:

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Which of the following is the most common cause of hepatocellular carcinoma?

a) Chronic hepatitis B infection

b) Chronic hepatitis C infection

c) Alcohol

d) Smoking

Question 9:

Which of the following are the precursor lesions for hepatocellular carcinoma?

a) 1, 3, 4

b) 2, 3, 5

c) 1, 3, 5

d) 1, 2, 4

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Question 10:

A 25-year-old woman presents with chronic abdominal discomfort. Imaging reveals a solitary well-encapsulated hepatic mass with a central fibrous scar and stellate calcification. Further investigations reveal elevated neurotensin levels and negative hepatitis B serology. Which of the following is incorrect regarding this condition?

a) Histology reveals oncocytic hepatocytes separated by collagen bundles

b) It is associated with a relatively good prognosis

c) Majority of these tumors are resectable

d) It is associated with liver cirrhosis

Question 11:

Which of the following agents is not associated with the development of hepatic angiosarcoma?

a) Arsenic

b) Vinyl chloride

c) Thorotrast

d) Benzene

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Question 12:

Which of the following is the most common tumor of the liver?

a) Hepatocellular carcinoma

b) Cavernous hemangioma

c) Metastatic tumor

d) Hepatic adenoma

Question 13:

A 53-year-old patient with anorexia and weight loss is found to have non-tender hepatomegaly on physical examination. CT scan of the abdomen shows multiple nodules in the liver and investigations reveal elevated ALP and AST levels, with no elevations in AFP. Which of the following is the most likely cause?

a) Hepatic adenoma

b) Hepatocellular carcinoma

c) Cholangiocarcinoma

d) Metastatic liver tumor

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Question 14:

Patients with which of the following conditions are not at risk for cholangiocarcinoma?

a) Non-alcoholic fatty liver disease

b) Primary sclerosing cholangitis

c) Typhoid carrier state

d) Chronic hepatitis B infection

Question 15:

What does Klatskin tumor refer to?

a) Extrahepatic cholangiocarcinoma

b) Fibrolamellar hepatocellular carcinoma

c) Intrahepatic cholangiocarcinoma

d) Gall bladder adenocarcinoma

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Question 16:

Which of the following statements is incorrect regarding gallbladder carcinoma?

a) The common type is adenocarcinoma

b) Gallstones are the most important risk factor

c) Her2 overexpression is seen in about 2/3 of the cases

d) It usually has a good prognosis

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Answer Key

Question No.	Correct Option
1	c
2	d
3	c
4	b
5	a
6	d
7	b
8	a
9	d
10	d
11	d
12	c
13	d
14	c
15	a
16	d

Detailed Explanations

Solution to Question 1:

Cavernous hemangioma is the most common benign tumor of the liver.

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It appears as a red-blue, soft nodule, usually < 2 cm in diameter. It may be mistaken radiographically or intraoperatively for a metastatic tumor.

Solution to Question 2:

The given clinical scenario is suggestive of hepatic adenoma. °-catenin-activated adenomas have a high risk of malignant transformation.

Hepatic adenomas are benign tumors of hepatocytes. Spontaneous rupture of the hepatic adenoma may cause intraabdominal bleeding, which is a surgical emergency.

Hepatic adenomas are classified into 3 subtypes:

• HNF1-α-inactivated adenomas -

• No risk of malignant transformation

• Often associated with oral contraceptive pill use (OCP) and MODY-3

• °-catenin-activated adenoma -

• High risk of malignant transformation

• Associated with oral contraceptive pills (OCP) and anabolic steroids usage

• Inflammatory adenomas -

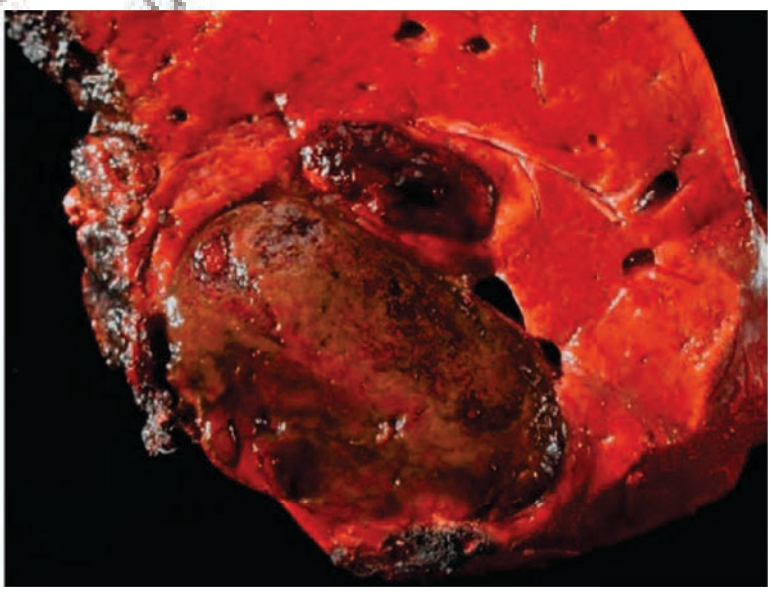
• Associated with non-alcoholic fatty liver disease (NAFLD)

• Upregulation of C-reactive protein (CRP) and serum amyloid A

• 10% may have concomitant °-catenin activating mutations

• Moderate risk of malignant transformation

The gross specimen of hepatic adenoma is shown below.



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Solution to Question 3:

Dysplastic nodules are associated with liver cirrhosis.

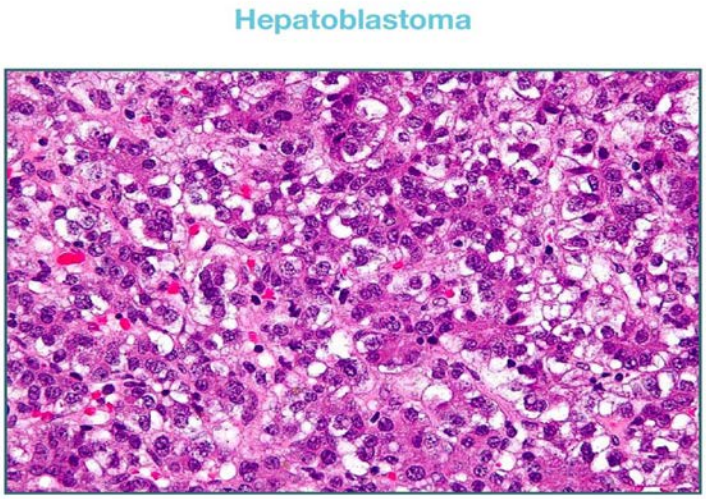
High grade dysplastic nodules may eventually develop into hepatocellular carcinoma in viral hepatitis and alcoholic liver disease.

Solution to Question 4:

The given clinical history and elevated serum alpha-fetoprotein level are suggestive of hepatoblastoma.

Hepatoblastoma is the most common malignant liver tumor of early childhood, usually < 3 years. Serum alpha-fetoprotein (AFP) is the most important clinical marker for hepatoblastoma. It remains the key clinical marker of malignant change, response to the treatment, and relapse.

Histological section of hepatoblastoma showing proliferating hepatoblasts consisting of round epithelial type cells is given below.



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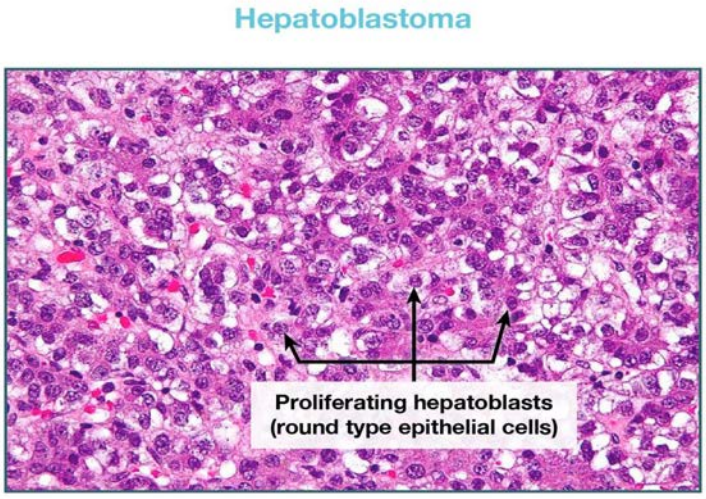

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Solution to Question 5:

Hypertension is not a risk factor for hepatoblastoma.

Risk factors for hepatoblastoma include:

- Prematurity and low birth weight (LBW)
- Beckwith–Wiedemann syndrome
- Familial adenomatous polyposis (FAP)

Solution to Question 6:

Pure fetal histology hepatoblastoma is associated with a very good prognosis. They may be cured by surgical resection without adjuvant chemotherapy.

Prognostic factors in hepatoblastoma include:

Prematurity and low-birth weight (LBW) are associated with hepatoblastoma but do not affect its outcome.

Good prognosis	Bad prognosis
Low tumor stagePure fetal hi stology	High tumor stageLow AFP le velsSmall cell undifferentiate d histologyRhabdoid features Vascular invasion

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Solution to Question 7:

Gardner syndrome, a variant of familial adenomatous polyposis (FAP) syndrome is associated with hepatoblastoma.

Activation of WNT signaling plays a major role in hepatoblastomas. This occurs by a variety of mechanisms including mutations in APC gene. Hence, patients with FAP syndromes frequently develop hepatoblastomas.

The following syndromes are associated with hepatocellular carcinoma:

• Hereditary tyrosinemia

• Alpha-1 antitrypsin defeciency

• Familial hemochromatosis

Solution to Question 8:

The most common cause of hepatocellular carcinoma is chronic hepatitis B virus infection. More than 85% of cases of hepatocellular carcinoma occur in countries with high rates of chronic hepatitis B virus infection.

Risk factors for hepatocellular carcinoma are:

• Hepatitis B virus

• Hepatitis C virus

• Alcohol

• Aflatoxin

• Alpha-1 antitrypsin deficiency

• Hemochromatosis

• Nonalcoholic steatohepatitis

• Tyrosinemia

• Smoking

Activation of °-catenin and inactivation of p53 are the two most common early mutational events seen in hepatocellular carcinoma.

Solution to Question 9:

Focal nodular hyperplasia and nodular regenerative hyperplasia are not precursors for hepatocellular carcinoma (HCC).

The precursors of HCC inlcude:

• Hepatocellular adenoma - especially those with °-catenin-activating mutations

• Small cell and large cell change - cellular dysplasias

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• Dysplastic nodules - low-grade and high-grade

Solution to Question 10:

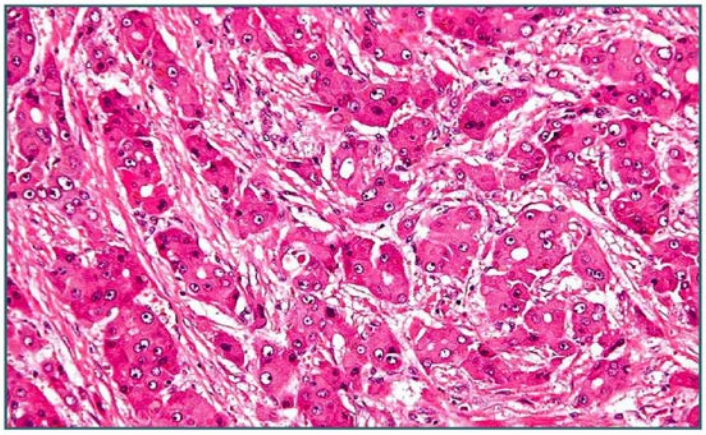
The given clinical scenario is suggestive of fibrolamellar carcinoma. It is usually not associated with liver cirrhosis.

Fibrolamellar carcinoma is a distinctive and rare variant of hepatocellular carcinoma (HCC). It usually occurs < 35 years of age. There is no gender predilection and no identifiable predisposing conditions. It has a good prognosis compared to the classical HCC. Majority (50-75%) of these tumors are resectable.

It usually presents as a single large, hard scirrhous tumor with fibrous bands coursing through it. Microscopically, it is composed of oncocytes growing in nests or cords separated by parallel lamellae of dense collagen bundles.

The histological section of fibrolamellar carcinoma is given below. It shows malignant-appearing, oncocytic hepatocytes separated by dense bundles of collagen.

Fibrolamellar Carcinoma of Liver



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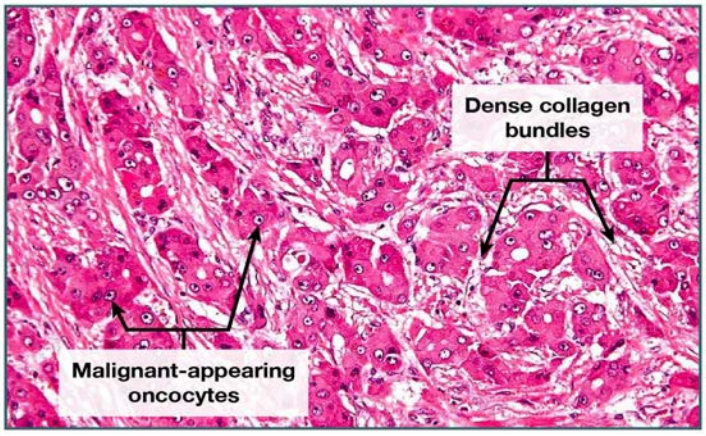
Fibrolamellar Carcinoma of Liver



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Solution to Question 11:

Hepatic angiosarcoma is associated with exposure to arsenic, thorotrast and vinyl chloride.

Angiosarcoma is a malignant endothelial neoplasm. There is equal gender predilection. The tumor may occur at any site, but most often involves skin, soft tissue, breast and liver.

Various hepatic tumors and associated etiological agents are given below:

Tumor	Etiological agents
Hepatocellular adenoma	Oral contraceptives, anabolic steroids
Hepatocellular carcinoma	Alcohol, thorotrast
Cholangiocarcinoma	Thorotrast
Angiosarcoma	Thorotrast, vinyl chloride, arsenic

Solution to Question 12:

The most common tumors of the liver are metastatic tumors.

The common primary sources of liver metastasis are:

- Colon carcinoma
- Breast carcinoma
- Lung carcinoma

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• Pancreatic carcinoma

Solution to Question 13:

The given clinical scenario is suggestive of a metastatic liver tumor.

Metastases are the most common malignant neoplasms of the liver. The most common primary sources are the colon, breast, lung, and pancreas, although any cancer at any site of the body may spread to the liver.

Patients with metastases typically have multiple nodules replacing the normal liver parenchyma. There may be no clinical or laboratory evidence of hepatic insufficiency. Often, the only telltale sign of secondaries in the liver will be hepatomegaly.

Solution to Question 14:

Typhoid carriers are not at risk of developing cholangiocarcinoma.

Cholangiocarcinoma is the second most common primary malignant tumor of the liver after hepatocellular carcinoma. It is a malignancy of the biliary tree, arising from bile ducts within and outside of the liver.

The risk factors for cholangiocarcinoma include the following:

• Infestation by liver flukes (particularly Opisthorchis and Clonorchis)

• Primary sclerosing cholangitis, and other chronic inflammatory diseases of the large bile ducts

• Chronic hepatitis B and C infections

• Cirrhosis

• Inflammatory bowel disease

• Diabetes mellitus, obesity, non-alcoholic fatty liver disease (NAFLD)

• Alcohol and tobacco

• Precursor lesions -

• Biliary intraepithelial neoplasias

• Mucinous cystic neoplasms

• Intraductal papillary biliary neoplasia

Solution to Question 15:

Klatskin tumors are extrahepatic cholangiocarcinomas located in the perihilar region.

These tumors are located at the junction of the right and left hepatic ducts. Distal tumors arise in the common bile duct posterior to the duodenum. Regardless of the site, the prognosis is poor.

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Solution to Question 16:

Gallbladder carcinoma carries a poor prognosis because it is typically detected late due to non-specific symptoms.

Carcinoma of the gallbladder is the most common malignancy of the extrahepatic biliary tract. Most carcinomas of the gall bladder are adenocarcinomas.

Gallbladder cancer is at least twice as common in women than in men. The most important risk factor for gallbladder cancer (besides gender and ethnicity) is gallstones, which are present in 95% of cases. Her-2/neu is overexpressed in around 2/3 of the cases, and therefore, they can be targeted for therapy.

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Gall Bladder and Pancreas

Question 1:

What is the most common congenital anomaly of the gallbladder?

a) Agenesis

b) Choledochal cyst

c) Bilobed gall bladder

d) Phrygian cap

Question 2:

A 24-year-old man presented with severe right upper quadrant pain for 8 hours associated with nausea and vomiting. A diagnosis of acute cholecystitis was made and he underwent laparoscopic cholecystectomy. The specimen is shown below. This finding is associated with all the following conditions except:

a) Chronic hemolytic syndromes

b) Ileal resection

c) Biliary infection

d) Hyperlipidemia syndromes

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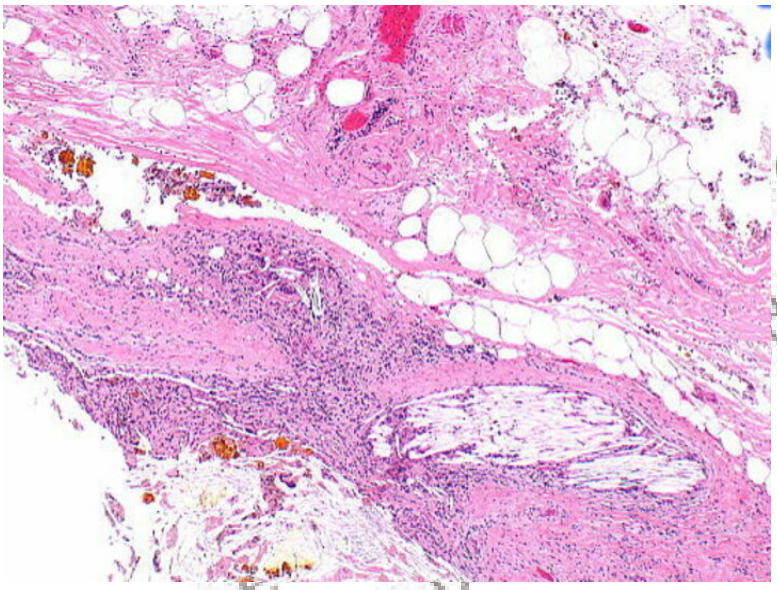
Question 3:

A 52-year-old man was rushed to the ER with right upper quadrant pain for the last 6 hours. He had been diagnosed with gallstones 10 years ago but had not undergone any treatment. Imaging revealed gallbladder wall thickening. He underwent a cholecystectomy which revealed a shrunken and nodular gallbladder with a thick wall. The following was noted on microscopy. This condition is associated with:



a) Dystrophic calcification of the gallbladder wall

b) Gallbladder stasis and ischemia

c) Rupture of Rokitansky-Aschoff sinuses

d) Infection by gas-forming organisms

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Question 4:

What is the most common congenital anomaly of the pancreas?

a) Annular pancreas

b) Ectopic pancreas

c) Pancreas divisum

d) Agenesis

Question 5:

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A 19-year-old boy presented with severe abdominal pain for the last 24 hours with radiation to the upper back. He has had multiple similar episodes since his childhood. Family history revealed similar episodes in the father. Investigations revealed elevated serum levels of amylase and lipase. Which of the following statements is not true about the given condition?

a) It is commonly associated with mutations in the PRSS1 gene

b) This boy has a 40 % lifetime risk of developing pancreatic cancer

c) It may be associated with mutations in the CFTR gene

d) Hypocalcemia is an important triggering factor this condition

Question 6:

A 65-year-old man presented with vague abdominal pain, anorexia, weight loss for the last 6 months. He also reported spontaneously appearing and disappearing painful, linearly arranged nodules at different locations on his body. On examination, thrombophlebitis and epigastric tenderness were noted. Investigations revealed elevated serum CEA and CA 19-9. Which of the following genetic mutations is most frequently associated with this condition?

a) BRCA -2

b) K-RAS

c) PRSS1

d) SPINK1

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Question 7:

A pathologist was studying a biopsy specimen from a patient with pancreatic cancer. He observed that it resembled ovarian stroma. What is it likely to be?

a) Serous cystic neoplasm

b) Mucinous cystic neoplasm

c) Intraductal papillary mucinous neoplasm

d) Solid pseudopapillary neoplasm

Question 8:

All of these are characteristic features of pancreatic carcinoma except:

a) Cigarette smoking is a risk factor

b) Carcinoma of body of pancreas often present with jaundice

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c) They elicit intense desmoplastic response

d) Perineural invasion is common

Question 9:

Patients with which of the following have the highest risk of pancreatic cancer?

a) FAMMM syndrome

b) Familial adenomatous polyposis

c) Hereditary pancreatitis

d) Peutz-Jeghers syndrome

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Answer Key

Question No.	Correct Option
1	d
2	d
3	c
4	c
5	d
6	b
7	b
8	b
9	d

Detailed Explanations

Solution to Question 1:

The most common congenital anomaly of the gallbladder is the Phrygian cap. It refers to an inward folding of the fundus of the gallbladder. It is named for its resemblance to a conical hat.

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The other common congenital anomalies of the gallbladder are:

• Agenesis - absence of all or any portion of the hepatic or common bile ducts

• Biliary atresia - hypoplastic narrowing of biliary channels

• Choledochal cysts - congenital dilations of the intra and/or extrahepatic biliary system

Solution to Question 2:

The given image shows pigmented gallstones, which are not associated with hyperlipidemia syndromes.

Pigmented gallstones are made of bilirubin and calcium salts. They can occur in:

• Chronic hemolytic syndromes

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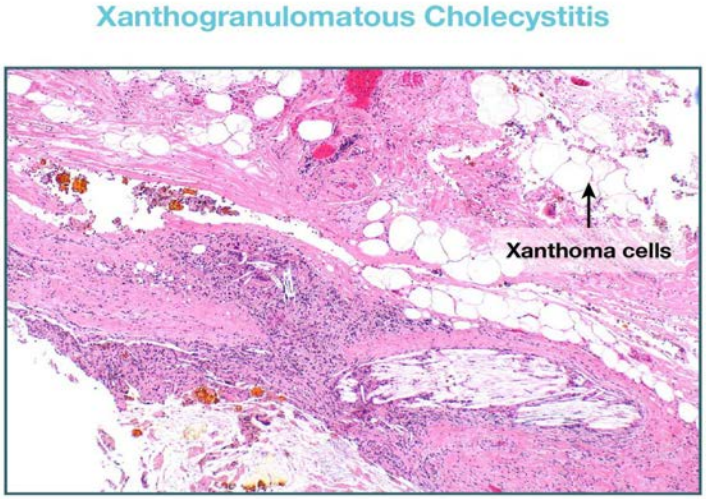
- Ileal resection
- Biliary infection
- Cystic fibrosis with pancreatic insufficiency

Cholesterol stones are made of crystalline cholesterol monohydrates. Dyslipidemia is a risk factor for the development of cholesterol gallstones.

The following image shows cholesterol gallstones:

Solution to Question 3:

This clinical scenario of chronic cholecystitis and image showing lipid-laden xanthoma cells are suggestive of xanthogranulomatous cholecystitis. This condition results due to the rupture of Rokitansky–Aschoff sinuses.



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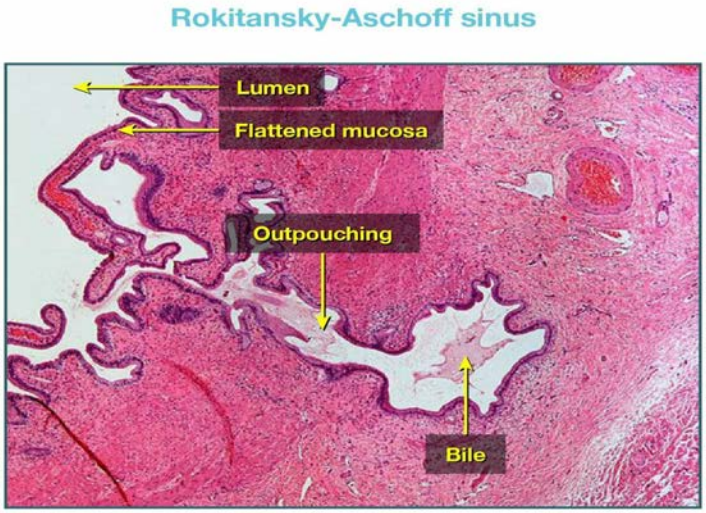
Rokitansky–Aschoff sinuses are bile-filled outpouchings of the gallbladder mucosa through the gallbladder wall. They develop in reaction to chronic inflammation of the gallbladder. Eventually, they may rupture into the wall of the gallbladder. This results in the accumulation of macrophages that have ingested biliary phospholipids, which are called xanthoma cells.



Chronic cholecystitis may have other sequelae:

• Porcelain gallbladder - dystrophic calcification of the gallbladder wall

• Hyalinizing cholecystitis - replacement of the gallbladder wall by dense fibrosis, with or without calcification (leads to higher incidence of gallbladder carcinoma)

• Hydrops of the gallbladder - atrophic, obstructed, dilated gallbladder containing clear fluid

Acute cholecystitis includes the following variants:

• Emphysematous cholecystitis - acute infection of the gallbladder by gas-forming organisms

• Acalculous cholecystitis - due to gallbladder stasis and ischemia

Solution to Question 4:

Pancreas divisum is the most common congenital anomaly of the pancreas.

The pancreas develops by fusion of the larger dorsal and smaller ventral pancreatic buds. The dorsal duct is the dominant duct during development and it drains into the minor papilla. The ventral duct drains into the major papilla. After fusion, the following ducts are formed:

• Main pancreatic duct (of Wirsung) - formed by fusion of ducts of dorsal and ventral buds, drains into the major papilla

• Accessory pancreatic duct (of Santorini) - formed by the proximal portion of the dorsal duct, drains into the minor papilla

In pancreas divisum, the ventral and dorsal ducts fail to fuse. Hence, the majority of the pancreas continues to drain through the dominant dorsal duct that enters the duodenum at the minor

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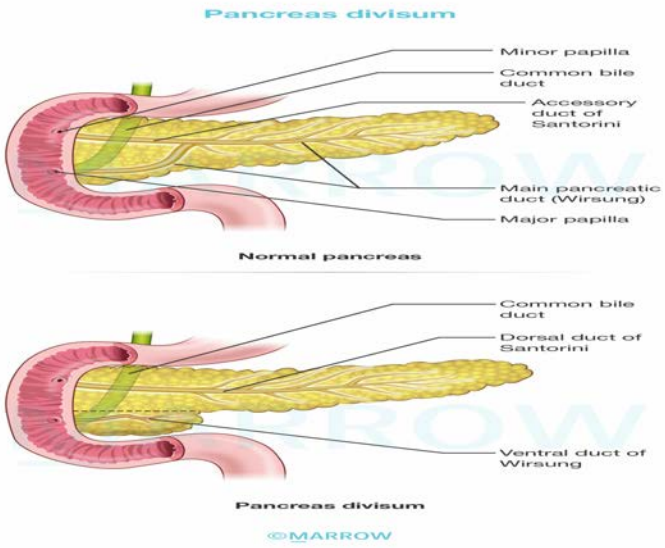
papilla while the ventral duct, along with the bile duct, drains into the major papilla. These patients are more prone to pancreatitis.



The other congenital anomalies of the pancreas are:

• Annular pancreas - band-like ring of normal pancreatic tissue encircling 2nd part of duodenum, may cause obstruction

• Ectopic pancreas - common in stomach, duodenum, and jejunum (found in about 2% of postmortem exams)

• Agenesis - rarely seen, associated with mutations of PDX1 (homeobox gene)

Solution to Question 5:

This clinical scenario in a young patient with positive family history of similar episodes is suggestive of hereditary pancreatitis. Acute episodes of pancreatitis can be precipitated by hypercalcemia, not hypocalcemia.

The following genes are implicated in hereditary pancreatitis:

• Gain-of-function mutation in trypsinogen gene (PRSS1) - most common

• Loss-of-function mutation in trypsin inhibitor gene (SPINK1)

• Loss of CFTR - abnormal secretions that promote protein plugging, duct obstruction, leading to pancreatitis

Hereditary pancreatitis is associated with a 40% lifetime risk of developing pancreatic cancer.

Solution to Question 6:

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The presence of the above clinical symptoms with migratory thrombophlebitis (Trousseau syndrome) and elevated serum levels of CEA and CA 19-9 in an elderly man point to a diagnosis of pancreatic cancer. The most frequently associated mutation with this condition is K-RAS.

It is attributed to the production of platelet-aggregating factors and procoagulants from the tumor or its necrotic products. Both venous and arterial thrombi can occur. Venous thrombi can embolize to the lungs.

Molecular alterations involved in pancreatic carcinogenesis are:

Following genes are associated with an inherited predisposition to pancreatic cancer:

• BRCA2 mutation - pancreatic cancer, breast cancer, prostate cancer, and ovarian cancers

• PRSS1 mutation - pancreatic carcinoma secondary to hereditary pancreatitis

Gene	Type	Chromosome
KRAS(most common oncogene)	Oncogene (activated by point mutation)	12p
CDKN2A(most common tumor-suppressor gene)	Tumor suppressor gene	9p
TP53	Tumor suppressor gene	17p
SMAD4	Tumor suppressor gene	18q

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Solution to Question 7:

Mucinous cystic neoplasms of the pancreas have dense stroma, similar to the ovarian stroma.

These tumors have large cystic cavities filled with thick, tenacious mucin. They are lined by columnar, mucin-producing epithelium with dense stroma. This results in similarity to ovarian stroma.

They usually arise in the tail of the pancreas and can be precursors to invasive carcinomas. They are associated with mutations in the KRAS oncogene, and the tumor-suppressor genes TP53 and RNF43.

Solution to Question 8:

Patients with carcinoma of the head of the pancreas develop jaundice due to obstruction of the biliary tract.

Cigarette smoking doubles the risk of pancreatic cancer and is the leading preventable cause. The clinical features depend on the location of the tumor.

• Head - painless, palpable gallbladder with mild jaundice is suggestive of malignancy (according to Courvoisier's law)

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• Body and tail - may remain asymptomatic until later stages as they do not impinge on the biliary tract and do not cause jaundice

Other common pathological features of this condition are:

• Desmoplastic reaction - growth of fibrous or connective tissue

• Perineural invasion, as well as lymphatic and large vessel invasion

Solution to Question 9:

Patients with Peutz–Jeghers syndrome have the highest risk of pancreatic cancer.

Hereditary syndromes and their associated risk of pancreatic cancer:

FAMMM: Familial atypical multiple mole melanoma

HNPCC: Hereditary nonpolyposis colorectal cancer

Syndrome	Germ-line mutation	Estimated increased risk (fold) of
Peutz–Jeghers syndrome	STKII (LKB1)	~132
Hereditary pancreatitis	PRSS 1/SPINK1	~ 53
Cystic fibrosis	CFTR	~ 30
FAMMM syndrome	p16/CDKN2A	~13-38
Hereditary breast and ovarian cancer	BRCA 2	~3.5-10
HNPCC /Lynch syndrome	MLH1, MSH2, MSH6, PMS2	~9-30

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Esophagus

Question 1:

What is the most common site of fistulization in GIT?

a) Esophagus

b) Rectum

c) Anal canal

d) Ileum

Question 2:

What is the most frequent site of ectopic gastric mucosa?

a) Upper esophagus

b) Lower esophagus

c) Pancreas

d) Meckel's diverticulum

Question 3:

A 57-year-old man came with complaints of difficulty in swallowing and a persistent feeling of something stuck in his throat. He also reports bad breath and regurgitation of food particles. Barium swallow revealed the following. This condition occurs due to a defect in which of the following?

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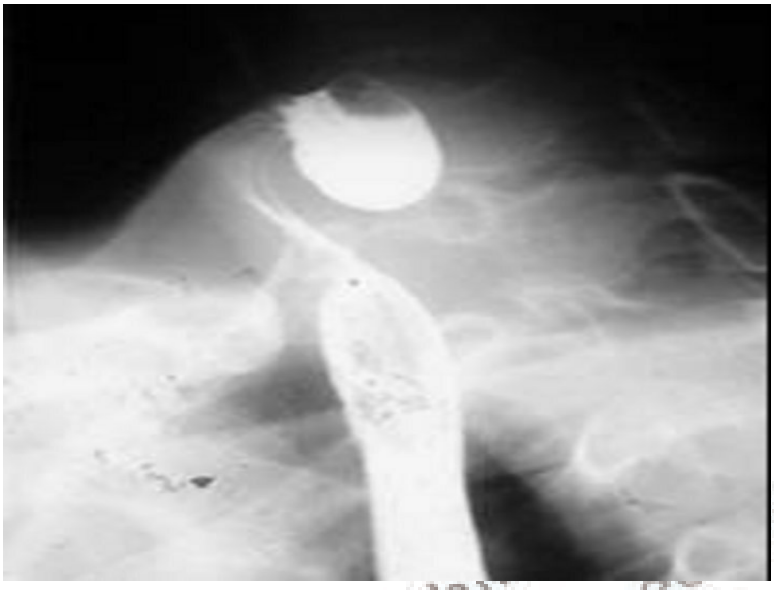

a) Laimer–Hackermann's triangle

b) Killian–Jamieson area

c) Zenker's triangle

d) Killian's triangle

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Question 4:

All of the following may be seen in patients with Plummer-Vinson syndrome except:

a) Cheilosis

b) Iron-deficiency anemia

c) Glossitis

d) Progressive dysphagia

Question 5:

A 45-year-old woman presented with complaints of difficulty in swallowing solid foods. An upper GI endoscopy revealed the following finding just above the gastroesophageal junction. What is the likely diagnosis?

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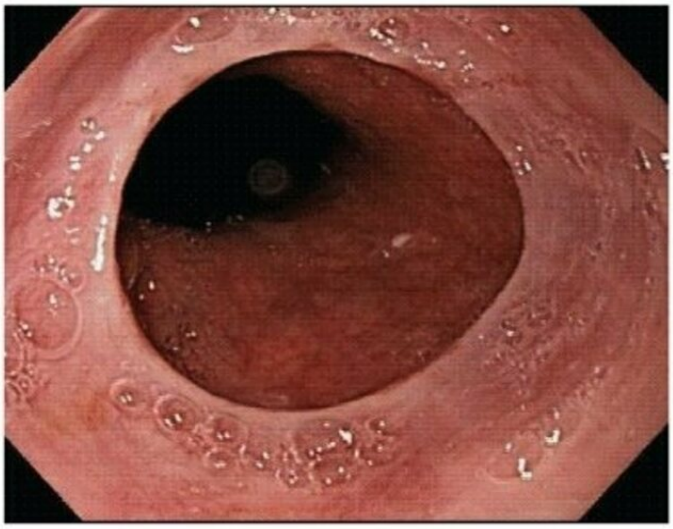

a) Type A ring

b) Type C ring

c) Type D ring

d) Type B ring

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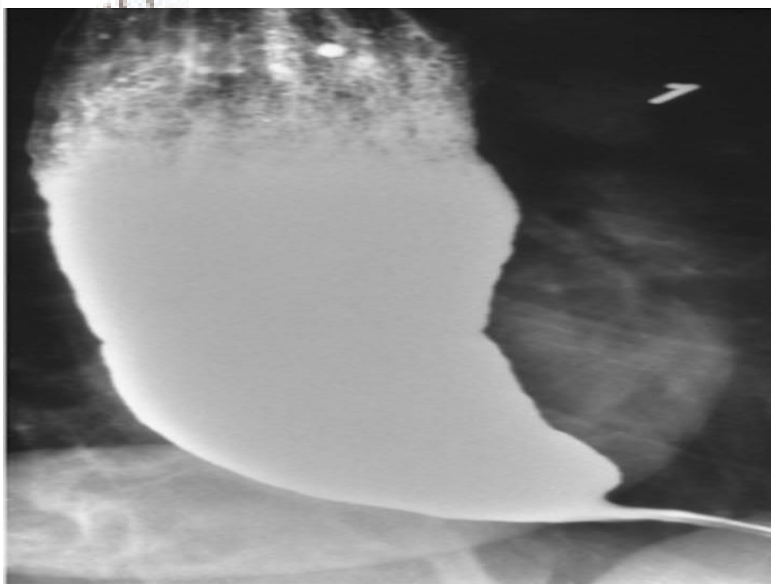
Question 6:

A 52-year-old woman is being evaluated for dysphagia and chest pain. She traveled to Brazil on a business trip 5 months ago. Barium swallow reveals the following finding. Which of the following could have caused this condition?



a) Leishmania donovani

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b) Trypanosoma cruzi

c) Trypanosoma brucei

d) Schistosoma haematobium

Question 7:

Which of the following statements is true about the pathology of achalasia cardia?

a) Relaxation of lower esophageal sphincter

b) Defective peristalsis

c) Decreased release of NO and VIP in the distal part of esophagus

d) Decreased tone of the lower esophageal sphincter

Question 8:

A mother brought her 8-year-old son to the OPD with complaints of refusal to eat and poor weight gain. The child complained that food often gets stuck in his throat. Endoscopy revealed the following finding. What is the likely diagnosis?

a) Gastroesophageal reflux disease

b) Eosinophilic esophagitis

c) Achalasia cardia

d) Plummer-Vinson syndrome

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Question 9:

Which of the following is incorrect about eosinophilic esophagitis?

a) Majority of patients have associated atopic conditions

b) Feline esophagus is an endoscopic finding

c) Treatment of choice is systemic steroids

d) May be associated with food products like cow's milk and soy products

Question 10:

A 47-year-old woman comes to you with progressive heartburn and difficulty in swallowing. She also describes episodes of painful blanching and bluish discoloration of her fingers and toes on exposure to cold. The following findings are noted on examination. Antibodies to which of the following are most likely to be seen in this patient?

a) Centromeric proteins

b) Histidyl-t-RNA synthetase (Jo-1)

c) Ribonucleoprotiens

d) Histones

Question 11:

A 50-year-old man presented with blood in his vomitus. He gives a history of binge drinking followed by multiple episodes of vomiting the prior night. He is hemodynamically stable.

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Which of the following is incorrect about this condition?

a) It is due to longitudinal mucosal tears

b) The gastroesophageal musculature fails to relax

c) The tears cross the gastroesophageal junction

d) It requires surgical intervention

Question 12:

What is the most frequent cause of esophagitis?

a) Pill esophagitis

b) Eosinophilic esophagitis

c) Infectious esophagitis

d) Reflux esophagitis

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Question 13:

Which organism can cause esophageal infections in healthy individuals?

a) Cytomegalovirus

b) Herpes-simplex virus

c) Candida

d) Aspergillus

Question 14:

Punched-out ulcers in the esophagus are caused by:

a) Herpes-simplex virus

b) Cytomegalovirus

c) Candida

d) Acid

Question 15:

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A 28-year-old patient with haematemesis is found to have the following finding on upper GI endoscopy. He has traveled to Zambia several times over the past 3 years. What could be the likely cause of this condition?

a) Fascioliasis

b) Schistosomiasis

c) Ecchinococcosis

d) Leishmaniasis

Question 16:

All are true about Barrett oesophagus except:

a) Complication of chronic GERD

b) Seen in 10% of individuals with symptomatic GERD

c) Increases risk of squamous cell carcinoma

d) Intestinal metaplasia

Question 17:

A 60-year-old man with chronic dyspepsia underwent upper GI endoscopy. The biopsy findings are shown below. What is the special stain that has been used?

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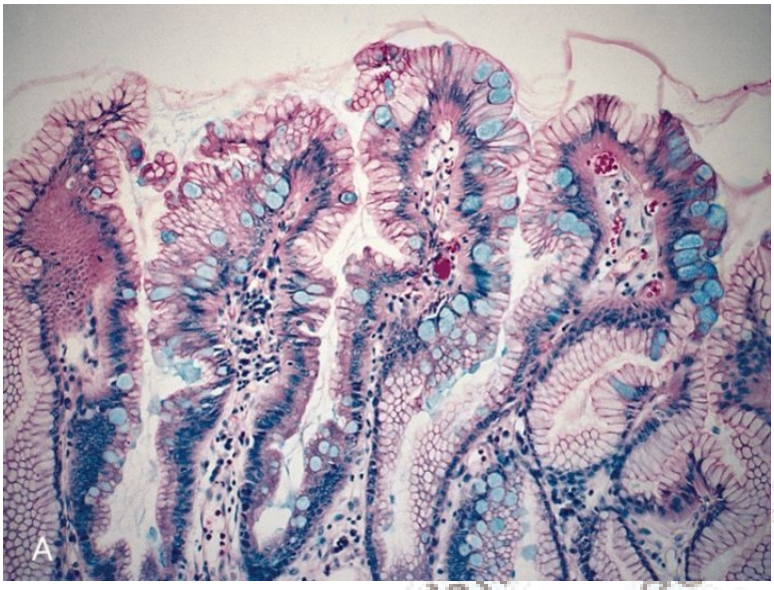

a) Periodic acid Schiff

b) Alcian blue

c) Combined Alcian blue-PAS

d) Mucicarmine

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Question 18:

Which of the following statements is false?

a) The most common site of extranodal lymphoma in GIT is the esophagus

b) The most common benign tumour of esophagus is leimyoma

c) The most common esophageal cancer overall is squamous cell carcinoma

d) The most common esophageal cancer in Western countries is adenocarcinoma

Question 19:

Which of the following is not a predisposing factor for esophageal cancer?

a) Mediastinal fibrosis

b) Diverticula

c) Caustic alkali burn

d) HPV

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Question 20:

A patient with recurrent gastritis has been diagnosed with Helicobacter pylori infection. Which of the following is true in this patient?

a) Increased risk of adenocarcinoma of esophagus

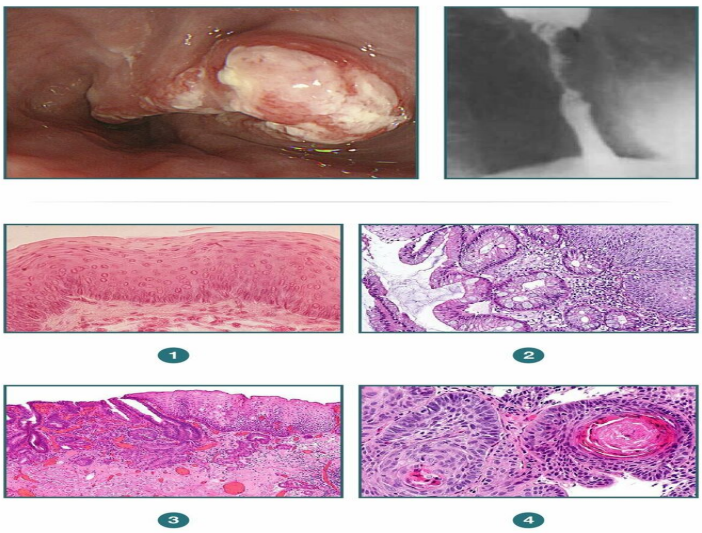
b) Decreased risk of adenocarcinoma of esophagus

c) Increased risk of squamous cell carcinoma of esophagus

d) Decreased risk of squamous cell carcinoma of esophagus

Question 21:

Endoscopic and barium swallow images of a lesion in the oesophagus of a patient are as shown below. What is the expected histopathological finding?



a) Image 2

b) Image 1

c) Image 4

d) Image 3

Answer Key

Question No.	Correct Option

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1	a
2	a
3	d
4	d
5	a
6	b
7	c
8	b
9	c
10	a
11	d
12	d
13	b
14	a
15	b
16	c
17	b
18	a
19	a
20	b
21	c

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Detailed Explanations

Solution to Question 1:

The esophagus is the most common site of fistulization in the gastrointestinal tract (GIT).

A tracheoesophageal fistula (TEF) is an abnormal fistula communication between the esophagus and trachea. The fistula is usually present near the tracheal bifurcation, with or without esophageal atresia. A blind proximal pouch with a distal tracheooesophageal fistula is the most common type of tracheoesophageal fistula (Type C).

10% of the patients have associated VACTERL anomalies (vertebral, anorectal, cardiac, tracheal, esophageal, renal, and limb).

Solution to Question 2:

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The most frequent site of the ectopic gastric mucosa is the upper third of the esophagus, where it is referred to as an inlet patch.

It is congenital and mostly asymptomatic. Occasionally, it can release acid, which can result in dysphagia, esophagitis, Barrett esophagus, or, rarely, adenocarcinoma.

Solution to Question 3:

The given clinical scenario and barium swallow image are diagnostic of Zenker's diverticulum. It occurs due to a defect in the Killian's triangle (Killian's dehiscence).

Killian's triangle is an anatomical triangular area bordered superiorly by the firm oblique fibers of the thyropharyngeus muscle and inferiorly by the horizontal fibers of the cricopharyngeus muscle. It is located immediately above the upper esophageal sphincter.

Although the Killian-Jamieson diverticulum is an anterolateral defect, it is rarely symptomatic.

Solution to Question 4:

Paterson–Brown–Kelly or Plummer–Vinson syndrome is associated with non-progressive dysphagia, especially with incompletely chewed food.

This syndrome is common in women aged >40 years. The other components of this syndrome are:

• Post-cricoid webs in the upper esophagus

• Iron-deficiency anemia

• Glossitis

• Cheilosis

Esophageal webs are idiopathic, semi-circumferential lesions composed of fibrovascular connective tissue and overlying epithelium. They are usually limited to the proximal esophagus and may cause obstruction. They are associated with:

• Plummer–Vinson syndrome

• Gastroesophageal reflux disease

• Chronic graft-versus-host disease

• Blistering skin diseases

The images below show endoscopic and barium swallow appearances of esophageal webs.

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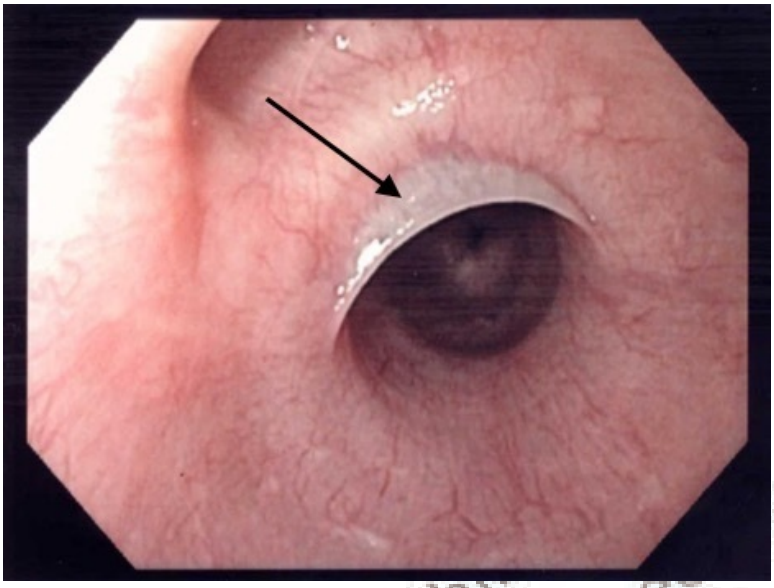

Solution to Question 5:

The given image shows an esophageal ring. Rings located above the gastroesophageal junction are classified as type A esophageal rings.

Esophageal rings are circumferential and thick. They include mucosa, submucosa, and occasionally, hypertrophic muscularis propria. There are 3 types:

Steakhouse syndrome refers to intermittent food impaction causing complete obstruction due to the presence of Schatzki rings.

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Type A rings	Type BorSchatzki rings	Type C rings
Caused by normal physiologic smooth muscle contractions	Most common typeAssociated with hiatus hernia	Rare findingsIndentations on radiographic studies due to diaphragmatic crural pressure
Seenabovethe gastroesophageal junction (GEJ) in the distal esophagusCovered by squamous mucosa	Located at thesquamocolumnarjunctionCovered by gastric cardia-type mucosa	Found in the mostdistalportion of the esophagus

Solution to Question 6:

The given clinical scenario and barium swallow showing the bird-beak appearance are suggestive of achalasia cardia. With respect to this patient's travel history, Chagas' disease due to infection with Trypanosoma cruzi must be suspected.

The infection destroys the myenteric plexus which results in failure of peristalsis and esophageal dilatation. Duodenal, colonic, and ureteric myenteric plexuses can also be affected by Chagas' disease.

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Solution to Question 7:

Achalasia cardia is characterized by decreased release of NO(nitric oxide) and VIP(vasoactive intestinal polypeptide) in the distal part of esophagus.

Normally, NO and VIP are secreted by the inhibitory neurons of the Auerbach's plexus in the distal esophagus. This leads to relaxation of the lower esophageal sphincter (LES). In achalasia cardia, these inhibitory neurons degenerate leading to decreased release of NO and VIP. This causes increased LES tone.

The triad of achalasia cardia is as follows:

• Incomplete relaxation of LES

• Increased tone of LES

• Absent peristalsis (aperistalisis)

Solution to Question 8:

The given clinical scenario and image showing multiple stacked esophageal rings are characteristic of eosinophilic esophagitis.

Differentiating features between eosinophilic esophagitis and GERD:

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Factors	Eosinophilic esophagitis	GERD
Dominant symptoms	Dysphagia	Heartburn and regurgitation
Food impaction	Common	Uncommon
Gender	Male predominance	Male = female
Age	Children, young adults	Middle age
Esophageal findings on endo scopy	EdemaMultiple stacked rings (feline esophagus) and longit udinal furrowsPunctate exud atesStrictures and narrow-cal iber esophagusCrepe-paper e sophagusNormalfindings in< 10%patients	Erosions and ulcersStrictures Barrett's esophagus and aden ocarcinomaNormalfindings o n endoscopy inmajorityof pat ients
Ambulatory pH testing	Negative or positive	Positive
Histology	≥15 eosinophils/hpf	<7 eosinophils/hpf
Etiology	Atopic or immune-mediated, acid reflux is not prominent	Acid reflux
Primary treatment	Proton-pump inhibitors (PPI s)Steroids (topical)Eliminatio n diet	AntacidsH2receptor blockers Proton-pump inhibitors (PPI s)

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Solution to Question 9:

Treatment of choice are proton pump inhibitors, which when started as primary therapy is effective in 30 - 50 % of affected individuals.

Additionally, elimination of allergenic proteins from diet as it is is associated with atopy and exposure to food allergens like cow's milk and soy products.

Swallowed topical steroids are used as well.

Immunocompromised patients are treated with acyclovir, famciclovir or valacyclovir.

Factors	Eosinophilic esophagitis	GERD
Dominant symptoms	Dysphagia	Heartburn and regurgitation
Food impaction	Common	Uncommon
Gender	Male predominance	Male = female
Age	Children, young adults	Middle age
Esophageal findings on endo scopy	EdemaMultiple stacked rings (feline esophagus) and longit udinal furrowsPunctate exud atesStrictures and narrow-cal iber esophagusCrepe-paper e sophagusNormal findings in <10% patients	Erosions and ulcersStrictures Barrett's esophagus and aden ocarcinomaNormal findings on endoscopy in majority of patients
Ambulatory pH testing	Negative or positive	Positive

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Factors	Eosinophilic esophagitis	GERD
Histology	≥15 eosinophils/hpf	<7 eosinophils/hpf
Etiology	Atopic or immune-mediated, acid reflux is not prominent	Acid reflux
Primary treatment	Proton-pump inhibitors (PPIs)Eliminationofallergensin dietSteroids(topical)	AntacidsH2receptor blockers Proton-pump inhibitors (PPIs)

Solution to Question 10:

The symptoms of the patient in the above case scenario and the image showing calcinosis are the characteristic findings of the CREST syndrome or limited scleroderma. Patients with this condition characteristically have antibodies directed against centromeric proteins (anti-centromere antibodies).

CREST syndrome is characterized by the following:

- Calcinosis
- Raynaud phenomenon
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasia

In the esophagus, progressive atrophy and fibrous replacement of the muscularis propria leads to hypomotility and dysphagia. The lower 2/3 of the esophagus develops a rubber-hose–like inflexibility. The associated dysfunction of the lower esophageal sphincter gives rise to gastroesophageal reflux, Barrett metaplasia, and stricture.

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Solution to Question 11:

This clinical scenario is suggestive of a Mallory–Weiss tear. They require only conservative management and healing tends to be rapid and complete.

They are longitudinal mucosal tears that may cross the gastroesophageal junction (GEJ). Forceful retching or vomiting along with failure of reflex relaxation of the gastroesophageal musculature results in tears involving the mucosa and submucosa. It usually occurs secondary to conditions like acute alcohol intoxication or hyperemesis gravidarum.

Boerhaave syndrome is a much more serious disorder characterized by transmural rupture of the distal esophagus. This results in acute mediastinitis with severe chest pain, tachypnea, and shock. Such patients generally require urgent surgical intervention.

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Solution to Question 12:

The most frequent cause of esophagitis is reflux of gastric acid into the lower esophagus.

The most common cause of gastroesophageal reflux is transient lower esophageal sphincter relaxation. Reflux esophagitis leads to chronic gastroesophageal reflux disease (GERD). This can cause Barrett's esophagus and eventually can cause adenocarcinoma.

Solution to Question 13:

Esophagitis in healthy individuals can be caused by the Herpes simplex virus. However, it is relatively uncommon.

In immunosuppressed individuals, infections can be caused by:

- Herpes simplex virus
- Cytomegalovirus
- Candida

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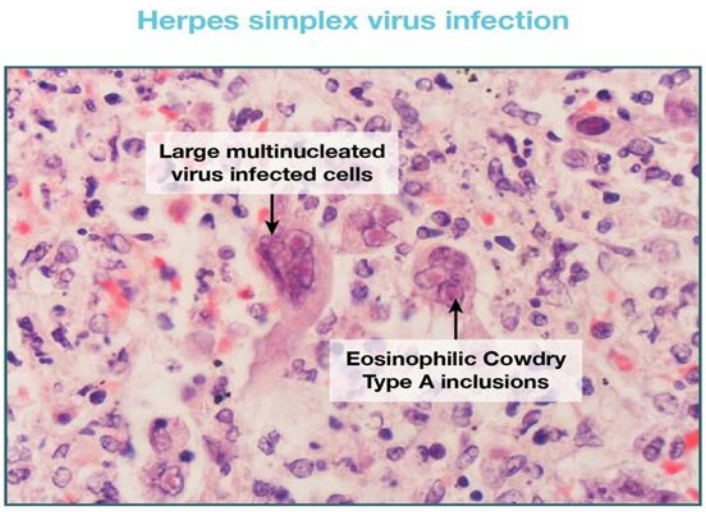
Solution to Question 14:

Infection with Herpes simplex virus (HSV) typically results in punched-out ulcers in the esophagus.

HSV esophagitis commonly occurs in immunocompromised patients. For diagnosis, the biopsy sample should be taken from the edge of the ulcer. The following microscopic findings are noted:

- Ballooning degeneration
- Ground-glass changes in nuclei
- Cowdry type A intranuclear inclusion bodies



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Note: CMV esophagitis causes shallow ulcerations. The biopsy is taken from the base of the ulcer and shows characteristic nuclear and cytoplasmic inclusions bodies.

Solution to Question 15:

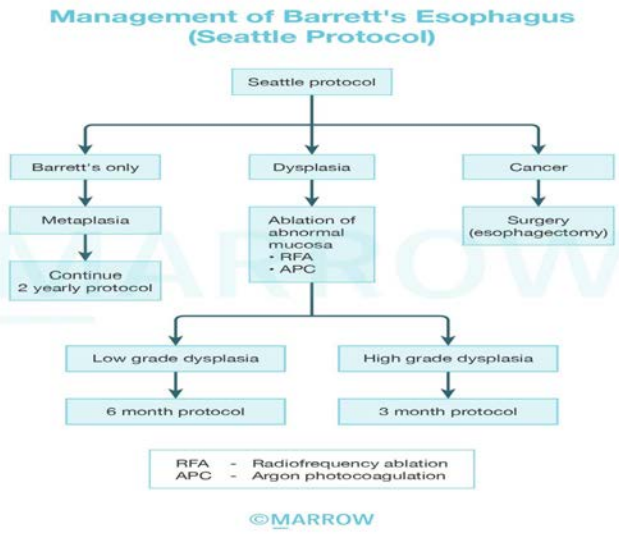
This clinical scenario and image showing bleeding esophageal varices are suggestive of hepatic schistosomiasis. It is the second most common cause of varices worldwide.

Liver cirrhosis, mostly in association with alcoholic liver disease, is the most common cause of varices.

Solution to Question 16:

Barrett's esophagus increases the risk of esophageal adenocarcinoma, not squamous cell carcinoma.

Barrett's esophagus is a complication of GERD and it is estimated to occur in as many as 10% of individuals with symptomatic GERD. Microscopically, it is seen as the replacement of the squamous esophageal epithelium with goblet cells (intestinal metaplasia).



The following images show endoscopic and microscopic images of Barrett's esophagus:

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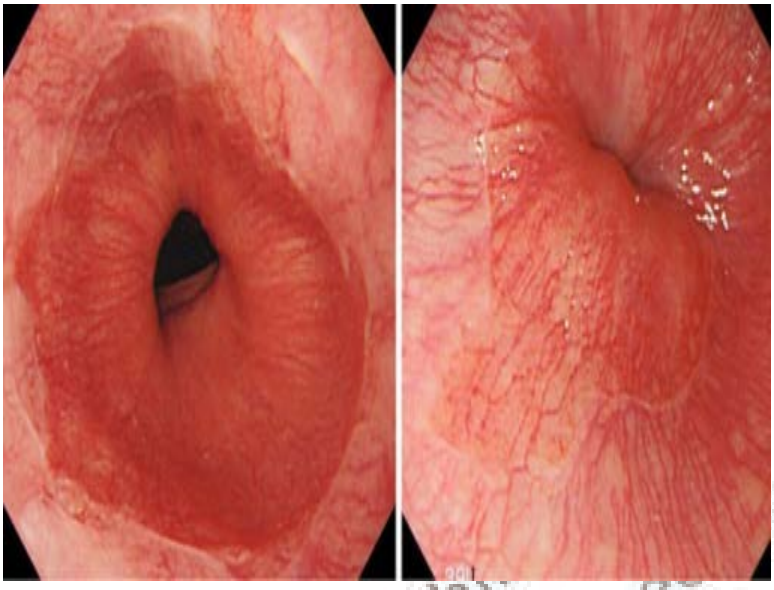
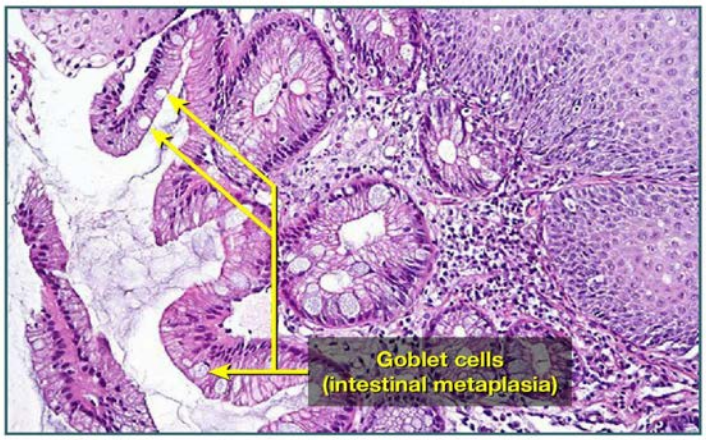


Barrett's Esophagus



Solution to Question 17:

The given image is of Barrett's esophagus showing intestinal metaplasia. The special stain used here is Alcian blue, which stains the acid mucin present in the goblet cells.

The following stains are used for mucin:

Stain	Type of mucin	Color stained
Periodic acid Schiff (PAS)	Neutral mucin	Magenta pink
Alcian blue	Acid mucin	Blue
Combined Alcian blue-PAS	Acid mucinNeutral mucin	BlueMagenta pink

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Stain	Type of mucin	Color stained
Mucicarmine	Acid mucin	Rose-red

Solution to Question 18:

The most common site of extranodal lymphoma in GIT is the stomach, not the esophagus.

Solution to Question 19:

Mediastinal fibrosis does not predispose to esophageal carcinoma. Risk factors for esophageal carcinoma include the following:

- Alcohol and tobacco use
- Poverty
- Caustic alkali burns
- Diverticula
- Achalasia
- Tylosis
- Plummer–Vinson syndrome
- Frequent consumption of very hot beverages
- Radiation exposure to the mediastinum
- Human papillomavirus (HPV) infection - squamous cell carcinomas

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Solution to Question 20:

Helicobacter pylori infection is associated with decreased risk of esophageal adenocarcinoma.

Long-standing H. pylori gastritis (chronic inflammation) causes multifocal gastric mucosal atrophy, which in turn leads to reduced parietal cell mass, acid secretion. This leads to reduced incidence of Barrett's esophagus and decreased risk of esophageal adenocarcinoma.

H. pylori infection, however, increases the risk of gastric adenocarcinoma.

Solution to Question 21:

The given images showing an esophageal exophytic growth on endoscopy and apple core appearance in the middle 1/3 of the esophagus on barium swallow are suggestive of squamous cell carcinoma. The characteristic histopathological finding in this condition are nests of stratified

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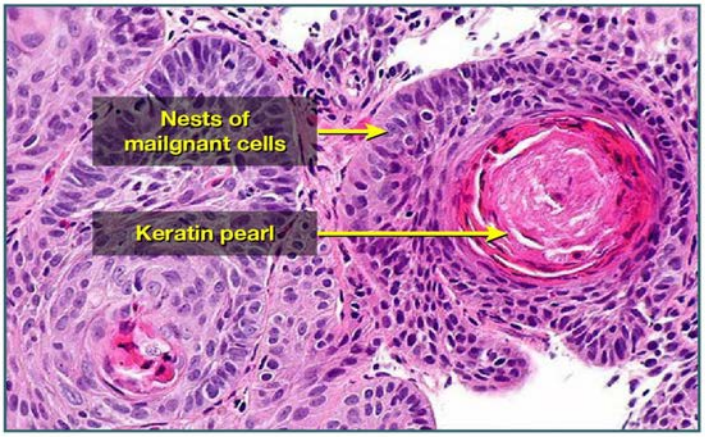
malignant cells and keratin pearls, which are noted in image 4.

Squamous cell carcinoma



Normal Esophagus

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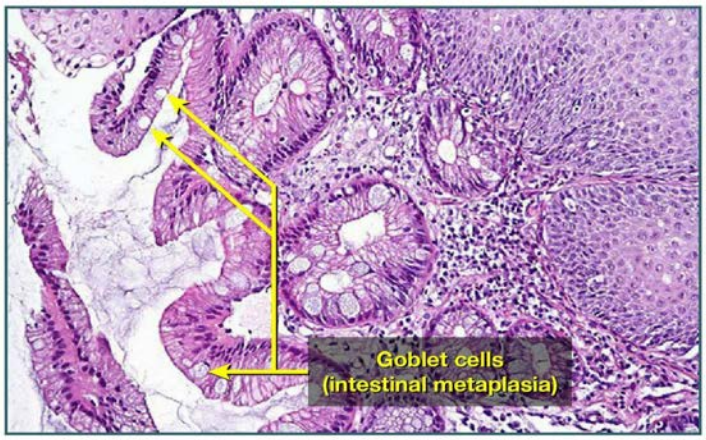
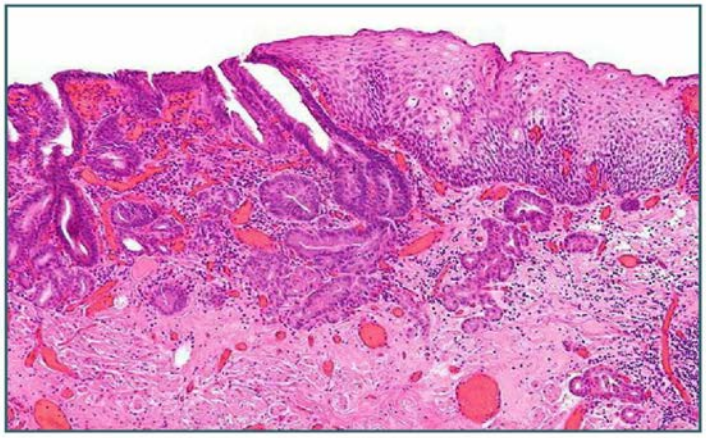
Barrett's Esophagus



Adenocarcinoma



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Stomach

Question 1:

A 3-weeks-old baby presents with projectile non-bilious vomiting after every meal. Abdominal examination reveals prominent peristalsis in the epigastrium and an olive-sized mass is felt on deep palpation of the right upper abdomen. Which of the following drug exposures is associated with this condition?

a) Azithromycin

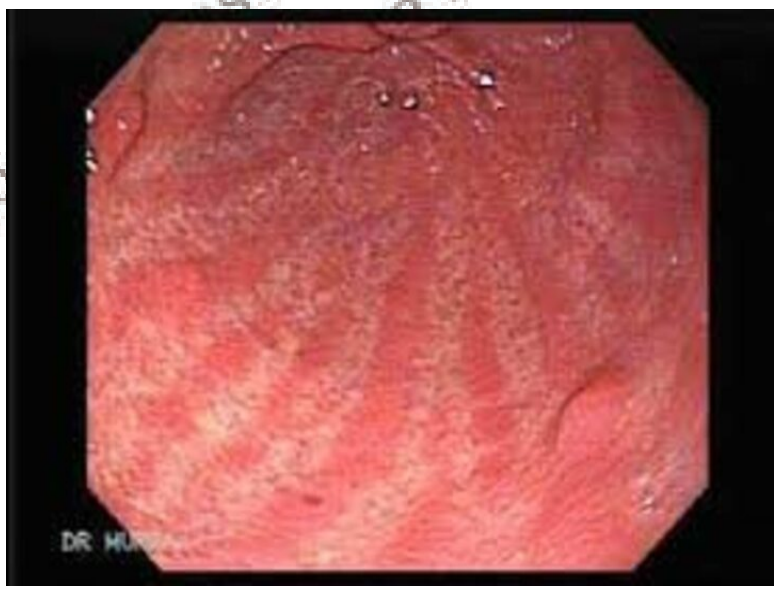
b) Tetracycline

c) Chloramphenicol

d) Metronidazole

Question 2:

Endoscopy of a patient with chronic upper gastrointestinal bleeding showed the following finding. What is the likely diagnosis?



a) Dieulafoy lesion

b) Vascular ectasia

c) Carcinoma stomach

d) Chronic gastric varices

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Question 3:

A 60-year-old man with hypertension and diabetes mellitus is on dialysis for chronic renal failure. Which of the following forms of gastritis is the patient at risk of development?

a) Acute gastritis

b) Chronic antral gastritis

c) Lymphocytic gastritis

d) Hypertrophic gastritis

Question 4:

What is the most common cause of chronic gastritis?

a) Infection

b) Acid hypersecretion

c) Alcohol

d) Autoimmune

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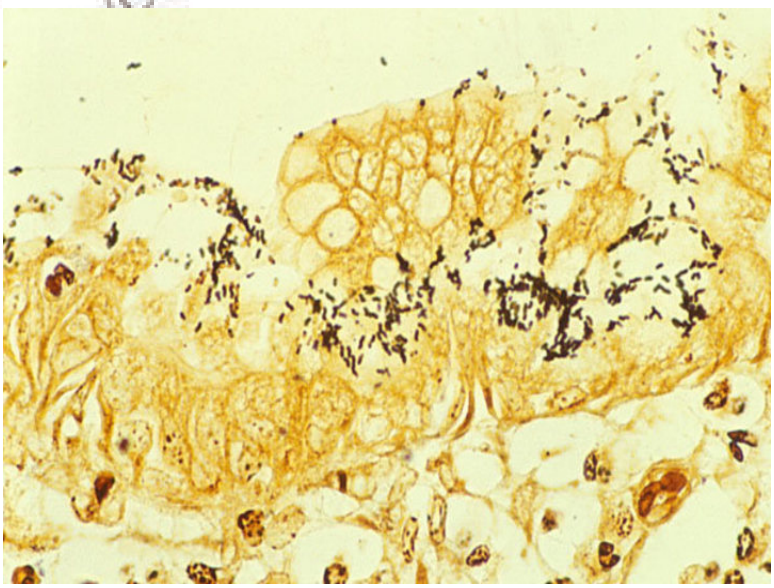
Question 5:

A patient with a history of peptic ulcers underwent an upper GI endoscopic biopsy of the stomach. The biopsy was stained with a special stain as shown in the image. Identify the special stain used.



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a) Gomori's methanamine silver stain

b) Warthin-Starry silver stain

c) Masson-Fontana stain

d) Periodic Acid Schiff stain

Question 6:

A 34-year-old man presents with nausea and upper abdominal pain. He experiences vague discomfort mostly in the afternoon and night, which is relieved by food. The urea breath test is positive. Upper GI endoscopy reveals a small ulcer with a clean base in the duodenum. From which of the following sites should the biopsy be taken to confirm the diagnosis?

a) Antrum

b) Fundus

c) Duodenum

d) Lesser curvature

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Question 7:

In patients with autoimmune gastritis, what part of the stomach is least likely to get involved?

a) Body

b) Fundus

c) Antrum

d) Cardia

Question 8:

What is the most common site of peptic ulcers?

a) Anterior wall of the duodenum

b) Posterior wall of the duodenum

c) Lesser curvature of the stomach

d) Antrum of the stomach

Question 9:

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A 55-year-old man presents with periodic abdominal pain. The pain is associated with meals and is relieved by antacids. Physical examination is unremarkable. Endoscopy shows a mucosal ulcer. What is the most common complication of this condition?

a) Perforation

b) Bleeding

c) Malignant tranformation

d) Obstruction

Question 10:

A 26-year-old man with severe burns is most likely at risk of developing which of the following ulcers?

a) Curling's ulcer

b) Cushing's ulcer

c) Marjolin's ulcer

d) Buruli's ulcer

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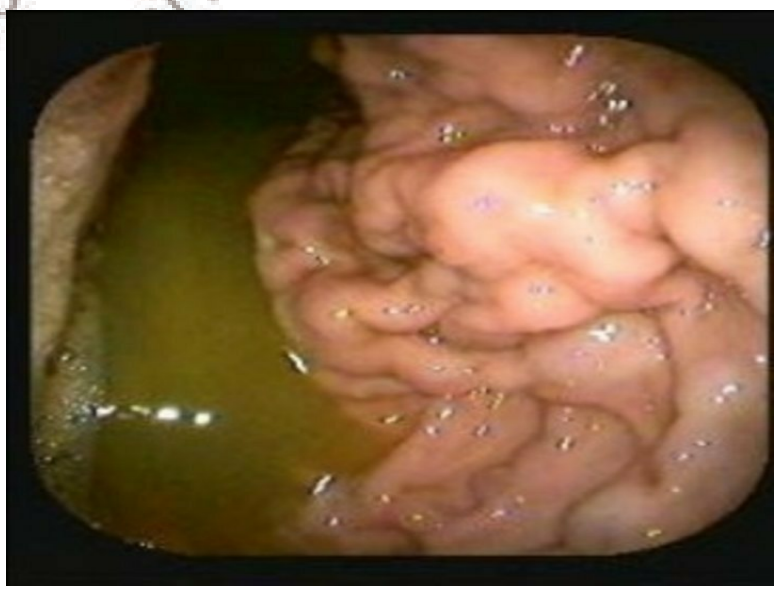
Question 11:

The upper gastrointestinal endoscopy of a patient is shown below. Excessive secretion of which of the following is associated with this condition?



a) TGF alpha

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b) PDGF beta

c) PDGF alpha

d) TGF beta

Question 12:

Fundic gland polyps are associated with which of the following conditions?

a) Chronic gastritis

b) Zollinger-Ellison syndrome

c) Peutz-Jeghers syndrome

d) Familial adenomatous polyposis

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Question 13:

What is the most common site of gastric adenoma?

a) Antrum

b) Fundus

c) Body

d) Lesser curvature

Question 14:

All are predisposing factors for the development of gastric adenoma except:

a) Chronic gastritis

b) Intestinal metaplasia

c) Familial adenomatous polyposis

d) Zollinger-Ellison syndrome

Question 15:

Which germline loss-of-function mutation is strongly associated with patients diagnosed with familial gastric cancer?

a) CDH1

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b) P53

c) APC

d) PTEN

Question 16:

Linitis plastica is seen in which of the following?

a) Chronic gastritis

b) Intestinal-type gastric carcinoma

c) Diffuse-type gastric carcinoma

d) Gastric maltoma

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Question 17:

All are true about diffuse gastric cancer except:

a) Loss of E-cadherin

b) Bulky tumor

c) Signet-ring cells

d) TP53 mutation

Question 18:

A 55-year-old woman with severe unintentional weight loss was found to have gastric cancer. This cancer is least likely to metastasize to which of the following sites?

a) Supraclavicular lymph nodes

b) Right axillary lymph nodes

c) Ovary

d) Pouch of Douglas

Question 19:

What is the most common translocation seen in patients with gastric MALToma?

a) t(11;18)

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b) t(1;14)

c) t(14;18)

d) t(11;14)

Question 20:

A 68-year-old woman with long-standing chronic gastritis undergoes an endoscopic biopsy. The biopsy showed dense lymphocytic infiltration with lymphoepithelial lesions in the gastric glands. The cells of this tumor are likely to express all of the following markers except:

a) CD10

b) CD43

c) CD19

d) CD20

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Question 21:

Which of the following is least likely to be secreted by gastrointestinal carcinoid tumors?

a) Polypeptide YY

b) Cholecystokinin

c) Substance P

d) Noradrenaline

Question 22:

At which site are the most aggressive carcinoid tumors of the gastrointestinal system seen?

a) Stomach

b) Appendix

c) Jejunum

d) Colon

Question 23:

A 50-year-old woman presents with complaints of abdominal pain and diarrhea. On examination, her face appears flushed and her pulse is 120/min. Increased levels of 5-HIAA

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are observed in a 24-hour urinary sample. Which of the following is not a prognostic factor for this condition?

a) Degree of histological differentiation

b) Mitotic rate

c) Type of hormone secreted

d) Ki-67 proliferative index

Question 24:

A 62-year-old man underwent resection of a localized gastrointestinal tumor arising from the stomach. Histopathological examination showed a gain-of-function mutation in the KIT gene and positivity for CD117 and CD34. What is the most likely origin of the tumor?

a) Kulchitsky cells

b) Smooth muscle cells

c) Enterochromaffin cells

d) GI pacemaker cells

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Question 25:

What is the most specific marker for a gastrointestinal stromal tumor?

a) CD 117

b) CD 34

c) DOG-1

d) S-100

Question 26:

Which of the following is an epithelial tumor of the stomach?

a) Carcinoid tumor

b) Lymphoma

c) Gastrointestinal stromal tumor

d) Gastric adenocarcinoma

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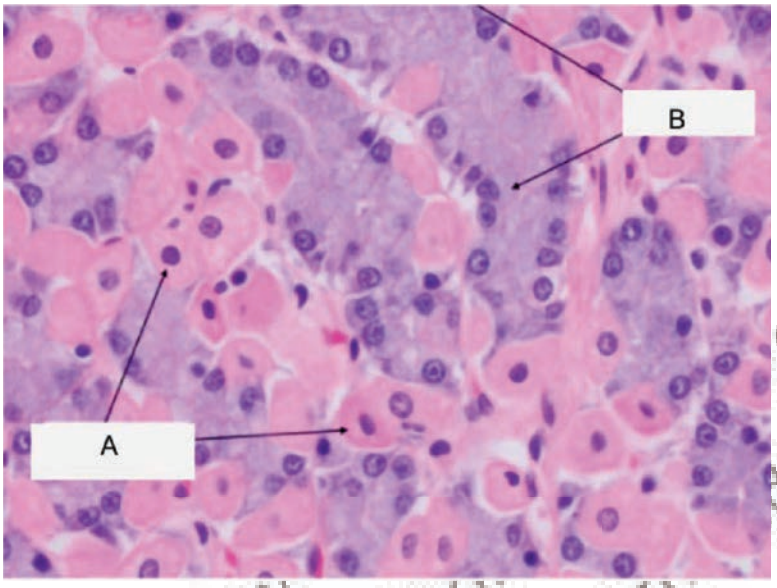
Question 27:

The absence of the structure marked as A will present with all except:



a) Pernicious anemia

b) Carcinoid syndrome

c) Vit B12 Deficiency

d) Zollinger ellison syndrome

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Answer Key

Question No.	Correct Option
1	a
2	b
3	a
4	a
5	b
6	a
7	c
8	a
9	b
10	a
11	a

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12	d
13	a
14	d
15	a
16	c
17	b
18	b
19	a
20	a
21	d
22	c
23	c
24	d
25	c
26	d
27	d

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Detailed Explanations

Solution to Question 1:

The given scenario is suggestive of congenital hypertrophic pyloric stenosis. It is associated with exposure to azithromycin.

Risk factors for congenital hypertrophic pyloric stenosis:

• Turner syndrome

• Trisomy 18

• Erythromycin or azithromycin exposure in the first 2 weeks of life either orally or via mother's milk.

Hyperplasia of the pyloric muscularis propria obstructs the gastric outflow tract.

It is three to five times more common in males. Generally presents between 3rd and 6th weeks of life as new-onset regurgitation, projectile, non-bilious vomiting after feeding. Physical examination reveals a firm, ovoid, 1 to 2 cm abdominal mass. In some cases, abnormal left to right hyperperistalsis is seen.

Treatment is the surgical splitting of the muscularis (Ramstedt pyloromyotomy).

Solution to Question 2:

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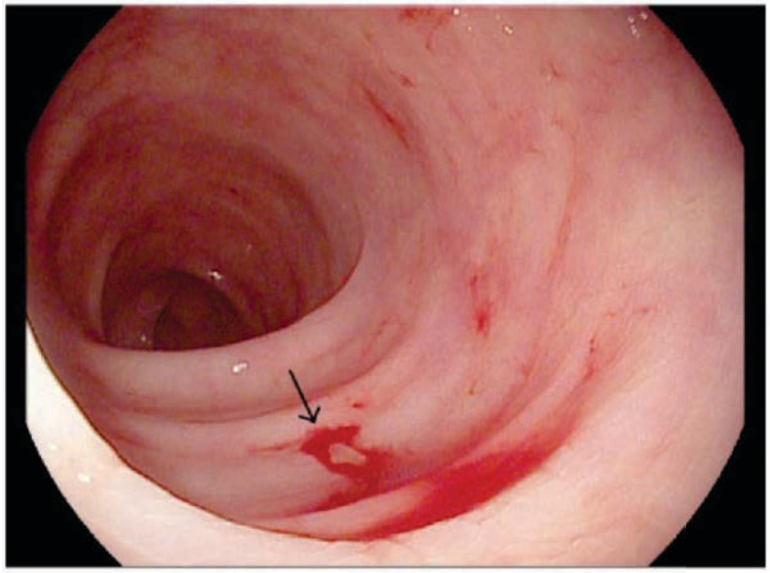
The endoscopy findings of the watermelon stomach are suggestive of gastric antral vascular ectasia (GAVE).

In GAVE, endoscopy reveals longitudinal stripes of edematous erythematous mucosa that alternate with less severely injured, paler mucosa giving the appearance of watermelon. GAVE is responsible for 4% of non-variceal upper gastrointestinal bleeding.

Dieulafoy lesion is a non-stress-related cause of GI bleeding. It is due to a submucosal artery that does not branch properly within the wall of the stomach. It is shown in the image below.



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Solution to Question 3:

Patients with renal failure develop acute gastritis as a consequence of uremia.

In uremia, gastric injury is due to inhibition of gastric bicarbonate transporters by ammonium ions.

Causes of acute gastritis:

• Alcohol

• Non-steroidal anti-inflammatory drugs (NSAIDs)

• Smoking

• Ischemia/shock

• Steroid use

• Uremia

• Chemical ingestion

• Stress

Histologically, the presence of neutrophils above the basement membrane in direct contact with epithelial cells signifies acute gastritis.

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Solution to Question 4:

The most common cause of chronic gastritis is infection with the bacillus Helicobacter pylori.

Causes of chronic gastritis:

• Helicobacter pylori - 1st most common

• Autoimmune gastritis - 2nd most common

• Radiation injury

• Chronic bile reflux

• Mechanical injury (e.g., an indwelling nasogastric tube)

• Systemic diseases such as Crohn disease, amyloidosis

• Graft-versus-host disease

Options B and C: Acid hypersecretion and alcohol ingestion are the causes of acute gastritis.

Note: Autoimmune gastritis is the most common cause of diffuse atrophic gastritis.

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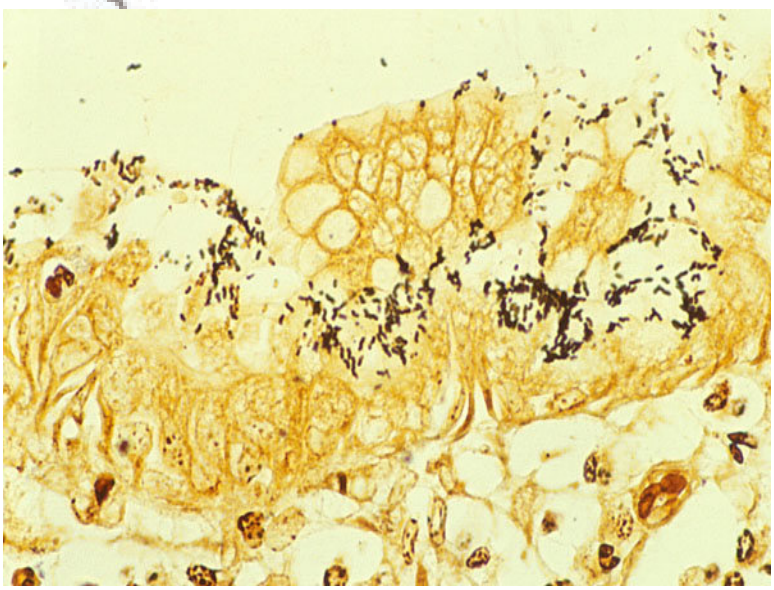
Solution to Question 5:

The given slide shows the GI mucosa, which has been stained with Warthin-Starry silver stain, demonstrating the Helicobacter pylori bacilli.

On antral biopsy, H. pylori organisms are seen abundantly within the surface mucus layer, but they are difficult to visualize with routine hematoxylin (H&E) stains. Organisms are most easily demonstrated with special stains like Warthin-Starry silver stain or Giemsa stain.

The image given below is GI biopsy stained with Warthin-Starry silver stain.



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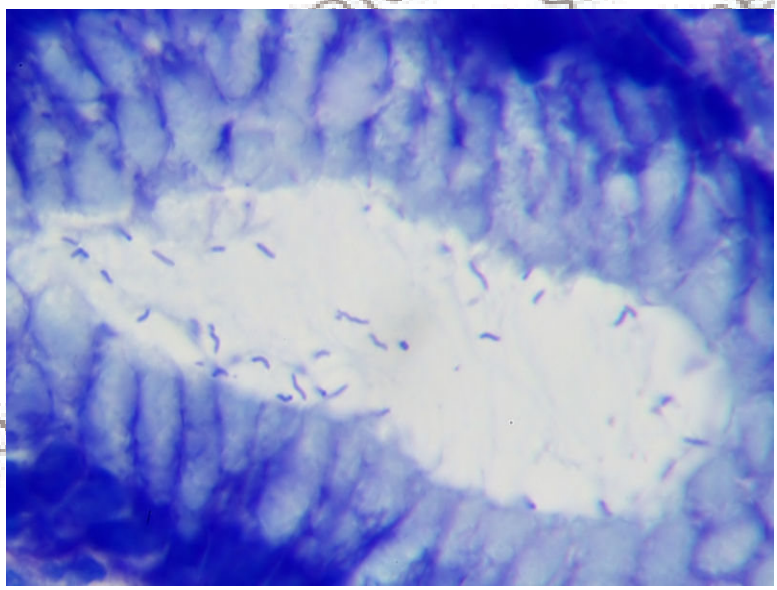
The below image is a Giemsa stain showing Helicobacter pylori in a case of chronic gastritis.



Solution to Question 6:

The given scenario is suggestive of H. pylori gastritis. The preferred site for biopsy is the antrum as H. pylori are most often found in the antrum of the stomach.

H. pylori display tropism for gastric epithelia and are generally not found in the duodenal epithelium. Long-standing H. pylori gastritis may extend to involve the body and fundus, resulting in patchy mucosal atrophy.

The below image is a Warthin-Starry silver stain showing Helicobacter pylori colonized on the surface of the regenerative epithelium of the antrum.

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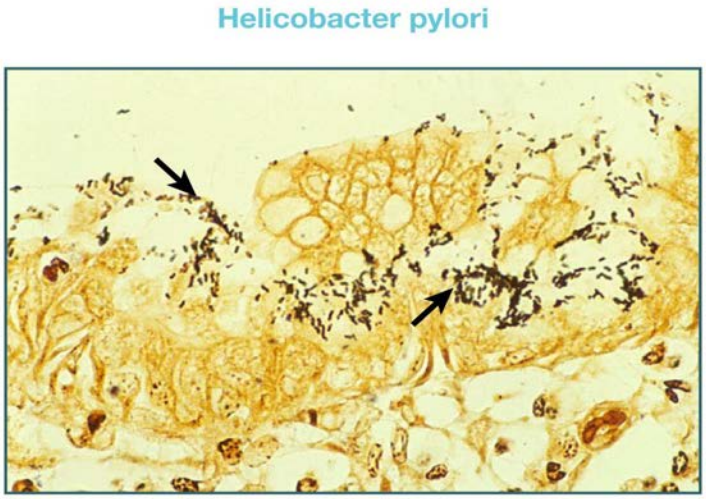

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Solution to Question 7:

Autoimmune gastritis typically spares the antrum.

Autoimmune gastritis causes diffuse mucosal damage of the acid-producing mucosa, within the body and fundus. It accounts for less than 10% of cases of chronic gastritis. CD4+T cells directed against parietal cell components, including the H+/K+ ATPase, are considered to be the principal agents of injury in autoimmune gastritis.

Characteristic features of autoimmune gastritis:

• Antibodies to parietal cells and intrinsic factor

• Reduced serum pepsinogen I concentration

• Hypergastrinemia

• Endocrine cell hyperplasia leads to carcinoid tumors

• Vitamin B12 deficiency (pernicious anemia)

• Defective gastric acid secretion (achlorhydria)

Solution to Question 8:

The most common site of peptic ulcer is the anterior wall of the proximal duodenum, within a few centimeters of the pyloric valve.

Gastric peptic ulcers are predominantly located along the lesser curvature near the interface of the body and antrum.

Locations of peptic ulcers (in decreasing order of frequency):

• Duodenum (first part)

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• Stomach (lesser curvature near the junction of body and antrum)

• Gastroesophageal junction in gastroesophageal reflux disease (GERD) or Barrett's esophagus

• Margins of jejunostomy

• Stomach, duodenum, and/or jejunum in patients with Zollinger–Ellison syndrome

• Ileal Meckel's diverticulum containing ectopic gastric mucosa

The below image shows a peptic ulcer with a round to oval, sharply punched-out defect, and clean mucosal margin

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Solution to Question 9:

The most common complication of peptic ulcers is bleeding.

An ulcer on the posterior wall of the duodenum causes bleeding from the gastroduodenal artery. Gastric ulcer on the lesser curvature of the stomach causes bleeding from the left gastric artery.

Other complications are perforation, obstruction, and malignant transformation.

Note: The most common cause of death in peptic ulcers is perforation followed by bleeding. Perforation accounts for two-thirds of ulcer deaths.

Solution to Question 10:

Curling's ulcers are associated with severe burns or trauma.

Curling's ulcers occur in the proximal duodenum. Systemic hypotension or reduced blood flow caused by stress-induced splanchnic vasoconstriction results in gastric mucosal injury.

Note: Cushing's ulcers arise in individuals with intracranial disease. They occur in the stomach, duodenum, and esophagus and carry a high incidence of perforation.

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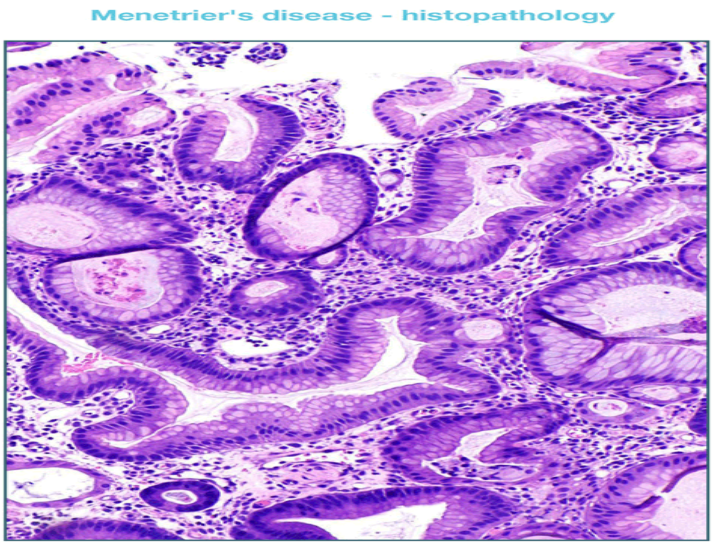
Solution to Question 11:

The given endoscopy image showing irregular enlargement of the gastric rugae in the body is suggestive of Ménétrier disease. It is due to excessive secretion of transforming growth factor α (TGF-α).

Menetrier disease is one of the causes of hypertrophic gastropathy. It is associated with diffuse hyperplasia of the foveolar epithelium and hypoproteinemia due to protein-losing enteropathy. There is an increased risk of gastric adenocarcinoma in adults.

Below histological image shows hyperplasia of foveolar mucous cells. The glands are cystically dilated and elongated with a corkscrew-like appearance.



Solution to Question 12:

Fundic gland polyps are associated with familial adenomatous polyposis (FAP).

Fundic gland polyps may also occur sporadically or with proton pump inhibitor use. They occur in the gastric body and fundus.

They may be asymptomatic or associated with nausea, vomiting, or epigastric pain.

Dysplasia and neoplasia may occur in FAP-associated fundic gland polyps. Another gastric polyp associated with FAP is gastric adenoma.

The below histological image of fundic gland polyp shows cystically dilated, irregular glands lined by flattened parietal and chief cells. Inflammation is typically absent or minimal.

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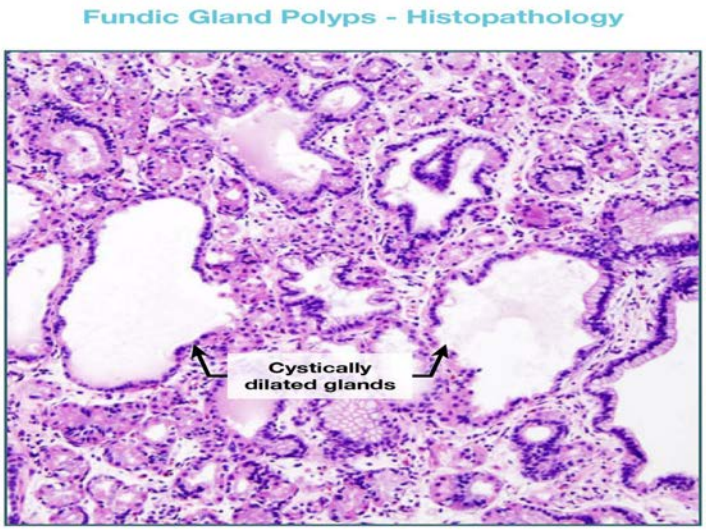

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Solution to Question 13:

The most common site of gastric adenoma is the antrum.

Gastric adenomas are premalignant neoplastic lesions. Patients are usually between 50 and 60 years of age. Males are affected three times more often than females.

The majority of adenomas are composed of intestinal-type columnar epithelium that exhibits varying degrees of dysplasia.

Solution to Question 14:

Zollinger–Ellison syndrome is not a predisposing factor for the development of gastric adenoma. It may predispose to carcinoid tumors.

Risk factors for gastric adenoma:

• Chronic gastritis with atrophy

• Intestinal metaplasia

• Familial adenomatous polyposis

The risk of adenocarcinoma in gastric adenomas is particularly increased in lesions greater than 2 cm in diameter. Overall, carcinoma may be present in up to 30% of gastric adenomas.

Solution to Question 15:

Familial gastric cancer (diffuse type) is strongly associated with germline loss-of-function mutations in the tumor suppressor gene CDH1. It encodes the cell adhesion protein, E-cadherin.

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Half of the sporadic diffuse gastric cancer cases occur due to loss-of-function mutations in CDH1. In the remaining cases, E-cadherin expression is decreased, due to hypermethylation and silencing of the CDH1promoter. Thus, the loss of E-cadherin is a key step in the development of diffuse gastric cancer.

Sporadic intestinal-type gastric cancers are strongly associated with increased signaling via the Wnt pathway (loss-of-function mutation of APC/gain-of-function mutation of ° -catenin).

Mutation of TP53 is also found in the majority of sporadic gastric cancers of both types.

Solution to Question 16:

Linitis plastica or leather bottle stomach or Brintons's disease is seen in diffuse gastric cancer.

Diffuse gastric cancer is an infiltrative tumor and often evokes a desmoplastic reaction that stiffens the gastric wall. When there are large areas of infiltration, diffuse rugal flattening and a rigid, thickened wall may impart a leather bottle appearance as shown below.

Solution to Question 17:

The diffuse-type gastric adenocarcinoma does not form bulky tumors. It grows in a diffuse infiltrating pattern that stiffens the gastric wall (linitis plastica). In contrast, the intestinal type tends to form bulky masses.

Loss of E-cadherin is the key step in the development of diffuse gastric cancer, resulting in discohesive cells. These single cells have large, intracytoplasmic mucin vacuoles that push the nucleus to the periphery, creating a signet-ring cell morphology. Mutation of TP53 is found in a majority of sporadic gastric cancers of both diffuse and intestinal types.

The below H&E-stained smear shows normal gastric mucosa (red arrow) and the characteristic signet cells (green arrows) in a patient with diffuse gastric adenocarcinoma.

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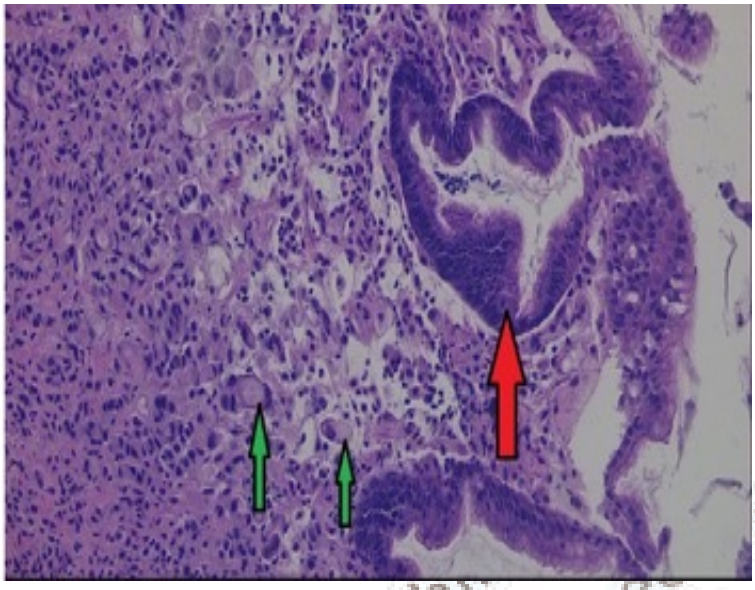

Note: Loss of E cadherin is also seen in lobular carcinoma of the breast.

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Solution to Question 18:

Right axillary lymph nodes are least likely to be involved in gastric cancer metastasis.

Sites most commonly involved in gastric cancer metastasis include the following:

- Supraclavicular sentinel lymph node (Virchow node)
- Periumbilical nodes (Sister Mary Joseph nodule)
- Left axillary lymph node (Irish node)
- Ovary (Krukenberg tumor)
- Pouch of Douglas (Blumer shelf)

Solution to Question 19:

The most common translocation in gastric MALToma is t(11;18)(q21;q21).

Three translocations are associated with gastric MALToma:

- t(11;18)(q21;q21) - Most common
- t(1;14)(p22;q32)
- t(14;18)(q32;q21)

Solution to Question 20:

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The given scenario is suggestive of gastric MALToma. The tumor cells express the B-cell markers CD19 and CD20. They do not express CD5 or CD10.

They are positive for CD43 in about 25% of cases, a T-cell marker that can be diagnostically helpful.

Solution to Question 21:

Gastrointestinal carcinoid tumors can secrete all of the above-mentioned secretory products except noradrenaline.

Carcinoid products at different sites:

- Stomach - Histamine, somatostatin, serotonin
- Duodenum - Gastrin, somatostatin, cholecystokinin
- Jejunum and ileum - Serotonin, substance P, polypeptide YY
- Colon - Serotonin, polypeptide YY.

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Solution to Question 22:

The most aggressive carcinoid tumors of the GIT are seen in the jejunum and ileum.

Carcinoid tumors occur throughout the GI tract. The most common site is the appendix followed by the ileum and rectum.

Ileal carcinoid with metastasis to the liver cause carcinoid syndrome because the vasoactive substances escape the filtering actions of the liver. This is characterized by cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis.

The behavior of the carcinoid tumors differs according to their location:

- Foregut carcinoid tumor
- Stomach; duodenum, proximal to the ligament of Treitz; and esophagus
- Gastric carcinoid tumors originate from gastric enterochromaffin-like (ECL) cells
- Well-differentiated neuroendocrine tumors
- Variable behavior
- Rarely metastasize and are generally cured by resection
- Gastric carcinoid tumors without predisposing factors are often more aggressive
- Midgut carcinoid tumor
- Arise in the jejunum and ileum
- Often multiple
- Tend to be aggressive

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• Hindgut carcinoid

• Arise in the appendix and colorectum

• Appendiceal tumors are usually < 2 cm in diameter and are almost always benign

• Metastasis of rectal carcinoid tumors is uncommon

Gastric carcinoid tumors may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-I, and Zollinger–Ellison syndrome.

Solution to Question 23:

The given scenario is suggestive of carcinoid tumors. The most important prognostic factors include the degree of histological differentiation, mitotic rate, and Ki-67 proliferative index.

The diagnosis of carcinoid tumor is made by increased levels of 5-hydroxy indole acetic acid (5-HIAA) in a 24-hour urine sample. It is positive in larger tumors or if metastases are present.

Note: The most important prognostic factor for esophageal carcinoma and stomach carcinoma is the depth of invasion.

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Solution to Question 24:

The given clinical scenario is suggestive of a gastrointestinal stromal tumor (GIST). It arises from the interstitial cells of Cajal, or pacemaker cells, of the gastrointestinal muscularis propria.

It is the most common mesenchymal tumor of the abdomen. The peak age of incidence is 60 years.

In sporadic GIST, the most common mutations seen are gain-of-function mutation in KIT (75-80%) and PDGFRA mutation (8%). Inherited/germline GIST is seen in Carney–Stratakis syndrome. It is due to loss-of-function mutation of SDH which has increased risk for GIST and paraganglioma.

GIST at a younger age is associated with the following:

• Carney triad:

• Gastric GIST

• Paraganglioma

• Pulmonary chondroma

• Neurofibromatosis type 1

Grossly, it usually forms a solitary, well-circumscribed, fleshy mass covered by ulcerated or intact mucosa.

Histologically, the tumor is composed of spindle cells (most common), epithelioid cells, or mixed cell types.

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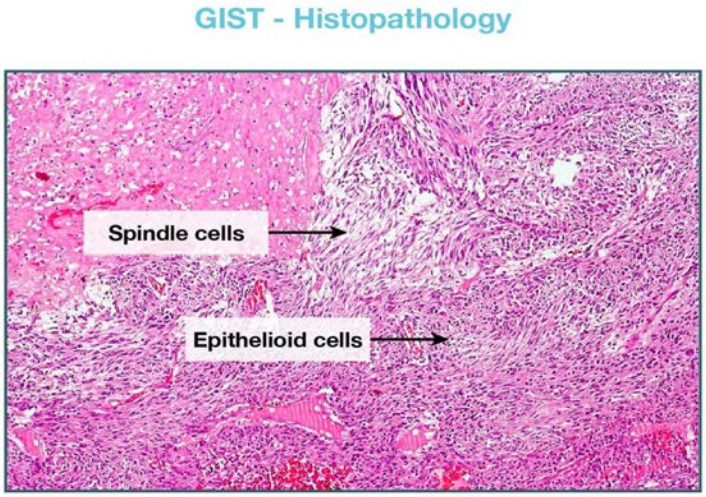
The below image shows microscopy of GIST composed of bundles, or fascicles, of spindle-shaped tumor cells



Complete surgical resection is the primary treatment for localized gastric GIST.

Imatinib, a tyrosine kinase inhibitor used to treat CML, can be used to treat GIST with mutations in KIT or PDGFRA.

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Solution to Question 25:

The most specific marker for gastrointestinal stromal tumor (GIST) is DOG-1.

KIT (CD117) is the best diagnostic marker (most sensitive marker) of GIST. However, 5–10% of GIST lack KIT expression. DOG-1 is expressed in all GIST, including CD117-negative cases. Hence, DOG-1 marker is most specific for GIST.

Solution to Question 26:

Gastric adenocarcinoma is an epithelial tumor of the stomach.

Adenocarcinoma is the most common malignancy (90% cases) of the stomach.

Option A: Carcinoid tumor is a neuroendocrine tumor.

Option B: Lymphoma is a lymphoid tumor.

Option C: GIST is the most common mesenchymal tumor of the abdomen.

Solution to Question 27:

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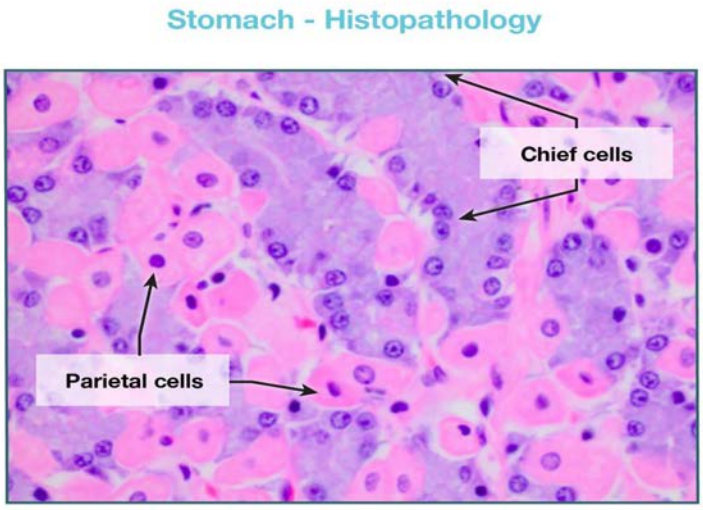
The eosinophilic appearing cells marked as A are the parietal cells, the absence of which is not associated with Zollinger-Ellison Syndrome. The cells marked as B are Chief cells.

Zollinger-Ellison Syndrome is caused by gastrin-secreting neuroendocrine tumors, which leads to parital cell hyperplasia. Gastrinomas are almost always found in the small intestine or pancreas. The most remarkable feature found in the stomach is an increase in oxyntic mucosal thickness due to massive parietal cell hyperplasia.



Other options:

Option A and C: Pernicious anemia is an autoimmune disease characterized by the presence of autoantibodies that impairs the production or activity of the intrinsic factor (IF) that is released from the parietal cells, which is required for the uptake of vitamin B12. There are three types of autoantibodies namely, type I, II, and III. The action of each of these include:

• Autoantibody type I prevents the binding of vitamin B12 to the intrinsic factor (IF).

• Autoantibody type II prevents the binding of vitamin B12-IF complex to the ileal receptors.

• Autoantibody type III acts against the α and ° subunits of the gastric proton pump, which impairs the production of intrinsic factor.

These patients also develop chronic atrophic gastritis, characterized by loss of parietal cells, infiltration of lymphocytes and plasma cells, and megaloblastic changes in mucosal cells.

Option B: Gastric carcinoid tumors originate from gastric enterochromaffin-like (ECL) cells. They are referred to as well-differentiated neuroendocrine tumors. The peak incidence of carcinoid tumors is in the 6th decade. These tumors occur throughout the GI tract, most commonly in the appendix, ileum, and rectum, in decreasing order of frequency.

Gastric carcinoid tumors may be associated with endocrine cell hyperplasia, autoimmune chronic atrophic gastritis, MEN-I, and Zollinger–Ellison syndrome. Ileal carcinoid may cause carcinoid syndrome which is characterized by cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis.

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Small Intestine

Question 1:

What is the most common cause of intestinal obstruction in children younger than 2 years of age?

a) Adhesions

b) Congenital hernia

c) Volvulus

d) Intussusception

Question 2:

A 30-year-old man presented with a history of long-standing diarrhea. Serologic evaluation showed positive anti-tissue transglutaminase antibodies. Duodenal biopsy showed crypt hyperplasia, villi atrophy, and CD8+ cells in lamina propria. Which of the following HLA alleles is associated with this condition?

a) HLA-DR3

b) HLA-DR4

c) HLA-DQ8

d) HLA-DQ4

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Question 3:

A 34-year-old male patient presented to the clinic with a history of diarrhea and poor appetite. He has been having 4-5 episodes of non-bloody, loose stools per day for the last 3 months. A duodenal biopsy is taken and the histopathology is as shown below. Which of the following is the most common cancer associated with this condition?

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a) B cell lymphoma

b) Carcinoid

c) T cell lymphoma

d) Small intestinal adenocarcinoma

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Question 4:

Malabsorption is not due to intestinal mucosal defects in which of the following disorders?

a) Tropical sprue

b) Whipple disease

c) Cystic fibrosis

d) Crohn disease

Question 5:

A 33-year-old man presented to the ER with severe abdominal pain. He gives a history of fever for the past 2 weeks. On examination, faint salmon-colored macules were noted on the trunk and abdomen. Which of the following diseases would you suspect?

a) Typhoid

b) Infective endocarditis

c) Amoebiasis

d) Leishmaniasis

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Question 6:

Which of the following phases is impaired in patients diagnosed with Whipple's disease?

a) Lymphatic transport

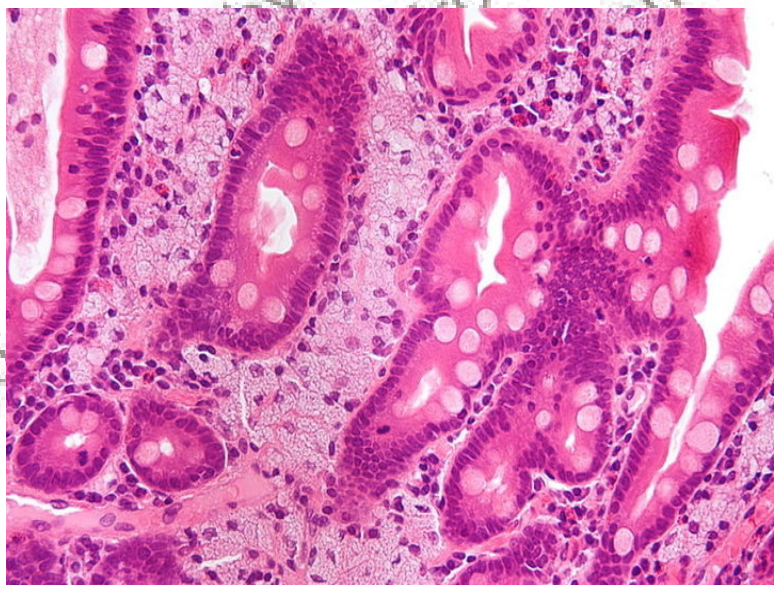
b) Terminal digestion

c) Intraluminal digestion

d) Transepithelial transport

Question 7:

A 35-year-old HIV-positive man is referred for evaluation of malabsorption. A duodenal biopsy shows the following finding. Which special stain can be used further to confirm the diagnosis?



a) PAS stain

b) Acid fast stain

c) Alcian blue stain

d) Mucicarmine stain

Question 8:

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A 2-year-old boy was brought by his parents with complaints of vomiting, watery diarrhea, and fever. A rapid ELISA test for rotavirus was positive. Which of the following viral proteins causes damage to the intestinal epithelium?

a) NSP1

b) NSP2

c) NSP3

d) NSP4

Question 9:

Which of the following is the most common parasitic pathogen in humans?

a) Roundworm

b) Hookworm

c) Plasmodium

d) Giardia

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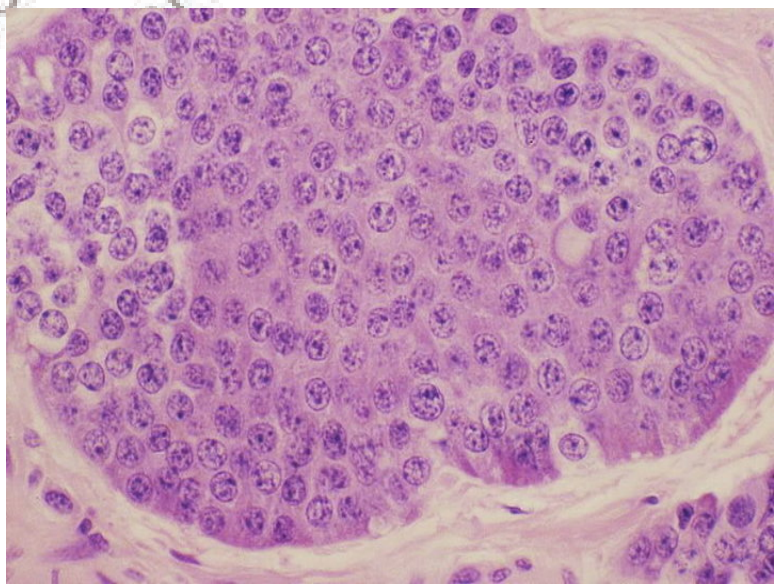
Question 10:

A 55-year-old man who presented with diarrhea and flushing was found to have an ileal tumor. The histological image of the resected specimen is given below. Which of the following markers will these cells be positive for?



a) C-KIT

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b) S-100

c) Synaptophysin

d) DOG1

Question 11:

A 10 month old infant is brought to the OPD with complaints of intractable diarrhea. His past history is significant for autoimmune thyroiditis. On examination, eczematous rashes were seen on the chest and back. Sequencing of which of the following genes would help to arrive at a definitive diagnosis?

a) PTPN22

b) FOXP3

c) MTP

d) CETP

Question 12:

A 7-day-old infant was brought with complaints of profuse watery diarrhea and severe dehydration. On detailed evaluation, labs showed metabolic acidosis and electron microscopy of small bowel biopsy showed characteristic intracellular microvillus inclusions. Mutations in which of the following genes is associated with this condition?

a) Microsomal triglyceride transfer protein

b) MYO5B

c) SMAD4

d) FOXP3

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Answer Key

Question No.	Correct Option
1	d
2	c
3	c
4	c

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5	a
6	a
7	b
8	d
9	d
10	c
11	b
12	b

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Detailed Explanations

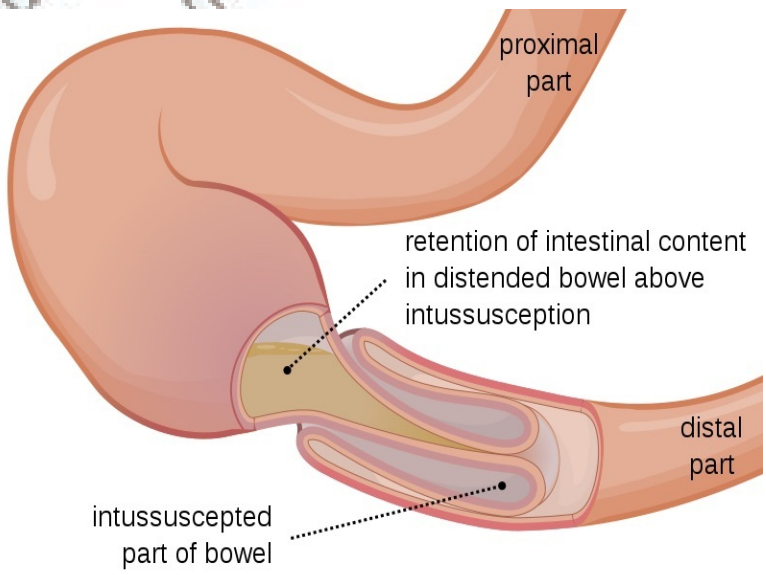
Solution to Question 1:

The most common cause of intestinal obstruction in children < 2 years of age is intussusception.

Intussusception occurs when a segment of the intestine, constricted by a wave of peristalsis, telescopes into the immediately distal segment. It is usually idiopathic at younger ages. However, it can be associated with viral infections and rotavirus vaccines, perhaps due to reactive hyperplasia of Peyer patches.

Untreated intussusception may progress to intestinal obstruction, compression of mesenteric vessels, and infarction.

Note: The most common form of congenital intestinal atresia is imperforate anus. It occurs due to failure of the cloacal diaphragm to involute.



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Solution to Question 2:

The given scenario is suggestive of celiac disease or gluten-sensitive enteropathy. It is associated with HLA-DQ2 and HLA-DQ8 alleles.

It is an immune-mediated enteropathy triggered by the ingestion of gluten-containing foods such as barley, rye, oats, and wheat (mnemonic: BROW) in genetically predisposed individuals.

In these individuals, digestion of the gluten-containing diet leads to the formation of gliadin peptides. These peptides result in the following immune reactions:

• They can activate the epithelial cells to express certain cytokines (IL-15), which result in CD8+ T cell proliferation

• They undergo deamidation and interact with HLA-DQ2 or HLA-DQ8 on the antigen-presenting cells. This leads to CD4+ T cell stimulation and further cytokine production

These mechanisms result in epithelial tissue damage.

Antibodies associated with celiac disease are:

• Anti-gliadin antibodies

• Anti-tissue transglutaminase antibodies (anti-ttG)

• Anti-endomysial antibodies

Microscopic findings include:

• Villi atrophy and flattening

• Crypt hyperplasia

• Increased intraepithelial T cells

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Solution to Question 3:

The given scenario and histopathology findings are suggestive of celiac disease. Enteropathy-associated T-cell lymphoma is the most common cancer associated with celiac disease.

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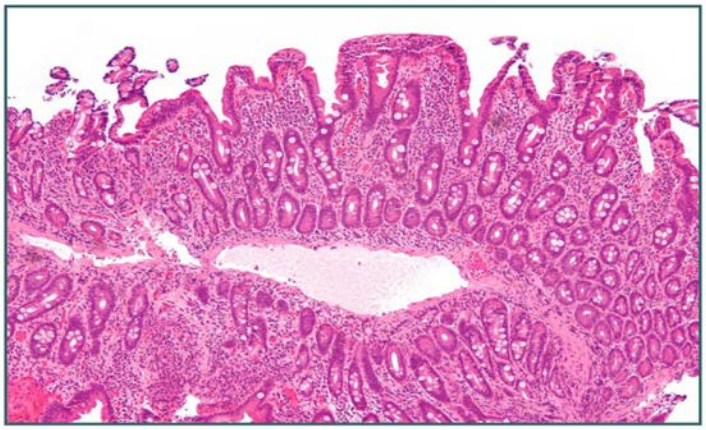
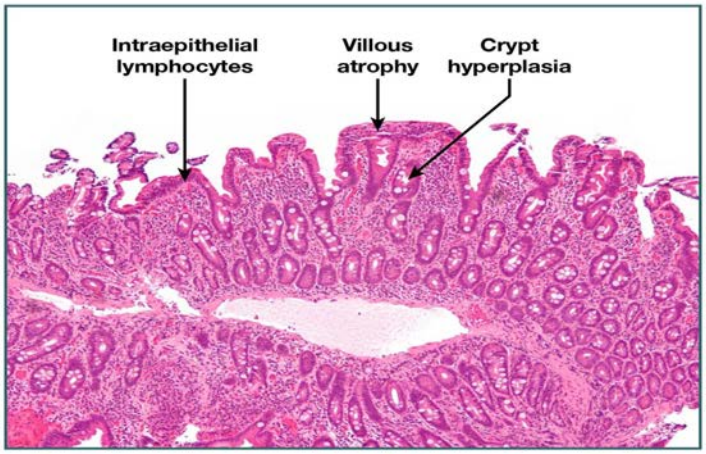
Celiac disease



Celiac disease



Small intestinal adenocarcinoma is also associated with celiac disease.

Celiac disease or celiac sprue or gluten-sensitive enteropathy is triggered by the ingestion of gluten, which is the major storage protein of wheat and similar grains. It usually affects the 2nd part of the duodenum or proximal jejunum.

Antibodies associated with celiac disease are:

• Anti-gliadin antibodies

• Anti tissue transglutaminase antibodies

• Anti endomysial antibodies

MARSH's score is used to assess celiac disease histologically.

Dermatitis herpetiformis occurs in about 10% of patients with celiac disease.

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Solution to Question 4:

In cystic fibrosis, malabsorption occurs due to exocrine pancreatic insufficiency, not intestinal mucosal defects.

Cystic fibrosis is caused by pathogenic mutations in the CFTR gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein.

The absence of CFTR protein interferes with Na^+, HCO_3^-, and water secretion resulting in defective luminal hydration. This causes the formation of pancreatic intraductal concretions and causes exocrine pancreatic insufficiency.

Solution to Question 5:

The given clinical scenario of faint salmon-colored macules is suggestive of rose spots that are seen in typhoid fever.

Rose spots are small erythematous maculopapular lesions that are seen on the chest and abdomen. In the second week of illness, abdominal pain develops and rose spots may be seen, as shown in the following image.

Note: Typhoid ulcers are oval ulcers oriented along the axis of the ileum and carry the risk of perforation. They usually develop in the 3rd week of typhoid.

Solution to Question 6:

In Whipple's disease, the cause of malabsorption is impaired lymphatic transport.

In Whipple disease, clinical symptoms occur because organism-laden macrophages accumulate within the small intestinal lamina propria and mesenteric lymph nodes, causing lymphatic obstruction. These bacteria-laden macrophages also accumulate within mesenteric lymph nodes,

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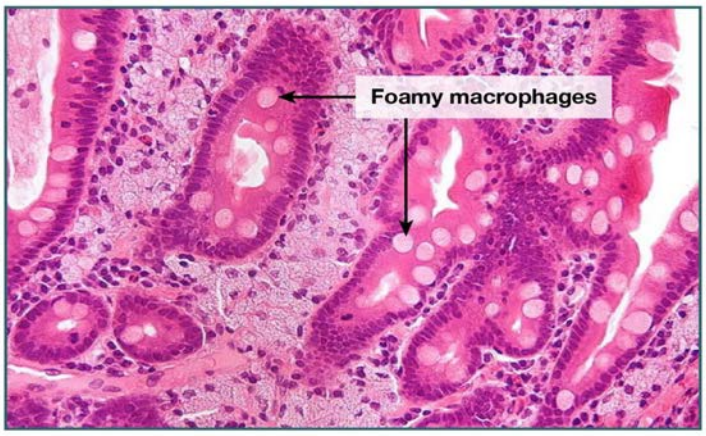
synovial membranes of affected joints, cardiac valves, brain.

The clinical presentation of Whipple disease is usually a triad of diarrhea, weight loss, and arthralgia.

Solution to Question 7:

This clinical scenario and image showing distended foamy macrophages inside the lamina propria are characteristic of Whipple's disease. The diagnosis can be confirmed by acid-fast staining.



Distended foamy macrophages inside the lamina propria of the duodenum can be seen in:

• Whipple's disease

• Intestinal tuberculosis, particularly in immunocompromised hosts

As both organisms are PAS-positive, PAS staining cannot differentiate between the two diseases. On the other hand, acid-fast staining can be used to confirm the diagnosis, as only mycobacteria are acid fast, whereas Tropheryma whipplei is not.

Solution to Question 8:

Rotavirus damages the intestinal epithelium by a viral factor called non-structural protein 4 (NSP4), which can induce epithelial apoptosis.

Rotavirus is a common cause of severe childhood diarrhea and diarrheal mortality worldwide. Rotavirus selectively infects and destroys mature enterocytes in the small intestine. This causes repopulation of the villus surface by immature secretory cells.

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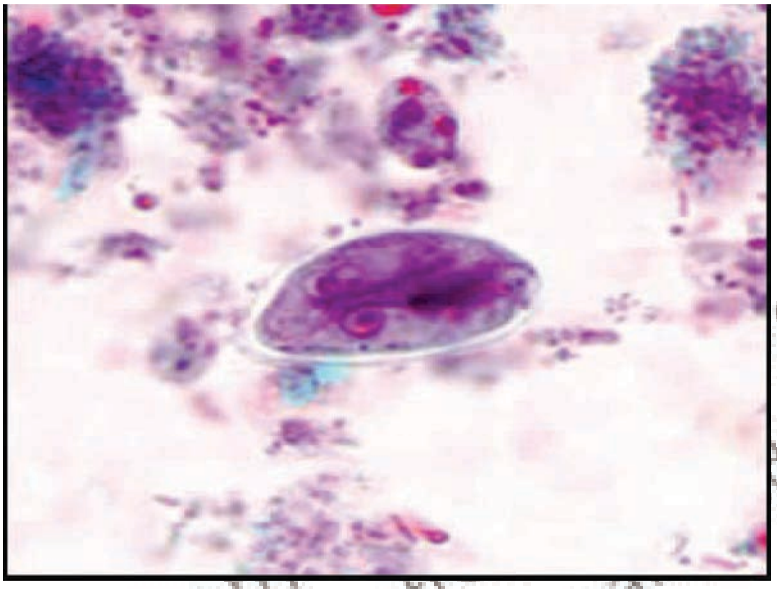
Solution to Question 9:

Giardia lamblia is the most common parasitic pathogen in humans.

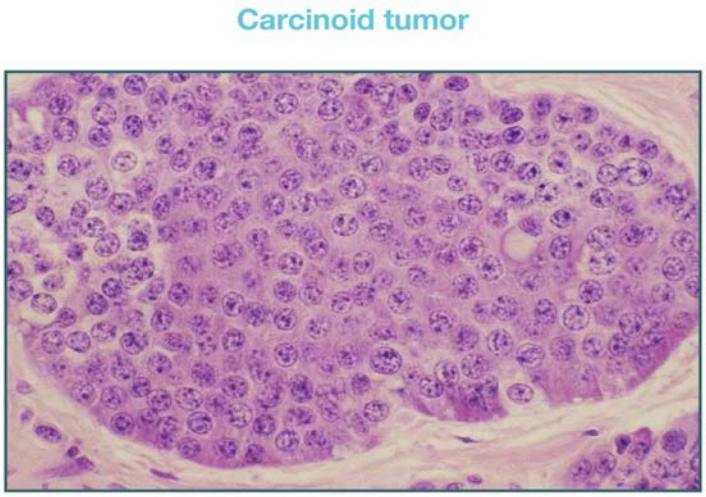
The following image shows teardrop (pear)-shaped Giardia with paired nuclei:



Solution to Question 10:

The given history and histological image are diagnostic of ileal carcinoid. The tumor cells are typically positive for synaptophysin on immunohistochemistry.

Histology of carcinoid typically reveals islands and nests of uniform cells with scant, pink granular cytoplasm and salt and pepper chromatin. Electron microscopy reveals cytoplasmic dense-core neurosecretory granules.



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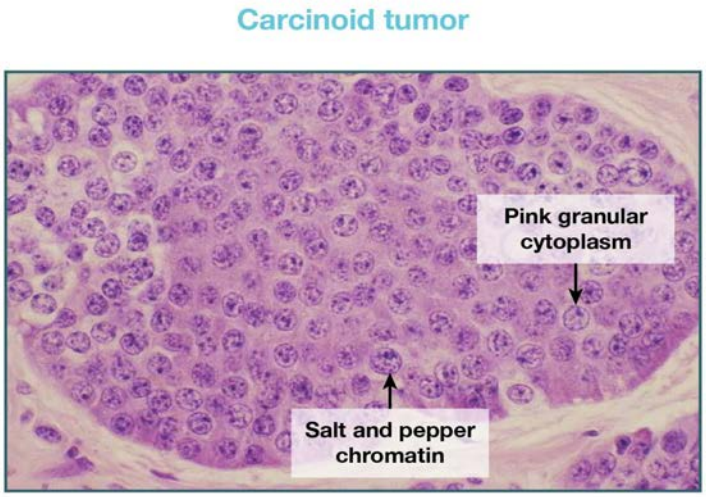

Carcinoid tumors most commonly occur in the gastrointestinal tract. The most common sites in decreasing order of frequency are the appendix, ileum, and rectum. These tumors may cause carcinoid syndrome, which is characterized by cutaneous flushing, sweating, bronchospasm, colicky abdominal pain, diarrhea, and right-sided cardiac valvular fibrosis.

Immunohistochemical (IHC) markers for carcinoid tumors are:

- Neuron-specific enolase
- Synaptophysin
- Chromogranin A
- Leu 7

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Solution to Question 11:

The given scenario is suggestive of autoimmune enteropathy or IPEX syndrome. Definitive diagnosis requires gene sequencing to identify mutations in the FOXP3 gene.

FOXP3 is a transcription factor expressed in CD4+ regulatory T cells.

Autoimmune enteropathy is an X-linked disorder characterized by severe persistent diarrhea and autoimmune disease in young children. A particularly severe familial form is termed IPEX an acronym denoting immune dysregulation, polyendocrinopathy, enteropathy, and X-linked inheritance.

The classic presentation of IPEX is a triad of:

- Failure to thrive with severe chronic diarrhea due to an autoimmune enteropathy
- Autoimmune endocrinopathy (neonatal type 1 diabetes or thyroiditis)
- Dermatitis (usually eczematous)

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Solution to Question 12:

The given scenario is suggestive of microvillus inclusion disease (MVID) which is associated with MYO5B gene mutations.

Microvillus inclusion disease or Davidson disease is an autosomal recessive disorder due to mutations of MYO5B gene. This gene encodes a motor protein that is required for the transport of normal nutrients, ions, water, and plasma membrane components. Hence, it leads to defective vesicular transport that causes deficient brush-border assembly.

Clinical features of MVID are:

• Profuse watery, secretory diarrhea - before 3 months of age (often in the first few days of life)

• Metabolic acidosis

• Hypotonic dehydration

Diagnosis of MVID include:

• Electron microscopy -

• Inclusion containing microvilli in the apical cytoplasm of the intestinal cells.

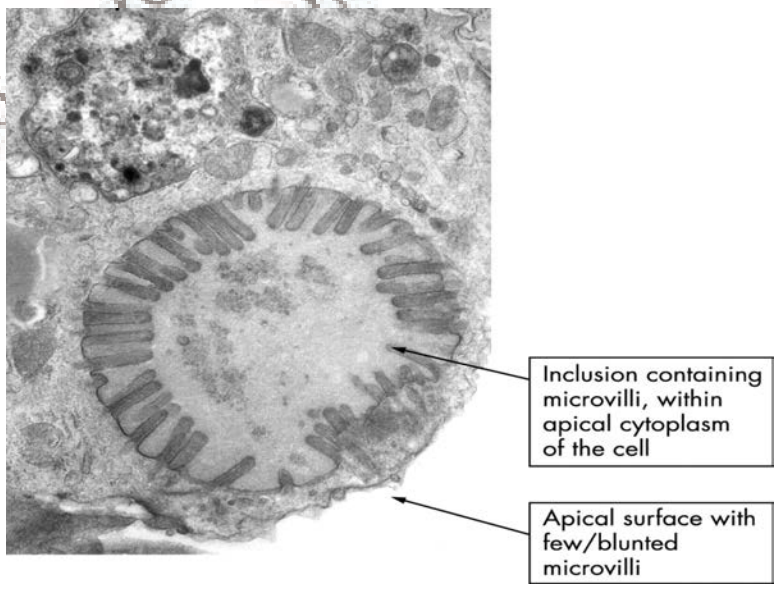
• Brush border microvilli are poorly developed with only a few/blunted microvilli

• Immunostaining of villin (the brush border protein)

• CD10 immunohistochemistry to detect microvillus inclusions

Treatment is total parenteral nutrition and small bowel transplantation.

The following electron microscopy image shows characteristic intracytoplasmic inclusions that are lined by intact microvilli along the absorptive surfaces of the intestinal cells.



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Large Intestine - Non-Neoplastic Conditions

Question 1:

Match the following conditions with their most commonly involved sites.

a) 1-B, 2-D, 3-A, 4-C

b) 1-B, 2-C, 3-A, 4-D

c) 1-C, 2-A, 3-D, 4-B

d) 1-D, 2-B, 3-C, 4-A

Question 2:

Which of the following is true about the pathogenesis of Hirschsprung disease?

a) Failure of migration of neural crest cells

b) Loss of ganglion cells

c) Visceral myopathy

d) Obstruction by inflammatory stricture

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Question 3:

A male infant, with a history of not passing meconium, presented with abdominal distension 2 days after birth. Barium enema showed marked colonic dilation above a narrow segment in the sigmoid region. A biopsy specimen from the narrowed region demonstrated absence of ganglion cells. This disease may be associated with which of the following conditions?

a) Down's syndrome

b) Turner syndrome

c) Edwards syndrome

d) Patau syndrome

Question 4:

What is the most common site of volvulus?

a) Transverse colon

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b) Sigmoid colon

c) Terminal ileum

d) Descending colon

Question 5:

What is the most common site of gastrointestinal ischemia?

a) Ileum

b) Duodenum

c) Jejunum

d) Colon

Question 6:

Campylobacter infection can result in all of the following complications except:

a) Reactive arthritis

b) Guillain-Barre syndrome

c) Erythema nodosum

d) Aplastic crisis

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Question 7:

A pathologist is examining the following histopathological specimen from a patient with watery diarrhea and abdominal pain. What is the most probable diagnosis?

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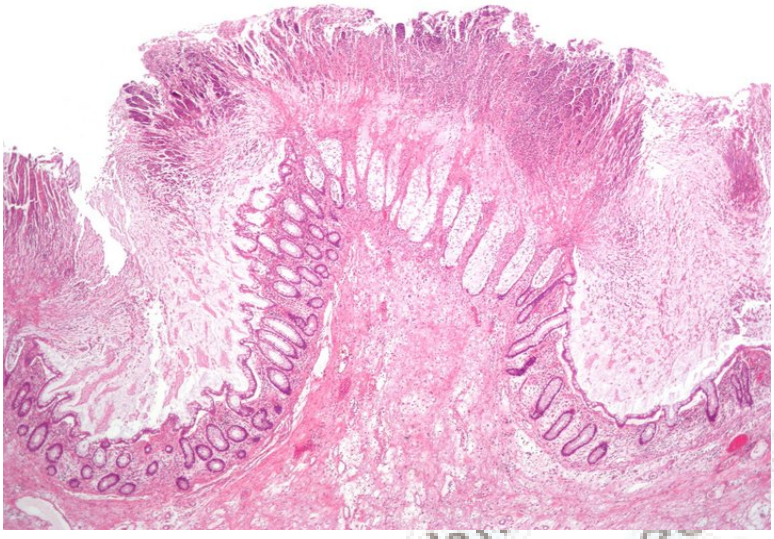

a) Whipple's disease

b) Clostridium difficile colitis

c) Acute exacerbation of Crohn's disease

d) Celiac sprue

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Question 8:

A 30-year-old man presented with loose stools and right lower abdominal pain for the past 6 months. Endoscopy was done which showed skip lesions with a cobblestone appearance. Histopathological examination showed aphthoid ulcerations and focal crypt abscesses. Which of the following genes is associated with this condition?

a) NOD1

b) NOD2

c) NOD3

d) NOD4

Question 9:

An endoscopy was performed on a patient who presented with lower abdominal pain and severe diarrhea. Which of the following is not associated with this condition?

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a) Uveitis

b) Erythema nodosum

c) Clubbing of fingertips

d) Primary biliary cirrhosis

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Question 10:

Which of the following gross findings would you see in the resected bowel segment of a patient with ulcerative colitis?

a) Mucosal bridge

b) Serpentine ulcers

c) Stricture

d) Mural thickening

Question 11:

p-ANCA is positive in which of the following conditions?

a) 2, 3, 4, and 5

b) 3, 4, and 5 only

c) 1, 2, 4, and 5

d) 1, 2, and 3 only

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Question 12:

A pathology resident notes flask-shaped ulcers in an intestinal biopsy sample. This is characteristic of infections caused by which of the following?

a) Mycobacterium tuberculosis

b) Salmonella typhi

c) Giardia lamblia

d) Entamoeba histolytica

Question 13:

Microscopic colitis encompasses which of the following?

a) 1 and 2 only

b) 3 and 4 only

c) 1 and 4 only

d) 2, 3, and 5

Question 14:

A 19-year-old boy with suspected acute appendicitis underwent laparoscopic appendectomy and the resected specimen was sent for histopathological examination. Presence of which of the following is considered confirmatory of this condition?

a) Neutrophilic infiltration in the mucosa

b) Neutrophilic infiltration of the muscularis propria

c) Lymphocytic infiltration in the mucosa

d) Eosinophilic infiltration of the muscularis propria

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Answer Key

Question No.	Correct Option
1	a
2	a
3	a

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4	b
5	d
6	d
7	b
8	b
9	d
10	a
11	c
12	d
13	c
14	b

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Detailed Explanations

Solution to Question 1:

The most common sites of the following conditions are:

A true diverticulum is a blind outpouching of the alimentary tract that communicates with the lumen and includes all three layers of the bowel wall. The most common true diverticulum is Meckel's diverticulum. It most commonly occurs in the ileum. It occurs as a result of the failed involution of the vitelline duct, which connects the lumen of the developing gut to the yolk sac.

The following image shows a Meckel's diverticulum.

Condition	Site
1. True diverticulum	B. Ileum
2. Acquired diverticulum	D. Sigmoid colon
3. Crohn's disease	A. Terminal ileum
4. Polyps	C. Colorectum

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On the other hand, false or acquired diverticula either lack the muscularis entirely or have an attenuated muscularis propria.

Though Crohn's disease most commonly occurs in the terminal ileum, it may occur in any area of the GI tract.

Polyps are most common in the colorectal region. They can be sessile (without stalk) or pedunculated (with stalk). Intestinal polyps can be classified as non-neoplastic or neoplastic in nature. The nonneoplastic polyps can be further classified as inflammatory, hamartomatous, or hyperplastic. The most common neoplastic polyp is an adenoma.

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Solution to Question 2:

Hirschsprung disease occurs due to the failure of migration of the neural crest cells to the bowel wall.

During normal embryogenesis, the neural crest cells migrate from the caecum to the rectum. The enteric neuronal plexuses develop from these migrated neural crest cells.

In Hirschsprung disease, there is an arrest in the migration of these cells, which leads to the development of a distal intestinal segment that is devoid of Meissner (submucosal) and the Auerbach (myenteric) plexus. Hence this segment is referred to as the aganglionic segment.

As a result, there is a lack of coordination in the peristaltic contractions and functional obstruction, which further leads to the dilation of the intestine proximal to the affected segment, leading to congenital megacolon. Diagnosis is confirmed by demonstrating the absence of ganglion cells in biopsy sections.

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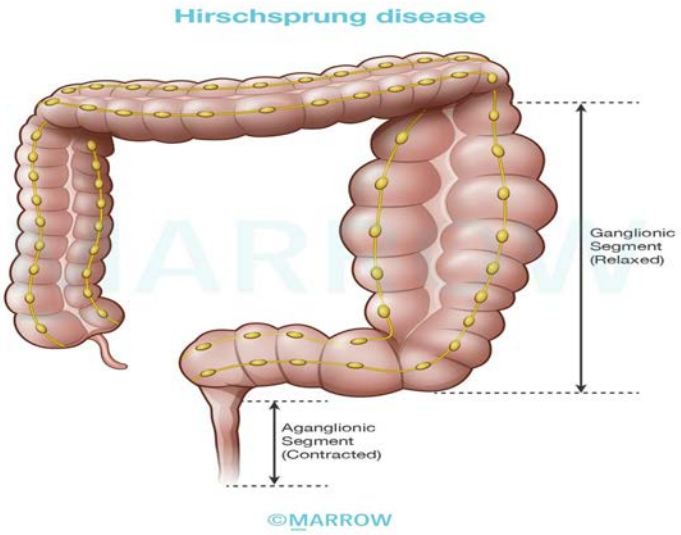

Some conditions may cause acquired megacolon. These include:

- Chagas disease, due to the loss of ganglion cells
- Visceral myopathy
- Obstruction by neoplasm or inflammatory stricture
- Toxic megacolon complicating ulcerative colitis
- Functional psychosomatic disorders

Solution to Question 3:

The given scenario is suggestive of Hirschsprung disease. It is associated with Down's syndrome.

Hirschsprung disease is also known as congenital aganglionic megacolon. 10% of all cases occur in children with Down's syndrome.

The premature arrest of normal migration of neural crest cells from the cecum to the rectum produces aganglionosis of the distal intestinal segment. This causes functional obstruction of the affected bowel and proximal dilation. The absence of ganglion cells in the affected segment in biopsy confirms the diagnosis.

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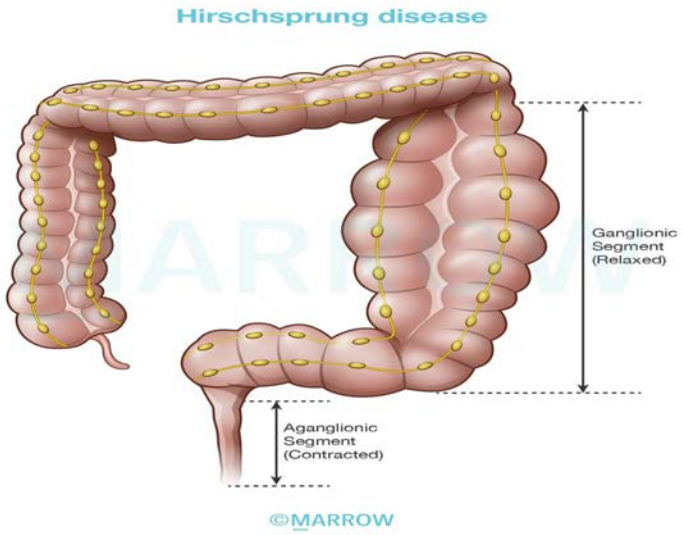

Gastrointestinal abnormalities associated with Down's syndrome include:

- Duodenal atresia
- Annular pancreas
- Hirschsprung disease

Gastrointestinal abnormalities associated with Edwards syndrome (trisomy 18) include:

- Meckel's diverticulum
- Malrotation

Gastrointestinal abnormalities associated with Patau syndrome (trisomy 13) include:

- Omphalocele
- Incomplete rotation of the colon
- Meckel's diverticulum

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Solution to Question 4:

The most common site of volvulus is the sigmoid colon.

The twisting of a loop of the bowel about its mesenteric point of attachment is termed volvulus. Segments involved in volvulus in the decreasing order of frequency are:

- Sigmoid colon
- Cecum
- Small bowel
- Stomach
- Transverse colon

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Solution to Question 5:

The most common site of gastrointestinal ischemia is the colon.

Intestinal segments at the end of their respective arterial supplies are particularly susceptible to ischemia. These are termed watershed zones. These include:

• Splenic flexure - where the superior and inferior mesenteric arterial circulations terminate

• Junction of sigmoid colon and rectum - where the inferior mesenteric, pudendal, and iliac arterial circulations end

Solution to Question 6:

Aplastic crisis is associated with parvovirus infection, not Campylobacter infection.

Campylobacter infection can cause:

• Reactive arthritis, primarily in patients with HLA-B27

• Erythema nodosum

• Guillain–Barré syndrome (GBS)

Molecular mimicry has been implicated in the pathogenesis of GBS because serum antibodies to Campylobacter jejuni lipopolysaccharide crossreact with peripheral and central nervous system gangliosides.

Solution to Question 7:

The given histopathological image shows superficially damaged crypts with a typical pattern of mucopurulent exudates (neutrophils) emanating from a crypt that resembles a volcanic eruption. This is pathognomonic of Clostridium difficile colitis.

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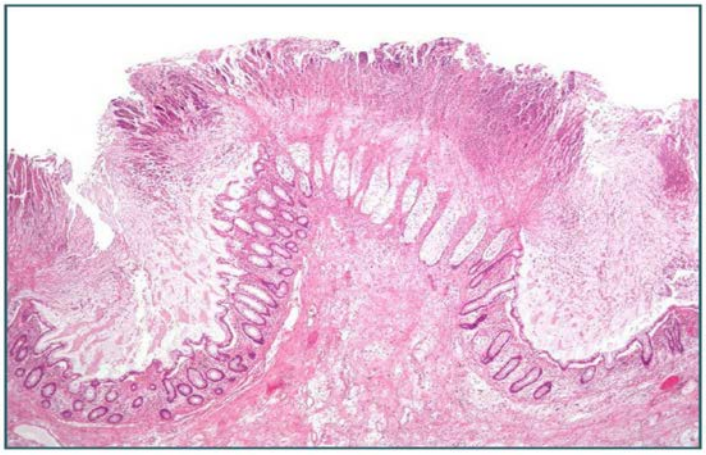
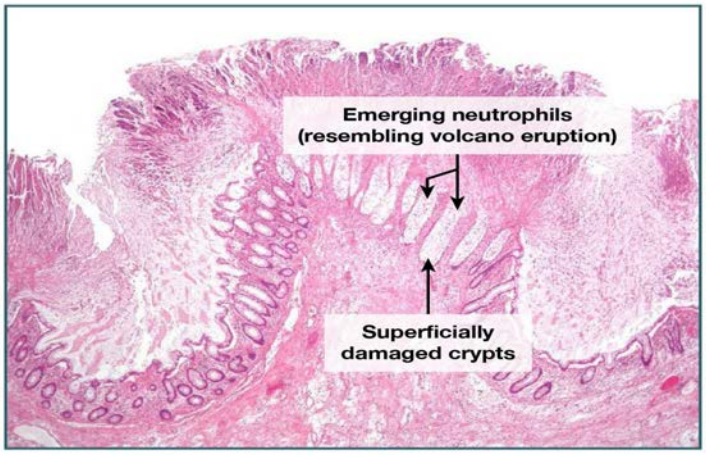
Clostridium difficile colitis



Clostridium difficile colitis



In this condition, disruption of the normal colonic microbiota by antibiotics allows C. difficile overgrowth.

Risk factors for Clostridium difficile colitis are:

• Antibiotic use

• Advanced age

• Gastric suppression- PPIs, H2 receptor blockers

• Immunosuppression

Solution to Question 8:

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The given scenario is suggestive of Crohn's disease. It is strongly associated with mutations in the nucleotide oligomerization binding domain 2 (NOD2) gene.

Crohn's disease occurs due to the host response against microbes. NOD2 encodes an intracellular protein that binds to bacterial peptidoglycans and activates the NF-κB pathway. Antibodies against the bacterial protein flagellin may be seen in NOD2-associated disease.

Other Crohn's disease-related genes are autophagy-related 16-like (ATG16L1), and immunity-related GTPase M (IRGM), which are critical for cellular responses to intracellular bacteria.

Crohn's disease most commonly involves the terminal ileum but can affect all parts of the GIT. The following microscopic changes may be seen:

• Aphthoid ulcerations

• Focal crypt abscesses

• Non-caseating granulomas can be found in all layers of the bowel, lymph nodes, mesentery, peritoneum, liver, and pancreas

Note: Ulcerative colitis-associated genes are ECM1 and HNFA.

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Solution to Question 9:

The given scenario along with cobblestone appearance on endoscopy is suggestive of Crohn's disease. This condition is associated with primary sclerosing cholangitis, not primary biliary cirrhosis.

Extraintestinal manifestations of Crohn's disease include the following:

• Uveitis

• Migratory polyarthritis

• Sacroiliitis

• Ankylosing spondylitis

• Erythema nodosum

• Clubbing of the fingertips

• Primary sclerosing cholangitis (less frequently than ulcerative colitis)

• Cutaneous granulomas form nodules referred to as metastatic Crohn's disease (a misnomer since there is no cancer)

Solution to Question 10:

In ulcerative colitis, regenerating mucosa often bulges into the lumen to create pseudopolyps and the tips of these polyps may fuse to create mucosal bridges.

Features characteristic of ulcerative colitis are:

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• Proctocolitis/ backwash ileitis

• Mucosa and superficial submucosal involvement

• Broad-based ulcers

• Pseudopolyps and mucosal bridges

• Toxic megacolon

Note: Granulomas, strictures, and mural thickening are features of Crohn's disease.

Solution to Question 11:

Henoch-Schönlein purpura is associated with IgA immune complex deposition in the small vessels, not p-ANCA.

The following conditions are positive for perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA):

• Ulcerative colitis

• Crohn's disease

• Churg–Strauss syndrome

• Microscopic polyangiitis

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Antibodies	Ulcerative colitis	Crohn's disease
p-ANCA	Present in majority (75 %)	Present in minority (11 %)
Antibodies toSaccharomyces cerevisiae	Absent	Present

Solution to Question 12:

Flask-shaped ulcers are characteristic of amoebiasis, which is caused by Entamoeba histolytica.

It most often affects the cecum and ascending colon. Parasites may also penetrate splanchnic vessels and embolize to the liver to produce amoebic liver abscesses.

Image showing flask-shaped ulcers of amoebiasis:

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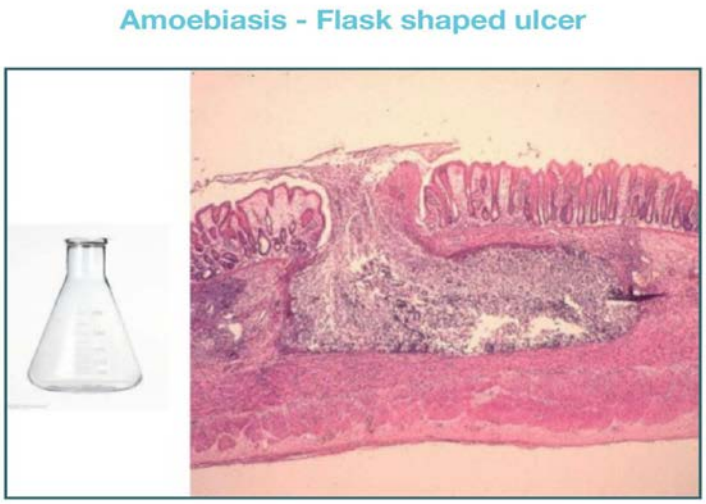

Option A: In TB, ulcers are perpendicular to the axis of the intestine (transverse ulcers).

Option B: In typhoid, ulcers are oriented along the axis of the intestine (longitudinal ulcers).

Option C: Ulceration is not a feature of giardiasis.

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Solution to Question 13:

Microscopic colitis encompasses two types of disorders - collagenous colitis and lymphocytic colitis.

Lymphocytic colitis shows a strong association between celiac disease and autoimmune diseases, including Graves disease and rheumatoid arthritis.

These idiopathic diseases both present with chronic, non-bloody, watery diarrhea without weight loss.

Collagenous colitis	Lymphocytic colitis
Dense subepithelial collagen layer	Subepithelial collagen layer i s of normal thickness
Increased numbers of intraep ithelial lymphocytes	Higher ratio of intraepithelial lymphocytes

Solution to Question 14:

The diagnosis of acute appendicitis is confirmed by the presence of neutrophilic infiltration of the muscularis propria.

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Surgical exploration is done when clinical suspicion for appendicitis is high but imaging studies are negative, nondiagnostic, or unavailable. In such situations, appendicitis can only be diagnosed intraoperatively or pathologically.

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Large Intestine - Neoplastic Conditions

Question 1:

What is the most common malignancy of the GI tract?

a) Gastric adenocarcinoma

b) Gastrointestinal stromal tumor

c) Adenocarcinoma colon

d) Carcinoid tumor of appendix

Question 2:

Which of the following patients is at an increased risk of developing malignancy?

a) A 50-year-old man with hyperplastic polyps

b) A 30-year-old woman with inflammatory polyps

c) A 10-year-old girl with retention polyps

d) A 40-year-old man with sessile serrated polyps

Question 3:

Which of the following sites is most commonly involved in patients with juvenile polyps?

a) Sigmoid colon

b) Jejunum

c) Transverse colon

d) Rectum

Question 4:

A 5-year-old child was admitted to the hospital with a history of prolapsing rectal mass and painless rectal bleeding. The histopathological image of the mass is as shown below. What is the most likely diagnosis?

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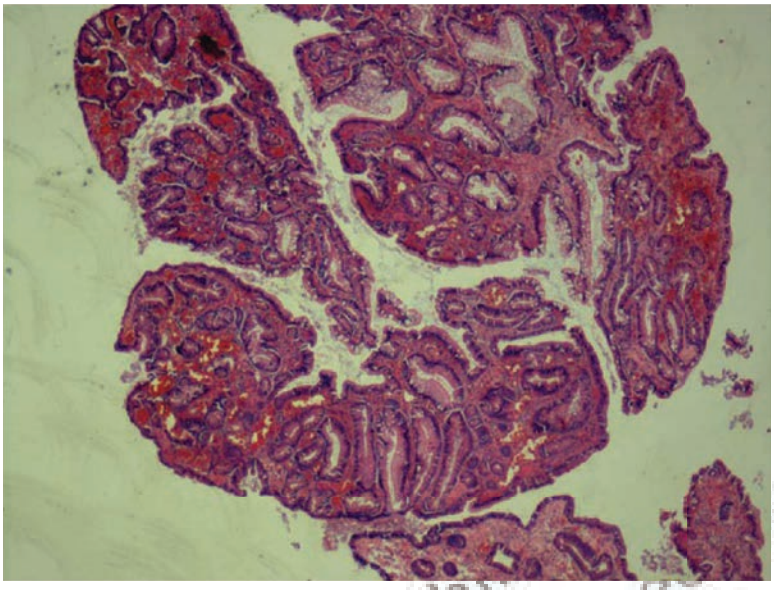

a) Peutz Jegher syndrome

b) Villous adenoma

c) Juvenile polyp

d) Tubular adenoma

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Question 5:

Patients with which of the following diseases have the highest risk of developing colorectal cancer?

a) Juvenile polyposis syndrome

b) Ulcerative colitis

c) Familial adenomatous polyposis

d) Peutz-Jeghers syndrome

Question 6:

What is the minimum number of polyps necessary for the diagnosis of familial adenomatous polyposis?

a) 40

b) 10

c) 80

d) 100

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Question 7:

Indirect ophthalmoscopy of an infant revealed congenital hypertrophy of the retinal pigment epithelium. This is seen as an extraintestinal manifestation in association with which of the following conditions?

a) Classic FAP

b) Turcot syndrome

c) Peutz-Jegher syndrome

d) Attenuated FAP

Question 8:

Which of the following is incorrect about Peutz-Jeghers syndrome?

a) It has an autosomal recessive inheritance

b) Baseline colonoscopy must be done at 20 years of age

c) There is increased risk of ovarian and uterine cancer

d) It is associated with loss-of-function mutations in STK11

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Question 9:

A 60-year-old man presented with complaints of chronic diarrhea, loss of weight, and hair loss. On examination, pallor, nail atrophy, and abnormal skin pigmentation were noted. On endoscopic evaluation, multiple sessile polyps were visualized in the small bowel and colon. What is the most likely diagnosis?

a) Bannayan-Ruvalcaba-Riley syndrome

b) Cronkhite-Canada syndrome

c) Gardner syndrome

d) Peutz-Jeghers syndrome

Question 10:

Which of the following acts as the initiating mutation in the majority of sporadic colon cancers?

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a) Gain-of-function mutation of APC

b) Loss-of-function mutation of APC

c) Gain-of-function mutation of TP53

d) Loss-of-function mutation of TP53

Question 11:

A 70-year-old man with hematochezia and weight loss is diagnosed with colorectal cancer. Which of the following is the most important prognostic factor for this condition?

a) Site of lesion

b) Tumor histology

c) Age of patient

d) Lymph node status

Question 12:

A 52-year-old lady has just been diagnosed with endometrial carcinoma. On taking history, she revealed that both her mother and her elder sister had been diagnosed with synchronous colorectal and endometrial cancer in their forties. She should be tested for mutations in which of the following genes?

a) APC

b) MSH

c) MYH

d) BRAF

Question 13:

Which of the following is incorrect about tumors of the appendix?

a) The most common tumor is carcinoid

b) Primary adenocarcinoma is usually serous

c) Goblet cell variant of carcinoid is more aggressive

d) Peritoneal dissemination can result in pseudomyxoma peritonei

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Answer Key

Question No.	Correct Option
1	c
2	d
3	d
4	c
5	c
6	d
7	a
8	a
9	b
10	b
11	d
12	b
13	b

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Detailed Explanations

Solution to Question 1:

Adenocarcinoma of the colon is the most common malignancy of the GI tract.

Tumors in the proximal colon often grow as polypoid, exophytic masses. These tumors rarely cause obstruction.

Carcinomas of the distal colon tend to be annular lesions that produce napkin-ring constrictions and luminal narrowing.

Solution to Question 2:

Patients with sessile serrated polyps are at an increased risk of developing malignancy.

Histologically, sessile serrated polyps appear like hyperplastic polyps, but a serrated architecture throughout the full length of the glands and lateral growth is the differentiating feature. They lack cytological features of dysplasia.

Solution to Question 3:

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The most common site of juvenile polyps is in the rectum.

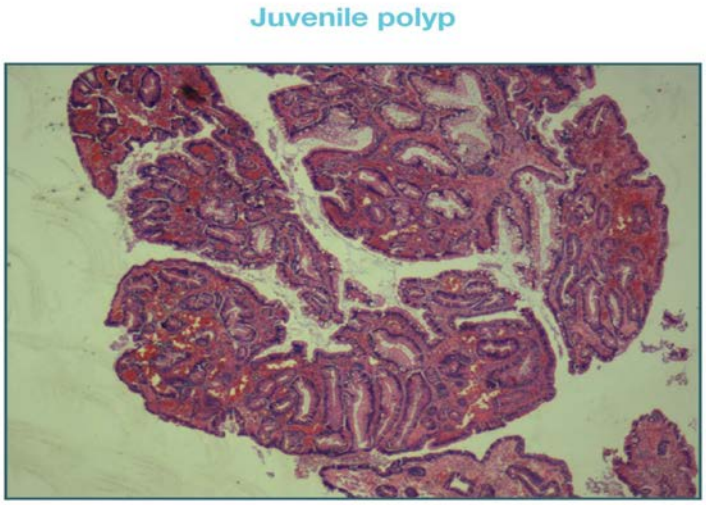
Juvenile polyps are focal malformations of the epithelium and lamina propria. They may be sporadic or syndromic. They typically present with rectal bleeding in children < 5 years.

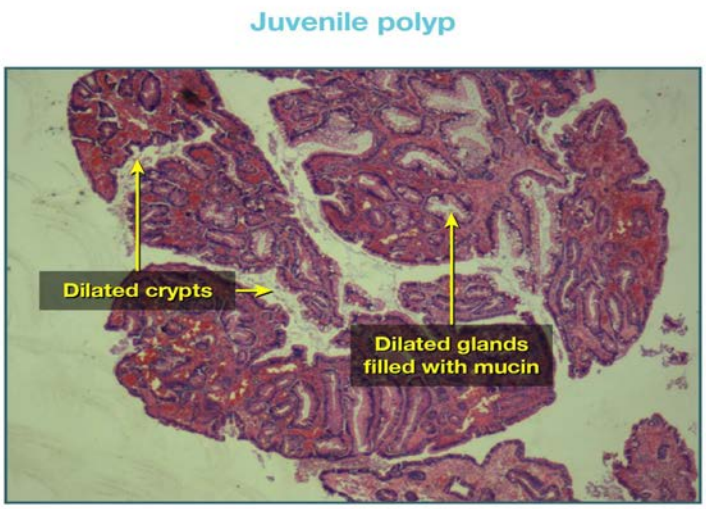
• Sporadic juvenile polyps - solitary lesions, also called retention polyps

• Juvenile polyposis - autosomal dominant syndrome with multiple hamartomatous polyps that have malignant potential

Solution to Question 4:

The clinical features and the histopathological image showing characteristic cystically dilated crypts and glands are suggestive of a juvenile polyp.





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Juvenile polyps are malformations of epithelium and lamina propria commonly located in the rectum. It is seen in children <5 years of age. The typical presentation is painless rectal bleeding. Sometimes there may be a proliferating rectal mass.

The disease may be sporadic or syndromic.

• Sporadic juvenile polyp occurs as a single mass and is called retention polyp.

• Juvenile polyposis syndrome is characterized by multiple hamartomatous polyps, which may be premalignant.

Morphologically, both of these types are indistinguishable.

• Gross appearance: They appear as pedunculated, smooth reddish lesions, and with cystic spaces.

• Microscopic appearance: The cysts appear as dilated glands filled with mucin and inflammatory debris.

Note: Complex glandular architecture and the presence of smooth muscle cutting through the lamina propria are seen in Peutz-Jeghers polyps.

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Solution to Question 5:

Patients with familial adenomatous polyposis (FAP) have the highest risk of developing colorectal cancer. 100% of untreated patients with FAP develop colorectal carcinoma, often before the age of 30 years.

Solution to Question 6:

The diagnosis of familial adenomatous polyposis (FAP) requires ≥100 polyps.

The current definition of familial adenomatous polyposis (FAP) requires evidence of any one of the below:

• Germline mutation in APC gene

• ≥100 colorectal adenomatous polyps (classical definition)

• Any colorectal adenomas < 30 years in a patient with a family history of FAP

• Intra-abdominal desmoid fibromatosis, osteoma of the mandible, or multiple epidermoid cysts in a patient with a family history of FAP

Colorectal adenocarcinoma develops in 100% of untreated FAP patients, often before age of 30 years and nearly always by age of 50 years.

Attenuated FAP is a less severe form of FAP with the following features:

• Usually <100 adenomas

• First appear usually in late childhood

• Adenomas usually ≤1 cm until adulthood

• Adenomas fewer and later

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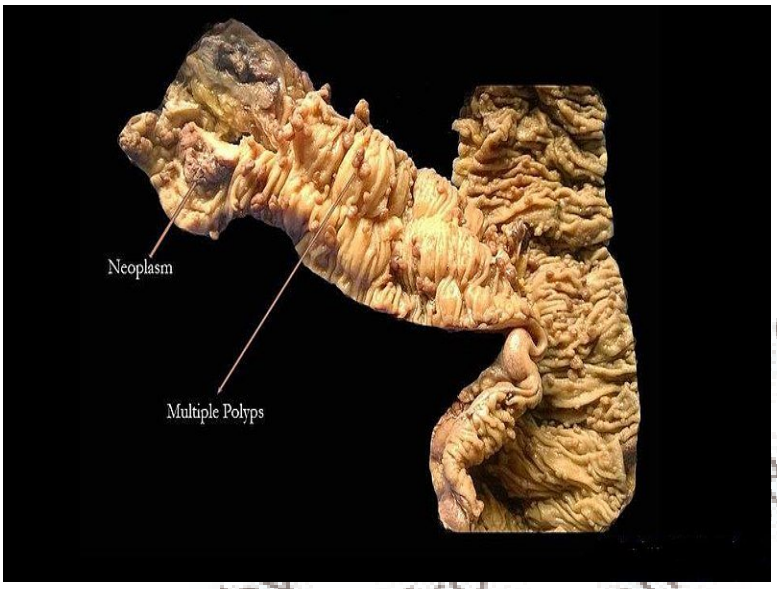
• Adenomas and carcinomas 60–75% right-sided

• The mean age of carcinoma is 55 years

The following image shows a gross specimen of familial adenomatous polyposis (FAP):



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Solution to Question 7:

Classic FAP and Gardner's syndrome are associated with congenital retinal pigment epithelium (RPE) hypertrophy.

Congenital hypertrophy of the RPE can be generally detected at birth and is, therefore, an adjunct to the early screening of FAP.

Solution to Question 8:

Peutz-Jeghers syndrome is an autosomal dominant syndrome.

It is commonly associated with germline heterozygous loss-of-function mutations in the gene STK11.

It is characterized by:

• Multiple gastrointestinal hamartomatous polyps

• Mucocutaneous hyperpigmentation

• Increased risk of gastrointestinal and extraintestinal malignancies (including ovarian and uterine cancer)

Baseline colonoscopy and upper endoscopy for screening are done at 20 years of age, followed by annual flexible sigmoidoscopy thereafter.

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Solution to Question 9:

The given scenario of intestinal polyps, cutaneous pigmentation, and diarrhea points toward a diagnosis of Cronkhite–Canada syndrome.

It is a non-hereditary polyposis syndrome that occurs at a mean age of 50 years.

Clinical features include:

• Diarrhea and abdominal pain

• Nail atrophy, hair loss, and cutaneous hyperpigmentation

• Cachexia and anemia

• Characterized by hamartomatous polyps of the stomach, small intestine, and colon due to abnormalities in the nonpolypoid mucosa

Solution to Question 10:

The majority of sporadic colon tumors typically include loss of function mutation of APC gene, early in the neoplastic process (the classic adenoma-carcinoma sequence).

About 10-15% of sporadic colon cancers involve the microsatellite instability pathway, which is associated with DNA mismatch repair defects (Lynch syndrome).

Solution to Question 11:

The two most important prognostic factors of colorectal cancer are the depth of invasion and the presence of lymph node metastases.

The liver is the most common site of metastasis from the colon due to its portal drainage.

Solution to Question 12:

The given scenario is suggestive of hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome. She should be tested for mutations in MSH genes.

It occurs due to defective DNA mismatch repair. It is caused by inherited mutations in genes that encode proteins responsible for the detection, excision, and repair of errors that occur during DNA replication. They include MLH1, MSH2, MSH6, and PMS2 or EPCAM genes.

It is the most common syndromic cause of colon cancer. It tends to occur at younger ages than sporadic colon cancers and often involves the right colon. Familial clustering of cancers occurs at several sites including:

• Colorectum, small bowel, and stomach

• Endometrium and ovary

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- Ureters
- Brain
- Hepatobiliary tract and pancreas
- Skin

Solution to Question 13:

Primary adenocarcinoma of the appendix is usually of mucinous type.

Peritoneal dissemination of mucinous tumors can cause pseudomyxoma peritonei.

The most common tumor of the appendix is carcinoid tumor. This neoplasm, which is almost always benign, most frequently forms a solid bulbous swelling at the distal tip of the appendix. Goblet cell variant of carcinoid tumor is more aggressive.

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Congenital anomalies, ARDS, Infections

Question 1:

What are neuroendocrine cells in the bronchial mucosa called?

a) Type I pneumocytes

b) Type II pneumocytes

c) Clara cells

d) Kulchitsky cells

Question 2:

In which of the following are the pores of Kohn located?

a) Terminal bronchiole

b) Lung capillary

c) Alveoli

d) Respiratory bronchiole

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Question 3:

Which of the following is false about alveolar epithelium?

a) Type 1 cells are not involved in surfactant production

b) Type 1 cells form the lining epithelium of alveoli

c) Type 2 cells are involved in the repair of the epithelium

d) Type 2 cells are involved in gaseous exchange

Question 4:

Ciliocytophthoria is seen in:

a) Acute respiratory infection

b) Kartagener syndrome

c) Situs inversus

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d) Cystic fibrosis

Question 5:

What is the most common site of foregut cyst?

a) Middle mediastinum

b) Anterior mediastinum

c) Posterior mediastinum

d) Superior mediastinum

Question 6:

Which of the following is not a reversible disorder?

a) Compression atelectasis

b) Resorption atelectasis

c) Obstructive atelectasis

d) Contraction atelectasis

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Question 7:

An infant born to a diabetic mother develops difficulty in breathing within 30 minutes of birth. Within a few hours, cyanosis becomes evident. Fine rales are heard over both lung fields. A chest x-ray film shows ground-glass picture. Which of the following is incorrect about this condition?

a) It is associated with respiratory failure and poor prognosis despite treatment

b) There is deficiency of surfactant produced by type II alveolar cells

c) Increased corticosteroid release lower the risk of developing RDS

d) On microscopy, hyaline membranes with fibrin and necrotic cell debris are seen

Question 8:

A newborn baby born at term was noted to have respiratory distress. Radiography revealed diffuse ground-glass opacities in all lung fields. Exogenous surfactant administration resulted in a brief improvement, but his condition continued to worsen once surfactant therapy was

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stopped. Which is the most common genetic mutation associated with this disorder?

a) ABCA3

b) Surfactant Protein B

c) GM-CSF

d) Surfactant Protein C

Question 9:

A 76-year-old woman is brought to the casualty with high-grade fever, dysuria, and flank pain. On examination, she is disoriented with suprapubic and costovertebral angle tenderness. Her BP is 70/40 mm Hg, pulse rate is 130/min, and her temperature is 103 ºF. She becomes increasingly hypoxic after admission and requires ventilation. What is the likely reason for respiratory failure?

a) Alveolar proteinosis

b) Diffuse interstitial inflammation

c) Diffuse pulmonary hemorrhage

d) Diffuse alveolar damage

Question 10:

A 68-year-old man presented with episodes of shortness of breath and coughing at night that awaken him from sleep. He was diagnosed with COPD 7 years ago. On examination, distended neck veins were observed and S3 was heard on auscultation. Bronchoalveolar lavage of this patient is given below. Identify the marked cells.

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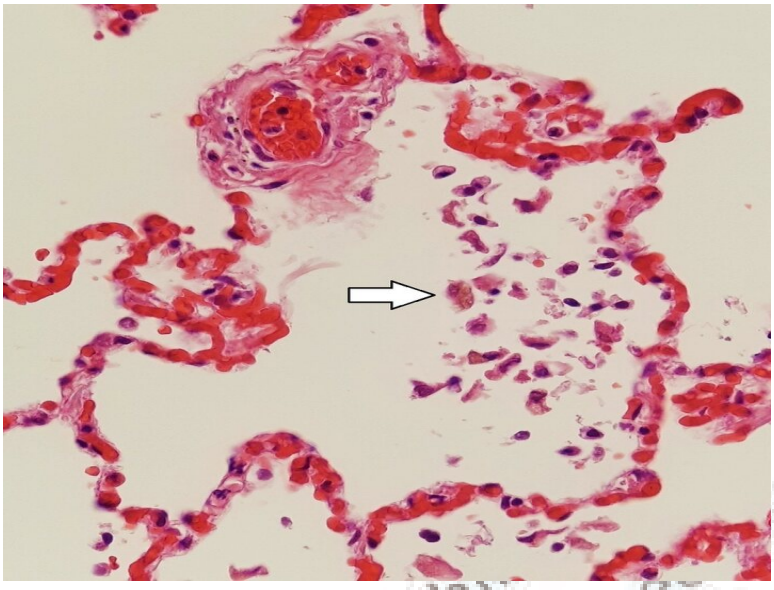

a) Inflammatory cells

b) Siderophages

c) Type I pneumocytes

d) Cardiac smooth muscle

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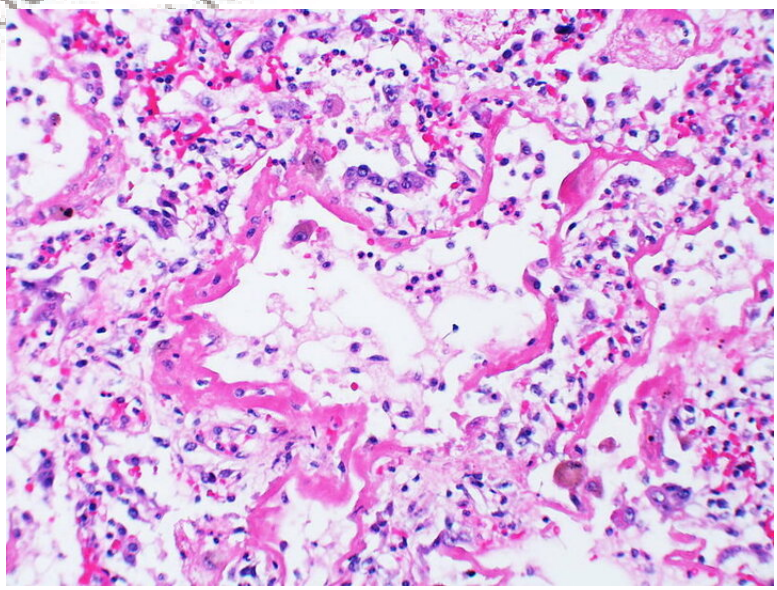
Question 11:

A pathologist is examining the following histopathological section of an alveolus. All of the following can be associated with this finding except:



a) Pneumonia

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b) Burns

c) Near-drowning

d) Heart failure

Question 12:

Which of the following occurs in the stage of gray hepatization in pneumonia?

a) Accumulation of WBCs in the alveoli

b) Accumulation of RBCs in the alveoli

c) Serous exudate in the alveoli

d) Accumulation of fibrin in the alveoli

Question 13:

Which of the following is not seen in patients with viral pneumonia?

a) Presence of interstitial inflammation

b) Predominance of alveolar exudates

c) Bronchiolitis

d) Multinucleate giant cells in the bronchiolar wall

Question 14:

A 65-year-old HIV-positive man presented with fever and breathlessness for 2 weeks. Imaging shows dense infiltration in the lower lobe and the lung biopsy showed the following finding. What is the diagnosis?

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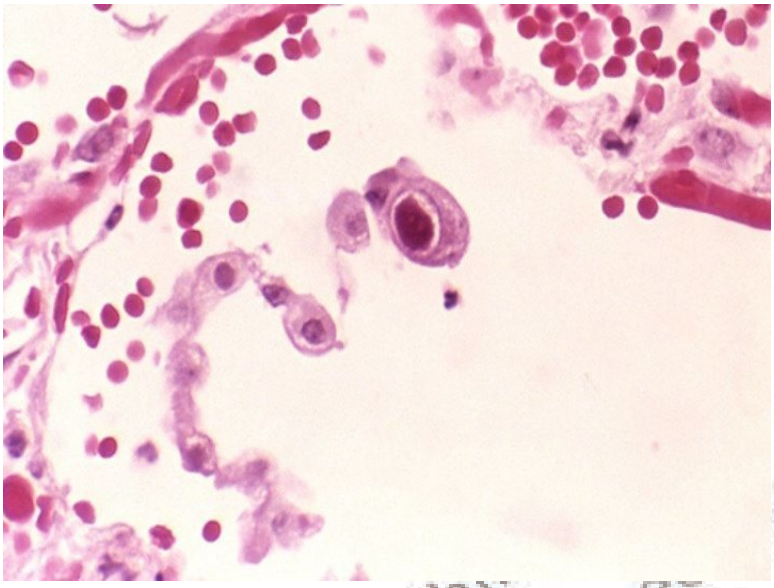

a) Small-cell lung cancer

b) CMV-associated organizing pneumonia

c) Cryptococcal pneumonia

d) Tuberculosis

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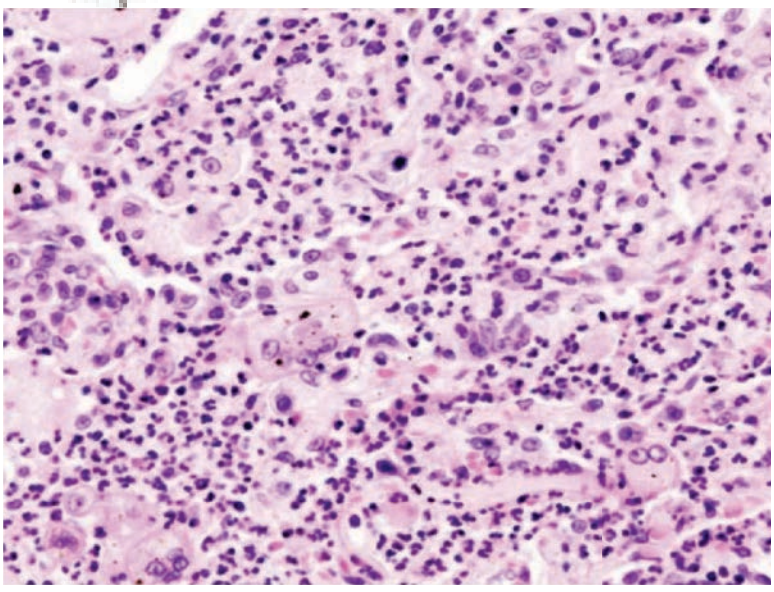
Question 15:

A 28-year-old woman underwent an emergency LSCS under general anesthesia to deliver a term, healthy infant. Two hours later, she developed sudden tachypnea, cyanosis, and massive pulmonary edema and died despite resuscitative measures. The histopathological picture of her lung is shown below. What is the likely cause of death?



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a) Mendelson's syndrome

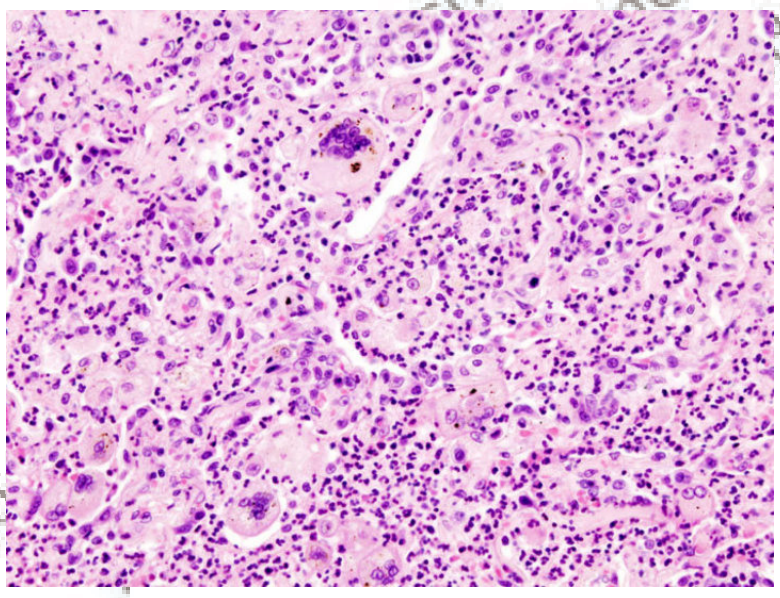
b) Cryptogenic organizing pneumonia

c) CMV pneumonia

d) Pneumocystis carinii pneumonia

Question 16:

A 35-year-old depressed man came with complaints of sudden onset breathlessness, with desaturation. Chest x-ray showed bilateral diffuse infiltrates with predominant involvement of right middle and lower lobes. The patient could not be revived despite treatment. On autopsy, the lungs appeared grossly normal. The histopathology image of the lung is as shown below. Which among the following is the appropriate cause?



a) Necrotizing TB granuloma

b) Vegetative matter aspiration pneumonia

c) Sarcoid granuloma

d) Severe fungal pneumonia

Question 17:

A 25-year-old man presented with fever, productive cough, and breathlessness of 2 months duration. CECT chest revealed bilateral upper lobe fibrotic lesions and enlarged mediastinal lymph nodes. Lymph node biopsy revealed the following. What is the most probable diagnosis?

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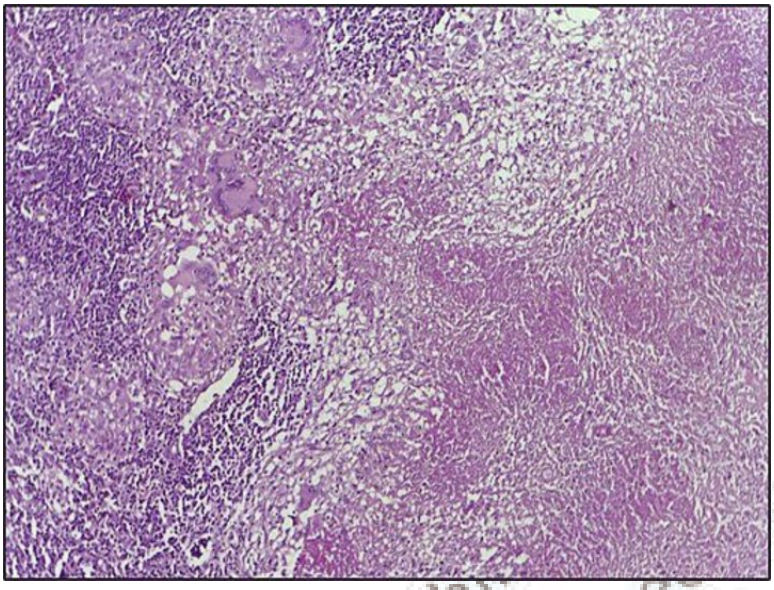

a) Sarcoidosis

b) Tuberculosis

c) Lymphoma

d) Silicosis

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Question 18:

A 38-year-old man comes to the emergency department due to several weeks of occasional hemoptysis, weight loss, and fever. He has lost 7 kg over the past 3 months. Sputum culture grows acid-fast bacilli and his chest X-ray is shown below. What is this lesion called?

a) Gohn's focus

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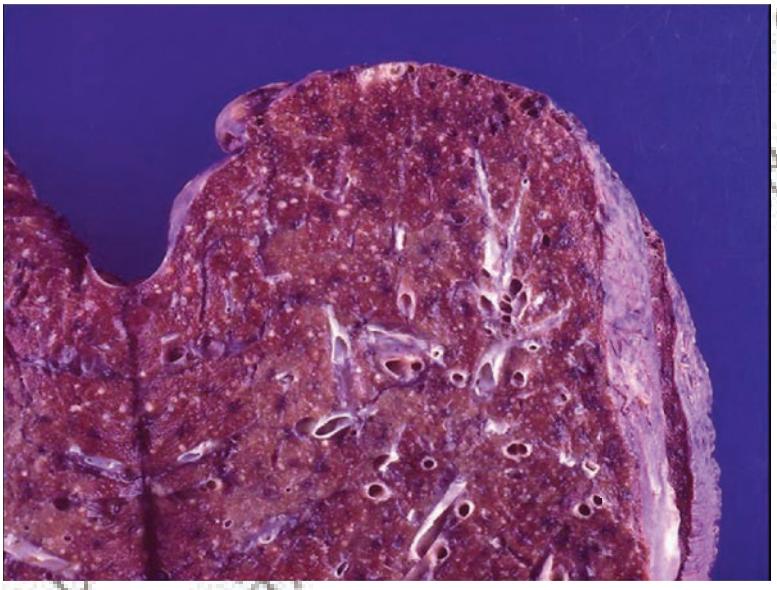
b) Puhl's focus

c) Assmann's focus

d) Simon's focus

Question 19:

A 61-year-old man presented with fever, night sweats, and weight loss. The patient subsequently died a few weeks later. Gross specimen of the lung is shown below. Which of the following is the most likely diagnosis?



a) Emphysema

b) Miliary tuberculosis

c) Pulmonary fibrosis

d) Bronchiectasis

Question 20:

A 48-year-old patient with a history of IV drug abuse had presented to the casualty with shortness of breath and fever with chills. Clinical examination had revealed marked hepatosplenomegaly and diffuse rales in all lung fields. His spot HIV test was positive. The admission chest X-ray and a repeat X-ray taken 3 days later are shown below. The patient died a few hours after the 2nd X-ray was taken. Which of the following statements regarding his diagnosis is true?

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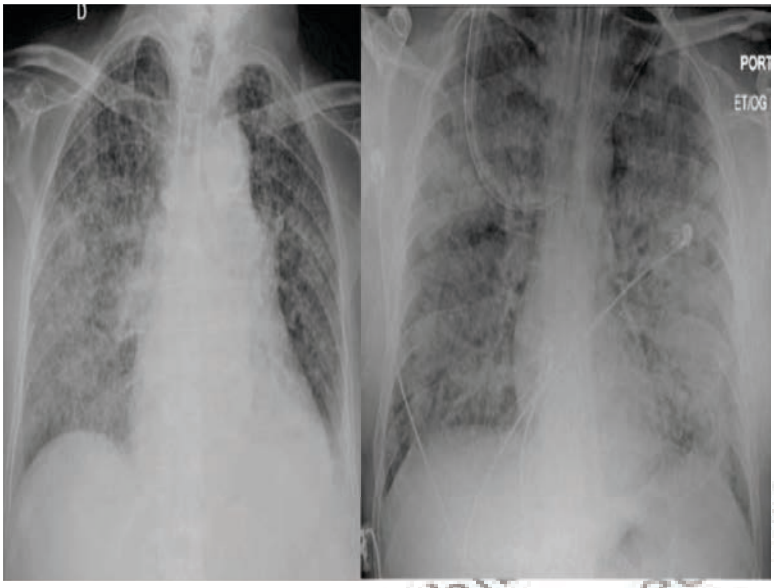

a) The cause of death likely a malignant pleural effusion

b) The spread is mostly due to lymphatic dissemination

c) Pancytopenia may be seen due to infiltration of the bone marrow

d) It is a form of disseminated extrapulmonary tuberculosis

Question 21:

A 52-year-old woman diagnosed with COVID-19 developed severe shortness of breath and died 5 days after admission. What lung pathology can be expected in this patient on autopsy?

a) Fibrin thrombi in capillaries

b) Diffuse alveolar damage

c) Endothelial dysfunction

d) Pulmonary infarction

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Answer Key

Question No.	Correct Option
1	d
2	c
3	d
4	a

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5	a
6	d
7	a
8	a
9	d
10	b
11	d
12	d
13	b
14	b
15	a
16	b
17	b
18	c
19	b
20	c
21	b

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Detailed Explanations

Solution to Question 1:

Neuroendocrine cells in the bronchial mucosa of the lungs are called Kulchitsky cells.

Bronchial mucosa contains a population of neuroendocrine cells that have neurosecretory-type granules and can release a variety of factors including serotonin, calcitonin, and gastrin-releasing peptide (bombesin).

The main cell types of the bronchial mucosa are:

• Clara cells - non-ciliated cuboidal epithelial cells that secrete important defence markers and serve as progenitor cells after injury

• Type I pneumocytes - seen in the alveolar epithelium and are responsible for gas exchange

• Type II pneumocytes - seen in the alveolar epithelium and produce surfactants

• Basal cells

• Neuroendocrine (Kulchitsky-type) cells

• Ciliated cells

• Serous cells

• Goblet cells

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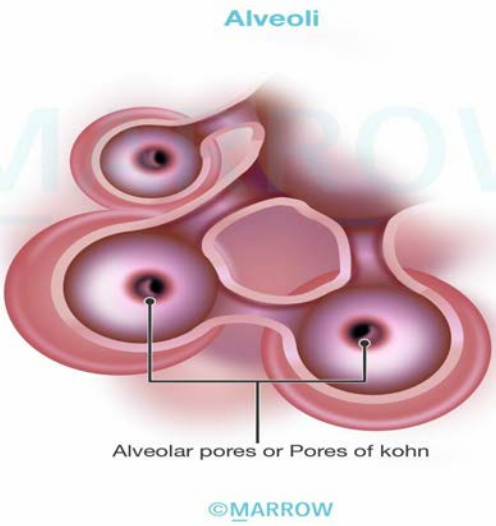
Solution to Question 2:

Pores of Kohn (alveolar pores) are seen in the alveolar wall.

They are the interalveolar connections that permit the passage of bacteria and exudate between adjacent alveoli. This plays an important role in the pathogenesis of lobar pneumonia. During the gray hepatization phase, fibrin also spreads through these pores.

When the lung is partially deflated, collateral ventilation can also occur to some extent through these pores.



Solution to Question 3:

Type II pneumocytes are not involved in gaseous exchange. They are only involved in repair and surfactant production.

Alveolar epithelium is a continuous layer of two cell types:

The following image shows types of cells in the alveoli.

Type I pneumocytes	Type II pneumocytes
Flattened, plate-like	Rounded
The lining epithelium of alveoli (covers 95% of the alveolar surface)Gaseous exchange	Synthesize surfactantRepair of the alveolar epitheliumRegeneration of type I cells

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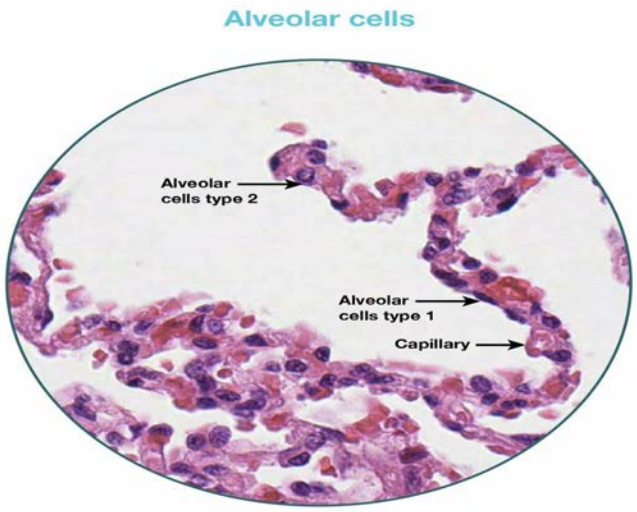

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Solution to Question 4:

Ciliocytophthoria refers to the degeneration of ciliated cells. It occurs in viral infections, such as acute respiratory infections.

Options B and C: Kartagener syndrome is also known as primary ciliary dyskinesia/ immotile cilia syndrome. It occurs due to a defect in the dynein arm of cilia. It is characterized by the triad of:

- Sinusitis
- Situs inversus
- Bronchiectasis

Option D: In cystic fibrosis ciliary ultrastructure remains normal.

Solution to Question 5:

Foregut cysts are most often located in the hilum or middle mediastinum.

They are the congenital cysts that arise from abnormal detachments of primitive foregut. Foregut cysts are classified as bronchogenic, esophageal, or enteric. The most common type of foregut cyst is bronchogenic cyst.

Microscopically, the cyst is lined by ciliated pseudostratified columnar epithelium.

Solution to Question 6:

Contraction atelectasis is an irreversible disorder. It occurs when focal or generalized pulmonary or pleural fibrosis prevents full lung expansion.

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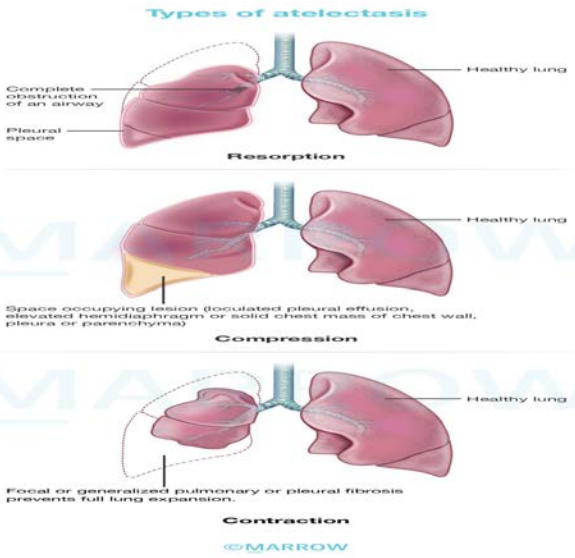
Atelectasis refers either to an incomplete expansion of the lungs (neonatal atelectasis) or to the collapse of the previously inflated lung.

The main types of atelectasis in adults are:

• Resorption atelectasis stems from complete obstruction of an airway. Over time, the air is resorbed from the dependent alveoli, which collapse. E.g. mucous plugs, foreign body aspiration

• Compression atelectasis occurs whenever significant volumes of fluid, tumor, or air accumulate within the pleural cavity. E.g. pneumothorax, pleural effusion.

• Contraction atelectasis occurs when focal or generalized pulmonary or pleural fibrosis prevents full lung expansion.



Solution to Question 7:

This clinical scenario is characteristic of neonatal respiratory distress syndrome (RDS) or hyaline membrane disease. With treatment, it rarely leads to respiratory failure and has a good prognosis.

The fundamental defect is a deficiency of pulmonary surfactant, produced by type II pneumocytes.

Microscopically, the hyaline membranes are largely made up of fibrin admixed with necrotic cell debris. Grossly, the lungs are of normal size, solid, airless, reddish-purple, and they usually sink in water.

Corticosteroids help in surfactant production and are given prophylactically to at-risk pregnant women.

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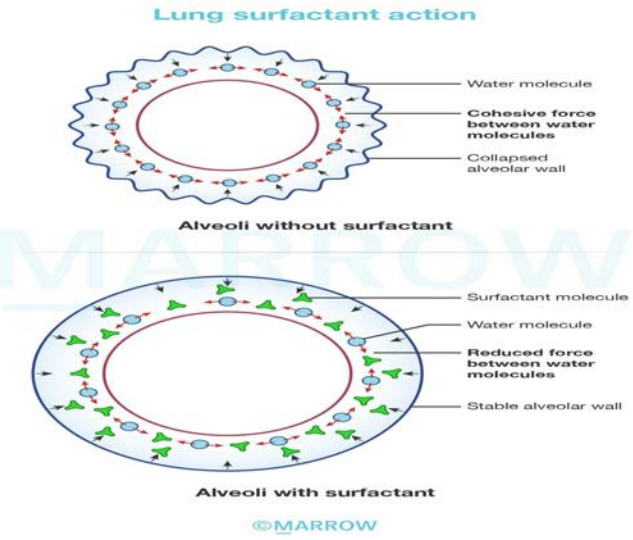

MARROW
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Solution to Question 8:

The above scenario is suggestive of surfactant dysfunction disorder. It is most commonly caused by mutations of ABCA3 gene.

In this disorder, lack of production of surfactant leads to severe respiratory failure in neonates. There is transient improvement with administration of exogenous surfactant, but it worsens once surfactant therapy is stopped. This condition occurs due to mutations in genes encoding proteins involved in surfactant trafficking or secretion such as:

- ATP binding cassette protein member 3 (ABCA3)
- Surfactant protein C
- Surfactant protein B

Solution to Question 9:

This clinical scenario is suggestive of urosepsis. This presentation is likely the result of acute respiratory distress syndrome (ARDS) or shock lung. It is characterized histologically by diffuse alveolar damage.

It is also known as acute lung injury and is clinically characterized by the abrupt onset of significant hypoxemia and bilateral pulmonary infiltrates in the absence of cardiac failure. Chest x-ray shows diffuse bilateral infiltrates, known as white-out appearance. The prognosis is poor with mortality up to 40%.

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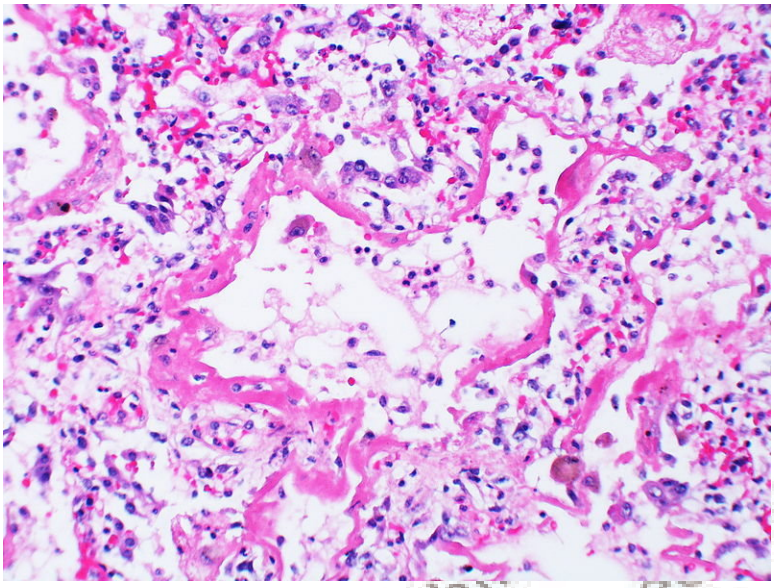
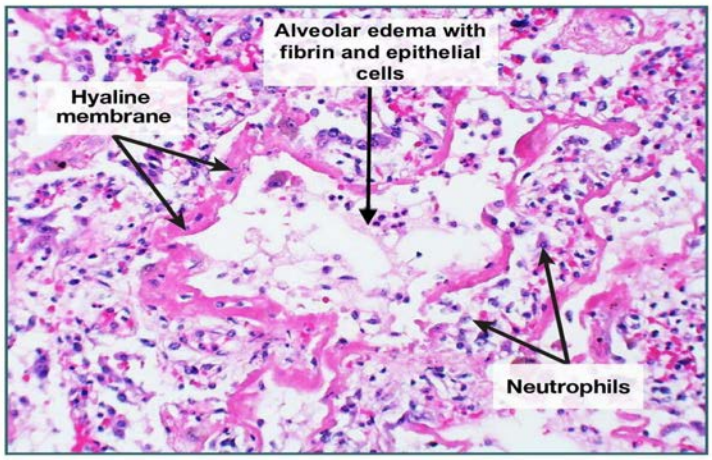


Acute Respiratory Distress Syndrome (ARDS)



Solution to Question 10:

The given scenario is suggestive of heart failure. The image shows heart failure cells, which are siderophages or hemosiderin-containing macrophages.

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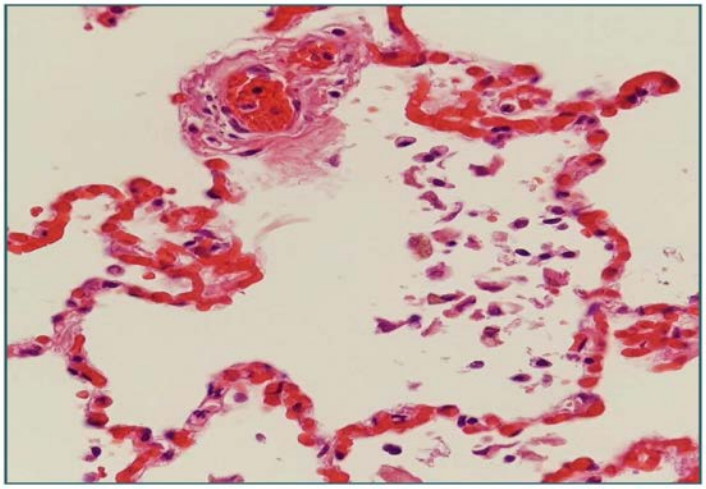
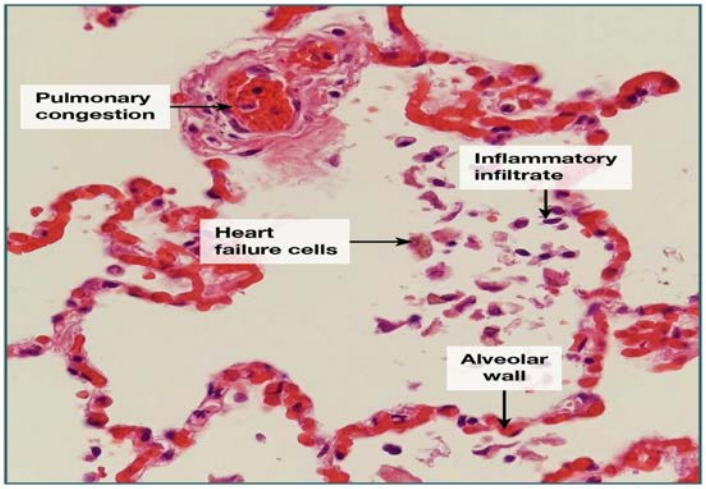
Heart failure cells



Heart failure cells



They are seen in the alveoli of patients with chronic pulmonary edema. The alveolar walls become thickened and fibrosed. These pigmented macrophages result in a brown induration of the lung.

The following image shows siderophages.

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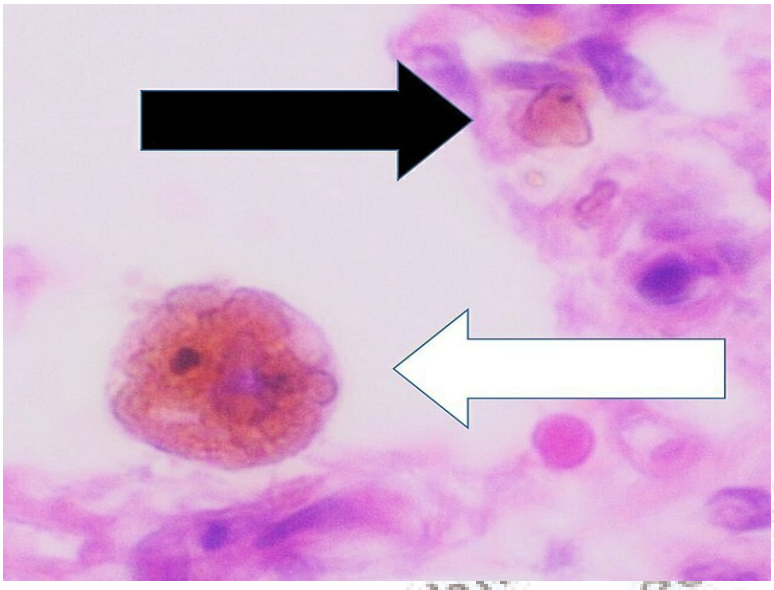

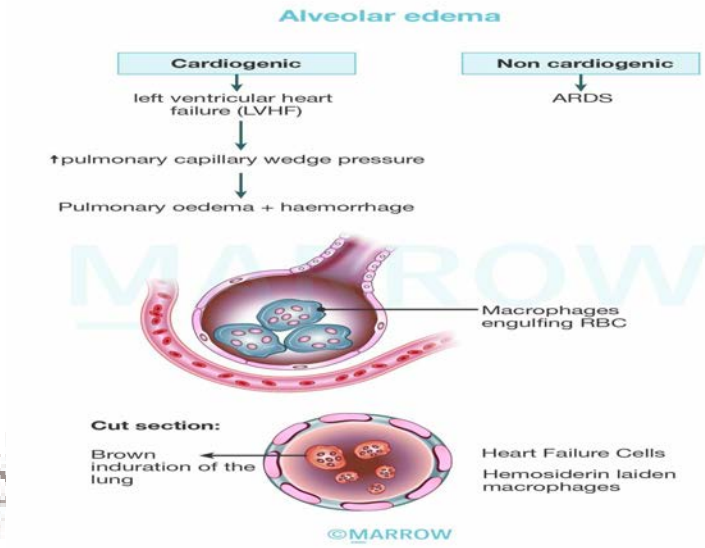

Solution to Question 11:

The given image shows diffuse alveolar damage which is the characteristic histologic finding of acute respiratory distress syndrome (ARDS). Heart failure is not associated with ARDS.

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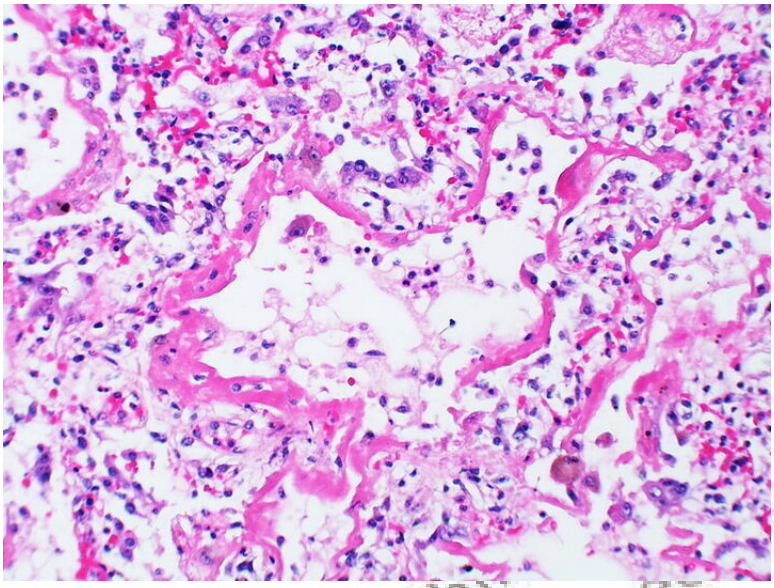

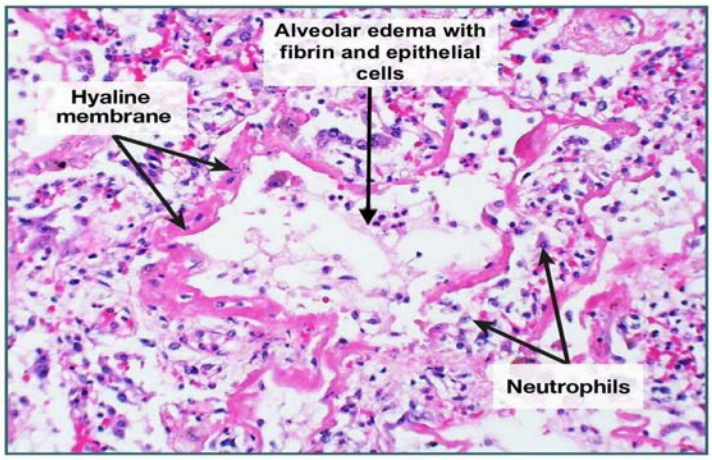

ARDS is characterized by bilateral pulmonary infiltrates and hypoxemia in the absence of heart failure. The causes of ARDS are:

- Sepsis
- Diffuse pulmonary infections
- Infectious - viral, Mycoplasma, and Pneumocystis, miliary tuberculosis
- Gastric aspiration
- Mechanical trauma, including head injuries, burns
- Near-drowning

Solution to Question 12:

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In the stage of gray hepatization in pneumonia, there is an accumulation of fibrin along with disintegration of RBCs within the alveoli.

Bacterial pneumonias can be classified morphologically as:

• Lobular pneumonia (bronchopneumonia) - patchy consolidation of the lung

• Lobar pneumonia - consolidation of an entire lobe

Stages of lobar pneumonia are as follows:

Stages	Duration	Description
Congestion	1-2 days	RBCs andexudatefluid in the alveoli
Red hepatization	2-4 days	Accumulation ofneutrophils, RBCsandfibrinin the alveoli
Gray hepatization	4-8 days	The disintegration of RBCs with thepersistenceoffibrinosuppurativeexudate
Resolution	9-10 days	Most common outcome

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Solution to Question 13:

The predominance of alveolar exudates is a feature of bacterial pneumonia, not viral pneumonia.

Solution to Question 14:

The given image shows a cytomegalic pneumocyte containing characteristic intranuclear basophilic inclusion surrounded by a clear halo known as owl's eye appearance. Along with the given clinical scenario, it is suggestive of cytomegalovirus (CMV) pneumonia.

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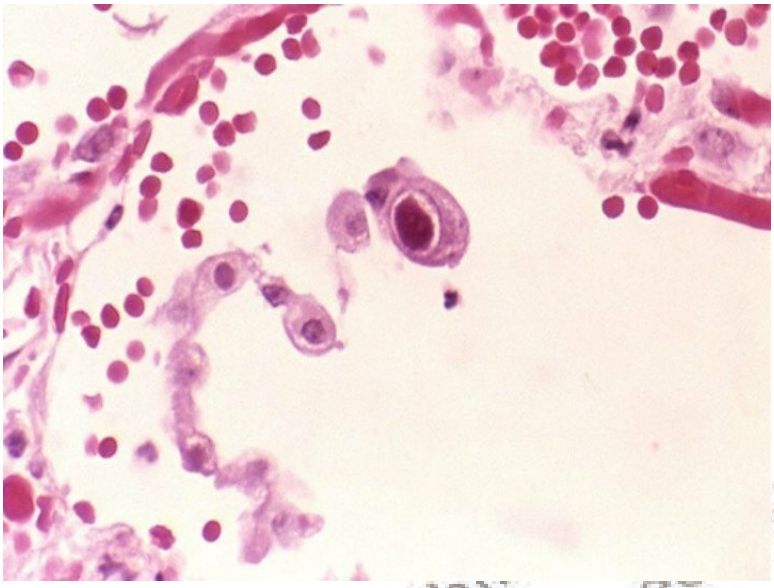
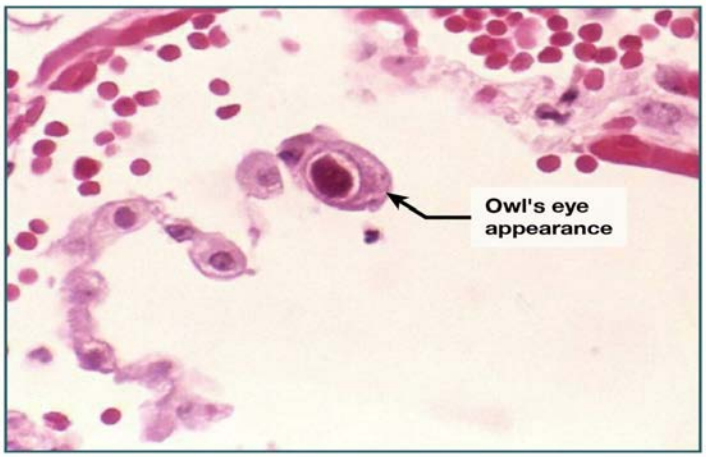


CMV Pneumonia - Lung Biopsy



CMV is a °-group herpesvirus. It causes the following conditions:

• Immunocompetent individuals - asymptomatic or mononucleosis-like infection

• Neonates - devastating systemic infections

• Immunosuppressed individuals - serious, life-threatening, disseminated CMV infections of the lungs (pneumonitis) and gastrointestinal tract (colitis)

Option A: Small-cell carcinoma has small cells with scant cytoplasm, salt-and-pepper chromatin with inconspicuous nucleoli.

Option C: In cryptococcal infection, encapsulated yeasts are seen on direct microscopy.

Option D: Tuberculosis is associated with well-defined epithelioid granuloma.

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Solution to Question 15:

The given scenario and image showing massive neutrophilic infiltration are suggestive of Mendelson's syndrome or aspiration pneumonitis.

Mendelson's syndrome is a chemical pneumonitis caused by the aspiration of sterile gastric contents during general anesthesia, especially during pregnancy. The most common cause of maternal mortality associated with general anesthesia is either due to a pulmonary aspiration or a failed endotracheal intubation.

The risk factors for Mendelson's syndrome include:

• Gastric volume > 25 mL (0.4 mL/kg)

• Gastric pH < 2.5

Incidence of aspiration can be reduced by administration of:

• Non-particulate antacids like sodium citrate 30-45 minutes prior to intubation

• H2 receptor antagonists like intravenous ranitidine

• Metoclopramide 1-2 hours prior to induction

Option B: Cryptogenic organizing pneumonia is a type of ILD associated with Masson bodies and plugs of loose connective tissue on histology.

Option C: CMV pneumonia is associated with the owl's eye appearance on histology.

Option D: PCP pneumonia is associated with black-walled cysts on silver staining.

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Solution to Question 16:

The given histopathological image clearly shows a granuloma with refractile granules indicative of a foreign body. It is seen in aspiration pneumonia due to vegetative matter (such as food).

In this condition, the chest x-ray shows bilateral diffuse infiltrates especially in the right middle and lower lobes. Patients with altered sensorium are at high risk (stroke, medications).

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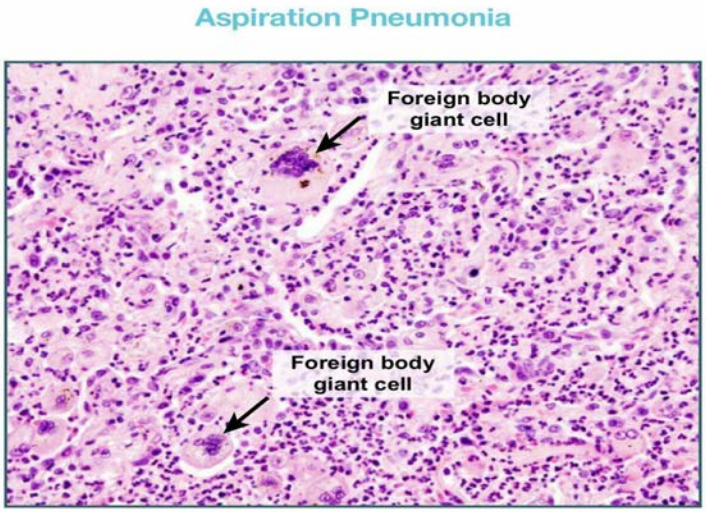

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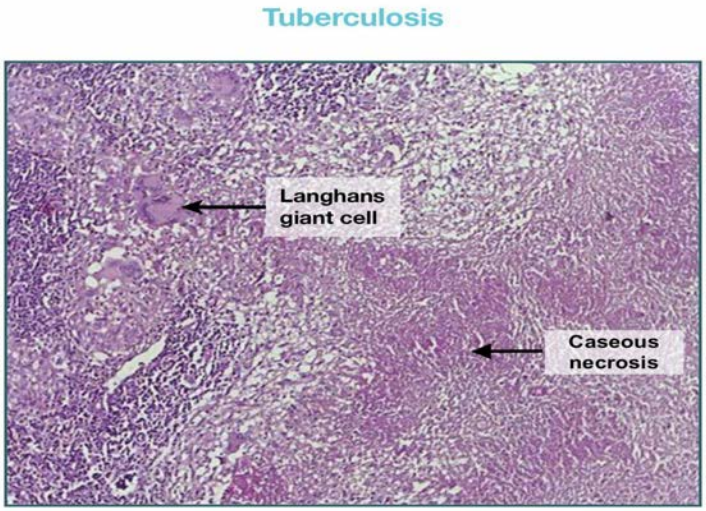
Solution to Question 17:

The given image shows the presence of granulomas of epithelioid cells with central caseous necrosis and Langhan's giant cells. These findings point towards the diagnosis of tuberculosis.

Langhan's giant cells show horseshoe or slipper-shaped arrangements of nuclei.



Solution to Question 18:

The given x-ray of this patient with tuberculosis shows an infraclavicular lesion. It is known as Assmann's focus.

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Primary tuberculosis occurs on first exposure and involves lower part of upper lobe and upper part of lower lobe. The following findings may be seen:

• Ghon's focus - focus of infection located subpleurally

• Ghon's complex - Ghon's focus with lymph node involvement

• Ranke complex - a calcified Ghon's complex

Secondary tuberculosis occurs due to the reactivation of TB. It affects the apex. The following findings may be seen:

• Puhl's complex - supraclavicular lesion

• Assmann's complex - infraclavicular lesion

Disseminated or miliary tuberculosis is characterised by 1-2 mm disseminated lesions all over the lung. The following findings may be associated:

• Simon's focus - early hematogenous seeding in the apex of lungs

• Rich focus - tuberculous caseous foci in brain, meninges and spinal cord

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Solution to Question 19:

The given clinical scenario and the gross image showing individual lesions which are small (2-mm) foci of yellow-white consolidation scattered through the lung parenchyma is suggestive of miliary tuberculosis.

Miliary tuberculosis (TB) refers to the widespread dissemination of Mycobacterium tuberculosis via hematogenous spread. It occurs when organisms draining through the lymphatics enter the venous blood and circulate back to the lung. Miliary TB may infect any number of organs, including the lungs, liver, and spleen.

The adjective 'miliary' is derived from the resemblance of these foci to millet seeds. Mantoux test is negative in miliary TB.

Solution to Question 20:

The given history, clinical features, and chest X-Ray point towards a diagnosis of miliary tuberculosis. Pancytopenia may be seen due to infiltration of the bone marrow in such cases.

The second X-ray shows acute respiratory distress syndrome (ARDS). Chest x-ray appearance of ARDS varies depending on the severity and typically appears as bilateral diffuse alveolar opacities with dependent atelectasis in some cases. The opacities may have a patchy ground-glass appearance. The cause of death here is likely ARDS. (option A)

In immunodeficient individuals (eg.- patient having HIV), there may occur widespread dissemination of M. tuberculosis, via the hematogenous route (option B) that leads to the seeding of bacteria in various organs (hepatosplenomegaly). This is known as miliary TB.

It is a form of disseminated pulmonary tuberculosis, and not extrapulmonary (option D)

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The risk factors of miliary TB include-

- Extremes of age
- Alcohol use
- Malignancy
- HIV
- Corticosteroids
- Connective tissue disease
- Renal failure
- Diabetes, and pregnancy

Solution to Question 21:

Diffuse alveolar damage may be seen in patients suffering from COVID-19, on histological analysis. It is the most common lung finding in COVID-19 pneumonia.

Other COVID-19 related histopathological changes in the lungs include:

- Hyaline membrane formation
- Desquamation of pneumocytes
- Fibrin deposits in lungs
- Inflammation with mononuclear cells

However, diffuse alveolar damage is not specific to COVID-19. It may be seen in all cases of acute respiratory distress syndrome (ARDS) including pneumonia, burns, near drowning, etc.

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Obstructive and Restrictive lung diseases

Question 1:

Which of the following conditions does not involve the bronchus?

a) Emphysema

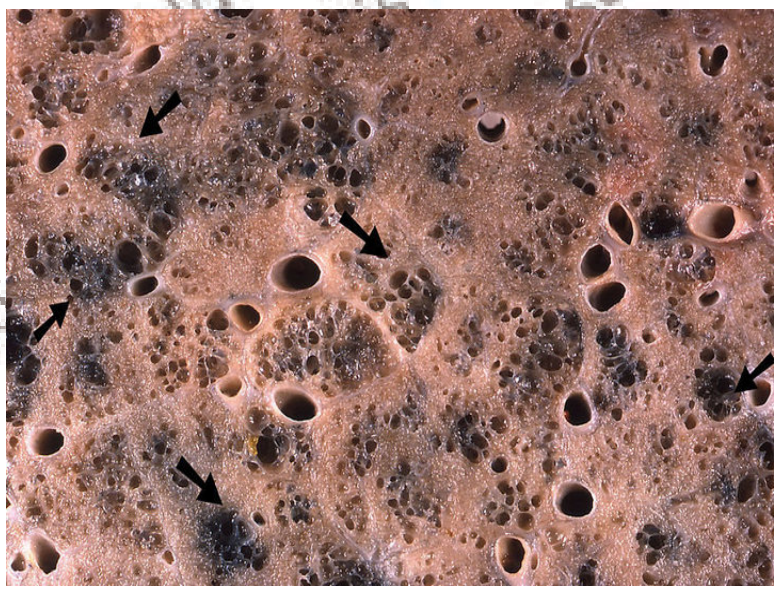
b) Bronchial asthma

c) Bronchitis

d) Bronchiectasis

Question 2:

A patient with severe emphysema underwent lung volume reduction surgery. The resected specimen is shown below. What type of emphysema is this?



a) Panacinar

b) Centriacinar

c) Paraseptal

d) Irregular

Question 3:

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In patients with COPD, the emphysematous damage is most likely to involve which of the following structures?

a) Respiratory bronchiole

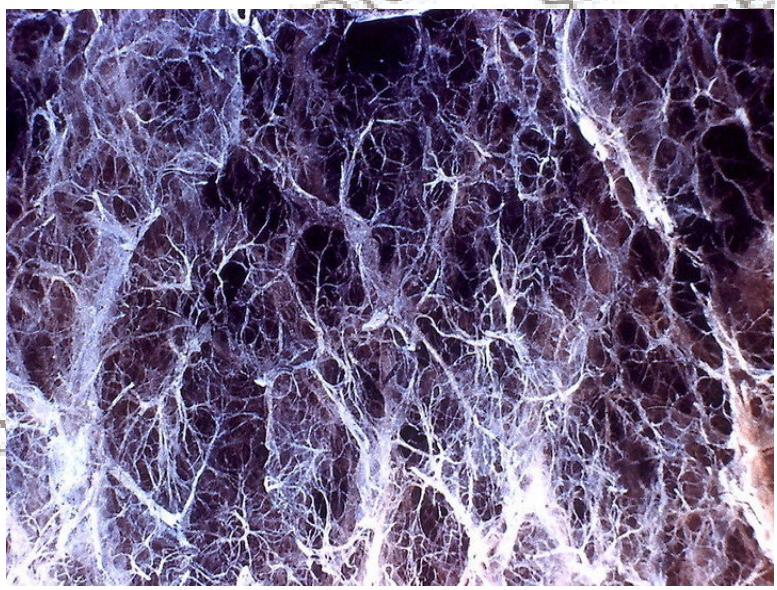
b) Terminal bronchiole

c) Alveoli

d) Alveolar ducts

Question 4:

A 30-year-old woman with a long history of dyspnea, chronic cough with sputum, and wheezing died of respiratory failure following a bout of lobar pneumonia. She was not a smoker or an alcoholic. The lung at autopsy is shown in the image below. Which of the following is most likely to cause the pathological changes shown?



a) Alpha-1-antitrypsin deficiency

b) Cystic fibrosis

c) Mutation in dynein arms

d) Antibodies against type-IV collagen

Question 5:

A 25-year-old man is being evaluated for dyspnea and cough for 2 months. He is not a smoker. Workup revealed emphysematous changes at lung bases. He reports that his father and uncles were diagnosed with liver failure and lung disease at relatively young ages. Where

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is the gene encoding the defective protein located?

a) Chromosome 11

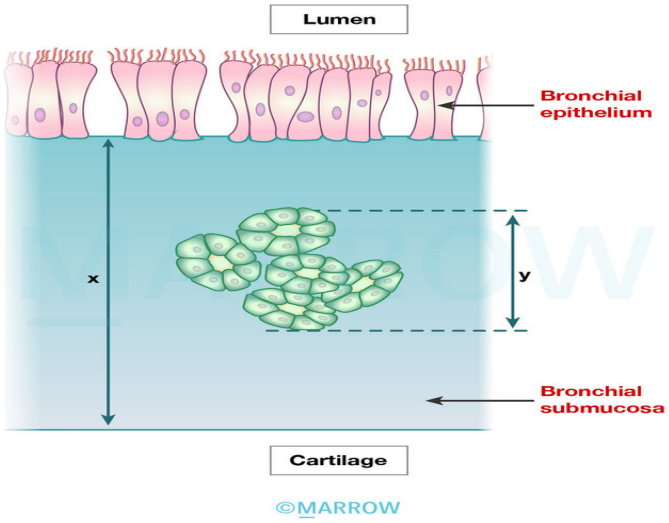
b) Chromosome 13

c) Chromosome 15

d) Chromosome 14

Question 6:

What is the normal value of y/x in the following representation?



a) 0.2

b) 0.8

c) 0.6

d) 0.4

Question 7:

A 55-year-old man was brought to the ED with fever, cough with expectoration, and difficulty in breathing for 1 day. He is a chronic smoker and he has had similar progressive symptoms for the last 4 years. Past PFT findings showed reduced FEV1 and increased RV with normal diffusion capacity. Which of the following is the most common organism implicated in this condition?

a) Staphalococcus aureus

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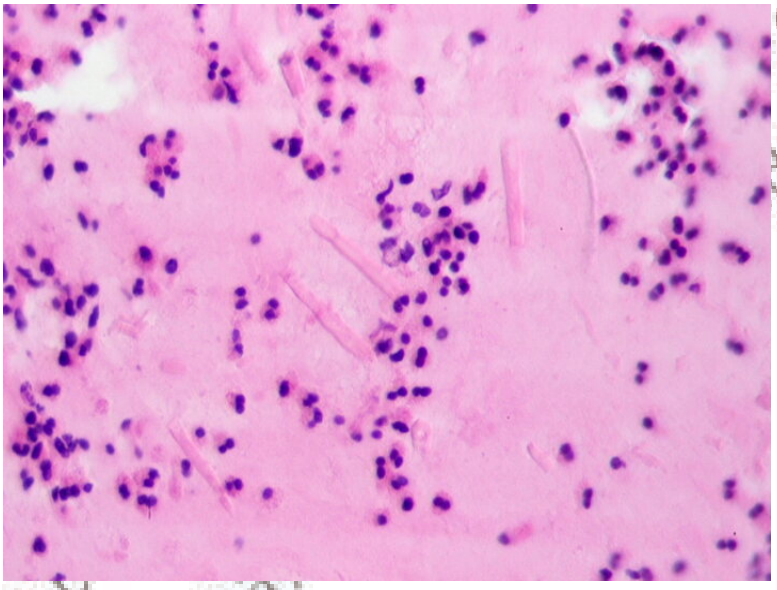
b) Hemophilus influenzae

c) Moraxella

d) Pneumococcus

Question 8:

A middle-aged woman presented with recurrent episodes of breathlessness, wheeze, and chest tightness. Auscultation of the chest revealed bilateral wheeze. Sputum microscopy reveals the following. What is the most likely diagnosis?



a) Sarcoidosis

b) Bronchial asthma

c) Chronic bronchitis

d) Asbestosis

Question 9:

A resected specimen of a lung is shown below. What is the likely diagnosis?

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a) Emphysema

b) Bronchiectasis

c) Interstitial lung disease

d) Anthracosis

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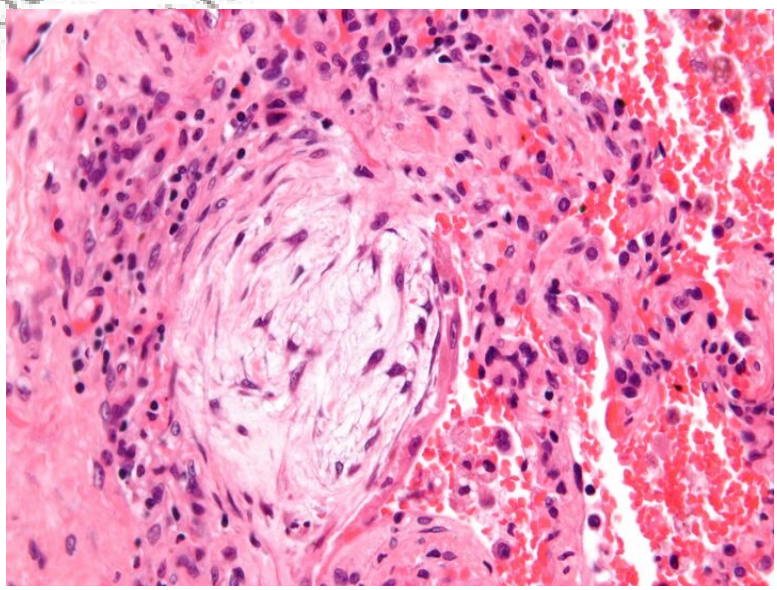
Question 10:

Transbronchial biopsy from a patient showed the following microscopic finding. What is the likely diagnosis?



a) Sarcoidosis

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b) Asbestosis

c) Silicosis

d) Cryptogenic organizing pneumonia

Question 11:

What is the most common pneumoconiosis in the world?

a) Silicosis

b) Asbestosis

c) Anthracosis

d) Farmer's lung

Question 12:

What is the most common manifestation of asbestosis?

a) Pleural plaque

b) Mesothelioma

c) Lung cancer

d) Pleural effusion

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Question 13:

A patient working in a factory presented with lung fibrosis and thickening of pleura. Biopsy was done. Diagnosis from the histopathology picture is:

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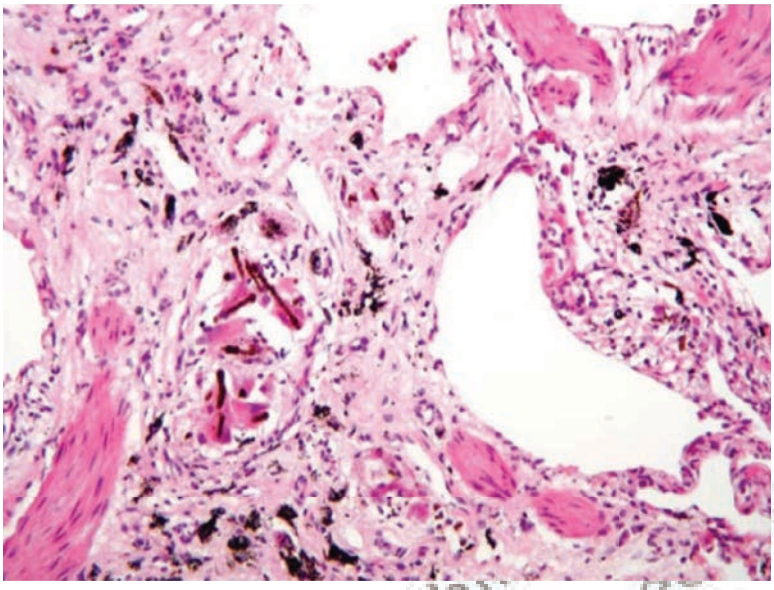

a) Asbestosis

b) Silicosis

c) Tuberculosis

d) Mesothelioma

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Question 14:

Patients A, B, and C presented to the OPD with symptoms of progressive dyspnea and cough. Further history and workup revealed the following findings. Who among them is more susceptible to developing tuberculosis?

a) Patients A and B

b) Patient B only

c) Patients A and C

d) Patient C only

Question 15:

A 60-year-old man presented with dyspnea and cough. Chest X-ray revealed irregular linear densities, particularly in both lower lobes. Histopathological examination of lung biopsy is shown below. This patient has a higher risk of developing:

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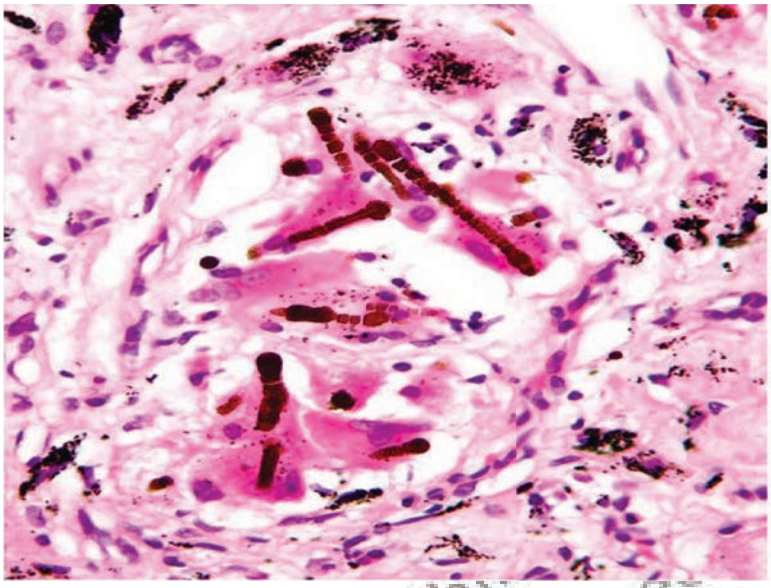

a) Centrilobular emphysema

b) Pneumonia

c) Occupational asthma

d) Lung carcinoma

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Question 16:

A 45-year-old woman presents with complaints of low-grade fever, dry cough, and progressive dyspnea. Examination reveals the following painless skin lesion. Chest X-ray shows bilateral hilar lymphadenopathy. Lung biopsy shows non-caseating granulomas. Which of the following is not a feature of this condition?

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a) CD4/CD8 T-cell ratio > 3.5

b) Impaired dendritic cell function

c) Monoclonal hypergammaglobulinemia

d) Anergy to common skin test antigens

Question 17:

What is the most common gene mutation associated with pulmonary hypertension?

a) BMPR1

b) BMPR2

c) BMPR3

d) BMPR4

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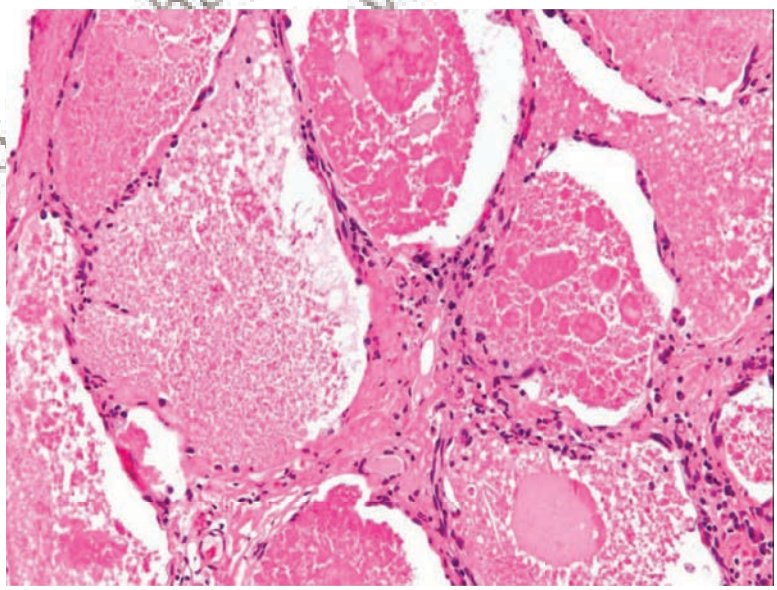
Question 18:

A 57-year-old man presented with a persistent dry cough and progressive dyspnea. HRCT showed a crazy-paving pattern. Microscopy of BAL aspirate is shown below. Antibodies against which of the following are seen in this condition?



a) Lecithin

b) Protein A

c) Protein B

d) GM-CSF

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Question 19:

Match the following:

a) 1-b, 2-d, 3-a, 4-c

b) 1-d, 2-b, 3-c, 4-a

c) 1-a, 2-b, 3-c, 4-d

d) 1-a, 2-b, 3-d, 4-c

Question 20:

A 70-year-old patient presented with cough, fatiguability, and weight loss. He was diagnosed with squamous cell carcinoma (SCC) on bronchoscopy. The resected specimen had a hilar lymph node that was 1cm in size and showed a black pigment. What is the black pigment likely to be?

a) Anthracotic pigment

b) Melanin

c) Lipochrome

d) Hemosiderin

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Answer Key

Question No.	Correct Option
1	a
2	b
3	a
4	a
5	d
6	d
7	b
8	b
9	b
10	d

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11	a
12	a
13	a
14	b
15	d
16	c
17	b
18	d
19	b
20	a

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Detailed Explanations

Solution to Question 1:

Emphysema does not involve the bronchus, it involves the acinus.

Chronic obstructive pulmonary disease (COPD) includes both emphysema and chronic bronchitis.

Other obstructive lung diseases include:

• Bronchial asthma - characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli

• Bronchiectasis - destruction of smooth muscle and elastic tissue by chronic necrotizing infections leading to permanent dilation of bronchi and bronchioles

Emphysema	Chronic bronchitis
Irreversibleenlargementof th e airspaces distal to thetermi nal bronchioledue to wall des truction (without obvious fibr osis)	Mucushypersecretion and pe rsistentinflammationin thelar ge airways
Patients with this condition a re known aspink puffers	Patients with this condition a re known asblue bloaters

Solution to Question 2:

The given gross image is characteristic of centriacinar emphysema.

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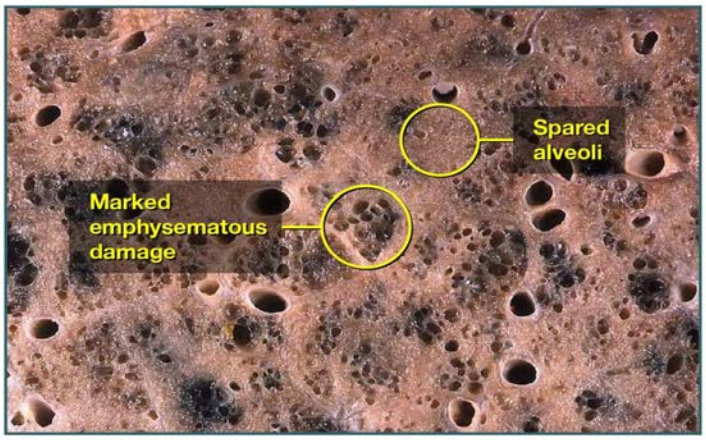
Centriacinar Emphysema

Centriacinar Emphysema



In paraseptal emphysema subpleural spaces are mainly affected (shown below).

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In panacinar emphysema all air spaces within acini are evenly enlarged (shown below).

Solution to Question 3:

Patients with chronic obstructive pulmonary disease (COPD) usually have centriacinar emphysema which involves respiratory bronchioles.

Emphysema is classified into four major types:

- Centriacinar
- Panacinar
- Paraseptal
- Irregular

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Solution to Question 4:

The above gross specimen shows emphysematous damage involving enlargement of the entire acinus suggestive of panacinar emphysema. It is caused due to alpha-1-antitrypsin deficiency.

In panacinar (panlobular) emphysema, the acini are uniformly enlarged from the level of the respiratory bronchiole to the terminal blind alveoli. It occurs commonly in the lower zones and in the anterior margins of the lung and is most severe at the bases.

The image below shows panacinar emphysema.

Solution to Question 5:

The above scenario is suggestive of α1-antitrypsin deficiency. The α1-antitrypsin is encoded by the proteinase inhibitor (Pi) locus on chromosome 14.

α1-AT is a polymorphic gene located on chromosome 14. It is part of a larger family of structurally unique serine protease inhibitors, referred to as serpins. The most common clinically significant mutation in α1-antitrypsin deficiency is PiZZ.

α1-antitrypsin, normally present in serum, tissue fluids, and macrophages is a major inhibitor of proteases (particularly elastase) secreted by neutrophils during inflammation. The absence of α1-antitrypsin activity results in excessive digestion of elastic tissue by elastase.

Patients with α1-antitrypsin deficiency have a markedly increased tendency to develop panacinar emphysema.

Solution to Question 6:

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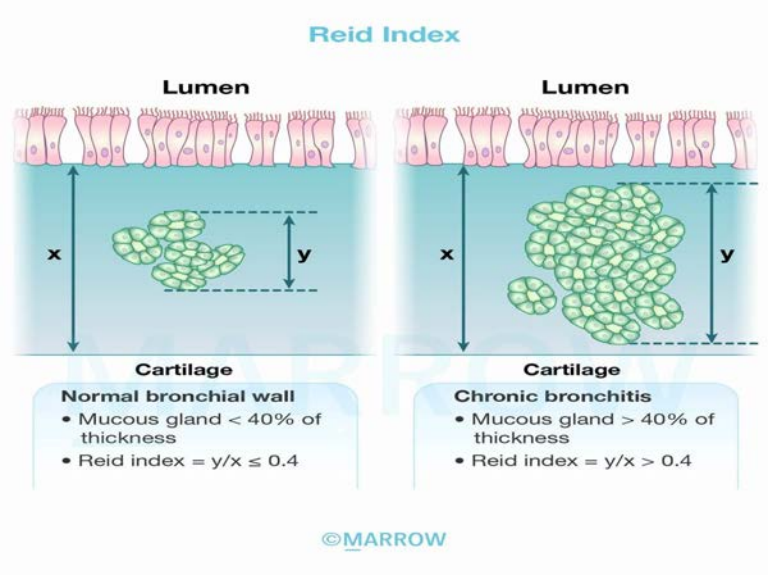
In the above image, y/x denotes the ratio of the thickness of the submucosal gland layer to that of the bronchial wall. This is called as Reid index and it is normally 0.4.

It is increased in chronic bronchitis.



Chronic bronchitis is defined by the presence of a persistent productive cough for at least 3 consecutive months in at least 2 consecutive years. The single most important cause is cigarette smoking. The distinctive features of chronic bronchitis are as follows:

• Hypersecretion of mucus

• Hypertrophy of submucosal glands

• Goblet-cell hyperplasia

• Inflammation

Difference between clinical presentation of emphysema and chronic bronchitis:

	Predominant Bronchitis	Predominant Emphysema
Age (year)	40-45	50-75
Dyspnea	Mild; late	Severe; early
Cough	Early; copious sputum	Late; scanty sputum
Infections	Common	Occasional
Respiratory insufficiency	Repeated	Terminal
Cor pulmonale	Common	Rare; terminal
Airway resistance	Increased	Normal or slightly increased
Elastic recoil	Normal	Low
Chest radiograph	Prominent vessels; large hear t	Hyperinflation; small heart
Appearance	Blue bloater	Pink puffer

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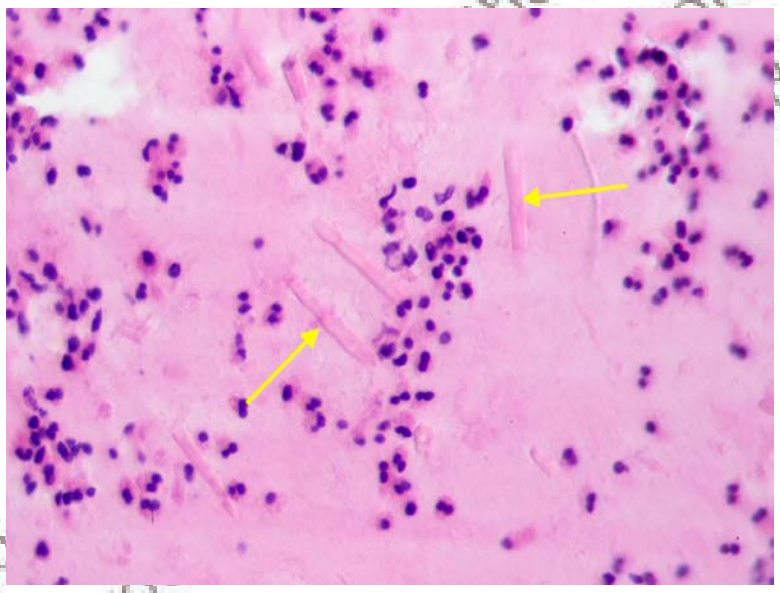
Solution to Question 7:

The above clinical scenario gives a picture of acute exacerbation of COPD. The most common bacterial cause of acute COPD exacerbation is Haemophilus influenzae.

Moraxella is the second most common bacterial cause of acute exacerbation of COPD.

Solution to Question 8:

The given clinical scenario and the sputum microscopy showing Charcot–Leyden crystals (arrows in below image), lakes of mucus, and numerous eosinophils, are diagnostic of bronchial asthma.



Asthma is characterized by reversible bronchoconstriction caused by airway hyperresponsiveness to a variety of stimuli. Atopic asthma is caused by a TH2 and IgE-mediated immunologic reaction to environmental allergens (type-1 hypersensitivity reaction). Triggers for non-atopic asthma are less clear but include viral infections and inhaled air pollutants.

Genetic susceptibility for developing asthma:

• Chromosome 5q - site of the susceptibility locus for asthma

• IL-13 gene polymorphisms (on 5q chromosome) - most consistent associations with asthma or allergic disease

• IL-4 receptor gene variants - associated with atopy, elevated total serum IgE, and asthma

The sputum of patients with bronchial asthma shows:

• Charcot–Leyden crystals - made of an eosinophilic membrane protein called galectin 10

• Curschmann spirals - spirals of mucus plugs from subepithelial mucous gland ducts or bronchioles

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• Creola bodies - desquamated epithelial cells

• Numerous eosinophils

Note: The hygiene hypothesis was previously used to explain the development of asthma and other hypersensitivity disorders.

Solution to Question 9:

The image above shows markedly distended bronchi involving the middle and lower lobe of the lung which is seen in bronchiectasis.

Bronchiectasis is a suppurative lung disease with abnormal and irreversible dilatation of the bronchi. It is an end-stage condition of various diseases that result in destruction of the bronchial wall and its surrounding supporting tissues.

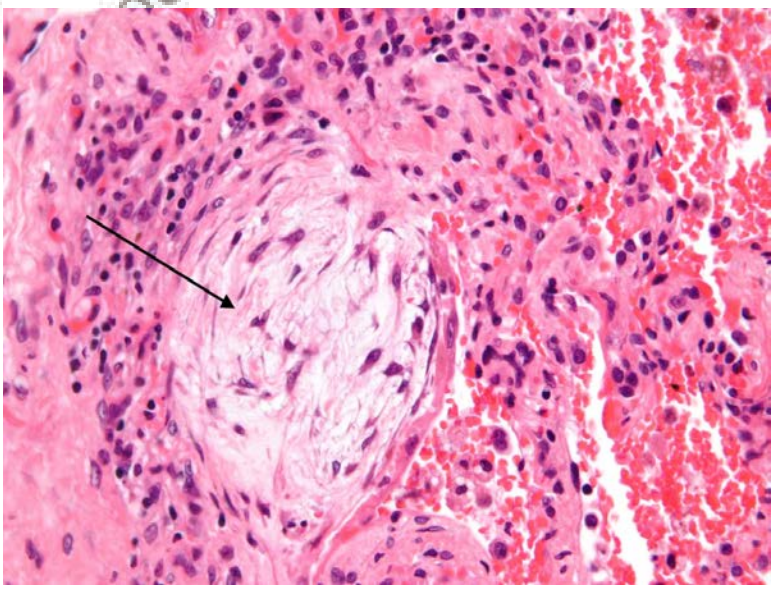
The normal clearing mechanisms are impaired, either due to congenital causes or due to bronchial obstruction. This results in pooling of secretions, secondary infection, and inflammation, often with necrosis, fibrosis, and eventually cystic dilation of airways up to four times the normal size.

Note: Kartagener syndrome is a primary ciliary dyskinesia characterized by the classical triad of situs inversus, chronic sinusitis, and bronchiectasis.

Solution to Question 10:

The image above shows alveolar spaces filled with balls of fibroblasts (Masson bodies). This is characteristically seen in cryptogenic organizing pneumonia (COP).

Masson bodies are polypoid plugs of loose organizing connective tissue within alveolar ducts, alveoli, and bronchioles along with foci of fibrosis.



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The clinical presentation of COP is the development of nonspecific systemic and respiratory symptoms. It is associated with filling of the lung alveoli that is visible on a chest X-ray as patchy unilateral or bilateral consolidation.

COP was previously known as bronchiolitis obliterans organizing pneumonia (BOOP).

Solution to Question 11:

Silicosis is the most common pneumoconiosis in the world.

Silicosis is caused by the inhalation of crystalline silica (e.g., quartz). Individuals involved with the concrete work, sandblasting, stone carvers, and jewelers using chalk molds are at high risk.

Pneumoconioses encompass a group of chronic fibrosing diseases of the lung resulting from exposure to organic and inorganic particulates, most commonly mineral dust.

Solution to Question 12:

Pleural plaques are the most common manifestation of asbestos exposure.

They are well-circumscribed plaques of dense collagen, often containing calcium. They develop most frequently on the parietal pleura and over the domes of the diaphragm. They do not contain asbestos bodies, and only rarely occur in persons without prior asbestos exposure.

Asbestos occurs in two distinct forms - serpentine chrysotile (more common) and amphibole (more pathogenic). Exposure may result in the following conditions:

- Localized fibrous plaques or, rarely, diffuse pleural fibrosis
- Pleural effusions
- Parenchymal interstitial fibrosis (asbestosis)
- Lung carcinoma
- Mesotheliomas
- Extrapulmonary neoplasms including laryngeal, ovarian, and colon carcinomas

The image below shows fibrous pleural plaques seen on the diaphragmatic pleural surface in asbestosis.

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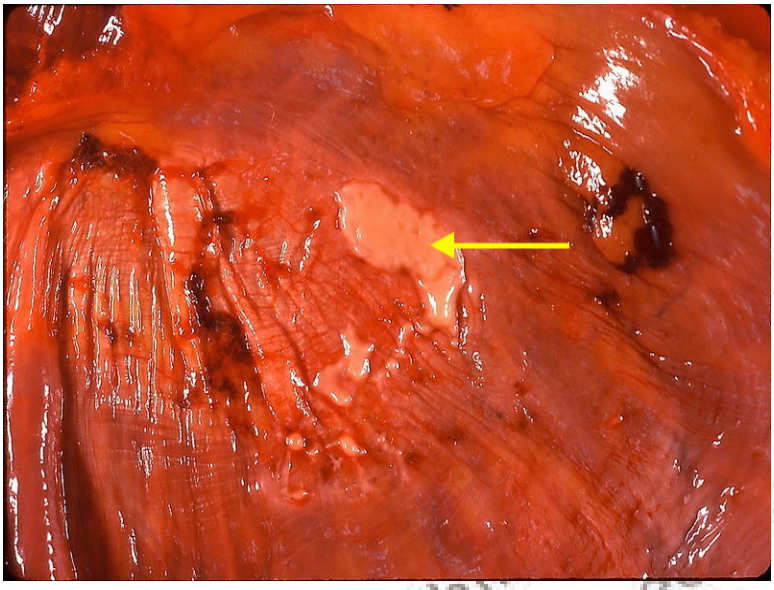
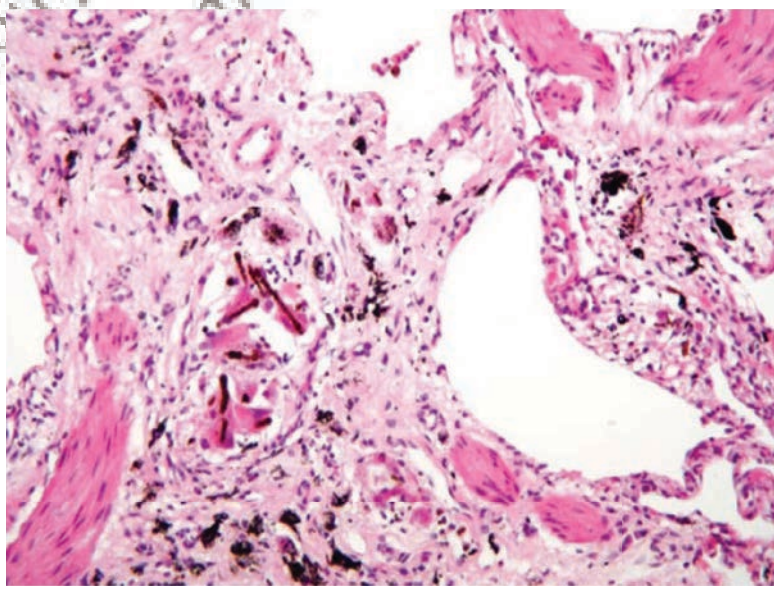


Solution to Question 13:

This clinical scenario and image showing typical asbestos bodies are suggestive of asbestosis.

Asbestosis is a type of pneumoconiosis associated with asbestos exposure. The disease-causing capabilities of the different forms of asbestos depend on concentration, size, shape, and solubility. This condition is marked by diffuse pulmonary interstitial fibrosis.

Asbestos bodies are a typical finding. They are golden brown, fusiform, or beaded rods with a translucent center. They consist of asbestos fibers coated with an iron-containing proteinaceous material and arise when these fibers are phagocytosed by macrophages.



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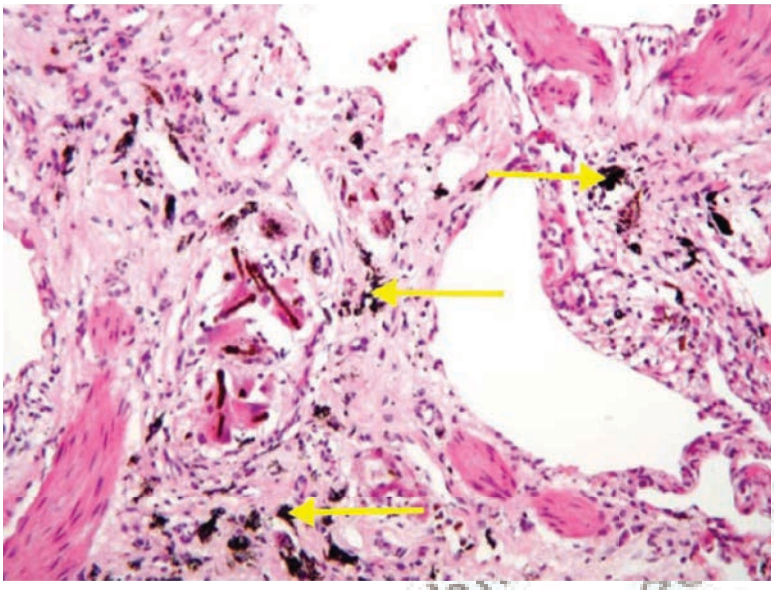

Other inorganic particulates may become coated with similar iron-protein complexes and are called ferruginous bodies.

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Solution to Question 14:

Patient B is a worker in the sandblasting industry with eggshell calcification on x-ray. This is suggestive of silicosis. Patients with silicosis have a higher risk of tuberculosis as the crystalline silica impairs the ability of pulmonary macrophages to kill phagocytosed mycobacteria.

The given clinical picture of patient A is classical of asbestosis and that of patient C is suggestive of anthracosis.

Features	Anthracosis	Silicosis	Asbestosis
Mineral dust	Coal	Silica:AmorphousCrystalline	Asbestos:SerpentineAmphibolic
Radiology	Nodules in initial stagesProgressive massive fibrosis	Bilateral hilar lymphadenopathyEggshell calcification	Pleural plaquePleural effusionInterstitial lung fibrosis
Microscopic	MaculeNodule	Non-caseating granuloma	Asbestos bodyFerruginous body
TB risk	-	+	-
Carcinoma risk	-	+	+++++

Solution to Question 15:

The image shows golden-brown, beaded rods with a translucent center called asbestos bodies which are seen in asbestosis. These patients are at risk of developing both lung

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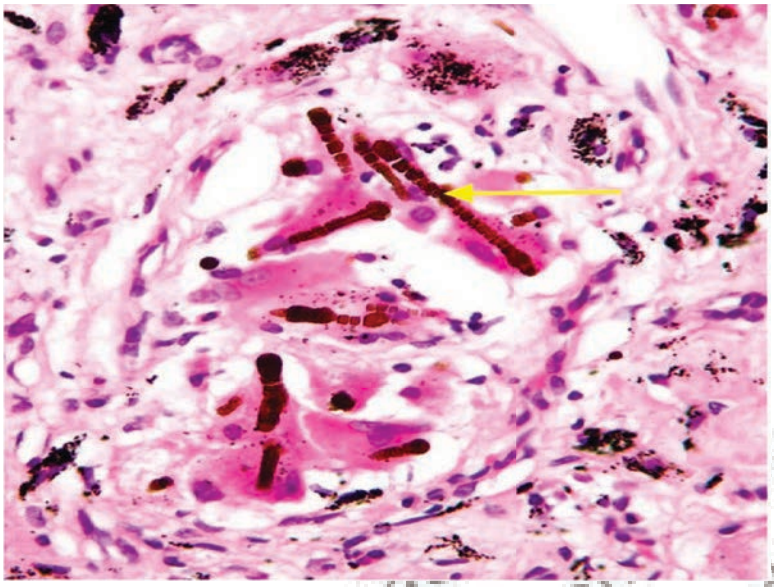
carcinoma and mesothelioma.



Asbestosis is marked by diffuse pulmonary interstitial fibrosis and the presence of multiple asbestos bodies.

Option A: Centrilobular emphysema may develop in simple coal workers' pneumoconiosis.

Option B: Increased susceptibility to tuberculosis is seen in silicosis.

Option C: Occupational asthma may be triggered by fumes (epoxy resins, plastics), organic and chemical dust (wood, cotton, platinum), gases (toluene), or other chemicals (formaldehyde, penicillin products).

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Solution to Question 16:

The given clinical scenario and image showing the lesion of lupus pernio point towards sarcoidosis. It is a multisystemic disease characterized by polyclonal hypergammaglobulinemia.

Lupus pernio is seen in cutaneous sarcoidosis and presents as infiltrated erythematoviolaceous plaques involving the nose, cheeks, ears, lips, forehead, and fingers. On the cheeks, telangiectasia is characteristic. It is usually painless. As it does not ulcerate, it is not as mutilating as lupus vulgaris.

Immunological abnormalities include:

• Polyclonal hyperglobulinemia

• A CD4/CD8 ratio > 3.5

• T- cell expansion and macrophage activation

• Impaired dendritic cell function

• Anergy to common skin tests.

The hallmarks of sarcoidosis include:

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• B/L hilar lymphadenopathy

• Non-caseating granulomas

• Lupus pernio

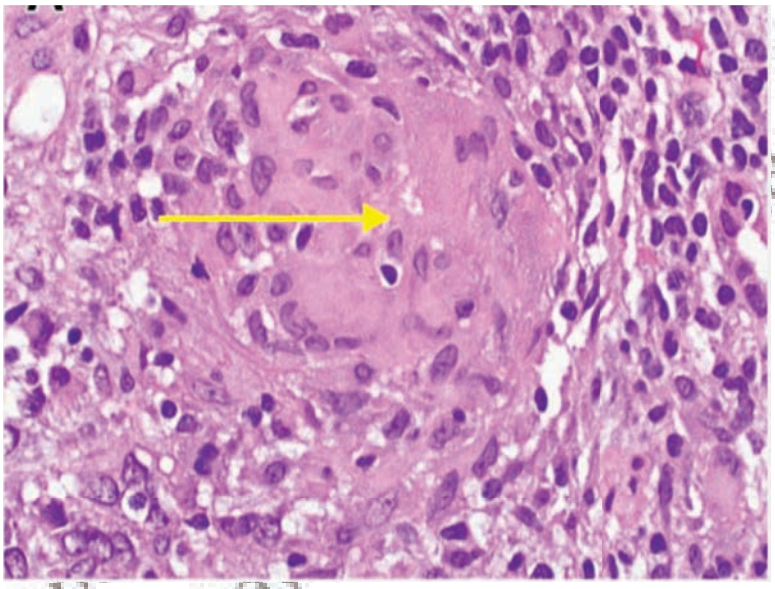
• Erythema nodosum (acute sarcoidosis)

Syndromes associated with sarcoidosis are:

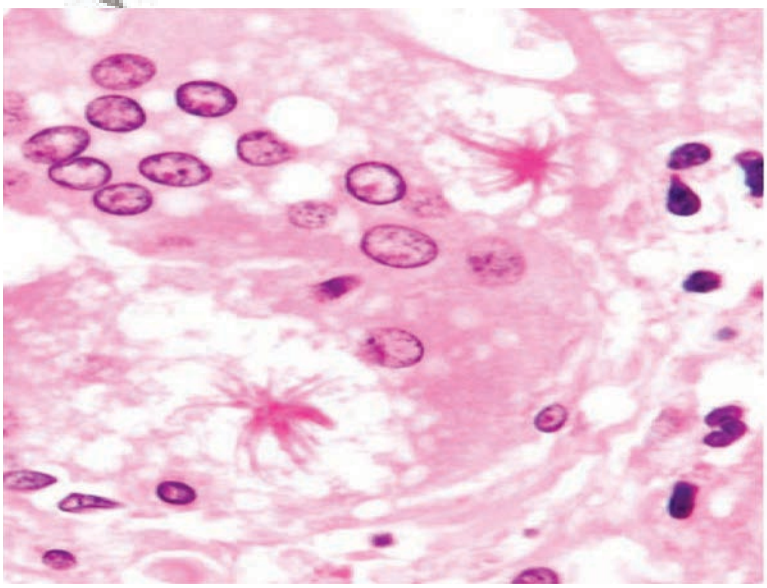
• Mikulicz syndrome - sarcoidosis combined with uveoparotid involvement

• Lofgren's syndrome - acute presentation of sarcoidosis, consisting of arthritis, erythema nodosum, and bilateral hilar adenopathy

The image below shows the characteristic non-caseating sarcoid granuloma.



The image below shows stellate inclusions known as asteroid bodies that are found within giant cells in approximately 60% of the granulomas.



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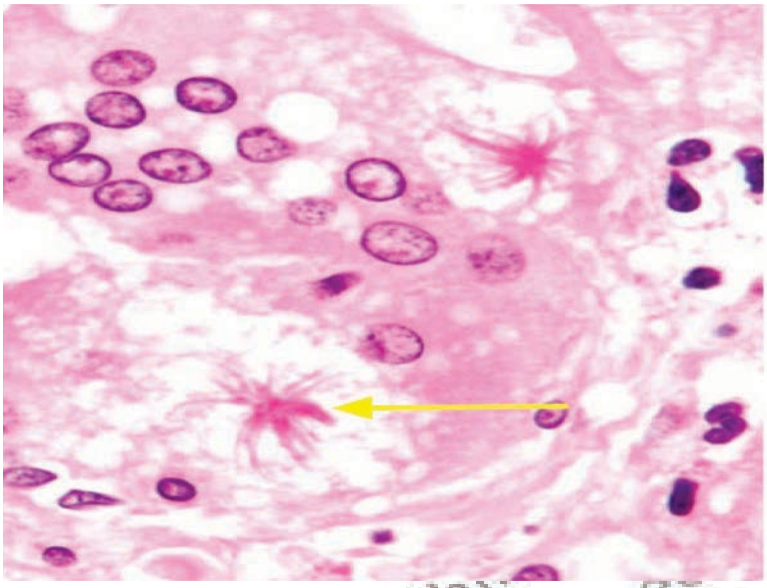
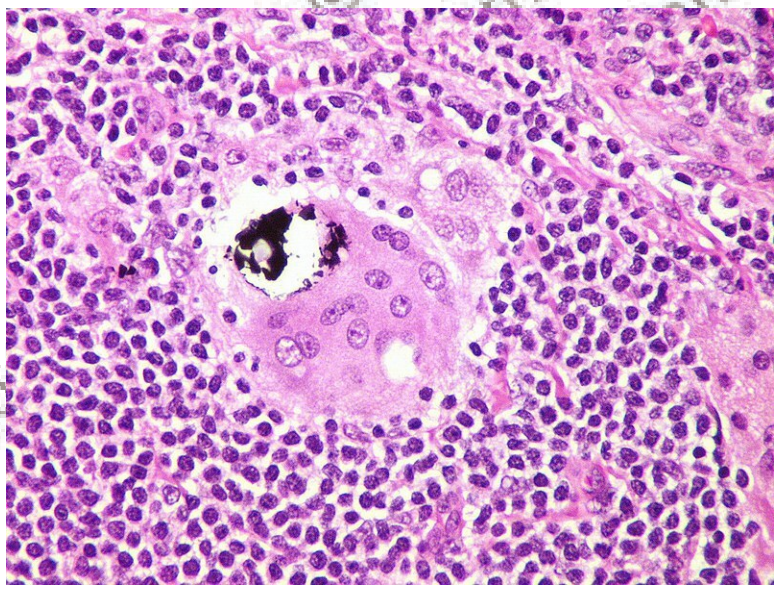


The image below shows laminated concretions composed of calcium and proteins known as Schaumann bodies that are found within giant cells in approximately 60% of the granulomas.



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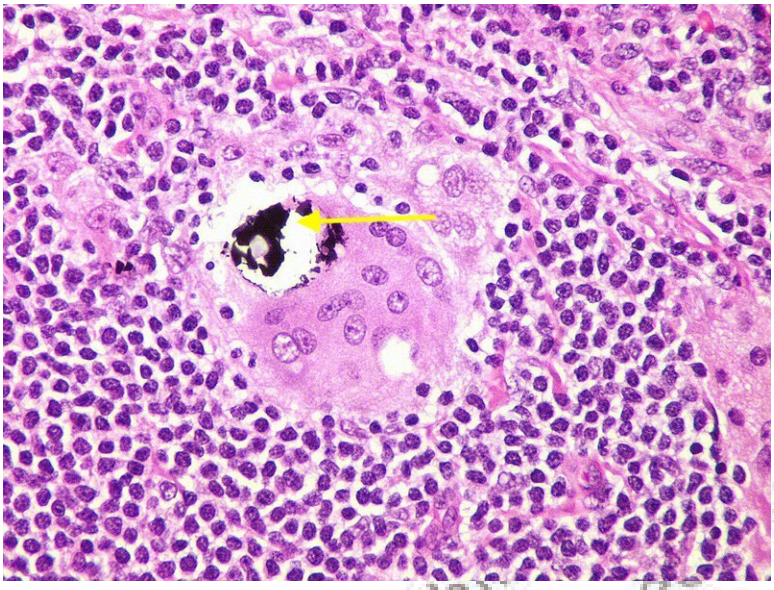

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Solution to Question 17:

Bone morphogenetic protein receptor 2 (BMPR2) is the most common gene mutation in pulmonary hypertension. Inactivating mutations in this gene are found in 75% of the familial cases of pulmonary hypertension, and 25% of sporadic cases.

The BMPR2 receptor is a cell surface protein belonging to the TGF-° receptor superfamily. It is involved in the regulation of growth, differentiation, and apoptosis of pulmonary artery endothelial and smooth muscle cells.

Due to the mutation, there is enhanced proliferation and reduced apoptosis of vascular endothelial and smooth muscle cells leading to pulmonary hypertension.

Solution to Question 18:

The given scenario and microscopy showing alveoli filled with a dense, amorphous, protein-lipid granular precipitate are suggestive of autoimmune pulmonary alveolar proteinosis (PAP). It is caused by circulating neutralizing antibodies specific for granulocyte-macrophage colony-stimulating factor (GM-CSF).

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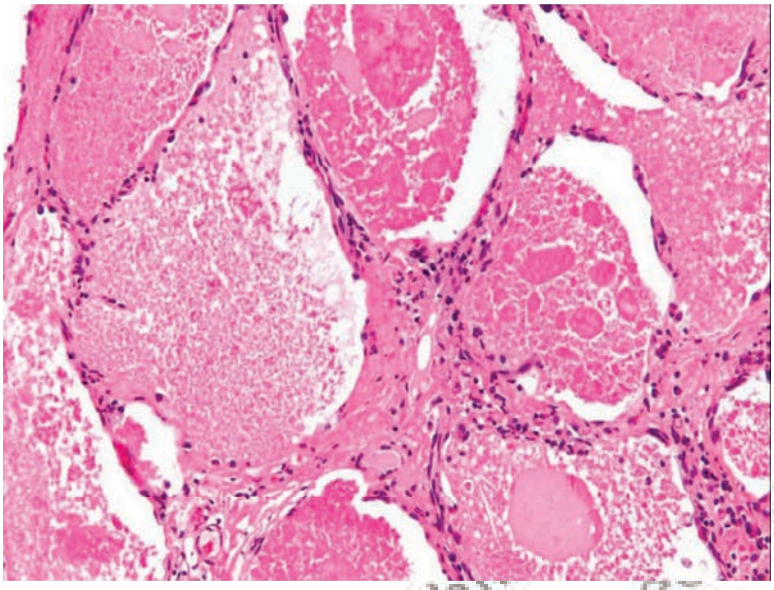

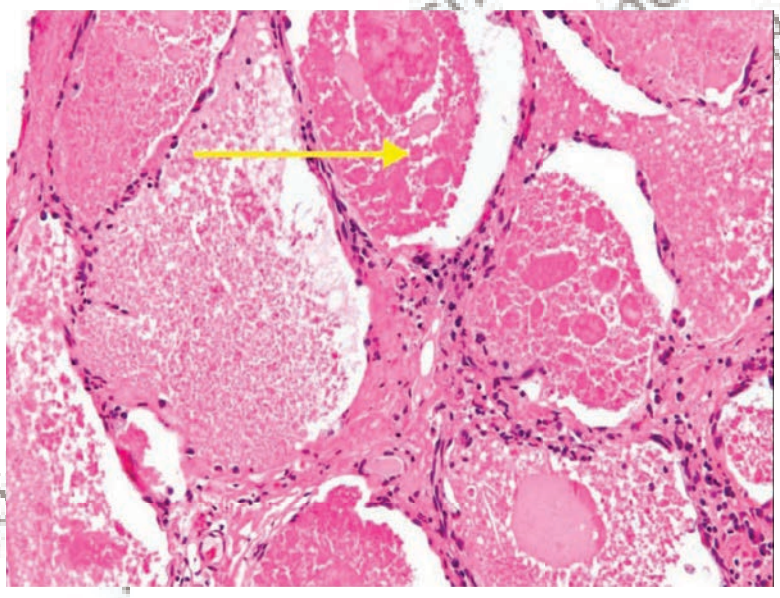

PAP is a condition characterized by the accumulation of surfactants in alveoli and terminal airways. It can be due to impaired clearance or abnormal production of surfactants.

PAP can be of three forms:

• Primary (most common): There is impaired GM-CSF-dependent surfactant clearance by the alveolar macrophages. It can be due to:

• Autoantibodies against GM-CSF (acquired/idiopathic/autoimmune PAP)

• Mutation in GM-CSF receptors (hereditary PAP)

• Secondary: There is a reduction in the number or ability of alveolar macrophages that causes impaired surfactant clearance. It can be due to:

• Silicosis

• Immunodeficiency disorders

• Hematopoietic disorders and malignancies

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• Congenital: It affects neonates and children. There is abnormal surfactant production due to mutation in the genes coding for:

• Surfactant protein B

• Surfactant protein C

• ATP binding cassette protein member 3

Solution to Question 19:

The correctly matched associations of the following conditions are:

• Silicosis: Crazy paving pattern

• Mesothelioma: Malignant pleural effusion without mediastinal shift

• Caplan syndrome: Initially demonstrated in coal workers

• Asbestosis: Basal lobes are involved

Caplan's syndrome also called rheumatoid pneumoconiosis, is a combination of rheumatoid arthritis and pneumoconiosis. It manifests as pneumoconiotic nodules along with features of seropositive rheumatoid arthritis. Caplan syndrome was first described in coal miners and later in patients with silicosis too.

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	Silicosis	Asbestosis	Malignant mesothelioma
Exposure	Crystallinesilica	Asbestos	Most specific neoplasm as sociated withasbestosexpo sure
Radiologic/ Gross findi ngs	Simple silicosis - small ro undedopacitiesin upper lo besComplicated silicosis - Larger opacities > 1cm an deggshell calcificationof h ilar lymph nodesAcute sili cosis - ground-glass opaci ties on X-ray andcrazy pa ving patternon HRCT (int erlobular septal thickenin g with background of gro und-glass opacity)	X-ray shows peripheralret icular opacitiespredomina ntly in thebasal lobesHRC T shows subpleural fibroti c lines, irregular opacities, tractionbronchiectasis, an dhoneycombing	Diffuse gelatinous,greyish -pink lesionarising either from the visceral or pariet al pleura.
Clinical manifestations	Increased risk of developi ng TB and bronchogenic c arcinoma	It mainly affects the lower lobesPFT shows arestricti ve patternwith a decrease in lung volumes and diffu sing capacity	Strong male predilection 3:1Can causemalignant pl eural effusion

Solution to Question 20:

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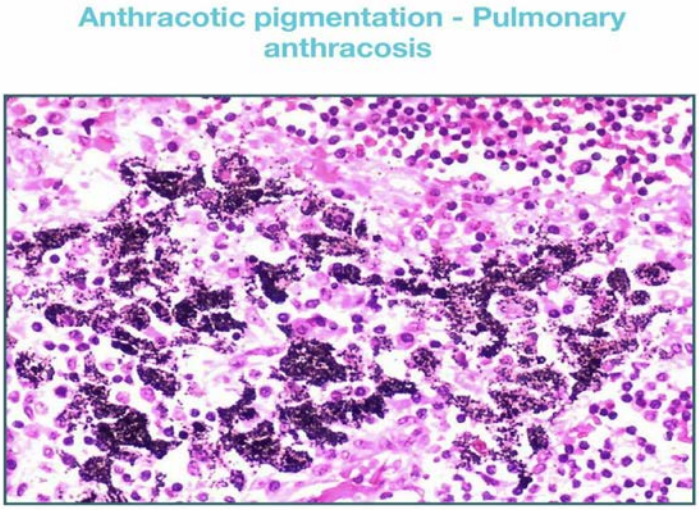
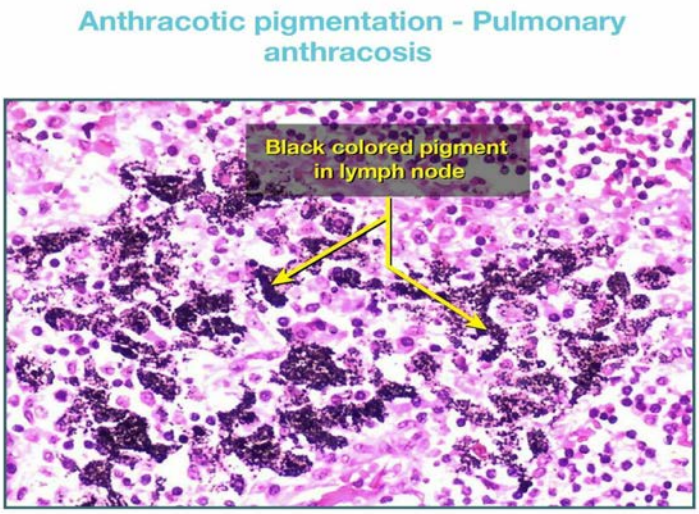
The black-colored pigment in the hilar lymph node of the resected bronchoscopic specimen is likely to be an anthracotic pigment.

The black color is due to the deposition of carbon particles. The inhaled carbon particles are engulfed by the lung macrophages and then transported to the hilar lymph nodes.
This accumulates and causes the blackening of the lung tissues or anthracosis.

It is commonly seen in people who work in environments where there is high air pollution with carbon particles, such as coal mines. It is also the most common exogenous pigment found in the human body as a result of air pollution in urban areas. The aggregates of the carbon dust may induce fibroblastic reaction or emphysema that may lead to a condition called coal worker's pneumoconiosis.

The following image shows anthracosis with deposition of black carbon particles, within the cytoplasm of macrophages.





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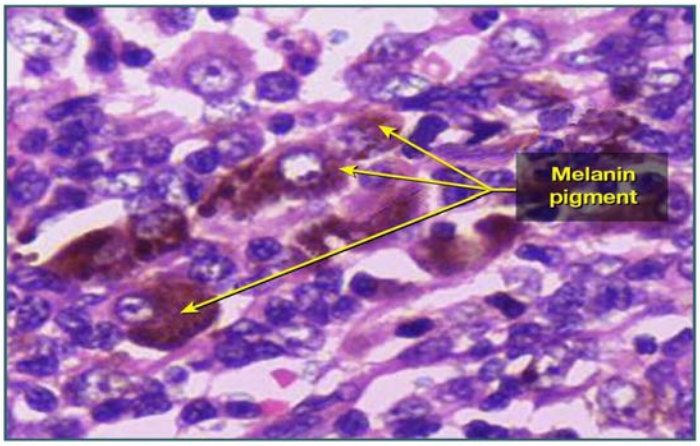
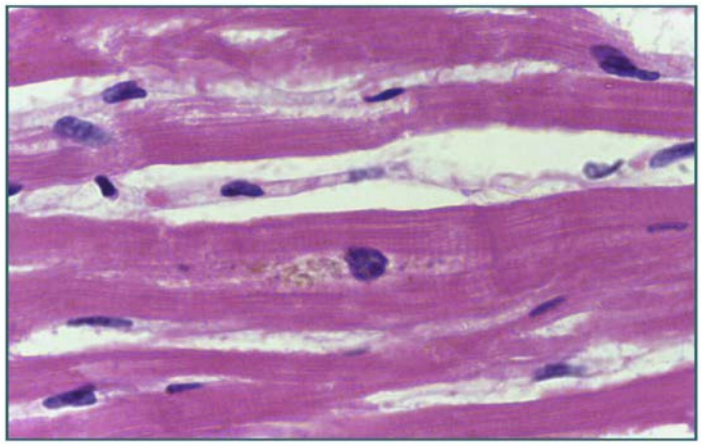
Option B: Melanin is brown-black in color which occurs as a result of oxidation of tyrosine in melanocytes, as shown in the following histopathology of a lymph node.

Melanin pigment



Option C: Lipochrome or lipofuscin (brown lipid) is seen as a yellow-brown pigment in histopathological sections of the liver and heart of normal aging patients, patients with severe malnutrition, and cancer cachexia. It is derived through lipid peroxidation and indicates free radical injury and lipid peroxidation. The following image shows a cardiac myocyte with fine yellow-brown lipofuscin granules in the perinuclear region.

Lipochrome accumulation in cardiac myocyte



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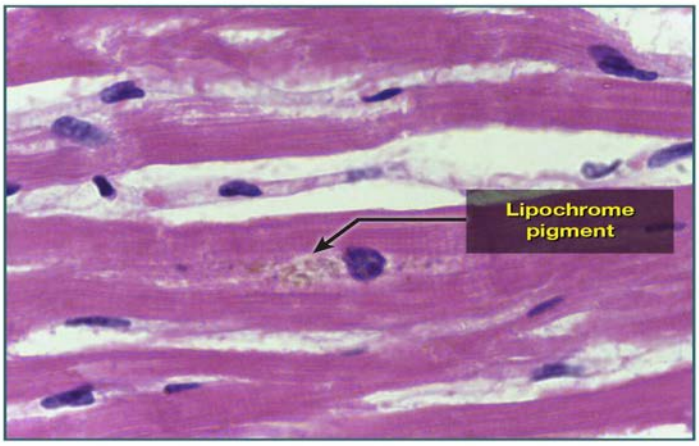
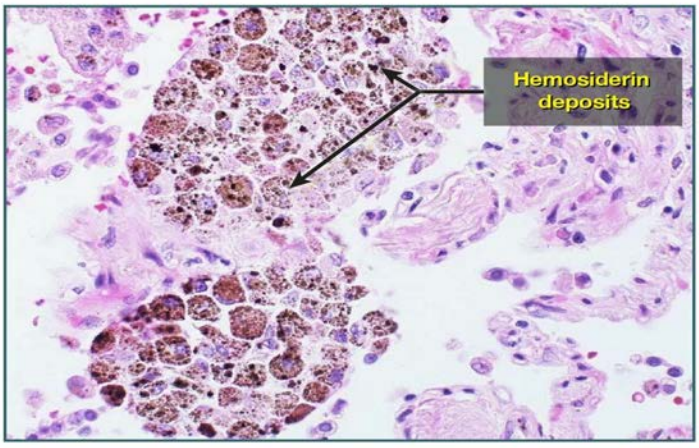
Lipochrome accumulation in cardiac myocyte



Option D: Hemosiderin is a hemoglobin-derived golden-yellow colored pigment seen in conditions associated with iron overload such as hemochromatosis. The following image shows extensive intra-alveolar hemosiderin deposition following pulmonary hemorrhage.

Hemosiderin pigment



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Lung tumors

Question 1:

Which of the following statements is incorrect?

a) The most common cancer worldwide is lung cancer

b) The most common malignant tumors of the lung are metastases

c) The most common cause of cancer mortality worldwide is lung cancer

d) The lung is the most common site of metastatic neoplasms

Question 2:

Which of the following is the most common symptom seen in patients with lung cancer?

a) Cough

b) Dyspnea

c) Weight loss

d) Chest pain

Question 3:

Histopathological findings of a lung tumor biopsy are shown below. Which of the following is the most sensitive and specific marker of this tumor?

[Image unavailable]

a) P40

b) P63

c) P53

d) TTF-1

Question 4:

Which is the most aggressive type of lung cancer?

a) Small cell carcinoma

b) Squamous cell carcinoma

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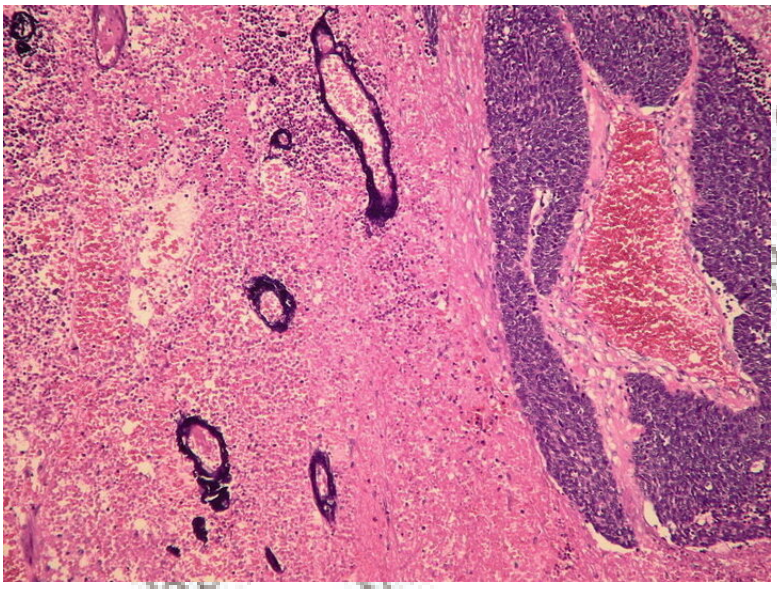
c) Adenocarcinoma

d) Broncho alveolar carcinoma

Question 5:

A 53-year-old man who is a chronic smoker is diagnosed with lung carcinoma. Histopathology of the lung tissue is shown in the image below. What is the most likely diagnosis?



a) Small-cell carcinoma

b) Squamous cell carcinoma

c) Adenocarcinoma

d) Broncho alveolar carcinoma

Question 6:

Non-smoker patients with lung carcinoma are most likely to have a mutation in which of the following genes?

a) KRAS

b) EGFR

c) TP53

d) ALK

Question 7:

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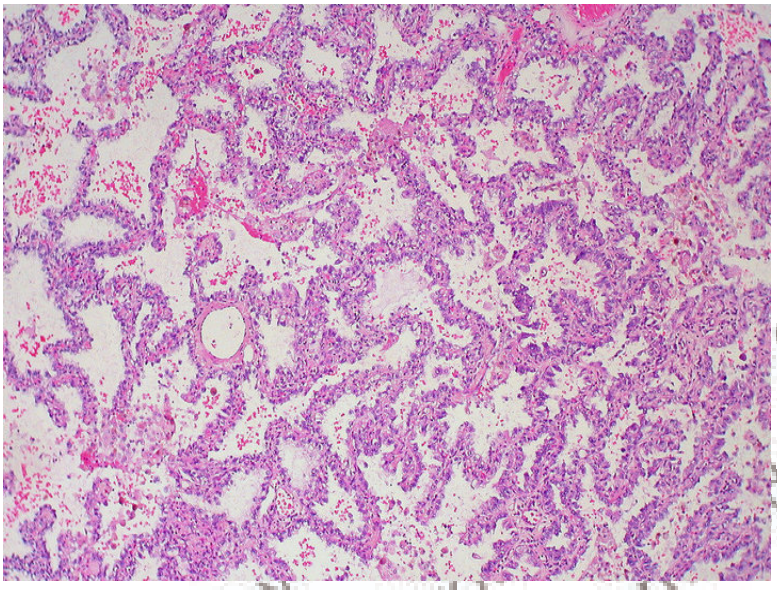
A woman presents to the OPD with complaints of bloody cough, dyspnea, and weight loss. During the evaluation, a CT-guided lung biopsy reveals the following picture. What is the most likely diagnosis?



a) Squamous cell cancer

b) Small-cell cancer

c) Adenocarcinoma

d) Carcinoid

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Question 8:

Which of the following immunohistochemical markers would be positive in a patient with adenocarcinoma lung?

a) Fibrillary protein

b) Chromogranin

c) Synaptophysin

d) Thyroid transcription factor

Question 9:

A 75-year-old man presents with a cough and shortness of breath. He has been working in a shipping factory for 30 years. On x-ray, a mass is seen in the right apical region of the lung. A biopsy sample is taken from the mass. Which of the following tumor markers is likely to be positive in this tumor?

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a) Calretinin

b) Napsin A

c) PSA

d) CA-19-9

Question 10:

A 59-year old man presented with persistent wheezing, episodes of hemoptysis, and dry cough. Bronchoscopy revealed a mass occluding the left bronchus. Biopsy of the specimen revealed polygonal cells with fine stippled chromatin and eosinophilic cytoplasm arranged in nests. The tumor was positive for CD 56, synaptophysin, and chromogranin. What is the cell of origin of this tumor?

a) Type 2 pneumocyte

b) Clara cell

c) Paneth cells

d) Kulchitsky cell

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Question 11:

What percentage of patients with bronchial carcinoids present with carcinoid syndrome?

a) 10%

b) 30%

c) 70%

d) 20%

Question 12:

A solitary coin lesion was seen on a routine X-ray of a patient. After evaluation, he was diagnosed with lung hamartoma. Which of the following is the most common tissue seen in these lesions?

a) Bone

b) Cartilage

c) Fat

d) Smooth muscle

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Answer Key

Question No.	Correct Option
1	a
2	a
3	a
4	a
5	a
6	b
7	c
8	d
9	a
10	d
11	a
12	b

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Detailed Explanations

Solution to Question 1:

According to Globocan 2020, the most common cancer worldwide is breast cancer. However, lung cancer remains the leading overall cause of cancer mortality.

Lung cancers:

• The most common malignant tumors of the lung are metastases/ secondaries.

• The most common primary malignant tumor of the lung is bronchogenic cancer.

• The most common histology is adenocarcinoma (43.8%), followed by squamous cell (26.2%).

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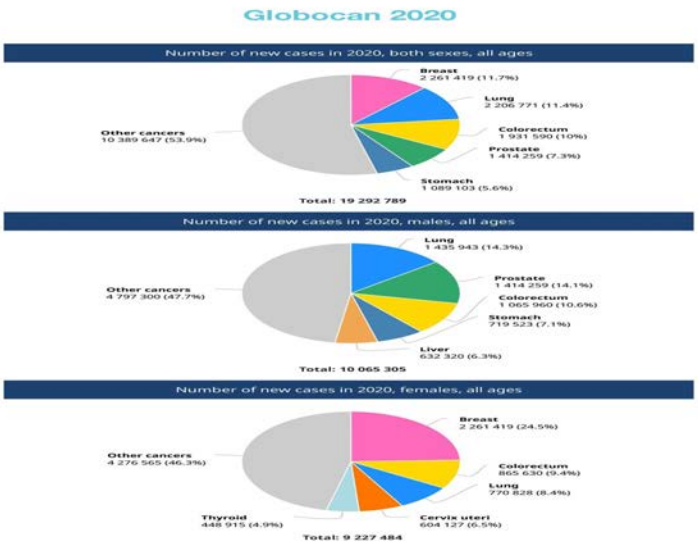

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Solution to Question 2:

The major presenting complaints of lung cancer patients are cough (75%), weight loss (40%), chest pain (40%), and dyspnea (20%).

Paraneoplastic syndromes associated with lung cancer:

SIADH: Syndrome of inappropriate antidiuretic hormone secretion

ADH: Antidiuretic hormone

ACTH: Adrenocorticotropic hormone

Paraneoplastic syndrome	Causal mechanism	Type of cancer
SIADH	Inappropriate ADH secretion	Small-cell carcinoma
Cushing syndrome	ACTH or ACTH like substanc e	Small-cell carcinoma
Carcinoid syndrome	Serotonin and Bradykinin	Small-cell carcinoma
Hypercalcemia	Parathyroid hormone-related peptide	Squamous cell carcinoma
Lambert-Eaton myasthenic s yndrome	Auto-antibodies directed to t he neuronal calcium channel (possibly elicited by tumor io nic channels)	Small-cell carcinoma (rarely i n other lung cancers)
Acanthosis nigricans	secretion of epidermal growt h factor	Lung carcinoma
Hypertrophic pulmonary oste oarthropathy	Unknown	Lung carcinoma

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Solution to Question 3:

The given image shows keratin pearls and islands of large polygonal malignant cells. These as seen in squamous cell carcinoma of the lungs. P40 is the most sensitive and specific marker for squamous cell carcinoma (SCC) of the lungs.

Other markers include cytokeratin 5/6 and P63.

TTF-1 and napsin-A are the markers for adenocarcinoma.

Chromogranin, synaptophysin, and CD56 are the markers for small cell lung carcinoma.

Note: The 2015 World Health Organization Classification of Lung Tumors has made a recommendation that at least one antibody each for squamous (P40 or P63) and glandular (e.g. TTF-1) differentiation should be used for an initial workup. Thus a simple panel of TTF-1 and p40 may be able to classify most non-small cell carcinoma-not otherwise specified cases.

Solution to Question 4:

Small-cell carcinoma of the lung is the most aggressive type of lung cancer.

This tumor originates from neuroendocrine progenitor cells (Kulchitsky cells), which are present in the lining bronchial epithelium.

Histopathological examination of small cell lung carcinoma shows:

• Clusters of small cells with scant cytoplasm

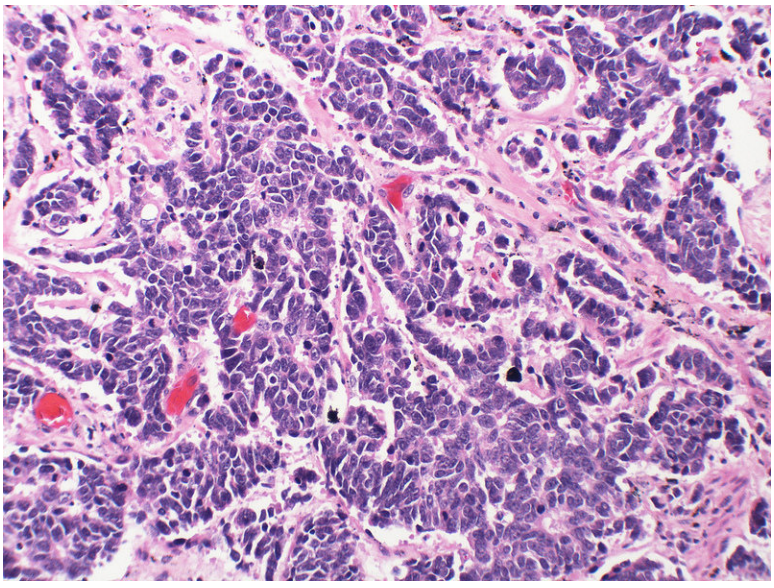
• Ill-defined cell borders

• Finely granular nuclear chromatin (salt and pepper pattern)

• Absent or inconspicuous nucleoli

The cells are round, oval, or spindle-shaped, and nuclear molding is prominent.

The image below shows the histopathological findings of small cell lung carcinoma.



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Solution to Question 5:

The given clinical features and the histopathology showing the Azzopardi effect are suggestive of a small cell carcinoma of the lung.

Azzopardi effect is described as basophilic staining of vascular walls due to encrustation by DNA from necrotic tumor cells.

Solution to Question 6:

Non-smoker patients with lung carcinoma are most likely to have a mutation in the EGFR gene.

Molecular genetics of lung cancer:

Histological type	Mutated genes
Adenocarcinoma	Tyrosine kinase genes (EGFR, ALK, ROS, MET, RET)orKRASgene
Squamous cell carcinoma	TP53CDKN2A/p16FGFR1 gene amplificationLoss of RB gene
Small cell carcinoma	TP53Loss of RB gene3p deletionMYC amplification

Solution to Question 7:

The given clinical scenario is suggestive of adenocarcinoma lung.

It is the most common form of lung cancer. It is an invasive malignant epithelial tumor with glandular differentiation. The tumor cells produce mucin. It is usually located peripherally (it arises from the terminal bronchiole).

Molecular genetics show frequent mutations in EGFR, ALK, ROS, MET, and RET (Receptor tyrosine kinase genes) or KRAS mutations.

Histologically, lepidic growth patterns are seen. It refers to the pattern of spread of the tumor in which the tumor cells “crawl” along normal-appearing alveolar septae and resembles butterflies resting on a fence.

Adenocarcinomas grow in various patterns, including acinar, lepidic, papillary, micropapillary, and solid with mucin formation. Tumor cells are positive for mucin and thyroid transcription factor-1 (TTF-1)

Tumors 3 cm or less in diameter characterized by lepidic growth pattern without stromal invasion are now called adenocarcinoma in situ (formerly called bronchoalveolar carcinoma).

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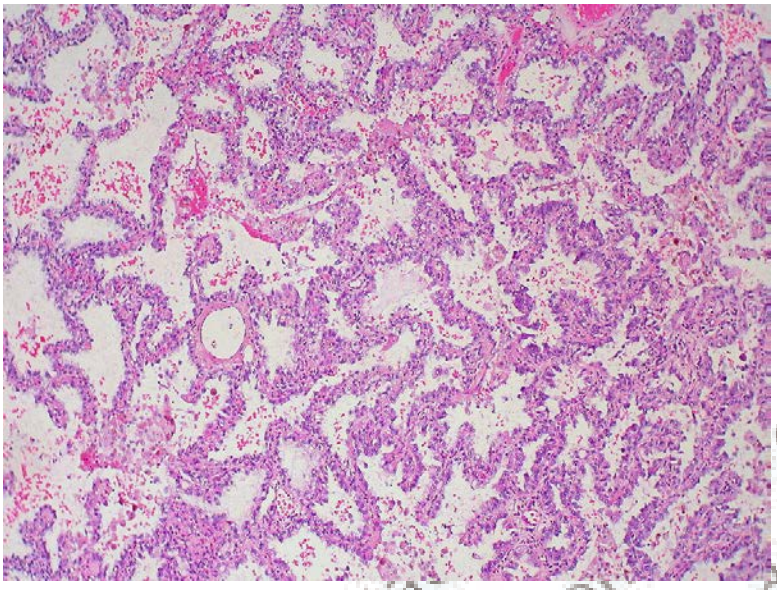
The image below shows histopathological findings of adenocarcinoma of the lung.



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Solution to Question 8:

Thyroid transcription factor-1 (TTF-1), mucin, and napsin-A are positive in adenocarcinoma lung.

TTF-1 is required for normal lung development. It can be used to distinguish primary adenocarcinoma of the lungs (TTF-1 positive) from other histological types of lung cancers, metastatic adenocarcinoma, and mesothelioma (TTF-1 negative).

P40 and P63 are the markers for squamous cell carcinoma.

Chromogranin, synaptophysin, and CD56 are the markers for small cell lung carcinoma.

Solution to Question 9:

Calretinin is most likely to be positive in this tumour as the given clinical scenario points to the diagnosis of malignant mesothelioma.

Malignant mesothelioma is a rare malignant tumour of the pleura, associated with heavy asbestos exposure (shipping factory). The lifetime risk of developing mesothelioma in heavily exposed individuals is as high as 7% to 10%.

It has strong male predilection (3:1). There is a long latent period of 25 to 45 years for the development of asbestos-related mesothelioma.

The image below shows a lung autopsy sample with mesothelioma.

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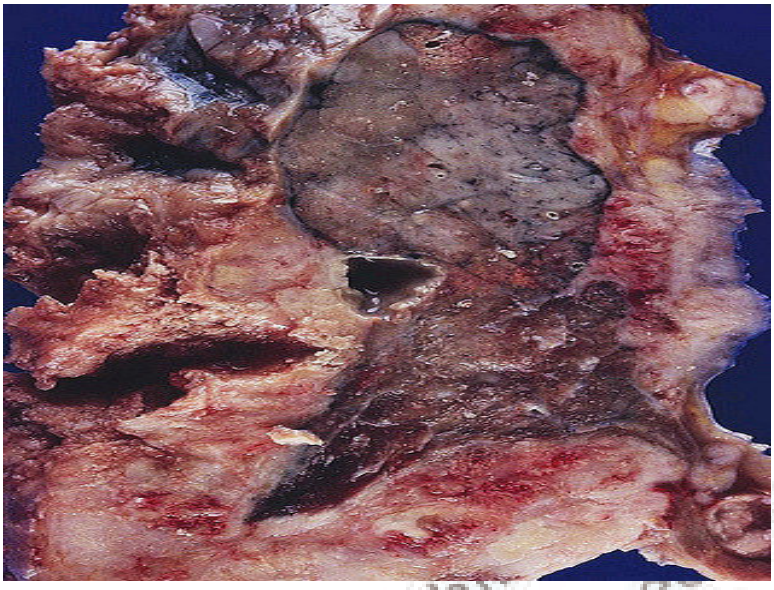
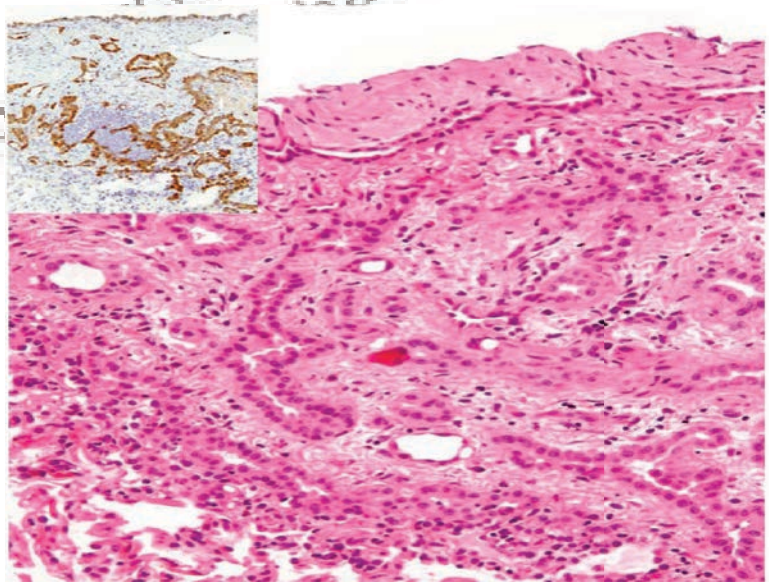


Grossly, it appears as a diffuse lesion arising either from the visceral or parietal pleura. The affected lung becomes ensheathed by a thick layer of soft, gelatinous, grayish pink tumor tissue.

Microscopically, they are of three types: epithelioid (60%), sarcomatoid (20%), and mixed (20%).

Electron microscopy in mesothelioma will show numerous long, slender microvilli and abundant monofilaments but absent microvillous rootlets and lamellar bodies.

The image below shows the epithelioid type of mesothelioma showing cuboidal, columnar, or flattened cells forming tubular or papillary structures resembling adenocarcinoma. Inset shows strong positivity for Calretinin immunostain.



Solution to Question 10:

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The given clinical scenario is suggestive of bronchial carcinoid. Bronchial neuroendocrine tumors (NETs) arise from Kulchitsky cells.

WHO divides neuroendocrine neoplasms into four categories:

• Typical carcinoid

• Atypical carcinoid

• Large-cell neuroendocrine carcinoma

• Small-cell carcinoma

Carcinoid tumors are low-grade malignant epithelial neoplasms that represent 1% to 5% of all lung tumors. It is not related to smoking. Carcinoids may occur in patients with multiple endocrine neoplasia type 1.

On gross examination, these tumors grow as fingerlike or spherical polypoid masses that project into the lumen of the bronchus or as collar button lesions, penetrating the bronchial wall to fan out in the peribronchial tissue.

Histologically, the tumor is composed of organoid, trabecular, palisading, ribbon, or rosette-like arrangements of cells separated by a delicate fibrovascular stroma. On electron microscopy, the cells exhibit the dense-core neurosecretory granules.

Immunohistochemistry shows positivity for serotonin, neuron-specific enolase, bombesin, calcitonin, or other peptides.

10% of the cases may produce carcinoid syndrome.

Most carcinoids follow a relatively benign course and have good prognosis.

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Solution to Question 11:

Approximately, 10% of bronchial carcinoids give rise to the carcinoid syndrome.

Most bronchial carcinoids follow a relatively benign course, do not have secretory activity and do not metastasize to distant sites.

Classic carcinoid syndrome is characterized by intermittent attacks of diarrhea, flushing, bronchospasm and cyanosis.

Carcinoid syndrome is due to excessive production of serotonin, a specialised product of tryptophan metabolism by argentaffin cells (cells in the carcinoid tumor). It is then metabolised and excreted in urine.

If urinary levels of 5- HIAA exceed 25 mg/day, a diagnosis of carcinoid syndrome can be made.

Solution to Question 12:

Cartilage is the most common connective tissue in lung hamartoma.

Pulmonary hamartoma consists of nodules of connective tissue intersected by epithelial clefts. There are islands of cartilage, fat, smooth muscle, and entrapped respiratory epithelium in

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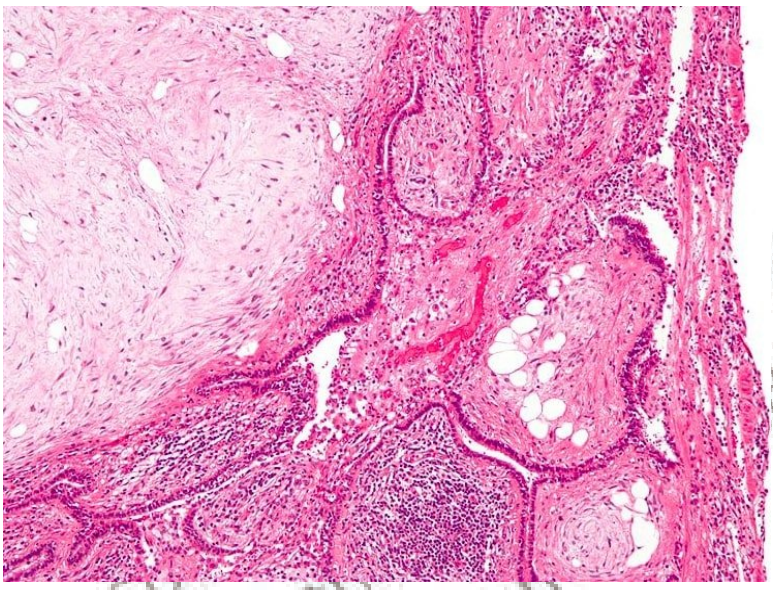
pulmonary hamartoma.

It is a benign clonal neoplasm associated with chromosomal aberrations involving either 6p21 or 12q14-q15.

Lung hamartoma is usually discovered as an incidental coin lesion on a routine chest radiograph.

The given below is an image of lung hamartoma.



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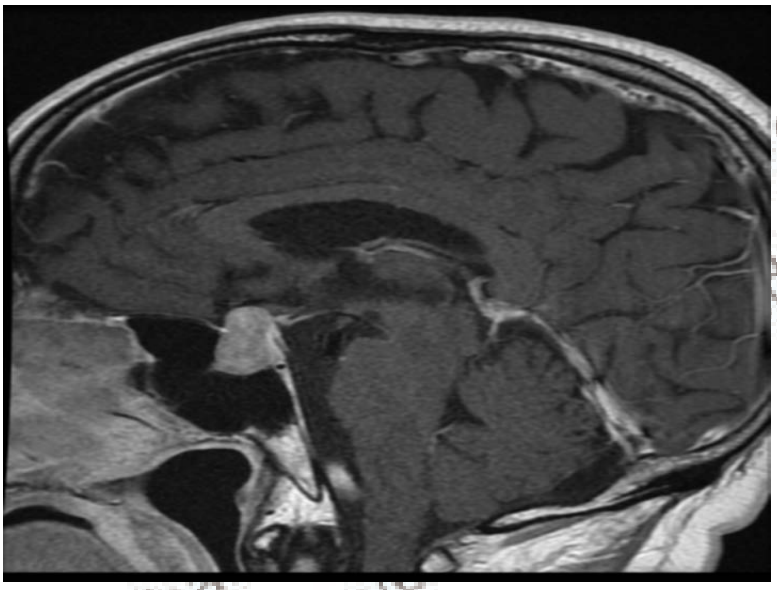
Pituitary ,Parathyroids and Pancreas

Question 1:

A 30-year-old woman is being evaluated for chronic headaches, infertility, and galactorrhea. MRI of the brain shows the following finding. What is the likely diagnosis?



a) Corticotroph adenoma

b) Gonadotroph adenoma

c) Lactotroph adenoma

d) Somatotroph adenoma

Question 2:

Presence of which of the following features is required to diagnose a patient with pituitary carcinoma?

a) Nuclear pleomorphism

b) Atypical mitotic figures

c) Rapidly growing mass

d) Presence of craniospinal metastasis

Question 3:

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Which of the following cells secrete parathyroid hormone?

a) Chief cells

b) Oxyphil cells

c) C-cells

d) Parafollicular cells

Question 4:

What is the most common cause of asymptomatic hypercalcemia?

a) Malignancy

b) Sarcoidosis

c) Primary hyperparathyroidism

d) Secondary hyperparathyroidism

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Question 5:

A 40-year-old woman presented with bone pain and abdominal cramps for the past 1 week. She has had multiple prior hospital admissions for management of recurrent renal calculi. Investigations revealed elevated serum calcium and PTH levels with reduced phosphate levels. Which of the following is the most common pathological change responsible for this condition?

a) Adenoma

b) Diffuse hyperplasia

c) Nodular hyperplasia

d) Ectopic glandular tissue

Question 6:

A 47-year-old woman was evaluated for chronic backache and abdominal pain. Investigations revealed the following. What is the most likely bone finding seen in this condition?

a) Osteoporosis circumscripta

b) Fraying and cupping of metaphysis

c) Osteitis fibrosa cystica

d) Punched out lytic lesions

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Question 7:

A 46-year-old woman is referred with recurrent episodes of hypoglycemia. During the evaluation, she is found to have high serum levels of insulin. Measurement of which of the following can help in reaching the diagnosis?

a) Proinsulin

b) C-peptide

c) Pre-proinsulin

d) Insulin-like peptide

Question 8:

Patients with which of the following chromosomal anomalies are least likely to develop diabetes mellitus?

a) Trisomy of chromosome 21

b) XXY karyotype

c) XO karyotype

d) Trisomy of chromosome 18

Question 9:

A pathologist is studying a Congo red-stained slide of pancreatic tissue. He observes it under polarized light and notes the following finding. This finding is commonly associated with which of the following conditions?

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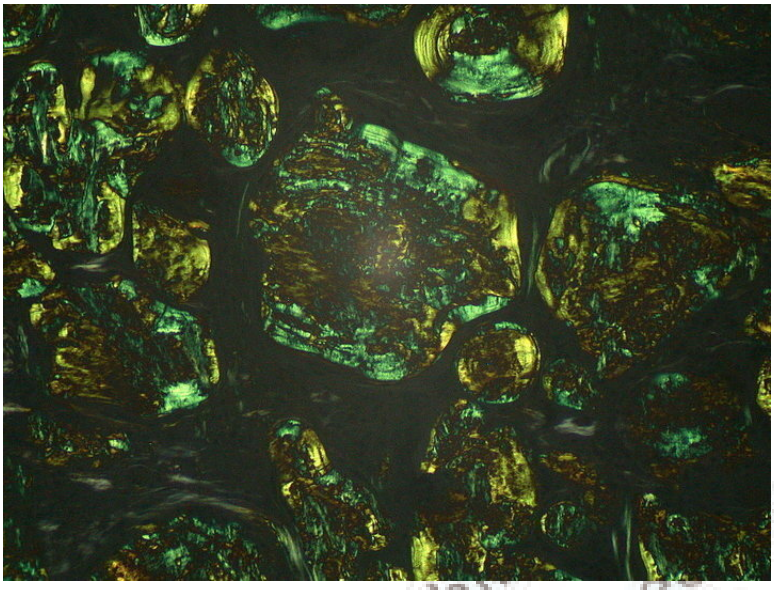

a) Type 1 diabetes mellitus

b) Type 2 diabetes mellitus

c) Maturity onset diabetes in young

d) Type 3C diabetes mellitus

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Question 10:

Which of the following is not a detrimental effect of advanced glycation end-products in patients suffering from diabetes mellitus?

a) Deposition of excess basement membrane material due to TGF-° release

b) Generation of reactive oxygen species in endothelial cells

c) Increased anticoagulant effect on endothelial cells and macrophages

d) Increase in vascular smooth muscle cells and extracellular matrix

Question 11:

What is the most common pancreatic endocrine neoplasm?

a) Glucagonoma

b) Insulinoma

c) Gastrinoma

d) VIPoma

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Question 12:

A 39-year-old man was referred to a higher center for further evaluation of peptic ulcer disease refractory to high doses of proton pump inhibitors. There is a history of pituitary and parathyroid tumors in his family members. Serum gastrin level was found to be 1690 pg/ml (normal < 100) and a neuroendocrine tumor is suspected. Which of the following is false about this condition?

a) It is associated with intractable jejunal ulcers

b) This patient likely has a solitary tumor

c) Most tumors are locally invasive

d) Tumors usually originate in Passaro's triangle

Question 13:

A patient with longstanding diabetes mellitus came with complaints of bulky stools. Ultrasound abdomen showed the presence of multiple gallstones. Hypersecretion of which of the following leads to this presentation?

a) Somatostatin

b) Glucagon

c) Amylin

d) Growth hormone

Question 14:

A patient presented with profuse watery diarrhoea and muscle cramps for the past few weeks. The diarrhoea was intractable to antibiotics and stool culture was negative for organisms. He also complained of indigestion and frequent bloating. On investigation, he was found to have microcytic hypochromic anaemia. Serum potassium was 2.4 mmol/L. Upper GI endoscopy was normal. Excess of which of the following hormones leads to this condition?

a) VIP

b) Gastrin

c) Serotonin

d) Pancreatic polypeptide

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Answer Key

Question No.	Correct Option
1	c
2	d
3	a
4	c
5	a
6	c
7	b
8	d
9	b
10	c
11	b
12	b
13	a
14	a

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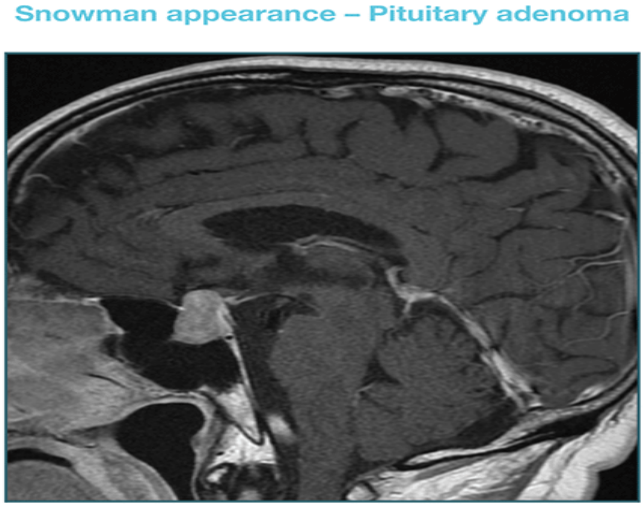
Detailed Explanations

Solution to Question 1:

This clinical scenario and brain MRI showing a pituitary adenoma are suggestive of a lactotroph adenoma (prolactinoma).



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Pituitary adenomas are usually found in adults. The most common genetic alterations in this condition are mutations in G proteins (particularly GNAS).

Depending on their size, they are classified as:

• Microadenomas - diameter < 1 cm

• Macroadenomas - diameter > 1 cm

They may be functioning or non-functioning. The most common type of functioning pituitary adenomas are prolactinomas.

The clinical features of prolactinoma include:

• Due to mass effect -

• Features of raised intracranial tension

• Visual field disturbances (bitemporal hemianopia) - due to compression of optic chiasm

• Hypopituitarism - due to compressed hypophyseal stalk

• Due to hyperprolactinemia -

• Galactorrhoea

• Amenorrhoea or oligomenorrhoea

• Infertility

• Loss of libido

• Gynecomastia

Serum prolactin concentrations tend to correlate with the size of the adenoma. The normal range of serum prolactin is 5-20 µg/L. The diagnosis of prolactinoma is most likely to be associated with a prolactin level >200 µg/L.

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Solution to Question 2:

The following features are required for the diagnosis of pituitary carcinoma:

• A pituitary tumor that has metastasized to distant sites, either craniospinal or systemic sites (and/or)

• Presence of a pituitary tumor that is not contiguous with the primary sellar tumour

Pituitary carcinoma is extremely rare (< 1% of total tumors). They are associated with activating mutations of the HRAS oncogene.

The diagnosis of pituitary carcinoma cannot be made based on histologic appearance alone. Though pituitary adenomas normally show cellular monomorphism and the absence of a reticulin network, they can have some overlapping features with malignant tumors such as:

• Atypical adenomas - show pleomorphism and atypical mitosis

• Invasive adenomas -

• Non-encapsulated

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• Show local invasion into cavernous and sphenoid sinuses, dura, brain

• However, they remain confined to the primary tumor site

Solution to Question 3:

Parathyroid hormone (PTH) is secreted by the chief cells of the parathyroid glands.

The function of the parathyroids is to regulate calcium homeostasis. This gland is composed of two cell types:

• Chief cells -

• Polygonal cells with uniform nuclei and pink cytoplasm

• Water-clear appearance - due to presence of large amounts of cytoplasmic glycogen

• Secretory granules containing PTH

• Oxyphil cells - Slightly larger cells with acidophilic cytoplasm with no known function.

The following image shows the normal histology of the parathyroid gland:

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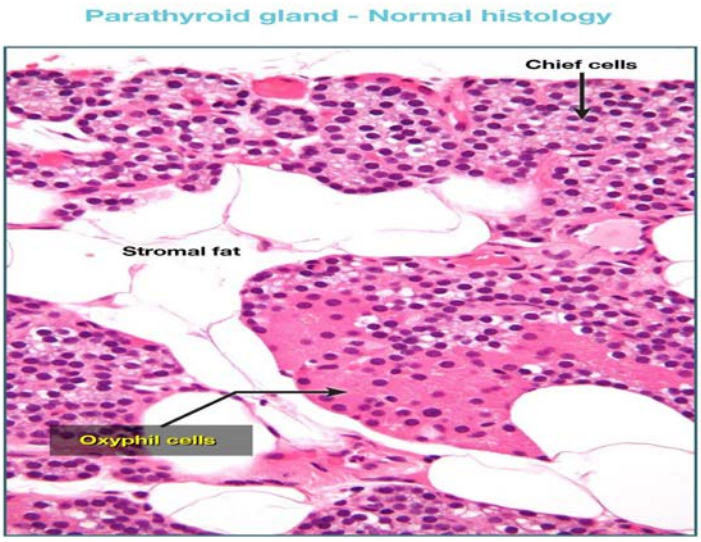

C-cells or parafollicular cells are present in the thyroid. They secrete calcitonin.

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Solution to Question 4:

The most common cause of asymptomatic hypercalcemia (isolated hypercalcemia without signs or symptoms) is primary hyperparathyroidism. It is also the most common cause of hypercalcemia overall.

Primary hyperparathyroidism results in autonomous overproduction of parathyroid hormone (PTH), resulting in elevated levels. It usually results from an adenoma or hyperplasia of parathyroid tissue.

The most common cause of symptomatic hypercalcemia is malignancy. The most common mechanism through which osteolytic tumors induce hypercalcemia is the secretion of the PTH-related peptide (PTHrP).

Solution to Question 5:

The given clinical picture is highly suggestive of primary hyperparathyroidism. The most common cause is a sporadic, solitary parathyroid adenoma.

Parathyroid tumors may be associated with cyclin D1 gene inversions and MEN1 mutations. Hyperparathyroidism refers to elevated parathyroid hormone (PTH). It is classified into:

• Primary - autonomous overproduction of PTH

• Secondary - compensatory hypersecretion of PTH in response to prolonged hypocalcemia

• Tertiary - persistent hypersecretion of PTH even after correction of prolonged hypocalcemia. (e.g. after renal transplant)

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The classical symptoms and signs of primary hyperparathyroidism are due to hypercalcemia as well as increased parathyroid hormone (PTH) levels. The features of hypercalcemia are as follows:

The features of elevated PTH levels are as follows:

• Osteitis fibrosa cystica

• Osteopenia/osteoporosis

• Hyperuricemia and gout

• Pseudogout

• Increased production of calcitriol

• Nephrolithiasis

• Hypophosphatemia

• Anemia

The clinical signs associated with primary hyperparathyroidism can be remembered with the mnemonic - “bones, stones, groans, moans with fatigue overtones”

System	Clinical features
Musculoskeletal	Bone painSkeletal deformitiesPathological fracturesMyalgia and arthralgia
Renal	Renal stones(Calcium oxalate > calcium phosphate)Nephrocalcinosis Polyuria and dehydrationRenal failure
GIT	ConstipationNausea, vomiting, anorexiaAbdominal painPeptic ulcer diseaseAcute pancreatitis
Neuropsychiatric	Anxiety, depressionCognitive dysfunctionIrritabilityHallucinations
Cardiac	Short QT intervalBradycardia Hypertension
Ectopic calcification	Cornea: Band keratopathyExtravascular tissues: calcinosis Small arteries: calciphylaxis

Solution to Question 6:

The clinical scenario and lab findings point towards a diagnosis of hyperparathyroidism. The bone finding associated with this condition is osteitis fibrosa cystica.

This condition is also called brown tumor or von Recklinghausen disease of bone.

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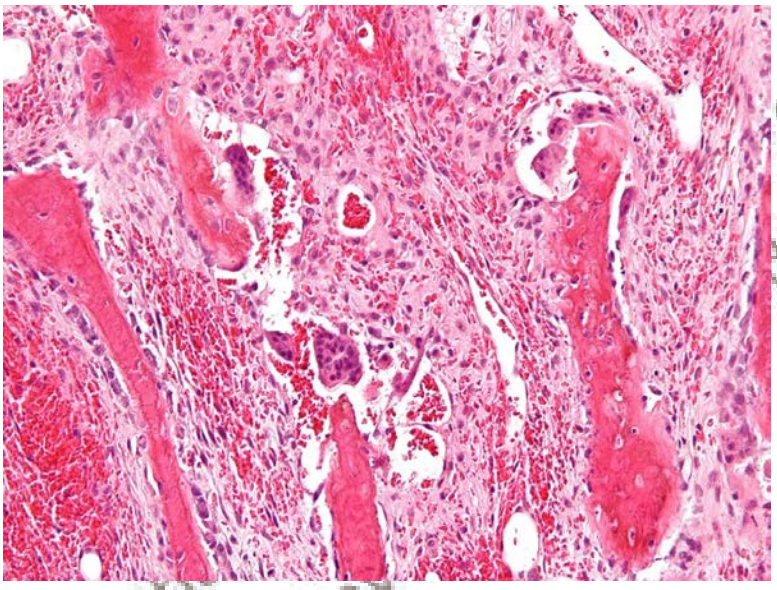
In hyperparathyroidism, high levels of PTH result in increased osteoclast activity. This results in bone loss which predisposes to microfractures and secondary hemorrhages. This results in the following changes:

• An influx of macrophages that form giant cells

• Mass of reparative fibrous tissue

• Increased vascularity, hemorrhage, and hemosiderin deposition - results in brown color

The image given below is showing a brown tumor with numerous giant cells with interstitial hemorrhage, hemosiderin.



Option A: Osteoporosis circumscripta is a large, well-defined lytic lesion seen in the skull of patients with Paget's disease.

Option B: Fraying and cupping of the metaphysis of the bones are classically seen in patients suffering from rickets.

Option D: Punched out lytic lesions of the bone are seen in patients with multiple myeloma.

Solution to Question 7:

This clinical scenario is suggestive of hypoglycemia due to hyperinsulinemia. As C-peptide is a marker of endogenous insulin secretion, its levels would help in identifying the source of insulin:

• High C-peptide - excess insulin production (insulinoma)

• Normal/ low C-peptide - exogenous insulin administration (factitious disorder)

The precursor molecule of insulin is pre-proinsulin, which gets cleaved to form proinsulin. This proinsulin gets cleaved to form insulin and C-peptide (by-product). Hence, both are secreted in equimolar quantities during insulin secretion. Hence, the level of C-peptide corresponds to the level of endogenous insulin.

The levels of C-peptide decrease with the loss of °-cell mass in type 1 diabetes.

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Solution to Question 8:

Edward's syndrome or trisomy 18 is not associated with diabetes mellitus.

Genetic syndromes associated with diabetes mellitus include:

• Down's syndrome (trisomy 21)

• Klinefelter's syndrome (XXY karyotype)

• Turner's syndrome (XO karyotype)

• Prader–Willi syndrome (deletion of paternal chromosome 15)

Other causes of diabetes mellitus include:

• Genetic defects in insulin action -

• Type A insulin resistance

• Lipoatrophic diabetes

• Exocrine pancreatic defects -

• Chronic pancreatitis

• Pancreatectomy/trauma

• Neoplasia

• Cystic fibrosis

• Hemochromatosis

• Fibrocalculous pancreatopathy

• Endocrinopathies -

• Acromegaly

• Cushing syndrome

• Hyperthyroidism

• Pheochromocytoma

• Glucagonoma

• Infections -

• Cytomegalovirus

• Coxsackie B virus

• Congenital rubella

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Solution to Question 9:

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The image shows a Congo red-stained biopsy specimen with apple-green birefringence under polarized microscopy. It is indicative of amyloid accumulation within the pancreatic islets. This is commonly associated with type 2 diabetes mellitus.

Amyloid deposition begins in and around capillaries and between cells. In advanced stages, the islets may be virtually obliterated and fibrosis may also be observed.

Solution to Question 10:

Advanced glycation end products (AGEs) result in increased procoagulant effects on endothelial cells and macrophages, not anticoagulant effects.

AGEs are formed by nonenzymatic reactions between intracellular glucose-derived dicarbonyl precursors with the amino groups of proteins. They bind to a specific receptor (RAGE) that is expressed on inflammatory cells (macrophages and T cells), endothelium, and vascular smooth muscle.

The detrimental effects of the AGE-RAGE signalling axis within the vascular compartment include:

• Release of cytokines and growth factors, including TGF-° - leads to deposition of excess basement membrane material

• Generation of reactive oxygen species in endothelial cells.

• Increased procoagulant activity on endothelial cells and macrophages.

• Enhanced proliferation of vascular smooth muscle cells and synthesis of extracellular matrix

These effects are responsible for the microvascular and macrovascular complications in diabetes mellitus.

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Solution to Question 11:

Insulinoma (°-cell tumors) is the most common pancreatic endocrine neoplasm. It produces sufficient insulin to induce clinically significant hypoglycemia.

The three most common and distinctive clinical syndromes associated with functional pancreatic endocrine neoplasms are as follows:

• Hyperinsulinism

• Zollinger–Ellison syndrome (hypergastrinemia)

• Multiple endocrine neoplasias (MEN)

Solution to Question 12:

The given clinical scenario is suggestive of a gastrin-producing tumor or gastrinoma (Zollinger-Ellison syndrome). The family history of pituitary and parathyroid tumors is suggestive

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of MEN1 syndrome. This syndrome is associated with multifocal gastrinomas.

On the other hand, sporadic gastrinomas are usually single.

Gastrinomas usually arise in the duodenum, peripancreatic soft tissues, pancreas. The site of origin is the duodenum when ZES is associated with MEN1. Most tumors are locally invasive and metastasize early.

Hypergastrinemia gives rise to extreme gastric acid secretion and peptic ulceration, that is refractory to proton pump inhibitors. It results in multiple ulcers in duodenum, stomach, and uncommon areas like jejunum.

Solution to Question 13:

The given scenario is suggestive of a δ-cell tumor or somatostatinoma. It results in hypersecretion of somatostatin.

Somatostatin inhibits pancreatic and biliary secretions. Patients with somatostatinoma usually present with vague abdominal pain along with the triad of:

• Gallstones - due to bile stasis

• Diabetes mellitus - due to inhibition of insulin secretion

• Steatorrhea - due to inhibition of pancreatic exocrine secretion and bile secretion

Solution to Question 14:

The given scenario is suggestive of WDHA syndrome. It is due to hypersecretion of VIP (vasoactive-intestinal peptide).

WDHA syndrome includes the following features:

• Watery diarrhea

• Hypokalemia (Serum K+< 3.5 mmol/L)

• Achlorhydria (bloating, indigestion, iron deficiency)

Neural crest tumors, such as neuroblastomas, ganglioneuroblastoma, ganglioneuromas, and pheochromocytomas can also be associated with VIPoma syndrome.

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Thyroid Glands

Question 1:

What is the most common cause of endogenous hyperthyroidism?

a) Graves' disease

b) Adenomatoid goiter

c) Pituitary adenoma

d) Multinodular goiter

Question 2:

A 32-year-old lady presents with loss of weight, tremors of the hand, and irritability for the past 4-5 months. Examination findings and investigations are given below. All of the following contribute to these eye findings except:

a) Lymphocytic infiltration in the retroorbital space

b) Glycosaminoglycan deposition

c) Orbital adipose tissue infiltration

d) Sympathetic overactivity

Question 3:

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Which of the following disorders does not lead to hyperthyroidism?

a) Thyroid hormone resistance

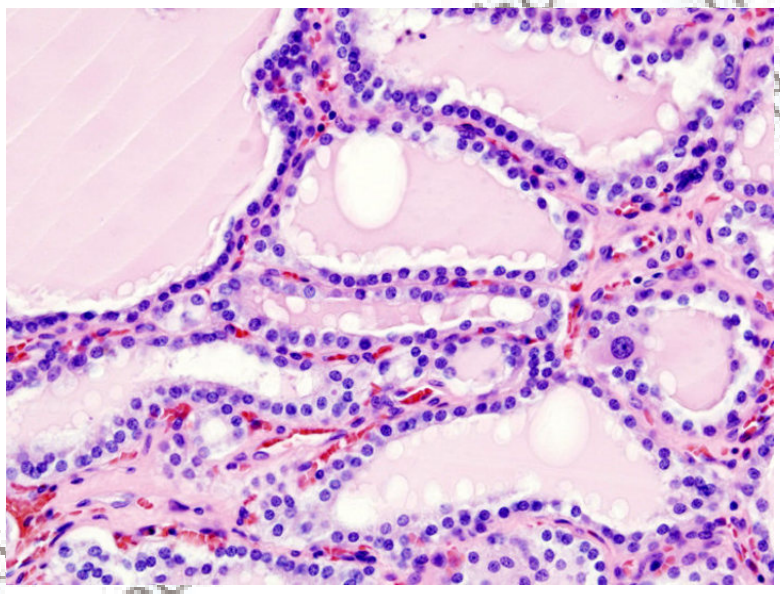
b) Plummer disease

c) TSH secreting pituitary adenoma

d) Hashimoto thyroiditis

Question 4:

What is the finding seen in the following histopathological examination of a biopsy specimen from a patient with an enlarged thyroid?



a) Dense lymphoid infiltrate with germinal centre

b) Fibroreticular proliferation

c) Vacuolated cytoplasm

d) Follicular hyperplasia with scalloping colloid

Question 5:

A 50-year-old woman presented with diffuse thyroid swelling for the past 6 months. She says that it has increased in size over the last 1 month. Investigations reveal elevated TSH levels. Histopathological examination is done, as shown below. What is the most likely diagnosis?

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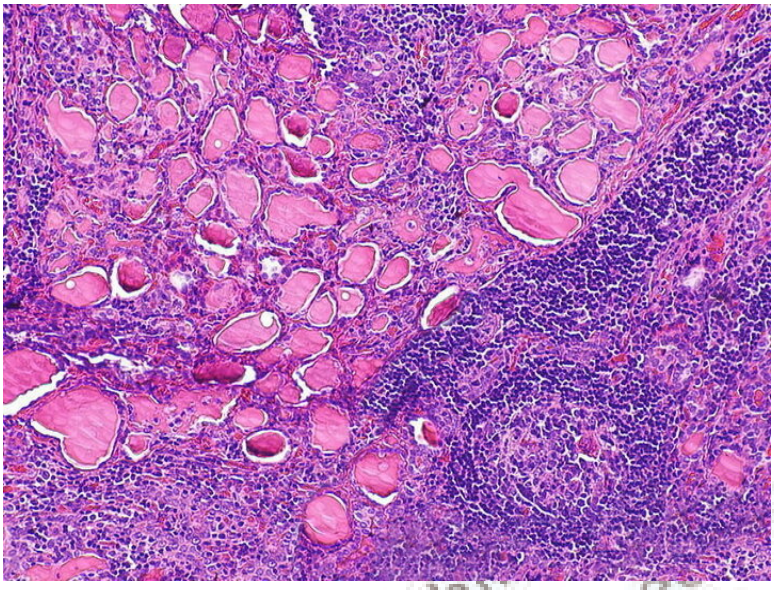

a) Granulomatous thyroid disease

b) Hashimoto's thyroiditis

c) Medullary carcinoma of thyroid

d) Papillary carcinoma of thyroid

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Question 6:

Which of the following findings will you not observe in a thyroid gland biopsy taken from a patient suffering from Hashimoto thyroiditis?

a) Atrophic thyroid follicles

b) Well-developed germinal centres

c) Oncocytic metaplasia

d) Orphan Annie eye nuclei

Question 7:

What is the most common cause of hypothyroidism in iodine-sufficient areas of the world?

a) Autoimmune hypothyroidism

b) Dyshormonogenetic goiter

c) Wolff Chaikoff effect

d) Iatrogenic hypothyroidism

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Question 8:

A 48-year-old woman presented with fever, malaise, and painful enlargement of the thyroid gland after a few days following viral fever. On investigation, thyroid antibodies were normal and serum T4 was slightly raised. Which of the following is the most probable diagnosis?

a) Subacute lymphocytic thyroiditis

b) Riedel's thyroiditis

c) Subacute granulomatous thyroiditis

d) Hashimoto's thyroiditis

Question 9:

Which of the following statements about solitary thyroid nodule is incorrect?

a) They are more common in women

b) These are mostly benign

c) Solitary nodules are more likely to be malignant than are multiple nodules

d) Nodules in younger patients are less likely to be malignant

Question 10:

Which of the following is the most common thyroid cancer?

a) Papillary

b) Follicular

c) Anaplastic

d) Medullary

Question 11:

A patient with a long-standing history of thyroglossal cyst develops a neck swelling. The biopsy of the lesion is given below. What is the probable diagnosis?

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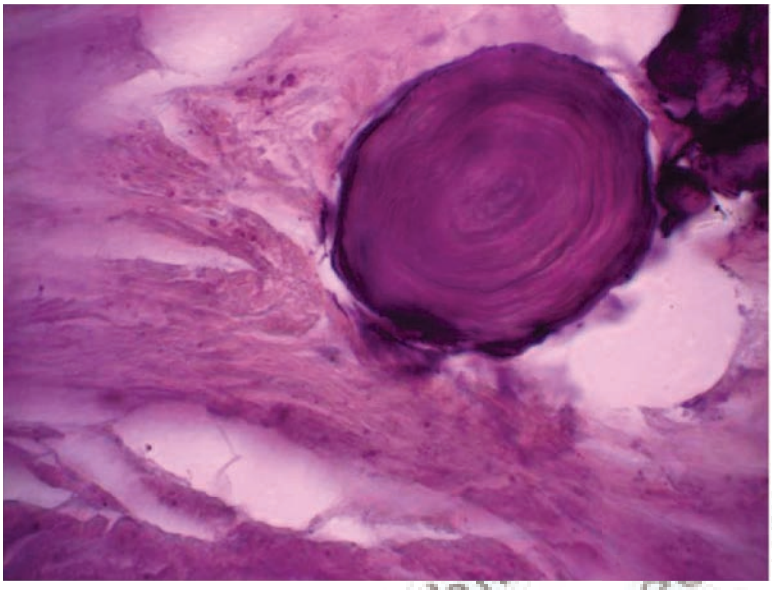

a) Papillary carcinoma

b) Follicular neoplasm

c) Anaplastic carcinoma

d) Medullary carcinoma

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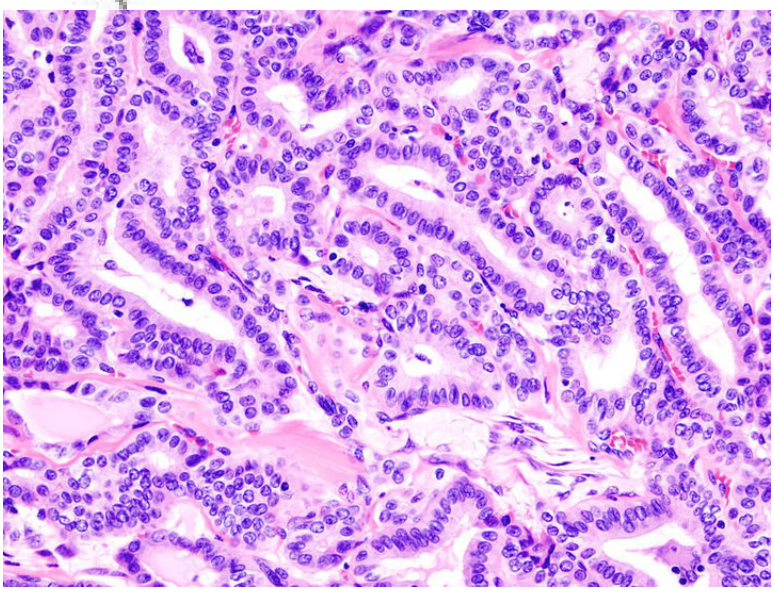
Question 12:

A 30-year-old woman presented with a solitary, non-tender, firm nodule on the left side of her neck. Thyroid function tests were within normal limits. A fine-needle biopsy revealed malignant cells. The tumor was excised and examined under light microscopy as shown below. What is the most probable diagnosis?



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a) Undifferentiated carcinoma

b) Follicular carcinoma

c) Medullary carcinoma

d) Papillary carcinoma

Question 13:

Which of the following statements regarding papillary carcinoma of the thyroid is incorrect?

a) It is the most common form of thyroid carcinoma

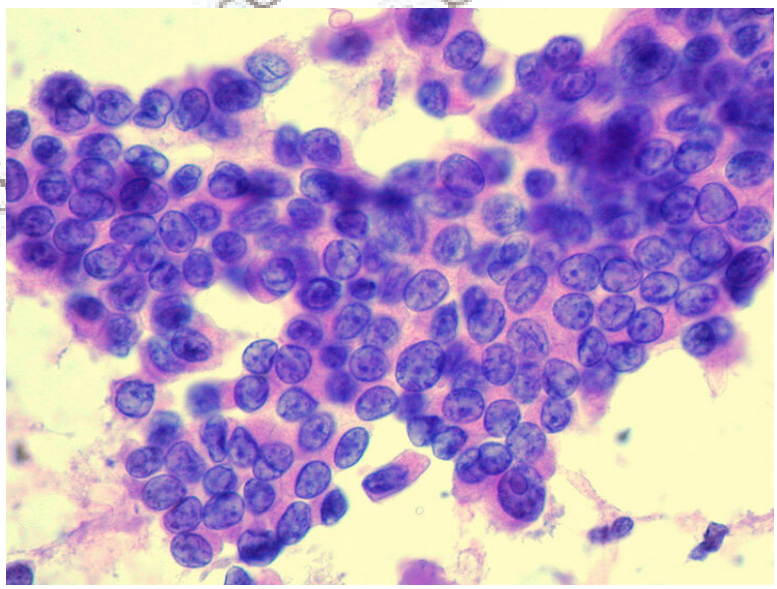
b) Diagnosis can be made based on nuclear features, even in the absence of typical architecture

c) It is associated with previous exposure to ionizing radiation

d) Hematogenous spread is common

Question 14:

A pathologist is studying the following FNAC from a patient's thyroid nodule. Which is the most common site of metastasis for this condition?



a) Lung

b) Liver

c) Brain

d) Bone

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Question 15:

In patients with papillary carcinoma of the thyroid, which of the following genes may be involved?

a) 1, 5

b) 1, 2, 5

c) 2, 3, 4

d) 1, 2, 3

Question 16:

Which of the following is the most common variant of papillary thyroid cancer?

a) Tall cell

b) Follicular

c) Clear cell

d) Diffuse sclerosing

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Question 17:

Which of the following patients is likely to have the best prognosis?

a) A 30-year-old man with papillary carcinoma thyroid

b) A 45-year-old woman with follicular carcinoma thyroid

c) A 78-year-old man with anaplastic carcinoma thyroid

d) A young man with MEN- II syndrome having medullary carcinoma thyroid

Question 18:

A 56-year-old woman coming from a hilly area presents with a hard swelling in the neck which moves up with deglutition and does not move with protrusion of the tongue. The biopsy of the frozen section is given below. What is your diagnosis?

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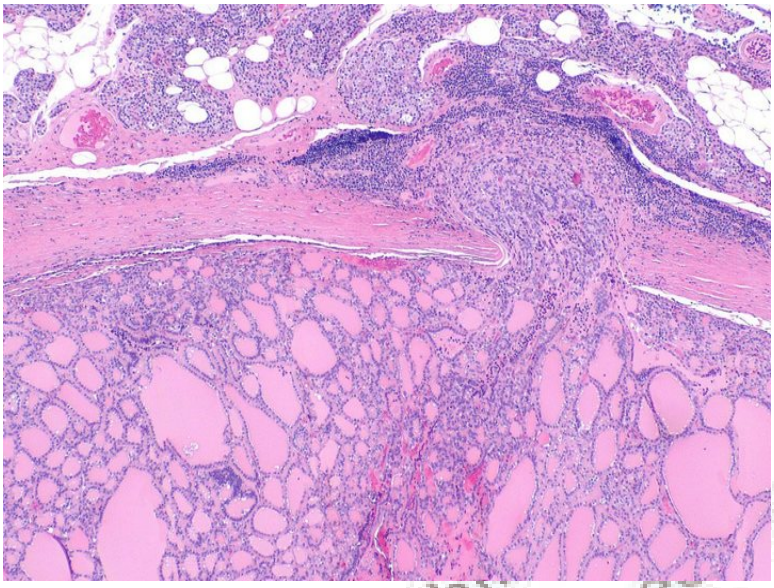

a) Follicular adenoma of thyroid

b) Follicular carcinoma of thyroid

c) Anaplastic carcinoma of thyroid

d) Medullary carcinoma of thyroid

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Question 19:

Which of the following mutations may be found in patients with follicular carcinoma?

a) RAS

b) GNAS

c) RET

d) BRAF

Question 20:

Which of the following is not a proto-oncogene implicated in carcinoma of thyroid?

a) RAS

b) RET

c) BRAF

d) p53

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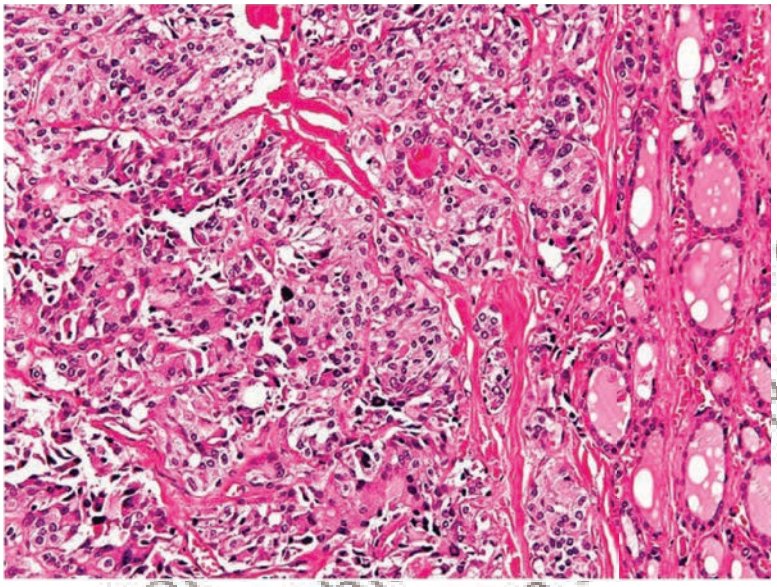
Question 21:

A middle-aged woman presents with thyroid swelling. The histology of the swelling is as shown below. Investigations reveal elevated calcitonin levels. Which of the following is associated with this condition?



a) Cowden syndrome

b) Sipple syndrome

c) Wermer syndrome

d) Werner syndrome

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Answer Key

Question No.	Correct Option
1	a
2	d
3	d
4	d
5	b
6	d
7	a
8	c
9	d

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10	a
11	a
12	d
13	d
14	a
15	d
16	b
17	a
18	b
19	a
20	d
21	b

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Detailed Explanations

Solution to Question 1:

Graves' disease is the most common cause of endogenous hyperthyroidism.

It is an autoimmune disorder due to the production of TSH-receptor stimulating immunoglobulins (TSI) which cause hyperthyroidism.

It is characterized by the triad of:

• Thyrotoxicosis

• Infiltrative ophthalmopathy (exophthalmos)

• Dermopathy (pretibial myxedema)

Glycosaminoglycan deposition, lymphoid infiltrates, and fatty infiltrates are responsible for ophthalmopathy and dermopathy.

Grossly, there is a diffuse enlargement of the thyroid gland and a beefy deep red parenchyma. Histology shows tall crowded follicular cells with scalloped margins and lymphoid infiltrates. Laboratory features include elevations in free T3 and T4 and decreased TSH.

Solution to Question 2:

The given clinical scenario along with the given image showing exophthalmos is suggestive of Graves' ophthalmopathy. Sympathetic overactivity of Muller's muscle results in a wide, staring gaze and lid lag, but not exophthalmos.

Exophthalmos is characterized by abnormal protrusion of the eyeball. It is due to increased volume of the retroorbital connective tissues and extraocular muscles because of:

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• Marked lymphocytic infiltration of the retro-orbital space

• Inflammation with edema and swelling of extraocular muscles

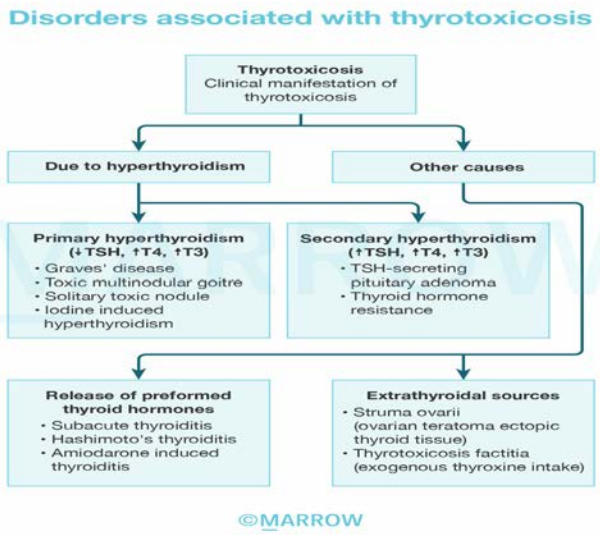
• Accumulation of hydrophilic glycosaminoglycans such as hyaluronic acid and chondroitin sulfate

• Increased numbers of adipocytes (fatty infiltration)

Solution to Question 3:

Hashimoto thyroiditis is not associated with hyperthyroidism. It is associated with transient thyrotoxicosis, followed by chronic hypothyroidism.

Thyrotoxicosis is a hypermetabolic state caused by elevated circulating levels of free T3 and T4. On the other hand, hyperfunctioning of the thyroid gland itself is referred to as hyperthyroidism.



Solution to Question 4:

The given image shows follicular hyperplasia with a scalloping colloid. The clinical scenario along with the image is suggestive of Graves' disease.

In Graves' disease, the thyroid is diffusely hyperplastic. The follicles are lined by tall columnar epithelial cells that project into lumina. The cells actively resorb the colloid in the center of the follicle which results in a scalloped appearance of the edges of the colloid.

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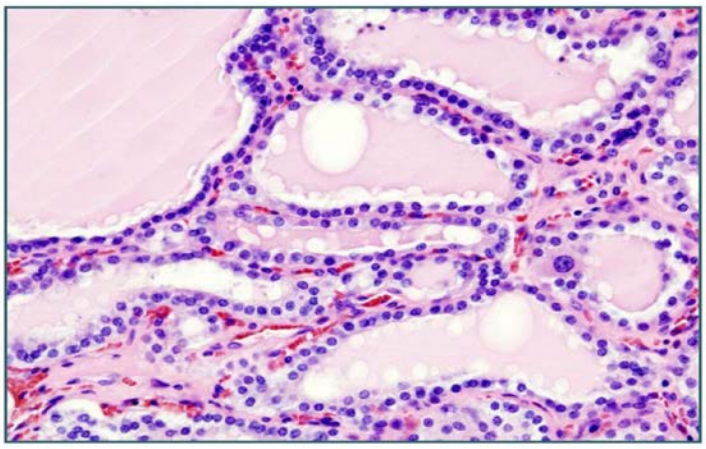
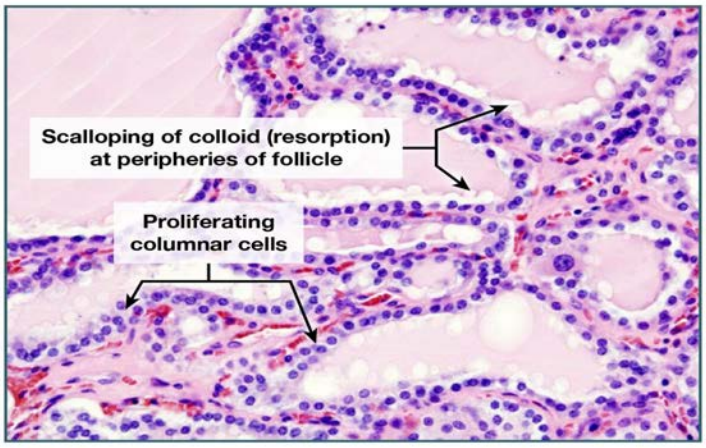
Graves' Disease - Histology



Graves' Disease - Histology



Solution to Question 5:

The given clinical picture and image showing Hurthle cells are suggestive of Hashimoto's thyroiditis.

In this condition, the following microscopic features are seen:

• Intense lymphocytic infiltrate containing small lymphocytes, plasma cells, and well developed germinal centers

• Atrophied thyroid follicles

• The epithelial cells lining the follicles contain eosinophilic granular cytoplasm (oncocytes)

• This is called oncocytic metaplasia

• These cells are called Hurthle cells

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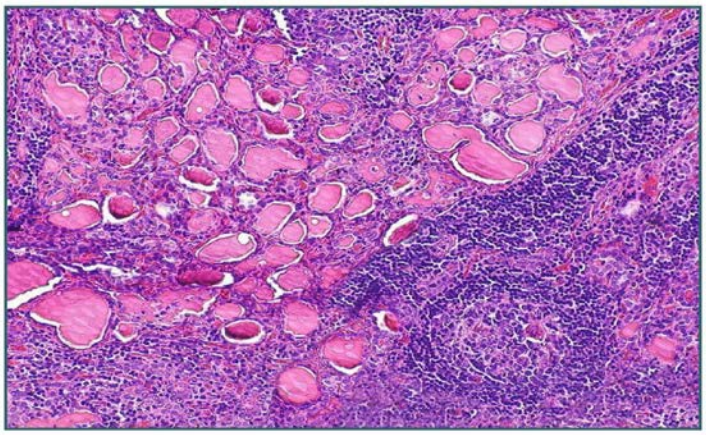
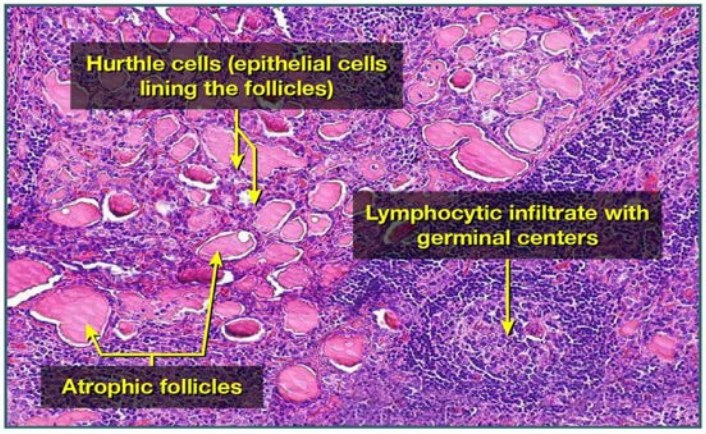
• Ultrastructurally, these cells have numerous mitochondria

Hashimoto's Thyroiditis



Hashimoto's Thyroiditis



Hashimoto's thyroiditis is an autoimmune disease, characterized by the gradual destruction of the thyroid gland leading to thyroid failure. It is commonly seen in women between 45 to 65 years of age. It is caused by the presence of circulating autoantibodies against thyroglobulin and thyroid peroxidase.

Morphologically, there is a diffuse enlargement of the thyroid gland, with an intact capsule. It is well demarcated from the adjacent structures.

Note: Oncocytes can arise in various tissues and are referred to as follows:

• Hurthle cells/ Ashkenazy cells - thyroid gland

• Oxyphilic cells - parotid gland

• Apocrine metaplasia - breast

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Solution to Question 6:

Orphan-Annie eye nuclei are a feature of papillary carcinoma of the thyroid, not Hashimoto's thyroiditis.

Hashimoto thyroiditis is an autoimmune disease that results in the destruction of the thyroid gland and gradual and progressive thyroid failure.

It is the most common cause of hypothyroidism in areas of the world where iodine levels are sufficient.

The thyroid gland is often diffusely enlarged, painless, with some degree of hypothyroidism. This may be preceded by transient thyrotoxicosis (Hashitoxicosis). It is associated with an increased risk of:

• Other autoimmune conditions

• Extranodal marginal zone B-cell lymphomas

• Papillary carcinoma

Histologically, the following findings are seen:

• Intense lymphocytic infiltrate containing small lymphocytes, plasma cells, and well developed germinal centers

• Atrophied thyroid follicles

• The epithelial cells lining the follicles contain eosinophilic granular cytoplasm

• This is called oncocytic metaplasia

• These cells are called Hurthle cells

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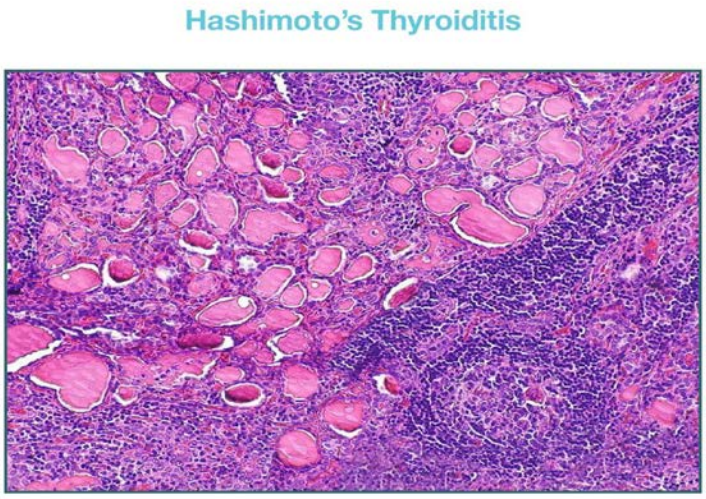

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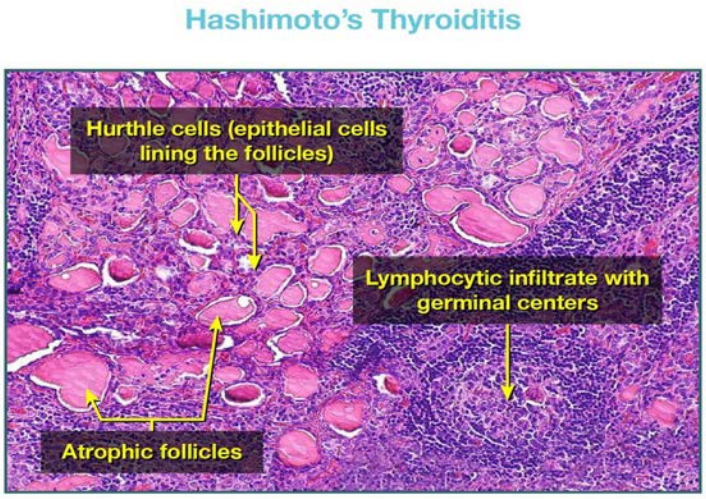

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Solution to Question 7:

Autoimmune hypothyroidism is the most common cause of hypothyroidism in iodine-sufficient areas of the world.

The thyroid gland is typically enlarged. The circulating autoantibodies found in this disorder are:

- Antimicrosomal antibodies
- Antithyroid peroxidase antibodies
- Antithyroglobulin antibodies

Note: Wolff-Chaikoff effect refers to iodine-induced hypothyroidism.

Solution to Question 8:

The given clinical condition is suggestive of subacute granulomatous thyroiditis.

It is the most common cause of a painful thyroid. It is also known as painful subacute thyroiditis, de Quervain thyroiditis, or migratory thyroiditis (this is because the pain can shift to different locations in the thyroid).

Option A: Subacute lymphocytic thyroiditis (postpartum thyroiditis) is typically painless. It often occurs after pregnancy and is characterized by lymphocytic inflammation in the thyroid.

Option B: Riedel's thyroiditis is a rare disorder characterized by a painless, rapidly growing thyroid mass with extensive fibrosis involving the thyroid and contiguous neck structures.

Option C: Hashimoto thyroiditis is an autoimmune disease that presents as painless enlargement of the thyroid associated with some degree of hypothyroidism in middle-aged women.

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Solution to Question 9:

Nodules in younger patients are more likely to be malignant than those in older patients.

The solitary thyroid nodule is a palpably discrete swelling within an otherwise apparently normal thyroid gland. A higher incidence is seen in areas with endemic iodine deficiency. They are more common in women than in men.

Malignant transformation is more common in:

• Solitary nodules > Multinodular goiter

• Solitary nodules in males > females

• Cold nodules > Hot nodules

However, benign neoplasms are more common than thyroid carcinomas by a ratio of nearly 10:1.

Solution to Question 10:

The most common thyroid cancer is papillary carcinoma.

Major subtypes of thyroid carcinoma and their relative frequencies are as follows:

• Papillary carcinoma - most common

• Follicular carcinoma

• Medullary carcinoma

• Anaplastic carcinoma - least common

Thyroid carcinomas are derived from the thyroid follicular epithelium, except medullary carcinoma which is derived from parafollicular C cells.

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Solution to Question 11:

The given image shows psammoma bodies, which are seen in papillary carcinoma of the thyroid. This type of carcinoma is associated with a history of long-standing unresected thyroglossal cyst.

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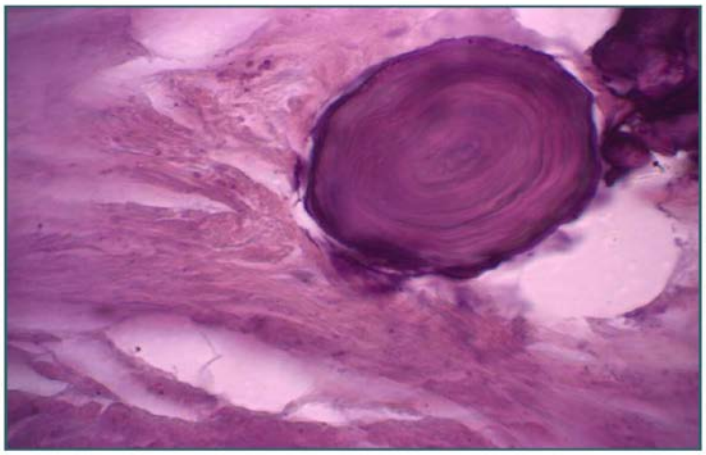
Psammoma bodies



Psammoma bodies are concentrically calcified structures often present within the cores of papillae in papillary carcinoma of the thyroid. These structures are almost never found in follicular and medullary carcinomas. They arise from:

• Infarction and dystrophic calcification of papillae tips

• Calcification of intra-lymphatic tumor thrombi.

Psammoma bodies are seen in:

• Papillary carcinoma (thyroid, kidney, endometrium, lungs)

• Prolactinoma

• Meningioma

• Papillary serous cystadenocarcinoma of the ovary

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Solution to Question 12:

The presence of empty appearing nuclei, also called Orphan Annie eye nuclei as seen in the above image is diagnostic of papillary carcinoma of the thyroid.

Microscopic features of papillary thyroid carcinoma include:

• Branching papillae with fibrovascular stalk

• Covering epithelium is simple or stratified cuboidal

• Orphan Annie eye nuclei -

• Empty-appearing nuclei due to dispersed chromatin

• They are diagnostic, regardless of papillary architecture

• Psammoma bodies - concentric calcified structures

• Foci of lymphatic invasion

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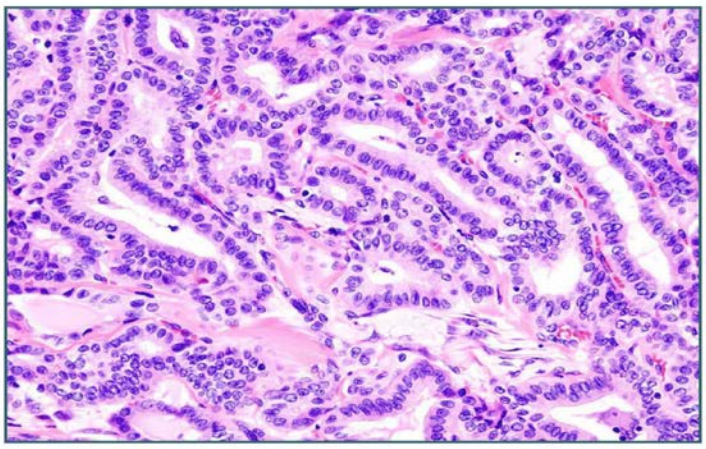
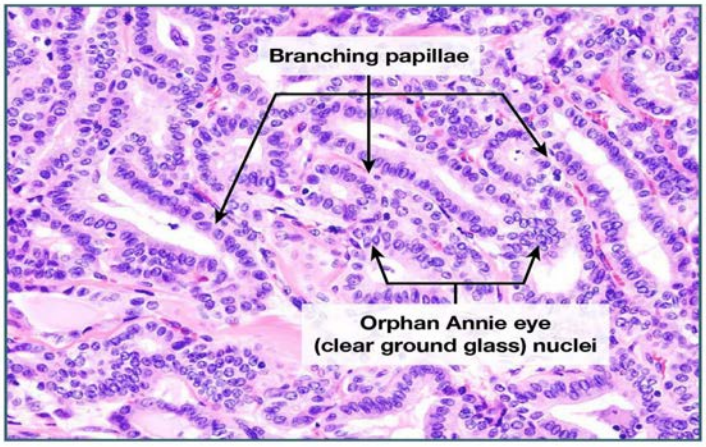
Papillary Carcinoma of Thyroid



Papillary Carcinoma of Thyroid



Note: Orphan Annie refers to a comic book character with empty appearing eyes, as shown below.

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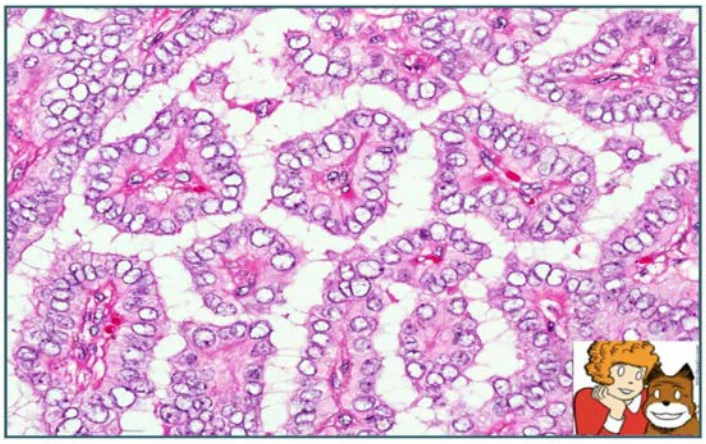
Papillary Carcinoma of Thyroid

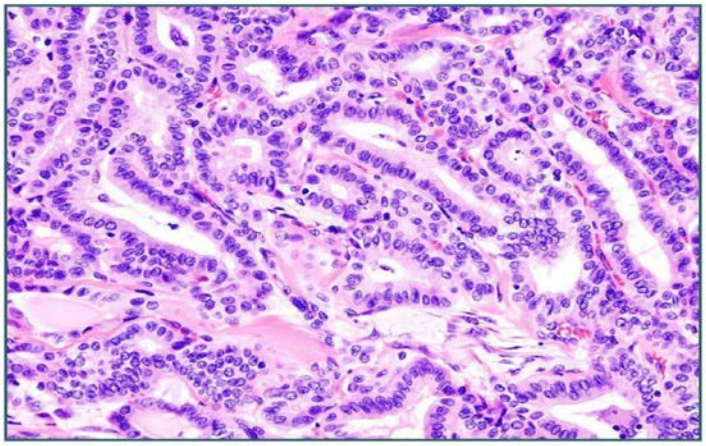


Solution to Question 13:

Hematogenous spread is rare in papillary carcinoma of the thyroid. Metastases to lymph nodes are more commonly associated with this condition.

It is associated with previous exposure to ionizing radiation. The presence of nuclear features such as Orphan Annie eye nuclei (empty-appearing nuclei) are diagnostic, regardless of papillary architecture.

Papillary Carcinoma of Thyroid



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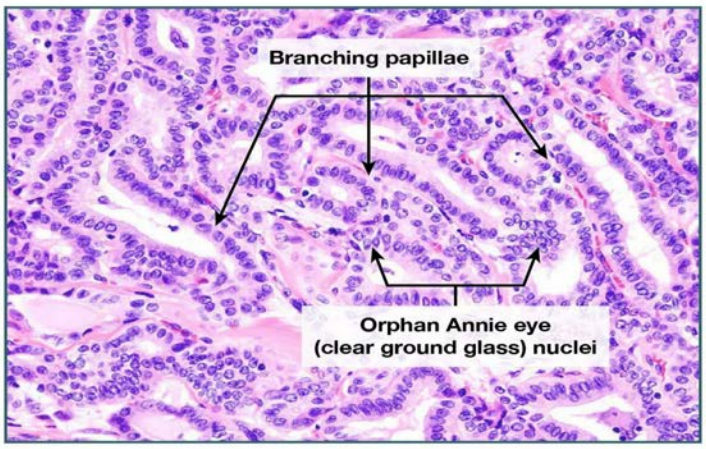
Papillary Carcinoma of Thyroid



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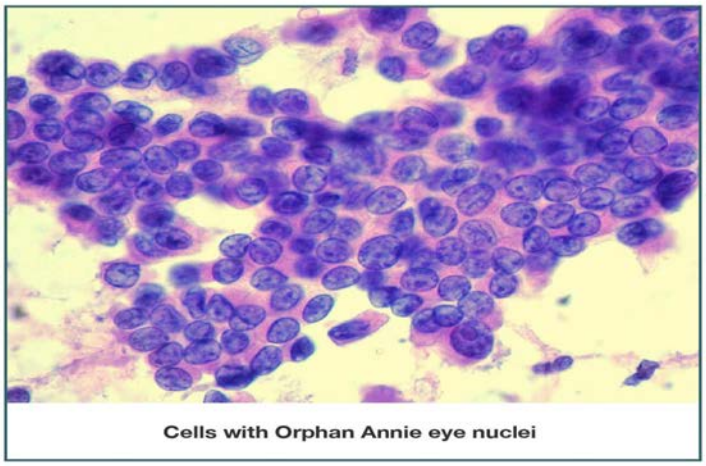
Solution to Question 14:

The FNAC image is suggestive of papillary carcinoma of the thyroid. Among the given options, the most common site of metastasis is the lungs.

Papillary Carcinoma of Thyroid



The histological features of papillary carcinoma of the thyroid are:

- Papillary architecture
- Nuclear findings (enough to diagnose the condition even in the absence of papillary architecture)
- Nuclear overlapping, grooving, crowding
- Ground-glass appearance (Orphan Annie eye nuclei)
- Dusty and pale chromatin

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• Intranuclear inclusion bodies

The most common mode of spread overall is through the lymphatic route, with lymph node metastases being common at initial presentation.

Solution to Question 15:

Papillary carcinoma of the thyroid is associated with gain-of-function mutations in the following genes:

• NTRK1 (receptor tyrosine kinase)

• RET (receptor tyrosine kinase)

• BRAF (serine/threonine kinase)

Solution to Question 16:

The most common variant of papillary carcinoma of the thyroid is the follicular variant.

It has the following features:

• Characteristic nuclear features of papillary carcinoma

• Almost entirely follicular architecture

• Can be either -

• Encapsulated - favorable prognosis (or)

• Poorly circumscribed and infiltrative - requires aggressive treatment

The variants of papillary carcinoma include:

Variant	Description
Tall-cellvariant	50% of cells withheight 2 tim es the widthSeen inolderindi vidualsHave higher frequenci es of vascular invasionExtrat hyroidal extension, and cervi cal and distant metastases
Diffuse sclerosingvariant	In younger individuals, inclu ding childrenDiffuse fibrosist hroughout the glandLymph n ode metastasesare present in almost all cases.Lacks BRAF mutations
Cribriformvariant	Associated withfamilial aden omatous polyposis(FAP)Beta-cateninmutation

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Variant	Description
Columnar-cellvariant	Elongated nuclei with pseudo stratificationof the nucleiPoo r prognosis
Solidvariant	More common in childrenAss ociated with Chernobyl nucle ar accident

Note: According to the latest WHO classification of thyroid tumors, the non-invasive encapsulated follicular variant of papillary thyroid carcinoma (FVPTC) has been renamed as non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) to better reflect the indolent course of this tumor. This was done to prevent potential overtreatment and reduce the burden to patients of a cancer diagnosis.

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Solution to Question 17:

Papillary thyroid cancers have the best prognosis, with a 10-year survival rate seen in more than 95% of the patients.

The prognosis of papillary thyroid cancers is dependent on several factors, including age (being less favorable among patients older than 40 years), the presence of extrathyroidal extension, and presence of distant metastases.

The thyroid cancer with the worst prognosis is anaplastic carcinoma.

Solution to Question 18:

The given clinical scenario along with the given histopathological image showing uniform sheets of cells with capsular invasion by tumor cells is suggestive of follicular carcinoma thyroid.

The following images show follicular carcinoma of the thyroid.

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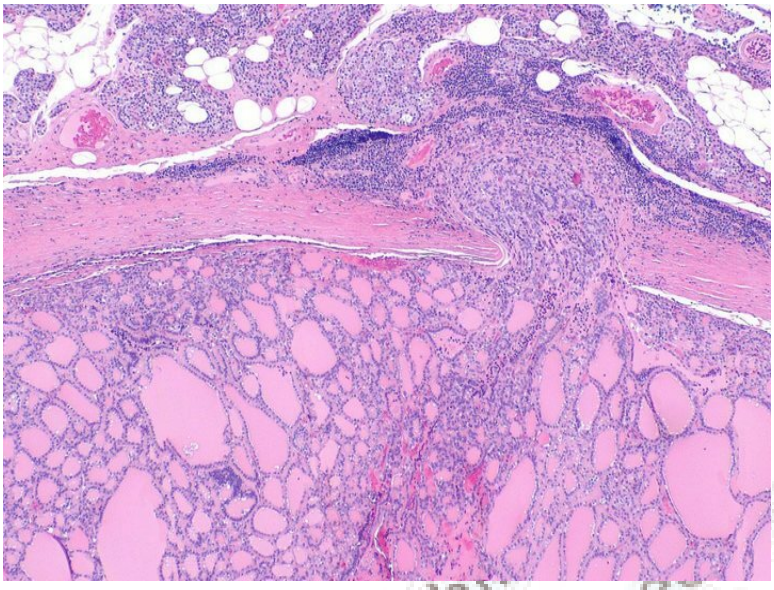
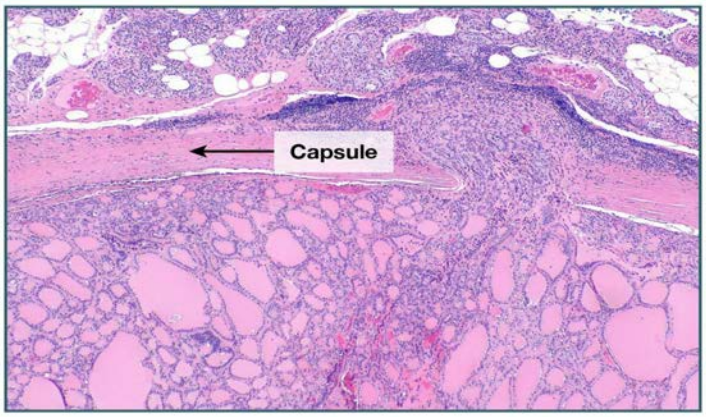


Follicular carcinoma thyroid showing capsular invasion



Option A: In follicular adenoma, there is no capsular invasion.

Option C: Anaplastic carcinoma is associated with rapidly progressive swelling with obstructive features and undifferentiated cells on histopathology.

Option D: In medullary carcinoma, amyloid stroma is seen on histopathology.

Solution to Question 19:

RAS mutations are associated with follicular carcinoma.

It is also associated with acquired mutations in the PIK3CA gene (PI3K/AKT arm of the receptor tyrosine kinase signaling pathway) and the PAX8-PPARG fusion gene.

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Solution to Question 20:

p53 is is a tumor-suppressor gene and not an oncogene.

The following are the proto-oncogenes implicated in carcinoma of the thyroid.

Proto-oncogene	Tumor
RAS	Papillary thyroid carcinomaFollicular thyroid carcinomaHurthle cell carcinoma
RET	Papillary thyroid carcinoma Medullary thyroid carcinoma
MET	Papillary thyroid carcinomaFollicular thyroid carcinoma
BRAF	Papillary thyroid carcinomaTall-cell poorly differentiated cancerAnaplastic carcinoma

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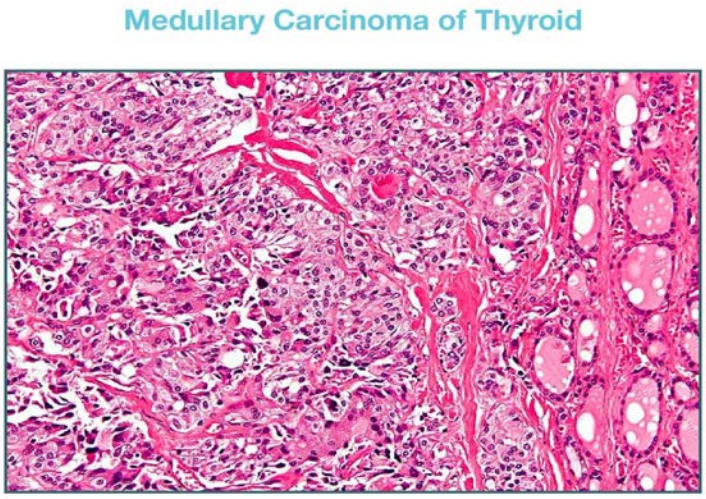
Solution to Question 21:

The given clinical scenario and histological appearance showing amyloid stroma are suggestive of medullary carcinoma of the thyroid. This condition can occur in the setting of MEN2A (Sipple syndrome) or MEN2B.



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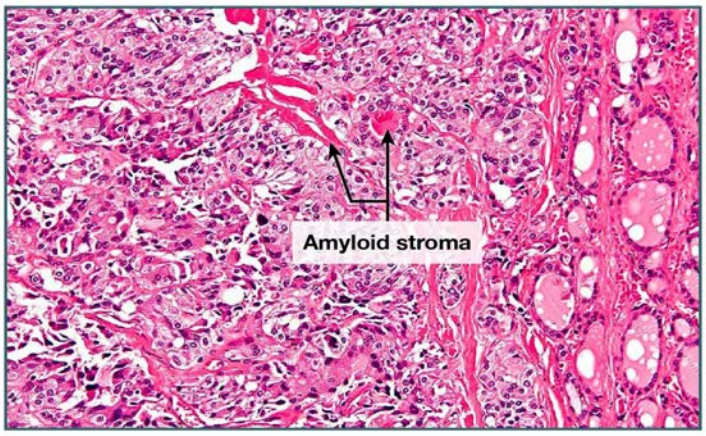
Medullary Carcinoma of Thyroid



Medullary carcinomas of the thyroid are neuroendocrine neoplasms derived from the parafollicular cells or C cells of the thyroid. They may be:

• Sporadic (70%)

• Familial or associated with MEN2 syndromes (30%) -

• More aggressive and metastasize more frequently than sporadic

• Usually bilateral and multicentric

Both forms can be associated with RET mutations.

These tumors may present with:

• Mass in the neck

• Dysphagia

• Hoarseness

• Diarrhea due to the secretion of VIP

• Cushing's syndrome due to ACTH secretion

Histopathology shows polygonal to spindle-shaped cells, which may form nests, trabeculae, and even follicles. Acellular amyloid deposits derived from calcitonin polypeptides are present in the stroma. These lesions secrete calcitonin and carcinoembryonic antigen.

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The Adrenals

Question 1:

A 40-year-old woman presents to the OPD with rapid weight gain and easy bruisability over the past 1 month. She was started on oral prednisolone for dermatomyositis 2 months ago. On examination, moon facies and abdominal striae are noted. Her BP is 160/110 mm Hg. Which of the following pathological changes is seen in this condition?

a) Corticotroph cells with homogenous and pale cytoplasm

b) Accumulation of keratin filaments in adrenal cells

c) Eosinophilic inclusion bodies in adrenal cells

d) Basophilic nuclear inclusion bodies in corticotroph cells

Question 2:

What is the most common clinical feature of Cushing syndrome?

a) Hypertension

b) Obesity

c) Facial plethora

d) Hirsutism

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Question 3:

A 27-year-old woman is brought to the casualty with severe abdominal pain, diarrhea, and dizziness for the past 3 days. On examination, the following findings are noted. Blood pressure is 80/50 mm Hg and blood glucose is 48 mg/dl. Which of the following would you expect in this patient?

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a) High ACTH and low renin levels

b) High ACTH and high renin levels

c) Low ACTH and normal renin levels

d) Low ACTH and low renin levels

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Question 4:

A 6-year-old boy was referred with fever, altered sensorium, and non-blanching rash for the past 2 days. He developed rapidly progressive shock and DIC. Despite resuscitation measures, he died. The following appearance of his adrenals was noted on autopsy. All of the following can cause this condition except:

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a) Neisseria gonorrhoeae

b) Streptococcus pneumoniae

c) Pseudomonas aeruginosa

d) Haemophilus influenzae

Question 5:

What is the most common cause of primary hyperaldosteronism?

a) Bilateral adrenal adenoma

b) Ectopic aldosterone-producing tumors

c) Nodular adrenal hyperplasia

d) Unilateral adrenal adenoma

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Question 6:

What is the underlying pathology in patients with Conn's syndrome?

a) Micronodular hyperplasia

b) Adrenal adenoma

c) Macronodular hyperplasia

d) Paraneoplastic syndrome

Question 7:

Patients with which of the following conditions are not at risk of developing adrenocortical carcinoma?

a) Li Fraumeni syndrome

b) Beckwith-Wiedemann syndrome

c) MEN1 syndrome

d) MEN2B syndrome

Question 8:

A 7-year-old boy is brought for the evaluation of recurrent seizures over the last 3 months. Past history is significant for chronic oral candidiasis for 2 years. On examination, nail

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dystrophy is noted. Further investigation reveals serum calcium of 6.9 mg/dl and prolonged QT interval. What is the likely diagnosis?

a) Autoimmune polyendocrinopathy type 1

b) Autoimmune polyendocrinopathy type 2

c) Multiple endocrine neoplasia type 1

d) Multiple endocrine neoplasia type 2B

Question 9:

A 24-year-old woman presented with recurrent episodes of palpitations, headaches, and sweating. Her BP was 155/95 mm Hg and HR was 135/min. Investigations revealed elevated 24-hour urinary metanephrines and a right adrenal mass on CT abdomen. She should be examined for the presence of all of the following except:

a) Retinal hemangioblastoma

b) Marfanoid habitus

c) Lisch nodules

d) Shagreen patch

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Question 10:

Which of the following is most commonly involved in Wermer syndrome?

a) Parathyroid

b) Pituitary

c) Pancreas

d) Adrenal

Question 11:

Which of the following is an indicator of malignant transformation in a patient with pheochromocytoma?

a) Pleomorphism

b) High mitotic activity

c) Vascular invasion

d) Lymph node metastases

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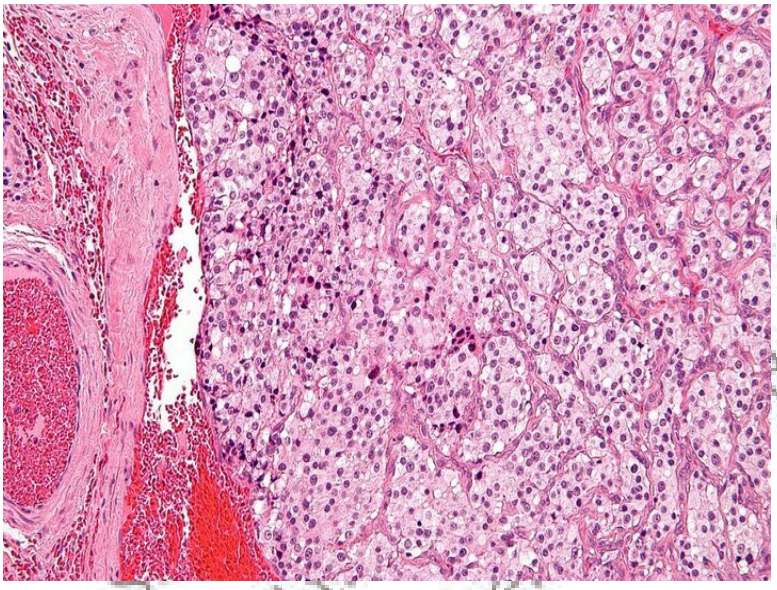
Question 12:

A pathologist is studying the following slide from the biopsy of a patient with an abdominal mass. What is the likely diagnosis?



a) Paraganglioma

b) Liposarcoma

c) Rhabdomyoma

d) Desmoid tumor

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Question 13:

A 38-year-old woman was being evaluated for persistent hypertension. Workup revealed a tumor located near the bifurcation of the aorta. Surgical excision was done and HPE examination revealed a zellballen pattern of cells. Where did this tumor likely originate from?

a) Organ of Zuckerkandl

b) Organ of Rosenmüller

c) Organ of Giraldes

d) Organ of Corti

Question 14:

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What mutation is likely to be seen in patients with familial paraganglioma syndrome?

a) SDH

b) NF1

c) RET

d) VHL

Question 15:

A 21-year-old young man presents with a neck mass. Past history is significant for surgical removal of a pheochromocytoma 6 months ago. On examination, a marfanoid habitus is noted along with the following finding. Which of the following should the patient be screened for?

a) Papillary thyroid carcinoma

b) Paraganglioma

c) Medullary thyroid carcinoma

d) Parathyroid adenoma

Question 16:

What gene is mutated in polycythemia paraganglioma syndrome?

a) RET

b) SDHB

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c) SDHD

d) EPAS1

Answer Key

Question No.	Correct Option
1	a
2	b
3	b
4	a
5	c
6	b
7	d
8	a
9	d
10	a
11	d
12	a
13	a
14	a
15	c
16	d

Detailed Explanations

Solution to Question 1:

This clinical scenario is suggestive of iatrogenic Cushing's syndrome. In this condition, the normal basophilic cytoplasm of the corticotrophs of anterior pituitary becomes homogeneous and pale. This is termed the Crooke hyaline change and is due to the accumulation of intermediate keratin filaments in the cytoplasm.

This change occurs due to high levels of circulating glucocorticoids in Cushing's syndrome.

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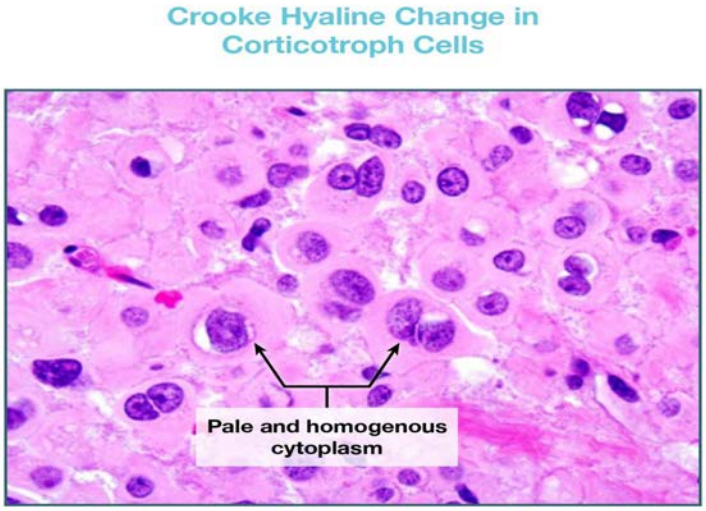

Based on the cause of Cushing's syndrome, the following pathological changes are seen in the adrenals:

• Iatrogenic - atrophy of zona fasciculata and zona reticularis (as zona glomerulosa functions independently of ACTH)

• ACTH-dependent - diffuse hyperplasia (due to high ACTH levels)

• ACTH-independent - nodular hyperplasia, adenoma, or carcinoma

Note: Eosinophilic inclusion bodies in adrenal cells are called spironolactone bodies. They are seen in Conn's syndrome.

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Solution to Question 2:

Obesity is the most common clinical feature of Cushing's syndrome.

Clinical features of Cushing's syndrome are attributed to the glucocorticoid, mineralocorticoid, and sex steroid actions of cortisol. They include:

System	Clinical features
Body fat	Centralortruncal obesity(most common)Buffalo hump (fat deposition behind the neck)Moon facies
Skin	Purple striae (over abdomen & flanks)Acne and HirsutismEasy bruisingFacial plethoraHyperpigmentation
Musculoskeletal	Proximal myopathyOsteoporosis

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System	Clinical features
Metabolic	Poorly controlled hyperglycemiaDyslipidemia
Reproductive	OligomenorrheaAmenorrhea
Renal	Hypokalemic alkalosis
CVS	AtherosclerosisDiastolic HypertensionEdema
Hematologic	Hypercoagulable stateLymphopeniaNeutrophiliaEosinopenia
CNS	DepressionPsychosisAnxiety

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Solution to Question 3:

The clinical scenario and the image showing hyperpigmentation of palmar creases and oral mucosa are suggestive of primary adrenal insufficiency. It presents with low aldosterone, high renin, and high ACTH levels.

In primary adrenal insufficiency, lack of aldosterone production results in compensatory rise in ACTH and renin levels. The high ACTH results in hyperpigmentation. The most common causes are autoimmune in developed countries and tuberculosis in developing countries.

In secondary adrenal insufficiency, there is pituitary dysfunction leading to low ACTH levels. Renin and aldosterone levels are normal, as they function independently of ACTH.

Solution to Question 4:

This clinical scenario and image showing bilateral adrenal hemorrhage are suggestive of Waterhouse-Friderichsen syndrome. Neisseria gonorrhoeae is not a cause of this condition.

It is caused by highly virulent organisms such as:

• Neisseria meningitidis or meningococci (classically)

• Streptococcus pneumoniae or pneumococci

• Pseudomonas aeruginosa

• Haemophilus influenzae

• Staphylococcus species

This condition is more common in children. Overwhelming bacterial infection leads to bilateral adrenal hemorrhage, thereby causing acute adrenal insufficiency. This is likely a result of direct bacterial seeding of small vessels and endothelial dysfunction caused by microbial products and inflammatory mediators.

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It usually presents with rapidly progressive hypotension and shock and disseminated intravascular coagulation (DIC) with widespread purpura. Without prompt recognition and treatment, death occurs within hours to a few days.

Solution to Question 5:

Bilateral nodular hyperplasia of the adrenal glands is the most common cause of primary hyperaldosteronism.

Adrenal adenoma is the second most common cause. It is usually solitary, but multiple adenomas may occur occasionally. Other rare causes include:

• Ectopic aldosterone-producing tumors

• Familial idiopathic hyperaldosteronism - due to germline mutations of KCNJ5 (encodes a potassium channel)

Solution to Question 6:

The underlying pathology in patients with Conn's syndrome is adrenal adenoma.

Hyperaldosteronism may be primary or secondary.

Primary hyperaldosteronism is due to autonomous overproduction of aldosterone with resultant suppression of RAAS. It can occur due to adrenal hyperplasia, adenoma, or carcinoma. It presents with the following features:

• Hypertension (most common)

• Hypokalemia

• Metabolic alkalosis

• Polyuria (due to ANP)

• Polydipsia (due to polyuria)

• Muscle weakness

It is confirmed by elevated ratios of plasma aldosterone concentration to plasma renin activity (PAC / PRA).

When primary hyperaldosteronism is due to an aldosterone-secreting adenoma, it is called Conn syndrome. Patients are usually treated with spironolactone followed by surgical removal of adenoma. In patients treated with spironolactone, the adenomas contain eosinophilic cytoplasmic inclusions called spironolactone bodies.

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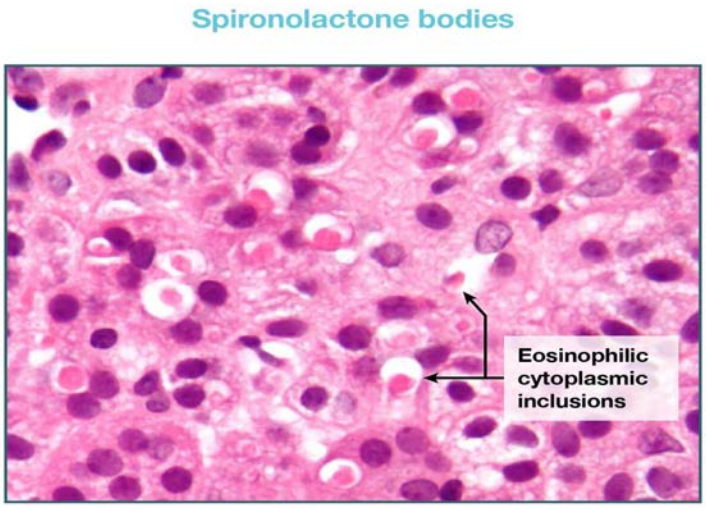

In secondary hyperaldosteronism, aldosterone release occurs in response to the activation of the renin-angiotensin system (RAAS).

Solution to Question 7:

MEN2B syndrome is associated with pheochromocytoma and medullary carcinoma of thyroid, not adrenocortical carcinoma.

Adrenocortical carcinoma is associated with the following hereditary cancer syndromes:

- Li–Fraumeni syndrome - due to germline TP53 mutations
- Beckwith–Wiedemann syndrome - a disorder of epigenetic imprinting
- MEN1 syndrome - due to mutations of MEN1 gene

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Solution to Question 8:

This clinical scenario is suggestive of autoimmune polyendocrinopathy (APS) type 1. It is also called APECED (autoimmune polyendocrinopathy, candidiasis, and ectodermal dystrophy).

It is caused by mutations in the autoimmune regulator (AIRE) gene. This gene usually increases tolerance of central T-cells to peripheral tissue antigens. When this function is lost, the T-cells become more prone to mount immune reactions against tissue antigens, promoting autoimmunity. These patients develop autoantibodies against IL-17 and IL-22, which are crucial for defense against fungal infections.

It presents in childhood with the following features:

• Chronic mucocutaneous candidiasis

• Ectodermal dystrophy (abnormalities of the skin, dental enamel, and nails)

• Organ-specific autoimmune disorders such as -

• Autoimmune adrenalitis

• Autoimmune hypoparathyroidism

• Idiopathic hypogonadism

• Pernicious anemia

Autoimmune polyendocrine syndrome (APS) type 2 usually presents in early adulthood as a combination of the following:

• Adrenal insufficiency

• Autoimmune thyroiditis or type 1 diabetes

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Solution to Question 9:

This clinical scenario is suggestive of pheochromocytoma. This patient does not need to be examined for a shagreen patch. It is a feature of tuberous sclerosis syndrome, which is not associated with pheochromocytoma.

Familial syndromes associated with pheochromocytoma are:

Even patients with no family history must be evaluated for findings of these genetic syndromes, as they may occur sporadically in some cases.

Syndrome	Clinical manifestations
Neurofibromatosis	Café-au-lait spotsAxillary and inguinal frecklingOptic nerve gliomaLisch nodules

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Syndrome	Clinical manifestations
von Hippel-Lindau (VHL) syndrome	HemangioblastomasRenal cell carcinomaPancreatic endocrine neoplasms
MEN2A syndrome	Medullary thyroid carcinoma Parathyroid hyperplasia
MEN 2B syndrome	Medullary thyroid carcinoma MarfanoidhabitusMucocutaneous ganglioneuromatosis

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Solution to Question 10:

Primary hyperparathyroidism is the most common manifestation of Wermer's syndrome or MEN-1 syndrome.

MEN1 syndrome is due to germline mutations in the MEN1 tumor-suppressor gene, which encodes a protein called menin. The most commonly secreted products are pancreatic polypeptides.

Solution to Question 11:

The definitive diagnosis of malignancy in pheochromocytomas is based exclusively on the presence of metastases to regional lymph nodes as well as distant sites like liver, lung, and bone.

Capsular and vascular invasion may be encountered even in benign lesions. Malignant pheochromocytomas are histologically and biochemically the same as benign ones. Hence, typical histological criteria like cellular atypia, mitotic spindles, and vascular invasion are insufficient to confirm malignancy in pheochromocytomas.

Solution to Question 12:

The given histopathology slide shows nests of cells arranged in an organoid pattern, with fibrovascular septae, and finely granular cytoplasm. This is called the zellballen pattern. It is typically seen in paragangliomas and pheochromocytomas.

Paragangliomas are benign neuroendocrine tumors arising from paraganglia in the neck or abdomen. They are composed of chief and sustentacular cells arranged in an organoid pattern.

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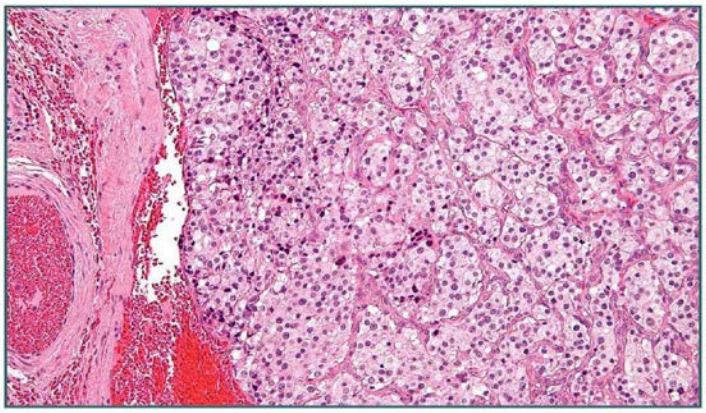
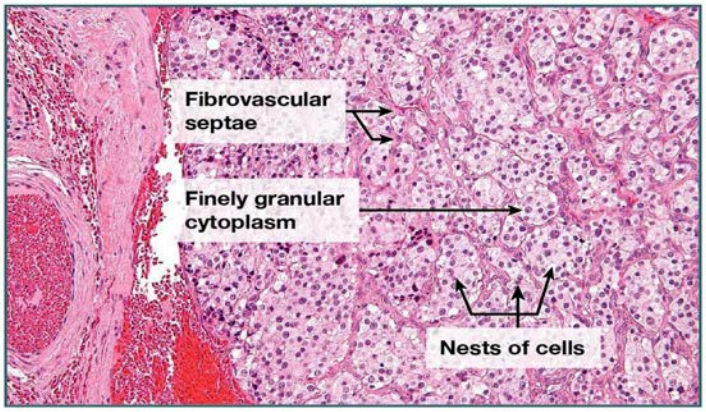
Zellballen Pattern -
Pheochromocytoma and Paraganglioma



Zellballen Pattern -
Pheochromocytoma and Paraganglioma



Solution to Question 13:

This clinical scenario is suggestive of a paraganglioma (ectopic pheochromocytoma) located in the abdomen. They commonly arise from the organ of Zuckerkandl, located at the bifurcation of the aorta. It is part of the vertebral paraganglia (clusters of chromaffin cells along the autonomic nerve chains).

Other sites of origin of paragangliomas include:

• Urinary bladder - rarely

• Carotid and aortic bodies

• Ganglion nodosum of the vagus nerve

• Jugulotympanic ganglia

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Solution to Question 14:

Familial paraganglioma is most likely associated with mutations in the SDH (succinate dehydrogenase) gene.

The SDH complex is involved in mitochondrial electron transport and oxygen sensing. It is believed that SDH mutations also lead to the upregulation of HIF-1α, which is a key oncogenic driver in this type of tumor.

Solution to Question 15:

This clinical scenario and image showing mucosal neuromas are suggestive of MEN2B syndrome. This condition is associated with medullary carcinoma of the thyroid.

The MEN syndromes are a group of inherited diseases of multiple endocrine organs. Tumors occur at a younger age than sporadic tumors, either synchronously (at the same time) or metachronously (at different times).

MEN2 syndrome occurs due to abnormal activation of the RET gene. Medullary carcinoma is seen in both MEN 2A and 2B syndromes. However, it tends to be more aggressive and metastasizes more frequently in MEN2B syndrome.

Note: RET gene is deactivated in Hirschsprung disease.

Solution to Question 16:

Polycythemia paraganglioma syndrome occurs due to germline mutations in the EPAS1 gene. This syndrome presents with neuroendocrine tumors and early-onset polycythemia.

RET gene mutation is seen in MEN2A and MEN2B syndromes.

SDHD and SDHB mutations are seen in hereditary paraganglioma 1 and hereditary paraganglioma 4 syndromes respectively.

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The Breast

Question 1:

Which of the following lesions does not arise from the terminal duct lobular unit of the breast?

a) Sclerosing adenosis

b) Blue dome cyst

c) Carcinoma breast

d) Periductal mastitis

Question 2:

Which of the following lesions arise from the large ducts of the breast?

a) 3 and 5

b) 1 and 5

c) 2 and 4

d) 1 and 3

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Question 3:

A 28-year-old lactating mother presents with pain in her left breast. On examination, you notice her nipple is erythematous and tender with a purulent exudate. Which of the following is the most common cause of this condition?

a) Pseudomonas aeruginosa

b) Streptococcus viridans

c) Streptococcus pneumoniae

d) Staphylococcus aureus

Question 4:

Which of the following diseases is most strongly associated with a history of smoking?

a) Granulomatous mastitis

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b) Fat necrosis

c) Periductal mastitis

d) Carcinoma breast

Question 5:

A 30-year-old woman presented with a painless palpable lump in her left breast. She had sustained a traumatic blow to her left breast 1 month back. Mammography showed a radiolucent cystic lesion with rimmed calcification. What is the most likely diagnosis?

a) Lymphocytic mastopathy

b) Sclerosing adenosis

c) Fat necrosis

d) Hyalinized fibroadenoma

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Question 6:

Which of the following is a proliferative breast lesion?

a) Papilloma

b) Cysts

c) Mild hyperplasia

d) Adenosis

Question 7:

All of the following lesions are proliferative breast lesions without atypia except:

a) Duct ectasia

b) Radial scar

c) Sclerosing adenosis

d) Florid hyperplasia

Question 8:

What is the most common clinical presentation seen in patients with duct papilloma?

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a) Retraction of nipple

b) Painless lump

c) Bloody nipple discharge

d) Eczema and itching of nipple

Question 9:

A young man presents to your clinic with the following finding. Which of the following is not associated with this condition?

a) Klinefelter syndrome

b) Seminoma

c) Sertoli cell tumor

d) Alcohol

Question 10:

A biopsy was performed on a female patient who presented with a lump in her right breast. Presence of which of the following findings is not associated with an increased risk of cancer?

a) Florid hyperplasia

b) Fibroadenoma with complex features

c) Sclerosing adenosis

d) Apocrine change

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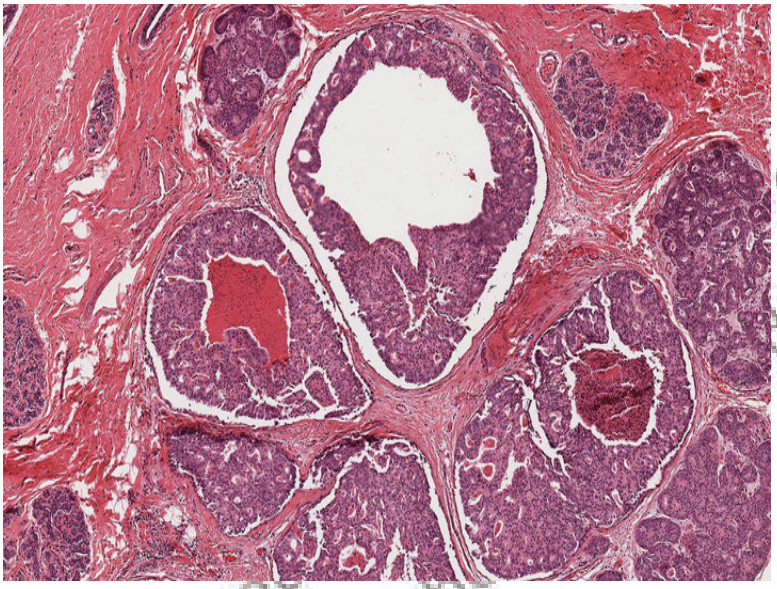
Question 11:

While undergoing a routine mammogram, a 45-year-old woman was found to have clusters of microcalcification in her right breast. A needle biopsy was done and revealed the following. Which of the following markers can be used to rule out invasive disease?



a) ER

b) HER2

c) p53

d) p63

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Question 12:

A 55-year-old woman presents with persistent soreness and itching in her right nipple. On examination, the following finding is noted. What would be the next best step in her management?

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a) Prescribe antibiotics

b) Biopsy of the nipple

c) Prescribe cortisone cream

d) Observation and follow-up

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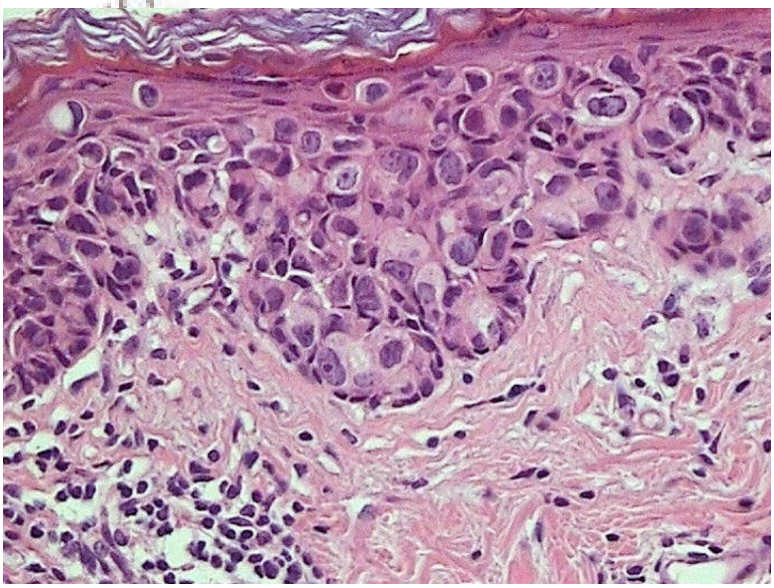
Question 13:

Histopathological examination of a middle-aged woman who presented with redness and itching over the nipple of her left breast is given below. Which of the following statements is incorrect about her condition?



a) The cells are ER positive

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b) Underlying carcinoma is poorly differentiated

c) Prognosis depends on the underlying carcinoma

d) The cells show overexpression of HER2

Question 14:

Which of the following is not a risk factor for breast cancer?

a) Dense breast

b) Post-menopausal obesity

c) Early pregnancy

d) Early menarche

Question 15:

What is the most common site of carcinoma in the breast?

a) Upper inner quadrant

b) Upper outer quadrant

c) Lower outer quadrant

d) Subareolar region

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Question 16:

On which of the following chromosomes is the BRCA2 gene located?

a) Chromosome 13

b) Chromosome 11

c) Chromosome 17

d) Chromosome 12

Question 17:

Immunohistochemical testing was performed on a biopsy sample taken from a patient with breast cancer. It revealed lack of expression of ER, PR, and HER2. Which of the following genes is most commonly mutated in this condition?

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a) RET

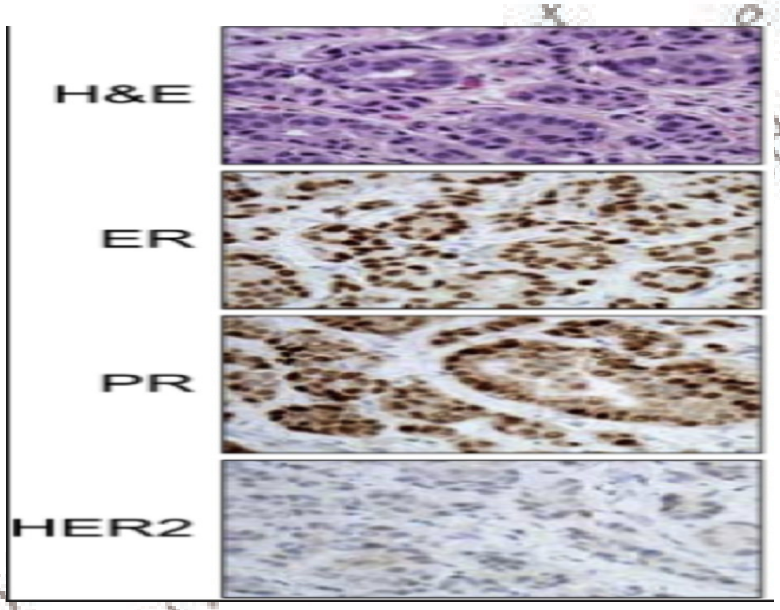
b) MYC

c) TP53

d) PIK3CA

Question 18:

A 44-year-old woman has been diagnosed with breast carcinoma. Immunohistochemistry staining of a tissue biopsy specimen of this patient is given below. Which of the following statements is true regarding her condition?



a) BRCA 1 mutation is most probable

b) It is not associated with tP53 mutations

c) Poor response to paclitaxel

d) Good response to trastuzumab

Question 19:

Immunohistochemistry test of a breast cancer patient was reported negative for ER and HER2. This molecular subtype includes all of the following except:

a) Secretory carcinoma

b) Spindle cell carcinoma

c) Adenoid cystic carcinoma

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d) Mucinous carcinoma

Question 20:

Patients with all of the following conditions have ER-positive and HER2-negative tumors except:

a) Lobular carcinoma

b) Tubular carcinoma

c) Mucinous carcinoma

d) Secretory carcinoma

Question 21:

Which of the following breast cancers most commonly presents as an occult primary carcinoma?

a) Micropapillary carcinoma

b) Mucinous carcinoma

c) Medullary carcinoma

d) Lobular carcinoma

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Question 22:

Which of the following is not a feature of lobular breast carcinoma?

a) Often bilateral

b) Multicentricity within the same breast

c) Loss of E-cadherin

d) Extensive desmoplasia

Question 23:

A 53-year-old woman with breast cancer is found to have TNM staging of T4dN0M0. Which of the following statements is true regarding her condition?

a) There is loss of e-cadherin expression

b) It has a relatively favorable prognosis

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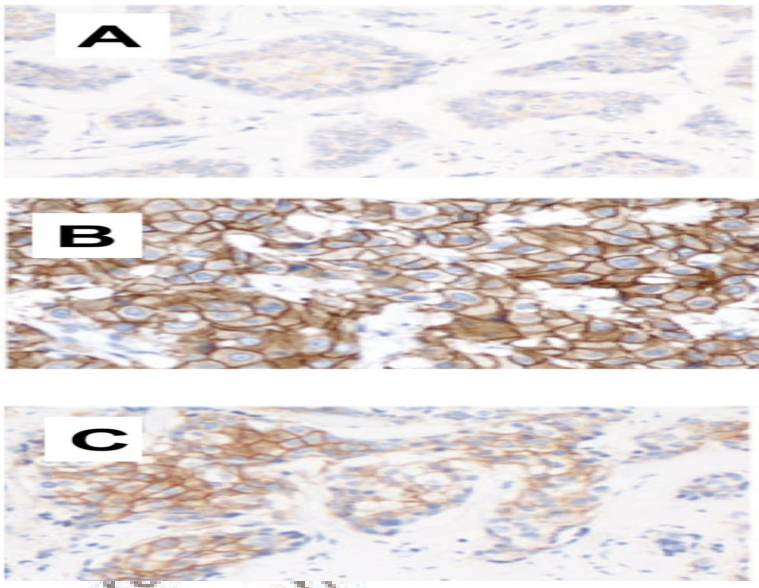
c) There is obstruction of dermal lymphatics by neoplastic cells

d) History of trauma to the breast is usually present

Question 24:

Immunohistochemistry for HER2 protein expression is performed in 3 patients with breast carcinoma, with the following results. Which of the following patients should be subjected to fluorescence in-situ hybridization?



a) Patient A

b) Patient C

c) Patients B and C

d) Patients A and C

Question 25:

A middle-aged woman is diagnosed with low-grade mucinous carcinoma of the breast. IHC showed HER2 overexpression and a low Ki67 index. Which of the following would be considered as a poor prognostic factor?

a) Low grade

b) Low Ki67 index

c) Her2 overexpression

d) Mucinous carcinoma

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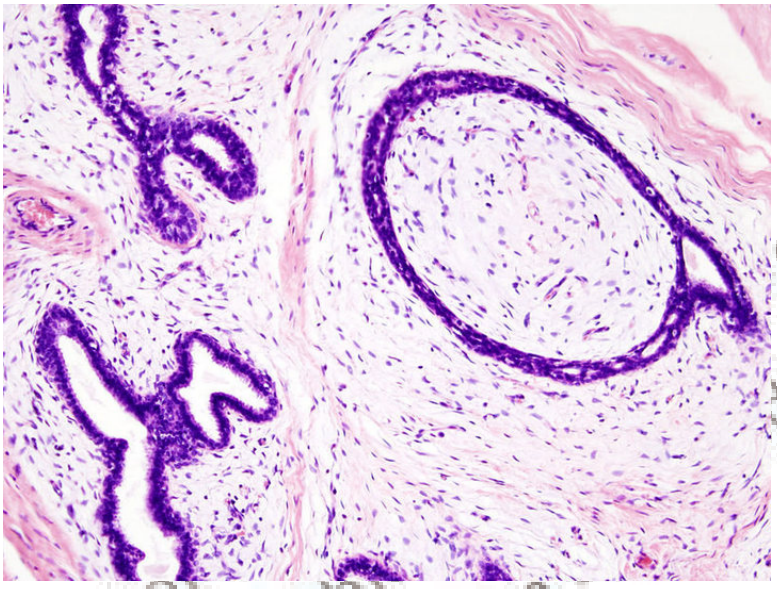
Question 26:

A 30-year-old woman on cyclosporin-A following renal transplantation developed multiple bilateral breast lumps that regressed after cessation of treatment. ■Her biopsy finding is shown below. What is the most likely diagnosis?



a) Fat necrosis

b) Phyllodes tumour

c) Fibroadenoma

d) Sclerosing adenosis

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Question 27:

A 58-year-old woman presented with a large, rapidly growing painless breast lump. On examination, a smooth, multinodular breast lump was noticed. Microscopic examination of the core biopsy sample is shown below. Which of the following is an incorrect statement regarding this condition?

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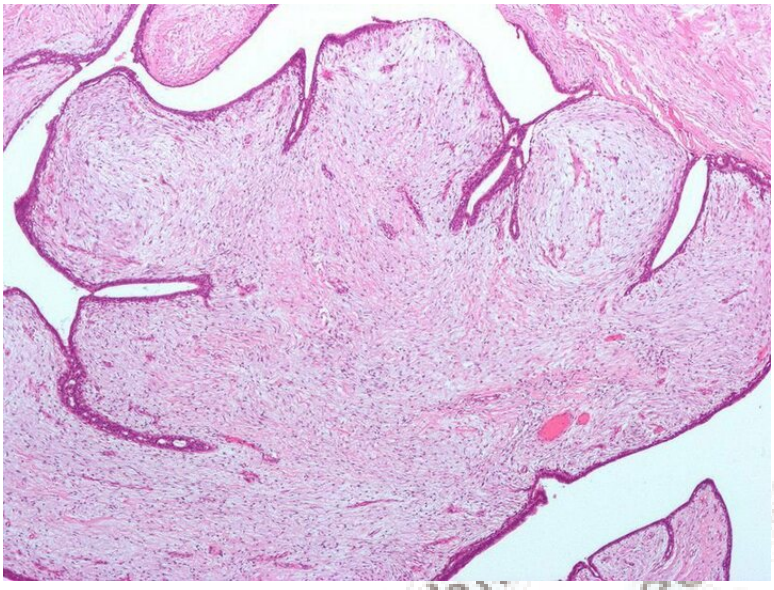

a) Lymphatic spread is rare

b) Stromal cellularity is increased next to the epithelium

c) Absence of epithelial elements suggests malignancy

d) Both epithelial and stromal components can metastasize

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Question 28:

What is the most common stromal malignancy in the breast?

a) Leiomyosarcoma

b) Liposarcoma

c) Angiosarcoma

d) Fibrosarcoma

Question 29:

BRCA-2 mutation does not predispose to the development of which of the following conditions?

a) Renal cell carcinoma

b) Male breast cancer

c) Prostate cancer

d) Pancreatic cancer

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Question 30:

A 35-year-old woman presents with a lump in the upper outer quadrant of her breast. Histopathological examination of the mass showed cells in mucin pools and faint nuclei. What is the most likely diagnosis?

a) Colloid carcinoma

b) Papillary carcinoma

c) Medullary carcinoma

d) Lobular carcinoma

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Answer Key

Question No.	Correct Option
1	d
2	d
3	d
4	c
5	c
6	a
7	a
8	c
9	b
10	d
11	d
12	b
13	a
14	c
15	b
16	a
17	c
18	c
19	d
20	d
21	d
22	d

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23	c
24	b
25	c
26	c
27	d
28	c
29	a
30	a

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Detailed Explanations

Solution to Question 1:

Periductal mastitis arises from the large lactiferous ducts.

It is also known as squamous metaplasia of lactiferous ducts, recurrent subareolar abscess, or Zuska disease.

The terminal duct lobular unit (TDLU) is the basic functional and histopathological unit of the breast. Successive branching of large ducts eventually leads to the TDLU. Sclerosing adenosis, blue dome cyst, and carcinoma breast arise from the TDLU.

Solution to Question 2:

Duct ectasia and Paget's disease arise from the large ducts of the breast.

Normal anatomy of the breast includes ducts, lobules, and stroma. Successive branching of the large ducts eventually leads to the terminal duct lobular unit.

Atypical hyperplasia arises from the terminal ducts and lobules, whereas, fibroadenoma and phyllodes tumors arise from the intralobular stroma.

Solution to Question 3:

The given clinical scenario is suggestive of acute mastitis. The most common cause of acute mastitis is Staphylococcus aureus.

Acute bacterial mastitis typically occurs during the 1st month of breastfeeding (lactational breast abscess). It is caused by a local bacterial infection when the breast is most vulnerable due to cracks and fissures in the nipples.

Staphylococcal acute mastitis typically results in localized abscesses.

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Option A: Breast abscess caused by Pseudomonas aeruginosa is uncommon, only a few cases have been documented in immunocompromised patients.

Options B and C: Streptococcal infections tend to spread throughout the breast in the form of cellulitis.

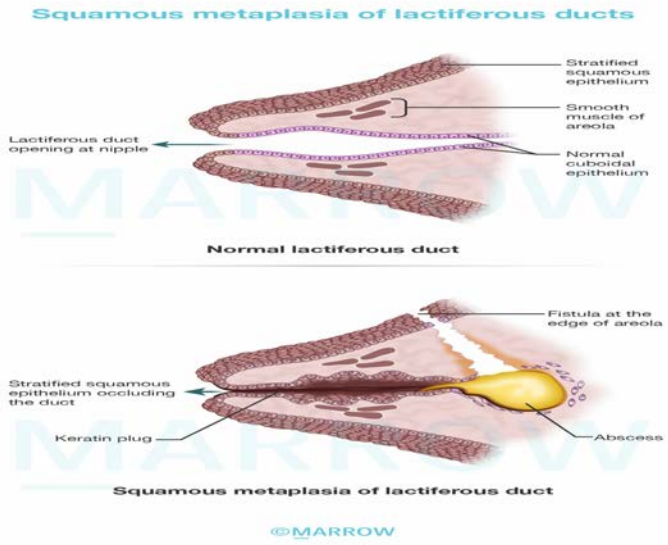
Solution to Question 4:

Periductal mastitis is strongly associated with a history of smoking. More than 90% of the affected individuals are smokers.

Periductal mastitis is also called recurrent subareolar abscess or squamous metaplasia of lactiferous ducts or Zuska disease. In this condition, a relative deficiency of vitamin A associated with smoking or toxic substances in tobacco smoke alters the differentiation of the ductal epithelium.

Histologically, there is keratinizing squamous metaplasia of the nipple ducts. Keratin shed from these cells is trapped and plugs (keratin plug) the ductal system, causing dilation and eventually rupture of the duct. This results in keratin spillage into the surrounding periductal tissue forming a chronic granulomatous inflammatory response.

It presents with a painful erythematous subareolar mass that clinically mimics bacterial abscess. It has a high recurrence rate.



Solution to Question 5:

The typical history of a breast lump following trauma and mammography findings of a radiolucent cystic lesion with rimmed calcification suggests a diagnosis of fat necrosis.

About half the affected women with fat necrosis of the breast have a history of breast trauma or previous surgery. It can present as a painless palpable mass, skin thickening or retraction, or

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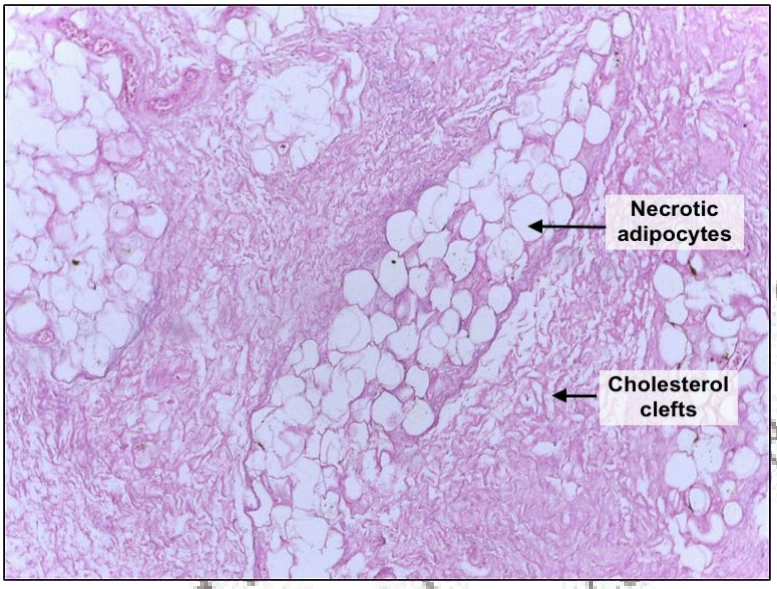
mammographic densities or calcifications.

Histologically, necrotic adipose tissue with foamy macrophages, multinucleated giant cells, and chronic inflammatory cells are seen often with hemosiderin deposits, fibrosis, and calcification.

The following image shows an area of fat necrosis within breast tissue.



Note: Calcifications are seen on mammography in the following conditions -

• Apocrine cysts

• Hyalinized fibroadenomas

• Sclerosing adenosis

• Duct ectasia

• Breast carcinoma- shows irregular densities and small, numerous, clustered calcification (microcalcifications).

Solution to Question 6:

Papillomas are classified under proliferative breast diseases without atypia.

Proliferative breast lesions without atypia are not clonal and usually have no genetic changes. Thus they are predictors of risk but are not true precursors of carcinoma.

Benign epithelial lesions are classified into three groups, according to the subsequent risk of developing breast cancer. These are:

• Non-proliferative breast changes

• Proliferative breast disease without atypia

• Atypical hyperplasia

Note: Lobular carcinoma in situ (LCIS) has recently been classified as a benign lesion with associated risk for developing carcinoma in the future but not as a malignancy capable of

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metastases.

Solution to Question 7:

Duct ectasia is a non-proliferative breast change.

Radial scar, sclerosing adenosis, and florid hyperplasia belong to proliferative breast lesions without atypia.

Proliferative breast lesions without atypia are not clonal and are not commonly found to have genetic changes. Thus they are predictors of risk but unlikely to be true precursors of carcinoma.

Solution to Question 8:

The most common clinical presentation seen in patients with duct papilloma is nipple discharge. More than 80% of large duct papillomas produce a nipple discharge.

Papillomas grow within a dilated duct and are composed of multiple branching fibrovascular cores. It can be serous or bloody.

• Serous discharge - due to intermittent blockage and release of normal breast secretions or irritation of the duct by the papilloma

• Bloody discharge - due to torsion of the stalk, causing infarction

Solution to Question 9:

The image given depicts gynecomastia. Seminoma is not a cause of this condition.

Gynecomastia occurs due to increased estrogenic action. The most common causes of gynecomastia include:

• Cirrhosis of the liver

• Alcohol

• Marijuana, heroin

• Antiretroviral therapy

• Anabolic steroids

• Klinefelter syndrome (XXY karyotype)

• Functioning testicular neoplasms such as Leydig cell or Sertoli cell tumors

Microscopically, there is an increase in the dense collagenous connective tissue. It is associated with epithelial hyperplasia of the duct lining with characteristic tapering micro-papillae. Lobule formation is almost never observed.

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Solution to Question 10:

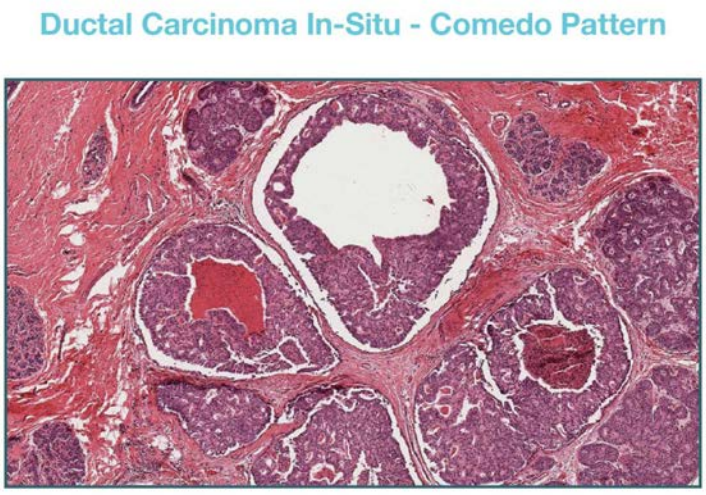
Apocrine change does not increase the risk of cancer as it is a non-proliferative change.

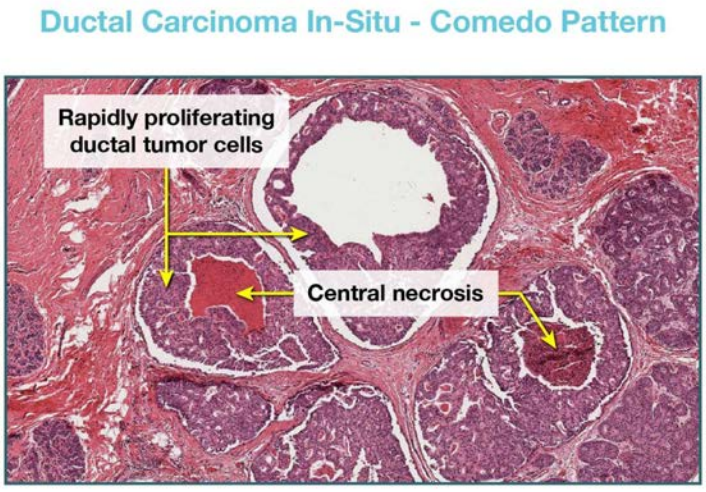
Moderate or florid hyperplasia, fibroadenoma with complex features, and sclerosing adenosis are classified under proliferative disease without atypia with a 1.5- to 2-fold increased risk of carcinoma.

Both breasts are at increased risk, although the risk to the ipsilateral breast may be slightly higher.

Solution to Question 11:

The given image is suggestive of the comedo type of ductal carcinoma in situ (DCIS). Myoepithelial cell markers like p63 can differentiate DCIS from invasive carcinoma.





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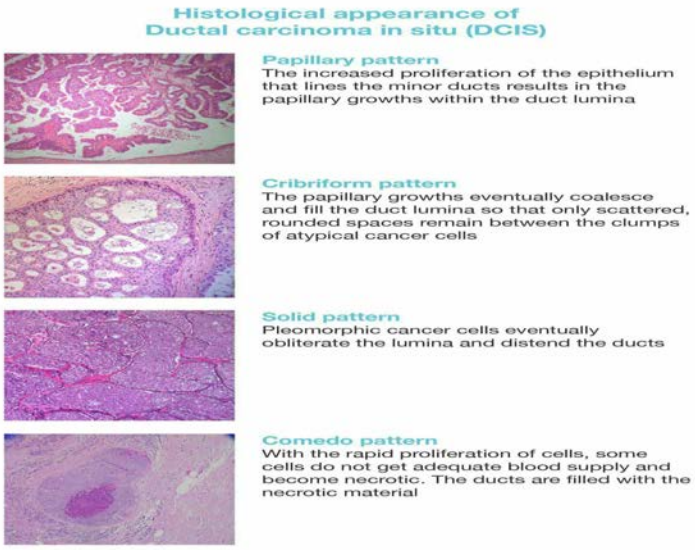
DCIS is a malignant clonal proliferation of epithelial cells limited to ducts and lobules by the intact basement membrane. It is rarely palpable and is almost always detected by mammography.

Myoepithelial cells (basal cell layer) are preserved in involved ducts or lobules in DCIS. Hence the myoepithelial cell markers like p63, basal cytokeratin (CK 5/6), calponin will be positive in DCIS whereas it will be absent in infiltrating ductal carcinoma. However, myoepithelial markers may be diminished in high-grade DCIS compared to surrounding normal ducts or lobules.

Once the tumor cells penetrate through the basement membrane and grow within the stroma, they are considered to be invasive carcinoma.



Note: Lobular carcinoma in situ (LCIS) has recently been classified as a benign lesion with associated risk for developing carcinoma in the future but not as a malignancy capable of metastases.

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Solution to Question 12:

The given scenario showing a red eczematous rash over the areola of the breast is suggestive of Paget's disease of the nipple. The next best step in management is biopsy of the nipple.

Paget's disease can be mistaken for eczema, and hence, biopsy of the nipple should be the initial management of choice. Paget cells are readily detected by nipple biopsy.

Solution to Question 13:

The given clinical scenario and image showing Paget's cells (malignant cells with abundant pale cytoplasm and pleomorphic nuclei) are suggestive of Paget's disease of the nipple. These cells are ER-negative.

Paget's disease of the nipple is a rare form of ductal carcinoma in-situ (DCIS). The characteristic Paget's cells are scattered individually throughout the squamous epithelium. They do not breach

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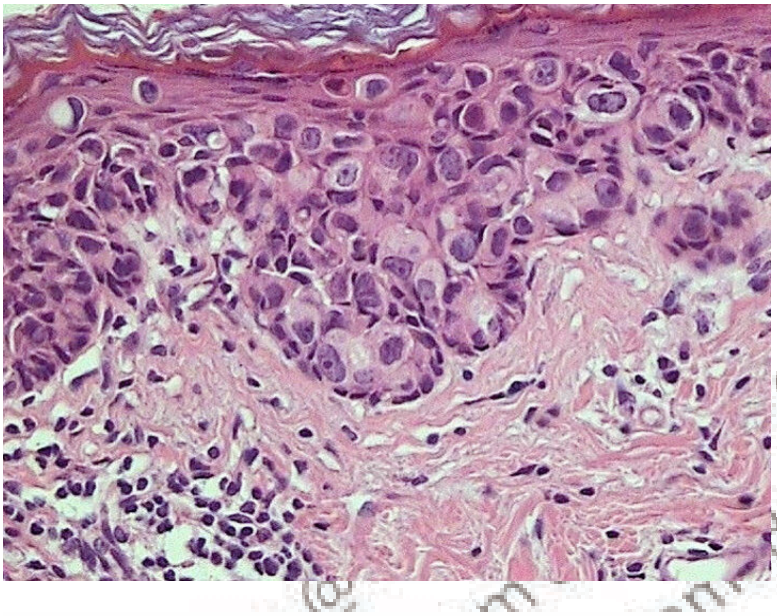
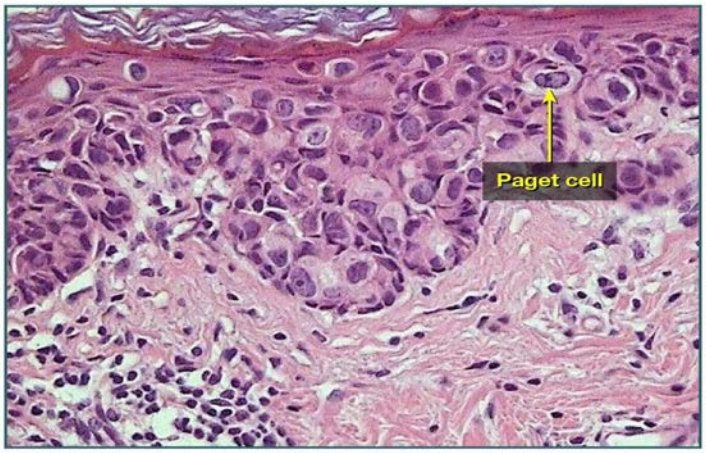
the basement membrane but extend via the lactiferous sinuses into the nipple skin.

The following images show Paget's cells that do not breach the basement membrane.



Paget's disease of the nipple



It presents as a unilateral erythematous eruption with a scale crust. A palpable mass is seen in about half the patients with this disease.

The underlying carcinomas are usually poorly differentiated, ER-negative, and overexpress HER2. The prognosis of Paget's disease depends on the features of the underlying carcinoma.

Paget's disease may mimic the following conditions:

• Eczema (clinical appearance) - can be differentiated by the presence of malignant cells on biopsy

• Superficial spreading melanoma (histological appearance) - Paget's cells are PAS-positive and diastase resistant unlike melanoma cells

Note: Paget's disease of the bone is a distinct condition that results in abnormal bone metabolism due to osteoclastic overactivity.

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Solution to Question 14:

Early full-term pregnancy (younger than 20 years) is protective against breast cancer. It halves the risk of developing breast cancer compared to that of nulliparous women.

Women with very dense breasts on mammography have a four- to six-fold higher risk of both ER-positive and ER-negative breast cancer compared to women with low density.

Obese women under the age of 40 years have a decreased risk as a result of anovulatory cycles and lower progesterone levels. In contrast, postmenopausal obese women are at an increased risk, which is attributed to the synthesis of estrogens in fat depots.

Early menarche, late menopause, and nulliparity are risk factors of breast cancer due to hyperestrogenemia. Exercise and breastfeeding are protective against breast cancer.

Solution to Question 15:

The upper outer quadrant is the most common site of carcinoma in the breast.

Approximately 50% of carcinomas are located in the upper outer quadrant, 10% in each of the remaining quadrants, and about 20% in the central or subareolar region.

A palpable mass is the most common clinical sign of invasive breast carcinoma.

Triple assessment is recommended for the diagnosis of any palpable breast lump. It includes:

- Clinical examination
- Radiological assessment (mammography/USG)
- Pathological assessment (FNAC/biopsy)

Techniques of palpation for breast examination are:

- Vertical strip/lines pattern
- Circular pattern
- Wedges or radial spokes pattern

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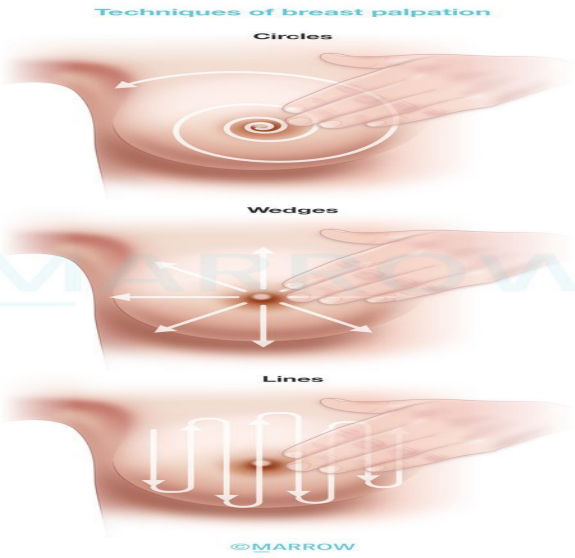

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Solution to Question 16:

BRCA2 gene is located on the long arm of chromosome 13 (13q12.3).

Mutations in BRCA1 and BRCA2 are responsible for 80 to 90% of single gene familial breast cancers and about 3% of all breast cancers.

ER-positive, HER2-negative cancers (luminal type) is the most common subtype of breast cancer in individuals who inherit germline mutations in BRCA2. This gene is associated more frequently with male breast cancer.

Single gene mutations associated with familial breast cancer can be categorized into:

• High penetrance germline mutations (>4 fold increased risk) - BRCA1, BRCA2, TP53, PTEN, STK11, CDH I, PALPB2

• Moderate penetrance germline mutations (2-4 fold increased risk) - ATM, CHEK2

Solution to Question 17:

The given scenario is suggestive of triple-negative breast cancer (ER-negative, PR-negative, and HER2-negative). TP53 is the most commonly mutated gene in triple-negative breast cancer (TNBC).

Common gene mutations in the 3 major molecular types of invasive breast carcinoma are:

Molecular Subtype	Common gene mutations
Luminal (ER+/HER2 -)	Luminal A: PIK3CA (more co mmon), TP53Luminal B: PIK 3CA (more common), TP53

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Molecular Subtype	Common gene mutations
HER2 Positive (HER 2+)	TP53 (more common), PIK3CA
TNBC (ER-/ HER2-)	TP53 (more common), PIK3CA

Solution to Question 18:

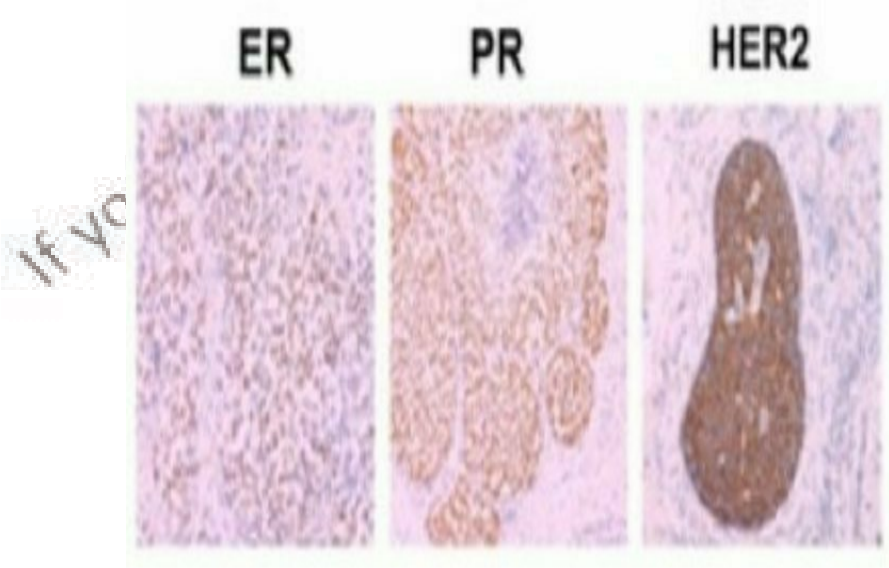
The given immunohistochemistry (IHC) staining shows positive ER, PR (brown nucleus), and negative Her-2 (no membrane-bound brown stain) expression, which is suggestive of luminal A molecular subtype. It shows a poor response to paclitaxel.

Hormone receptors (ER, PR) are present in the nucleus. Therefore ER, PR–positive breast cancer cells will stain dark in the nucleus on IHC. Her-2 receptors are membrane-bound receptors, and hence, cells having these receptors are darkly stained on the membranes.

Luminal A type is more commonly associated with BRCA2 mutations.

Hormone receptor-positive tumors are responsive to hormonal chemotherapeutic agents like tamoxifen and aromatase inhibitors. In Her-2 negative cases, trastuzumab is not effective as it is a recombinant humanized monoclonal antibody directed against HER-2.

The following image shows ER/ PR/ Her-2 positivity:



Note: At least 10% of luminal type A breast cancers express tp53 mutations. tP53 mutations are associated with triple-negative tumors as well.

Solution to Question 19:

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Carcinomas with immunohistochemistry ER and HER2/v negative are all of the above except mucinous carcinomas. Mucinous carcinomas are usually ER-positive and HER2/neu negative (luminal A type)

ER-negative, HER2-negative (triple-negative) molecular subtype commonly includes the following histological subtypes:

- Medullary
- Adenoid cystic
- Secretory
- Metaplastic
- Spindle cell
- Squamous
- Matrix-producing

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Solution to Question 20:

ER-positive, HER2-negative status on immunohistochemistry is suggestive of the luminal type of breast carcinoma, which does not include secretory carcinoma.

The ER-positive, HER2-negative molecular subtype (luminal type) commonly includes the following histological subtypes:

- Well and poorly differentiated lobular carcinoma
- Tubular carcinoma
- Mucinous carcinoma
- Papillary carcinoma

Secretory carcinomas are usually ER-negative and Her2/neu negative (basal type).

Solution to Question 21:

Lobular carcinoma is the most common type of breast carcinoma to present as an occult primary carcinoma.

Lobular carcinoma of the breast is seen bilaterally and with multicentricity. Loss of E-cadherin is the hallmark of lobular carcinoma. They also have characteristic patterns of metastatic spread, often involving the peritoneum and retroperitoneum, leptomeninges (carcinomatous meningitis), gastrointestinal tract, ovaries, and uterus.

The histological hallmark of lobular carcinoma is the presence of discohesive infiltrating tumor cells, often arranged in a single Indian file pattern or in loose clusters or sheets.

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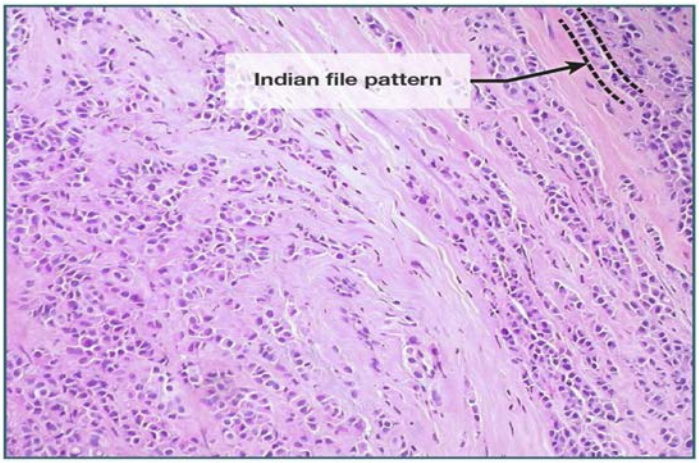
Lobular carcinoma of breast



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Solution to Question 22:

There is no or very slight desmoplastic response seen in lobular carcinomas.

Desmoplasia refers to collagenous stromal proliferation induced by tumor cells which is essential for tumor growth and spread. It results in hard and stony tumors. However, this is not seen in lobular carcinoma. This is likely due to the loss of expression of CDH1, the gene that encodes e-cadherin (normally maintains intercellular adhesiveness). This also results in disaggregation of cells.

Lobular carcinomas are often bilateral and multicentric. It shows characteristic metastatic spread, often involving:

- Peritoneum and retro peritoneum
- Leptomeninges (carcinomatous meningitis)
- Gastrointestinal tract
- Ovaries
- Uterus

Histopathological image of invasive lobular carcinoma of breast showing discohesive cells with few signet ring cells.

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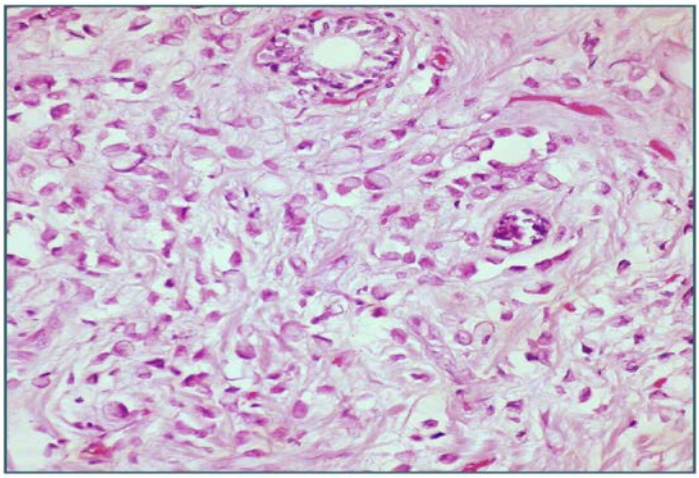
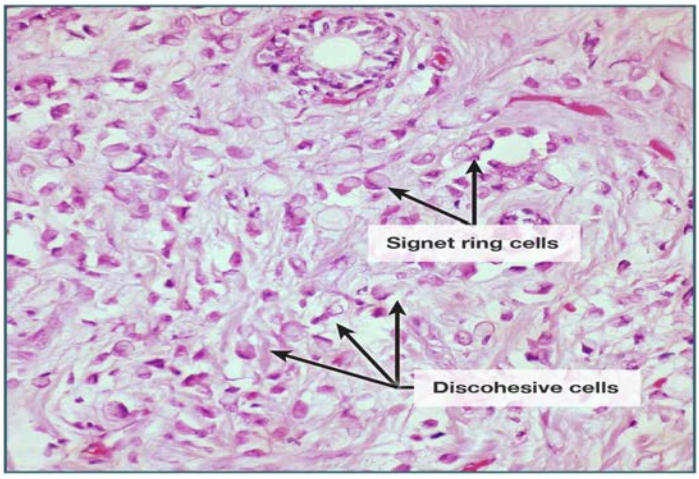
Lobular Carcinoma of Breast



Lobular Carcinoma of Breast



Note: Individuals with heterozygous germline mutations in CDH1 (loss of E-cadherin) also have a greatly increased risk of gastric signet-ring cell carcinoma.

Solution to Question 23:

T4d in the TNM staging of carcinoma breast points toward a diagnosis of inflammatory breast carcinoma. It shows extensive invasion and proliferation of tumor cells within the dermal lymphatics leading to obstruction.

Inflammatory breast cancer is the most aggressive subtype of breast cancer. The hallmark of this condition is the overexpression of e-cadherin. This results in increased tumor cohesion and the formation of tumoral clumps which can result in emboli. It has a particularly poor prognosis.

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These tumors are usually of high grade but do not belong to any particular molecular subtype. More than half (60%) are ER-negative and 40% to 50% overexpress HER2. There is no association with trauma.

Due to lymphatic obstruction, it results in brawny induration, erythema with a raised edge, and edema called peau d'orange appearance. This may mimic non-neoplastic inflammatory lesions like mastitis. A breast lump may or may not be present.

The following image shows a peau d'orange appearance of the right breast.

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Solution to Question 24:

The immunohistochemistry (IHC) pattern of patient C reveals moderately strong circumferential staining (faint brown color) in >10 % of cells, which is classified as 2+ or equivocal staining. Hence, she should be subjected to fluorescence in situ hybridization (FISH) to confirm HER2-positive gene amplification status.

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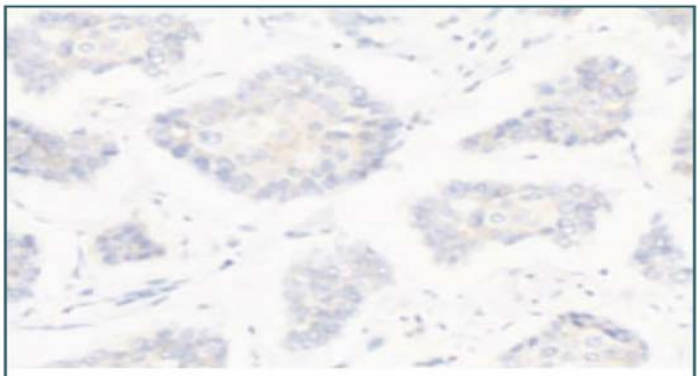
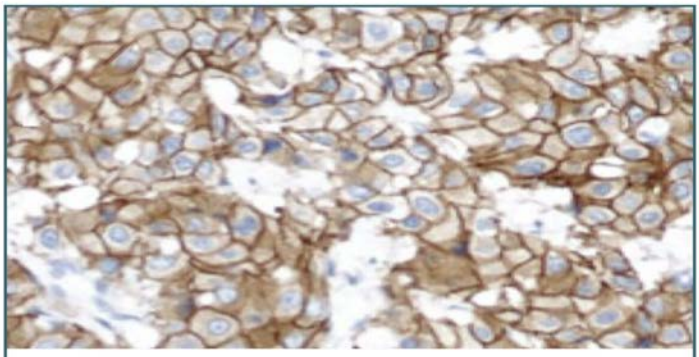
Patient A



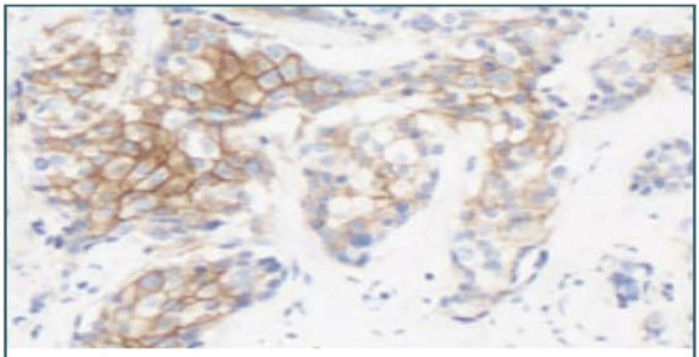
1+
HER2-negative

Patient B



3+
HER2-positive: Strong circumferential membrane staining in >10% cells

Patient C



2+
Equivocal – moderately strong circumferential staining in >10 % of cells

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The following are classified as HER2-positive tumors:

• Tumors that show 3+ staining on IHC (here FISH is not needed).

• Tumors with 2+ staining on IHC, followed by HER2-gene amplification confirmed by FISH

Once HER2-positive status is confirmed, targeted therapy against HER2 can be initiated with trastuzumab or lapatinib.

Solution to Question 25:

HER2 overexpression in a patient with carcinoma breast is associated with poor survival.

The main importance of HER2 status is as a predictor of response to agents that target this receptor.

Prognostic and predictive factors in breast carcinoma:

	Good prognosis	Bad prognosis
Extent and spread	In situ carcinoma	Invasive carcinomaLocally advanced diseaseLymphovascular invasionDistant metastasis
Size	Size <1 cm	Size >2 cm
Histological subtype	Tubular carcinomaMucinous carcinomaLobular carcinoma Papillary carcinomaAdenoid cystic carcinoma	Metaplastic carcinomaMicropapillary carcinoma
Histologic grade	Low grade	High grade
Molecular subtype	Luminal A subtype	Her2-enriched and basal subtype
Proliferation rate(Ki67 index & mitotic counts)	Low proliferation rate	High proliferation rate

Solution to Question 26:

This clinical scenario and image showing duct proliferation are suggestive of fibroadenomas. The use of cyclosporin-A after transplantation is associated with fibroadenomas that regress after cessation of the treatment.

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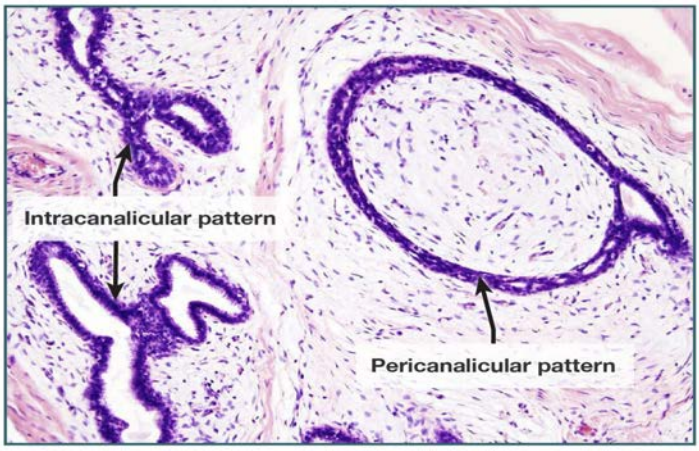
Fibroadenoma of Breast



Fibroadenomas are the most common benign tumor of the female breast. Nearly 2/3 cases are associated with mutations in the MED12 gene.

They are frequently multiple and bilateral and usually occur in women <30 years of age. They are solid, well-defined, highly mobile masses (also known as breast mice).

Fibroadenomas can be classified into 2 types:

• Without complex features - classified as a non-proliferative condition

• With complex features -

• Associated with cysts > 0.3 cm, sclerosing adenosis, epithelial calcifications, or papillary apocrine change

• Classified as proliferative changes without atypia

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Solution to Question 27:

The given clinical scenario and image are suggestive of phyllodes tumor. Here, only the stromal component is involved in metastasis.

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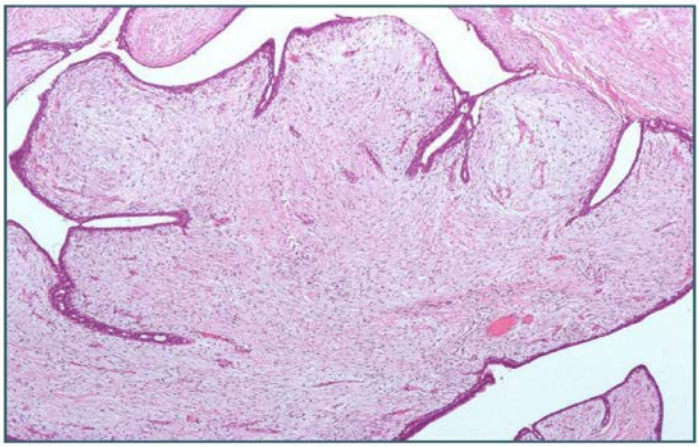
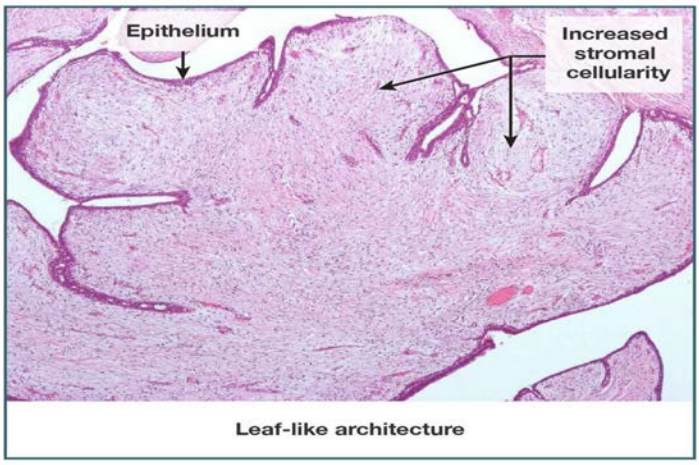
Phyllodes Tumor



Phyllodes Tumor



Phyllodes tumor is a fibroepithelial tumor arising from the intralobular stroma. It presents as a smooth, rapidly growing, multinodular, painless breast lump that is usually palpable. It most commonly presents in the 6th decade of life and is associated with:

• Gain in chromosome 1q

• HOXB13 overexpression

Phyllodes tumors show stromal cellularity next to the epithelium (subepithelial or periepithelial regions). This feature helps to differentiate it from intracanalicular fibroadenoma.

The prognosis of phyllodes tumors depends on their histological grade. Most phyllodes tumors are low grade, with limited stromal cellularity. They recur only occasionally and do not metastasize.

The features of malignant (intermediate and high grade) phyllodes tumors are:

• Markedly increased stromal cellularity

• Stromal overgrowth - absence of epithelial elements

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- Nuclear atypia
- Increased mitosis (>10/ 10 hpf)
- Highly recurrent

Regardless of the grade, lymphatic spread is rare in phyllodes tumors. Hence, axillary lymph node dissection is contraindicated.

Solution to Question 28:

Angiosarcoma is the most common stromal malignancy in the breast.

It arises in the interlobular stroma and accounts for < 0.05% of breast malignancies. It is a high-grade tumor with a poor prognosis. It can either be sporadic or occur in association with radiation therapy. The mean age of affected individuals is 35 years.

Solution to Question 29:

BRCA-2 mutation does not predispose to the development of renal cell carcinoma.

BRCA-2 mutation predisposes to the development of prostate and pancreatic cancer. It is also associated with an increased risk of male breast cancer.

Solution to Question 30:

The given scenario is suggestive of colloid or mucinous carcinoma of the breast.

Colloid carcinoma is an invasive breast carcinoma, which shows intracellular and extracellular mucin deposition.

On histopathological examination, extracellular type shows tumor cells with faint nuclei, arranged in clusters, floating in lakes or pools of mucin. In intracellular type, nuclei are pushed to the periphery to form a signet ring appearance.

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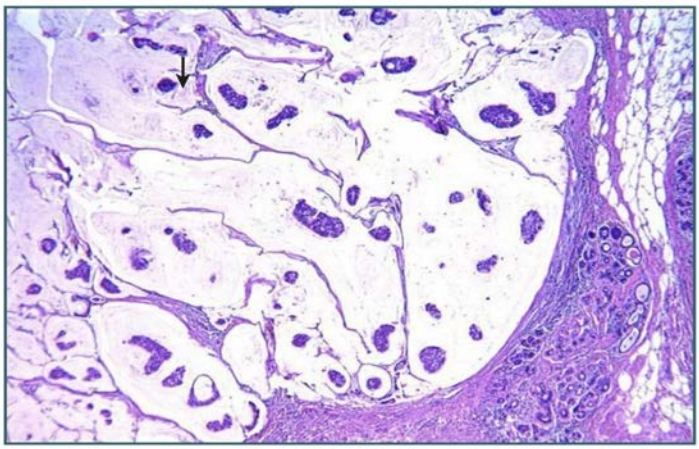
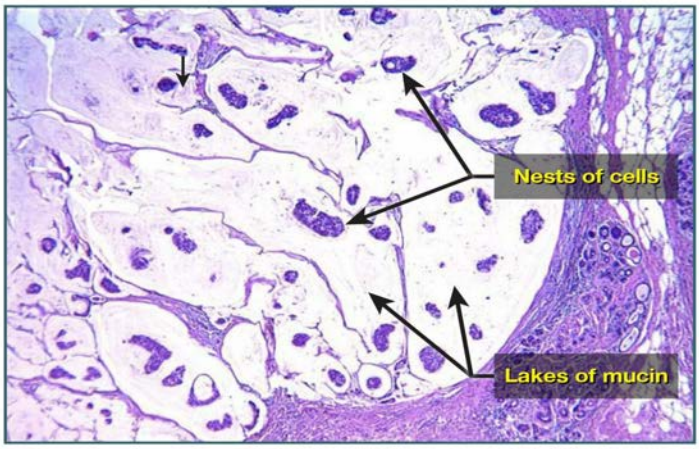
Colloid Carcinoma of Breast



Colloid Carcinoma of Breast



Option B: Microscopic image of papillary carcinoma of the breast showing true papillae with a leaf-like arrangement of fibrovascular tissue lined by the tumor cells is shown below.

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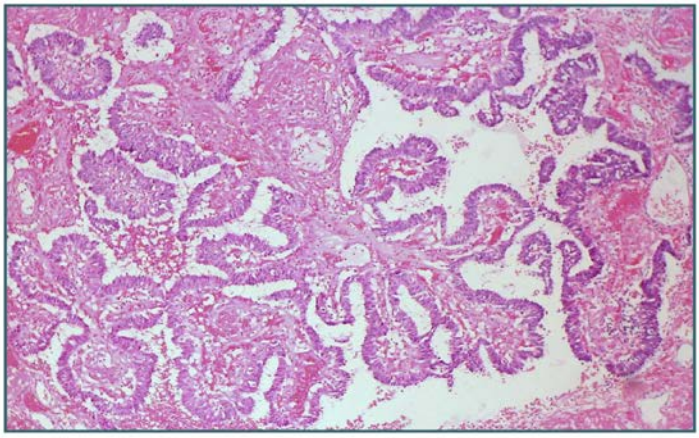
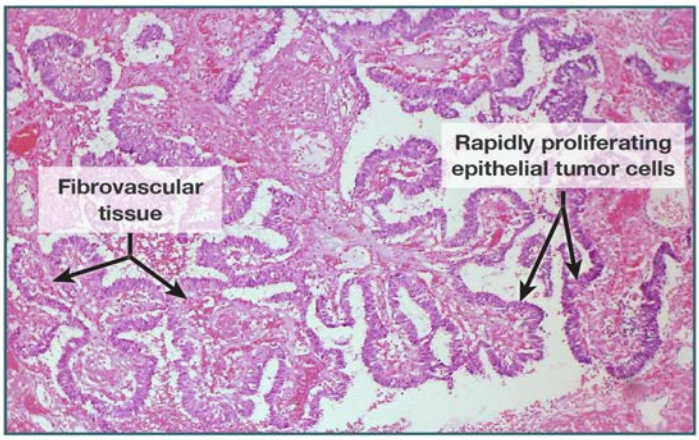
Papillary Carcinoma of Breast



Papillary Carcinoma of Breast



Option C: Microscopic image of medullary carcinoma of the breast consisting of sheets of highly pleomorphic cells with mitotic figures (anaplastic cells), lymphoplasmacytic infiltrate is shown below.

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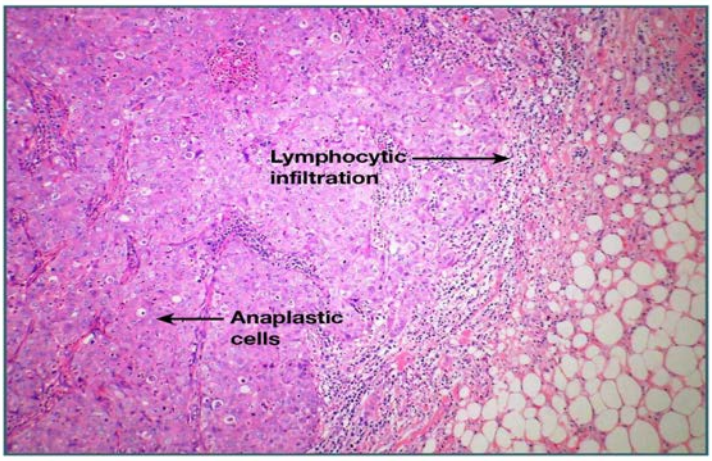
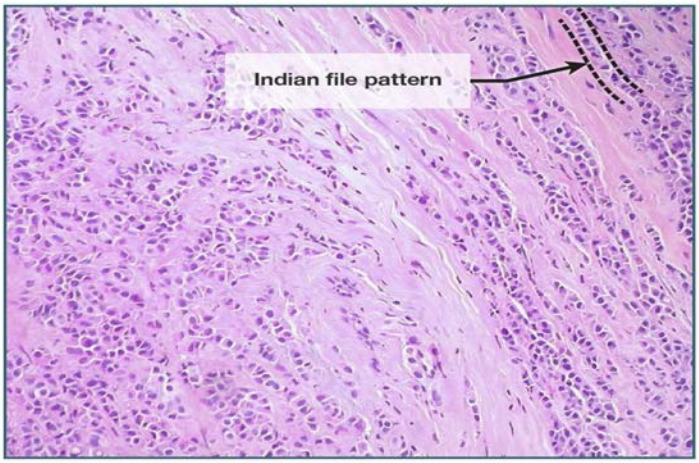
Histology of medullary carcinoma breast



Option D: Microscopic image of lobular carcinoma of the breast shows infiltrating small monomorphic discohesive tumor cells arranged in an Indian-file or single-file pattern is shown below.

Lobular carcinoma of breast



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Developmental disorders,infections and tumors of bone

Question 1:

What are the specialized multinucleated macrophages in bone called?

a) Osteocytes

b) Chondroblasts

c) Osteoclasts

d) Histiocytes

Question 2:

Which of the following is not a marker of bone resorption?

a) Osteocalcin

b) Urine free deoxypyridinoline

c) Crosslinked-N-telopeptides

d) Tartrate resistant acid phosphatase

Question 3:

Which of the following is the most common benign bone tumor?

a) Osteoblastoma

b) Chondroblastoma

c) Osteochondroma

d) Osteiod osteoma

Question 4:

A woman delivered a child who died a few minutes after birth. The infant was found to have blue sclera and fractures of the right humerus, ulna, and femur at birth. What is the most probable diagnosis?

a) Osteogenesis Imperfecta Type I

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b) Osteogenesis Imperfecta Type II

c) Osteogenesis Imperfecta Type III

d) Osteogenesis Imperfecta Type IV

Question 5:

A 29-year-old woman gives birth to an infant with less than 5th percentile length. The head and torso are of normal size but extremities are short. The head circumference is at the 95th percentile, and frontal bossing is seen. What is the most likely diagnosis?

a) Hypophosphatemic rickets

b) Achondroplasia

c) Ehlers-Danlos syndrome

d) Osteogenesis imperfecta

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Question 6:

Which of the following is also called marble bone disease?

a) Osteogenesis imperfecta

b) Vrolik's syndrome

c) Albers-Schönberg disease

d) Paget disease of bone

Question 7:

An infant is being evaluated for multiple fractures over the last 3 months. On examination, hydrocephaly, cranial nerve defects, and hepatosplenomegaly are noted. Imaging reveals generalized sclerosis and a bone-in-bone appearance. Which of the following is the most likely enzyme to be deficient in this condition?

a) Carbonic anhydrase II

b) Acid phosphatase

c) Creatine kinase

d) Phosphorylase

Question 8:

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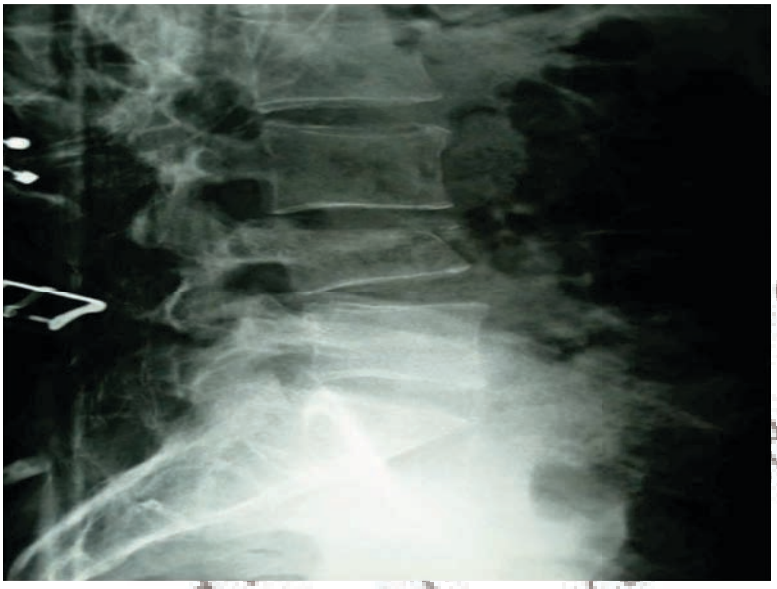
A 60-year-old postmenopausal woman presents with sudden severe back pain. There is no history of trauma. X-ray findings are given below. MRI shows thinning of trabecular plates of the vertebrae and vertebral collapse. Levels of which of the following will be increased in her condition?



a) RANKL

b) OPG

c) IFNg

d) IL-8

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d.

Question 9:

In patients with which of the following conditions will you see a histologically normal bone?

a) Osteomalacia

b) Osteoporosis

c) Paget's disease

d) Hyperparathyroidism

Question 10:

A patient presents with back pain, recurrent headaches, and increasing head size. On evaluation, raised alkaline phosphatase and a mosaic pattern of lamellar bone is seen. Which of the following statements is false about this condition?

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a) Onset is in late adulthood

b) It occurs due to mutations in the SQSTM1 gene

c) It is polyostotic in about 15% of cases

d) Sarcoma occurs in less than 1% of all individuals

Question 11:

In patients with hyperparathyroidism, which of the following is least expected?

a) Osteoporosis

b) Brown tumors

c) Dissecting osteitis

d) Osteopetrosis

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Question 12:

A 7-year-old child presented with fever, pain, and swelling around the knee joint for 3 days. Lab investigations showed a WBC count of 23,500/mm3. An MRI was done, which demonstrated an intramedullary abscess of the proximal tibia. Which of the following is the most common causative organism of this condition?

a) Streptococcus pyogenes

b) Staphylococcus aureus

c) Salmonella

d) Klebsiella

Question 13:

Patients with sickle cell disease are particularly susceptible to osteomyelitis caused by which of the following?

a) Staphylococcus aureus

b) Haemophilus influenzae

c) Streptococcus pyogenes

d) Salmonella enteritidis

Question 14:

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A patient who is a known case of TB presents to the orthopedic OPD with a 4-month history of progressively worsening back pain. He also complains of fatigue and irregular fever for 2 weeks. X-ray reveals lytic destruction of the anterior portion of the vertebral body and increased anterior wedging. All of the following are the complications of his condition except

a) Scoliosis

b) Paraplegia

c) AA amyloidosis

d) Brodie's abscess

Question 15:

A 25-year-old man presents with back pain that is unresponsive to aspirin. Radiographs show a well-demarcated lesion in the posterior spine. A biopsy is done and the histopathological finding is given below. Which of the following is the most likely diagnosis?

[Image unavailable]

a) Osteosarcoma

b) Osteoid osteoma

c) Osteoblastoma

d) Chondroblastoma

Question 16:

A 17-year-old man presents with progressive swelling of the upper end of the humerus. He also complains of arm pain and weight loss for 3 months. X-ray findings are given below. Which of the following is associated with a higher risk of developing this condition?

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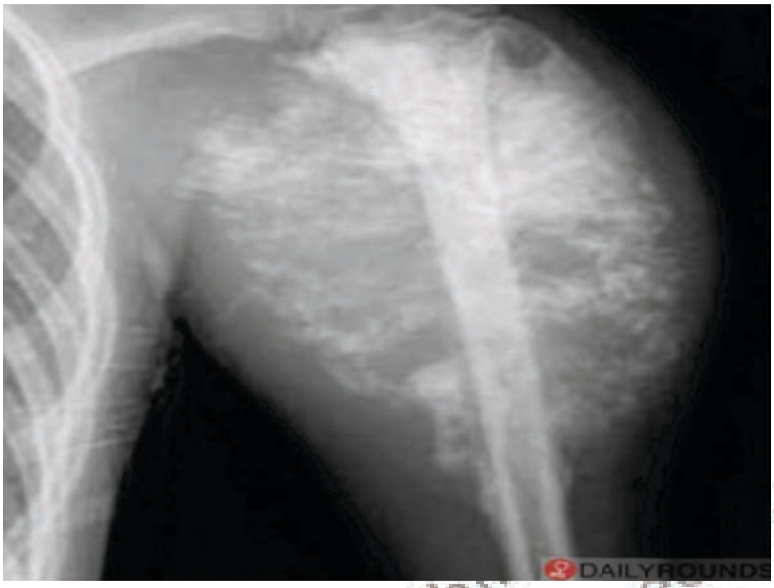

a) Germline mutation of p53

b) Translocation (X;18)

c) Translocation (12;16)

d) 1p rearrangements

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Question 17:

Which of the following statements is false about osteosarcoma?

a) It usually arises in the diaphyseal region of long bones

b) It has a bimodal age distribution

c) Codman triangle is characteristic of the tumor

d) Most common subtype is osteoblastic and high grade

Question 18:

Which of the following bone tumors is characteristically seen in patients with Ollier disease and Maffucci syndrome?

a) Enchondromas

b) Osteochondromas

c) Osteiod osteomas

d) Chondrosarcomas

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Question 19:

Which of the following statements is not true about chondrosarcoma?

a) Conventional central tumors constitute about 90% of chondrosarcomas.

b) Clear cell and the mesenchymal variants occur in older patients.

c) Chondrosarcomas commonly arise in the axial skeleton.

d) In multiple hereditary exostosis, osteochondromas progress to chondrosarcoma.

Question 20:

Which of the following can progress to become chondrosarcoma?

a) 1, 2 and 5

b) 1, 3 and 5

c) 2, 3 and 4

d) 1, 2 and 3

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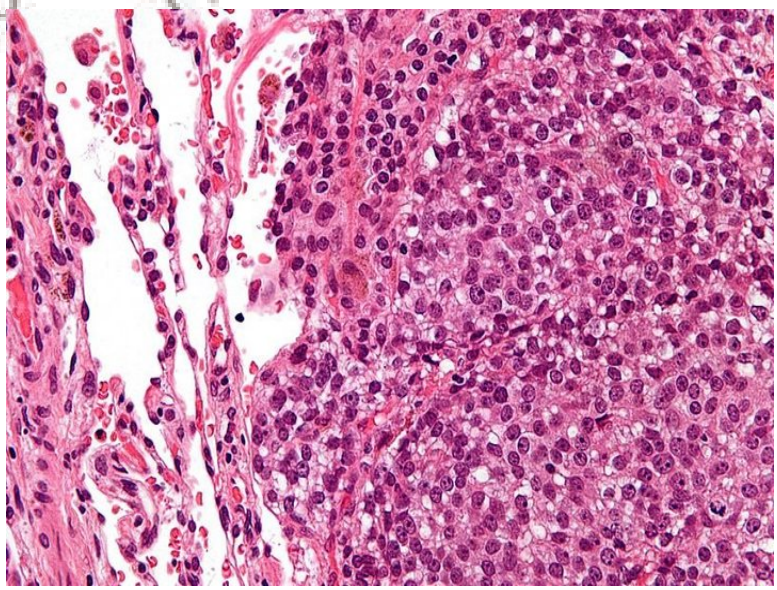
Question 21:

A plain radiograph of a patient shows a destructive lytic tumor that extends into the surrounding soft tissues with a characteristic onion-skin appearance. A biopsy image is shown below. Which of the following is not true about the tumor?



a) It is the second most common group of bone sarcomas in children

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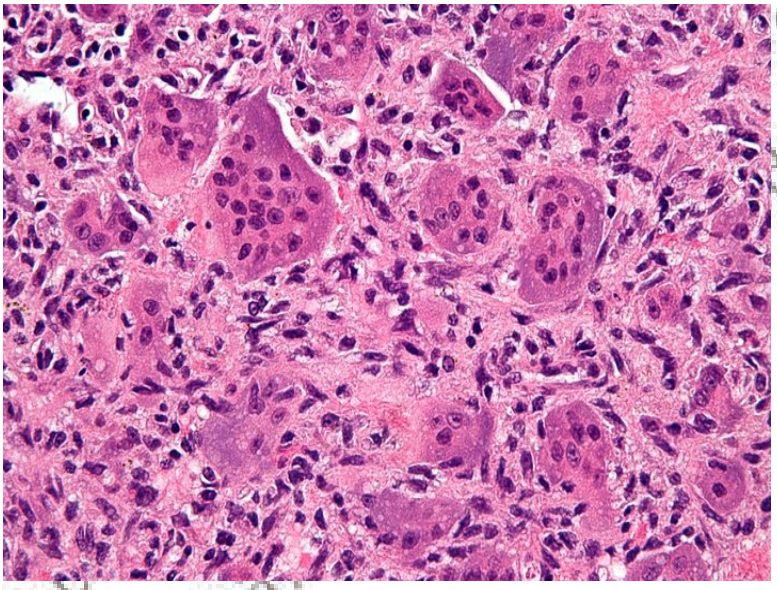
b) It arises in the epiphysis of long tubular bones

c) Most of these tumours contain a (11;22) (q24;q12) translocation

d) The amount of chemotherapy-induced necrosis is an important prognostic finding

Question 22:

A 30-year-old woman presents with a 1-month history of pain in the left knee, which is tender on palpation. X-ray shows a 5 cm mass in the distal femoral epiphysis, with a soap bubble appearance. Microscopy is as seen below. What is the most likely diagnosis?



a) Chondroblastoma

b) Osteoclastoma

c) Osteosarcoma

d) Osteochondroma

Question 23:

A 19-year old man presents with back pain for 2 months. MRI of the spine reveals a bony cystic mass at the L1 vertebra. Biopsy shows multiple, blood-filled cystic spaces separated by septae, composed of multinucleated osteoclast-like giant cells and reactive woven bone. There is no cartilage or necrosis. What is the likely diagnosis?

a) Osteoclastoma

b) Aneurysmal bone cyst

c) Chondroblastoma

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d) Fibrous cortical defect

Question 24:

A 60-year-old patient complains of severe back pain for 2 months, which worsens at night. An MRI shows multiple osteoblastic secondaries on the vertebrae. Which of the following tumors could be the primary source of these lesions?

a) Renal cell carcinoma

b) Prostatic adenocarcinoma

c) Adenocarcinoma lung

d) Multiple myeloma

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Answer Key

Question No.	Correct Option
1	c
2	a
3	c
4	b
5	b
6	c
7	a
8	a
9	b
10	c
11	d
12	b
13	d
14	d
15	c
16	a
17	a
18	a
19	b

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20	d
21	b
22	b
23	b
24	b

Detailed Explanations

Solution to Question 1:

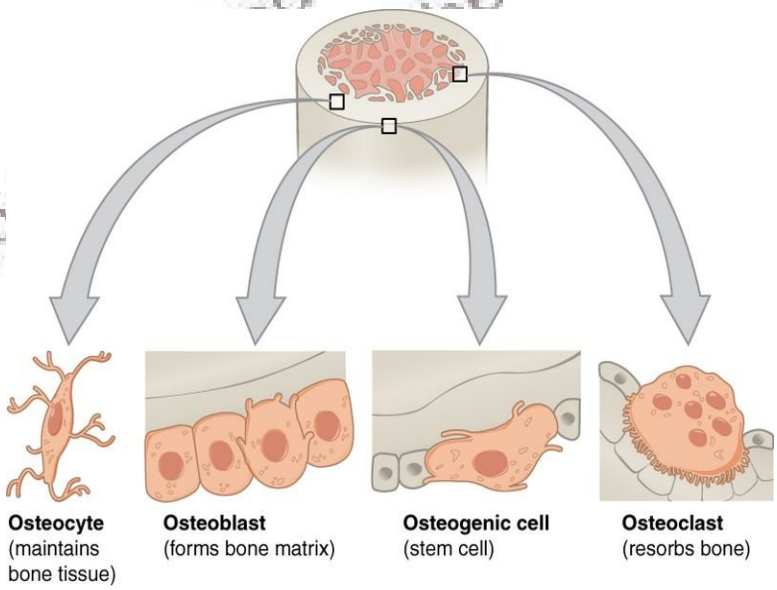
Osteoclasts are specialized multinucleated macrophages derived from circulating monocytes that are responsible for bone resorption.

Osteocytes are formed when osteoblasts are embedded in the matrix within lacunae and canaliculi. They control calcium and phosphate levels in the microenvironment.

Osteoblasts are mesenchymal cells that rim the bony spicule, responsible for bone synthesis and mineralization.

Chondrocytes are specialized cells that produce and maintain the extracellular matrix of cartilage.

The image given below shows different cells present in a bone.



Solution to Question 2:

Osteocalcin is not a bone resorption marker.

It is a protein secreted only by osteoblasts. Thus, it is a bone formation marker (osteoblastic marker).

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Solution to Question 3:

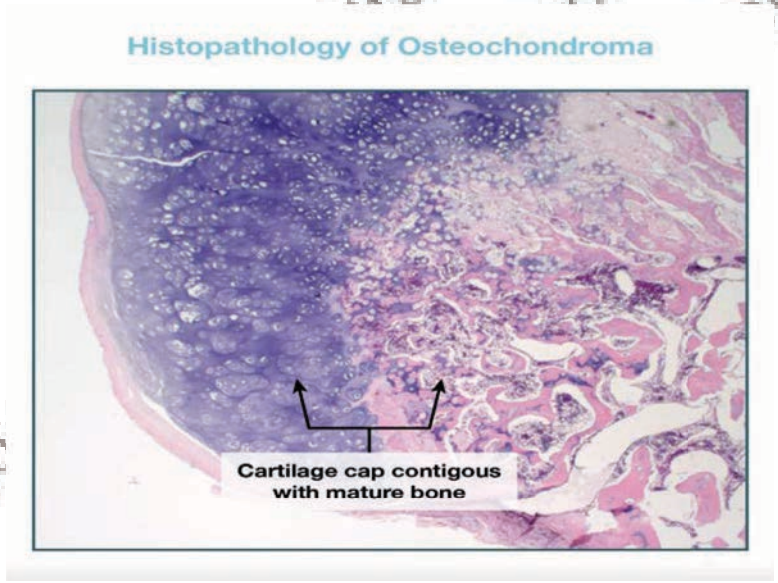
Osteochondroma, also known as exostosis, is the most common benign bone tumor.

It is a benign cartilage-capped tumor. 85% of osteochondromas are solitary. The remainder is seen as part of the multiple hereditary exostosis syndromes, an autosomal-dominant hereditary disease.

Lesions arise from the metaphysis near the growth plate of long tubular bones, especially near the knee. They are either sessile or pedunculated and range in size from 1 to 20 cm. Histologically, the cap is composed of benign hyaline cartilage varying in thickness and is covered peripherally by perichondrium.

Osteochondromas can progress to chondrosarcoma.

The image below shows the histopathological specimen of osteochondroma, displaying a cartilage cap lined by perichondrium contiguous with mature bone.



Solution to Question 4:

The given clinical scenario is suggestive of osteogenesis imperfecta type II.

The type II variant of osteogenesis imperfecta (OI) is uniformly fatal in utero or during the perinatal period. Type II OI is characterized by extraordinary bone fragility with multiple intrauterine fractures.

Osteogenesis imperfecta (brittle bone disease) is caused by deficiencies in the synthesis of type I collagen. It can be separated into four major clinical subtypes that vary widely in severity. The severity of the disease is based on the location of the mutation within the protein.

Individuals with type I OI have a normal life span, but experience childhood fractures that decrease in frequency following puberty.

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Solution to Question 5:

This given clinical scenario is suggestive of achondroplasia.

Achondroplasia is the most common skeletal dysplasia and a major cause of dwarfism. It has autosomal dominant inheritance.

It occurs due to the gain of mutation in fibroblast growth factor receptor (FGFR3). This leads to abnormal cartilage proliferation at growth plates and affects endochondral bone growth. Infants present with:

• Short stature

• Rhizomelic shortening of limbs

• Frontal bossing

• Midface deficiency

The condition is not associated with changes in longevity, intelligence, or reproductive status.

The image below shows a baby affected with achondroplasia. Note the prominent forehead, triangular face, and body asymmetry in the image (a); a low nasal bridge in the image (b); trident hands in the image (c); and scoliosis in the image (d).

Solution to Question 6:

Albers-Schönberg disease or osteopetrosis is also known as marble bone disease.

The term osteopetrosis reflects the stone-like quality of the bones. The bones are abnormally brittle and fracture easily, like a piece of chalk. It occurs due to reduced bone resorption and diffuse symmetric skeletal sclerosis because of impaired formation or function of osteoclasts.

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Note: Osteogenesis imperfecta is also called brittle bone disease. Paget's disease is also called osteitis deformans; it presents with mosaic pattern of lamellar bone.

Solution to Question 7:

The given clinical scenario is suggestive of osteopetrosis. It occurs due to autosomal recessive defects in the gene for the enzyme carbonic anhydrase II.

Carbonic anhydrase II is required by osteoclasts and renal tubular cells to generate protons from carbon dioxide and water (acidification). The absence of carbonic anhydrase II prevents osteoclasts from acidifying the resorption pit and dissolution of calcium hydroxyapatite within the bone matrix. It also blocks the acidification of urine by the renal tubular cells. This leads to reduced bone resorption and diffuse symmetric skeletal sclerosis.

Due to deficient osteoclast activity, bones involved by osteopetrosis lack a medullary canal giving it a bone-in-bone appearance. The ends of long bones are bulbous (Erlenmeyer flask deformity) and misshapen. The neural foramina are small and compress the exiting nerves, leading to cranial nerve palsies.

Extensive extramedullary hematopoiesis leads to leukopenia and prominent hepatosplenomegaly. As carbonic anhydrase II is widely expressed, mutations of this gene result in a condition called marble brain disease or Guibaud-Vainsel syndrome.

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Solution to Question 8:

The given clinical scenario is suggestive of osteoporosis. Cytokines stimulate osteoclast recruitment and activity in osteoporosis by increasing the levels of RANKL.

RANKL helps in diminishing the expression of osteoprotegerin (OPG), increasing osteoclast proliferation, and preventing osteoclast apoptosis.

Decreased estrogen levels after menopause actually increase both bone resorption and formation. However, the latter does not keep up with the former, leading to a high turnover. Decreased estrogen appears to increase the secretion of inflammatory cytokines such as IL-6, TNF-α, and IL-1.

Solution to Question 9:

Histologically normal bone with decreased density is the hallmark feature of osteoporosis.

In advanced osteoporosis, both the trabecular bone of the medulla and the cortical bone are markedly thinned leading to progressive microfractures.

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Option A: Inadequate mineralization in osteomalacia leads to a thickened osteoid matrix.

Option C: Paget's disease presents with a mosaic pattern of lamellar bone.

Option D: Dissecting osteitis cystica is seen in severe hyperparathyroidism.

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Solution to Question 10:

Paget disease is monostotic in about 15% of cases and polyostotic in the rest of them.

Paget disease (osteitis deformans) is a disorder of increased, but disordered and structurally unsound, bone mass. The onset is in late adulthood (average age at diagnosis, 70 years).

It occurs due to mutations in the SQSTM1 gene. This increases the activity of NF-κB, which then increases osteoclast activity.

Three sequential phases exist:

• Initial osteolytic stage

• Mixed osteoclastic-osteoblastic stage

• Final burned-out quiescent osteosclerotic stage

The axial skeleton or proximal femur is involved in up to 80% of the cases. The typical x-ray findings are as follows:

• Enlargement of the craniofacial skeleton: leontiasis ossea or lion face

• Invagination of the skull base (platybasia)

• Chalk stick-type fractures in the long bones of the lower extremities

The pathological hallmark is a mosaic pattern of lamellar bone, seen in the sclerotic phase as shown below. It shows a jigsaw-like pattern produced by unusually prominent cement lines, which join haphazardly oriented units of lamellar bone.

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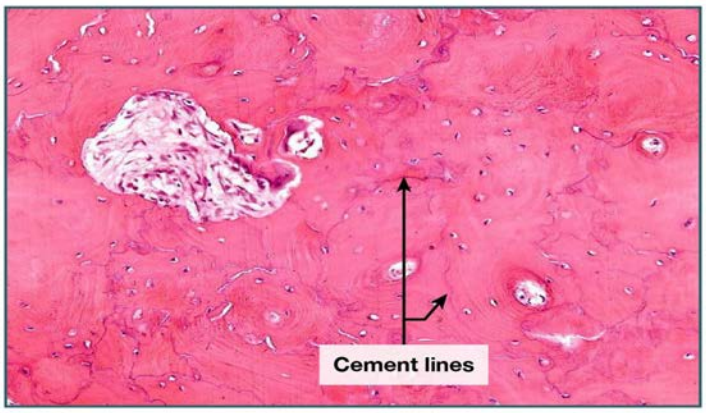
Paget's Disease -
Mosaic pattern of lamellar bone



Laboratory findings show elevated serum alkaline phosphatase and urinary hydroxyproline (normal serum calcium and phosphorus).

Following tumors can develop in the affected bones in Paget's disease:

• Benign tumors -

• Giant cell tumors

• Giant cell reparative granuloma

• Extra-osseous masses of hematopoietic tissue

• Sarcoma (osteosarcoma or fibrosarcoma) - most dreaded complication. Occurs in < 1 % of all individuals with Paget disease, and in 5% to 10% of those with the severe polyostotic disease.

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Solution to Question 11:

Osteopetrosis does not belong to the clinical spectrum of hyperparathyroidism.

The features of hyperparathyroidism are as follows:

• Osteitis fibrosa cystica

• Osteopenia/osteoporosis

• Hyperuricemia and gout

• Pseudogout

• Increased production of calcitriol

• Dissecting osteitis and brown tumors

• Nephrolithiasis

• Hypophosphatemia

• Anemia

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Hyperparathyroidism leads to significant skeletal changes related to unabated osteoclast activity. Increased osteoclast activity is most prominent in cortical bone, but the medullary bone is not spared. Osteoclasts may tunnel into and dissect centrally along the length of the trabeculae, creating the appearance of railroad tracks, diagnostic of dissecting osteitis. Generalised osteoporosis may be seen in the phalanges, vertebrae, and proximal femur.

Brown tumor presents with bone loss leading to microfractures and secondary hemorrhages which causes influx of macrophages and ingrowth of reparative fibrous tissue. Generalized osteitis presents with increased bone cell activity, peri-trabecular fibrosis, and cystic brown tumors.

Solution to Question 12:

The given clinical picture is suggestive of acute pyogenic osteomyelitis. Staphylococcus aureus is the most common cause of culture-positive pyogenic osteomyelitis.

Osteomyelitis denotes inflammation of bone and marrow, almost always secondary to infection. Organisms may reach the bone by

• Hematogenous spread

• Extension from a contiguous site

• Direct implantation

The common causative organisms include:

• Staphylococcus aureus - the most common cause overall

• Pseudomonas aeruginosa - most common cause in IV drug abusers

• Salmonella - common in patients of sickle cell anemia

• Haemophilus influenzae - was a common causative organism in children, less common now due to vaccination

• Streptococcus pyogenes - most common in neonates

• Escherichia coli, Klebsiella- most common cause in patients with genitourinary tract infections

Solution to Question 13:

Salmonella enteritidis is commonly implicated in osteomyelitis in patients with sickle cell anemia.

The common causative organisms include:

• Staphylococcus aureus - the most common cause overall

• Pseudomonas aeruginosa - most common cause in IV drug abusers

• Salmonella - most common in patients of sickle cell anemia

• Haemophilus influenzae - was a common causative organism in children, less common now due to vaccination

• Streptococcus pyogenes - neonates

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• Escherichia coli, Klebsiella- most common cause in patients with genitourinary tract infections

Solution to Question 14:

The patient is most likely suffering from TB osteomyelitis. Brodie's abscess is not a complication of this condition.

In tuberculous osteomyelitis, weight-bearing joints - spine (Pott's disease), hips, and knees, are most commonly affected.

Complications of tuberculous osteomyelitis include:

• Scoliosis or kyphosis (gibbus)

• Neurologic deficits secondary to spinal cord and nerve compression leading to paraplegia -

• Tuberculous arthritis

• Sinus tract formation

• Psoas abscess - may be due to paravertebral “cold” abscess

• AA amyloidosis

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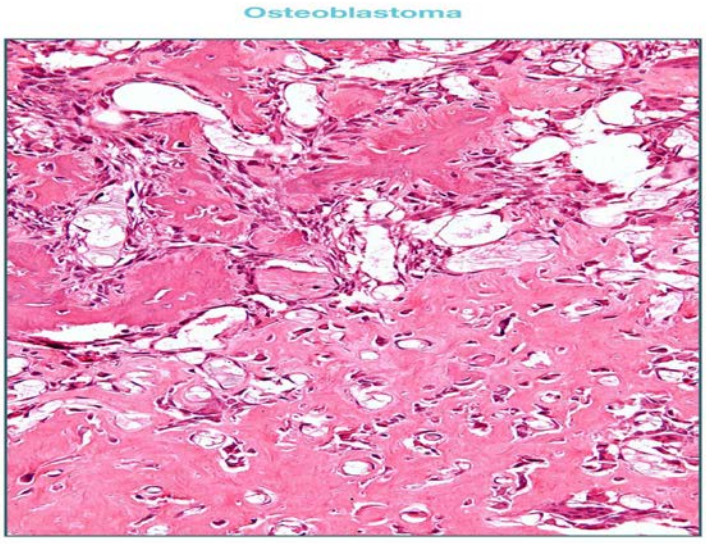
Solution to Question 15:

The given clinical scenario is suggestive of osteoblastoma.

Histopathology shows well-circumscribed lesions composed of randomly interconnecting trabeculae of woven bone that are prominently rimmed by a single layer of osteoblasts. Stroma surrounding the neoplastic bone consists of loose connective tissue that contains many dilated and congested capillaries.

The image below shows the histopathological findings in osteoblastoma.



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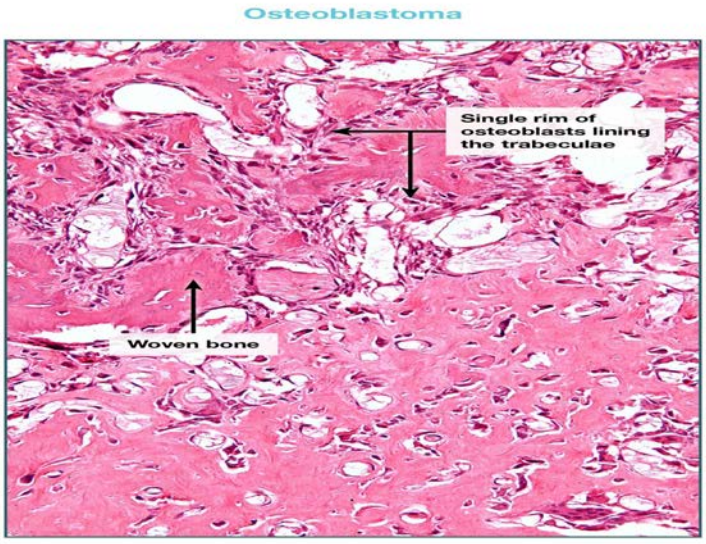

Osteoid osteoma and osteoblastoma are benign bone-producing tumors that have identical histologic features. The differentiating features between them are given below:

Osteoid osteoma	Osteoblastoma
Less than 2 cm in diameter	Larger than 2 cm in diameter
Predilection for the appendicular skeleton	involves the posterior spine (laminae and pedicles)
Thick rind of reactive cortical bone is seen on radiography	Usually, no marked bony reaction is seen on radiography
Pain that is relieved by aspirin and other non-steroidal anti-inflammatory agents	Pain which is unresponsive to aspirin

Solution to Question 16:

The given history and classic sunburst appearance on the X-ray are highly suggestive of osteosarcoma. Mutation of p53 (Li-Fraumeni syndrome) is associated with a greater risk of sarcomas, particularly osteosarcoma.

The image given below shows sunburst pattern seen in osteosarcoma.

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Option A: Translocation (X;18) is characteristic of synovial sarcoma.

Option B: Translocation (12;16) is characteristic of myxoid liposarcoma.

Option D: 1p rearrangements are characteristic of conventional chondrosarcoma.

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Solution to Question 17:

Osteosarcomas usually arise in the metaphyseal region of the long bones of the extremities. It commonly occurs in the knee (i.e., distal femur or proximal tibia).

The most common subtype is primary, intramedullary, osteoblastic, and high grade. It is a malignant tumor in which the cancerous cells produce an osteoid matrix or mineralized bone. It occurs in all age groups but has a bimodal age distribution.

The formation of fine lace-like neoplastic bone by the tumor cells is diagnostic histopathologically of osteosarcoma as shown below.

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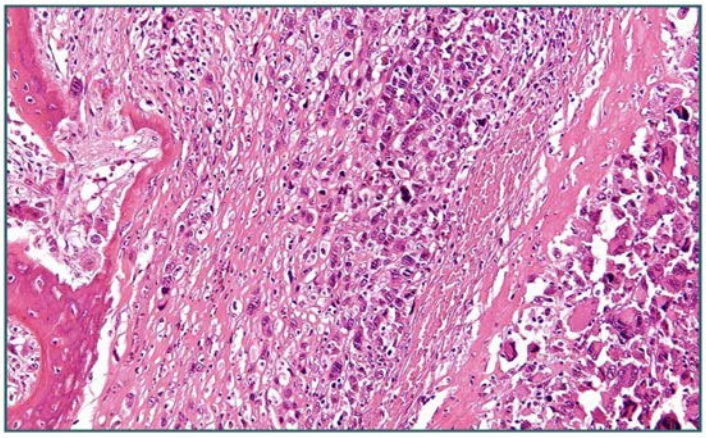
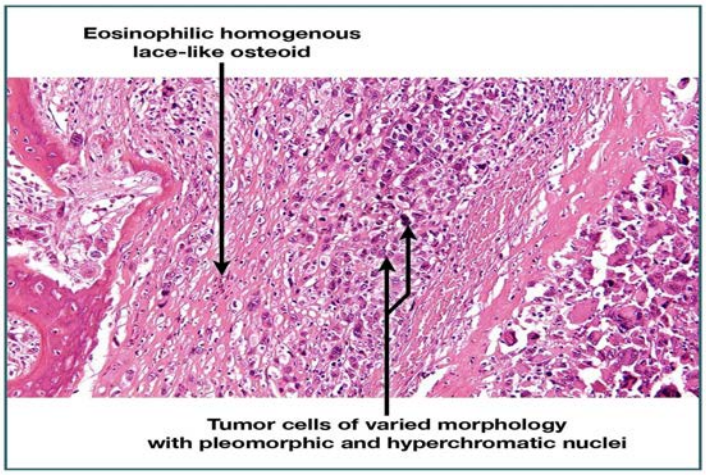
Osteosarcoma



Osteosarcoma



Radiography shows a large destructive, mixed lytic and blastic mass with infiltrative margins, which breaks through the cortex and lifts the periosteum, resulting in reactive periosteal bone formation. The triangular shadow between the cortex and raised ends of the periosteum, known radiographically as the Codman triangle, is characteristic of osteosarcoma. This is shown in the radiograph below.

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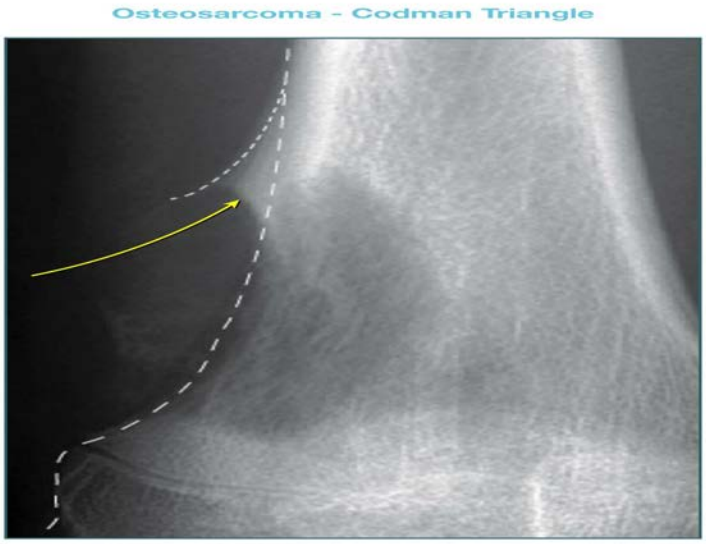

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Solution to Question 18:

Ollier disease and Maffucci syndrome are nonhereditary disorders characterized by multiple enchondromas. Maffucci syndrome is, in addition, distinguished by the presence of spindle-cell hemangiomas.

Enchondromas are benign tumors of hyaline cartilage that usually occur in bones of enchondral origin. They are usually diagnosed in individuals 20 to 50 years of age. They present as solitary metaphyseal lesions of tubular bones of the hands and feet.

The radiographic features consist of circumscribed lucencies with central irregular calcifications, a sclerotic rim, and an intact cortex. They are usually smaller than 3 cm. They are gray-blue and translucent, composed of well-circumscribed nodules of hyaline cartilage containing cytomorphologically benign chondrocytes.

The enchondromas in Ollier disease and Maffucci syndrome are sometimes more cellular than sporadic enchondromas and exhibit cytologic atypia, making them more difficult to distinguish from chondrosarcomas.

The image below displays the histopathological picture of an enchondroma showing lobules of hyaline cartilage encased by bone and covered by perichondrium (fibrous tissue).

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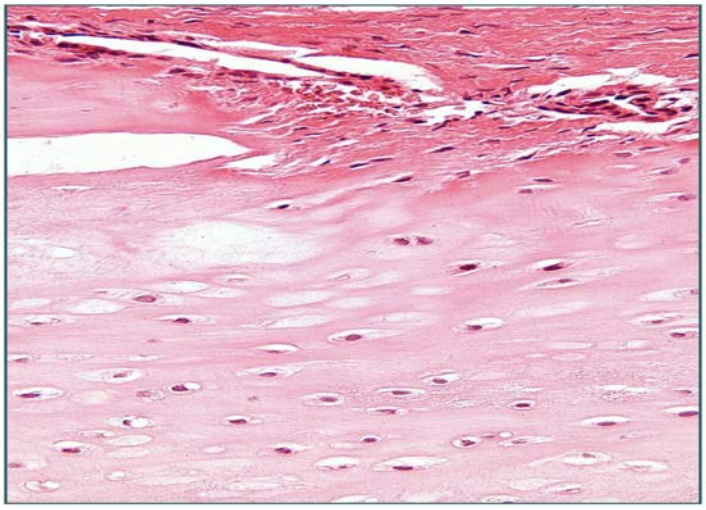
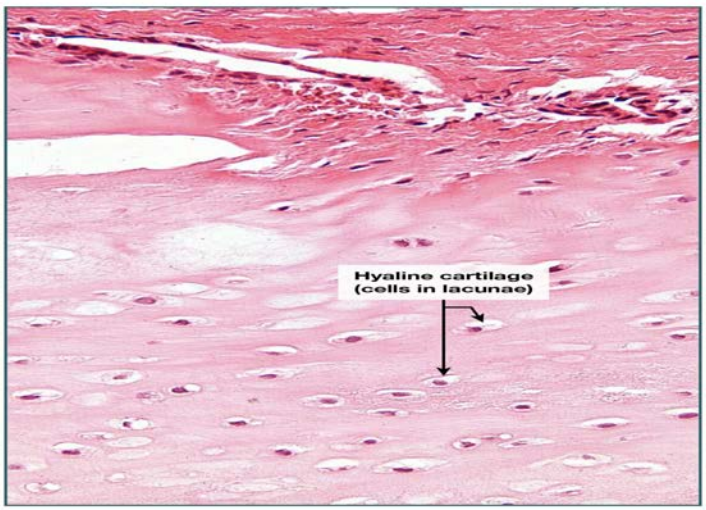
Enchondroma



Enchondroma



Solution to Question 19:

The clear cell and the mesenchymal variants of chondrosarcoma occur in younger patients (teens or 20s).

Chondrosarcomas are malignant tumors that produce cartilage. They commonly arise in the axial skeleton, especially the pelvis, shoulder, and ribs.

They are subclassified histologically as following variants:

• Conventional (hyaline cartilage producing) - 90% cases

• Clear cell

• Dedifferentiated

• Mesenchymal

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In multiple hereditary exostosis, osteochondromas can progress to chondrosarcoma. Increased thickness of the cartilage cap has been reported as an indicator of potential malignancy. The average age of secondary chondrosarcoma is younger than patients with primary tumors.

Solution to Question 20:

Osteochondromas, multiple enchondromas, and synovial chondromatosis can progress to become chondrosarcoma.

The average age of patients with secondary chondrosarcoma is 35 years (less than that of those with primary tumors). These tumors most commonly affect the pelvic bones. The increased thickness of the cartilage cap (normally 1–3 mm) is considered an indicator of potential malignancy.

Multiple enchondromas in the setting of Ollier's disease or Maffucci's syndrome carry a significantly higher risk of transformation to secondary chondrosarcoma than solitary enchondromas. Histological findings of abundant myxoid change, cyst formation, and permeation of existing trabeculae suggest malignancy.

Secondary malignancy in synovial chondromatosis has been reported, but it is rare.

Solution to Question 21:

The given clinical scenario is suggestive of Ewing sarcoma. It arises in the diaphysis of long bones, especially the femur and the flat bones of the pelvis.

Ewing sarcoma follows osteosarcoma as the second most common group of bone sarcomas in children. It generally affects patients < 20 years. Boys are affected slightly more frequently than girls. Usually, the tumor arises in the diaphysis of long tubular bones, especially the femur and the flat bones of the pelvis.

Fever, elevated sedimentation rate, anemia, and leukocytosis may be seen. Plain radiographs show a destructive lytic tumor with permeative margins that extend into the surrounding soft tissues. The characteristic periosteal reaction produces layers of reactive bone deposited in an onion-skin fashion. It arises in the medullary cavity and usually invades the cortex, periosteum, and soft tissue.

On microscopy, sheets of uniform, small, round cells with scant cytoplasm are seen, which may appear clear because they are rich in glycogen. The presence of Homer–Wright rosettes indicates a greater degree of neuroectodermal differentiation.

The image given below shows the histopathological findings in Ewing sarcoma.

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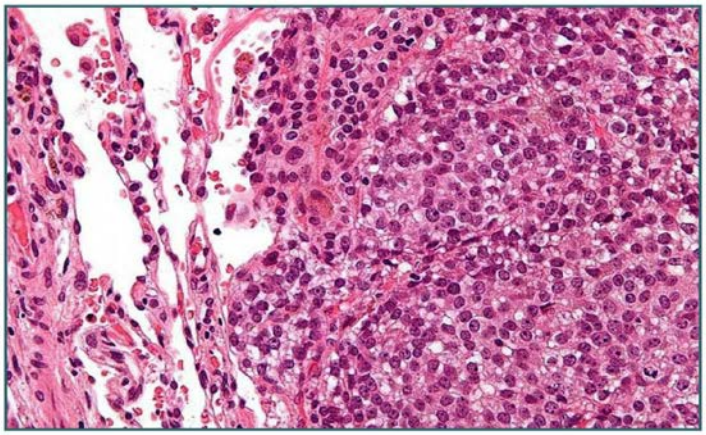
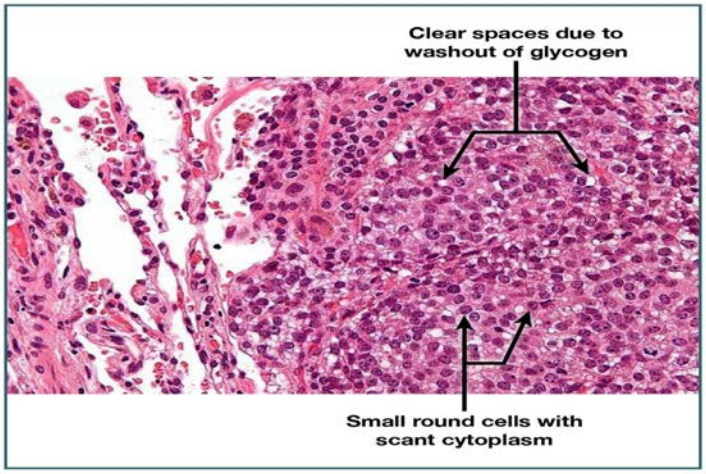
Ewing Sarcoma



Ewing Sarcoma



Most Ewing sarcoma family tumors contain an (11;22) (q24;q12) translocation. Variant translocations fuse the EWS to other members of the ETS transcription factor family. CD99(MIC2), FLI1, and NSE would be positive in ES/PNET.

Solution to Question 22:

The given clinical scenario is suggestive of osteoclastoma/ giant-cell tumor (GCT) of bone.

GCT is a relatively uncommon benign, but locally aggressive, neoplasm that usually arises in individuals in their 20s to 40s. The neoplastic cells express high levels of RANKL. It promotes the proliferation of osteoclast precursors and their differentiation into mature osteoclasts via RANK expressed by these cells.

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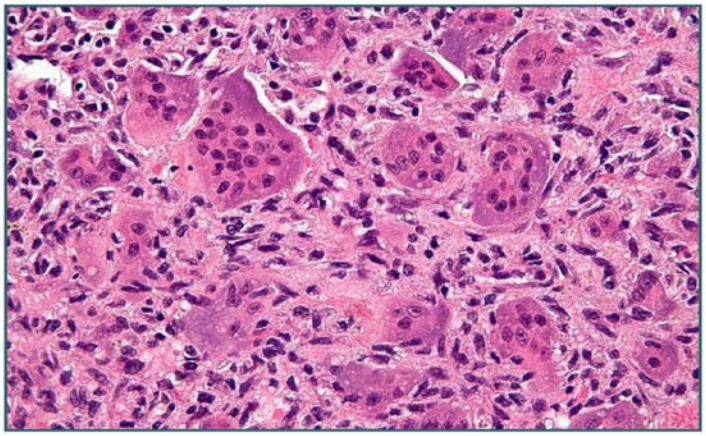
GCTs arise in the epiphysis but may extend into the metaphysis. The majority arise around the knee (distal femur and proximal tibia). Most are solitary, multicentric tumors in the distal extremities. The tumors destroy the overlying cortex, producing a bulging soft tissue mass delineated by a thin shell of reactive tissue.

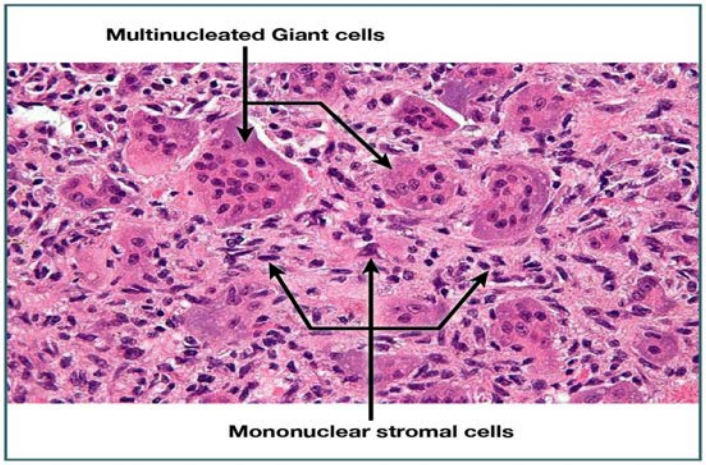
Histopathologically, sheets of uniform oval mononuclear cells and numerous osteoclast-type giant cells are seen with 100 or more nuclei. Necrosis and mitotic activity may be prominent.

The image given below shows the histopathological findings seen in osteoclastoma.

Osteoclastoma



Osteoclastoma



Typically, they are treated with curettage, but 40% to 60% recur locally.

Up to 4% of tumors metastasize to the lungs, but these sometimes spontaneously regress and they are rarely fatal. The RANKL inhibitor, denosumab, has shown promise as adjuvant therapy in GCT.

Note: The E mnemonic for GCT:

• Epiphyseal

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- Eccentric
- Egg-shell crackling
- Expansile

Solution to Question 23:

The given clinical scenario is suggestive of an aneurysmal bone cyst.

It affects all age groups, but generally occurs during the first 2 decades of life and has no sex predilection. It usually occurs in the metaphysis of long bones and the posterior elements of vertebral bodies.

This is a tumor characterized by multiloculated blood-filled cystic spaces separated by septae, composed of multinucleated osteoclast-like giant cells and reactive woven bone. Radiographically, an aneurysmal bone cyst is seen as an eccentric, expansile, lesion with well-defined margins. Most lesions are completely lytic and often contain a thin shell of reactive bone at the periphery.

The spindle cells of aneurysmal bone cyst frequently demonstrate rearrangements of chromosome 17p13, leading to USP6 overexpression.

The majority of secondary aneurysmal bone cysts arise in association with:

- Benign neoplasms
- Giant-cell tumor of the bone (most common)
- Chondroblastoma
- Osteoblastoma
- Fibrous dysplasia
- Osteosarcoma

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Solution to Question 24:

Prostatic adenocarcinoma is associated with predominantly osteoblastic secondaries to the bones (vertebral column).

The radiographic appearance of bone metastases may be purely lytic (bone destroying), purely blastic (bone-forming), or mixed lytic and blastic. Most cancers are associated with predominantly one pattern or the other.

Parathyroid hormone-related protein (PTHrP) and transforming growth factor-° (TGF-°) are implicated in osteolytic secondaries, while proteins such as endothelin-1 and morphogenetic proteins are implicated in osteoblastic lesions.

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Joints and soft tissue pathology

Question 1:

A 77-year-old woman presents with pain and limited movement of the left hip and knee for 10 years. The pain has increased in severity in the past 1 year. The x-ray of the hip is given below. Laboratory tests do not show RF or ANA in her serum. Which of the following is the most likely diagnosis?

a) Ankylosing spondylitis

b) Rheumatoid arthritis

c) Osteoarthritis

d) Reactive arthritis

Question 2:

A 28-year-old woman presents with complaints of joint pain and progressive loss of joint motion. On examination, symmetric joint swelling of the hands is seen. A subcutaneous nodule is seen over her right forearm. Microscopy of the excised nodule shows the findings given in the image below. Which of the following lab findings will be seen in this patient?

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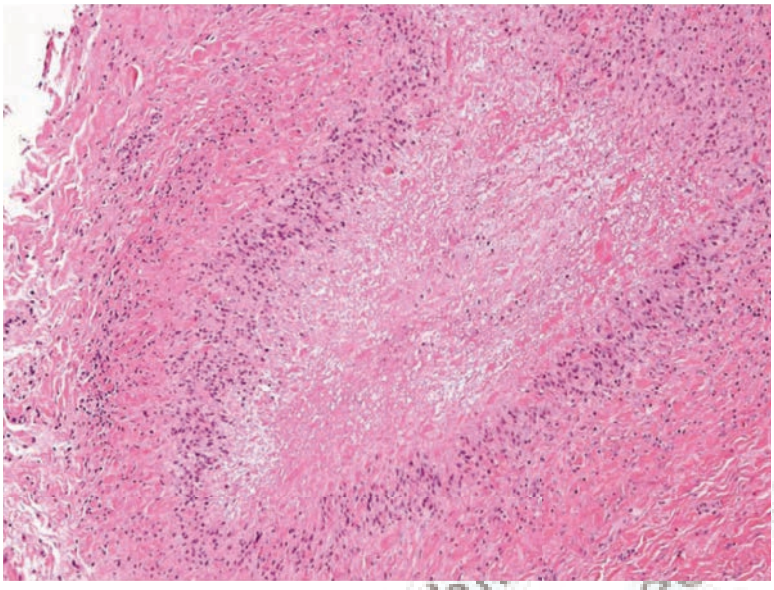

a) Positive Borrelia-Burgdorferi serologic test

b) Uric acid crystals in joint aspirate

c) Serum positive for rheumatoid factor

d) Calcium pyrophosphate crystals in joint aspirate

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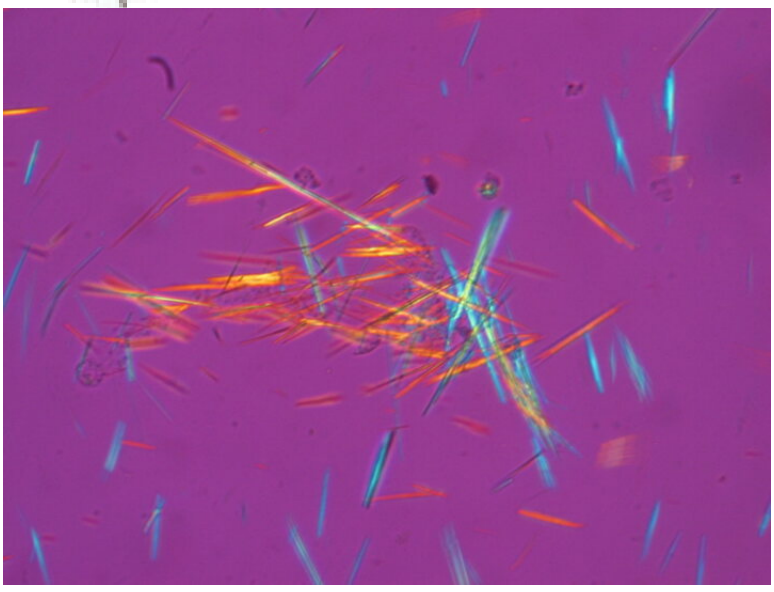
Question 3:

An obese 35-year-old man with renal failure presents with excruciating joint pain in the right knee. It is associated with localized hyperemia. Joint aspiration is done which shows dense neutrophilic infiltrate and the following finding under polarised light. Which of the following is the most likely diagnosis?



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a) Rheumatoid arthritis

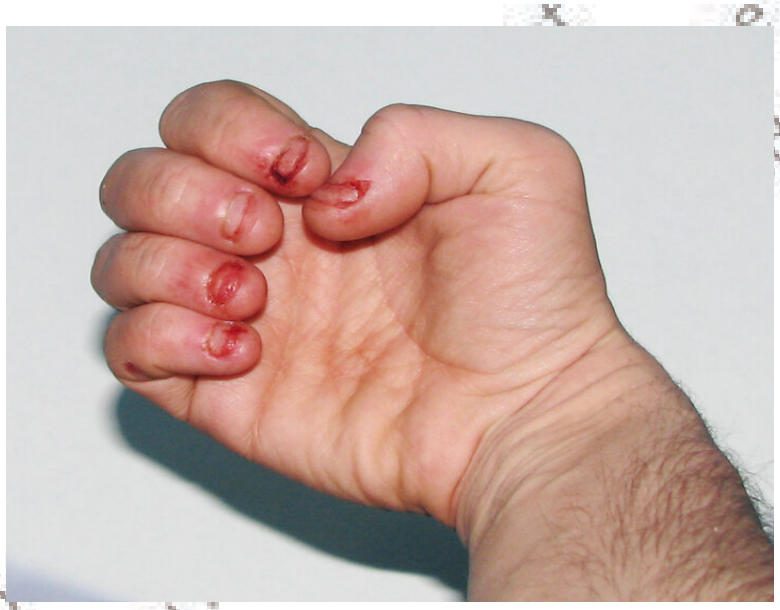
b) Gout

c) Ankylosing spondylitis

d) Septis arthritis

Question 4:

A 3-year-old child with knee pain is found to have uric acid crystal deposition in his joints. On examination, excessive nail-biting is seen as shown below. Congenital deficiency of which of the following enzyme is responsible for this condition?



a) Xanthine oxidase

b) Hypoxanthine-guanine phosphoribosyltransferase

c) Adenosine deaminase

d) PRPP amidotransferase

Question 5:

A 50-year-old patient presents with left knee pain, redness, and swelling for 3 days. Joint aspiration is performed and microscopic findings under polarised light are given in the image below. What is the most likely diagnosis?

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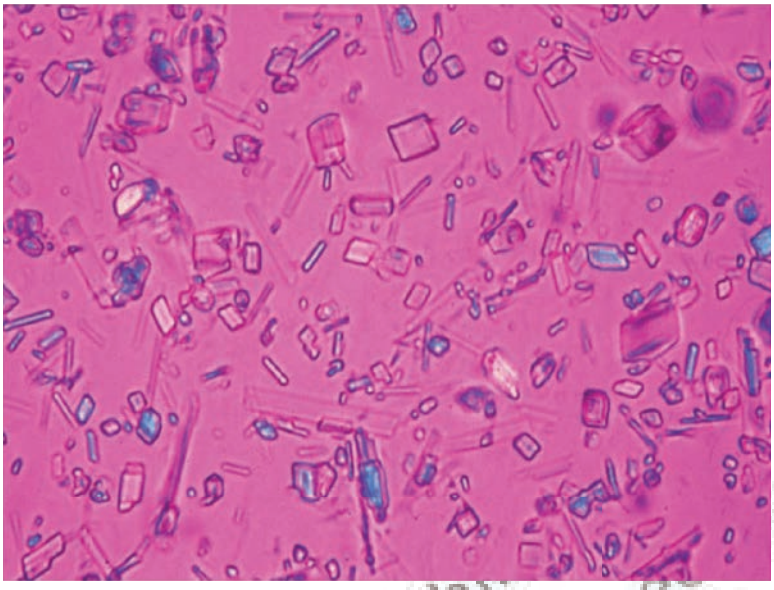

a) Psoriatic arthritis

b) Ankylosing spondylitis

c) Gout

d) Pseudogout

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Question 6:

Which of the following statements is not true about liposarcoma?

a) Amplification of 12q13-q15 is characteristic of well differentiated liposarcoma.

b) The key gene in the amplified region of chromosome 12q is MDM2.

c) The pleomorphic variant is usually indolent and rarely metastasizes.

d) Myxoid liposarcoma shows delicate 'chicken-wire' or 'crow's feet' vasculature.

Question 7:

A 50-year-old man presented with a retroperitoneal mass. Biopsy from the lesion is shown in the image below. Molecular analysis revealed t(12;16). What is the most likely condition?

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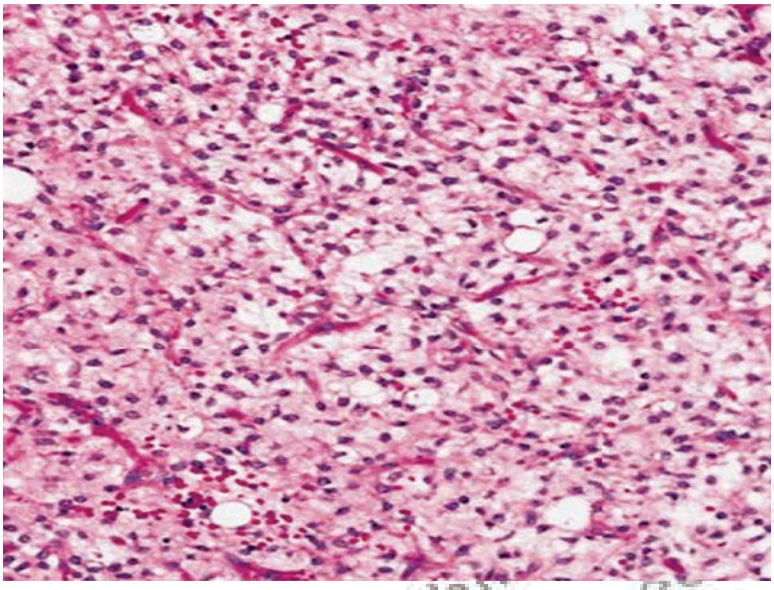

a) Myxoid Liposarcoma

b) Lipoma

c) Spindle lipoma

d) Polymorphic lipoma

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Question 8:

A 30-year-old man presented with a 2-cm, rapidly growing, painful, subcutaneous mass on his left arm. Microscopy revealed immature proliferation of fibroblasts and myofibroblasts with abundant mitotic figures. Immunohistochemistry was positive for vimentin and muscle-specific actin. What is the most likely diagnosis?

a) Pleomorphic sarcoma

b) Desmoid tumor

c) Nodular fasciitis

d) Fibrous histiocytoma

Question 9:

A 40-year-old man presented with a swelling in the floor of his mouth for 6 months. Intraoral examination revealed a soft, painless, non-tender mass in the left floor of the mouth, extending posteriorly into the supraglottic region. On histopathological examination, spider cells were seen. What is the most likely diagnosis?

a) Pleomorphic Adenoma

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b) Leiomyoma

c) Rhabdomyoma

d) Schwannoma

Question 10:

A 17-month-old girl presented with abnormal vaginal bleeding. A gynecological examination showed abnormal vaginal tissue protruding through the introitus. Histopathological analysis showed sheets of spindled cells in a myxoid stroma, which stained positive for desmin and Myo-D1. What is the most likely diagnosis?

a) Liposarcoma

b) Rhabdomyosarcoma

c) Ewing sarcoma

d) Osteosarcoma

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Question 11:

A 26-year-old man presents with left knee pain for 6 months. MRI shows a well-circumscribed 4-cm mass superior to the patella within soft tissue. Biopsy shows a biphasic pattern of spindle cells and epithelial cells forming gland-like structures. Karyotype shows t(X,18) translocation. What is the most likely diagnosis?

a) Leiomyosarcoma

b) Rhabdomyosarcoma

c) Synovial sarcoma

d) Dermatofibrosarcoma

Question 12:

A 13-year-old boy presents with fever, pain, and swelling in the left mid-thigh region. X-ray shows lamellated periosteal reaction resembling an onion skin. A biopsy from the lesion is shown in the image below. What is the most likely diagnosis?

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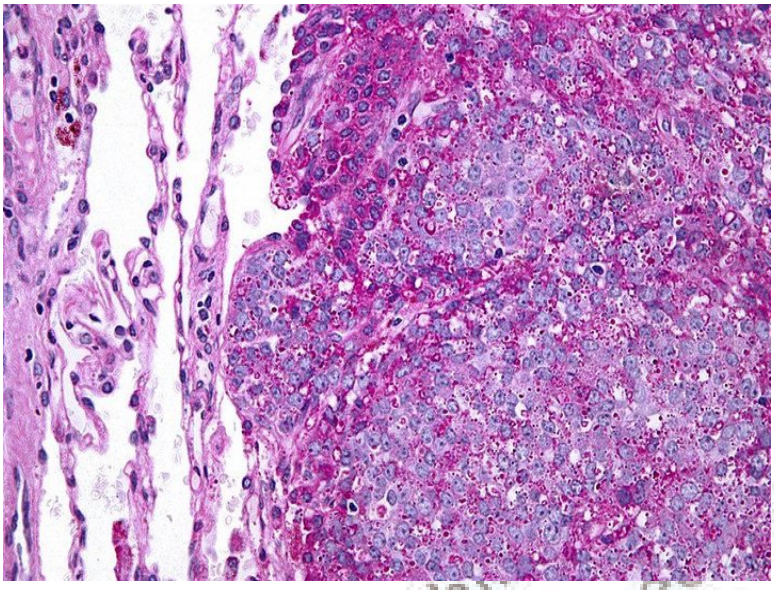

a) Desmoplastic small round cell tumour

b) Small cell osteosarcoma

c) Ewing's sarcoma

d) Embryonal Rhabdomyosarcoma

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Question 13:

Acid mucin is stained by _____.

a) PAS

b) Alcian blue

c) Masson trichrome

d) PTAH

Question 14:

A 36-year-old man with a history of blunt trauma to the left upper arm presents with swelling and redness 3 weeks later. There is a 4-cm mass in the outer aspect of the upper left arm in the soft tissue. Radiographs show a radiolucent center and surrounding irregular bone formation. What is the most likely diagnosis?

a) Chondroblastoma

b) Osteochondroma

c) Myositis ossificans

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d) Chondrocalcinosis

Question 15:

An 18-months-old child is brought to you with complaints of fever with chills and right knee pain for 3 days. On examination, his knee is warm and swollen with localized erythema. Joint aspiration showed 60,000 /mm3 WBCs. Which of the following organisms is the most likely cause of his condition?

a) Staphylococcus aureus

b) Haemophilus influenza

c) Neisseria gonorrhea

d) Streptococcus pyogenes

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Answer Key

Question No.	Correct Option
1	c
2	c
3	b
4	b
5	d
6	c
7	a
8	c
9	c
10	b
11	c
12	c
13	b
14	c
15	a

Detailed Explanations

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Solution to Question 1:

The x-ray image of the hip shows narrowing of the joint space and subchondral sclerosis which is diagnostic of osteoarthritis (OA), also called degenerative joint disease.

OA is the most common type of joint disease, which is characterized by the degeneration of joint cartilage. This results in structural and functional failure of synovial joints. Osteoarthritis can be classified into 2 types:

• Primary OA: Insidious onset, without apparent initiating cause, as an aging phenomenon

• Secondary OA: Predisposing conditions such as joint deformity, a previous joint injury, or an underlying systemic disease such as diabetes, ochronosis, hemochromatosis, or marked obesity.

The knees and hands are more commonly affected in women and the hips in men. OA lesions occur due to the degeneration of the articular cartilage and its disordered repair. Inflammatory cells are sparse, but cytokines and diffusible factors, particularly TGF-° (which induces matrix metalloproteinases), TNF, prostaglandins, and nitric oxide, have been implicated in OA.

Solution to Question 2:

The given clinical scenario is suggestive of rheumatoid arthritis. The patient's serum will test positive for rheumatoid factor.

Microscopy of the excised nodule shows a necrotizing granuloma with a central zone of fibrinoid necrosis surrounded by a prominent rim of activated macrophages and numerous lymphocytes and plasma cells.

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of autoimmune origin that principally attacks the joints, producing nonsuppurative, proliferative, and inflammatory synovitis. The inflammation progresses to the destruction of the articular cartilage and ankylosis of the joints.

In RA, the synovium contains germinal centers with secondary follicles and abundant plasma cells, which produce antibodies, some are autoantibodies. Many of the autoantibodies produced in the lymphoid organs are specific for citrullinated peptides (CCPs). 80% of patients have serum IgM or IgA autoantibodies that bind to the Fc portions of their own IgG. These autoantibodies are called rheumatoid factor and may also deposit in joints as immune complexes

The characteristic histologic features of RA include:

• Synovial cell hyperplasia and proliferation

• Dense inflammatory infiltrates

• Increased vascularity due to angiogenesis

• Fibrinopurulent exudate on the synovial and joint surfaces

• Osteoclastic activity in underlying bone

• Subcutaneous nodule: necrotizing granulomas with a central zone of fibrinoid necrosis surrounded activated macrophages, lymphocytes, and plasma cells

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This altogether leads to a mass of edematous synovium called pannus, which grows over the articular cartilage and causes its erosion.

Solution to Question 3:

The most likely diagnosis is gout. Aspirate from the joint shows dense neutrophilic infiltrate and crystals that are long, slender, needle-shaped, and negatively birefringent.

Gout is marked by transient attacks of acute arthritis initiated by crystallization of monosodium urate (MSU) within and around joints. This results in the production of cytokines that recruit leukocytes. Macrophages phagocytose the MSU and the inflammasome activates caspase-1, which is involved in the production of some biologically active cytokines.

The distinctive morphologic changes in gout are acute arthritis, chronic tophaceous arthritis, tophi in various sites, and gouty nephropathy. Tophi are the pathognomonic hallmark of gout. These are large aggregations of urate crystals surrounded by an intense inflammatory reaction of foreign body giant cells which may appear in the articular cartilage, ligaments, tendons, bursae, earlobes, fingertips, or kidneys.

Gouty nephropathy refers to the renal complications caused by MSU crystals or tophi in the renal medullary interstitium or tubules. Complications include uric acid nephrolithiasis and pyelonephritis.

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Solution to Question 4:

The given clinical scenario is suggestive of Lesch-Nyhan syndrome. In this condition, there is a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

Lesch–Nyhan syndrome is charecterised by neurological and behavioral abnormalities such as lip and finger biting and head banging.

It also causes the overproduction of uric acid, leading to gouty arthritis and impaired kidney function. It is classified as secondary gout.

Solution to Question 5:

The given clinical scenario is suggestive of calcium pyrophosphate crystal deposition disease (CPPD), also known as pseudo-gout and chondrocalcinosis.

The image shows aspirated crystals which are rhomboid, 0.5 to 5 µm in the greatest dimension, and positively birefringent (yellow).

It usually occurs in individuals older than 50 years of age and becomes more common with old age.

CPPD is classified into sporadic (idiopathic), hereditary, and secondary types. It is caused by germline mutations in the pyrophosphate transport channel. The secondary form is associated

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with

• Previous joint damage

• Hyperparathyroidism

• Hemochromatosis

• Hypomagnesemia

• Hypothyroidism

• Ochronosis

• Diabetes

Inflammation is usually milder than in gout. CPPD may produce acute, subacute, or chronic arthritis that can be confused with osteoarthritis or rheumatoid arthritis. The joint involvement may be monoarticular or polyarticular; the knees, followed by the wrists, elbows, shoulders, and ankles, are most commonly affected.

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Solution to Question 6:

The pleomorphic variant of liposarcoma is usually aggressive and frequently metastasizes.

Liposarcoma is one of the most common sarcomas of adulthood seen mainly in people in their 50s to 60s in the deep soft tissues of the proximal extremities and in the retroperitoneum.

Amplification of 12q13-q15 and t(12;16) are characteristic of well-differentiated and myxoid liposarcomas, respectively. One of the key genes in the amplified region of chromosome 12q is MDM2, which is a potent inhibitor of p53.

Well-differentiated liposarcoma contains adipocytes with scattered atypical spindle cells. Myxoid liposarcoma contains an abundant basophilic extracellular matrix, arborizing capillaries ("chicken-wire" or "crow's feet" vasculature), and primitive cells reminiscent of fetal fat.

The well-differentiated variant is relatively indolent, while the myxoid/round cell type is intermediate in its malignant behavior.

Solution to Question 7:

The given clinical scenario is suggestive of myxoid liposarcoma.

The image shows abundant ground substance, with branching capillaries and a few immature adipocytes.

Liposarcoma is the most common sarcoma in adults and is usually seen in the 5th to 6th decade of life. They commonly occur in the deep soft tissues of the proximal extremities and in the retroperitoneum.

Histologically the liposarcomas are divided into three subtypes:

• Well-differentiated liposarcoma: It consists of mature adipocytes and scattered spindle cells with hyperchromatic nuclei. It is associated with amplification of 12q13-q15.

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• Myxoid liposarcoma: It contains abundant basophilic extracellular matrix with branching capillaries. Few immature adipocytes are found scattered within the matrix. It is associated with t(12;16).

• Pleomorphic liposarcoma: It consists of sheets of anaplastic cells with bizarre nuclei and few immature adipocytes.

Among the three subtypes, the pleomorphic liposarcoma is the most malignant and often metastasizes, while the well-differentiated is least malignant. Myxoid liposarcoma has intermediate malignancy behaviour.

Solution to Question 8:

The given clinical scenario is suggestive of nodular fasciitis.

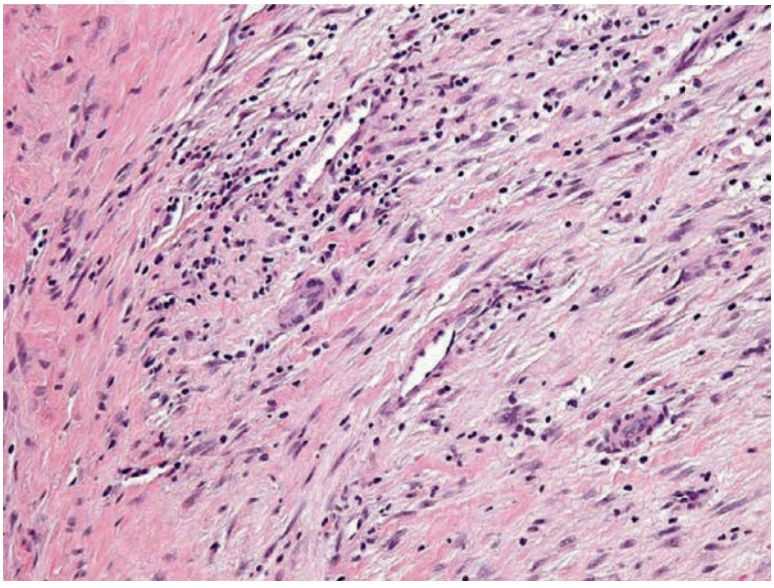
Nodular fasciitis is a self-limited fibroblastic and myofibroblastic proliferation that typically occurs in young adults in the upper extremity. Etiology is unclear but a history of trauma is present in approximately 25% of cases. The tumors grow rapidly over a period of several weeks, typically no larger than 3 cm. It typically regresses spontaneously and if excised, rarely recurs.

Microscopically, it is richly cellular and contains plump, immature-appearing fibroblasts and myofibroblasts, arranged randomly or in short fascicles reminiscent of tissue culture fibroblasts. A gradient of maturation from cellular, loose, and myxoid to organized and fibrous is typical. The cells vary in size and shape (spindle to stellate) and have conspicuous nucleoli; mitotic figures are abundant.

Immunohistochemistry shows positivity for vimentin, smooth muscle actin, and muscle-specific actin.

Desmoid tumours are firm and poorly demarcated masses which infiltrate the surrounding muscle, nerve and fat. Histologically, fibroblasts are arranged in long parallel fascicles amid dense collagen. (Option 2)

The image below shows the histopathological findings of nodular fasciitis.



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Solution to Question 9:

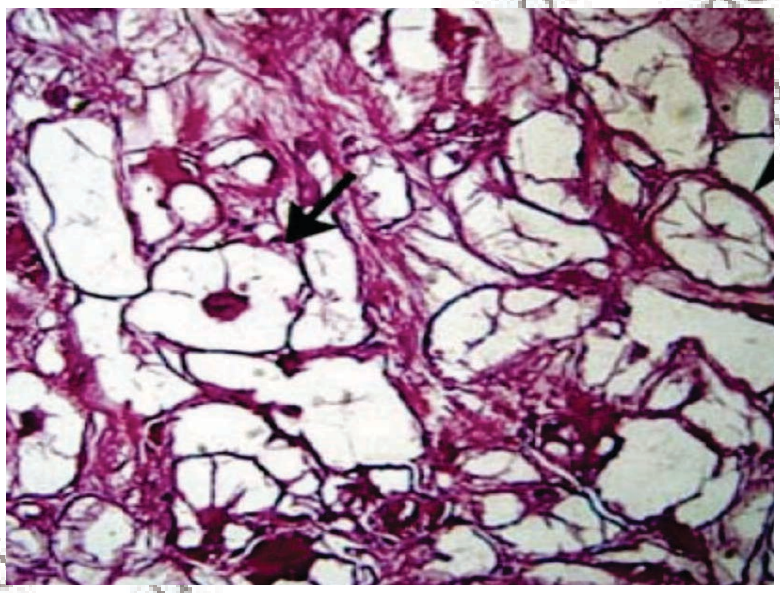
The given clinical scenario is suggestive of rhabdomyomas.

Rhabdomyoma is a benign neoplasm of skeletal muscle that mainly occurs in the head and neck region. Although the mass is usually asymptomatic, it may compress or displace the tongue or may cause partial obstruction of the pharynx.

Rhabdomyomas can be classified into cardiac (most common) or extracardiac.

Spider cells are seen in this condition. These are large, rounded, polygonal cells with glycogen vacuoles separated by strands of cytoplasm extending between the cell membrane and nucleus.

The image given below shows spider cells.



Solution to Question 10:

The given clinical scenario is suggestive of sarcoma botryoids, which is a variant of embryonal rhabdomyosarcoma. It is a malignant mesenchymal tumor with skeletal muscle differentiation.

Rhabdomyosarcomas are the common soft tissue sarcomas of childhood and adolescence, classified into four subtypes: alveolar, embryonal, pleomorphic, and spindle-shaped/ sclerosing.

• Embryonal rhabdomyosarcoma: It contains sheets of both primitive round and spindled cells in a myxoid stroma. Sarcoma botryoids is a variant that occurs in the walls of hollow, mucosal-lined structures, such as the nasopharynx, common bile duct, bladder, and vagina.

• Alveolar rhabdomyosarcoma: consists of the network of fibrous septae that divide the cells into clusters or aggregates, creating a crude resemblance to pulmonary alveoli.

• Pleomorphic rhabdomyosarcoma - consists of large, sometimes multinucleated, bizarre eosinophilic tumor cells.

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• Spindle cell/sclerosing rhabdomyosarcoma - Consists of fusiform cells with vesicular chromatin arranged in long fascicles or in a storiform pattern.

On immunohistochemistry, they are positive for desmin, myoglobin, myogenin, MyoD1, and vimentin. Pleomorphic rhabdomyosarcoma is seen predominantly in adults.

The botryoid variant of embryonal rhabdomyosarcoma has the best prognosis, while the pleomorphic subtype is often fatal.

Solution to Question 11:

The given clinical scenario is suggestive of synovial sarcoma.

It can be present in locations (chest wall, head, and neck) that lack synovium. Most lesions occur in people in their 20s to 40s. Patients usually present with a deep-seated mass that has been present for several years.

Most synovial sarcomas show a characteristic chromosomal translocation t(x;18)(p11;q11) producing SS18-SSX1, SS18-SSX2, or SS18-SSX4 fusion genes.

They are morphologically classified into monophasic or biphasic:

• Monophasic synovial sarcoma consists of uniform spindle cells with scant cytoplasm and dense chromatin growing, in short, tightly packed fascicles.

• Biphasic type consists of a spindle cell component with gland-like structures composed of cuboidal to columnar epithelioid cells. Tumor cells, especially in the biphasic type, are positive for epithelial markers (e.g., keratins), differentiating them from most of the other sarcomas.

Solution to Question 12:

The given clinical scenario is suggestive of Ewing's sarcoma.

It is a malignant bone tumor that occurs primarily in children and young adults, in the age group of 10-20 years. It usually affects the long bones, such as the femur, tibia, or humerus. Occasionally, the tumor may begin in the muscles or soft tissues (extraosseous Ewing's sarcoma).

Microscopically, solid sheets of small uniform round cells with PAS-positive magenta pink colored cytoplasm are characteristic of Ewing's Sarcoma/PNET. The cells show PAS positivity due to the presence of large amounts of cytoplasmic glycogen. This is an important feature for the differential diagnosis of Ewing's with other small round cell tumors.

Solution to Question 13:

Acid mucin is stained by Alcian blue.

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Solution to Question 14:

The given clinical scenario is suggestive of myositis ossificans (MO).

It is a pseudo-inflammatory tumor that originates from skeletal muscle and corresponds to a heterotopic, metaplastic, nonmalignant bone tumor.

It is a highly inflammatory, rapidly growing, and painful muscular mass, which is seen following muscular trauma. The late stage is characterized by a typical zonal pattern (zonal phenomenon). It consists of three zones:

• Innermost zone: made of proliferating fibroblasts and myofibroblasts with areas of hemorrhage and necrosis

• Intermediate zone: contains osteoblasts with the immature osteoid formation

• Peripheral zone: the mature bone

Solution to Question 15:

The given clinical scenario is suggestive of septic arthritis. The most common organism implicated in this condition in children < 2 years is Staphylococcus aureus.

Since the advent of the Haemophilus influenzae vaccine, the predominant causes of septic arthritis among children <5 years of age have been S. aureus, Streptococcus pyogenes (group A Streptococcus), and (in some centers) Kingella kingae.

Causative organism of bacterial arthritis:

Note: H. influenza arthritis predominates in children younger than 2 years of age, particularly in areas with low Hib immunization rates, but it is not the most common organism.

Age group /Condition	Most common Organism
Overall	S. aureus
Gram-negative bacteria in yo ung children	Kingella kingae
Adolescents	Neisseria gonococcus
After surgical procedure	Staphylococcus aureus
Prosthetic joints	Coagulase-negative Staphyloc occi
Sickle-cell disease	Salmonellasp
Complement deficiency	Neisseria gonococcus

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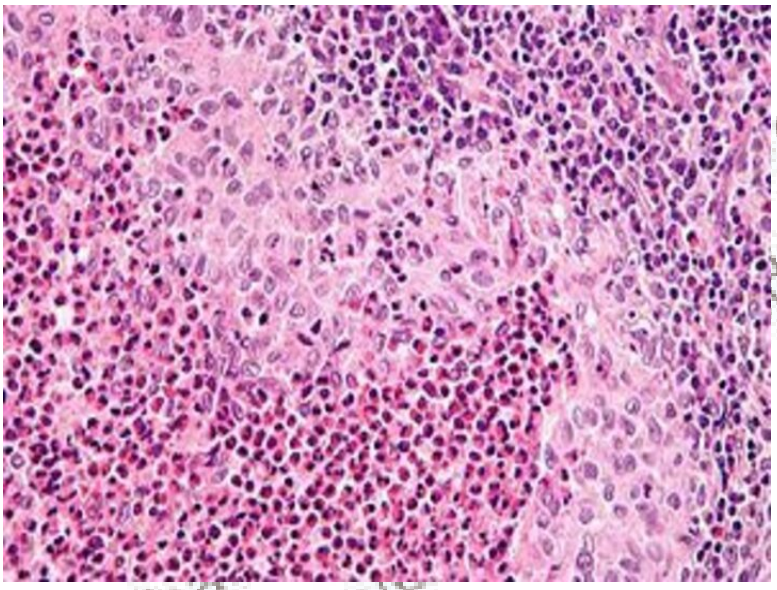
Skin pathology

Question 1:

A child was brought with complaints of an eczematous lesion on the scalp. A biopsy from the lesion was taken. The cells stained positively for CD1a and CD207. What are these cells?



a) Dendritic cell

b) T-lymphocyte

c) Keratinocyte

d) Neuroendocrine cell

Question 2:

An elderly man presented with a rapidly growing lesion as shown below. A biopsy from this lesion showed malignant cells. The immunohistochemical staining was positive for CK-20. The tumor cells in this condition originated from which of the following cells?

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a) T-lymphocytes

b) Melanocytes

c) Langerhans cells

d) Merkel cells

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Question 3:

A histopathological examination of melanocytic nevus in a patient showed nests of large round pigmented cells superficially. At the deeper extent of the lesion, it showed fascicles of non-pigmented cells resembling neural tissue. What does this signify?

a) Benign nature of nevus

b) Coexisting nerve tumor

c) Risk of malignant transformation into melanoma

d) Neural invasion of tumor cells

Question 4:

Which of the following driver mutations is not associated with given skin malignancy?

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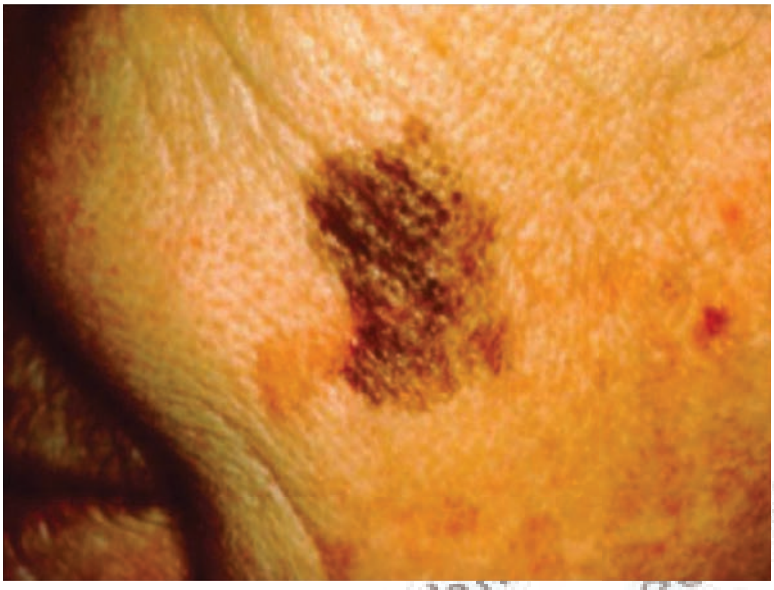

a) Mutations in cell cycle regulators

b) Mutations in receptor tyrosine kinase signalling pathway

c) Mutations that activate telomerase

d) Mutations in hedgehog signalling pathway

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Question 5:

What is the most common type of melanoma?

a) Nodular melanoma

b) Acral lentiginous melanoma

c) Lentigo maligna melanoma

d) Superficial spreading melanoma

Question 6:

An elderly European man presented with a slowly progressing lesion on his scalp for 2 years. Immunohistochemistry revealed tumor cells that were positive for the S-100 marker. All are favorable prognostic factors for his condition except:

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a) Thin tumor depth

b) Few mitoses (< 1 per mm2)

c) Brisk tumor infiltrating lymphocyte response

d) Regression

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Question 7:

Which of the following conditions is not associated with FGFR3 mutations?

a) Seborrheic keratosis

b) Acanthosis nigricans

c) Thanatophoric dwarfism

d) Melanomas

Question 8:

A patient presented with multiple, small, pink nodular growths on the temples. A biopsy from the lesion showed the following. What is the likely diagnosis?

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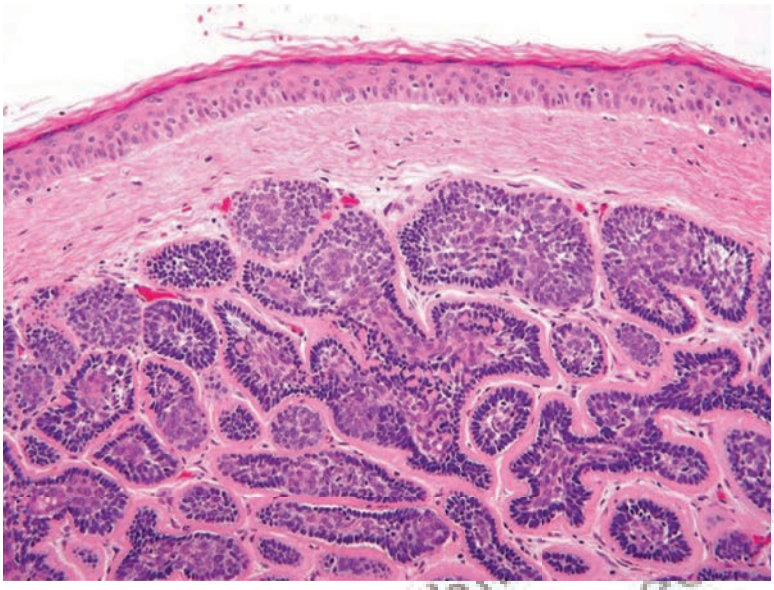

a) Trichilemmoma

b) Cylindroma

c) Basal-cell carcinoma

d) Spiradenoma

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Question 9:

Histopathological examination of a biopsy taken from a rough, scaly macular lesion from a patient's forearm showed neoplastic dyskeratosis. What is the probable diagnosis?

a) Darier's disease

b) Warty dyskeratoma

c) Familial benign pemphigus

d) Actinic keratosis

Question 10:

A biopsy from a chronic oropharyngeal lesion of a patient showed the following. Which of the following is not a risk factor for developing this condition?

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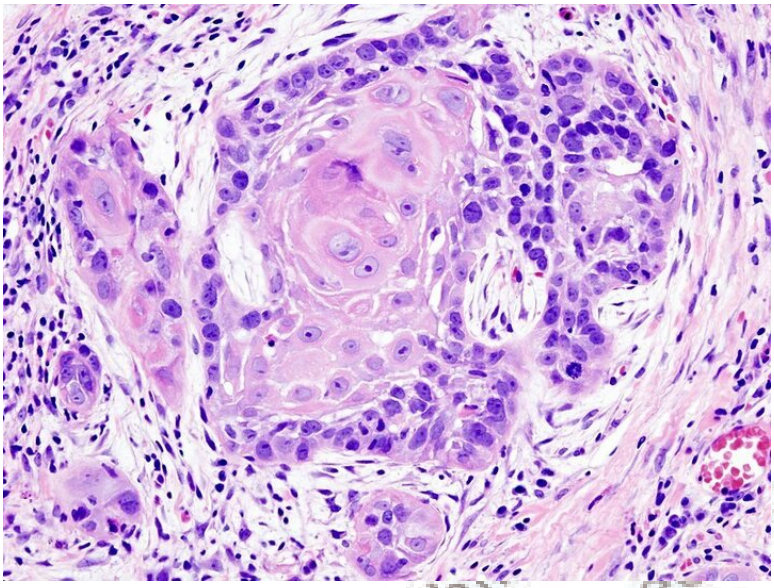

a) Exposure to UV light

b) Chronic ulcers

c) Ionising radiation

d) Epstein–Barr virus

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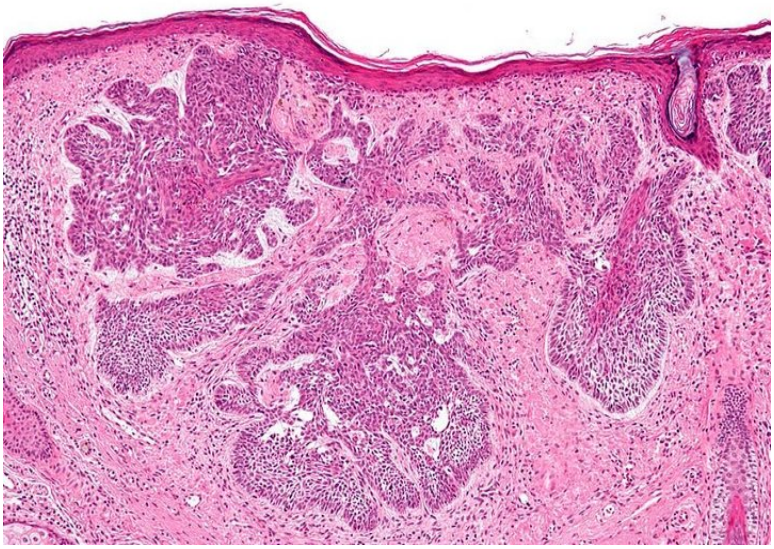
Question 11:

A 60-year-old man presents with a pearly papule over the face containing prominent dilated subepidermal blood vessels and surface ulceration. A histological picture of the tumor is shown below. All are true about the tumor except:



a) Incidence is increased in xeroderma pigmentosum

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b) Presence of multiple such tumors is seen in Gorlin syndrome

c) It may be multifocal

d) Metastasis is common

Question 12:

The clinical picture and a biopsy from the skin lesion of a patient are shown below. This condition is associated with which of the following?

a) Langerhans cell histiocytosis

b) Benign fibrous histiocytoma

c) Mycosis fungoides

d) Mastocytosis

Question 13:

A child was brought with urticarial lesions on the forearm. On examination, Darier's sign was positive. The cells responsible for this condition can be stained with all of the following except:

a) Masson–Fontana stain

b) Toluidine blue

c) Leder stain

d) CD 117

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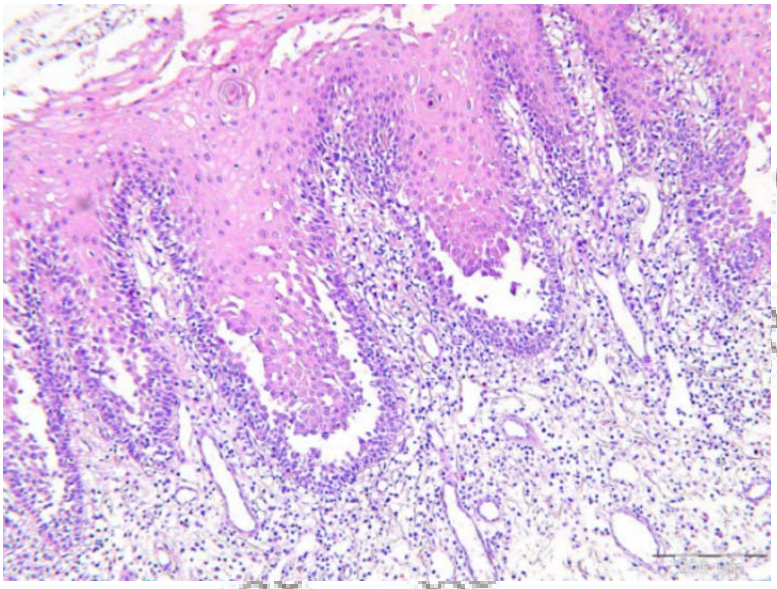
Question 14:

A 40-year-old woman presents with oral ulcers and bullae over the mucosa and skin. On examination, the bullae are flaccid and filled with clear fluid. Histopathology of the lesion shows the following. What is the most likely diagnosis?



a) Pemphigus vulgaris

b) Bullous pemphigoid

c) Dermatitis herpetiformis

d) Pemphigus foliaceus

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Question 15:

A 30-year-old woman presented with painful blisters on the skin and oral mucosa. Direct immunofluorescence is given below. Which of the following is false regarding the same?

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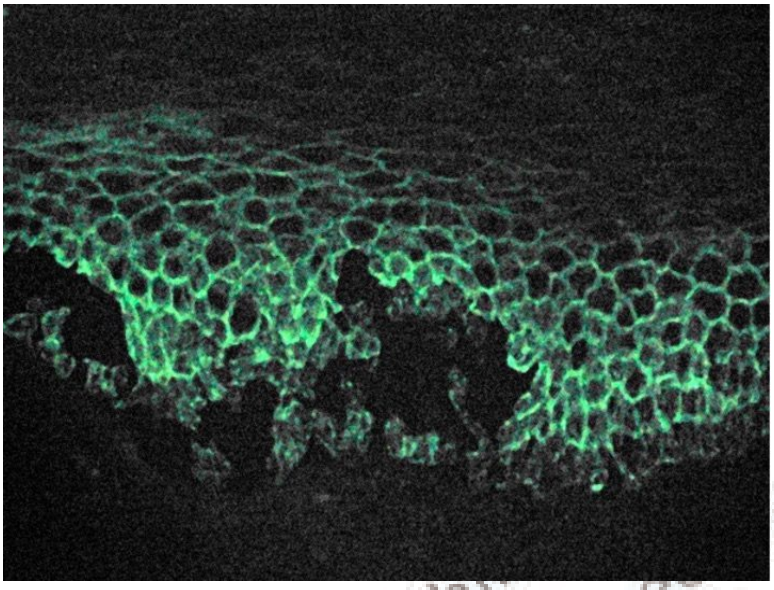

a) Antibodies against desmoglein 3

b) Antibodies against desmoglein 1

c) Suprabasal acantholytic blister is a characteristic feature

d) Antibodies against hemidesmosomes

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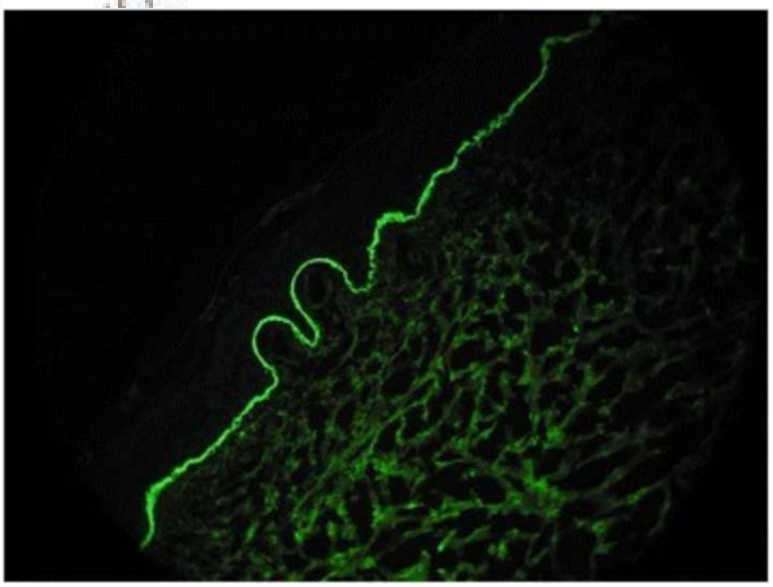
Question 16:

A 70-year-old woman presents with multiple tense itchy blisters on the trunk and thigh region. Histopathology demonstrates subepidermal, non-acantholytic blisters. Direct immunofluorescence for IgG and C3 shows the following. What is the most likely diagnosis?



a) Pemphigus vulgaris

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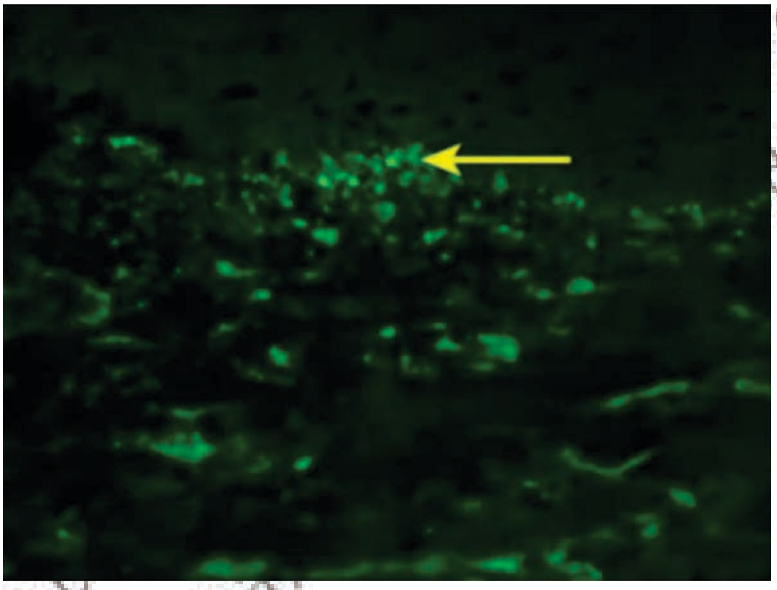
b) Dermatitis herpetiformis

c) Bullous pemphigoid

d) Pemphigus foliaceus

Question 17:

A 28-year-old man with gluten sensitivity presents with severely itchy papulovesicular lesions on extremities, knees, elbows, and buttocks for one year. Direct immunofluorescence staining of the lesions showed IgA deposition as follows. What is the most probable diagnosis?



a) Bullous pemphigoid

b) Pemphigus vulgaris

c) Dermatitis herpetiformis

d) Epidermolysis bullosa acquisita

Question 18:

A 36-year-old male with skin-colored umbilicated papules. Microscopy is as shown below. The most likely diagnosis is_____.

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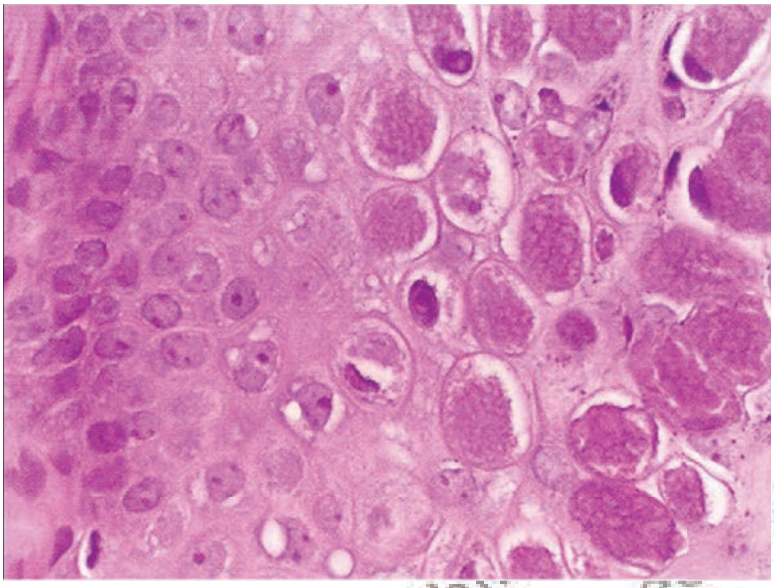

a) Herpes virus

b) Verruca vulgaris

c) Molluscum contagiosum

d) Lichen planus

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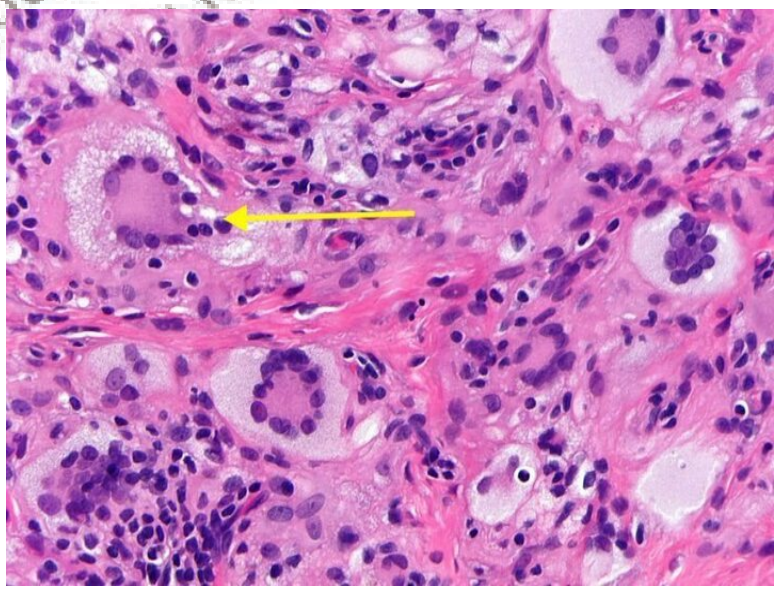
Question 19:

A pathology resident notes the following cells while examining a histopathological section. It may be seen in all of the following conditions except:



a) Xanthoma

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b) Fat necrosis

c) Dermatofibroma

d) Sarcoidosis

Question 20:

A 35-year-old man presented with a single hypoaesthetic and a hypopigmented patch on the lateral aspect of the forearm. Microscopy of a biopsy sample from the lesion revealed granulomatous inflammation but acid-fast bacilli were not identified. What is the likely diagnosis?

a) Tuberculoid leprosy

b) Lepromatous leprosy

c) Cutaneous tuberculosis

d) Histioid leprosy

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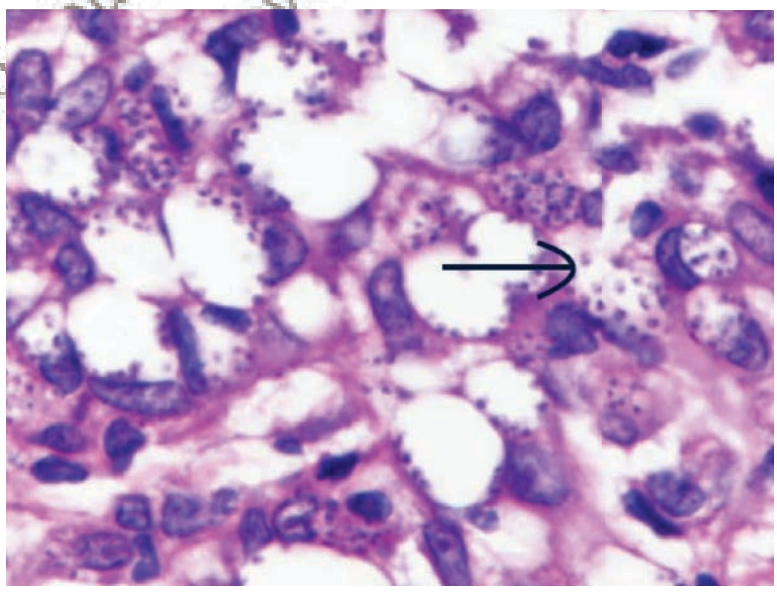
Question 21:

A 25-year-old man from the eastern part of India presents with a shallow and slowly expanding ulcer with heaped-up borders over the face. Biopsy reveals granulomas and the following finding. What is the most likely diagnosis?



a) Leishmaniasis

b) Tuberculosis

c) Lepromatous leprosy

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d) Primary syphilis

Question 22:

Max Joseph's space is a histopathological feature of which of the following conditions?

a) Psoriasis vulgaris

b) Lichen planus

c) Erythema multiforme

d) Mastocytosis

Question 23:

A 35-year-old man presents with the following lesions. Which of the following finding is likely to be seen in histopathology?

a) Papillary tip microabscess

b) Munro microabscess

c) Pautrier's microabscess

d) Eosinophilic microabscess

Answer Key

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Question No.	Correct Option
1	a
2	d
3	a
4	d
5	d
6	d
7	d
8	b
9	d
10	d
11	d
12	c
13	a
14	a
15	d
16	c
17	c
18	c
19	d
20	a
21	a
22	b
23	b

Detailed Explanations

Solution to Question 1:

The above scenario is suggestive of Langerhans cell histiocytosis. The image shows Langerhans cells with abundant, often vacuolated cytoplasm and vesicular nuclei containing linear grooves or folds and surrounding eosinophils. They stain positive for CD1a and S-100. They are intraepidermal dendritic cells.

The image below shows Langerhans cells.

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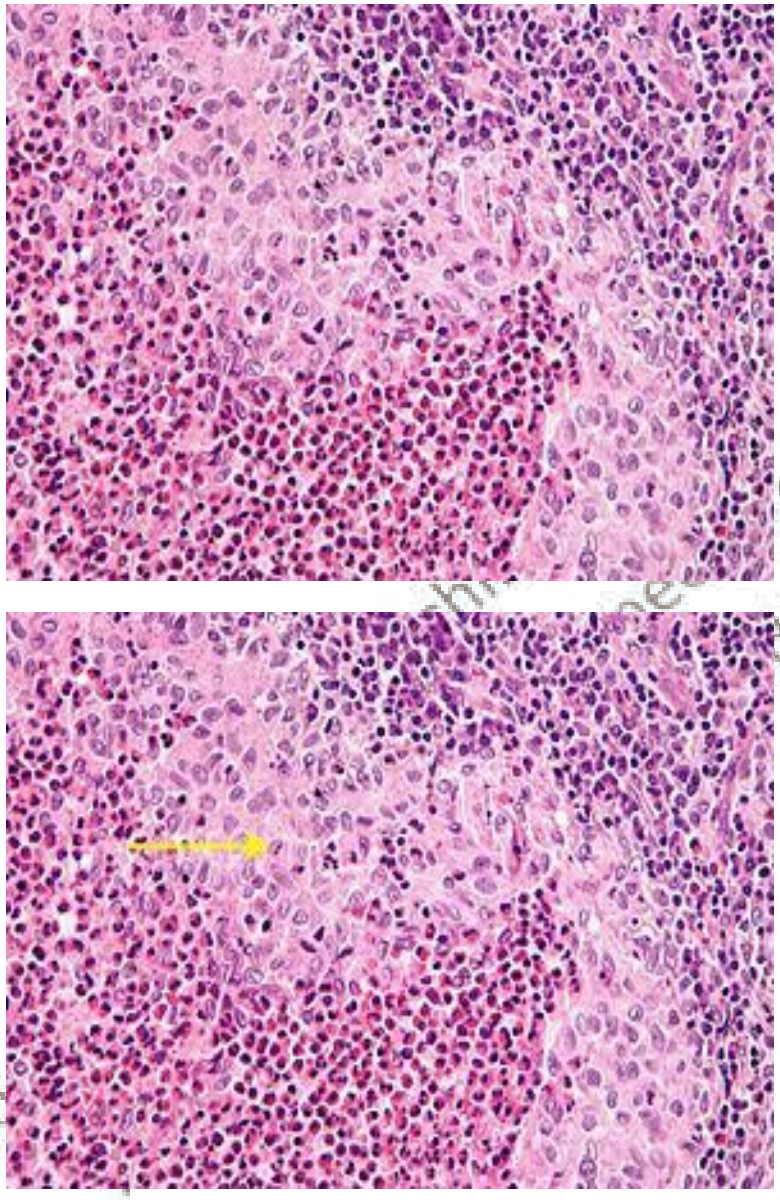

Clonal proliferation of Langerhans cells leads to Langerhans cell histiocytosis, a histiocytic and dendritic cell neoplasm.

These cells secrete factors that augment innate immune responses, and also the antigen-presenting cell of the skin, thereby stimulating the adaptive immune system.

Solution to Question 2:

The above scenario is suggestive of Merkel cell carcinoma. It arises from Merkel cells.

These cells are located in epithelial basal cell layer and have neuroendocrine and mechanoreceptor functions.

Merkel cell carcinoma is a rare and aggressive neuroendocrine tumor of the skin, most commonly found in white men and diagnosed at a mean age of 70 years. A rapidly growing, flesh-colored

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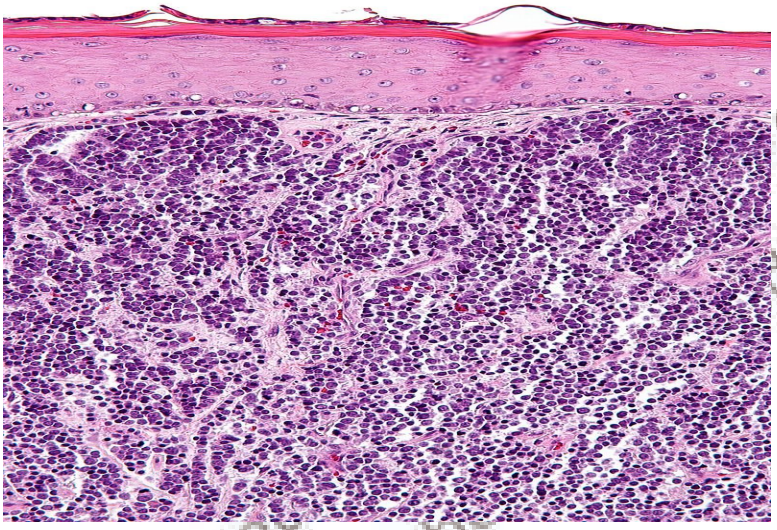
papule or plaque characterizes the disease. About 80% of the cases are seen associated with Merkel cell polyomavirus.

Regional lymph nodes are involved in 30% of the patients and 50% will develop systemic disease. CK-20 is a specific marker for Merkel cell carcinoma. Wide local excision is usually necessary.

The image below shows Merkel cell carcinoma composed of uniform small round cells having granular chromatin and scant cytoplasm.



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Solution to Question 3:

Nevus cells often become non-pigmented and resemble neural tissue as they grow deep into the dermis. This change is called neurotization and suggests the benign nature of the nevus.

This morphological change in nevus cells occurs due to progressive loss of tyrosinase activity and acquisition of cholinesterase activity in deeper “nervelike” nevus cells.

Melanocytic nevi (moles) are common benign neoplasms caused by acquired activating mutations in components of the RAS signaling pathway.

Based on the location, it may be junctional nevi, intradermal nevi, or compound nevi.

Melanocytic nevi are thought to progress through a series of morphologic changes over time. Superficial nevus cells are larger, tend to produce melanin, and grow in nests. Deeper nevus cells are smaller, produce little or no pigment, and appear as cords and single cells. At the deepest extent of the lesions, these cells often acquire fusiform contours and grow in fascicles resembling neural tissue (neurotization).

Melanocytic nevi with neurotization indicate normal maturation change and help in differentiating benign nevi from melanomas (which lacks such features).

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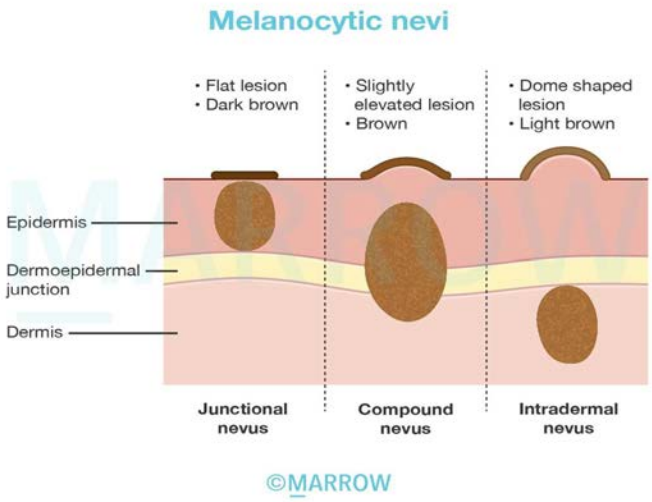

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Solution to Question 4:

The above image is suggestive of melanoma. Mutations in the hedgehog signaling pathway are associated with basal cell carcinoma.

All other mutations are associated with melanoma.

Melanoma is a highly aggressive malignancy linked to UV exposure.

Most sporadic melanomas are associated with mutations in cell cycle regulators (p16/INK4a, CDK4), proteins in receptor tyrosine kinase signaling pathway (KIT, RAS, BRAF), and telomerase (TERT mutation).

Dysplastic nevus syndrome is an autosomal dominant condition with inherited CDKN2A mutation that can lead to familial melanoma.

Solution to Question 5:

The superficial spreading type of melanoma is the most common type of melanoma.

The progression of melanoma may be described as:

• Radial growth phase: the horizontal spread of melanoma within the epidermis and superficial dermis

• Acral lentiginous - unrelated to sun exposure

• Lentigo maligna (Hutchinson freckle) - sun-exposed regions

• Superficial spreading (most common)

• Vertical growth phase: the tumor cells invade downward into the deeper dermal layers as an expansile mass (nodular)

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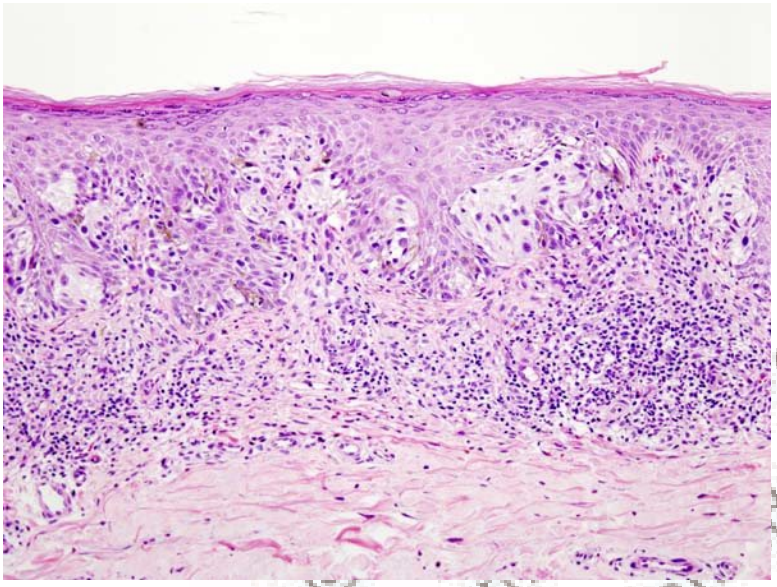
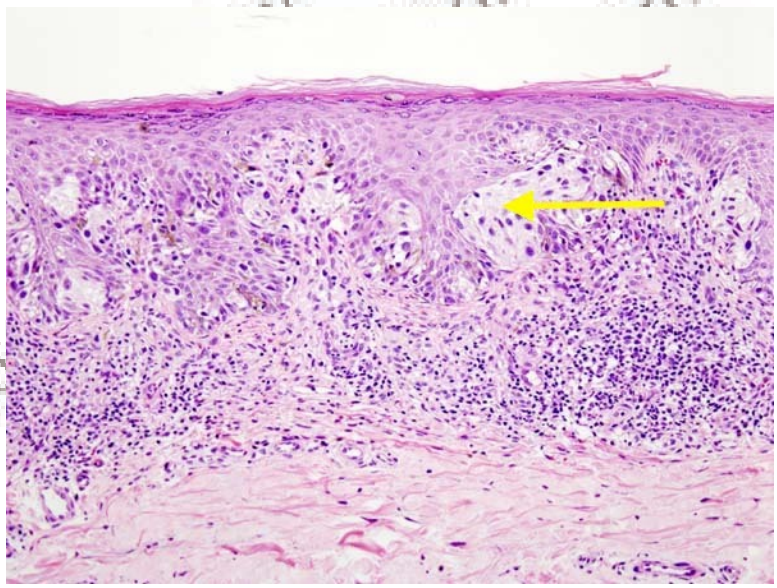
The image below shows melanoma in the radial growth phase. It shows the irregular nested and single-cell growth of melanoma cells within the epidermis and an underlying inflammatory response within the dermis.





The image below shows melanoma cells that have large nuclei with irregular contours. The chromatin is characteristically clumped at the periphery of the nuclear membrane with prominent red (eosinophilic) nucleoli.

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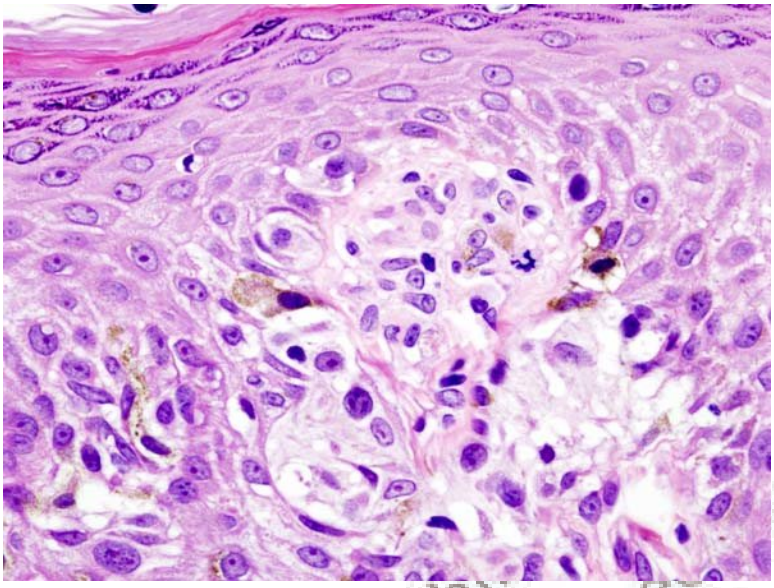
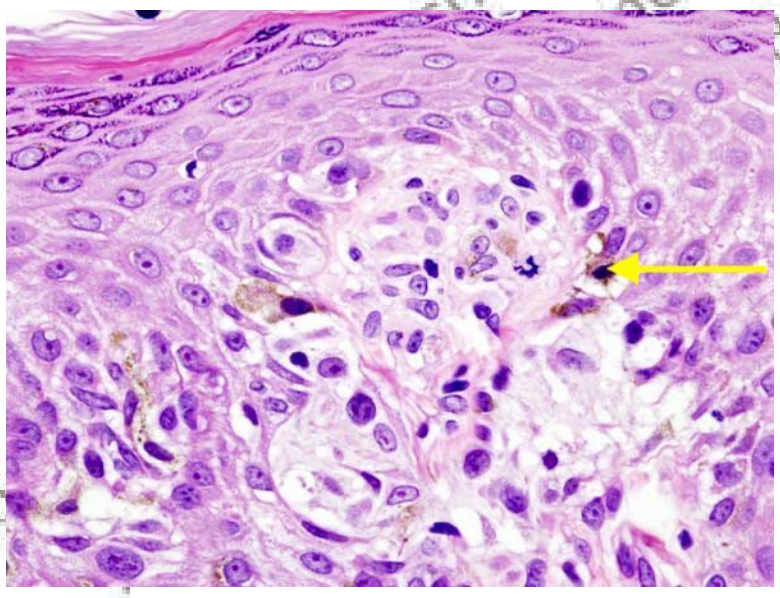
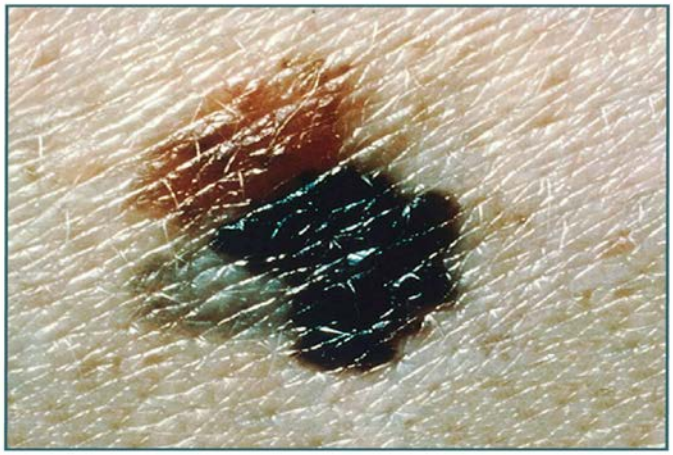




Superficial spreading melanoma



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Solution to Question 6:

The above image is suggestive of melanoma. The absence of regression is a favorable prognostic factor in melanomas.

Immunohistochemistry markers for melanoma are:

• S-100

• HMB (Human Melanoma Black)-45

• LDH

• MELAN-A

Regression is defined as partial or complete disappearance of a previously documented tumor in the absence of therapeutic interventions or physical trauma. Microscopically, it is characterized by the replacement of melanoma cells by dense inflammtory cell infiltrate or dermal fibrosis.

This phenomenon explains some apparent discrepancies between expected and observed prognosis based on tumor thickness and also the cases of metastatic melanoma with occult primary.

Determinants of a more favorable prognosis in melanoma include:

• Thinner tumor depth

• No or very few mitoses (< 1 per mm2)

• A brisk tumor infiltrating lymphocyte response

• The absence of regression

• Lack of ulceration

• Absence of metastases in the sentinel lymph node

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Solution to Question 7:

Mutations in the FGFR3 gene are not described in melanomas.

Fibroblast growth factor receptor-3 (FGFR3) is a receptor tyrosine kinase.

Defects in the FGFR3 gene have been associated with several conditions:

• Hypochondroplasia

• Thanatophoric dwarfism

• Seborrheic keratosis

• Acanthosis nigricans

• Bladder cancer

• Craniosynostosis

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• Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN)

Solution to Question 8:

The above image shows a jigsaw puzzle appearance which is seen in cylindroma (turban tumor/Spiegler's tumor).

Cylindroma is a familial autosomal dominant disorder. It is due to the loss of the cylindromatosis gene, CYLD on chromosome 16q12-13. It has also been reported to follow radiotherapy epilation of the scalp.

The lesions are frequently multiple, smooth, firm, pink to red, and somewhat pedunculated. They are mostly seen on the scalp. Histologically, it contains mosaic■like masses - a jigsaw appearance. Malignant transformation is very rare.

Surgery is the treatment of choice.

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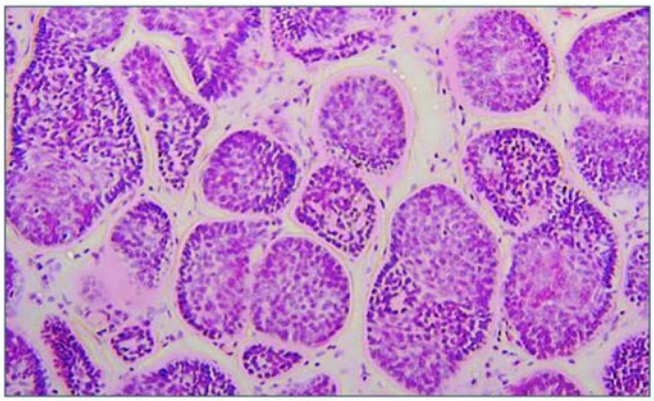
Jigsaw-puzzle appearance of cylindroma



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Cylindroma

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Note: Genetic syndromes associated with adnexal tumors:

• Germline mutations in CYLD - familial cylindromatosis, familial trichoepithelioma

• Brooke–Spiegler syndrome - associated with trichoepithelioma, cylindroma, spiradenoma

• Muir–Torre syndrome - sebaceous adenomas

• Cowden syndrome - multiple trichilemmomas

Solution to Question 9:

Neoplastic dyskeratosis is seen in actinic keratosis.

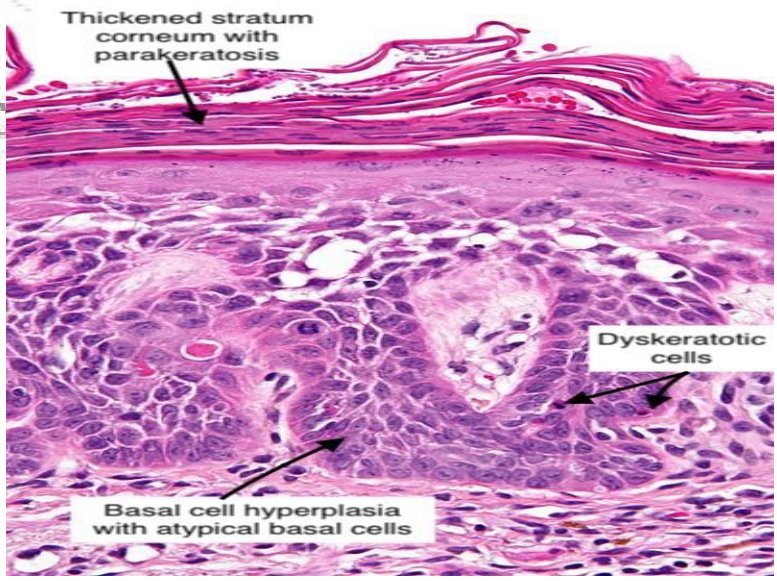
Dyskeratosis is premature keratinization of individual keratinocytes. These cells usually have pink or reddish cytoplasm. It can be benign or malignant.

• Benign dyskeratosis - seen in Darier's disease, warty dyskeratoma, and familial benign pemphigus

• Neoplastic dyskeratosis - seen in Bowen's disease, squamous cell carcinoma, and actinic keratosis

Actinic keratoses usually occur in sun-damaged skin and are considered precursor lesions of squamous cell carcinoma. Some lesions produce so much keratin that a cutaneous horn develops.

The image below shows the histology of actinic keratosis. It shows atypical basal cells, dyskeratotic cells, and parakeratosis in the stratum corneum (cells with a retained nucleus).



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Actinic keratoses

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Solution to Question 10:

The above image shows keratinous pearls and atypical tumor cells suggestive of squamous cell carcinoma. Human papillomavirus (HPV) subtypes 5 and 8 may predispose to squamous cell carcinoma, but not Epstein–Barr virus (EBV).

Risk factors for squamous cell carcinoma:

- Exposure to UV light
- HPV subtypes 5 and 8
- Epidermodysplasia verruciformis
- Industrial carcinogens (tars and oils)
- Chronic ulcers and draining osteomyelitis
- Old burn scars (Marjolin ulcers)
- Ingestion of arsenicals
- Ionizing radiation
- Tobacco and betel nut chewing (in the oral cavity)
- Precursor lesions:
- Actinic keratosis
- Xeroderma pigmentosum

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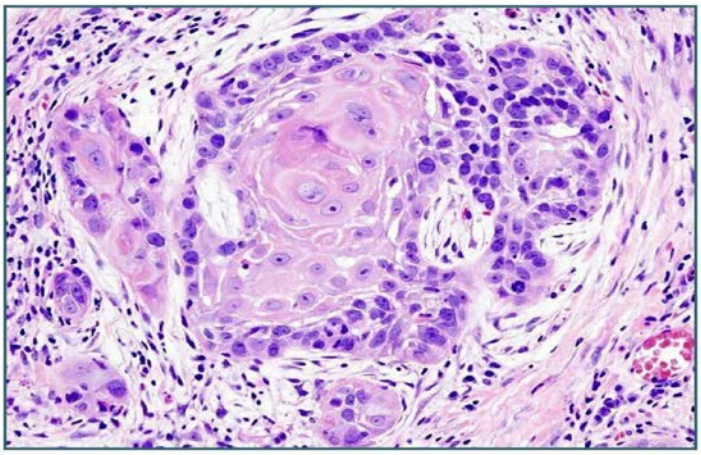
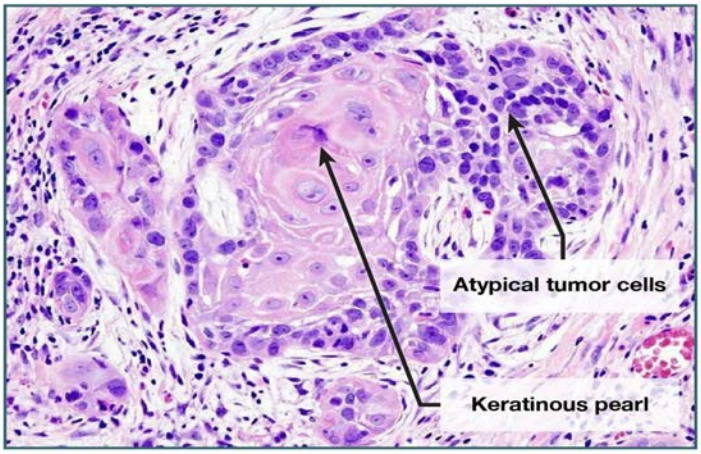
Squamous Cell Carcinoma



Squamous Cell Carcinoma



The image below shows an SCC lesion in the oral cavity.

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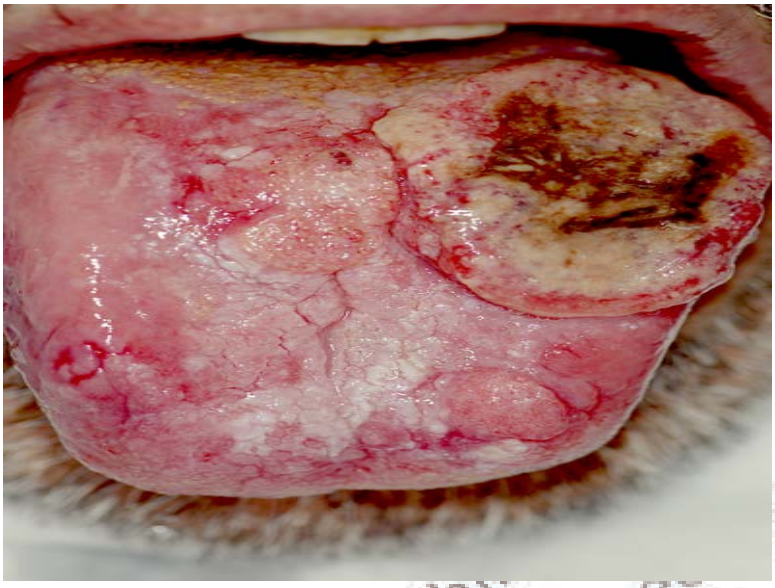

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Solution to Question 11:

The clinical presentation and histology are suggestive of basal cell carcinoma (BCC). It is a locally aggressive cutaneous tumor, and metastasis is very rare.

It occurs in sun-exposed areas with increased incidence in the setting of immunosuppression and in disorders of DNA repair, such as xeroderma pigmentosum.

BCCs usually present as pearly papules and locally invasive ulcers (rodent ulcers).
Histologically, the tumor cells resemble those in the normal basal cell layer of the epidermis with peripheral palisading and retraction cleft.

It is associated with mutations that activate the hedgehog pathway signaling.

Gorlin syndrome is an autosomal-dominant disorder with multiple basal cell carcinomas, medulloblastomas, ovarian fibromas, and odontogenic keratocysts, pits of the palms, and soles.

The image below shows the histopathology of BCC.

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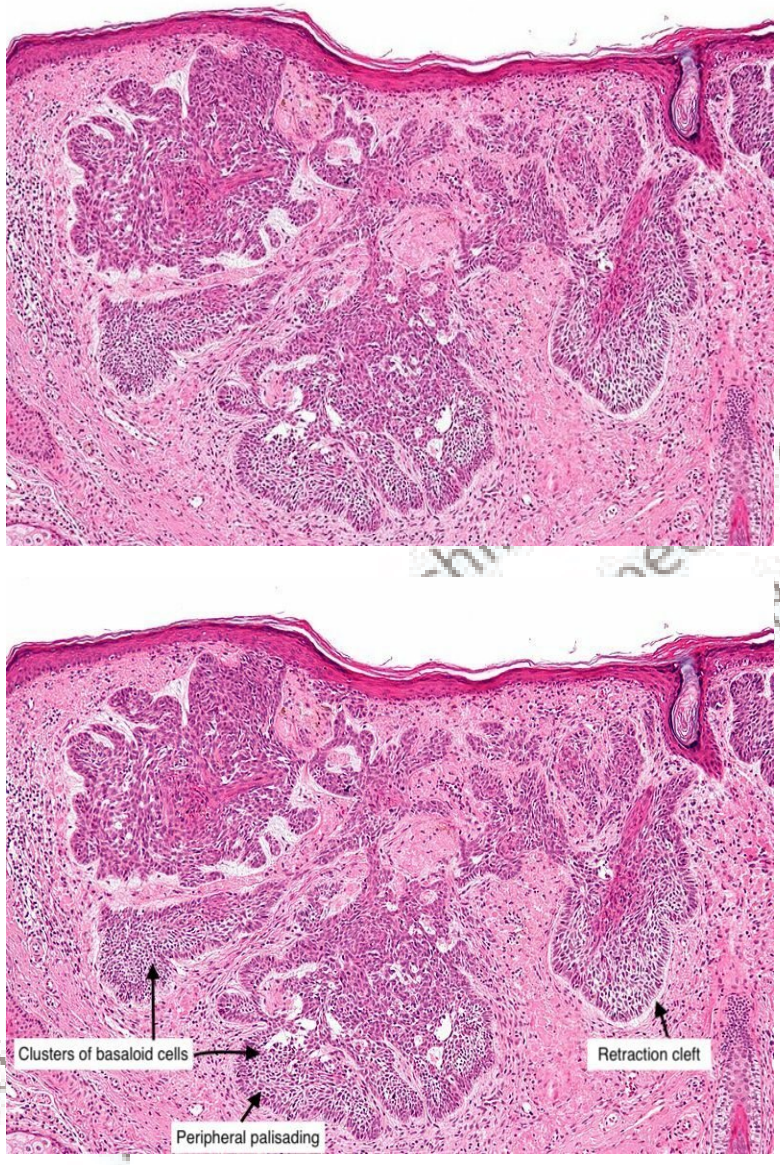

Solution to Question 12:

The clinical image shows diffuse erythema and scaling of the entire body surface (erythroderma) and histopathology shows the presence of lymphocytes in the epidermal cell layer (epidermotropism). This is suggestive of Sézary syndrome which is a disseminated and severe form of mycosis fungoides (cutaneous T-cell lymphoma).

Mycosis fungoides is a cutaneous T-cell lymphoma (CD4+ T-cells) that presents in the skin. It remains localized to the skin for many years, but it may eventually evolve into a systemic lymphoma.

The image of mycosis fungoides showing hallmark features - Sezary Lutzner cells showing epidermal infiltration (epidermotropism),

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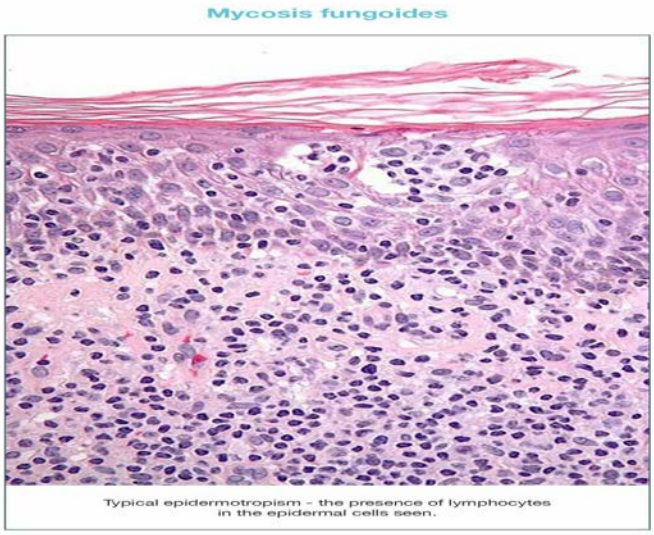

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Solution to Question 13:

The above scenario is suggestive of urticaria pigmentosa caused by cutaneous mastocytosis. The Masson-Fontana stain is used to demonstrate melanin in nevus and malignant melanoma.

Darier's sign is seen in urticaria pigmentosa. It refers to the development of urticaria and erythema around the lesions after mild trauma, including scratching or rubbing of the lesion.

Mast cells may be difficult to differentiate from lymphocytes in routine, hematoxylin, and eosin (H&E)–stained sections. Special metachromatic stains (toluidine blue or Giemsa) are used to visualize their granules.

Stains for mast cells:

• Toluidine blue

• Giemsa

• Tryptase

• Leder stain (Chloracetate esterase)

• CD 117

The image below shows mast cells stained with toluidine blue.

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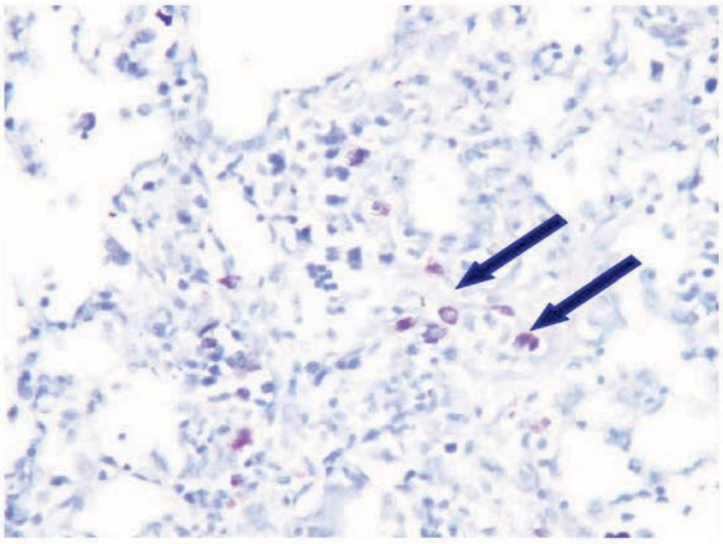

Positive Darier's sign in a nodule of urticaria pigmentosa in a young child.

A Presence of papular lesion

B Linear wheal after stroking

Solution to Question 14:

The above image shows the suprabasal splitting of the epidermis (acantholysis) giving rise to the row of tombstones appearance. This is suggestive of pemphigus vulgaris.

Pemphigus vulgaris is the most common type of pemphigus. It involves the mucosa and skin. Autoantibodies against desmoglein 1 and 3 are present.

Pemphigus is a blistering disorder caused by autoantibodies that result in the dissolution of intercellular attachments within the epidermis and mucosal epithelium.

Variants of pemphigus:

• Pemphigus vulgaris

• Pemphigus vegetans

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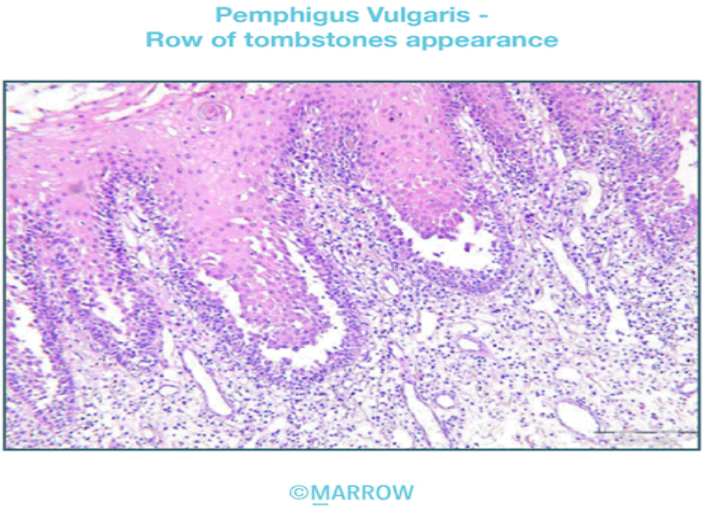
• Pemphigus foliaceus - autoantibodies are against Dsg1 alone, leading to superficial, subcorneal blisters.

• Pemphigus erythematosus

• Paraneoplastic pemphigus - in association with various malignancies, most commonly non-Hodgkin lymphoma



Solution to Question 15:

Antibodies against hemidesmosomes is the false statement as the given image shows a characteristic fish-net appearance on direct immunofluorescence, which is diagnostic of pemphigus vulgaris. The antibodies are against the desmosomal adhesion proteins such as desmogleins 1 and 3.

This pattern is due to intraepidermal intercellular deposition of IgG and C3.

The first-line investigation in pemphigus vulgaris is the Tzanck smear. It allows us to visualize the histology by collecting material from the floor of a fresh blister that is stained with Giemsa or any Romanowsky stain. Tzanck cells are seen on microscopy.

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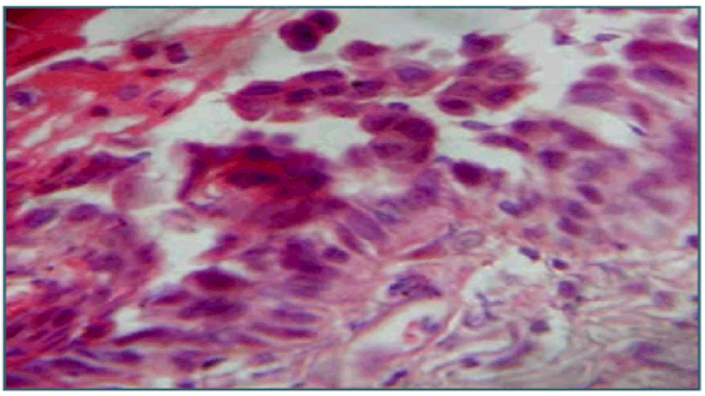
Tzanck cells



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Direct immunofluorescence microscopy (DIF) is the most accurate test.

Antibodies against hemidesmosomes that link basal keratinocytes to the underlying basement membrane are seen in bullous pemphigoid.

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Solution to Question 16:

The above image showing linear IgG and C3 deposits on direct immunofluorescence (DIF) microscopy is characteristic of bullous pemphigoid.

Bullous pemphigoid is characterized by tense itchy bulla in the flexor areas and trunk which do not rupture easily. In bullous pemphigoid, the antibodies are formed against bullous pemphigoid antigens (BPAGs)- BP 180 and BP 230, which are components of hemidesmosomes.

The separation of bullous pemphigoid from pemphigus is based on the identification of subepidermal, nonacantholytic blisters that are Nikolsky negative.

Nikolsky's sign is elicited by applying firm tangential sliding pressure with a finger on lesional or perilesional skin. If the lesion is opened (i.e., skin sloughed off), then the Nikolsky's sign is present/positive.

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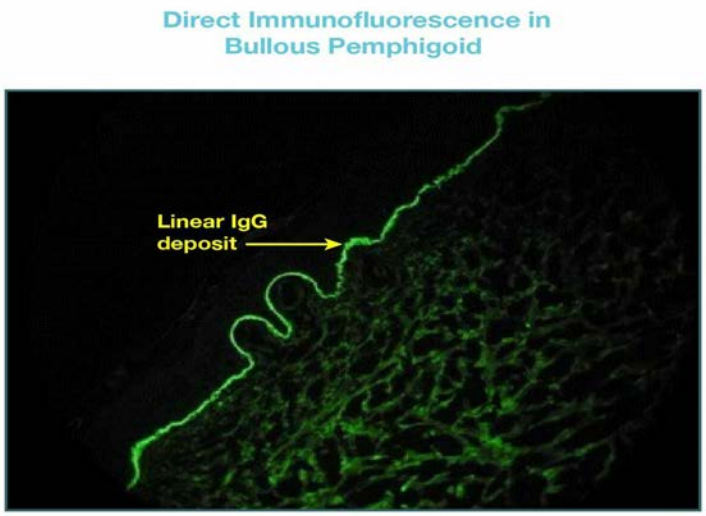

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Solution to Question 17:

The above image showing granular deposits of IgA on direct immunofluorescence is suggestive of dermatitis herpetiformis or Duhring's disease. These deposits localize in the tips of dermal papillae.

Dermatitis herpetiformis presents as grouped vesicles and papules. These lesions are commonly located over the extensor aspects of knees, elbows, buttocks, back, scalp which are associated with intense pruritus.

It is associated with gluten-sensitive enteropathy or celiac disease. It is also associated with HLA DQ2/DQ8/B8. Deposition of IgA antitransglutaminase antibodies in the dermal papillae results in true subepidermal blisters and vesicles.

The characteristic microscopic feature is subepidermal blisters with papillary tip microabscesses containing neutrophils.

The initial treatment of choice for dermatitis herpetiformis is a gluten-free diet.

The image below shows subepidermal vesicles, with papillary neutrophil microabscesses, with neutrophil, eosinophil and lymphocytes infiltrates in the superficial dermis in case of dermatitis herpetiformis.

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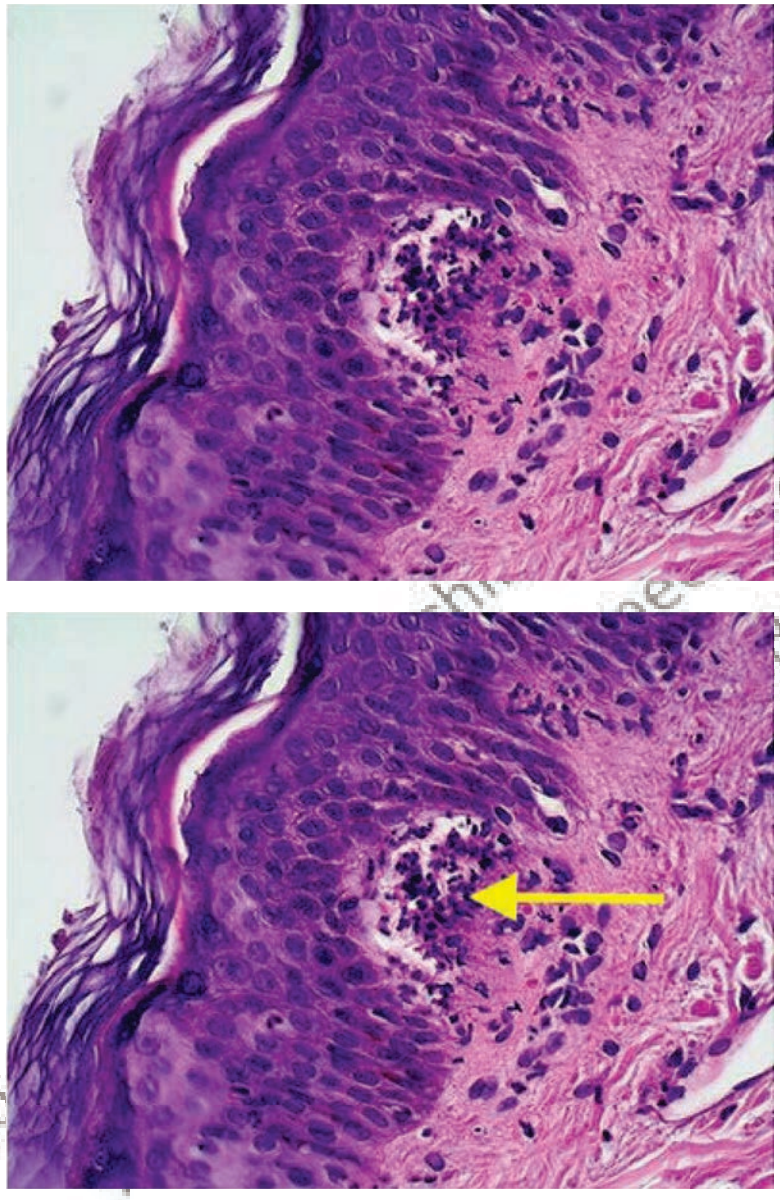

The image below shows vesicular lesions of dermatitis herpetiformis.

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Solution to Question 18:

The given microscopic image shows large, ellipsoid, homogeneous, cytoplasmic inclusion in cells of the stratum granulosum and the stratum corneum classically seen in molluscum contagiosum.

Molluscum contagiosum is a common, self-limited viral disease of the skin caused by a poxvirus. Poxvirus is brick-shaped and is about 300 nm in size, the largest pathogenic poxvirus in humans

Tzanck smear shows intracytoplasmic molluscum bodies (Henderson–Patterson bodies), the largest known inclusion bodies (30–35 µm).

Individual lesions are firm, pruritic, pink to skin-colored umbilicated papules (shown below). A curd-like material can be expressed from the central umbilication

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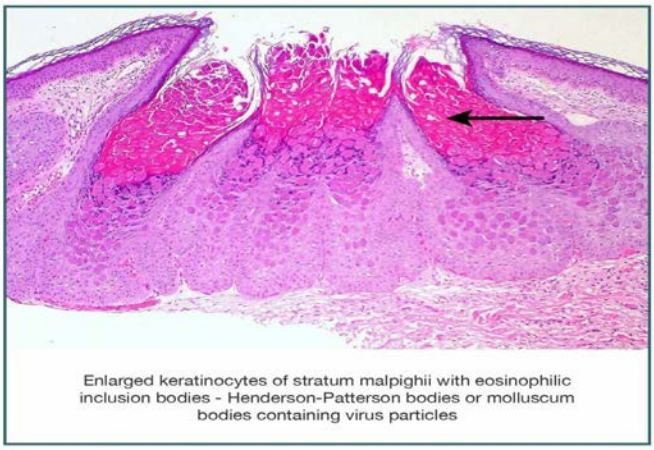
Molluscum contagiosum



Enlarged keratinocytes of stratum malpighii with eosinophilic inclusion bodies - Henderson-Patterson bodies or molluscum bodies containing virus particles

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Solution to Question 19:

The image above shows Touton giant cells having a central ring of nuclei while the peripheral cytoplasm is clear due to accumulated lipid. These cells are formed by the fusion of lipid-containing macrophages. They are not seen in sarcoidosis.

These cells are seen in:

- Fat necrosis
- Xanthoma
- Xanthogranulomas
- Dermatofibroma

The cardinal histopathologic feature of sarcoidosis is the non-caseating epithelioid granuloma with occasional other microscopic features:

- Schaumann bodies - laminated concretions composed of calcium and proteins
- Asteroid bodies - stellate inclusions enclosed within giant cells

Solution to Question 20:

The most likely diagnosis is tuberculoid leprosy.

On microscopic examination, tuberculoid leprosy has granulomatous lesions closely resembling those found in tuberculosis. Because of the strong host defense, bacilli are almost never found, hence the name paucibacillary leprosy.

Leprosy or Hansen disease is a slowly progressive infection caused by Mycobacterium leprae, mainly affecting the skin and peripheral nerves.

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Solution to Question 21:

The image shows many histiocytes containing Leishman–Donovan bodies and surrounding chronic inflammatory cells classically seen in cutaneous leishmaniasis.

Cutaneous leishmaniasis presents with a shallow and slowly expanding ulcer, often with heaped-up borders.

On microscopic examination, the lesion shows granulomatous inflammation, usually with many giant cells and few parasites.

Diffuse cutaneous leishmaniasis is characterized by a single skin nodule, which continues spreading until the entire body is covered by nodular lesions. Microscopically, they contain aggregates of foamy macrophages stuffed with leishmania.

Solution to Question 22:

Max Joseph's space is a histopathological feature of lichen planus.

Histological features of lichen planus:

• Orthokeratosis, parakeratosis, thickening of the stratum granulosum.

• Acanthosis with the formation of colloid bodies (also known as Civatte bodies/Sabouraud bodies)

• Liquefactive degeneration of the stratum basale, with separation from the underlying lamina propria, as a result of desmosome loss, creating small spaces (Max Joseph spaces)

• Infiltration of T cells in a band-like pattern into the dermis "hugging" the basal layer (interface dermatitis)

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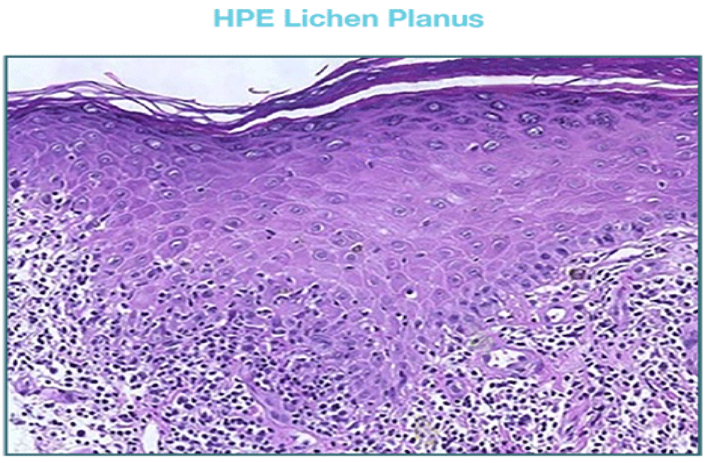

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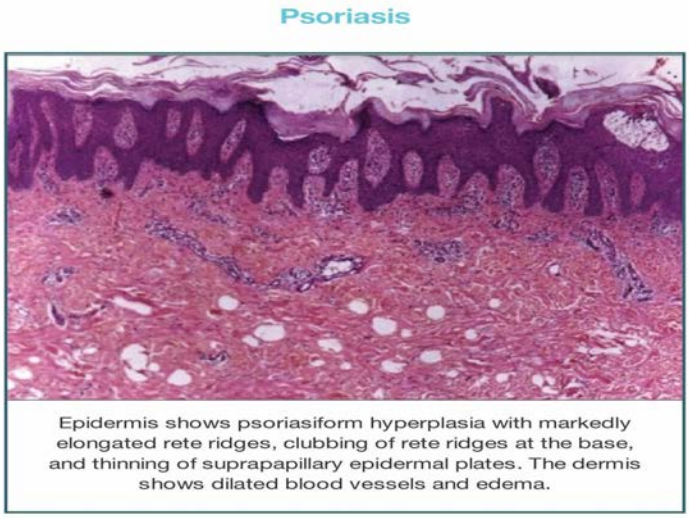
Solution to Question 23:

The image shows silvery-white scaly lesions on the extensor aspect of the knees suggestive of psoriasis. Munro microabscesses are seen in psoriasis.

Psoriasis is a chronic inflammatory dermatosis that appears to have an autoimmune basis. The lesions are pink to salmon-colored plaque covered by loosely adherent silver-white scales. Auspitz sign and Koebner phenomenon can be demonstrated. Nail changes include pitting, dimpling, separation of the nail plate, onycholysis, thickening, and crumbling.

Microscopy shows thinning of stratum granulosum, supra papillary plates, and neutrophils forming small aggregates within the superficial epidermis (spongiform pustules) and within the stratum corneum (Munro microabscesses).



Some types of microabscesses and their examples are given below:

Predominant cell	Name of microabscess	Disease
Neutrophilic microabscess	Papillary tip microabscessMunro microabscess (superficial)Spongiform pustules of Kogoj (deep)	Dermatitis herpetiformisPsoriasisPsoriasis
Lymphocytic microabscess	Pautrier's microabscess	Mycosis fungoides
Eosinophillic microabscess		Pemphigus vegetans

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Infective & Vascular CNS pathology

Question 1:

Which cells constitute the resident monocyte-lineage population of the CNS and accumulate in response to injury?

a) Oligodendrocytes

b) Microglial cells

c) Astrocytes

d) Stellate cell

Question 2:

Which of these are the earliest morphologic markers of neuronal cell death?

a) White neurons

b) Red neurons

c) Gliosis

d) Axonal reaction

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Question 3:

A 45-year-old male who is a known diabetic and hypertensive suffers a stroke. During this episode, which of the following cells are the least susceptible to injury, considering the stroke was transient and not severe?■

a) Watershed zones of cerebral cortex

b) Pyramidal cells of hippocampus

c) Purkinje cells of cerebellum

d) Astrocytes of cerebral cortex

Question 4:

A 50 year old man died of an unknown condition. On autopsy, a sample of the brain was taken as a specimen, and the following fibres were seen on microscopic examination. These

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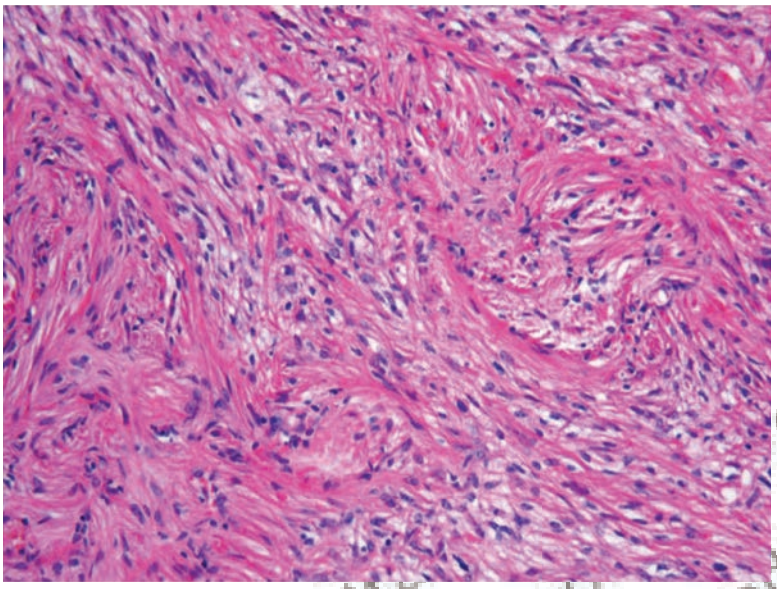
fibres are not seen in which of the following conditions?



a) Alexander disease

b) Pilocytic astrocytoma

c) Pick disease

d) Longstanding gliosis

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Question 5:

Hemorrhage of which of the following areas of the brain are called ganglionic hemorrhages?

a) Basal ganglia and cerebral hemisphere

b) Thalamus and pons

c) Basal ganglia and thalamus

d) Basal ganglia only

Question 6:

A patient is rushed into the ER with complaints of sudden excruciating headache and projectile vomiting. CT angiography shows the presence of Charcot-Bouchard microaneurysms. These are caused by which of the following?

a) Congenital

b) Hypertension

c) Atherosclerosis

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d) Trauma

Question 7:

A 66-year-old man with chronic hypertension presents to the ER with altered mental status and elevated blood pressure of 210/110 mm Hg. You suspect intracranial hemorrhage. What is the most common site of hemorrhage seen in such cases?

a) Putamen

b) Thalamus

c) Pons

d) Cerebellum

Question 8:

A patient with a known history of autosomal dominant polycystic kidney disease, presents to the ER with a sudden, severe headache, photophobia and nausea. What type of aneurysm would you suspect in this patient?

a) Saccular

b) Fusiform

c) Mycotic

d) Dissecting

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Question 9:

Which of the following statements is not true about CADASIL?

a) It shows autosomal recessive inheritance.

b) It is characterized by mutations in the NOTCH3 gene.

c) It presents with subcortical infarcts.

d) Recurrent strokes and dementia are seen.

Question 10:

A patient presented to the emergency department with high fever, photophobia and neck stiffness. A lumbar puncture was performed and findings are given below. Which of the

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following is the most common cause of this condition?

a) Enterovirus

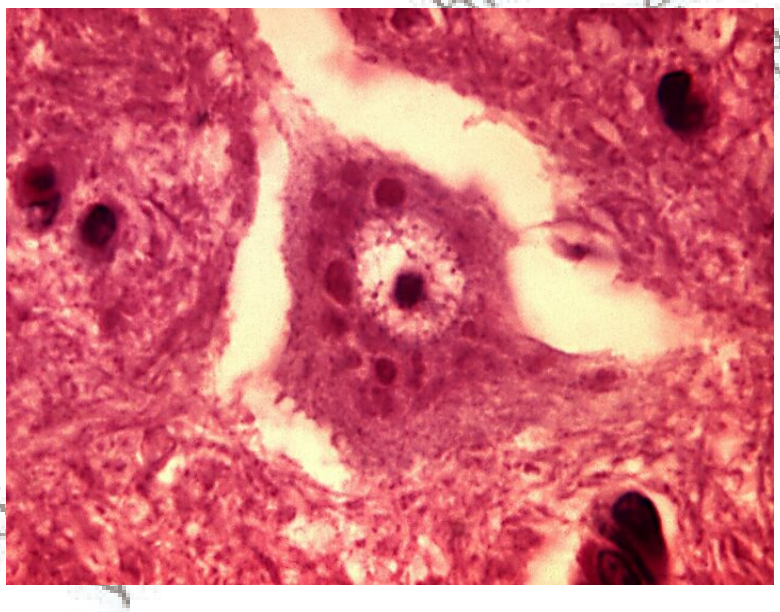
b) Herpes simplex 1 virus

c) Herpes simplex 2 virus

d) West nile virus

Question 11:

A 34-year-old man is admitted with a history of altered sensorium and abnormal behavior. The patient subsequently died and on autopsy, the following findings are seen in the Purkinje cells of the cerebellum. What are these called?



a) Henderson-Patterson bodies

b) Negri bodies

c) Owl-eye inclusions

d) Guarnieri bodies

Question 12:

Progressive multifocal leukoencephalopathy is caused by which of the following?

a) Rabies

b) Measles

c) JC virus infection

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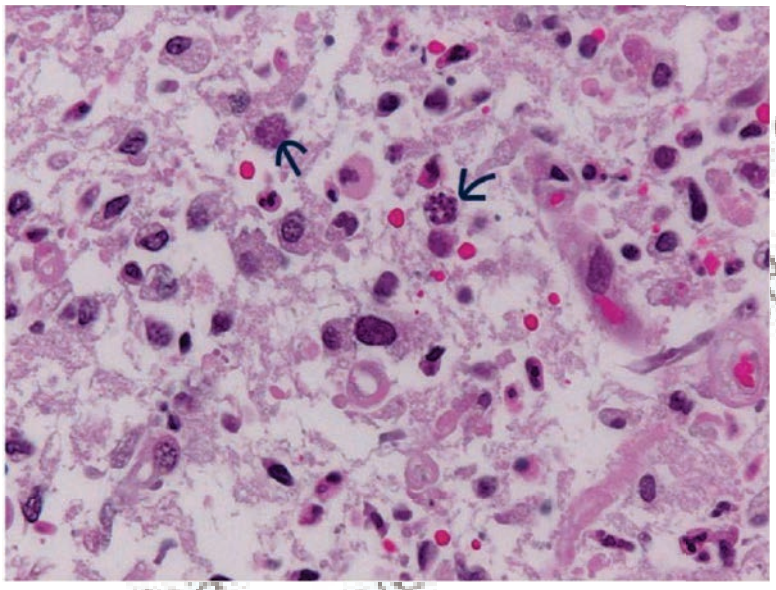
d) CMV infection

Question 13:

A 35-year-old immunocompromised patient presented with fever, headache, and neurological deficits. MRI showed multiple enhancing lesions and a stereotactic biopsy of the lesion was done. What is the most likely diagnosis?



a) Cerebral malaria

b) Cerebral toxoplasmosis

c) Herpes simplex encephelitits

d) Progressive multifocal leukoencephalopathy (PML)

Question 14:

A 40-year-old man with bronchiectasis presents with progressive focal neurologic deficits and symptoms related to increased intracranial pressure. On lumbar puncture, the CSF is found to have a high white cell count and an increased protein concentration, but the glucose content is normal. What is the most likely diagnosis?

a) Brain abscess

b) Viral meningitis

c) Neurosyphilis

d) Lyme disease

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Question 15:

Which of the following is incorrect regarding the common locations of CNS infections?

a) Tuberculosis - basal part of the brain

b) HSV - frontal and temporal lobes

c) HIV - frontal and parietal lobes

d) CMV - choroid plexus

Question 16:

Which of the following statements is false regarding prion diseases?

a) Creutzfeldt Jakob Disease is most commonly sporadic

b) Spongiform neurons are seen in fatal familial insomnia

c) Startle myoclonus is seen in Creutzfeldt Jakob Disease

d) The disease causing isoform of prion protein is PrPC

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Question 17:

A 15 year old boy is brought to the ER with complaints of seizures, spasticity of limbs and cognitive decline since two weeks. He has no history of recent illness, but mentions suffering from a high fever with a rash 5 years ago. What condition had he likely suffered from?

a) Measles

b) Chicken pox

c) HSV infection

d) Scarlet fever

Question 18:

Berry aneurysm occurs due to:

a) Endothelial injury of vessel due to HTN

b) Arterial internal elastic lamina defect

c) Endothelial layer defect

d) Adventitia defect

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Answer Key

Question No.	Correct Option
1	b
2	b
3	d
4	c
5	c
6	b
7	a
8	a
9	a
10	a
11	b
12	c
13	b
14	a
15	c
16	d
17	a
18	b

Detailed Explanations

Solution to Question 1:

Microglia are mesoderm-derived phagocytic cells that serve as the resident monocyte-lineage population of the CNS and accumulate in response to injury.

They respond to injury by:

• Activation and proliferating

• Developing elongated nuclei (rod cells), as in neurosyphilis

• Forming aggregates around small foci of tissue necrosis (microglial nodules)

• Congregating around cell bodies of dying neurons (neuronophagia)

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Solution to Question 2:

Red neurons are the earliest morphologic markers of neuronal cell death.

Acute neuronal injury refers to a spectrum of changes that accompany acute CNS hypoxia / ischemia or other acute insults and reflect the earliest morphologic markers of neuronal cell death. They are evident by about 12 to 24 hours after an irreversible insult.

Morphologic features consist of:

• Shrinkage of the cell body

• Pyknosis of the nucleus

• Disappearance of the nucleolus

• Loss of Nissl substance

• Intense eosinophilia of the cytoplasm.

Stages of neuronal injury and their pathological features are given below:

Stages	Time	Features
Early change	12–24 hr	Red neuron
Subacute change	24 hr–2 weeks	Necrosis, macrophages, vascular proliferation, gliosis
Repair	2 weeks +	Removal of necrosis, gliosis completed, loss of CNS architecture

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Solution to Question 3:

Astrocytes are more resistant to focal cerebral ischemia than neurons, and die by delayed necrosis.

The cells most susceptible to ischemia are:

• Pyramidal cell layer cells of the hippocampus (especially area CA1, also referred to as Sommer sector)

• Purkinje cells of the cerebellum

• Pyramidal neurons of the cerebral cortex(the watershed zones)

Solution to Question 4:

The image shows the presence of rosenthal fibres. Rosenthal fibres are not seen in Pick's disease.

Rosenthal fibers are thick, elongated, brightly eosinophilic, irregular structures that occur within astrocytic processes. They contain two heatshock proteins (αB crystallin and HSP27) as well as ubiquitin.They are typically found in regions of longstanding gliosis and are characteristic of a

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type of glial tumor—pilocytic astrocytoma.

Alexander disease is a leukodystrophy associated with mutations in the gene encoding GFAP. In this condition, abundant rosenthal fibers are found in periventricular, perivascular, and subpial locations.

Solution to Question 5:

Hemorrhages in the basal ganglia and thalamus are commonly designated ganglionic hemorrhages. Those that occur in the lobes of the cerebral hemispheres are called lobar hemorrhages.

Solution to Question 6:

Charcot–Bouchard microaneurysms are caused by chronic hypertension. They are most commonly seen within the basal ganglia.

Solution to Question 7:

The given clinical condition is suggestive of hypertensive intraparenchymal hemorrhage. The most common site (50-60%) of hypertensive hemorrhage in the brain is the putamen.

Hypertension is the most common cause of intracerebral hemorrhage.

Solution to Question 8:

In a patient with a known history of autosomal dominant polycystic kidney disease, the most common type of intracranial aneurysm is saccular aneurysm.

Although the majority occur sporadically, genetic factors may be important in their pathogenesis of saccular aneurysms. There is an increased incidence of saccular aneurysm in individuals with certain Mendelian disorders like autosomal dominant polycystic kidney disease, Ehlers–Danlos syndrome type IV, neurofibromatosis type 1 [NF1], and Marfan syndrome, fibromuscular dysplasia of extracranial arteries, and coarctation of the aorta. Other predisposing factors include cigarette smoking and hypertension.

The most frequent cause of clinically significant subarachnoid hemorrhage is rupture of a saccular (berry) aneurysm in a cerebral artery.

Solution to Question 9:

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Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an autosomal-dominant disorder caused by mutations in the NOTCH3 gene.

This leads to the misfolding of the extracellular domain of the NOTCH3 receptor that is preferentially expressed in vascular smooth muscle. It is clinically characterized by recurrent strokes (usually ischemic, less often hemorrhages) and dementia.

Arteries in the CNS and in other tissues such as skin show concentric thickening of the media and adventitia, loss of smooth muscle cells, and the presence of basophilic, periodic acid Schiff (PAS)-positive deposits. Deposits contain the misfolded NOTCH3 protein. These appear as osmiophilic compact granular material on electron microscopy and are consistently detected in the walls of affected vessels.

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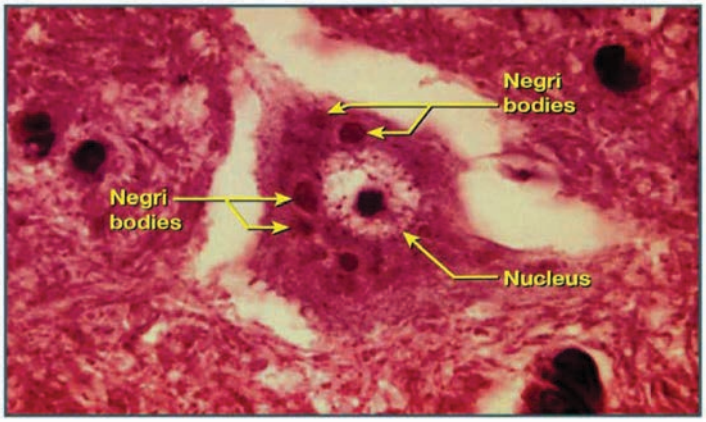
Solution to Question 10:

The above clinical scenario is suggestive of aseptic meningitis. Enterovirus is the most common cause, accounting for around 90% of the cases.

Solution to Question 11:

The image shows characteristic Negri bodies found in the Purkinje cell of the cerebellum. These are the pathognomonic microscopic finding in rabies. This patient's clinical features of altered sensorium and abnormal behavior are suggestive of rabies.

Negri bodies are cytoplasmic, round to oval, eosinophilic inclusions that can be found in the pyramidal neurons of the hippocampus and Purkinje cells of the cerebellum. The rabies virus can be detected within Negri bodies by ultrastructural and immunohistochemical methods.



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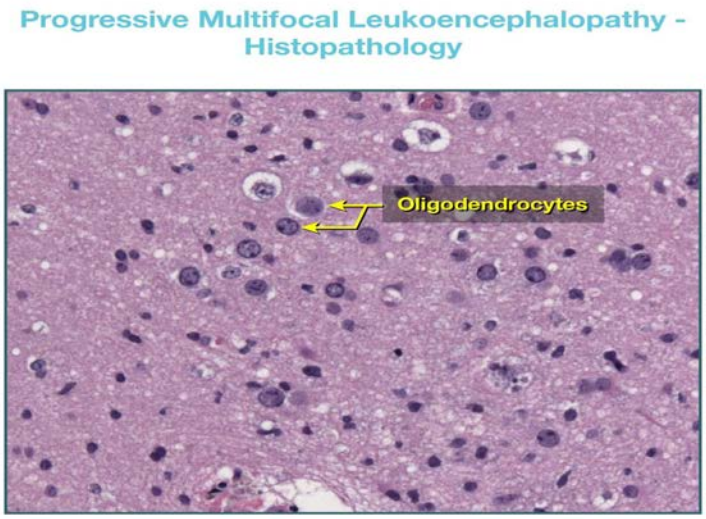
Solution to Question 12:

Progressive multifocal leukoencephalopathy (PML) is an encephalitis caused by the JC polyomavirus.

The disease occurs almost exclusively in immunosuppressed individuals, most commonly among patients with acquired immunodeficiency syndrome (AIDS). The most prominent symptoms are clumsiness, progressive weakness, and visual, speech, and personality changes.

Since the virus preferentially infects oligodendrocytes, demyelination is its principal pathologic effect. It affects the subcortical white matter, particularly that of the parietal and occipital lobes. On microscopic examination, enlarged oligodendrocyte nuclei containing glassy amphophilic viral inclusions are seen.

The image below shows a brain biopsy of a progressive multifocal leukoencephalopathy patient, showing oligodendrocytes with nuclear enlargement and glassy chromatin.



Solution to Question 13:

The above image shows lymphocytes, macrophages and eosinophils surrounding the toxoplasma bradyzoites encased in cysts. Along with the case scenario, the most likely diagnosis is cerebral toxoplasmosis.

Cerebral toxoplasmosis is an opportunistic infection commonly found in the setting of HIV-associated immunosuppression. Toxoplasmosis of the CNS produces brain abscesses, which are found most often in the cerebral cortex (near the grey-white junction) and deep gray nuclei.

Lesions of acute cerebral toxoplasmosis exhibit central necrosis, petechial haemorrhages surrounded by acute and chronic inflammation, macrophage infiltration, and vascular proliferation. Both free tachyzoites and encysted bradyzoites may be found at the periphery of the necrotic foci. Chronic lesions consist of small cystic spaces containing scattered lipid and hemosiderin-laden macrophages that are surrounded by gliotic brain.

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Option A: In cerebral malaria caused by P. falciparum, brain vessels are plugged with parasitized red cells. Around the vessels, ring hemorrhages and small focal inflammatory reactions (called malarial or Dürck granulomata) are seen.

Option C: Herpes simplex encephalitis is necrotizing and often hemorrhagic. Cowdry type A intranuclear viral inclusion bodies may be found in both neurons and glia.

Option D: Progressive multifocal leukoencephalopathy (PML) is an encephalitis caused by the JC polyomavirus. The disease occurs almost exclusively in immunosuppressed individuals. The virus preferentially infects oligodendrocytes and hence demyelination is its principal pathologic effect. The enlarged oligodendrocyte nuclei contain glassy amphophilic viral inclusions.

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Solution to Question 14:

Brain abscess is the most likely diagnosis in the above patient with progressive focal neurologic deficits and increased intracranial pressure.

Predisposing conditions for brain abcess:

• Acute bacterial endocarditis, which may give rise to multiple brain abscesses.

• Congenital heart diseases with right to left shunt.

• Chronic pulmonary disease, as in bronchiectasis.

• Systemic disease with immunosuppression.

Organisms involved are:

• Streptococcus spp. and Staphylococcus spp. (most common aerobic organisms)

• Bacteroides fragilis and Peptostreptococcus spp.(most common anaerobic organisms).

Foci of organisms in brain abscess:

• Direct implantation of organisms

• Local extension from adjacent foci (mastoiditis, paranasal sinusitis)

• Hematogenous spread (from primary foci of heart, lungs, bones of extremities, dental extraction)

CSF analysis in brain abscess:

Note: In Robbins and Cotran's Pathology of Diseases- edition 9 page no.1273, it is given that in a typical brain abscess patient, the glucose in the CSF will be normal.

Parameters	Observation
WBC	Increased
Proteins	Increased
Glucose	Decreased (but it will be normal in a significant proportion of individuals)

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Solution to Question 15:

HIV encephalopathy is seen in subcortical regions of the brain and not in frontal and parietal lobes. It is characterized by defects in short-term memory and executive function. It is also known as subcortical dementia.

CNS manifestations seen in AIDS:

- Aseptic meningitis
- HIV-associated neurocognitive disorder (HAND)
- HIV encephalopathy
- AIDS dementia complex
- Myelopathy
- Pure sensory ataxia
- Paresthesia/dysesthesia
- Myopathy
- Peripheral neuropathy
- Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Mononeuritis multiplex
- Distal symmetric polyneuropathy

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Solution to Question 16:

The disease causing isoform of prion protein is PrPSc.

Prions are the proteinaceous infectious particle that lacks nucleic acid, composed entirely of alternatively folded proteins that undergo self-propagation. They bind to the normal, cellular isoform of the prion protein (PrPC) which is rich in α-helix, and stimulate conversion of PrPC into the disease-causing isoform PrPSc which contain less α-helix and a high amount of °-structure. ° structured proteins are resistant to digestion by human cellular enzymes. Transmission of prion disease may be sporadic, familial or iatrogenic.

This group of diseases include:

- Creutzfeldt Jakob disease
- Gerstmann Sträussler Scheinke syndrome
- Fatal Familial Insomnia
- Kuru disease
- Scrapie in sheep and goats

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• Bovine spongiform encephalopathy in cows

Most common prion disease in humans is CJD, which is most commonly sporadic. CJD is characterized by a constellation of dementia, myoclonus, and periodic electrical bursts in EEG.

Autoclaving at 134 degree Celsius for 5 hours or treatment with 2 N NaOH for several hours is recommended for sterilization against prions (tip: 1234-5 for prions).

Solution to Question 17:

The patient is most likely suffering from subacute sclerosing panencephalitis (SSPE), a delayed late complication of measles.

Subacute sclerosing panencephalitis (SSPE) is a rare, progressive clinical syndrome characterized by cognitive decline, spasticity of limbs, seizures and psychosis. It occurs in children or young adults, months or years after an initial, early-age acute infection with measles.

The pathogenesis of SSPE is not well understood but may involve persistent infection with a genetic variant of measles virus within the central nervous system.

Solution to Question 18:

Berry aneurysm occurs due an arterial internal elastic lamina defect.

As an aneurysm develops, it typically forms a neck with a dome and the arterial internal elastic lamina disappears at the base of the neck. The media thins and connective tissue replaces the smooth-muscle cells. The site of rupture is most often the dome. Here the wall thins, and the tear that allows bleeding is usually ≤0.5 mm long.

Risk of aneurysm rupture is higher if:

• Aneurysm is >7 mm in diameter

• Aneurysm at the top of the basilar artery

• Aneurysm at the origin of the posterior communicating artery

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Degenerative, Toxic & Metabolic CNS disorders

Question 1:

Which of the following is a risk factor for Alzheimer's disease?

a) Apo E1

b) Apo E2

c) Apo E3

d) Apo E4

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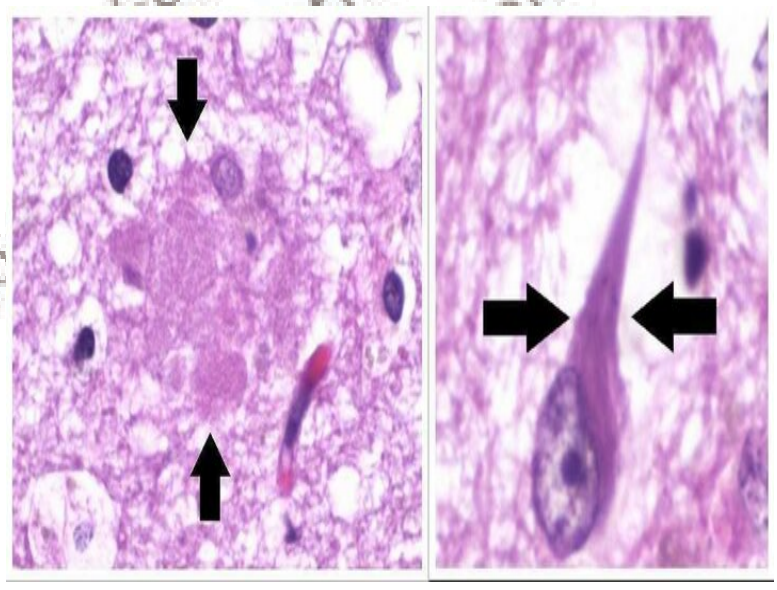
Question 2:

During the autopsy of a 78-year-old man who had progressive memory loss for 2 years, the following histologic finding was noted in the brain tissue. Which of the following mechanisms is most likely responsible for this condition?



a) Aggregation of A° peptide

b) Conformational change in the prion protein

c) Mutations in the tau gene

d) Deposition of Lewy bodies

Question 3:

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With respect to Alzheimer's disease, which of the following pairs is incorrectly matched?

a) APP – Chromosome 21

b) PS1- Chromosome 14

c) PS2– Chromosome 9

d) Apo E – Chromosome 19

Question 4:

Patients with which of the following diseases develop features of androgen insensitivity?

a) Spinal bulbar muscular atrophy

b) Amyotrophic lateral sclerosis

c) Multiple system atrophy

d) Huntington's disease

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Question 5:

In which of the following conditions can neurofibrillary tangles be found?

a) 3, 4 and 5

b) 1 and 5 only

c) 2, 3 and 4

d) 1, 2 and 5

Question 6:

A 43-year-old man who presented with tremors, bradykinesia, ■lack of coordination, and progressive declining cognitive functions was diagnosed with punch drunk syndrome. This condition is likely due to the deposition of which of the following in his brain?

a) Alpha synuclein

b) Tau proteins

c) Poly-glutamate inclusions

d) A° peptide

Question 7:

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A 62-year-old man is brought with tremors of his hands at rest. His son says that he has difficulty initiating movements and seems to be moving very slowly. On examination, shuffling gait, pill-rolling tremors, and rigidity on passive arm movement are noted. Which of the following is not seen in this condition?

a) Pick cells and Pick bodies

b) Mutations of alpha-synuclein

c) Pallor of the substantia nigra

d) Lewy bodies within neurons

Question 8:

LRRK2 mutation is associated with which of the following conditions?

a) Alzheimer disease

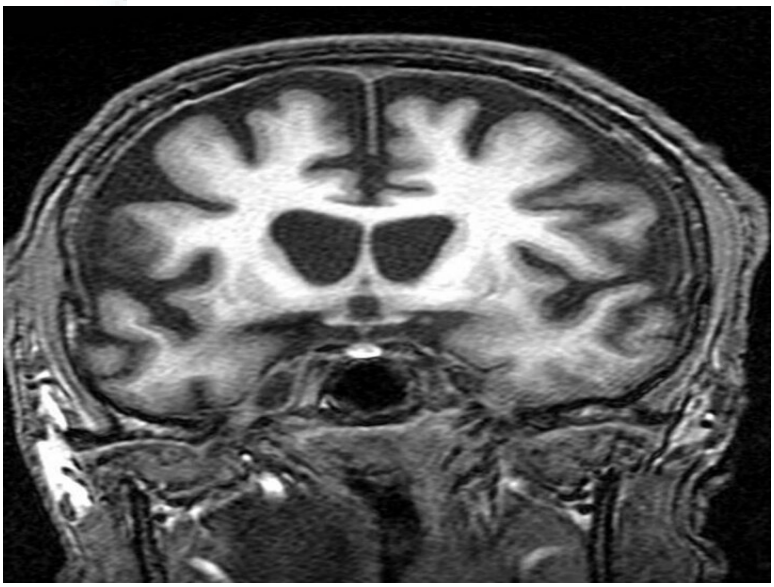
b) Parkinson's disease

c) Frontotemporal dementia

d) Multiple system atrophy

Question 9:

A wife brings her 52-year-old husband to the OPD with complaints of involuntary, sudden, jerky movements of his hands. She also tells that he has been occasionally forgetting the route to his office. His older brother also developed similar complaints last year. MRI revealed the following findings. Which of the following is incorrect about this condition?



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a) It has an X-linked recessive mode of inheritance

b) The phenomenon of anticipation is seen

c) Severity is related to the length of the CAG repeats

d) There is degeneration of GABAergic neurons

Question 10:

In patients with Huntington's disease, the mutated gene is located on which chromosome?

a) 4

b) 16

c) 17

d) 2

Question 11:

A 10-year-old boy was brought to the OPD with difficulty in climbing stairs and walking long distances. His parents say that he has received complaints at school due to progressively worsening handwriting. On examination, pes cavus is noted. Investigations revealed scoliosis and hypertrophic cardiomyopathy. Which of the following is incorrect regarding this condition?

a) Autosomal recessive inheritance

b) Presence of extensor plantar reflex

c) Expansion of a GAA trinucleotide repeat

d) Association with chromosome 19

Question 12:

While studying a spinal cord section, a pathology resident noted that the nuclei of the Schwann cells of the dorsal root ganglia were enlarged nearly 5 times the normal size. This finding is seen in which of the following conditions?

a) Machado-Joseph disease

b) Friedreich ataxia

c) Ataxia-telangiectasia

d) Amyotropic lateral sclerosis

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Question 13:

Match the following:

a) 1-b, 2-d, 3-a, 4-c

b) 1-c, 2-d, 3-a, 4-b

c) 1-d, 2-a, 3-b, 4-c

d) 1-b, 2-c, 3-d, 4-a

Question 14:

Bergmann gliosis is due to the loss of which of the following?

a) Purkinje cells

b) Pyramidal cells

c) Astrocytes

d) Oligodendrocytes

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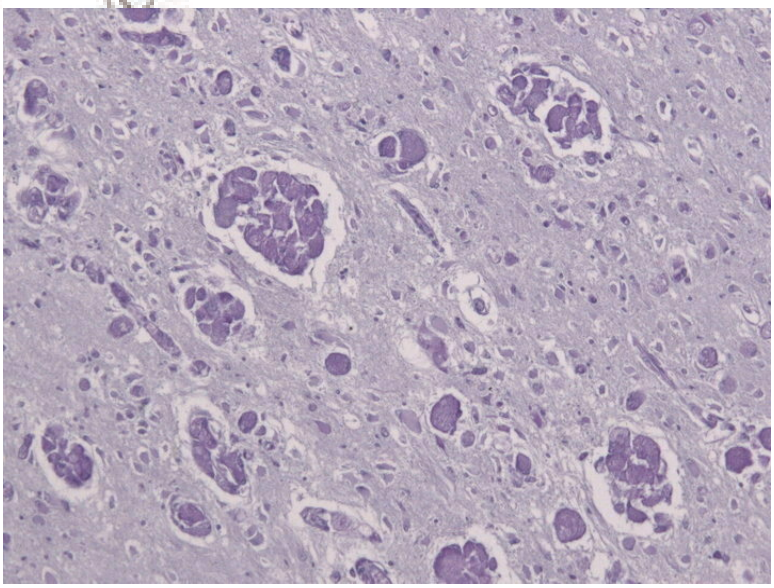
Question 15:

A 5-month-old baby was brought to the OPD with complaints of irritability, stiffness, and weakness of limbs. On examination, there was hypertonia of limbs. After a few months, the baby died due to the rapid progression of the disease. A brain autopsy was done and the following cells were seen. What are these cells?



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a) Macrophages

b) Adipocytes

c) Hepatocytes

d) Astrocytes

Question 16:

A 35-year-old man presented with frequent falls and tingling in his extremities. On examination, an unsteady gait with a positive Romberg sign was noted. Additionally, there was loss of proprioception and vibration sense and deep tendon reflexes in the lower limbs. Blood investigations revealed the following. Deficiency of which of the following vitamins is the likely cause of this condition?

a) Thiamine

b) B12 only

c) B12 and folic acid

d) Vitamin E

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Question 17:

Korsakoff syndrome is caused by the deficiency of which vitamin?

a) B1

b) B3

c) B6

d) B12

Answer Key

Question No.	Correct Option
1	d
2	a
3	c
4	a
5	d

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6	b
7	a
8	b
9	a
10	a
11	d
12	c
13	b
14	a
15	a
16	b
17	a

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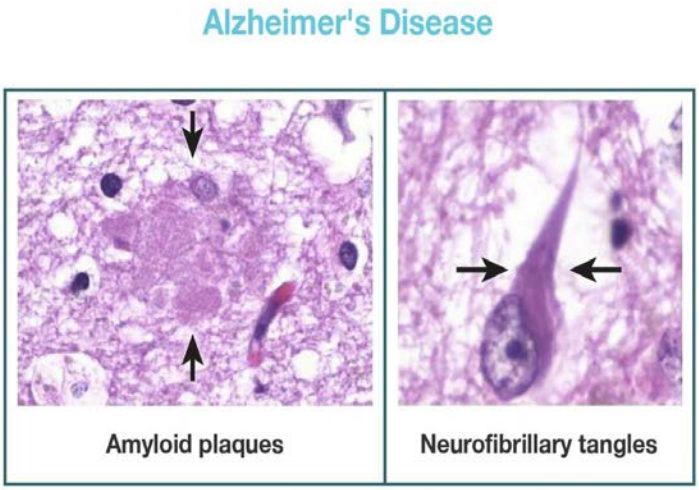
Detailed Explanations

Solution to Question 1:

Apolipoprotein E4 is a risk factor for Alzheimer's disease.

Solution to Question 2:

The clinical scenario and the images showing amyloid plaques and neurofibrillary tangles are diagnostic of Alzheimer's disease (AD), complicated by cerebral amyloid angiopathy (CAA). The formation and aggregation of A° peptides are responsible for AD.



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Amyloid precursor protein (APP) is neurotrophic and neuroprotective. It is present in astrocytes and neuroglia. This protein is cleaved at 3 sites by secretase enzymes (α, °, and γ), and the products are known as A° peptides.

In Alzheimer's disease, A° peptides get aggregated in the form of amyloid plaques, which stain positive for Congo red. These get deposited within the neural tissue (A° 42) and the cerebral arterioles (A° 40 protein, causing CAA), which causes neuronal dysfunction, and is the first sign of AD.

Normally, tau proteins within the neurons stabilize microtubules, however, in AD, these get hyperphosphorylated and lose their function. Hyperphosphorylated tau proteins combine with cytoplasmic fibrils, to form neurofibrillary tangles (NFTs) and get abnormally accumulated around the neuronal nucleus.

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Solution to Question 3:

In Alzheimer's disease, presenilin-2 (PS2) is present on chromosome 1, not chromosome 9.

The following gene loci are seen in Alzheimer's disease:

Gene locus	Chromosome	Significance
Amyloid precursor protein	21	Down syndrome region
Presenilin-1	14	Early-onset familial AD
Presenilin-2	1	Early-onset familial AD
Apoprotein E4	19	Risk of developing AD

Solution to Question 4:

Spinal bulbar muscular atrophy results in androgen insensitivity.

It is an X-linked lower motor neuron disorder caused by CAG repeats in the gene encoding the polyglutamine tracts of the androgen receptor. It presents with progressive weakness and wasting of limb and bulbar muscles and features of androgen insensitivity like gynecomastia and reduced fertility.

Disease	Pathological protein
Huntington's disease	Huntington (Polyglutamine)
Spinocerebellar ataxia(SCA1, 2, 6, 7, 17 and DRPLA)	Various proteins (Polyglutamine containing)
Amyotrophic lateral sclerosis	SOD1, TDP-43, FUS

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Disease	Pathological protein
Spinal-bulbar muscular atrophy	Androgen receptor (Polyglutamine containing)

Solution to Question 5:

Neurofibrillary tangles (NFTs) are found in:

• Normal aging

• Subacute sclerosing panencephalitis

• Alzheimer's disease

NFTs are aggregates of hyperphosphorylated tau proteins (microtubule-associated proteins) found in numerous diseases known as tauopathies. NFTs can also be seen in relatively lower numbers in elderly people without dementia.

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Solution to Question 6:

Punch drunk syndrome is due to accumulation of tau proteins in the brain.

This condition is also called dementia pugilistica or chronic traumatic encephalopathy. It is a dementing illness that develops following repeated head trauma in boxers and other athletes. Affected brains are typically atrophic, with enlarged ventricles. They show accumulation of tau--containing□ neurofibrillary tangles in a characteristic pattern involving the superficial frontal and temporal lobe cortex.

Solution to Question 7:

This clinical scenario is suggestive of Parkinson's disease. This condition is not associated with Pick cells and Pick bodies. They are seen in Pick's disease or frontotemporal dementia.

In Parkinson's disease, there is loss of the substantia nigra neurons projecting to the striatum. This leads to pallor of the substantia nigra as well as a decrease or absence of dopamine in the striatum. This leads to slowing of movements and tremors.

Lewy Bodies are seen within the neurons of affected patients. They are filamentous projections of the protein α■synuclein or ubiquitin. They are present in surviving neurons and can be found in the cortex.

Solution to Question 8:

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Mutations in the gene encoding LRRK2 (leucine rich repeat kinase 2) are a common cause of autosomal dominant Parkinson's disease. They are also found in some sporadic cases of the disease.

Solution to Question 9:

The MRI shows bilateral atrophy of caudate nuclei with compensatory dilatation of lateral ventricles, also known as boxcar ventricles. Along with the clinical features, it is suggestive of Huntington's disease (HD). It has an autosomal dominant mode of inheritance.

It is commonly seen in the 4th and 5th decades of life. It is a degenerative disease of the caudate and putamen (striate neurons) caused by trinucleotide (CAG) repeats in the huntingtin gene on chromosome 4. The severity of the disease depends on the number of repeats. With more repeats, the disease becomes more severe. The disease also manifests at an earlier age, a phenomenon called anticipation.

The caudate nucleus is dramatically atrophied, with accompanying atrophy of the putamen, cortex, and hydrocephalus ex vacuo of the 3rd ventricle. The medium-sized GABAergic neurons are especially affected.

It causes chorea and dementia. Motor problems like chorea typically precede dementia.

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Solution to Question 10:

In Huntington's disease, the affected HTT gene is located on chromosome 4.

The coding region has a trinucleotide repeat (CAG/ glutamine). The severity and age of onset of the disease depend on the number of repeats increases. This phenomenon is called anticipation.

Solution to Question 11:

The given clinical scenario is suggestive of Friedrich's ataxia. It is associated with mutations of genes on chromosome 9q13.

It is an autosomal recessive disease caused by the expansion of a GAA trinucleotide repeat in the gene encoding frataxin. The clinical features are given by the mnemonic FRIEDRICHS:

- F - Frequent falls (ataxia), foot deformity (pes cavus or overarched foot)
- R - Recessive
- I - Iron accumulation in mitochondria
- E - Eye movements (nystagmus)
- D - Dorsal column (loss of fine touch, vibration, position)
- R - Reflexes (deep tendon) lost, with extensor plantar reflex
- I - Incoordination

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- C - Cerebellar involvement
- H - Hypertrophic cardiomyopathy (HCM)
- S - Scoliosis (with kyphosis), staggering gait

Solution to Question 12:

In ataxia-telangiectasia, the nuclei of the Schwann cells of the dorsal root ganglia are enlarged to nearly 2-5 times the normal size. This finding is seen in the Schwann cells of dorsal root ganglia, peripheral nerves, endothelial cells, and pituicytes. These cells are called amphicytes.

Ataxia-telangiectasia is due to mutations of the ATM gene, located on chromosome 11q. It predominantly affects the cerebellum with the loss of Purkinje and granule cells. There is also degeneration of the dorsal columns, spinocerebellar tract, anterior horn cells, and peripheral neuropathy.

Telangiectatic lesions are found in the CNS as well as in the conjunctiva and skin of the face, neck, and arms. The lymph nodes, thymus, and gonads are hypoplastic.

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Solution to Question 13:

The given pathological findings are seen in the following conditions:

Pathologic findings	Conditions
Bunina bodies	Amyotrophic lateral sclerosis
Pick bodies	Frontotemporal dementia
Lewy bodies	Parkinson's disease
Verocay bodies	Schwannoma

Solution to Question 14:

Bergmann gliosis is due to the loss of Purkinje cells.

It occurs in advanced cases of chronic alcoholism. There is a loss of Purkinje cells and proliferation of the adjacent astrocytes between the depleted granular cell layer and the molecular layer of the cerebellum.

Solution to Question 15:

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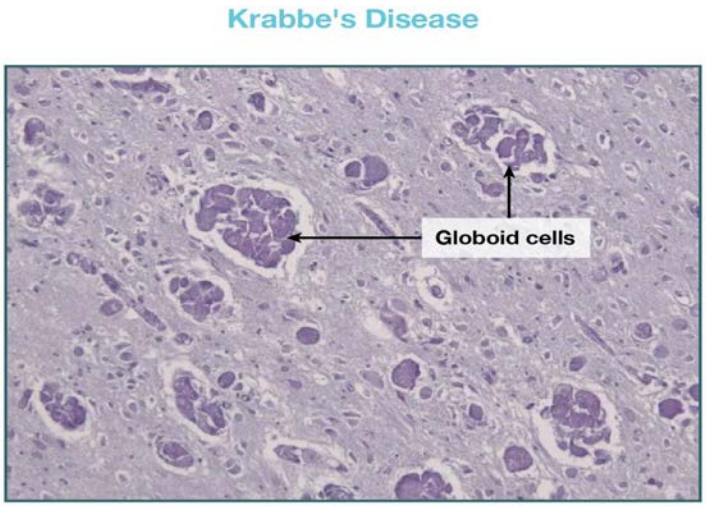
The clinical scenario showing motor symptoms and rapid progression to death, an autopsy of the brain showing globoid cells is highly suggestive of Krabbe's disease. The globoid cells are macrophages.



Krabbe's disease or globoid cell leukodystrophy is a neurodegenerative disorder with severe myelin destruction due to a deficiency of galactocerebroside °-galactosidase.

The onset of symptoms is between 3 to 6 months of age, dominated by motor signs such as stiffness and weakness. Survival beyond the age of 2 years is uncommon. The brain shows loss of myelin and oligodendrocytes with a similar process affecting the peripheral nerves.

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Solution to Question 16:

The given clinical scenario with involvement of the dorsal column and investigations showing macrocytic anemia is suggestive of subacute combined degeneration (SACD) of the spinal cord. It is due to a deficiency of vitamin B12 which is involved in myelin synthesis.

The most severely affected regions are the posterior columns at the cervical and upper thoracic levels.

The clinical features include:

• Peripheral nerve and spinal cord involvement

• Paresthesias in the hands or feet

• Weakness and unsteadiness of gait

• Loss of vibration or joint position sense in the legs

• Mental slowing, depression, confusion, delusions, and hallucinations

MRI spine shows diffuse myelopathy and areas of demyelination. Treatment involves a replacement regimen of vitamin B12 intramuscular daily injections of 1000 µg for the first week followed by weekly 1000 µg injections for 1 month. Monthly injections are given thereafter.

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While vitamin E deficiency can also cause SACD, it is rare and is associated with hemolytic anemia.

Solution to Question 17:

Korsakoff syndrome is caused by the deficiency of thiamine.

This syndrome is characterized by pronounced anterograde and retrograde amnesia along with impairment in visuospatial, abstract, and other types of learning. It is usually completely or partially permanent in about half the patients.

Wernicke's encephalopathy refers to the acute form of thiamine deficiency. It is characterized by nystagmus and ophthalmoplegia, mental status changes, and unsteadiness of stance and gait. It is a medical emergency and IV or IM thiamine should be initiated immediately.

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CNS Tumours

Question 1:

Which of the following is the most common primary malignant brain tumor in children?

a) Medulloblastoma

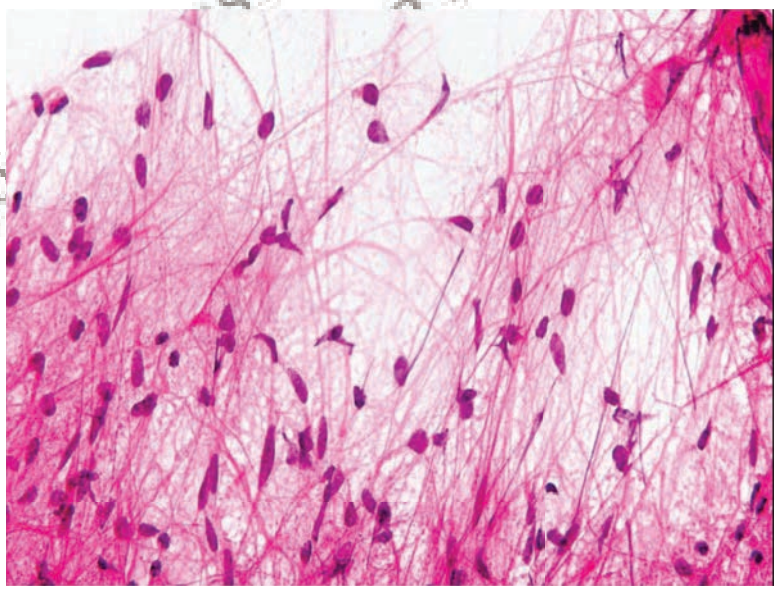
b) Oligodendroglioma

c) Pilocytic astrocytoma

d) Ependymoma

Question 2:

A 6-year-old child is brought with complaints of unsteadiness and gait disturbance. On neurological examination, nystagmus, areflexia, and hypotonia are noted. Contrast-enhanced MRI of the brain shows enhancing nodule within the wall of a cystic mass. The mass is resected and histology shows the given finding. Which of the following statements is incorrect regarding this tumor?



a) BRAF mutation is seen in this tumor

b) It is GFAP positive

c) It is usually slow growing

d) It belongs to WHO grade II tumors

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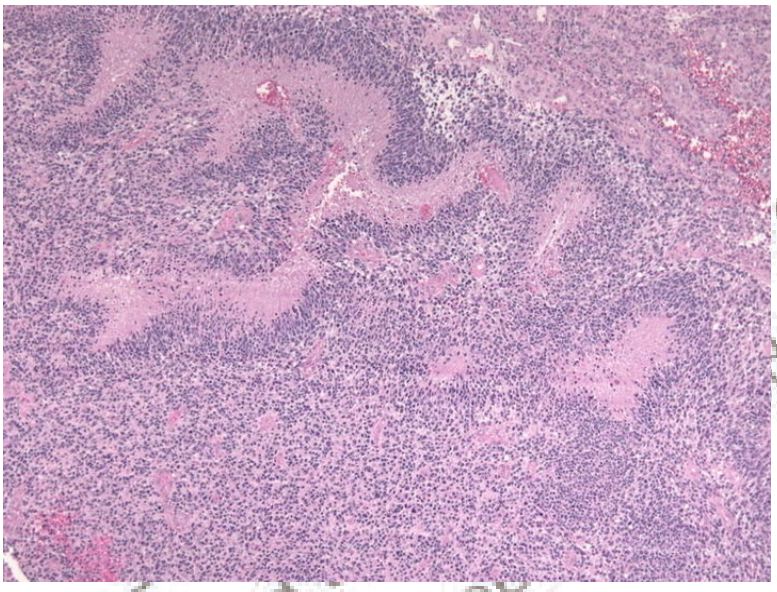
Question 3:

A 65-year-old patient presents with headache, seizures, and focal neurological deficit. Imaging shows a tumor in the right frontal lobe which crosses the midline and the histological section of the resected tumor is shown below. Which of the following molecular subtypes does this tumor belong to?



a) IDH - wild type

b) IDH - mutant type

c) P53 - wild type

d) P53 - mutant type

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Question 4:

A 40-year-old patient presents to the OPD with recurrent seizures, headache, and projectile vomiting. MRI brain reveals cortical-based heterogeneous tumor with calcification in the frontal lobe. The histological section of the resected tumor shows perineuronal satellitosis. Which of the following is the most common genetic alteration noted in this tumor?

a) Mutation of the isocitrate dehydrogenase genes

b) Deletion of portions of chromosomes 1p and 19q

c) Loss of 9p

d) Mutation in CDKN2A

Question 5:

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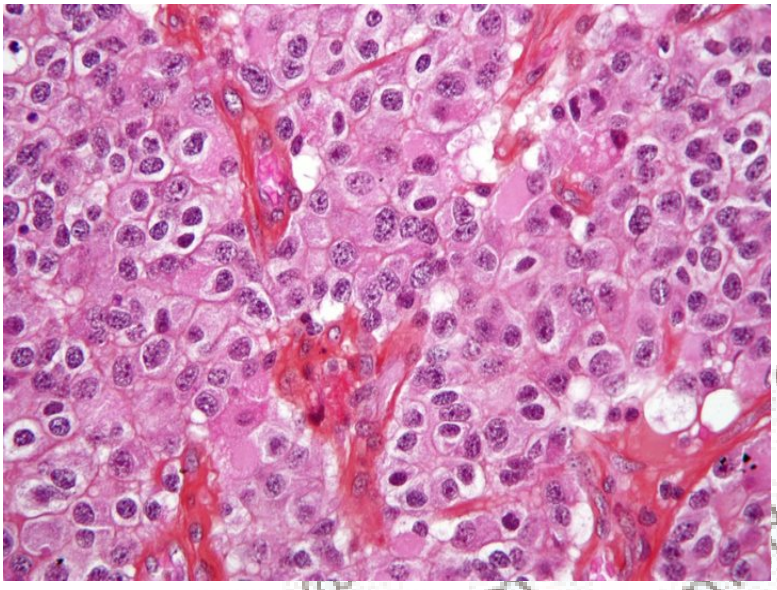
The histological section of an intracranial space-occupying lesion resected from a patient is given below. Which of the following tumors shows this pattern?



a) Pleomorphic Xanthoastrocytoma

b) Medulloblastoma

c) Oligodendroglioma

d) Ependymoma

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Question 6:

Which of the following statements is incorrect regarding oligodendroglioma?

a) It shows perinuclear halos and perineuronal satellitosis

b) Tumor showing IDH1 and IDH2 mutation carries good prognosis

c) It commonly involves the white matter of the cerebral hemispheres

d) Tumor showing co-deletion of 9p and 10q is chemosensitive

Question 7:

The spinal MRI of a 30-year-old patient with neurofibromatosis type 2 shows an ependymoma. Which of the following is true regarding this tumor?

a) Ependymoma is predominantly a spinal tumor

b) Ependymoma in children commonly arises from the roof of the fourth ventricle

c) CSF seeding of metastasis is commonly seen

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d) Posterior fossa ependymoma mostly presents with ataxia

Question 8:

The fluorescence in situ hybridization done in a patient with supratentorial ependymoma shows positivity for RELA fusion protein. What is the prognosis of this molecular subtype?

a) Excellent

b) Worst

c) Variable

d) Intermediate

Question 9:

An obese patient is being evaluated for recurrent low back pain radiating to both the lower limbs. Imaging shows a myxopapillary ependymoma located in the spinal cord. Which of the following statements regarding this tumor is incorrect?

a) It belongs to WHO grade 2 tumors

b) It commonly arises from the filum terminale

c) It consists of mucopolysaccharides and a papillary core consisting of blood vessels microscopically

d) It follows an aggressive clinical course

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Question 10:

A 12-year-old boy presents with complaints of headache, projectile vomiting, and blurring of vision. CT scan shows a mass lesion in the posterior cranial fossa. His medical records are unremarkable, except for a family history of colon cancer in three of his relatives. What is the most probable syndrome that this patient has?

a) Gorlin syndrome

b) Turcot syndrome

c) Lynch syndrome

d) Neurofibromatosis

Question 11:

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Which of the following statements regarding medulloblastoma is incorrect?

a) It belongs to WHO Grade II tumors

b) Drop metastases is a common complication

c) It is an extremely radiosensitive tumor

d) Isochromosome 17q signals a poor prognosis

Question 12:

A 40-year-old smoker diagnosed with small cell carcinoma of the lung 1 year back now develops seizures, short-term memory loss, and psychiatric symptoms. Which of the following paraneoplastic conditions can be attributed to this presentation?

a) Subacute cerebellar degeneration

b) Limbic encephalitis

c) Opsoclonus myoclonus

d) Lambert Eaton syndrome

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Question 13:

A 28-year-old pregnant woman is diagnosed with a meningioma. which of the following growth patterns does the tumor exhibit in the subsequent trimesters of her pregnancy?

a) The tumor grows rapidly throughout her pregnancy

b) The tumor shrinks throughout her pregnancy

c) The tumor grows rapidly in first trimester and shrinks thereafter

d) The size of the tumor exhibits no change throughout her pregnancy

Question 14:

The MRI of a woman presenting with recurrent headaches is given below. Microscopy of the resected tumor shows psammoma bodies and the tumor cells express progesterone receptors. Which of the following is the most common cytogenetic abnormality noted in this tumor?

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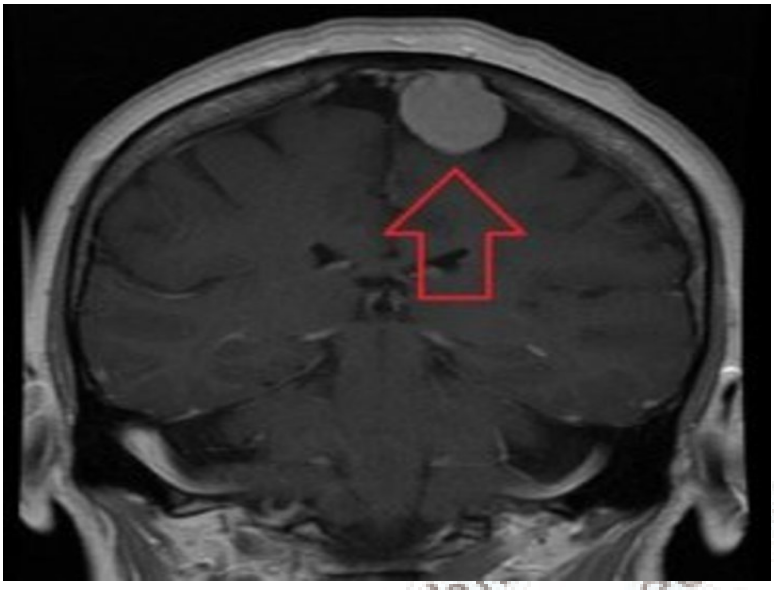

a) 22q deletion

b) 9p deletion

c) 17q deletion

d) 1p deletion

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Question 15:

Which of the following tumors is most commonly associated with meningeal carcinomatosis?

a) Breast carcinoma

b) Lymphoma

c) Malignant melanoma

d) Colon carcinoma

Question 16:

Which of the following types of herniation is characterised by duret hemorrhages?

a) Transtentorial herniation

b) Subfalcine herniation

c) Tonsillar herniation

d) Cingulate herniation

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Question 17:

Which of the following structures is involved in tonsillar herniation?

a) Brainstem

b) Cerebellum

c) Temporal lobe

d) Cingulate gyrus

Question 18:

Which of the following is the most common CNS neoplasm in immunosuppressed patients?

a) Medulloblastoma

b) Astrocytoma

c) Glioblastoma

d) Lymphoma

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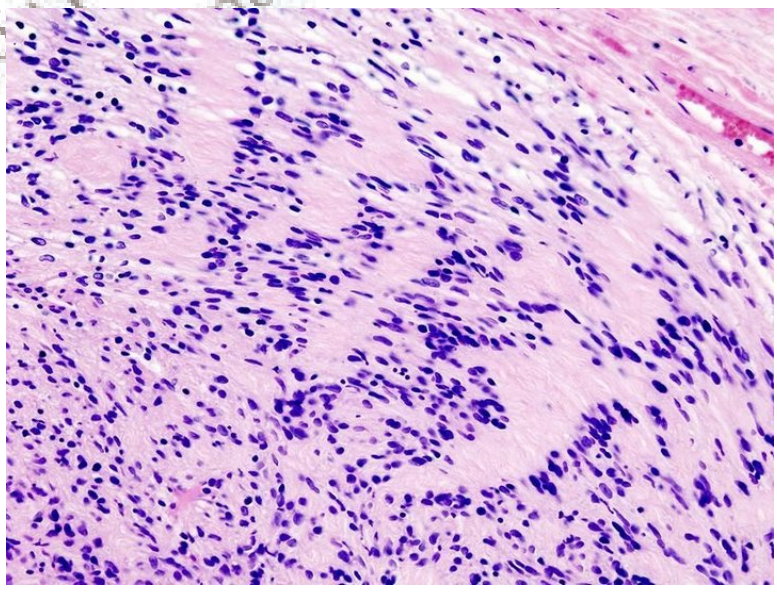
Question 19:

A 14-year-old patient presents with bilateral proptosis. The biopsy from the region shows this pattern. What is the likely diagnosis?



a) Leiomyoma

b) Schwannoma

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c) Rhabdomyosarcoma

d) Fibromatosis

Question 20:

CSF spread can occur in patients with all of the following tumors, except:

a) Medulloblastoma

b) Ependymoma

c) Oligodendroglioma

d) Meningioma

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Answer Key

Question No.	Correct Option
1	a
2	d
3	a
4	a
5	c
6	d
7	a
8	b
9	d
10	b
11	a
12	b
13	a
14	a
15	a
16	a
17	b
18	d
19	b
20	d

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Detailed Explanations

Solution to Question 1:

Most common primary malignant brain tumor in children is medulloblastoma.

Solution to Question 2:

The given clinical history and the image showing Rosenthal fibers is diagnostic of pilocytic astrocytoma. It belongs to WHO grade I tumors.

Pilocytic astrocytoma typically occurs in children and young adults and is usually located in the cerebellum. It is usually a slow-growing tumor and if it occurs in the cerebellum, it can be resected. If it extends into the hypothalamic region from the optic tract, it can have a more ominous clinical course because of its location.

It is often cystic, if solid, it may be well circumscribed. It is often biphasic with both loose microcystic and fibrillary areas.

The tumor is composed of bipolar cells with long, thin hair-like processes that are GFAP-positive and form dense fibrillary meshworks. Rosenthal fibers and eosinophilic granular bodies are characteristic findings under microscopy. BRAF mutation is seen in this tumor.

Solution to Question 3:

The clinical history and histological image are suggestive of primary glioblastoma, IDH - wild type.

The given histological image shows foci of necrosis with pseudo-palisading of malignant nuclei and endothelial cell proliferation, which are characteristic of glioblastoma (previously called glioblastoma multiforme).

According to the WHO classification of CNS diseases 2016, glioblastomas are classified as follows:

1. Glioblastoma, IDH - wild type:

• About 90% of the cases

• Primary or de novo glioblastoma

• Over 55 years of age

2. Glioblastoma, IDH - mutant type:

• About 10% of the cases

• Secondary glioblastoma, with a history of prior lower-grade diffuse glioma

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• Arises in younger patients

3. Glioblastoma, NOS, where full IDH evaluation cannot be performed.

Solution to Question 4:

The clinical picture is suggestive of oligodendroglioma and the most common genetic alterations in oligodendroglioma are mutations of the isocitrate dehydrogenase (IDH1 and IDH2) genes.

IDH1 and IDH2 gene mutations are seen in upto 90% of oligodendroglioma and they are associated with a better prognosis. Deletions of portions of chromosomes 1p and 19q are seen in up to 80% of the cases.

Solution to Question 5:

The histological image shows fried egg appearance of cells and is seen in oligodendroglioma.

Oligodendroglioma is an infiltrating glioma comprised of cells that resemble oligodendrocytes. It commonly occurs in the fourth and fifth decades. The lesion is found mostly in the cerebral hemispheres, with a predilection for white matter.

The tumor is composed of sheets of regular cells with spherical nuclei containing finely granular chromatin (similar to normal oligodendrocytes) surrounded by a clear halo of vacuolated cytoplasm giving a fried egg appearance. Tumor cells infiltrating the cerebral cortex often collect around the neurons (perineuronal satellitosis).

Fried eggs in pathology:

• Oligodendroglioma on histopathology

• Hairy cell leukemia on bone marrow biopsy

• Seminoma / Dysgerminoma on light microscopy

• Mycoplasma pneumonia fried egg colonies on Eaton agar

Solution to Question 6:

Oligodendroglioma showing co-deletion of 9p and 10q is chemoresistant.

Mutations in oligodendroglioma and their responsiveness to chemotherapy:

Mutations	Chemo-radiation
IDH 1, IDH 2	sensitive
1p, 19q codeletion	sensitive

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Mutations	Chemo-radiation
9p loss, 10q loss,CDKN2A mutation	resistant

Solution to Question 7:

Ependymoma is predominantly a spinal tumor in adults and is commonly associated with neurofibromatosis type 2.

CSF dissemination is uncommon despite the relationship of the ependymoma with the ventricular system.

Posterior fossa ependymoma often manifests with hydrocephalus secondary to progressive obstruction of the fourth ventricle.

	Tumor site	Recurrence
Adults	Spinal cordSupratentorialPosterior fossa	Rare
Children	Infratentorial(floor of the fourth ventricle)	Frequent

Solution to Question 8:

RELA fusion protein positive ependymoma carries the worst prognosis.

This highlights the importance of immunohistochemistry in the role of prognosis of ependymoma.

Solution to Question 9:

Myxopapillary ependymoma is a slow-growing tumor and do not follow an aggressive clinical course.

Myxopapillary ependymoma belongs to WHO grade 2 tumors histologically as of the 2021 WHO clasiffication of central nervous system tumors. It occurs commonly in the filum terminale of the spinal cord and contains papillary elements in a myxoid (acidic and neutral mucopolysaccharides) background, admixed with ependymoma-like cells microscopically.

Solution to Question 10:

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The given clinical features and the family history of colon cancer point to the diagnosis of Turcot syndrome.

Turcot syndrome is a rare hereditary disorder clinically characterized by the occurrence of primary tumors of the colon and the central nervous system.

Two types of tumors are seen in Turcot syndrome. The first is characterized by childhood cerebellar medulloblastoma caused by mutations in the APC gene. The second type is characterized by gliomas, particularly glioblastoma multiforme, arising in both children and adults and is related to mismatch repair gene mutations.

Familial carcinoma syndromes and the common malignancies associated with them:

- Gorlin syndrome: Medulloblastoma and multiple early-onset basal cell carcinomas
- Lynch syndrome: Gastrointestinal and genito-urinary tumors and rarely gliomas in the brain
- Neurofibromatosis: Schwannoma

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Solution to Question 11:

Medulloblastoma belongs to WHO grade IV tumors.

Medulloblastoma accounts for 20% of brain tumors in children. It occurs predominantly in children and exclusively in the cerebellum. Drop metastasis through CSF dissemination is a common complication. It is an extremely radiosensitive tumor.

Molecular classification of medulloblastoma:

Group	Molecular alteration	Prognosis
WNT type	Monosomy 6 and beta - catenin overactivity	Best
SHH type	Mutation in sonic hedgehog pathway	Intermediate
Group 3	Isochromosome 17q with MYC amplification	Worst
Group 4	Isochromosome 17q without MYC amplification, but sometimes with MYCN amplification	Intermediate

Solution to Question 12:

The given clinical history is suggestive of limbic encephalitis.

Limbic encephalitis is characterized by subacute dementia. Histologically, it is characterised by perivascular inflammatory cuffs, microglial nodules, neuronal loss, and gliosis evident in the anterior and medial portions of the temporal lobe.

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Some of these patients have a circulating ANNA1 antibody (antiHu) that is most commonly associated□ with small cell carcinoma of the lung. Another group of these patients have a circulating antibody that recognizes the NMDA receptor and cross-reacts with hippocampal neurons.

Solution to Question 13:

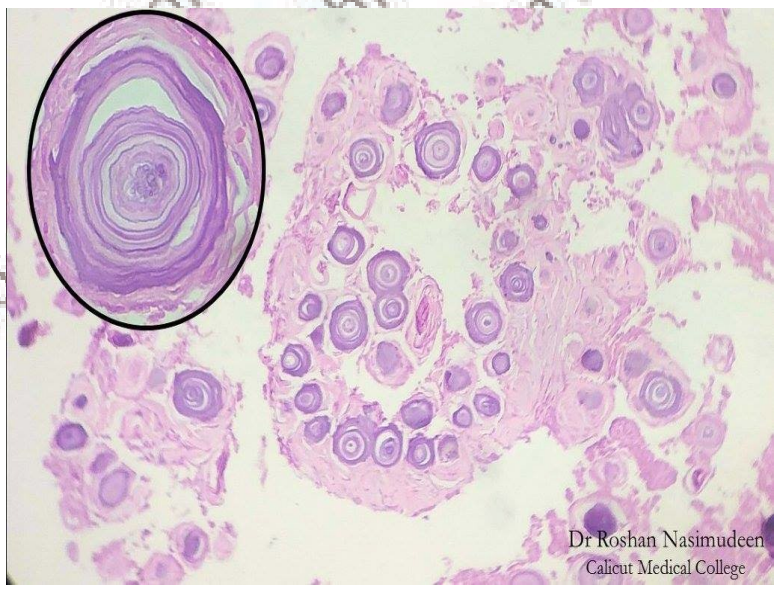
Meningiomas express progesterone receptors and grow more rapidly during pregnancy.

Meningiomas are usually slow growing tumors. They show a moderate female predominance.

The common sites of involvement of meningiomas are:

- The parasagittal aspect of the brain convexity
- Dura over the lateral convexity
- Wings of the sphenoid
- Olfactory groove
- Sella turcica
- Foramen magnum.

The histological section of meningioma showing psammoma bodies is given below:



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Solution to Question 14:

The given MRI showing homogeneously enhancing extra - axial, dural based tumor and the microscopic findings are highly suggestive of meningioma. The most common cytogenetic abnormality in meningioma is 22q deletion.

Meningioma is predominantly a benign tumors of adults, usually attached to the dura. It arises from the meningothelial cells of the arachnoid. 50% - 60% of the sporadic meningioma harbors

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mutations in the NF2 gene (in chromosome 22q12) resulting in the absence of functional merlin protein. In meningioma without NF2 mutations, the most common mutations occur in TNF receptor - associated factor 7 (TRAF7).

Solution to Question 15:

Breast carcinoma is commonly associated with meningeal carcinomatosis.

Meningeal carcinomatosis presents as tumor nodules studding the surface of the brain, spinal cord, and intradural nerve roots.

Solution to Question 16:

Duret hemorrhages are characteristic of transtentorial herniation.

Transtentorial (uncinate, mesial temporal) herniation occurs when the medial aspect of the temporal lobe is compressed against the free margin of the tentorium. Progression of transtentorial herniation is often accompanied by secondary hemorrhagic lesions in the midbrain and pons, termed Duret hemorrhages. These linear or flame - shaped lesions usually occur in the midline and paramedian regions and are believed to be due to the distortion or tearing of penetrating veins and arteries supplying the upper brainstem.

With increasing displacement of the temporal lobe, the third cranial nerve is compromised, resulting in pupillary dilation and impairment of ocular movements on the side of the lesion. The posterior cerebral artery may also be compressed, resulting in ischemic injury to the territory supplied by that vessel, including the primary visual cortex.

When the extent of herniation is large enough, the contralateral cerebral peduncle may be compressed, resulting in hemiparesis ipsilateral to the side of the herniation. The compression in the peduncle in this setting is known as the Kernohan notch.

Solution to Question 17:

Cerebellum is involved in tonsillar herniation.

Tonsillar herniation refers to the displacement of the cerebellar tonsils through the foramen magnum. This pattern of herniation is life-threatening because it causes brainstem compression and compromises vital respiratory and cardiac centers in the medulla.

Solution to Question 18:

Primary central nervous system lymphoma is the most common CNS neoplasm in immunosuppressed individuals, including those with AIDS and immunosuppression after transplantation.

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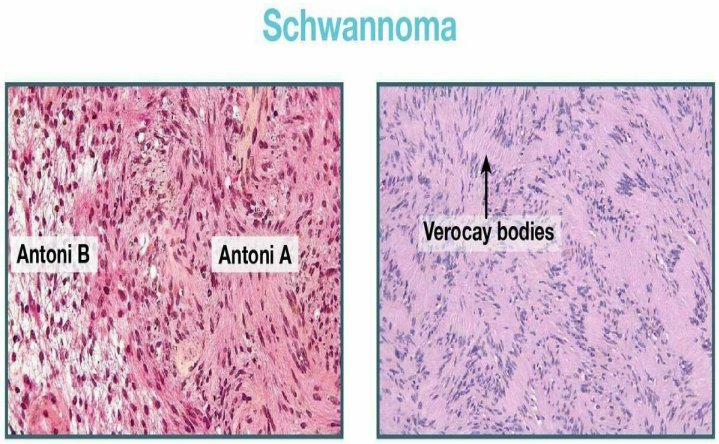
The vast majority of primary central nervous system lymphomas are of B-cell origin. Overall, primary central nervous system lymphomas are aggressive and have worst outcome. The Epstein-Barr virus plays an important role in the pathogenesis of HIV-related primary central nervous system lymphoma.

Solution to Question 19:

The given clinical history and biopsy picture is characteristic of schwannoma.

The biopsy specimen in schwannoma shows hypocellular (Antoni B) and hypercellular areas (Antoni A). Antoni A area has the nuclei of tumor cells aligned in palisading rows. The nuclear-free zones that lie between nuclear palisading are known as Verocay bodies.

The histological section of a schwannoma showing Antoni A, Antoni B and Verocay bodies is given below:



Solution to Question 20:

Most of the meningiomas are benign tumors and very rarely metastasize to CSF.

The primary intracerebral malignancies that may cause metastases to the subarachnoid space are:

- Glioblastoma (GBM)
- Anaplastic astrocytoma
- Medulloblastoma
- Ependymoma
- Pineoblastomas
- Oligodendroglioma

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Leptomeningeal metastases, also known as carcinomatous meningitis, refer to the spread of malignant cells through the CSF space. These cells can originate both in primary CNS tumors (e.g. drop-metastases), as well as from distant tumors that have metastasized (hematogenous spread).

The most common secondary tumors that spread to CSF are breast cancer > lung cancer > melanoma > GI malignancies.

Contrast MRI is the investigation of choice and shows leptomeningeal enhancement and tumor scattered over the brain in a ‘sugar-coated’ manner.

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Peripheral nerves & Neuromuscular pathology

Question 1:

What is the most common cause of peripheral neuropathy?

a) Nutrition deficiency

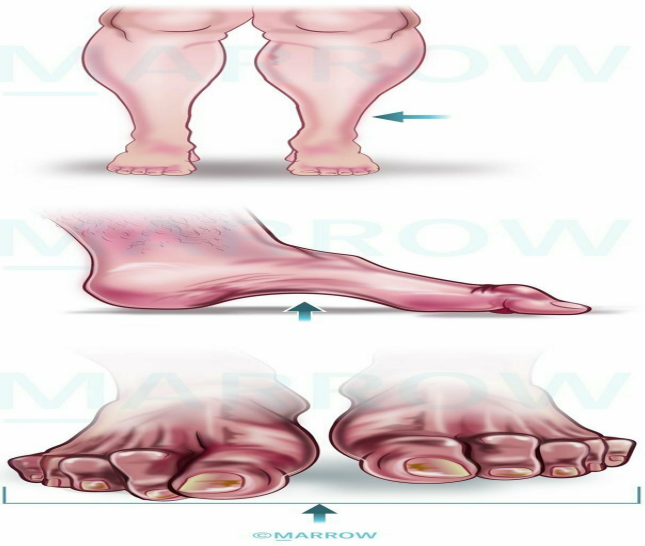
b) Paraneoplastic syndrome

c) Diabetes mellitus

d) Drug-induced

Question 2:

A 20-year-old man presents with distal leg weakness with no complaints of tingling or numbness. On examination, you note reduced muscle stretch reflexes below the knee along with the following findings. This condition is associated with which chromosome?



a) 17

b) 19

c) 1

d) 13

Question 3:

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A 32-year-old woman comes with complaints of double vision that gets worse after she reads a book or watches television. She also has drooping of the eyelids that gets better after a nap. Serology is positive for anti-acetylcholine receptor antibodies. Which of the following is more commonly associated with this condition?

a) Thymoma

b) Thymic hyperplasia

c) Medullary carcinoma of thyroid

d) Small cell lung carcinoma

Question 4:

A 52-year-old man presents with mild ptosis and proximal lower limb weakness. Nerve conduction studies show incremental response following brief exercise. Further investigations reveal antibodies against presynaptic P/Q voltage-gated calcium channels. Which of the following malignancies is associated with this condition?

a) Small cell lung cancer

b) Thymoma

c) Medullary thyroid cancer

d) Parathyroid cancer

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Question 5:

What is the most common inflammatory myopathy in children?

a) Dermatomyositis

b) Polymyositis

c) Inclusion body myositis

d) Viral myositis

Question 6:

A 51-year-old woman presents with complaints of weakness for 2 months. She reports that she has difficulty rising from a chair and combing her hair every morning. Physical exam reveals decreased strength in the shoulders and hip. Muscle biopsy findings are shown below. What is the likely diagnosis?

[Image unavailable]

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a) Dermatomyositis

b) Polymyositis

c) Inclusion body myositis

d) Viral myosistis

Question 7:

A patient with gastric carcinoma develops proximal muscle weakness. Biopsy findings are suggestive of dermatomyositis. Which of the following antibodies are most likely to be present in this patient?

a) Anti-Mi2 antibodies

b) Antiribosomal P antibodies

c) Anti-P155/P140 antibodies

d) Anti-Jo1 antibodies

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Question 8:

A patient with muscle weakness is found positive for antibodies against cN1A. What is the likely diagnosis?

a) Dermatomyositis

b) Polymyositis

c) Inclusion-body myositis

d) Viral myositis

Question 9:

An 8-year-old boy was brought with progressive muscle weakness and walking difficulties. The following finding was noted on examination. Genetic testing revealed a dystrophin gene mutation. On which chromosome is the affected gene located?

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a) X

b) Y

c) 21

d) 22

Question 10:

NARP syndrome is a?

a) Lysosomal storage disorder

b) Mitochondrial function disorder

c) Glycogen storage disorder

d) Golgi body transport disorder

Question 11:

Which of the following are mitochondrial disorders?

a) 2, 4, 5

b) 1, 3, 4

c) 1, 2, 3

d) 2, 3, 5

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Question 12:

Hypokalemic periodic paralysis is most commonly caused by the mutation of genes encoding which of the following ion channels?

a) Sodium

b) Calcium

c) Potassium

d) Chloride

Question 13:

In a child diagnosed with myotonia congenita, which of the following ion channel is likely to be mutated?

a) Sodium

b) Calcium

c) Potassium

d) Chloride

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Question 14:

Glial hamartia is a feature of which of the following conditions?

a) Neurofibromatosis type 1

b) Neurofibromatosis type 2

c) Tuberous sclerosis

d) Von Hippel-Lindau syndrome

Question 15:

A pathologist is examining a histopathological slide showing pseudo-Meissner corpuscles. This finding is seen in which of the following conditions?

a) Diffuse neurofibroma

b) Plexiform neurofibroma

c) Superficial cutaneous neurofibroma

d) Wallerian degeneration

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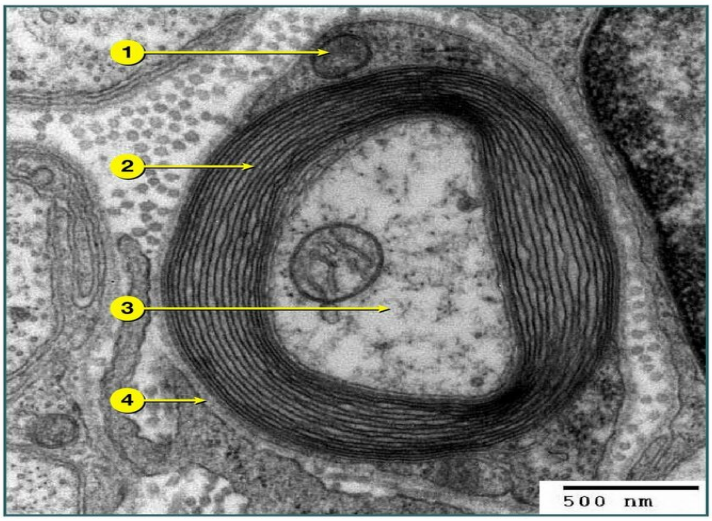
Question 16:

An electron microscopic picture of a cut section of a nerve fiber is given. Identify the area which will be affected in the most common variant of Guillain-Barré syndrome.



a) 1

b) 2

c) 3

d) 4

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Answer Key

Question No.	Correct Option
1	c
2	a
3	b
4	a
5	a
6	a
7	c
8	c

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9	a
10	b
11	d
12	b
13	d
14	b
15	a
16	b

Detailed Explanations

Solution to Question 1:

The most common cause of peripheral neuropathy is diabetes mellitus.

The most common pattern of diabetic neuropathy is an ascending, distal symmetric, sensorimotor polyneuropathy (glove and stocking type).

The most common type of hereditary neuropathy is Charcot-Marie-Tooth (CMT) disease.

Solution to Question 2:

The given clinical scenario is suggestive of Charcot–Marie–Tooth (CMT) disease. It is most commonly associated with chromosome 17.

It is the most common type of hereditary neuropathy. The most common variant of this condition is CMT1A. It is caused by a duplication of a region on chromosome 17 that includes the peripheral myelin protein 22 (PMP22) gene.

It usually presents in the first to third decade of life with distal leg weakness, e.g., foot drop with no numbness or tingling. There is reduced sensation to all modalities with reduced muscle stretch reflexes. Atrophy of the muscles below the knee leads to inverted champagne bottle legs.

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Solution to Question 3:

The given clinical scenario is suggestive of myasthenia gravis. It is most commonly associated with thymic hyperplasia (65% of cases).

Thymoma is seen in around 10% of patients with myasthenia gravis.

Myasthenia gravis is a neuromuscular disorder that is characterized by weakness and the fatigability of skeletal muscles. It is due to the autoantibody-mediated destruction of the acetylcholine receptors (AChRs) at the neuromuscular junction. This consequentially leads to a decreased transmission at the neuromuscular (myoneural) junction.

There is a characteristic pattern of muscle involvement. Lid and extraocular muscles (diplopia and ptosis) are involved early in the disease course. The facial muscles weakness can produce a snarling expression, weakness in chewing, and nasal timbre to the voice. Weakness increases with repeated use of the muscles and improves with rest. The reflexes are normal in this condition.

Solution to Question 4:

The given clinical scenario is suggestive of Lambert-Eaton myasthenic syndrome (LEMS). It is associated with small-cell lung carcinoma.

It is an autoimmune disorder caused by antibodies that block acetylcholine release by inhibiting a presynaptic calcium channel. In contrast to myasthenia gravis, rapid, repetitive stimulation (muscle activity) results in an increase in muscle response and strength.

Patients typically present with weakness of their extremities. In about half the cases, there is an underlying malignancy; most often, neuroendocrine carcinoma of the lung (Small cell lung carcinoma). The stimulus for autoantibody formation in paraneoplastic cases may be the expression of the same calcium channel in the neoplastic cells.

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Patients without cancer often have other autoimmune diseases, such as vitiligo or thyroid disease. Treatment consists of drugs that increase acetylcholine release by depolarizing synaptic membranes (pyridostigmine), plasmapheresis, and immunosuppressive agents, similar to myasthenia gravis.

Solution to Question 5:

Dermatomyositis is the most common inflammatory myopathy in children.

Two types of dermatomyositis are known—juvenile and adult.

	Juvenile dermatomyositis	Adult dermatomyositis
Age of onset	7 years	4th to 6th decade
Common associations	CalcinosisLipodystrophy	Cardiac and lung involvement tUnderlying malignancy(15-25%)Myositis-specific antibodies
Prognosis	Better	Worse

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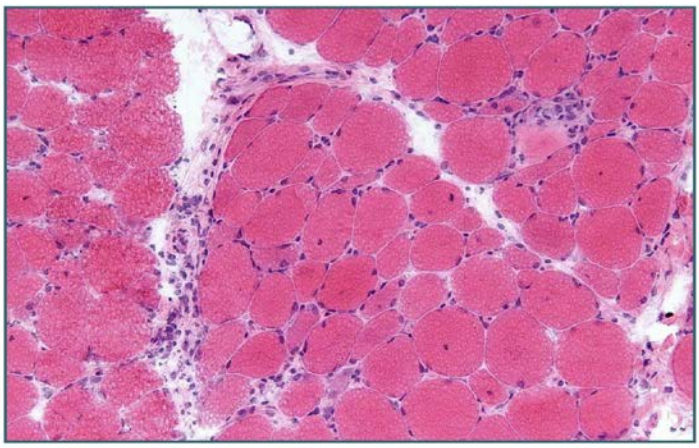
Solution to Question 6:

The muscle biopsy shows myofiber atrophy accentuated at the edges of the fascicles (perifascicular atrophy). The biopsy along with the history is suggestive of dermatomyositis. It is associated with perimysial CD4+ cellular infiltrates.

Dermatomyositis is an immunologic disease in which damage to small blood vessels contributes to muscle injury.

Dermatomyositis Biopsy Findings



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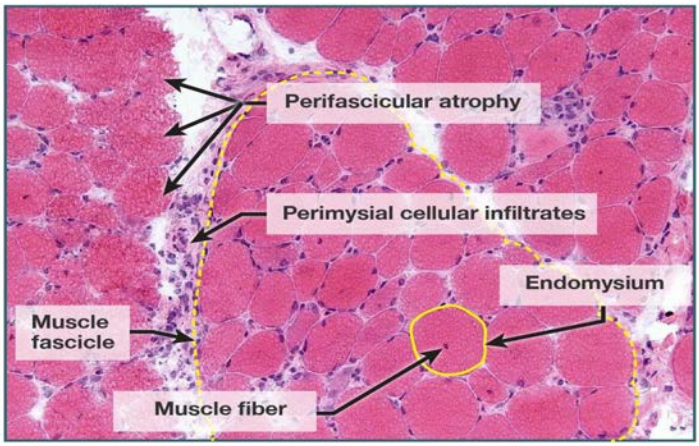
Dermatomyositis Biopsy Findings



Note: Viral myositis occurs 1-7 days after a viral infection (HIV-1, coxsackievirus). Muscle weakness and tenderness are seen. There are raised CK levels, muscle necrosis without inflammation, and positive urine myoglobin.

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Solution to Question 7:

This patient has developed paraneoplastic dermatomyositis. Anti-P155/P140 antibodies (directed against several transcriptional regulators) are associated with paraneoplastic dermatomyositis and juvenile dermatomyositis.

It presents as gradual, symmetric muscle weakness and myalgias, typically affecting the proximal muscles first. Fine movements controlled by distal muscles are affected late in the disease. Myopathic changes and elevation in serum creatine kinase levels suggest muscle damage.

Dermatomyositis- Cutaneous features

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Solution to Question 8:

Antibodies to cN1A are seen in inclusion-body myositis.

It is the most common inflammatory myopathy in patients >65 years.

Patients present with slowly progressive muscle weakness that tends to be most severe in the quadriceps and the distal upper extremity muscles. Dysphagia from esophageal and pharyngeal muscle involvement can also occur.

Laboratory studies usually show modestly elevated creatine kinase levels. Most myositis-associated autoantibodies are absent but are positive for antibodies to cN1A.

Solution to Question 9:

The given clinical history and the image showing pseudohypertrophy of calf muscles are highly suggestive of Duchenne's muscular dystrophy. It is an X-linked recessive condition.

Duchenne's and Becker's muscular dystrophy are caused by loss-of-function mutations in the dystrophin gene on the X chromosome. It is one of the largest human genes. Dystrophin provides mechanical stability to the myofiber during muscle contraction. Defects in the complex may lead to small membrane tears that permit the influx of calcium, triggering events that result in myofiber degeneration.

Duchenne's muscular dystrophy is associated with deletions or frame-shift mutations that result in the total absence of dystrophin. Immunohistochemical studies for dystrophin show the absence of the normal sarcolemmal staining pattern.

In contrast, the mutations in Becker's muscular dystrophy typically permit the synthesis of a truncated version of dystrophin, which retains some function. Immunohistochemical studies for dystrophin show reduced staining.

Solution to Question 10:

NARP syndrome - Neuropathy Ataxia Retinitis Pigmentosa syndrome is described as a mitochondrial function disorder.

NARP syndrome is due to a point mutation of the mitochondrial ATPase-6 gene. It has 2 phenotypes:

• NARP

• Maternally inherited Leigh syndrome (MILS)

It is characterized by moderate, diffuse cerebral and cerebellar atrophy and symmetric lesions of the basal ganglia on MRI. The severity of the syndrome corresponds to the mutant mitochondrial DNA load in the tissues.

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Solution to Question 11:

The following conditions are mitochondrial disorders:

• Myoclonic epilepsy with ragged red fibers

• Leber hereditary optic neuropathy

• Kearns-Sayre syndrome

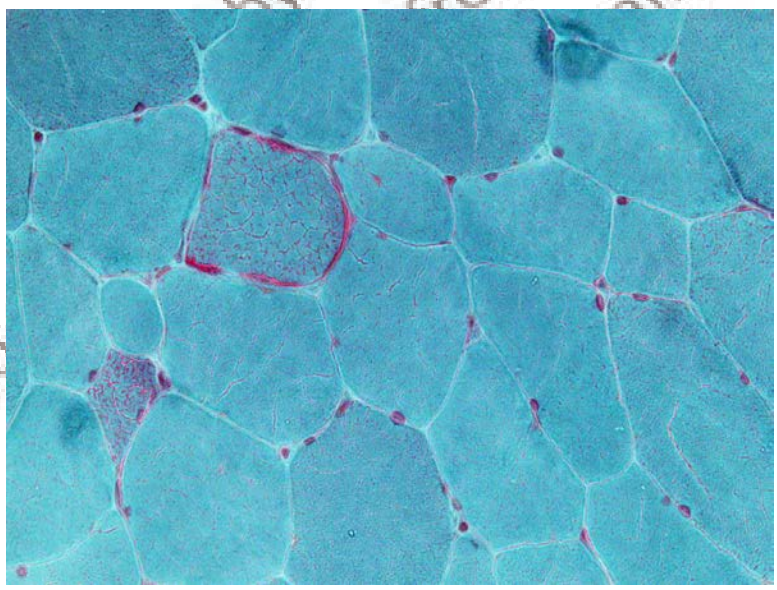
The proteins and tRNAs in the mitochondria may be encoded by 2 sets of genes:

• Nuclear genome - Mendelian inheritance patterns

• Mitochondrial genome (mtDNA) - maternally inherited, as the oocyte contributes all the mitochondria in the embryo

Mitochondrial disorders are caused by mutations in the mitochondrial genome.

The most consistent pathologic change in skeletal muscle is abnormal aggregates of mitochondria. These are seen preferentially in the subsarcolemmal area of affected myofibers, producing a ragged red fibers appearance, as shown below.



Solution to Question 12:

Hypokalemic periodic paralysis is most commonly caused by the mutation of the genes encoding calcium channels (CALCL1A3).

It is an autosomal dominant ion channel myopathy with an onset in adolescence. Males are usually affected more than females. It presents as proximal muscle weakness. Ocular and bulbar muscles are less likely to be involved.

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The diagnosis is established by a low serum potassium level during an attack, after excluding secondary causes.

Ion channel myopathies include the following:

Ion channel affected	Manifestation
CALCL1A3	Hypokalemic periodic paralysis
KCNJ2	Andersen–Twail syndromeAutosomal disorderPeriodic paralysis, heart arrhythmias, and skeletal abnormalities
SCN4A	Myotonia and periodic paralysis
CLC1	Myotonia congenita
RYR1	Congenital myopathy (central core disease)Malignant hyperthermia

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Solution to Question 13:

Mutations affecting the chloride channel CLC1 cause myotonia congenita. The resulting deficiency of CLC1 is responsible for the characteristic myotonia in myotonic dystrophy.

Ion channel myopathies:

Ion channel affected	Manifestation
CALCL1A3	Hypokalemic Periodic Paralysis (HypoKPP).
KCNJ2	Andersen–Twail syndrome, an autosomal disorder associated with periodic paralysis, heart arrhythmias, and skeletal abnormalities
SCN4A	Myotonia and periodic paralysis
CLC1	Myotonia congenita
RYR1	Congenital myopathy (central core disease) and malignant hyperthermia

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Solution to Question 14:

Glial hamartia are seen in neurofibromatosis type 2 (NF 2). These are microscopic nodular collections of glial cells at abnormal locations, often in the superficial and deep layers of the cerebral cortex.

NF2 is associated with the following:

• Bilateral eighth-nerve schwannomas

• Multiple meningiomas

• Gliomas - typically ependymomas of the spinal cord

• Nonneoplastic lesions - schwannosis, meningioangiomatosis, and glial hamartia

Option A: NF 1 is associated with neurofibromas of all types, malignant peripheral nerve sheath tumors, gliomas of the optic nerve, other glial tumors, hamartomatous lesions, and pheochromocytomas.

Option C: Tuberous sclerosis is associated with hamartomas within the CNS in the form of cortical tubers and subependymal nodules. Other lesions include subependymal giant-cell astrocytoma, renal angiomyolipomas, retinal glial hamartomas, pulmonary lymphangioleiomyomatosis, cardiac rhabdomyomas, and cysts in the liver, kidneys, and pancreas.

Option D: Von Hippel–Lindau disease is associated with hemangioblastomas of the CNS and cysts involving the pancreas, liver, and kidneys, and have a propensity to develop renal cell carcinoma and pheochromocytoma.

NOTE: A hamartia is not considered to be a tumor and is distinct from a hamartoma. A hamartoma is a benign neoplasm characterized by tissue misarrangement similar to a hamartia.

Solution to Question 15:

Focal collections of pseudo-Meissner corpuscles or tactile-like bodies (cells mimicking the appearance of Meissner corpuscles) is a feature of diffuse neurofibroma.

Note: Meissner corpuscles consist of a cutaneous nerve ending responsible for transmitting the sensations of fine, discriminative touch and vibration.

Solution to Question 16:

The most common variant of Guillain-Barré syndrome is acute inflammatory demyelinating polyneuropathy (AIDP). The area affected in this condition is the myelin sheath (marked as 2 in the image).

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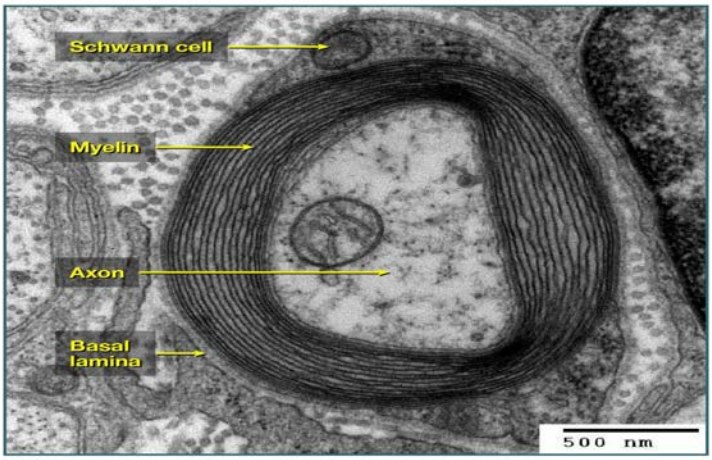
Myelinated Axon -
Electron microscopy appearance



Guillain-Barré syndrome (GBS) is an acute autoimmune disease that causes fulminant polyradiculoneuropathy. It is a T-cell mediated immune response.

GBS is usually associated with a history of upper respiratory infection (URI) or acute gastroenteritis (AGE) 1-3 weeks prior. The causative organisms may be Campylobacter jejuni, cytomegalovirus, Epstein-Barr virus, and Mycoplasma pneumoniae.

It presents with the following features:

• Ascending motor paralysis (lower limbs > upper limbs)

• Sensory deficits may or may not be seen

• Deep tendon reflexes - absent

• Transient bladder dysfunction - severe cases

• Autonomic manifestations - loss of vasomotor control, postural hypotension, cardiac dysrhythmias

Histological examination shows inflammation of peripheral nerves, manifested as perivenular and endoneurial infiltration by lymphocytes, macrophages, and a few plasma cells. On electron microscopy, an early effect on myelin sheaths is seen. There is segmental demyelination induced by the actions of activated macrophages.

There are several types of Guillain–Barre syndrome:

• Demyelinating

• Acute inflammatory demyelinating polyneuropathy (AIDP) - most common

• Axonal

• Acute motor axonal neuropathy (AMAN)

• Acute motor-sensory axonal neuropathy (AMSAN)

• Regional GBS syndromes: Miller–Fisher syndrome (MFS)

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