Cell Injury

Stress: Cell adaptation

1. Hypertropy (↑ in size)
   Eg:
   Sk. Muscle: Athletes
   Cardiac muscle: Athletes
   Uterus: Pregnancy
   Breast: Puberty, lactation.

2. Hyperplasia
   Uterus - Pregnancy
   Breast - puberty, preg-

   Endometrial → BPH Hyperplasia

In uterus (preg), trophy > Plasia.

3) Metaplasia:
   Stem cell reprogramming
   Stimulus: Chronic irritation

Types:
- Epithelial
  - Squamous (m/c)
    - Reab: Smoker, Vit A def.
    - Biliary / Panc: stones
    - Bladder: Stones, Schistosomiasis
    - Endocervix: HPV
  - Columnar
    - Barret's esophagus
    - ↓
    - Columnar cells in esophagus (lower)
    - Stain: Alcian Blue.
    - Progressive
    - Dysplasia → Adenocarcinoma
- Connective tissue
  - Myositis osificans

4) Atrophy:
   ↓ In size or number

MILD INJURY

10:15

- Reversible
- M/c → Mild ischemia → Mild hypoxia.
  - ↓ ATP → ↓ Na^+ K^+ ATPase pump
  - ↑ Lactate → pH ↓ → Chromatin condensation
- Morphology:
  Em change:

- Loss of Microvilli
- Cyto. Memb. Blebs
- Organelle swell

Mitochondria

ER → Robosome detachment → Protein → TG → FFA

LM findings:

- Cell swelling (Cloudy)
- Fat vacuoles seen

IRREVERSIBLE INJURY *19:07*

Necrosis: Severe / Persistent ischemia

Sever / Persistent Hypoxia → ATP depetion → ↑ Na^+, Intracellular Ca ↑ → Large Flaccutent amorphous density → Activates enzymes

- ATPase → ATP breakdown
- Protease + Phosphatase → PM + lysomemb. Broken → Hydrolytic Enzyme → Tissue damage → Neuro infiltration (Acute inflammation)
- Endonuclease → Pyknosis → Karyorrexis → Karyolysis

- Stains pink (↑ Eosinophilia)
- ↓ Blue (↓ Basophilia)

- Myelin figures

Necrosis types:

1) Coagulative (m/c)
   - Tomb stone app
   - Moth eating app
   - Glossy app

Eg: Ischemia to all solid organs (exc. CNS)

- Thermal
- Zenker's degeneration
- Dry gangrene.

2) Liquid (Colliquative)

   Pus: Necrosis + Neutrophil

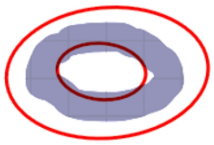
   Eg: Ischemia to CNS
   - Coag. Necrosis + Bacteria
   - Wet gangrene.

3) Caseous Necrosis (Coag > Liq)

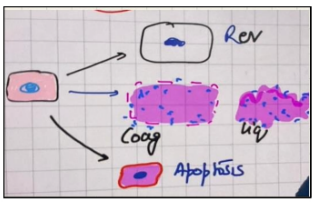
   TB, Histo, Coccidiodomycosis.

4) Fatty Necrosis:
   - Acute pancreatitis
   - Trauma

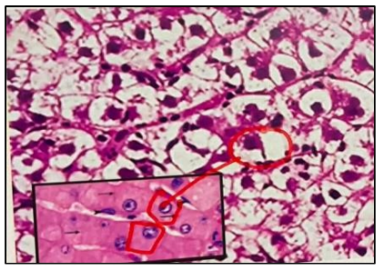
5) Fibrinoid:

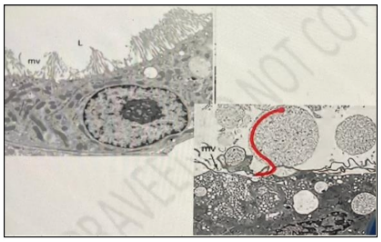


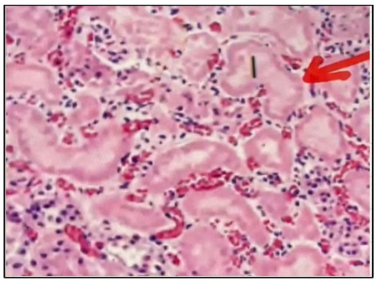
Vasculitis, I/c deposits, Malig. Hyperthermia



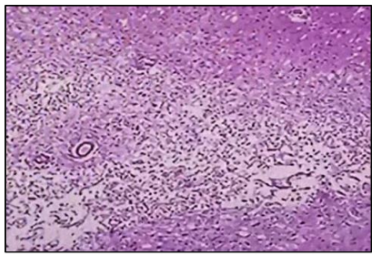
Hydropic change





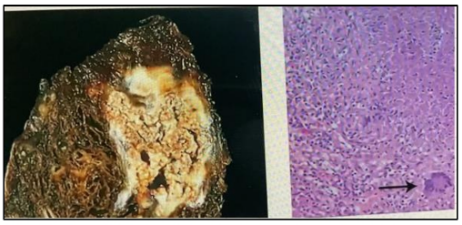


Coagulative Necrosis



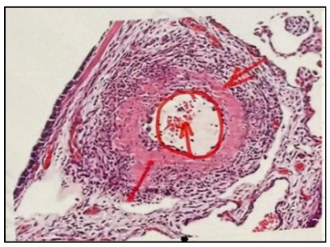
Cerebral Ischemia

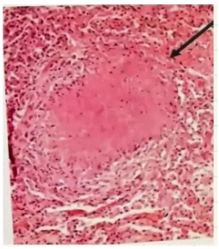
Caseous Necrosis



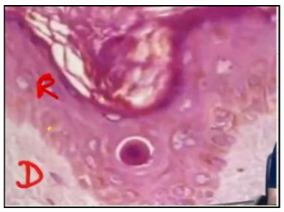
Saponification (Fatty Necrosis)

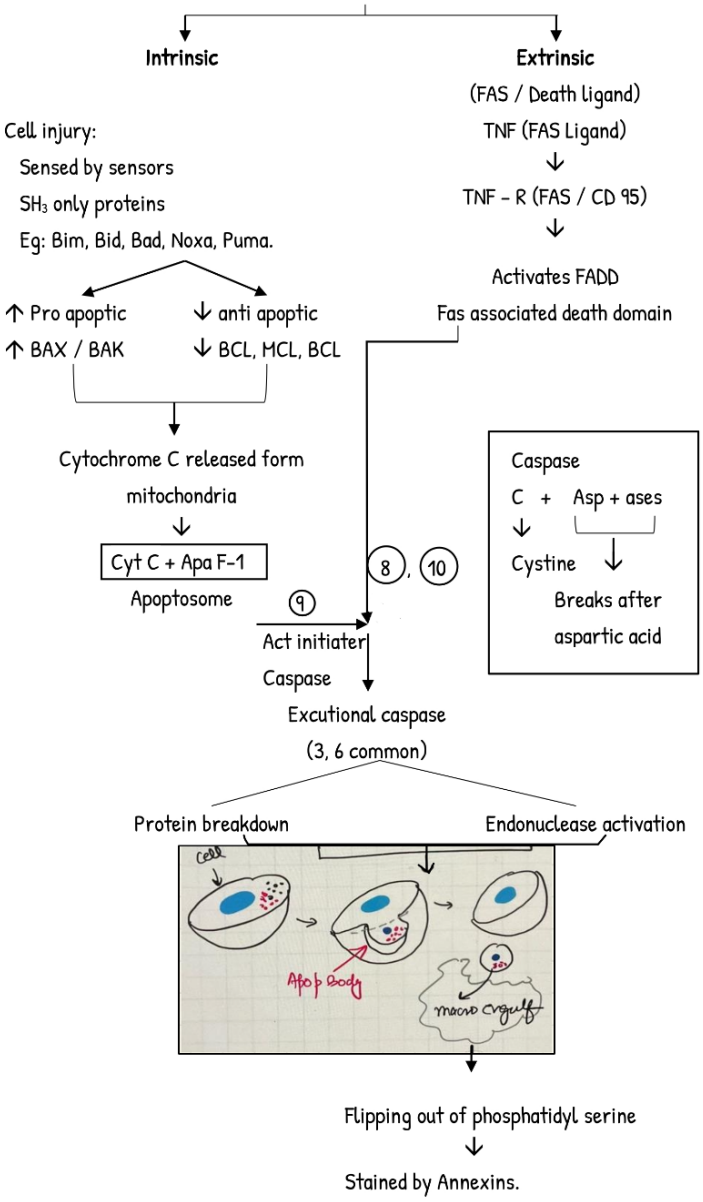
Fibrinoid necrosis

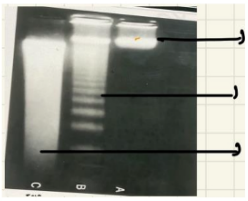




Apoptosis:




Intrinsic
Extrinsic
(FAS / Death ligand)
TNF (FAS Ligand)
Cell injury:
Sensed by sensors
SH3 only proteins
Eg: Bim, Bid, Bad, Noxa, Puma.
TNF - R (FAS / CD 95)
Activates FADD
Fas associated death domain
↑ Pro apoptic
↑ BAX / BAK
↓ anti apoptic
↓ BCL, MCL, BCL
Cytochrome C released form
mitochondria
Cyt C + Apa F-1
Apoptosome
8, 10
9
Act initiater
Caspase
Caspase
C + Asp + ases
Cystine
Breaks after
aspartic acid
Excutional caspase
(3, 6 common)
Protein breakdown
Endonuclease activation
Cell
Apop body
macro engulf
Flipping out of phosphatidyl serine
Stained by Annexins.



Normal

Apoptosis (Step ladder pattern)

Necrosis

NECROPTOSIS

55:00

Steatohepatitis
Ac. Pancreatitis
Reperfusion injury
Parkinson disease

↑ INF
↓
FAS + FADD

Act C-8
↓
Apoptosis

Activates
RIP 1/3

↑ ROS + ATP depletion
↓
Necrosis

Pyroptosis

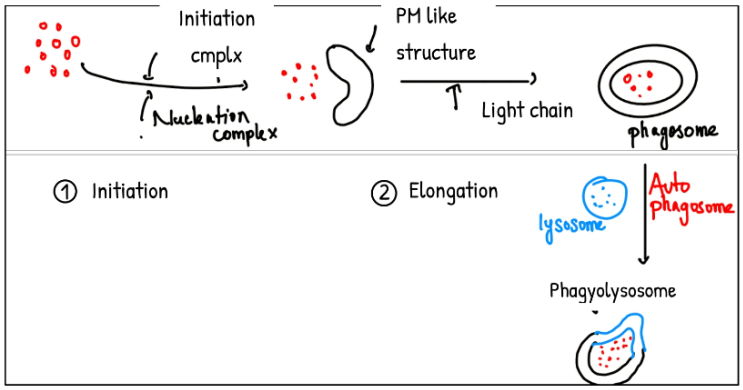
Fever + Apoptosis
In viral inf, cell death
↓
Activace NOD like Receptor
↓
Inflammasome
↓
Pro IL - 1 → IL - 1 → Fever
↓
Activate C-I/II (4, 6)
(Apoptosis)

Ferroptosis:

↑ in Intracellular Iron
↓
↑ ROS → Cell death (Necrosis)

Autophagy:

- Eat up self
- Cannibalism of organelles
- Seen in starvation, Cancer, Neurodegenerative condition



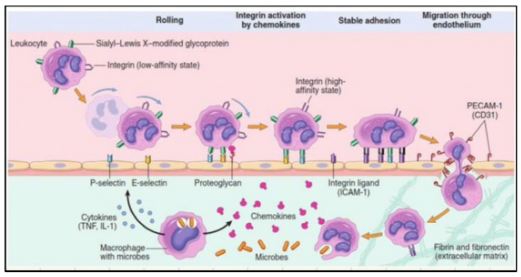
Inflammation

Acute:

a) Vascular events: Vasodilation
↑. Vasc. permeability

Mech.	Mediator	Response time
Endothelial contraction	Histamine	Immediate / Transient
Endothelial retraction	IL - 1 TNF - ∝	Delayed - prolonged
Endothelial damage	→ Direct:- Bacterial burns → Prolonged sun (U.V rays) → WBC mediated.	Sustained long lived / Late

b) Cellular events:



1) Margination Vasodilation

	Endoth	RBC
2) Rolling		↓ (LAD-2)
	E - Selectin	Sialyl lewis x gp
	P - Selectin	Sialyl lewis x gp
3) Adhesion	ICAM - 1	LFA - 1, MAC - 1 (β_2 integrin)
	VCAM-1	VLA - 4 (β_1 integrin)
4) Diapedesis	PECAM-1 (CD31)	PECAM-1 CD-31

LAD-1: Infection + delayed. Sep of umb. stump

LAD - 2: Infection + Bombay phenotype blood group

5) Chemotaxis:

Chemokines: C5a
LTB_4
IL - 8
Bact. Product 1

6) Phagocytosis:

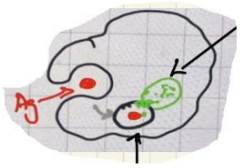
6a. Recognition: Mannose - R
Scavenger - R.

6b. opsonisation:

Opsonins eg: C_{3b}, C_{4b}, C_{5b}.

(Opsonizers): IgG (Fc-R)
C-RP
Fibrinogen.

6c.. Engulfment.

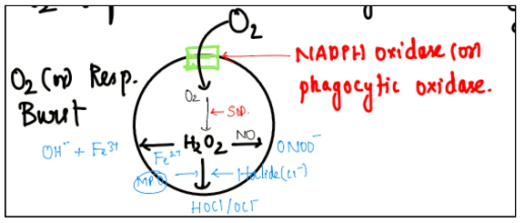


Lysosome
Fusion: LYST gene
Phagolysosome

Phagosome

In Chediak Higashi syndrome , LYST gene (-)

7) Killing: O_2 dependent. PHOX gene ← (-) Chronic granuloma disease



Most efficient free radical bactericidial: OCT

Most efficient free radical bactericidial system: MPO-H_2O_2 halide.

O_2 independent killing:

1° / Azurophillic	2° / specific
MPO	Alk PO_4 are
Defensin	Collagenase
Lysozyme	Gelatinase
P-proteinase 3	Transcobalamin
N - N - elastase	Lactoferrin
G - Cathepsin - G	

Mediators of inflammation:

Cell derived

- Pre. Formed
  - Histamine
  - Serotonin
  - 1° / 2° granules
- Synth. De- Novo
  - 4. NO Arginine → NO, Citrilline
  - 5. Platelet activating fact.
  - 6. Interleukin, Cytokines
    - Eg: IL-1, TNF - α
  - 7. Arachidonic acid metabolites
    - (PG. LKT)
- Plasma derived.
  - 8. Complements
  - 9. Kinin
  - 10. Coagulation

Antiinflammatory mediators:

T	TGF - β	
L	IL - 10	IL - 4, 13,: (pro & anti)
I	Lipoxins	

CHRONIC INFLAMMATION *37:30*

Persistent Ag:
- Infections
- Autoimmune ds.
- Hypersensitivity reactions
- Foreign body.

Mechanism:

Neutrophils Can't destroy → M.Tb (Chronic Ag)

↓

Macrophage

T cells
IL - 12
IFN - γ
M. Macro
(Classically activated)
Lysosomal enz ↓ROS. IL-1
Inflam + microbial
activation

T cell
IL-10
M_2 macro
(Mech. activated)
IL - 10
TGF - β
Anti - inflammatory reaction Repair.
(Fibrosis + angiogenesis)

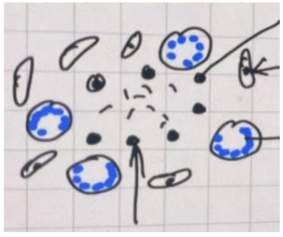
- Tissue destruction + Repair
  Occurs simultaneously in chronic inflammation

Chronic inflammation:

Macrophage
T - cells
B - cells
Antibody, plasma cells
Mast cells, eosinophils.

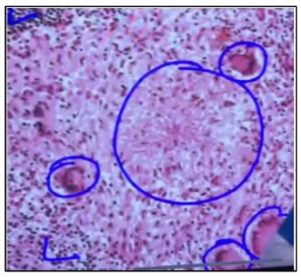
Cell: Type IV Hs: Th_1 cell

Granuloma:



Lympho
Epitheloid cells (modified micro)

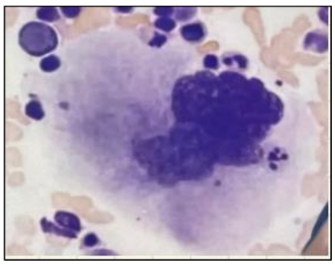
Giant cells (fused macro)



Caseating granuloma

Emperipolesis:

- Chronic inflammation
- Hodgkins
- Rosai dorfman's disease.



Repair and Regeneration

- Fibrosis seen in Repair
- No fibrosis in Regeneration

Healing (Skin)

1° Intention:

- Surgical wound
- D_0: Blood clot
- D_1: Neutrophil opp.
- D_3: a. Neutrophil → macrophage
  b. G.T → Fibroblast + vessels
  c. Collagen appears (type III)
- D_5: a. Macrophage prominent
  b. G.T prominent
  c. Vessels prominent
  d. Colalgen: bridges gap
  e. Thick epithelilzation

- Max. collagen: end of 2nd month.
- Aft 1 month: Remodification of collagen.

Wound Strength
a) Type 3 → replaced by Type - I
   Enz: Matrix & Metallic protinase
b) Cross linking of collagen - I
   Enz: Hydroxylation of Lysine / proline
   (Vit C - co - factor)

With suture: 70%
On end of 2nd week: 10%
On end of 1st m: 30%
On end of 3rd m: 70-80%

2° Intention:

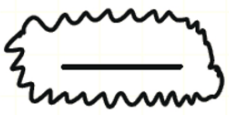
Abundant inflammation

Abundant G.T, vessels.

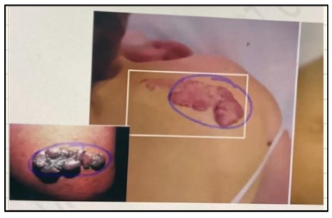
Hallmark: Myofibroblast: Fibroblast which can contract.

Abundant collagen → can cause scar.

Scars:

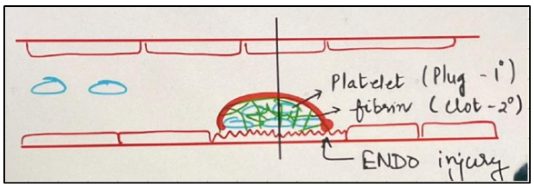
Keloid		Hypertrophic scar
		
Extend away, forms after 2 month	→	Within 2 m
Color: darker	→	Same colour
Never regress	→	Can regress
Surgery, Triamcilone inj.	→	Wait & watch.
Collagen I > III	→	Col III >
Familial / Genetic	→	None
Site: Pinna,	→	None

Keloid & Hypertrophic sca

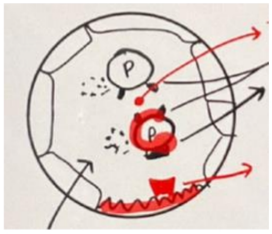


Hemodynamics & Bleeding

Bleeding



1° plug:



Fibrinogen / vw
Gp II b/III a
gpIb / IX
→ aggregation (A)

VWF (Ehdo, Platelet) → adhesion (B)

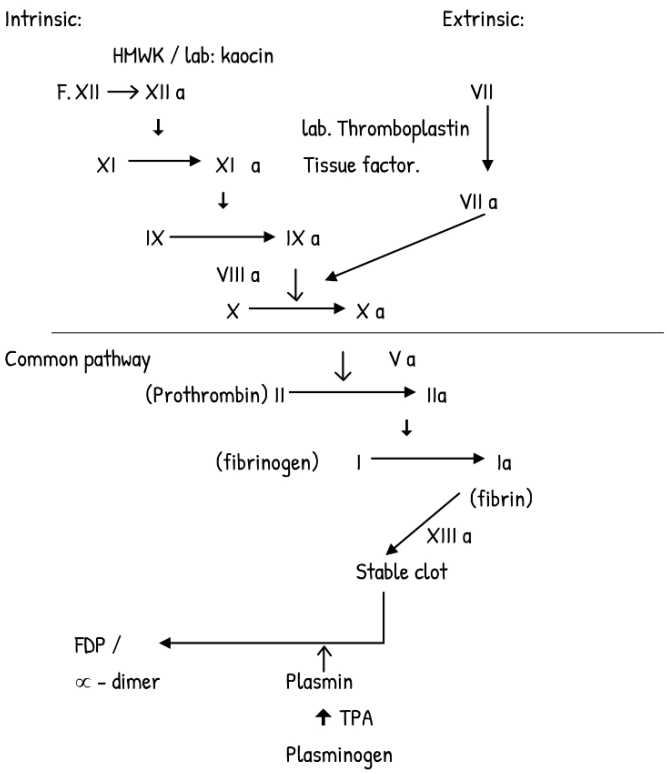
Platelet granules

α	δ (Dense)
Factor I	Den: adenosine di PO_4
Factor V	S : Seratonin
Factor VII	E : Epinephrine
Platelet factor 4	Calcium
PDGF	

Helps in aggregation

Deficiency	Defect	Disease
• VWF	Adhesion > aggregation	VWD
• Gp Ib / IX I → II →	Adhesion B G	Bernard Solier synd
• Gp IIb / IIIa	Aggregation	Glanzman Thrombesthenia

2° plug: Stable clot



Case 1:	↑ PT (N)apTT	Factor 7 deficiency, Warfarin dose, Vit K deficiency
Case 2:	(N) PT ↑ apTT	Factor XII, XI, IX, VIII def.
Case 3:	↑ PT ↑ apTT	↑ PT: IP + EP ↑ apTT: F. X, V, II, I def.

inactive

Vit K factors: F 2, 7, 9, 10, protein, S, C

in Liver

(1st factor to ↓ is f7 (shortest t ½ - 4 hrs

So ↑ PT only)

Y Carboxylation of glu acid to factors

inhibits

Warfarin

Warfarin dose: PT - INR

PT INR = $\left(\frac{\text{PT patient}}{\text{PT control}}\right)^{ISI}$

INR: International Normalised ratio

VWF:

Function: Platelet adhesion & aggregation

Stabilise factors VIII

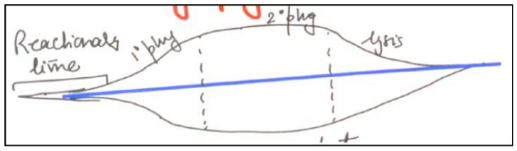
So, in VWD, Factor VIII is also deficient

So, ↑ aPTT only

Thrombo electrography (TEG)

Take plasma ➜ allow it to clot

1° plug ➜ 2° plug ➜ lysis



Max. amplitade depends on 1° plug (platelets)

DIC

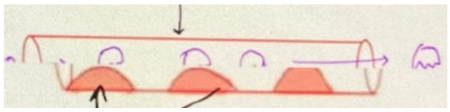
18:00

Disseminated Intravascular Coagulation

Tissue injury: Endothelial injury

Hyperactivation of coagulation pathway

↓



Helmet cells
(Schistocytes)

↓

Microclots

Consume platelets
Consume coag. Factors } C.F Bleeding

↓

Fibrinolysis

Fibrin degraded product
D - dimer

Lab investigation:

- ↓ platelet count
- ↑ PT / ↑ apTT.
- FDP
- D-Dimer

If FDP / d-dimer: -ve → Rule out DIC

Treatment:

Remove 1° cause

Fresh Frozen plasma

Genetics

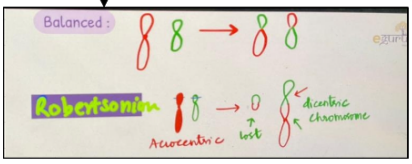
MUTATION

00:20

Change in DNA

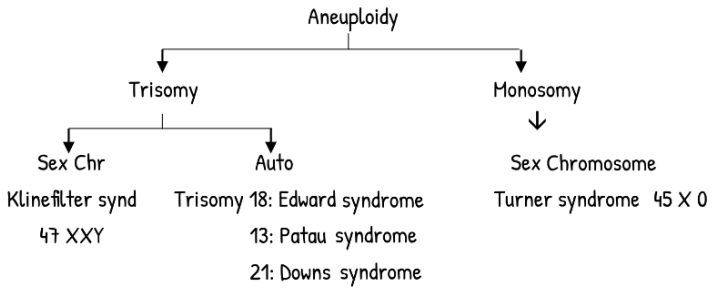
- Gene
  - Point
    - Replacement / Substitution
  - Frame shift
    - Deletion
    - Insertion
- Chromosome
  - Structural
    1) Deletion
       - 22q del (CATCH 22)
       - 5p del cri du chat
    2) Insertion
    3) Inversion
    4) Duplication
    5) Ring Chr
    6) Iso Chr
    7) Translocation
  - Numerical
    - N = 23
      - Euploidy
        - Total number is exact multiple of n
        - Eg: 3n, 4n, 5n
    - 2n = 46
      - Aneuploidy
        - Total number is not exact multiple of n
        - Eg: 2n +1 = 47 Trisomy
        - 2n-1=45 monosomy

Non disjunction of chr. During meiosis (47)



Mosaicism: >2 sets of chromosome in same person. (2n. 2n + 1)

Cause: Non dysjunction during mitosis

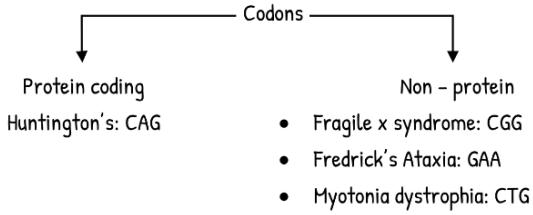


INHERITANCE PATTERN OF SINGLE GENE MUTATION *13:56*

A. Mendelian (Classical): AD, AR, XD, XR
B. Non mendelian (non classical):
   1. Mitochondrial
   2. Trinucleotide repeatsa
   3. Genomic imprinting ✓
   4. Germline mosaicism ✓

1) Mitochondrial:
   - Only ova can transmit ds
   - Threshold effect: C/f appear only after mutated mitochondrial DNA are more than cut off.
   - K kearn Syndromedro
   - L Leigh Syndrome
   - M Merf Syndrome
     Melas Syndrome
   - N Narp Syndrome
   - O Opthalmoplegia Syndrome

2) Trinucleotide repeats:



Fragile X Syndrome:

CGG	CF
15-55 →	(N)
55-200 →	Premutation → Ataxia / Tremor
>200 →	Large ears, Testis, Mandible Mental Retardation.

3) Imprinting / Silencing:
   - Fails to express
   - Mech: Epigenetics: Preferential expression of genes from either parent.
   - Chr. 15: Deletion (70%), imprinting (20%)

Paternal chrom	Maternal chromosome
P.W.S	A.G.M.S

Uniparental disomy (10%)
- Maternal disomy: P.W.S
- Paternal disomy: A.G.M.s

4) Germline Mosaicism:
   Eg: Tuberous sclerosis, Achondroplasia, O.I
- Somatic cell gene: (N)
- But germline cell genes: mutated.
- (N) parent can transmit ds. To pregnancy.

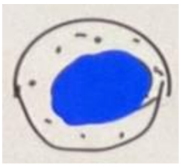
Immune System

INNATE IMMUNITY

00:45

(1st line defense)

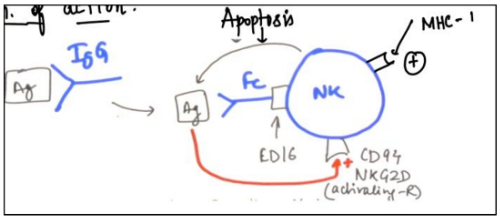
1. NK cells: Natural killer cells
   - 1st line of defence - Virus infected } → lack MHC - 1
     - Tumor cells



Large granular lymphocytes

- CD16 (Fe - R of IgG)
  56: NCAM
  Destroy: Apoptosis

Mech. of action:



2. Pattern Recognition - Receptions : Various
   Eg: Toll like receptors (TLR): Pathogen
   Nod like receptors (NLR): Necrotic cells
   Rig like receptors (RLR): Virus
   C - lectin Receptors (CLR): Fungus
   Mannose - Receptors : Bacteria

Family	Ag recognized
2	TB, Gram +
3	DNA, RNA Virus
4	Gram -ve
Five 5	Flagella
9	Protozoa (CPG DNA)

ADAPTIVE IMMUNE RESPONSE

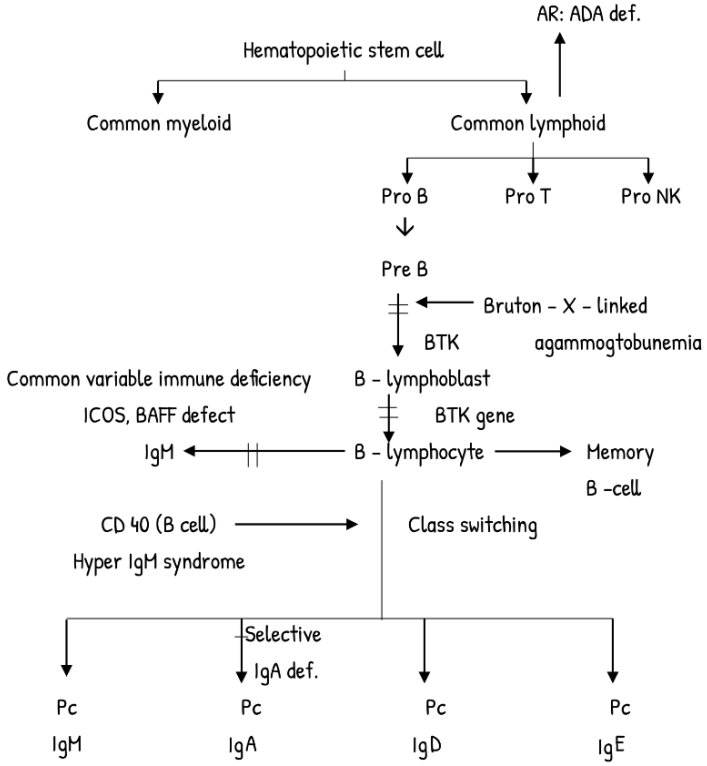
7:15

Lymphocytes:

B – Humoral

T – Cell mediated – CD_4T

CD_8T



2) Witcoh Aldrich syndrome:

T: Thrombocytopenia

E: Eczema

I: Infections

Defect: WASP gene (Chr. X p 11)

T cell defect

1. Di George syndrome: Chr 22q 11 del
   Fail in development of 3rd / 4th pharyngeal pouch

↓

Hypoplasia - Thymus: T cell lost
- Parathyroid: hypocalcemia: Tetany
- Def heart / vessels

C/f

C	Cardiac Anomoly
A	Anomolous face
T	Thymus hypotrophy
C	Cleft plate
H	Hypo. Ca

T – LYMPHOCYTES 18:08

- CD_4T cells: T - Helper cells
- CD_8T cells: Cyto toxic
- Y & T cell: GIT mucosa: Prevent Ag entry
- Suppressor T cells: CD_4 & CD_{25}.

↓

Suppresses Autoimmunity

Apc: Cells which present Ag to T cells

Site	APC MHC I/II
• Lymph node	Dendritic - mature most potent immature
• Skin	Langerhans cells
• Tissue	Histiocytes / macrophages
• Blood	B lymphocytes
• GIT	M - cells

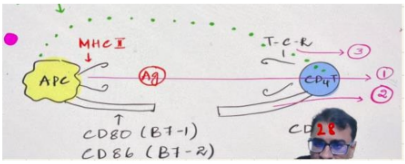
Major Histocompatibility complex:

- On chromosome 6 P
- Codes for HLA.

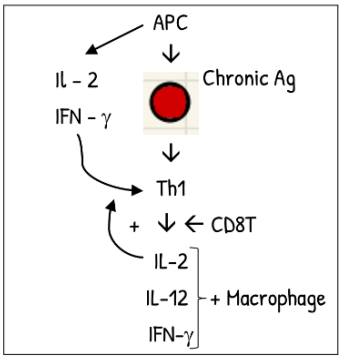
MHC

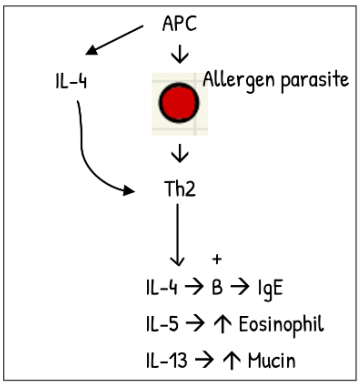
Class I		Class II
All nucleated cells	Site	All APCs platelets
Intracellular Ag	Identify	Extracellular Ag
CD_8T	Presents Ag to	CD_4T

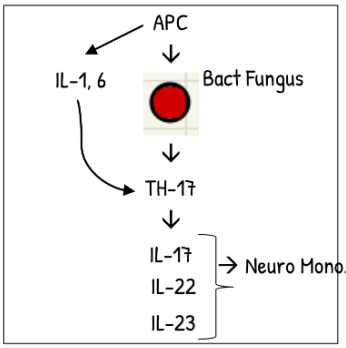
Cytokines



Types of Th cells:







HYPERSENSITIVITY REACTIONS

28:49

Type 1 HSN: (Allergy, Anaphylaxis, Atropy, Asthma, Utericaria)

Th_2

↓

IL-4 → B → IgE

Histamine

Platelet activating factor

PL on mast cells

↓ P. lipases ← (-) Steroids

A.A

Cox → PGD_2, PGE_2 → ↓ Bronchospasm, Vasodilation

Lox ← (-) Ziletuidn

LTB_4 → Chemokine

↓

[LTC_4, $LT D_4$] ← LTR [-Kast] antagonist Bronchospasm.

- ↑ Vascular permeability

After 2 hrs: Late phase

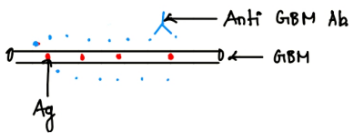
Th_2 → IL-5: ↑ Eosinophil → MBP, ECP
→ IL-13: ↑ Mucin

TYPE – 2 HYPERSENSITIVITY *33:19*

Antibody mediated:

- A: a O
- LT B_4
- IL - 8

a) Inflammation type:



"Glomerulonephritis"

Eg:

- Good pasture syndrome — Anti GBM Ab (Col IV α3) NC end
- Phemphigus (Anti - Dsg Ab)
- Rheumatic Carditis (Ab 'M' protein Ab)
- ANCA vasculitis

b) Ab → Opsonization & phagocytosis
Eg: ABD incompatibility
Rh incompatibility
ITP incompatibility

c) Ab ↴
Activate receptor: TSI: Graves disease
Inhibit - Receptor: Ach - R: Myasthenia gravis
Parietal cells: Pernicious Anemia

3) Type – III Hypersensitivity:
   - Circulating Ag + Ab
   - Immune complex deposits

   a) Circulating immune complex (I/C)
   ↓
   b) Filter out at glomerulus / Joints (small I/C)
   ↓
   c) Activate C_{5a} → Inflammatory damage
   - Glomerulonephritis + Arthritis

Eg: All Glomerulonephritis / except Good pasterns
   S – SLE, Serum sickness
   H – HSP
   A – Arthus reaction
   R – RA
   P – PAN

4) TYPE IV HYPERSENSITIVITY *39:00*

- Cell mediated, delayed 48-72 hrs
- Th cells: IL-2 → Th1, CD8T

(TH1) IL-12 JF } Macrophage
IFN – γ }

Eg:
- All granulomas
- Type IDM
- Contact dermatitis
- Type I Lepra (II: III hsn)
- Montaux reaction

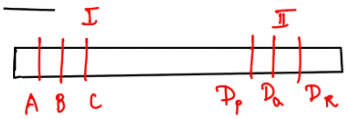
GRAFT REJECTION *69:31*

	Hyperacute	Acute	Chronic
Time:	Mins – hrs	Weeks – months	Months – years

Mech:	**Preformed** Anti donor HLA Ab in receipient (Type 2>3 hsn)	**Post transplant** • Anti donor Ab (Type 2 hsn) • Type IV hs.	**Post transplant** • T cells against donor cells Type 4 Hsn C/I: Organ atrophy Fibrosis

Types of graft:
Auto → Self
Iso → Identical twins
Allo → Same species
Xeno → diff species

HLA alleles:



3 genes x 2 = 6 alleles.

GVHD / Runts disease:
- Immunocompetant Donor T cells
  ↓
- Attacks & destroy immunosuppressed recipient tissues
- < 100 days: Acute
- > 100 days: Chronic
- C/f:
  1st : Skin Rash
  Jaundice (Liver)
  Bloody diarrhea (GIT)

AMYLOIDOSIS *80:08*

Amyloid: Starch like deposition (amylase like)
Stained: Congo Red
Seen by: Polarized M/C: Apple green birefringence
E/M: Long unbranching fibrils
X ray crystallography: β plated sheets

Biopsy: Abd. Fat aspiration (more convenient)
Rectal Bx (Best)

Types of Amyloidosis:

Localized:

1. Alzimer: Aβ
2. Med - Ca Thyroid: Acal
3. Insulinoma: AAPP (polypeptide)
4. Isolated atrial amyloidosis: AANP

Generalized:

1) 2° Amyloid to inflammatory
Malignant
Auto immune disease
} AA associated (or) SAA

2) Dialysis associated: $A\beta_2$ Microglobulin
3) Senile poly neuropathy: ATTR (wild type)
4) Familial cardiac amylord: ATTN (mutated)
5) Familial Mediterranean fever: AR.
Mut PYRIN gene → SAA.

MORPHOLOGY *56:31*

- M/c organ: Kidney (Nephrotic > Nephritic)
- Heart: Arrythmia
Restrictive cardiomyopathy
- Hepatomegaly
- Malabsorbtion
- Spleen → Red pulp → lardaceous
White pulp → Saga spleen

Neoplasia

Developmental Malformation:

Hamartoma (Premalignant)	Choriostoma (ectopic)
Abnormal tissue @ (N) Site	Normal tissue at Ab (N) site
Eg: Dysplastic ling tissue in lungs	Eg: (N) gastric mucosa in pancreas. Meckel's diverticulum

Def =	**Dysplasis** Disordered growth	**Anaplasia** (hallmark of malig) Loss of differentiation
• Profil rate	↑	↑↑↑
• Mitotic rate	↑	↑↑↑
• Nucleo cyto ratio (N:C ratio)	↑	↑↑↑
• Hyperchromatism	+	+++
• plemorphism	+	+++

Dysplasia	**In cervix**	**Bethesda**
Starts lower 1/3rd mild ↓	CIN – 1	Low grade SIL (LSIL)
Lower 2/3 → ↓m	Moderate CIN – II →	MSIL
Full thickness Or Ca in Situ	→ Severe CIN-III	

Sq. cells

HPV infection: →  → Koilocytes Hyperchromatic nuclei

Protein ↓

$E_6 \xrightarrow{\ominus} P_{53}$

$E_7 \xrightarrow{\ominus} Rb$

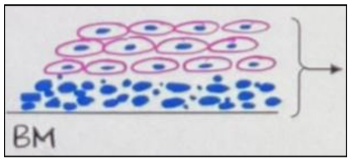
Tumor

If partial inhibition HPV → Anogenital Warts

If complete inhibition (16, 18) → Ca: Vulva, vaginal, cervical, oral,

(31, 33) Tonsilar carcinoma

DYSPLASIA 05:05



Dysplasia
Starts lower 1/3rd: Mild

CIN: Cervical intra epithelial neoplasm

SIL: Squamous intra epithelial lesion

CELL CYCLES 6:43

A. Cell cycle inhibitors (Brakes)

CIP / KIP	INK 4a
(CDK NA)	(CDKNB)
Acts on G_1 – S & G_2 – M	Acts on G_1 – S only
Eg: P21, 27, 57	P14, 16 (P17, 18, 19)

G1 – S or G2 – M
↓
Checks for mut
↓ GADD45
Apoptosis ←(–) BAK, BAX Repair (+)→ cell cycle

B. Cell cycle proliferators (accelerators):

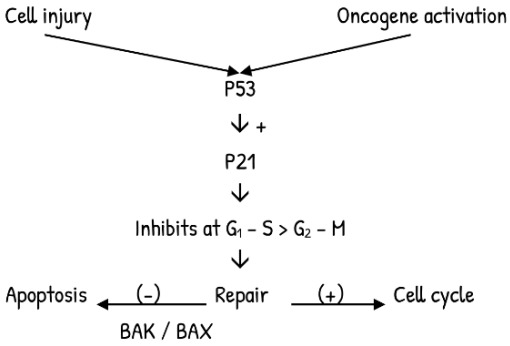
Cyclin ↔ CDK (cyclin dependent kinase)

D – 4/6 E – 2	G_1 – S
A – 2/1 B – 1	G_2 – M

Tumor suppressor gene (loss):

1. P53 on Chr. 17 β:
   Guardian of genome / Molecular policeman of genome.

MOA:



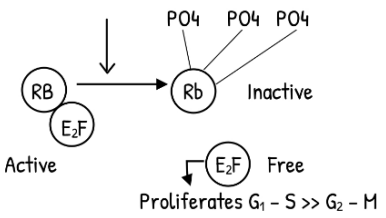
1) Tumor suppressor gene (loss):
   1. P53 on Chr. 17.
      a) Germline (inherited / familial) – Li fraumeni syndrome
         B – Breast, Brain
         L – Lung
         A – Adrenal
         S – Stomach, Skin
         T – Tumor
      b. sporadic mut

   2. Rb gene on (Chr 13q): E_2F: Elongation factor – 2

2) Rb gene on Chr. 8q
   - E_2F
   - Governor of proliferation

MOA:

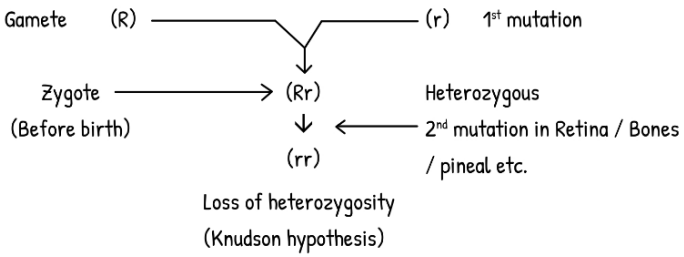
Rb. Gene
Growth Factor (EGF)
↓
Gr. Factor receptor (EGFR)
↓
Cyclin D → CDK 4/6.
↓



Mutation / loss of Rb gene:

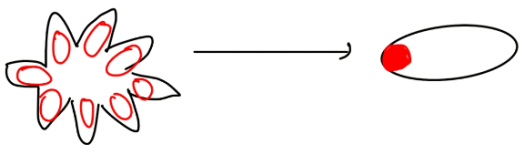
- Sporadic R = (N) allele
- Familial / Germline γ = Mutated allele.

(n) RR



Eg: Familial Rb. Mutation → M/c 2° tumor in Rb: Osteosarcoma

- Trilateral Rb → B/L Rb + pineoblastoma.



Flower arrangement: flure

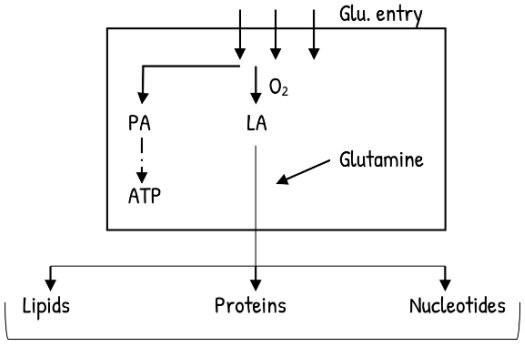
- Flexner winter steiner rosette (True):

HALLMARKS OF CANCERS 25:28

- Self sufficiency in growth signal
- Tumor suppressor gene loss
- Evasion of apoptosis: anti apoptotic genes +ve
  BCL 1 (+) → MZL

BCL 2 (+) → PL
BCL 6 (+) → DLBCL

- A: Altered cellular metabolism: Warberg / glycolysis / Glucose hunger



↑ Synthesis of tumor cells

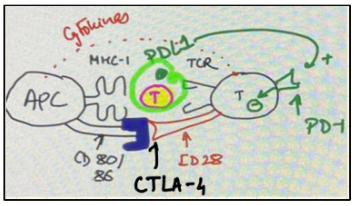
- L: limiters replication potential:

↑
Telomerase: ↑ maintain Telomere length
↑ (N) Somatic cell divides 60-80 times
P53 loss (Hay flich limit)
(TERT gene mutation)

- Angiogenesis: TGF - β
VEGF
Angiogenesis

- Tumor immunity:
Tumor: mutated gene → Mutated protein destroyed ↑ (Foreign Ag) by host immune cells
How tumor avoids host immunity
a) Do not exp. Aq : escape Ab. Killing
b) Do not exp. MHC I: escape CD8T killing
c) Immunomodulation:

- Metastasis: distant & discont. Spread of tumor



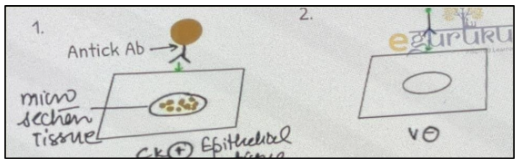
- Cancer immunotherapy: Ab. Against POL – I
- Anti CTLA – 4 Ab – Idilimumab
  Anti PD-1 Ab – Nivolumab
  Nti PDL – 1 AB – Atezolizumab.

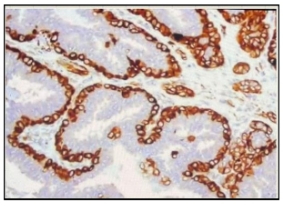
Diagnosis:
Tissue specimen:
Cytology:

- FNAC
- Imprint cytology
- Exfoliate cytology – PAP smear (95% ethanol)

Biopsy:

- Fixation: Preservation of morphology
- MC: 10% Formalin
- Em: Glutaraldehyde
- GI Biopsy, sperm morphology: Bovins fluid.
- Special stain: IHC





IHC

IHC	Tumor
Cytokeratin	Carcinoma
Vimentin	Sarcoma
Desmin	RMS
HMB 45	Melanoma
S-100, CD-207	LCH
GFAP	Glioma
Neuron sp. Enolase, Cromogranin, Synaptophysin	Neuroendocrine tumor

EM:

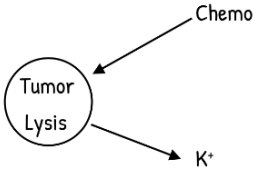
Birbeck granules
"Tennis Racquet appearance"

New:

- FCM/IPT
- Liquid Bx / Circulating tumor cells
  ↓ Tumor cells + mut. Genes in blood

  Specific marker against tumor cells in blood

Tumor Lysis Syndrome

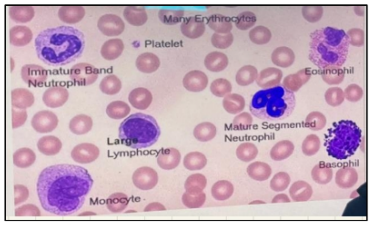


Finding: ↑ K
↑ PO_4 → ↓ Ca
↑ V.A

Treatment: I.V hydration
Uricosuric drugs
→ Probencic acid
→ Allopurinol
→ Rasburicase

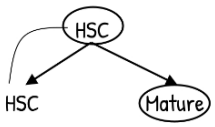
Acute Leukemia

(N) Peripheral Smear:



HSC: Hematopoietic stem cell

1) Trans differentiation / developmental plasticity
2) Asymmetric division



3) Self renewal
4) Not sessile – (N) site BM (0.1%)

In stress → Peripheral Blood.

Hematopoiesis:

Yolk sac – 3 week IU life

↓

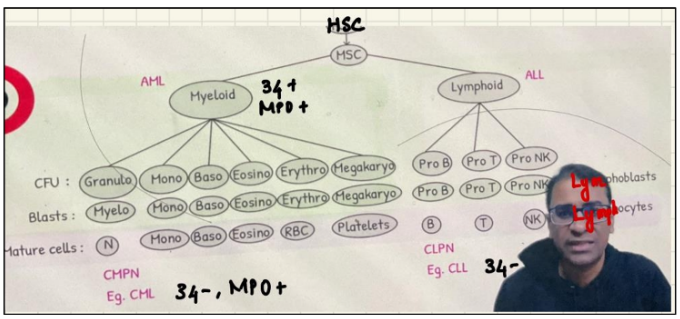
Liver – 3 month

↓

BM – 4 month

At birth: All bones At

Puberty: Flat bones Sternum, Ribs, Vertebra, Iliac.



CD Marker:
Blasts - CD_{34}
WBC - CD_{45}

Lymphoid

- B - Cd 19, 20, 21, 22, 23, 24
- T - CD 1, 2, 3, 4, 5, 6, 7, 8
- NK - CD 16, 56
- Mono - CD 14, 64
- Immature cells → Acute tumors Eg: AML
  (All cells before blasts cell stage)
- Mature cells → Chronic tumors.
  Eg: Mature myeloid - CMPN

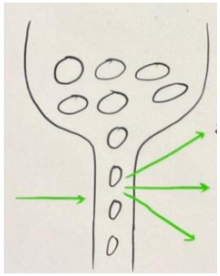
Bone Marrow:
C/O: Fatigue } 7 days
Fever }
O/E: Hepatosplenomegaly 3cm - 5cm
Lab: TLC: 2L/μL
PC: 20,000/μL
BM: Hyper cellular, Blasts % = 22%
Cut off AC Leukemia ≥ 20%

AML	ALL
Chloroma	CNS infiltration
Gum hyperplasia	Testis infiltration
CBC + P.S	Mediastenal L. Nodes

Stains:

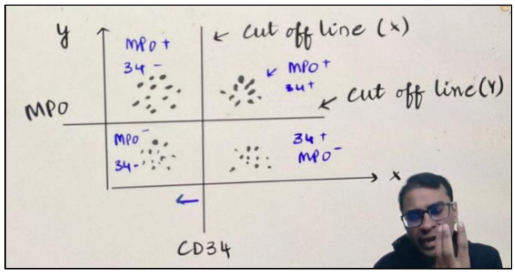
	MPO	SBB	PAS	NSE
Mydoid	+	+	-	
Lymphoid	-	- (ALL-L3)	+	
Monocytic	+/-	-	-	
Erythroblasts: PAS +ve				

Flow cytometry:



SS
Side ∝ granules scatter
Forward ∝ Size S
FS

Immunophenotyping: (IPC)



CLASSIFICATION OF ACUTE LEUKEMIA 24:52

A. FAB: L_1, L_2, L_3
B. WHO 2018:

All with recurrent cytogenic aberration

Good prognosis	Poor prognosis
T (12, 21)	t (5, 14)
Trisomy 4, 10, 17	t (9, 22)
	T (V, 11) (V - Variable)

Provisional entity:
B - ALL with t (BCR - ABL)
Early T - AL L

AML:
FAB → M_0 → M_7
WHO 2018: AML

1) AML with recurrent cytogenic aberration

	Good prognosis	Bad prognosis
Blast cut-off req < 20%	t (8, 21)	t (1, 22)
	t (15, 17)	t (6, 9)
	t (16, 16) or CEBPA mutation	FLT-3 mutation
	NPM-1 mutation	

Provisional entity: AML with BCR-ABL

2) AML with Myelodysplasia "MDS": poor prog.
   5q del / Mono. Chr 5
   Morphology of dysplasia → MDS

3) AML in down's syndrome: (AML-MF)
   GATA-1

4) AML therapy related

5) AML: Nos (M_0 - M_7)

APML: Acute promyelocyte leukemia

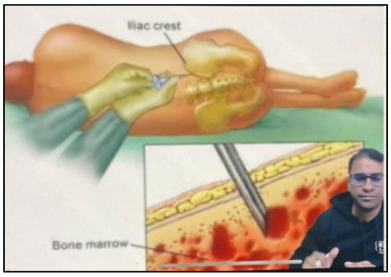
Myeloblast → Promyelocyte → Metamyocytes
↑ APML (-)
↓
T (15, 17)
T (PML-RARA)
↑⊗
ATRA
↓
Band
↓
Neutrophil

Bone Marrow aspiration needle

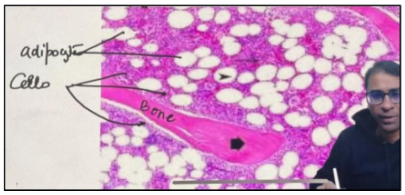
Side screw: SALAH

Acute Leukemia

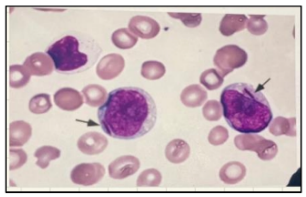
Topic Notes: 5



BM Biopsy



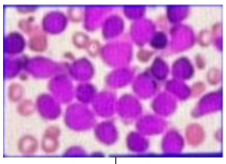
AML Morphology



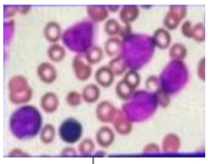
Cluster of Auer

Rods: Faggots

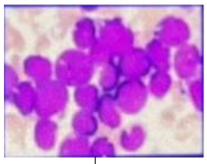
FAB Classification of ALL (1976)



L_1: Small monomorphic



L_2: Large, heterogeneous



L_3: Burkitt cell-type

CMPN & Lymphoma

Tumor of mature myeloid cells.

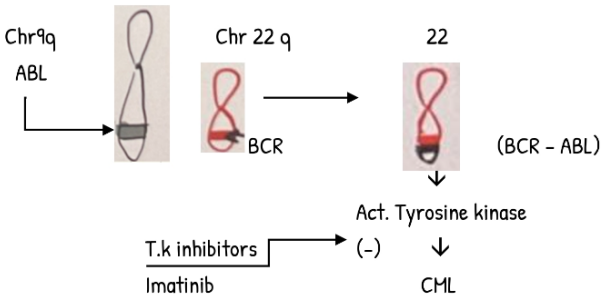
WHO 2018:

1. CML: Chronic myeloid leukemia
2. PCV: Polycythemia vera
3. ET: Essential thrombocythemia
4. PMF: Primary myelofibrosis
5. CNL: Ch. Neutrophilic leukemia
6. CEL: Ch. Eosinophilic leukemia

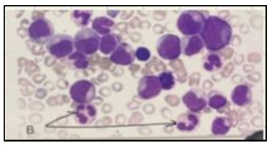
CML

2:24

Philladelphia chromosome.



PS: 'Garden party' appearance
Myeloid Bulge (N, Bands, meta, myelo, pro myeloblasts)
Basophilia



d/d of garden party appearance:

CML	Leukemoid reaction (Sepsis, GM CSF)
LAPSCOLE low (<25) • PNH • Her rickets	High (>125) • PCV, CML (AP, BC) • AML • Preg. Chld

3 Phases of CML:

=Acute leuke
↑

	Chronic	Acceleration	Blast crisis
% Myeloblast	0-9%	10-19%	≥20%
% Basophils	0-19%	>20%	-

Polycythemia Vera:

All major or 1st 2 major + minor

Major:

1. Hb → 16.5gm% (M)
   → 16 g% (F)

   Or

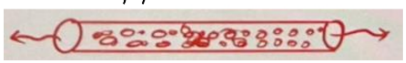
   Hct > 49%

   > 48%

2. Pan myelosis
3. Mut: JAK2, MPL
4. Mut: JAK2, MPL, Cat - R

Minor:

1. Rule of 2° Polycythemia (↓ EPO levels)



C/f: Headache, syncope, thrombosis

Treatment:

- Therapeutic phlebotomy
- Anti coag.

Essential Thrombocythemia:

All Major + 1st 3 Major + Minor.

Rule out 2° causes: Infection, vasculitis, IDA.

Major:

- ↑ Platelet > 4.5 lakhs / pL.
- ↑ BM Megakaryocyte

- Rule out CML / PCV
- JAK - 2, MPL.

Minor
- Rule out 2° causes.

Rx:
If thrombosis: Salicylates.

PRIMARY MYELOFIBROSIS 21:30

- 2 Stages.
  (1) Cellular in BM, ↑↑ TLC
  (2) Fibrotic in BM ↓↓ TLC

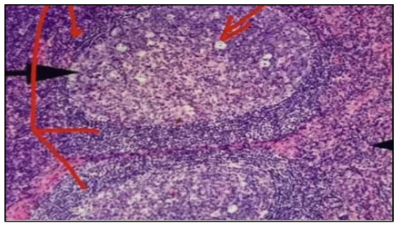
Mut: JAK-2, MPL, Calveticulin Cal - R

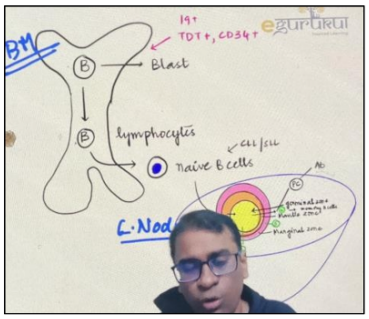
PS:
Tear drop RBC + OCC n RBC, myelobast
Leukoerythroblastosis.

Case:
46/M: Fatigue, headache
Hb: 19.5 gm%, PL: 7 lakhs
TLC: 30,000/UL

If pH^+ - CML
pH^- Epo level ↓, JAK 2 → PCV
Epo level ↑, → 2° PCV

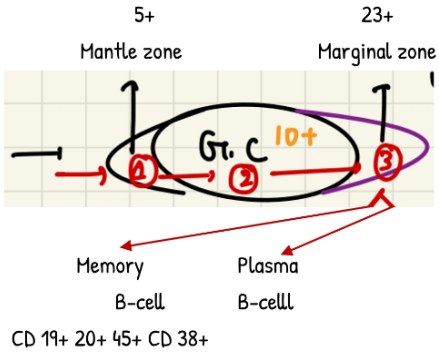
LYMPHOMA 26:30





Basics:

Naïve B cell → L. Follicle →
CD5+



Mantle zone:	CLL MZL
G.C:	Follicular L. DLBCL Burkitts
Marginal zone:	C.L.L MZL.

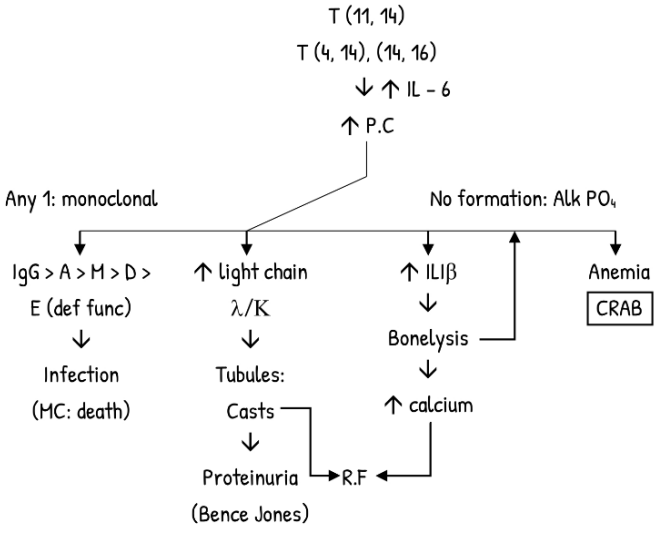
Diagnosis:
Biopsy + IHC + Mutations

(CLPN) Lymphoma	Mut	19+, 20+, 45+ IHC	Biopsy / Histology
1. CLL / SLL	Ch. 13 q del	5+, 23+	Pseudofollicular pattern

2. Mantle	BCL-1 (Ch. 11) T (11, 14)	5+	Mantle zone proliferation
3. Follicular	BCL – 2 + (Chr. 18) T (14, 18)	10+	True follicular pattern
4. DLBCL (Diffuse large B cell lymphoma	BCL – 6 + (Chr.3) T (3, 14)	10+	Diffuse effacement by medium – large cells
5. Burkitts	C – MYC (Chr-8) T (8, 14); (2, 8); (8, 22)	10+	Starry sky app.
6. Marginal zone lymp	BCL – 20	20+	(+) H. pylori Autoimmune disease
7. Hairy cell leuk 	BRAFF mut.	11C, 25, 103, FMC-7	Fried egg appearance TRAP+ Annexin A_1+

PLASMA CELL MYELOMA

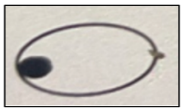
16:07



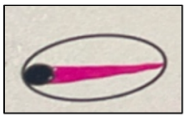
↑ IgM due to MYD mutation

↳ Walden storm macro: Headache, Blurry vision, Ab (N) Coagulation

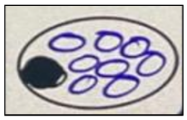
Morpho:



PC

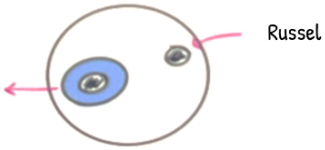


Flame cell



Mott

Inclusions:



New

Any 1: MM

B_2 Microglobulin Serum / urine	→ Prognostic

S: > 60% PC

LI: Light chain (I.V) = > 100

M: MRI ≥ 2 lytic lesion of > 5 mm size

T – CLPN

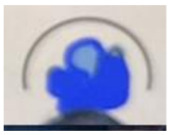
24:46

1. Adult T cell lymphoma: HTLV – 1

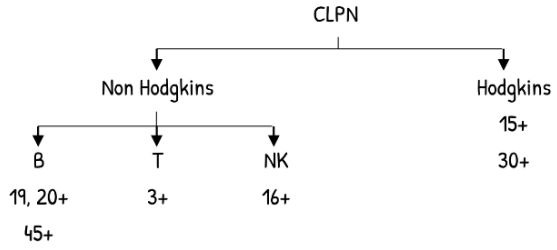
Clover lymphoma

2. Anaplastic T cell lymphoma: Alk gene + Doughnut cell

3. Sezary syndrome / mycosis fungoidosis:
   (Cutaneous)



Cerebriform nuclei



HODGKIN'S LYMPHOMA

55:00

	Classical	Non – Classical
CD20	-	+
CD15/30	+	-
PAX5	+	+
BCL 6	+/-	+/-

Reed Steen berg cell

Classical Hodgkins lymphoma

1. Mixed cellularity:
   (MC – India)
   - Mononuclear cell
   - EBV + (70% cases)

2. Nodular sclerosis: (MC world)

→ Fibrosis
Lacuner cell

EBV 0-5%

3. Lymphcocyte rich

4. Lymphocyte depleted
   (EBV in 90% cases)
   Worst prognosis

Rx: A: Adriamycin
B: Bleomycin
V: Vinblastine
D: Dacarbazine

Non classical HL:

1. Nodular lymphocyte predominant H.L (rare)
   - EBV – 0% cases
   - Best prognosis
   - Popcorn cells

CD20 (+)
15 (-)
30 (-)

Treatment:
R – Rituximab
C – Cyclophosphamide
H – Hydroxy daurorubicin
O – Oncovin
P – Prednisolone.

RBCS & Anemia

BM
Proerythroblast
↓
Basophilic erythroblast
(early)
↓
Poly chromatic erythroblast
↓
Orthochromatic erythroblast
(Late)

RBC
↑
Reticulocyte

Spleen nucleus.

RETICULOCYTE

03:16

Reticulocyte supra vital stain

NBM
BCB
CV

↑ ed
Hemolytic

(> 2.6%)
>5%)

N: 0.5 - 2%

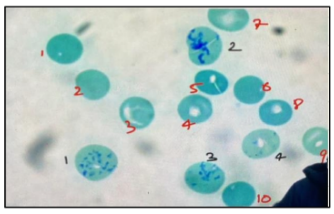
Low (<0.5%)
Hypo proliferative

% Retic = Retic / 100 RBCs

$$CRC = \% \text{ Retic} \times \frac{Hb/HCT\ (Pt)}{Hb/HCT\ (N)}$$

R = 4 % $\frac{4}{10}$ x 100 = 40%

Rbc = 10



1) MCV: 80-95FL
2) MCH: avg Hb per RBC

$$MCH = \frac{Hb}{RBC\ count}\ (30 \pm 3pg)$$ ↓ in hypochromia

3) MCHC = Avg. Hb per unit volume of RBC

$\frac{Hb}{PCV\ (HCt)}$ (30 ± 2g/dl) ↑ in H.S

4) RDW: Anisocytosis (n=12-16)

Intravascular hemolysis	Extravascular hemolysis
Hemoglobinemia →	X
Hemosiderinuria →	X
Hemoglobinuria →	X
Hb + Hapto: ↓ hapto →	Normal
↑ Bilirubin	↑↑ Bilirubin
↑↑ LDH	↑ LDH
X ←	Splenomegaly
Cause: (Intracorpuscular)	Memb defect: HS, HE
→ PNH	Enzy. Defect: G-6PD def. PKD.
→ PCH	Hb. Defect: Thalassemia, SCA.
→ IHA	IHA

Extra corpuscular

- Micro haemolytic anemia
- HVS
- TTP
- DIC
- HELLP syndrome
- Vasculitis

1. PNH: Rx: C5 Inhibitors

   Def in PIG A gene → def gpi Eculizumab

   ↓

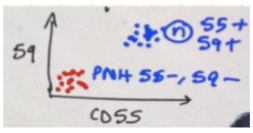
   Loss of CD55 & 59 on RBC → ↑ ed 'C' activation

   ↑ Lysis: of RBC, WBC, Platelets more at night, infection (↓ PH)

   1) Pancytopenia + hyper cellular BM
   2) IVH
   3) Thrombosis (Hep Vein)

Diagnosis:

- Flow: Abs CD55/59
- FLAER
- HAMS
- Sucrose lysis test



Immunohemolytic Anemia:

Ab

IgG (37° c) Warm Ab	IgM (4° - 22°c) Cold Ab
1°	1°
2°:	2° Infections
• Autoimmune ds	Viral: M. pneumoniae
• Drugs: α -m-DOPA, Penicillin	Influenza EBV
• CLL	Multiple myeloma

Diagnosis: Coombs Test

HEMOLYTIC UREMIC SYND. *23:00*

Hemolytic uremic synd.	Thrombotic thrombocytopenic purpura
1. MAHA	1) MAHA
+	+
2. Thrombocytopenia	2) Thrombocytopenia
+	3) Neurological defects
3. R.F (↑urea/ ↑creat)	ADAM TS 13 def
D+ Shigella, EHEC	↓
D- def. of factor I	↑↑ VWF multimers
↓	Schistocytes
Endothelial injury	↓
→ MAHA	MAHA

Treatment:
Symptomatic (HUS)
Recom. ADAM Ts 13 (TTP)

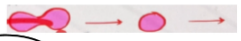
Heriditary Spherocytosis:

- (AD)
- Defect in Ankyrin > Band - 3> Spectrin

MC defect

Max hemolysis: α - Spectrin loss
MC defect in HE: Spectrin loss

(N) RBC

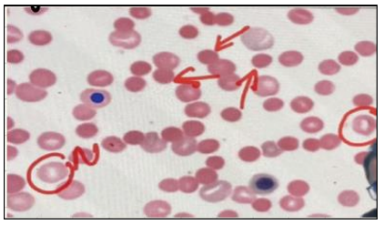


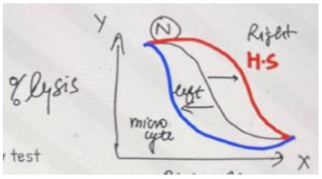
dest by EVH spleen

Biconcave ↑S. area

D/d: IHA → Coombs +ve
Severe burns
Toxins, G6PD def.

Spherocyte:





% NaCl
↑ ed fragility
↓ ed fragility

Diagnosis:

1. Osmotic fragility test
   N RBC lysis: 0.5 - 0.3% NaCl
- In Sphero lysis: above 0.5 - 0.9%

- In micro lysis: below 0.3 - 0.1%

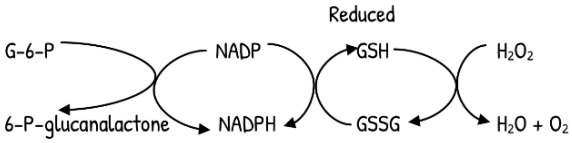
Confirm: Mutation analysis
Splenectomy: ↓ hemolysis
↑ Spherocytes

G-6-P D deficiency:

XR > AR

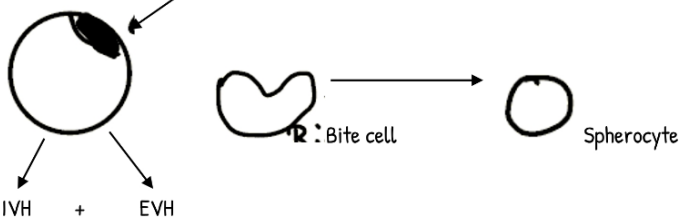
G-6-P $\xrightarrow{\text{G-6-P D}}$ 6-P - Gluconalactone

HMP Shunt:



In G-6-P D def,

↑ oxidative stress
↓
↑ lipid peroxidation
↓ Heinz body (Supravital sign)



+ EVH

Blister RBC

Prinaguive, Quinine, Chloroquine, sulphadexine

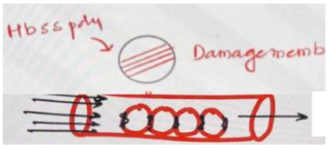
s) ↑ ed hemolysis — Dmg, Infections, Fava Bean

↑ ed hemolysis → Drugs: Quinine, Chloroquine, Primaquine
→ Infection
→ Fava bean

3. Sickle cell Anemia (Hbs):

β chain (6th position) Glutamic acid (-)ve → valine nee

(Change in charge, Solubility, Structure)



Ischemia

Reversible (to O_2 / hydration)

- Pain dactylitis Hand – Foot synd
- Infection – chest, bone
  ↓
  Salmonella typhi

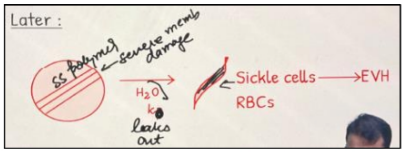
Reversible (to O_2 / hydration)

- Pain dactylitis Hand – Foot synd
- Infection – chest bone Osteomyelitis
  ↓ Etio
  Ac. Chest synd Salmonella typhi

Treatment:

- O_2; i.v Fluids
- Hydroxy urea
- Crizanlizumab: P – selectin Ab → ↓ Vaso occlusion
- L – glutamine: ↓ Free Radicals.
- Voxeletor: ↑ O_2 affinity of Hb.

Later:



Test:

Sickling - Nameta Bisulphite

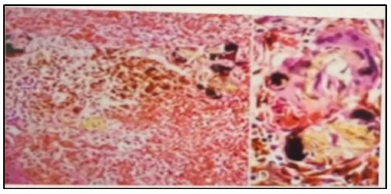
Hb - electrophoresis

Hb - HPLC

Mutation: Best

GAMMA GANDY BODIES: Congestive splenomegaly: Fe + Ca + giant cells

(PCV, CML, Sickle cell, Portal HTN)



4. Thalassemia: AR

Def: $\frac{\alpha \text{ gene}}{\text{Chrib}}$: α thalassemia

(N) $\alpha\alpha/\alpha\alpha$: (n)

4α gene

α-/α-α Thal trait

Defect:

(-) deletion

--/-- BART

α - /-- HbH

β gene → misense mut. (Splicing mutation) promoters mut.

↓

β^+

-β gene termination mut.

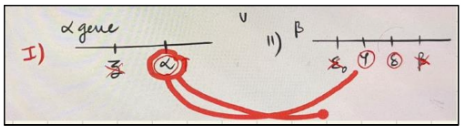
β_1

(N) Adult Hb:

HbA = $\alpha_2\beta_2$	96.5 - 97.5%
A2 = α_2 S_2	2.5 - 3.5 %
F = α_2 γ_2	<1%

Diagnosis: Hb - HPLC

Gene mutation analysis



In β thalassemia: excess α combines with

β thalassemia trait: ↓HbA, ↑A_2

HbA ↓ δ = ↑A_2

Y = ↑F

Hereditary persistence of fetal Hemoglobin (HPFH)

↑ HbF, Hb: (N)

β thal major: ↑↑ HbF, ↑ HbA_2

HbA↓↓

Severe anemia + Jaundice

RBC:

Microcytic - hypo chromic

Target cells

Howell jolly bodies

Cabot rings

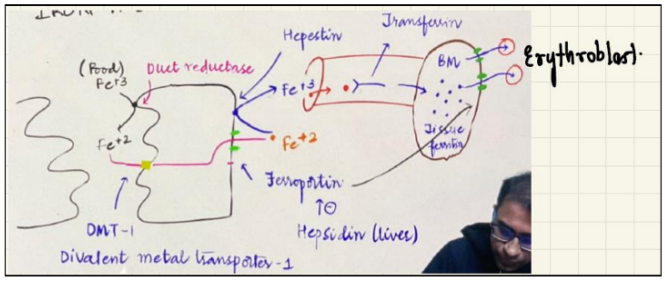
Nucleated RBCs

Basophilic Stippling

Nutritional Anemia

FE DEFICIENCY ANEMIA

52:32



	Thal. Trait	Mild IDA
	No hemolysis	↓ RBC production
MCV	↓	↓
Mentzer index	<13	>13

Iron profile:

	(N)	IDA	ACD	SA (iron overloaded)
S. Iron (Transferrin bound)	100 ug/dl (50-150)	↓	↓	↑
Ferritin (most sensitive)	50-150 mg/ml	↓	↑	↑
Transat (%)	33%	↓	↓	↑
TIBL	300 ug/dl	↑	↓	↓

$$TIBC \propto \frac{1}{ferritin}$$

ACD inflammation : ↑ IL - 6, 1, TNF - α

↓

↑ ferritin → ↓ TIBC

↓

↑ Hepcidin → ↓ ferroportin

Sideroblastic Anemia: Def in porphyrin synthesis

Globin → Hb ↓

↑ Iron – Heme → Hb ↓

↓

Porphyrin ↓  Ring sideroblast

Rx: B_6 Cofactor of ALA syndrome

↑ ALA → ↑ Heme

Macrocytic Anemia:

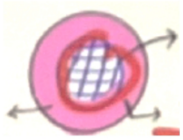
Macrocytic

Megaloblastic	**Non – megaloblastic**
BM: large blasts	BM: normoblast
Defective nuclear maturation	Toxic effect of alcoholism
B_{12} deficiency	Hypothyroidism
Folic acid deficiency	

RBC:

WBC: hyper segmented neutrophils ≥ 6 lobes

BM:



Seivelike (Immature chromatin)

Mature cytoplasm

Nucleo cytoplasmic asynchrony

Lab diagnosis:

- Homocysteine $\xrightarrow[\text{Folate}]{\text{Vit } B_{12}}$ Methionine

  M.M CoA $\xrightarrow[B_{12}]{}$ Succinyl CoA.

  If Vit B_{12} ↓, Homocysteine ↑
  Succinyl CoA ↓
  M.M. CoA ↑

C/f: Hyperpigmentation of knuckles.

HYPOPROLIFERATIVE ANEMIA *90:58*

Aplastic Anemia	Pure red cell aplasia (PRCA)
Pancytopenia + Hypo cellular BM Retic % = ↓ M: E Ratio = (n)	Severe anemia + Absent Erythroblasts in BM ↓ 99:1

Myeloid: erythroid = 3 : 1
(BM)

Etiology:

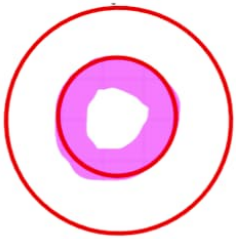
→ Fanconi synd.
→ Dyskeratosis congenita

1°:
→ Diamond Blackfan synd.
2°:
→ Thymoma
→ lymphoma

→ Diamond Schwachman synd.

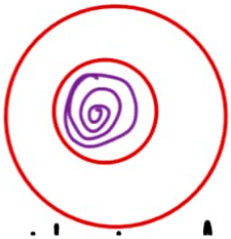
Arteriosclerosis:

Hyaline



Smooth homogenous pink deposition

Hyperplastic



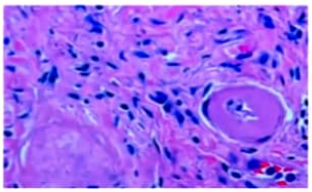
Proliferation of collagen and S.M

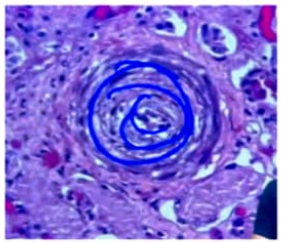
Concentric lamination

Malignant

Eg: Benign HTN

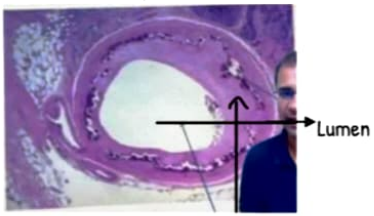
DM





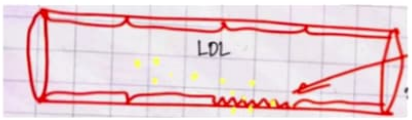
Monckeberg medial calcific sclerosis

Muscular Artery



Calcification in T. media + I.E.L

3) Atherosclerosis



Endo injury

Mod

Non mod

LDL

↓

LDL – O (Free radical)

↓

Engulfed by macro / mono / LMC / Foam cells.

↓

PDGF & TFG – β

↓

Recruit SMC & collagen

↓

Atheromatous plaque

Site:

Abd. Aorta	Gangrene
Coronary art	MI
Cerebral art	Stroke
Popliteal art	Gangrene
Mesenteric	Rare.

Other effects:

- Haemorrhage (rupture in thin plaque)
- Thrombosis, Embolism
- Aneurysm
- Dissection

Aneurysm:

Mc site: Abd. aorta.

(b/w renal art. & Bifurcation of iliac art.)

Etiology: mc: Atherosclerosis

Other: Syphillis (Leutic) → obliteration of vasovasorum

↓

Ischemic fibrosis (Tree bark)

Site: Abd. Aorta.

Myotic aneurysm:

Etiology: Bact (pyogenic)

- S. aureus
- Salmonella gastroenteritis.

Dissection:

Mc. Etiology: HTN > Atherosclerosis

CMN (Cystic medial necrosis)

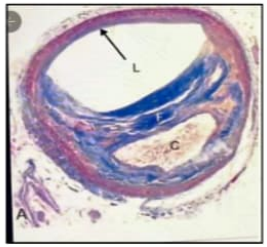
Mc. Site: Abd. aorta > Arch. > Descending.

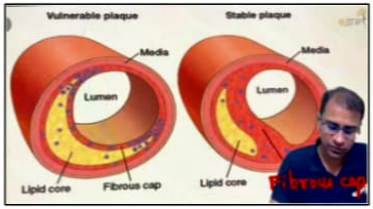
CMN:

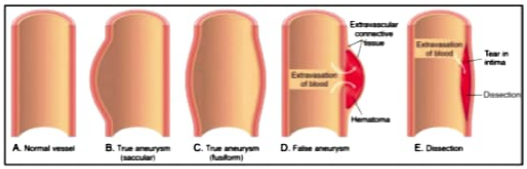
- Degeneration of T. media
- Replaced by mucoid like subs.

Etiology:

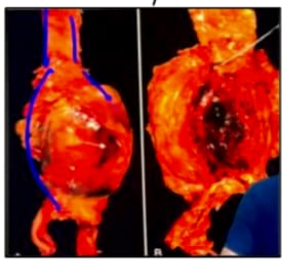
- Ehler Danlos (Collagen def.)
- Marfans
- Loeys Deitz syndrome
- Vit - C def.
- Pregnancy
- AT

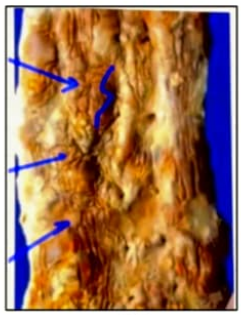




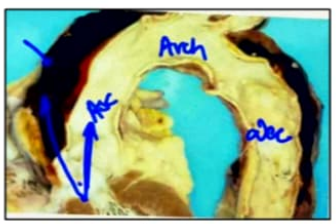


Aneurysm





3 Syphillis



Dissection

CMN

VASCULITIS

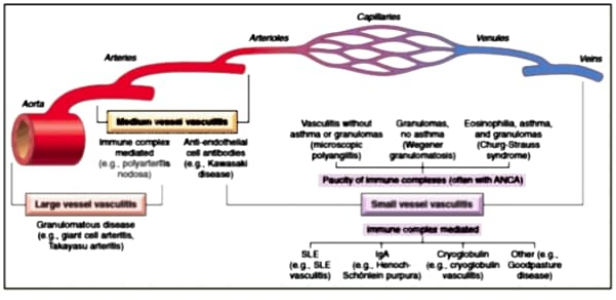
25:00

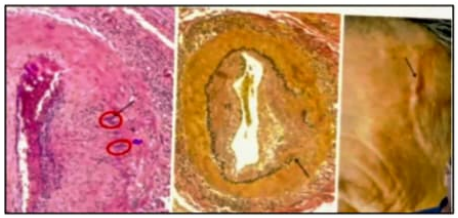
- Inflammation of vessels.

Classification:

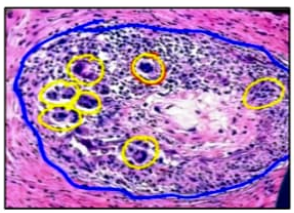
Large	Medium	Small
G: Giant cell Arteritis	P: PAN (Type 3)	
T: Takayasu Arteritis	K: Kawasaki (Type 2) Disease	

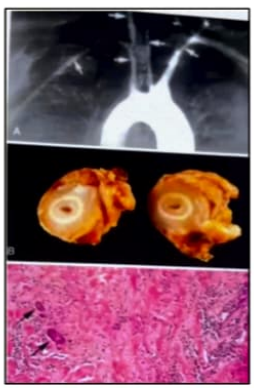
Immune complex		ANCA mediated
Type 3 HSN	Type 2	• Churg strauss
• HSP	3	• Wegener's granulomatosis
• SLE	4	
	Type 2	• Microscopic polyartheritis





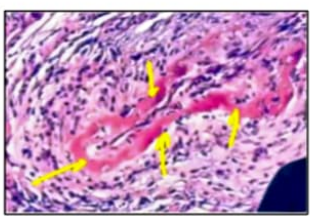
Giant cell arteritis





Takayasu arteritis

PAN:



Kawasaki disease:

>5d. of fever

C → Conjunctivitis (Non purulent)

R → Rash (Polymorphic)

E → Edema (hands / toe)

A → Adenopathy

M → Mucosal tongue

Other: MI + Carotid artery aneurysm.

Small vessel:

HSP: MC vasculitis in children

C/f: 1-2 d. after viral illness

1. Glomerulo nephropathy
2. Joint: Arthritis
3. Skin: Palpable purpura
4. Mescentric cap: Colic abd. Pain.

Diag:

Purpura: Leuko cytoclastic vasculitis

IgA deposits in vessel (specific)

Pauci immune (ANCA) Antineutro cytoplasmic Ab

↓

IFA

P - ANCA

(MPO)

Enz. Tissue damage

IFA

C-ANCA

(Proteinase 3)

C: Churg straus

M: Micro polyangitis

Wegener's

	Churg	Wegeners	Mic poly
ANCA	P	C	P
CF	Asthma + Allergic Rhinitis Eosinophilia	Upper RTI Necrotizing Cavitation in lungs	X
Granuloma	+	+	X

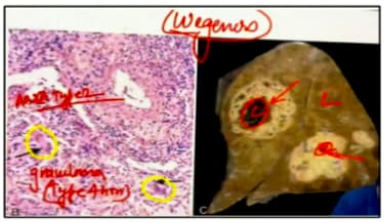
RPGN	+	+	+

Bechets: Small + med. Vasculitis

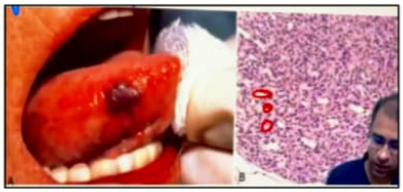
1) Oral apthous ulcer
2) Genital warts
3) Uveitis

Buirgero / Thromboangitis obliterans

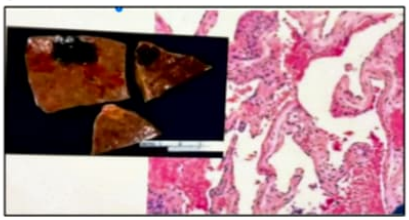
- (Med + small vessel) ➜ Radial / Tibial artery
- HLA B5, Heavy smokers
- Intermittent claudication
- In step foot claudication
- Raynaud's phenomenon: pain on cold extremities.



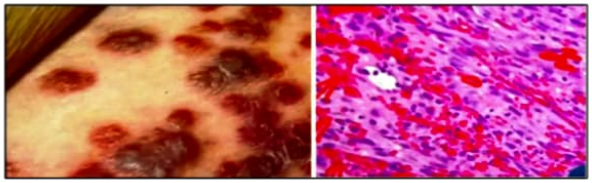
Capillary Hemangioma:



Cavernous Hemangioma



Kaposi sarcoma



Heart

Vegetations:

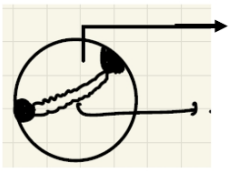
	RHD	NBTE	LSE	I.E
Etiology	Grp. A β Hemolytic Strepto (1, 3, 5, 8)	Mal. Nut Cancers S – Stomach L – Lung A – Adeno Ca. P – Panc.	Ag + Ab Immune compl of S.L.E	S. Aureus
Valve	M	M	M	Aortic
Site	Along line of closure	Along line of closure	On both side	Large friable bulky on valve cusps.
Destruction	No	No	No	yes

I.V drug abusers: Right side (Tricuspid)

RHD:
Pancarditis
Acute:

1) Pericardium — Bread & Butter
2) Myocardium — Ascoff body
3) Endocardium — Vegetations: MR
   LA wall: Thick patch
   (Mc. Callum patch)

Chronic:



Fibrosed / calcified

Fish mouth app.

I.E	Acute	Subacute
Etio:	Virulent S. aureus Native	Avirulent <12m: S. epi >12m: S. viridians
C/f:	Death	Damaged / prosthetic

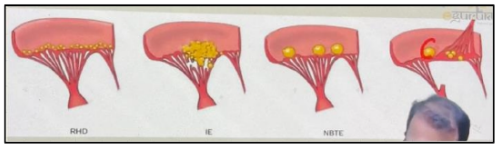
Other lesions:

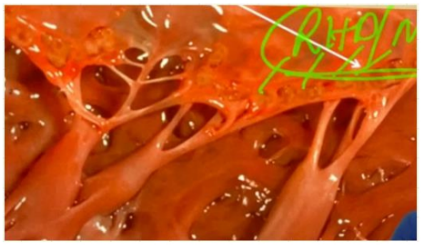
Retina: Roth

Palm / Soles: Painless

Fingers: Painful ➜ osler's nodes.

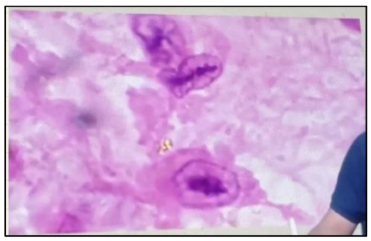
(Janeway)

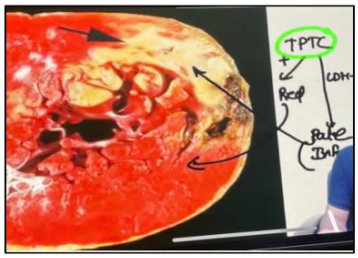


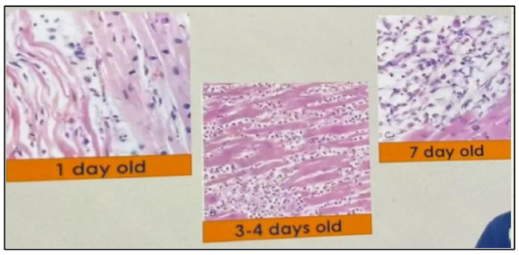


RHD

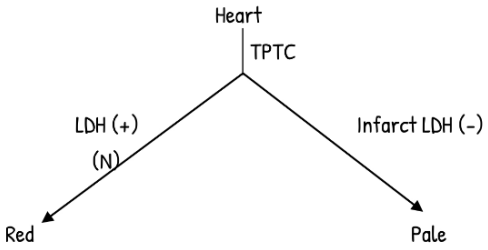
Anitschow cells







Morphological changes in MI:



MI:

< 30 min ➜ Reversible injury

>30 min ➜ Irreversible injury

Time	Gross	LM	EM
<30 min	-	-	Loss of macrosome Cytoplasmic bleb Ribosome detachment
30 min - 4 hr	-	Waviness of myofibrils	M. figure Amorph density
12-24 hr		Neutrophil	
24-72 hr		Brisk Neutrophil	
D_3 - d_7		Macrophage	
D_7 - D_{14}		G.T	
> d_{14}		Collagen	

Heart completely heals in 6-8 weeks

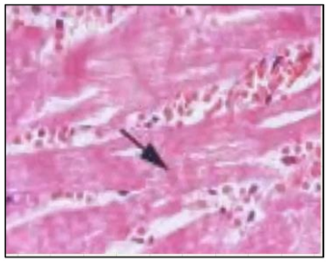
Reperfusion injury:

After infarction → Blood reflow to infarcted area

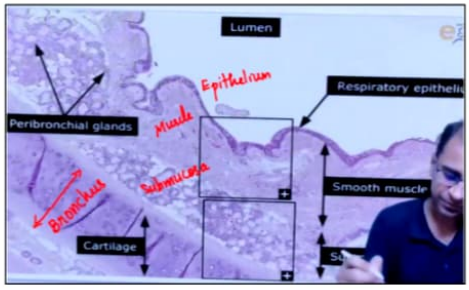
→ Free radical injury

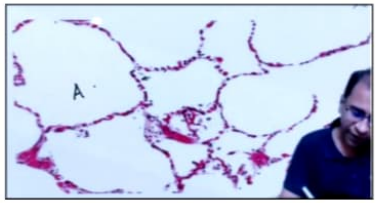
→ Ca. inflow: surrounding (N) area to contraction

Contraction Band Necrosis

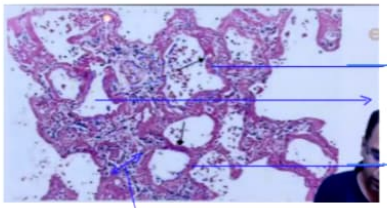


Lungs





ARDS



Neutrophils

Alveolar collapse

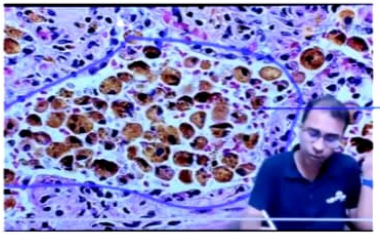
Hyaline deposition

Edema

↓

Hyaline membrane disease

- Edema not related to heart = Non - Cardiogenic pulmonary edema



Cardiogenic pulmonary edema

↓

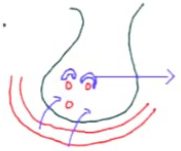
Heart failure cells = Hemosiderin laid macrophages

Other edema in lungs

Alveolar edema

Non - cardiogenic
→ ARDS / HMD

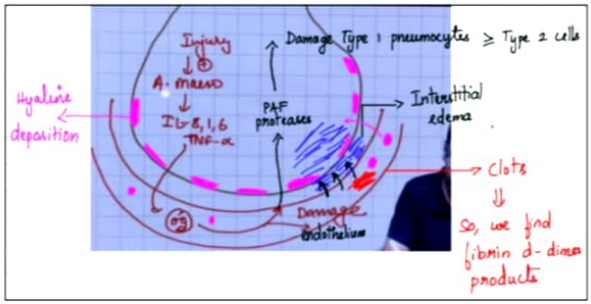
Cardiogenic
→ Let ventricular failure
↓
↑ Pulmonary cap. Wedge pressure
↓
RBC and fluid moves into alveoli
↓
Macrophages engulf RBC
↓
Hemosiderin = Heart failure ceills Laden Macrophages



Macrophages engulf this

ARDS / HYALINE MEMBRANE DISEASE 05:36

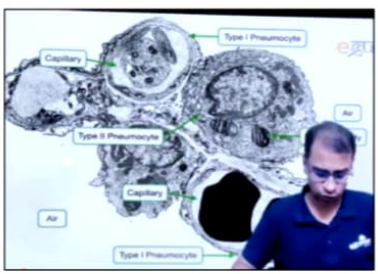
- Sepsis
- Pulmonary infection [COVID-19, Viral, Bac, TB, S.aureus]
- Head trauma
- Gastric aspiration
- Others: Toxic gases
  Near drowning
  Acute pancreatitis
  Uremia
  Severe burns
  TRALI
  Massive blood transfusion



- Type 1 pneumocytes ≥ type 2 (late damage)
  Attacked → Alveolar collapse
  Respiratory distress
  Due to damage, hyaline proteins also move out
  Deposited = Hyaline membrane disease

- Hyaline = Fibrin + Necrosed Type - 1 ≥ 2 cells

- Stage A : Exudative stage
  B : Proliferation of type 2 → relay type 1 cells
  C : Fibrosis



CHRONIC PULMONARY DISEASE 15:41

- Can be
  - Obstructive
  - Restrictive

Obstructive Involve

- Emphysema = Acinus (Distal to terminal bronchiole)
- Asthma = Bronchus ± Bronchioles
- Chronic bronchitis = Bronchus only
- Bronchiectasis

- Emphysema + Chronic bronchitis = COPD
- Obstruction = Obstruction to outflow of Air
  Restrictive = Obstruction to inflow of Air

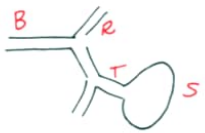
	FEV_1	FVC	FEV_1 / FVC
Restrictive	↓	↓	Normal
Obstructive	↓	Normal / ↓	↓

EMPHYSEMA

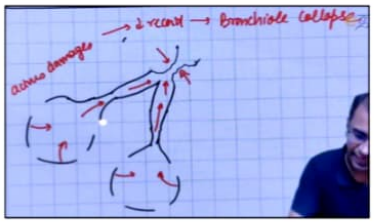
19:47

- Dilation and destruction of acinus = Pink puffers

Centriacinar	Pan acinar	Paraseptal
[B]	[T, R]	[s]
Etio: Smoking	α_1 antitrypsin def	TB
Acinus: Proximal	Proximal + distal affected	Distal acinus affected
Lungs: Apex	Base	Peripheral



B = Bronchus
T = Terminal bronchiole
R = Respiratory bronchiole
S = Alveolar sac



Bronchiole collapse → Obstruction to Airflow

α_1 Antitrypsin def

- Antitrypsin (Protease inhibitor = PI)
  ↓
  Deficiency
  ↓
  Alveolar damage

- PI gene = on chromosome 14
- PI deficiency = protease deposition on liver (Form globules)
  ↓
  PAS +, Diastase - R

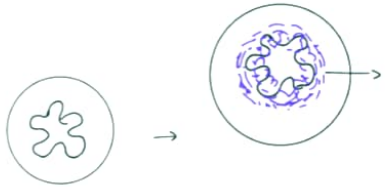
ASTHMA

27:07

- Type - 1 HSN reaction
  ↓
  Inflamm. Obstruction to air flow

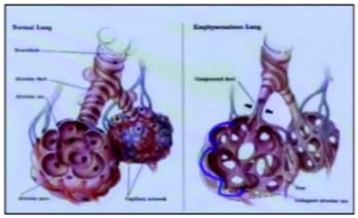
- Sputum microscopy C = Creola body
  (Damaged Resp cells)
  C = Charcot leyden crystals
  (Eosino crushing)
  C = Curschmann spirals
  (Impacted mucin plugs)

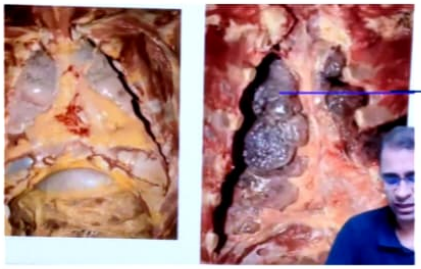
Histopath:



↑^{sec} mucin production
↓
Remodification of airway
↓
- ↑ wall thickness
- ↓ lumen

Blocks up the airways





Bullae formation

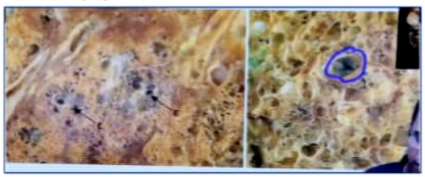
↓

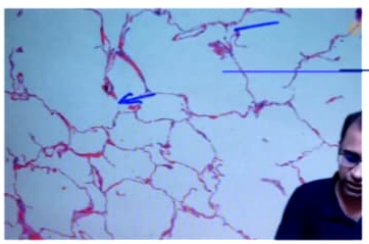
Ruptures

↓

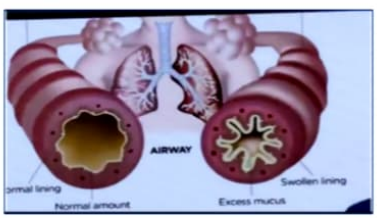
Spontaneous pneumothorax

Emphysema (Centri - & Pan - acinar)

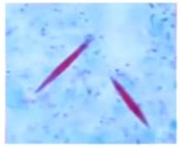




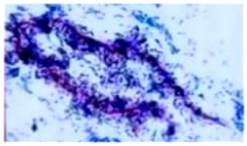
Alveoli dilated



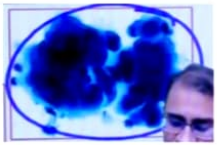
Sputum findings in Bronchial Asthma



Charcot ledyden crystals



Curschmann spirals



Creola body

CHRONIC BRONCHITIS

33:40

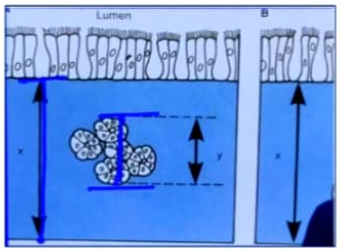
- ≥ 3 month of chronic productive cough in last 2 consequent years
- Chronic irritation, smoking, silica, dust

  ↓

  ↑ Mucin (↑ in mucin glands in sub mucosa)

  ↓

  ↓ airway clearance
- Reid index = $\frac{\text{Mucin gland layer}}{\text{Bronchial wall layer}}$
- If ≥ 0.4 → chronic bronchitis



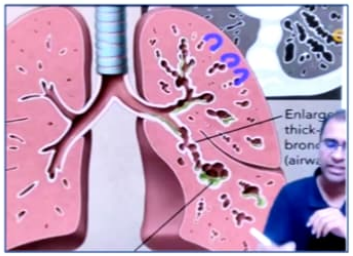
Cartilage

Normal bronchial wall

- Mucus gland < 40% of thickness

BRONCHIECTASIS

38:08



- Whole wall thickened
- Chronic necrotizing destruction of elastic and smooth muscle of bronchi

↓

By necrotizing infection

- Pseudomonas

  S. Aureus

  Aspergillus

  Foreign body

  Autoimmune disease → Inflammatory damage

  Congenital disease → ↑ pulmonary infection

1) Cystic fibrosis = CFTR mutation
2) Kartagener syndrome = 1° ciliary dyskinesia

↓

- Bronchiectasis
- Sinusitis
- Situs inversus

RESTRICTIVE LUNG DISEASE *41:37*

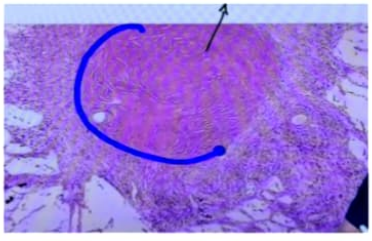
Pneumoconiosis

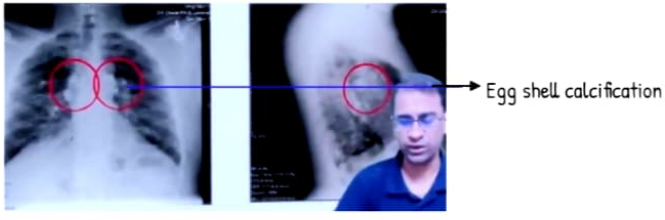
- Chronic fibrosing lung disease due to inhalation of organic / inorganic dusts, fumes, vapours.
- Caplan syndrome = RA + Pneumoconiosis

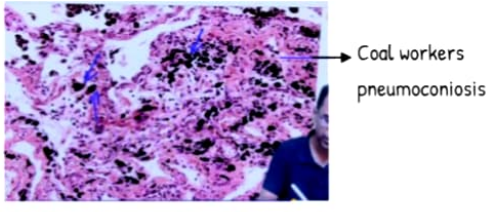
Coal worker (Anthracosis)	**Silicosis**	**Asbestosis**
Mineral Dust coal mines	Silica • Amorphous • Crystalline	Asbestos • Serpentine • Amphibole / crochidolite
	More pathogenic	
Lungs Upper lobe **Microscopy:**  Coal Macule  Nodule	Upper lobe Silica Nodule	Lower lobe Asbestos body [As + Fe + gp] Ferrugenous body [Others + Fe + gp]

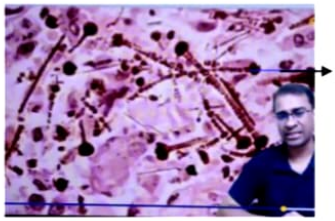
Gross	-	• B/L hilar L. Node enlargement • Egg shell calcification	• Pleural plaques • Effusion • Lung fibrosis

- ↑ TB risk = Silicosis
  ↓
  ↓ T cells
  ↓
  TB
- Lung tumor = Asbestosis > Silicosis
  ↓
  Adeno Ca > malignant mesothelioma

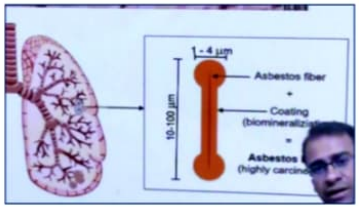


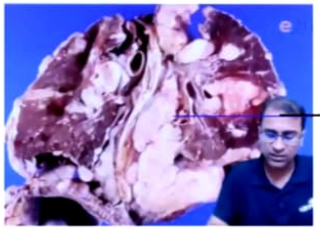




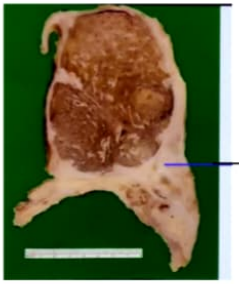


Asbestos bodies





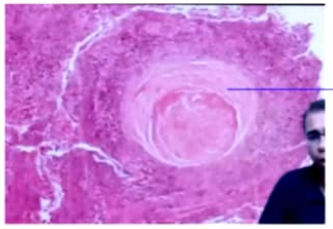
Malignant mesothelioma



Pleural involvement

↓

Asbestosis



Silicotic nodule

LUNG TUMORS

52:50

Smoking, radiation exposure, asbestosis, silicosis

1) Squamous cell ca
   - M C in smokers
   - MC in India
   - Common site = Bronchus (Central)
   - Micro = Keratin pearl + Malignant squamous cells
   - Mut = p53, p63 (IHC)

2) ADENOCARCINOMA

54:51

- MC in world, females, young age
- Acinus (Peripheral) involved
- Micro:

Malignant glands

- Mutation = EGFR - 1 (Good)
  K-RAS (Bad prognosis)
- IHC = TTF - 1
- Pre malignant lesion = Bronchio alveolar variant
  (or) Adeno Ca - in - situ
  ↓
  Best prognosis
  ↓
  No invasion

Lepidic pattern

- EM = ↑ type - 2 pneumocytes = ↑ surfactant

3 NEURO ENDOCRINE TUMOR

58:42

- IHC = S+
  C+
  NSE +
  CD 56+

Benign

- Tumor lets
- Typical carcinoids

Malignant

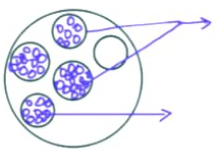
- Atypical cancer
- Small cell cancer (SCC)
- Large cell cancer

CARCINOIDS

1:00:26

- Kulchitshy cell
- Diarrhea
  Flushing
  Cyanosis

- Micro:



Tumor nest

Salt and pepper chromatin = EM

↓

Neurosecretory granules

- M/c site of Tracheo bronchial tree

  ↓

  Ileum
- If Mitotic rate < 2 / npf: Typical
  >2 / npf: Atypical

SMALL CELL CANCER

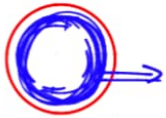
01:03:00

- Worst prognosis
- Occurs in smokers

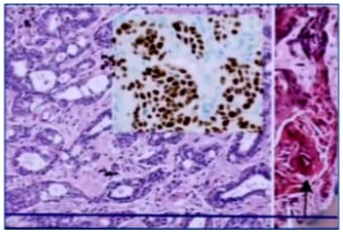
- MC with paraneoplastic syndrome
  (Excep: Hypercalcemia not seen here
  ↓
  Seen in squamous cell cancer)

- Micro: Salt and pepper chromatin
  ↓
  "Nuclear moulding"

DNA leaks out →

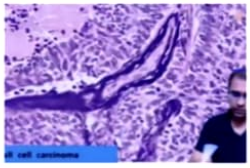


Azopardi effect

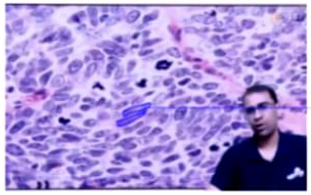


Adenocarcinoma

Squamous cell carcinoma



Small cell carcinoma
↓
Azopardi effect



Spindle shaped cells

↓

Salt and pepper chromatin

MALIGNANT MESOTHELIOMA

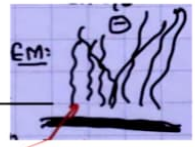
01:08:19

- Seen in asbestosis

Malignant mesothelioma	Adeno carcinoma
• CK 5/6+	• CK 8/9+
• TTF - 1 (-)	• TTF - 1 (+)

M.M

CK 5/6 +



Malignant Mesothelioma

Long microvilli

Absent rootcells

Adeno Ca

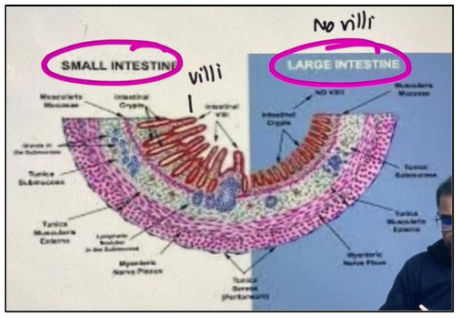
CK 8/9+

TTF - 1 (+)

Short / plump Microvilli

Adeno carcinoma

GIT

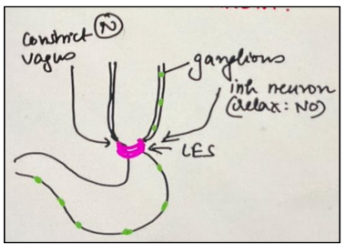


Aganglionosis: Absence of ganglion

1) Esophagus: Congenital: Achalasia cardia
   Acquired: Chagas disease (T. Cruzi)

2) Intestine: Congenital: Hirschsprung disease
   Acquired: Chagas disease
   Toxic megacolon (V.C)

Achalasia Cardia:



Triad

1. Absence of ganglion: Aperistalsis
2. Loss of inhibitory neuron: LES fails to relax
3. Vagal supply intact: ↑ LES tone

Hirsch Sprung Disease:

Loss of RET gene

↓

Premature arrest in descent of neutral crest cells

↓

Distal intestine: lack ganglion.

Involved	Segments	C.F
Rectum	Short. Seg	Asymptomatic / mild
Rec + S.C + Prox. Colon	Long. Seg.	Obstruction, distension, pain abdomen.
		New born: fails to pass meconium.

Affected segment

No ganglions

No infolding

No peristalsis

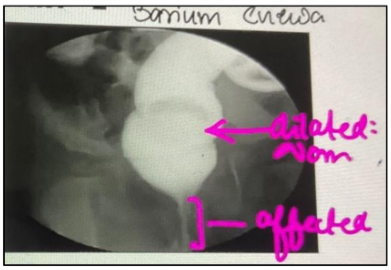
Screening: Anorectal manometry

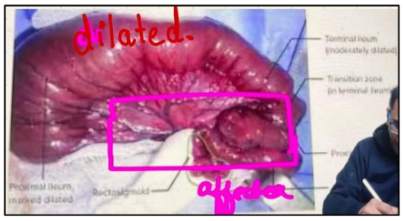
Diagnosis: Rectal Bx:

- Absence of ganglion Calretinin (-)
- Hypertrophied nerves Ache (+)

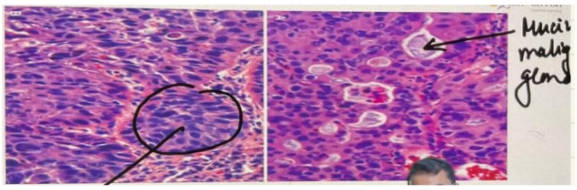
Treatment:

Resection anastomosis





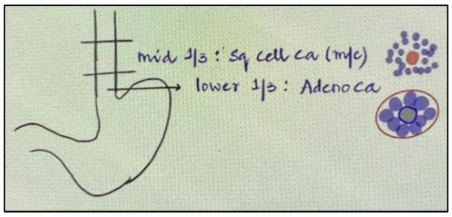
ESO CA: SQUAMOUS CELL AND ADENO CA



Malig. Sq. Cell nest

ESOPHAGEAL TUMORS

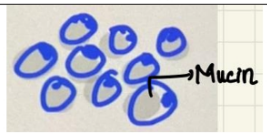
12:49



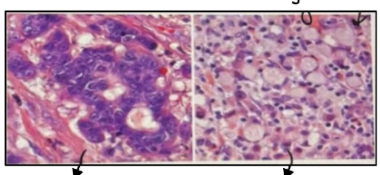
Stomach tumor:

Epithelial	Mesenchymal	Lymphoid
Adeno ca (m/c)	GIST (m/c)	MALTOMA (m/c)
Sq. Cell ca	Leiomyoma	DLBCL

Adeno Ca.: Class → Laureus.

Intestinal type	Diffuse type
• M/c: Malignant glands • Cells: Cohesive  • Mut. APC / β Catenin P53 mutation WNT pathway.	 Non – cohensive cells Signet ring ↑ ed ↑ Invasion ↑ Metastasis: Krukenberg to ovary tumor. M/c: CDH – 1 loss ↓ E – Cadherin loss.

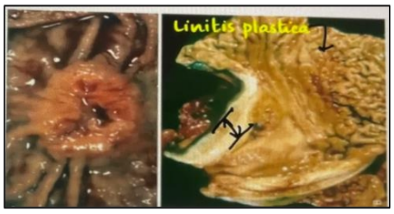
ADENO CA OF STOMACH No glands



Malig glands Intestinal Diffuse (Signet Ring)

ADENO CA OF STOMACH

Malig ulcer 0



GIST: Gastrointestinal stromal tumor

Origin: Interstitial cells of CAJAL
(Pacemaker cells)

Mutation:

- CK 17 + CD117
- PDGFR - α mut
- DOG - 1 (Best)

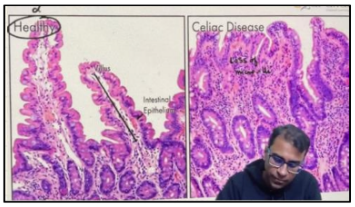
T/t: Imatinib

Carneg: triangle: GIST + Paraganglioma + pulmonary chondroma

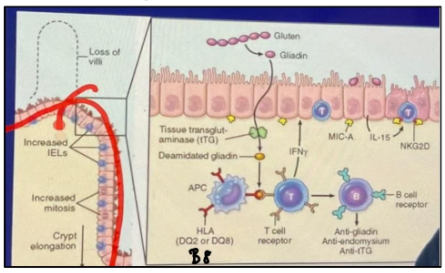
Carneg. Shatakis syndrome: SDH loss pediatric.

1. Celiac disease:

- Hypersensitivity to Gluten — Brow, Barley, Rye, Oat, Wheat
- HLA DQ - 2 / B-8



Pathogenesis of Celiac Disease



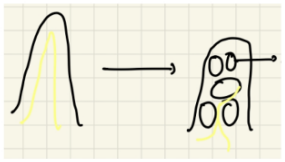
- Anti endomysium Ab: most specific
- Anti TTh Ab → Most sensitive
- Anti gliadin Ab: Cross react with skin
  ↓ pruritic
- Associated: Dermatitis herpetiformis
  ↑ Al ds
  ↑ T - cell lymphoma risk

Rx: Avoid gluten.

2) Tropical Sprue:

- E. coli. Giardia
- Mild villous disease
- Rx: Antibiotics

3) Whipple disease:
Etiology: Trophyrema whippeli (actinomycete)

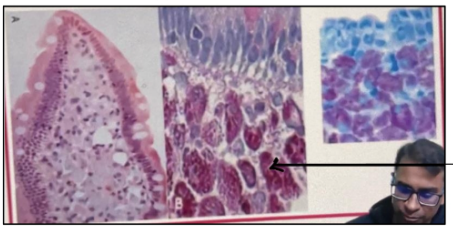


Swollen macrophage with partially digested bacilli
PAS +
Diastase - R
↓
Compress lacteals
↓
Fat malabsorption

C/F:

- GIT: Fat absorption
- CNS: Seizures, dementia
- Joint pain

Whipple's Disease



PAS +, Diastase Resistant + partially digested bacilli.

Colorectal polyps:

Benign

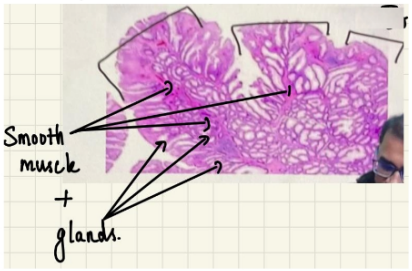
Hamartomatous
Hyper plastic
Inflammatory

Malignant

Adenomatous polyp

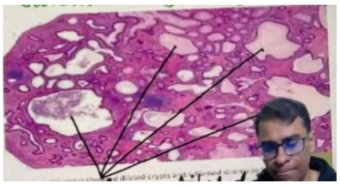
Juvenile		**Peutz Jeghar**
Rectum	Site	Jejunum
< 5 yr	Age	5-15 yr
SMAD - 4	Mut.	STK - 11
J.P synd.	Syndrome	P.J. Syndrome
	→ AD	C.F: Perioral Hyperpigmentation
	→ Premalignant	↑ed Risk of Ca at other site.
	→ Multiple	

Peutz Jeghers



Bronchus: Arborizing pattern.

Juvenile Polyps Syndrome



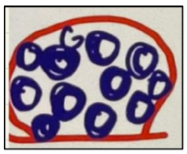
Cystic large dilated

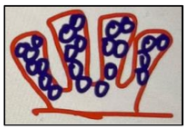
Adenomatous polyp:

M/c: Dysplasia

3 pattern

Tubular | Villous | Tubulo – Villous





Mutations:

- APC gene (M/c
- Myth gene (DNA repair) – number 40-60
- Attenuated PAP

FAP

33:41

- Familial adenomatous polyposis Coli
- AD inheritance, APC gene mutations
- Number > 100
- Hyperpigmentation of Retina.

FAP + Syndromes:

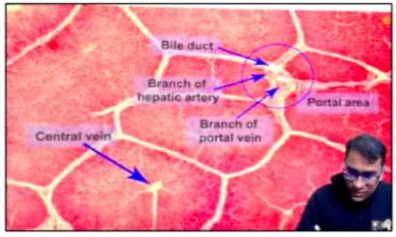
- Gardner syndrome ➜ FAP + Desmoid + Osteoma + Supernumeric unerupted teeth
- Turcot syndrome ➜ FAP + Medulloblastoma / Glioblastoma

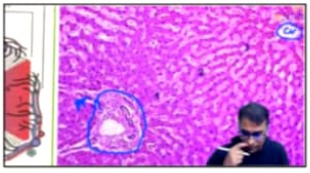
HNPCC:
(Lynch synd.)

- Mismatch. Repair mutation
- Non heriditary.

Liver

Normal Liver:

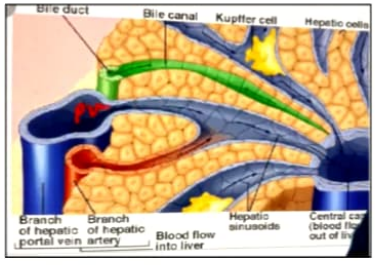


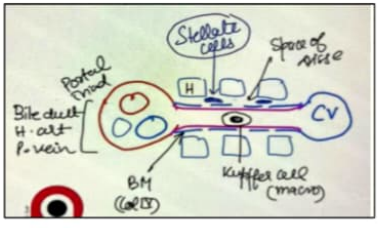


Zone 1

Zone 2

Zone 3





Liver

CONGESTION: *06:17*

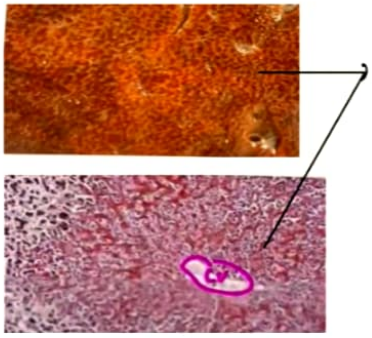
Cause: Right heart failure

Acute: Hydropic change in centrilobular area

Chronic: Nutmeg liver

Red: Contrilobular necrosis + Sinusoidal dilation

Pale: Periportal fibrosis



Congestion

ALCOHOLIC LIVER DISEASE

20:44

Alcohol consumption: 60-80gm/day: Alcoholic hepatitis

>160 gm/day: Alcoholic cirrhosis

Risk: HBV, HCV, HIV

F>M

Iron overload

Patho: Alc dehydrogenase

1. Alc → acetaldehyde → Toxic to liver

NADP NADPH

Lipid deposition ← fatty acid synthesis

Morph:

1. Steatosis (fatty liver) - micro or macro vesicular
2. Steato hepatitis - Ballooning degeneration
   Neutrophil infiltration
   Malory denk body (1)

W - Wilson

A - ALD

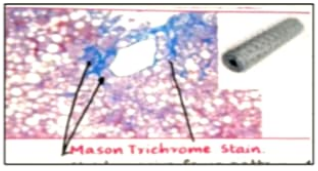
I - ICC

T - α AT def

HC - HCC

3. Steato fibrosis:
    - Perisinusoidal fibrosis
    - Chicken wire fence pattern
    - Collagen in space of disse

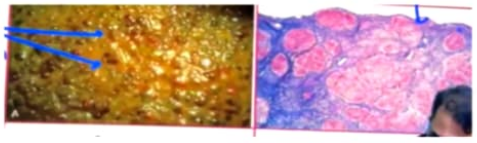
Stain: Masson Trichome



Nodular

Size

- <3mm micro
- >3mm macro



Gross Microscop

LENNAC CIRRHOSIS

NAFLD

16:52

Non Alcoholic fatty liver

- Alcohol < 20g / week
- Etio: Syndrome x (Met syndrome)

	NAFLD	ALD
• Alcohol H/O	-	+
• GGT	↑	↑↑↑
• AST: ALT ratio	1:1	3:1

Treatment:

Life style modification

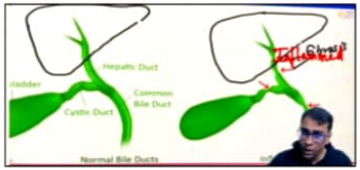
AUTOIMMUNE CHOLANGIOPATHY

24:04

	1° Biliary Cirrhosis	1° Sclerosing cholangitis
Bile duct	Intra hepatic	Intra + extra hepatic
Ab	Anti mito. Ab	Atypical P-ANCA

Biopsy	Florid duct lesion	Collagen prolif. Onion skin app.
Risk of Cholangio Ca	↑↑↑	↑

Primary Sclerosing Cholangitis (PSC)



Liver tumors:

HCC:

- ALD, NASH, metabolic
- PSC, PBC
- ↑ estrogen
- Aflatoxin

Tumor markers: α FP

IHC: Glypican, Hep par - 1

	HCC	HCC - (FL)
Prognosis	Poor	Good prog
Age	60-70 yr	20-30 yr
M : F	2-3:1	1:1
LFP	↑↑↑	Normal
		Neurotensin ↑

Fibrolamellar variety

↓

M/c: Collagen fibres b/w hepatocytes (pink) oncocytes

CHRONIC LIVER DISEASE

32:00

Cirrhosis: Diffuse transformation of liver into regenerating nodules surrounded by fibrous tissue

Etio: ALD

NAFLD

HBV, HCV

Autoimmune – Hepatitis, Chalangiopathy: PBC, PSC

Met liver ds – Wilsons: ↑ Cu toxicity

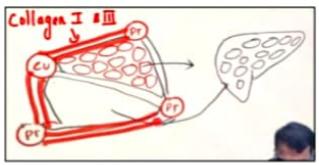
α_1 AT def

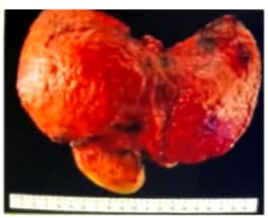
Hemo chromatosis

Parasitic

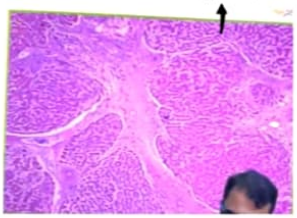
+

Etio → hep. Damage → Kupffer cells →
Stellate cells → fibrosis





Cirrhosis



Effect of Cirrhosis:

1. Portal HTN → Perisinusoidal firbrosis
   → Contriction of sinusoids
   a. Ascites: ↑ Hydrostatic Press (HP), ↓ Oncotic pressure
   b. Opening of porto systemic collaterals
      - Esophageal varices
      - Rectal varices
      - Caput medusae
   c. Congestive splenomegaly: Pancytopenia
2. CLD: Change in NO level
   NO decreases in liver

Compensatory NO ↑ es in splanchnio / systemic vessels

a. Hepatopulmonary syndrome: Hypoxemia, resp. distress.

b. Hepatorenal syndrome
→ ↑ Urine creatinine
→ Renal failure

Liver do: ↓↓ Estrogen catabolism
↓
Males → ↑ Estro levels

- Hypo gonadism
- Loss of hair / libido
- Gynacomastia

Urine – Crystals

URINE

00:30

Crystals:

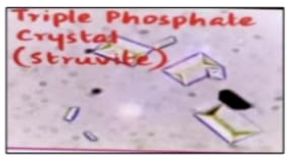
Acidic Urine
- Ca oxalate (M/C) → Envelope
- uric acid → Envelope

Envelope → Calcium oxalate = Most common

Alk
- Triple PO_4 Struvite → Coffin lid

Casts:

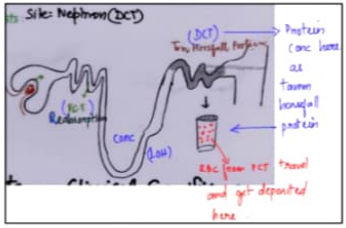
Triple phosphate crystal (struvite)



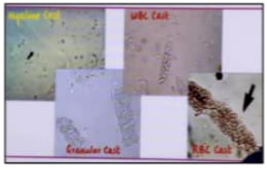
CASTS

01:19

- In Nephron

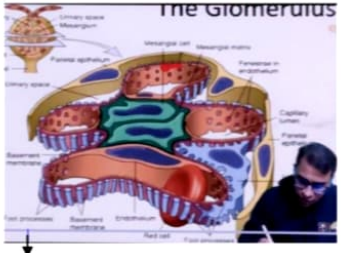


- Different types of casts

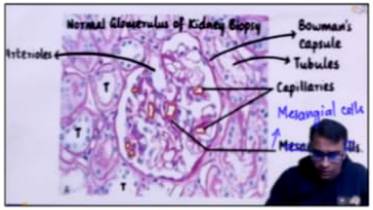


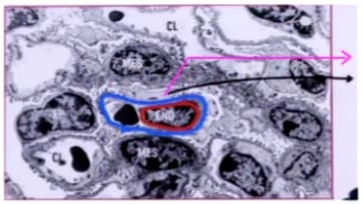
Glomerulonephritis:

- Hyaline → Physiological = Pregnancy
  Dehydration
  → Pathological = Nephrotic syndrome
- RBC = Glomerulonephritis
- WBC = AC. Tubula interstitial nephritis
- Epithelial casts = PCT necrosis (ATN)
- Granular (Muddy brown) = ATN
  Tubulo interstitial nephritis
- Broad casts = Chronic renal failure



Visceral epithelum





GB memb

Podocyte

END: Endothelium

MES: Mesangial cells

Filtration from endothelium

↓

GBM

↓

Mesangial cell

GLOMERULONEPHRITIS

08:57

- Inflammation of glomerulus

Type - 2

HSN

↓

Local immune complex disease

↓

Type 3

HSN

Circulating immune complex disease

↓

CAMP

Activation

↓

= C5a

↓

Chemotaxis

↓

Neutrophil infiltration + Damage to GBM

C_{3b} → Opsonisation

↓

Platelet activation

↓

PDGF / TFG - β → cell proliferation in glomerulus

Nephritic	Nephrotic
• Proteinuria < 3.5 g/d	• > 3.5 g/d
• Edema = Mild	• Severe
• HTN =	
• Uremia = More severe	• Milder
• Hematuria =	
• PSGN RPGN IgA Nephropathy MPGN	• MCD MGN FSGS IgA Nephropathy MPGN

NEPHRITIC

12:18

↓

Post streptococcal GN

- Group A β - haemolytic streptococci (12, 4, 1)
- 7-21 days after pharyngitis (or) pyoderma
- No response to antibiotics
- Type 1 HSN

RHD

- 1, 3, 5, 18
- No pyoderma
- Responds to B. penicillin
- Type - 2 HSN

Treatment:

Corticosteroid = 95% responds

↓ 4% = goes to chronicity

1% = RPGN

Kidney biopsy done

Kidddney Bx: PSGN

LM

Endo & Exo capillary proliferation

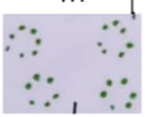
EM

Sub epithelial humps

↓

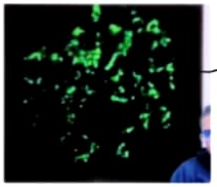
IC deposition

FM → Granular / lumpy bumpy deposits



↓

Starry sky appearance

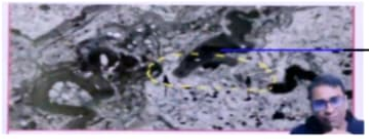


Starry sky app.

RAPIDLY PROGRESSING GLOMERULO NEPHRITIS [RPGN] *16:32*

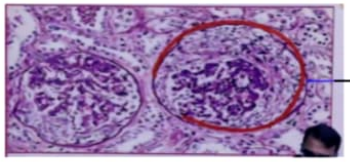
- Any GN progressing to acute renal failure within 4 weeks

I	II	III
• Anti GBM antibody	• Immune complex deposition	• Pauci immune (ANCA)
• Good pasture syndrome	• MGN, HSP, MPGN, SLE, FSGS, IgA nephron PSGN	• Churg strauss • Wegner's • Micro polyangitis



Rupture of basement membrane

Electron Microscopy: Rupture GBM. (EM)



Crescents
↓
Proliferation of parietal epithelium
+ WBC + fibrin

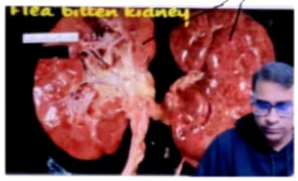
Light Microscopy: Crescents

- Crescents → will compress → ↓ GFR
  ↓
  Acute renal failure
  ↓
  HTN ← RAAS activation

Morpho: RPGN

- Gross: Flea Britten kidney
- LM: Crescents
- EM: GBM Rupture

Petichial haemorrhagic spots → Flea Britten kidney



IG A NEPHROPATHY

22:10

- Seen in 25% cases of Henoch Scholein Purpura (HSP)
- Gross hematuria = 1-2 days after pharyngitis
  [Note: If 1-3 weeks after pharyngitis = PSGN]

- Treatment: Steroids
  ↓
  25% of patients will be steroid resistant
  ↓
  Do Kidney Biopsy

LM	Ig G.M also	EM
Mesangial Proliferation (mesangio Proliferative GN)	FM ↑ IgA & C3 in mesangium	Mesangial dense deposits

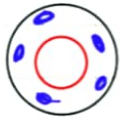
Membrano Proliferative GN (MPGN)

- Infections
  ↓
  HCV + Cryoglobulinemia, HBV, HIV, kala azar

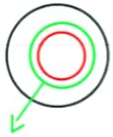
- Auto immune infections
- Drugs
- Malignancy

MPGN

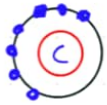
Type - I	II
• Both classical and alternate pathway	• Alternate pathway only
• All complements low	• C_1, C_2, C_4 = Normal
• IC deposition = Sub endothelial deposits	• Intra membranous deposits



↓ Another memb comes



Double contour tram track appearance



↓

Dense deposit disease

- All proliferation of GBM + Mesangium + Capillary occurs
- C_3 glomerulopathy = Activation of C_3 without IC deposition
  = Poor prognosis

NEPHROTIC SYNDROME

29:58

- Proteinuria (1^{st} → Albumin
  ↓ Next
  Transferrin = IDA
- Vit D def
- Thrombosis = Loss of protein C, S, Antithrombin - 3
- Hyper lipidemia & lipiduria
  Lipid breaks TG
  ↓
  FFA
  ↓
  Hyperlipidemia
- Later, loss of globulin proteins = Non specific proteinuria
  ↓
  Infection

MINIMAL CHANGE DISEASE

32:14

- Sudden onset of proteinuria (No prior history)
- Treat: Steroid (99% respond)

↓ 1% not respond

Do kidney biopsy

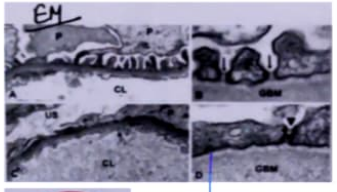
LM	FM	EM
X	X	Effacement / destruction of foot process

↓

Podocytopathy

D/d: Diabetic
MGN
FSGG

- MCD



Normal

MCD

Effaced foot process

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGN)

34:24

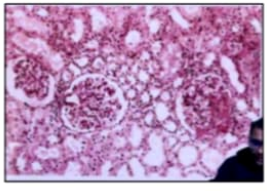
2. FSGS (Focal Segmental Glomerulosclerosis):

↓ ↓ ↓

<50% of glomeruli Involved — Part of glomerulus — Fibrosis

50% diffuse → Focal

Global → Entire glomerulus → Segmental



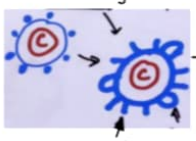
FSGN

- Reflux nephropathy = M/C
- HTN
- IV drug abuser
- Post renal ablation
- Sickle cell anemia
- Massive obesity

MEMBRANOUS GLOMERULO NEPHRITIS (MGN) *37:13*

Morpho:	LM	FM	EM
Kid Bx:	Diffuse GBM thickening	IgG / M+C3 deposition	• Podocytopathy + I/C in sub epithelium

Kidney biopsy



Spike + Dome app

→ Spike and Dome appearance.

DIABETIC NEPHROPATHY *39:17*

Glomerulus

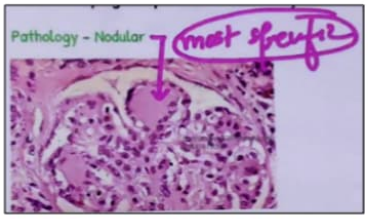
↑ Glucose
↓
Adhere to GBM & Damage
↓
GBM thickening + ↑ Permeability

- Diffuse GBM thickening
  ↓
  ↓ GFR
  ↓
  Microalbuminuria

- Diffuse mesangial proliferation
  ↓ Leads to
  Modular glomerulosclerosis
  (Kimmelstiel Wilson nodule = Inter capillary)

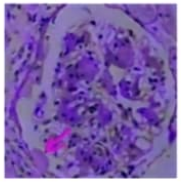
- Fibrin caps
- Capsular drops

- Tubules = Protein dep: Resorption droplets
  Glycogen dep: Armani ebstein crystals

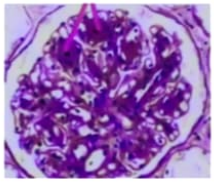


Kimmel stiel Wilson nodules

Nodular G.



Capsular drops



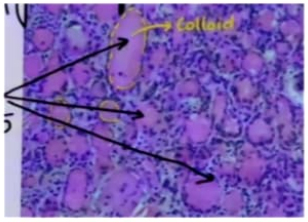
K.W lesion

Tubulo interstitial disease

- Chronic pyelonephritis

Tubulo intestinal as Ch. Pyelonephritis

Colloid like depsosits

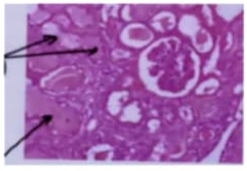


Chronic pyelonephritis on Biopsy

- Thyroidisation of tubule (colloid like deposits)

Colloid line

Thyroidisation of tubule
(colloid like deposits)



Pyelonephritis

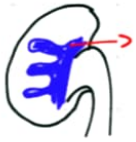
- Involvement of tubules + Interstitium + Renal pelvis

Acute ↓

- Micro: • Infiltration of Neutrophils
  +
  • Edema
- Complica:
  - Papillary necrosis
  - Pyonephros
  - Perinephric abscess

Chronic ↓

- Fibrosis
- Thyroidisation
- Xantho granulomatous Pyelonephritis



Stag horn calculi ↓ Proteus E. Coli

Causes

- Smoking
- Aniline dye
- Petroleum
- Estrogen exposure

RENAL TUMORS

48:44

	Clear cell Ca 80% of cases	Papillary Ca 15% cases	Chromphob Ca Rare	Belini Ca Rare
Origin	PCT	DCT	CD	CD
Gene	VHL	MET	Multiple	Chromosome
Chromosome number	3p ↓	7 ↓	Loss ↓	↓
Micro	 Clear vacuoles pid+glycogen	 Papilla	-	-

Prognosis	Intermediate	Intermediate	Best	Poor

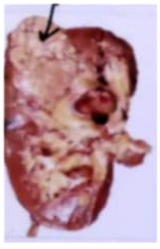
VHL

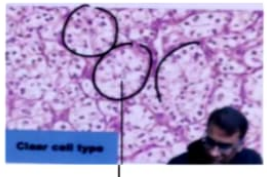
- Hemangioblastoama H
- Inc risk of RCC I
- Pheochromocytoma P
- Port urine stain P
- Eye E
- Lung L

Others [X PII translocation]

- Clear cell + papillary Pattern
  → TFE gene
  Medullary Ca (in sickle cell anemia)
  ↓
  Worst prognosis

Renal cell carcinoma





Clear vacuoles

Cns Tumors

Cells:

- Neurons:
  - Neurocytoma
  - Ganglioneuroma
- Glial cells (Supporting cells)
  - Microglial (Modified macrophage of CNS)
  - Macroglial
    - Astrocyte: Astrocytoma
    - Oligodendrocyte: Oligodendroglioma
    - Ependymal cells: Ependymoma.

Glioma

- Astroglioma
  - Grade I — Pilocytic
    - Localized
    - Benign
    - Prognosis – good
    - Rx: Local excision
  - II — Atypical
  - III — Anaplastic
  - IV — Glioblastoma
    - Multiformae
    - Localy invasive
    - Malignant
    - Poor prognosis
    - Rx: Surgery +
    - Chemo + Radio
    - Site: Cerebellum.
- Oligodedroglioma
- Ependymoma

GBM:

IDH Mutation

- Mutation (2°)
  - Good prognosis
  - Chemoresponsive
  - FDA: Enasidenib
- No mutation (1°)
  - Poor prognosis

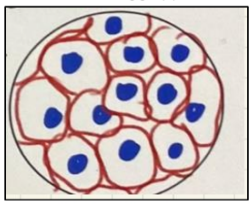
2) Oligodendroglioma:

Site: Frontal lobe

Calcification: Common

M/c:

Fried egg app



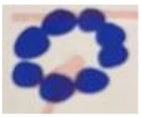
3) Ependymoma

Site: Ventricles, spinal canal

Mutation: NF – 2

M/c: Rossette

True



Pseudoperivascular

Other CNS Tumors:

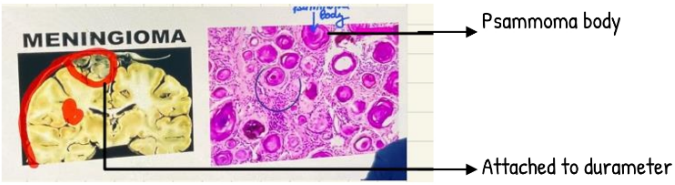
Meningioma: WHO Gr I, II, III

Grade – I → Psammomatoes

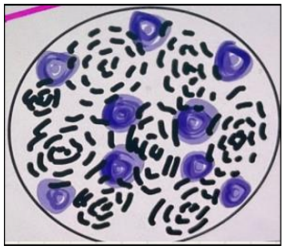
Grade – II → Atypical

Grade – III → Anaplastic

- Origin: Arachinoid cap. Cells
- Mutation: NF 2



- Localizing sign
- Diff. clinical features based on site
- M/c: Whorled.



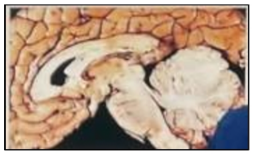
Psammoma body

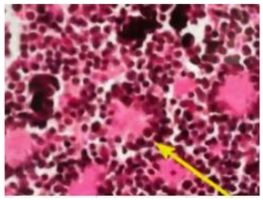
2) Medulloblastoma:

- 100% arises from cerebellum
- WHO Grade IV tumor
- Mc. Malignant Brain tumor of children.
- Origin: PNET → Primitive Neuroectodermal tumor.

CNS	Periphral
Medulloblastoma	Neuroblastoma
Pineoblastoma	Eving's sarcoma

MEDULLOBLASTOMA





Homer Wright Rossette.
Medulla blastoma

- **Mutation**: WNT / SHM pathway (Gorlin syndrome)
  1. Most common tumor of CNS- metastasis
  2. Most common primary tumor of CNS-meningioma

3. Most common primary intracranial tumor of CNS- glioma (astrocytoma)
4. Most common malignant tumor of CNS-glioma (glioblastoma)
5. Most common malignant tumor in children- 4 medulloblastoma closely followed by pilocytic astrocytoma
6. Most common primary CNS tumor in children: Pilocytic astrocytoma.

Peripheral Nr. Sheath tumor:

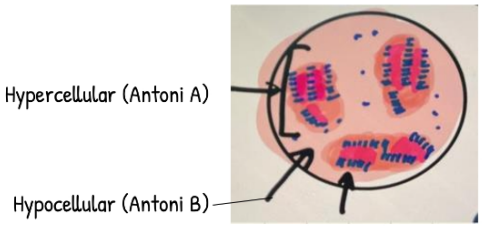
1) Schwanoma: Vestibular
   - M/c site: CN 8^{th} > 5^{th}
   - Nuclear factor → 2 mutation
   - C/f: Tinitis, hearing loss, acoustic neuroma.
   - NF - 2 mut (chr. 22q)

     M → Multiple

     I → Inherited

     S → Schwanoma

     M → Meningioma



Verocay body

2) Neurofibroma:

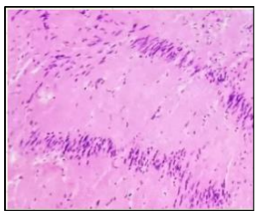
   Spindle shaped tumor cells + fibrous tissue (collagen)

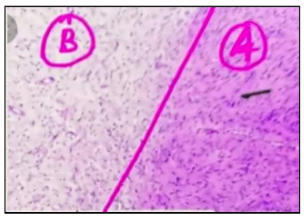
   NF-1 (Chr. 17q)

N	Neurofibroma
O	Optic Nerve glioma
S	Sphenoid dysplasia
P	Plexiform Neurofibroma
A	Axillary freckling
C	Café aulait spots
E	Eye Iris: Lisch. Nodules

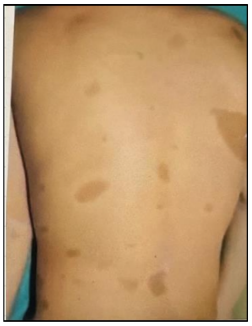
CNS Tumors

Topic Notes: 5





Verocay body

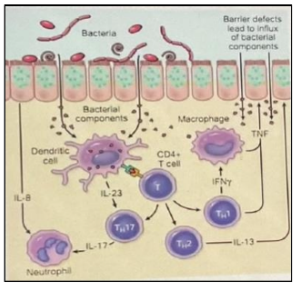


Café au lait spots.

Lisch. Nodules

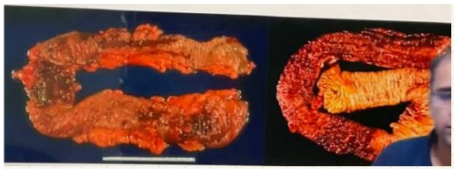
IBD

Pathogenesis:



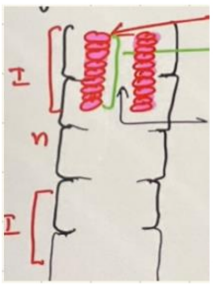
Types:

CROHNS ULCERATIVE COLITIS



CROHNS' DISEASE *3:45*

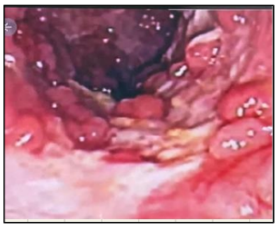
- Ileocecal region
- LI, SI or LI + SI
- Transmural (full thickness)
- Segmental (skip) lesion

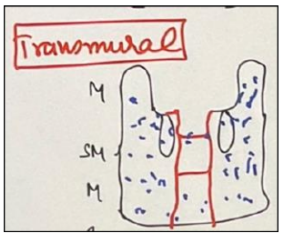


1st lesion: Apthous ulcer

Surpentine ulcer

Bulging of (n) area ⟶ cobble stone app





Ulcer → fissure → fistula perforation

Heal by fibrosis

- Mc Hallmark: Non caseating granuloma.
- Crypts:

Crypt abcess — Cryptitis

ULCERATIVE COLITIS

10:22

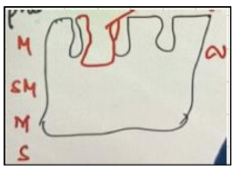
- Rectum / sigmoid colon
- Entire colon involved (Pancolitis)

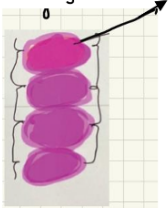
↓

- Backwash ileitis

Morphology:

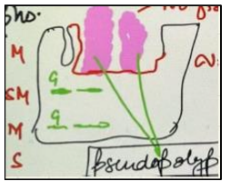
- Superficial involvement →
- No skip lesions
- Large broad based ulcer





- No fissure / fistula / perforation / stricture

M/c:- → Cryptic abcess
→ Cryptitis
→ Crypt distoration
→ Pseudopoly p. seen
(Regenerative mucosa)



In complicated case: U.C can go deep
↓
Destroy both ganglions
↓
Toxic megacolon.

Extra intestinal complication:

- Sacroileitis
- Eye - uvetis
- PSC (in U.C)
- A.S

Treatment

Anti inflammatory agents

Smoking → relieves pain in ulcerative colitis
↳ aggrevates pain in Gohn's disease