Structured Notes According to

PATHOLOGY

Revision friendly **Fully Colored Book/Structured Notes**

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LIST OF IMPORTANT TOPICS

Cell injury

- Patterns of irreversible cell injury, free radical injury and pigmentation

Inflammation

- Cellular events
- Chemical mediators
- Granulomatous inflammation

Neoplasia

- Genetic mechanism of carcinogenesis
- Tumour markers
- Diagnostic techniques

Hematology

- Anaemia and iron profiles
- Hemolytic anaemia
- Bleeding disorders classification and diagnosis
- Leukaemia and lymphomas

Genetics

- Mode of inheritance
- Techniques for diagnosis of genetic disorders

Respiratory system

- Cancers
- Obstructive and restrictive lung diseases

Immunity

- General concepts
- Auto immune diseases
- Immune deficiency diseases
- Amyloidosis

- **GIT**
  - Cancers
  - Malabsorption diseases

- **CVS**
  - Vasculitis
  - Ischemic heart disease

- **Kidney**
  - Nephrotic & nephritic syndromes
  - Cancers

- **Male and Female Genital Tract**
  - Cancers with histological findings

- **CNS**
  - Degenerative diseases
  - Cancers

- **Liver**
  - Hepatitis markers
  - Cirrhosis

- **Endocrine**
  - Thyroid disorders and histology
  - Diabetes

- **Miscellaneous topics**
  - Images strictly to be revised from Robbins and Review of Pathology by Gobind Garg/ Sparsh Gupta

LEARNING OBJECTIVES

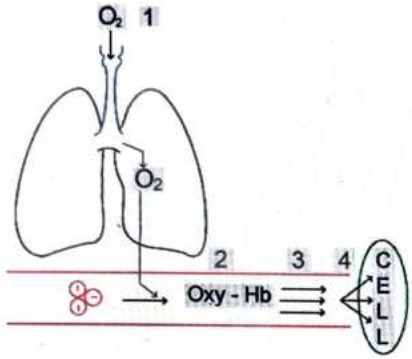
Unit 1 CELL INJURY

- **Concept of Cell Injury**
  - Hypoxia
  - Reversible cell injury
  - Irreversible cell injury
- **Cellular Adaptation**
  - Atrophy
  - Hypertrophy
  - Hyperplasia
  - Metaplasia
- **Irreversible Cell Injury Part 1**
  - Pathophysiology
  - Coagulative Necrosis
  - Liquefactive / Colliquative Necrosis
  - Caseous Necrosis
  - Fat Necrosis
  - Fibrinoid Necrosis
  - Gangrene
- **Irreversible Cell Injury Part 2**
  - Apoptosis
  - Pathways of Apoptosis
  - Caspases
  - Clinical Significance of Apoptosis
  - Pyroptosis
  - Necroptosis / Programmed Necrosis
- **Free Radical Injury**
  - Fenton Reaction
  - Causes of Free Radical Injury
  - Antioxidants
- **Ferroptosis**
- **Pigmentation**
  - Melanin
  - Hemosiderin
  - Lipofuscin
  - Calcification

1 CONCEPT OF CELL INJURY

HYPOXIA

- MC cause of cell injury: Hypoxia (↓ O_2)



Types

- Hypoxic hypoxia
  - High altitudes
  - COPD
- Anemic hypoxia
  - Anemia
  - CO poisoning
- Stagnant hypoxia
  - MC cause
  - Arterial obstruction → ischemia → ↓ oxygen
  - Venous obstruction
- Histo-toxic hypoxia
  - Cyanide poisoning

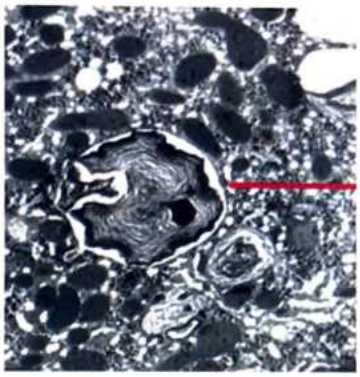
Important Information

- **Sensitivity to Oxygen deprivation: Neurons (most sensitive) >> skeletal muscle cells >> fibroblast (least sensitive/resistant)**

REVERSIBLE CELL INJURY

00:07:03

- ↓ O_2 → Mitochondria affected → ↓ ATP
- 1st organelle affected in reversible cell injury: Mitochondria
- Cell membrane
  - ↓ ATP → ↓ Na^+-K^+ ATPase pump activity → ↑ Na^+ accumulation → ↑ water → cell swelling (1st microscopic change)
  - Cell swelling is also known as hydropic change
  - Myelin figures in cytoplasm (due to damage of phospholipid) is seen



Myelin figures

- Endoplasmic reticulum
  - RER is responsible for protein synthesis and requires energy. On ATP depletion it results in
    → ↓ Protein concentration
    → ↑ Misfolded proteins accumulation
- Metabolic changes
  - ↑ Lactic acid/pyruvic acid (due to absence of TCA cycle)
  - ↓ Glycogen
- Nucleus: clumping of chromatin
- ↓ ATP → ↑ Ca^{2+} → enters mitochondria → amorphous/mitochondrial densities
  - Seen MC in prolonged cell injury
- Liver & Cardiac tissues show fatty change (accumulation of triglycerides in cytoplasm) in reversible cell injury.

Previous Year's Questions

Q. All are features of reversible cell injury EXCEPT? (AIIMS 2019)

A. Endoplasmic reticulum swelling
B. Dense deposition of mitochondria
C. Bleb formation
D. Detachment of ribosome

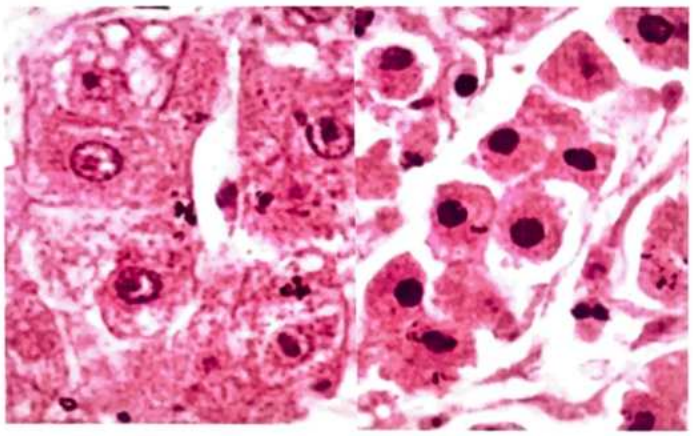
IRREVERSIBLE CELL INJURY

00:15:41

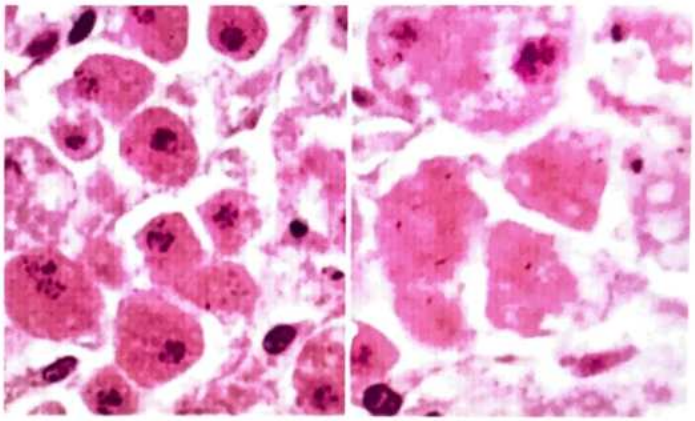
- Persistent hypoxia → ↓ mitochondrial function → ↓↓↓ ATP → ↑↑ Ca2+
- Increased calcium results in
  - Mitochondrial densities → cell death (higher in no compared to reversible cell injury)

- Activation of
  - Lysosomal enzymes (cell death)
  - Phospholipase (membrane damage)
  - Nucleases ("smear" pattern in gel electrophoresis)
    - → Nucleic acid condensation: Pyknosis
    - → Nucleic acid material fragmentation: Karyorhexis
    - → Complete breakdown of nuclear material: Karyolysis

- In heart
  - Reversible cell injury (angina) → cell swollen → membrane intact
  - Irreversible cell injury (MI) → membrane damage → troponin leak into blood



Normal Pyknosis



Karyorhexis Karyolysis

Apoptosis

- Longer duration of injury → ↑↑ mitochondrial permeability → leakage of cytochrome C → cell death

2 CELLULAR ADAPTATIONS

ATROPHY

00:01:11

- Atrophy → absent growth
- Associated with ↓ Size & ↓ function of cells
- Reversible change

Examples

- Physiological Atrophy
  - Uterus after parturition
  - Organ Atrophy (fetal development) → notochord
- Pathological Atrophy
  - Denervation atrophy → polio virus infection (Anterior horn cell of spinal cord)
  - Inadequate Nutrition → protein energy malnutrition
  - Disuse atrophy → seen after fracture (nonuse of muscles)
  - Chronic ischemic atrophy → brain (Alzheimer's disease)

HYPERTROPHY

00:06:37

- Hypertrophy: ↑ size of the cell → ↑ function of the cell
- Reversible in nature

Examples

- Physiological
  - Uterine hypertrophy → pregnancy
  - Skeletal muscles → weight lifting
- Pathological
  - Cardiac hypertrophy → HTN, Valvular disease

HYPERPLASIA

00:09:13

- Hyperplasia → ↑ number of cells

Important Information

- Simultaneous hypertrophy & hyperplasia can be seen in gravid uterus

Examples

- Physiological
  - Uterus & breast → Pregnancy
  - BM → Hemolytic anemia
- Pathological
  - Prostatic hyperplasia → ↑ DHT formation in elderly; benign condition
  - Endometrial hyperplasia → can progress to endometrial carcinoma

METAPLASIA

00:17:54

- Change in nature of cells in presence of stress factor
- On stress → stem cells change in nature → metaplasia
- Benign & Reversible in nature

Examples

- Epithelial metaplasia
  - In lungs smoking can lead to squamous metaplasia

P/S ciliated columnar ⇄ Squamous epithelium

  - If the change persists for longer → cancer (squamous cell carcinoma of lung)
  - In stomach, GERD can cause intestinal columnar metaplasia of esophagus (Barrett's esophagus)

$$\text{Squamous epithelium} \xrightarrow{acid\ reflux} \text{Intestinal columnar epithelial cells}$$

- Connective tissue metaplasia
  - Myositis Ossificans → after trauma due to hemorrhage the muscle replaced by bone like tissue

Previous Year's Questions

Q. A 45 years old person who is chronic smoker came to the clinic with complaints of cough. The physician examines the patient and takes a biopsy. The picture in the biopsy was as the description below. Which of the following cellular changes has happened in this patient? (NEET – Jan - 2020)

A. Hyperplasia
B. Dysplasia
C. Metaplasia
D. Anaplasia

3 IRREVERSIBLE CELL INJURY 1

PATHOPHYSIOLOGY

Irreversible cell injury

Mitochondrial Dysfunction
↓
CYT C LEAKAGE INTO CYTOPLASM
↓
APOPTOSIS
↓
CELL DEATH

Necrosis
↓
↓↓↓↓ ATP [d/t Hypoxia]
↓
Energy dependent Ca2+ pumps
↓
↑↑ Ca^{2+} inside the cell

- Mitochondrial Densities → Cell Death ←
- Enzyme Activation → Cell Death ←
  - Lysosomal enzymes
  - Phospholipase
  - Nucleases breaks nucleic acid

NECROSIS

- Morphological changes in a tissue after cell death occurs

SUBTYPES

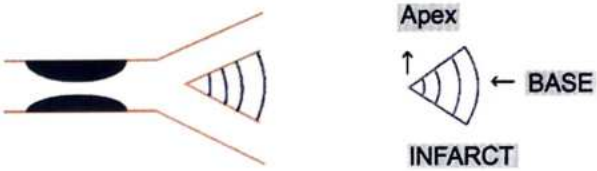
COAGULATIVE NECROSIS

- MC type of necrosis seen microscopically
- MC cause → ischemia
- Denaturation of proteins, inactivation of hydrolytic enzymes and intact structural outline

Important Information

- Coagulative necrosis is associated with "Tombstone Appearance" → can be seen in all organs except CNS
- Seen in Zenker's degeneration → coagulative necrosis in skeletal muscle, associated with typhoid infection

- Neutrophilic infiltration is classically noted in COAGULATIVE necrosis (for clearing dead cells)



Previous Year's Questions

Q. A wedge shaped are in the adrenal gland is affected. On HPE nucleus is not seen but cellular outlines are intact. Which type of necrosis is being described?
(JIPMER – Nov - 2018)

A. Coagulative
B. Liquefactive
C. Fibrinoid
D. Caseous

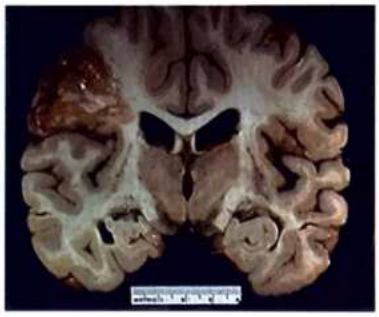
Infarct

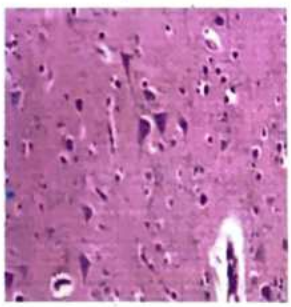
- Localized area formed due to ischemia, usually triangular in shape
- Apex of infarct points in the direction of site of obstruction
- Subtypes of Infarct-
  - White Infarct
    → Seen in organs with end-arterial blood supply, particularly in solid organs
    → Eg: Heart, Kidneys
  - Red Infarct
    → Seen in Organs with loose Connective tissues

→ Seen in Organs with Dual blood supply like Lungs/ Liver

LIQUEFACTIVE/COLLIQUATIVE NECROSIS 00:09:06

- Hydrolytic enzyme activation → Damage to tissues (liquefied)





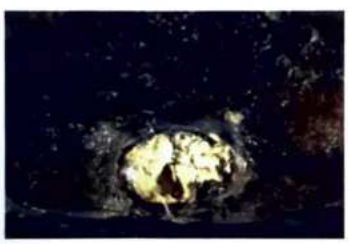
Normal

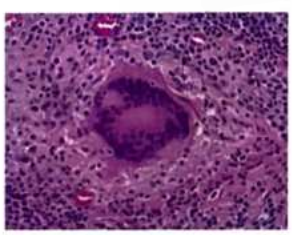
Necrosis

- Structural outline not preserved microscopically
- Examples
  - CNS Ischemia → damage to glial cells leading to hydrolytic enzyme activation
  - Infections → associated with pus formation in Staphylococcus aureus infection

CASEOUS NECROSIS

- 'Cheese - like' necrotic material
- Actually a combination of COAGULATIVE and liquefactive necrosis, with coagulative necrosis being the predominant contributor
- Seen in organisms with high lipid content like TB. It is also seen in other conditions like fungal infections (Histoplasmosis, coccidiodomycosis) and syphilis.
- Granulomatous reaction present.





Langhans cell

- Microscopic appearance: Langhans Giant cell/monocytic/lymphocytic infiltrations are seen
  - Associated with tubercular focus

FAT NECROSIS

- Associated with organs with high fats or with high concentration of lipases
- Seen with injury to breast tissue, omentum tissue injury and pancreatitis

Acute Pancreatitis

Gall Stones / Alcohol

↓

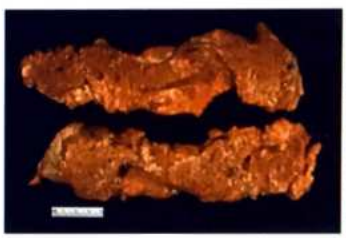
Lipase activation

↓

Lipids → Fatty Acids + Ca^{2+}

Saponification ('Chalk-like' yellow white deposits)

- Sr. Ca^{2+} level (↓↓) is an important prognostic factor to assess the severity of pancreatitis

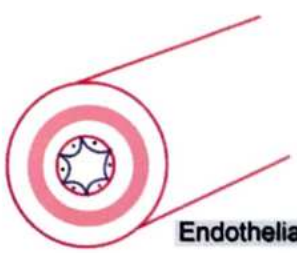


Fat necrosis

Important Information

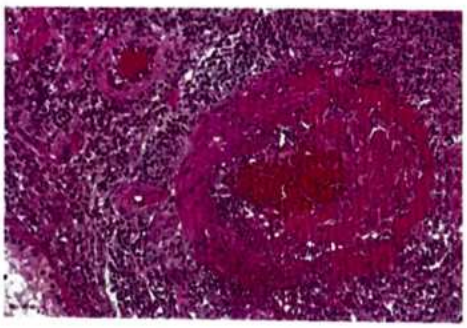
- In Pancreatitis, there is involvement of 2 types of necrosis
  - Pancreas → liquefactive necrosis
  - Peri-pancreatic fat → fat necrosis

FIBRINOID NECROSIS 00:22:13



Endothelial cells

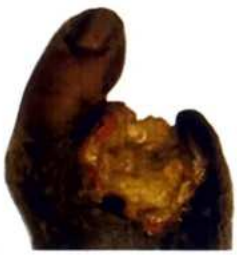
Endothelial Cell Injury
↓
Immune Complex formation
↓
Entry or leakage of plasma protein to the vessel wall
↓
Inside the vessel wall (seen as pinkish appearance in the vessel), there is deposition of plasma protein
↓
Fibrinoid Necrosis



- Can be seen in
  - Malignant Hypertension
  - Aschoff Body in cardiac tissue
  - Immune Complex Disorder/Type 3 Hypersensitivity Reaction (PAN/HSP)

GANGRENE

00:25:43



Dry gangrene Wet gangrene

Dry gangrene	Wet gangrene	Gas gangrene
• Ischemia (Decreased blood supply) • Coagulative necrosis	• Ischemia + secondary infections • Liquefactive necrosis	• Sub type of wet gangrene • Associated with clostridium welchii/clostridium perfringens • Clostridiuim welchii produces gas in the subcutaneous tissue

4 IRREVERSIBLE CELL INJURY 2

APOPTOSIS

- Apoptosis is a type of caspase-dependent programmed cell death.
- It is controlled by genes, and it affects a single cell or a small group of cells.

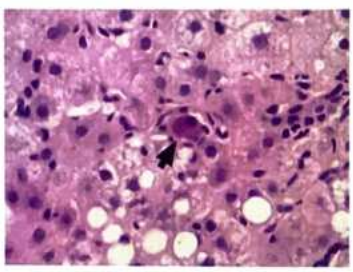
Pro - apoptotic genes	Anti - apoptotic genes	Sensors
• BAK gene • BAX gene • P53 gene • Glucocorticoids	• BCL-2 gene • BCL - XL gene • MCL-1 gene (responsible for resistance to chemotherapy) • Sex Steroids	• BiM gene • BAD gene • PUMA gene • NOXA gene

Physiological Apoptosis is seen in

- Embryogenesis
  - Removal of tail cells present in developing fetus
  - Separation of fingers due to death of cells present between fingers. If apoptosis fails to occur, fingers will not separate resulting in a condition known as Syndactyly.
- Females of Reproductive Age group- During menstrual cycle, hormone (Estrogen) promotes formation of new layer of endometrium and shedding, as per its levels in various part of the cycle.
- Self Reactive B & T Cells

Pathological apoptosis is seen in

- DNA Damage → in response to a person's exposure to radiation or drugs.
- Viral infections of hepatitis → "Councilmann Body"



Apoptotic body

- Accumulation of misfolded proteins → Alzheimer's disease, Parkinsonism

Pathways of apoptosis 00:08:18

Intrinsic / mitochondrial pathway	Extrinsic pathway
↓ Growth factors ↓ BCL-2 inactivation ↓ BCL-2 replaced by BAK / BAX ↓ Mitochondrial permeability ↓ ↑ Cytochrome-C in cytoplasm ↓ Activation of APAF-1 (Apoptosome) ↓ ↑ Activation of Caspase 9 ↓ Stimulate Caspase 3/ 6/ 7 ↓ ↑ Activation of Proteases & Endonucleases ↓ Cell Death	FAS –L / TNF α Release (in severe damage) ↓ FAS –L / TNF α + FAS –L / TNF-R ↓ Trimerization ↓ Activation of FADD ↓ Pro CASPASE 8/ 10 → Caspase 8/ 10 ↓ ↑ Activation of Caspase 3 /6 /7 ↓ ↑ Activation of Proteases & Endonucleases ↓ Cell Death

- APAF-1 → Apoptosis Activating Factor 1, also called as apoptosome
- FADD → Fas Associate Death Domain
- IAP → Inhibitor of Apoptotic- protein, inhibits intrinsic pathway

Previous Year's Questions

Q. BCL 2 protein is located in which of the following site? (JIPMER – May - 2018)

A. Cell membrane
B. Mitochondria
C. Nucleus
D. Cytosol

Caspases

- Cysteine containing special proteases acting on targets at the aspartic acid residues.

Caspase type	Intrinsic pathway	Extrinsic pathway
Initiator	Caspase 9	Caspase 8 (Worms), Caspase 10 (Humans)
Executioner	Caspase 3/6/7	Caspase 3/6/7

Previous Year's Questions

Q. APAF I is involved in the activation of which of the following caspases (AIIMS – June - 2020)

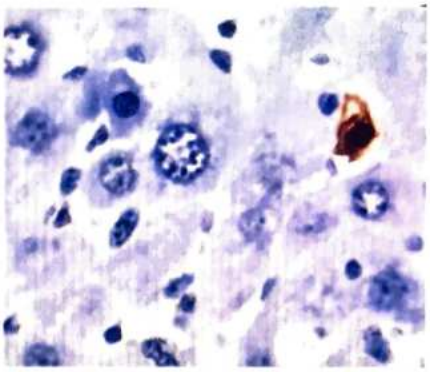
A. Caspase 8
B. Caspase 9
C. Caspase 3
D. Caspase 10

Salient Features of Apoptosis

- Cell shrinkage: Cell size decreases due to damage to structural proteins
- Chromatin Condensation
  - Caused due to endonuclease activation
  - Hallmark feature associated with apoptosis
- No cell membrane damage as there is no activation of phospholipase enzyme
- No Inflammation

Tests to Detect Apoptosis

- Tunel Technique



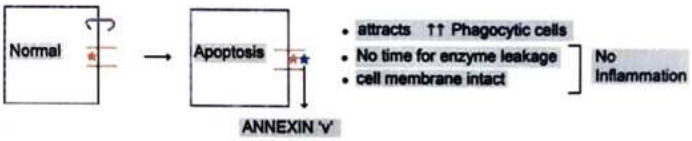
Tunel staining

  - Used for diagnosis of apoptosis
  - dUTP dye is used and fragments of DNA are visualized by light microscope
- Gel Electrophoresis: Apoptotic nucleic acid are found to be in Step-Ladder Pattern

Important Information

- Normal nucleic acid → Single Band
- Necrotic nucleic acid → SMEAR Pattern

Staining



- Done by using ANNEXIN 'V' which attaches to flipped molecules or by using DAPI Stain.
- Molecules which can flip over, and hence are expressed more at the time of apoptosis, include:
  - Phosphatidyl Serine
  - C1q
  - Thrombospondin

Clinical Significance of Apoptosis 00:26:00

- Excessive apoptosis is seen in

- Neuro-degenerative disorders
- Viral infections

- Reduced apoptosis is seen in
  - Autoimmune disorders

Important Information

- **Neurons are unique in the aspect that they do not have APAF-I. They instead secrete AIF (Apoptosis Initiating Factor) which directly activates proteases and endonucleases without Caspase activation.**

PYROPTOSIS

- It is a special type of apoptosis, with noted cellular swelling and inflammation.

Infections
↓
Intra-cellular Receptors (NOD-like Receptors)
↓
Inflammasome formed (multi molecular protein complex)

Caspase I	Caspase II
↓	↓
IL-1	Cell death
↓	
Fever	

- Other Caspases which have an action similar to Caspase 1 would be Caspase 11, 4/5.
- Efferocytosis is the name of the process through which molecules like C1q and Thrombospondin attract phagocytes during apoptosis.

NECROPTOSIS/ PROGRAMMED NECROSIS

00:34:32

- It is a Caspase-Independent programmed cell death.

TNF + TNF-®
↓
RIP 1 / 3 [Receptor Interacting Protein Kinase]

Phosphorylation of MLKL Protein — No Caspase activation
↓
CM damage & Inflammation ⊕

- Conditions where necroptosis is seen
  - Physiological → Mammalian Growth Plate
  - Pathological → Pancreatitis, Reperfusion injury, Parkinsonism, Steatohepatitis

5 FREE RADICAL INJURY

- Free radicals are chemical molecules with an unpaired electron (e^-) in its structure
- They have a high amount of energy in them and are highly reactive.
- They can cause damage to cell membrane, proteins and DNA.
- It is an auto-catalytic reaction while inflicting damage to DNA
- Proteins and most importantly Lipids, there is a release of more free radicals which further causes cellular damage and death.

> **Important Information**
>
> - Lipid Peroxidation, caused by free radicals, is implicated in aging and cancer Development (Due to damage to nucleic acids, resulting in mutations)

Fenton Reaction 00:03:52

$(Fe^{2+} \rightarrow Fe^{3+})$

Super oxide ion $(O_2^-) \rightarrow$ $O_2 \rightarrow$

Hydrogen Peroxide (H_2O_2) ⟶ Hydroxyl - Radical (OH^-)

↓

Free radical

↓

Damage to DNA / Proteins / Lipids

↓

Auto Catalytic Reaction

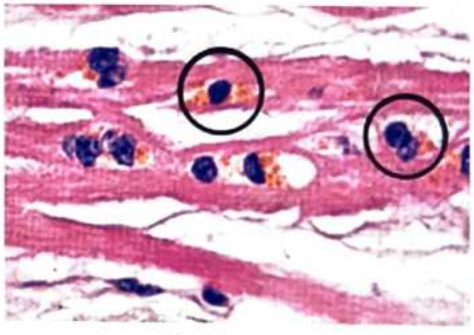
↓

Cell death

- Most Dangerous Free Radical Hydroxyl
- Fenton's reaction is associated with free radical formation in the presence of the metal Fe.
- Normal cells are able to protect themselves from free radical injury through Superoxidase dismutase
  - It converts superoxide ion to hydrogen peroxide
- Hydrogen peroxide conversion to water is by
  - Catalase enzyme
  - Reduction by Glutatione peroxidase, which adds H2 from reduced glutathione (GSH) to form Glutathione disulfide (GSSG)

Causes of Free Radical Injury

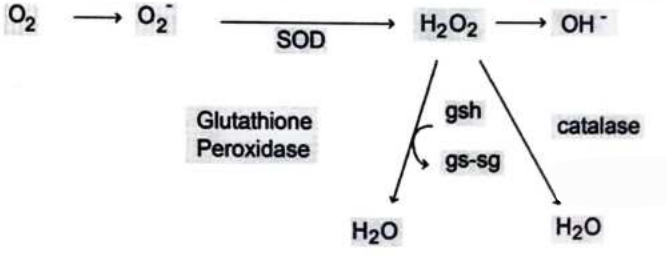
- Radiation injury: Ionizing radiation falls on water and releases hydroxyl radical
- Oxidative stress: Involved in aging, cancer and inflammation
- Reperfusion Injury
- Transitional metals in excess → Iron (Hemochromatosis), Copper (Wilson's disease)
- Chemicals: Carbon Tetrachloride used in dry cleaning factory (CCl_4), Paracetamol overdose



Lipofuscin

- Tell-Tale Sign → peri-nuclear deposition of brown colored lipid-derived pigment called Lipofuscin in Free Radical Injury (Aging).

ANTI-OXIDANTS 00:17:31



Superoxide Dismutase

- SOD has two subtypes
  - Mitochondrial: Manganese is present as a co-factor

- Cytoplasmic: Copper and Zinc are present as co-factors
- Decreases free radical damage in brain.
- Mutation in SOD1 gene causes Amyotrophic Lateral Sclerosis

Catalase

- Converts hydrogen peroxide to water.
- It is also present in certain bacteria.

Glutathione peroxidase

- Requires reduced glutathione (GSH) to help the cell.
- During oxidative stress, GSSG: GSH Ratio increases.

Vitamins A, E & C

- Vitamin C is found to be the most important as it aids in neutralizing the hydroxyl free radical

Plasma Proteins Binding With Metals

- Transferrin/ Lactoferrin/ Ferritin binding with Iron
- Ceruloplasmin binding with Copper

6 PIGMENTATION

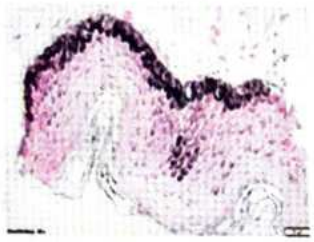
- Endogenous pigment
- Exogenous Pigment
  - Coal dust inhalation → Anthracosis (Asymptomatic)
  - Tattooing

ENDOGENOUS PIGMENT

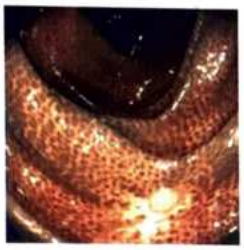
00:01:52

Melanin

- Endogenous black pigment
- Provides Hair & Skin Color
- Tyrosine derived pigment
- Protects skin from UV rays
- Identified by Masson Fontana stain
- Pseudo-melanin is seen on large bowel of patients who are on chronic laxative therapy (senna) → PAS positive substance & present inside the macrophages



Masson Fontana stain



Melanosis Coli

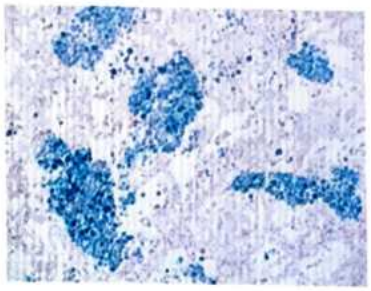
Homogentisic Acid

- Deficiency of homogentisic acid oxidase → deposition of HA in cartilage/skin/bone/connective tissue (Ochronosis)
- Seen in Alkaptonuria urine turns black on exposure to air

Hemosiderin

- Iron derived pigment (Fe → ferritin)
- Excess iron is stored in the form of ferritin
- Seen in
  - Hemochromatosis
  - Repeated blood transfusion (thalassemia)
  - Chronic Hemolytic anemia

- Pearls reaction: on application of Prussian blue, ferritin is unbound from protein and react with potassium ferrocyanide ferricyanide (blue violet color)

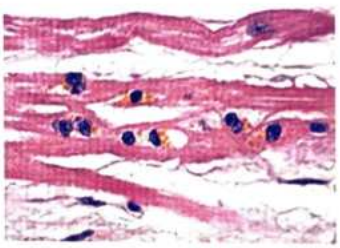


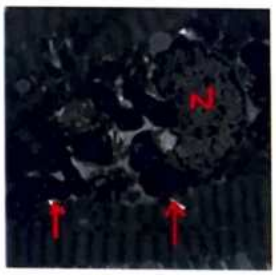
Hemosiderin

Lipofuscin

00:09:21

- Aka lipochrome/wear & tear pigment/pigment of Ageing
- Lipid derived pigment
- Produced by lipid peroxidation/free radical injury
- Indicator of free radical injury: Lipofuscin
- Lipochrome: Golden brown color, peri-nuclear in location & deposited in lysosomes





Lipofuscin

- Seen in ageing/PEM/Cachexia
- Maximum lipofuscin deposition is seen in heart & liver

Previous Year's Questions

Q. Staining of lipids is best seen in which of the following conditions? (INICET Nov 2020)

A. Frozen section
B. Liquid paraffin
C. Formalin fixed
D. Karnovsky stain

Ageing

- DNA damage → DNA helicase defect (Werner syndrome)
  - Wermer syndrome → associated with MEN
- Protein misfolding
- Telomere Length
  - Normal cell undergoes 60-70 divisions → Hayflick's limit
  - Telomerase (responsible for maintaining telomere length) → over activity is seen
    - → Physiological → germ cells
    - → Pathological → cancer cells
- Associated with brown atrophy → lipofuscin

Sirtuins

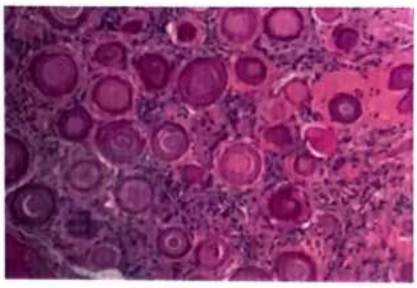
- Sirtuin 6 → ↑ life span
  - ↓ Free radical injury
  - ↑ Insulin sensitivity
  - ↓ Insulin like growth factor pathway
- Can be increased by calorie restriction/wine intake

CALCIFICATION

00:22:51

Dystrophic Calcification	Metastatic Calcification
• S.Ca^{2+} → normal	• S.Ca^{2+} ↑↑↑
• Deposits in Dead/Degenerated tissues	• Deposits in living tissues
Conditions associated • Rheumatic heart disease • Atherosclerosis • TB , Monckeberg Sclerosis • Tumors ○ M – Meningioma/ Mesothelioma ○ O – ovary ○ S – Salivary gland } papillary Ca ○ T – Thyroid gland } ○ P – Prolactinoma ○ G - Glucagonoma	Conditions associated • Hyperparathroidism ○ 1° → parathyroid adenoma ○ 2° → CKD • ↑↑ Vitamin D ○ Intoxication ○ Sarcoidosis (↑ 1α-Hydroxylase) ○ Williams syndrome • Milk-Alkali syndrome • Cancers → Breast Ca/MM

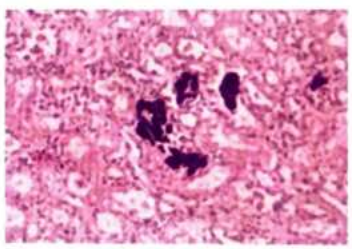
- Ca^{2+} deposition is seen as Psammoma bodies



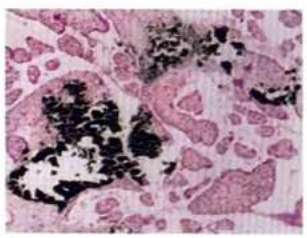
- Ca^{2+} deposits in mitochondria in majority of cells → Lime Catcher Organelle
  - Exception: Renal cells → Deposits in Basement membrane
- Preferential calcium deposition organs: lungs > stomach > SA/PV
- Calcium has special affinity for tetracycline → used to assess bone turnover (Tetracycline Labelling)

Microscopic appearance

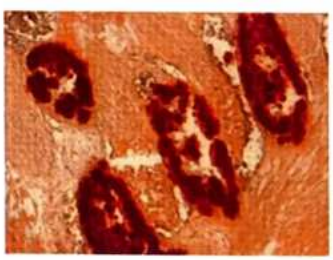
- H&E stain → Basophilic appearance of Ca^{2+}
- Von-kossa stain → stains Ca^{2+} in black color & picks up large amount of Ca^{2+}
- Alizarian Red stain → helps in smaller deposition of Ca^{2+}



H&E Stain



Von-Kossa stain



Alizarian Red stain

Previous Year's Questions

Q. Dystrophic calcification seen in which of the following conditions? (AIIMS - May - 2019)

A. Myositis ossificans
B. Paget's disease
C. Metastasis
D. Sarcoidosis

7 FERROPTOSIS

INTRODUCTION

00:00:14

- Specific signals results in the iron accumulation and lipid peroxidation.
- Defence mechanism: reduced form of glutathione - dependent antioxidants

MECHANISM

00:00:54

- Excess amount of iron or malfunctioning glutathione → results in more amount of reactive oxygen species(ROS)→ High chances of Lipid peroxidation → membrane damage → Cell death
- Fact 1 : started with specific signals
- Fact 2: It can be prevented by reducing concentration of intracellular iron; which distinguish from necrosis.
- Targeted organelle affected : Mitochondria

Two specific findings

00:02:19

- Loss of mitochondrial cristae
- Outer mitochondrial membrane: complete rupture/damage

MCQ Question

00:03:10

- Role played by iron dependent pattern of cell injury:
  - lipid peroxidation causing the injury in permeability in cell death
  - Free radicals exhaust the defensive mechanism of the cell.
- Two specific findings of mitochondria:
  - Loss of mitochondrial cristae and rupture of outer mitochondrial membrane

CLINICAL QUESTIONS

1. A 49 Yr old male complaints of sudden onset of difficulty in breathing when he climbs up the stairs associated with diaphoresis and palpitations. Patient is a known case of Hypertension for 15 years on irregular compliance to antihypertensive drugs. ECG taken which revealed LVH. ECHO was done which revealed Ejection fraction of 40%. All of the following are transcription factors activated by signal transduction pathways of the given pathology, except:

A. GATA 4
B. NFAT
C. MEF 2
D. MLL 1

Solution

- In the given clinical scenario, Patient has Cardinal symptoms of Heart failure,
  - Palpitations
  - Diaphoresis
  - Dyspnea on exertion
- Patient is a known case of Hypertension with poor compliance to Antihypertensive drugs which lead to Left Ventricular Hypertrophy which concomitantly explains Heart failure, Echocardiography revealed an ejection fraction of 40%, which is usually seen in chronic pressure and volume overload conditions.
- Signalling pathways which trigger hypertrophy activate a set of transcription factors such as:
  - GATA 4
  - Nuclear factor of activated T-cells (NFAT)
  - Myocyte enhancer factor-2 (MEF2).
- These transcription factors work in coordination to increase the synthesis of muscle proteins that are responsible for hypertrophy.
- CARD→ MLL 1 (Mixed lineage leukemia protein-1) is a gene involved in acute leukemia.

Reference

- Robbins & Cotran Pathologic Basis of Disease 10th ed pgs-57,58

LEARNING OBJECTIVES

Unit 2 INFLAMMATION

- **Introduction to Inflammation & Vascular Changes**
  - Vascular Changes Seen in Inflammation
  - Mechanism of Vascular Leakage
  - Stasis
  - Virchow's Traid
- **Intravascular Cellular Changes**
  - Margination
  - Rolling
  - Adhesion
  - Leucocyte Adhesion Disorders
  - Trans-Migration
- **Extravascular Cellular Changes**
  - Chemotaxis
  - Phagocytosis
  - Recognition of Target Cell
  - Engulfment
  - Killing
  - Chediak-Higashi Syndrome
- **Oxygen Dependent & Independent Bacterial Killing**
  - Oxygen Independent Killing
  - Oxygen Dependent Killing
  - Chronic Granulomatous Disease
- **Neutrophil Extracellular Trap**
- **Preformed Chemical Mediators**
  - Histamine
  - Serotonin
  - Lysosomal Enzymes
- **Freshly Formed Chemical Mediators**
  - Nitric Oxide
  - Arachidonic Acid Metabolites
  - Anti-Inflammatory Drugs
  - Cytokines
  - Pyrogens
  - Chemokines
  - Interferons
- **Plasma Chemical Mediators**
  - Kinin System
  - Complement System
  - Regulatory Complement Protein
- **Chronic Inflammation & Wound Healing**
  - Different Macrophages
  - Role of lymphocytes
  - Granulomatous inflammation: Giant cells, types and Features
  - Wound healing: Abnormal Healing

8 INTRODUCTION TO INFLAMMATION & VASCULAR CHANGES

BASIC CONCEPTS

- It is the response seen in vascularized connective tissues
- This response is usually protective, but sometimes harmful

Injury
↓
Response of body
↓
Changes in blood vessels & cells (connective tissue)

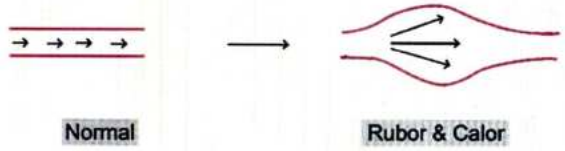
Subtypes

- Acute → Short duration, Neutrophils are involved
- Chronic → Long duration, Mono-nuclear WBCs (Lymphocytes/ Monocytes)

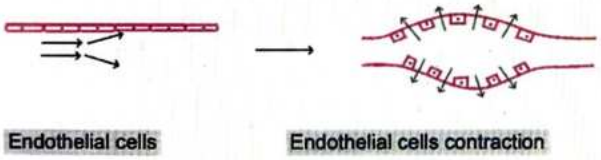
VASCULAR CHANGES SEEN IN INFLAMMATION

00:01:11

- Vasoconstriction → 1st change in blood vessels
- Vasodilation → Primarily caused by Histamine



- ↑ Vascular Permeability



- With contraction of endothelial cells, space in between endothelial cells increases and contents get leaked out.
  - Fluids
  - Cells
  - Proteins

  } exudate → swelling/edema (Tumor)

Important Information

- Most characteristic feature of Acute Inflammation: Vascular permeability
- MC mechanism involved: Endothelial cell contraction

Mechanisms of Vascular Leakage 00:03:33

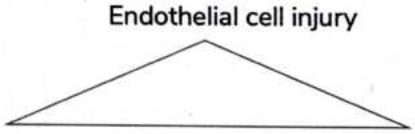
Mechanism	Type of response	Example
EC contraction	Immediate Transient Response	Thorn Prick
Direct EC injury	Immediate Sustained Response	Severe Burn, Septicemia
EC retraction	Delayed Transient Response (Cytokine-mediated)	Bacterial Infections
EC damage	Delayed Prolonged Leakage	Late Sun Burn

Stasis

↑ Vascular permeability
↓
↑ Hem concentration
↓
↓ Blood Flow
↓
Stasis
↓
↑ Chances of thrombosis/clot formation

- Inflammation is a 'pro-thrombotic' state

Virchow's Triad

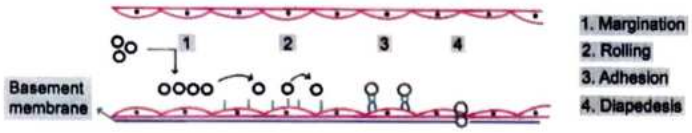


Previous Year's Questions

Q. Virchow triad includes all except?
(FMGE - Jun - 2018)

A. Endothelial injury
B. Stasis of blood flow
C. Hypercoagulability
D. Platelet thrombus

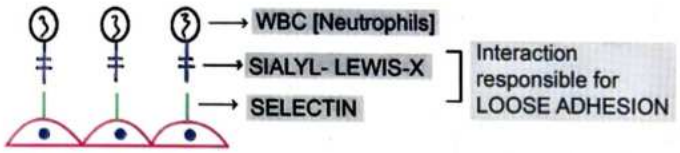
9 INTRAVASCULAR CELLULAR CHANGES



Margination

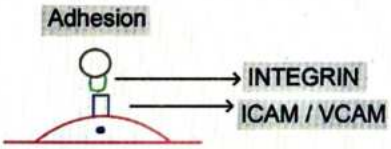
- WBC starts to move towards from margin

Rolling



- Aka Loose adhesion
- It is an interaction between selectins in endothelial cells and Sialyl-Lewis X molecule in WBC
- Selectins aka CD62
- Subtypes of Selectins
  - E → present on endothelial cells
  - P → present on Platelets, Endothelial cells
  - L → present on Lymphocytes
- Weibel Palade Body
  - E-selectin is present intracellularly in endothelial cells in low affinity state
  - It contains Von-Willebrand factor & Selectins

Adhesion

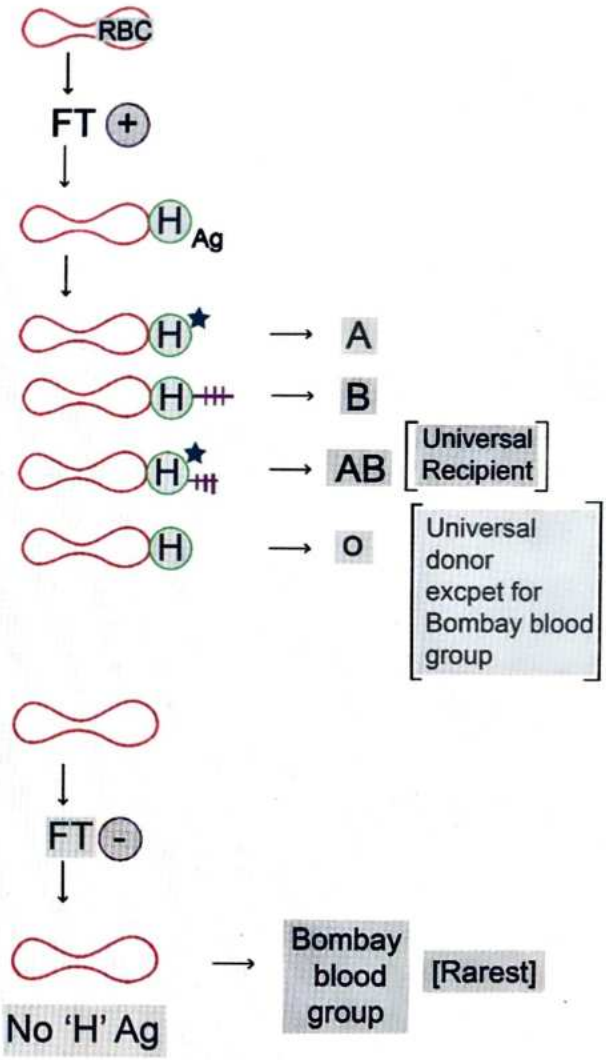


- Firm Adhesion
- Integrins in WBC, ICAM/VCAM in endothelial cells are responsible for adhesion
  - ICAM (Inter cellular adhesion molecules)
  - VCAM (vascular cellular adhesion molecules)
- Integrins also known as CD11a/LFA

Leucocyte Adhesion Disorders (LAD) 00:15:48

- Characterized by
  - ↑ Risk of infections
  - Neutrophilia
  - No pus formation

LAD I	LAD II
• Integrin defect • Delayed Separation of umbilical cord	• Selectin defect (Sialyl-Lewis X) • Fucosyl transferase enzyme defect ○ Short stature ○ Bombay blood group



Role of FT enzyme

Trans-Migration 00:25:08

- Aka Diapedesis → WBC
- CD31: Present on surface of platelet & endothelial cell → Homotypic interaction
  - Aka PECAM (Platelet Endothelial cell adhesion molecule)

- Trans-migration causes predominant involvement of venules
  - Exception: pulmonary circulation/lung (takes place in capillaries)
- Trans-migration
  - < 24hrs → neutrophils
  - > 24hrs → macrophage
  - Exception: trans-migration in parasitic infection → eosinophil, trans-migration in viral infection → lymphocytes

Important Information

- In pseudomonas infection, initial 2-4days is characterized by predominant neutrophil trans-migration

10 EXTRAVASCULAR CELLULAR CHANGES

CHEMOTAXIS

- Chemical mediators are released to help aide movement of more WBCs towards the bacteria.
- This is an example of unidirectional/ targeted movement.
- Chemicals Responsible
  - Bacterial Products → Exogenous
  - C5a (Complement Protein)
  - LTB4 (Leukotriene-B4)
  - IL-8 (Interleukin-8)

  } Endogenous
- Major action of steroids → Chemotaxis Inhibition, Used in Autoimmune conditions

PHAGOCYTOSIS

00:06:24

- Steps in Phagocytosis

A. Recognition
B. Engulfment
C. Killing

A. RECOGNITION OF TARGET CELL

WBC		MICROBES
↓		↓
Mannose binding receptor	↔	Mannose
Scavenger receptor	↔	some particles

- Leukocyte activation occurs prior to phagocytosis.
- It maybe mediated by certain second-messengers like IP3/DAG.
- Phagocytosis is facilitated by Opsonisation.
- Opsonisation are chemicals which cover the bacteria and are preferentially killed.
  - Examples of Opsonins: Fc fragment of IgG, C3b, Fibrinogen/C-Reactive Protein

Antibody formation

Precursor B-cell
↓
B-Cell Tyrosine Kinase
Activated B-Cell
↓
Plasma Cell
↓
Immunoglobulin

- Bruton's disease refers to defect in BTK enzyme, affecting boys.
  - There is reduced antibody secretion → Hypo-gammaglobulinemia or Agammaglobulinemia
  - Opsonisation is defective in this condition.

C-Reactive Peptide

- Formed by the liver
- Is a plasma protein and is different from C-Peptide released by beta-cells of pancreas
- Is implicated in inflammatory conditions and Coronary Artery Disease

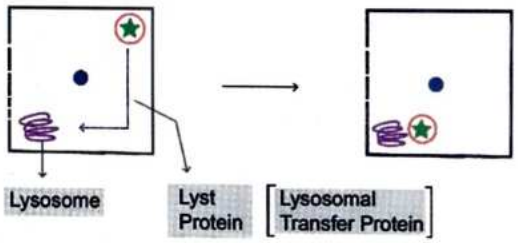
Important Information

- C-RP in Microbiology, is basically denoting the Carbohydrate Ag derived from the Pneumococcus (S. pneumonia)

B. ENGULFMENT

- Through pseudopod formation
- Due to actin polymerization

C. KILLING



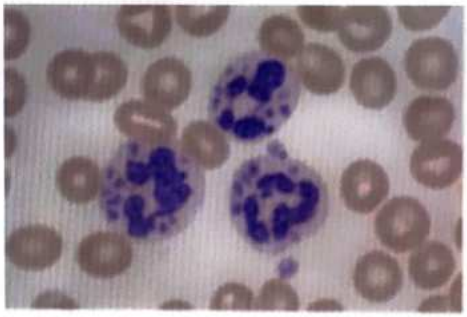
↓
Defect
↓
Chediak-Higashi Syndrome

Chediak-Higashi Syndrome

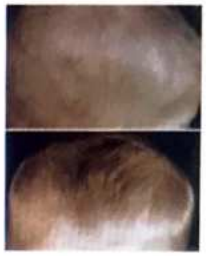
00:19:12

- LYST protein is required for normal function of
  - Neutrophils
  - Platelets
  - Melanocytes
  - Neural cells

- Clinical features
  - C → CNS Features
  - HE → Hemorrhage
  - DI → Decreased Immunity (Recurrent Infections)
  - AK → Albinism



Giant granules



Albinism

- Peripheral Blood Smear in C-H Syndrome shows giant granules in the cytoplasm

11 OXYGEN DEPENDENT & INDEPENDENT BACTERIAL KILLING

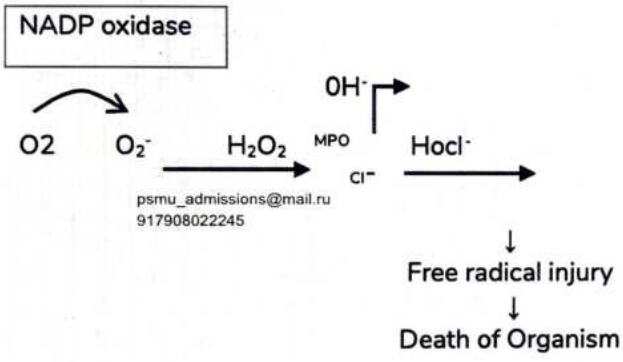
OXYGEN INDEPENDENT KILLING

00:00:56

- Cathelicidin
- Lysozymes
- Lactoferrin
- Major basic protein
  - Present predominantly in eosinophils
  - Toxic for Parasite
- Defensins: cationic protein rich in arginine

OXYGEN DEPENDENT KILLING

- Can take place by 2 mechanisms
  - O_2 derived free radicals
  - NO derived free radicals
- $O_2^- + NO \rightarrow ONOO^-$ (Peroxynitrite) → damage to bacteria
  - Important mechanism for macrophage, especially against mycobacterium



- During infection, sudden increase in oxygen requirement occurs → Respiratory burst
- NADPH oxidase aka Respiratory burst oxidase/phagocytic oxidase

CHRONIC GRANULOMATOUS DISEASE

00:09:51

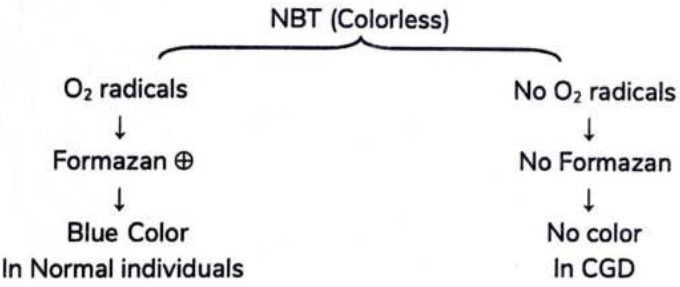
- Deficiency of NADPH Oxidase
- It is of 2 types
  - X-linked recessive (gp91PHOX) → defect of component in the membrane
  - Autosomal Recessive (gp47/67PHOX) → cytoplasmic protein defect

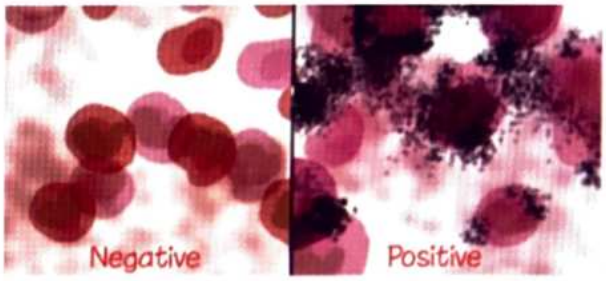
Clinical features

- ↑ Infections
- Formation of granuloma in different organs
- Infections by Catalase positive organism

Diagnosis

- Nitro-Blue Tetrazolium Test





  - Presence of granules is normal finding (positive)
- DHR test → flow cytometry
- Cytochrome 'C' reduction assay → tells amount of functional enzyme

Treatment

- Bone Marrow transplant
- IFN-γ

Important Information

- MPO-Halide system is the most efficient bactericidal method used by neutrophils
- MPO deficiency → mild infections

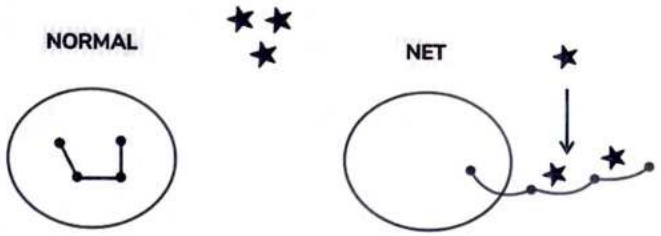
12 NEUTROPHIL EXTRACELLULAR TRAP

- Extracellular fibrillary network
- Stimuli
  - Infectious pathogens
  - Inflammatory mediators

Arginine

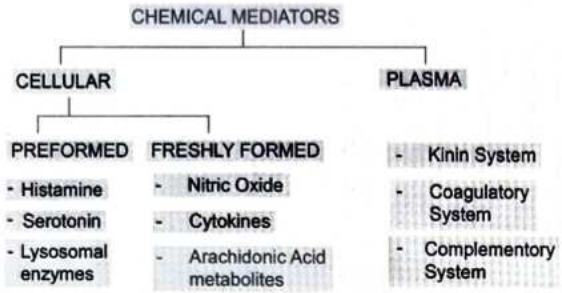
ROS $\xrightarrow{\oplus}$ Arginine Deiminase

Citruline



- Citroline is responsible for Chromatin De-condensation in neutrophils
- Chromatin comes out of nucleus and it contains anti-bacterial property (elastse, MPO) → Kills the bacteria
- Chromatin cannot return inside the cell → Death of Neutrophil
- Exposure of chromatin material → ↑ risk of autoimmune diseases
  - ANA → SLE

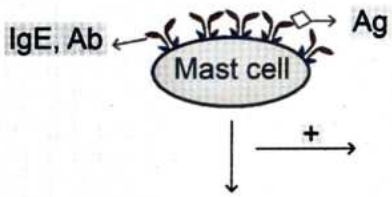
13 PREFORMED CHEMICAL MEDIATORS

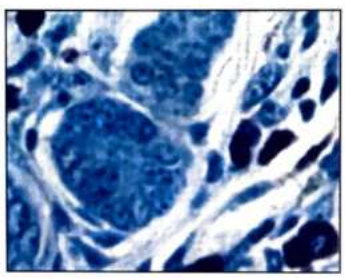


CELLULAR PREFORMED MEDIATORS

HISTAMINE

- Source
  - Mast cells (Richest Source)
  - Basophils
  - Platelets
- Functions
  - Vasodilation
  - Increase in Vascular Permeability
  - Bronchospasm
  - Itching
- Mast cells have receptors to bind to IgE antibody.
- IgE Cross linking leads to histamine release.





Toluidine blue

- Acidic Proteoglycans in Mast cells interact with the basic dye Toluidine Blue and the dark blue color here and help detect histamine release

Stimuli for Histamine release

- Physical factors - Temperature (Hot/Cold Urticaria)
- Viruses (Rhinoviruses)
- Anaphylotoxins
  - Bee venom (Mellitus) / Insect venom
  - Complement proteins (C2a/C3a/C4a/C5a)
- Drugs
  - Morphine
  - D-tubo curarine
- Allergens

Important Information

- Vancomycin: To be given slowly via IV. Rapid injection can cause Red Man Syndrome

SEROTONIN (5- HYDROXYL TRYPTAMINE)

00:07:45

- Source
  - GIT (Richest source, present in Enterochromaffin cells)
  - Platelets
  - CNS
- Functions same as histamine

LYSOSOMAL ENZYMES

- Responsible for oxygen dependent killing of bacteria
- Has two types of granules:
  - Primary: known as Azurophilic granules
  - Secondary: Alkaline phosphatase present in WBCs

Important Information

- Phospholipase A2 is present in both granules
- LAP score: In cases where Activated WBCs / Leukocytes are in elevated numbers, the score is increased.
- Example: Benign infections, Leukemoid reaction

14 FRESHLY FORMED CHEMICAL MEDIATORS

NITRIC OXIDE (NO)

00:00:31

$$\text{L - Arginine} \xrightarrow{\text{eNOS}} \text{Nitric oxide}$$

- NO Vasodilation & inhibition of platelets
- Isoforms
  - eNOS → Endothelial Cells
  - iNOS → Inducible/Inflammation
  - nNOS → Neurons

NO

$$O_2^- \longrightarrow ONOO^-$$

- Peroxinitrite causes damage to microbes

Previous Year's Questions

Q. Which of the following amino acid is required for the formation of nitric oxide in blood vessels?
(FMGE – Aug - 2020)

A. Citrulline
B. Arginine
C. Histidine
D. Tryptophan

ARACHIDONIC ACID METABOLITES

00:03:37

Phospholipids
↓
Phospholipase A2 (rate limiting enzyme)
Arachidonic Acid (EFA)
↓
COX
$PgG_2 = PgH_2$

PgI_2 (prostacyclin)
- Vasodilation
- Inhibition of platelets

$PgD_2/E_2/F_{2a}$
- Vasodilation
- Permeability
- Pain (PgE_2)
- Pyrexia (PgE_2)
- Mucus (PgD_2)

Thromboxane A_2
- Platelet aggregation
- Vasoconstriction

- Other Essential FA
  - Linoleic Acid (most essential)
  - Linolenic Acid
  - DHA present in Breast milk essential for development of brain

Previous Year's Questions

Q. Which of the following causes vasodilation?
(AIIMS – Nov - 2019)

A. Thromboxane A2
B. Prostaglandin E2
C. Histamine
D. Serotonin

Anti-Inflammatory Drugs
- Steroids act on Phospholipase A_2
- NSAIDs act on COX enzyme

COX-1 (Constitutive function)	Stomach → Pg (protective function)
COX-2 (Inflammation)	Kidneys (physiological function)

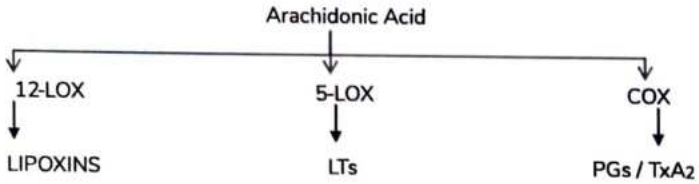
- Aspirin
  - Inhibit COX-1/COX-2 → Non-Selective
  - Anti-inflammatory action
  - Side effects → gastritis

AA
↓
5-LOX
Leukotrines
↓
LTA_4

LTB_4
- Chemotaxis
- Binding to EC

$LTC_4/D_4/E_4$
- ↑ Permeability
- Bronchospasm

- Leukotrienes aka SRS-A (Slow Reacting Substance of Anaphylaxis)
- 5-LOX inhibitor → Zileuton
- LT Receptor antagonist → Montelukast



- Lipoxins requires Neutrophils platelets & Inhibit inflammation

Important Information

- Fish oil is a good source of Lipoxins. it ↓ Inflammation → ↓ Incidence of CAD

CYTOKINES

00:27:48

- Pleiotropy → more than one action by one cytokine
- Redundancy → more than one cytokines having common action
- It has Local & Systemic actions

SYSTEMIC ACTIONS

- CNS → Sleepiness, ↓ appetite, ↑ COX activity (fever)
- BM
  - ↑ Neutrophil/lymphocyte/eosinophil in bacterial, viral and parasitic infections respectively
  - Shift to the left
  - Leukemoid reaction

Liver

- Positive Acute Phase Reactants
  - Hepcidin → iron inhibitory protein (negative regulator of iron balance)
  - Ferritin
  - SAA Protein → ↑ in 2° Amyloidosis
  - Fibrinogen → ESR
    → ESR α Fibrinogen
    → ESR = 0 → Afibrinogenemia
  - CRP → increased in sepsis (New marker: Pro-calcitonin)
  - Thrombopoietin → ↑ platelets
- Negative Acute Phase Reactants
  - Albumin
  - Transferrin
  - Anti-Thrombin
  - TTR

TNF-α

- Systemic effects (↓↓↓ appetite → cachexia)
- Macrophage activation → bacteria killing
- TNF-α antagonist therapy → ↑ risk of TB

Pyrogens

00:46:13

- Exogenous → Bacterial toxins
- Endogenous → IL-1/IL-6/TNF-α/CNTF (Ciliary Neuro Trophic Factor)

Anti-Inflammatory Cytokines

- IL-10
- TGF-β
- IL-6
- IL-4
- Adiponectin

} has dual action

Cytokines: Individual Actions

- IL-1 → Systemic Effects of inflammation
- IL-2 → Autocrine action
- IL 3 → Hematopoiesis
- IL-4/5 → B-cell replication & Differentiation
- IL-6 → Systemic Effects of Inflammation
- IL-7 → B/T cell maturation (defect can cause SCID)
- IL-11 → ↑ Platelets
- IL-17 → secreted by T-cells, responsible for recruitment of neutrophils

CHEMOKINES

00:52:51

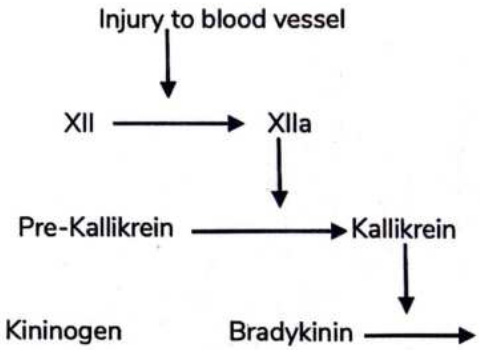
- α chemokine → CXC
  - Example: IL-8 (CXCL8) → attracts neutrophils
- ß chemokine: CC
  - MCP-1 → attracts monocytes
  - EOTAXIN → attracts Eosinophils
  - RANTES → regulates T-lymphocytes
- γ chemokines: C
  - Example: Lymphotactin → attracts Lymphocytes
- Fractalkine: CX_3C → required for chemotaxis & in process of adhesion of monocytes & T-cell to endothelial cells
- Chemokines act through 2 receptors
  - CCR5 receptor → ß chemokine
  - CXCR4 receptor → α chemokine
  - These receptors help in entry of HIV into Host cells (Maraviroc blocks CCR5 receptor)

INTERFERONS

	Source	Action	Clinical use
IFN-α	Leucocytes	Anti-viral	Viral infections
IFN-ß	Fibroblast	Immunomodulatory	Multiple sclerosis
IFN-γ	T cells	Macrophage activation	Chronic Granulomatous Disease

15 PLASMA CHEMICAL MEDIATORS

KININ SYSTEM

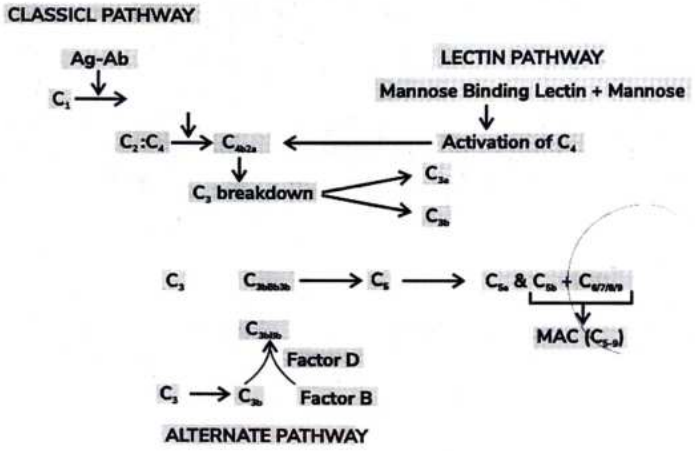


- Bradykinin causes
  - ↑ Permeability (most important)
  - Pain
  - Smooth muscle contraction (lungs)
- Bradykinin is destroyed by ACE (Angiotensin Converting Enzyme)
  - ACE inhibitor → ↑ Bradykinin concentration
  - Side effect: Dry cough
- Kallikrein is also associated with
  - Complement activation
  - Plasmin

COMPLEMENT SYSTEM

00:05:45

- It consists of > 20 proteins (C_1 - C_9)
- Complement proteins are responsible for innate & adaptive immunity



- Alternate pathway
  - Activated by endotoxin (LpSA)/venom/(IgA >> IgD)
  - Properdin & factor H/I also at take part in alternate pathway

Important Information

- **Classical pathway: Levels of $C_1/C_2/C_3/C_4$ → reduced**
- **Alternate pathway: $C_1/C_2/C_4$ → normal: C_3 → reduced**

- Role of important proteins
  - C3a → Anaphylatoxin
  - C3b → opsonin
  - C5a → Anaphylatoxin/Chemotaxis
  - C5b → MAC → destruction of antigen

Deficiency	Diseases
C_1 / C_2/ C_4 (Early complement proteins)	↑ Autoimmune disorder (SLE)
C_3	pyogenic infections
C_5 / C_6 / C_7 / C_8 (Late complement proteins)	Neisseria infection Toxoplasmosis
C_9	No disease

- C_2 is the MC complement protein deficiency

Regulatory Complement Proteins

00:23:49

- C_1 inhibitor deficiency → hereditary angioedema
  - F >>> M
  - Edema (Oral/larynx/GIT)
  - Non pitting edema
- CD_{55}/CD_{59} defect → PNH (Paroxysmal Nocturnal Hemoglobinuria)
- CD_{46}/Factor H&I defect
  - Excessive activation of Alternate pathway → atypical HUS
- Factor H defect → ARMD (Age Related Macular Degeneration)

16 CHRONIC INFLAMMATION & WOUND HEALING

- 3 components
  - Ongoing inflammation
  - Tissue destruction (Hallmark feature)
  - Healing
- Cell for Chronic Inflammation is monocyte (circulation) → macrophage (tissue)

Different Macrophages

- Kidney - Mesangial cell
- Liver - Kupffer cell
- Bone - Osteoclast
- Placenta - Hoffbauer cell
- Brain - Microglia/gitter cells
- Spleen - Littoral cell

Important Information

Types of Macrophages

- M_1 type activated by INF γ secreted by T-cells and it ↑ inflammation
- M_2 type activated by IL-4 & IL-13 and it ↓ inflammation by promoting tissue fibrosis

Role of lymphocytes 00:06:01

- TH1 cells: Responsible for INF γ secretion → activation of M1 macrophage
- TH2 cells: Responsible for IL-4/IL-13 secretion → activation of M2 macrophage
- TH17 cells: Responsible for IL-17 secretion → recruitment of neutrophils

GRANULOMATOUS INFLAMMATION

- Type of Chronic Inflammation
- Associated with formation of microscopic structure "granuloma" (macrophages surrounded by lymphocytes)
- No of lymphocytes in granuloma is minimal → naked granuloma

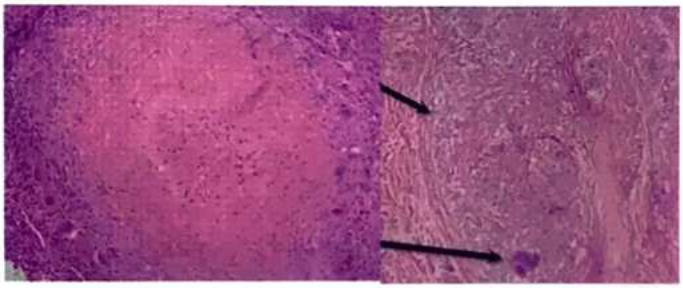
Granuloma conditions

- TB: Caseating Granuloma (soft granuloma)
- Sarcoidosis: Non-Caseating Granuloma/Hard granuloma/Naked granuloma
- Syphilis: Gumma
- Malaria: Durck Granuloma
- Q-Fever: Doughnut Granuloma
- IBD
  - Crohn's disease: Granuloma
  - Ulcerative colitis: No Granuloma
- Cat scratch disease: Stellate Granuloma
- Vasculitis: Temporal arteritis/Takayasu arteritis/Churg Strauss syndrome/Wegner's granulomatosis

Giant cells

- Upon INF γ macrophages are activated and modified into "Epitheloid Cell" – has secretory function.
- Multiple epitheloid cells fuse to form "giant cells"

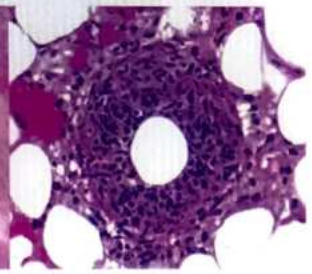
Giant cell type	Features
Langhans Giant Cells	• Seen in TB • Inverted U/ Horse shaped nuclei
Foreign Body Giant Cells	• Seen with sutures & talc
Warthin-Finkeldey Giant Cells	• Seen in measles • Eosinophilic inclusions are seen
Reed-Sternberg Giant Cell	• Owl-eye appearance • Seen in Hodgkin's Lymphoma
Touton Cell	• Peripheral cytoplasm has foamy appearance due to lipid deposition • Seen in Xanthoma



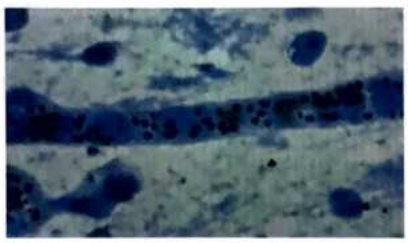
Caseating granuloma – TB

Sarcoidosis

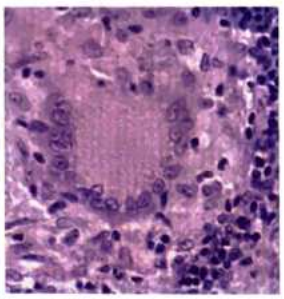
Cat-Scratch Disease



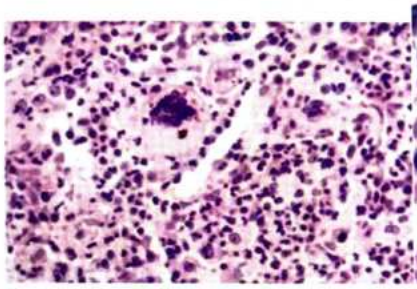
Q fever



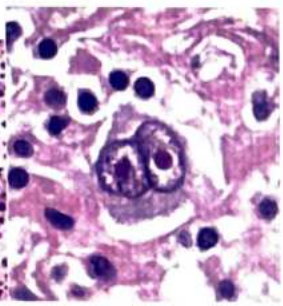
Cerebral malaria



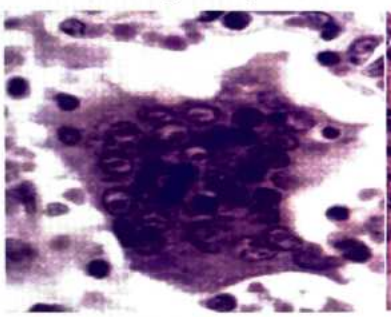
Langhan's GC



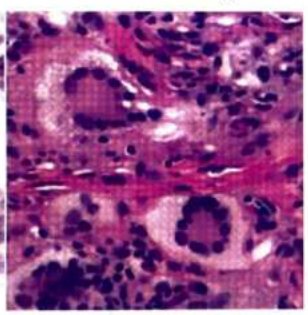
Foreign Body GC



Reed-Sternberg cell



Warthin-Finkeldey cell



Touton GC

WOUND HEALING

- Wound healing takes place by 2 steps
  - Primary union
  - Secondary union
- Primary Union
  - Damage predominantly in the epithelial lining
  - Minimal loss of Connective tissue
  - Seen in clean, surgical, uninfected wound
- Secondary Union
  - Seen with blunt object injury
  - More loss of connective tissue resulting in scar formation

Day	Feature
0	Blood Clot
1	Blood Clot + Neutrophilic infiltration
2	Thin Epithelial Layer
3	• Granulation tissue (collagen III) • Composed of Macrophages + Fibroblasts + Blood vessels
4/5	GT + collagen deposition (max angiogenesis)
14	↑↑ collagen + Fibrous tissue deposition

- In secondary union, due to ↑ release of inflammatory chemicals resulting in the conversion of fibroblast → myofibroblast
- Myo-Fibroblast
  - Contains actin
  - It has the contraction ability: Scar Contraction / wound contraction

Previous Year's Questions

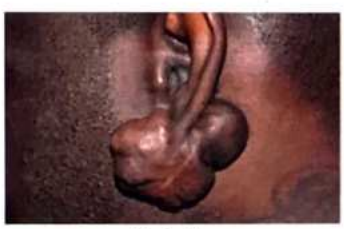
Q. Secondary healing mechanism is? (FMGE 2018)
A. Granuloma formation
B. Scab formation
C. Granulation Tissue
D. Neovascularization

Collagen Remodeling 00:37:42

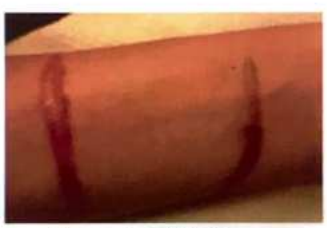
- Collagen III → Collagen I (Zn)
- It depends on
  - Vit C
  - MMP (Matrix metallo-Proteinases)
- Strength of the wound after 1 week: 10%
- Strength of the wound never becomes 100%

Abnormal Healing

- Keloid: Extra deposition of granulation tissue vertically goes beyond margins
  - MC site for keloid formation: Sternum
- Hypertrophic Scar: Extra deposition of granulation tissue vertically but it is within the margin



Keloid



Hypertrophic Scar

CLINICAL QUESTIONS

1. A 43-year-old man complains of a 1-week history of abdominal pain and yellow discoloration of his sclera. Physical examination shows right upper quadrant pain. Laboratory studies show increased serum levels of alkaline phosphatase (520 U/dL) and bilirubin (3.0 mg/dL). A liver biopsy revealed portal fibrosis, with scattered foreign bodies consistent with schistosome eggs. Which of the following inflammatory cells is most commonly to predominate in the portal tracts in the liver of this patient?

   A. Basophils
   B. Eosinophils
   C. Macrophages
   D. Monocytes

Solution

- Eosinophils are recruited in parasitic infestations and would be expected to predominate in the portal tracts of the liver in the patients with schistosomiasis.
- Eosinophils have leukotrienes and platelet-activating factor, as well as acid phosphatase and eosinophil major basic protein.
- Plasma cells are differentiated in to B lymphocytes that secrete large amounts of monospecific immunoglobulin.
- Diagnosis: Schistosomiasis

Reference

- Robbins 10th ed, Pg 397-398

LEARNING OBJECTIVES

Unit 3 IMMUNITY 1

- **Basics of Immune System Activation**
  - Innate Immunity
  - Adaptive Immunity
  - Activation Of Immune System
  - APC
  - MHC (Major Histocompatibility Complex)
  - T-Cell Activation
- **Hypersensitivity Reaction**
  - Type 1 Hypersensitivity Reaction
  - Type 2 Hypersensitivity Reaction
  - Opsonization & Phagocytosis
  - Inflammation
  - Cellular Dysfunction
  - Type 3 Hypersensitivity Reaction
  - Type 4 Hypersensitivity Reaction
  - Tuberculin Test
  - CD T-cell Activation

17 IMMUNITY

Immunity	
Innate Immunity	**Adaptive Immunity**
• Non-specific • No memory	• Specific • Memory is present

INNATE IMMUNITY

00:05:22

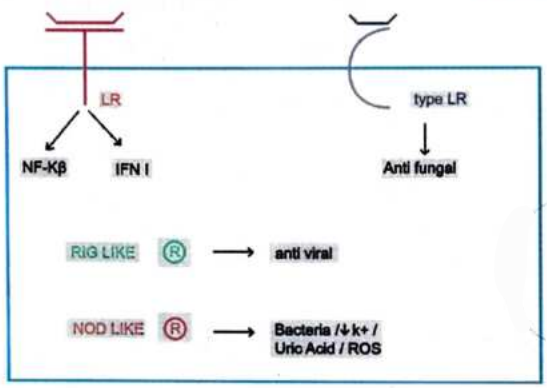
- Barriers
  - Anatomical barriers (Intact skin)
  - Physiological barriers (lysozyme is saliva, sweat)
- Protein molecules
  - C-reactive protein/Lectin/complement proteins
- Cells
  - Neutrophils
  - Macrophages
  - NK cells
    - → Recognizes and cause damage to virus infected/mutated cells

Important Information

- Bacteria: PAMP (required for infectivity of the bacteria)
- Inflammation (injured/necrotic cells): DAMP

PATTERN RECOGNITION RECEPTORS

00:11:39



Plasma membrane receptors

- Toll Like Receptor activation leads to secretion of
  - Nuclear factor κβ activation associated with ↑ recruitment of WBC at the site of injury
  - Interferon I have anti-viral effect
- C-type Lectin Receptor
  - Effective against fungal infections

Cytosolic receptors

- Rig like receptors: Defense against virus
- NOD like receptors
  - Identifies bacteria, potassium efflux, uric acid & reactive oxygen species
  - Inflammasome associated with activation of caspase 1 and release of IL-1 (fever)

ADAPTIVE IMMUNITY

00:19:21

B-Cells

- Upon activation coverts into activated B-cells/Plasma cells.
- Responsible for antibodies secretion.
- Contribute to Humoral immunity
- Effective against extracellular organism like bacteria

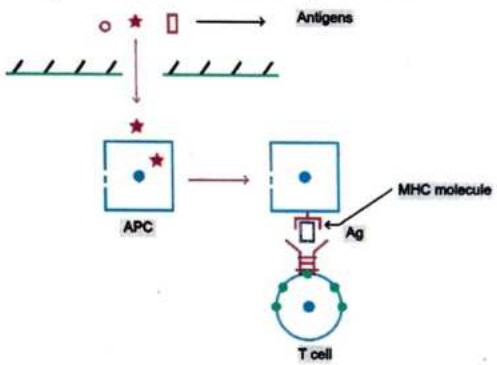
T-Cells

- Contribute to Cellular immunity
- Effective against intracellular microbes like virus & fungi

ACTIVATION OF IMMUNE SYSTEM

00:22:37

- Antigen (Ag)
  - Proteinaceous: T-cell dependent
  - Carbohydrate/lipid: T-cell independent



- Clonal selection: only a particular type of T-cell is activated depending on the structure of the presenting antigen.
- T-cells
  - Effector T-cell (actively fights the infection)
  - Memory T-cell (Marker: CR45RO)

APC

00:27:32

- Professional APC's (higher expression of MHC molecules)
  - B-cells (on direct stimulation by carb/lipid Ag it results in T-cell independent Ab secretion)
  - Macrophages ($CD_{13/14/15/33}$)
  - Dendritic cells
    - → Skin: Langerhans cell
    - → Lymph node/spleen: follicular dendritic cell (used by HIV as reservoir)
- Non-Professional APC's (lower expression of MHC molecules)
  - Thymic epithelial cells
  - Endothelial cells
  - Fibroblast
  - Glial cells
  - Pancreatic β-cells

MHC (MAJOR HISTOCOMPATIBILITY COMPLEX)

Previous Year's Questions

Q. HLA is located on?

(FMGE 2018)

A. Short arm chromosome 6
B. Long arm chromosome 6
C. Short arm chromosome 3
D. Long arm chromosome 3

- Present on chromosome 6p
- Present on surface of APC, responsible for presentation of processed antigenic peptide to immune cell in the body.

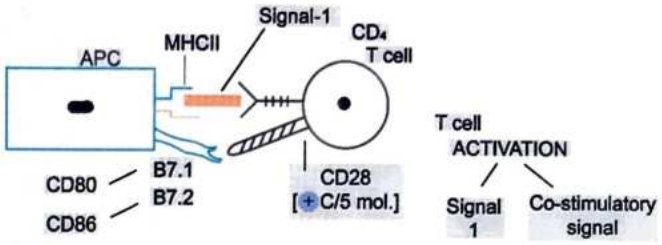
- Antigen binding cleft of MHC I made of α1, α2 (Distal α chains)
- Antigen binding cleft of MHC II made of α1, β1 (Distal α/β)
- Antigen + MHC I → CD_8 T-cells (MHC I dependent/MHC I restricted cells)
- Antigen + MHC II → CD_4 T-cells (MHC II dependent cells)
- MHC I is present on all nucleated cells and platelets are the only non-nucleated cells with MHC I.
- Alloantisera is used to detect MHC I
- Mixed Leukocyte Reaction (MLR) is used to detect MHC II
- CD_4: CD_8 T-cells → 2:1
- MHC is also known as HLA. And certain HLA associated with specific disorders

Important Information

- HLA B-27 is associated with ankylosing spondylitis
- HLA DR3/DR4 is associated with type I DM
- HLA DQ2/DQ8 is associated with celiac sprue

T-CELL ACTIVATION

00:40:56



- T-cell activation requires both signal 1 and costimulatory signal
- External antigen: generation of both signal 1 and costimulatory signal
- Self-antigen: generation of only signal 1 and not the costimulatory signal (T-cell Anergy)
  - Associated with self-tolerance
- Negative costimulatory signal: CTLA-4/PD-1 molecule of T-cell (↓ activation of T-cell upon self-antigen)

Previous Year's Questions

Q. Co-stimulatory factor of T-cell include all except.

(JIPMER 2018)

A. B7.1
B. B7.2
C. B7.3
D. CD 40

Cancer cells

00:51:54

- Cancer cells have ↑ expression of PD-L1/L2 molecule (program death ligand) and binds with PD-1 molecule results in inactivation of T-Cells
- Immune checkpoint blockade treatment is developed (monoclonal antibody blocks the interaction between PD-L1/L2 and CTLA-4/PD-1 molecule)
- Used in malignant melanoma, hodgkins and solid cancer
  - Side effect: ↑ risk of auto-immune disorders

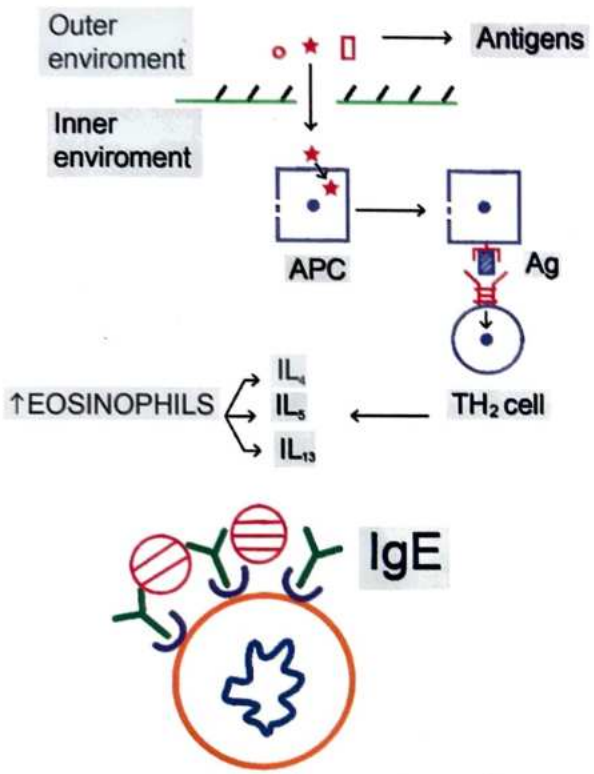
18 HYPERSENSITIVITY REACTIONS

- Hypersensitivity reaction → Tissue damage
- Gel combs classification → 4 subtypes of hypersensitivity reactions

TYPE 1 HYPERSENSITIVITY REACTION

00:01:24

- Aka Immediate type HR



First Exposure/Sensitization

- IL-4 → IgE → attaches to mast cell → modified mast cells
- IL-5 → ↑ Eosinophils
- IL-13 → ↑ Mucus

Re-exposure

Mast cells + IgE
↓
Ag exposure
↓
Crosslinking of IgE antibody
↓
Mast cell activation
↓
Degranulation
↓
Early phase: Histamine/proteases/ECF; NCF
Late phase: Cytokines/AA metabolites

- AA metabolites
  - PgD_2
  - LTs
- Cytokines
  - IL-2
  - TNF α
  - IL-5 → recruitment of eosinophils → release of MBP/ECP → Tissue damage

Examples

- A: Allergies → atopy (difference in genetic makeup that makes immune system to react in exaggerated manner)
  - Asthma: exposure to house dust (in western countries – pollen grains)
  - Hay fever
  - Food: peanuts/seafood
- B: Bee Sting (Melittin)
- C: Casoni's Test, P-K reaction, Theobald-Smith phenomena
- D: Drugs → Penicillin → Anaphylaxis

Previous Year's Questions

Q. A Boy presents in the emergency because of development of allergy due to pollen inhalation. Which of the following cells is important in the pathogenesis of this condition? (FMGE Aug 2020)

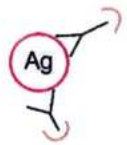
A. NK cell
B. Neutrophil
C. Helper T cell
D. Cytotoxic T cell

TYPE II HYPERSENSITIVITY

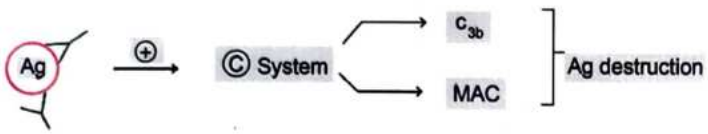
00:19:27

- Aka Antibody Mediated HR/Cytolytic HR

OPSONISATION & PHAGOCYTOSIS



- IgG (opsonin Ab) → Neutrophils, Macrophages → Phagocytose the Ab
- Ag + Ab → complement system activation → C3b attachment → attracts phagocytic cells
- MAC formation → damage to the antigen



Examples

- Blood transfusion reaction
- Erythroblastosis Fetalis/ Rh incompatibility of newborn
  - Mother → Rh –ve; Father → Rh +ve
- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Autoimmune leucopenia

INFLAMMATION

- Ag
- Ab

} Complement activation → C3a/C5a → WBCs → Tissue damage

Examples

- Acute rheumatic fever
  - Ab formation against bacteria
  - Structure of bacteria is similar to normal cardiac tissue/joints
  - Cross react → carditis/arthritis
- ANCA vasculitis
- Goodpasture syndrome
  - Ab → Non-collagenous part of α chain
  - α-chain is also present in BM of lungs & kidney
- Pemphigus Vulgaris

CELLULAR DYSFUNCTION

- Aka type 5 HR
- Ab → ↑↑↑ Stimulation of receptor → Graves disease (hyperthyroidism)
- Ab → ↓↓↓ Stimulation of receptor → Myasthenia gravis
- Examples of cellular dysfunction
  - Pernicious anemia
  - Insulin resistant DM

Examples of Type II HR

- MY - Myasthenia gravis
- Blood - Blood transfusion Reactions, Rh incompatibility
- Group - Good pasture Syndrome; Graves disease
- IS - Immune Hemolytic Anemia; Immune Thrombocytopenia; Insulin resistant DM
- R - Rheumatic Fever
- H - Hyperacute graft rejection
- Positive - Pernicious anemia; Pemphigus vulgaris

How to remember

- **Conditions associated with type II HR → My Blood Group Is RH Positive**

Previous Year's Questions

Q. A 55 – year old patient presented with difficulty in breathing and rashes after ingestion sea food: He has shown similar reaction in the past following consumption of the same food items. Which of the following hypersensitivity reaction do you relate with this? (FMGE Dec 2020)

A. Type I
B. Type 2
C. Type 3
D. Type 4

TYPE III HYPERSENSITIVITY REACTION

00:41:47

- Aka immune complex disease

Ag → Ab formation → Ag-Ab complex (Phase 1)
5-7 days ↓
Deposition of I/C (Phase 2)
(Glomerulus/serosa/LN/Skin/Synovium)
10-14 days ↓
Clinical features (Phase 3)

- Most dangerous immune complex are medium sized

How to remember

- **Conditions associated with type III HR → SHARP**

Examples

- S - Serum Sickness, SLE
- H - Henoch-Schonlein Purpura
- A - Arthus Reaction (Localized type 3 HR & involves

BV)

- R - Reactive Arthritis, Type 2 Lepra reaction
- P - Post Streptococcal Glomerulonephritis/Polyarteritis nodosa
- SLE
  - Chronic phase
  - Acute phase
    → I/C → Complement Activation occurs → ↓↓↓ Serum C_3
- Damage to endothelial cells → Plasma protein deposition in BV wall → Fibrinoid necrosis
- Presence of neutrophilic infiltration is also seen

TYPE IV HYPERSENSITIVITY REACTION

00:55:34

- Aka cell mediated HR
  - CD $\frac{4}{4}$-cell
  - CD $\frac{8}{8}$-cell

Delayed Type HR

- 1st Exposure: 2 mechanisms (Ag → APC → T_H/TH_1 cell)

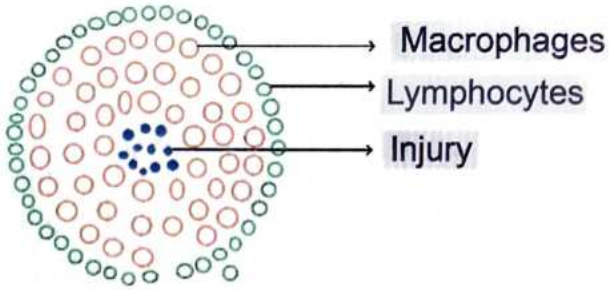
IL-12 → Helper T-cell → Differentiates into TH_1 → IFN γ → ↑ TH_1

(or)

Ag + APC → IL-1/6/23 → Naïve T-cell → Differentiates into TH_{17} cell → Memory cells

- Re-exposure

Ag → Memory cell → IL-2/ IFN γ → ↑ TH_1 → ↑ Lymphocytes → Macrophage activation → Granuloma



Important Information

- Granuloma associated with TH_1cell → consists more number of activated macrophages
- Granuloma associated with TH_2cell → consists more number of neutrophils

Tuberculin test (Mantoux test)

0.1ml of PPD → Inject intradermal into forearm → Check horizontal diameter of induration after 72hrs → If >10mm, Mantoux positive

- Helps in assessing
  - Exposure to Mycobacterium
  - Sufficient immune system activity
- Lepromin test/Mantoux test → delayed type IV HR

How to remember

- Conditions associated with Type IV HR → RAM Chandra If DM/Psoriasis/Leprosy/TB

Examples

- RA - Rheumatoid Arthritis
- M - Multiple sclerosis
- Chandra - Contact Dermatitis
  - Female → chemicals
  - Poison ivy
- If → IBD
- DM (Type 1)/Psoriasis/Leprosy/TB

CD_8T-cell activation

01:11:29

CD_8T-cell activation

Perforins (↑ permeability) Granzyme ↓ Activation of caspase ↓ Destroys target cell	↑↑FAS-L expression ↓ Fas receptor ↓ Extrinsic pathway of apoptosis activation ↓ Destroys target cell

Example

- Graft rejection
- CD_8-cells → virus **infected cell / cancer cells**
- Hepatitis
- Type 1 DM → **CTLs** → **Insulitis**
- CD_8-cells → **INF γ**

Important Information

- **Killing of virus infected/cancer cells**
  - **MHC I dependent: CD_8T-cells**
  - **MHC independent: NK cells**

CLINICAL QUESTIONS

1. You are an Intern in OBG Department, you receive a case of Term Teenage Pregnancy in labor with Cephalo-Pelvic Disproportion. Your Resident doctor instructs you to get the blood investigations done ready as the patient is to be taken for an Emergency LSCS procedure, especially the resident asked u to get the Blood Grouping and Rh typing done first. Which of the following potentially represents the most dangerous situation?

A. Rh+ve mother with 2nd Rh-ve child
B. Rh-ve mother with 2nd Rh+ve child
C. Rh+ve mother with 1st Rh-ve child
D. Rh-ve mother with 1st Rh+ve child

Solution

- Rh-ve mother with 2nd Rh+ve child can result in the development of hemolytic disease of newborn or erythroblastosis fetalis. So, it is a dangerous condition.
- In hemolytic disease of the fetus and newborn (erythroblastosis fetalis), there is an antigenic difference between the mother and the fetus, and IgG anti-erythrocyte antibodies from the mother cross the placenta and cause destruction of fetal red cells.
- This condition is a type II hypersensitivity reaction.
- *This is Not to be confused with Hemorrhagic disease of the newborn* which is a coagulation disturbance in the newborns due to vitamin K deficiency. As a consequence of vitamin K deficiency there is an impaired production of coagulation factors II, VII, IX, X, C and S by the liver.

Reference

- Robbins 10th/pg 210 table 6.3

LEARNING OBJECTIVES

Unit 4 IMMUNITY II

- **Concepts of Tolerance & Basics of Autoimmune Disorder**
  - Central Tolerance
  - Peripheral Tolerance
  - Autoimmune Disorders
- **Autoimmune Disorder 1; SLE**
  - Risk Factors
  - Features Of Organ Involvement
  - Antibodies In Sle
  - Conditions Resembling Sle
- **Autoimmune Disorder 2**
  - Sjogren Syndrome
  - Systemic Sclerosis / Scleroderma
  - Limited Scleroderma
  - Diffuse Scleroderma
  - Autoantibodies
  - Mixed Connective Tissue Disease
  - IgG_4 Related Disease
  - Dermatomyositis
  - Polymyositis
- **Concepts of Organ Transplant**
  - Immune Activation
  - Hyper Acute Transplant Rejection
  - Acute Transplant Rejection
  - Chronic Graft Rejection
  - Reducing Risk of Rejection
  - Graft Versus Host Disease
- **Immunodeficiency Disorders**
  - Di-George Syndrome
  - Bruton's Disease
  - Common Variable Immunodeficiency Disease
  - IgA Deficiency
  - Hyper IgM Syndrome
  - Hyper IgE Syndrome
  - X-Linked Lymphoproliferative Syndrome
  - Ataxia Telangiectasia
  - Wiskott Aldrich Syndrome
  - Severe Combined Immunodeficiency Syndrome
- **Amyloidosis**
  - Primary Amyloidosis
  - Secondary Amyloidosis
  - Hemodialysis Associated Amyloidosis
  - Localized Amyloidosis
  - Hereditary Amyloidosis
  - Organs Affected in Amyloidosis

19 CONCEPT OF TOLERANCE & BASICS OF AUTOIMMUNE DISORDER

- ↓ Response of immune system to antigens [Self]
- Self-tolerance: proper response of immune system to self-antigen
- Activation of immune system against self-antigen → auto-immune diseases

Types
- Central tolerance
- Peripheral tolerance

CENTRAL TOLERANCE
00:01:37

- Take place in LN/Bone marrow
- Deletion / Negative selection
  - Clonal deletion: deletion of Self-reactive B/T cells at the time of development by Apoptosis
  - T-cell → AIRE gene defect (autoimmune regulatory gene) → AI poly-endocrinopathy
- Receptor Editing
  - Seen in B cells

PERIPHERAL TOLERANCE
00:05:39

Anergy (Functional hypo-responsiveness)
- B-Cell ↓: CD40 – CD40L (↓)
- T-Cell ↓: CD28 – B.7 (↓)
- Self-antigen → ↑↑ CTLA-4/PD-1
- Cancer cells also use this mechanism for survival
- New anti-cancer therapy: Immune surveillance

T-Regulatory cell
- Example: Fetus at pregnancy
- They secrete
  - IL 10 & TGF β
  - CTLA-4 & PD 1 → ↓ activation of B & T cell
- CD4 T-cells
  - IL-2 receptor/ CD25 polymorphism → ↑ Multiple sclerosis
  - FOXP3 defect: IPEX syndrome

Important Information
- I - Immune dysregulation
- P - Poly-endocrinopathy
- E - Enteropathy
- X - X-linked Syndrome

Antigen Sequestration
- Immune Privileged Sites
  - **B - B**rain except chemoreceptor trigger zone/ Area postrema
  - **E - E**ye except optic nerve
  - **T - T**estis (Seminiferous Tubules) except epididymis

How to remember
- BET

- In Trauma in B/E/T is exposed → Orchitis, Opthalmitis

Previous Year's Questions
Q. Immune privilege site is. (JIPMER 2019)

A. Optic nerve
B. Seminiferous Tubule
C. Area postrema
D. Spinal cord

Deletion of self-reactive B/T-cells
- Done by process of programmed cell death
- ↑ Expression of FAS ligand/FAS receptor interaction → Apoptosis
- Self-reactive B/T cells have ↑ Bim (increases apoptosis)
- Defect in interaction → No Apoptosis → Auto Immune Lympho Proliferative Syndrome (ALPS)

AUTOIMMUNE DISORDERS
00:19:37

Genetic Factors
- ↓ Tolerance
- HLA genes defects → HLA B-27 (ankylosing spondylitis)
- Non-HLA genes defects
  - PTPN-22 gene defect
    - → Responsible for controlled lymphocyte proliferation in normal individuals
    - → Defect → ↑ No of self-reactive lymphocyte → ↑ Auto-Immune Disease
  - NOD-2 (sensor for GI bacteria) → malfunction → IBD

→ IBD is not a classical example of auto-immune disorder rather a hyperactivity of immune system against GI commensals

- IL-2 Receptor is responsible for normal function of T regulatory cells
  → IL-2 Receptor defect → ↓ T Regulatory Cells → MS/T1DM

Infections

- ↑↑ APC activation (due to ↑ Co-stimulatory Signal)
- Molecular mimicry (Rheumatic fever)
- Spreading of cryptic epitope
  - Example: In RF, hidden Ag is exposed in neighboring areas of diseased part
- Polyclonal B-Cell Activation
  - Example: EBV & HIV
  - Viral infection → B-cell activation → some B-cells are spontaneously mutated → Auto Ab formation
- Hygiene Hypothesis
  - ↓ Infections → ↓IL-2 → ↓ maintenance of T Regulatory Cells → ↑ Autoimmune Disorders

Miscellaneous Factors 00:33:07

- Hormones (female >>> male)
- UV light (SLE0
- Release of sequestered Ag (B/E/T)
- Drugs

Important Information

- **Drugs increasing autoimmune disorders**
  - S - Sulfonamide
  - H - Hydralazine
  - I - Isoniazid
  - P - Procainamide

20 SYSTEMIC LUPUS ERYTHEMATOSUS

- Associated with failure of self-tolerance
- Multisystem disorder

> **Important Information**
>
> - Pathology: Damage to any blood cells (Type 2 HR) + damage to organ by I/C deposition and subsequent inflammation (Type 3 HR)

RISK FACTORS

- Genetic factors
  - HLA DQ polymorphism
  - Deficiency of complement proteins ($C_1/C_2/C_4$)
- Environmental factors
  - UV rays
  - Female predominant (hormonal and genes specifically located in 'X' chromosome)
- Drugs
  - Immunologic factors
  - Hyper activation of B & T-Lymphocyte

SLICC Clinical Immunologic Criteria

> 4 criteria [at least 1 clinical and 1 laboratory]

Clincal	Labortory
1. Acute cutaneous lupus 2. Chronic cutaneous lupus 3. Oral or nasal ulcers 4. Non scarring alopecia 5. Arthritis 6. Serositis 7. Renal 8. Neurologic 9. Hemolytic anemia 10. Leukopenia [<4000/mm^3] 11. Thrombocytopenia [<100,000/mm^3]	1. ANA above lab ref range 2. Anti-dsDNA above lab ref range [or 2x ref range if tested by ELISA] 3. Anti-SM 4. Antiphosphliopid antibody 5. Low complement [C3,C4,CH50] 6. Direct coombs' test [do not count in the presence of hemolytic anemia]

- Acute cutaneous lupus: photosensitive skin rash (malar rash on Nose Bridge)
- Chronic cutaneous lupus: discoid rash
- Oral or Nasal ulcers: painless
- Arthritis: ≥2 more peripheral joint involvement in which there's no damage to articular cartilage
- Serositis: pericarditis, pleuritis
- Renal: massive proteinuria or RBC cast in the urine
- Neurologic: decline in the brain function or seizures or epilepsy
- CH50 is indicator of activation of classical pathway
- Low complement levels indicate "active phase" of the disease
- Standalone criteria – presence of ANA/anti-ds DNA Ab + biopsy proven lupus nephritis

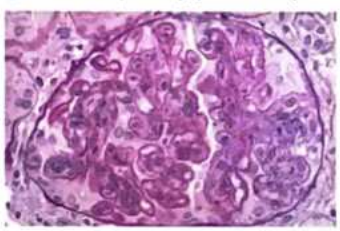
FEATURES OF ORGAN INVOLVEMENT

00:10:55

- Non-specific fever, weight loss, fatigue
- Oral cavity: painless aphthous ulcer
- Joint: non-erosive arthritis and no deformity
  - Musculoskeletal involvement in the commonest involvement in SLE
- Skin: malar/butterfly rash, photosensitive
  - Degeneration of basal layer of epidermis
  - Immunofluorescence: Ig at dermo-epidermal junction
- Lungs: pleuritic (MC) > interstitial fibrosis
  - Shrinking lung syndrome: weakness of diaphragm resulting in small lung
- Cardiac: pericarditis (MC) >> Libman Sacks Endocarditis (Mitral/Aortic valve involvement)
  - Accelerated atherosclerosis
- Spleen: "Onion skin appearance" due to fibrosis around penicilliary artery

> **Important Information**
>
> - Onion peel appearance in blood vessel of kidney - malignant HTN
> - Onion peel appearance of bile ducts - primary sclerosing cholangitis

- Kidney: glomerulonephritis, tubule-interstitial nephritis
  - Type 4/diffuse proliferative glomerulonephritis is the most common and most severe
  - Sub-endothelial I/C deposition → circumferential thickening of the capillary (wire loop lesion)



- Full-house phenomenon: Immune-complex are associated with Ig/M/A, C3 protein and λ/κ light chains
- CNS: decline in cognitive function
- Blood: anemia in these patients is due to
  - Abnormal Ab (AIHA)
  - Anemia associated with chronic disease – most important cause

ANTIBODIES IN SLE

00:25:25

Previous Year's Questions

Which of the following cannot be diagnosed with +ve ANA?

(AIIMS 2018)

A. Drug induced lupus
B. SLE
C. Scleroderma
D. Sjorgen syndrome

- Anti-nuclear antibody: Most sensitive for diagnosis of SLE
- Anti-ds DNA/Anti smith antibody: most specific for the diagnosis of SLE
  - Predicts disease activity (Anti-ds DNA antibody)
  - Correlates with nephritis and vasculitis
- Anti-Ribosomal P antibody: associated with development of psychosis
- Predictor of SLE in pregnancy
  - Anti-Ro antibody: Neonatal lupus (congenital heart block)
    - → Can also be found in subacute cutaneous lupus, Sjorgen syndrome
    - → Associated with ↓ nephritis
  - Anti-β2 gp antibody: It is directed against phospholipid of endothelial cells, platelets and placental vessels resulting in recurrent abortions
    - → Increased risk of DVT/HVT/stroke
    - → Associated with APLA (Antiphospholipid Antibody Syndrome)

Previous Year's Questions

Q. Which antibody is associated with reduced risk of lupus nephritis in SLE?

(JIPMER 2018)

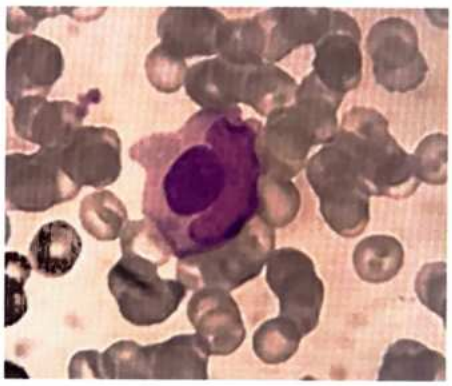
A. Anti-ribosomal P antibody
B. Anti-histone antibody
C. Anti-Ro antibody
D. Antinuclear antibody

- APLA
  - ↑aPTT is seen
  - Primary: unknown cause
  - Secondary: SLE (MC)

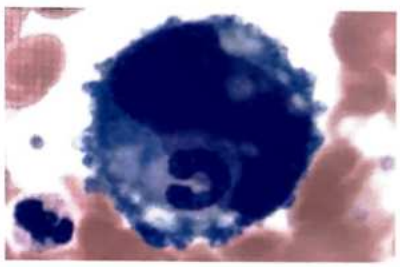
Important Information

- **Antibodies are directed against cardiolipin and Anti-β2 gp**
- **Cardiolipin antigen associated with false +ve VDRL (syphilis)**
- **DRVVT (Dilute Russell Viper Venom Test) helps in detection of auto-Ab**

- LE Cell: Neutrophil and macrophages has denatured nuclear material (LE body) of another cell
  - Found in SLE >> RA, drug induced lupus



- TART cell: Macrophage that phagocytosed intact chromatin containing nuclei.
- Emperipolesis: Intact cell within cytoplasm of another cell
  - Found in Rosai Dorfman Disease, HL, CML/AML, MDS, MPD



Band cell within Megakaryocyte

- Organism used in IF detection of antibody: Crithidia

psmu...@mail.ru
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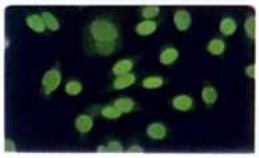
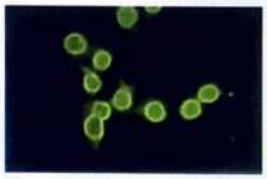
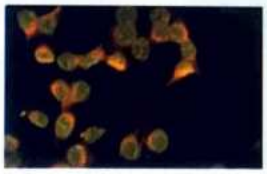
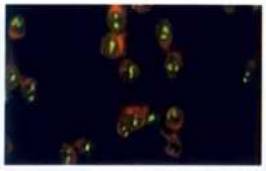
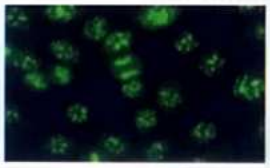
Pattern	Antigen	Image
Homogenous or diffuse nuclear staining	Chromatin, histones	
Rim or peripheral staining	Double stranded DNA	
Speckled pattern (MC and least specific pattern)	Antibody against extractable (non-DNA) nuclear antigens like ribonucleoprotein, Sm antigen, SS-A and SS-B reactive antigen	
Nucleolar pattern (seen in systemic sclerosis)	RNA (Bright fluorescence is seen within the nucleoli)	
Centromeric pattern (seen in CREST syndrome)	Centromeres	

21 AUTOIMMUNE DISORDERS - 2

SJOGREN SYNDROME

00:00:29

- Characterized by Lymphocytic infiltration of lacrimal glands & Salivary glands leading to fibrosis overtime

Clinical features

- Females
- Dry eyes/Dry mouth Syndrome → sicca syndrome
  - Gritty sensation of eyes and thickened secretion in conjunctiva
  - Saliva has antibacterial property, hence its absence can lead to bad breath, difficulty in swallowing and speech.
  - Parotid gland enlargement
- Sicca Syndrome can be 1°/2°
  - Associated with Rheumatoid Arthritis (cause of 2° Sicca Syndrome)

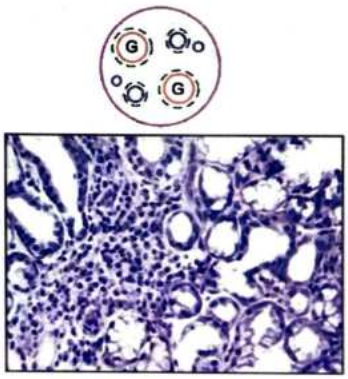
DIAGNOSIS

Auto antibodies

- They are non-confirmatory
- ANA +ve
- Anti RO Ab [SS-A] +ve
- Anti La Ab [SS-B] +ve
- Anti RO Ab: Associated with
  - Vasculitis
  - Nephritis
  - ↑ duration of disease

Lip Biopsy

- Confirmatory (IOC)
- Lymphocytic infiltration in and around glands & blood vessels
- ↑ Risk of marginal zone lymphoma (also seen in Hashimoto's thyroiditis)



Previous Year's Questions

A 47yr old female presents with arthralgia, difficulty in swallowing the food and gritty feeling in the eye. He is also found to be having increased titers of ANA. Which of the following is the likely diagnosis? (FMGE 2020)

A. Rheumatoid arthritis
B. SLE
C. Serum sickness
D. Sjorgen syndrome

SYSTEMIC SCLEROSIS (SCLERODERMA)

00:10:18

- Characterized by
  - ↑ Fibrous tissue deposition → skin & other organs
  - Damage to blood vessels

Variants

- Linear Scleroderma / Morphea
- Limited Scleroderma

Limited Scleroderma

- Initial involvement of Blood vessels [Raynaud's phenomenon]
- Affected blood vessels are narrowed → ↓ blood supply → pale white → blue → red
- Skin of Fingers/face/fore arm involved
- Late involvement of systemic visceral organs
- Anti-centromere Ab +ve
- CREST syndrome
  - **C** - Calcinosis
  - **R** - Raynaud's phenomenon
  - **E** - Esophageal dysmotility
  - **S** - Sclerodactyly
  - **T** - Telangiectasia

Previous Year's Questions

Anti-centromere antibodies are seen in which of the following? (AIIMS 2018)

A. Drug induced lupus
B. SLE
C. Sjorgen syndrome
D. Scleroderma

Diffuse Scleroderma

- Skin + early visceral involvement
- Organ involvement
  - Esophagus: Dysphagia
  - GIT: malabsorption
  - Cardiac: pericarditis, pericardial **effusion, fibrosis**
  - Lungs: PAH (cause of death); Pulmonary **Fibrosis**
  - Kidney: ↑ **risk of renal failure**

Autoantibodies

- Anti-ANA Ab **+ve**
- Anti–DNA Topoisomerase **I Ab [Anti - SCL 70 Ab ⊕]**: specific antibody
  - Associated with ↑ **chances of**
    - → Peripheral Vascular Disease
    - → Lung involvement
- Anti-RNA Polymerase **III Ab**
  - **Associated with systemic sclerosis**
  - **3 important manifestations**
    - → **R - Renal**
    - → **N - Neoplasia**
    - → **A - Acute onset**

Important Information

- **Anti U_3 RNP Ab: Associated with systemic sclerosis**
- **Anti U II/I2 RNP Ab: Associated with ↑ risk ILD**

MIXED CONNECTIVE TISSUE DISEASE

00:23:45

- Mixed Features of **SLE/Sclerosis/Polymyositis**
- Anti - U_1 RNA Ab
- Less severe renal involvement
- Better response to steroids

Ig G_4 RELATED DISEASE

- **Middle aged male → Plasma cells + T cells + Obliterative phlebitis**

↓

Ig G4

- Associations
  - Idiopathic retro peritoneal fibrosis/Ormond's disease
  - Riedel's thyroiditis
  - Mikulicz syndrome
  - Autoimmune **pancreatitis**
  - Kuttner's **Tumor (chronic sialadenitis)**
- Storiform pattern **of fibrosis is seen**
  - Also seen in Malignant Fibrous Histiocytoma
- **Treatment: Rituximab**

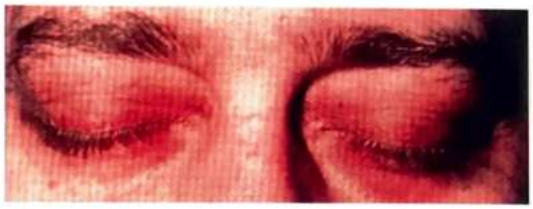
DERAMATOMYOSITIS

00:31:06

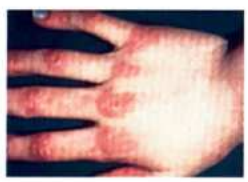
- Skin + Muscles + **Surrounding Blood vessels**
- 1° or associated **with cancers (stomach cancer)**

Clinical features

- Skin
  - Heliotrope rash
  - Gottron papules (seen on extensor surface)
- Muscle
  - **Proximal muscles involved early**
  - **Distal muscles involved later (↑ Creatinine Kinase value)**



Heliotrope rash

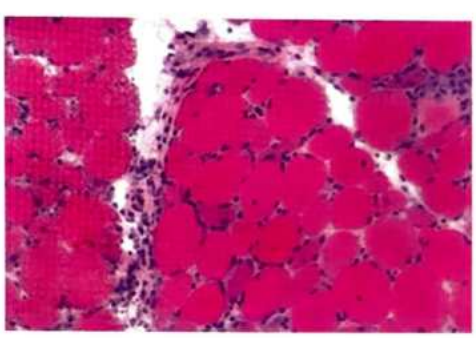


Gottron Papule

Diagnosis

- Auto Anti Bodies
  - ANA +ve
  - Anti Jo 1 Ab +ve: Mechanic hand
  - Anti Mi2 Ab +ve: skin features
  - Anti P 155 Ab +ve: Paraneoplastic syndromes
  - Anti P 140 Ab +ve: Juvenile Dermatomyositis

Biopsy



CD_4 T-cells

↓

Peri Mysial Inflammation

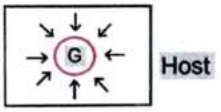
&

Peri Fascicular Atrophy

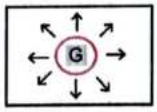
POLYMYOSITIS 00:38:52

- Skeletal muscle inflammation
- No skin involved
- Biopsy: Endomysial Inflammation (CD_8 T-Cells)

22 ORGAN TRANSPLANTATION



Transplant Rejection



Graft Vs Host Disease

Types of graft 00:02:01

- Auto-graft: self
  - Example: skin graft, Hair transplant, bone transplant
- Allograft: Different individual of same species
  - Example: Kidney transplant
- Iso-graft/Syngraft: Identical twin
- Xenograft: Different species
  - Example: Cardiac valves from pig & cow

Important Information

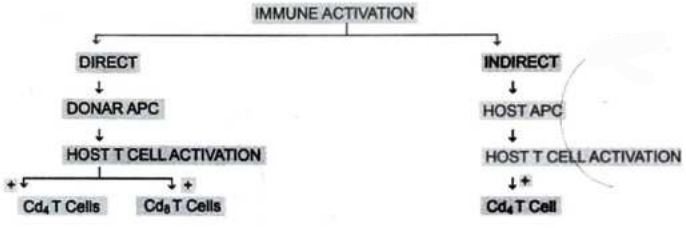
- **Auto-graft: Least chance of rejection**
- **Xenograft: Maximum chance of rejection**

Previous Year's Questions

Q. An elderly diabetic male patient underwent kidney transplantation from his twin brother. The type of grafting is? (FMGE – Dec – 2020)

A. Allograft
B. Isograft
C. Xenograft
D. Autograft

IMMUNE ACTIVATION 00:04:13



- Direct pathway is responsible for acute cellular rejection.
- Indirect pathway is responsible for chronic cellular rejection.

HYPER ACUTE TRANSPLANT REJECTION 00:05:47

- Rejection occurs within minutes to hours
- H/O previous transplant, blood transfusion, multiparous
- Occurs due to preformed Ab – IgM (against ABO/HLA)
- Preformed Ab → Endothelial Cell damage → Thrombus

Previous Year's Questions

Which graft rejection can be reversed once it is established? (JIPMER 2019)

A. Hyper-acute rejection
B. Acute rejection
C. Chronic rejection
D. Acute on chronic rejection

ACUTE TRANSPLANT REJECTION

- Rejection occurs within Days to weeks (< 6 months)
- Reversible
- Acute cellular rejection: Activation of CD4/CD8 T-Cells results in
  - Tubular injury (Type 1 injury)
  - Endothelial injury – vasculitis, endothelitis (Type 2 injury)
- Acute humoral rejection: Ab → activation of complement system → C_4D deposition in glomeruli (used as marker)

CHRONIC GRAFT REJECTION

- Rejection occurs in months to years (> 6 months)
- MC type of transplant rejection
- Cellular: ↑ smooth muscle proliferation/fibrosis → narrowing of lumen → "Graft Arteriosclerosis"
  - Example: Glomerulo-sclerosis (deposition of fibrous tissue at glomerulus, duplication of BM)
- Humoral: Ab formation

REDUCING RISK OF REJECTION 00:12:29

HLA MATCHING

- HLA-A, HLA-B, HLA-C, HLA – DQB1, HLA - DRB1 (most important)
- Total score of matching = 10
- In practice HLA-A/B/C & DRB 1 considered predominantly (score = 8)

- In adults, Score 6 out of 8 is suitable for transplantation
- In cord blood, HLA-A/B/DRB 1 → 4 out of 6 should be matched

DRUGS

- Steroids
- Mycophenolate mofetil (MMF)
- Tacrolimus
- IV Ig
- Plasmapheresis
- Acute cellular rejection has the best response to drugs
- S/E of Drugs
  - ↑ Risk of opportunistic infections (CMV, EBV, Polyoma virus, HPV)
    - → CMV: nephritis, ocular complications
    - → EBV: Post transplant B-cell lymphoma
    - → HPV: ↑ squamous cell cancer
  - ↑ Cancers

NATURE

- HLA matching is important for kidney transplantation
- Transplantation of heart, lungs and liver: HLA matching is not required as certain other factors are more important such as
  - Time of organ harvestation from donor
  - Anatomical size of the organ

GRAFT VERSUS HOST DISEASE

00:20:32

- Cause
  - Immuno-compromised host
  - Immuno-competent Graft
- GVHD is seen in
  - HSCT (Hematopoietic stem cells transplantation) is the MC reason for graft vs host disease
  - Liver transplantation
  - Un-irradiated Blood Transfusion

	Skin	Liver	Intestine
Acute GVHD (<100 days)	Rash	Jaundice	Bloody diarrhea
Chronic GVHD (>100 days)	Fibrosis	Cholestatic jaundice	Esophageal stricture
	Thymic involution, ↓ lymphocytes in LN		

T-Cells

- T-cells are responsible for causing GVHD
- T-cells has also beneficial role
  - ↓ EBV infected B-cells
  - ↓ Leukemia cells
  - Engraftment of transplanted HSC

Previous Year's Questions

Cell responsible for "Graft Versus Host Disease" is. (JIPMER 2017)

A. Donor T-cell
B. Host T-cell
C. Donor B-cell
D. Host B-cell

HSCT Transplantation

- MC cause of GVHD
- Immunodeficiency: MC complication of HSCT
  - Cause of death: CMV Pneumonitis
- GVHD Can be reduced by Autologous BMT/HSCT

23 IMMUNODEFICIENCY DISORDERS

- Primary → genetic defect, early presentation
  - Leukocyte disorders → LAD I/II, CHS, CGD, MPO deficiency
  - ↓↓ complement proteins → C2
  - Lymphocytes → B/T-Cells
- Secondary → acquired
  - PEM
  - Infections (HIV)
  - H/O of splenectomy
  - Immunosuppressive drugs

DI-GEORGE SYNDROME

00:04:32

- T-Cell defect
- Associated with 22q11 deletion → TBX1 gene → ↓↓ 3/4th pharyngeal pouch → ↓ PTH
- 3/4th pharyngeal pouch are associated with development of thymus gland, ultimobranchial body, parathyroid gland.
- Manifestations
  - Congenital cardiac defect
  - Abnormal facies
  - T-Cells ↓
  - Cleft lip/palate
  - Hypocalcemia
  - 22q11 deletion
- Aka Velo-cardial facial syndrome

BRUTON'S DISEASE

00:07:44

- B-Cell malfunction
- Associated with B-Cell Tyrosine Kinase defect
- Boys (male >> female)

Precursor B-Cell
↓ BTK
Immature B-cells
↓
B-Cells
↓
Plasma cells
↓
↓Ab

- X-Linked hypogammaglobulinemia

Clinical features

- Presents around 6 months (mother's antibodies are present in circulation for up to 6 months)
- ↓↓ Ig → Infection (strep pneumonia/H.Influenza)
- T-Cells → normal
- Underdevelopment of lymphoid areas (splenic follicles, LN, Tonsils)
- ↓ IgA → ↑ enterovirus/giardia
- Fulminant infections are caused by
  - Poliovirus: Paralytic poliomyelitis
  - Echovirus: Encephalitis

COMMON VARIABLE IMMUNODEFICIENCY DISEASE

- Involvement of B-Cells >> T-Cells
- Precursor B-Cell → Immature B-Cell → B-Cell (BAFF receptor) → PC
- Underactivity of BAFF receptor/ICOS/TACI
- Problem at the level of plasma cell formation → ↓ Ig → sino-pulmonary infection/bacterial/viral/giardia infections
- Difference from Bruton's disease
  - B-Cells → normal in number
  - Hyperplasia of B-Cell location (LN/Spleen)
  - Male = Female
  - Late presentation
- ↑ Risk of autoimmune disorders → RA
- ↑ Risk of cancer → stomach cancer/lymphoid cancer

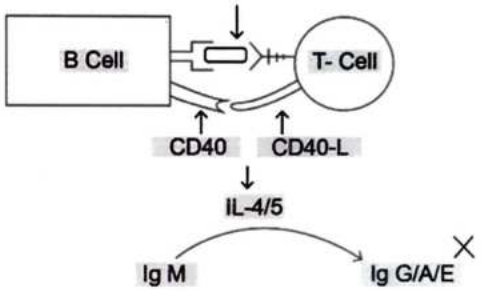
IgA DEFICIENCY

00:21:43

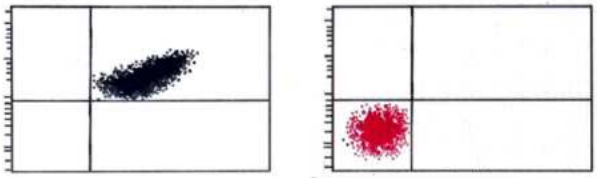
- MC immunodeficiency disorder
- IgA → ↑ Infections (lungs/GIT)
- Also associated with IgG2/IgG4 deficiency
- Presentation
  - ↑ Allergy
  - H/O blood transfusion → IgA → Anaphylaxis
  - ↑ Autoimmune disorders (SLE/RA)

HYPER IgM SYNDROME

- Involvement of B-Cells & T-Cell → improper interaction
- Associated with X-Linked inheritance → CD40 Ligand
- AR → B-Cell(CD40/AID)



- ↑↑↑ IgM
  - Anemia
  - Thrombocytopenia
  - Leukopenia
- ↓ IgG → ↑ Infections/P.Jioverci infections
- B-Cells & T-Cell → Normal



Normal (CD 40)

Previous Year's Questions

Q. Which of the following diseased in diagnosed with help of the flowcytometry pattern?

(AIIMS Nov 2019)

A. Bruton disease
B. Bare lymphocyte syndrome
C. Hyper IgM syndrome
D. Severe combined immunodeficiency disease

HYPER IgE SYNDROME

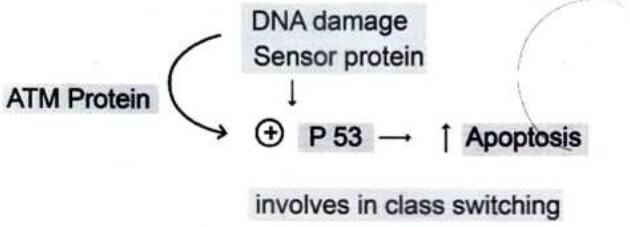
- Aka Job Syndrome
- Characterized by ↑ IgE levels
- ↓↓ TH_{17} → cold abscess (staph aureus)
- AD inheritance

X-LINKED LYMPHOPROLIFERATIVE SYNDROME

- SLAM/SLAM associated protein → required for normal function of B/T/NK Cells
- Defect in SLAM/SLAM associated protein → ↑ risk of EBV → Fulminant Infectious mononucleosis
- Associated with ↑ risk of B-Cell cancers

ATAXIA TELANGECTASIA

00:38:04



- Defect in ATM gene which is present at Chromosome 11 → functions as DNA Damage sensor

Clinical features

- Ataxia
- Dilated tortuous BV
- Neurological deficits
- ↓ Immunity (↓IgA/↓ IgG_2)
- ↑ Tumors

WISKOTT ALDRICH SYNDROME

- X-Linked inheritance
- Defect in WASP protein → Xp11 defect
- Triad of
  - Recurrent infections
  - ↓ Platelets (Small sized platelets)
  - Eczema
- Ab changes
  - ↓↓ IgM
  - ↑↑ IgE
  - IgA → Normal/↑

SEVERE COMBINED IMMUNO DEFFICIENCY DISEASE (SCID)

- ↓↓ B/T-Cells

X linked SCID	AR SCID
• Defect in Cytokine receptor → γ chain • IL-7 → B/T cells • IL-15 → NK cells • IL-2/4/9/11 • ↓ CMI • B-Cell → ↓ Ig	• ADA deficiency → ↑ deoxyadenosine → damage to B & T cells • RAg • JAK-3 → ↓↓ γ chain

Clinical features

- ↑ Bacterial/protozoal Infections
- ↑ Viral/Fungal infections

Treatment

- Hematopoietic stem cell transplantation

24 AMYLOIDOSIS

- Group of conditions associated with Inflammation /Extra-cellular Fibrillary protein deposition
- Amyloid depositions → pressure atrophy in organs
- It is made if
  - Fibrillary protein (95%)
  - 'P' Protein (5%)

GENERALISED / SYSTEMIC AMYLOIDOSIS

PRIMARY AMYLOIDOSIS

- MC clinical association → plasma cell dyscrasia
- Also associated with multiple myeloma
- Abnormal plasma cell → Abnormal Ig (light chain > heavy chain)
- In plasma cell dyscrasia → overproduction of λ subtype of light chain
- Chemical nature of amyloid: AL (λ)

SECONDARY AMYLOIDOSIS (REACTIVE)

- It is associated with
  - Chronic inflammation (RA/TB/IBD)
  - Cancers (RCC/Hodgkin's lymphoma)
- In both these conditions → ↑ IL-6/1 → Liver → SAA → migrates from serum into tissues
- Chemical nature of amyloid: AA

HEMODIALYSIS ASSOCIATED AMYLOIDOSIS

- Associated with chronic renal failure
- Earlier used hemodialysis machines contain semi-permeable membrane → unable to filter β_2 microglobulin → amyloid
- Chemical nature of amyloid: $A\beta_2m$
- Has special affinity to joints (wrist, knee)

LOCALIZED AMYLOIDOSIS

00:09:04

Senile Cerebral Amyloidosis

Amyloid Precursor Protein $\xrightarrow{\beta/\gamma \text{ secretase}}$ Aβ-plaque

Aβ-plaque

↓

Damage to Meynert nucleus

↓

Interferes with neurotransmitter Ach

↓

Memory loss

- Clinically known as Alzheimer's disease
- Chemical nature of Amyloid: Aβ (APP)
- Gene for APP located on chromosome 21
- Down syndrome (Trisomy 21) → ↑ APP → ↑ Aβ → development of neuronal degeneration at early age

Medullary Thyroid Cancer

- Arises from Para Follicular cells → secretes calcitonin → excess of calcitonin deposits as amyloid
- Chemical nature of amyloid: ACal
- Calcitonin levels can be used as a diagnostic marker

Type 2 DM

- Involvement of pancreatic β-cells
- Deposition of Islet Associated Pancreatic Peptide (IAPP) → ↓ insulin
- Chemical nature of Amyloid: AIAPP

Isolated Atrial Amyloidosis

- Stretching of atrial wall → ANF (Atrial Natriuretic Factor → amyloid
- Chemical nature of Amyloid: AANF

HEREDITARY AMYLOIDOSIS

00:15:33

Familial Mediterranean Fever

- AD condition
- Characterized by inflammation along with the release of IL-1 → Liver → Pyrin
- Pyrin is pyrexia causing protein & involvement of serosal surface (serositis/pleuritis)
- Inflammation → ↑SAA protein
- Chemical nature of amyloid: AA (Pyrin)
- Good response to NSAIDs & colchicine is seen

Familial Amyloidotic Neuropathies

- TTR responsible for transport of thyroxine & vitamin A derivatives
- Altered TTR protein → interferes with nerve activity
- Chemical nature of Amyloid: ATTR

Systemic Senile Amyloidosis

- In elderly, deposition of normal TTR in all organs of the body (especially heart) → Systemic Senile Amyloidosis
- Difference from familial amyloidotic polyneuropathy is that it has abnormal TTR deposition
- Chemical nature of Amyloid: ATTR

ORGANS AFFECTED IN AMYLOIDOSIS

00:19:48

Cardiac tissue

- MC associated with 1° amyloidosis
- Amyloid is deposited on Sub-endocardial tissue and interferes with electrical conductivity of heart → arrhythmia (MC clinical manifestation)
- Amyloid deposition between cardiac fibers → cardiac fibers unable to relax → Restrictive Cardiomyopathy
- MC cause of restrictive Cardiomyopathy → Amyloidosis

Kidney

- MC & most severely affected organ from amyloidosis
- MC seen with 2° amyloidosis
- Initial Amyloid deposition is seen in Mesangial matrix, followed by progressive involvement of glomerulus
- Renal venules are not affected
- Nephrotic syndrome occurs leading to massive proteinuria

Liver

- Presence of hepatomegaly
- 1st part of the liver to be involved is 'Space of Disse' → Ito cell (responsible for vitamin A metabolism)

Spleen

- Involvement of Splenic Sinuses/Red Pulp → Lardaceous Spleen
- Involvement of Splenic Follicles/White Pulp → Sago Spleen

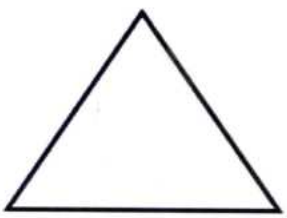
Skin

- Amyloid deposition around blood vessel → weak connective tissue → fragile BV → "Pinch purpura"
- Periorbital bleeding → Raccoon eyes
- Subcutaneous tissue is also involved → Abdominal fat aspiration (helps in diagnosis)

Joints

- Knee Joint Involved
- Wrist Joint involved → carpal tunnel Syndrome → median nerve affected
- Can be seen after dialysis

Carpal tunnel syndrome



Tenosynovitis Scapulo-Humeral Periarthrtis

GIT

- Tongue → Nodules → ↑ tongue size (macroglossia)
- Mucosa involvement → Tissues can be taken Oral/Rectal mucosa
  - Rectal mucosa biopsy is preferred
- Abdominal fat aspiration > rectal mucosa > oral mucosa

Previous Year's Questions

Q. True/false amyloidosis? (AIIMS May 2019)

A. A beta 2 microglobulin is accumulated in senile amyloidosis.

B. Malignancy is the most common cause of amyloidosis in western counties.

C. Mostly it contains kappa light chains.

D. Apple green under UV light when stained with congo red.

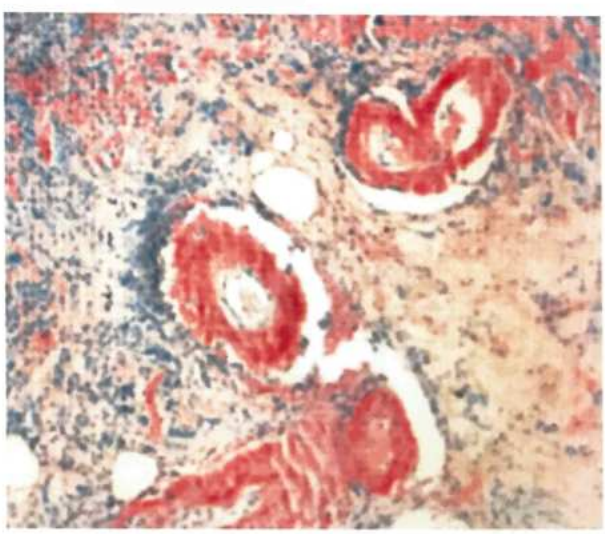
DIAGNOSIS

00:32:51

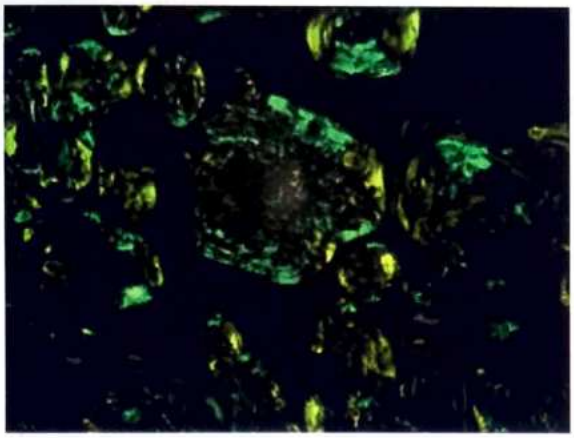
- Localized → biopsy from affected organ
- Abdominal Fat Aspiration → most sensitive test
- Biopsy → Rectal Mucosa

Staining

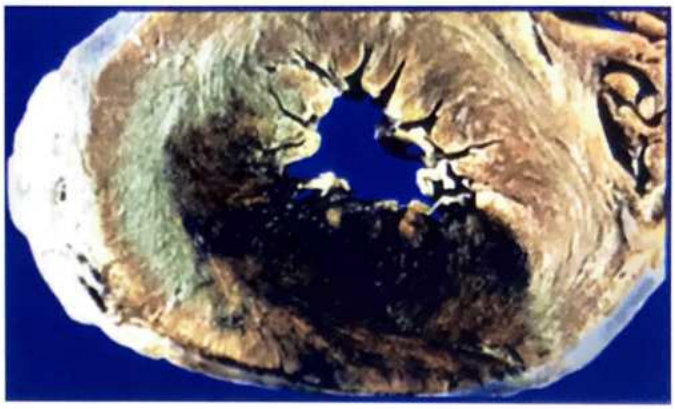
- Congo red
  - Under normal light: Pink red appearance
  - Under polarized light: Apple green birefringence (characteristic)
- PAS ⊕
- Thioflavin T/S → provides immunofluorescence to amyloid protein



Congo red stain



Apple green birefringence



Gross specimen

- Scintigraphy → done with the help of radiolabeled SAP

- Electron Microscopy → Non-branching Fibrils are observed
- Spectroscopy/Crystallography → β-plated structure
- Organ → Shows waxy appearance & ↑ size of organ
  - Iodine → Mahogany Brown appearance → washed with dilute H_2SO_4 → Blue color

CLINICAL QUESTIONS

1. A 59-year-old female comes to her primary care physician with chief complaints of dyspnea on working and intractable coughing. She reported no fevers, chills, night sweats, or hemoptysis, however, did relate an approximate 20-pound weight loss over 6 weeks prior to presentation. The patient's general exam was within normal limits except for multiple, scattered erythematous to violaceous and tender skin nodules on her bilateral extremities. Her lungs were clear to auscultation and she had no palpable adenopathy. Punch biopsy of a right pretibial skin lesion showed a well-formed sarcoid type of granuloma with septal thickening and fibrosis True regarding granulomas seen here are all except-

A. Large central area of necrosis is common

B. Compact non cosseting granulomas

C. Giant cells are seen

D. Schaumann bodies and asteroid bodies may be seen

Solution

- Granulomas found in sarcoidosis are non-caveating, compact, with tightly clustered collection of epithelioid histiocytes
- They contain the following:
  - Asteroid Bodies
  - Schaumann bodies and
  - Birefringent crystals

Reference

Robbins, Pathologic Basis of Disease, 10e, p. 696-698

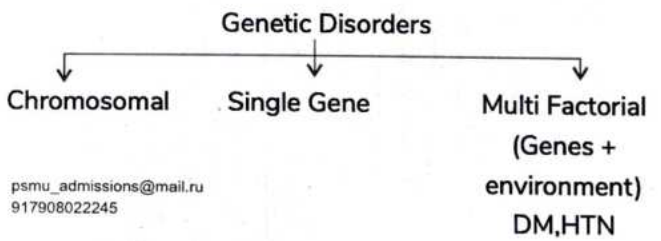
LEARNING OBJECTIVES

Unit 5 GENETICS

- **Introduction to Genetics**
  - Chromosomal Disorders
  - Karyotyping
  - Structural Defects
- **Single Gene Disorders**
  - Autosomal Dominant Disorders
  - Autosomal Recessive Disorders
  - Y-Linked Disorders
  - X-Linked Recessive Disorders
  - X-Linked Dominant Disorders
- **Non-Classical Inheritance Disorders**
  - Genomic Imprinting
  - Prader Willi Syndrome
  - Angelman Syndrome
  - Mitochondrial Inheritance
  - Triple Repeat Mutations
  - Fragile X Syndrome
  - Sherman's Paradox
- **Specific Cytogenic Disorders**
  - Down Syndrome
  - Screening
  - Turner Syndrome
  - Noonan Syndrome
  - Klinefelter Syndrome
  - Lyon's Hypothesis

25 INTRODUCTION TO GENETICS

- Genes → present on Chromosomes
- Allele → two different set of genes acquired (from 1 parent each)
- No of genes discovered: 20,000
- % of genes for coding proteins: 1.5%



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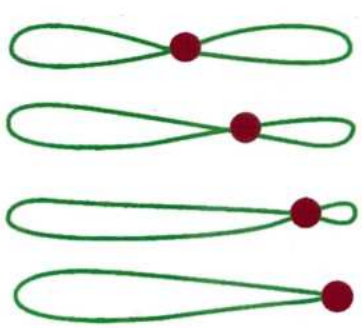
CHROMOSOMAL DISORDERS

00:02:34

- On number → Diploid/ Haploid/ Aneuploidy
  - Euploidy → multiples of 'n' (2n, 3n)
  - Aneuploidy → not exact multiple of 'n'
- Structural Defect

Subtype of chromosomes

- Based on Sex determination
  - Autosomes: chromosome 1 to 22
  - Sex Chromosomes: X/Y
- Based on centromere

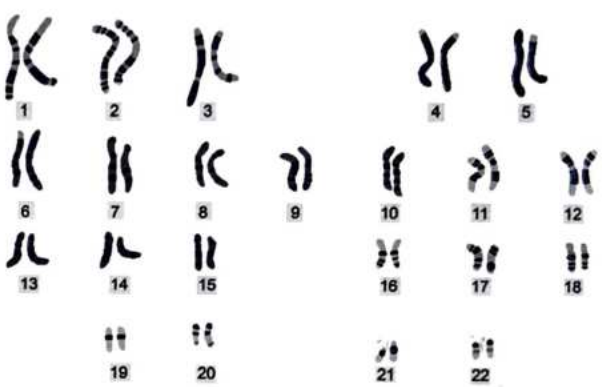


  - Metacentric: centromere present in the middle
  - Sub-metacentric: centromere present slightly on one side of middle (example: X chromosome)
  - Acro-Centric: centromere present towards one end (example: Y/13/ 14/15/ 21/22 chromosome)
  - Telocentric: centromere present right at the tip (not seen in humans)

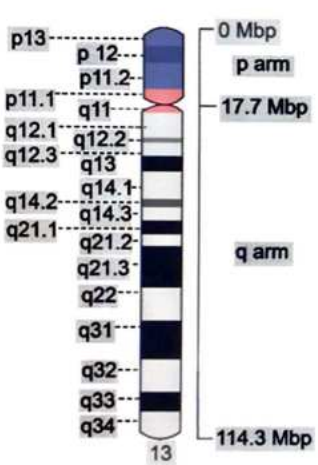
Karyotyping

00:08:27

- Study of Chromosomes (to detect problem of chromosomal number)
- Samples
  - Amniotic cells
  - Skin Fibroblasts
  - Epithelial cells of buccal mucosa
  - Peripheral blood lymphocytes



- Chemical: colchicine metaphasic arrest
- Autosomes are arranged depending on length in descending order
- Sex chromosome is not revealed



- Chromosome has short arm 'q' and long arm 'p'
- Example: 13q14.5
  - 13 → chromosome number
  - 1 → represents region
  - 4 → represents band
  - 5 → represents sub-band
- Carnoy's Fixative is used → Methanol: Glacial acetic acid (3:1)
- G banding → MC Banding pattern

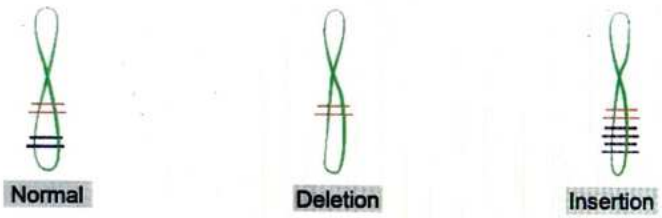
Important Information

- Light microscope → 5 mega base-pairs can be seen
- Metaphase arrest → 400-800 sets
- Prophase arrest → 1500 sets

STRUCTURAL DEFECTS

00:16:37

- Change in number of genes



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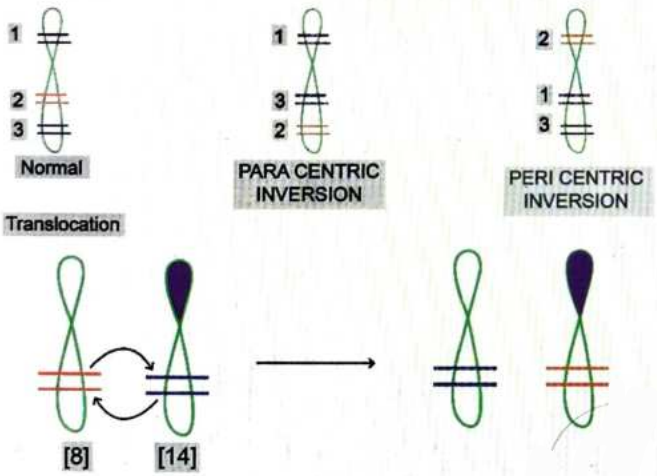
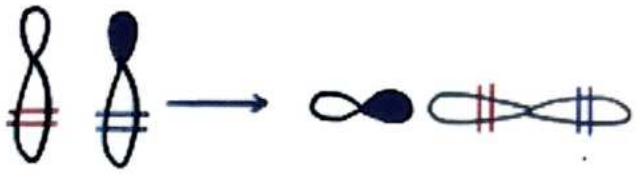
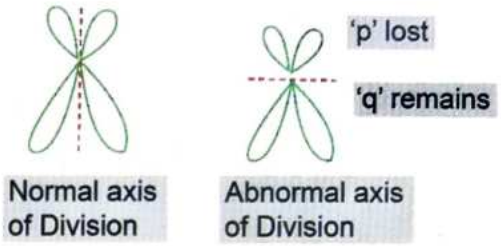
  - Change in position of genes: Inversion
  - Example: inversion (16) → AML-M4



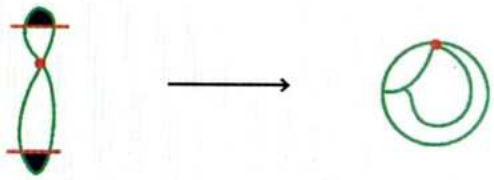
- Balanced Translocation
  - Equal amount of genetic material is exchanged
  - No loss of genetic material
  - t(8; 14) → Burkitt's Lymphoma



- Robertsonian Translocation
  - Acrocentric chromosome is affected
  - Change in genetic material is seen
  - Chromosome 14/21 → Down's syndrome
- Isochromosome



  - Due to abnormal axis of division
  - Same set of genes in one daughter cell
  - MC isochromosome seen in humans → xq
  - MC isochromosome associated with cancers 17q
  - MC ischromosome associated with testicular tumor → 12p
- Ring chromosome

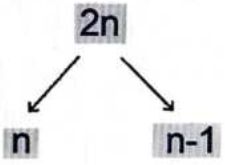


  - Defect at the edge of chromosome → loss of genetic material → 2 ends will fuse with each other
  - Example: Turner Syndrome → 46xy(x)

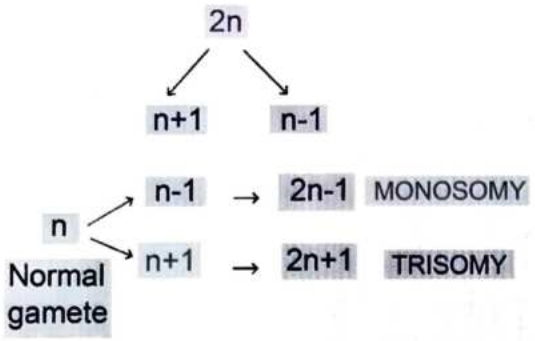
Aneuploidy

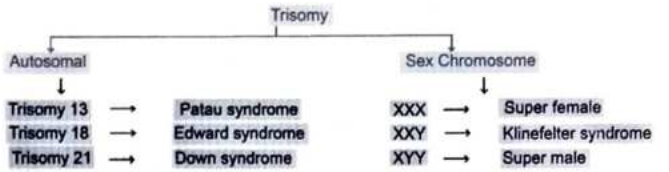
00:28:49

- Anaphase lag

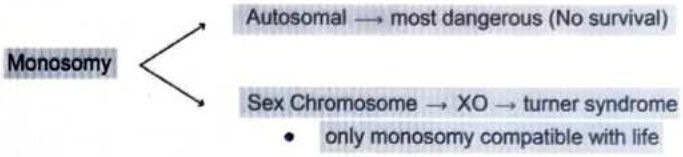


- Meiotic Non-Disjunction (unequal distribution of chromosome)





- MC Trisomy 16



26 SINGLE GENE DISORDERS

- Normal gene → 2 alleles

Hair Color	Homozygous Trait	Heterozygous Trait	
Genotype	AA ↓ A (Black)	aa ↓ A (Golden)	Aa ↓ A (Black)
Phenotype			

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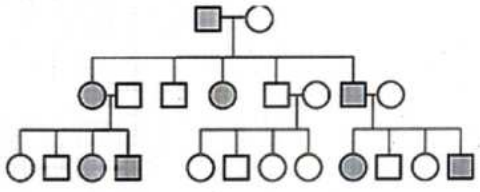
- Dominant Allele (A) → expressed even in heterozygous trait
- Recessive Allele (a) → expressed only in homozygous trait
- Co-Dominance → Both alleles are expressed
  - Example: Blood grouping, HLA / MHC genes

AUTOSOMAL DOMINANT DISORDERS

00:06:12

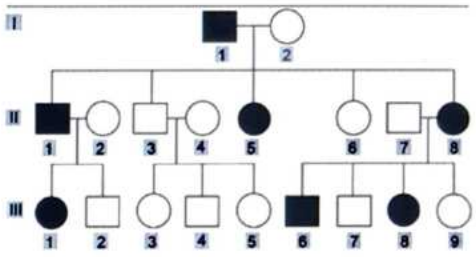
- Expressed even in heterozygous State
- 50% progeny affected
- Vertical inheritance (at least 1 parent affected)



- Female = male affected
- Structural proteins are affected
- Loss of Function mutation >> Gain of Function mutation
- Incomplete penetrance (Every individual with defective gene will not affected → one functional allele can be present)
- Variable expressivity → Different levels of severity
- Pleiotropy (> 1 system involved)
  - Example: Marfan syndrome

Previous Year's Questions

A 25yr old man presents for routine physical examination. The patient is 6ft 5inches tall and on examination he was found to have early diastolic murmur. His family pedigree is given below. Which of the following mode of inheritance by which disease is likely to be transmitted? (NEET 2020)



A. AD disorder
B. AR disorder
C. X-linked recessive disorder
D. X-linked dominant disorder

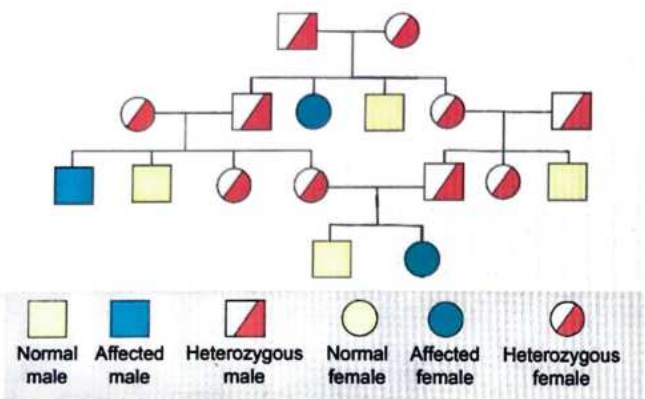
Conditions with AD inheritance 00:17:03

- VO → VWD; VHL Syndrome
- Familial → Familial adenomatus Polyposis
- Hyperchol → Familial Hypercholesterolemia
- Poora → Adult Polycystic kidney Disease
- D → Dystrophia myotonica
- → Osteogenesis imperfecta
- M → Marfan syndrome; MEN
- I → Intermittent porphyria
- N → Neurofibromatosis 1,2
- A → Achondroplasia
- N → Noonan syndrome (chromosome 12)
- T → Tuberous sclerosis
- Hota → Huntington disease
- Hai → Hereditary spherocytosis

AUTOSOMAL RECESSIVE DISORDERS

00:21:14

- Expressed only in homozygous state
- Female = male affected
- Horizontal inheritance (siblings are affected)



- Enzymatic proteins are affected
- Complete penetrance
- ↑ in consanguineous marriage
- Examples
  - Inborn Errors of metabolism
  - Friedrich's ataxia
  - Sickle cell anemia
  - Thalassemia
  - Wilson's disease
  - Hemochromatosis
  - Homocystinuria
  - Alkaptonuria

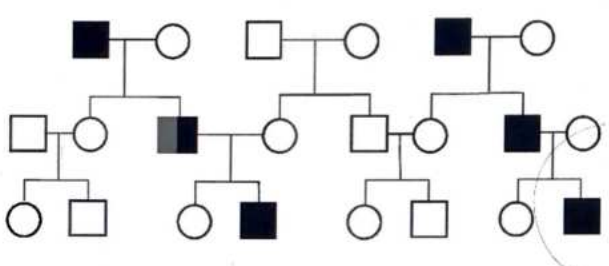
SEX LINKED INHERITANCE

00:27:07

- XLR → MC sex linked pattern of inheritance

Y Linked Disorders

- Aka Holandric inheritance
- Only male are affected
- Patient → Son transmission



- Hair on pinna/webbed toes
- Y chromosome → acrocentric chromosome → ↓ Fertility

Important Information

- X-linked disorders: Father to son transmission is 'zero'

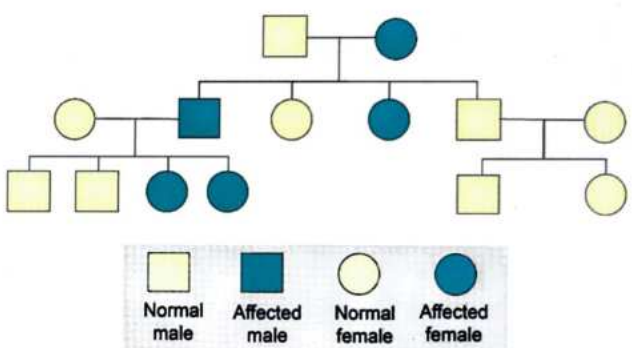
X Linked Recessive Disorders

- X linked genes → encodes enzyme genes
- Seen MC in males
- Females: xx^d → heterozygous (no disease manifestation)

- Examples
  - Less → Lesch - Nyhan Syndrome
  - H → Hemophilia A & B
  - C → CGD
  - G is → G6PD deficiency
  - Detected in → Duchene muscular dystrophy; DI
  - A → Agammaglobulinemia (Bruton Disease)
  - Fragile → Fragile X Syndrome
  - Women → Wiskott-Aldrich Syndrome

X-Linked Dominant Disorders

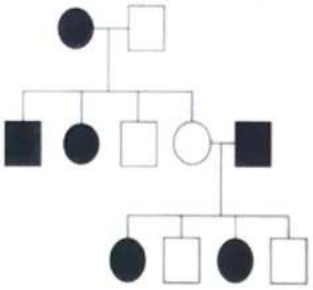
00:36:08



- Affects male → Transmission to Daughters
- Affected daughter Xxd → 50% Progeny
- Less common
- Examples
  - A → Alport syndrome
  - V → Vit D resistant Rickets
  - I, P } Incontinentia Pigmenti
  - Rett syndrome

Previous Year's Questions

Read the pedigree chart and identify the pattern of transmission. (JIPMER 2017)



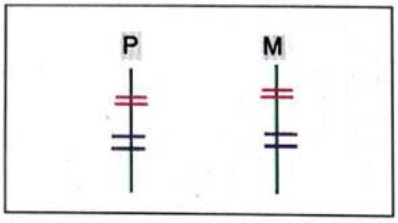
A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X-linked recessive

27 NON-CLASSICAL INHERITANCE DISORDERS

GENOMIC IMPRINTING

00:00:28

- Differential gene expression based on parent of origin
- Epigenetic regulation: gene silencing
  - DNA methylation
  - Histone deacetylation; methylation
- Inactivation is before fertilization



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Chromosome 15

- Normal
  - Maternal gene imprinted
  - Paternal gene is active (SNORP)

PRADER WILLI SYNDROME

Etiology

00:03:59

- Deletion of paternal chromosome (MC cause)
- Uniparental Disomy (maternal chromosome)
- ↓↓ SNORP (Small nucleolar RNA Proteins)

Clinical features

- Mental Retardation
- Obesity
- Hypotonia
- Hypogonadism

ANGELIMAN SYNDROME

- Normal
  - Paternal gene imprinted
  - Maternal gene is active (UBEZA)

Etiology

- Deletion of maternal chromosome (MC cause)
- Uniparental disomy (paternal chromosome)

Clinical features

- S → Seizures
- A → Ataxia
- R → Retardation (Mental)
- I → Inappropriate laughter

} Happy Puppets

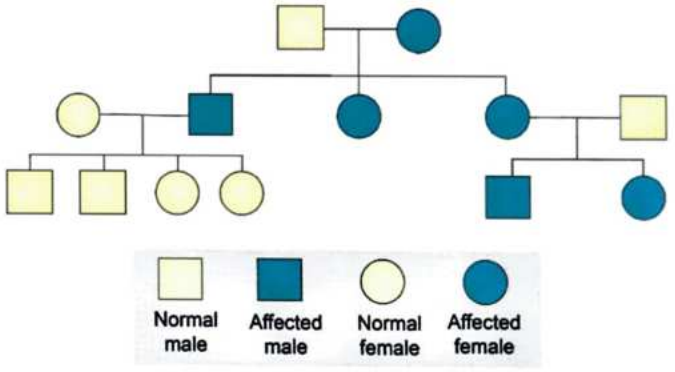
Genomic Imprinting

- Genomic Imprinting can be checked → methylation status of marker gene & FISH
- Genomic Imprinting also seen in
  - McCune Albright Dystrophy
  - Beckwith-Wiedemann syndrome
  - Huntington's disease
  - Myotonic dystrophy
  - Tumorigenesis

MITOCHONDRIAL INHERITANCE

00:12:29

- Aka maternal inheritance
- Mitochondrial DNA is present in ovum & not in sperms



- Heteroplasmy: normal and defective mtDNA in a single cell
- Involvement of cardiac muscle/skeletal muscle/kidney/CNS/Liver is seen
- Governed by Law of population genetics
- Examples
  - MELAS → Mitochondrial Encephalopathy, Lactic Acidosis, Stroke
  - Leigh's Disease
  - NARP SYNDROME → Neuropathy, Ataxia, Retinitis Pigmentosa
  - Leber's Optic Neuropathy

GERMLINE MOSAICISM

- AD
  - 1 Affected parent → Normal
  - No parent Affected → Rare

Person
↓
Normal
↓
Post zygotic mutation affecting gonadal cells
↓
Progeny affected

- Examples: osteogenesis imperfecta, Tuberous Sclerosis

TRIPLE REPEAT MUTATIONS

00:19:47

- Presence of Long nucleotide repeats (cytosine/guanosine)
- Seen in Neuro degenerative disease
- Dynamic in nature
- Amplification of nucleotide repeats at the time of gametogenesis with next generation
- Next generation can have disease presentation earlier anticipation

Amplification
↓
Pre-mutation
↓
Mutation

- Coding regions → Huntington's/Kennedy's disease/SCA 1,2,3,6,7/Haw River syndrome
  - All have CAG repeats
  - SCA 3: Machado Joseph disease
  - SCA 6: Voltage gated calcium channel is affected
- Non-coding regions
  - Fragile X syndrome: CGG repeats
  - Myotonic dystrophy: CTG repeats
  - Friedrich's ataxia: GAA repeats

FRAGILE X SYNDROME

00:27:48

- Problem at Xq
- FMR-1 gene loss of function mutation
- 2nd MC cause of Mental retardation
- Manifestations → 'X' large
  - Large Face
  - Large mandible
  - Large Testicular tissue (Macro-orchidism)
  - Large everted ears
- High arched palate/MVP/Hyper-extensible joints can also be seen
- CGG Repeats → oogenesis
  ♂ (6-55) → next generation (55-200) → Grandson (200-400)
- Can be detected by PCR test

Previous Year's Questions

All are seen in fragile X syndrome except.

(JIPMER 2018)

A. Testicular enlargement
B. Mental retardation
C. Trinucleotide repeats
D. Genomic imprinting

Sherman's Paradox

- Chances of developing MR far more in grandson by Anticipation
- Nucleotide repeats → Pre-mutation → Mutation

Important Information

- **Permutation of Fragile X syndrome in**
  - **Female → primary ovarian failure**
  - **Male → tremor/ataxia/ ↑ risk of parkinsonism**

28 SPECIFIC CYTOGENETIC DISORDERS

DOWN SYDROME

- Trisomy 21
- MC chromosomal disorder
- MC inheritable cause of mental retardation

Genetic Basis

- Meiotic Non-Disjunction
  - MC cause (95%)
  - Associated with ↑ maternal age
  - Occurs at Meiosis I
    - → Except for Trisomy 18 (affects Meiosis II)
  - Extra chromosome → maternal origin
- Robertsonian Translocation
  - Affects chromosome 14/21
  - No association with maternal age
  - It is a familial condition
- Mosaicism
  - Aka mitotic non-disjunction
  - Least common cause
  - Unequal distribution of chromosome during mitosis
  - No association with maternal age

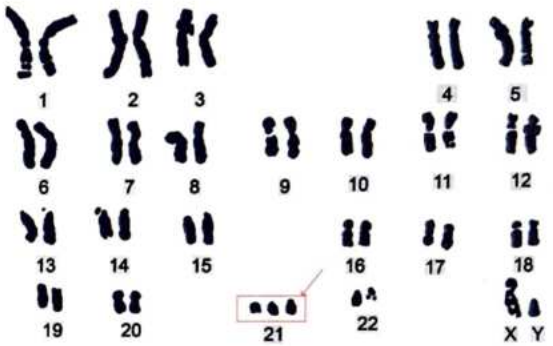
Clinical features

- C → congenital cardiac defect (AV septal defect)
- H → Hypotonia
- I → Increased gap between great toe & second toe (sandle toe)
- L → Leukemia (ALL; AML-M7)
- D → duodenal atresia
- H → Hirschsprung disease
- A → Alzheimer's disease
- S → Simian crease (Single palmar crease)
- P → Protruding Tongue
- R → Rolling of eyes
- O → Occiput (flat)
- B → Brushfield Spots
- L → Low nasal bridge
- E → Epicanthal Folds
- M → Mongolian slant

Screening

00:13:25

- Sporadic Down syndrome → meiotic non-disjunction
  - Chances of having 2nd baby in down syndrome are much lower
- Familial Down syndrome → Robertsonian translocation
  - Chances of having 2nd baby and down syndrome are much higher
  - t(14;21), t(21;22), t(21;21) → 100% chance of recurrence
- Radiological exam → ↑ Nuchal thickness
- Triple test
  - AFP ↓
  - HCG ↑
  - Estriol ↓
- Quad test → triple test + Inhibin α ↑↑
- Invasive
  - CVS → done at 9-11 weeks
  - Amniocentesis → done at 14-16 weeks
- Non-invasive
  - Next generation sequencing of chromosome 21 linked genes in total cell free fetal DNA in maternal blood



Previous Year's Questions

Which of the following is not a part of quadruple test?
(AIIMS 2018)

A. AFP
B. Estradiol
C. βHCG
D. Inhibin B

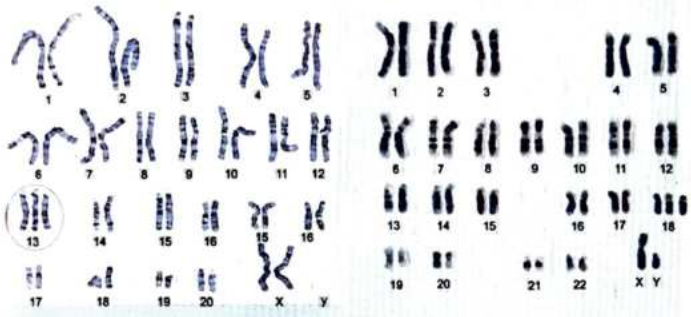
FEATURES OF OTHER TRISOMIES (13/18)

00:22:00

Common manifestations

- congenital cardiac defects
- Renal defects
- Mental Retardation
- Rocker Bottom Feet (Convexity towards ground)

Patau Syndrome	Edward Syndrome
• Polydactyly • Palate defects • Eye defects • Microcephaly	• Extra Prominent occiput • Micrognathia (small chin) • overlapping fingers



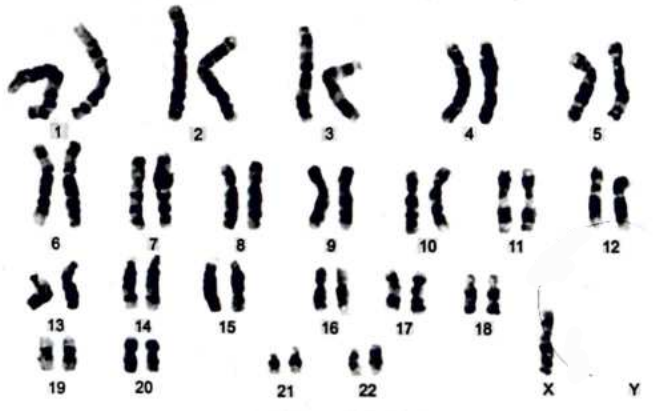
TURNER SYNDROME

00:26:15

- Loss of 'X' chromosome
  - 45XO (classical)
  - Mosaicism (46XX/45XO)
  - Ring chromosome → 46Xr(X)/46Xi(X)

Clinical features

- MC cause of primary amenorrhea
- C → Cardiac defects (Bicuspid aortic valve, coarctation of aorta, Aortic dissection)
- L → Lymphedema
- O → Ovaries (streak), ↓ fertility, ↑ cancer risk
- W → Webbed neck
- N → Nipples (widely spaced/shield chest)
- S → Short stature (SHOX gene defect), short 4th metacarpal
- ↑ Risk of metabolic syndrome



'0' Barr Body

Noonan syndrome

- Female = male
- AD inheritance
- Chromosome 12 defect → PTPN11 gene
- Presence of learning disability
- Normal karyotype
- Cardiac defects can be present

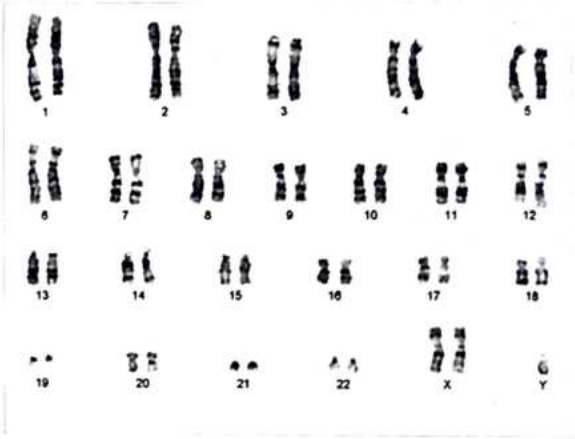
KLINEFELTER SYNDROME

00:39:19

- Male Phenotype → 47 XXY
- MC genetic cause of infertility

Clinical feature

- Tall stature
- ↓ IQ
- Hypotonia
- 1' Barr body
- Feminine features
  - Gynecomastia
  - Testicular atrophy (↓ Testosterone, ↑ FSH/LH)



- ↑ Auto immune disorders (SLE)
- ↑ Cancers (Testicular tumors, ductal breast carcinoma)
- ↑ Congenital cardiac defects (MVP)

Defective Gametogenesis

- ↑ Maternal age
  - Down syndrome
- ↑ Paternal age
  - Marfan syndrome
  - Osteogenesis imperfecta
  - NeuroFibromatosis
  - Achondroplasia

- 22q11 deletion → DiGeorge syndrome
  - Thymus/parathyroid gland dysfunction
  - Abnormal facies
  - Congenital cardiac defect

- ↑ risk of schizophrenia/bipolar disorder
- 5p deletion → Crides chat syndrome
  - Strange cry
  - Development abnormalities
  - Eyes → coloboma

Lyon's Hypothesis 00:50:18

- Only '1' x chromosome → active
- 2nd Inactivation (Xist gene → DNA methylation)
- Barr Body
  - Perinuclear structure → interphase
  - No of Barr Bodies

Normal Male	XY	0
Normal Female	XX	1
Turner Syndrome	XO	0
Klinefelter Syndrome	XXY	1
Super Female	XXX	2

Previous Year's Questions

Which of the following is a manifestation of 22q11 mutation syndrome? (AIIMS 2018)

A. Hypercalcemia
B. Conotruncal abnormalities
C. Thymic hyperplasia
D. Dysmorphogenesis of 1st & 2nd pharyngeal pouches

CLINICAL QUESTIONS

1. A 2-month-old female child brought with complaints of being pale and not accepting feeds. Parents gave history of blood transfusion at birth. Her hemoglobin level was 3.2gm/dl and the reticulocyte count (0.2%). Bone marrow study showed reduction in red cell precursors. Genetic screening revealed mutation in ribosomal protein S19 (RPS19) gene in both child and father. What is the likely diagnosis?

A. Schwachman diamond syndrome
B. Diamond blackfan anaemia
C. Dyskeratosis congenita
D. Congenital amegakaryocytic thrombocytopenia

Solution

- Diamond blackfan anemia
  - Autosomal dominant condition
  - Congenital abnormalities,
  - Severe macrocytic anemia,
  - Reticulocytopenia
  - Selective depletion of erythroid precursors in the bone marrow.
- Schwachman diamond syndrome
  - Autosomal recessive
  - Biallelic mutation in SBDS gene.
  - Bone marrow failure,
  - Exocrine pancreatic insufficiency
  - ↑ risk of myelodysplasia and leukemia
- Dyskeratosis congenita
  - Inherited bone marrow failure syndrome
  - Triad- skin pigmentation, nail dystrophy, and mucosal leukoplakia.
  - X linked and autosomal condition.
  - Bone marrow aplasia
  - Pulmonary fibrosis
  - Liver disease
  - Neurologic and eye abnormalities
  - Increased predisposition to cancer
- Congenital amegakaryocytic thrombocytopenia
  - Autosomal recessive condition
  - Mutation in thrombopoietin (TPO) receptor c-mpl.
  - Aplastic anemia by 5 yrs of age.

Reference

https://rarediseases.info.nih.gov/diseases/640/congenital-amegakaryocytic-thrombocytopenia

LEARNING OBJECTIVES

Unit 6 HEMATOLOGY: Red Blood Cells

- **Hematopoiesis Basic Concepts**
  - Hematopoietic Stem Cell
  - Haematopoiesis / Erythropoiesis
- **RBC Development & Classification of Anemias**
  - Stages of RBC development
  - Normoblast
  - Erythropoietin
  - Reticulocyte
  - RBC's
  - Microcytic Anemia
  - Macrocytic Anemia
- **Microcystic Anemia Part 1**
  - Iron Deficiency Anemia
  - Causes of Iron Deficiency
  - Stages of Iron Deficiency
- **Microcystic Anemia Part 2**
  - Anemia of Chronic Disease
  - Sideroblastic Anemia
  - Iron Profile
- **G6PD Deficiency & Hereditary Spherocytosis**
  - Hereditary Spherocytosis
  - Normal physiology of RBC
  - Diagnosis
  - G6PD Deficiency
  - Genetics
  - Advantages of G6PD Deficiency
- **Hemolytic Anemia: Basic Concepts**
  - Clinical features
  - RBC Destruction
  - Types of Haemolytic anaemia
  - Causes of hemolytic Anemia
- **Hemoglobinopathies - Sickle Cell, Alpha & Beta Thalassemia**
  - Sickle cell anaemia; features, diagnosis and treatment
  - Thalassemia: types, mutation, classification of mutation, screening test, diagnosis and treatment
- **Megaloblastic Anemia**
  - Vitamin B12 Deficiency
  - Blood / BM Findings
  - CNS changes
  - Pernicious Anemia
  - Folate Deficiency
  - Metabolism of B12
- **Autoimmune Hemolytic Anemia**

- Immune Mediated Hemolytic Anemia
- Warm AIHA
- Cold AIHA
- Associations of cold agglutinin disease (IgM)
- Cold Hemolysin Type

- Miscellaneous Disorders
  - Aplastic Anemia: Causes, Clinical features, Diagnosis, Treatment, Classification of Aplastic Anemia
- Paroxysmal Nocturnal Hemoglobinuria
  - PNH
  - Flaer-Flow Cytometry
  - Disorders Related with PNH

29 BASIC CONCEPTS OF HEMATOPOTESIS

- **HEMATOPOIETIC STEM CELL [HSC]** 00:00:13
  - Identified by a molecular marker CD34
  - Pluripotent cell L can give rise to multiple types of cells]
  - Hematopoiesis starts at the Time of fetal life
    - → At 3 weeks HSC is present in Yolk sac and Mesoderm
      - Mesoderm of Aorta, Gonads, mesonephros
    - → At 3 months HSC is present in Liver spleen and Lymph nodes
    - → At Birth HSC is present in bone marrow of All the Bones
    - → At puberty: bone marrow of Axial skeleton and ends of long bones

Hematopoiesis / Erythropoiesis 00:02:55

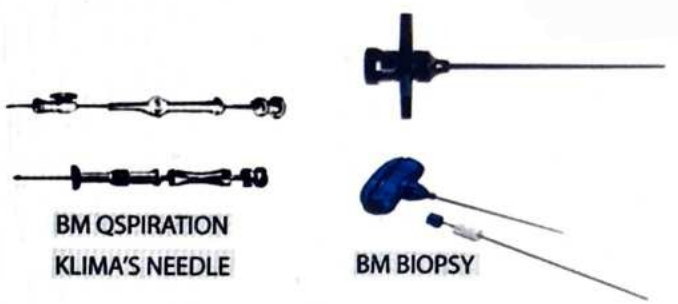
HSC
↓
MSC

Myeloid SC / Trilineage SC	Lymphoid SC
• 20 µ in size • 3-4 nucleoli • Granular cytoplasm	• 20 µ in size • 0-2 nucleoli • Condensed nucleus • Non granular cytoplasm

Refer Flow Chart 29.1

RBC	→ Erythropoietin [EPO]	←	DARBOPOIETIN
Platelets	→ IL 11	←	OPRELVEK IN
GM- CFU	→ GM - CSF	←	SARGRAMOSTIM
G- CFU	→ G - CSF	←	FILGRASTIM

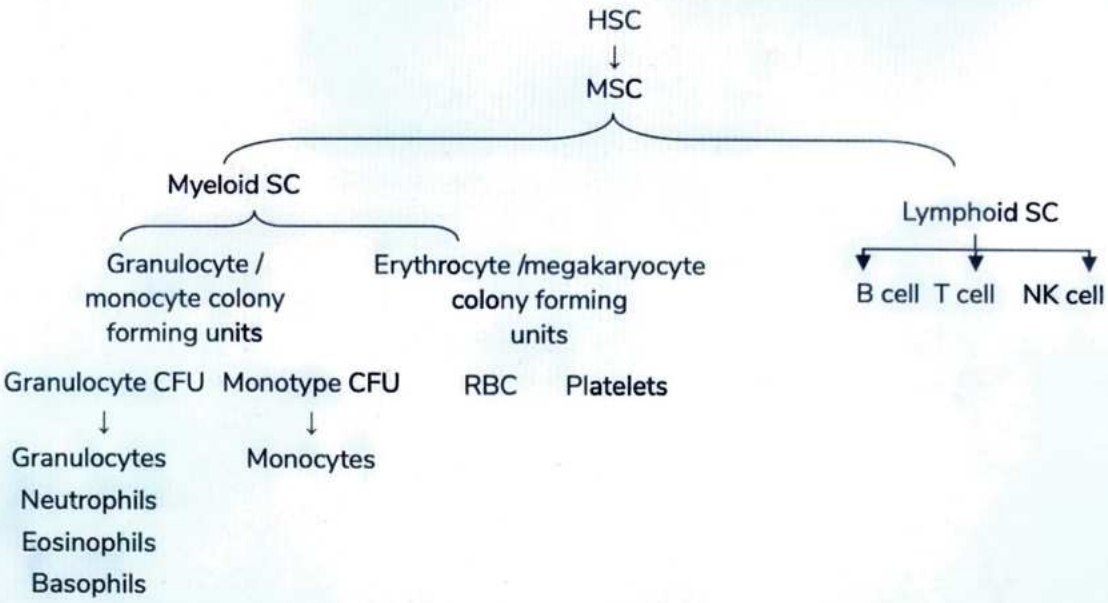
BM Examination 00:06:35



1. Bm Aspiration: Cell morphology, Enumeration
- Needles used
  - KLIMA/SAL H'S NEEDLE
  - SALAH'S NEEDLE
- Size of needle: 14 to 18 gauge
- Volume of sample: 0.2 to 2 ml
- Anticoagulant used: EDTA
  - EDTA prevent the clotting of blood and does not alter the morphology

2. Bm Biopsy: For cellularity, Fibrosis, infiltrative disorders affecting the BM
- Needles used
  - TREPHINE NEEDLE
  - JAMSHEDI'S NEEDLE
- Ideal Site of BM BIOPSY
  - Adults: posterior superior iliac spine [PSIS] except in obese people [ASIS]
  - Child: Anterior end [Tibia]
  - M/c S/E: Local site soreness
- BM examination can be carried out in Individuals having a reduced Platelet count or mild clotting factor deficiency
- Pancytopenia Seen in
  - Aplastic Anemia
  - D/t damage to HSC
- Myeloproliferative Disorders: ↑RBC /Platelets / WBC

Flow Chart 29.1



30 RBC DEVELOPMENT & CLASSIFICATION OF ANEMMIA

DEVELOPMENT

Stages of RBC development

00:00:24

Myeloid Stem Cell
↓
CFU-E
↓
Erythroblast
↓
Normoblast
↓
Reticulocyte
↓
RBC

- From top to bottom there is
  - ↑ Differentiation
  - ↓ Size
  - ↓ Size Of Nucleus
  - ↑ Hb Concentration

- Hb detected firstly in Erythroblast [only by e-microscope]

Normoblast

- Early: has a bluish cytoplasm so K/a Basophilic Normoblast
- Intermediate: Aka Polychromatophilic Normoblast, Hb can be detected by routine staining
- Late: Aka Ortho chromatophilic Normoblast

Erythropoietin

- Required for the normal development of RBC
- Predominant source: Kidney (peritubular capillary cells) > Liver
- Half-life: 6 to 9 hrs
- Maximum receptors of erythropoietin is present on: CFU-E

Erythroferrone

- Secreted by normoblast
- Increase absorption of iron in the body by reduction in concentration of Hepcidin

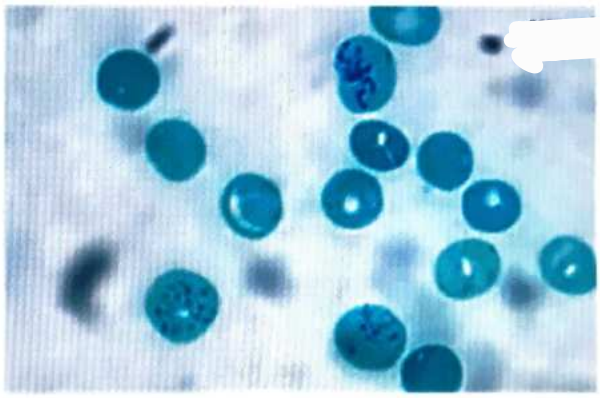
RETICULOCYTE

00:06:36

- First Non - Nucleated Cell in the RBC development
- Detection Requires Supra Vital Staining [detected Only in Living State]
  - New Methylene blue
    → Preferred/ best stain
    → Mesh like appearance
  - Brilliant cresyl blue
- Normal: 1- 2%
- Time for maturation: 1 day
- Absolute retic count: no of reticulocyte in $1mm^3$ blood
- Corrected Reticulocyte Count:

$$\frac{\text{Reticulocyte count} \times \text{Hb [patient]}}{\text{Hb [normal]}}$$

  - Used to estimate compensatory increase of reticulocytes in certain conditions
- In very severe anemia reticulocyte production index must be calculated
- Retic production index: $\frac{\text{CRC}}{\text{Maturation time correction (2)}}$



Previous Year's Questions

Q. Formula for calculating reticulocyte production index? (JIPMER May 2019)
A. Retic X patient hematocrit 4/5
B. Corrected reticulocyte count
C. Reticulocyte percentage X RBC count
D. Reticulocyte counted X100/no. of red cells

HCT value	Correction factor
45	1
35	1.5
25	2.0
15	2.5

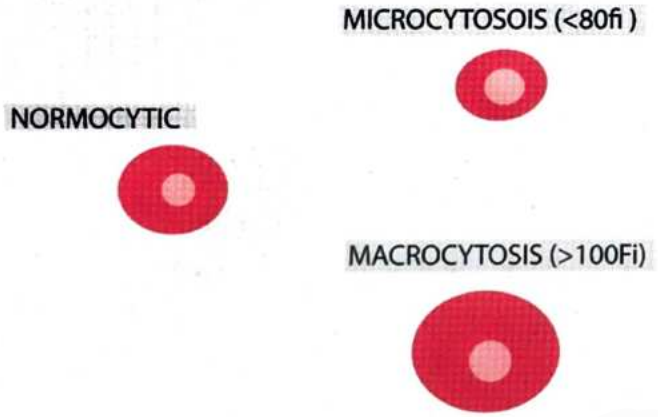
- Reticulocyte count Estimation gives Bm Activity aka 'Poor Man's Bm Aspiration'
- RPI <2.5 indicates: Decreased proliferation/ Decreased Maturation
- RPI > 2.5 indicates: hemolytic anemia
- Increased Reticulocyte count
  - Hemolytic anemia
  - Fe/FA/ B12 Supplementation
- Decreased Reticulocyte count
  - Aplastic anemia
  - Deficiency of Iron /FA/B12
  - Leukemias / Metastasis
  - Myelofibrosis

RBC's

00:21:16

- Normal size: 7-8 µ
- Bi concave Shape
- More Hb at periphery than center
- Shape & Flexibility maintained by
  - Spectrin: most imp
  - Band
  - Ankyrin

Parameters	
• MCH	27-33 Pg
• MCV	80-100 FL
• MCHC	$\frac{MCH}{MCV}$



- $MCV = \frac{Hematocrit \times 10}{RBC\ count}$
- Hereditary spherocytosis: MCHC value is Higher
- Poikilocytosis: Change is shape of RBC's
- Anisocytosis: Change is size of RBCs
- Parameter to check for Anisocytosis: RDW
  - RDW: range in which the volumes of RBCs are present
  - Normal RDW = 11.5 – 14.5
  - When anisocytosis increase RDW also Increase
- B12 deficiency / megaloblastic Anemia: MCHC → Ⓝ

ANEMIA – CLASSIFICATION

00:28:29

1. Size of RBC

a. Microcytic Anemia
- **S** - Sideroblastic Anemia
- **I** - Iron deficiency Anemia
- **T** - Thalassemia
- **A** - Anemia of chronic disease
- **L** - Lead poisoning
- Copper deficiency

b. Macrocytic Anemia (> 100Fl)
- **L** - Liver disease
- **H** - Hypothyroidism
- **M** - Myelodysplastic Syndrome
- **C** - Cell maturation disorder
  - B12 deficiency
  - FA deficiency
  - Alcohol
- Fanconi's Anemia

c. Normocytic Anemia
- Kidney disease
- Anemia of chronic disease: early stages
- Myelofibrosis
- Metastasis

31 MICROCYTIC ANEMIA PART-1

IRON DEFICIENCY ANEMIA

- MCC of microcytic anemia

Iron Metabolism

Refer Image 31.1

- % Transferrin saturation= 33%
- Serum iron = 100-120microgram/dl
- TIBC = 300 – 360 microgram/dl
- Stain for hemosiderin = Prussian Blue
- Absorption: chief site is duodenum
- Pure Vegetarians Have Higher Chances of Iron Deficiency

Causes of Iron Deficiency 00:10:13

- ↓ Intake
- ↓ Absorption: Malabsorption, diarrhea
- ↑ Requirement
  - Growing Children
  - Reproductive Age Group
  - Pregnancy
  - Lactation
  - Blood loss
  - Accidents / trauma
  - Hook worm infection
  - Peptic ulcer disease
  - Colon cancer

Previous Year's Questions

Q. Which of the following interfere with iron absorption? (FMGE June 2019)

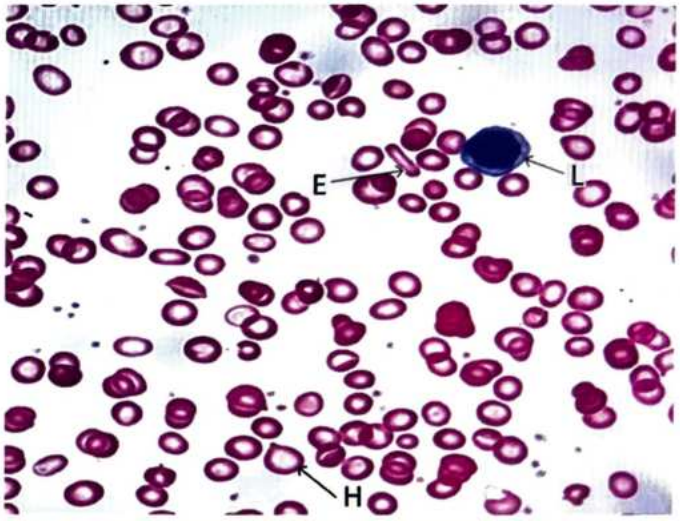
A. Vitamin C
B. Phytates
C. Oxalate
D. Myoglobin

Stages of Iron Deficiency

1. ↓ Negative Iron Balance
- ↓ BM IRON
- ↓ Serum Ferritin

2. Iron profile
- S. Ferritin: ↓
- Serum Iron: ↓↓
- % TF Saturation: ↓
- TIBC: ↑

3. Iron Deficiency Anemia
- RBCs Affected
  - Microcytic Hypochromic Anemia
  - Anisocytosis
  - Poikilocytosis: Pencil cell, Target cells



Previous Year's Questions

Q. Which of the following findings are there in iron deficiency anemia? (AIIMS Nov 2019)

A. ↑ TIBC, ↓ Ferritin, ↓ Transferrin saturation
B. ↑ TIBC, ↑ Ferritin, ↓ Transferrin saturation
C. ↓ TIBC, ↓ Ferritin, ↓ Transferrin saturation
D. ↓ TIBC, ↓ Ferritin, ↑ Transferrin saturation

Clinical Features

- Fatigue: Stunted growth
- Koilonychia

Diagnosis 00:16:20

1. BM Examination
- Gold Standard

- ↓↓ Staining in Prussian blue

2. Blood
- ↓ Hb
- ↓ MCH / MCV / MCHC
- RDW - ↑↑

3. Iron Profile
- S. Ferritin: ↓
- S. Iron: ↓
- % TF Saturation: ↓
- TIBC: ↑

4. Free Erythrocyte Protoporphyrin [FEP]→↑↑↑

5. MENTZER INDEX= $\frac{\text{MCV}}{\text{RBC COUNT}}$

- 13 – IDA
- < 13 - Thalassemia trait
- Distinguishes b/w microcytic anemias [IDA vs Thalassemia Trait]
- D/D of microcytic Hypochromic Anaemia
  - **S** - **S**ideroblastic Anaemia
  - **I** - **I**DA
  - **T** - **T**halassemia trait
  - **A** - **A**naemia of chronic disease

How to remember

- SITA

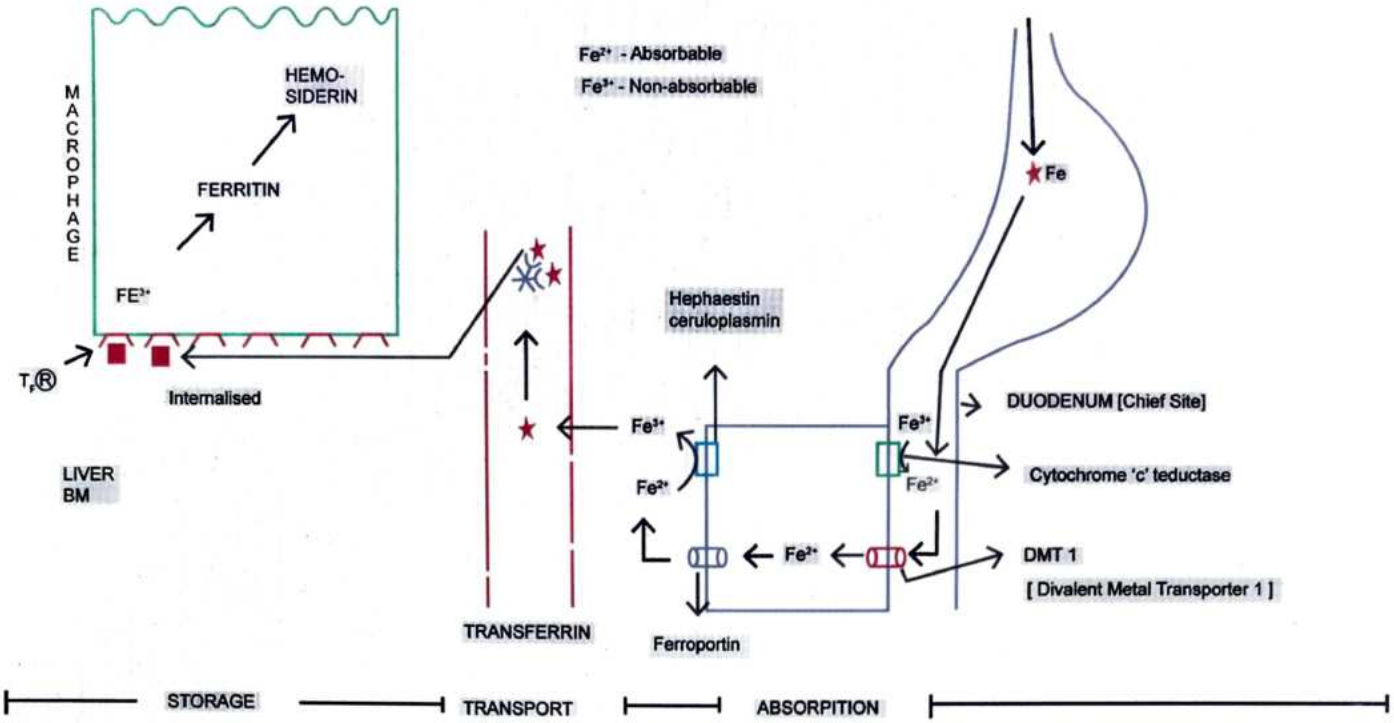
6. $\frac{\text{S. Tf receptor}}{\text{Log (feritin)}}$

- Value is > 1.5 in IDA
- Value is < 1.5 In Anemia of chronic disease

Treatment

- Treat 1° cause
- Iron supplementation - oral / parental
  - Improvements can be seen in clinical symptoms as early as 3 to 4 days of initiation of iron supplementation
  - Iron supplementation is associated with Brisk erythropoiesis

Image 31.1


MACROPHAGE
HEMO-SIDERIN
FERRITIN
FE³⁺
T_F®
Internalised
LIVER BM
Fe²⁺ - Absorbable
Fe³⁺ - Non-absorbable
Hephaestin ceruloplasmin
Fe³⁺
Fe²⁺
TRANSFERRIN
Ferroportin
Fe
DUODENUM [Chief Site]
Cytochrome 'c' teductase
DMT 1
[Divalent Metal Transporter 1]
STORAGE
TRANSPORT
ABSORPTION

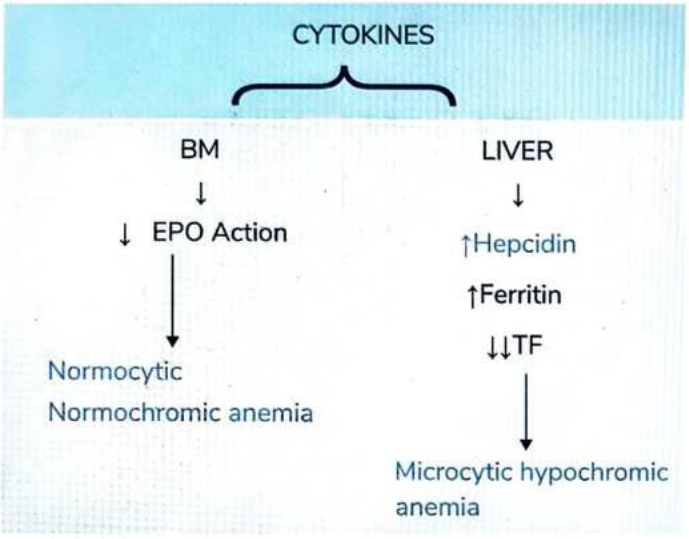
32 MICROCYTIC ANEMIA PART-2

ANEMIA OF CHRONIC DISEASE

00:00:18

Risk factors

- Chronic Infection - TB
- CHRONIC INFLAMMATION - RA } IL-6/IL 1/TNF-α
- Cancer



- Normocytic Normochromic anemia > Microcytic hypochromic anemia
- HEPCIDIN → inhibits Iron metabolism

Previous Year's Questions

Q. Which types of anemia is seen in patients of rheumatoid arthritis? (FMGE Dec 2017)

A. Normocytic and Hypochromic anemia
B. Microcytic and Hypochromic anemia
C. Normocytic and normochromic anemia
D. Macrocytic anemia

Diagnosis

00:07:09

1. Iron profile

	AOCD	DA
• S Ferritin	↑↑	↓↓
• % T_F Saturation	↓↓	↓↓
• S. Iron	↓↓	↓↓
• TIBC	↓↓	↑↑

2. $\frac{S.T_FR}{Log\ [Ferritin]}$

- <1.5: AOCD
- >1.5: IDA

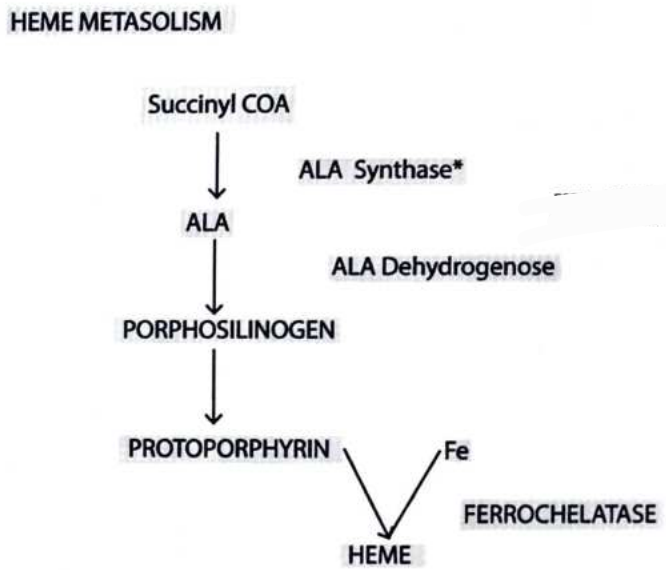
Treatment

- Does not response to Iron supplementation
- Treat 1 cause
- In cancer patients – Erythropoietin

SIDEROBLASTIC ANAEMIA

00:12:16

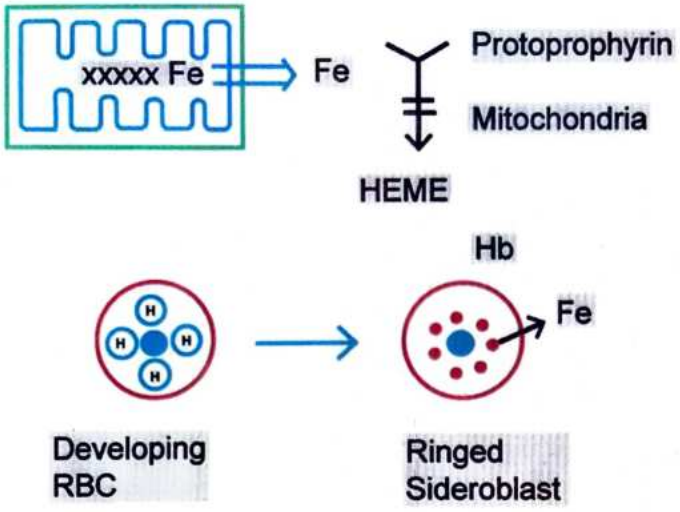
Heme Metabolism



Causes

1. Congenital: Enzyme defects
2. Acquired [more common]

- B_6 deficiency
  - Primary
  - Isoniazid / dietary
- Alcohol: M/c
- Lead poisoning: Damages ALAD &Ferrochelatase
- Copper deficiency



- Fe → damage to RBC Precursor→ Leakage of Iron → Iron Overload
- On BM examination Ringed sideroblasts can be seen
- Ringed sideroblast are seen in
  - Sideroblastic anemia
  - Myelodysplastic syndrome
  - Thalassemia
  - Megaloblastic anemia (B_{12}/ Folic acid deficiency)
  - Hemolytic anemias

Iron Profile

00:22:04

- S. ferritin: ↑↑
- S. iron: ↑↑
- % TF saturation: ↑↑
- TIBC: ↓↓

Summery Table of Microcytic Hypochromic Anemia

	IDA	ADCD	SID.AN.	THAL.TRAIT
S. FERRETIN	↓	↑	↑	N
S. IRON	↓	↓	↑	N
% TF SATURATION	↓	↓	↑	N
TIBC	↑↑	↓	↓↓	N

33 HEREDITARY SPHEROCYTOSIS AND G6PD DEFICIENCY

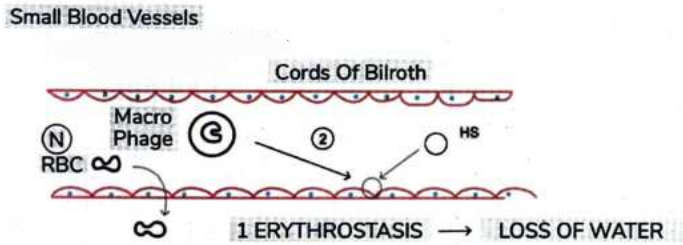
HEREDITARY SPHEROCYTOSIS

00:00:23

- Autosomal dominant

Normal Physiology of the RBC

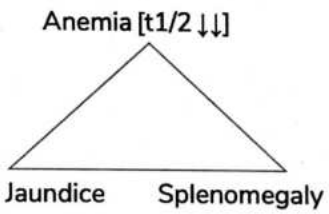
- Shape is Biconcave
- Biconcavity is due to membrane proteins
  - Spectrin: Most important membrane protein contributing to shape of the RBC
  - Ankyrin
  - Band 3
  - Band 4.1
  - Glycophorin: most abundant
- Size: 7 to 8 microns
- Normal lifespan: 100 – 120 days
- Most important membrane proteins that is affected in HS: Ankyrin > Band 3 >Spectrin
- As RBC change spherical, it can't pass through splenic Cords of Bilroth as they lose their flexibility, this leads to
  - Destruction of RBC by splenic macrophages: Extravascular Hemolytic anemia
  - Erythrostasis



Clinical Features

00:06:34

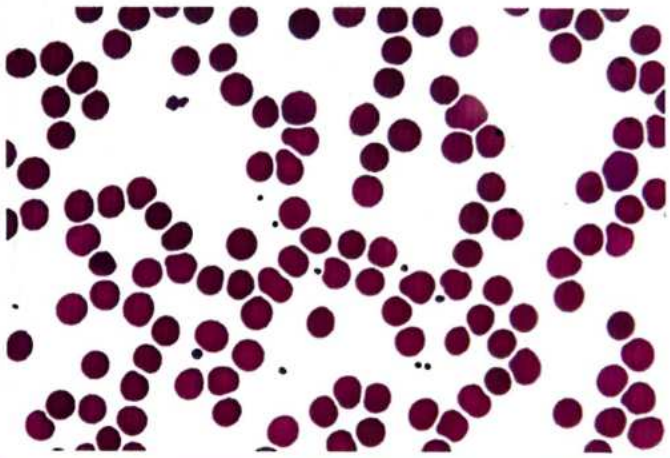
- Extravascular hemolytic anemia
- Splenomegaly
- Jaundice



Diagnosis

00:07:43

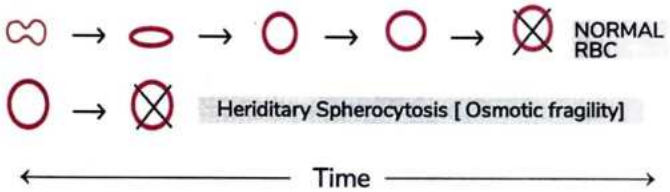
1. BM Examination → ↑ Cells / ↑ reticulocytes
2. Blood
   - ↓ Hb / ↑ LDH / ↓ S. Haptoglobin
   - MCH → (N)
   - MCV → ↓
   - MCHC → ↑↑↑ $\left[\frac{MCH}{MCV}\right]$
   - P/SMEAR Shows Spherocytes [no central pallor]



Important Information

- Conditions where spherical RBCs can be seen are
  - Autoimmune Hemolytic anemia: Most important cause
  - Hereditary spherocytosis
  - G6PD deficiency
  - ABO incompatibility

3. Osmotic Fragility Test/ Pink test [RBC in hypotonic solution]



4. AUTOHEMOLYSER [0.9% Nacl [Kept RBC for 48 hrs]]
- Normal: < 4% RBC destruction
- HS: > 15% RBC destruction

5. Osmotic Gradient Ektacytometry
- Can detect the shearing stress of RBC
- Can be done infants also
- Best, most specific

6. Flow cytometry
- Dye → 5'EMA (Eosin's Maleimide Dye) is used

Previous Year's Questions

Q. Eosin-5-maleamide flow cytometry is used for diagnosis of (JIPMER May 2018)
A. G6PD
B. Hereditary spherocytosis
C. Sickle cell anemia
D. Alpha thalassemia

Treatment 00:19:12

1. ELECTIVE SPLENECTOMY
- Increases the risk of infection caused by capsulated organism
- Severity of anemia ↓
- Shape of RBCs will not change

Complications 00:21:00

- Aplastic Crisis: ↑ BMA →↑ Erythroid Precursors → Susceptible to Parvo Virus
- ↑ INFECTIONS [post Splenectomy]
- HS → Chromic Hemolysis → Pigment gallstones

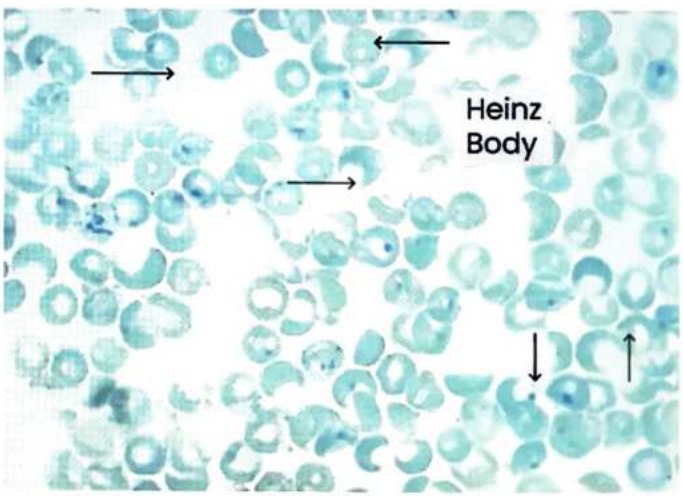
G6PD DEFICIENCY 00:21:57

- M/c metabolic disorder in the RBC contributing to Hemolytic anemia
- G6PD → ↑NADPH → ↑gSH
  H_2O_2
  H_2O
  Gssg
- Decreased G6PD leads to Increased Susceptibility for being damaged by Oxidative stress → Denaturation of Hb Chains → gets precipitated inside the RBC (Heinz Body)
- Findings: Bite Cell/ Degmacyte, Spherocyte, Blister Cell, Heinz bodies

HEINZ BODY

Direct Damage to RBC membrane ↓ I/V Hemolysis	↓Flexibility of RBC ↓ in Splenic circulation ↓ E/V HEMOLYSIS

- Stain for Heinz Bodies: Supravital stain
  - M/c supravital stain used: Crystal violet



Previous Year's Questions

Q. Blister cells are seen in? (JIPMER Nov 2017)
A. Thalassemia
B. Chronic liver disease
C. Sickle cell anemia
D. G6PD disease

Important Information

- Howell Jolley Body vs Heinz Body
  - Howell Jolley bodies are picked up in routine staining. Background RBCs will be having pinkish appearance but in Heinz bodies background RBCs are bluish
- Heinz Body vs Reticulocyte
  - Reticulocytes will be having a meshwork like appearance but in Heinz bodies there will be a dot like or Granule like appearance
  - Stain intensity in case of Heinz body is far less in comparison to reticular meshwork in case of reticulocyte
- Degmacyte: Bite cell
- Drepanocyte: Sickle cell

Risk factors 00:33:46

- Infections: Pneumonia, Sepsis, Infective Endocarditis
- Drugs: Anti-malarial [primaquine], Sulfa drugs, Nitrofurantoin, Nalidixic acid, Rasburicase
- Foods: Fava beans

Clinical Symptoms

- Clinical symptoms develop 48 – 72 hrs after exposure to risk factors
- Clinical symptoms include
  - Anaemia leading to fatigue
  - Drop in Hematocrit value/ Drop in the Hb value
  - Altered color of urine

Genetics

- Self-limiting disease
- Males >> Females
- X Linked Recessive Disorder

Variants

- Unstable enzyme
- ↓↓↓ t1/2

G6PD-B >	G6PD – A⁺ >	G6PD – A⁻ >	G6PD - M
↓	↓	↓	↓
Normal t½	↓ t½	↓↓t½	↓↓↓↓t½
↓			↓
Most Common			Most severe hemolysis

Diagnosis 00:41:12

1. History
2. Blood investigation
   - Peripheral smear
     - Special stain: Heinz bodies
     - Routine stain: Bite cells/ Degmacyte, Blister cells, Spherocytes
3. G6PD Level Estimation
   - Electrophoresis
   - Fluorescent spot test
     - Screening test
     - Most reliable and sensitive screening test
   - MetHb reduction Assay

Advantage of G6PD deficiency

- G6PD Deficiency: Rapid clearance of RBC so protects against P. falciparum infection

Treatment

- Self-limiting Condition

Important Information

- Any complication that is normally associated with Chronic hemolytic anemia is not seen in these patients
- Splenomegaly and Gall stones are not seen in G6PD deficiency

Previous Year's Questions

Q. Which of the following is true about G6PD deficiency? (AIIMS June 2020)

A. Resistant to hemolysis in hypotonic saline
B. Spectrin is involved in pathogenesis
C. Presence of spherical cells may be seen
D. It causes chronic hemolysis

34 BASIC CONCEPTS OF HEMOLYTIC ANEMIA

Clinical features 00:00:15

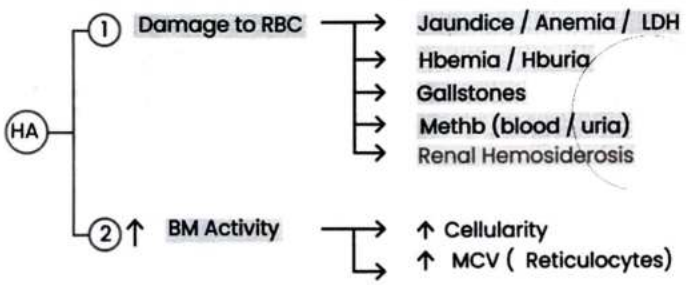
Refer Image 34.1

1. Increase in BM activity
- Cause
  - Increase cellularity of BM
  - Increase in Reticulocytes
  - Myeloid erythroid ratio reduced
2. RBC Destruction
- Because of Excessive damage of the RBCs
  - Patient develops anemia
  - Increase in serum LDH
  - Increase in UCB causing Jaundice
  - Formation of Calcium Bilirubinate: forms Pigment gall stones, Associated with presence of Chronic hemolytic anemia
- Haptoglobin and Hemopexin are reduced in hemolytic anemia

Important Information

- Reduced haptoglobin without hemolytic anemia: Pregnancy and liver dysfunction

- Free Hb in blood is k/a hemoglobinemia
- Free Hb in urine: hemoglobinuria
- Renal Hemosiderosis: manifestation found in patients having Hemolytic anemia
- Free Hb $\xrightarrow{Fe^{2+}Fe^{3+}}$ Methemoglobin → Methemoglobinemia & Methemoglobinuria



Types of Hemolytic anemia 00:11:39

- Based on site of RBC damage it is classified into 2
  - Intravascular hemolytic anemia: Inside Systemic Circulation
  - Extravascular Hemolytic anemia: Inside Liver and spleen

Intravascular hemolytic anemia	Extravascular Hemolytic anemia
• No hepatosplenomegaly	• Hepatosplenomegaly +
• Hemoglobinemia +++	• Hemoglobinemia +
• Hemoglobinuria +	• Hemoglobinuria ±
• S. haptoglobin ↓↓↓	• S. haptoglobin ↓

Important Information

- Intravascular hemolytic anemia with False normal value of Heptoglobin is seen with Bile duct obstruction

Causes of HA 00:16:27

Refer Table 34.1

Image 34.1

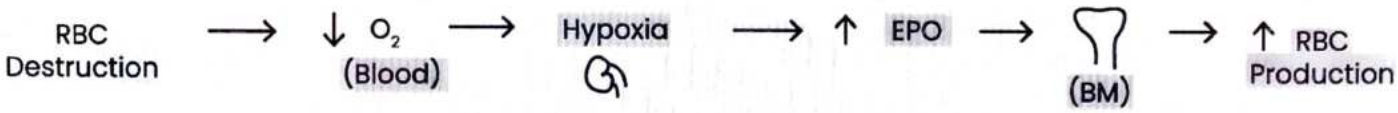


Table 34.1

Intracorpuscular Causes	Extracorpuscular causes
• Inherited ○ Hereditary spherocytosis ○ G6PD deficiency, Hexokinase deficiency ○ Hemoglobinopathies like SCA, thalassemia	• Immune mediated ○ ABO/ Rh incompatibility ○ Autoimmune HA
• Acquired ○ Paroxysmal Nocturnal hemoglobinuria	• Non-immune mediated ○ Clostridial Toxin ○ Snake venom toxin ○ Sequestration ○ Mechanical Damage → Angiopathic hemolytic anemia → Prosthetic cardiac valves → March Hemoglobinuria

35 HEMOGLOBINOPATHIES: SICKLE CELL ANEMIA & THALASSEMIA

SICKLE CELL ANEMIA

00:00:28

- It is a qualitative disorder of hemoglobin

PATHOPHYSIOLOGY

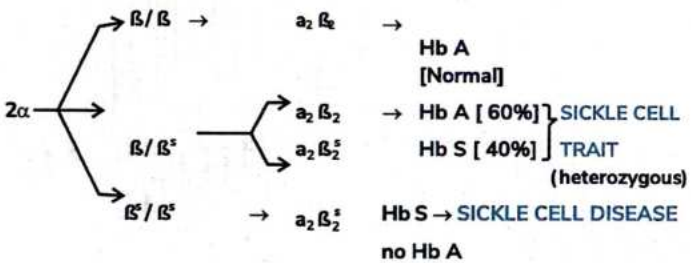
- Point mutation →
  - Glutamic Acid [Norma] (β) Polar AA
  - β6 AMINO Acid Valine [Sickle cell anemia] (β^s) Neutral AA

How to remember

- Glutamic acid Goes and valine velcomes

Hb → TETRAMER → 2a → HbA_2 $\alpha_2\delta_2$

→ 2ß → Hb F $\alpha_2\gamma_2$

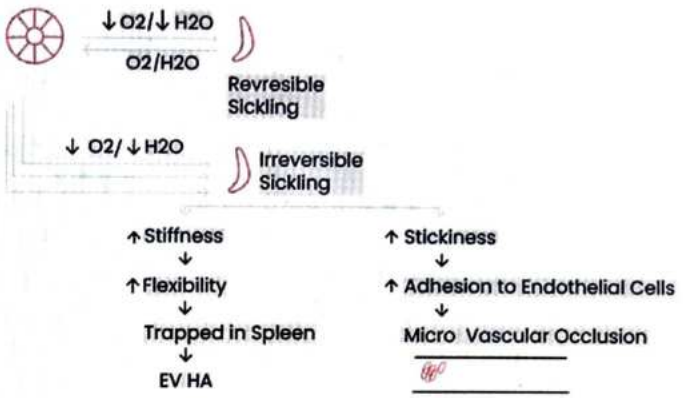


Important Information

- Sickle cell trait patients – Asymptomatic
- Sickle cell disease – symptomatic
- More the β mutation, more the symptoms

Hemoglobin S

00:03:20



Clinical Features

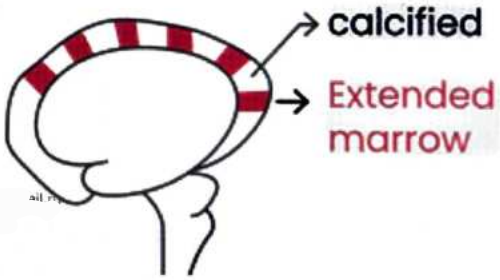
00:04:25

- Geographically more common in Africans
- Anemia / retarded growth
- Abdominal discomfort – Splenomegaly (In later stages)

Complications

00:05:10

- Most Common complication -Vaso-occlusion crisis - leading to ischemia in different organs of the body
- Bones
  - Small bones of hands & feet→ HAND-FOOT SYNDROME/DACTYLITIS
  - Long bones →Avascular necrosis of neck of femur
  - SKULL



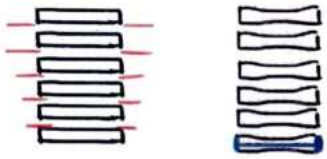
Calcified area

Hair on end appearance
crew cut appearance

Important Information

- Crew cut appearance – Thalassemia major > Sickle cell anemia

- Vertebral column – backache



H-Shaped Vertebra / COD fish vertebra / Fish mouth Vertebra

- CNS → TIA, Stroke
- SKIN → Chronic non healing Leg ulcers (In medial malleolus)
- SPLEEN → ↑↑ Size initially → Occlusion of veins
  - Leading to congestive Splenomegaly - Gandy gamma body Ca^{2+} deposition + fibrosis
  - Later→ Arterial occlusion→ Ischemic damage → FIBROSIS OF SPLEEN
  - AUTO SPLENECTOMY (Reduction in size of spleen)
- PENIS - Painful undesirable erection → PRIAPISM
- PULMONARY CIRCULATION - ACUTE CHEST SYNODROME
  - Pain in Chest
  - Dyspnea
  - ↓O2 in blood

Important Information

- Patient becomes symptomatic when there is
  - Infection
  - Dehydration
  - Hypoxemia (any kind)

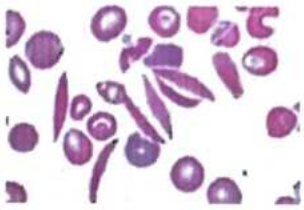
Previous Year's Questions

Q. A boy after playing football complaining fatigue and abdominal pain. He also had a history of hand swelling in past. On ultrasonography, h has shrunken spleen. What is the likely diagnosis of this patient? (NEET – Jan - 2020)

A. Sickle cell anemia
B. Iron pancreatitis
C. Acute pancreatitis
D. Intermittent porphyria

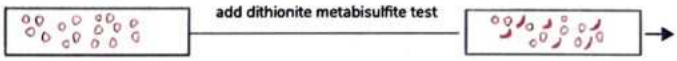
DIAGNOSIS 00:09:42

- BLOOD →
  - ↓Hb
  - ↑↑↑ TLC
  - ↓↓↓ ESR
  - Peripheral Smear Shows → Sickled Cells, Normal Rbc, HJ Body, Target Cell



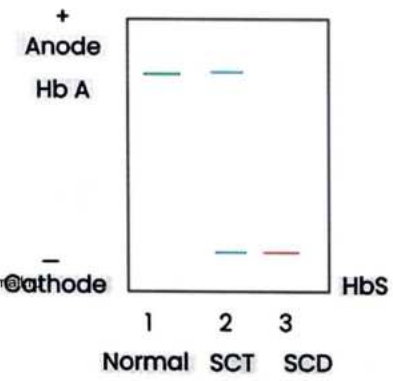
Drepanocyte

- DITHIONITE/METABISULFITE TEST
  - To check if RBC have sickling tendency by creating artificial hypoxemia can't distinguish b/w SCT/SCD



- OSMOTIC FRAGILITY TEST
  - SCA→↓ Osmotic Fragility
  - seen in all Hemoglobinopathies
  - Thalassemia (Both beta and alpha)
  - Severe IDA

- Hb ELECTROPHORESIS
  - Glutamic acid [Polar] [HbA] valine [Neutral] [HbS]



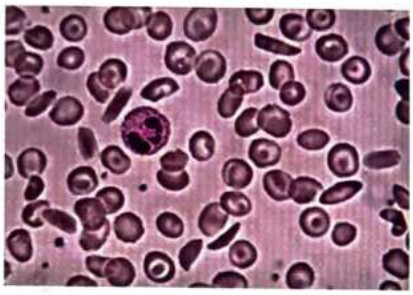
  - Limitation: Require expertise
- Genetic analysis - IOC
- HPLC - HIGH PERFORMANCE LIQUID CHROMATOGRAPHY
  - Can differentiate the types of Hb
  - Quantity of Hb S can be known
  - IOC (If genetic analysis is not in option)

Other complications 00:15:42

APLASTIC CRISIS	BM hyperactivated due to compensatory mechanism	Parvo virus infection
SEQUESTRATION CRISIS	↑↑↑↑ Splenic Size d/t ↑blood in spleen	Hypovolemia

TREATMENT 00:16:44

- Routinely sickle cell anemia patient presents with stunted growth, but if the patient presents with complications associated with it – Symptomatic treatment is given



Sickle cell Anemia – Drepanocyte/Sickle cell

Important Information

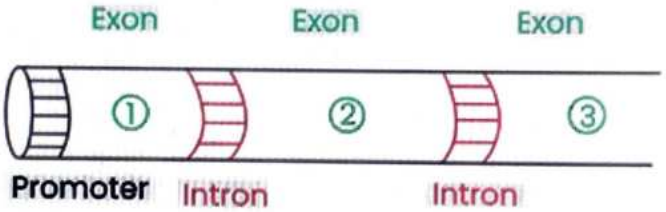
- Sickle cell of RBC – due to the amount of Hb S present in the RBC

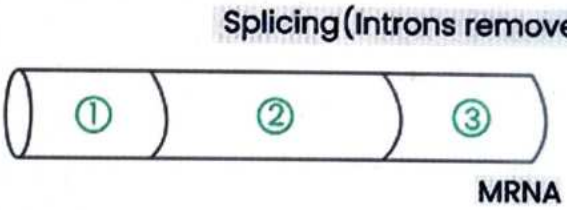
THALASSEMIA 00:18:20

- Quantitative disorder of Hb
- Hb
  - 2 α chains → 4 α genes – chromosome 16 - HBA1/HBA2 gene
  - 2 ß chains → 2 ß genes - chromosome 11 – HB B gene
- α THALASSEMIA → d/t gene deletion
- β THALASSEMIA → d/t gene mutation [More common]

ß THALASSEMIA 00:21:45

- NORMAL Adult → Hb A ($\alpha_2\beta_2$) (95%) /Hb F ($\alpha_{2\gamma_2}$) (1%) / Hb A_2 (α_{22}) (3%)
- β gene isoforms
  - β^{+} → normal β chain Formulation
  - β^{+-} partial β chain formulation
  - β^{o-} no β chain formulation





↓
RIBOSOMES
↓
Translation
↓
β FORMATION

- INTRON → Intervening region
- EXON → Expressive Sequence
- PROMOTOR → Increases the no. of β Chains

Important Information

- Whenever there is a problem in the promoter region or splicing defect, there will be a interference in the proper amount of production of the β chains

MUTATION 00:25:15

Important Information

- Mutation leading to the alteration of one aminoacid to other – Missense mutation
- Mutation leading to the stop codon – Non sense mutation
- Mutation that do not cause any change – Silent mutation

Classification of the mutation in Thalassemia

- SPLICING MUTATIONS [Intron > Exon] → $\beta^{+}>>>\beta^{\circ}$
- PROMOTER MUTATIONS → β^{+}
- CHAIN TERMINATION MUTATION → β°

Common

- Most common mutation in thalassemia is Nonsense mutation
- Most common mutation involved in partial synthesis of β chain – Splicing mutation
- Commonest mutation associated with β thalassemia in India – IVS-1-5 (g→c)
- Other mutation
  - 619 bp deletion
  - IVS – 1 (g→T)
  - Codon 41/42 – frameshift mutation
  - Codon 8/9 – frameshift mutation

CLINICAL POSSIBILITIES 00:29:12

- β/β → NORMAL → 14-17g/dl
- β/β^{+} or β/β° → THALASSEMIA MINOR / THALASSEMIA TRAIT
  - Mild
    - → Hb > 10 g/dl
    - → Asymptomatic
    - → No H/o blood transfusion
- β^{+}/β^{+} THALASSEMIA INTERMEDIA
  - Moderate
    - → Hb → 8-9 g/dl
    - → on & off Blood transfusions
- $\beta^{\circ}/\beta^{\circ}$ or β°/β^{+} or β^{+}/β^{+} → THALASSEMIA MAJOR (Cooley's anemia)
  - Severe
    - → Hb < 7 g/dl
    - → Regular blood transfusions
    - → Transfusion dependent thalassemia

Previous Year's Questions

Q. An 18 years old patient's hemogram shows Hb 12 g%, RBC count of 6 million, decreased MCV (56), decreased MCH (29) AND RDW OF 14. What is the most probable diagnosis? (JIPMER – Nov- 2017)

A. Iron deficient stores
B. Folate deficiency
C. Beta thalassemia trait
D. Normal lab parameters

ß THALASSEMIA MAJOR

00:34:55

Relative excess of α chains
↓
α - chain precipitation

In bone marrow, Direct damage to normoblast
↓
No. of actual RBC & (INEFFECTIVE ERYTHROPOIESIS)

Escape in circulation
↓
Trapped in spleen
↓
EVHA

SEVERE ANEMIA

ANEMIA +++
↓
↑↑EPO

?BM ACTIVITY

EXTRAMEDULLARY HEMATOPOIESIS

Liver / Spleen / BONES
↓
Hepatosplenomegaly

Facial and skull Bones involvement

FACIAL BONES INVOLVEMENT

- Frontal Bossing
- Malocclusion of teeth

} CHIPMUNK FACIES

CHIPMUNK FACIES

Blood Transfusion 00:39:40

- Regular blood transfusion → ↑ Iron → Iron overload
- Erythroferrone
  - ↑BM ACTIVITY - ↑erythroid precursors - Erythroferrone - ↓hepcidin - Iron overload
- Iron is involved in the generation of free radicals (Fenton's reaction)

IRON OVERLOAD leading to 2°hemochromatosis

Heart Pituitary Pancreas Liver Parathyroid

- CARDIAC/ENDOCRINE FAILURE → DEATH

Important Information

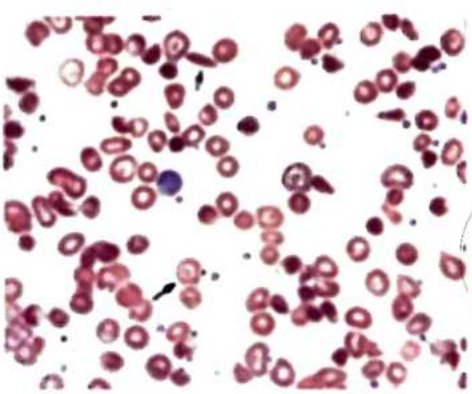
- Erythroferrone - Hormone acting on the liver to suppress Hepcidin
- Hepcidin acts negatively Iron regulator
- I° hemochromatosis – genetic defect at the level of iron
- 2° hemochromatosis – Extra amount of iron because of other causes

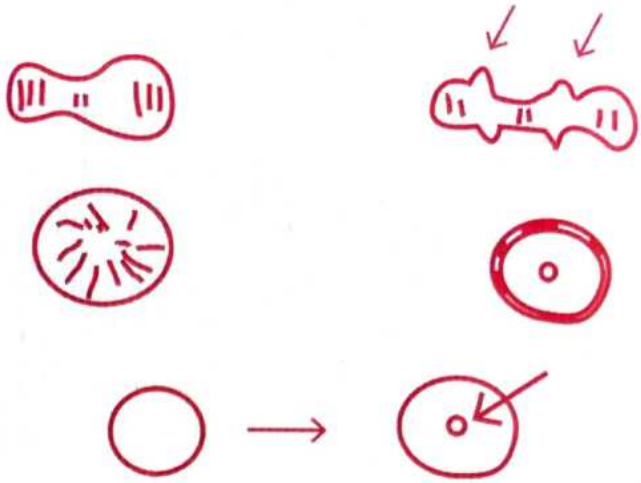
DIAGNOSIS 00:44:00

- BLOOD
  - Hb/MCV/MCH/MCHC ↓↓

PERIPHERAL SMEAR

- Microcytic hypochromic
- Anisocytosis
- Poikilocytosis
- Target cells (Differentiating feature from IDA)
- Basophilic stippling [d/t abnormal Ribosomes]
- Howell jolly bodies (Remanants of DNA)
- Nucleated RBC





Target cells – (Codocyte)

Important Information

- Target cells – (Codocyte)
  - It is due to the extra amount of membrane relative to the hemoglobin
  - It is also said that the abnormal Hb because of α chain tetramer formation – This abnormal Hb preferentially deposits in centre.

Important Information

- Basophilic stippling seen in
  - Sideroblastic anemia
  - Thalassemia major
  - Megaloblastic anemia
  - Lead poisoning

- OSMOTIC FRAGILITY↓↓
- Hb HPLC (2nd best) > Hb electrophoresis - Protein detection

α	β →	$\rightarrow \alpha_2\beta_2$	→ ↓↓↓HbA
	γ →	$\rightarrow \alpha_{2\gamma2}$	→ ↑↑↑ HbF (Highly suggestive)
	δ →	$\rightarrow \alpha_2\delta_2$	→ ↑HbA_2

- Globin gene sequencing (Molecular test) – Best (but expensive and not available) - Definitive diagnosis
  - It can detect thalassemia even in the presence of co-existing hemoglobinopathies
  - The result will not be interfered with recent blood transfusion
  - These two points were not possible by protein detection
  - Hence, Molecular test far more superior than protein detection

- Radiodiagnosis

CREW CUT / HAIR ON END APPEARANCE

Important Information

- Crew cut/hair on end appearance of skull in thalassemia is due to expansion of diploic spaces

Treatment 00:57:38

- Regular Blood transfusion – Packed RBC's
- To control the iron overload, iron chelators are given
- Allogenic Bone marrow transplant – Definitive treatment

THALASSEMIA TRAIT / MINOR 00:59:50

- ↓ Intensity
- Mild anemia
- No H/O Blood transfusion
- Peripheral Smear → Mild +
- ♂♀T.trait →AR → Thalassemia major [25%]

SCREENING test 01:04:10

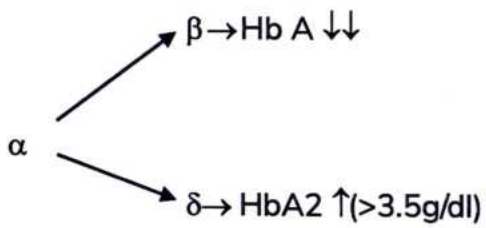
- NEST ROF TEST
  - NE – Naked eye
  - ST – Single tube
  - R – Red cell
  - OF – Osmotic Fragility
  - TEST
- OSMOTIC fragility → ↓
- Procedure
  - Mix Hypotonic Saline [5 ml] with 0.2 ml Blood
  - Wait for 30 minutes

Check the visibility of black line

Important Information

- R.B.C which are affected in case of thalassemia are relatively resistant in terms of osmotic fragility
- Therefore, they are not easily lysed so the black line is not visible
- But, this screening is based on the observer

- Diagnosis confirmed by Hb HPLC



- Differentiation between Thalassemia Trait VS IDA

	Thalassemia Trait	IDA
RDW (Anisocytosis)	N	↑↑↑
Mentzer index $\frac{MCV}{RBC\ count}$	<13	>13
HPLC	↑↑ HbA_2	↓Hb A

Treatment

- No treatment needed for these patients since they are asymptomatic.

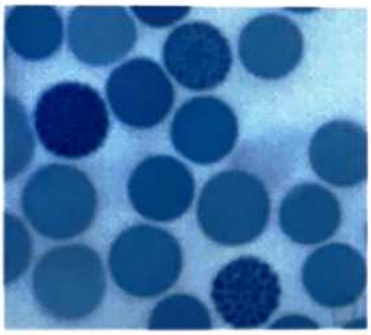
ALPHA THALASSEMIA

01:13:48

- Due to GENE DELETION
- Chromosome 16 → 4 α genes → 2 α Chains

CLINICAL POSSIBILITIES 01:15:05

- αα / αα → Normal [100% α Chains]
- αα / α_ → Asymptomatic
  - Silent Carrier - 75% α Chains
- α thalassemia trait
  - α_ / α_ → Mild
    - → 50% α Chains
    - → Trans gene deletion
  - αα/__ → Mild
    - → Southeast Asians
    - → 50% α Chains
    - → CIS α Thalassemia
    - → Marriage not advised
- α_/__ →
  - 25% α chains - β4 TETRAMER [Hb H]
  - High precipitation → Golf ball appearance – EVHA
  - High o2 affinity → Tissue hypoxia



Golf ball appearance – Supravital staining

- __/__ → Fetal life
  - γ_4 TETRAMER [BARTS Hb] - high o2 affinity
  - Intrauterine Death in 3rd trimester → Non-Immune Hydrops Fetalis
  - The fetus survives 1st two trimesters because of the formation of ξγ Hb

Important Information

- Immune hydrops fetalis – Rh incompatibility
- Non-immune hydrops fetalis – α thalassemia

36 MEGALOBLASTIC ANEMIA

Introduction 00:00:12

- Macrocytic Anemia: ↑ Size
- Megaloblastic anemia: ↑ Size & (Nuclear Immaturity) N:C Asynchrony

Etiology

- Vitamin B12 deficiency: ↑Risk of B12 deficiency in vegans
- FA deficiency
- Drugs

VITAMIN B12 DEFICIENCY 00:01:25

Source

- Animal food : Milk, Meat
- Gut bacteria

Normal Functioning requires

- Intrinsic Factor [parietal cells]
- Pancreatic enzymes [Duodenum]
- Ileum [Site]

Normal Function required For :

- Rapid division of cells
- DNA Synthesis
- Homocysteine → Methionine
- Methyl malonyl COA→Succinyl coA [required for myelin Synthesis]

Etiological factors

- ↓ Intake: vegans [x no milk]
- ↓ Absorption: ↓ Intrinsic factor – pernicious anaemia
  - Pancreatic disease
  - Ileal disease
  - Bacterial overgrowth syndrome
  - Abdominal surgery
- ↑Requirement
  - Children
  - Pregnancy
  - Lactation
  - Fish tape worm [Diphyllobothrium latum] Infection

Clinical feature 00:10:00

1. Blood / BM Findings

- Changes
  - Pancytopenia
  - Hyper cellular BM
  - Ineffective Erythropoiesis
- RBC Abnormalities :
  - Macro - Ovalocytosis [Earliest Manifestation]
  - Basophilic Stippling
  - Howel Jolly Bodies (DNA Remnants)
  - Cabot Ring
- WBC Abnormalities:

  - > 5% - ≥ 5nuclei – Megaloblastic anemia
  - BM :↓ DNA: Immature cells : ↓ inhibits Mature cells
  - PLATELETS : ↑↑ Size → Abnormal Shape

2. GIT Changes:

- Epithelial size: Mucosal Atrophy
- Tongue→Smooth: Beefy Tongue

3. CNS

- ↓Myelin
  - PNS: Paresthesia
  - CNS: subacute combined degeneration of spinal cord
- Peripheral neuropathy
- Ascending / descending tract Involvement
  - Sub acute combined degeneration of spinal cord [SACD] [also seen in neurosyphilis]
  - Dorsal column >> Antero – lateral Spinothalamic tract

Clinical features:

- Anemia + mild Jaundice + Neurological Features
- Hyper-pigmentation of knuckles

Diagnosis 00:21:15

1. Serum Vit B12: ↓↓

- S. Homocysteine: ↑
- S.mm coA →methyl malonylemia[Blood] methyl malonyluria [Urine]

2. BM:

- Hypercellular BM } Ineffective
- ↓↓↓Reticulocytes } Erythropoiesis

3. Blood

- ↑MCV
- ↑ MCH
- MCHC: Normal & unaffected [MCV / MCH]

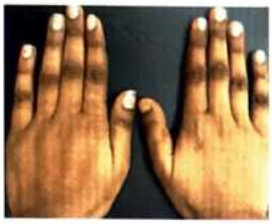
- Basophilic Stippling+[Abnormal RBC precursor]
- Howell Jolly bodies +
- Cabot ring +
- Hypersegmented neutrophils

Rx:- 00:25:03

- B12 supplementation [oral/i/m]
- 1% absorbed by non intrinsic pathway - High dose of B_{12} given.

Previous Year's Questions

Q. A 20 years female with easy fatigability and pallor. Findings of her hand has been shown below. What is your likely diagnosis? (INICET – Nov - 2020)



A. Aplastic anemia
B. B12 deficiency
C. Iron deficiency anemia
D. Hypo albuminemia

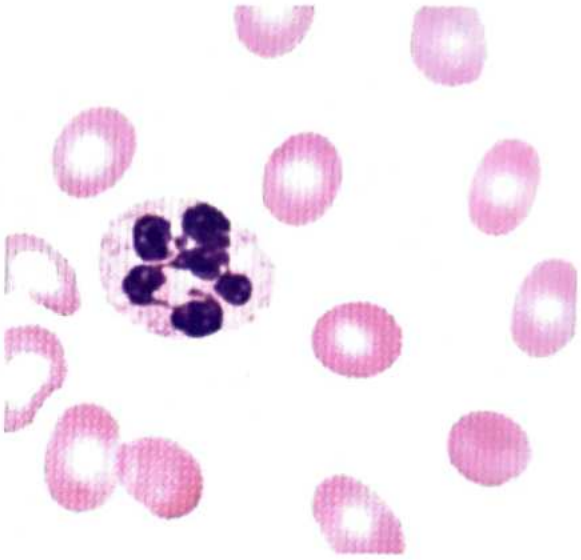
Important Information

- B12 deficiency there is demyelination affecting dorsal column of spinal cord called as sub-acute combined degeneration of spinal cord.

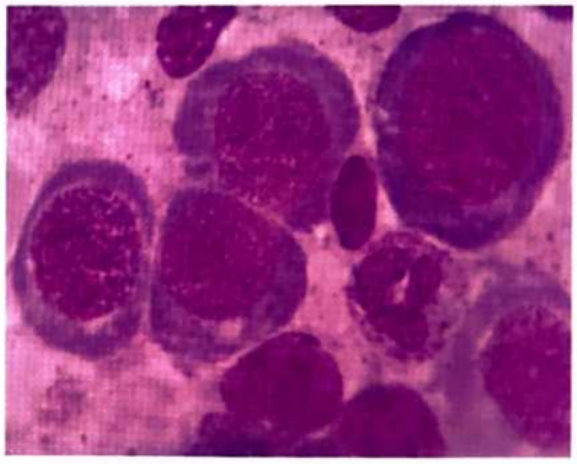
Previous Year's Questions

Q. A 30 years old women came with complaints of easy fatigability, exertional dyspnea and weight loss. She also has a complaint of frequent fall. Physical examination revealed there was b/L decreases in vibration sense. Her hemoglobin levels were 8.2g%. she was treated with folate. Her anemia improved but neurological symptoms worsened. Which of the following is the most probable reason for the condition? (NEET - Jan - 2020)

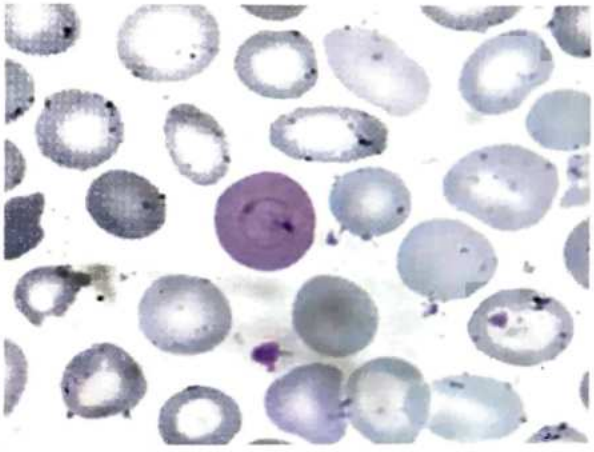
A. Folate not absorbed
B. Folic acid deficiency unmasked pyridoxin deficiency
C. Deficiency of folate reductase in CNS
D. Folate therapy cause rapid use of B12 stores aggravating symptom



Hyper-segmented neutrophil; Macro - Ovalocytosis; Howel Jolly Bodies



Sieve- Like Chromatin(Megaloblast)



Cabot Ring & 8-Figure like structure

PERNICIOUS ANEMIA

00:27:36

- Auto-reactive T cells: auto Ab; Auto immune disorder
  - I: ↓ [Intrinsic Factor + B12] [most specific]
  - II: Ileal
  - III: parietal cells
- ↓↓ B12 absorption
- Atrophic Gastritis: Intestinalization occurs [predominant in fundus / Body] → Ca Stomach: ↑ cancer

Diagnosis

00:32:17

- Auto Ab
- S. B12 ↓↓
- Histamine stimulation: Achlorhydria
- Schilling Test
  - done for cause of B12 deficiency
  - not done for diagnosis of B12 deficiency

Treatment

00:36:48

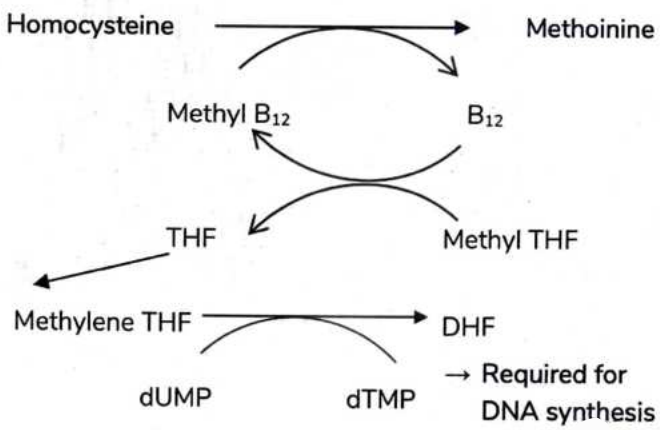
- B12 Supplementation
  - In pernicious anemia: Life time
  - In other causes: For Specific period
  - In treatment with B12 : Reversal
  - Blood picture: Reversal
  - neurological C/F: no further aggravation / no reversal
  - Cancer: higher than normal

FOLATE DEFICIENCY

00:37:54

- Poly glutamate form of folate [DIET]
- mono glutamate form absorbed in SI [JEJUNUM] : chr 21
  - Converts into active form in blood - methyltetra hydrofolate Q

Folic acid synthesis & absorption



Clinical Significance

- Folate Trap - FA trapped as Methyl THF form

Metabolism of B12

- Oral Cavity: B12 + Heptocorin
- Stomach [Pepsin]: B12 + Intrinsic factor
- Duodenum: IF-B12 complex
- Jejunum: IF-B12 complex + gut bacteria
- Ileum: B12 enters systemic circulation
- B12 is bound to dietary protein
- In stomach, it binds to salivary protein (haptocorin) and free from dietary protein
- It binds to intrinsic factor and detaches from haptocorin under activity of pancreatic enzymes
- In the presence of gut bacteria, it enters ileum, internalize with help of receptor (cubilin) and enters the systemic circulation

Etiology

- ↓ Intake: Drugs which ↓ absorption
- ↓ absorption: alcohol
- ↑ requirements: methotrexate & OCPs, phenytoin
- Chr 21: Location for FA (R)

Clinical Features

00:43:57

- Megaloblastic anemia
- no neurological manifestations
- ↑chances of Neutral tube defect → Pre conceptionally Q FA given

Diagnosis

00:44:20

- S. Folate levels : ↓↓
- RBC Folate : ↓↓ [Best test]
- Figlu test [Forminino glutamate]

FA
Histidine → ↑FIGLU → Glutamate
↓
Urine

Megaloblastic Anemia

B_{12}	↓FA
NS (+)	NS (-)
MMCoA↑	MMCoA – (N)

- Vit B_{12} +FA , never FA alone [in case of megaloblastic Anemia]

37 EXTRACORPUSCULAR HEMOLYTIC ANEMIA

IMMUNE MEDIATED HEMOLYTIC ANEMIA

Autoimmune hemolytic anemia

- It is of 2 types
- Warm AIHA (antibodies attached at 37° C)
  - IgG >>> IgA
- Cold AIHA (antibodies attach at low temperature)
  - IgM >>> IgG

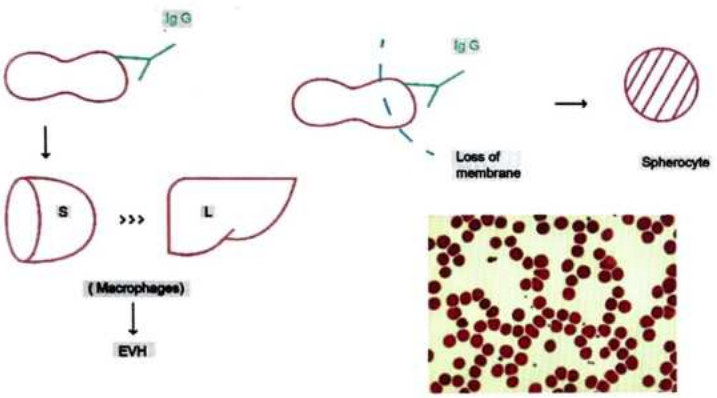
WARM AIHA

00:06:00

- IgG/IgA: Bind at temperature of 37°

Causes

- Idiopathic
- Auto-immune disorders (SLE, rheumatoid arthritis)
- Malignancies (CLL)
- Drugs
  - α-Methyldopa
  - Penicillin/quinidine



Clinical feature

- Jaundice
- Anemia
- Splenomegaly
- Spherocyte in PBS

Diagnosis

- ↑ LDH/↑ unconjugated bilirubin/↓ Hb
- Blood
  - PBS: spherocytes
  - Presence of auto-antibodies and could be present in 2 locations
    - → On RBC surface: Direct Coombs test
    - → Serum (free): Indirect Coombs test

> **Important Information**
>
> - Clinical features of hereditary spherocytosis and idiopathic AIHA are similar. The only differentiating factor is that "spherocytosis is Coombs test negative"

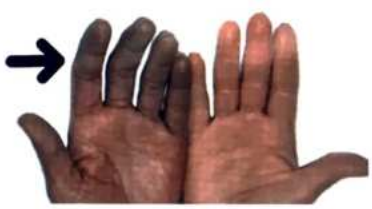
COLD AIHA

00:20:57

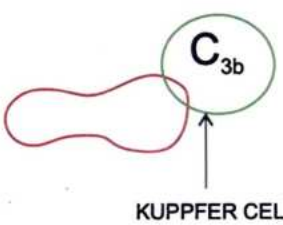
- Antibodies attach at lower temperatures (<37°C)
- It has 2 variants

COLD AGGLUTININ DISEASE

IgM → 'I' antigen of RBC
↓
Binds to RBC at cold temperature
↓
Clumping/agglutination of RBC
↓
Acrocyanosis
At body temperature (37°C) → detachment of IgM



- IgM → Complement proteins → C3b attachment → destruction on hepatic circulation (EVH)



Clinical features

- Jaundice
- Anemia

- Acrocyanosis at exposure to lower temperature
- Hepatomegaly

Associations of cold agglutinin disease (IgM)
- Mycoplasma infections
- Malignancies
- Infectious mononucleosis
- Waldenstrom macroglobulinemia

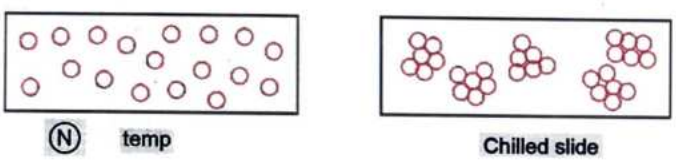
Previous Year's Questions

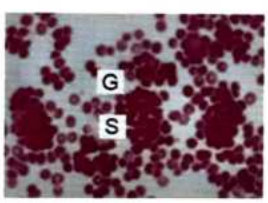
Q. Cold agglutinin are directed against which of the following RBC antigens?

(JIPMER 2019)

A. I antigen
B. P antigen
C. Le antigen
D. Re antigen

Diagnosis
- Cold slide test

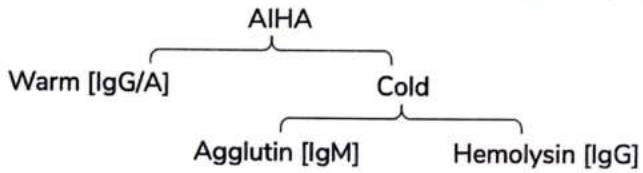




COLD HEMOLYSIN TYPE
- Formation of IgG → 'P' antigen of RBC
- Binds at lower temperature at 4°C → complement activation at 37°C → MAC formation → destruction of RBC (Intravascular hemolysis) → Hburia

- Cold hemolysin aka Paroxysmal Cold Hemoglobinuria (PCH)
- Cold hemolysin Ab: Donath-Landsteiner Ab
- It can be seen with viral infections in children
  - Syphilis

AIHA SUMMARY 00:43:28



Warm
- IgG/IgA
- Associated with idiopathic, drugs, SLE & RA
- Destruction of RBC mainly occurs in spleen

Cold
- Cold agglutinin disease
  - IgM
  - Site of destruction is liver
  - Associated with attachment of Ab at lower temperature
  - Extravascular hemolysis

- Cold hemolysin
  - IgG
  - Associated with attachment at of Ab lower temperature and activation of complement at core temperature (Biphasic Ab)
  - Intravascular hemolysis

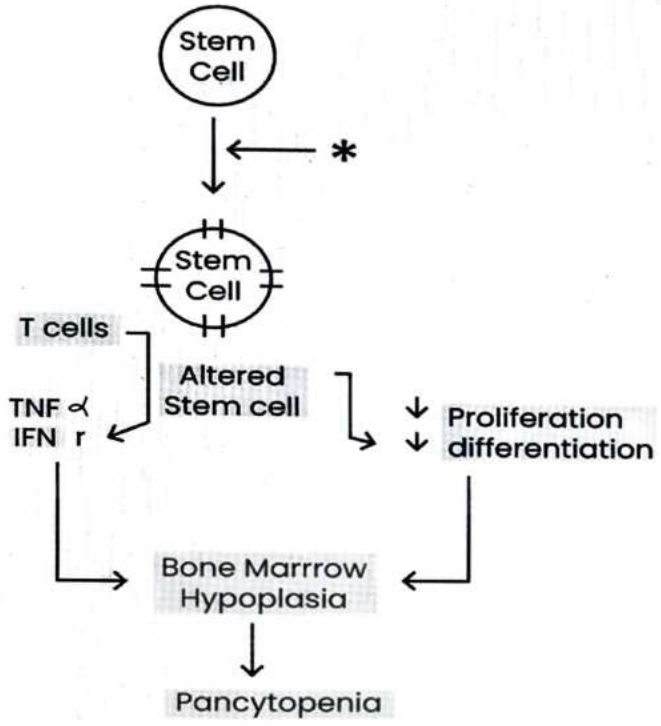
38 MISCELLANEOUS DISORDERS

APLASTIC ANEMIA

Introduction

00:00:15

- Associated with Hematopoietic stem cell defect: Pancytopenia



Important Info

- Drugs
- Anti Thymocyte Globulin [ATG] } ↓T Cell→useful in Aplastic anemia
- Cyclosporine activity }
- AA can progress to
  - MDS
  - AML
- AA also a/w PNH [dlt T cell activity against GPI - linked protein]

Causes

00:05:54

- Inherited
  - Telomerase defect
  - Fanconi Anemia
    - → AR
    - → Defect in DNA Repair genes
    - → Hypoplasia [Kidney | Spleen]
    - → Bone defects [Radius | thumb]
    - → Fanconi Syndrome is a/w Renal Tubular Damage [different from FA]
- Acquired
  - Immune Mediated
  - Idiopathic [MCC]
- Chemicals
  - Dose Related : Alkylating Agents / Anti Metabolites / Chloramphenicol
  - Dose Unrelated: [IDIOSYNCRATIC S/E] [even 1 Single dose can cause AA]
    - → Gold salts
    - → Chloramphenicol
- Physical
  - Radiation
  - Viruses [EBV, VZV, CMV]

Clinical features

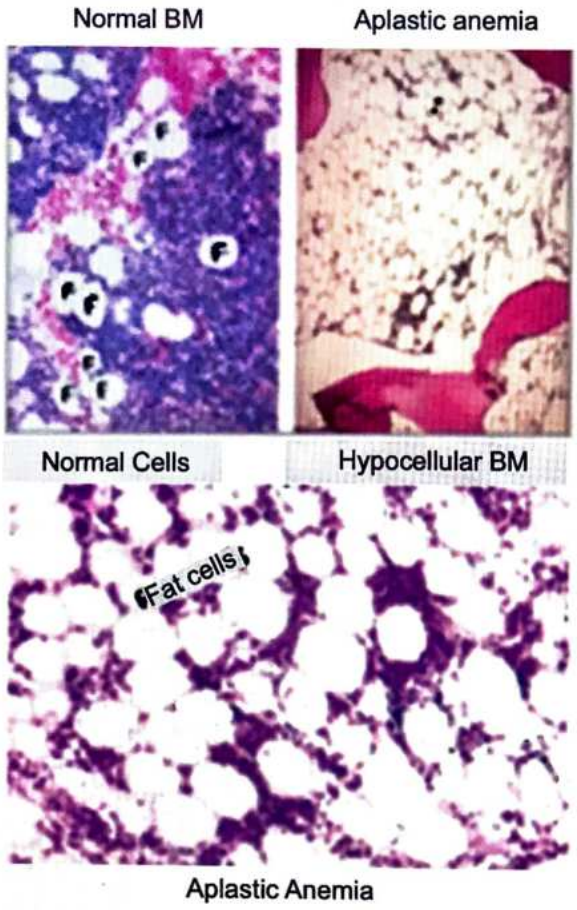
00:13:05

- No age predilection
- No sex predilection
- Features of pancytopenia
  - Fatigue
  - Fever
  - Hemorrhage [bleeding manifestations]
- Splenomegaly never seen

Diagnosis

00:14:25

- Blood
  - Pancytopenia
  - Reticulocytopenia
  - macrocytic, normochromic RBCs
- BM Aspiration: Dry TAP
- BM Biopsy 00:17:44
  - ↑ Cellularity
  - This Feature differentiates AA from
    - → MDS: hyper-cellular
    - → Aleukemic leukemia: hyper –cellular



Aplastic Anemia

Treatment 00:19:32

- TDC: Bone marrow Transplantation
- Drugs: Anti Thymocyte Globulin [ATG]
- Cyclosporine

Classification of Aplastic Anemia 00:20:20

- Non-Severe / Moderate AA
  - BM cellularity <25%
- Severe AA
  - BM cellularity < 25%
  - +
  - Any 2 out of 3
    - Absolute neutrophil count <500/mm3
    - Platelet count <20000/mm3
    - Reticulocyte count <60000/mm3
- Very Severe AA
- Severe AA with absolute neutrophil count< 200/mm^3
- Common cause of death in patients in severe & very severe AA: Septicemia

Previous Year's Questions

Q. All the following are criteria for diagnosing severe aplastic anemia except? (JIPMER – Nov – 2017)

A. Bone marrow cellularity < 25%

B. Reticulocyte < 60,000/mm^3

C. Platelet < 20,000/mm^3

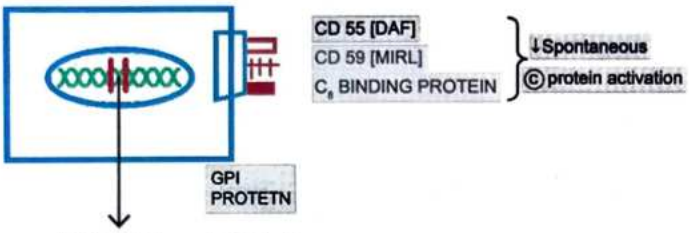
D. Absolute neutrophil count < 1500/mm^3

39 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA [PNH]

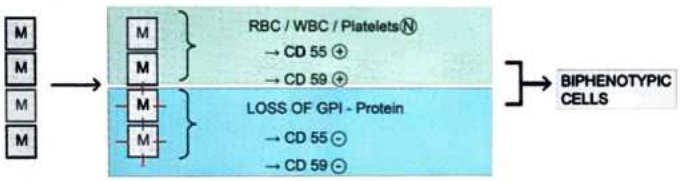
Paroxysmal Nocturnal Hemoglobinuria

00:00:18

- Acquired Incorpuscular Hemolytic Anemia [only cause]



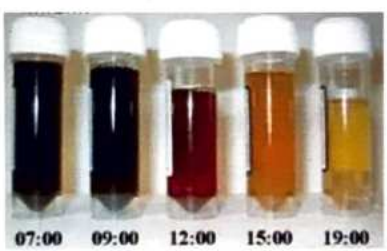
  - PIG - A Gene [x Chr]
  - [Phosphatidylinositol glycan complementation A gene]
- Synthesizes GPI Link protein [Transmembrane protein]
- Serves as ANCHOR
- CD 59 is also k/a
  - DAF: Decay Accelerating Factor
  - MIRL: Membrane Inhibitor of Reactive Lysis
- IN PNH , PIGA gene defect +



- Myeloid Stem Cells
  - Complement → Destruction Of → Pancytopenia: Activation RBC / WBC / Platelets

> **Important Information**
>
> - There is Defect GPI linked protein therefore problem in functioning of CD59/CD55 and complement related protein.

- RBC Destruction
  - [Night] → ↓RR→↑ Co2→↑ H+ [ACIDOSIS]



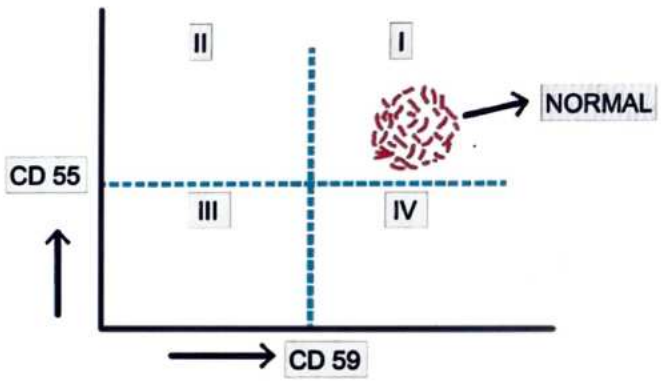
C System
↓
RBC Damage
↓
IV HEMOLYSIS
↓ Hb URIA
[altered color of Urine]

- WBC: Dysfunction: ↑ Infections♀, ↓ LAP score♀
- Platelets : ↓ platelet count
  - Altered function
  - ↑ Aggregation: Free Hb [dlt IVH]
  - ↑ THROMBOSIS +
    - → cerebral veins / Hepatic veins: DEATH
    - → Budd Chiari Syndrome

Diagnosis

00:15:00

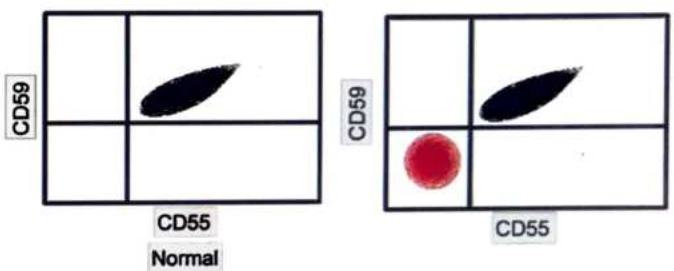
- Blood sample: Pancytopemia
- Screening Test
  - (I) Ham's acidified serum Test
    - Blood + Acid → RBC destruction
  - (ii) Sucrose Lysis Test
    - Blood + Sugar → RBC destruction
- I-Normal person [CD59, CD55 ⊕]
- III –Abnormal low level of CD59, Cd55



FLAER- FLOW CYTOMETRY [IOC]

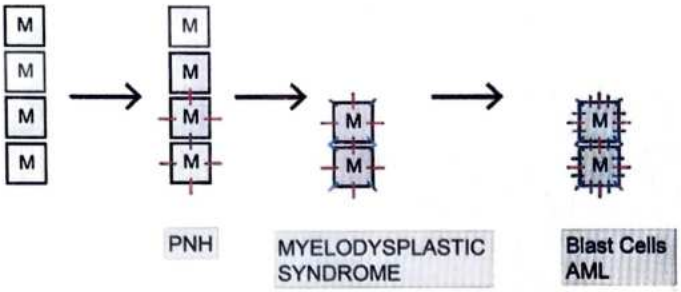
00:18:30

- Fluorescein-labelled Pro-Aerolysin
- PNH- 2 different cells
  - CD59, Cd55 ⊕
  - CD59-, Cd55-
  - Biphenotypic Appearance



Disorders Related with PNH 00:21:58

- PNH can progress to



- PNH also a/w APLASTIC ANEMIA 00:25:19
- Auto Ab +
  - GPI - P: PNH
  - Stem cell Ag: Aplastic Anemia

Treatment

- PNH: ↑↑ © Proteins Damage
- Decrease activity of Complement system
  - C5 Convertase Inhibitor : Eculizumab
- In young patients: allogenic SCT
  - Stem Cell Transplantation [definitive R_1]

CLINICAL QUESTIONS

A 10 Yr old boy, Anemic who is on long-term oral iron supplements, complaints of fatigue, weakness once when he stops iron intake. On lab investigation, Hypoferremia (+). Clinically patient's Growth and Neurocognitive development are Normal for his age. The type of Anemia that is described above is characterized by all of the following, except:

A. Low hepcidin level

B. *TMPRSS6* gene mutations

C. Normal serum ferritin

D. Refractoriness to oral iron therapy

Solution

- Iron-refractory iron deficiency anemia (IRIDA):
  - Anemia with variable degree of microcytic hypochromicindices
  - Low-normal to normal serum ferritin
  - Very low serum iron and transferrin saturation (TSAT)
  - Inappropriately high serum hepcidin levels compared todegree of anemia
  - Oral iron refractoriness as per standard criteria for evaluationof response to oral iron
  - Presence of homozygous of compound heterozygous mutations in *TMPRSS6* gene

Reference

- Robbins, Pathologic Basis of Disease, 10/e, pg.656; https://doi.org/10.1016/j.phoj.2017.08..003

LEARNING OBJECTIVES

Unit 7 WBC

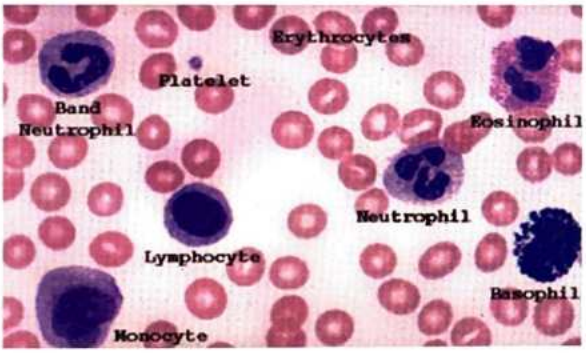
- **Introduction to WBC disorders**
  - Differential leukocyte count
  - WHO classification of lymphoid neoplasm & myeloid leukemia
  - Acute leukemia
- **Acute leukemias: ALL and AML**
  - Acute Myelogenous Leukemia
  - Classifications of AML
  - Acute Lymphoblastic Leukemia
  - Provisional Entities of B-cell & T-cell
- **Chronic Myeloid Leukemia**
  - Chronic Myeloid Leukemia
  - Diagnosis
  - Philadelphia chromosome
  - Treatment
- **Chronic Lymphocytic Leukemia**
  - Chronic Lymphocytic Leukemia
  - Pathogenesis of CLL
  - Diagnosis
  - Treatment
- **Myeloid Disorders**
  - Manifestation of Myelodysplastic syndrome (MDS)
  - Sub-types of MDS
  - Diagnosis of MDS
  - Treatment of MDS
- **Lymphoma: HL & NHL**
  - Hodgkin lymphoma
  - Subtypes of Hodgkin lymphoma
  - Non-Hodgkin lymphoma
  - Hairy cell leukemia
  - Cutaneous T-cell lymphoma
- **Basics of Plasma Cell Dyscrasias**
  - Plasma cell
  - Protein electrophoresis
  - Monoclonal gammopathies
- **Plasma cell Disorders**
  - Multiple Myeloma
  - Differential diagnosis Of Multiple Myeloma
  - Lymphoplasmacytic Lymphoma
  - Heavy chain disease

40 INTRODUCTION TO WBC DISORDERS

- Normal TLC: 4000 – 11000 cells/µl

DLC

- Neutrophils (50-70%)
  - Increased in bacterial infection/sterile inflammation/ acute inflammation/ burns
- Lymphocyte (20-40%)
  - Increased in Viral/ Bordetella infection, chronic inflammatory conditions
- Monocyte (8-10%)
  - Monocytosis occurs with lymphocytosis
  - Chronic inflammation/TB/Rickettsia/Malaria/SLE/IBD
- Eosinophil
  - Increased in allergic conditions (hay fever/allergy), parasitic infections/ HL/Athero-embolism
  - Eosinophilic casts in urine can be seen
- Basophils (rarest) → Increased in CML
- Band neutrophil
  - Usually present in BM → ↑↑ Seen in PBS indicates "shift to the left"

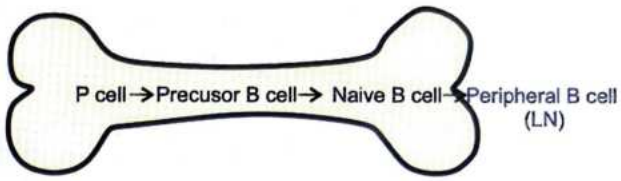


Wright staining smear

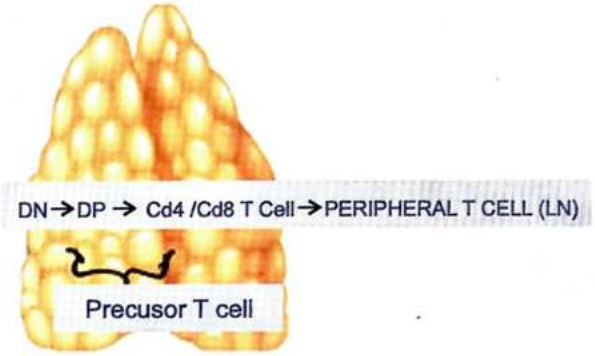
↑ WBC

- Leukocytosis → seen in mild infections
- Leukemoid reaction → seen in pneumonia/IE/Kawasaki disease/septicemia
  - Mature WBC identified by LAP score→↑↑ in leukemoid reaction
- Leukemia/lymphoma→ proliferation of immature cells (↓↓ LAP score)
  - Leukemia: involvement of BM, blood
  - Lymphoma: presence of cancer cells in different organs
  - Associated with pancytopenia /lymphadenopathy/ hepatosplenomegaly

WHO classification of Lymphoid neoplasm



- Precursor B-cell: pre B-cell ALL
- Peripheral B-cell: BL/DLBCL/ML/MZL/FL/HCL



- Precursor T-cell → Pre T-cell ALL
- Peripheral T-cell
  - Mycosis Fungoides
  - Enteropathy associated T-cell lymphoma
  - Anaplastic large cell lymphoma
  - Hodgkin lymphoma

WHO classification of myeloid leukemia 00:15:11

- Acute myeloid leukemia
- Myelodysplastic syndrome
- Myeloproliferative neoplasm

WHO classification of macrophages

- Langerhans cell histiocytosis

Precursor cell→ peripheral cell (less rate of multiplication)

↓ ↓

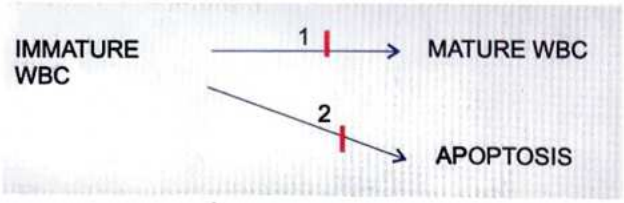
Acute leukemia chronic leukemia

ACUTE LEUKEMIA

Risk factors

- Ionizing radiation

- Chemicals → benzene, smoking, drugs
- Genetic factors
  - Down syndrome: ALL >> AML ($AML\text{-}M_7$)
  - Klinefelter syndrome
  - Neurofibromatosis 1
  - Fanconi's anemia
  - Bloom syndrome
  - Ataxia telengectasia
  - Kostmann syndrome
- Infectious organism → EBV, HTLV-1, HHV-8



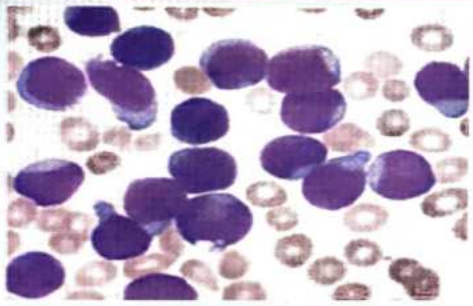
- BM examination
- Immunophenotyping/flow cytometry → Best method for diagnosis
- Cytogenetic analysis
- Molecular analysis

Clinical features

- Fever
- Bleeding
- Fatigue
- Pallor
- Hepatomegaly/splenomegaly/lymphadenopathy
- Bone tenderness

Diagnosis

- PBS → ↑↑ TLC

Lymphoblast	Myeloblast
	
• Lymphoid progenitor cell: condensed nucleus • ↑ Lymphoblast → ALL • Special Stain for lymphoblast: Tdt/PAS +ve	• Myeloid progenitor cell: less condensed nucleus, presence of granules • ↑ Myeloblast (>20%) → AML • Special Stain for myeloblast: MPO/NSE +ve

41 ALL & AML

ACUTE MYELOGENOUS LEUKEMIA

- MC affected: 60 years

AML-FAB CLASSIFICATION

- M_0 - Minimally differentiated AML
- M_1 - AML without maturation
- M_2 - AML with maturation
- M_3 - Acute Promyelocytic Leukemia
- M_4 - Acute Myelocytic Leukemia

} MPO +ve

- M_5 - Acute Monocytic Leukemia (NSE +ve)
- M_6 - Acute Erythroleukemia (PAS +ve)
- M_7 - Acute Megakaryocytic Leukemia (CD46 & CD61)

Previous Year's Questions

Q. A 50yr old child presents with gum bleeding and fatigue. His PBS shows marked leukocytosis with 70% cells showing MPO positivity. Diagnosis?
(FMGE 2020)

A. AML
B. ALL
C. CLL
D. CML

- MC clinical manifestation: fatigue
- Stains used for myeloblast: MPO, NSE, PAS
- MC type of AML: M_2 (AML with maturation)/ myeloblastoma/ chloroma/ granulocytic sarcoma
  - Tumor cells have more predilection for involvement skin and retro-orbital tissue → proptosis
  - M2 shows positivity for lysozyme, CD45 & CD43
  - Associated chromosomal t(8;21)
- AML M3 associated with chromosomal t(15;17) → ↓ Vitamin A → DIC
  - Vitamin A is given
- AML M4 associated with chromosomal t(16;16)
  - Gingival hyperplasia and leukemia cutis is seen
- AML M5 presents with skin infiltration and gum hypertrophy
  - MC type of AML in infants
- AML M7 is associated with Down syndrome
  - Responsible for causing myelofibrosis

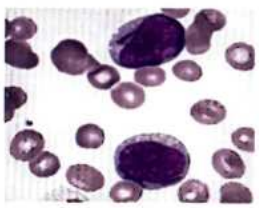
Important Information

- **Myeloblasts with Auer rods (azurophilic granules) is seen maximally in M_3 (acute promyelocytic leukemia)**
- **Group of Auer rods: Faggot cells**

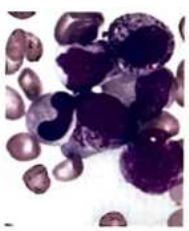
WHO CLASSIFICATION

00:08:49

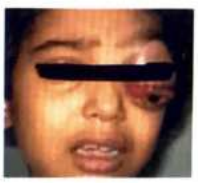
- AML with specific genetic defects: t(8;21) t(16;16), PML-RAR α, nucleophosmin mutation, t(11;V)
  - Diagnosis of AML can be made with < 20% and very good prognosis
- AML with myelodysplasia related changes (deletion of 5q/7q)
  - Intermediate prognosis
- AML therapy related with Alkylating agent, Topoisomerase inhibitor
  - Poor prognosis
- AML (NOS)
- Myeloid sarcoma
- Myeloid proliferation related to Down syndrome (GATA1 mutation)



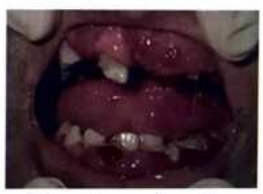
Auer rods



Faggot cells



Proptosis in M2 AML



Gum hypertrophy

00:14:26

Diagnosis

- Peripheral blood smear
- Bone marrow examination
- IOC: Flow cytometry
- Cytogenetics molecular study

ACUTE LYMPHOBLASTIC LEUKEMIA

00:15:24

- MC leukemia in children

Clinical features

- Abrupt onset
- Pallor
- Fatigue
- Bleeding: Petechiae, gum bleeding, purpura
- ↑ Infection
- Hepatomegaly, splenomegaly, lymphadenopathy
- In male, testicular mass
- Mediastinal mass
- Sternal tenderness
- Brain lesion presents as headache, vomiting, CN compression

Previous Year's Questions

Q. A 4 yr old child presents with the development of fever, petechial spots and complaint of fatigue. He is also having presence of pallor, hepato-splenomegaly as well as tenderness. The clinical situation descried above is most correctly associated with which of the following?

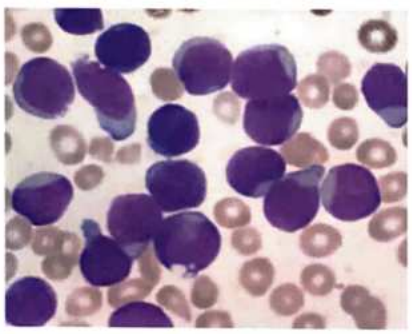
(FMGE 2020)

A. AML
B. ALL
C. CLL
D. CML

Pathogenesis

- Genetic defect: B cell ALL >>> T cell ALL

B cell ALL	T cell ALL
• Hyperploidy/hypoploidy • t(12;21), t(9:22), t(1;19) • EBF/PAX 5 mutation (loss of function) • ETV6/RUNX 1 mutation	• NOTCH mutation (gain of function)



Lymphoblast

- Staining for acute lymphoblastic leukemia: Tdt, PAS
- D/D for pre T-cell ALL: thymoma (cytokeratin - marker)
- CD10 aka Calla molecule

Pre B-cell ALL	Pre T-cell ALL
• More common • BM +++ • Max → 3 years • ↓ cell lines • CD 10/19/20 (+) • Better prognosis	• Less common • Thymus +++ • Max → puberty • Retrosternal mass • CD 1/2/5/7 (+) • Poor prognosis

PROGNOSTIC FACTORS IN ALL

00:31:02

Good Prognosis	Bad Prognosis
• Hyperploidy (>50), t(12;21), Trisomy 4/7/10	• Hypoploidy, MLL/KMT2A translocation, t(9;22), t(1;19), t(4;11), t(5;14)
• White race	• Black race
• Age of presentation: 1-10 years	• Age of presentation: <1year, >10years
• Female	• Male
• Less blast count (<100000)	• More blast count
• Pre B-cell ALL	• Pre T-cell ALL
• Drug response – most important • Remission <14 days	• Non-responsive to drugs • Remission >14 days

- Minimal Residual Disease: Residual cancer cells not picked by light microscopy

Treatment

00:39:31

- Drugs
- Bone marrow transplantation
- CAR-T therapy (Chimeric Antigen Receptor T-cell therapy) targets CD19
  - S/E: cytokine storm

PROVISIONAL ENTITIES (INICET INFO)

B-cell

- Philadelphia like ALL: BCR-ABL-1 like

- Associated with TK activating rearrangements → ABL1, JAK2, PDGFRB
- CRLF2 overexpression (Down syndrome) → TSLPR (detected by flow cytometry)
- IKZF 1 deletion
- All are associated with poor prognosis

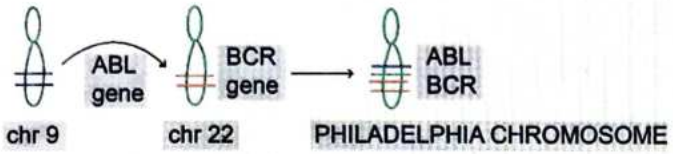
- B-cell ALL with iAMP 21
  - Seen in children
  - ≥ 5 copies of RUNX1 gene

T-cell

- Early T-cell precursor ALL (ETP-ALL)
  - Cells have CD7 (+) but CD1a/CD8 (-)
  - ≥ 1 stem cell/myeloid marker (+)
  - NOTCH 1/CDKN 1,2 mutations (-)
- NK cell lymphoblastic leukemia

42 CHRONIC MYELOID LEUKEMIA

- Myelo-proliferative disorder
- It is a problem of pluripotent hematopoietic stem cells
- Associated with Radiation exposure
- Overactive enzyme: Tyrosine Kinase
- Genetic defect: t (9;22)



t(9;22)
↓
BCR-ABL gene
↓
↑ Cell replication (WBC >>> Platelets)

- BCR-ABL fusion gene → Aka Philadelphia Chromosome. It is associated with
  - CML - 210 kda protein
  - ALL (B-Cell) - 119 kda protein
  - CNL - 213 kda protein

Clinical Features 00:06:04

- Age group: 25-60 years
- Non-specific symptoms: Fatigue, weight loss, night sweats
- Massive Splenomegaly > Hepatomegaly > Lymphadenopathy

Tri-phasic leukemia

- Chronic phase (Blasts <10%, non-specific symptoms)
- Accelerated phase (Blasts 10-19%)
  - Spleen size ↑↑
  - Basophils ↑
  - Cytogenetic changes
  - Response to TKI
    - Hematologic resistance to 1st TKI
    - → Hematologic/cytogenetic/molecular evidence of resistance to 2 sequential TKI
    - → Patient acquiring ≥ 2 mutation in spite being on TKI therapy
- Blast phase (Blasts ≥20%)
  - Anemia
  - Extra-medullary blasts
- Sudden ↑↑ size of LN is suggestive of blast phase
- On conversion to acute leukemia
  - AML (70% cases)
  - ALL (30% cases)

Additional mutations

- Trisomy 8
- Philadelphia chromosome duplication
- Iso-chromosome 17q

WORK-UP 00:16:06

Blood Examination

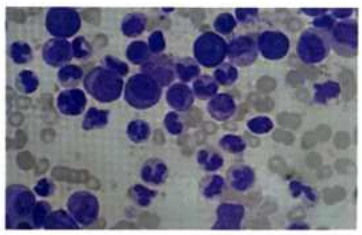
- ↑↑ TLC: DLC, Peripheral smear
  - ↑ Eosinophils
  - ↑↑↑ Basophils

Important Information

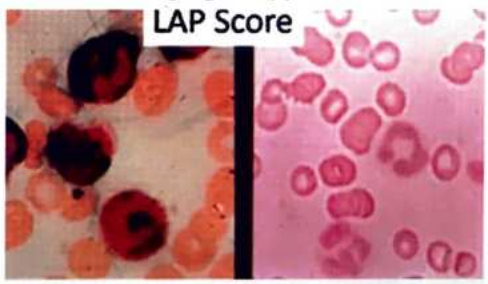
Leukemoid Reaction

- Benign condition
- TLC (50.000)
- No basophilia/eosinophilia
- Infectious features

- Serum B_{12} levels ↑↑
- LAP score: ↓↓ (also seen in PNH)
- CLL: Convent girl appearance; CML: College girl appearance

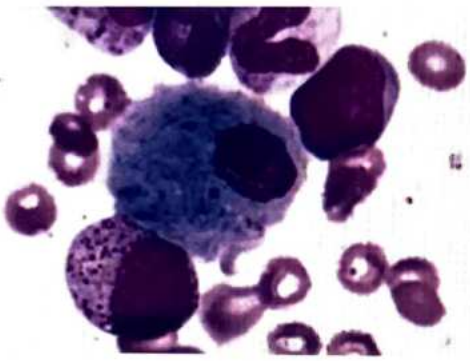


"College girl" appearance



BM Examination

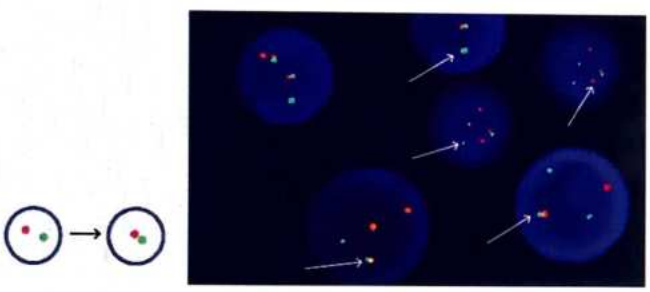
- ↑ Cellularity
- Reticulin +++
- Sea-blue histiocyte
- Pseudo - Gaucher Cells (seen in CML/ MM/ ALL/ MD/ Thalassemia)
  - No cytoplasmic inclusions
  - No iron staining



Pseudo-Gaucher cells

Philadelphia Chromosome

- Most Confirmatory test
- Demonstrated by FISH (Fluorescent In Situ Hybridization) → BCR-ABL gene Fusion



BCR-ABL fusion gene → FISH
↓
mRNA → PCR
↓
Fusion protein → Western Blot

Previous Year's Questions

Q. A patient presented with headache & fever. His investigations revealed Hb-16g/dL, TLC of 21000/μL, platelet count of 350,000. His DLC showed neutrophils (25%), lymphocyte (20%), metamyelocytes & myelocytes 40% and eosinophils 5%. Which of the following is the next best investigation for this patient? (AIIMS 2017)

A. JAK 2 mutation
B. EPO level
C. Philadelphia chromosome
D. Bone marrow biopsy

TREATMENT

00:32:31

Oncogene Addiction

- Philadelphia Chromosome → ↑ Tyrosine Kinase activity → cancer cells
- TK inhibitor: Imatinib

PROGNOSTIC SCORES

SOKAL Index

- **S** - Size of spleen
- % of circulating blasts
- **K** - Klonal cytogenetic defects
- **A** - Age
- **L** - Level of platelets

Hassford Score

- Instead of clonal evaluation → % of eosinophil & basophils is considered

43 CHRONIC LYMPHOCYTIC LEUKEMIA

- Aka Small Lymphocytic Lymphoma (SLL)
- B-cell cancer
- MC leukemia in adults
- Etiology Unknown (Not associated with Radiation)

Genetic Mutations 00:02:09

- 11q deletion
- 13q deletion (MC)
- 17p deletion
- 12q Trisomy
- NOTCH gene (gain of function)
- Somatic Hyper-mutation (slow rate of growth)
- ZAP–70 ↑↑

PATHOGENESIS

- This type of leukemia arises from
  - Naïve B-Cell
  - Post-germinal B-Cell
- B-Cell → Plasma Cell → Ig
- B-Cell mutation → Abnormal Plasma cells → Abnormal Ig

Previous Year's Questions

Q. Tumor cells in Chronic Lymphocytic Leukemia or Small Lymphoblastic Lymphoma (CLL/SLL) arise from which of the following? (AIIMS 2017)

A. Mature B-cell
B. Naive B-cell
C. Centrocytes of Germinal center
D. Progenitor B-cell

B-Cell features

- These B-Cells have higher rate of replication → Infiltration of bone marrow, lymph node & spleen
- Secretion of cytokines: TNF-α, TGF-β (Responsible for ↓ normal BMA)
- Protein affected: Vimentin (Responsible for maintaining cytoskeletal integrity) → fragile

Ig Features

- Hypo-gammaglobulinemia
- Abnormal Ig: ↑↑↑ Infections
- Auto Abs
  - AIHA
  - AIT / Auto Immune Thrombocytopenia)

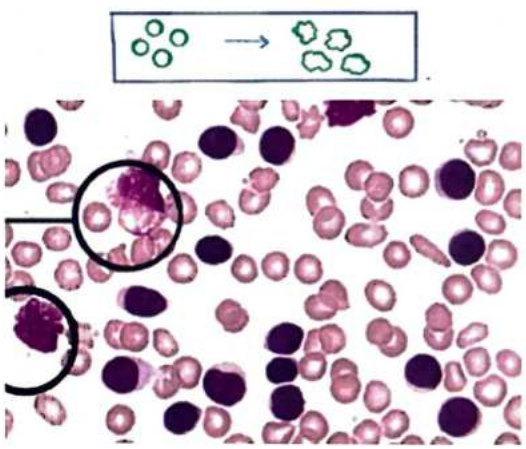
Clinical Features 00:09:35

- Elderly (>60 yrs)
- Fever, Weight loss, Night sweats
- LN enlargement
- Fatigue
- Pallor
- Asymptomatic mostly, incidental finding

WORK-UP 00:11:40

Blood Examination

- Anemia, ↑ TLC (Lymphocytosis)
- Absolute lymphocyte count (ALC): > 5000 Cells/µl
- Auto-Ab → Coomb's test (both direct & indirect positive)
- Peripheral smear: Smudge Cells & convent girl appearance



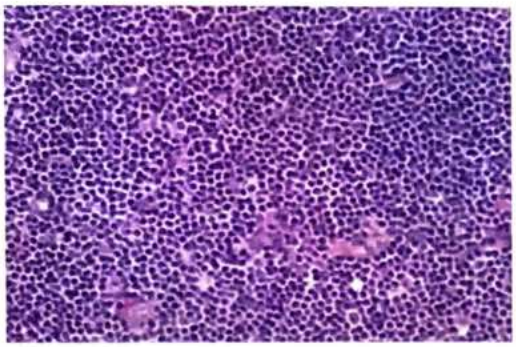
Smudge cells/Basket cells/Parachute cells

BM examination

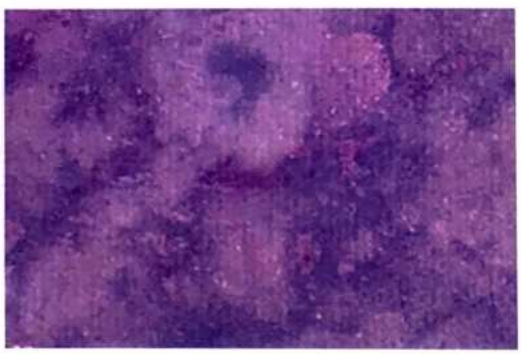
- Hypercellular
  - ↓ Myeloid cells
  - ↓ Erythroid cells
  - ↑ Lymphoid cells

LN Biopsy

- Effacement of LN due to infiltration by tumor cells
- ↑ Mitotically active cells result in focal accumulation "Proliferation centres" (Aka Pseudofollicle)



Non-Conspicuous Nucleoli



Effaced LN

Flow-cytometry

- IOC
- B-cell cancer
  - CD 10/19/21/23 +ve
  - CD 20/5 +ve
- Mantle Lymphoma: CD 5 +ve, CD 23 -ve

Important Information

- Richter syndrome: CLL/SLL → Additional Mutation → LN & splenic tissue enlargement → DLBCL (Diffuse Large B-Cell Lymphoma)

PROGNOSTIC FACTORS

00:27:13

Poor Prognosis

- 11q deletion
- 17p deletion (worst prognosis)
- 12q trisomy
- ZAP 70 ++
- NOTCH mutation
- Absence of Somatic hyper mutation

Good Prognosis

- 13q deletion

TREATMENT

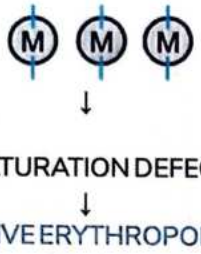
00:29:05

- Fludarabine (DOC)
- Rituximab (Anti CD20)
- Ibrutinib (B-Cell tyrosine Kinase enzyme)

44 MYELODYSPLASTIC SYNDROME

Definition 00:00:17

- Maturation defect at the level of myeloid cells leading to dyserythropoiesis



- Dyserythropoiesis leading to hypercellular bone marrow and pancytopenia blood picture
- In these patients, there is increased risk of AML

SUB TYPES 00:01:55

- 1° MDS
  - Elderly [means age 70 years]
  - Idiopathic
- 2° MDS – known cause
  - Also referred as Treatment associated MDS (t-MDS)
  - H/O exposure to anticancer Drugs/Radiations $\xrightarrow{2\text{-}8yrs}$ MDS
  - GENETIC DEFECTS
    - → Epigenetic modification
      - DNA methylation
      - Histone modification
      - Chromatin looping
    - → Nuclear transcription factors
    - → Trouble in RNA splicing

Cytogenic abnormalities 00:04:25

- Chromosome 5q deletion → Seen in Adults [MC overall]
- Monosomy 7 → Seen in children
- P53 gene
- Trisomy 8 [MYC]

Important Information

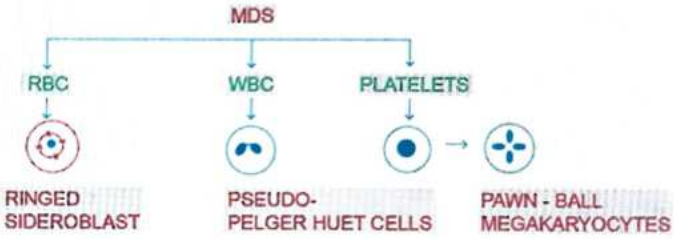
- Most common cytogenic abnormality seen in India – complex karyotype
- Most common cytogenic abnormality seen in western countries– 5q deletion

CHIP – Clonal Hematopoiesis of Indeterminate Potential 00:09:09

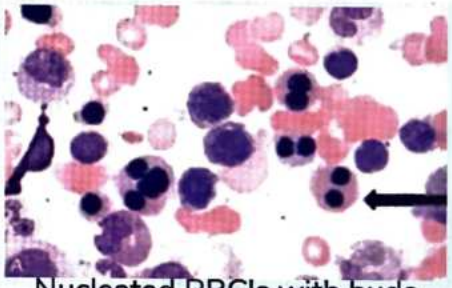
- Mutation at the primitive levels of the cells
- Pro-inflammatory state
- Associated with MDS and atherosclerosis

DIAGNOSIS 00:10:25

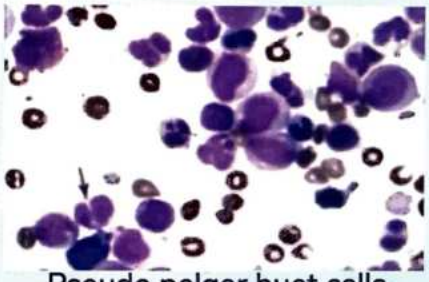
- Bone Marrow EXAMINATION
  - Hyper cellularity
  - Megaloblastic RBC
  - Nuclear budding anomaly
  - Ringed Sideroblasts
  - Pseudo pelger huet cells – MDS/AML/CML
  - Pawn - ball megakaryocytes



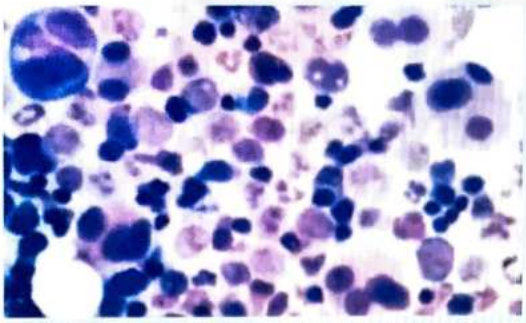
- PERIPHERAL SMEAR → Pancytopenia & abnormal cells



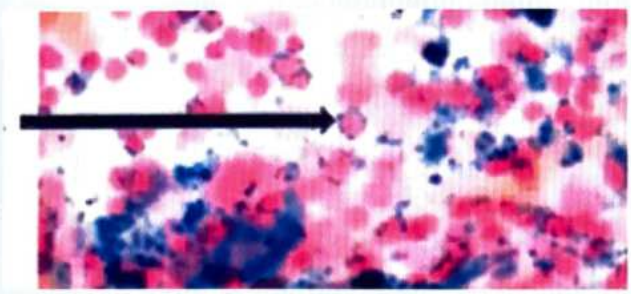
Nucleated RBC's with buds



Pseudo pelger huet cells



Pawn - ball megakaryocytes



Ringed sideroblasts

Important Information

- Ringed sideroblast can also be seen in lead poisoning, administration of anti-tubercular drugs mainly isoniazid, sideroblastic anemia

Clinical features 00:17:44

- Elderly with Fatigue
- Petechiae (Bleeding tendency – Decreased platelets)
- Fever (Decreased WBC)
- Anemia (Decreased RBC)

TREATMENT 00:18:35

- ALLOGENEIC BM TRANSPLANTATION → for young patients
- AZACITIDINE/DECITABINE→ DNA Methylation inhibitors
- LENALIDOMIDE → for 5q deletion
- ANTIBIOTICS
- REPEATED BLOOD TRANSFUSIONS

Important Information

- Repeated mutations in the myeloid cells will lead to acute myeloid leukemia [If Blasts > 20%]
- Mostly associated with 2° MDS – Patient will Progress to AML within few months
- AML is differentiated from MDS with the help of lineages

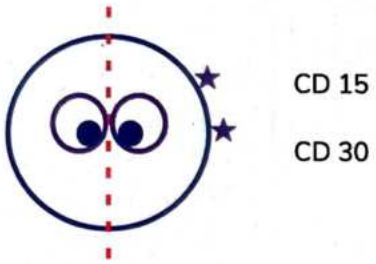
45 LYMPHOMAS: HL & NHL

HODGKIN LYMPHOMA

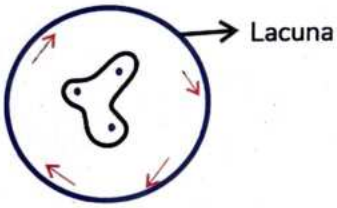
00:00:19

- Predominant LN involvement & extra nodal involvement is uncommon
- B-Cell origin → Germinal center/post GC
- EBV → ↑↑ PD-L1/L2

Reed Sternberg Cell

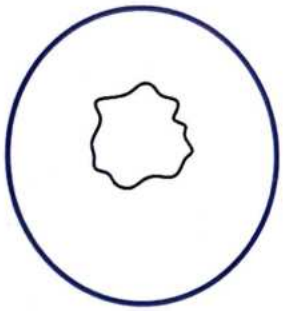


- Size: 15-45μ
- Owl-Eye Appearance
- Molecules expressed: CD15/30/45, PAX-5
  - Best marker: Cd30
- Variants of RS Cell
  - Non-classical RS cell → CD15/30 ⊖ & CD20/BCL-6 ⊕
  - Lacunar RS Cell: Presence of empty area (lacuna) around the nucleus caused by cytoplasm retracts



  - Mono Nuclear Cell: prominent nucleus & nucleolus without any cytoplasm retraction

  - Lympho- histiocytic cell/ non-classical RS cell: Presence of nuclear indentation → popcorn cell → CD 15/30 ⊖ & Cd20 ⊕



- Cytokines secreted by RS cells
  - IL-5: ↑ Eosinophils
  - TGF-β: deposition of fibrous tissue/collagen
  - M-CSF: ↑ monocytes
  - IL-10: ↓ local immunity
  - IL-13: ↑ RS cells

Important Information

- RS cells in the background of inflammatory cells is diagnostic of Hodgkin's lymphoma
- No diagnostic value if RS cell is present without any inflammatory cells

Clinical features

- Painless lymph node enlargement (rubbery discrete)
  - MC affected LN: cervical LN
- Non-specific constitutional 'B' symptoms
  - Fever
  - Night Sweats
  - Weight Loss (>10% in last 6 months)
- Atypical symptoms
  - Pain on alcohol consumption
  - Secondary amyloidosis

Diagnosis

- Excisional LN biopsy
  - Examined microscopically & using flow cytometry
  - Tumor burden is reduced
- PET/CT → Used for staging

Classical HL	Non-Classical HL
• RS cell: CD15/30 ⊕	• RS cell: CD15/30 ⊖ • CD20, BCL-6 ⊕

SUB-TYPES OF HODGKIN LYMPHOMA

00:15:51

Nodular Sclerosis HL

- Males = females
- Young adults are affected
- MC HL subtype globally
- Presence of Lacunar RS cells → Formation of nodule like structures by TGF-β secretion
- Rarely associated with EBV
- Best prognosis among classical variants

Mixed Cellularity HL

- MC HL in India
- Bimodal distribution: Young adults or > 55yrs
- Patients present with lot of 'B' Symptoms
- Associated with EBV infection

Lymphocyte Depleted HL

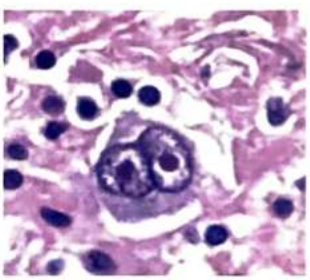
- Seen in Elderly individuals
- H/O HIV infection & strongly associated with EBV
- Bad prognosis
- Presence of Atypical Histiocytes → Hodgkin Cells

Lymphocyte Rich HL

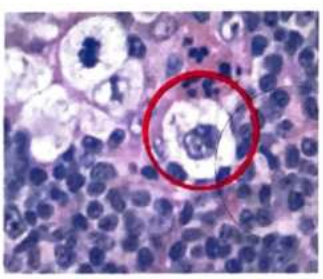
- Seen in Elderly
- Presence of mononuclear RS cells
- Can also be associated with EBV

Lymphocyte Predominant HL

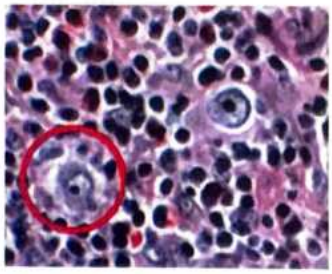
- No association with EBV
- Early presentation → overall best prognosis
- RS Cells → CD20 ⊕
- Aka lympho-histiocytic cell/popcorn cell



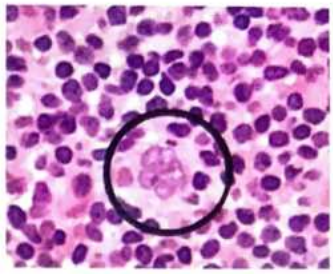
RS Cell



Lacunar cell



Mononuclear RS cell



Non-classical RS cell

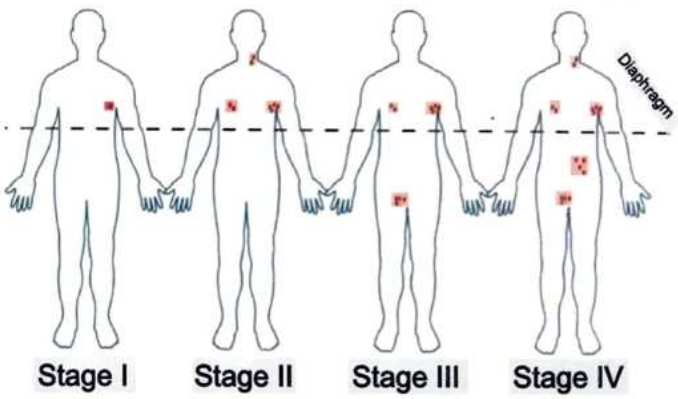
- Metastasis: Nodal disease >> Spleen

Previous Year's Questions

Q. Which of the following is incorrect statement about nodular lymphocyte predominant Hodgkin's lymphoma: NLPHL is? (INICET Nov 2020)

A. EBV negative
B. CD15/30 negative
C. CD 20+
D. Poor prognosis compared to classical variant

Ann Arbor staging of HL



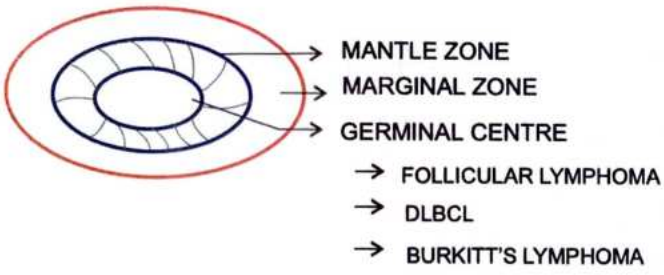
- Stage I: 1 LN or 1 extra lymphatic site
- Stage II: 2 or more LN on one side of diaphragm
- Stage III: Both the sides of diaphragm are involved
- Stage IV: Diffuse involvement

Treatment

- Adriamycin
- Bleomycin
- Vinblastine
- Dacarbazine
- Nivolumab
- Pembrolizumab

NON-HODGKIN LYMPHOMA

00:29:42



Previous Year's Questions

Q. Which of the following is the least likely cause of a bone marrow showing a dry tap?

(INICET Nov 2020)

A. Hairy cell leukemia
B. Myelodysplastic syndrome
C. Follicular lymphoma
D. Acute megakaryocytic leukemia

MANTLE ZONE LYMPHOMA

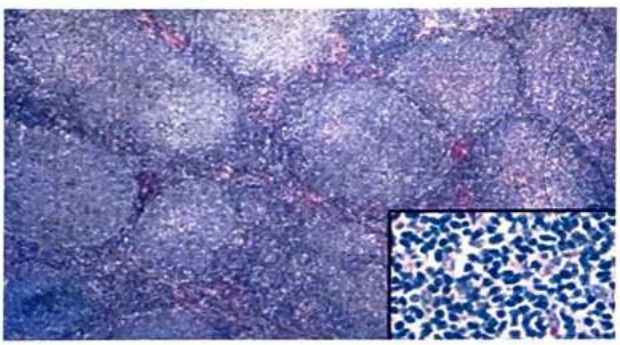
- Cell-origin: naive B-cells
- Associated with t(11;14) → → ↑↑↑ bcl-1 (Cyclin D_1) → diffuse lymphadenopathy
  - Chromosome 14 contains Ig gene
  - Chromosome 11 contains Cyclin D1 gene
- Flow cytometry
  - CD19/20/ Cyclin D1 ⊕
  - CD5 ⊕/CD 23 ⊖ → differentiates from CLL
  - New marker: SOX-11→best marker (Used in diagnosis of Cyclin D1 –ve lymphoma)

MARGINAL ZONE LYMPHOMA

- Associated with t(11;18)/H.pylori/autoimmune disorder
- Site of origin: MALT → MALToma
  - Present in GIT, Lungs

FOLLICULAR LYMPHOMA

- MC indolent tumor
- Most aggressive tumor among NHL→Burkitt's lymphoma
- MC NHL → DLBCL
- Characterized by t(14;18)→ ↑↑ bcl-2 (anti-apoptotic gene)
- Can also have additional mutation: MLL gene
- Flow cytometry → Cd19/ 20/ BCL-2 ⊕; Cd5 ⊖
- FL → DLBCL/ BL (poor prognosis)
- Characteristic feature: Presence of buttock cells (due to nuclear cleaving)



Centrocytes/centroblasts

DIFFUSE LARGE B-CELL LYMPHOMA

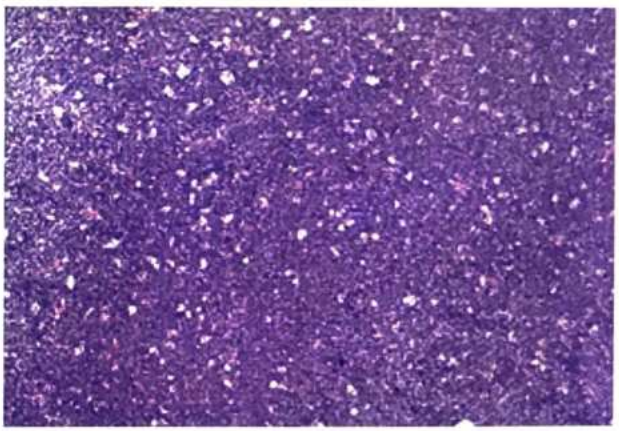
00:40:23

- MC type of NHL
- Aggressive tumor
- Etiology→Idiopathic (50%); ↑↑ BCL-6 (30%); follicular lymphoma (20%)
- Flow cytometry: CD10/19/20/BCL-6/sIg
- Variants
  - Immunodeficiency associated lymphoma: AIDS/ transplantation → EBV
  - 1° effusion lymphoma → caused by Kaposi Sarcoma Herpes Virus/HHV-8

BURKITT'S LYMPHOMA

00:43:43

- Associated with t(8;14)/t(2;8)/t(8;22)
- Chromosome 8: ↑↑ C-MYC → ↑↑↑ proliferation
- ↑ Rate of destruction → Tumor lysis syndrome



Starry sky appearance

- LN biopsy: Hyperchromatic nuclei containing tumor cells with macrophages in between → Starry sky appearance

Sub-Types

- Endemic
  - Seen in Africans

- 100% association with EBV
- Affects jaw & maxilla

- Sporadic: Involvement of GIT → abdominal mass
- HIV → ↑↑ BCL-6

Previous Year's Questions

Q. A 5 years old boy came with a clinical presentation of cervical lymphadenopathy. Microscopic picture of lymph node biopsy shows starry sky appearance. Which of the following translocation is unlikely to be seen in this condition? (JIPMER May 2019)

A. t (2:8)
B. t (8:22)
C. t (8:14)
D. t (11:18)

HAIRY CELL LEUKEMIA

- B-cell tumor
- Male >> Female
- Involvement of BM/Spleen/Liver → Pancytopenia, ↑ Atypical infections
- Majority of lymphoma → white pulp involvement
  - Exception: hairy cell leukemia/hepato-splenic lymphoma → red pulp affected
- Red pulp affected → splenomegaly/↑ infections

Diagnosis

- Blood: Pancytopenia; hairy cells (seen in phase contrast microscopy)
  - TRAP staining
- BM: Dry tap; Honeycomb/fried egg appearance in biopsy
- FC: CD11/25/103
  - Best marker: Annexin A_1

Previous Year's Questions

Q. True regarding hairy cell leukemia is? (JIPMER Dec 2019)

A. Characterized by mild splenomegaly
B. Pancytopenia is the characteristic finding
C. Mono cytosis seen
D. Hairy cells are TRAP negative

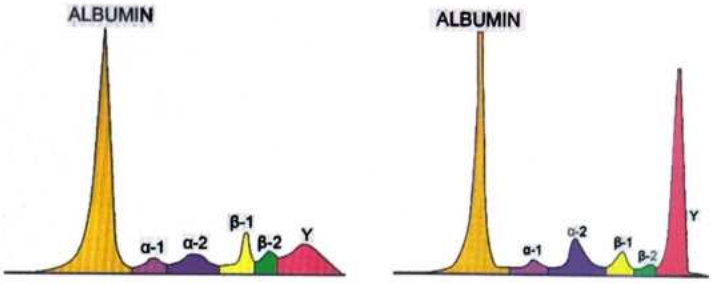
CUTANEOUS T-CELL LYMPHOMA

00:54:08

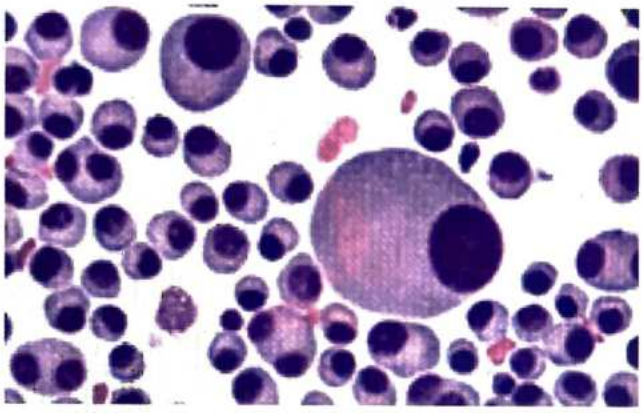
- Origin: CD_4 T-cell
- Predilection of Skin involvement → epidermotropism
- Blood involvement: SEZARY Syndrome
- Skin involvement: Pautrier's Microabscess/mycosis fungoides
- Presence of cerebriform nuclei
- Hallmark cells: horseshoe nucleus (anaplastic large cell lymphoma)
  - Associated with ALK gene mutation on chromosome 2p
- Can be CD 30 ⊕

46 PLASMA CELL DYSCRASIAS

- B Cell → Plasma Cells → Ig secretion
- Heavy chain→ 5 chains made of gamma, alpha, Mu, delta, epsilon
- Light chain → 2 chains made of kappa and lambda
- Type of heavy chain produced in max concentration: gamma chain (IgG)
- Type of light chain produced in max concentration: kappa > lambda

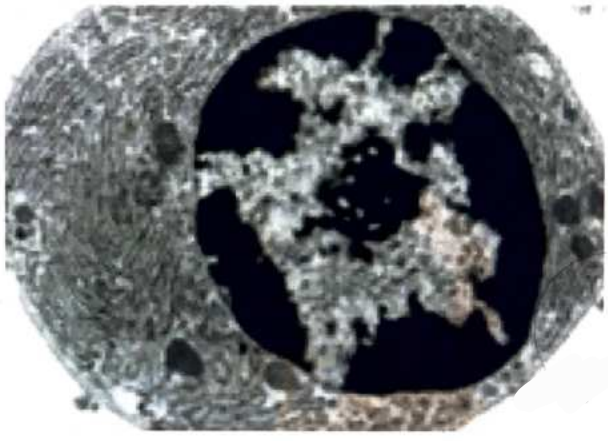


Normal 'M' spike pattern



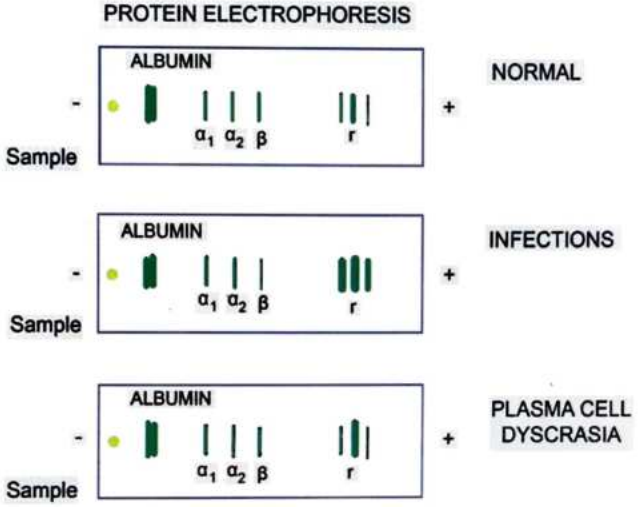
Normal Bone Marrow – Plasma cell

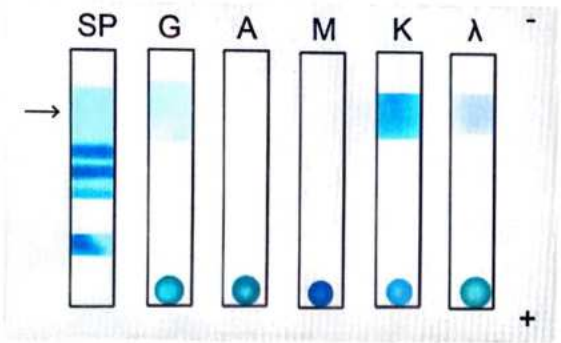
- Plasma cell has eccentric nucleus
- Peri nuclear 'Hof' around the nucleus is due to the presence of golgi apparatus.
- Basophilic cytoplasm is due to RER.



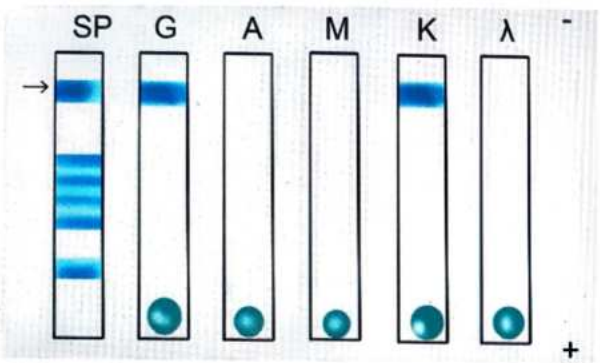
Cartwheel nucleus/clock face nucleus

- Normal plasma cell → CD19/38/45/138 (+)
- Infections → stimulate plasma cells → Ig+++ (polyclonal Ab)
- B cell mutation→ Mutation of Plasma cells→ over production of one particular light and heavy chain (monoclonal Ab)
- M spike is due monoclonal Ab
- Plasma cell cancer aka monoclonal gammopathies /paraproteinemia
- Normal serum viscosity: 1.4 – 1.8 CP units
- Plasma cell cancer viscosity: > 4 CP units (Hyper-viscosity Syndrome)
- Protein electrophoresis is of 2 types
  - Quantitative estimation – Protein Electrophoresis
  - Qualitative estimation-Immuno Fixation Electrophoresis





Normal



Plasma cell cancer

- In normal individuals
  - For heavy chain, max thickness is seen in G > A > M
  - For light chain, max thickness is seen in κ > λ
- In plasma cell cancer
  - Predominantly only one particular type of heavy chain gamma γ and one particular type of light chain κ is produced (monoclonal proliferation of plasma cells)

MONOCLONAL GAMMOPATHIES 00:21:25

- Monoclonal gammopathy of unknown significance (MGUS)
  - Most common
- Plasma cell myeloma
  - Made of multiple myeloma/smoldering myeloma/ solitary plasmacytoma
  - Overproduction of light chain >>> heavy chain
- Lymphoplasmacytic lymphoma
  - Associated with ↑ plasma cells/lymphocytes/mast cells
  - Maximum chance of causing hyper viscosity feature
- Heavy chain disease
  - Overproduction of heavy chain >>> light chain

47 PLASMA CELL DISORDERS

MULTIPLE MYELOMA

- Post-germinal center cell malignancy
- Abnormal plasma cells→abnormal Ig (light chain >> heavy chain)

Mutations

- 13q deletion (MC)
- t(11;14) → Ig, Cyclin D1
- ↑↑ MYC gene (proto-oncogene)
- Chromosome 17p deletion

PATHOGENESIS

- Abnormal plasma cell secrete IL-6 → proliferation of plasma cells (autocrine). It is responsible for causing changes by
  - Replacement of Normal BM cells → Pancytopenia
  - IL-6/TNF-α/MIP/DKK4
  - 'M' proteins

IL-6/TNF-α/ MIP/ DKK4

- Lytic lesions caused by
  - ↑ Osteoclast activity
  - Normal Osteoblast activity
- Vertebral column > Ribs > sternum > Pelvis > Skull
- Symptoms: Pathological fracture/Backache/pain on deep inspiration
- Serum Alkaline Phosphatase → Normal
- S.Ca^{2+} ↑↑ → kidney damage

'M' proteins

- IgG >> IgA >> IgM
- ↑ ESR
- ↑ Bleeding
- ↑ Viscosity of Blood → CNS (IgG_3/IgA)
- Cryoglobulin → tingling/numbness/acrocyanosis
- Kidney
  - λ_2/λ_3 → Amyloidosis
  - Light chains are filtered into urine → RTA damage (Proximal renal tubular damage)
  - Bence - Jones protein proteinuria
- ↑↑ Infections → cause of mortality

DIAGNOSIS

00:18:25

- BM Biopsy → IOC

International Myeloma working group criteria

Clonal BM Plasma Cells ≥ 10% (or) biopsy proven bony/ extra medullary plasmacytoma

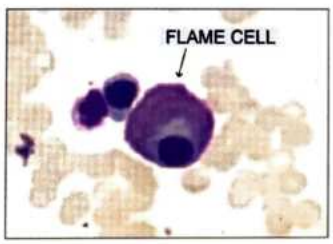
+

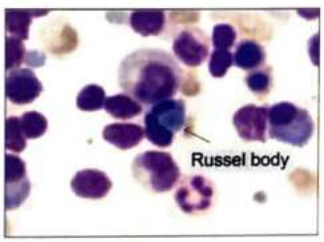
Any one of Myeloma defining events

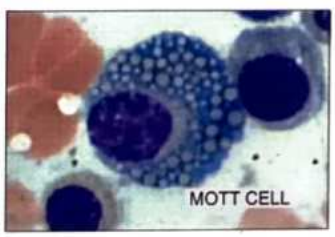
- Related organ/ tissue impairment
  - **C**alcium ↑↑ (>11mg/dl)
  - **R**enal Insufficiency (s.creatinine > 2mg/dl)
  - **A**nemia (< 10gm/ dl)
  - **B**ony lesions (≥1 osteolytic lesion)
- Biomarkers
  - **S** - Sixty (≥ 60% clonal BM cells)
  - **Li** - Light chain (involved: uninvolved → ≥ 100)
  - **M** - MRI (>1 Lesion of size ≥5mm)
- Morphology
  - Flame cells → Reddish inclusions in cytoplasm
  - Mott cell → grape like inclusions
  - Russel body → tubular or round inclusions in cytoplasm
  - Dutcher body → intra-nuclear inclusions

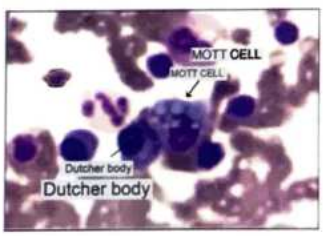
Mott cells

Flame cells









- Flowcytometry
  - Normal: CD19/38/45/138 ⊕
  - Multiple myeloma: CD19/45 ⊖; CD38/56/138 ⊕
- IHC marker: overexpression of cyclin D1

Blood

- Anemia
- Neutropenia
- ↑↑ ESR
- ↑↑ $S.Ca^{2+}$
- Normal S.Alkaline phosphatase level
- S.IL-6 ↑↑
- S.ß2 microglobulin ↑↑ (correlates with prognosis)
- Electrophoresis: 'M' spike (IgG)

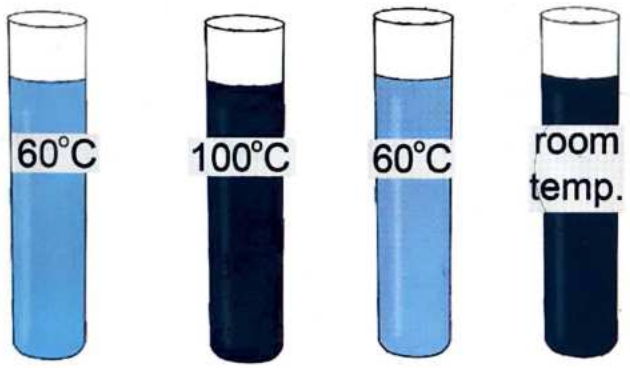
Previous Year's Questions

Q. An elderly patient presents with complaint of fatigue lower back and presence of headache for last weeks. Lab investigation revealed elevated value of ESR and his radiograph revealed the presence of multiple punched out lesion in the skull. Which of the following is the best investigation for this patient? (FMGE Aug 2020)

A. Serum electrophoresis showing IgG
B. Serum levels of CA 15-3
C. Whole body scan
D. CT read with contrast.

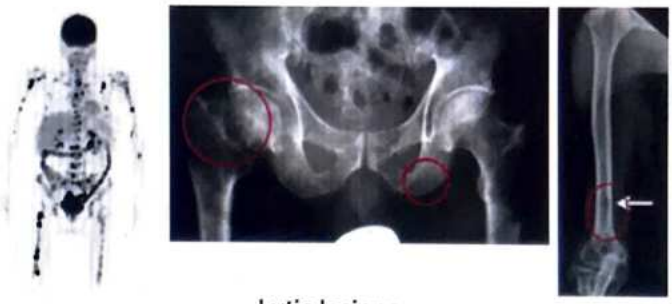
Urine

- Bence - Jones proteins
- Heat-coagulability test: At 40-60°C proteins gets precipitated
- 1 % patient → Non secretary MM

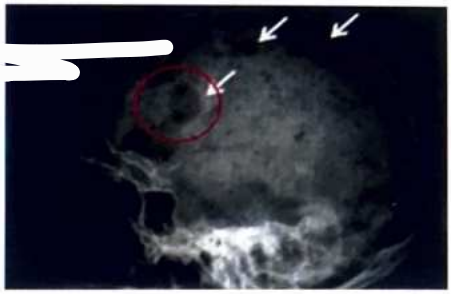


Radiological

- PET scan
- X-ray: osteolytic lesions



Lytic lesions



Punched out lesions

Important Information

Diagnosis of Plasma Cell Leukemia

- Absolute PC count >2000/µl
- PC >20% cells in peripheral blood smear

Treatment

- Lenalidomide + Boritezomib + Dexamethasone

Prognosis

- Good prognostic factor: t(11;14)
- Poor prognostic factor
  - ↑↑ MYC
  - 17p deletion
  - ↑↑ $S.\beta_2$ microglobulin
  - ↑↑ Anemia/bony lesions/kidney dysfunction

D/D OF MULTIPLE MYELOMA

00:44:42

MGUS

- < 10% BM plasma cells
- No myeloma defining events
- Prevalence

- 50 yrs (3%)
- 70 yrs (5%)

- 1 % per year progression to MM

Smoldering Myeloma

- BM plasma cells → 10-59%
- No myeloma defining events
- No amyloidosis

Multiple myeloma

- ≥ 10% plasma cells
- Myeloma defining events

Solitary Plasmacytoma

- Single lesion of clonal plasma cells
- Can be present in
  - Bone → same involvement as MM (↑ Risk of MM)
  - Soft tissue → lungs/sinus/oropharynx (Radiotherapy/ surgical resection can be done)
- Difference from MM
  - Normal BM
  - Normal skeletal screen
  - No CRAB criteria

LYMPHOPLASMACYTIC LYMPHOMA 00:51:51

- Aka Waldenstrom's Macroglobulinemia
- MYD 88 gene defect

- M' Spike → IgM (Macroglobulinemia)
- Presence of lymphocytes/PC/mast cell proliferation
- Light chains (κ) = heavy chains (μ)
- IgM → ↑ viscosity
  - MC plasma cell dyscrasia with hyper-viscosity syndrome

Multiple myeloma	Lymphoplasmacytic lymphoma
• IgG >> IgA	• IgM
• Proliferation of Plasma cells only	• Proliferation of Plasma cells/Lymphocytes/ Mast cells
• CRAB criteria ⊕	• CRAB criteria ⊖
• Infiltration of liver/LN/ spleen is not seen	• Infiltration of liver/LN/spleen is present
• Cold agglutininΘ	• Cold agglutinin ⊕

Treatment

- Plasmapheresis
- Rituximab

HEAVY CHAIN DISEASE 01:00:00

- Predominant production of heavy chain antibody
- As → α HCD/ Seligmann's Disease (MC)
  - Jejunum >> respiratory
  - Associated with Mediterranean lymphoma → ↑ intestinal parasitic load
- U → μ HCD
  - Associated with CLL
- FG → γ HCD/Franklin disease
  - Presentation as fever/LN ↑↑/hepato-splenomegaly
  - Associated with RA
  - Can develop palatal edema

Previous Year's Questions

Q. Palatal edema is significant for?

(JIPMER May 2018)

A. Alpha heavy chain disease.
B. Gamma heavy chain disease.
C. Mcu heavy chain disease.
D. Light chain disease.

CLINICAL QUESTIONS

1. A 5-year-old boy with no relevant pre-existing medical issues appeared with perianal soreness and a 5-day-old fever. A general pallor and a perianal abscess were discovered during the examination. Hemoglobin (Hb) was 5.0 g/dL, leukocytes were 0.209 x 109/L, neutrophils were 0.006 x 109/L, and platelets were 4.9 x 109/L on the initial complete blood count (CBC). The results of a bone marrow biopsy (BMB) and bone marrow aspirate (BMA) revealed severely hypoplastic bone marrow with no cancer cells. It was later determined that it was a case of ALL. Except for the following, all of the following are positive prognostic markers for paediatric acute lymphoblastic leukaemia:

A.CNS disease at diagnosis
B. Initial WBC count of 50000/cumm
C. Hyperdiploidy
D.t(12;21)

Solution

- Favourable prognostic markers include
  - Age between 1 and 10 years,
  - A low white cell count at diagnosis,
  - Hyperdiploidy,
  - Trisomy of chromosomes 4, 7, and 10, and the prese[illegible]1).
- Several factors are associated with a worse prognosis:
  - Infancy, older age at diagnosis (presentation in adolescence or adulthood)
  - Translocations involving the MLL gene [t(4;11)]
  - Higher WBC count at diagnosis (peripheral blood blast counts greater than 100,000/cumm)
  - Presence of CNS disease at diagnosis
  - Hypodiploidy

Reference

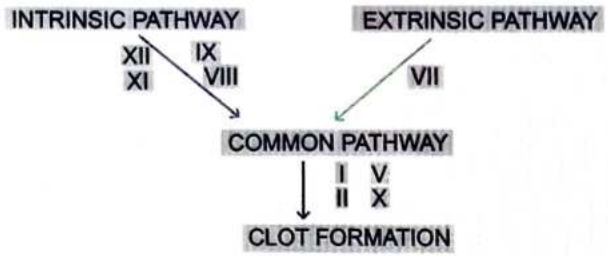
- Robbins & Cotran Pathologic Basis of Disease 10th ed pgs 596, 597

LEARNING OBJECTIVES

Unit 8 PLATELET AND BLOOD TRANSFUISON

- **Concepts of bleeding disorders**
  - Haemostasis
  - Defect in Blood Vessel
  - Normal Physiology
  - Platelet Bleeding Disorder: Functional platelet disorders, Ristocentin agglutination test, Platelet defects, Coagulation defects
- **Introduction to platelet disorders**
  - Functional Defect
  - Quantitative defect/ thrombocytopenia
- **Basic concepts of Angiopathic hemolytic anemia**
  - Definition and subtypes
- **Clotting factor disorders and concepts of factor inhibitors**
  - Haemophilia
  - Concept of factor inhibitors
- **Blood transfusion and blood grouping**
  - Blood transfusion: Whole Blood Components, Indications, Complications of Blood Transfusion, Massive Blood Transfusion
  - Blood Grouping; ABO Blood Grouping, A/ B/ H antigens, Other Blood Groups
- **Von Willebrand disease**
  - Von Willebrand Factor: Source
  - Acquired form of Von Willebrand Disease
  - Sub Types of Von Willebrand Disease
  - Clinical Features
  - Diagnosis
  - Ristocetin Test
- **Platelet disorders**
  - ITP [Immune Thrombocytopenic Purpura]: Sub Types, Pathogenesis, Diagnosis, Treatment
  - Hemolytic Uremic Syndrome: Sub Types, Clinical Features , Investigations
  - Thrombotic Thrombocytopenic Purpura [TTP]: Causative Factors, Clinical Features, Pathogenesis, Treatment
  - Disseminated Intra Vascular Coagulation [DIC]: Risk Factors, Pathogenesis, Diagnosis, Clinical Features, Treatment

48 CONCEPT OF BLEEDING DISORDERS



Hemostasis

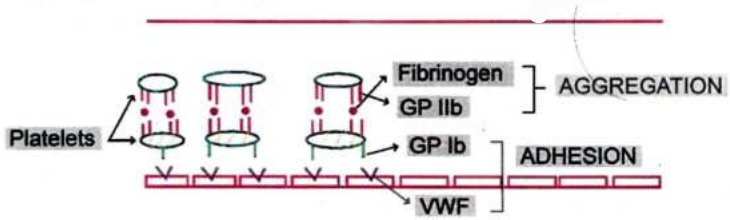
- Blood vessels - vasoconstriction (Serotonin, endothelin)
- Platelets - Temporary plug/clot
- Coagulation cascades - Permanent plug/clot

Defect in Blood Vessel

- Vitamin C deficiency → poor functioning of collagen → peri-follicular hemorrhages
- Senile purpura
- HHT (Hereditary Hemorrhagic Telangiectasia)

Normal Physiology

- Adhesion 00:04:05
  - On trauma, enhanced expression of GP-Ib on platelets and VWF on WB body of endothelial cells.
  - Adhesion: GP-Ib + VWF
- Activation
  - Platelets are smooth surfaced, disc shaped & enucleated cells
  - On activation: Spiky appearance. It contains alpha granules & delta granules (ADP, epinephrine, serotonin, TXA2 & Ca^{2++}) and they release their contents
- Aggregation
  - Due to activation of platelets, there's enhanced expression of GP-IIb
  - GP-IIb is responsible for platelet-platelet interaction (temporary plug)
  - Fibrinogen, a plasma proteins helps in platelet aggregation
  - Activation of coagulation cascade is responsible for permanent plug.



PLATELET BLEEDING DISORDER

- ↓ Platelet count - Thrombocytopenia disorder
  - Normal Platelet count: 150,000 – 450,000 per cubic mm
- Functional platelet disorder

FUNCTIONAL PLATELET DISORDERS 00:12:49

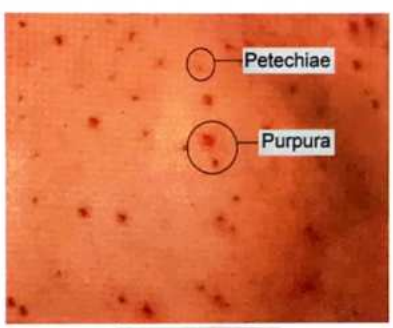
Important Information

- **Adhesion: VWF, GP-Ib**
- **Activation: TxA_2, ADP**
- **Aggregation: GP-IIb, Fibrinogen**

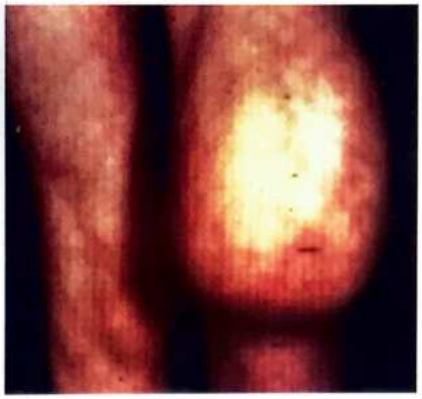
- Adhesion Defects
  - GP-Ib defect: Bernard Soulier Disease
    → Peripheral Smear: Big size platelets present
  - VWF defect: Von Willebrand Disease
- Activation defects
  - Aspirin: ⊖ TXA_2
  - Clopidogrel: ⊖ ADP
  - Vorapaxar: ⊖ PAR-1 receptor
- Aggregation defect
  - GP-IIb defect: Glanzmann's Disease/Glanzmann Thrombasthenia
  - Fibrinogen defect: hypofibrinogenemia, afibrinogenemia

Ristocentin Agglutination Test

- Ristocetin - ↑ interaction of GP-Ib and VWF in normal individuals
- RAT test is abnormal in Von Willebrand Disease, Bernard Soulier Disease



Platelet bleeding



Clotting Factor bleeding

PLATELET BLEEDING	CLOTTING FACTOR BLEEDING
• Superficial bleeding (mucosa/skin)	• Deep tissue bleeding (joints/muscles)
Investigations	**Investigations**
• Bleeding time • Platelet count ↓↓/normal • RAT • PFA-100	• Prothrombin time < INR • aPTT/PTTK • Thromboelastography

PLATELET DEFECTS

00:21:36

- Superficial bleeding (Skin/mucosa)
- Petechiae (< 1 mm)/ purpura (1-2 mm)
- Hematuria
- ↑ Menstrual loss
- Gum bleeding
- Melena

COAGULATION DEFECTS

- H/O Trauma
- Deep Tissue Bleeding
  - Joints - Hemarthrosis
  - Muscles - Hematoma

ADD ON INFO

00:28:35

- Samples
  - Platelet bleeding disorder: platelet rich plasma
  - Clotting factor bleeding: platelet poor plasma

Previous Year's Questions

In a platelet poor plasma sample, calcium and tissue thromboplastin is added. This is used to assess which of the following pathway? (AIIMS 2017)

A. Extrinsic
B. Intrinsic
C. Fibrinolytic
D. Common

Clotting factor bleeding

- Plastic syringe should be used
- Within 2hrs
- Blue Vacutainer with 3.2% Tri-sodium citrate (anticoagulant) is used → 1:9
  - 1 part of anticoagulant
  - 9 part of patient blood
- Performed at room temperature (20-24°C)

49 INTRODUCTION TO PLATELET DISORDERS

00:00:15

Platelet Defects

↑ BT	↑ BT
Normal platelet count	↓ Platelet count
↓	↓
Functional Defect/ Qualitative Defect	Quantitative Defect / Thrombocytopenia

Functional Defect 00:03:29

1. BS defect
2. VWD
3. Glanzmann's disease
4. ↓ Fibrinogen
5. Drugs

Quantitative defect/ thrombocytopenia 00:04:35

- ↓ Platelets ⟶ stimulation of BM

Stimulation of BM	
↑Activity	↓ Activity
↓	↓
Megakaryocytic Thrombocytopenia	Amegakaryocytic Thrombocytopenia

- Normal Platelets: 1.5 Lakh - 4.5 Lakh /mm3
- Thrombocytopenia: < 1 lakh / mm3

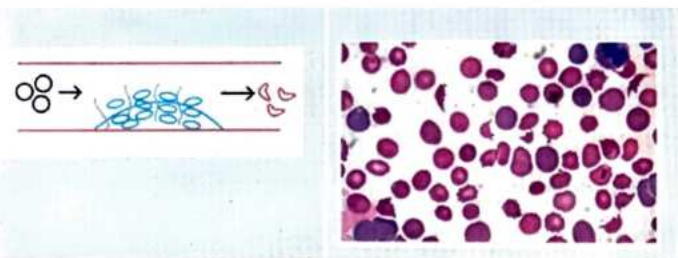
00:08:36

Megakaryocytic Thrombocytopenia	Amegakaryocytic Thrombocytopenia
1. Immune mediated (Coombs +ve)	• BM Failure [Fibrosis | Radiation]
• ITP	• B12 / FA Deficiency
• Dengue	• Leukemia
• SLE	• Drugs [Anti-cancer Drugs]
• B cell cancers	• Aplastic Anaemic
• Drugs [Quinidine / Heparin]	
2. Non-Immune causes (Coombs -ve)	
• DIC	
• HUS	
• TTP	

50 ANGIOPATHIC HEMOLYTIC ANEMIA: BASIC CONCEPTS

Definition: 00:00:17

- Pathology in the blood vessels leading to the Physical damage of RBCs



Important Information

- M.C condition associated with microangiopathic hemolytic anemia is DIC

SUB TYPES

- MACRO ANGIOPATHIC HA 00:01:44
  - Anemia caused by systemic circulation vessels or large vessels
  - a/w Prosthetic cardiac valves [Aortic valve >>> Mitral valve]
  - a/w Severe Aortic Stenosis
  - a/w Synthetic vascular graft
  - a/w Cavernous Hemangioma
- MICRO ANGIOPATHIC HEMOLYTIC ANEMIA 00:05:35
  - Similar situations in small blood vessels
  - a/w HUS / TTP / DIC
  - a/w Eclampsia
  - a/w Scleroderma
  - a/w Malignant HTN
  - a/w March hemoglobinuria [Soldiers]

51 CLOTTING FACTOR DISORDERS

HEMOPHILIA

Important Information

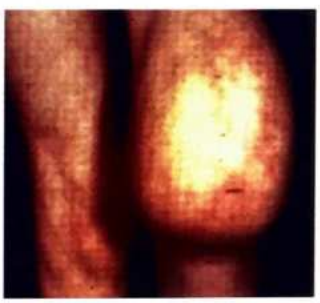
- MC inheritable cause of bleeding: Von-Willebrand Disease
- MC inheritable cause of life threatening bleeding: Hemophilia A

Sub Types
- Hemophilia A: ↓↓ Factor 8 (XLR)
- Hemophilia B: ↓↓ Factor 9 (XLR)
- Hemophilia C: ↓↓ Factor 11 (AR)

HEMOPHILIA – A

00:03:05

- Male >> Female
- X-linked recessive condition
- Gene: F8 gene → inversion of intron 22 sequence
- H/O trauma → Tissues
  - Joints
  - Muscle: Pseudo-tumor syndrome



Target joint

Diagnosis
- P/C: Normal
- PT: Normal
- BT: Normal
- aPTT: Elevated
- Factor 8 level
  - 90%: ↓↓↓ Factor 8
  - 10%: Normal (Functional defect of factor 8)
- Factor 8 Source
  - Liver: Sinusoidal Endothelial cells (Kupffer cells)
  - Kidney: Tubular Epithelial cells
- For proper formation of clot, only 30-50% of factor 8 is required
  - Mild: 6-50% of factor 8 level
  - Moderate: 2-5% of factor 8 level
  - Severe: < 1% of factor 8 level

Treatment 00:10:25
- Desmopressin
- Humate (rVIII)
- Cryoprecipitate (factor 1/8/13/VWF)
  - Contains 80U of factor 8

Previous Year's Questions

Investigation to distinguish between pregnancy acquired hemophilia A and lupus anticoagulant? (JIPMER 2019)

A. Factor 8 assay
B. dRVVT test
C. VWF assay
D. aPTT

HEMOPHILIA B [CHRISTMAS DISEASE]

00:11:56

- X Linked Recessive
- Associated with ↓↓ Factor IX levels

Diagnosis
- BT – Normal
- PT – Normal
- P/C – Normal
- aPTT - ↑↑↑
- Factor VIII – Normal
- Factor IX - ↓↓

Treatment
- Recombinant Factor IX
- Fresh Frozen Plasma

HEMOPHILIA C
- ↓↓ Factor 11
- Autosomal Recessive

CONCEPT OF FACTOR INHIBITORS

00:15:24

- Abs against factors given → ↓ clotting Factor activity
- Idiopathic

Causes

- Recipients of clotting factors
- Pregnancy/female
- Auto immune disorders
- B-cell cancer

Clinical features

- Similar to Hemophilia
- ↑↑ aPTT

↑↑ aPTT

Add Heparinase → ↑↑ aPTT

↓

Normal aPTT

↓

- Hemophilia (Factor deficiency)
- Factor Inhibitor

MIXING STUDY [Distinguishes Hemophilia & Factor inhibitor]

- 1:1 of Patient & normal plasma

aPTT test	Factor deficiency	Factor Inhibitors	Lupus anticoagulant
Immediate	Normal	Normal	↑↑
Late	Normal	↑↑	↑↑

Treatment

- Immune-tolerance induction
- Rituximab

52 BLOOD TRANSFUSION AND BLOOD GROUPING

BLOOD TRANSFUSION

Introduction

00:00:46

Healthy voluntary	350 ml in CHITRA BAG ®	+ Anti coagulant Solution [49ml]

- 450 ml Blood → 63 ml anti coagulants

Anticoagulants Solutions

00:01:52

Anti Coagulants Solution	Shelf Life	
• ACD	Acid Citrate Dextrose	21 Days
• CPD	Citrate Phosphate Dextrose	21 Days
• CPD-A	Citrate Phosphate Dextrose - Adenine	35 Days
• SAGM	Saline Adenine Glucose mannitol & Citrate & Phosphate	42 Days

- Saline: Isotonic
- Adenine: ATP generation
- Glucose : RBC nutrition
- Mannitol: ↓ Lysis
- Citrate: ↓ ca2+ → ↓ clot formation
- Phosphate: Buffer [maintains PH]

Whole Blood Components

00:07:28

Refer Table 52.1

Cryoprecipitate rich in
- VMF
- Factor 8
- Factor 13
- Fibrinogen

FFP rich in
- Other clotting factors

Indications

1. Whole blood transfusion
   - Massive Blood transfusion
   - Exchange transfusion
   - 1 Unit transfusion: ↑ 1 gm | dl Hb & 3% ↑ HCT
2. Packed RBC indication: Anemia
3. Frozen RBCs with Glycerol (↓ lysis) indicated for Autologous transfusion
4. Platelets indication: ↓ Platelet count
5. FFP Indications: Burns, Clotting factors deficiencies
7. Cryoprecipitate indications: Clotting factors deficiencies

Properties of Blood Transfusion Set

00:16:58

- Transfusion needle: 18-19 gauge
- Filter:
  - 170-200 μ
  - micro aggregates can enter

Important Information

- Transfusion of fresh frozen plasma or cryoprecipitate should be started as early as possible and finished within 20 min.

	Start	Finish
Whole blood	within 30 min	4 hrs
FEP	ASAP	within 20 min
Cryoprecipitate	ASAP	within 20 min

Platelets 00:21:10

- Random donor Platelets: ↑↑ 5000 - 10000 with 1 unit
- S/E: ↑ Alloimmunization 1 unit / 10 kg BW
- Single Donor Platelets: Plateletpheresis
  - 6 Units can be obtained from a single donor
  - ↓ Immune Reactions
  - Transient hypocalcemia can occur
  - Peri oral numbness / tingling

Complications of Blood Transfusion 00:26:40

Donor

- Pain, bruise, hematoma
- Vasovagal Syncope
  - Countered by
    - → raising the foot end of donor
    - → Supplementing with fluids
- Apheresis → Citrate
  - Transient hypocalcemia
  - Prevented by Slow infusion
  - Rx by oral Ca2+ supplementation

Recipients

- Fever
  - > 1°C than normal
    - Aka febrile Non-Hemolytic Transfusion Reaction [fNHTR]
    - MC blood transfusion Reaction
- Acute Hemolytic Transfusion Reaction / Mismatched Transfusion Reaction ♀
  - d/t mismatching [mostly dlt clerical error]
  - Acute Reaction
  - Takes place with

    whole blood, Platelets, FFP } should be ABO compatible

Clinical features

- In conscious patient
  - High grade fever with chills & rigors
  - Flank pain [Hemoglobinemia & Hemoglobinuria ⊕]
- Oozing of blood from venipuncture [in comatose patient]

Management

- Stop BT
- Maintain IV Line with saline
- Blood Bank bag → Sampling of patient for mismatch
- Anaphylactic Reaction
  - ↑ risk with Ig A deficiency
- TRALI [Transfusion Related Acute Lung Injury]
  - Seen with in 6 hrs of FFP infusion
  - D/t antibodies against WBCs
  - Non - Cardiogenic pulmonary edema ⊕
- Post Transfusion Purpura
  - Seen with platelet transfusion after 7-10 days
- Graft VS Host Disease
  - D/t immuno-competent donor T cells
  - Seen after 8-10 days
  - Skin > Intestines > Liver involvement
- Infections
  - Maximum with Platelets
  - Malarial trophozoites transmits through all components
  - Seen with Bacteria
    - → Yersinia enterocolitica
    - → Pseudomonas
    - → Coagulase negative Staphylococcus
  - Prevented by Screening

Massive Blood Transfusion 00:46:45

- > 1 Blood volume in 24 hrs
- > 50% Blood volume within 3 hrs

Complications

1. Hypothermia [prevented by inline warmers]
2. Electrolyte Disturbances

- ↑↑ K+
- Citrate: ↓↓ ca2+

:  → HCO_3^- → Metabolic Alkalosis

3. Dilutional Coagulopathy

- DIC → Death
- 1: 1:1 PROTOCOLQ → Protective against
- RBC: Plasma : Platelets Dilutional Coagulopathy related mortality

Alternatives of blood

- Hb solutions
- Perfluoro carbons / Artificial Blood } has ↓ t 1/2
  - Used at Balloon angioplasty

BLOOD GROUPING

ABO Blood Grouping 00:54:17

- MC Blood grouping System
- A/B antigen genes Located on: Chromosome 9
- H antigen genes Located on: Chromosome 19
- Full expression of these genes occur at: 1 year of Age
- ABO antigens are Glycoproteins
- ABO Antigens expressed on the surface of RBCs & Platelets

Refer Table 52.2

A/B/H antigens

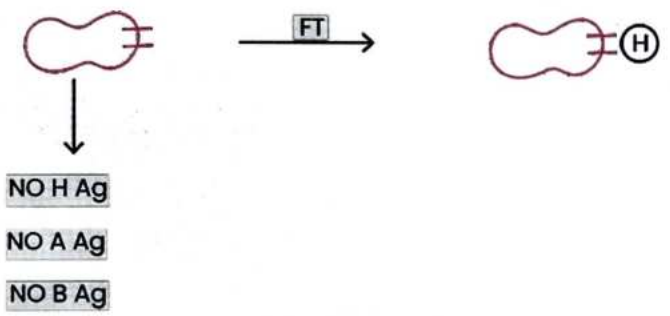
- Secretors [80%]
  - Saliva | Sweat / Plasma / Semen

- Except CSF
- Non - Secretors
- Mc specimen used to check secretors & non – secretors: Saliva

Blood Group	Ag on RBC	Ab in plasma
A	A, H	Anti-B Ab
B	B, H	Anti-A Ab
AB	A, B, H	No Ab
O	H	Anti-A & anti B Ab

- AB: Universal recipient
- O: Universal donor
- Safest blood group for transfusion in emergency: O^-
- Safest plasma for transfusion in emergency: AB^+

Bombay Blood Group 01:06:59



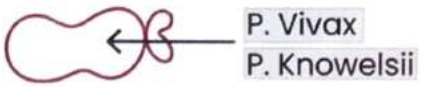
- Fucosyltransferases enzyme defect
- Discovered by BHENDE[Q]
- Rare blood group
- Anti A/B/H Ab in plasma
- Even 'O' can't be given to these patients
- Safest for transfusion for these patient → Bombay blood
- Detected by Reverse Grouping: detection of Ab in plasma

Other Blood Groups

1. Rhesus / Rh

- Antigens expressed since birth 01:11:37
- C/D/E Antigens
- D: Most important
- Genes Located on chromosome 1
- 85%: Rh ⊕
- 15%: Rh ⊖
- Rh - incompatibility: Clinical significance
  - Hemolytic Disease of Newborn
  - Ig G Antibodies
  - D/t mismatch b/w Rh group of mother with fetus

2. Duffy Antigen



- Duffy ⊖ RBCs have resistance to P. vivax / P. Knowlesii infection

3. P. Antigen

- A/w parvovirus 19 infection
- P antigen negative → resistant to Parvovirus B19 Infection
- Auto – Ab against P antigen: Donath Landsteiner Ab [Biphasic Ab]
  - Attaches at 4°C
  - Hemolysis at body temp
- Seen in Paroxysmal Cold Hemoglobinuria

4. I Antigen

- Ab Formation → RBC agglutination → Col 01:18:04 Disease
- Cold Agglutinin Disease is associated with infection caused by EBV

5. Lewis Antigen

- Mc cause of incompatibility during Pretransfusion testing
- Gene Located on chromosome 19
- Ab: Ig M^Q
- Do not cross placental barrier
- Do not cause hemolytic disease of newborn

6. KELL Antigen

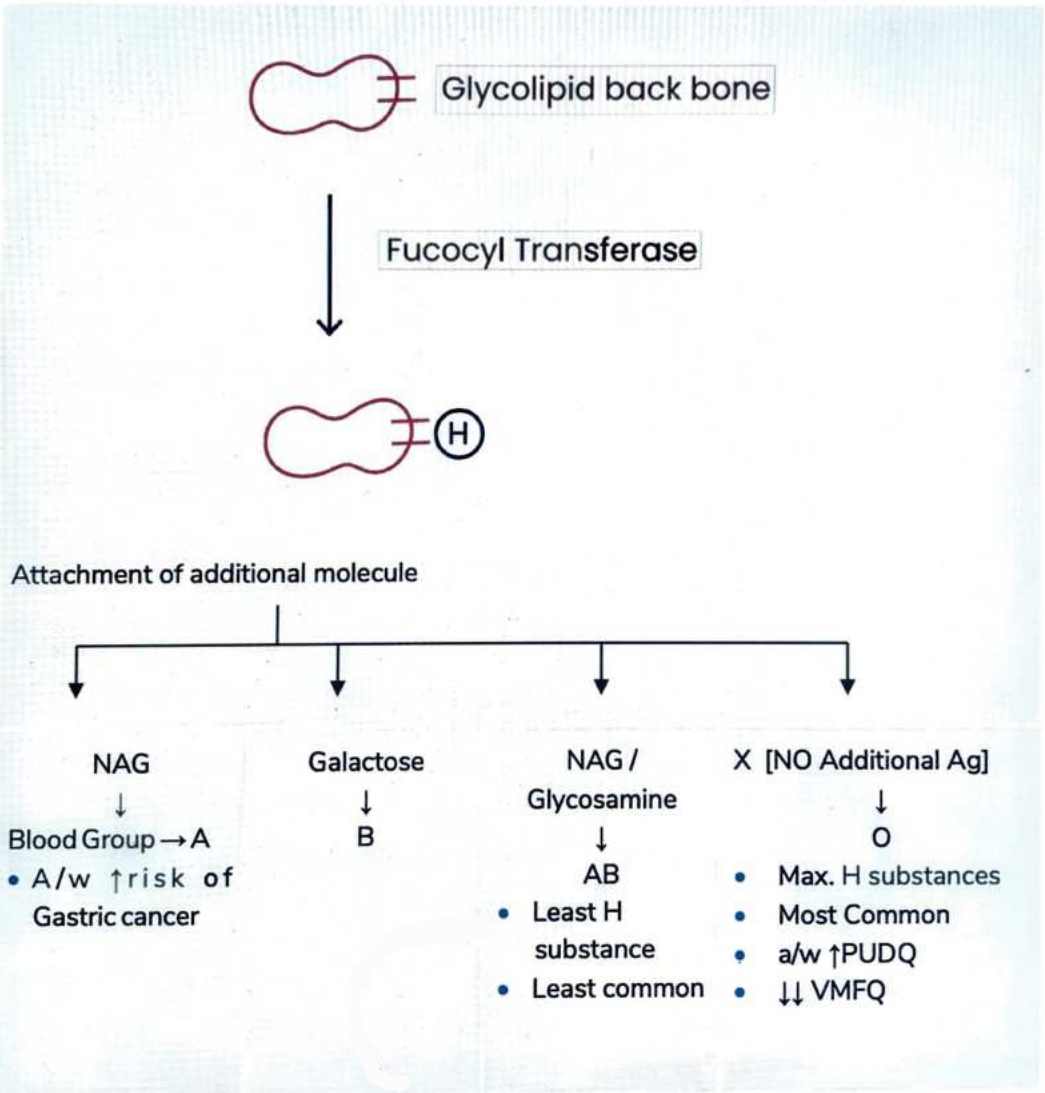
- KELL Ag + Kx Ag
- Deficiency of Kx protein causes McLeod Phenotype
  - ↓ RBC life Span
  - Cardiac defects ⊕
  - Muscular dystrophy ⊕
  - Acanthocytes ⊕

Table 52.1

42 Days ← [2-6° C]^{Q} Whole Blood [< 6 hrs] Processing

Packed RBC	Platelets	FFP	Cryoprecipitate
↓	↓	↓	↓
Stored at 2-6° C	20-24° C	-18° C	-18° C
	↓	↓	↓
	5 days	1 year	1 year

Table 52.2



53 VON WILLEBRAND DISEASE

Introduction 00:00:12

- Most common inheritable cause of bleeding: vWD

Von Willebrand Factor: Source

- Endothelial cells [Weibel-Palade Body]
- Megakaryocytes
- Hepatocytes [small quantity]
- Gene Located on chr. 12

Functions 00:01:50

- Transport of Factor 8
  - t 1/2: 2.4 hrs
  - t 1/2 with VWF : 12 hrs
- Platelet Adhesion

↓VMF

- ↓ Platelet Adhesion
  - ↓
  - ↑ BT
  - PC – Normal
- ↓ Intrinsic pathway Activity
  - ↓
  - ↑ a PTT
  - Normal PT

Acquired form of Von Willebrand Disease

- L.P.D (Lymphoproliferative Disorders): MGUS /Monoclonal gammopathy of undetermined significance (MC Plasma cell dyscrasia)♀
- **HEYDE Syndrome:** valvular defect (AS) + GI bleeding

Sub Types of Von Willebrand Disease

- TYPE I VWD: ↓ VWF [MC]♀ → Autosomal Dominant
- TYPE II VWD: Normal VWF → Qualitative Defect♀
- TYPE III VWD : ↓↓↓ VWF [most severe] ♀ → Aut. Recessive

Type 2 VMD: Sub Types

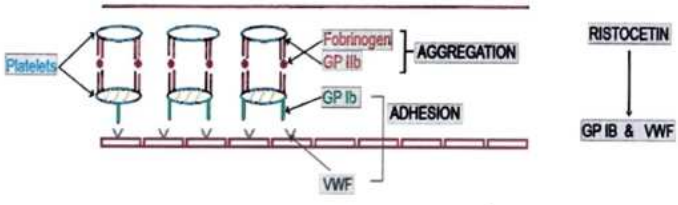
- Type 2A♀ [MC]
- Type 2B
- Type 2M
- Type 2N: Factor 8 ↓↓↓; Autosomal Hemophilia
- Autosomal Dominant

Clinical Features 00:12:36

- **Positive family history**
- **Mucosal bleeding**
  - Petechiae / Purpura
  - Epistaxis / melena
- Tissue bleeding [rare]

Diagnosis 00:14:36

- P/C: N
  - PT: N
  - BT: ↑
  - aPTT: ↑
- VMF levels: ↓
- Ristocetin Agglutination Test [RAT] [Confirmatory test]



Ristocetin Test

- Formalin-Fixed Platelets + Plasma
- Ristocetin [Person]
  - RCO: Ristocetin Cofactor activity; quantitative test, most specific
  - RIPA: Ristocetin induced platelet aggregation; functional test/qualitative test
- Normal: RAT [elicited by AGGREGO meter]
- VWD: RAT
- VMD
  - ↑ BT & ↑ aPTT → RAT ⊖
  - Ⓝ PT & Ⓝ P/C → VWF ASSAY

Previous Year's Questions

Q. True for Von-Willebrand disease? (FMGE - Jun - 2018)

A. Normal PTT
B. Decreased platelets
C. Normal PT
D. Normal BT

Rx

00:18:00

- Desmopressin for mild form
- Recombinant vWF
- Cryoprecipitate ♀ for Severe form

54 PLATELET DISORDERS

ITP [IMMUNE THROMBOCYTOPENIC PURPURA]

00:00:46

Sub Types

- **ACUTE ITP**
  - Short duration history
  - Severe
  - Sudden onset
  - Seen in children
  - H/O viral infection
  - PC < 20,000
- **CHRONIC ITP**
  - Longer duration History
  - Less Severe
  - seen in adults
  - Sub-types:
    - → 1° / Idiopathic : spleen size normal
    - → 2° [SLE / HIV | CLL]: spleen size ↑

Pathogenesis 00:04: 51

- ITP→Ab formation→against Platelet Ag → Circulation → Splenic Phagocytosis

C/F 00:07: 04

- Petechia
- Purpura
- Hemorrhagic Bullae [more in Acute ITP]
- Gum bleeding
- Hematuria
- Melena
- Normal sized spleen

Diagnosis 00:08:22

- ITP is diagnosis of exclusion
- BT ↑ / P/C ↓
- PT : Normal
- a PTT: Normal
- ↑ Mean platelet volume
- Coombs Test
- BM Examination → Active → Megakaryocytic Thrombocytopenia ♀

Treatment 00:12:13

- Symptomatic Mx for Acute ITP
- Chronic ITP
  - Steroids
  - IV Igs
  - Splenectomy - removal of B cells → no antibody formation

HEMOLYTIC UREMIC SYNDROME

00:13:28

Sub Types

1. Typical HUS: H/o Acute Gastroenteritis
   - Caused by: E. coli 0157 / H7, Shigella dysenteriae
     - Both release a toxin which is responsible for forming Platelet rich Thrombi
2. Atypical HUS
   - Mutation of Complimentary Proteins [CD 46 / factor H, I] → Platelet rich Thrombi
   - Drugs [Mitomycin / Ticlopidine]

Clinical Features 00:18:47

- Classical Triad [K / A / T or R / A / T syndrome]

1. Renal Failure
2. Microangiopathic HA
3. Thrombocytopenia

- Child with H/O Bloody Diarrhea → Renal Dysfunction + Purpura

Investigations

- ↑ BT
- PT } Normal
- a PTT
- ↓ PC

THROMBOTIC THROMBOCYTOPENIC PURPURA [TTP]

00:26:14

- Liver ⟶ ADAM TS 13 [metalloprotease] ⟶ Damage to VWF Clumps

Causative Factors

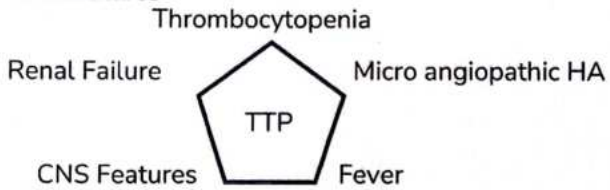
1. Deficiency of Adam Ts 13 K/a Upshaw - Schulman Syndrome
2. Ab formation against ADAM TS 13 M/c

- Seen with Auto immune disorders & certain Drugs [Mitomycin Ticlopidine]
- In Both deficiency and Ab formation against Adam Ts 13 there is an↑ VWF clumping causing ↑ Platelet Right Thrombi

Clinical Features

- Pentad
  - Thrombocytopenia
  - Microangiopathic Hemolytic anemia
  - Renal failure
  - Fever
  - CNS features

00:32:29



Pathogenesis

- Congenital / Deficiency
- Autoantibodies against Adam Ts 13

Treatment

- Treated by Plasmapheresis

DISSEMINATED INTRA VASCULAR COAGULATION [DIC]

00:36:45

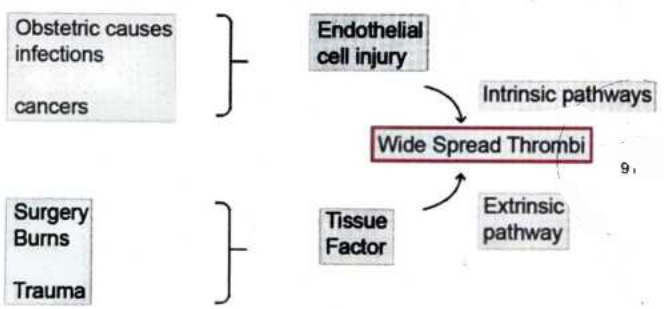
Definition

- Thrombo - Hemorrhagic disorder
- Acute | Sub acute | Chronic disorder

RISK FACTORS 00:38:20

- OBSTETRIC CAUSES [MC]
  - Retained placenta
  - Dead Fetus
  - Amniotic fluid embolism 00:39:20
- INFECTIONS – Usually in severe infections like Infective endocarditis
- CANCERS – Stomach/Colon/Pancreas/AML - M3
- BURNS | SURGERY | TRAUMA

PATHOGENESIS 00:42:58

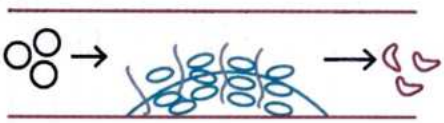


1° EVENT → WIDE SPREAD THROMBI

VASCULAR OCCLUSION ↓

- Ischemic damage
- Micro angiopathic HA

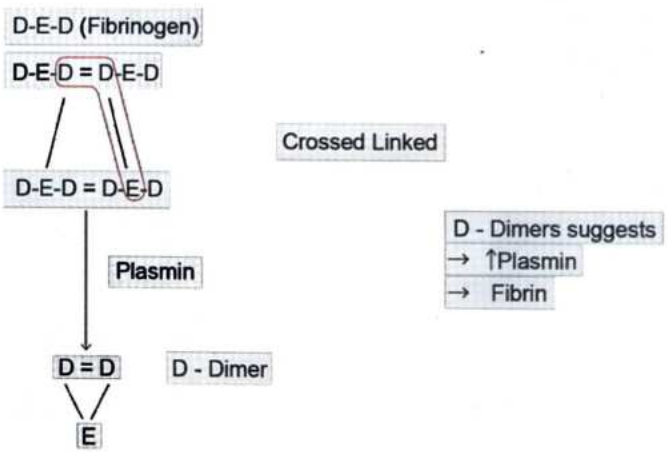
Platelets / Clotting factor Consumption ↓ Plasmin Activation ↓ ↑Bleeding [2° event]



Fragmented RBC& (Schistocytes)

DIAGNOSIS 00:54:48

- ↓Hb/↑LDH/↑PC/↑UC Bilirubin
- PERIPHERAL SMEAR shows SCHISTOCYTES [MAHA] / Helmet cells
- ↑BT/↑PT/↑aPTT
- D-DIMER ASSAY [Specific] – also ↑ in PTE



Clinical Features 01:02:46

- BRAIN → MC affected^{Q} → Confusion, altered sensorium, Dizziness, Coma
- HEART → ↓CO / Dyspnea
- KIDNEY → Acute tubular necrosis
- LUNGS → difficulty in =breathing, hypoxemia
- ADRENAL GLAND → Hemorrhage [Meningococcemia]

↓

WATERHOUSE - FRIDERICHSEN SYNODROME

Previous Year's Questions

Q. Which among the following laboratory investigation is best to reveal bleeding in disseminated intravascular coagulation? (AIIMS May - 2018)

A. Increased PT
B. Increased aPTT
C. Decreased fibrinogen
D. Increased FDPs

TREATMENT

01:06:32

- TREAT PRIMARY CAUSE
- Symptomatic management - FFP
- ANTI COAGULANTS
- Despite the BEST EFFORTS, DIC a/w HIGH MORTALITY

CLINICAL QUESTIONS

A 40-year-old female presented with acute painful swelling of left leg. USG of left leg showed deep venous thrombosis. Which of the following abnormality is least likely to be involved in this condition?

A. Factor V Leiden mutation
B. Prothrombin gene mutation
C. Hypohomocysteinemia
D. Protein C deficiency

Solution

- Factor V Leiden mutation results in an abnormal form of factor V that is resistant to protein C.
- It is associated with increased risk for recurrent thromboembolism.
- The most common thrombophilic genotypes - point mutations in the factor V gene (Factor V Leiden) and prothrombin gene (G20210A variant).
- Anticoagulant deficiencies such as antithrombin III, protein C, or protein S are rare genetic causes of primary hypercoagulability.
- Inherited or acquired causes of elevated homocysteine levels (hyperhomocysteinemia) can be prothrombotic.
- Prothrombotic effects of homocysteine may be due to ester linkages formed between homocysteine metabolites and a variety of proteins, including fibrinogen.

Reference

- Robbins & Cotran Pathologic Basis of Disease 10th ed pg 127

LEARNING OBJECTIVES

Unit 9 GASTROINTESTINAL TRACT

- **Introduction to GIT**
  - Layers if GIT: mucosa, submucosa, muscularis propria, serosa
- **Acute and chronic gastritis**
  - Acute gastritis: Causes and Microscopic feature
  - Chronic gastritis: microscopic feature, Causes, Type A gastritis, Type B gastritis
- **Congenital GIT anomalies**
  - Tracheoesophageal fistula; clinical features
  - Clinical features of infantile hypertrophic pyloric stenosis
  - Hirschsprung disease
- **GIT disorders part 1**
  - Alcohol induced esophageal disorders and Achalasia cardia
  - Esophagus
  - Esophageal cancer: Introduction, variants of esophageal carcinoma, Risk factors for SCC and adenocarcinoma, Clinical features, diagnosis, Metastasis, treatment
- **GIT disorders part 2**
  - Stomach basics gastritis and gastropathy: Cells, Gastropathy, Menetrier's disease, Zollinger Ellison syndrome
  - Peptic ulcer disease
  - Gastric tumors
- **GIT disorders part 3**
  - Malabsorption disorders
  - Inflammatory bowel disease: Crohn's disease, Ulcerative colitis
  - Intestinal polyps, colon, and Anal cancer
- **Carcinoid tumors: clinical features, cardiac involvement, diagnosis, treatment**

55 INTRODUCTION TO GIT

LAYERS OF GIT

00:00:43

Mucosa/Epithelium

- Oral cavity: Squamous epithelium
- Esophagus: Stratified squamous non-keratinized epithelium
- Stomach/Intestines: Columnar epithelium
- Anal Canal: Squamous epithelium

Important Information

- **Malignancy arising from epithelium: Carcinoma**
- **Malignancy arising from glandular/columnar epithelium: Adenocarcinoma**

Sub-mucosa

- It contains Meissner's Plexus: Secretory & absorptive in function

Muscularis Propria

- Inner: Circular layer of muscles
- Outer: Longitudinal layer of muscles
- In between 2 layers, Auerbach's/Myenteric Plexus → motor/peristaltic activity

Serosa

- It is absent in esophagus
- Gallbladder do not have submucosa & muscularis mucosa

56 ACUTE & CHRONIC GASTRITIS

ACUTE GASTRITIS

Causes

- Alcohol consumption
- Drugs (NSAID, anti-cancer drugs)
- Uremia (↓ bicarbonate secretion)
- Stress
  - ICU patients
  - Burns → hypovolemia → interfere with gastric epitherlium regeneration → curling ulcer (MC location: duodenum > stomach)
  - ↑ ICT → ↑ pressure on vagus nerve → parasympathetic stimulation → ↑ acid secretion → Cushing ulcer in stomach

Microscopic feature

- Neutrophil infiltration at the level of lamina propria

CHRONIC GASTRITIS

00:06:04

Microscopic feature

- Deposition of lymphocytes and plasma cells at the level of gastric mucosa

Causes

- Autoimmune: Type A gastritis
- H.pylori infection: Type B gastritis
- Chemicals (NSAID, bile reflux): Type C gastritis
- Radiation
- Graft vs Host disease
- Crohn's disease

Type A gastritis	Type B gastritis
• Autoimmune • Body/fundus of stomach • CD4 T-cells ↓ Achlorhydria ↓ ↑↑ Gastrin (Neuroendocrine hyperplasia) ↓ ↑ Tumor • Risk for Type 1 DM/ Hashimoto / pernicious anemia • Auto-Ab present • Chronic inflammation ↓ Intestinal metaplasia ↓ ↑ stomach cancer	• Bacterial infection • Natural host: humans • Associated with urease secretion/ Cag.A/VAC-A → ↑ stomach cancer • Antrum of stomach • Clinical feature ○ ↑ HCL → Duodenal ulcer ○ Cag .A ↓ Pangastritis + multifocal atrophy ↓ ↓HCL ↓ Adenocarcinoma ○ Reactive T-cells ↓ B-Cell proliferation ↓ MALToma (post-germinal B cell)

Previous Year's Questions

Q. Which of the following not a pathological feature of H.Pylori chronic gastritis? (JIPMER 2019)

A. Eosinophilic gastritis
B. Intraepithelial neutrophil deposits
C. Affects intestinal gland formation in the stomach
D. Sub-epithelial plasma cell deposits

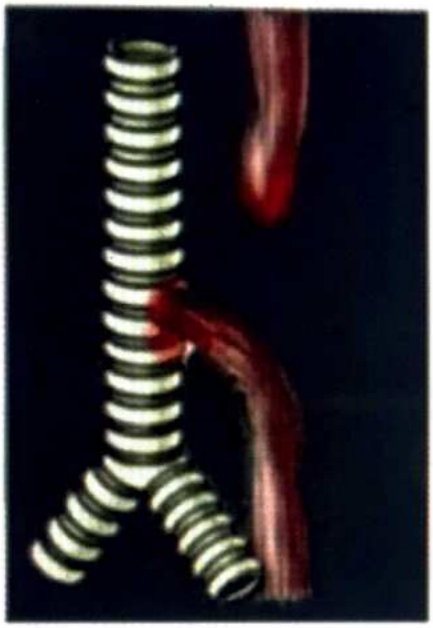
57 CONGENITAL GIT ANOMALIES

TRACHEO- ESOPHAGEAL FISTULA 00:00:12

- Fistula is an abnormal connection present between two epithelial surfaces- esophagus and trachea.
- can be b/w 2 tubings or b/w 1 tubing & Skin
- congenital defect

Most Common Variant

- upper end of esophagus end in a blind pouch



- Lower end of esophagus communicates with part of trachea just above the bifurcation.

CLINICAL FEATURES 00:01:12

- Poly hydramnios
- Abdominal distension
- Aspiration [pneumonia]

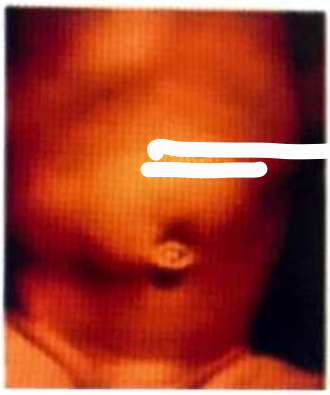
Suspected When

- When newborn baby not able to Swallow milk
- When not able to pass NG tube in new born baby

Treatment

- Surgical Mx

INFANTILE HYPERTROPHIC PYLORIC STENOSIS 00:03:10



- Earlier Name: Congenital Hypertrophic Pyloric Stenosis
- But this condition , not present at the time of birth, so name is changed

Associated with

- Trisomy 18 [Edward Syndrome]
- Trisomy 21 [Down Syndrome]
- Exposure to Erthyromycin [motilin receptor agonist] in 1st two weeks of life

CLINICAL FEATURES 00:03:47

- present at 3-6 wks after birth
- more common in Male babies
- New onset regurgitation
- Non - bilious , projectile vomiting after Feeding
- Demands refeeding
- OLIVE LUMP [1-2 cm Firm , ovoid , abdominal mass]

Diagnosis

- USG

Treatment

- Surgical Mx: Pyloromyotomy

HIRSHSPRUNG DISEASE 00:05:11

- Also Known as CONGENITAL AGANGLIONIC MEGACOLON
- Prevalence -1 : 5000 live births

Parthenogenesis:

Due to Failure of migration of neural crest cells into the bowel

↓

Absence Of gangl ionic cells [particularly Nitric oxide releasing cells] in bowl

↓

Affected part of bowel not able to relax

↓

Proximal part of affected bowel will be dilated

- Short segment hirshprung disease:
- Long segment hirshprung disease:
- MC site involved:
- If it involves part of large intestine
- If it involves entire colon
- Rectum[Q]

Genetics

- loss/under activity of RET gene[Q]
- in 10% a/w Down Syndrome[Q]

Clinical features

- Failure of passage of meconium leading to abdominal distension
- constipation
- Dilatation of segment leads to thinning of bowel wall
  - cecum is prone for rupture

Diagnosis

- confirmed by RECTAL SUCTION BIOPSY[Q]
  - Absence of ganglionic cells
  - nerve fibers are hypertrophied

58 GIT DISORDERS PART-1

ALCOHOL INDUCED ESOPHAGEAL DISORDERS

00:00:11

Mallory - Weiss Tear	Boerhaave Syndrome
• Mucosal involvement • 90% of the cases have tear below GEJ & 10% in lower esophagus	• Muscle layer affected • 3-5cms above GEJ particularly on posterolateral part of the left side
	

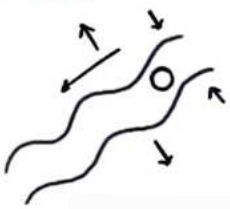
Treatment: Surgical management

Mackler's triad
- Chest pain
- Vomiting
- Sub cutaneous emphysema → Hamman's crunch heard on Auscultation

Important Information
- Esophageal varices: Painless hematemesis
- Mallory-Weiss Tear & Boerhaave Syndrome: Painful hematemesis

ACHALASIA CARDIA

00:05:02

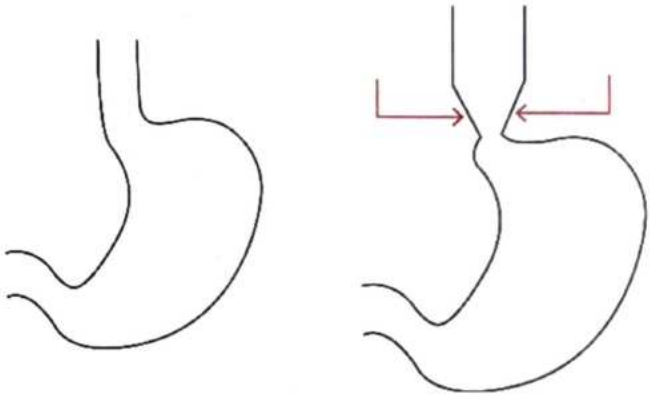


- MC motility disorder of esophagus
- Normal peristaltic activity occurs due to coordinated activity between stimulatory and inhibitory neuron
  - Stimulatory neuron secrete Ach
  - Inhibitory neuron secrete NO / VIP

Pathology
- Selective Loss of inhibitory neurons → ↑↑ Muscle tone
- MC Involvement: LES

Triad
- ↑ LES tone
- Incomplete LES relaxation
- Aperistalsis

Etiology
- Primary / Idiopathic
- Secondary
  - Chagas disease caused by T-cruzi
  - Varicella Zoster virus
  - Esophageal Cancer
  - Scleroderma



Clinical feature
- MC presentation: Dysphagia (Liquids >>> Solids)
- Weight loss
- Regurgitation → pulmonary abscess (MC complication)
- ↑ Risk of squamous cell cancer of esophagus

Investigations
- IOC: Manometry
- Barium Swallow: "Bird-Beak" Appearance

Allgrove syndrome/Triple A disease

- Achalasia
- Alacrimia
- ACTH resistance adrenal insufficiency

Treatment

- Ca^{2+} channel blocker
- Nitrates
- Botulinum toxin (↓ presynaptic release of Ach → ↓LES tone)
- Definitive treatment: Heller's Myotomy + partial Fundoplication

ESOPHAGUS

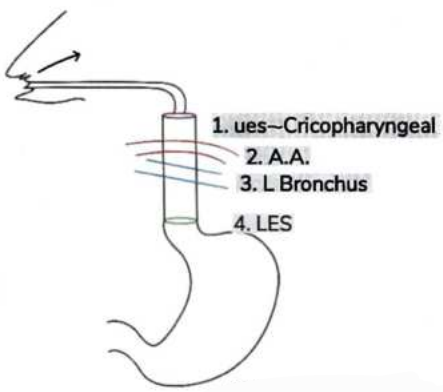
00:14:38

Important Information

- **Length of esophagus in adult: 25 cm**
- **Length of esophagus in new born: 10 cm**

- Esophagus extends from $C_6 - T_{11}$ vertebra
- Serosa is absent in esophagus.

4 Constrictions of esophagus



Constrictions	Distance From Incisor teeth
• UES (cricopharyngeus)	• 6" (15cm)
• Aortic Arch	• 9" (22.5cm)
• Left Bronchus	• 11" (27.5cm)
• LES	• 16" (40cm)

- Maximum narrowing: UES
  - MC cause of rupture: Iatrogenic (instrumentation)

LES

- It helps in unidirectional movement of food from esophagus to stomach
- ↓ LES tone → regurgitation of contents → epithelial damage
- Epithelium: Stratified Squamous non-keratinized (acid-sensitive)

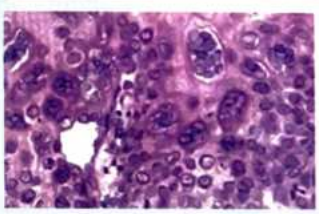
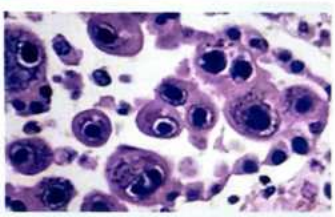
ESOPHAGITIS

00:20:53

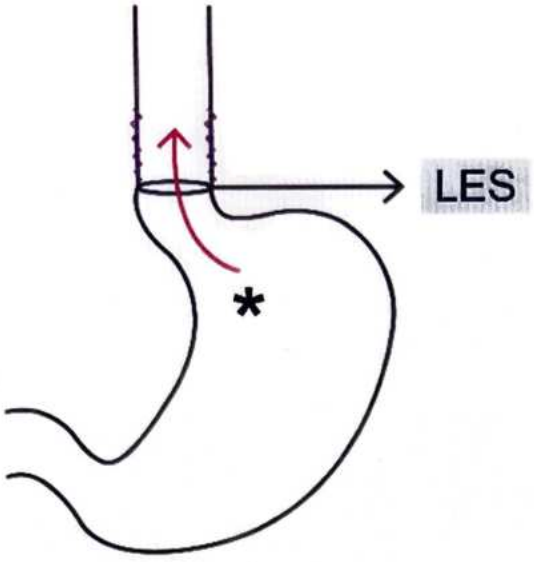
- Inflammation of esophageal lining

Causes

- Chemicals esophagitis
  - Bisphosphonates
  - Doxycycline
  - Alkali/acid
- Infections
  - Candida
  - HSV (Punched out ulcer)
  - CMV (Shallow ulcer)
    - → Overall best site for biopsy, sample tissue is taken from edge of the ulcer
- Reflux esophagitis (MC cause)

HSV Esophagitis	CMV Esophagitis
	
•Multinucleate squamous epithelial cells •Eosinophilic Cowdry 'A' inclusions	• Basophilic intra-nuclear/intra-cytoplasmic inclusions • "Owl-eye" appearance

REFLUX ESOPHAGITIS



- Cause: Transient Lower Esophageal Sphincter Relaxation

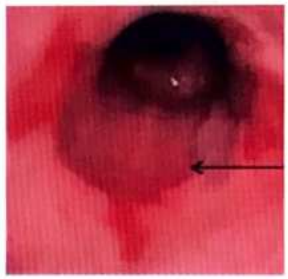
Risk Factors
- Smoking
- Alcohol
- Obesity
- Over eating
- Pregnancy
- Hiatal Hernia
- Chocolates, Coffee
- Fatty food

Clinical Features
00:31:18
- Retro Sternal pain (Burning character)
- Nausea
- Sour brash (due to acid in oral cavity)
- Teeth discoloration

Diagnosis
- 24 hour pH study - IOC
- Endoscopy + Biopsy
  - Metaplasia: On acid exposure, Stratified Squamous Non-Keratinized Epithelium (SSNKE) → Intestinal columnar epithelium

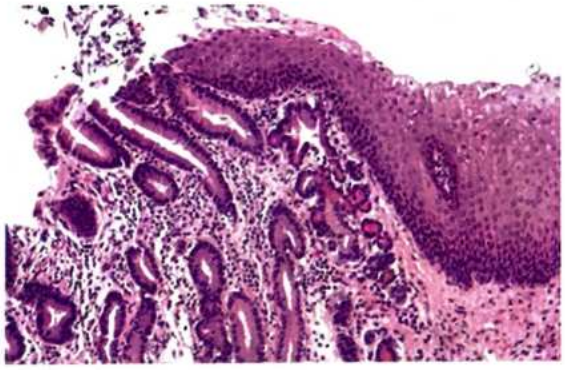
Barret's esophagus
- Intestinal columnar metaplasia → Adenocarcinoma
- Short segment Barret esophagus: <3cm
- Long segment Barret esophagus: >3cm
- Intestinal columnar epithelium has presence of Goblet cells, responsible for secretion of acidic mucin (stained by Alcian Blue)

- Barret's esophagus and stricture formation are 2 common complications of reflux esophagitis

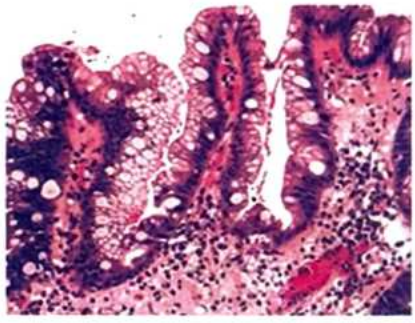


Red-velvety mucosa in Barret's esophagus

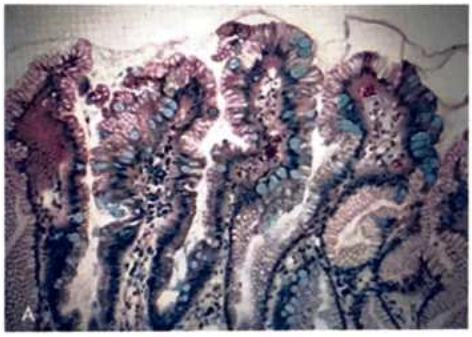
Histopathology



Squamous-columnar junction



Routine stain



Alcian blue stain

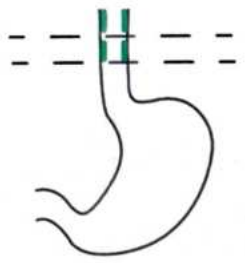
Treatment

- PPIs (DOC)
- Pro-kinetic Drugs → Stimulate peristalsis
- Surgery: Fundoplication (Strengthens LES)

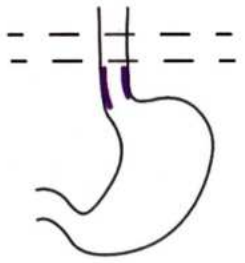
ESOPHAGEAL TUMORS

00:42:52

- Benign tumor: Leiomyoma (MC)
  - Male >> female
  - MC part involved: Middle or lower 1/3rd of esophagus
- Malignant
  - Squamous cell cancer
  - Adenocarcinoma



SQUAMOUS CELL CANCER



ADENOCARCINOMA

Previous Year's Questions

Q. Which is the most common site of the carcinoma of esophagus? (FMGE 2017)

A. Lower 1/3rd
B. Middle 1/3rd
C. Upper 1/3rd
D. GE Junction

Clinical Features

00:53:52

- Progressive dysphagia (Solids >>> Liquids)
- Hoarseness of voice (recurrent Laryngeal nerve involvement)
- Malignant TEF

Diagnosis

- IOC: Endoscopy + Biopsy → Additional narrowing to 4 natural constrictions
  - Adeno carcinoma: glands ⊕
  - Squamous cell carcinoma: keratin pearls ⊕

Squamous cell carcinoma	Adenocarcinoma
MC in India and worldwide	MC in USA
Middle 1/3rd	Lower 1/3rd

Risk factors
• Smoking & Alcohol
• Nitrosamines (Smoked Foods)
• Chronic achalasia cardia
• Hot beverages
• Radiation
• Tylosis Et Palmaris (congenital hyperkeratosis)
• Ectodermal Dysplasia
• Celiac Disease
• Mursik (contains acetaldehyde)
• HPV
• Plummer Vinson Syndrome/ Patterson Kelly Brown Syndrome
  ○ Iron deficiency anemia
  ○ Atrophic glossitis
  ○ Esophageal web
	Risk factors
	• Whites
	• Long standing GERD
	• Barret's esophagus
	• Smoking & Alcohol
	• Obesity
	• Scleroderma
	• Radiation
	• H.pylori
	  ○ Gastric atrophy → ↓ HCL → ↓ Barret esophagus

Genetic mutations

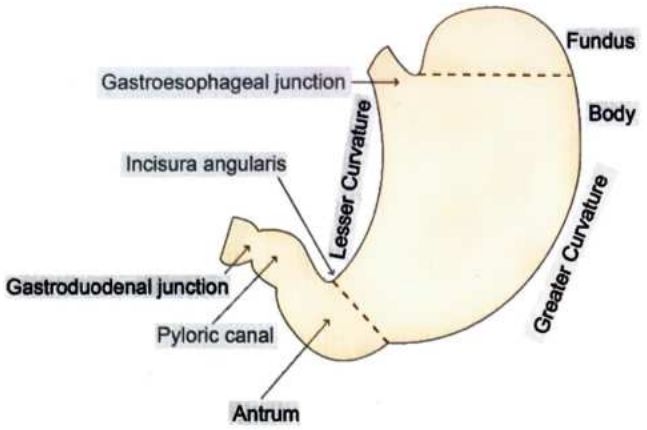
- SOX-2 amplification
- Cyclin D_1 gene underactivity
- P53 / notch gene

Genetic mutations

- P53 mutation → cyclin D/E ↑

59 GIT DISORDERS PART -2

STOMACH BASICS & GASTROPATHY



Cells

00:01:02

- Parietal Cells: It secrets
  - Intrinsic Factor → required for absorption of vitamin B_{12}
  - HCL (Ach / Histamine / Gastrin)
- Chief Cells: Secrets pepsinogen
- Foveolar Cells: Secrets mucus (protective)
- G - Cells
  - Located in antrum
  - Secrets GASTRIN → HCL (HCL has feedback inhibition on G-Cells)

Factors in Stomach

Damaging Factors	Protective Factors
• HCL • H.pylori	• Epithelial regeneration (stress) • HCO_3^- (uremia) • Mucus • PGs (COX inhibitors - NSAIDS)

Previous Year's Questions

Q. Gastrin is the marker of which carcinoma?
(JIPMER Nov 2018)

A. Medullary cancer of thyroid
B. GIST
C. Gastric carcinoma
D. Pancreatic neuroendocrine tumor

GASTROPATHY

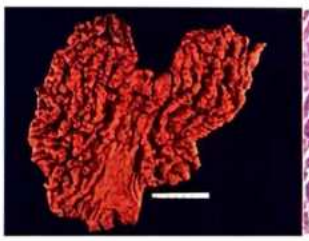
Gastric cell mucosal injury → WBC infiltration (gastritis)
↓
Inflammation & epithelial regeneration present but no WBC infiltration
↓
Gastropathy

MENETRIER'S DISEASE

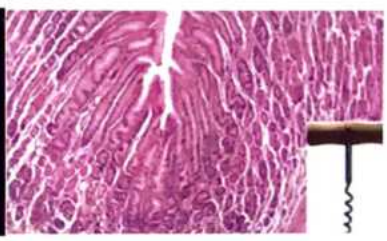
- Middle age male (40-60yr)
- ↑↑↑ TGF-α → ↑ epithelial cell Proliferation
- Presence of prominent gastric Rugal folds → Bag of worm appearance
- Protein-losing enteropathy (due to ineffective tight junctions)
- ↑ risk of stomach cancer

Microscopic Findings

- ↑↑↑ Foveolar cells & presence of focally dilated glands → Cork screw appearance



Bag of worm appearance



Cork screw appearance

ZOLLINGER ELLISON SYNDROME

- Associated with gastrin secreting tumor → gastrinoma (malignant)

- It has 2 variants
  - Sporadic (75%): Solitary
  - Familial (25%)
    → Associated with MEN-I
    → Multiple tumors

Clinical features
- ↑ gastrin → ↑↑ acid → duodenal ulcers
- Diarrhea

Microscopic findings
- ↑ parietal cells → ↑ oxyntic mucosa thickness

Diagnosis
- S.gastrin level > 1000pg/ml (diagnostic)
- ↑↑Basal acid output

Treatment
- Surgery
- Anti-cancer drugs
- PPI
  - Patient is refractory to anti-ulcer therapy

PEPTIC ULCER DISEASE
- Erosion: Defect is limited to epithelial lining
- Ulcer: Damage to complete mucosa

Causes
- H. Pyloriinfection
- NSAIDS
- Smoking
- Uremia

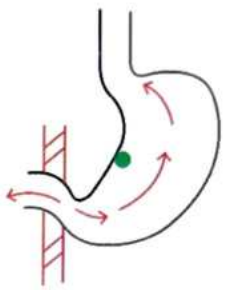
Location of ulcer
- 1st part of Duodenum (D_1)
- Gastric Antrum (Lesser Curvature)
- GEJ
- Meckel Diverticulum (presence of ectopic gastric mucosa → inflamed)

Important Information
- Blood group 'O' associated with ↑ risk of PUD
- Blood group 'A' associated with ↑ risk of gastric carcinoma

Refer Table 59.1

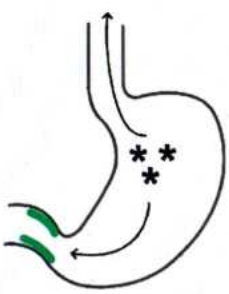
COMPLICATIONS OF PEPTIC ULCER 00:33:55

Bleeding
- MC complication of PUD
- Seen in both duodenal & gastric ulcer
- Bleeding ulcer (gastric) → blood moves in retrograde manner → hematemesis
- Bleeding ulcer (duodenal) → blood moves with peristalsis → blood + acid → Melena
- Ulcer present in posterior wall of D1 → Erosion of gastro-duodenal artery
- Source of bleeding in Duodenal ulcer: Gastro-duodenal artery
- Source of bleeding in gastric ulcer: Left gastric artery



Perforation
- MC seen with ulcer involving anterior wall of the duodenum
- MC complication causing mortality
- Associated with complications
  - Pancreatitis
  - Peritonitis
  - Poor prognosis & ↑ mortality

Gastric Outlet Obstruction



- Seen at D1
- Edema & scarring leads to narrowing of lumen → gastric outlet obstruction
- ↑ Intra gastric pressure → repeated vomiting
- Repeated vomiting is associated with
  - Loss of HCL → Metabolic alkalosis, hypochloremia
  - Loss of fluid → + RAAS → ↑ aldosterone → ↑ loss of K^+/H^+ → Hypokalemia & aciduria

Important Information

- "Paradoxical aciduria" is seen with gastric outlet obstruction as acid is lost in urine when metabolic alkalosis is present

- MC cause Gastric Outlet Obstruction in newborn: Infantile Hypertrophic Pyloric Stenosis
- MC cause of Gastric Outlet Obstruction in adults: stomach cancer > PUD

Malignancy
- GU: ↑↑ risk of malignancy
- DU: Benign

Previous Year's Questions

In gastric outlet obstruction in ulcer patient, the most likely site of obstruction? (FMGE 2018)
A. Antrum
B. Duodenum
C. Pylorus
D. Fundus

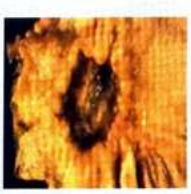
DIAGNOSIS

00:47:21

Urea Breath Test

Radiolabeled urea^{14} water consumption
↓
Urease in H.Pylori
↓
Urea^{14} → $^{14}CO_2$ (detected by breath analyzer)

Endoscopy + Biopsy
- IOC

Benign ulcer	Malignant ulcer
	
• Single, solitary ulcer (<4cm) • Clean base/folds • Location: Lesser curvature	• Big in size, multiple in no • Necrosis at the base of ulcer • Heaping up of margins • Location: Greater curvature

CLO test
- Done to detect the presence of H.Pylori
- Chemical indicator: Phenol Red
- If H.Pylori infection is present, it will release CO_2 & urease which break urea to NH_4 which reacts Phenol red → Discoloration

Previous Year's Questions

Q. Which of the following is not a pathologic features of H pylori chronic gastritis? (JIPMER – Dec – 2019)
A. Eosinophilic infiltrates
B. Intraepithelial neutrophil deposits
C. Affects intestinal gland formation in stomach
D. Subepithelial plasma cell deposits

TREATMENT
- For H.pylori infection → 1 PPI + 2 Antibiotics (Triple Drug Therapy)
- Negative H.pylori patients → only PPI's given

GASTRIC TUMORS

1. GASTRIC ADENOCARCINOMA

00:56:49

- MC malignant tumor of stomach

Risk Factors
- Smoked / salted food (Nitrates → Nitrites)
- Low social-economic status
- Previous gastric Surgery
- Partial antrectomy
- Pernicious anemia
- Atrophic gastritis
- H.pylori (Type 1 carcinogen)
- EBV
- Tobacco use
- Adenomatous polyp
- Menetrier's disease
- Blood group 'A'
- Nutrient deficiency

Genetic Factors
- p53 / Li fraumeni syndrome
- Underactivity of APC gene
- Over activity Of β- catenin
- CDH 1 mutation: Responsible for secretion of E – cadherin
  - Associated with familial gastric cancer
  - High risk for gastric adenocarcinoma and lobular carcinoma of breast
- $BRCA_2$ gene

- HNPCC/Lynch syndrome

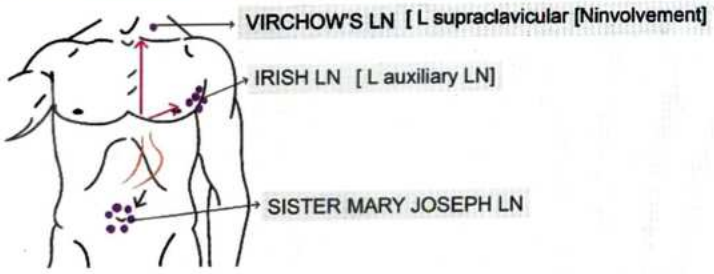
Site
- MC location Antrum (lesser curvature)
- Patients with pernicious anemia → fundus & body is affected predominantly

Clinical features
- RUQ discomfort (earliest)
- Post prandial heaviness/dyspepsia
- Weight loss (MC)
- Abdominal pain
- Paraneoplastic syndrome
  - Acanthosis nigricans
  - Leser Trelat sign (seborrheic keratosis)
  - Migratory thrombophelibitis
  - MAHA

Metastasis
- Hematogenous spread → liver > lungs/ovary
- Lymphatic spread → involvement of LN, Ovaries
  - B/L ovary involvement → Krukenberg Tumor (MC cause: stomach cancer)

Important Information

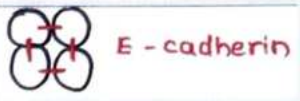
Lymph Node Involvement
- Left S/C LN → Virchow's LN
- Left Axillary → Irish LN
- Peri-umbilical area → Sister Mary Joseph LN
- Pouch of Douglas → Blumer's shelf



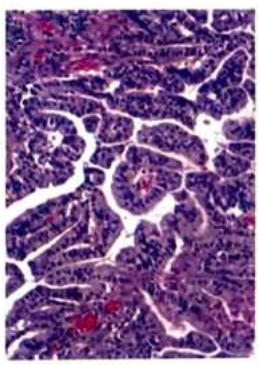
DIAGNOSIS 01:16:29
- IOC: endoscopy + biopsy

Classification of gastric adenocarcinoma
- Morphology: external/exophytic growth or flat growth or excavated/ulcerated lesion
- Depth of invasion
  - Early: Mucosa & Sub mucosa involved (better prognosis)
  - Late: muscle & Serosa also involved (poor prognosis)
  - Overall best prognosis: Superficial spreading type of stomach cancer

Lauren's Classification

Intestinal Type	Diffuse Type
• Intestinal gland like pattern • MC variant • Localized (exophytic/ulcerative lesion) • Elderly (male > female) • Better prognosis	 • CDH_1 mutation → loss of E-Cadherin activity → bond between tumor cells is lost → scattered tumor cells • Young (male = female) • Poor prognosis • Presence of mucinous vacuole → Signet ring appearance • Associated with desmoplasia → Linitis plastica

Linitis plastica/Leather bottle appearance



Intestinal type

Diffuse type

Important Information

- EBV is associated with proximal involvement of stomach, diffuse subtype and lymphocytic infiltration

Treatment
- Surgical excision
- Anti-cancer drugs
  - Epirubicin
  - Cisplatin
  - 5 Fluorouracil

2. GASTROINTESTINAL STROMAL TUMOR (GIST)

01:29:05

- MC mesenchymal Tumor of abdomen
- Common location: stomach > SI > LI > esophagus (rarest0
- Origin: Cell of Cajal (pacemaker of GIT)
  - Regulates peristaltic/motor activity
  - Located at muscularis propria
- It has 2 variants
  - Sporadic: C-KIT (70-80%) > PDgFRA > SDH
  - Familial: NF-1 gene
- Elderly (60years)
- Genetic mutations → ↑↑ TK activity → ↑ cell proliferation

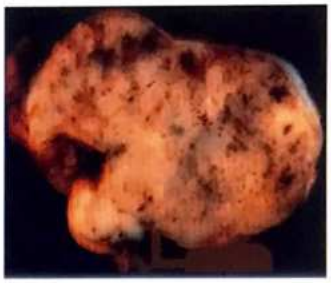
Carney Stratakis syndrome
- Autosomal dominant
- SDH mutation
- GIST + Paraganglioma

Carney's Triad
- Young female, non-hereditary
- GIST
- Paraganglioma
- Chondroma

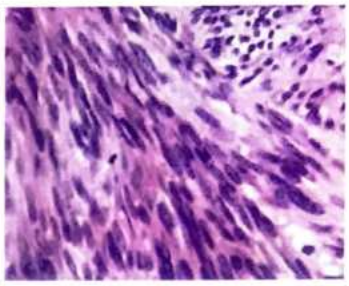
Clinical features
- Bleeding (MC)
- Abdominal Pain
- Incidental finding

Metastasis
- No Lymphatic spread
- Hematogenous spread → Liver (MC organ affected)

Diagnosis
- PET-CT or CECT scan



Whorled appearance



Spindle cells

- Gross appearance: Solitary, well circumscribed tumor
- Microscopic appearance: 3 subtypes
  - Spindle cell variant (MC)
  - Eptheliod variant
  - Mixed variant
- Immuno-histo-chemistry marker: DOG-1 > C-KiT/CD-117 > CD34

Treatment
- Targeted drug therapy: Tyrosine kinase inhibition → Imatinib (DOC)
- Surgery for smaller tumor

Prognosis 01:40:54
- Location: stomach (less aggressive)
- Mitotic index: (↑) → poor prognosis
- Size
  - 10 cm: ↑ chances of recurrence
  - < 5cm: minimal chance of recurrence

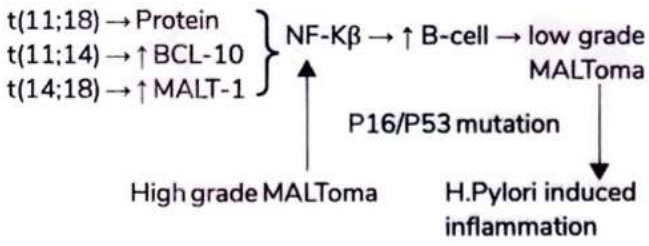
GI LYMPHOMAS

- MC extra-nodal site for NHL: GIT (Stomach)
- MC extra-nodal site of NHL in AIDS: CNS

WHO 2019 update
- MC overall subtype: Diffuse large B-cell Lymphoma
- MC location of MALToma: Stomach
- MC location of Follicular Lymphoma: Duodenum
- Preferred site for Enteropathy Associated T-cell Lymphoma: Jejunum
- Commonest site for Mantle cell Lymphoma: Ileum (can also be seen in jejunum & LI)

Allogenic BMT/organ transplantation
↓
Immunosuppressive therapy (cyclosporine)
↓
Suppression of T-cell
↓
B-cell proliferation in Bowel by EBV

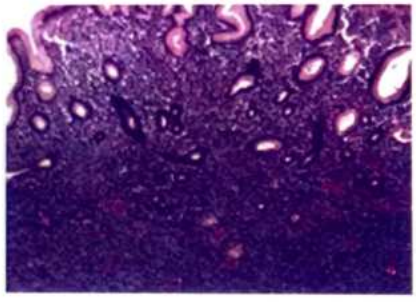
Gastric MALToma
- Aka Indolent Marginal gene B-cell Lymphoma
- Risk factor: H.pylori



- H.Pylori independent translocation/high grade MALToma caused by H.pylori → antibiotics ineffective

Clinical features

- Epigastric pain
- Dyspepsia



Lymphoepithelial lesion

Diagnosis

- Microscopic examination: "Lymphoepithelial lesion" → diagnostic feature of gastric MALToma
- IHC: marginal zone lymphoma → CD20⊕, CD5⊖ / CD23⊖
  - In 25% of patients → CD43⊕

Treatment

- Good response to antibiotics if low grade MALToma which is usually due to H. Pylori infection
- High grade MALToma: Anti-cancer drugs

Table 59.1

Duodenal ulcer	Gastric ulcer
Location & cause • Involvement of anterior wall of D_1 • H. pylori +++	**Location & cause** • Involvement of lesser curvature (incisura angularis) • H.pylori + / NSAIDS / smoking / alcohol
Clinical features • Epigastric pain • ↓ Pain with food (due to ↑ alkaline secretion of intestine stimulated by the food) • Weight gain	**Clinical features** • Epigastric pain • ↑ pain with food (due to ↑ secretion of acid) • Weight loss
Microscopic feature • Brunner gland hypertrophy +++ • Benign	**Microscopic feature** • No Brunner gland hypertrophy • Pre malignant

60 GIT DISORDERS PART-3

MALABSORPTION DISORDERS

- Chronic Diarrhea – Steatorrhea (MC characteristic finding)

1. CELIAC SPRUE

00:01:21

- Aka gluten sensitivity Enteropathy
- Genetic association: HLA DQ2/DQ 8

Gluten
ttg (tissue trans-glutaminase) ↓
Gliadin
↓
CD8 T-Cell → epithelial cell damage
CD4 T-Cell → Abnormal Ab (IgA)

Abnormal antibodies

- Anti tranglutaminase Ab (most sensitive)
- Anti-gliadin Ab (most specific)
- Anti-endomysial Ab

Cereals containing gluten: BROW

- **B – Barley**
- **R – Rey**
- **O – Oats**
- **W - Wheat**
- Skin manifestation: Dermatitis Herpetiformis (IgA deposited in dermal papillae)

Clinical features

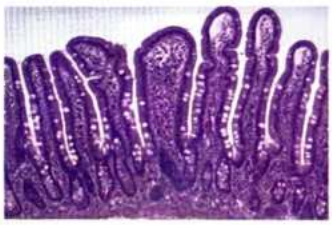
- Pediatric age group: 6 months
- Adult: 30-60 years
- Diarrhea
- Abdominal pain
- Flatulence
- Anemia, nutritional deficiency
- Stunting growth (failure to thrive in pediatric group)
- Associated with
  - T1DM
  - Sjorgen Syndrome
  - Thyroiditis
  - IgA nephropathy
  - Down syndrome
  - Turner syndrome

DIAGNOSIS

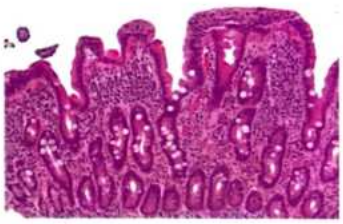
- Symptomatic upon starting cereals
- Serology for antibodies

Biopsy

- Confirmatory test: Biopsy
- Max exposure to gliadin: duodenum
- Biopsy taken from duodenum
- T-cell mediated injury → blunting of villi → ↑ no cells in crypts



Normal



Celiac sprue

Important Information

- In celiac sprue, overall mucosal thickness remains • villous atrophy • crypt hyperplasia

Associated malignancies

- ↑ Enteropathy associated T-cell lymphoma (EATL)
- SI adenocarcinoma
- Esophageal cancer (squamous cell carcinoma)

Treatment

- Cereal substitution: Maize, Rice, Quinoa
- For skin manifestation: Dapsone

Previous Year's Questions

Gluten sensitive enteropathy is strongly associated with (FMGE 2018)

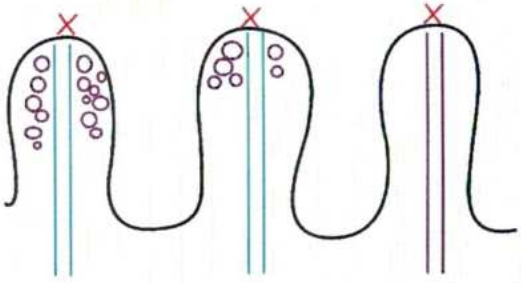
A. Blood group B
B. HLA - DQ3
C. HLA - DQ2
D. HLA - DQ4

2. ENVIRONMENTAL ENTEROPATHY 00:14:31

- Aka Tropical Sprue
- Contributes to 40% of cases
- E.coli infection
- No autoimmune disorder
- Total SI involvement deficiency of Fe/FA/vit-B_{12}
- Benign condition
- Good response to antibiotics (co-trimoxazole)
- Histopathology: villous blunting + complete lymphocytic infiltration

3. WHIPPLE'S DISEASE 00:18:12

- Causative organism: Tropheryma Whippelii → accumulation of macrophages in lamina propria



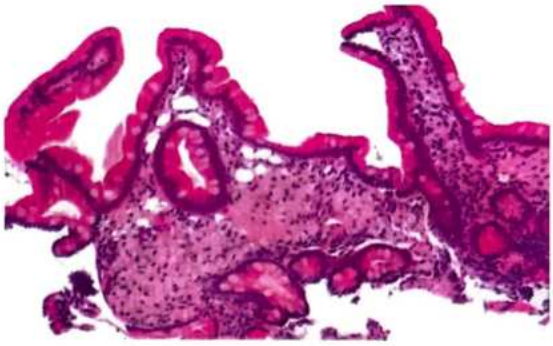
- Over-crowding of macrophages → compression of lacteals → impaired lymphatic drainage → diarrhea
- Hallmark finding: defective luminal transport

Clinical features

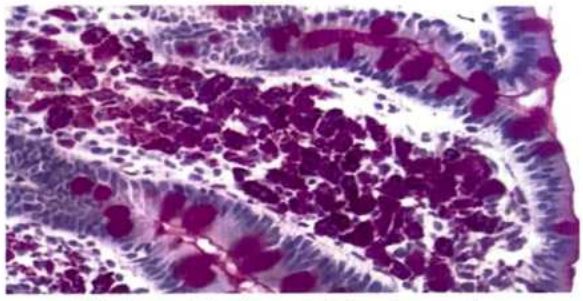
- Multi System Involvement: Intestine/Joints/LN/Cardiac
- Diarrhea
- Weight loss
- Loss of memory (indicates advanced stage)

Diagnosis

- Histopathology: Macrophage infiltration of lamina propria → foamy macrophages
- Electron microscopy: rod shaped appearance of bacilli
- PAS strain → diastase resistant granules (PAS +ve)



Foamy macrophage in LP



PAS +ve; Diastase resistant granules

Treatment

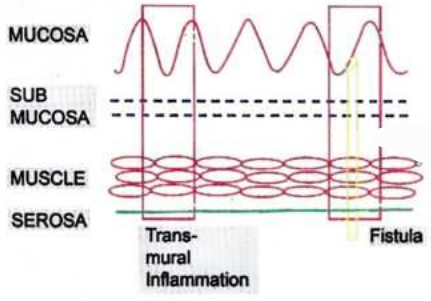
- Co-trimoxazole (trimethoprim + sulfamethoxazole)

INFLAMMATORY BOWEL DISEASE 00:24:44

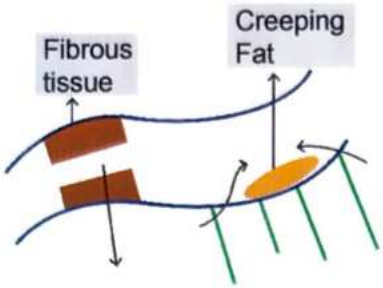
- Young female
- Abnormal immune response to gut bacteria → immune dysfunction
- Not an autoimmune disorder
- Extra-intestinal involvement: skin, joints, bile ducts, ocular tissue

1. CROHN'S DISEASE

- Any part of gut is involved
  - Ileum – MC site affected
  - Rectum - spared



- Presence of skip lesions & transmural inflammation
- Earliest manifestation: Apthous ulcer
- Cobblestone mucosa → edema and swelling of affected mucosa in between normal mucosa giving irregular appearance
- Fragile bowel wall → Fistula formation (MC location: Perianal)



- Extensive fibrosis can lead to intestinal obstruction
- Contraction of fibrous tissue → pulling of intestine with mesentery giving "creeping fat" appearance
- Radiology: string sign of Kantor
- TH_{17}/TH_1 cell → Granulomatous inflammation
- Presence of ASCA (Anti-Saccharomyces cerevisiae antibodies)
  - Associated with ↑ risk of kidney stone development due to ↑ absorption of oxalate
  - ↑ Risk of colon cancer

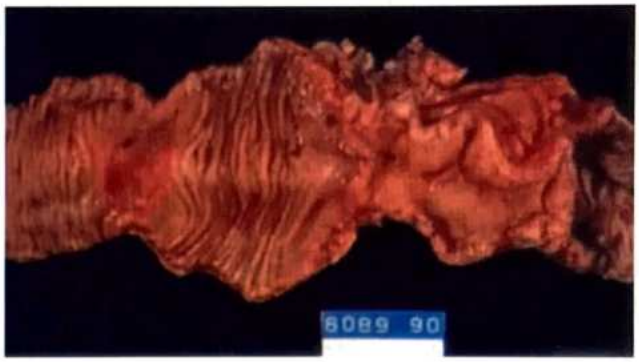
Important Information

Salient features of Crohn's Disease

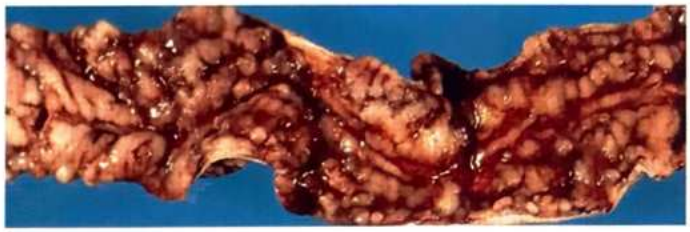
- S - Skip lesion
- I - Ileum
- S - String sign
- T - Transmural inflammation
- E - Extra Fibrosis, fistula formation
- R - Rectum spared

Clinical features

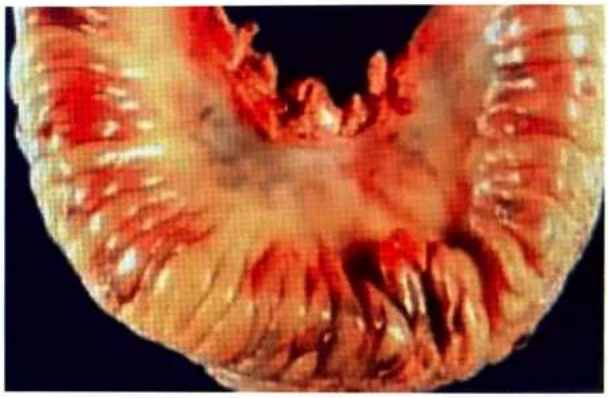
- GI
  - Colicky abdominal pain
  - Blood in stools
- Eye
  - Watery eyes
  - Photophobia
- Skin
  - Pyoderma gangrenosum
  - Skin lesions are associated with certain deposits and termed as "metastatic Crohn's disease"



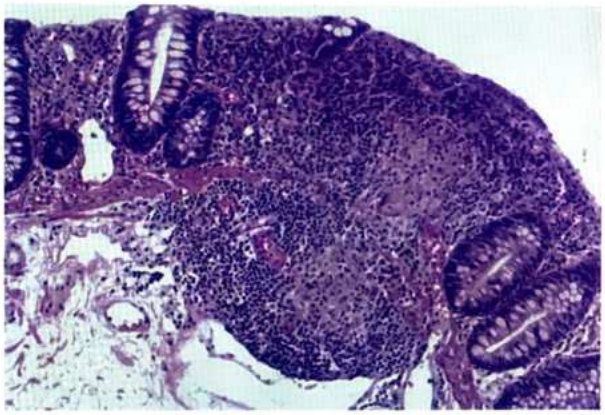
Skip lesions



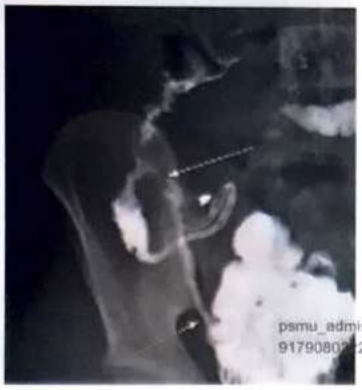
Cobblestone mucosa



Creeping fat



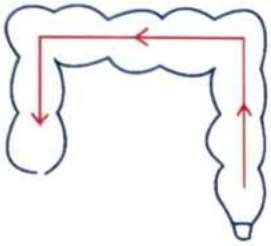
Granuloma formation



String sign of Kantor

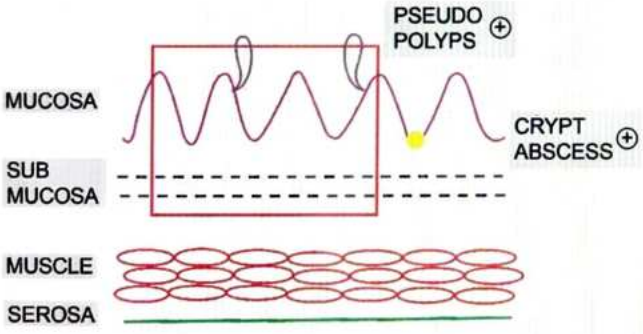
2. ULCERATIVE COLITIS

00:38:00



Retrograde spread

- Involvement LI (colon)
- Retrograde continuous Spread: Begins from Rectum → sigmoid colon → descending colon → transverse colon → ascending colon
- Complete colon is affected → Pancolitis
- In severe disease, a part of ileum is also involved → Backwash ileitis



- Inflammation is limited to mucosa & sub-mucosa → superficial ulcers
- ↓ Chance of fistula formation/fibrosis compared to CD
- Pseudo-polyps: Arises from unaffected mucosa and contains only mucosa & submucosa
- TH_2 Cell is involved → no granuloma formation

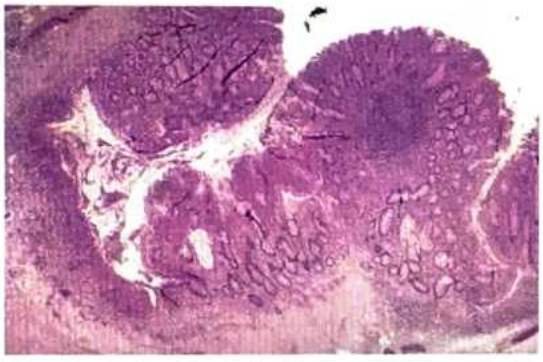
- Toxic Megacolon: In transverse colon, Due to toxins → ↓ neuronal activity in muscle layer → no peristalsis → accumulation of intestinal contents → Rupture
- Presence of crypt abscess
- Edema of mucosa → loss of haustrations → lead-pipe appearance
- Antibody involved: P–ANCA

Clinical features

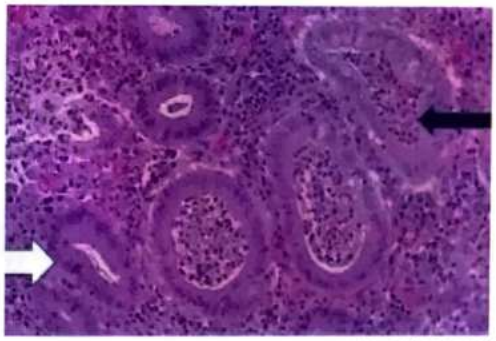
- Colicky abdominal pain
- Blood in the stools
- Primary Sclerosing Cholangitis → features of obstructive jaundice
- ↑ Risk of colon cancer (UC=CD)

Pancolitis

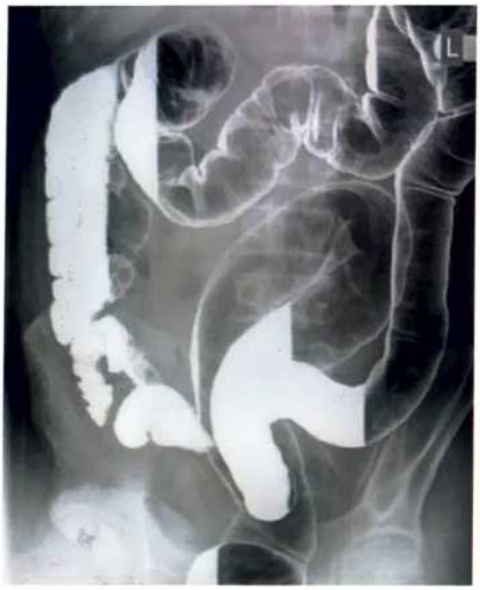
Pseudopolyps



Superficial inflammation



Crypt Abscess



Lead pipe appearance

INTESTINAL POLYPS COLON & ANAL CANCER

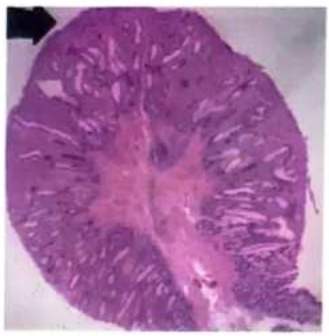
- Non-Neoplastic Polyps 00:49:31
- Neoplastic Polyps

1. NON - NEOPLASTIC POLYPS

- Inflammatory polyps
- Hyperplastic polyps
  - Usually associated with rectal ulcer
  - MC site: Rectum
- Hamartomatous polyps. Subdivided into
  - PJ polyp
  - Juvenile polyp

Juvenile Polyp

- 1st decade of life (Male > Female)
- Origin: Rectum
- Histology: Pedunculated polyp & numerous cystic dilated glands



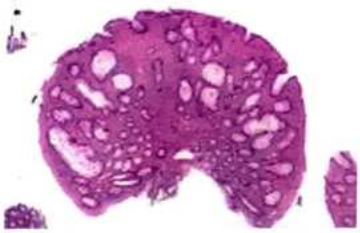
Presence of cystic dilated glands

Juvenile Polyposis Syndrome

- Associated with malfunction of SMAD 2/4 gene and TGF β
- Presence of multiple juvenile polyps
- ↑ Risk of cancers (both GI & extra-intestinal cancers)

Previous Year's Questions

A 5yr old child presented with rectal bleeding. He has polypoidal mass located in the rectum. The biopsy is shown in the image below. What is the most likely diagnosis? (NEET 2020)



A. Serrated adenoma
B. Villous adenoma
C. Angiodysplasia
D. Juvenile polyp

Peutz-Jeghers Polyp

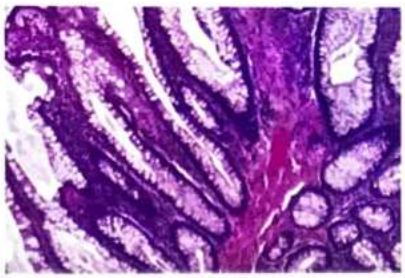
- Involvement of Jejunum
- Mean age: 11years (Teenage group)
- No risk of neoplasia

PJ syndrome

- Presence of multiple PJ polyps
- Hyperpigmentation of oral mucosa, lips and genitalia
- ↑ Risk of esophageal/colon/pancreatic/lung/genital cancers
- Associated with STK-11 >> AMP kinase gene

malfunction

- Histology: Arborizing pattern of smooth muscle



Arborizing pattern/ Christmas tree appearance

2. NEOPLASTIC POLYPS

00:56:22

- Adenomatous Polyp

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

- AD mode of inheritance
- APC gene present at Chromosome 5q → Tumor suppression gene)
- Mutation of APC gene → ↑↑ Adenomatous Polyps

Sub syndromes

- Classical FAP: ≥ 100 adenomatous polyp
  - Eye involvement: retinal pigment hypertrophy (new born screening can be done)
  - ↑ Risk of colon cancer at early age
- Turcot Syndrome: FAP + CNS tumors (medulloblastoma/glioma)
- Gardner Syndrome: FAP + soft tissue tumor (desmoid/osteoma/fibroma)
- MAP
  - MUYTCH associated polyposis
  - AR condition
  - Associated with malfunction of DNA repair genes → ↑ risk of cancer

COLON CANCER

01:02:01

- Elderly
- Presentation: iron deficiency anemia
- MC site: Rectum
- Subtype: Adeno carcinoma

GENETIC FACTORS

HNPCC/LYNCH syndrome

- HNPCC: Hereditary Non-Polyposis Colorectal Carcinoma syndrome
- Autosomal dominant condition
- DNA Repair genes defect → microsatellite instability → ↑ risk of colon & other cancers
- CEO syndrome
  - Colon cancer
  - Endometrial cancer
  - Ovarian cancer

Familial Adenomatous Polyposis (FAP)

- Mutation of APC gene → ↑↑ Adenomatous Polyps → ↑ Colon Cancer
- Variants: Classical/Gardner syndrome/Turcot syndrome/MAP
- Cancer presentation at much earlier age (<30yrs)

Previous Year's Questions

Q. False about familial polyposis colon cancer syndrome? (JIPMER Nov 2017)

A. Autosomal recessive transmission
B. Associated with fibroma and osteomas
C. Associated with brain tumors
D. 100% chance of colon carcinomas

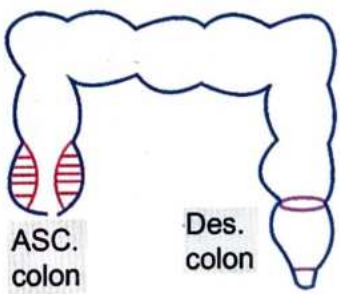
NON-GENETIC FACTORS

- ↑↑ Consumption of dietary lipids
- Pelvic radiation exposure
- Uretero-sigmoidoscopy
- Streptococcus Bovis

Protective factors

- Dietary fibers consumption
- NSAIDS

Clinical Features



- Involvement of either ascending colon or descending colon
- MC site: rectum
- Proximal colonic cancer → ↑ ulcerative lesions → chronic blood loss → unexplained anemia
- Descending colonic cancer → project into bowel lumen → narrowing of lumen → change in bowel habit

Important Information

Rectal carcinoma Triad

- **Bleeding P/R (MC presentation)**
- **Tenesmus**
- **Spurious diarrhea**

- Circumferential growth of cancer → irregularity of colon giving "Napkin ring appearance"

Diagnosis 01:13:37

- Colonoscopy + Biopsy (IOC)
- Occult Blood in stool detected by
  - Microscopic Examination of stool
  - GUAIAC test
- Tumor Markers: ↑↑ S.CEA (Carcino-Embryonic Antigen) → useful to detect recurrence
- Radiology: "Apple Core Appearance" on Barium enema
- Metastasis: liver > ovary in females (krukenberg tumor → signet ring appearance)

Previous Year's Questions

Q. A female presents with adenocarcinoma metastasis in liver with CK 20+ and CK T negative. Which of the following is the most likely site of primary in this patient?

(INICET Nov 2020)

A. Ovarian cancer
B. Colorectal cancer
C. Pancreatic cancer
D. breast cancer

ANAL CARCINOMA

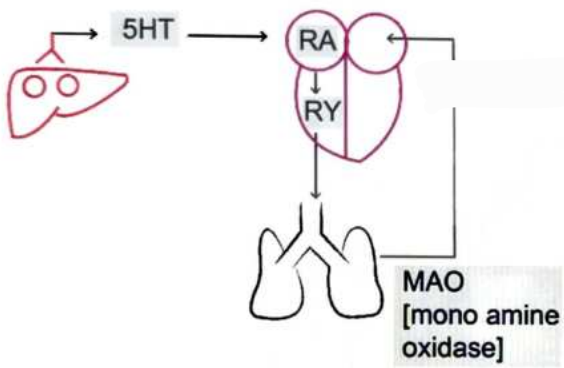
- Squamous cell carcinoma
- Surgery is not done due to risk of damage to sphincter
- TOC: chemo-radiation: Nigro's regime

61 CARCINOID TUMOR

- Arises from neuro-endocrine cells
- Markers: Chromogranin, NSE
- MC Site of origin: GIT > Bronchus
- It is characterized by Overproduction of 5-HT (Serotonin)
- Carcinoid tumor in ileum → 5-HT production → Liver (Metabolized) → urine excretion of 5-HIAA
- Carcinoid tumor in Midgut (malignant) → 5-HT → Metastasis in liver → 5-HT into systemic circulation (carcinoid syndrome)

Clinical features

- Systemic fibrosis
- Hepatomegaly
- Intestine (Diarrhea)
- Vasomotor (Flushing)
- Asthma like features



Cardiac Involvement

- Systemic fibrosis: Isolated Right heart involvement
- Tricuspid valve: Regurgitation / Insufficiency
- Pulmonary valve: Stenosis
  - **T** - **T**ricuspid love
  - **I** - **I**nsufficiency
  - **P** - **P**ulmonary valve
  - **S** - **S**tenosis

How to remember

- TIPS

Diagnosis 00:10:48

- Screening Test: 24hr HIAA Levels
- Plasma concentration of Chromogramin A Levels: Increased
- Biopsy & Electron Microscopy: shows Granules with presence of chromogranin A & Neuron specific enolase

Treatment

- Drugs for small tumors
- Surgery for big tumors

CLINICAL QUESTIONS

A 40-year-old woman presents with a 2-year history of difficulty swallowing and increasing fatigue. A CBC shows Iron-deficiency anemia. Upper endoscopy reveals an annular narrowing in the upper third of the esophagus. A mucosal biopsy shows no evidence of inflammation or neoplasia. Which of the following is the most likely diagnosis?

A. Achalasia
B. Barrett esophagus
C. Diverticulum
D. Esophageal **web**

Solution

- Plummer-Vinson syndrome is characterized by:
  - Cervical esophageal web/ rings
  - Mucosal lesions of the mouth and pharynx
  - Iron-deficiency anemia.

Reference

- Robbins 10th ed p757

LEARNING OBJECTIVES

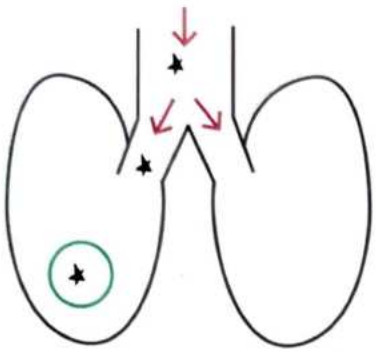
UNIT 10 RESPIRATORY SYSTEM

- **Obstructive Lung Disorders:**
  - Lung Abscess, Spirometry
  - Emphysema, Chronic Bronchitis
  - Bronchial Asthma
  - Bronchiectasis
- **Restrictive Lung Disorders:**
  - Idiopathic Pulmonary Fibrosis(IPF)
  - Non specific Interstitial Pneumonia (NSIP)
  - Cryptogenic Organizing Pneumonia (COP)
  - Desquamative Interstitial Pneumonia
  - Pneumoconiosis: Silicosis, Asbestosis , Coal Worker's Pneumoconiosis
  - Sarcoidosis
  - Hypersensitivity Pneumonitis
- **Pulmonary Hypertension**
  - Primary Pulmonary HTN, Secondary Pulmonary HTN
- **Infective Lung Disorders:**
  - Pulmonary Tuberculosis, Primary pulmonary TB
  - Secondary Pulmonary TB, Diagnosis
  - Pneumonia
  - Typical Pneumonia- Causative Organisms
- **Miscellaneous Topics (ARDS)**
  - Etiology
  - Clinical Features
- **Lung Tumors**
  - Bronchogenic Carcinoma: Risk Factors
  - Squamous Cell Carcinoma; Adenocarcinoma
  - Small Cell Carcinoma
  - Large Cell Cancer
  - Pleural Tumors
  - Solitary Fibrous Tumor
  - Pulmonary Hamartoma

62 OBSTRUCTIVE LUNG DISORDERS

BASIC CONCEPTS

LUNG ABSCESS

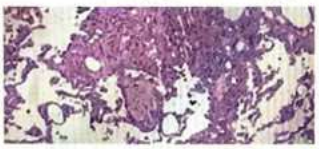


- Right bronchus is more aligned with trachea → FB impaction is more common in right lung.
- FB is the MC cause of lung Abscess → MC involves right lower lobe.
- Can also be seen due to
  - Pneumonia
  - Septicemia
  - Malignancy → improper drainage of secretion → contamination
- Pus settles down with air on top → air-fluid level on radiograph
- Food particles is the MC foreign body
- Anaerobes are MC microorganisms causing lung abscess.

Previous Year's Questions

Q. Patient with history of long-standing depressive illness comes to ER acute breathlessness. The X-ray shows diffuse infiltrates with predominance in right middle lobe and right lower robe. The patient did not survive and the following picture in the lungs was seen on autopsy. It is suggestive of?

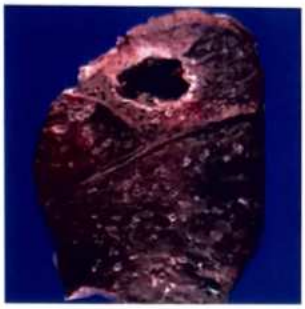
(AIIMS - Nov - 2017)



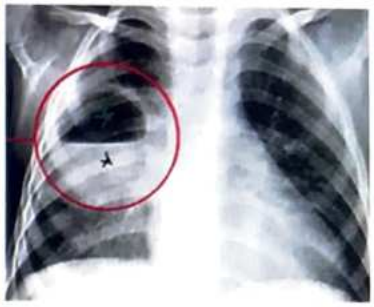
A. Severe neurosis with fungal hyphae, severe fungal pneumonia
B. Coagulation necrosis, tuberculosis
C. Vegetable matter, aspiration pneumonia.
D. Severe neurosis, severe necrotizing pneumonia.

Clinical features

- Fever
- Foul smelling sputum
- Hemoptysis



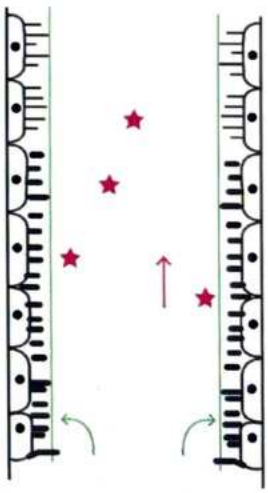
Cavitory lesios



Air-fluid level

- Other causes
  - Elderly → malignancy
  - Multiple lung abscesses → staph aureus infection

Normal Histology



- Lined by pseudo stratified ciliated columnar epithelium → nuclei are present in haphazard fashion, no true stratification
  - Except vocal cord where stratified squamous epithelium is present
- Presence of glands → secretion of mucus
  - ↓ Mucus → infections
- Dust / bacteria / Ag → attach to mucus → cilia (escalator

like action)
  - ↓ Ciliary activity → ↑ infections
- Acquired ciliary abnormality: Smoking
- Congenital ciliary abnormality: Defect in dynenin → Kartagener Syndrome
  - Also associated with ↓ fertility

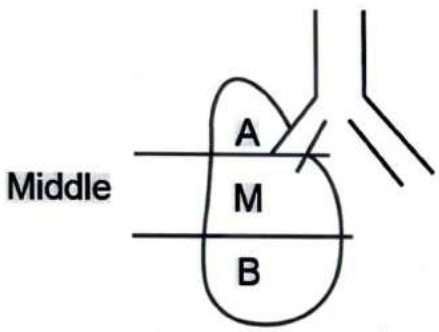
Important Information

Kartagener Syndrome Triad

- Bronchiectasis
- Situs inversus (Dextrocardia)
- Sinusitis

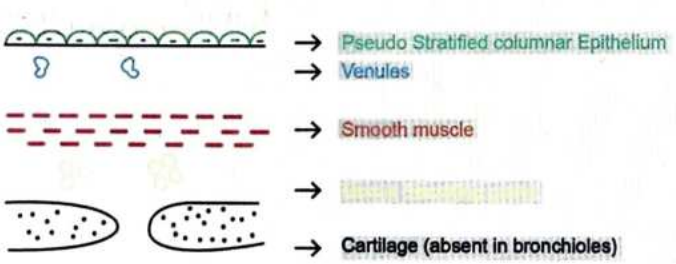
- ↓ Mucus secretion
  - Cystic fibrosis: CFTR defect → chloride channel defect → dry mucus → ↑ risk of infections

Lung physiology



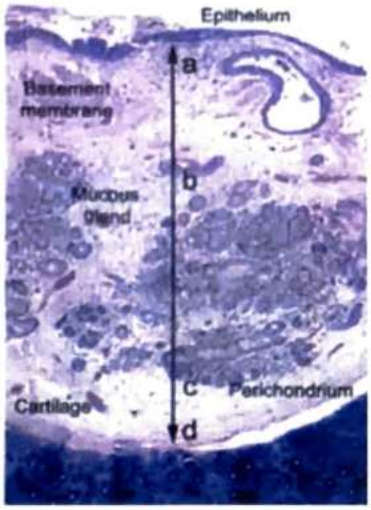
- Ventilation maximum at Base
- Perfusion maximum at Base
- Perfusion is maximum at Base
- V/p ratio is maximum at Apex
- VQ ratio: normal - 0.8 (cannot be >1)

Reid's Index



- Venules at lamina propria → provides ambient temperature to air

- Reid's Index: A/B
  - A: Thickness of mucus gland layer
  - B: Distance b/w epithelial cell & cartilage
- Normal value: 0.4 (increased in Pulmonary Bronchitis)



Reid's Index

- Smaller airway has no cartilage, ↓ glands
- Functional unit of lung: Acinus
- Between alveoli → pores of Kohn is present
  - Significance: Bacteria can travel from one alveolar sac to adjacent alveolar sac

Pneumocytes

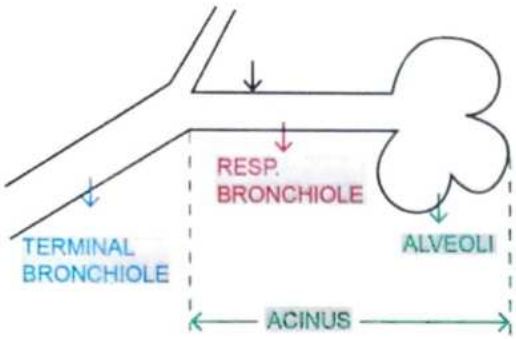
- Type 1 → contributes to majority of surface area
- Type 2
  - Present in more number
  - Secretes surfactant (DPPC) → ↓ surface tension at expiration
  - Alveolar repair

Spirometry 00:29:07

	Obstructive Disease	Restrictive Disease
FEV_1	< 80%	N/↓
FVC	N/↓	↓
FEV_1/ FVC	< 0.7	> 0.7
TLC	N/↑	↓

EMPHYSEMA

00:32:00



- Acinus involvement
- Abnormal permanent dilatation of airway beyond terminal bronchiole (acinus) → alveolar wall destruction with minimal fibrosis

Damaging factors

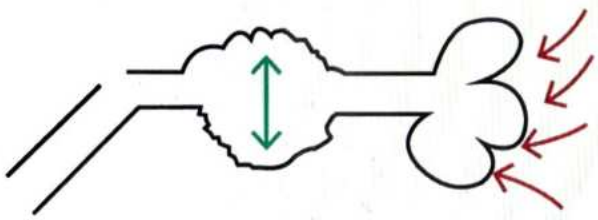
- Elastase (Neutrophils / Macrophages) → Elastin fibers damage
- Smoking associated with ↑ elastase
- Air pollution
- Pneumoconiosis

Protective Factors

- Anti-elastase activity
  - α_1 anti-trypsin (produced by liver)
  - α_1 macro globulin
- Gene for α_1 anti-trypsin: PiMM gene present on chromosome 14
- α_1 anti-trypsin deficiency
  - PiMZ gene defect (heterozygous) → ↓ α1 - anti trypsin (MC)
  - PiZZ gene defect (homozygous) → ↓↓↓ very low α1 anti-trypsin → emphysema
  - Also associated with α1 anti-trypsin misfolded proteins in liver → cirrhosis

ANATOMICAL CLASSIFICATION

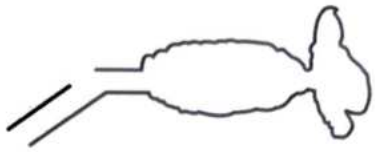
Centri-acinar emphysema



CENTRIACINAR EMPHYSEMA

- Proximal part of acinus is involved
- MC type of emphysema (associated with smoking)
- Upper lobes of lungs are affected
- MC type of emphysema seen clinically
- Alveoli are spared

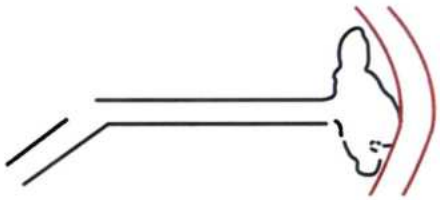
Pan Acinar Emphysema



PANACINAR EMPHYSEMA

- Complete acinus is involved
- MC associated with α1 - anti trypsin deficiency
- Base of the lung is involved
- They co-exist with cirrhosis

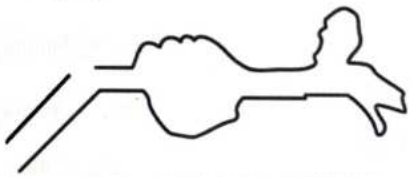
Distal Acinar Emphysema



DISTAL ACINAR EMPHYSEMA

- Seen more commonly in smoker
- Upper Lobe of lungs is involved
- Damage at the distal acinus → Bleb/bullae formation → damage at visceral pleura → air from acinus enters pleura → Spontaneous pneumothorax

Irregular Emphysema



IRREGULAR EMPHYSEMA

- Patchy involvement
- MC type of emphysema that is seen microscopically

Important Information

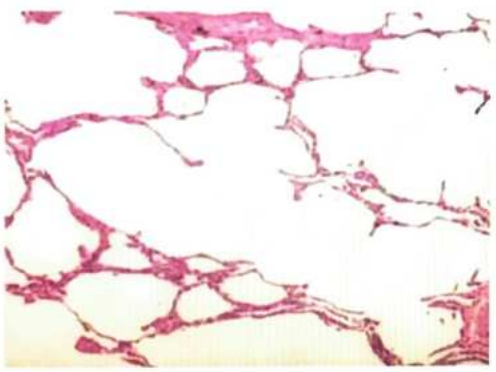
- NRF2 gene: works as sensor for oxidative molecules produced by smoking
- NRF2 → activates anti oxidative defense mechanisms
- Problem at NRF2 gene → more damage to the lungs

CLINICAL FEATURES

- Elderly
- Dyspnea
- Barrel chest
  - Loss of elastin fibers → loss of elastic recoil → air trapping → hyperinflation
  - CXR: flattening of diaphragm
- Weight loss
- Pink Puffers
- Long-term complication: Hypoxemia → pulmonary Hypertension → Cor pulmonale

Normal lung

Emphysema



Destruction of alveolar wall

CHRONIC BRONCHITIS

- Risk factor: H/O smoking

Pathogenesis

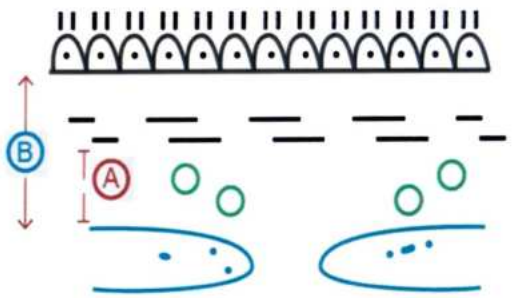
SMOKING
↓
INFLAMMATION
↙ ↘
2° INFECTION (H.Infulenza) ← ↑MUCUS PRODUCTION

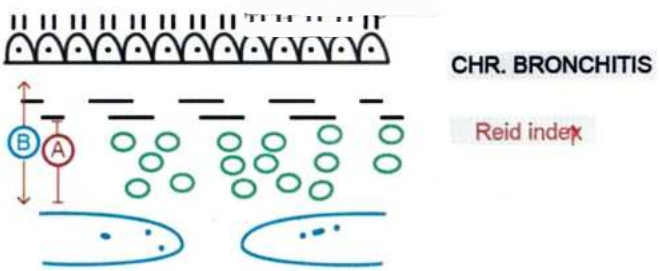
- Productive cough
- Mucus gland thickness ↑
- Airway obstruction

Clinical Features

- Productive cough (minimum duration of 3 months in 2 consecutive years)
- Fever
- Cyanosis
- ↑ Reid's index
- Hypoxemia (Blue bloaters) → Pulmonary HTN → Cor Pulmonale
- No associated amyloidosis
- Smoking → squamous metaplasia → ↑ cancer
- COPD → Emphysema + Chronic Bronchitis + Small airway disease
- Smoking → irritation of vagal afferents → ↑ Ach → Bronchospasm

$$\text{REID'S INDEX} = \frac{A}{B}$$





Treatment

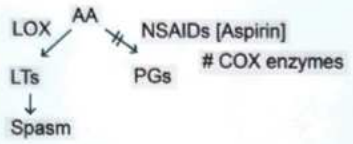
- O_2 Supplementation
- Ipratropium
- Mucolytic drugs
- Antibiotics

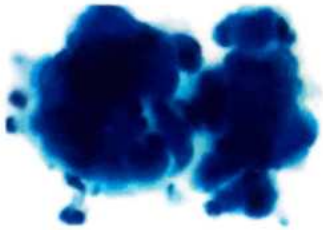
BRONCHIAL ASTHMA

01:15:20

- Reversible airway obstructive disorder

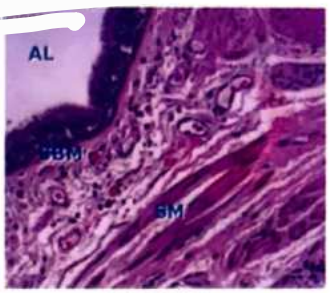
EXTRINSIC BA	INTRINSIC BA
• Type 1 HR • External antigen (House dust/pollens) • ↑↑ IgE • Childhood onset • H/O atopy	• Not due to HR • No association with External antigen • Normal IgE • Adults • No history of atopy • H/O viral infection → hyper-responsiveness • Exposure to Cold



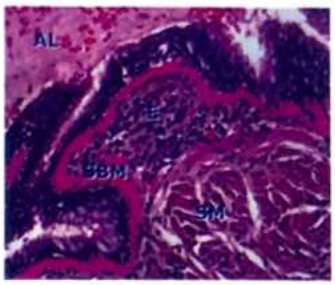


Creola Body

AIRWAY REMODELLING



NORMAL



ASTHMA

- ADAM 33 gene → responsible for proliferation of smooth muscle and fibroblasts
- YKL 40 protein correlates with severity of Asthma

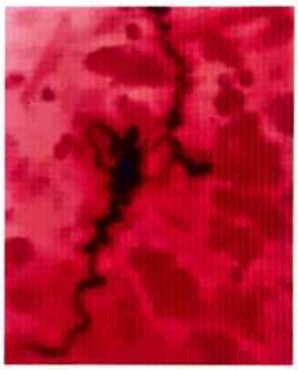
Treatment
- Steroids
- Bronchodilators: Terbutaline, Salbutamol
- Montelukast

Important Information

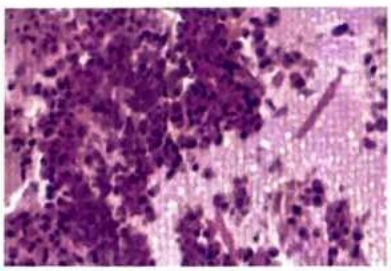
Samter's Triad
- Aspirin intolerance
- Asthma
- Adult nasal polyps (child with nasal polyp → CF)

Clinical features
- Dyspnea
- Wheezing
- Nocturnal cough

Diagnosis
- Spirometry
- Sputum examination
  - Charcot - Leyden Crystals is composed of galectin 10
- Airway remodeling



Curschmann Spirals



Charcot - Leyden Crystals

Previous Year's Questions

Q. Which of the following is not a feature of bronchial asthma? (FMGE - Dec – 2018)

A. Thickening of bronchial wall.

B. Increase in number of goblet cells glands.

C. Hypotrophy of smooth muscle

D. Increased IgE

BRONCHIECTASIS

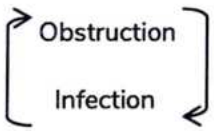
01:29:56

- Chronic necrotizing infection/inflammation → abnormal permanent dilatation of airways

Etiology
- Congenital risk factors
  - Kartagener Syndrome
  - Cystic Fibrosis
- Obstruction (FB or tumor) → inability to clear secretion → secondary infections
- Infections
  - TB

- Staph aureus
- ABP aspergillosis
- Miscellaneous factors
  - RA
  - GVHD

Pathogenesis



- Prolonged inflammation → wreaking of wall → dilatation of airway

Clinical features

Dilated airways across the lung

- Bronchorrhea
- Left sided Basal involvement is more
- HRCT → Tram track appearance (honeycomb lung)
- Fever
- Dyspnea
- Associated with secondary amyloidosis
- Benign condition

Treatment

- Mucolytics
- Antibiotics
- Supportive therapy

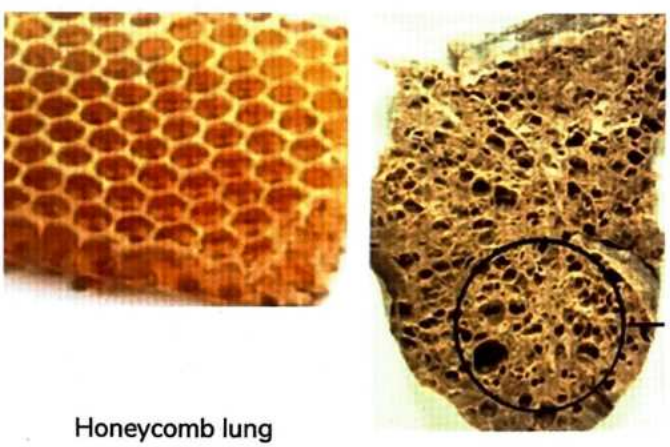
63 RESTRICTIVE LUNG DISEASE

Spirometry findings
- TLC ↓↓
- FVC ↓↓ → FEV1 (normal/↓)
- FEV1/FVC ↑↑
- Fibrosis
  - ↓ Compliance
  - ↓ Diffusion Capacity

ETIOLOGY

Extra parenchymal causes
- Chest wall disorders: obesity/kyphosis/scoliosis/ankylosing spondylitis
- Neuromuscular disorders: diaphragmatic palsy/MG/GBS/muscle dystrophy

Parenchymal causes
- Acute: ARDS
- Chronic
  - Fibrosing: IPF/NSIP/COP/ Pneumoconiosis → Irregular cystic cavities Honeycomb lung
  - Granulomatous: HP/Sarcoidosis
  - Eosinophilic: Loeffler Syndrome/Drug Allergy
  - Smoking related: Diphtheria/Respiratory Bronchiolitis



Honeycomb lung

IDIOPATHIC PULMONARY FIBROSIS (IPF)

00:08:18

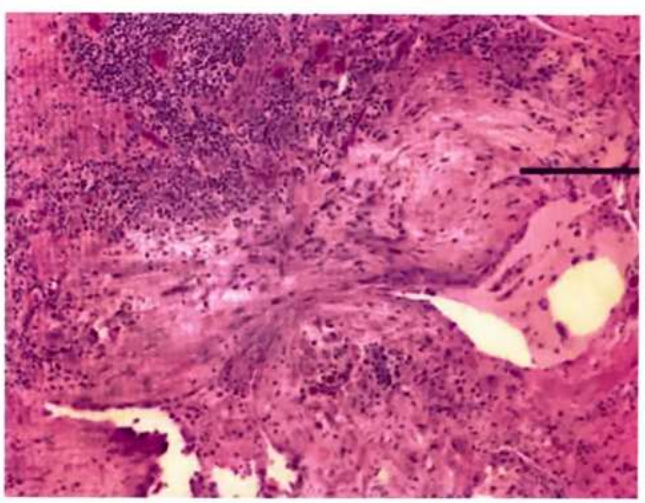
- Aka cryptogenic fibrosing alveolitis

Alveolar Epithelial Injury
↓
Alveolitis
↓
TGF-β
↓
Fibrosis

Risk Factors
- Age: Elderly
- Genetic Factors: Telomerase/mucin/Surfactant
- Environmental factors: GERD, Tobacco exposure

Clinical features
- Male > 50yrs
- Dry cough
- Dyspnea
- Dry inspiratory crackles
- R/O previous radiation exposure and drugs
  - Methotrexate
  - Bleomycin
  - Amiodarone

Diagnosis
- It is a diagnosis of exclusion
- Surgical biopsy → usual interstitial pneumonia. Characterized by
  - Patchy interstitial fibrosis (Heterogeneous: fibroblastic foci, collagen)
  - Architectural distortion → cyst → honeycombing
  - Site of biopsy: lower lobe (sub-pleural, along interlobular septa)
- HRCT scan
- IPF → death within 3yrs from diagnosis



Fibroblastic foci (sub-pleural, along interlobular septa)

Important Information

- UIP can also be seen in hypersensitivity pneumonitis. Rheumatoid arthritis

Treatment
- Lung transplant
- TGF β inhibitor: Pirfenidone
- Tyrosine kinase inhibitor: Nintedanib (↓ fibrosis)

NON SPECIFIC INTESTITIAL PNEUMONIA (NSIP)

00:22:56

- Idiopathic
- Connective Tissue disorders (exception Rheumatoid Arthritis)

Clinical features
- Elderly female
- 6th decade of life
- Non smoker
- Dyspnea
- Dry Cough

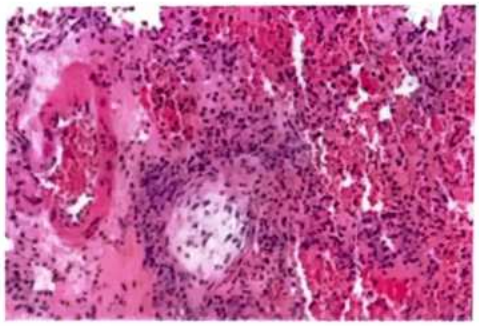
Diagnosis
- Radiology: HRCT scan Reticular opacities
- Surgical biopsy
  - NSIP → "Homogenous/uniform appearance"
  - Presence cellular NSIP (or) Fibrosing NSIP (poor prognosis)
    → Both never seen together
  - Distinguishing factors from UIP: No fibroblastic foci/variability/honeycombing
  - No granulomatous lesion/hyaline membrane

Treatment
- Steroids

CRYPTOGENIC ORGANISING PNEUMONIA (COP)

00:28:56

- Unknown etiology
- Clinical features: cough & Dyspnea
- Diagnosis: Surgical biopsy → presence of Masson body (plug of connective present in airway)
- Treatment: Good response to steroids

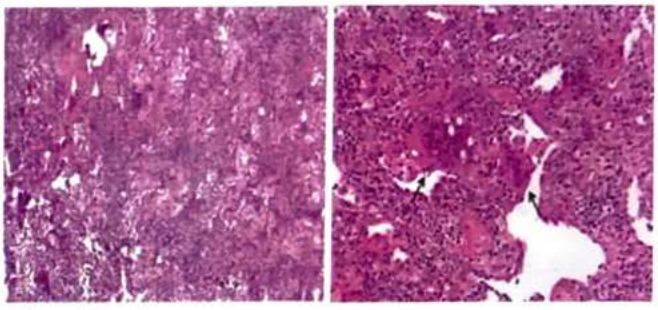


Masson body

DESQUAMATIVE INTERSTITIAL PNEUMONIA

00:31:01

- No Desquamation of pneumocytes
- Smoking → Pigmented alveolar macrophages (Smoker's macrophages)
- Mild interstitial Fibrosis
- Steroids provides good relief



Smoker's macrophage

- Respiratory bronchiolitis: Pigmented macrophages on respiratory bronchioles

PNEUMOCONIOSIS

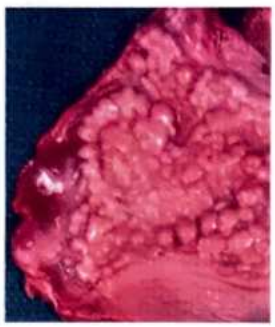
00:34:04

Inhalation of dust particles (1-5μ)
↓
Activation of alveolar macrophages
↓
Fibrosis
↓
Restrictive lung disorder

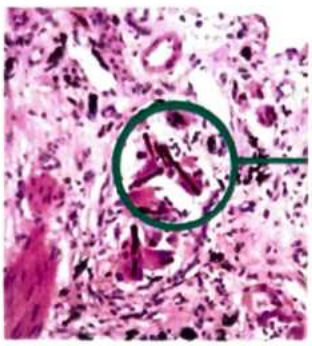
SILICOSIS
- MC pneumoconiotic disorder
- Exposure to silica/sand dust
- Upper lobe involvement
- ↑ Risk of TB/cancer
- On CXR, Egg shell calcification is seen
- Polaroid microscopy: Birefringent silica crystals

ASBESTOSIS

- Asbestos – chemical carcinogen
- Associated with fibrotic nodule formation in pleura → Pleural plaques (MC lesion)
- Interstitial fibrosis → asbestos body/ferruginous body (asbestos particle covered by proteinaceous material containing iron)
- ↑ Risk of cancer
  - Bronchogenic carcinoma (MC)
  - Malignant mesothelioma (Most Specific)



Pleural plaque



Ferruginous body

COAL WORKER'S PNEUMOCONIOSIS

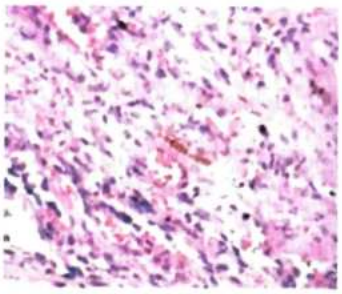
- Due to inhalation of coal dust
- Asymptomatic (anthracosis)
- Symptomatic (coal workers pneumoconiosis)
  - Cold nodule
  - Centriacinar emphysema
- Continuous exposure → Progressive Massive Fibrosis (complicated CWP)
- Black lung → prolonged exposure to coal dust
- CWP + RA → Caplan syndrome

OTHER TYPES OF PNEUMOCONIOSIS

- Byssinosis → Inhalation of cotton dust in textile industry
- Bagasosis → Inhalation of fungal contaminated sugarcane spores in farmers
  - Spray of 2 % Propionic Acid → ↓ risk of bagasosis
- Berylliosis → Exposure to beryllium in aerospace industry

Previous Year's Questions

Q. A worker was working in a factory from the past 20 years. Now presented with pleural thickening & fibrosis. Histopathology of lesion is shown in below image. Most likely diagnosis is which of the following? (AIIMS – May - 2018)



A. Asbestosis
B. Cotton fiber
C. Coal worker's disease
D. Silicosis

SARCOIDOSIS

00:48:20

- Immune dysregulation
- Presence of HLA A/B8
- Female >> Male
- Commonly seen in non-smokers

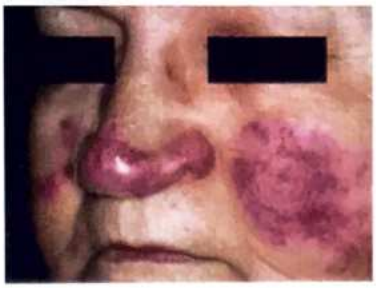
Pathogenesis

Unknown AG
↓
CD_4 T activation
↓
Cytokines
(TNF α → marker in BAL fluid)
↓
Non-caseating granuloma

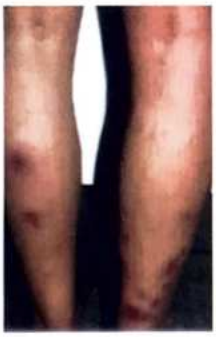
Clinical features

- Lungs
  - Dyspnea
  - Cough
  - Bilateral hilar lymphadenopathy "potato nodes"
- Skin
  - Lupus pernio
  - Erythema nodosum
  - Loffgren syndrome
    → Erythema nodosum
    → Arthralgia

→ B/L lymphadenopathy



Lupus pernio



Erythema nodosum

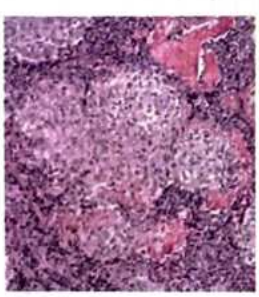
- Eyes: Uveitis (MC ophthalmologic manifestation)
- Mickulicz syndrome: Lacrimal gland/salivary gland destruction → dryness of eye and mouth
- Spleen/Liver/Bone marrow: presence of granuloma
- Endocrine: pituitary involvement
- Muscle: myalgia, fatigue

Important Information

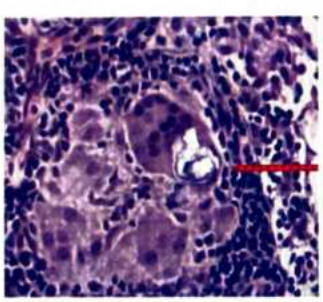
- MC cause non-infectious granulomatous hepatitis: Sarcoidosis

Diagnosis

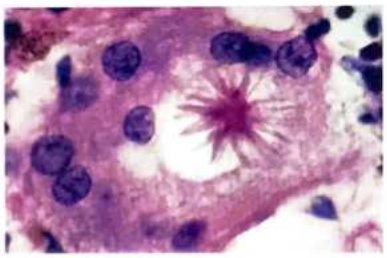
- Diagnosis by Exclusion
- ↑↑ S. ACE levels
- ↑ Activity of 1α – hydroxylase → ↑↑ Ca^{2+}
- Cutaneous anergy (↓ cell mediated immunity)
- BAL fluid
  - ↑ TNF α
  - ↑ CD_4:CD_8 T-cell ratio (5-15:1)
- LN biopsy: Non caseating granuloma
- Kveim test: Intra-cutaneous injection of spleen extract from known case of sarcoidosis → Non-caseating granuloma formation in 4-6 weeks



Naked granuloma



Schaumann body



Asteroid body

Treatment

- Spontaneous Remission
- Improvement on Steroids

HYPERSENSITIVITY PNEUMONITIS 01:06:03

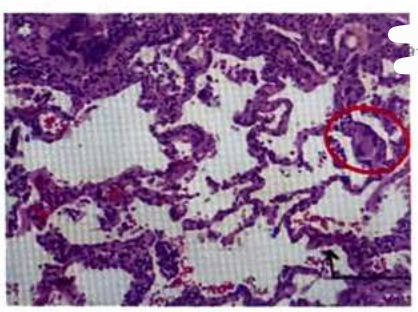
- Aka extrinsic allergic alveolitis
- Exposure to known Ag → interstitial pneumonitis & non-caseating granuloma

Acute Exposure (4-6 hrs after exposure)
↓
Immune Complex (Type 3 HR)
↓
Alveolitis

- Chronic Exposure → T-Cell activations → granuloma (Type 4 HR)
- Type 4 HR >> Type 3 HR

Clinical features

- Dyspnea
- Cyanotic manifestations
- Respiratory failure



Interstitial pneumonitis

- Farmer's lung → thermophilic actinomyctes
- Pigeon breeder's lung → bird protein
- Humidifier lung → bacteria

64 PULMONARY HYPERTENSION

Important Information

- Normal pulmonary artery pressure: 10mm Hg
- Pulmonary HTN: > 25 mmHg

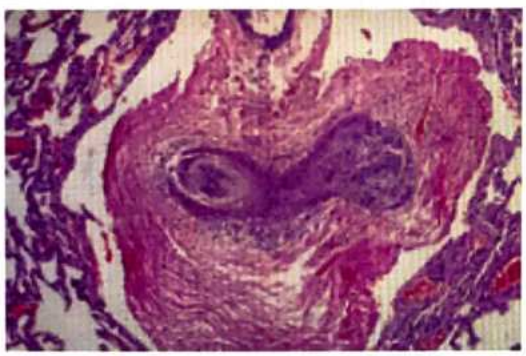
1° Pulmonary HTN 00:00:41

- Young female (20-40yrs)
- Inactivation mutation of BMPR 2 (Bone Morphogenic Protein Receptor)
- Normal gene → smooth muscle cell apoptosis
- Mutation → ↑↑ proliferation of smooth muscle cell → Pulmonary HTN

2° Pulmonary HTN

- Hypoxemia causes vasoconstriction
- Seen in high altitude/pulmonary disease
- Left ventricular Failure/mitral Stenosis
- Recurrent Pulmonary Embolism
- Obstructive sleep apnea

Microscopic appearance



Medial hypertrophy

- Medial hypertrophy (affects elastic & muscular arteries)
- Pulmonary artery atherosclerosis
  - Presence of plexiform lesion
- Right ventricular hypertrophy

Clinical features

- Dyspnea
- Fatigue
- Chest pain
- CXR → Tapering of pulmonary arteries

Treatment

- Administration of O_2
- Diuretics
- Vasodilators
  - Endothelin Antagonists
  - Prostanoids
- Lung transplantation

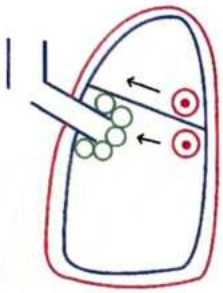
65 INFECTIVE LUNG DISORDERS

PULMONARY TUBERCULOSIS

- Causative organism: Mycobacterium tuberculosis hominis
- Mode of transmission: Droplet infection
- Obligate aerobe
- Cord factor → virulence
- LAM → inhibits phagocytosis

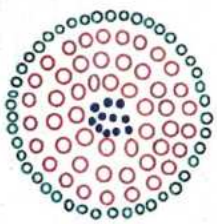
Primary pulmonary TB

- 1st entry of pathogen



Gohn's complex

- Ghon's focus: sub-pleural lesion near the inter-lobar fissure
  - 1st cell affected by Ghon's focus → alveolar macrophages
- Ghon's complex: Ghon's focus + Lymphatics + Hilar LN enlargement (occurs within 3 weeks)
- After 3 weeks: APC → TH1 cell → INF γ → macrophage activation
- Macrophage + IL-2 + TNF α → Granuloma formation → inactivation of bacilli



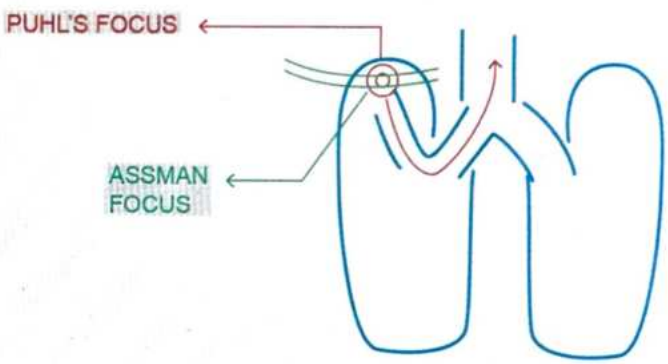
Macrophages covered by lymphocytes

- Raenke's complex: Fibro-calcified Ghon's complex
- Simon's focus: Apical lesion seen in immunocompromised individual
- In severely immunocompromised patients → dissemination of bacteria → progressive pulmonary TB

Primary TB

Secondary Pulmonary TB

00:12:55



- Occurs due to
  - Reactivation (MC) → ↓ immunity
  - Reinfection
- Apical Lesion is seen → due to maximum ventilation perfusion ratio

Apical lesion	
Delayed hypersensitivity	**Immunosuppression**

• Caseation
• Cavitation
• Hemoptysis
• No hilar lymphadenopathy
	• Lymphatic spread → lung → military pulmonary TB
	• Hematogenous
	• Aerogenous
	  ○ Endobronchial TB
	  ○ Laryngeal TB

Important Information

- MC blood vessel to bleed in Tuberculosis: Bronchial artery

- In secondary pulmonary TB
  - Supra-clavicular lesion → Puhl's focus
  - Infra-clavicular lesion → Assman focus

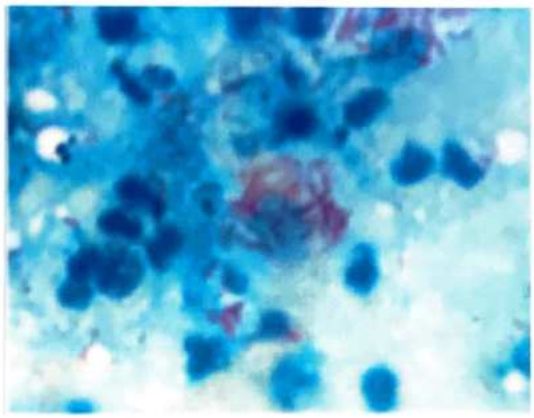
Secondary pulmonary TB

Clinical features
- Cough (> 2 weeks)
- Weight loss
- Low grade fever with rise in the evening
- Night sweats
- Hemoptysis
  - Uncommon Pulmonary artery involvement → Rasmussen's aneurysm

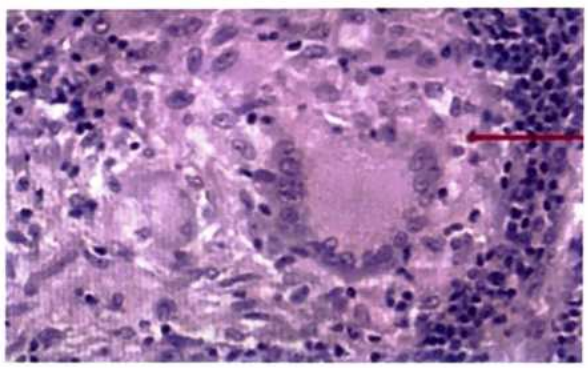
Refer Table 65.1

Millet-like foci (Miliary TB)

Diagnosis 00:34:15
- ↑↑ ESR
- Lymphocytosis
- Sputum Examination (Petroff's method/NALC method)
  - Early morning sample is preferred
  - Stain: ZN stain → acid fast bacilli
  - Culture
    - → LJ media
    - → BACTEC method (faster growth)
  - PCR: mycobacterial NA → CBNAAT
- Chest X-ray: pleural effusion
  - Straw colored fluid in pleural tap
  - ↑↑ ADA



Acid fast bacilli



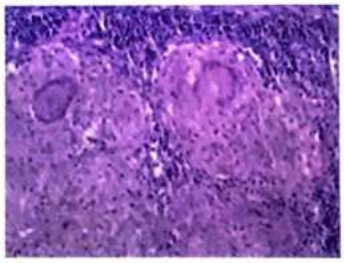
Langhans cell

Caseous necrosis

Treatment
- ATT
  - MDR-TB: Resistance to isoniazid/rifampicin
  - XDR–TB: Resistance 1st line ATT/1 Injectable fluoroquinolone/aminoglycosides

Previous Year's Questions

Q. A 11 years old boy came with history of cough for 15 days. On examination he was found to have cervical lymphadenopathy. The lymph node biopsy is shown below. Which of the following is the most appropriate diagnosis? (NEET - Jan - 2020)



A. Tuberculosis
B. Leprosy
C. Sarcoidosis
D. Syphilis

PNEUMONIA

00:42:12

- Infection of lung parenchyma

Refer Table 65.2

Laennec Stages of Typical Pneumonia

- Congestion (1-2 days): Vascular engorgement & presence of alveoli containing bacteria & WBCs
- Red hepatisation (3-4 days): Alveoli with RBCs & ↑ fluid → change in consistency
- Grey hepatisation (5-8 days): Lysis of RBC, massive fibrin deposition
- Resolution (>8 days): Causative organisms are removed by Phagocytic cells

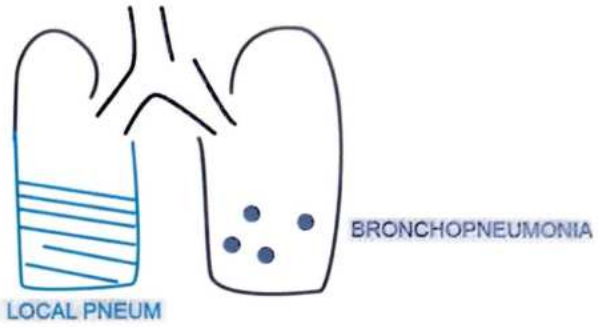
Previous Year's Questions

Q. A non-smoker patient has the presence of alveolar exudate. He presented with flu like symptoms which were followed by radiological evidence of consolidation in the lung. Which of the following is the likely organism is seen? (JIPMER - Nov - 2017)

A. Streptococcus pneumoniae
B. Staph aureus
C. Pseudomonas aeruginosa
D. klebsiella pneumonia

Types of Typical Pneumonia

- Lobar pneumonia: Extensive involvement of lung tissue, can be seen on chest X-ray
- Bronchopneumonia: Patchy involvement. Seen in children and elderly.
  - B/L involvement
  - Basal lobe is usually involved



Typical Pneumonia - Causative Organisms 00:54:58

Streptococcus pneumonia	• CAP (community Acquired Pneumonia) • Rusty Sputum
Staphylococcus aureus	• 2° pneumonia • Abscess formation
Klebsiella pneumonia	• Alcoholic → Aspiration • Red currant Jelly sputum
H.Influenzae	• Exacerbation of COPD • H/O Epiglottitis • type 'b' → Hib vaccine (offers protection)
Pseudomonas Aeruginosa	• ↓ immunity • Burns • Cystic Fibrosis • Nosocomial Pneumonia (VAP) → greenish pus

Atypical Pneumonia - Causative Organisms

Refer Table 65.3

Table 65.1

Organs affected by TB	
LN	2nd MC organ affected → Scrofula → Matted LN
CNS	Rich focus; TB meningitis (basal cistern, cobweb appearance)
Heart	Chronic constrictive pericarditis
Bone	Vertebral column involved → Potts spine → cold abscess
Kidney	TB pyelonephritis → sterile pyuria
Adrenal gland	Chronic adrenal insufficiency
Genital tract	Infertility; epididymis affected (In TB, epididymis → testicular tissue)
Liver	Simmond's focus
Pulmonary vein	Weigart Focus
Ear	Otitis media → multiple tympanic membrane perforations
Eye	Phlectenular conjunctivitis (Type 4 HR)
GIT	Ileum (ulcers/subacuteintestinal obstruction)

Table 65.2

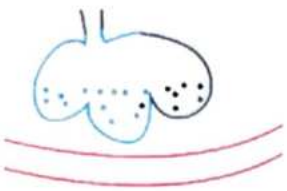
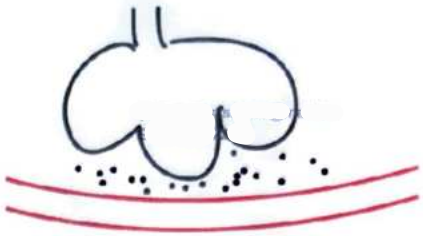
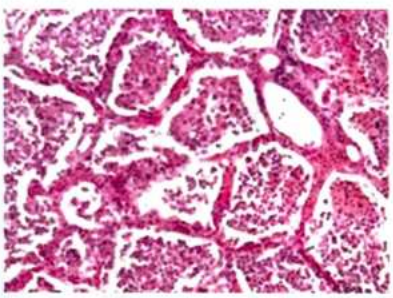
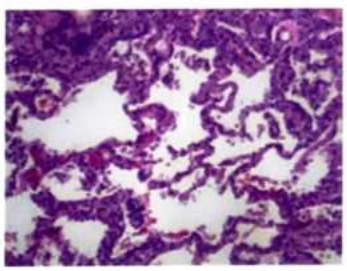
Typical Pneumonia	Atypical Pneumonia
	
• Aka air space pneumonia • Presence of alveolar exudate (most characteristic) • Neutrophilic infiltration	• Aka interstitial pneumonia • Interstitial tissue inflammation (most characteristic) • Mononuclear infiltration
 Alveolar exudate	 Alveolar septal involvement
Clinical features • High grade Fever • Chills/rigors • Productive Cough • Pleuritis • Dyspnea	**Clinical features** • Low grade fever • Dry cough • Less severe dyspnea • Malaise • Aka walking pneumonia

Table 65.3

Mycoplasma Pneumonia		• MC cause of atypical pneumonia • Cold AIHA • Hostel, military barracks → closed spaces
Chlamydia		• 2nd MC cause
Pneumocystis Jiroveci		• Fungal infection • Immunosuppression → AIDS • Silver stain is used
Coxiella Burnetii		• 'Q' fever
Legionella		• ICU → humidified air exposure • In normal individuals → Pontiac fever • Involvement of GIT/CNS is seen
Viruses	Influenza Type A	• MC viral atypical pneumonia • 2° infection → staph aureus
	RSV	• Children are affected • Bronchiolitis
	Measles	• ↓ Immunosuppression • Warthin–Finkeldey cells • Koplik spot
	CMV	• Post-transplant (kidney) • Immunosuppression • Presence of Owl-Eye Inclusions

66 ADULT RESPIRATORY DISTRESS SYNDROME

- Aka stiff lung / shock lung / hyaline membrane disease/ non-cardiac pulmonary edema
- Acute Respiratory Failure (< 7 days) + B/L Pulmonary opacities
- Diffuse alveolar damage (most characteristic feature)

Etiology 00:02:14

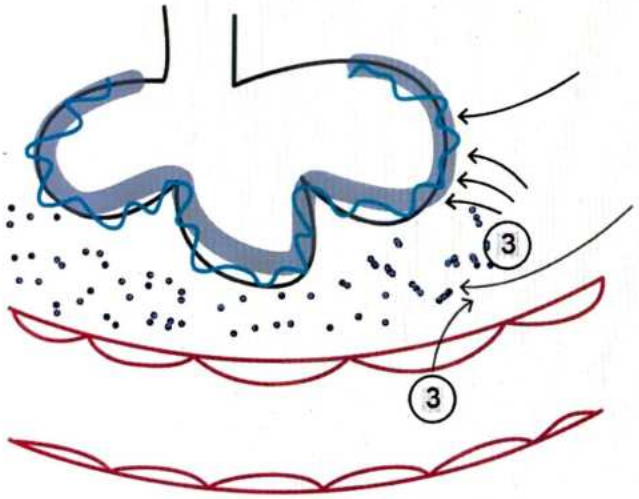
- Direct Lung Injury
  - Pneumonia (Viral)/gastric aspiration/inhaled gas
- Indirect Lung Injury
  - Gram –ve Septicemia/Mechanical trauma
  - TRALI/DIC/Fat embolism
  - Pancreatitis/drugs/burns
- MC cause of adult ARDS: Pneumonia

Pathogenesis

Endothelial Cell Injury

IL-8 → Neutrophils → Damage to alveolar epithelial cells (Type 1 > type 2) → ↓ Surfactant → Alveolar collapse

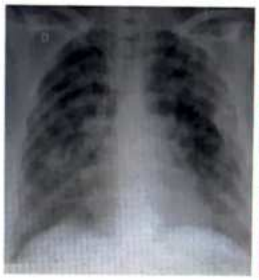
Alveolar interstitial space (exudative fluid) → Fibrin deposition/necrotic cells → Hyaline membrane → Stiff lung



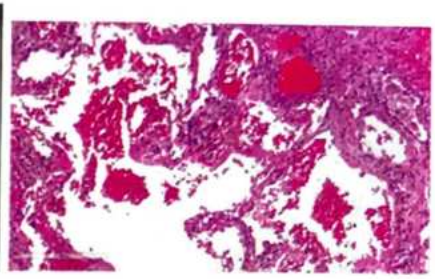
Clinical Features 00:12:22

- Respiratory Distress
- Hypoxemia
- Inflammatory pulmonary edema (exudative fluid)

Diagnosis



White out lung



Hyaline membrane

- CXR: white out lung
- Microscopic appearance
  - Diffuse alveolar damage
  - Hyaline membrane (fibrin + dead epithelial cells)
- PCWP: < 18 mmHg (NCPE)
- Macrophages → TGF β → fibrin

Treatment

- O_2 inhalation → Refractory
- Treat the Primary cause
- PEEP (Positive End Expiratory pressure)
- Steroids

67 LUNG TUMORS

BRONCHOGENIC CARCINOMA

RISK FACTORS

00:00:27

- Smoking
  - Female >> male
  - CYP1A1 polymorphism → ↑ risk of cancer
- Industrial Hazards: Asbestos
  - 15-20yrs exposure: bronchogenic carcinoma
  - 40yrs exposure: malignant mesothelioma
- Air pollution
- Genetic risk factors
  - p53/p16 mutation → ↑ risk for squamous cell carcinoma
  - Rb/myc mutation → ↑ risk for small cell lung cancer
  - EgFR/KRAS mutation → ↑ risk for adenocarcinoma of lung

Important Information

- Asbestos → atypical adenomatous hyperplasia → adenocarcinoma in-situ → MIA

Clinical features

- Cough
- Weight loss
- Dyspnea
- Hemoptysis
- Pleuritic pain
- Atelectasis
- Obstructive pneumonia
- RLN involvement → Hoarseness of voice
- Shoulder pain → involvement of C8/T1/T2
- Pancoast tumor: Tumor in apical lobe → compression of sympathetic plexus → Horner syndrome
  - Miosis
  - Anhydrosis
  - Ptosis
  - Enopthalmos
  - Loss of ciliospinal reflex

Diagnosis

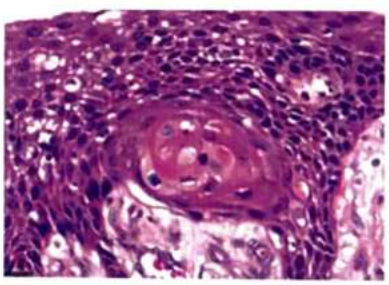
- Sputum examination → less sensitive
- PET-CT scan → Used to find extent of disease
- Bronchoscopy + Biopsy → IOC
  - HPE
  - Immunohistochemistry
  - Molecular testing

WHO 2015 Classification (Epithelial Tumors)

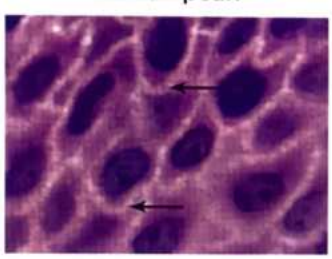
- Squamous Cell Cancer: keratinizing/non-keratinizing/Basaloid
- Adenocarcinoma: Lepidic/Acinar/Papillary/Solid
- Large Cell Cancer
- Neuroendocrine Carcinoma: DIPNECH/carcinoid tumor
  - Small cell/large cell carcinoma
  - DIPNECH: Diffuse Idiopathic Pulmonary Neuro-endocrine Cell Hyperplasia
- Mixed Carcinoma: Adenosquamous Carcinoma, combined small cell Carcinoma
- Others: Sarcomatoid/giant cell cancer/spindle cell Cancer
- NUT Carcinoma
  - $NUTM_1$ Gene → BRD4 (Chromosome 19p) – 70%
  - Chromosome 15q14 → BRD3 (Chromosome 9q) – 6%
  - Unknown gene - 24%

SQUAMOUS CELL CARCINOMA

00:19:19



Keratin pearl

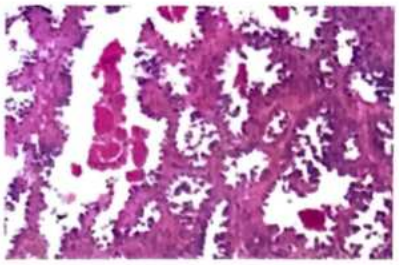


Intercellular keratin bridge

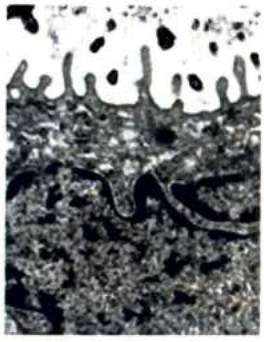
- IHC: p63/p40 +ve
- Seen in smokers
- Better prognosis (early detection due to larger proximal

airway involvement)
- Development of local cavitation
- Lipoid pneumonia
- Hypercalcemia (paraneoplastic syndrome)

ADENOCARCINOMA



- Presence of gland & mucin
- IHC markers: TTF-1, NAPSIN-A
- Overall MC Lung cancer globally
- Non-smokers can also be affected
- Mucin glands → Thrombophlebitis
- Clubbing (hypertrophic pulmonary osteo-arthropathy)
- Smaller/periphery airways are involved
- Origin: Bronchiole-alveolar cell



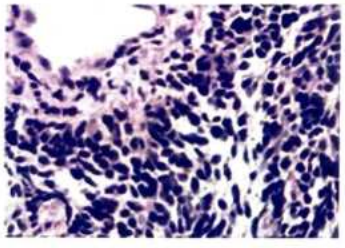
Adenocarcinoma

Malignant mesothelioma

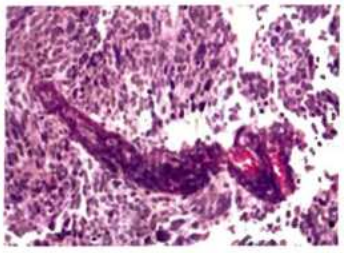
- On Electron microscopy
  - Adenocarcinoma has small, non-branching microvilli
  - Malignant has long, slender, branching microvilli

SMALL CELL CARCINOMA

00:28:09



Nuclear molding



Azzopardi effect

- Neuroendocrine carcinoma
- Presence of Neuro-secretory granules seen under electron microscopy
- IHC markers: Synaptophysin/CD-57/BCL-2/Chromogranin
- Involvement of larger airways is seen
- Highly aggressive in nature (poor prognosis)
- Neurosecretory granules → secrete active substances (ACTH → cushing syndrome, calcitonin → hypocalcemia)
- It can also be responsible for causing SVC syndrome

Microscopic appearance

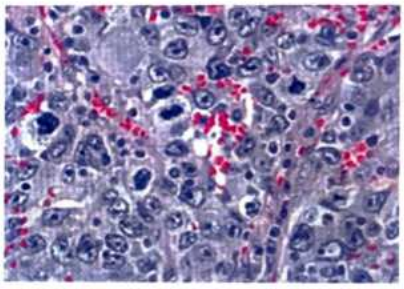
- Cells have small cytoplasm with majority being occupied by the nucleus → cells deform each other → nuclear molding
- Chromatin is finely dispersed → salt & pepper chromatin
- ↑ Mitosis
- Damage to cells → leakage of nuclear contents → staining of vascular endothelial cells (Azzopardi effect)

Important Information

- Small cell lung cancer is associated with Lambert Eaton Syndrome → antibodies produced against pre-synaptic calcium channel

LARGE CELL CANCER

00:34:24



- It is a diagnosis of exclusion
- Paraneoplastic syndrome: cells secrete estrogen → gynecomastia

Metastasis

- MC organ affected in lung cancer: adrenal gland
- MC organ affected in Small cell cancer: CNS

Treatment

- SCLC: Radiation/chemotherapy
- NSCLC: Specific therapy. Examples
  - Squamous cell carcinoma: immune checkpoint inhibitor therapy
  - Adenocarcinoma: Pemetrexed
- Patient with EgFR mutation will have better prognosis than those with K-RAS mutation

Previous Year's Questions

Q. Which is the most common tumor associated with superior vena cave syndrome? (FMGE - Dec - 2017)

A. Lung cancer
B. Lymphoma
C. Metastasis
D. Thyroid cancer

PLEURAL TUMORS

00:39:17

- Secondary tumor (metastasis) >>> primary tumor

Primary tumor	Secondary tumor
• Solitary fibrous tumor • Malignant mesothelioma	• MC cause of metastasis: Lung cancer • 2nd MC cause: Breast cancer • Ipsilateral involvement of pleura to lung/breast cancer

SOLITARY FIBROUS TUMOR

00:41:04

- Aka Benign Mesothelioma
- Asbestos exposure is not a risk factor
- Genetics: Chromosome 12 inversion → NAB-2 STAT 6 fusion gene

Dense fibrous tumor

- Gross appearance: Dense fibrous tumor
- Microscopic appearance: Presence of spindle cells resembling fibroblasts

	SFT	MM
CD34	⊕	⊖
Keratin	⊖	⊕

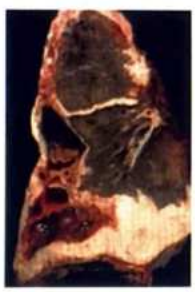
MALIGNANT MESOTHELIOMA

Risk Factors

- Asbestos exposure (Amphibole)
- Incubation period: 25-45yrs
- Radiation
- No association with smoking

Clinical Features

- Age group: 50-60yrs
- Chest pain
- Difficulty in breathing
- Pleural effusion
- Right Lung >>> Left Lung
- Involvement of Lung & Hilar lymph nodes are also seen.



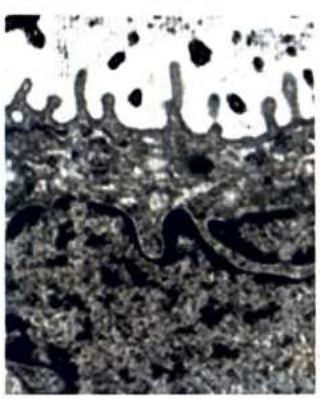
Lung encased by cancer

Variants

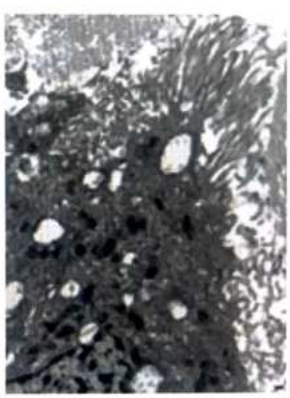
- Epithelioid type (MC)
- Sarcomatoid type
- Mixed / biphasic type

EPITHELIOD TYPE

- Tumor cells → forms papillary & tubular structures
- Resembles adenocarcinoma of lung
- Distinguished from Adenocarcinoma of Lung by Electron microscopy
  - Adenocarcinoma: Short & Non-branching microvilli
  - Mesothelioma: Long, thin, branching microvilli



Adenocarcinoma



Mesothelioma

IHC Markers	Adenocarcinoma	Mesothelioma
Calretinin (Marker of choice)	-	++
WT_1	-	++
CK5/6	-	++
MOC 31	++	-

Important Information

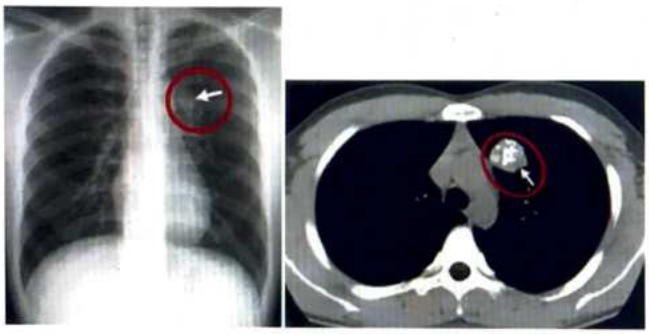
Malignant Mesothelioma

- Deletion of tumor Suppressor genes CDKN2A/INK4a on chromosome 9p
- It can be confirmed by FISH technique

PULMONARY HAMARTOMA

00:56:24

- True Neoplasm
- Nodules of Mesenchymal Tissue/Entrapped Respiratory Epithelium
  - Mesenchymal Tissue
    - → Connective tissue
    - → Fat
    - → Cartilage (predominant)
    - → Smooth muscles
    - → Genetics: t(3;12)
- Radiological finding: Pop-corn calcification
- Treatment: Surgical Excision



Pop-corn calcification

INFLAMMATORY MYOFIBROBLASTIC TUMOR

- Seen in pediatric population
- Genetics: ALK gene activation present on chromosome 2p23
- Gross appearance: Peripheral firm mass calcium deposition

Clinical features

- Fever
- Cough
- Chest pain
- Hemoptysis

Microscopic appearance

- Presence of spindle shaped cells (fibroblasts or myofibroblasts)
- Infiltration of lymphocytes & plasma cells
- Presence of peripheral Fibrosis

CLINICAL QUESTIONS

Q. A 60-year-old man, a heavy smoker, presents for treatment to stop smoking. On physical examination, he is thin and has a red complexion. He has cough with expectoration and a barrel-shaped chest. He has pursed his lips to facilitate his breathing and is sitting leaning forward. A diagnosis of emphysema is made. Which of the following is the most likely histological finding in the lungs?

A. Hypertrophy of smooth muscle of bronchus with proliferation of eosinophils
B. Leakage of protein-rich fluid into alveolar spaces with Diffuse alveolar damage
C. Destruction of alveolar walls with Dilation of air spaces
D. Hyperplasia of bronchial submucosal glands which secretes mucus

Solution

- Emphysema is an example of COPD.
- Due to the destruction of alveolar walls there is a lack of elastic recoil which causes trapping of air in alveoli, and, thus, on expiration obstruction of airflow occurs.
- In COPD, FEV1 is decreased, whereas FVC is normal or increased; therefore, patients with COPD have a decreased FEV1: FVC ratio.

Reference

- Robbins 10/e p 681

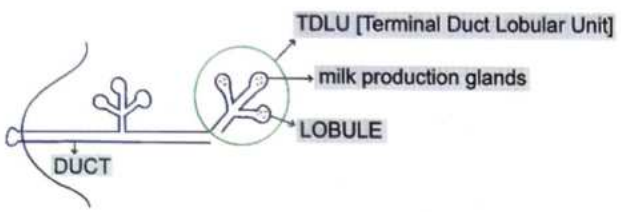
LEARNING OBJECTIVES

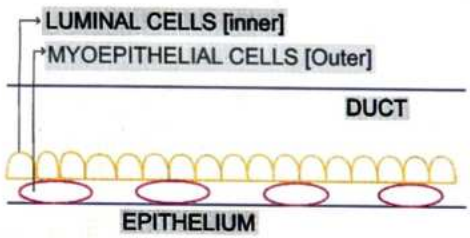
UNIT 11 BREAST

- **Breast disorders**
  - Inflammatory Conditions
  - Zuska's Disease
  - Mammary Duct Ectasia
  - Fat Necrosis
  - Lymphocytic Mastopathy
  - Benign Epithelial Lesions Of Breast Tissue
  - Breast Cancer; Pathogenesis
  - Types Of Breast Cancer
  - Carcinoma In Situ
  - Paget's Disease Of Nipple
  - Lobular CIS
  - Infiltrating Cancers ; Histological Classification
  - Inflammatory Breast Cancer
  - Prognostic Factors Of Carcinoma Breast

68 BREAST

- It is a modified apocrine gland
- Breast is hormone sensitive tissue
  - Estrogen: Alveolar duct growth
  - Progesterone: Alveolar cell differentiation
  - Prolactin: Lacto-genesis
  - Oxytocin: Milk ejection





- Functional unit of Breast tissue: TDLU (Terminal Duct Lobular Unit)
- Myoepithelial contraction is responsible for ejection of contents in the lumen

Breast pathology presentation
- Mass/lump
- Mastalgia
- Nipple discharge

Important Information
- Milk discharge - Galactorrhea (MC due to nipple stimulation)
- Purulent discharge - Acute mastitis
- Greenish discharge - Ectasia of mammary duct
- Blood discharge - Ca breast, Ductal Papilloma (MC cause)

INFLAMMATORY CONDITIONS
00:06:11

ACUTE MASTITIS
- H/O Breast feeding young female
- Cause: Entry of Staphylococcus aureus present in oropharynx of the baby into the breast tissue by fissure or cracks on the skin of nipple.

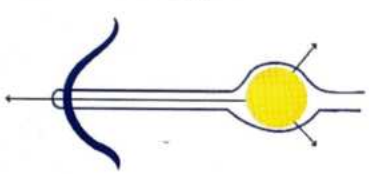
Clinical Features
- Pain
- Fever
- Swelling
- Redness
- Purulent discharge

Diagnosis
- Ultrasonography for confirmation

Treatment
- NSAIDs
- Antibiotics (Flucloxacillin/dicloxacillin)
- Aspiration
- Incision & Drainage
- Breast feeding is not contraindicated and can continue feeding from unaffected breast.

ZUSKA'S DISEASE
00:08:22
- Aka Peri-ductal mastitis (inflammation of tissue around the duct)
- H/O Smoking female/ vit A ↓↓
- Vitamin A is required for differentiation of columnar cells
- Smoking/Vit A deficiency → keratinizing squamous metaplasia → obstruction of duct → Rupture → local inflammation
- Fistula tract and retraction of nipples is possible

MAMMARY DUCT ECTASIA
00:10:52
- Seen in elderly female
- No association with smoking



- Abnormal dilation → accumulation of lipid laden macrophages → sub-areolar mass

Clinical feature
- Greenish discharge
- No pain

- No redness

Microscopic Examination
- Chronic granulomatous inflammation
  - Associated with infiltration of Lymphocytes, lipid laden macrophages & plasma cells
  - Aka Plasma cell mastitis

FAT NECROSIS 00:13:30
- Associated with history of Trauma & Surgery

Pathogenesis

Activation of Lipase
↓
Release of FFA from breast tissue
↓
FFA + Calcium
↓
Dystrophic calcification

Presentation
- Painless palpable mass
- Skin thickening
- On mammography, dystrophic calcification mimics malignancy

Histopathology
- Presence of lipid laden macrophages and foreign body giant cells

LYMPHOCYTIC MASTOPATHY 00:16:00
- Auto immune disorder
- Associated with autoimmune thyroid disease/Type 1 DM
- Mimics malignancy as there is presence of >1 breast mass

Microscopic feature
- Duct & lobular Atrophy
- ↑ Collagen deposition
- Lymphocytic infiltration

BENIGN EPITHELIAL LESIONS OF BREAST TISSUE 00:17:23
- Fibrocystic changes/non proliferative breast changes
  - Seen in < 50 years
  - Lumpy bumpy breast tissue
  - Risk of development of cancer: 3%
- Proliferative breast changes
  - Without Atypia (Risk of development of cancer: 5-7%)
  - With Atypia (Risk of development of cancer: 15-17%)
- Carcinoma in situ (Risk of development of cancer: 25-30%)

Non proliferative / fibrocystic breast changes
- Cysts: Bluish fluid in dome shaped cyst
- Fibrosis: Leakage of fluid cyst causing local inflammation & fibrosis
- Adenosis: ↑ no of acini per lobule
- Presentation due to irregularity in the breast tissue

Proliferative breast disease without atypia
- Epithelial hyperplasia
- Sclerosing adenosis
  - ↑ Collagen & Fibrosis
- Complex sclerosing lesion
  - Presence of Radial scar
- Intraductal papilloma
  - Incomplete compression: serous discharge
  - Complete compression: Bloody discharge
  - MC cause of bloody discharge

Proliferative breast disease with atypia
- It characterized monomorphic cells
- Atypical lobular hyperplasia (<50% acini involved per lobule)
- Atypical ductal hyperplasia

BREAST CANCER 00:22:37
- MC cancer in Females in India

Risk Factors
- ↑ Estrogen exposure
  - Female-99% & Males-1%
  - Early menarche & late menopause
  - Exogenous estrogen (HRT)
  - Obese post-menopausal female
  - Endometrial cancer
- Age: post-menopausal female
- Radiation exposure (during developmental stages)
- Family H/O: 1° Relatives
- Pregnancy
  - 1st pregnancy < 20yrs: protective
- Lactation: protective
  - Inhibition of ovulation
  - Maturation of cells in epithelium → ↓ risk of cancer
- Dietary
  - ↑ Lipids
  - Alcohol

PATHOGENESIS 00:28:45
Familial Breast Cancer (10-12%)
DNA Repair Genes
- BRCA 1 gene (17q) → female > male breast cancer

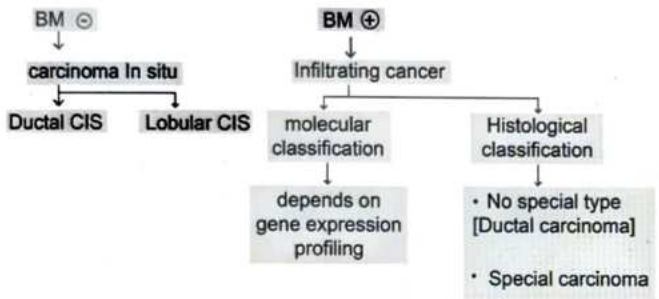
- Associated with basal-like & medullary cancer
- BRCA 2 gene (13q) → male > female breast cancer
  - Also associated with ovarian & prostate cancer
  - ↑↑ Fanconi Anemia
- p53 gene (17p) → sporadic breast cancer
  - Li-Fraumeni syndrome (↑ risk of leukemia & sarcoma)
  - Overall MC mutation for development of breast cancer
- CHEK2 gene → ↑ risk of breast/kidney/colon/thyroid cancer
- Associated with post-radiation exposure

Sporadic Breast Cancer (88-90%)

Estrogen Exposure + Genetic factors (p53 mutation)
↓
Potential cells
↓
↑ Risk of cancer

TYPES OF BREAST CANCER

00:38:41



CARCINOMA IN SITU

00:42:29

- Site of origin: TDLT

DUCTAL CIS

- No involvement of BM
- Cells in ducts (Basal cells or myoepithelical cells preserved)
- Secretion & Necrosis → Ca^{2+} deposition → mammography
- DCIS → Invasive cancer (1% per year)

Types

- Comedo DCIS
  - Presence of high grade tumor cells
  - Presence of central necrosis
  - Associated with linear/branching type of calcification in mammography
- Non-comedo DCIS
  - "Cribriform pattern" of calcium deposition
  - Micro-papillary pattern

Cribriform

Micropapillary

Treatment

- Mastectomy
- Radio therapy
- Tamoxifen

Previous Year's Questions

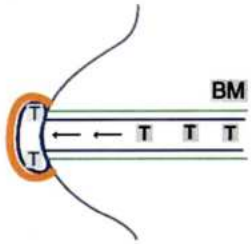
Which of the following shows breast necrosis and calcification? (FMGE 2017)

A. Comedo subtype of DCIS
B. Cribriform subtype of DCIS
C. Colloid carcinoma
D. Lobular carcinoma in-situ

PAGET'S DISEASE OF NIPPLE

00:49:19

- Type of DCIS

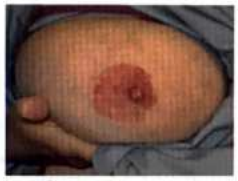


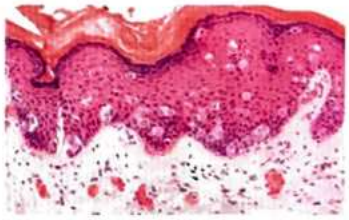
Scaly crust formation over nipple

- Unilateral lesion
- Aka "eczematoid lesion"
  - Intense pruritus
  - Ulceration of nipple
  - Palpable mass (50%): presence of underlying Invasive cancer

Microscopic finding

- Paget Cells have
  - Abundant cytoplasm
  - Prominent nucleus & nucleoli
  - Presence of Mucin
  - Positive HER 2 Expression
  - Negative for ER/PR





LOBULAR CIS

00:58:59

- Presence of malignant cells growing in discohesive fashion

E-cadherin Discohesive pattern

- CDH1 mutation → E-cadherin → Discohesive tumor cells
- No secretions & no necrosis (no calcification)
- Incidental finding
- Bilateral presentation
- Lobular carcinoma → Risk of Invasive cancer on both ipsilateral and contralateral side (1% per year)

Microscopic finding

- Presence of mucin positive signet ring cells
- ER/PR – positive
- HER 2 – negative

Treatment

- Bilateral mastectomy

INFILTRATING CANCERS

01:06:05

- site of MC cancer origin: TDLU
- >90% of breast cancers are adenocarcinoma
- 2 types of classification
  - Molecular classification: Based on Gene expression profiling
  - Histological classification: further divided into
    - → Special subtype
    - → No special type

MOLECULAR CLASSIFICATION

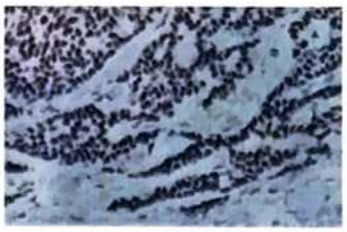
Refer Table 68.1

Important Information

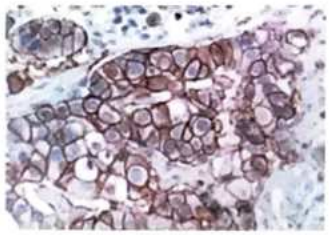
- Anti-Estrogen therapy is effective only in Luminal A&B subtype.
- HER 2/Neu antibody directed treatment is effective only in HER 2 enriched subtype

Immuno-histochemical staining

- ER/PR: overexpression of these receptors can cause darker nuclear stain
- HER 2/Neu: overexpression of these receptors can cause surface membrane staining



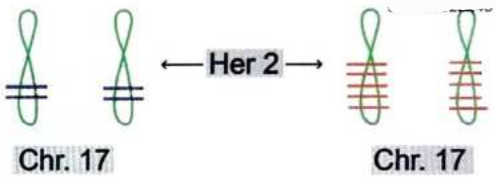
ER +ve in tumor cells



HER 2/Neu staining

Immunohistochemistry		
Negative score	Equivocal score	Positive score
0/1	2	3

- For equivocal score → FISH (Fluorescence in situ hybridization)
  - ↑ HER 2/Neu
  - $\frac{Her2/Neu}{CEP\,17}$ (Better Indicator)



Previous Year's Questions

In a known case of breast cancer, Fluorescent In-Situ Hybridization (FISH) for gene amplification will be done based on which of the following immuno-chemistry (IHC) staining for HER 2/Neu? (AIIMS 2017)

A. 1
B. 2
C. 3
D. Any of the above

HISTOLOGICAL CLASSIFICATION

01:21:40

NST INVASIVE CANCER

- Aka "ductal invasive cancer"
- MC sub type

Clinical feature

- Breast lump (MC)
- Upper outer quadrant (MC site due to ↑ breast tissue density)

- Skin retraction
- Nipple retraction
- Fixation of chest wall
- Peau d orange (due to cutaneous edema)

SPECIAL SUBTYPES

INVASIVE LOBULAR CARCINOMA

- ↓ CDH gene expression → ↓ E-Cadherin
- Bilateral & multifocal
- MC invasive cancer presenting as occult primary (hidden cancer)

Microscopic appearance

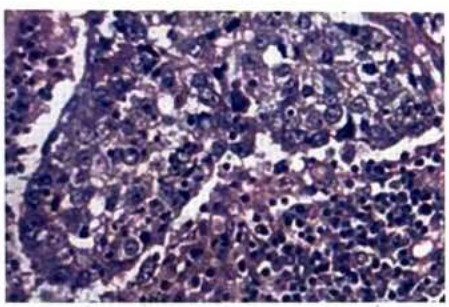
- Discohesive Cells: Indian File Pattern or Single file appearance
- Little stroma
- ↑ risk of association with development signet ring cell cancer of stomach (familial gastric carcinoma – CDH mutation)

MEDULLARY VARIANT

- Hyper-methylation of BRCA 1 gene promoter

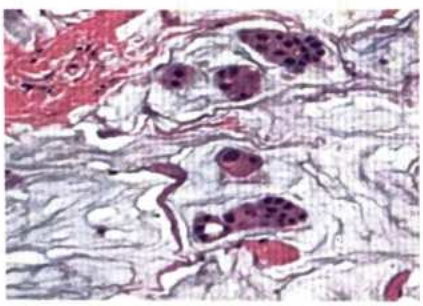
Microscopic appearance

- Sheets of cancer cells
- ↑ mitosis
- Lymphoplasmacytic infiltration



MUCINOUS VARIANT

- Tumor cells are present in a pool of mucin
- Soft, Gel-like consistency
- Elderly females
- Good prognosis



Tumor cells in the Mucin

OTHER VARIANTS

- Tubular variant
  - Best prognosis
  - Associated with well-formed tubules
- Papillary cancer
  - Least common/Rarest of special subtype

Previous Year's Questions

A middle aged female presented with a 4cm mass in upper outer quadrant of the breast. Biopsy showed densely packed cells with large lake of mucin. Which of the following is the most likely diagnosis in this patient? (NEET 2020)

A. Medullary carcinoma of breast
B. Colloid carcinoma of breast
C. Tubular carcinoma of breast
D. Papillary carcinoma of breast

INFLAMMATORY BREAST CANCER 01:35:45

- Associated with lymphatic obstruction → Redness & Swelling of breast
- Mimics mastitis/abscess
- No response to Antibiotics
- Poor prognosis

MALE BREAST CANCER

- 1% of all breast cancers

Risk Factors

- **B**: BRCA 2 >> BRCA 1
- **R**: Radiation
- **E**: Estrogen
- **A**: Age (60-70 years)
- **S**: Syndrome (Klinefelter Syndrome)
- **T**: Tumor in 1° relative

Clinical features

- Sub areolar mass
- Skin infiltration
- Nipple discharge

Microscopic appearance

- Example of ductal carcinoma subtype
- High expression of ER in male breast cancer

PROGNOSTIC FACTORS OF CARCINOMA BREAST 01:41:48

- CIS: Excellent prognosis
- Invasive cancer: variable prognosis
- Single most important factor of prognosis: Metastasis
- LN status: Axillary LN Status (Sentinel LN)
  - Sentinel LN involvement → extensive spread, poor

prognosis & extensive surgery
  - Sentinel LN not involved → localized tumor, better prognosis
- Size of tumor: Bigger size → ↑ metastasis
  - Exception: HER 2 enriched cancer
- Locally advanced disease: Skin/muscle involvement. Hence poor prognosis
- Inflammatory cancer: HER 2 positivity is associated with poor prognosis
- Lympho-vascular invasion: Poor prognosis
- Molecular sub types
  - Luminal A: Best prognosis
  - HER 2 Enriched: Worst prognosis
- Histological sub types
  - Tubular cancer: Best prognosis
- Grade: Nottingham score
  - Low score: low grade/good prognosis
  - High score: high grade/bad prognosis
  - Components
    - → Presence/absence of Tubule formation
    - → Mitotic counts
    - → Nuclear pleomorphism
- Aneuploidy: poor prognosis

Receptors

Estrogen Receptor	+	Better response to hormone therapy
	-	Better response to chemotherapy

- HER 2/Neu Receptor
  - Poor prognosis
  - Predicts the response to anti-HER 2 monoclonal antibodies
    - → Trastuzumab (Herceptin)
    - → Pertuzumab

Table 68.1

	Luminal A	Luminal B	HER 2 enriched	Basal like
ER/PR	+	+	-	-
HER 2/Neu	-	-	++	-
	Low proliferation rate	High proliferation rate		Triple negative cancer
Marker	K;67 - low	K;67 - High		
Prognosis	Best	Bad	Worst	
Other	- Elderly female - MC subtype	BRCA 2 mutation	Young female	- Young female - BRCA 1 mutation

CLINICAL QUESTIONS

Female 57-year-old who has not seen a doctor in more than twenty years, now came to OPD with left breast pain. On physical examination, the left breast is markedly erythematous, swollen. On palpation breast is warm to touch and tender. Also with significant dimpling of the breast (peau d'orange) and the left nipple is completely retracted. Which of the following is the most likely diagnosis?

A) Granulomatous mastitis
B) Micropapillary carcinoma
C) Fibrocystic disease of the breast
D) Inflammatory carcinoma

Solution:

- The presentation is that of **inflammatory carcinoma of the breast**, which typically has an extremely poor prognosis.
- The name "inflammatory" is a misnomer, as typically no inflammation is present.
- The underlying carcinoma is usually diffusely infiltrative and typically does not form a discrete palpable mass.
- In this variant, cancer cells have invaded the skin and suspensory ligaments of the breast, causing dimpling and distortion of the normal breast architecture.

Reference:

- Robbins & Cotran Pathologic Basis of Disease 10th ed pg 1058

LEARNING OBJECTIVES

UNIT 12 BONE DISORDERS

- **Bone Tumors**
  - Primary Bone Tumor
  - Osteosarcoma
  - Subtypes Of Osteosarcoma
  - Giant Cell Tumor
  - Chondrosarcoma
  - Ewing Sarcoma

69 BONE TUMORS

- Primary bone tumor
  - Benign (younger)
  - Malignant (elder)
- Secondary bone tumor/metastasis (MC)
- Bone biopsy: confirmatory test
- MC metastatic bone tumor in male: prostate cancer
- MC metastatic bine tumor in female: breast cancer (MC overall)
- Osteoblastic secondaries: prostate/carcinoid
- Osteoclastic secondaries: breast/lung cancer

Important Information

- Most of the secondary tumor/metastasis are multifocal, whereas renal cell carcinoma & thyroid cancer are unifocal and they have pulsatile metastasis.

PRIMARY BONE TUMOR

00:04:39

Type	Malignant	Benign
Hematopoietic	• Myeloma (MC) • Lymphoma	
Cartilage forming	•Chondrosarcoma	• Osteochondroma • Chondroma • Chondroblastoma • Chondromyxoid
Bone forming	• Osteosarcoma	• Osteoid osteoma • Osteoblast
Unknown origin	• Ewing sarcoma • Adamantinoma	• Giant cell tumor • Aneurysmal bone cyst
Notochordal	• Chordoma	

OSTEOSARCOMA

00:06:26

- 2nd MC primary malignant tumor
- Key feature: malignant cells are responsible for deposition of mineralized bone.

Risk factors

- Rb gene/P53 gene/MDM2 over activity/CDK4
- H/O pre-existing bone lesion: Paget's disease, bone infarct
- Chemical exposure: Alkylating agents and radiation exposure

Associations

- Osteosarcoma shows bimodal age distribution with
  - Primary: Young (75% cases)
  - Secondary: Elderly (25% cases) & H/O radiation exposure, benign bone tumor.
- Site: Femur (LE) >> Tibia (UE) >> Humerus (UE)
- MC involved bone part: Metaphysis

Clinical manifestations

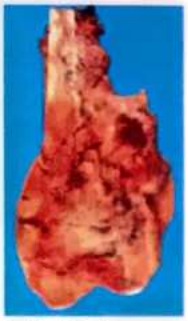
- Mass (around knee)
- Night pain
- Pathological fracture

Subtypes of osteosarcoma 00:14:47

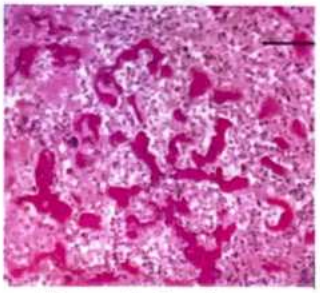
- Grade: High grade or low grade osteosarcoma
- Primary or secondary osteosarcoma
- Site
  - Intramedullary
  - Intracortical
  - Surface
    - → Parosteal: Surface of cortex
    - → Periosteal: Surface of periosteum
- Histologic subtype Osteoblastic
  - Chondroblastic
  - Fibroblastic
  - Telangiectatic
  - Small cell osteosarcoma
  - Giant cell osteosarcoma

Important Information

- MC subtype of osteosarcoma: High grade/primary/intramedullary/osteoblastic osteosarcoma



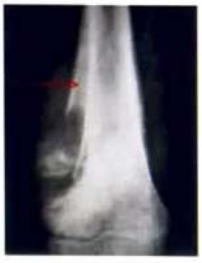
Bulky/gritty/necrosis



"Lace-like" pattern

- Diagnostic feature: Bone forming tumor cells
- Metastasis: bronchus >> bone to bone metastasis/brain
- Radio-resistant tumor. Hence the treatment is
  - Surgery
  - Methotrexate

Sunburst appearance



Codman's Triangle

Previous Year's Questions

Q. Gross specimen of bone tumor at the lower end of femur in 10 year old child is shown. Identify the most likely cause.

(INICET 2020)

A. Giant cell tumor
B. Osteosarcoma
C. Chondrosarcoma
D. Osteochondroma

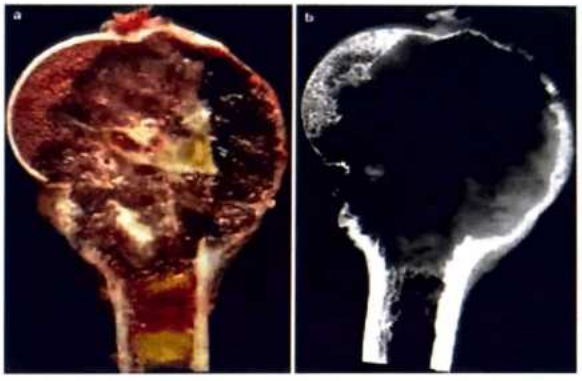
GIANT CELL TUMOR

00:25:08

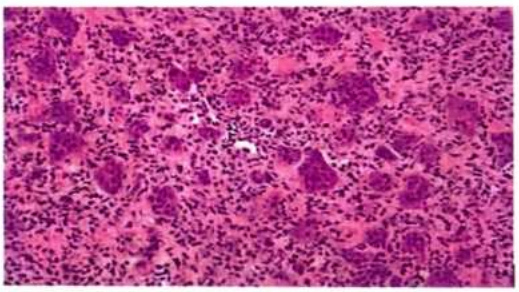
- Aka osteoclastoma
- It is benign in nature
- Origin: Osteoblast Precursor Cells → ↑ RANK ligand expression → ↑ osteoclast activity

Clinical feature

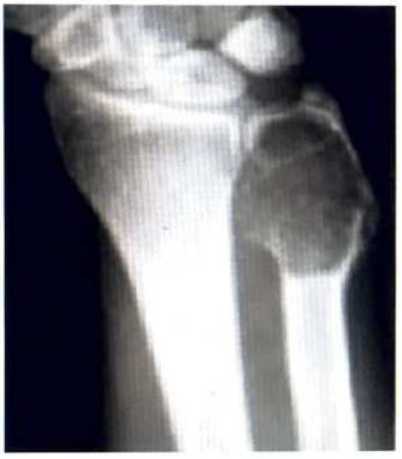
- MC affected bone area is epiphysis (extension into metaphysis can be seen)
- Age: 20-40 years
- MC affected joint: Knee
  - Lower end of femur > upper end of tibia
  - In upper limb, lower end of radius can be involved
- Pathological fracture
- Arthritis
- High chances of malignant transformation
- In 4-5% of patients, there's chance of pulmonary metastasis



Club shaped tumor



Giant cells surrounded by the tumor cells



Soap Bubble Appearance

CHONDROSARCOMA

00:29:26

- Malignant in nature
- Associated with cartilage formation
- Origin: Metaphysis (except clear cell chondrosarcoma)

Clinical feature

- Male, 40 years
- Pain
- Gradually enlarging mass
- Predilection of axial skeleton involvement
  - MC: pelvis
  - Shoulder and rib involvement can also be seen

Gene

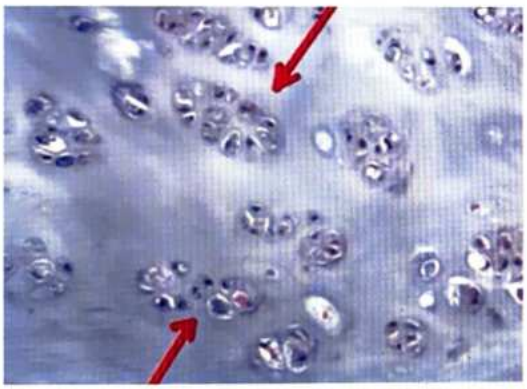
- IDH1/2 mutation
- EXT mutation (associated with multiple osteochondroma syndrome)

Important Information

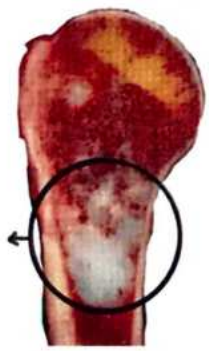
- MC type of chondrosarcoma: Grade I/Conventional/classical subtype/Intramedullary

Diagnosis

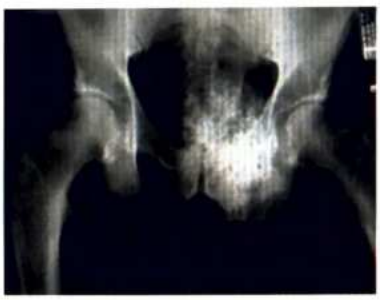
- Bone biopsy
- Common site for metastasis: Lungs > brain > kidney



Malignant Cartilage cells permeating Marrow



Cartilage deposition



Spotty calcification

Treatment

- Non-responsive to chemotherapy
- Surgery excision is the mainstay treatment

EWING SARCOMA

00:34:48

- Belongs to family of Small Round Blue Tumor cells
  - Neuroectodermal differentiation is not present
  - S-100, Neuron specific Enolase is absent
- Origin: diaphysis

Gene

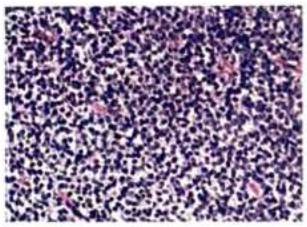
- t(11;22) → EWS-FLT_1 → ↑ cancer
  - EWS present in chr 22
  - FLT_1 present in chr 11

Clinical Feature

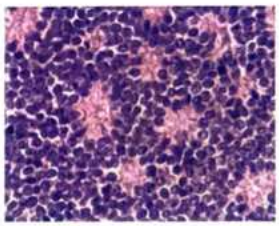
- < 20 years
- Pain
- Fever
- Tenderness
- Leukocytosis, ↑ ESR
- Mimics osteomyelitis

Diagnosis

- Immunohistochemical marker: CD99 (mic-2)
- Tumor cells are Rosette pattern with neurofibrillary material in the center

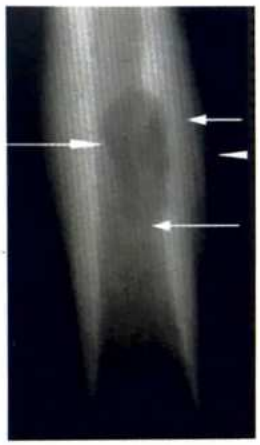


Small round blue cells



Homer-Wright Pseudorosettes

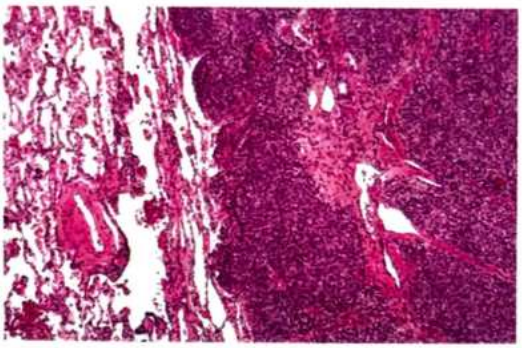
- True rosette/Flexner Winstersteiner rosette: Seen in retinoblastoma
- Ewing sarcoma shows "bone to bone metastasis"



Onion-Skin appearance (periosteal reaction)

CLINICAL QUESTIONS

A 9 years old boy presented to the orthopedics OPD with the chief complaints of the painful enlarging mass in the left lower limb. On examination it is tender and warm. X-RAY shows a destructive lytic tumor with permeative margins that extends into the surrounding soft tissue. Histopathology of the tumor is given below and large intracytoplasmic glycogen vacuoles are seen, associated with which of the following bone tumors?



A. Chondrosarcoma
B. Ewing sarcoma
C. Giant cell tumor
D. Aneurysmal bone cyst

Solution:

- **Ewing sarcoma**
  - Young age of presentation
  - Tumor arises in the diaphysis of long tubular bones
  - Presents as painful enlarging mass
  - Translocation (11;12) detected on F.I.S.H
  - Histology --> shows uniform, small round cells, they have scant cytoplasm, which appear clear because it is rich in glycogen and it is PAS+ ve

Reference:

- Robbins 10 edition page no 813

LEARNING OBJECTIVES

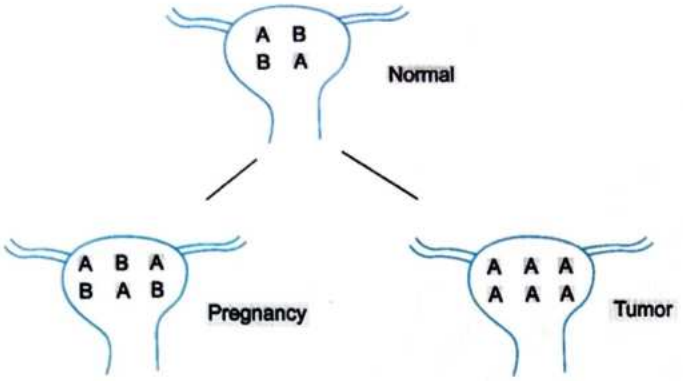
UNIT 13 NEOPLASIA

- **Basic concepts of Neoplasia**
  - Monoclonality
  - Important Terms
  - Features Of Neoplasia
  - Pathways Of Spread
  - Invasion
- **Genetics basis of Carcinogenesis part I**
  - Nuclear Transcription Factors
  - Signal Transduction Proteins
- **Genetics basis of Carcinogenesis part II**
  - Insensitivity to growth inhibitors & Functions
  - P53 Gene (Guardian of Genome)
  - APC gene
  - Altered Cell Metabolism
  - Sustained Angiogenesis
  - Evasion Of Immune Surveillance
- **Cancer genes**
  - Proto-oncogenes
  - Tumor suppressor genes
  - Hallmarks of cancer
- **Etiological factors of Neoplasia**
  - Radiation
  - Chemicals
  - Infectious organisms
- **Diagnosis of cancer**
  - Biopsy
  - Immunohistochemistry
  - Flowcytometry
  - Molecular and cytogenetic analysis
  - Tumor markers
- **Liquid biopsy**
  - Types of Biomarkers
  - Exosomes
- **Para-neoplastic syndromes**
  - Neuromuscular Disorder
  - Osseus; Soft Tissue
  - Endocrinopathies
  - Vascular; Hematological
  - Dermatological

70 BASIC CONCEPTS OF NEOPLASIA

MONOCLONALITY

00:01:22



Example

- In Female uterus, 2 isoforms of G6PD - A/B, G6PD A in 2 cells and G6PD B in 2 cells are present.
- In pregnancy, number of cells are increased being 20 cells with G6PD A and 20 cells with G6PD B (isoform A:B is unchanged)
- In cancer, number of cells are increased and are dominated by only one isoform A. This is known as monoclonality

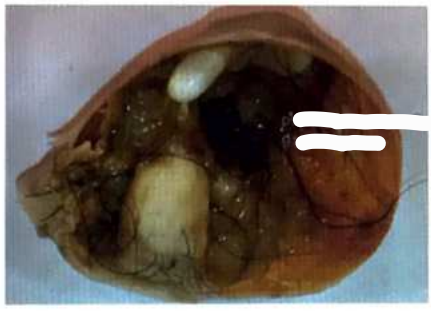
Important Information

- Desmoplasia: Increase in connective tissue /stromal content of tumor due to factors from epithelial cells or parenchymal cells.

IMPORTANT TERMS

00:04:44

- Carcinoma: malignant tumor arising from epithelial cells
  - Example: adenocaricnoma, squamous cell carcinoma
- Sarcoma: malignant tumor with origin from mesenchymal cells
  - Example: fibrosarcoma, chondrosarcoma
- Choristoma: normal tissue present at abnormal site
- Hamartoma: presence of abnormal tissue at normal anatomical site. It has neoplastic component.
- Pleomorphic tumor: different morphology of cells due to divergent differentiation
  - Example: salivary gland tumor
- Teratoma: origin from >1 germ cell layer.
  - Cell origin of teratoma: totipotent cells
  - MC site of origin: gonads
  - MC extra-gonadal site: midline area of embryonic rests
  - Teratoma of ovary: dermoid cyst



Kaleidoscopic pattern of dermoid cyst

FEATURES OF NEOPLASIA

00:11:17

Metastasis

- Most reliable feature of malignancy
- Most of the malignant tumors have metastasis. Exception
  - Glioma
  - Basal cell carcinoma (Rodent Ulcer/Tear ulcer)
- Microscopic features of Benign and malignant tumor of the thyroid are similar and can be distinguished with the help of metastasis
- Follicular carcinoma of thyroid → evidence of vascular invasion (blood vessels) is needed for the diagnosis.
  - Other example: Pheochromocytoma

PATHWAYS OF SPREAD

00:14:43

Direct seeding

- Tumor cell spread from the affected organ to the nearest body cavity.
- MC cavity affected: Peritoneal cavity (presenting as ascites)
- Tumor of appendix is associated with ↑↑ amount of mucin → pseudomyxoma peritonii

Lymphatic spread

- Associated with carcinoma. Exception
  - Kidney, liver, thyroid cancers have involvement of blood vessels

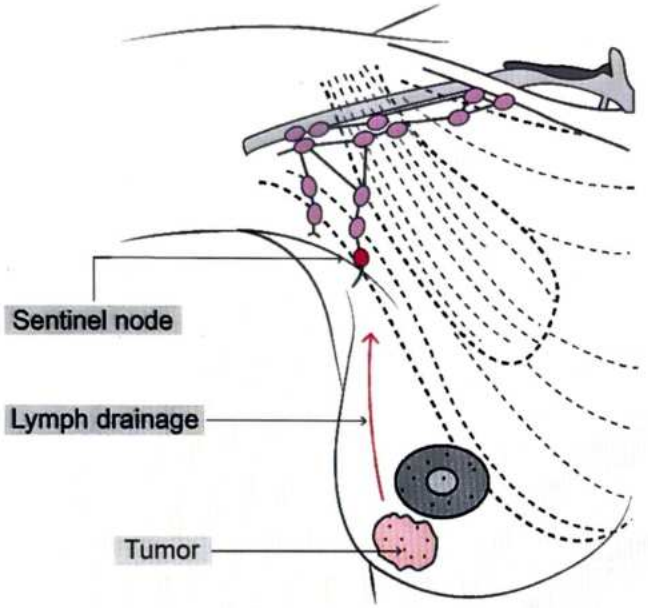
Previous Year's Questions

Which of the following malignancy is least commonly associated with lymphatic spread? (AIIMS 2018)

A. Basal cell carcinoma
B. Squamous cell carcinoma
C. Malignant melanoma
D. Merkel cell carcinoma

Sentinel lymph biopsy

- 1st lymph node present in the anatomical pathway of lymph node drainage



Example

- Tumor present in upper outer quadrant will have initial involvement of axillary lymph node.
- Biopsy of this LN, if negative → localized tumor
- If positive → indicates spread and extensive surgery is warranted.

Hematogenous spread

- Venous spread >> artery spread
- It is characteristic feature of Sarcoma. Except
  - Synovial cell sarcoma
  - Clear cell sarcoma
  - Alveolar Rhabdomyosarcoma
  - Epithelial cell sarcoma

CSF spread

- Drop metastasis: Medulloblastoma

Important Information

- Airway spread: Peripheral airway → large airway spread in adenocarcinoma in-situ

INVASION 00:25:16

- Tumor won't have local infiltration beyond 1-2mm without blood vessels
- Tumor cells secrete certain factors responsible for production of new blood vessels

RATE OF GROWTH

- 30 divisions are required for the tumor cells to produce clinical symptoms
  - 10^9 cells → 1g is the weight of the tumor
  - 10^{12} cells → 1kg is the weight of the tumor
- High growth rate is associated with "Glucose Hunger"
- Example: non-metabolizable radioactive glucose 18-FDG entry into tumor cell can be identified using PET scan.

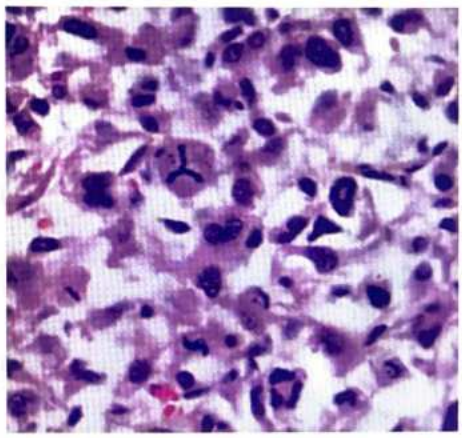
ANAPLASIA

- Hallmark feature of malignant transformation.

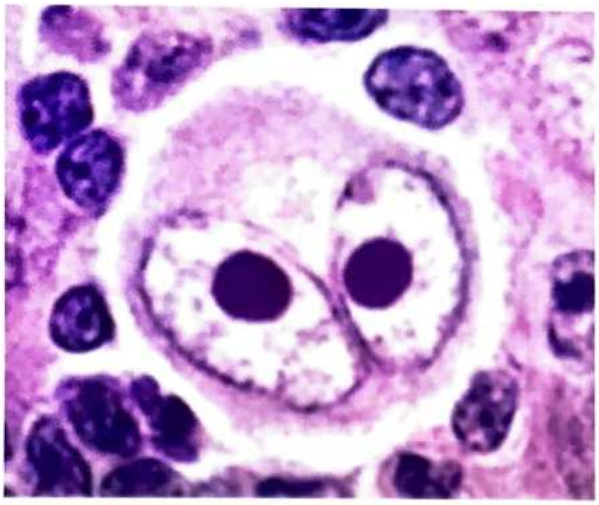
$$normal\ cell \xrightarrow{injury} metaplasia\ (benign, reversible) \rightarrow dysplasia \rightarrow anaplasia$$

Dysplasia

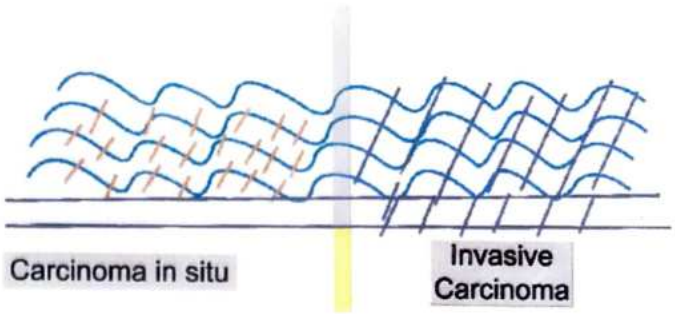
- Increase in nuclear cytoplasmic ratio
- Pleomorphism
- Reversible at initial stage (partially reversible stage)
  - Example: cervix → HPV → cervical cancer
- Associated with abnormal giant cells → RS cells in Hodgkin's lymphoma



Tri-polar mitotic spindle



RS cell

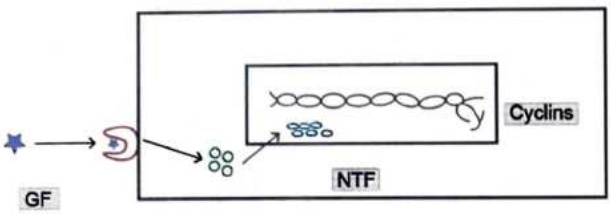


- Basement membrane is not affected in carcinoma in situ
- Basement membrane is affected in Invasive carcinoma

71 GENETIC BASICS OF CARCINOGENESIS 1

SELF SUFFICIENCY IN GROWTH SIGNAL

- Proto-oncogenes → oncogenes → onco-proteins



- GF → Transcription factors → nuclear transcription factors → alteration in activity of certain genes (Cyclins)

Previous Year's Questions

Q. Proto-oncogene to oncogene transformation takes place by which of the following? (AIIMS Nov 2019)

A. Point mutation
B. Promoter insertion
C. Amplification
D. Enhancer insertion

1. A, B, C and D
2. A and C
3. A and B
4. A, B and C

Growth Factors

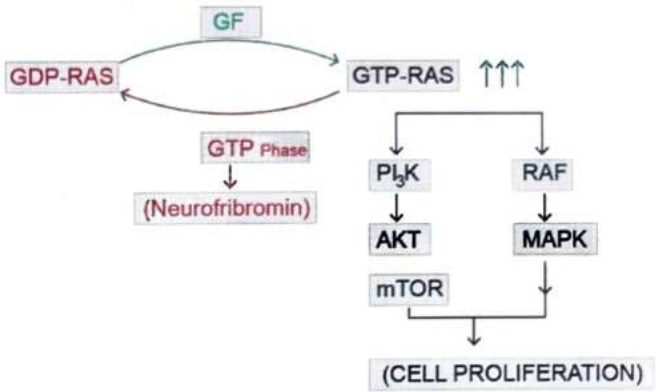
- PDGF (SiS) → glioma
- HGF → hepatocellular carcinoma

GF receptor

- Epidermal growth factor (↑ tyrosine kinase activity)
  - ERB B_1 gene: Lung cancer, Glioblastoma
  - ERB B_2: HER2/Neu gene → Breast cancer
    → Herceptin (tyrosine kinase inhibitor)
- RET gene: MEN II Syndrome
  - Pheochromocytoma
  - Medullary carcinoma Thyroid
- ALK: Adenocarcinoma lung, Anaplastic Lymphoma, Neuroblastoma
- FLT-3: ALL
- KiT: GIST, Seminoma

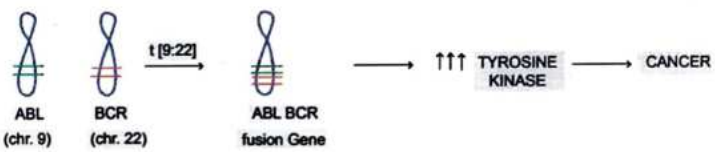
SIGNAL TRANSDUCTION PROTEINS 00:08:38

RAS gene



- K-RAS Colon cancer
- H-RAS → kidney & bladder cancer
- N-RAS → Melanoma

ABL gene



- t(9;22) → Philadelphia chromosome → CLL/ALL
- Oncogene addiction: Tumor cells are so much dependent/addicted on tyrosine kinase activity
- Targeted therapy: Imatinib
  - It is more effective against CML than ALL

BRAF gene

BRAF $\xrightarrow{\oplus}$ MAPK ⟶ ↑ cell proliferation

Seen in

- Hairy cell leukemia (100%): strongest association
- Benign nevus (80%)
- Melanoma (60%)

β-Catenin

- -catenin → ↑ MYC activity → ↑ cell proliferation
- Tumor suppressor gene (controls -catenin)
  - APC gene → underactivity → colon cancer
  - E-Cadherin

JAK-STAT

- Associated with development of Myeloproliferative disorders
- Polycythemia Vera
- Primary myleofibrosis
- Essential thrombocythemia

NUCLER TRANCRIPTION FACTORS 00:13:50

MYC gene

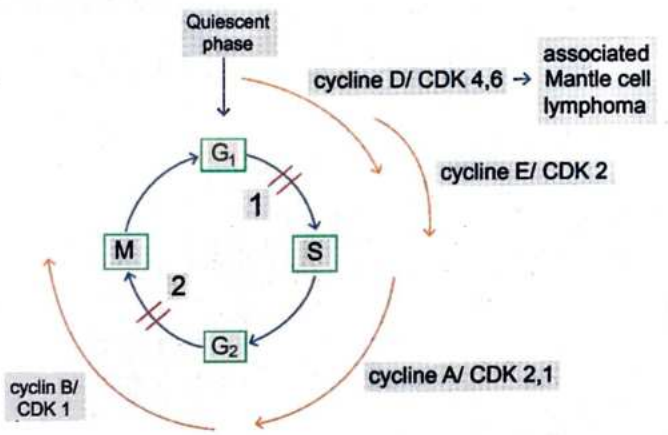
- Master regulator of cell proliferation
- C-MYC: Burkitt's lymphoma
- N-MYC: Neuroblastoma
- L-MYC: Lung cancer (small cell lung cancer)
- Hedgehog pathway (↑ MYC activity) → medulloblastoma

Cyclins

- Intermittent activity (Off/on) → CDKs
- Sequential activation of cyclins
  - D → 4, 6
  - E → 2
  - A → 2
  - B → 1

How to remember

- Sequential activation of cyclins: Dhoni Ek Akela Batsman



- G1/S: Rb/p53 gene
- G2/S: p53 gene (guardian of genome)
- p53 gene plays role in both checkpoints but greater activity checkpoint 1
- CDK4 over-activity → sarcoma, brain & gallbladder cancers
- Cyclin D_1 over activity → Mantle cell Lymphoma

CDK inhibitors	
Non-specific	**Specific**

• P21
  ○ P53 stimulates P21
• P27
  ○ TGF β controls P27
• P57
	• P15
	• P16/$CDKN_2A$
	  ○ Pancreatic cancer
	  ○ Glioblastoma
	  ○ Esophageal cancer
	• P18
	• P19 → inhibits cyclin dependent kinase 4/6 → cyclin D (important for proliferation) inhibition

Previous Year's Questions

Q. Arrange the cyclins and CDKs in cell cycle from G1 to S checkpoint?

(AIIMS Nov 2019)

A. CDK 2/cyclin E
B. CDK 4/cyclin D
C. CDK 1/cyclin B
D. CDK 2/cyclin A

72 GENETIC BASIS OF CARCINOGENESIS 2

INSENSITIVITY TO GROWTH INHIBITORS

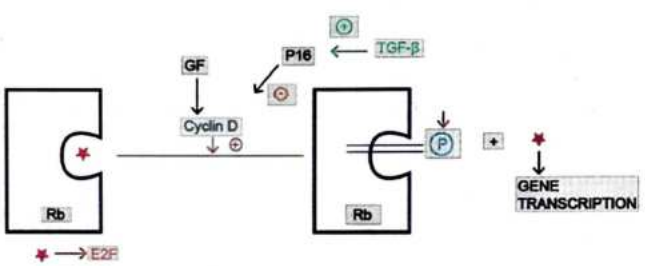
- Tumor Suppressor genes → ↓ hallmark of cancer
- Double-hit hypothesis
  - Both the alleles are underactive
  - It was proposed by Knudson: Rb gene

Functions 00:03:13

- Regulation of G_1/S Transition: Rb/p53 gene
- DNA Repair → BRCA 1/2 genes, MLH_1; MSH2/6
- Associated with microsatellite instability
- Mitogenic pathway ⊖ → APC genes, NF-1/2, PTEN gene, PTCH; SMAD 2/4
- Angiogenesis ⊖ → VHL gene, S-HDB, STK 11
- Invasion/ Metastasis ⊖ → CDH_1 gene

Retinoblastoma gene

- Located on chromosome 13q14
- Discovered by Knudson
- Governor of cell replication
- Sporadic Rb (MC)
  - Perfectly normal at birth
  - Sequential inactivation of both alleles one after another → retinoblastoma
  - Unilateral involvement
- Familial Rb
  - Germline mutation → born with one defective allele
  - 2nd allele becomes inactive later → Loss of heterozygosity
  - Bilateral involvement
  - ↑ risk of other cancers – osteosarcoma, breast cancer, bladder cancer
  - Trilateral Retinoblastoma → Pinealoblastoma + B/L Retinoblastoma



- These cyclins → ↑ cell proliferation

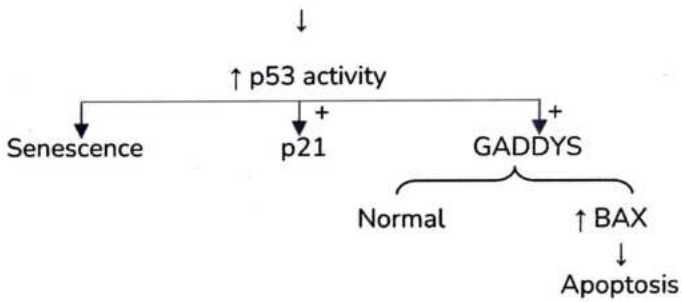
Important Information

- **Phosphorylation of Rb (tumor suppressor gene): inactivation**
- **Phosphorylation of RAS (proto-oncogene): activation**

- HPV 16/18 → E_7 protein → ↓ Rb gene → ↑ cervical cancer
  - It doesn't allow retinoblastoma back to hypo-phosphorylated form
  - E6 protein → ↓ p53 gene activity

P53 Gene (Guardian of Genome) 00:20:17

- Normal cells → MDM2 protein breakdown p53 → ↓ half-life DNA damage



- Normal variant: Wild type → Located on chromosome 17p
- Germline p53 gene mutation → ↑↑ cancers (Li Fraumeni Syndrome)
  - Chompret's criteria of Li Fraumeni Syndrome
    - → Sarcoma
    - → Osteosarcoma
    - → Adrenal Cortex tumor
    - → Breast tumor
    - → CNS tumor

- Sporadic p53 Gene Mutation
  - MC mutation associated with development of human cancers
  - Chemo/radio resistance

Previous Year's Questions

Q. Cell arrest due to DNA damage is done through which of the following gene?
(AIIMS May 2019)

A. Rb
B. P53
C. P16
D. Notch signal

BRCA
- DNA repair genes
- BRCA 1 → chromosome 17q → Female Breast cancer / ovarian cancer
- BRCA 2 → chromosome 13q → Male Breast cancer / Prostate cancer
- ↑ Risk of familial Breast cancer

MLH-1 & MSH-2/6
- Malfunction → microsatellite instability →↑ colon cancer

NF gene
- NF 1 → Chromosome 17q → Neurofibromin
- Underactivity of NF-1 gene → ↓ neurofibromin → neurofibromatosis 1 → JML
- NF2 → Chromosome 22q → Merlin →contact inhibition
- Mutation B/L Acoustic Neuroma/ Schwannoma

APC gene 00:33:37
- ↓β catenin →↓Adenomas
- Tumor suppressor located on chromosome 5q
- ↑ Risk of familial Adenomatous Polyposis →↑colon cancer
- Aka "Gate Keeper of Colonic Neoplasia"
- COX 2 inhibitor: ↓ risk of adenoma

PTCH gene
- Controls Hedgehog pathway
- Familial defect of PTCH gene → Gorlin syndrome
- Also associated with development
  - Medulloblastoma
  - Basal cell carcinoma/rodent ulcer/tear cancer

PTEN gene
- Location: Chromosome 10q
- Inhibits PI3K/ AKT pathway
- Mutation →↑cell proliferation due to loss of inhibition
- Familial variant is associated with Cowden syndrome

Important Information

- PTEN gene mutation is associated with BEST cancers
  - Breast cancer
  - Endometrial Cancer
  - Skin Appendages tumor
  - Thyroid Cancer

Previous Year's Questions

Q. An obese women with T2DM and HTN is diagnosed with endometrioid type of endometrial carcinoma. The most likely gene defect in this patient?
(AIIMS May 2019)

A. P53
B. PTEN
C. MSH2
D. BRCA2

SAMD 2/4
- Controls TGF-ß
- Mutation →↑risk of pancreatic Cancer
- Associated with Juvenile Polyposis

VHL gene
- HIF (Hypoxia inducible factor) →↑VEGF
- VHL gene → Normal →↓HIF →↓ VEGF
- Located On Chromosome 3p
- VHL syndrome
  - Kidney cancers
  - CNS tumor (cerebellar hemangioblastoma)
  - Pheochromocytoma

SDHB
- Associated with development of Paraganglioma, pheochromocytoma

STK 11 gene
- Mutation → PJ syndrome
  - GI polyps
  - ↑ GIT cancer
  - ↑ Risk of pancreatic Cancer

WT1 gene
- Responsible for epithelial mesenchymal transition
- Associated with development of Wilms tumor
- Located on chromosome 11p

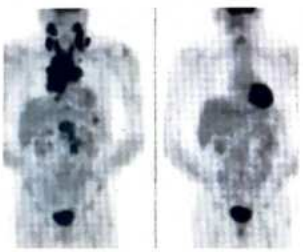
CHD_1 gene

- Normal: E.cadherin →↓ -catenin →↓ Cell proliferation
- High risk for stomach Cancer, Lobular Breast Cancer

ALTERED CELL METABOLISM

00:46:16

- In normal cell when there is available O_2, the glucose is utilized by glycolytic pathway → Krebs cycle
- Warburg effect → Aerobic glycolysis (cancer utilize only glycolytic pathway even in O_2 presence)
- Cancer cells → pyruvate + ↑ glutamine uptake → ↑cell proliferation
- Glucose hunger: ↑↑↑ glucose requirement by cancer cells compared to normal cells
- M_2 isoform of pyruvate kinase present

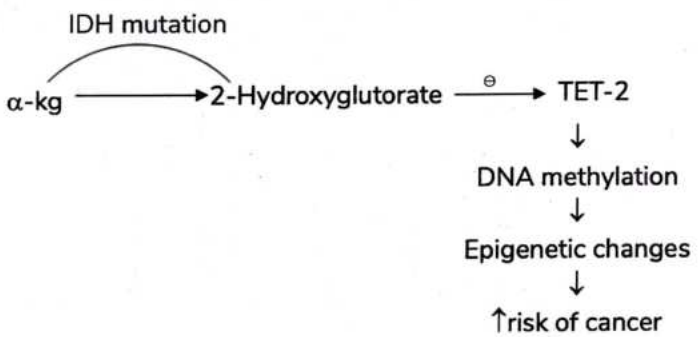


PET scan → ^{18}FDG

- Physiologically aerobic glycolysis can be seen in embryonic tissue, lymphoid cells during immune activation
- Altered Autophagy: alteration of ATG/Becklin gene according to the need of tumor cells

Onco-metabolism

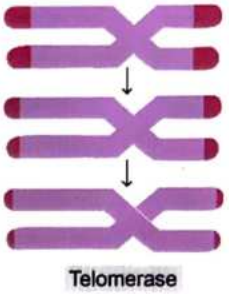
- IDH (Isocitrate Dehydrogenase)



- Oncometaboite: 2-Hydroxyglutorate
- IDH mutation seen in glioma, AML, cholangiocarcinoma
- Treated by Enasidenib (Mutant IDH inhibitor)

LIMITLESS REPLICATIVE POTENTIAL/ IMMORTALITY

- Hayflicks limit: Normal cell divides 60-70 times



- Telomere present at the end of chromosome
- With every replication telomere is progressive shortened
- Beyond critical level, cells cannot replicate
- Normal p53/Rb → Senescence
- Telomerase is a reverse transcriptase enzyme maintain the of telomere length.
- Physiologically, it is present in stem cells & germ cells
- Altered p53/Rb → NHEJ (Non-Homologous End Joining)

NHEJ

↓

Dicentric chromosome

↓

Chromosomal instability

No telomerase	Telomerase reactivation
↓	↓
Cell death	Cancer

Previous Year's Questions

Q. Hayflick's limit is defined as which of the following? (AIIMS June 2020)

A. Total number of times cells can divide before division stops.

B. Limitation of tumor growth due to aerobic environment.

C. Limitation of tumor growth due to anaerobic.

D. Limitation of untreated tumors occurring concurrently with shrinkage of tumors within the scope of the localized treatment.

Evasion of Apoptosis

- It is mainly due to changes in intrinsic pathway
- Apoptotic genes
  - BAX/BAK → ↑ apoptosis
  - BCL-2, BCL-XL, MCL-1 → ↓ apoptosis
  - BAD, BiD, PUMA → balancers/BH_3 proteins
- Evasion is due to

- Due to Loss of p53 function → ↑↑ MDM2
- Over expression of BCL-2 due to t(14;18) → follicular Lymphoma

- MiRNA is a tumor suppressor gene
  - MiRNA 15-16 deletion lead to over activity of BCL-2 → CLL
- In Breast cancer, Lung cancer → chemo-resistance
  - MCL1 over activity → ↓ apoptosis

Sustained Angiogenesis 01:05:16

- Without angiogenesis tumor can grows only 1-2 mm
- Hypoxia → Hif 1 α → ↑ VEGF → Neovascularization
- Factors
  - Stimulates Angiogenesis: VEgF, bFgF
  - Inhibits angiogenesis: Angiostatin, Endostatin, Thrombospondin ← p53
- Neovascularization
  - New blood vessels are Leaky → angiogram
  - Tumor spreads fast
- Drugs that inhibit angiogenesis
  - Bevacizumab
  - Thalidomide

INVASION AND METASTASIS

- Pro-Migratory phenotype: Tumor cells which has tendency to spread to distal parts

Steps

- Loosening of cell-cell contact → ↓ E-Cadherin
- Degradation of ECM
  - MMP 9
  - Cathepsin-D
- Attachment to novel ECM compartment → fibronectin, integrins
- Migration of tumor cells → CD44 → HEV

Important Information

- **Metastasis oncogenes (TWIST/SNAIL) → breast Cancer**
- **Metastasis suppressor genes (KISS) → melanoma**

- Epithelial mesenchymal Transition (EMT): for spread of tumor, epithelial properties are downregulated & mesenchymal properties are upregulated

Epithelial → mesenchymal
↓ E- cadherin ↑ Vimentin, smooth muscle Actin
↓ ⊕
Invasion & Metastasis

Previous Year's Questions

Q. Which of the following malignancy is least commonly associated with lymphatic spread? (AIIMS May 2018)

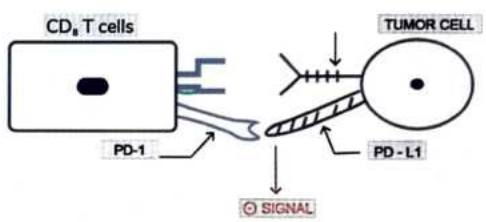
A. Basal cell carcinoma
B. Squamous cell carcinoma
C. Malignant melanoma
D. Merkel cell carcinoma

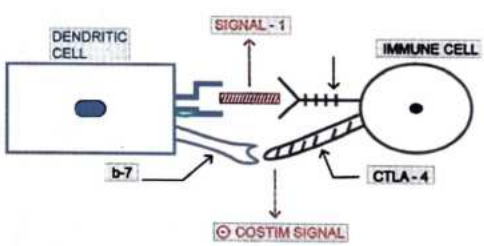
EVASION OF IMMUNE SURVEILLANCE 01:13:56

- Concept proposed by Lewis Thomas & M.Burnett
- Cytotoxic T-cells, NK cells, macrophages, TH_1 cells → important for destruction of tumor cells

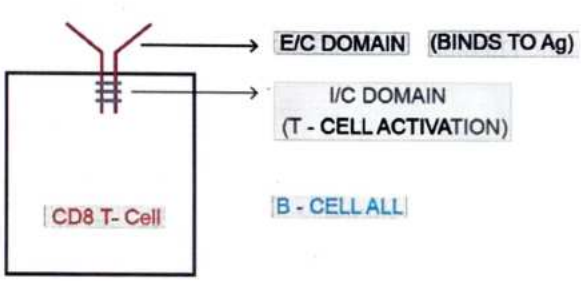
Cancer Immuno-editing

- Growth of Antigen -ve Variants
- Secretion of TgF-ß, IL-10, → ↓ inflammatory response
  - PgE2, VEgF → inhibit diapedesis
- ↓ MHC expression
- Immune checkpoint
  - PD-L1 ↓ response of CD_8 T cells
  - CTLA-4





Chimeric Ag Receptor T-cell (CAR-T cells)



- Modify the structure of T-cell receptor → mixed/chimeric molecule
- E/C domain (binds to tumor Ag)
- I/C domain (T-cell activation)
- This is also called live drug. Used in treatment of B-cell ALL

Genomic instability as enabler of malignancy

Defect in DNA repair		
Mismatch repair	**Nuclear Excision repair**	**Homologous recombination repair**
• Causes HNPCC/ Lynch syndrome • AD inheritance • C/E/O syndrome • Microsatellite instability	• AR • Xeroderma pigmentosum • UV → Pyrimidine dimers → DNA damage	• AR • Bloom syndrome • Fanconi's anemia (defective helicase) **Ataxia telangiectasia** • ATM gene → cerebellum (purkinje cells) • ↓ Immunity → thymic defects, IgA/G2 defects • ↑ cancers → ALL/HL/Breast cancer • BRCA1/2 gene → familial breast cancer

- ↑ Risk of Lymphoid Neoplasms: Defect in AiD, Rag1/2 gene defect lead to defective derangement →↑ B/T-cell neoplasam

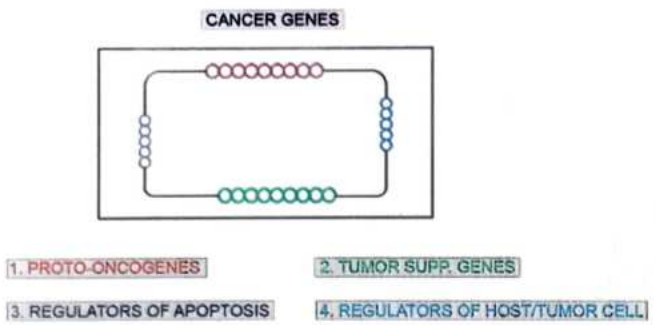
B-Cell —Ag Exposure→ AiD gene

T-cell —Ag Exposure→ Rag1/2 gene

Tumor promoting inflammation

- Inflammatory mediators: TGF- β
  - ↓ Immune cells migration to the site of tumor cells
  - Facilitates EMT
- M2 macrophages
  - Fibrin deposition
  - Stimulate angiogenesis
- Proteases → aids in spread
- COX-2: Adenomatous polyps - ↑ risk of colon cancer
  - Aspirin (Cox -2 inhibitor) is protective against development of colon cancer

73 CANCER GENES



Proto-oncogenes

- Physiological genes responsible for cell replication
- Gain of function mutation → cell proliferation
- Even one altered allele → ↑ Risk of cancer

Tumor suppressor genes

- Regulates cell replication rate → acts like brake of the cell
- Loss of function mutation: cancer
- It is of 2 types
  - Guardians: Repairs genetic damage (Example: p53 gene)
  - Governors (Example: Rb gene)
- Even though there is one altered allele → 2nd allele can ensure normal replication
- Both the copies of allele has to be affected to produce cancer

Regulators of apoptosis

- BAX, BAC, p53, BCL-2, BCXL
- Defect in apoptotic genes → mutated cells survive

HALLMARKS OF CANCER

00:04:57

- Self-sufficiency of growth signals
- Insensitivity to growth inhibitory signals
- Altered cell metabolism
- Limitless replication
- Evasion of apoptosis
- Invasion and metastasis
- Sustained angiogenesis
- Evasion of immune surveillance

Other factors

- Inflammation
- Genomic instability → caused by defect in DNA repair genes
- MMR gene → HNPCC syndrome
  - AD condition
- NER gene → Xeroderma Pigmentosum
  - AR condition
- Homologous recombination genes → Bloom syndrome/Fanconi's anemia/ataxia telangiectasia, BRCA1/2 gene
  - AR condition

ALD

B/T-Cells ⟶ Lymphoid neoplasm

RAG 1/2

74 ETIOLOGICAL FACTORS OF NEOPLASIA

RADIATION

00:00:55

- UV rays are non-ionizing radiation
- Sunlight → UV rays → Melanin (protective)
- UV C rays → dangerous, due to ozone layer never reaches earth
- UV B rays → DNA damage by Pyrimidine dimer
  - It is repaired by Nucleotide Excision Repair Genes (NER)
- Defective NER gene → Xeroderma Pigmentosum
  - ↑ Basal cell carcinoma
  - ↑ Squamous cell carcinoma
  - ↑ Melanoma

Ionizing Radiation

- MC reason of exposure to ionizing radiation: Diagnostic radiology
- Miners & radium → radiation exposure → ↑ cancer
- MC neoplasm due to radiation exposure → Myeloid Neoplasm
  - CLL has no association with radiation exposure
- H/O ionizing radiation exposure in childhood → papillary thyroid cancer development later
- Earlier thorium is used as radio-contrast material → angio-sarcoma of liver
- Radio-resistant tissues
  - GIT
  - Skin
  - Bone
- Radiation exposure → water in the cell → production of free radical → injury
  - Most powerful free radical: OH
- Platelets are not affected much due to radiation exposure as they contain less nuclear material

CHEMICALS

00:08:20

- Initiator: Normal DNA → abnormal DNA
  - Example: Alkylating agents, asbestos
- Promoters: Abnormal DNA → additional mutation → ↑ proliferation rate
  - Example: Estrogen, asbestos

Ames test

- To know carcinogenic potential of a particular chemical
- Rat liver extract in Petri dish → S.typhimurium is added → No growth
  - Chemical → no growth → safe
  - Chemical → growth → carcinogenic potential
- Smoking → PAH $\xrightarrow[\text{CYP1A1}]{}$ Benzopyrine epoxide
  - Genetic polymorphism can impact the outcome of exposure to chemical

Important chemicals

- Smoking: ↑ Risk of oropharyngeal cancer, GIT cancer, lung cancer, kidney/bladder cancer.
- Nitrites → Nitrosamines: ↑ Risk of GIT cancer
- Vinyl chloride: PVC → Angiosarcoma of liver
- Aflatoxin: Infected peanuts → Aflatoxin → liver cancer
- Asbestos: ↑ Risk of cancers in larynx/GIT/lung/kidney
  - Lung cancers – Bronchogenic carcinoma, Mesothelioma (long duration)
- Drugs: Alkylating agents (cyclophosphamide, busulphan)
- Dust particle: Silica → Lung cancer

INFECTIOUS ORGANISMS

00:22:58

- Fungus: Aflatoxin → Liver cancer
- H.pylori: chronic irritation of gastric epithelium → stomach cancer
  - Cag A toxin → Adenocarcinoma
  - MALToma → t(11;18)

Viruses

- Hepatitis B Virus → Liver cancer
  - Chronic inflammation → Regeneration cycles → Mutation → Cancer
  - HBx protein → ↑ risk of cancer
  - Insertional mutagenesis: HBV is a DNA virus → insertion to human DNA → Mutation
- EBV
  - LMP-1 → ↑ NF-Kβ
  - VIL-10 → ↓ T-cell activity
  - EBNA → ↑ Progression from G1 to S Phase because of ↑ Cyclin D activity
  - Can cause HL/NHL/BL Endemic/Anaplastic NPC/Angiocentric nasal NK/T-cell lymphoma
- HPV
  - Low risk subtype → warts
  - High risk subtype → ↑ cancers
  - E6 → ↓ p53 activity
    - → E7 → ↓ Rb gene activity
    - → Can cause cervical/anal/oropharyngeal/laryngeal papilloma
- HHV-8/Kaposi Sarcoma Herpes virus

- Kaposi Sarcoma (HIV)
- Primary effusion lymphoma
- Multi-centric Castleman disease

- HTLV 1
  - Origin: CD4 T-cell → adult T-cell leukemia
  - Associated with pathogenic TAX protein
  - Transmitted by sexual & parenteral route
- HCV: Core protein → ↑ Risk of liver cancer

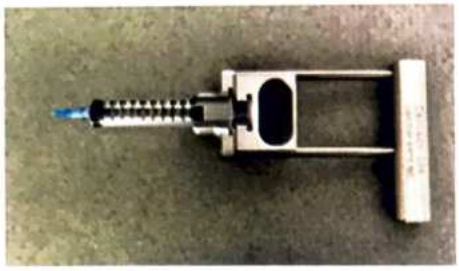
Parasites

- Schistosomiasis → urinary bladder
- Clonorchis Sinensis/Opisthorchis → Biliary tract carcinoma

75 DIAGNOSIS OF CANCERS

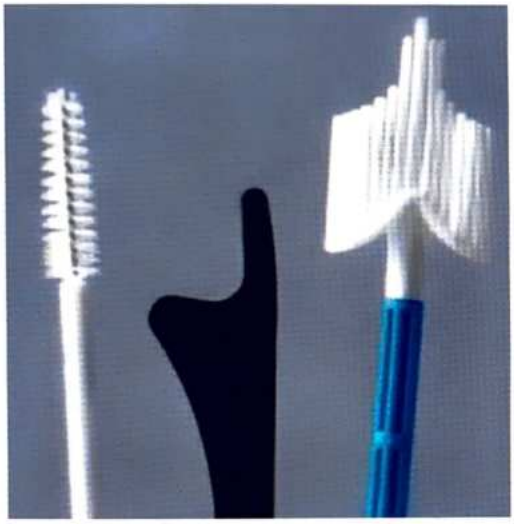
HISTOLOGICAL & CYTOLOGICAL METHODS

FNAC



- Needle size of 22-27G is used
- Follicular adenoma (benign) & follicular carcinoma (malignant) → cannot be differentiated by the FNAC

EXFOLIATIVE CYTOLOGY



Ayer spatula/Cytology brush

- Cells will spontaneously shed off or shed cells obtained by instruments like cytological brush Pap Smear

↓

Squamo-columnar Junction

↓

Fixed with ether + 95% ethanol (1:1)

↓

Exam for maturation index & nuclear features

Biopsy

00:06:57

- Biopsy is not done for testicular tumors → as it can spread the malignant tumor cells
- Fixative
  - Formalin: routinely used
  - 2% glutaraldehyde: used in electron microscopy

IMMUNOHISTOCHEMISTRY

00:09:36

- Tumor cells express cancer antigen on their surface, which are identified by fluorescent tagged Ab.
- Helps in diagnosis → Tg/PSA
- Used in diagnosis of undifferentiated tumors
  - Cytokeratin → carcinoma
  - Desmin → myogenic tumor (rhabdomyosarcoma)
  - Vimentin → mesenchymal tumor (Sarcoma)
  - GFAP → glial tumor (GFAP - Glial Fibrillary associated protein)
  - CD20 → B-cell lineage
- CUP: Carcinoma of Unknown Primary → CK7/CK20 is used in assessment

Refer flow chart 75.1

Organ specific IHC markers

- SOX-10/HMB-45/MELAN-A → Melanoma
- Hep-par 1/arginase 1/glypican 3 → liver cancer
- GATA-3/Mammaglobulin/gross cystic disease fibrous protein-15 → Breast cancer
- PSA/AMCAR/PSMA/NKX3-1 → Prostate cancer
- TTF-1/NAPSIN-A/SP-A1 → Lung adenocarcinoma
- Calretinin/WT_1/D2-40/Mesothelin → Mesothelioma
- Mesenchymal tumors
  - Factor VIII → Angiosarcoma
  - MyoD1 → Rhabdomyosarcoma
  - Smooth muscle actin → Leiomyosarcoma
- Thrombomodulin/Uroplankin III/CK20 → Urothelial tumor

In therapy

- Drugs are given based on IHC
- Example: Breast cancer with HER 2/Neu → poor prognosis
  - Trastuzumab is given

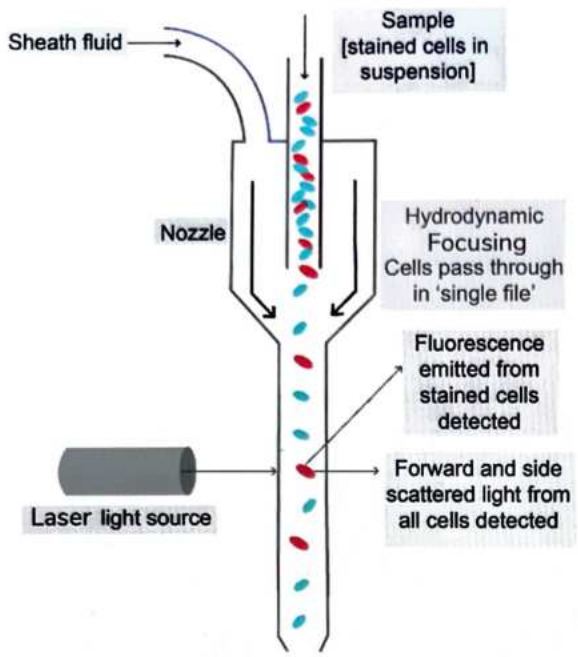
FLOWCYTOMETRY

00:21:36

- Useful in detection of CD molecules
- Multiple molecular markers can be analyzed

- Most helpful in leukemia

Flow Cytometry



Important Information

Flow-cytometry

- Forward scatter depends on size of the living cell
- Side scatter depends on granularity of the cells

MOLECULAR AND CYTOGENETIC ANALYSIS 00:24:45

- Useful in solid cancer with exception of cervical cancer, due to contamination of sample by microorganism

Uses

- Diagnosis of t(9;22) → FISH → CML
- Minimal residual disease → PCR (amplification of abnormal nucleic acid material) → CML
- Prognosis of the disease → ↑ Nmyc expression → poor prognosis of neuroblastoma
- Familial Screening → Breast cancer → BRCA1/2 → mastectomy
- Targeted drug therapy → CML → t(15;17) → ↑ Tyrosine kinase activity
  - Tyrosine kinase inhibitor → Imatinib

TUMOR MARKERS 00:33:33

- Helps in pointing a diagnosis, not confirming the diagnosis
- Helps in assessing
  - Response to therapy
  - Duration of remission
  - Development of Recurrence

Important Markers

- Ig → Multiple myeloma, plasma cell cancer
- PSA → prostate cancer
- HCG β → Choriocarcinoma/germ cell tumor
- Calcitonin → C cells → medullary thyroid cancer
- Catecholamines → pheochromocytoma/neuroblastoma
- AFP → Germ cell tumor/HCC
  - Altered value → Omphalocele/hepatitis/pregnancy
- CEA → Colon cancer >> pancreatic cancer
  - Non-cancerous conditions → IBD, Hepatitis, Bonchitis
- NSE; Chromogranin → small cell lung cancer/ neuroblastoma
- CA-125 → Ovarian cancer
- CA-15.3 → Breast cancer
- CA-19.9 → Pancreatic cancer >> colon cancer
- CA-72.4 → Stomach cancer
- CA27.29 → Breast cancer

Additional markers

- S-100 → LCH/Schwanomma/Malignant melanoma
- LDH → Lymphoma/dysgerminoma/Ewing sarcoma
- β_2 Micro globulin → Multiple myeloma
- CD-99 (mic-2) → Ewing's sarcoma
- ALK → Anaplastic T-cell lymphoma/adenocarcinoma & Inflammatory myofibroblastic of lung/Neuroblastoma
- Cell free DNA/CTC → p53 → liquid biopsy (blood serum)

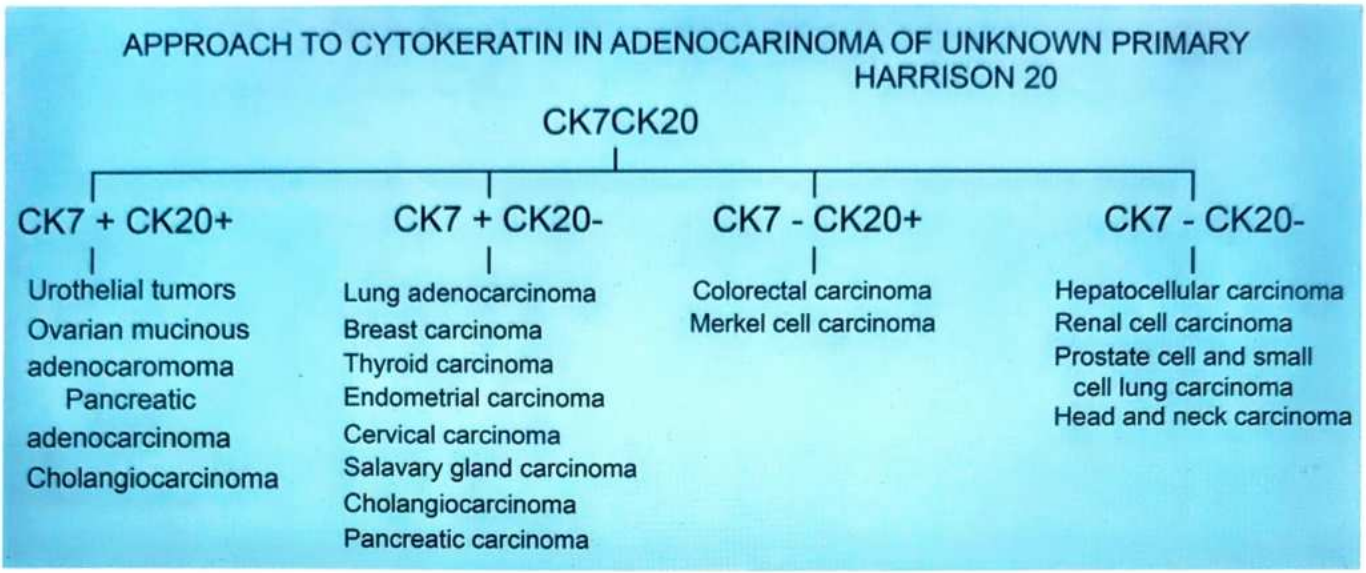
Previous Year's Questions

Q. Which of the following markers indicate an increased risk of recurrent carcinoma breast? (JIPMER Nov 2017)

A. CA 125
B. CA 19-9
C. CA 27-29
D. PSA

Flow chart 75.1

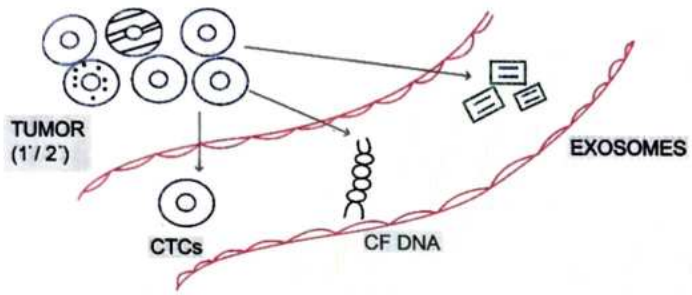
CUP: Carcinoma of Unknown Primary CK7/CK20 is used in assessment



76 LIQUID BIOPSY

- Non-invasive method used for molecular diagnosis of cancer
- Biomarkers detection in body fluids - Blood, plasma, urine, CSF, Ascitic fluid, BAL & breast milk

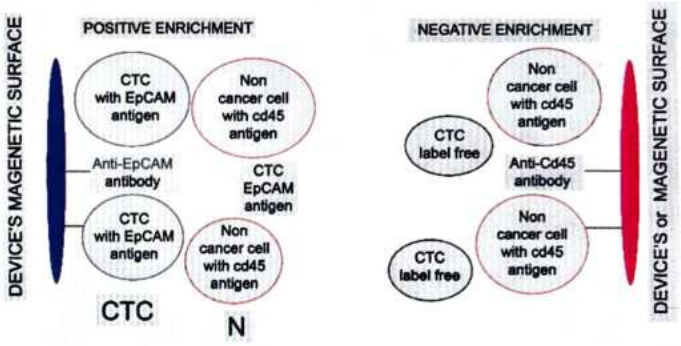
TYPES OF BIOMARKERS



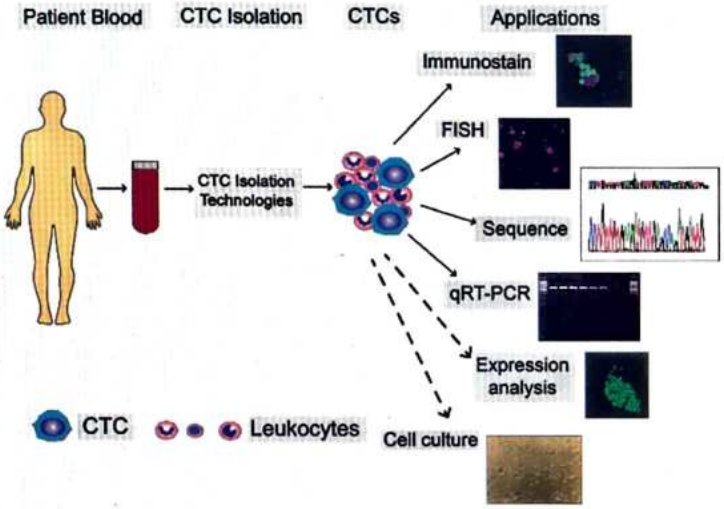
Standard tissue biopsy	Liquid biopsy
• Time intensive procedure	• Quick
• Localized sampling of tissues	• Comprehensive tissue profile
• Invasive & more complications	• Minimally invasive & less complications
• Not viable if tumor has been resected or can't be detected by imaging	• Allows for evaluation in absence of primary tumor or metastasis
• Tumor heterogeneity cannot be detected	• Tumor heterogeneity can be detected
• Repeated testing is cumbersome	• Repeated testing is easier, if needed

Circulating Tumor Cells

- CTC: 1-10 cells / µl → present in lesser no.
- Enrichment of CTC
  - Biological properties
    - → Positive Enrichment: Special tagged Ab that can attach to tumor antigen
    - → Negative Enrichment: Ab against CD45 of normal WBC is given → all unattached cells are tumor cells
  - Physical properties: Different techniques based on size/filter/density gradient media/Di-electrophoresis are used



- Nucleic acids extracted from CTC's can be studied by
  - Immunostaining
  - FISH
  - PCR
  - Sequencing → Next generation sequencing (Gold standard: Sanger sequencing)
  - Cell Culture
  - qRT- PCR



Cell free DNA (CfDNA)

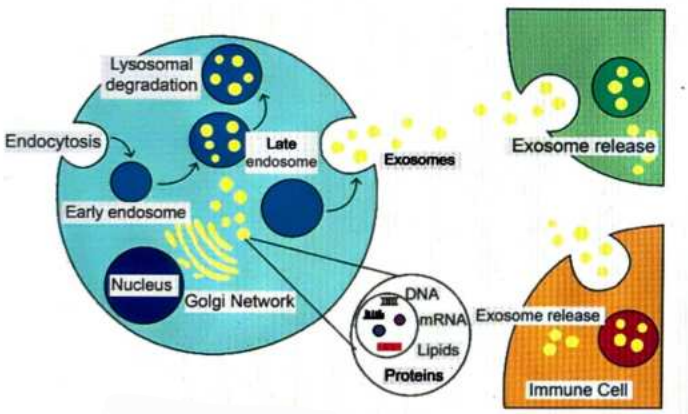
- Circulating DNA → released from tumor cells due to necrosis or apoptosis
- Cell free DNA → seen in both normal & abnormal cells
- Circulating Tumor DNA (Ct-DNA)
  - Special subtype on CfDNA secreted by tumor cells
  - Ct-DNA is directly proportional to tumor load
- Sample collection in K_3 EDTA tube
- Ct-DNA half life = 15min - 2.5hr
- Plasma separation within 1hr of collection
  - Preservatives → 96hrs
- Storage of plasma at -80°
- Analysis can be done by 2 methods
  - Targeted approach
    - → Digital PCR
    - → Real time PCR
    - → Targeted Next generation sequencing
  - Non-Targeted approach
    - → Whole genomic sequencing

mi-RNA

- Non-coding RNA → RNA silencing
- Sample: Serum >> Plasma
- Specific mRNA Quantification → qRT-PCR

EXOSOMES

00:22:29



- Membrane bound vesicles with presence of DNA/ RNA/ Proteins
- Endosomal origin
- Size: 40-100nm
- Function → Intercellular messenger
- Present in body fluids → Blood, plasma, CSF, BAL
- Analysis of RNAase (more specific & sensitive)

Tumor Educated platelets

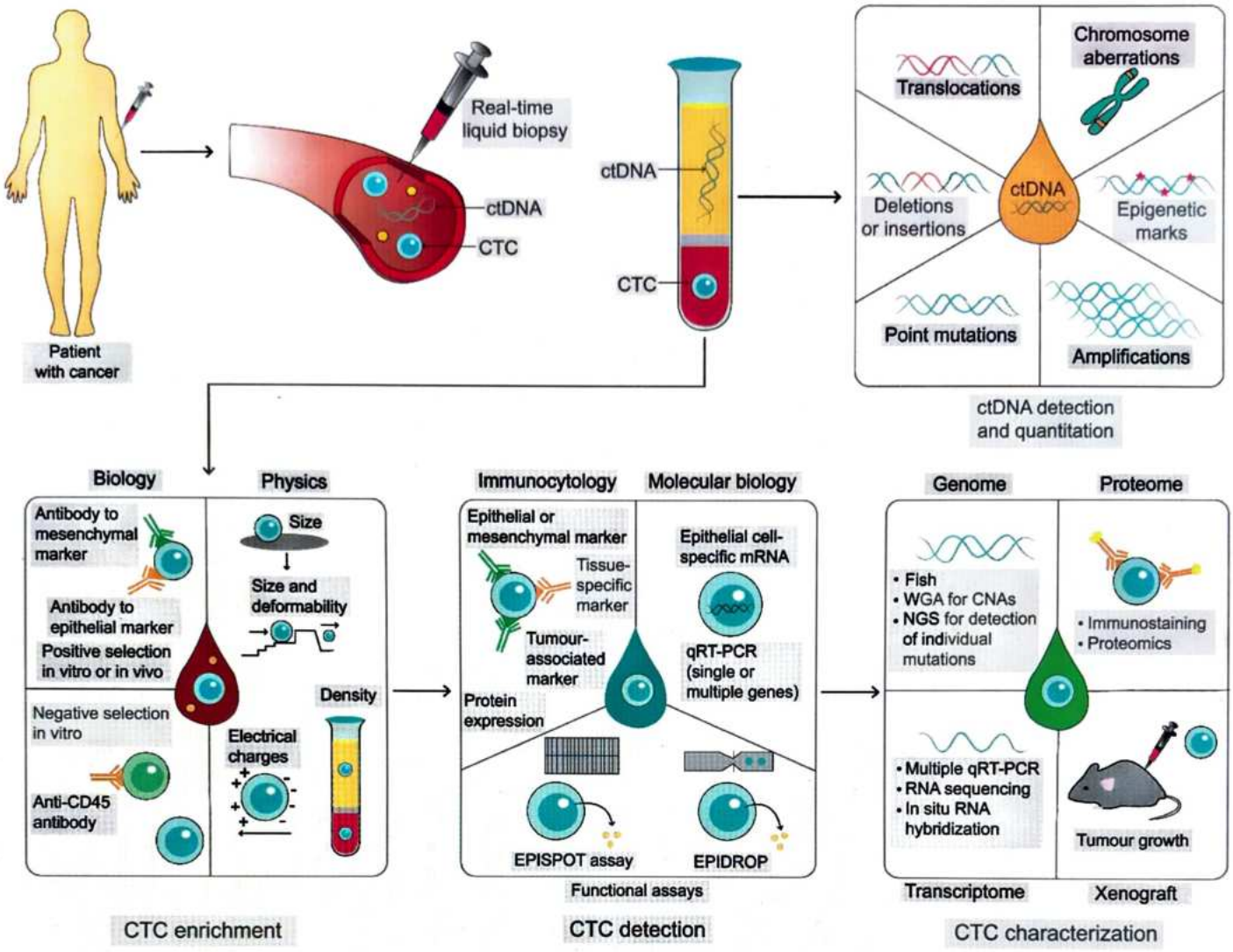
- PDGF → Secreted by platelets, responsible for epithelial mesenchymal transformation
- Involved in tumor invasion, angiogenesis
- RNA sequencing used to differentiate between normal platelets & tumor educated platelets

Uses

- Screening of cancer: Early Diagnosis/ Recurrence/ Prognosis
  - Example: EgFR presence in non-small cell lung cancer
- Drug Monitoring → to assess drug resistance
- Targeted therapy
- Newer targets

Refer Image 76.1

Image 76.1


Patient with cancer
Real-time liquid biopsy
ctDNA
CTC
ctDNA
CTC
Translocations
Chromosome aberrations
Deletions or insertions
ctDNA
Epigenetic marks
Point mutations
Amplifications
ctDNA detection and quantitation
Biology
Physics
Antibody to mesenchymal marker
Antibody to epithelial marker
Positive selection in vitro or in vivo
Negative selection in vitro
Anti-CD45 antibody
Size
Size and deformability
Density
Electrical charges
CTC enrichment
Immunocytology
Molecular biology
Epithelial or mesenchymal marker
Tissue-specific marker
Tumour-associated marker
Protein expression
Epithelial cell-specific mRNA
qRT-PCR (single or multiple genes)
EPISPOT assay
EPIDROP
Functional assays
CTC detection
Genome
Proteome
• Fish
• WGA for CNAs
• NGS for detection of individual mutations
• Immunostaining
• Proteomics
• Multiple qRT-PCR
• RNA sequencing
• In situ RNA hybridization
Tumour growth
Transcriptome
Xenograft
CTC characterization

77 PARANEOPLASTIC SYNDROME

NEUROMUSCULAR DISORDER

00:02:19

- Myasthenia Gravis
  - Ab against Ach Receptor (post synaptic) → muscle weakness
  - Seen in Thymoma, Lung cancer
  - Medically unresponsive → surgical removal of thymoma
- Lambert - Eaton Syndrome
  - Ab against ca2+ channel (pre Synaptic) → muscle weakness
  - Seen in Lung cancer (small cell cancer)
- Opsoclonus
  - Rapid eye movement
  - Seen in Neuroblastoma (In children), small cell lung cancer (adults)
- Limbic Encephalitis
  - Presence of Anti-HU Ab
  - Seen in small cell Lung cancer

Important Information

- MC lung cancer associated with paraneoplastic syndrome → oat cell lung cancer

- Subacute Cerebellar Degeneration
  - Anti-YO Antibodies
  - Seen in Endometrial cancer, ovarian cancer, Breast cancer

OSSEOUS: SOFT TISSUE

00:07:50

- Clubbing
  - Aka Hypertrophic Pulmonary Osteo-Arthropathy (HPOA)
  - seen in Lung cancer

ENDOCRINOPATHIES

- MC paraneoplastic Syndrome
- Hypercalcemia
  - Associated with tumor cell secretion of PgE2/PTHrP (PTH related Peptide) & ↑ Vit D
  - Asymptomatic hypercalcemia → primary hyperparathyroidism; symptomatic Hypercalcemia → cancer
  - Seen in Breast cancer, Squamous cells carcinoma of Lung, Kidney cancer
- Cushing Syndrome
  - Secretion of ACTH like substance
  - Seen in Lung cancer (small cell cancer, Carcinoid tumor
- SIADH
  - ↑ ADH
  - Seen in small cell Lung cancer, CNS Tumors
- Hypoglycemia
  - Seen in Fibrosarcoma, ovarian cancer
- Polycythemia
  - Due to ↑ EPO (Erythropoietin like Substance)
  - Seen in Hepatocellular carcinoma, Kidney cancer, Cerebellar hemangioblastoma

VASCULAR; HEMATOLOGICAL

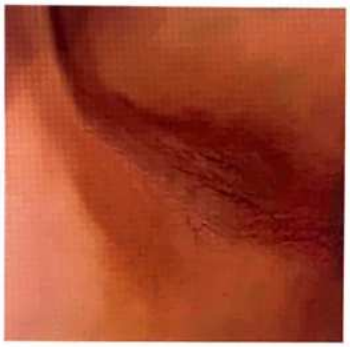
00:13:53

- Venous Thrombophlebitis
  - Causes Migratory Venous Thromboplebitis / Trousseau Sign
  - Seen in AML-M3 (secretion of mucin), Pancreas cancer, Adenocarcinoma of Lung
- Non Bacterial Thrombotic Endocarditis (NBTE)
  - Aka Marantic Endocarditis
  - Hyper-coagulable state → heart valves are involved
  - Seen in advanced cancer
- Anemia; Pure red cell Aplasia
  - Seen in Thymoma
  - Hypo-gammaglobulinemia (goods syndrome) is also seen
- DIC
  - Seen in AML-M3, Pancreatic Cancer, prostate cancer

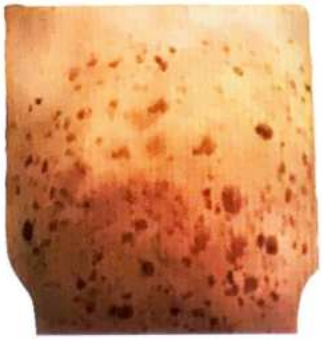
DERMATOLOGICAL

00:19:45

- Dermatomyositis
  - Contains Anti p-140/anti p-155 antibodies
  - Seen in Lung cancer, Breast cancer



Acanthosis nigricans



Seborrheic keratosis (sign of leser trelat)

- Acanthosis Nigricans
  - Seen in Stomach cancer, Lung cancer, Uterine malignancy
  - Also seen in insulin resistance
- Seborrheic Keratosis
  - Aka Sign of "Leser Trelat"
  - Seen in Stomach cancer, Colon cancer, Breast cancer

CLINICAL QUESTIONS

A 58-year-old guy complains of rapidly progressive weakness. His stools are really dark, The right lower quadrant of the body is full, according to physical examination. With a serum haemoglobin level of 7.4 g/dL, laboratory tests reveal iron deficiency anaemia. Occult blood is detected in stool samples. A cecum ulcer is discovered during a colonoscopy. Which of the serum tumour markers listed below is most likely to be beneficial in monitoring this patient after surgery?

A. Alpha-fetoprotein
B. Carcinoembryonic antigen
C. Chorionic gonadotropin
D. Chromogranin

Solution:

- In its early stages, colorectal cancer is asymptomatic. Occult blood in stools is the most prevalent symptom, especially when the tumour is in the proximal colon. ·
- CEA is commonly seen in colon adenocarcinomas, a glycoprotein that is secreted into the circulation and serves as a serologic marker for these tumours.
- CEA is also present in malignant tumours of the pancreas, lung, and ovary.
- AFP (choice A) is expressed by hepatocellular carcinoma and yolk sac tumors.
- Chromogranin (choice D) is expressed by neuroendocrine tumors.
- Chorionic gonadotropin (choice C) is secreted by choriocarcinoma.

Reference:

- Robbins 10th ed, Pg 335-6

LEARNING OBJECTIVES

UNIT 14 CVS, BLOOD VESSELS AND VASCULITIS

- **Vasculitis**
  - Large Vessel Vasculitis: Clinical Features Of Temporal Arteritis
  - Takayasu Arteritis
  - Medium Sized Vessel Vasculitis
  - Berger's Disease
  - Kawasaki Disease
  - Small Vessel Vasculitis
  - Microscopic Polyangiitis
  - Allergic Granulomatosis With Polyangiitis
- **Ischemic heart disease**
  - Clinical Features of Myocardial Infarction
  - Reperfusion Injury
  - Chronic Ischemic Heart Disease
- **Rheumatic fever and infective endocarditis**
  - Rheumatic Fever ; Pericarditis
  - Infective Endocarditis: Risk Factors, Clinical Features And Diagnosis
- **Cardiac tumors**
  - Myxoma
  - Rhabdomyoma

78 VASCULITIS

- Inflammation of blood vessels
- Inflammation + Edema (neutrophilic infiltration) → narrowing of lumen → Tissue ischemia and necrosis

LARGE VESSEL VASCULITIS

TEMPORAL ARTERITIS

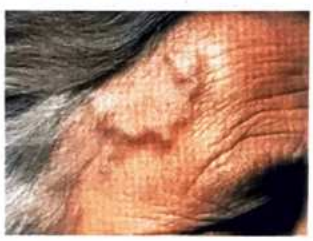
- MC vasculitis is adults (>50yrs)
- T-cell mediated damage → granuloma
- Superficial Temporal artery (terminal branch of ECA) is involved

Clinical features 00:03:13

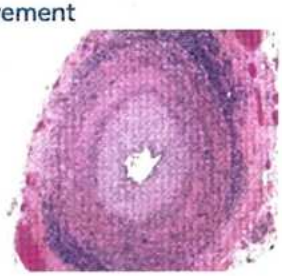
- Headache (MC symptom)
- Jaw claudication (most specific)
- Fever
- Malaise
- Polymyalgia Rheumatica → pain in Shoulder & Pelvic girdle
- Sudden onset blindness

Diagnosis

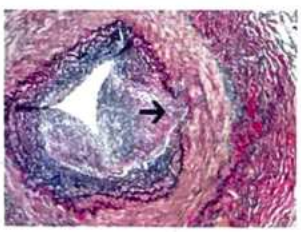
- ↑↑ TLC
- ↑↑ ESR
- Temporal Artery Biopsy
  - Presence of granuloma
  - Internal elastic lamina fragmentation
  - Minimum size of tissue should be at least 1cm
  - Absence of granuloma does not rule out the diagnosis → patchy involvement



Inflamed temporal artery



Reduction in lumen size



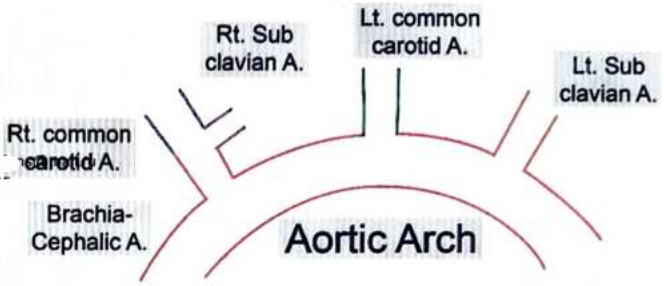
Fragmentation of internal elastic lamina (Van Gieson stain)

Treatment

- Steroids

TAKAYASU ARTERITIS 00:08:53

- Age of presentation: < 50yrs
- Involvement of aorta & subclavian vessel



- Aka aortic arch syndrome/pulseless disease/non-specific aorto-arteritis
- Involvement of Pulmonary Artery → PAH, cough & dyspnea
  - Renal Artery → activation of RAAS → Reno-vascular HTN
  - Cardiac vessels → MI

Important Information

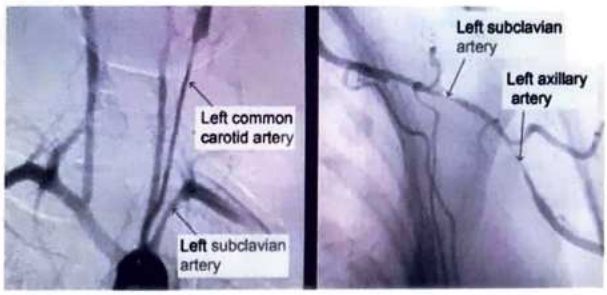
Reno-vascular HTN

- MC cause for young adults in India: Takayasu arteritis
- MC cause for young adults in USA: Fibromuscular dysplasia

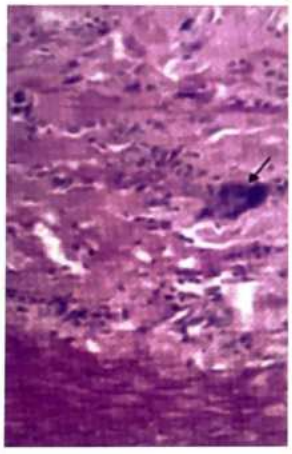
Clinical features

- Fever
- Malaise
- Feeble pulse
- ICA involvement → sudden onset of blindness

Diagnosis



Narrowing of lumen



Giant cells

- Angiogram → extreme Narrowing of affected vessel
- Granulomatous inflammation → giant cells

Treatment

- Steroids
- Poor prognosis

MEDIUM SIZED VESSEL VASCULITIS

00:16:12

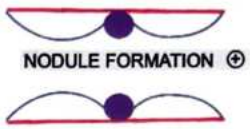
POLYARTERITIS NODOSA

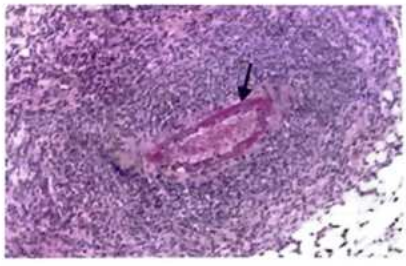
- Seen in Young Adults
- Presence of Immune complex formation → type 3 HR → Fibrinoid necrosis
- Associated with hepatitis-B infection → HBSAg + Ab → IC → organs

Clinical features

- Lungs are spared
- Kidney: Aneurysm/inflammation → HTN
- Small blood vessels are not affected → no glomerulonephritis
- GIT → abdominal pain, melena
- Skin → rash, ulcerative lesion
- Nerve → mononeuritis multiplex (MC systemic cause is DM)
- Joints → pain, difficulty in movement

Diagnosis





Fibrinoid necrosis

- Biopsy
  - Early Phase → Fibrinoid necrosis, Transmural inflammation
  - Late Phase → Fibrosis
  - Presence of nodule formation → string of pearl appearance
- MC cause of death → Renal Failure

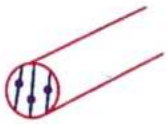
Previous Year's Questions

Q. ANCA negative vasculitis amongst the following is? (JIPMER Nov 2017)

A. Wegner granulomatosis
B. Churg Strauss syndrome
C. Polyarteritis nodosa
D. Microscopic polyangiitis

BUERGER'S DISEASE

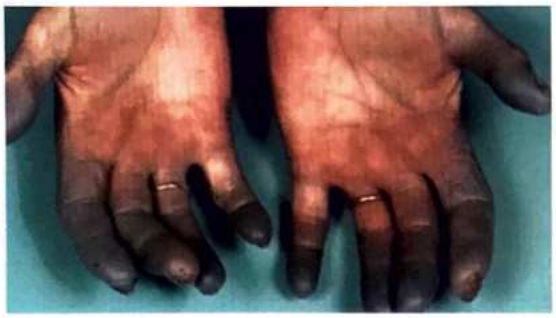
00:24:37



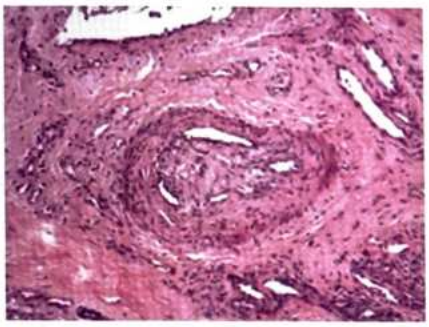
Thromboangitis obliterans

- Aka Thrombangitis Obliterans
- Seen in young male → smoker

- Genetics: HLAB 5/A9 → ↑↑ risk of Buerger's disease; HLAB12 → Protective
- Involvement of Arteries > veins > Nerves
  - Lymphatics not involved
  - Arteries involved: tibial artery, radial artery



Raynaud's phenomenon
- Tibial Artery involvement
  - ↓ Blood → Raynaud's phenomenon
  - Instep claudication



Rest pain (nerves are affected)

Microscopic appearance
- Micro-abscess formation
- Granulomatous inflammation

Treatment
- Quit smoking
- Vasodilator therapy
- Surgery

KAWASAKI DISEASE

00:33:12

- Kids < 4yrs age group
- Aka mucocutaneous LN syndrome

Clinical features

Fever +	• Conjunctivitis (non-exudative) • Rash • Edema of hands and feet • Adenopathy (unilateral; cervical) • Mucosal involvement (ulcer, strawberry tongue)

Pathophysiology

H/O viral infection
↓
T cell activation/anti-EC ab +
↓
Clinical Features

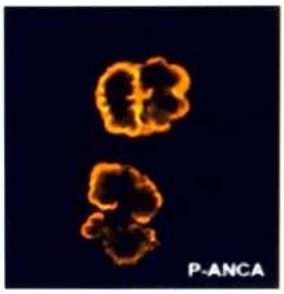
- Coronary artery vasculitis → myocardial infarction
- Diagnosis: ↑ P/C → ↑ risk of MI
- Treatment: IV Ig + aspirin

SMALL VESSEL VASCULITIS

00:39:13

ANCA: Anti-neutrophilic Cytoplasmic Ab

MPO [Ag]	Proteinase-3
↓	↓
P-ANCA	C-ANCA
↓	↓
Now k/a MPO-ANCA	Now k/a PR-3 ANCA



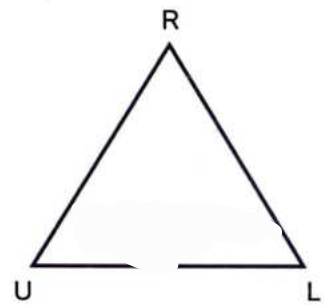
Conditions associated
- microscopic polyangiitis
- Churg-strauss syndrome
- Good pasture syndrome
- Ulcerative colitis (against nuclear envelop Ag)

Conditions associated
- Wegener granulomatosis

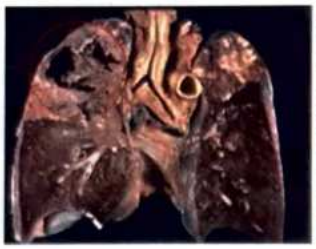
WEGENER GRANULOMATOSIS / GRANULOMATOSIS WITH POLYANGIITIS

- Characterized by presence of Necrotizing granuloma in URT, Lungs

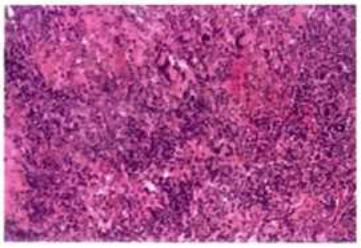
Rule of organ involvement



- Renal: Focal GN → Crescentic GN (RPGN) → renal failure
- URT
  - E - Otitis media
  - N - Septal perforation/saddle nose
  - T - strawberry gums/Sub-glottic Stenosis
- Lungs
  - Pneumonitis
  - Cavitatory lesions
  - Cough
  - Hemoptysis



Cavitatory lesion



Granulomatous inflammation

Diagnosis
- C-ANCA/PR-3 ANCA
- Biopsy
  - In kidney: Crescentic GN (RPGN)
  - In URT: necrotizing granuloma

Treatment
- Immunosuppressive therapy
- Cause of Death → Renal Failure

MICROSCOPIC POLYANGIITIS 00:52:52
- Neutrophilic inflammation → capillaries/venules (MC)/arterioles
- Aka hypersensitivity vasculitis / leukocytoclastic vasculitis
- Fragmented neutrophils are present around affected vessel

	PAN	MPA
small vessels	⊖	⊕
Lungs	⊖	⊕
Kidneys	⊕	⊕
Necrotizing gn	⊖	⊕
P-ANCA / MPO -ANCA	⊖	⊕

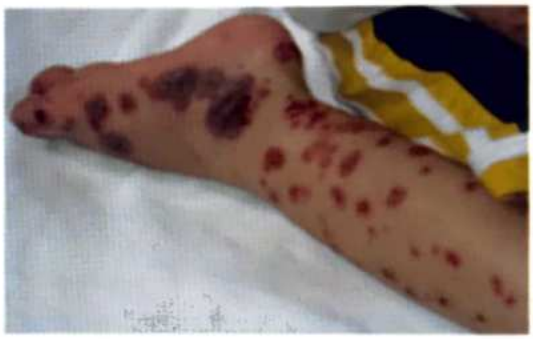
Microscopic appearance
- MPA: Same stage of inflammation
- PAN: early & late stage of inflammation co-exist
- No granuloma formation

Treatment
- Immunosuppressive therapy

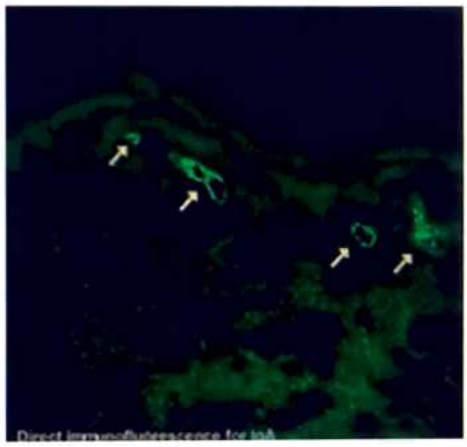
HENOCH-SCHONLEIN PURPURA
- MC vasculitis in pediatric age group
- Type 3 HR
- H/O URTI → ↑↑ IgA

Clinical features
- Kidney: Hematuria (microscopic)
- Skin
  - Rash on extensor surface, buttocks
  - Vasculitis → resembles purpura
  - P/C → Normal (non-thrombocytopenic purpura/anaphylactoid purpura)
- GIT: Abdominal pain
- Joints: joint pain/swelling

Diagnosis
- Normal platelet count
- Normal complement levels
- Skin biopsy → IgA Ab deposition at dermal papillae



Purpuric lesion

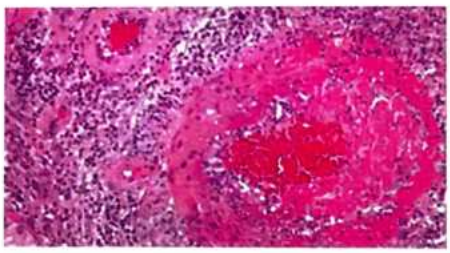


IgA Ab at dermal papillae

ALLERGIC GRANULOMATOSIS WITH POLYANGITIS

01:05:12

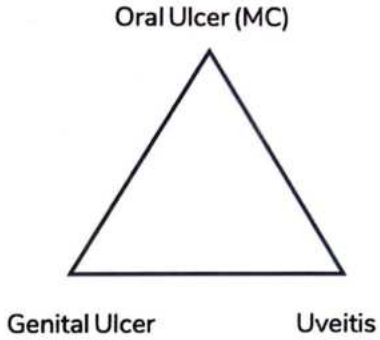
- Aka Churg-Strauss Syndrome
- Necrotizing Granulomatous inflammation → MPO-ANCA ⊕
- ↑↑ Eosinophils → Asthma/Allergic Rhinitis/Atopy
- Blood vessel inflammation
  - GIT: abdominal pain/discomfort
  - Skin: Rash
  - Heart: Cardiomyopathy (cause of death)



Large no of eosinophils

BEHCET'S DISEASE

- Aka Oculo-oral genital Syndrome
- Small vessel vasculitis
- TH_{17} → neutrophilic infiltration
- Associated with HLA B-5/B-51
- Presence of anti-EC Ab present → α-enolase
- Diagnosis by pathergy test



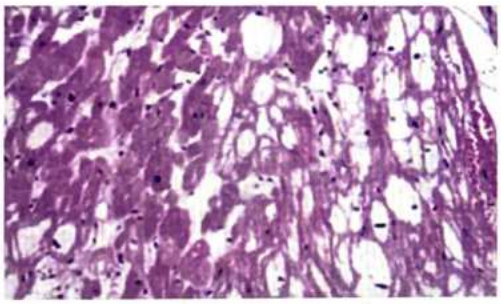
79 ISCHEMIC HEART DISEASE

- ↓ ATP → immediate change
- Loss of contractibility → < 2min
- ATP becomes
  - 50% of normal value within 10min
  - 10% of normal value within 40min
- Irreversible injury → 20min

Types of Ischemic heart disease

- Angina
  - Stable angina: fixed CA obstruction, symptomatic only during physical activity
  - Prinzmetal angina: coronary vasospasm → symptomatic
  - Unstable /pre-infarction angina: rupture of atherosclerotic plaque → MI
- MI
- Chronic IHD (HF)
- SCD → death within 1hr of cardiac symptoms onset

MYOCARDIAL INFARCTION



- Irreversible cardiac tissue injury
- Sub-lethal ischemia → associated with myocyte vacuolization
- Poor contractility (but myocytes are viable)

Ulceration/rupture/hemorrhage of atherosclerotic plaque
↓
↓ Blood supply
↓
Infarction

Subtypes of infarction

- Sub-endocardial MI
- Transmural MI
- Multifocal MI

Clinical features 00:05:29

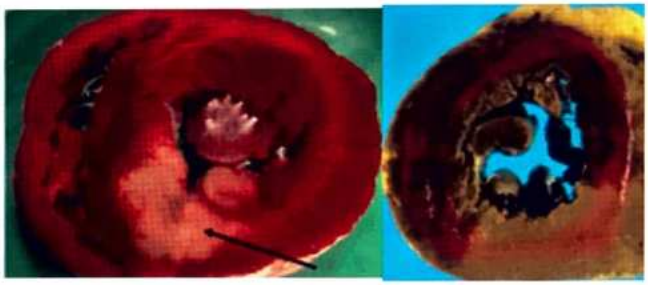
- Constricting/squeezing type of chest pain
- Levine Sign: Clenched Fist on chest
- MC type of MI: Anterior wall MI

Diagnosis

- ECG
- Blood sample
  - 1st enzyme to be elevated → HFABP
  - Myoglobin
  - CK-MB
  - Cardiac troponin
    - → Troponin T
    - → Troponin I → most sensitive/specific, marker of choice for re-infarction

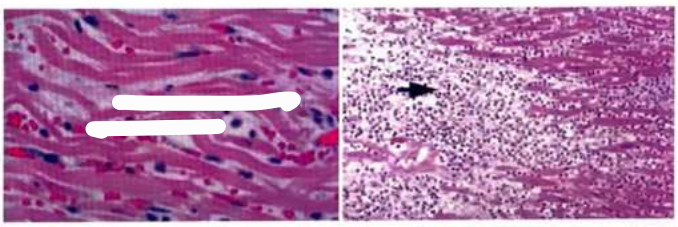
LDH

- Last enzyme to increase
- Normal: LDH1 (Heart) <<< LDH2 (blood)
- Flipping of LDH: LDH1 (Heart) >>> LDH2 (blood) → MI
- Reacts with Triphenyl Tetrazolium Chloride → brick red color



Biopsy

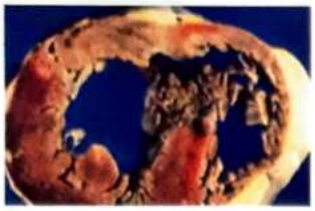
Refer Table 79.1



Waviness | Coagulative necrosis

Previous Year's Questions

Q. Gross section of myocardium following myocardial infarction is shown. What could be the duration following MI? (JIPMER Nov 2018)

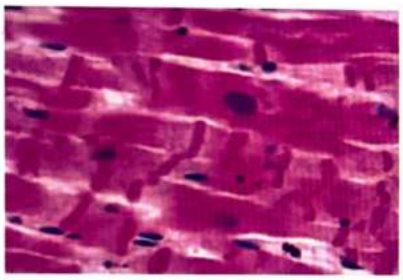


A. Immediate MI
B. 2 days
C. 2 weeks
D. Postmortem artefact

REPERFUSION INJURY

00:15:24

- Thrombolysis → influx of WBC/Free radicals/Ca^{2+}
- Patient worsens after thrombolytic therapy
- Viable myocyte exposure to calcium → Contraction Bands



Contraction bands in reperfusion injury

COMPLICATIONS

- Arrhythmias
- ↓HR
- Ventricular fibrillation → SCD
  - Death can occur within 1hr
- Cardiac failure

Cardiac rupture syndrome

- Occurs within intermediate time between loss of strength (↓ blood supply) & collagen deposition
- Seen after 3-7 days after MI
- Affects anterior wall of LV/Inter ventricular septum/mitral valve
- MC cardiac rupture: Ventricular wall rupture

Autoimmune pericarditis

- Aka Dressler syndrome
- Neo Antigens exposure → after 2-3 weeks after MI
- Neo Ag → Immune system activation → pericarditis
- Presents with chest pain (troponins differentiates it from reinfarction)

Ventricular Aneurysm

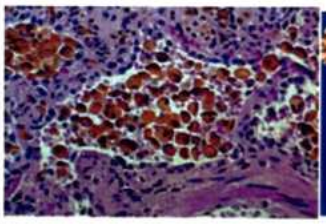
- Ventricular wall weakness → aneurysm
- Likely to form clot → thrombo-embolic manifestations

Chronic Ischemic Heart Disease

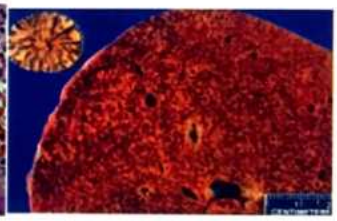
00:22:38

LVF	RVF

• Lungs: MC organ affected
  ○ Acute → dyspnea, PE
  ○ Chronic → "heart-failure" cells
• Kidney → RAAS activation, Azotemia
• CNS → Ischemic encephalopathy
	• MC cause: LVF
	• Cor pulmonale
	• Congestive hepatomegaly → nutmeg liver/cardiac cirrhosis
	• Congestive splenomegaly → GG body



Heart failure cells



Nutmeg liver

Table 79.1

< 4hrs	• "waviness" of fibers → caused by intercellular edema
4-12hrs	• coagulative necrosis starts
12-24hrs	• coagulative necrosis + neutrophilic infiltration, dark mottling is seen
1-3 days	• Brisk neutrophilic infiltration; coagulative necrosis → Infarct (yellow border)
3-7days	• Macrophage infiltration → Hyperemic border
7-10 days	• Deposition of Granulation tissue • Collagen deposition • Max yellow tan or red-brown appearance
4-6 weeks	• ↑ Collagen deposition • Scar formation → white

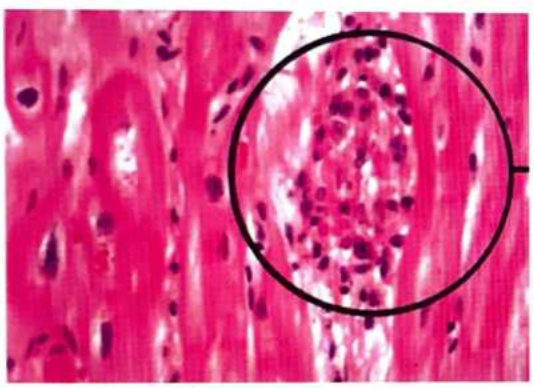
80 RHEUMATIC FEVER & INFECTIVE ENDOCARDITIS

RHEUMATIC FEVER

- H/O Group A β Hemolytic Streptococcus infection → Sore throat/pharyngitis
- Seen in 3% of children
- Associated with exposure to 'M' protein → immune system activation → Ab formation
- 'M' protein is similar to GP present in joints/heart/CNS/Skin
- Example of type 2 HR

Pancarditis

- Pericarditis → Bread & Butter Pericarditis (Serofibrinous exudate)
- Myocarditis → cardiac failure
- Presence of Aschoff body is seen around blood vessels
- Aschoff body: fibrinoid necrosis surrounded by eosinophilic collagen, macrophages, plasma cells
- Plump macrophages → Anitschkow cell

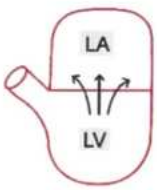


Aschoff body

Anitschkow cell

Important Information

- Anitschkow Cell can also be seen in
  - H/O Chemotherapy
  - Aphthous Stomatitis
  - Iron Deficiency Anemia



- Endocarditis: involvement of MV >> AV >> TV >> PV
- Acute: MR → McCallum plaque (located in left atrium; seen with MR)
- Chronic: MS → Button-hole/fish mouth stenosis
- Deposition of platelet/fibrin on apposed mitral valve → cardiac vegetation
- Small, sterile, firm, present along line of closure
- Marantic endocarditis: Small/sterile/firm/LOC/Emboli
  - Associated with AML-M_3/Carcinoma pancreas

Diagnosis

- Throat culture → ↑↑ anti-streptococcal Ab (Evidence of group A streptococcal infection)
- Major Criteria
  - Carditis → clinical/sub-clinical
  - Arthritis → migratory polyarthritis/mono-arthritis/polyarthralgia
  - Chorea
  - Erythema marginatum
  - Subcutaneous nodules
- Minor Criteria
  - Fever
  - Arthralgia (major criteria in high prevalence population)
  - ↑ESR (>30mm in 1hr)
  - ↑PR Interval (can be considered only when carditis is absent clinical/subclnical)
  - ↑CRP
- Initial ARF: 2 major or 1 major & 2 minor

- Recurrent ARF: 2 major or 1 major & 2 minor or 3 minor

Previous Year's Questions

Q. A 30-year-old male presented with severe dyspnea. His investigations showed mitral stenosis with left atrial enlargement. The histopathology report from his mitral valve is shown below. What is the likely diagnosis of these patients? (AIIMS Nov 2017)

A. Sarcoidosis
B. Fungal granuloma
C. Tuberculous
D. Rheumatic Heart disease

INFECTIVE ENDOCARDITIS

00:16:53

Normal individuals

- Normal Endothelial Lining – anti thrombotic in nature
- Temporary Bacteremia
- Activity of Immune System

Risk Factors

- Damage to Endothelial Lining → RHD/Congenital heart defect/artificial valve
- Prolonged bacterial Presence → Septicemia
- Immunosuppression → DM, Steroids

Acute IE

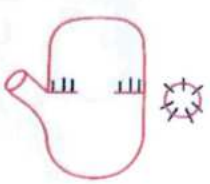
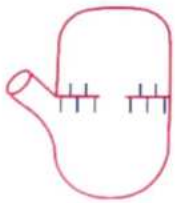
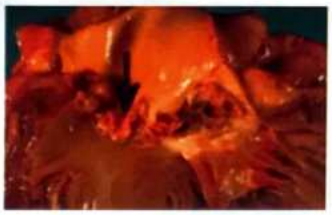
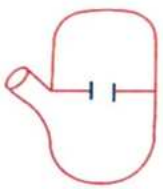
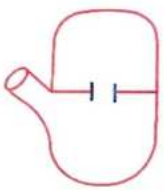
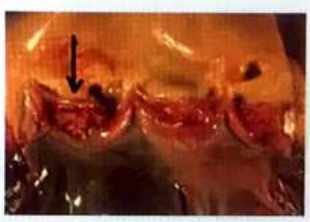
- Causative organism: staph aureus/streptococcus
- Nosocomial infection → Staphylococcus Aureus
- Damage to previously healthy valve

Sub-Acute IE

- Causative organism: Streptococcus viridians
- Previously damaged valve → infection by less virulent organism
- IV drug abusers → Staph aureus (TV affected)
- Valve surgery
  - < 2 months: staph epidermidis
  - 2 months: streptococcus
- HACEK bacteria → haemophilius/actinobacter/cardiobacterium/eikenella/kingella species

Clinical Features

- Fever
- Retinal Hemorrhage → Roth Spots
- Osler nodes → painful lesion in pulp of digits
- Janeway lesion → painless lesions in palm
- Murmurs (Changes from valve to valve) → characteristic

Infective endocarditis	Libman sack endocarditis (SLE)
	
• Large/bulky vegetation • non-sterile • Embolization can occur • Ring abscess is seen	• Lower surface is affected more • Small/sterile • No embolization
	
RHD	**NBTE (Marantic endocarditis)**
	
• Small/Sterile • Present along line of closure • No embolization	• Small/Sterile • Present along line of closure • High risk of embolization • Associated with AML-M3, Pancreatic cancer
	

Diagnosis by Modified Duke's Criteria

- Blood Culture → 1hr apart, 3 different sites
- Echocardiography

Previous Year's Questions

Q. Irregular, bulky and friable vegetation in cardiac valve is a finding of which of the following disorders?
(NEET Jan 2020)

A. Infective endocarditis
B. Rheumatic endocarditis
C. Libman sack endocarditis
D. Nonbacterial endocarditis

81 CARDIAC TUMORS

- Primary cardiac tumors
- Secondary cardiac tumors
  - Most common
  - MC metastasis: Bronchogenic carcinoma
  - Associated with involvement of Pericardium

	Malignant	Benign
In Adult	Angiosarcoma	Myxoma
In children	Rhabdomyosarcoma	Rhabdomyoma

MYXOMA

00:02:36

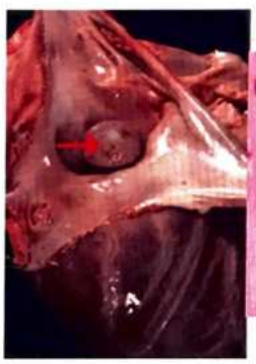
- MC primary benign cardiac tumor seen in adult
- Site of Origin
  - Mesenchymal stem cells
  - Atrium (LA >> RA): Fossa ovalis

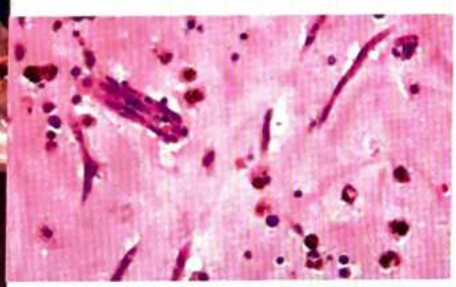
Clinical features

- On atrial contraction, the pedunculated mass hits the surface of the valve → tumor plop sound
- Ball valve mechanism of obstruction
- IL-6: Causes weight loss, fever
- Embolism

Microscopic finding

- Lepidic cells in acidic myxoid matrix





Types

- Sporadic: Single, MC (90%)
- Familial: Bilateral (10%)
  - Associated with Carney syndrome

Important Information

Carney syndrome Triad

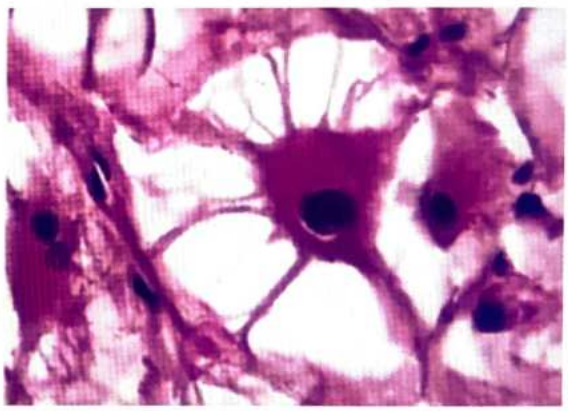
- Myxoma (cardiac & extra-cardiac site)
- Skin pigmentation
- Endocrine over-activity

- Other Associations
  - Mccune Albright syndrome ($GNAS_1$ gene mutation)
  - $PRKAR_1$ gene mutation

RHABDOMYOMA

00:07:52

- MC primary cardiac benign tumor in children
- Site of Origin: ventricles (RV = LV)
- Associated with TSC_1 & TSC_2 genes mutation
- Microscopic examination: Spider cells are seen (contains glycogen)



Spider Cells

Previous Year's Questions

Q. Most common tumor in a female diagnosed with tuberous sclerosis. (JIPMER 2018)

A. Rhabdomyosarcoma
B. Angiomyolipoma
C. Pulmonary lymphangio-leiomyomatosis
D. Optic Glioma

CLINICAL QUESTIONS

A 70-year-old man Rohan with advanced visceral cancer dies of extensive myocardial infarction. Autopsy also reveals sterile non-destructive vegetations along the mitral leaflet edges. The pathogenesis of this patient's vegetations is most similar to that of:

A. Hypercalcemia of malignancy
B. Distant metastases
C. Trousseau syndrome
D. Raynaud's phenomenon

Solution:

- The pathogenesis of non-bacterial thrombotic endocarditis (NBTE) often involves a condition of hypercoagulability that is the result of the procoagulant effects of the circulating cancer products;
- The resulting heart valve vegetation can also be referred to as endocarditis marantic.
- The pathophysiology of NBTE is similar to that of Trousseau's syndrome (migratory thrombophlebitis), which can also be induced by disseminated cancers such as mucinous adenocarcinoma of the pancreas and adenocarcinoma of the lungs, possibly related to the procoagulant effect of circulating mucin.
- Cancer metastases in the heart usually affect the pericardium or myocardium.
- Valve metastases are less common and would likely have shown invasive features on histological examination.

Reference:

- ***Robbins 10/e p564***

LEARNING OBJECTIVES

UNIT 15 KIDNEY & URINARY BLADDER

- **Congenital Renal Disorder**
  - Horse-Shoe Kidney
  - Adult Polycystic Kidney
  - Childhood Polycystic Kidney
  - Medullary Cystic Kidney
  - Medullary Sponge Kidney

- **Glomerular Disorder Part 1/Nephritic Syndrome**
  - Acute proliferative GN
  - Rapidly progressive GN
  - Berger's disease

- **Hereditary Nephritis**
  - Alport Syndrome
  - Thin BM Lesion
  - Good Pasture Syndrome

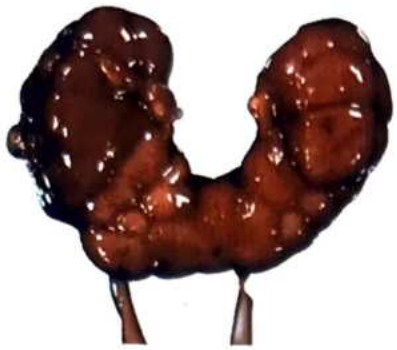
- **Glomerular disorder Part 2/ Nephrotic Syndrome**
  - Minimal Change Disease
  - Membranous Glomerulopathy
  - Membranoproliferative GN (MPGN)
  - Focal Segmental Glomerulosclerosis (FSGS)
  - Infections & Glomerular Lesions : HIV

- **Renal Stones/Nephrolithiasis**
  - Clinical features
  - Calcium oxalate stone
  - Struvite Stone , Uric Acid stone, Cystine stone
  - Diagnosis & Treatment

- **Renal Tumors**
  - Benign Tumors: Angiomyolipoma, Oncocytoma
  - Malignant Tumors: Renal Cell Carcinoma (RCC)

82 CONGENITAL RENAL DISORDERS

HORSE-SHOE KIDNEY



- MC congenital renal anomaly
- Prevalence: 1 in 500 live births
- Commonest site: Anterior to L4
- Ureters have abnormal rotation → ↑ risk of infections
- MC associated with
  - Edward syndrome
  - Down syndrome
  - Turner syndrome
- Radiologic appearance: hand joining sign/Flower vase appearance

ADULT POLYCYSTIC KIDNEY

- Autosomal Dominant inheritance
- B/L involvement

Genetics

- PKD_1 gene (chromosome 16p) → Polycystin 1 Protein (important for distal tubule)
- PKD_2 gene (chromosome 4q) → Polycystin 2 Protein (plays role in cell-cell interaction, tubular function)
- Mutation in above genes → increased cell proliferation → multiple cysts in kidney & other organs

Clinical features

- Asymptomatic
- Flank Pain
- Hematuria
- HTN
- Other organs affected: liver (MC), Spleen, pancreas, lungs
  - CNS is not involved

Complications

- CAD (cause of death)
- ↑ Nephrolithiasis (Uric acid stone)
- ↑ risk of cancer (Sarcomatoid type of renal cancer)

00:05:29

CHILDHOOD POLYCYSTIC KIDNEY

- AR inheritance
- Genetics: $PKHD_1$ gene → chromosome 6p
- Involvement of kidney & liver is seen
- Kidney: cystic lesions are present at right angle to the cortex (sponge appearance)
- Liver: ↑ risk of congenital hepatic fibrosis

00:07:07

MEDULLARY CYSTIC KIDNEY

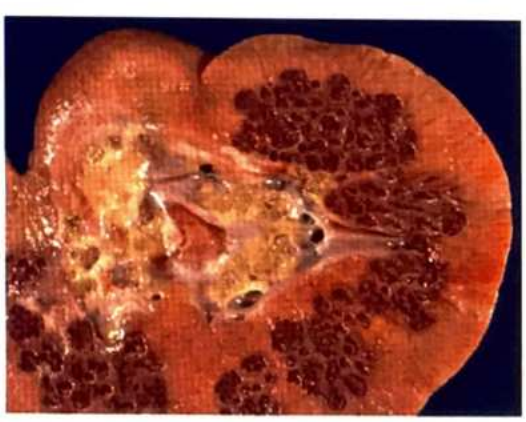
- Shrunken kidney → End Stage Renal Disease
- Presence of cortico-medullary cysts

Variants

- Adult variant
  - Aka Tubulo-interstitial kidney disease (ADTKD)
  - AD inheritance
  - Tubular & interstitial are involved → polyuria & nocturia
  - Glomeruli are preserved
  - Gene: $MCKD_{1/2}$ mutation
- Familial Juvenile Nephronophthisis → AR inheritance

MEDULLARY SPONGE KIDNEY

00:08:15



- Seen in adults; sporadic condition
- Kidney medulla affected
- Presence of cystic dilations involving collecting ducts → sponge like appearance
- ↑ Infections

- ↑ stones (Calcium oxalate & calcium phosphate) → Hematuria
- IVP → paint brush appearance

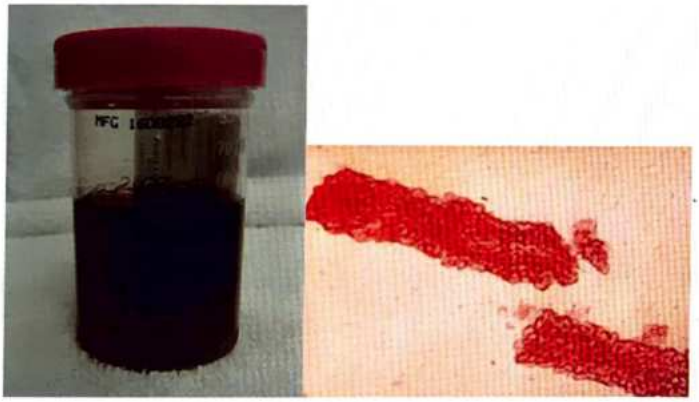
Previous Year's Questions

Q. Polycystic disease of kidneys EXCEPT? (FMGE June 2018)

A. Hematuria
B. Hypertension
C. Renal failure
D. Erythrocytosis

83 NEPHRITIC SYNDROME

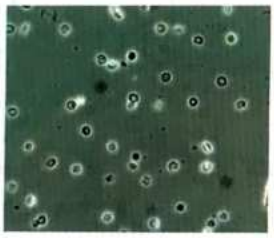
- Normal Glomerulus → GFR
  - Proteinuria⊖
  - Hematuria ⊖
- Inflammation of glomerulus → GN/Nephritic syndrome
  - ↓GFR → Oliguria (< 400ml/24hrs)
  - HTN (RAAS activation)
  - Proteinuria ⊕
  - Hematuria ⊕
    - → Smoky/cola-colored urine
    - → ≥3 RBC/hpf in at least 3 samples one week apart
- Tamm horsefall protein → hyaline cast (physiological)
- If RBC's are present in the urine, they attach to hyaline cast → RBC cast
- RBC's passing through inflamed glomerulus → change in shape of RBC (Dysmorphic RBC)



RBC casts

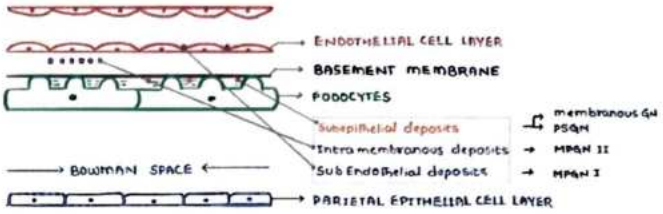
- RBC casts can be seen in
  - Glomerulonephritis
  - Malignant HTN
  - Vasculitis
  - Thrombotic microangiopathy

Isomorphic RBC



Dysmorphic RBC

- Isomorphic RBC → non-glomerular cause of hematuria (seen in Stones/Tumor)
- Dysmorphic RBC → glomerulonephritis



Acute Proliferative GN 00:11:41

- I/C formation against
  - Endogenous: SLE
  - Exogenous: Infections (streptococcus/staph aureus)

POST STREPTOCOCCAL GLOMERULONEPHRITIS (PSGN)

- MC GN in pediatric age group

Pathogenesis

H/O infection (skin/Sore Throat) with Group A β Hemolytic Streptococcus (12/4/1)

↓

Formation of I/C → SpeB (Streptococcal pyogenic exotoxin-B)

↓

Glomerulonephritis

- Type III HR
- Time taken for clinical features to develop: 10-14 days
- Transient ↓↓ C_3 levels (transient hypocomplementemia)
- Ab against streptococcus → IgG; Ab against staph → IgA

Clinical Features

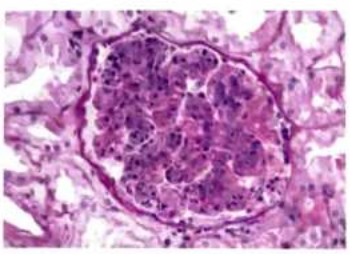
- Fever
- Malaise
- Altered color of urine (smoky/cola colored urine)
- Edema

Diagnosis

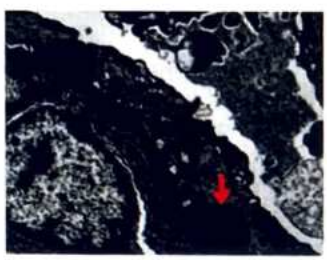
- Blood
  - Anti-DNase B Ab (preferred Ab)

- Anti-Streptolysin O Ab (significant in RHD)
- ↓ C3 protein

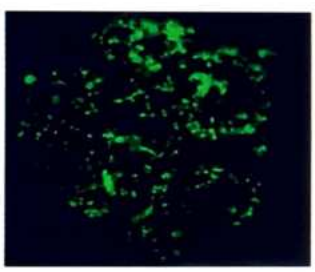
- Urine
  - Presence of RBC cast
  - Presence of Dysmorphic RBC
  - Proteinuria
- Renal Biopsy
  - Light Microscopy: All glomerulus are affected, hypercellularity (↑ cells)
  - Electronic Microscopy: Immune complexes are present at
    → Sub endothelial
    → Intra membranous
    → Sub epithelial humps → most characteristic
  - Immunofluorescence: Granular appearance (IgG/C3) → Starry sky/Lumpy-Bumpy appearance



Hypercellularity



Sub-epithelial humps



Starry sky appearance

Treatment

- Fluid restriction
- Antibiotics
- Minimal chance recurrence
- In children 90% recover; in adults 60% recover → rest progress to RPGN

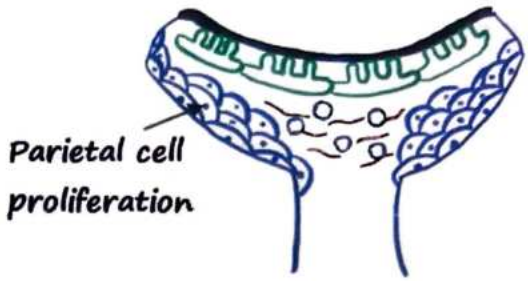
RAPIDLY PROGRESSIVE GN

00:31:19

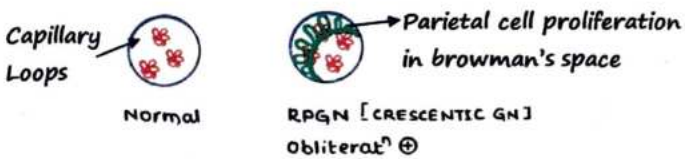
- Aka crescentic GN

onset of symptoms $\xrightarrow{\text{weeks/months}}$ ↓↓Renal function

Pathogenesis



Severe glomerular inflammation
↓
Leakage of Thrombin & cytokines
↓
Fibrin → fibrinogen
↓
Fibrin contributes to crescent formation
↓
Parietal cell proliferation
↓
↓ Bowman's space
↓
↓ GFR



- Composition of crescent
  - Parietal cell proliferation
  - Influx of WBCs
  - Deposition of fibrin

Sub Types

Refer Table 83.1

Previous Year's Questions

Q. Which of the following is correctly matched in different subtypes of rapidly progressive glomerulonephritis? (JIPMER May 2018)
A. Type I RPGN: IgA nephropathy
B. Type 2 RPGN: Anti-GBM antibody
C. Type I RPGN: Wegner's granulomatosis
D. Type 2 RPGN: SLE nephritis

Clinical features

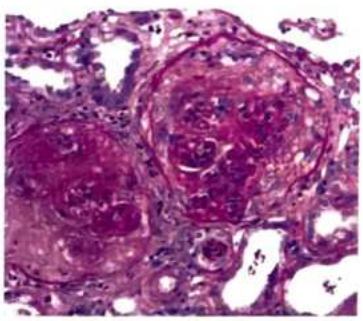
- Rapid deterioration of Renal Function
- HTN
- Proteinuria
- Oliguria

Diagnosis

- Blood: Proteinuria and other variable findings are
  - Type 1: Anti-GBM Ab
  - Type 2: ↓ complement levels
  - Type 2: presence of ANCA
- Kidney
  - Gross appearance: Due to RAAS, small blood vessels present on the cortical surface of the kidney rupture → "Flea-bitten kidney"
  - Microscopic appearance: Crescent formation
  - No of crescents ∝ prognosis of the disease

Important Information

- Flea-bitten kidney can also be seen in
  - Malignant HTN
  - Vasculitis
  - Leukemia/lymphoma
  - HUS/TTP
  - IE
  - PSGN



Crescent formation

Rupture of GBM

BERGER'S DISEASE

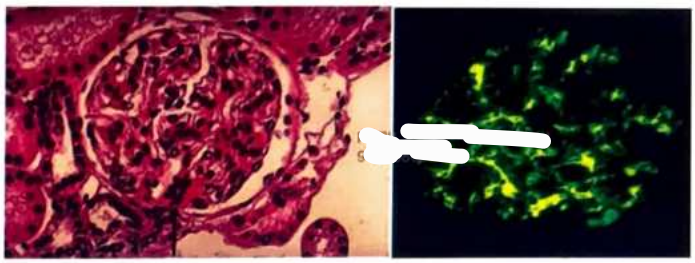
00:50:50

- Aka IgA Nephropathy
- MC GN → adults
- IgA → only monomeric form is present in the serum, polymeric form is removed by liver
- Cause: Presence of Galactose deficient IgA_1
- Primary disease: only kidney involvement
- Secondary disease: associated with celiac sprue, liver dysfunction

Pathogenesis

↑↑ Galactose deficient IgA_1 + IgG
↓
Immune complex formation
↓
Deposits in kidney (mesangium)
↓
Glomerulonephritis

- Marker: CD71 (receptor present on the surface of mesangial cell)
  - IgA_1 deposits on CD71 → Innocent bystander
- Activation of alternate complement pathway → Normal C_3 level



Mesangium is affected

Sore throat $\xrightarrow[<72hrs]{}$ Glomerulonephritis

Clinical features

- Synpharyngitic hematuria
- Gross hematuria
- Microscopic in 40% of patients
- Recurrent hematuria

Diagnosis

- Kidney biopsy: Involvement of mesangium
- ↑ Chance of recurrence (transplanted kidney is also affected)

PSGN	Berger's disease
• Pediatric	• Adults
• 10-14 days	• < 72hrs
• ↓ Serum complement levels	• Normal complement protein
• Sub-epithelial humps/granular IF appearance	• Mesangial involvement

Berger's disease	HSP
• Adults	• < 20yrs
• Predominant kidney involvement	• Multisystem involvement → rash, abdominal pain, joints &kidney involvement
• Recurrence is seen	• Skin rash → hematuria

Table 83.1

Type I RPGN	Type II RPGN	Type III RPGN
Anti-GBM Ab	Formation of I/C	Pauci-immune
Causes • Idiopathic • Good pasture syndrome	**Causes** • Idiopathic • Infections • HUS/TTP • IgA nephropathy • Cryoglobulinemia • MPGN	**Causes** • ANCA associated vasculitis o Wegner's granulomatosis o Microscopic polyangitis
Immunofluorescence • Liner IF	**Immunofluorescence** • Granular pattern	**Immunofluorescence** • No fixed pattern
Treatment • Plasmapheresis	**Treatment** • 1° cause	**Treatment** • Vasculitis management

84 HEREDITARY NEPHRITIS

- Presence of Collagen defect

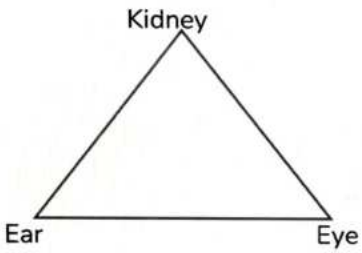
Collagen Sub-types
- Type 1: Bone (max tensile strength)
- Type 2: Cartilage
- Type 3: Blood Vessels
- Type 4: Kidney & Lungs BM

ALPORT SYNDROME

00:03:40

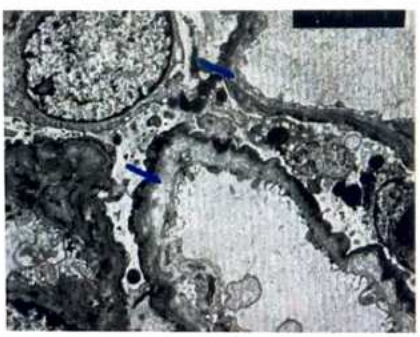
- Associated with defect in α5 chain of type IV collagen
- X-linked inheritance (85%) (XLD >> XLR)
- Autosomal (AR; AD)
- MC organ affected Kidney

Triad



- Kidney: Hematuria, RBC casts
- Ear: SNHL
- Eye: B/L Anterior Lenticonus, Corneal dystrophy

Diagnosis
- Renal Biopsy best tissue for examination
- Electron microscopy
  - Variable thickness of Basement membrane "Basket weave appearance"
  - Splitting of BM



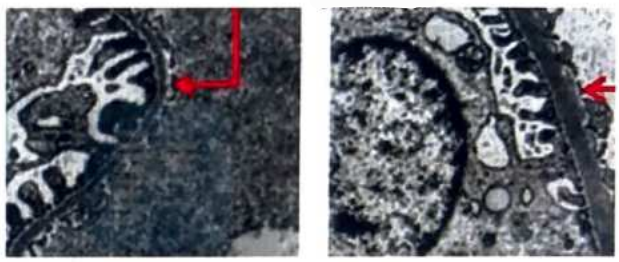
Basket wave appearance

- Age of presentation: 20-50yrs (RF)
- Recurrence is rare after renal transplant

THIN BM LESION

00:14:55

- MC cause of benign familial hematuria
- It is due to defect in α_3 & α_4 chain
- Normal Thickness: 300-400nm
- Thinning of BM 150-200nm
- AR Inheritance
- Asymptomatic Hematuria present
- Renal function is preserved good prognosis



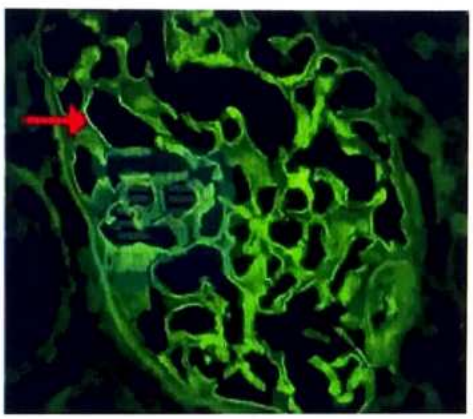
Thinning of BM

GOOD PASTURE SYNDROME

00:19:04

Auto-Ab (Type II HR)
↓
Ab against α3 chain
↓
Type collagen IV
↓
Interstitial hemorrhagic inflammation

- Kidneys: Hematuria
- Lungs: Hemoptysis



- Renal biopsy: Linear Immunofluorescence pattern
- Type I RPGN can progress to Renal Failure death

Treatment

- Plasmapheresis

85 NEPHROTIC SYNDROME

Pathogenesis

I/C + T-Cells (cytokines)
↓
Podocyte damage
↓
Massive proteinuria & ↑ Liver activity

Proteinuria

Massive proteinuria (>3.5g/day)
↓
Hypoalbuminemia (<3g/dl)
↓
↓↓ ANP (Na^+/H_2O retention)
↓
Edema

- Also associated with loss of certain proteins
  - ↓T_f → iron-resistant microcytic hypochromic anemia
  - Vitamin D protein → ↓ calcium
  - Igs → ↓ Infections
  - AT-III → ↓ Clot formation (DVT/RVT/PTE)
- Podocyte damage can be
  - Mild: selective proteinuria
  - Massive: non-selective proteinuria
- All the plasma proteins have ↓ concentration, except fibrinogen

↑ Liver activity

- ↑ Lipids in blood (hyperlipidemia)
- Loss of lipids in urine → lipiduria → lipid cast (can also be seen in hypothyroidism)
  - Lipid casts can have fragmentation → oval fat bodies
- Under polarized microscopy, cholesterol esters in urine → Maltese cross appearance

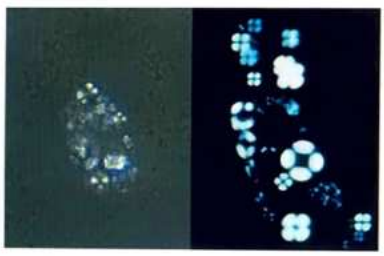
Important Information

- Maltese cross can be seen in
  - Nephrotic syndrome
  - Fabry's disease (Mulberry appearance is the characteristic finding)
  - In RBC's → Babesia microti infection

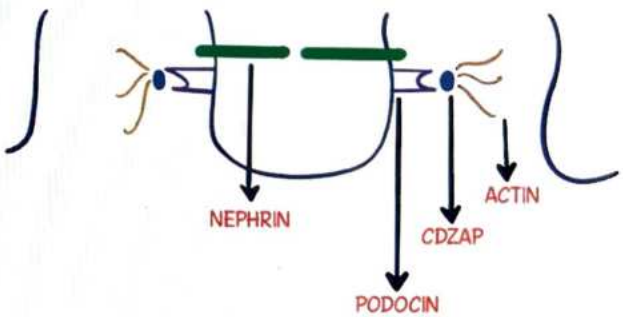
Peri-orbital edema

Frothy urine

Lipid cast



Maltese cross



Filtration slit

- Nephrin: $NPHS_1$ gene defect → congenital/Finnish nephrotic syndrome
- Podocin: $NPHS_2$ gene defect → FSGS (child)

MINIMAL CHANGE DISEASE 00:25:30

- MC cause of nephrotic Syndrome in Children (2-6yrs)

Immune dysfunction
↓
T-cell
↓
Podocytopathy
↓
Nephrotic syndrome
(Selective proteinuria)

- Immune dysfunction can be due to
  - RTI/Immunization/atopy
  - Hodgkin lymphoma
  - NSAIDs

Clinical features

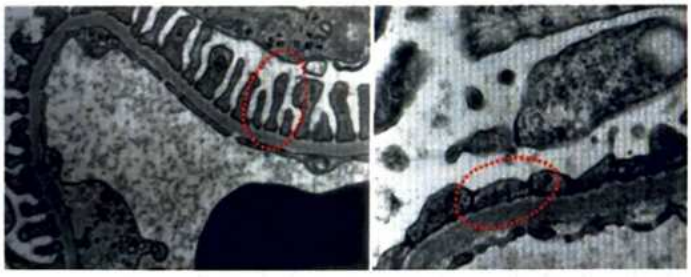
- Generalized edema
- Frothy urine

Diagnosis

- Urine

$$\frac{\text{urinary protein}}{\text{urine creatinine}}$$

  - 24hr urine sample
  - Oval Fat Bodies/Lipid Cast/Maltese cross can be present
- $S.C_3$ levels normal
- Renal Biopsy → most confirmatory test
  - LM: Normal
  - EM: Effacement of podocyte (Confirmatory)
  - IF: No I/C deposition (Nil Deposit Disease)



Normal Effacement of podocyte

- Presence of lipid in PCT cells → Lipoid Nephrosis

Treatment

- Steroids therapy → Excellent Response

Important Information

Congenital Nephrotic syndrome

- NPHS, gene mutation Nephrin
- Aka Finnish type NS
- No response to steroids

Previous Year's Questions

Q. Loss of foot process an electron microscopy is a classical feature in? (NEET Jan 2020)

A. Membranous nephropathy

B. Minimal change disease

C. IgA nephropathy

D. Rapidly progressive glomerulonephritis

MEMBRANOUS GLOMERULOPATHY 00:38:59

- MC cause of nephrotic Syndrome in Elderly

Etiology

- Idiopathic (MC)
- 2° causes
  - SLE
  - Hepatitis B/C, malaria, syphilis
  - Drugs: NSAIDS, Penicillamine
  - Cancers: solid cancer (melanoma/colon cancer/Breast Cancer)

Pathogenesis

HLA-DQA1
↓
Auto-Ab (IgG_4)
↓
Podocyte Ag (PLA_2R-M)
↓
I/C formation
↓
Podocytopathy

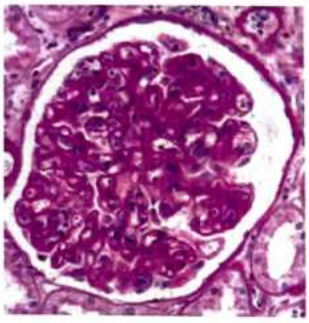
- Other podocyte Ag
  - THSP7A
  - NEP
- Heymann Nephritis → Rat kidney
  - Similar to membranous glomerulopathy in humans
  - Ab against Megalin

Clinical features

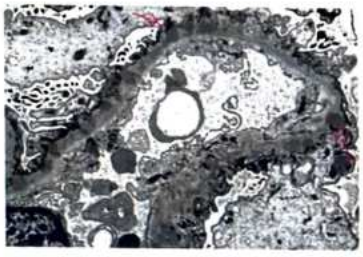
- Generalized Edema
- Excessive frothiness of urine
- Non-selective proteinuria
- ↑ Risk of DVT/RVT/PTE → nephrotic syndrome with maximum cause

Diagnosis

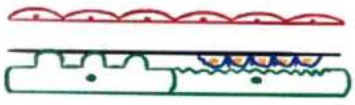
- Urine → urine protein: urine creatinine ratio
- Blood: PLA_2R Ab present → Prognostic factor
- Kidney Biopsy
  - LM: ↑↑ Thickness capillary BM
  - EM
    - → Effacement of podocytes
    - → Sub epithelial I/C deposits can be seen
  - IF → Granular appearance



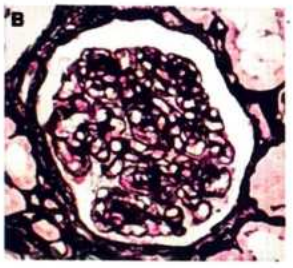
Thickened capillary wall



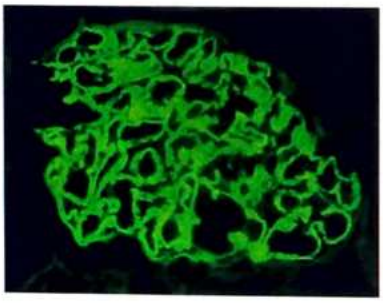
Subepithelial deposits



Spike-Dome appearance



Silver stain



Granular appearance

Treatment

- Steroids are not effective
- Poor prognosis
  - ↑ S.Creatinine
  - ↑↑ HTN
- Recurrence rate (40%) after renal transplant

Previous Year's Questions

Q. A patient has been diagnosed with a solid cancer of the bowel. He also experienced massive proteinuria after few months of initial diagnosis of cancer. Which of the following is a likely cause for development of the urinary finding? (FMGE Aug 2020)

A. focal segmental glomerulosclerosis

B. Minimal change disease

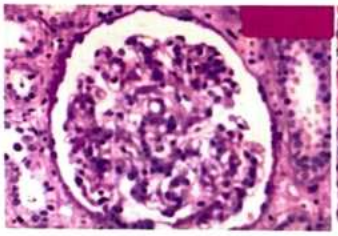
C. Membranous glomerulopathy

D. HPGN

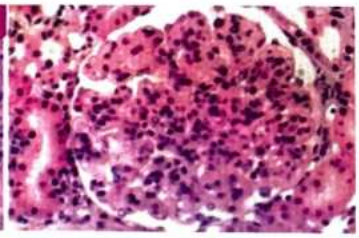
01:01:38

MEMBRANOPROLIFERATIVE GN (MPGN)

- Aka mesangiocapillary GN
- Mesangial cell proliferation + endo-capillary proliferation



Normal

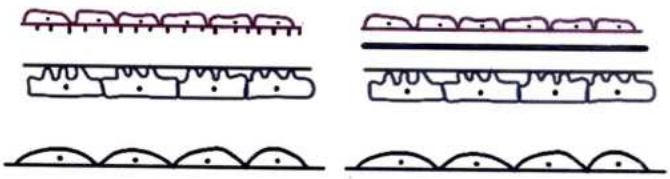


Lobular appearance

Etiology

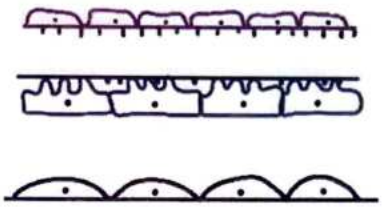
- 1°: Idiopathic
- 2° causes
  - Chronic I/C disorders (Malaria/Hepatitis B&C/IE/Cryoglobulinemia)
  - α_1 AT deficiency
  - Cancers (CLL, paraproteinemia)
  - Autoimmune Disorder (SLE, RA)

Traditional Classification



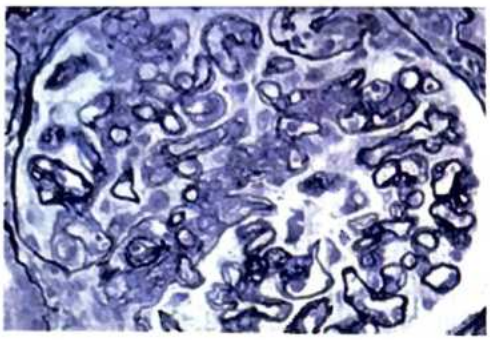
Subendothelial deposits

Dense deposits in BM



Subepithelial & sunepithelial deposits

- Double contour/tram track appearance can be seen in light microscopy & silver stain



Tram-track appearance

Current classification of MPGN (LM → IF → EM)

Ig⊕ MPGN (Ig/C_3⊕)	C_3 glomerulopathy (IgΘ; C_3⊕) → alternate pathway dysregulation Further subdivided into • C_3GN • Dense Deposit disease • CFHR (Complementary Factor H Regulatory gene defect)

↓

Classical/alternate complement pathway activation

↓

Deposition of C3/C1Q/C4 & Persistent hypocomplementemia

- EM: Sub-endothelial I/C
- Clinical features
  - Proteinuria
  - Hematuria
  - HTN
  - Fever/malaise

Dense Deposit disease

- C_3 involvement of mesangium in rings

Auto-Ab

↓

C_3NeF

↓

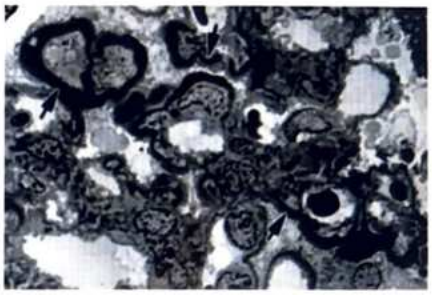
Alternate C_3 covertase

↓ +

C_3 → C_3b

(Persistent ↓C_3 levels)

- Associated with partial lipodystrophy
- Clinical features
  - Proteinuria >> hematuria
  - Nephrotic range
  - 10yrs → CKD
  - ↑ Rate of recurrence post-transplant
- EM: Ribbon like appearance

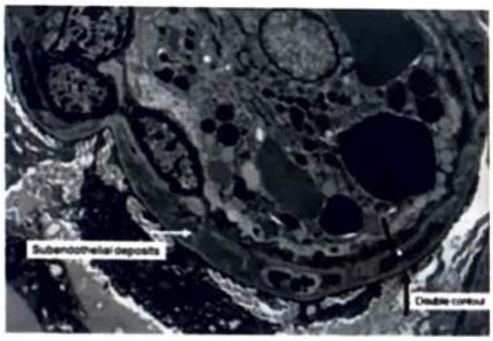


Ribbon like appearance

C_3GN

- Lighter electron dense material deposition
- Age: 30yrs
- Hematuria >> proteinuria

Refer Table 85.1



MPGN-Idiopathic

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

01:23:27

- Few glomeruli are involved
- Patchy involvement is seen

- MC cause of nephrotic syndrome among glomerular causes in adults

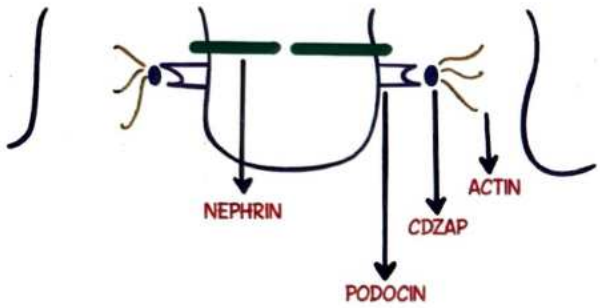
Etiology

- 1° → Idiopathic
- 2° causes
  - HIV/heroin/obesity/unilateral renal agenesis/sickle cell trait
  - HTN/reflux disease/IgA nephropathy
  - Inherited nephrotic syndrome

Important Information

- Polymorphism of $APOL_1$ gene → ↑ FSGS/Kidney failure & protection against trypanosome

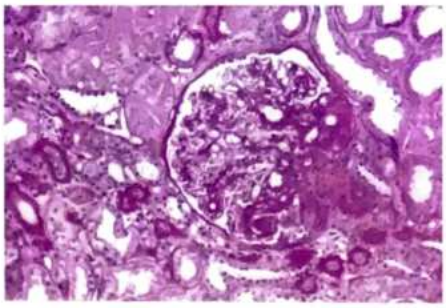
Pathogenesis



$NPHS_1$ gene mutation (13q)	$NPHS_2$ gene (1q)	α-actenin 4	TRPC-6
↓	↓	↓	↓
Nephrin	Podocin	AD FSGS (↑ renal failure)	Adult onset FSGS
↓	↓		
Congenital NS (Poor Prognosis)	AR FSGS (Childhood onset)		

Clinical features

- Non-selective Proteinuria
- ↑ HTN/Hematuria
- Renal failure in 10yrS

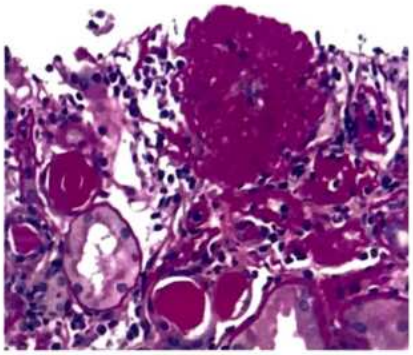


Hyalinosis

DIAGNOSIS

Renal Biopsy

- Cortico-medullary junction glomeruli are predominantly affected
- LM → Hyalinosis
- EM → Effacement of the podocytes
- IF → C_3 deposition



Collapsing variant

Variants of FSGS

- Glomerular tip variant → good prognosis
- Collapsing variant → Poor prognosis
  - Associated with HIV/SLE/Drugs (pamidronate)
  - Glomerular tuft collapses completely
  - Podocytes ↑ in size & number
  - Presence of Renal tubular Cysts
  - 2° causes → Tubulo-reticular inclusions (modified ER)
    → Produced by IFN-α action → seen in HIV/SLE

Treatment

- Poor response to steroids
- High chance of renal failure

INFECTIONS & GLOMERULAR LESIONS

HIV 01:37:46

- 50% of patients → HIVAN (HIV associated nephropathy)
- Collapsing Variant of FSGS
- No HTN/hematuria / ↑ lipids

- Active → HIVICK (HIV associated immune-complex disease)
- Treatment: anti-retro viral drugs, RAAS inhibitors

Other infections

- Syphilis: Associated with membranous glomerulopathy
- Hepatitis C: Cryoglobulinemic GN >> membranous glomerulopathy
- Hepatitis B carriers
  - Child: membrane GN
  - Adult: MPGN
- Malaria: MPGN
- Toxoplasmosis: MPGN

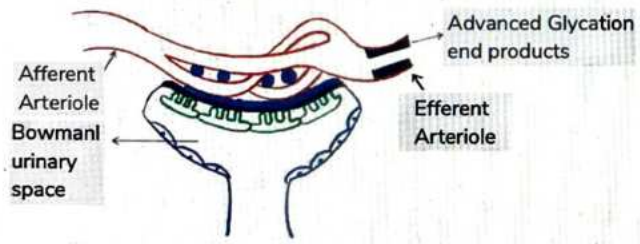
SYSTEMIC DISORDERS WITH NEPHROTIC SYNDROME

DIABETES MELLITUS

- MC systemic disease associated with nephrotic syndrome

Pathology

↑↑↑Glucose
↓
Non Enzymatic Glyosylation
↓
Advanced Glycation End Products
↓
Deposition in efferent vessels
↓
↑ Filtration Injury
↓
Nodular Glomerulosclerosis/Kimmelstein Wilson Lesion
↓
Diffuse Glomerulosclerosis
(↓ GFR)



- Nodular Glomerulosclerosis → most characteristic lesion
- DM is commonest cause of CKD globally
- Angiotensin II → Efferent vessel constriction
  - ACE Inhibitors
  - Angiotensin Receptor Blockers

Previous Year's Questions

Q. Most characteristic feature of diabetic nephropathy? (FMGE Dec 2018)
A. Kimmelstein Wilson change
B. Armani Ebstein Change
C. Focal segmental glomerulosclerosis
D Membranoproliferative glomerulonephritis

Renal Papillary Necrosis Causes

- DM (MC)
- Obstruction of urinary Tract
- Sickle cell disease
- Analgesics (↓ Pgs)

AMYLOIDOSIS

- 2° Amyloidosis affects Kidney
- Kidney → MC & most severely affected

Kidney
↓
Deposition at Mesangium
↓
Glomerular involvement
↓
Nephrotic Syndrome

SLE

- Associated with membranous glomerulopathy >>> MPGN
- Nephritic syndrome → diffuse proliferative GN (wire loop lesions)

Table 85.1

Ig ⊕ MPGN			C_3 Glomerulopathy
Polyclonal Pattern ⊕ ↓ Infection	Full House ↓ SLE	Monoclonal pattern ↓ Paraproteinemia	• **Alternate pathway** dysregulation • Eculizumab is used to treat these patients
If None ↓ Idiopathic MPGN Rx- Immunosuppressive Therapy			

86 RENAL STONE

Physiology
00:00:22

- In urine increased chances of precipitation of following substance
  - calcium
  - oxalate
  - Phosphate
  - Uric Acid
  - Drugs
- This precipitation is inhibited by following normally
  - citrate
  - osteopontin
  - Nephrocalcin
- Imbalance b/w precipitating factors & inhibitory factors lead to supersaturation of urine resulting in stone formation
- Other factors involved in stone formation
  - pH of urine
  - Hydration status
  - Certain infections

Clinical Features
00:02:14

- Abdominal pain – Flank [M/c]
- Renal colic [Hyperperistaltic ureteric muscle activity]
- Hematuria
- Stone pain radiates to
  - If stone is in upper 1/3rd of ureter
    - → Testicular tissue [in males]
    - → Labia majora [in females]
  - iliac fossa [if stone is present in middle 1/3rd]

Important Information

- Commonest cause of painful Hematuria in adults - Nephrolithiasis

  - groin region [if stone is present in lower 1/3rd]

Types of stones
00:05:18

Calcium oxalate stone - M/c kidney stone

- Radiopaque - can be seen early in X-ray
- pH independent

Causes

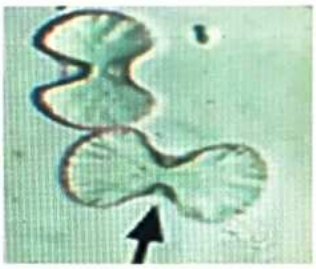
- Idiopathic Hypercalciuria [M/C/C]
- Hyperparathyroidism
- Hyperoxaluria

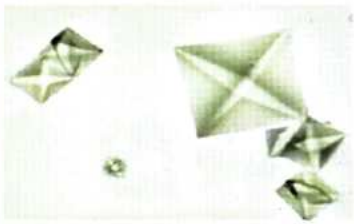
Randall plaque

- It is made up of $CaPO_4^{\circ}$; Calcium oxalate deposition occurs around it
- Present at tip of renal papillae

Appearance of calcium oxalate stone in urine

- Calcium oxalate monohydrate - Dumbbell shaped crystal
- Calcium oxalate dehydrate - Envelope / Bi-pyramidal shape





Important Information

- Poisoning associated with calcium oxalate stones – Ethylene glycol poisoning

Dumbbell shape Envelope / Bi-pyramidal shape

Previous Year's Questions

Q. The kidney stones whose development is seen most commonly is? (FMGE - Dec - 2017)

A. Calcium oxalate
B. Triple phosphate
C. Uric acid
D. Cysteine

Struvite Stone / Triple Stone 00:08:45

- Made up of magnesium, ammonium, phosphate
- Slow-growing stone
- Damages whole renal pelvis k/a Staghorn calculus
- Radiopaque
- Develops in alkaline pH
- A/w Proteus, Klebsiella Pneumoniae, Staphylococcus Saprophyticus urinary tract infection [pH is alkaline in these infections]
- In urine – coffin lid appearance

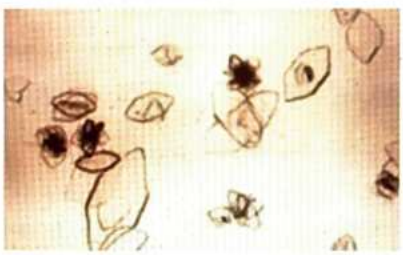
coffin lid appearance

Important Information

- Most of the stones are formed in acidic urine except Staghorn calculus
- Staghorn calculus – produced in alkaline urine and proteus involvement

Uric Acid stone 00:11:30

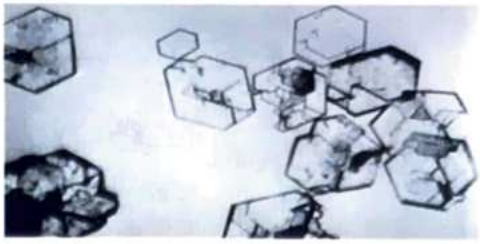
- A/w gout, Tumor Lysis Syndrome [anticancer drugs], Lesch-Nyhan Syndrome
- Develops in acidic pH
- Radiolucent
- Irregular in size



Uric Acid stone

Cystine stone 00:13:25

- A/w COLA disorders [Cystine, Ornithine, Lysine, Arginine]
- Cystine is dibasic component precipitate in urine when there is a defect in cystine transporter
- Children
- Formed in acidic urine
- Color change [green color] when come in contact with air
- Hexagonal shape (Benzene ring shape)



Cystine stone

Diagnosis of Nephrolithiasis 00:15:18

- NCCT scan [IOC] – Helical NCCT scan
- X-ray KUB cannot visualize 10% of stones containing uric acid stone
- Urine – Isomorphic RBC's – Kidney stones (MC) / tumors

Treatment 00:17:25

- NSAIDS to relieve pain
- Plenty of fluids
- Thiazide diuretics
- Surgery – Definitive treatment
  - < 2 cm - Exogenous shock wave Lithotripsy
  - > 2 cm - PCNL [Percutaneous Nephrolithotomy]

87 RENAL TUMORS

BENIGN TUMORS

Angiomyolipoma

- It can present with spontaneous hemorrhage
- Strongly associated with Tuberous Sclerosis
  - Epilepsy
  - Angiomyolipoma
  - Rhabdomyoma
  - Macules (shagreen patch)

Oncocytoma

- It consists of large eosinophilic cells with prominent mitochondria → Oncocytes

MALIGNANT TUMORS

RENAL CELL CARCINOMA (RCC) 00:03:23

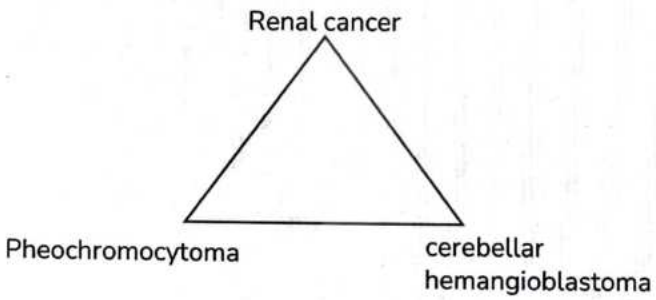
- Aka Hypernephroma / Grawitz Tumor
- Age of presentation: 6-7th decade
- Males > Female
- Upper pole of kidney is commonly involved

Risk Factors

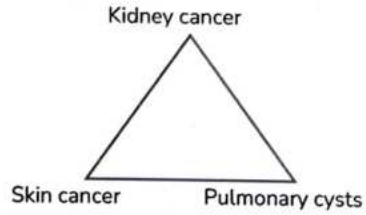
- Tobacco
- Asbestos
- HTN/Obesity
- Estrogen
- Sickle cell trait
- ESRD → Dialysis

Familial Variants

- VHL syndrome
  - VHL gene on chromosome 3p → ↓ HIF (Hypoxia Inducible factor)
  - VHL gene mutation → ↑ HIF → ↑ VGF → ↑ cancer



- Hereditary Leiomyomatosis + RCC → Fumarate Hydratase gene mutation
- Birt-Hogg Dube Syndrome



- Hereditary Papillary Cancer → MET gene mutation (proto-oncogene)

Previous Year's Questions

Q. Brit hogg dve syndrome is associated with increased risk of malignancy in which of the following organ? (JIPMER May 2018)

A. Stomach
B. Lung
C. Kidney
D. Ovaries

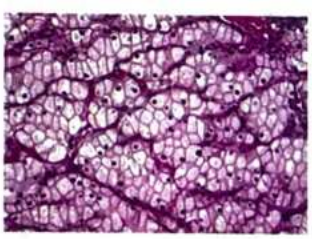
Clinical features

- Triad of RCC
  - Painless Hematuria
  - Palpable mass
  - Costo-vertebral pain
- Fever
- Weight loss
- Malaise
- Diagnosis: Renal Biopsy HPE

SUB TYPES

Clear Cell Cancer

- MC subtype
- It arises from proximal tubular cells
- Associated with VHL gene mutation
- Glycogen & lipids → clear cytoplasm in polygonal cells

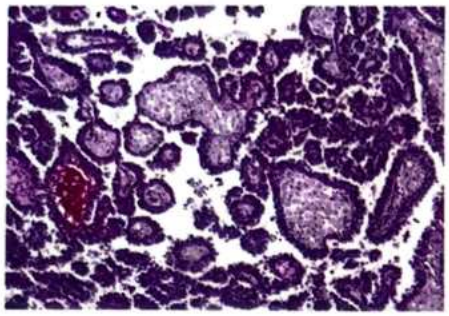


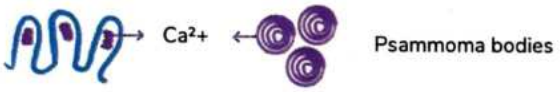
clear cytoplasm with granules

Polygonal cells

Papillary Cancer

- It arises from distal tubular cells
- Multifocal & B/L in nature
- Genetics: Trisomy 7/16/17
- Trisomy 7 → Sporadic & familial variants of papillary Cancer
- Presence of Papillae or finger-like projections → Ca^{2+} deposition (Psamomma body)





Papillae

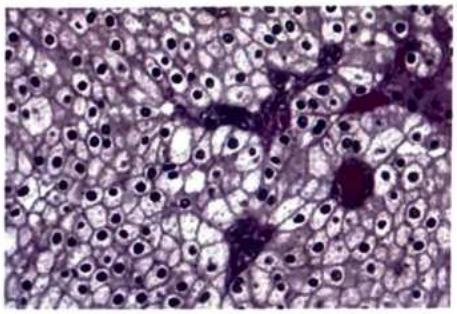
- It is associated with dialysis associated cystic disease

Previous Year's Questions

Q. Loss of Y chromosome is associated with which of the following renal cell carcinoma? (JIPMER Nov 2017)

A. Papillary
B. Chromophobe
C. Clear cell
D. Collecting duct carcinoma

Chromophobe Carcinoma



Perinuclear halo around tumor cell

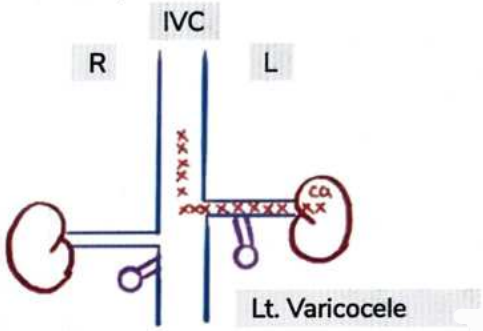
- Presence of peri-nuclear halo
- Associated with Hypoploidy/BHD Syndrome
- Best prognosis

Other variants

- Bellini Duct Carcinoma
  - It arises from collecting duct (medulla)
  - High degree of anaplasia is seen poor prognosis
- Medullary Carcinoma
  - Seen in patients with sickle cell trait
  - It arises from collecting duct
- XP 11 translocation cancer
  - TFE3 gene involved
  - Seen in young patients

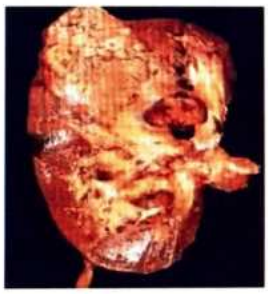
Metastasis

- Lungs (MC) > Bones > Liver > Adrenal gland
- RCC → Venous Spread

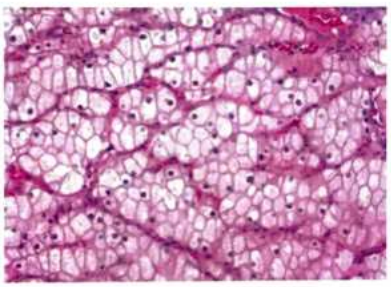


Paraneoplastic Syndrome

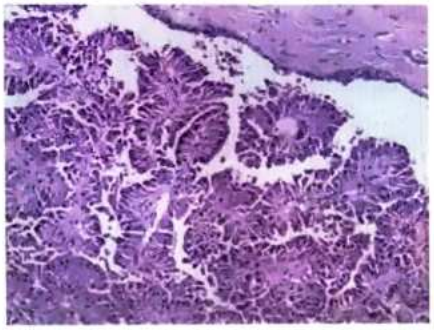
- ↑ESR
- Anemia
- Polycythemia
- ↑TLC → Leukemoid Reaction
- 2° Amyloidosis
- ↑Ca^{2+}/Feminization/masculinization
- Cushing syndrome
- Non-metastatic Hepatic dysfunction → Stauffer Syndrome



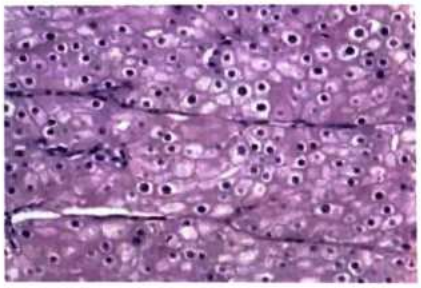
RCC



Clear cell variant of RCC

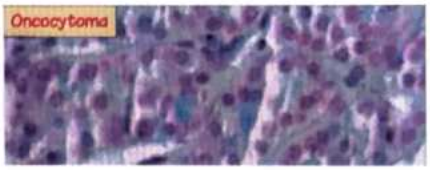


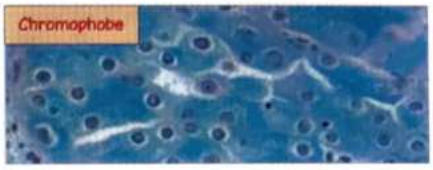
Papillary/chromophilic variant



Chromophobe variant

- Hale's colloidal iron stain → positive blue in cytoplasm of tumor cell
- CK7 positive
- Associated with BHD syndrome





CLINICAL QUESTIONS

1) A 45-year-old man presents with abdominal pain and hypertension. On physical examination, he is found to have an abdominal mass. Further workup confirms the diagnosis of adult polycystic kidney disease. Which of the following vascular complications is associated with this condition?

A. Arteriovenous fistula
B. Atherosclerotic aneurysm
C. Berry aneurysm
D. Luetic aneurysm

Solution:

- **Berry aneurysms,**
  - Occur in patients with adult polycystic kidney disease,
  - Small **saccular** lesions that develop at the site of congenital weakness of cerebral arteries, especially those of the **circle of Willis.**
  - Rupture of these aneurysms is the most common cause of **subarachnoid hemorrhage**.
  - **Arteriovenous fistulas** are often secondary to **trauma.**
  - **Dissecting aneurysm** is associated with hypertension or with diseases affecting the vascular media, most notably **Marfan syndrome.**
  - **Syphilitic (luetic) aneurysm** is associated with **tertiary syphilis.**

Reference:

- Robbin's 10th Ed./page-943

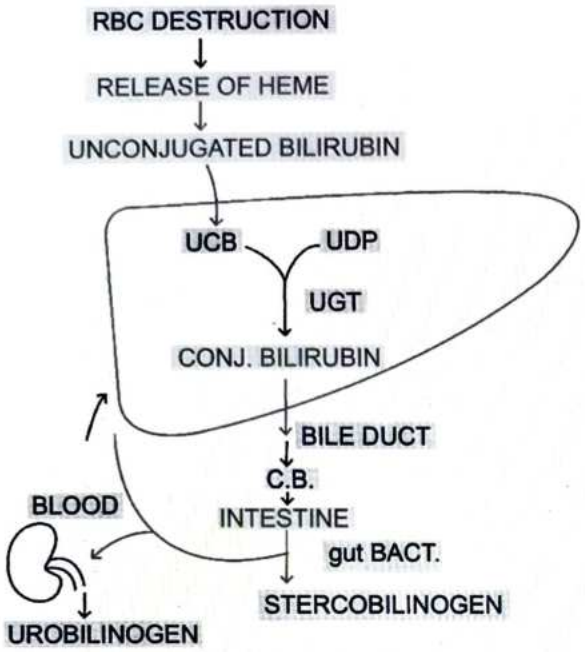
LEARNING OBJECTIVES

UNIT 16 LIVER, BILIARY SYSTEM & PANCREAS

- **Liver Disorders Part 1**
  - Conjugated Hyperbilirubinemia
  - Biliary tract disorders: Primary biliary Cholangitis
  - Primary sclerosing cholangitis
  - Cirrhosis
  - Alcoholic liver disease
  - Non-alcoholic fatty liver disease
  - Hepatitis
  - Hemochromatosis
  - Wilson's disease

- **Liver Disorders Part 2**
  - Benign Hepatic Tumors
  - Molecular Subtypes Of Hepatic Adenoma
  - Primary Malignant Tumors
  - Hepatocellulr Carcinoma /Hepatoma
  - Clinical features Of HCC
  - Fibrolamellar Variant of HCC

88 LIVER DISORDERS 1



- Jaundice: Bilirubin >2.5mg/dl
- Jaundice is examined at the level of sclera and mucous membrane → Bilirubin has ↑ affinity for elastin fibers
- Drug producing jaundice → Quinacrine (earlier used anti-malarial drug)

Important Information

- ↑ β-Carotene (in carrot) → Carotenoderma → yellowish discoloration seen only in skin and not in the sclera

Van den Bergh Test

- Normal bilirubin level: 0.1 – 1mg/dL
- Unconjugated Hyperbilirubinemia → UCB → >85% of TB
- Conjugated Hyperbilirubinemia (Direct) → CB → >15% of TB

UNCONJUGATED HYPERBILIRUBINEMIA

- ↑ RBC destruction
  - Hemolytic anemia, Hemorrhage, Ineffective Erythropoiesis (seen in pernicious anemia & thalassemia)
- Liver Immaturity
  - New Born → physiological jaundice (appears on 2nd day of life)
  - Breast feed → caused by presence of Pregnandiol/ β Glucoronidase
- ↓ UGT activity → Genetic Defects, Hepatocellular Disease

Genetic defects

- Gilbert Syndrome
  - ↓ Activity of UgT_1A_1 (25-30%)
  - No symptoms in childhood
  - Young Adult with Stress → Jaundice
  - Promoter region mutation → AR
  - 2Missense Mutation → AD
- Criggler Najjar Syndrome: ↓ Activity of UgT_1A_1 (AR condition)
  - Type 1 → no activity of UgT enzyme
    → ↑ UCB (Lipid soluble) → Crosses Blood-brain barrier → deposits in basal ganglia (kernicterus) → fatal
  - Type 2 → ↓ activity of enzyme
    → Enzyme inducer: Phenobarbitone → stimulate enzyme activity
    → Phototherapy: UCB → Lumirubin (water soluble) → excreted in urine

CONJUGATED HYPERBILIRUBINEMIA 00:16:09

Clinical features

- Jaundice
- Pruritus
- Dark colored Urine
- Clay colored stools
- Malabsorption → Steatorrhea

Causes

- Bile Duct Obstruction
  - Stones
  - Infections (clonorchis/Opisthorchis)
  - Cancer (in elderly patients)
- Biliary Tract Disease
  - Primary Biliary cholangitis
  - Primary Sclerosing cholangitis

Genetic Disease

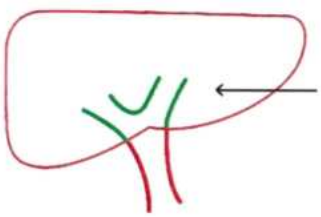
- Dubin-Johnson Syndrome
  - AR condition
  - Defect in MRP-2 (multiple drug resistance protein) → ↓ CB excretion
  - Hepatomegaly
  - Black/Dark pigmented liver → accumulation Epinephrine
- Rotor Syndrome
  - AR condition
  - Normal Liver, no pigmentation
  - Defect in Organic Anion Transporter (OAT B_1/B_3)

Enlarged, Black pigmented liver

BILIARY TRACT DISORDERS

00:20:56

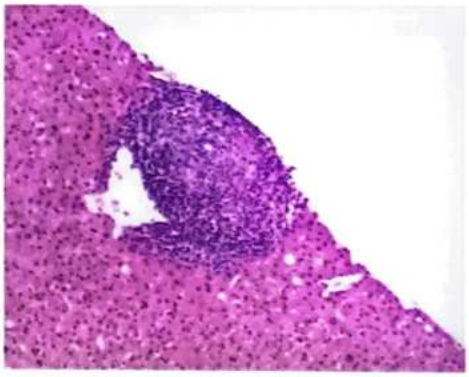
1° BILIARY CHOLANGITIS



- Small/medium intrahepatic bile duct → Granulomatous destruction
- Female >> Male
- Age of presentation: 50yrs
- Anti-mitochondrial antibody (AMA) → E_2-PD Complex (Pyruvate Dehydrogenase)
- Co-existence with Sjogren Syndrome is seen
- Long standing disease → ↑ cirrhosis/cancer

Diagnosis

- Liver biopsy
  - Florid Duct Lesion: Lymphocytic/plasmacytic infiltration in small/medium sized bile ducts +/- Granuloma



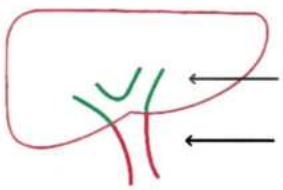
Florid duct lesion

Treatment

- Ursodeoxycholic acid
- Definitive treatment: Liver Transplant

1° SCLEROSING CHOLANGITIS

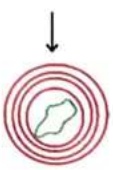
00:24:40



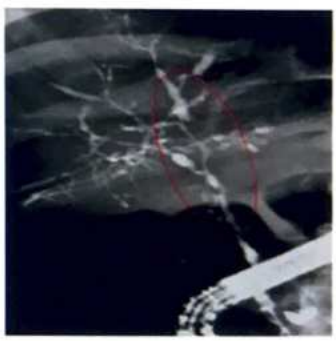
- Involvement of both intra-hepatic and extra-hepatic ducts is seen
- Male >>> female
- Age of presentation: 30yrs
- P-ANCA antibody produced against Nuclear envelop protein
- Associated with IBD (Ulcerative colitis)
- ↑ cirrhosis/cancer risk

Diagnosis

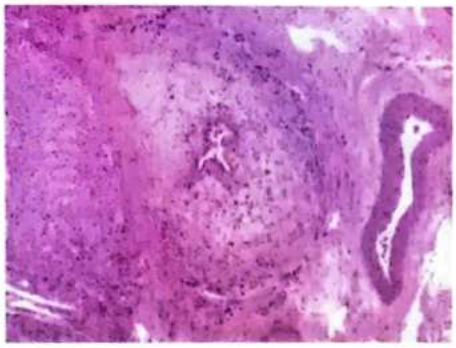
- Radiology: Bead like Appearance on cholangiogram
- Biopsy: concentric fibrosis in bile duct → "onion-skin periductal fibrosis"



ONION SKIN APPEARANCE



Beaded appearance



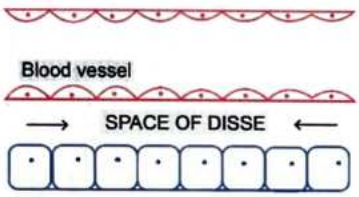
Periductal "onion-skin" fibrosis

Treatment
- Cholestyramine (Bile acid binding agent)
- Definitive treatment: Liver Transplant

CIRRHOSIS

00:31:38

- Characterized by 3 changes
  - Damage to liver parenchyma
  - Presence of bridging fibrous septa
  - Regeneration of Parenchymal nodules



- Space of Disse: Contains stellate/Ito cell required for metabolism of nutrients like vitamin A
- Ito cell → TGF-β → Myofibroblast
- On myofibroblast contraction
  - ↓ Blood flow → ischemia
  - Hampered exchange of substances

Etiological factors
- Alcohol (MC)
- Non-alcoholic fatty liver disease
- Hepatitis
- Metabolic disorders

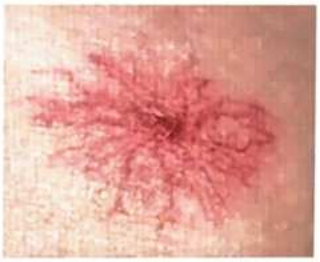
FEATURES

Portal HTN
- Congestive splenomegaly
- Ascites
- Opening of Porto-Systemic shunts
  - Esophageal varices → hematemesis
  - Hemorrhoids
  - Caput medusae

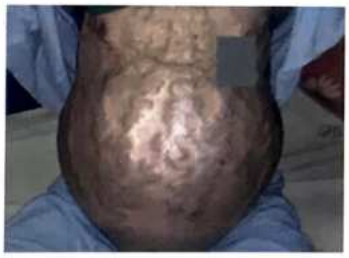
↓ Protein Synthesis
- ↓ Albumin → Ascites
- ↓ Clotting factors → ↑ Bleeding, ↑ PT, ↑ aPTT
- ↑ γ-globulins

↓ Metabolism
- ↑↑ Estrogen
  - Palmar erythema, Gynecomastia, gonadal atrophy, Spider-angioma
- ↑ NH3
  - In PNS, it can interfere with Neurotransmitter activity → Asterixis / Flapping tremors due to ↑ NH_3 levels
  - In CNS, it can lead to altered/reduced level of consciousness → Hepatic Encephalopathy

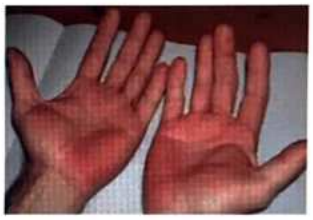
- Hepato-Renal & Hepato-Pulmonary Syndrome



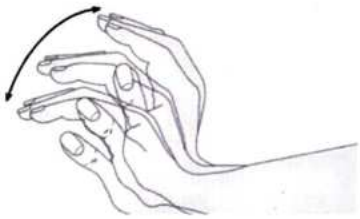
Spider angioma



Caput Medusae



Palmar erythema



Asterixis

Previous Year's Questions

Q. Which of the following is true about nodular regenerative hyperplasia? (JIPMER Nov 2018)
A. Nodule size 0.1 to 1cm
B. Fibrosis septa present
C. Portal hypertension seen in 50% of patients
D. AST and ALT are markedly elevated

ALCOHOLIC LIVER DISEASE

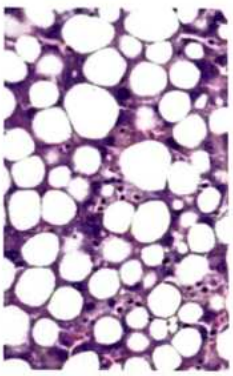
00:48:06

- MC cause of Cirrhosis worldwide
- Alcohol can cause
  - Fatty changes (steatosis)
  - Hepatitis (steato-hepatitis)
- Female >>> male
- Daily threshold: 80g of alcohol/day
- ↑ ALT, ↑↑↑ AST, AST/ALT > 2

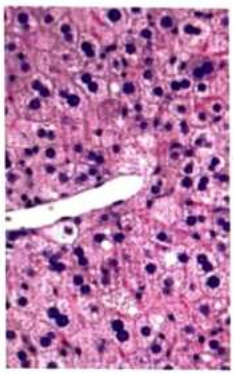
STAGES

Alcoholic Steatosis

- Fatty change inside the liver cell
- Reversible stage Liver accumulation of fat **droplets in** hepatocytes
- Aka fat droplets → micro/macro-vesicular **steatosis**
- Microvascular steatosis
  - Reye Syndrome
  - Acute fatty liver **of pregnancy**
  - Chronic viral hepatitis
  - Drugs: sodium valproate, **tetracyclines**
- Macro-vascular steatosis
  - ALD
  - Jejuno-ileal bypass
  - DM; Lipodystrophy
  - **Total parenteral nutrition**



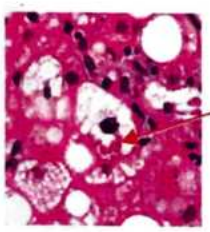
Macrovesicular fatty change

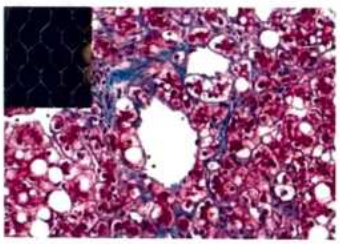


Microvascular fatty change

Alcoholic steato-hepatitis

- AST/ALT >2
- H/O Binge Drinking
- Associated with development of Peri-venular Fibrosis/chicken wire fibrosis
- Deposition of Cytokeratin 8/18 filaments → Mallory Denk Body
- Mallory Denk **Body** is not seen in 2° Biliary cirrhosis & Hemochromatosis





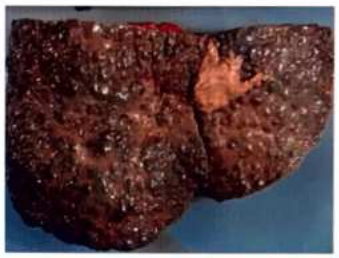
Chicken wire fibrosis

Important Information

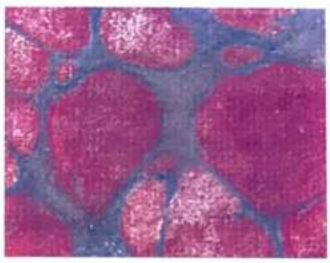
- Mallory Denk Body is also seen in
  - NAFLD
  - Indian childhood cirrhosis
  - Wilson's disease
  - Alcoholic liver disease, α_1-AT Deficiency
  - Tumors
  - Cholestasis (PBC)
  - Focal nodular hyperplasia

Alcoholic Liver Cirrhosis

- Aka Laennec Cirrhosis → fibrotic change on surface of the liver
- Nodular appearance of the liver
- Masson trichrome stain is used to pick collagen deposition



Laennec cirrhosis



Regenerating island of hepatocytes

NON-ALCOHOLIC FATTY LIVER DISEASE

01:04:29

- Idiopathic

Risk Factors

- Obesity
- Hyperlipidemia
- Insulin Resistance
- Diagnosis of Exclusion
- MC cause of Death: cardiovascular cause

Diagnosis

- AST/ALT < 2
- NAFLD → Non-alcoholic steato-hepatitis → Non-alcoholic liver cirrhosis (cryptogenic cirrhosis)
- Cryptogenic cirrhosis: NAFLD + AIH → some patients respond to steroids
- Microscopic appearance is similar to ALD

HEPATITIS

01:08:25

- HEPATITIS A → Acute liver disease
- HEPATITIS B, HEPATITIS C, HEPATITIS D } Acute/chronic liver disease

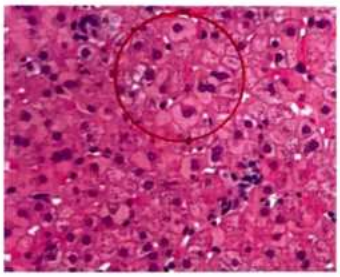
- HEPATITIS E → Acute liver disease

Hepatitis A
- Transmitted by Feco-Oral Route
- MC cause of Hepatitis in children

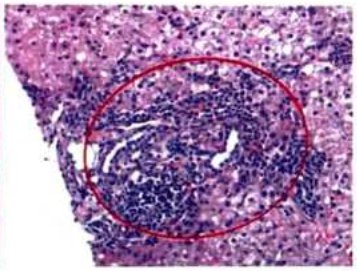
Hepatitis E
- Transmitted by Feco-Oral Route
- MC cause of Hepatitis in adults
- Fast progressing disease in pregnant female → high mortality
- MC cause of sporadic acute hepatitis in adults

Hepatitis B
- Can cause acute/chronic liver disease
- MC cause of hepatitis in patient with the H/O blood transfusion
- ↑ Chance of developing carrier state
- ↑ Risk of hepatocellular carcinoma
- HBs → Ground glass appearance
- HBc → Sanded nuclei
- HBe → Correlated with degree of infection

Hepatitis C
- Can cause acute/chronic liver disease
- Microscopic feature: focal fatty change (Hep C > Hep B)
- ↑ Chance of developing chronicity & cirrhosis



Ground glass appearance



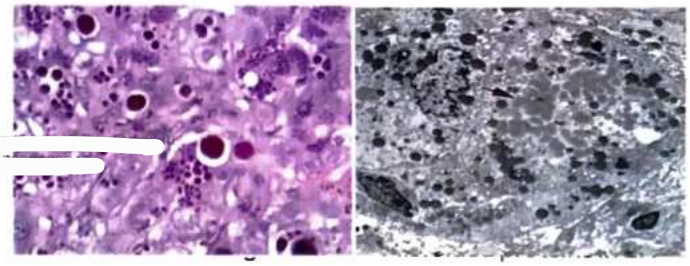
Periportal lymphocyte infiltration

Hepatitis D
- It is a defective virus
- Cannot produce infection alone, it requires Hepatitis B to cause chronic disease

Diagnosis
- ALT/AST > 2

A_1-ANTI TRYPSIN DEFICIENCY
- AR condition
- Genes for this condition are present on Chromosome 14

- In normal person → PIMM allele
- Abnormal (PIMZ/PIZZ) allele → misfolding of protein → cirrhosis & pan-acinar emphysema
- Predominantly symptoms are seen in PIZZ >>> PIMZ



Microscopic appearance
- PAS +ve, Diastase Resistant granules
- Mallory Denk Bodies

Previous Year's Questions

Q. α l- antitrypsin deficiency chromosome is located at? (JIPMER – Nov - 2017)

A. 10
B. 14
C. 17
D. 11

HEMOCHROMATOSIS
- Iron overload condition → free radical injury 01:21:32
- Hepcidin → negative iron Regulatory protein
- Hepcidin activity is influenced by HFE/HJV gene
- Can be primary or secondary

1°
- HFE gene defect on chromosome 6p
- HJV gene defect on chromosome 21
- Both the conditions lead to ↑ iron absorption

2°
- H/O repeated blood transfusions
- Africans (Bantu Tribe → iron utensil usage for cooking)
- Iron overload due to 2° cause → Hemosiderosis

Clinical features

Cirrhosis

Skin — Pancreas

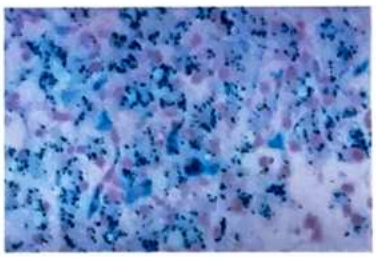
↓ Melanin + DM → Bronze Diabetes

- HPA axis dysfunction → ↓ gonadal function (Testicular atrophy)

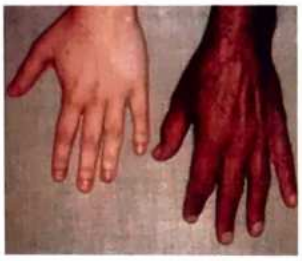
- Accumulation of crystals in joint → Pseudogout
- Cardiac: Restrictive cardiomyopathy → ↑ mortality

Diagnosis

- Fe profile
  - ↑↑ S. Iron
  - ↑↑↑ % TF Saturation
  - ↑↑ S. Ferritin
  - ↓↓ Total Iron binding capacity
- Liver Biopsy → confirmatory test
  - Prussian Blue Stain used → Bluish violet granules (Pearls Reaction)



Prussian Blue Stain



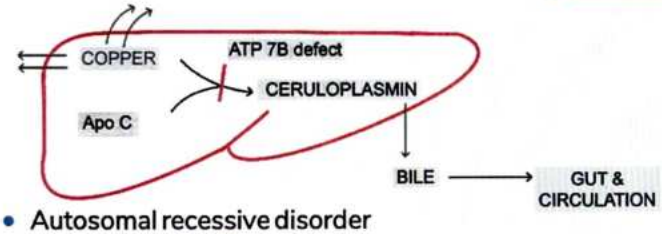
Hyperpigmentation

Treatment

- Iron chelators
- Phlebotomy

WILSON'S DISEASE

01:29:35



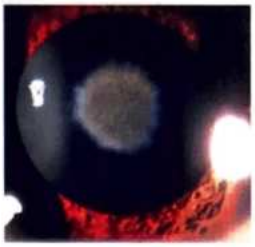
- Autosomal recessive disorder
- Genetics: ATP-7B gene defect (located on chromosome 13)

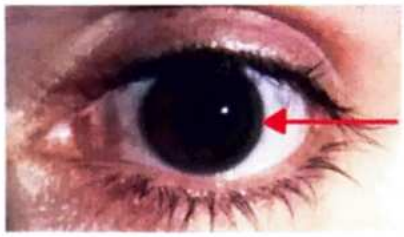
Clinical features

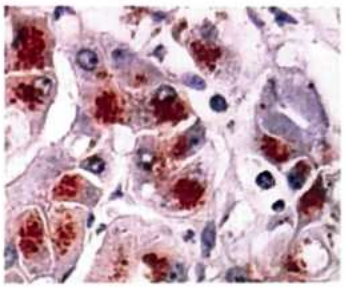
- Liver: Cirrhosis
- CNS
  - Parkinsonism
  - Alzheimer type 2 cells are seen
- Ocular
  - Sunflower cataract
  - DM membrane → KF ring

Diagnosis

- S.Copper levels → unreliable
- Urinary Copper (screening test)
- Liver exam: Copper level in dried Liver → >250 µg/g (confirmatory)
- Copper is seen with help of Rhodanine stain
- Treatment: Zinc administration → improves symptoms



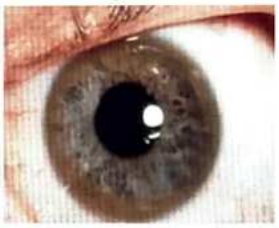




Rhodanine stain

Previous Year's Questions

Q. Comment on diagnosis? (FMGE Dec 2020)



A. NF-I
B. Arcus Senilis
C. Wilson disease
D Myotonic dystrophy

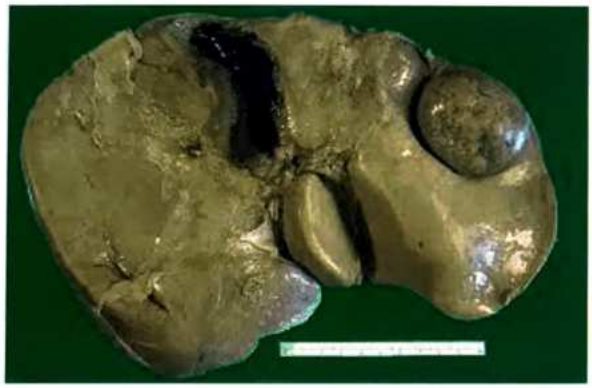
89 LIVER DISORDERS 2

BENIGN HEPATIC TUMORS

- Cavernous Hemangioma: MC benign tumor of liver

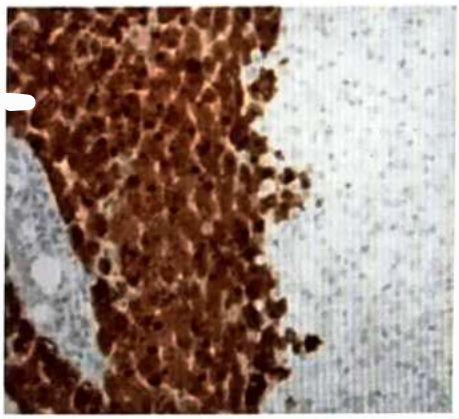
HEPATIC ADENOMA

- Female >>> Male
- Female with H/O OCP intake & Males with H/O intake of anabolic steroids
- In female → sudden ↑ size of tumor → abdominal pain
- During pregnancy, ↑ estrogen → ↑ size → rupture → abdominal hemorrhage

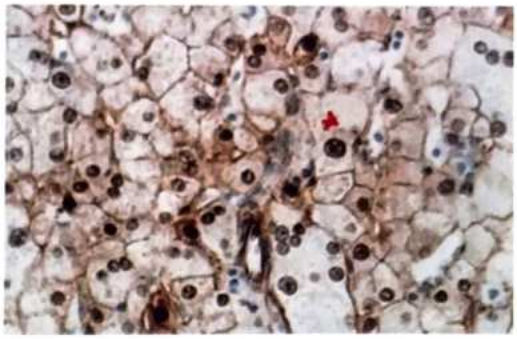


Hepatic adenoma

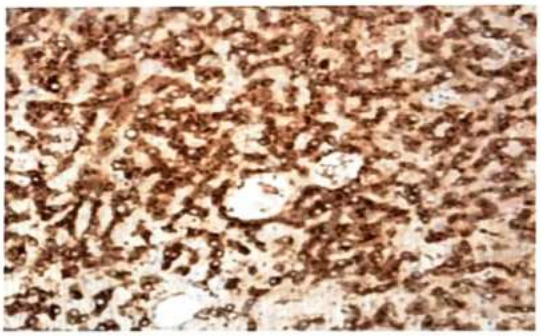
Molecular Subtypes of Hepatic Adenoma 00:03:12



- HNF-1α Inactivation
  - ↓ Liver Fatty Acid Binding protein expression (LFABP)
  - Seen in females
  - No atypia → lowest risk of progression to HCC
  - Also associated with MODY3



- β-catenin activation
  - Male = female
  - Subtype with maximum cellular atypia → ↑ risk of HCC
  - Most dangerous

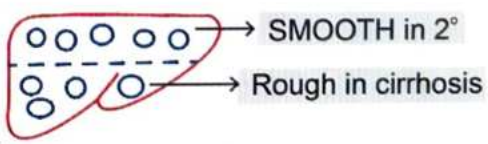


- Inflammatory Adenoma
  - MC molecular subtype
  - Activating mutation of IL-6 receptor → Co-receptor: gp130
  - ↑ CRP, ↑ SAA
  - Associated with NAFLD
  - 10% of patients have β-catenin activation → cancer

MALIGNANT HEPATIC TUMOR

Metastasis

- Metastatic tumor are more common than primary tumor
- MC cause of hepatic metastasis: Colon Cancer >>> Pancreatic/breast/lung Cancer
- ↑ size of the liver is seen



Important Information

- Nodules with intervening smooth area is suggestive of hepatic metastasis
- Nodules without any smooth area is seen in cirrhosis

PRIMARY MALIGNANT TUMORS 00:10:30

Hepatoblastoma

- MC primary malignant liver tumor in children (< 3yr)
- WNT pathway activation
- Associated with FAP (colon cancer) & Beckwith Wiedmann syndrome (Wilm's tumor)
- Treatment: surgery + chemotherapy
- Prognosis better than HCC

Angiosarcoma

- Uncommon tumor
- Risk Factors
  - Thorotrast
  - Arsenic
  - Poly vinyl chloride
- IHC marker: Factor VIII +ve

HEPATOCELLULR CARCINOMA / HEPATOMA 00:14:01

- MC 1° malignant liver tumor in adults

Risk factors

- Chronic Hepatitis
  - Hepatitis B (most important) → Family history of HCC/ ↑ viral load/ ↑↑ HBeAg/ Genotype C
  - Hepatitis C → associated with Genotype 1b
- Cirrhosis
- Alcohol: works in synergism with Hepatitis B/C & Smoking
- Aflatoxin: caused by aspergillus flavus infected Peanuts + Hepatitis B
- NAFLD: metabolic syndrome
- Metabolic Disorder
  - Hemochromatosis
  - α_1 AT deficiency
  - Wilson Disease
  - Hereditary Tyrosinemia
  - Autoimmune Hepatitis
- Endemic areas: 20-40yrs/50% cirrhosis/hepatitis B
- Western countries: >60yrs / 90 % after cirrhosis / hepatitis C Epidemic

Molecular Pathogenesis

- Telomerase stability (90%); TERT promoter: ↑ activity by hepatitis B infection
- β catenin activation (40%): ↑ replication of cells. Seen in association with hepatitis C, Alcohol
- p53 gene inactivation (60%): associated Aflatoxin exposure & Hepatitis B

Role of inflammation

$$CLD \xrightarrow{IL\text{-}6} Regeneration$$

- ↑ IL6 is responsible for
  - ↑ Proliferation of hepatocytes
  - ↓ Differentiation of liver cells

Precursor Lesions of HCC

- Cellular Dysplasia
  - Small cell change: N:C ↑↑↑ → ↑ risk of HCC
  - Large cell change: N:C ratio unaffected → Hepatitis B infection → ↑ risk of HCC
- Adenoma → β-catenin activation
- Dysplastic module
  - Low grade, lesser risk of cancer
  - High Grade, higher risk of cancer

Clinical features 00:27:21

- RUQ abdominal pain/discomfort (MC)
- Weight loss
- Malaise
- Male > female
- Hepatomegaly

Diagnosis

- IOC → Radiological
  - USG
  - 4 phase Multi-detector CT scan → Arterial hypervascularity + venous washout
- Biopsy is not gold standard
  - 3% risk of tumor seeding/bleeding
- Tumor Markers
  - AFP ↑↑↑ (non-specific)
  - Arginase-3 (Best tumor marker) → most Sensitive & Specific
  - Hep-par 1
  - Glypican – 3

Previous Year's Questions

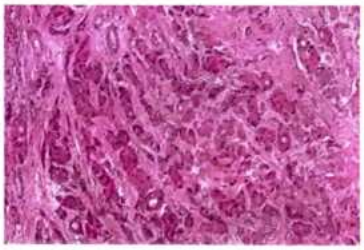
Q. AFP is raised in? (FMGE Jun 2018)
A. Renal carcinoma
B. Pancreatic carcinoma
C. Prostatic carcinoma
D. Hepatic carcinoma

Metastasis of HCC

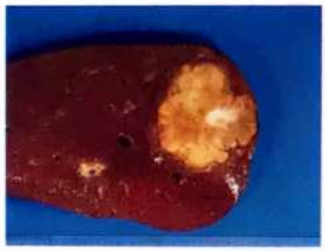
- Spread: Angioinvasive >> lymphatic route
- Angioinvasive
  - Intrahepatic Metastasis: involvement of portal vessels
  - Extrahepatic Metastasis: Lungs (MC site)/Right side of heart

Fibrolamellar Variant of HCC 00:34:01

- Young adults (20-40yrs)
- Male = Female (In India: F >> M)
- No association with Chronic Hepatitis/cirrhosis
- Preferential involvement of left lobe of liver
- AFP levels are normal
- Marker: Neurotensin
- Less growth: better prognosis
- Microscopic appearance: oncocytes + dense collagenous bands
- Presence of PRKACA-DNAJB$_1$ fusion oncogene is seen



Deposition of collagenous bands



Left lobe involvement

Treatment

- Sorafenib
- Liver transplantation

CLINICAL QUESTIONS

A 55-year-old man who is chronic alcoholic died after having an illness characterized by ascites, increasing jaundice, , and generalized wasting. Laboratory testing revealed hyperbilirubinemia, hypoalbuminemia, and mildly elevated liver enzymes. The appearance of the liver at autopsy is shown in the figure. The most likely diagnosis is

A. alpha 1-antitrypsin deficiency
B. Cirrhosis
C. Hepatitis A
D. Hepatitis C

Solution:

- Image shows the typical appearance of micronodular cirrhosis,
- Its most common cause is chronic alcoholism.
- Major clinical manifestations:
  - Jaundice
  - Ascites
  - Signs of hyperestrinism (palmar erythema, spider telangiectasia, gynecomastia, testicular atrophy)
  - Consequences of increased portal venous pressure (esophageal varices, distended abdominal

Reference:

- Robbins 10th ed pg 828-29

LEARNING OBJECTIVES

UNIT 17 GENITAL SYSTEM

- **Male Genital Tract Disorders Part 1**
  - Cryptorchidism
  - Orchitis
  - Testicular Tumors
  - Risk Factors For Gc Tumor
  - Seminoma
  - NSGCT
  - Choriocarcinoma
  - Non - Germ Cell Tumors

- **Male Genital Tract Disorders Part 2**
  - Prostate
  - Prostatitis
  - Benign Hyperplasia Of Prostate
  - Carcinoma Prostate

- **Female Genital Tract Disorders Part 1**
  - Cervical Intra Epithelial Neoplasia
  - Bethesda Classification
  - Cervical Cancer
  - Vagina

- **Female Genital Tract Disorders Part 2**
  - Endometrial Disorders
  - Endometrial Carcinoma
  - Myometrial Disorders
  - Leiomyosarcoma

- **Female Genital Tract Disorders Part 3**
  - Risk Factors Of Ovarian Tumors
  - Surface Epithelial Tumors
  - Mucinous Tumor
  - Serous Tumors
  - Endometroid Tumor
  - Teratoma
  - Ovarian Choriocarcinoma
  - Sex Cord Stromal Tumors
  - Gonadoblastoma / Mixed Tumor

90 MALE GENITAL TRACT DISORDERS 1

CRYPTORCHIDISM

00:00:33

- MC genito-urinary disorder in male child
- Failure of testicular descent (Right > Left)
  - Abdominal phase: Due to Mullerian Inhibitory Substances
  - Inguinal phase: Due to androgens working through genitofemoral nerve associated with release of C-GRP
- Failure of testicular tissue descent → exposed to routine body temperature
- Earliest microscopic change: BM thickened (spermatic tubules)
- Leydig cells are spared; atrophy
- Commonest site of undescended testis: Inguinal canal
- Incidental finding of empty scrotal sac

Complications

- Testicular Atrophy → ↓ Fertility
- Tumor (MC: Seminoma)
- Testicular Torsion

Treatment

- Surgical management: Orchiopexy done by 6 months - 2 years (no histological changes)

Important Information

- Orchiopexy done after histological/mutational changes → ineffective & still has ↑ risk of tumor

ORCHITIS

00:06:48

- Inflammation of testis + Epididymis

Causes

- E.Coli
- Chlamydia
- Mumps
  - Unvaccinated individuals
  - Involves testis, parotid salivary gland & pancreas
- TB
  - Inflammation of epididymis → inflammation of testis
  - Granulomatous orchitis & Presence of caseous necrosis
  - Granuloma can also be seen in autoimmune orchitis
    - → Painless testicular enlargement (MC symptom of malignancy)
    - → Testis is only involved
    - → No caseous necrosis
- Syphilis
  - Inflammation of testis → inflammation of epididymis

Features	Orchitis	Torsion
Scrotum elevation	↓↓ Pain	↑↑ Pain (Prehn sign)
Cremasteric reflex	+	-

TESTICULAR TUMORS

00:14:29

- Adult age group
- Clinical feature: Painless enlargement of testes
- Spread
  - Lymphatic → LN → Para aortic LN
  - Hematogenous Spread
    - → MC organ involved: Lungs >>> CNS/Liver/ Bones
- Biopsy is contraindicated (can cause dissemination of tumor cells)
- Testicular tissue is preserved in Bousin's fluid
- Germ cell tumor (95%) & Non-germ cell tumor

RISK FACTORS FOR GC TUMOR

00:18:53

Environmental factor

- Testicular Dysgenesis syndrome
  - Cryptorchidism (MC), Hypospadias, poor sperm quality
  - Associated with exposure to pesticides, non-steroidal estrogen

Genetic Defects

- KiT, BAK mutation
- Iso-chromosome 12p
  - Significance: conversion of Germ cell neoplasia in-situ (pre-invasive) → invasive cancer
- Klinefelter syndrome (↑ risk of mediastinal GC tumor)
- NANOG, OCT 3/4 transcription factor hyperactivity → ↑ cell proliferation

PATHOGENESIS

Cryptorchidism

Environmental factors

Germline variants

KiT

Primordial GC → Arrested Diff → GCN in-situ —Puberty/i12p, 7 years→ Invasive GCT

Classification of Testicular Tumors (WHO 2016)

Refer Table 90.1

- Germ cell tumors in without pre-invasive stage/ ITGCN
  - Spermatocytic seminoma
  - Pre pubertal Teratoma
  - Pre-pubertal Yolk sac tumor

SEMINOMA

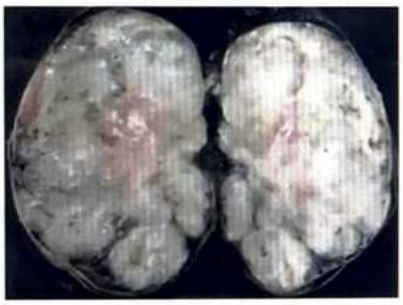
00:29:57

Variants

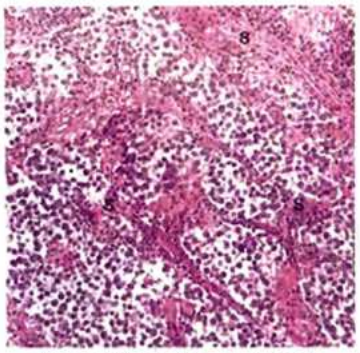
- Classical
- Anaplastic
- Spermatocytic

CLASSICAL SEMINOMA

- MC testicular tumor in adults
- It is a malignant tumor
- ↑↑ Expression of OCT3/4, NANOg, C- KIT
- Counter parts
  - Dysgerminoma (ovary)
  - Germinoma (Pineal gland)
- Tumor markers: PLAP / LDH/ β HCG
- Radio sensitive → Good prognosis
- Anaplastic Seminoma: Anaplasia & mitosis present



Grey white tumor



Round/Polyhhedral cells

Gross Features

- Grey white tumor
- Homogenous fleshy mass
- No hemorrhage or necrosis

Microscopic Features

- Sheets of round / polyhedral cells with watery/glassy cytoplasm (glycogen) with prominent nucleoli
- Lymphocytic infiltration in stroma

Previous Year's Questions

Q. Which of the following is the likely diagnosis in a 40 years old male with testicular tumor positive for PLAP and C-KIT? (JIPMER - Dec - 2019)

A. Seminoma
B. Teratoma
C. Embryonal cell tumor
D. Yolk sac tumor

SPERMATOCYTIC SEMINOMA

- Affects Elderly & has excellent prognosis
- Genetic defect: 9q gain of function
- No LN metastasis/ no i12p/no ITGN associations

Microscopic Features

- 3 types of cells
  - Small cells (2° spermatocytes)
  - Medium sized cells (normal spermatocytes)
  - Scattered giant cells
- No inflammatory infiltrates
- Not present at extra testicular sites

NSGCT

00:37:25

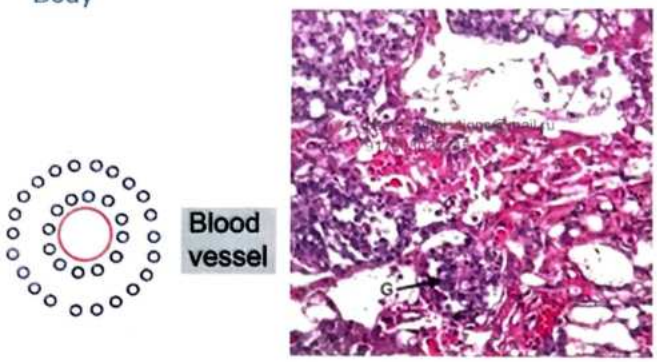
EMBRYONAL CANCER

- Age group: 20-40yrs
- Malignant tumor → resembles Primitive cells → form sheets, glands
- Tumor markers: ↑ β HCG/AFP
- Highly aggressive tumor
- Presence of Hemorrhage & necrosis, Mitosis ++, Pleomorphism ++
- Other Markers: OCT 3/4, Cytokeratin
  - KiT/podoplanin negative
- Treatment: Chemotherapy → some of the surviving tumor cells differentiates into Tetratoma

YOLKSAC TUMOR

- Aka Endodermal Sinus Tumor
- MC testicular tumor in a child < 3yrs of age

- 2 variants
  - Pre-pubertal: good prognosis, no association with i12p or GC neoplasia in situ
  - Post pubertal: Aggressive → poor prognosis, associated with i12p and GC neoplasia in situ
- Tumor markers: ↑ AFP, ↑ α_1 Anti trypsin, Cytokeratin
- Microscopic features: Schiller - Duval Body/Glomeruloid Body



Glomeruloid Body

CHORIOCARCINOMA

00:43:56

- Trophoblast derived
  - Cytotrophoblast
  - Syncytiotrophoblast → ↑ β HCG (α subunit HCG has resemblens with TSH/FSH/LH)
    → Atypical presentation: hyperthyroidism, gynecomastia
- Small palpable mass
- Early Spread/metastasis → Poor prognosis
- Treatment: chemotherapy (methotrexate)

TERATOMA

- Arises from > 1 germ cell layer → totipotent cells

Variants

- Pre-pubertal: Pure, benign and no association with i12p/ GCN in Situ
- Post-pubertal: seen in Adult
  - Mixed tumor
  - Malignant
  - Associated with i12p/ GCN in Situ

- Gross appearance: Large mass with heterogeneous appearance → Divergent differentiation/ kaleidoscopic pattern
- Teratoma with somatic malignant type transformation → Chemo-resistant & the treatment is surgical resection
  - ↑ Squamous cell Carcinoma (MC)
  - Adenocarcinoma
  - Sarcoma

Important Information

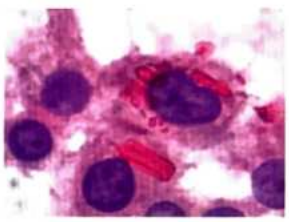
- Teratoma seen in male adults should always be considered as malignant until proven otherwise
- Ovarian teratoma in adults is benign

NON - GERM CELL TUMORS

00:54:03

LEYDIG CELL TUMORS

- Functional testicular tumors → Hormone secretion
  - Androgen → Precocious Puberty
  - Estrogen → Gynecomastia
- Testicular Mass and other clinical features depend on hormones
- Associated with
  - Klinefelter Syndrome
  - Cryptorchidism
  - Hereditary Leimyomatosis + RCC
- Microscopic appearance: presence of Reinke Crystals (rod shaped eosinophilic inclusion bodies) & lipid droplets



Reinke Crystals

SERTOLI CELL TUMOR

- Mostly silent tumor
- Causes ↑ Estrogen → Gynecomastia
- Seen in higher incidence on patients with
  - PJ syndrome
  - FAP syndrome (APC gene mutation)
  - Carney's complex (PRKAR1A mutation)

GONADOBLASTOMA

- Rare tumor
- Mixture of germ cells and stromal cells
- Uncommon Malignant transformation of germ cell seminoma

LYMPHOMA

- MC testicular tumor seen in Elderly > 60yr
- B|L tumor and Spermatic cord affected
- Microscopic Subtypes: Diffuse Large B Cell Lymphoma > Burkitt's Lymphoma > EBV +ve extra-nodal NK/ T cell Lymphoma
- CNS metastasis → poor prognosis
- ↑ Recurrence site: CNS

Table 90.1

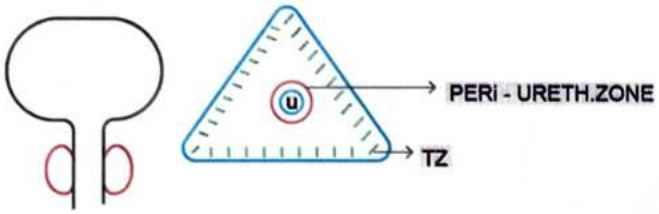
GCT from GC Neoplasia in-situ	GCT unrelated to GC neoplasia in-situ	Sex cord stromal tumors	Gonadoblastoma

• GC Neoplasia in-situ
• Seminoma: good prognosis
• **Non Seminoma GCT**
  ○ Embryomal Ca
  ○ Yolk sac Ca
  ○ Choriocarcinoma
  ○ Teratoma (Post puberty/ Somatic type malignancy)
• Mixed Germ cell tumor (60%)
	• Spermatocytic seminoma
	• Teratoma (Pre-pubertal)
	• Yolk Sac Tumor (Pre-pubertal
	• Mixed Teratoma/Yolk Sac Tumor
		• Leydig cell tumor
		• Sertoli cell tumor
			-

91 MALE GENITAL TRACT DISORDERS 2

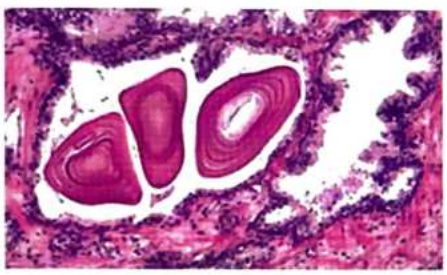
PROSTATE

00:00:16



- Peri-Urethral Zone → Early presentation
- Peripheral one → Late presentation

Microscopic appearance



Normal prostate

- Basal low cuboidal cell
- Inner secretory columnar cell
- Branching or Papillae
  - Benign condition with ↑ cells → ↑ branching or papillae formation
  - Loss of branching in prostate cancer
- Presence of Corpora Amylacea

PROSTATITIS

00:04:47

- Can be Acute or chronic condition

Clinical features

- Fever
- Dysuria
- Boggy / Tender Prostate on P/R examination

Causes

- In young: Chlamydia, Neisseria gonorrhea
- In elderly: Pseudomonas, E.Coli due to reflux of urine

Diagnosis

- Urine culture & microscopic examination
- Biopsy is Contraindicated

Treatment

- Appropriate antibiotic therapy

BENIGN HYPERPLASIA OF PROSTATE

- MC benign disease, seen in elderly male > 50yrs
- It is not pre-malignant condition
- Hormone Dependent: Androgen
  - Testosterone $\xrightarrow{5\text{reductase II}}$ DHT → ↑ Epithelial/stromal cells
  - Estrogen has facilitatory role
- Gross appearance: Nodularity
- Microscopic appearance: Hyperplasia of Stromal cells & glands
  - Outer cuboidal/ Basal layer
  - Inner columnar cell

Clinical features

- Urination problem → urethral compression
  - ↑ Frequency
  - Difficulty in starting & Stopping the micturition

Complications

- Bladder smooth muscle hypertrophy Bladder diverticula
- ↑ Risk of infections
- Hydroureter
- Hydronephrosis
- Acute urinary Retention (emergency)

Treatment

- Fenasteride (5α Reductase Inhibitors)
- Tamsulosin (Selective α_1 blockers)
- TURP (Transurethral Resection of Prostate) → Definitive treatment

CARCINOMA PROSTATE

00:16:38

- Elderly male

Risk Factors

- ↑↑ Age
- Exposure to Androgens/androgen receptor mutation → ↑↑ proliferation of cells
- Diet
  - ↑↑ Lipids → PAH (chemical carcinogen)
  - Protective factor: Glutathione S-transferase (hypermethylation lead to ↓ function)
  - ↓↓ Vitamin A/C, Soya foods

Genes

- Inherited factors: BRCA 2 gene mutation, Myc mutation, LYNCH syndrome, HOXB13
- Acquired factors
  - TMPRSS 2 (androgen promoter) → ERg fusion (transcription factor) → ↑ activity androgen → cancer
  - Loss of p27, PTEN & loss of activity of p53, Rb gene

Pathogenesis

Diet / Androgen / Germline mutation

↓

Normal Prostatic epithelium

↓

Fusion gene → ← gsTP methylation
PIN

↓

p27 loss → ← pTEN loss
Prostate carcinoma (↓Rb, ↓p53 → aggressive tumor)

Clinical features

- Asymptomatic
- Pain in Back / Pelvic area

Spread

- Peripheral zone → posteriorly
- Lymphatic spread → Obturator LN
- Hematogenous spread → Commonest organ affected: Bones
  - Lumbar Spine (MC) > Pelvis > Proximal femur
  - Batson's plexus is responsible for spread to spine (osteoblastic 2°)
- Back pain
  - Multiple myeloma → osteolytic lesions, normal S. Alkaline phosphatase
  - Prostate carcinoma → osteoblastic, ↑ S. Alkaline phosphatase
- Lungs & Liver involvement is uncommon
- Associated with Perineural invasion → malignant nature property

Important Information

- Peri-neural invasion with salivary gland tumor: adenoid cystic carcinoma

DIAGNOSIS

- DRE → nodularity in posterior area

Prostate Specific Antigen

- Physiological function – Liquefaction of Semen
- Sensitive but not Specific marker
- S. PSA Levels (normal < 4 ng/ml)
- S. PSA Levels >10 ng / ml likely of cancer
- PSA velocity: > 0.75 ng/ml
- Types
  - ↑↑ Free form: BHP
  - ↑↑ Bound form: cancer
- ↑↑ PAP

New markers

- NKX3-1
- AMACR (α - Methyacly coenzyme A racemase)
- TMPRSS 2 - ERG fusion DNA

Previous Year's Questions

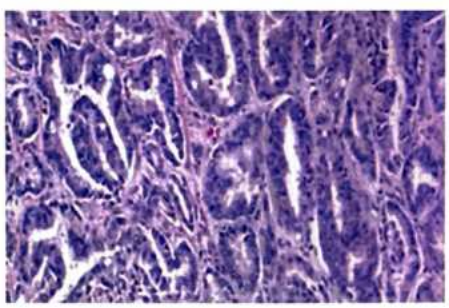
Q. NKX3-1 immunohistochemical used for diagnosis of?
(JIPMER – May - 2019)

A. Colorectal carcinoma
B. Pancreatic carcinoma
C. Prostate carcinoma
D. Renal cell carcinoma

Trans-rectal Needle Biopsy

- Confirmatory test
- Microscopic features
  - Adenocarcinoma (95%)
  - Presence of tumor cells forming invasive glands, prominent nucleoli
  - Single layer of cells and no basal cells

Osteoblastic secondaries



Crowded glands

Gleason grading

- Grade 1 – 5
  - Grade 1: Well differentiated
  - Grade 5: Poorly differentiated
- Patterns
  - 1° (dominant)

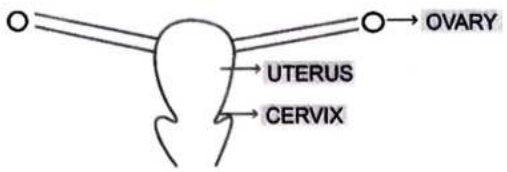
- 2° (2nd most frequent pattern)
- Score = Grading of 1° + Grading of 2°
- If single pattern, then score = grading of 1° + 1° (double the grading)

Treatment

- Surgery → orchiectomy (due to androgen)
- Anti-androgen therapy

92 FEMALE GENITAL TRACT DISORDERS 1

CERVIX



- Endocervix: columnar epithelium
- Exocervix: Squamous epithelium
- Transformation zone/squamo-columnar junction: preferred site for dysplasia

CERVICAL INTRA EPITHELIAL NEOPLASIA

00:02:20

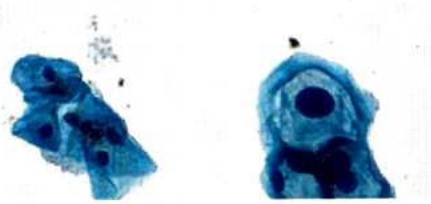
- Dysplastic changes present

Risk Factor

- HPV infection
  - Low risk sub types 6,11→ condyloma acuminata
  - High risk sub types 16, 18, 31, 33 → cancer
  - Most prevalent: HPV 16
- They secrete E_6, E_7 protein (interferes with tumor suppressor gene)
  - E_6 protein → ↓ p53
  - E_7 protein → ↓ Rb

Histology

- Presence of koilocytosis (perinuclear halo) → responsible protein E_5
- ↑ N:C ratio



Normal HPV infected cell

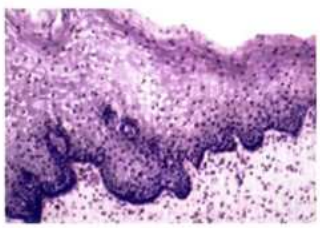
- Markers of proliferation: Ki67/P16

High risk of HPV infection

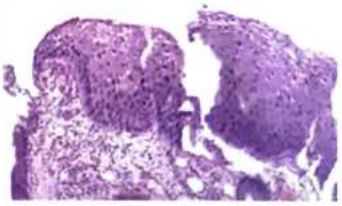
- Early age intercourse
- Multiple partners
- Multiparity
- High risk partner

Dysplasia

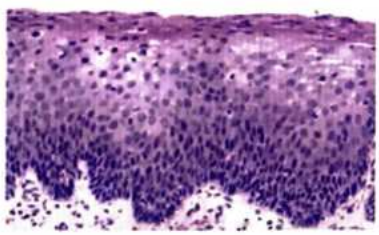
- Divided into CIN I, CIN II, CIN III



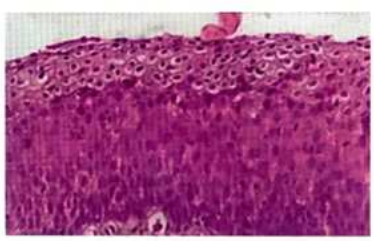
Normal cervical epithelium



CIN I (mild dysplasia, <33% involved)



CIN II (moderate dysplasia, <2/3rd involved)



CIN III (high grade dysplasia, >2/3rd involved)

- Complete layer of epithelium with dysplastic changes → carcinoma in situ

Bethesda classification 00:10:32

- Squamous Intraepithelial Neoplasia lesions (SIL)
  - Low grade SIL/CIN I
  - High grade SIL/CIN II / CIN III/ carcinoma in situ

LSIL $\xrightarrow[10yrs]{10\%}$ HSIL

HSIL $\xrightarrow[10yrs]{10\%}$ Cancer

CERVICAL CANCER

00:13:03

- 2nd MC cancer of females

Risk Factors

- HPV Infection
- Smoking (PAH)
- Immunodeficiency
- OCPs

Clinical features

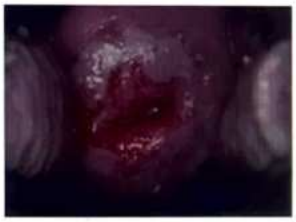
- Post-coital Bleeding
- Foul smelling discharge
- Cachexia
- Weight loss

Extension

- Vagina
- Bladder
- Lungs
- Ureter → obstruction → back pressure changes in kidney → post renal azotemia → renal failure → death
- MC cause of death: uremia > hemorrhage > infections

Screening

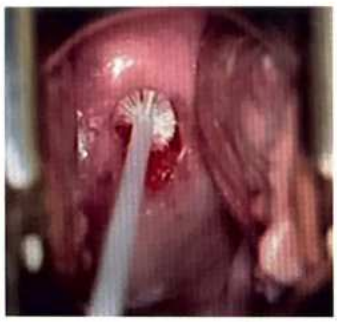
- For squamous dysplasia
- VIA & Colposcopy
  - VIA (visual Inspection after application of Acetic Acid) & colposcopy – best method
  - Dysplastic lesions + acetic acid → abnormal whitish, vascularity area (Mosaic pattern)



Dysplastic lesion

- PAP smear: Using Ayer's Spatula, cervical tissue is taken from TZ circumferentially → Fixation (ether: 95% ethanol) in 1:1 ratio → staining

PAP smear & Cytobrush



Liquid based cytology

- Liquid Based Cytology

  Cytobrush rotated 5 times clockwise at TZ

  ↓

  Sample fixed is liquid preservative

  ↓

  Processed & slide prepared

  - Brand name: Thin prep, sure path
  - Superiority of Liquid based cytology is due to
    - Immediate fixation
    - → Both microscopic & Automated evaluation can be done
    - → ↓ area & ↓ time

> **Important Information**
>
> - Liquid base cytology can be also be used for:
>   - Thyroid cyst fluid examination
>   - Body fluids – Pleural / urine
>   - Oval pathology lesions
>   - Brushing sample

- Colposcopy + Biopsy – confirmatory test

Microscopic appearance

- Squamous cell cancer (Large cell Keratinizing variant)
- Adeno carcinoma
- Mixed carcinoma

Prevention

- Screening
- Vaccination (effective against squamous cell cancer only) → pap smear is still advised

VAGINA

00:28:45

Embryonal Rhabdomyosarcoma

- Aka sarcoma Botryoides
- Children < 5yrs of age with H/O protrusion of mass from vagina
- Microscopic appearance: Presence of Tennis racket cells
- Markers: Myoglobin & Desmin

Clear Cell Adenocarcinoma

- Precursor lesion: vaginal adenosis
- Female with H/O intrauterine exposure of DES → Inhibits mullerian differentiation

Squamous Cell Cancer

- Extension of carcinoma cervix
- Etiology: HPV 16 Infection

93 FEMALE GENITAL TRACT DISORDERS 2

- Uterus has 2 **main components**
  - Myometrium
  - Endometrium
    - → Estrogen **(proliferative)**
    - → **Progesterone (Implantation)**

ENDOMETRIAL DISORDERS

00:01:32

ENDOMETRIOSIS

- Ectopic endometrial tissue (outside uterus)
- Age group: 25-35yr female
- MC ectopic site: ovary

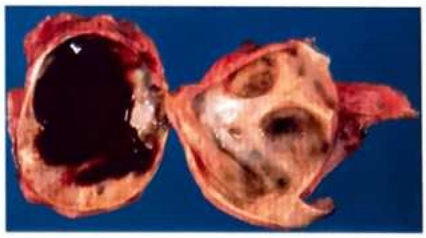
Location	Symptoms
• Ovary	• Chocolate Cyst, ↓ fertility
• Uterine ligament	• Dysmenorrhea, ↓ fertility
• Recto - uterine pouch • Bladder / Bowel	• Irritation of the tissue • Pain on urination & defecation
• Mucosa of fallopian tube	• ↓ Fertility
• Lungs/Nasal Mucosa (uncommon)	• Vicarious Epistaxis, Vicarious hemoptysis

Pathogenesis

- Sampson's regurgitation theory → MC accepted theory
- Ectopic cells survive by ↑ PGE_2 which
  - ↑ Aromatase
  - Inflammation
- ↑ Risk of ovarian cancer (↑ CA-125)

Important Information

- CA-125 contributes to non-cancerous conditions like endometriosis and TB of female genital tract



Chocolate cysts | Gun powder appearance

- Associated with Chocolate Cysts & presence Peritoneal Hemorrhagic spots giving "gun powder appearance"
- Adenomyosis: presence of endometrial tissue in myometrium
  - >2.5mm below Endomyometrial junction

ENDOMETRIAL HYPERPLASIA

- ↑↑ Estrogen → ↑↑ Endometrial glands → Bleeding
- It is a precancerous lesion
- Associated with PTEN gene mutation

Types

- Non-atypical EH → 1-3% risk of cancer
  - Follow up required
- Atypical EH → 23-48% Risk Of Cancer
  - Aka Endometrial Intra Epithelial Neoplasia
  - Hysterectomy is advised

ENDOMETRIAL CARCINOMA

00:17:13

Important Information

- MC cancer in females: Breast Cancer
- MC cancer of female genital tract: Cervical Cancer
- MC invasive cancer of female genital tract: Endometrial Cancer

Clinical features

- Irregular bleeding (MC) >> Post-menopausal bleeding
- Dirty vaginal discharge
- Commonest site of metastasis: Lungs

Classification

FEATURES	TYPE I (80-90%)	TYPE II
Age	55-65yrs	65-75yrs
Clinical Setting	• Estrogen ++ • Obesity • HTN/DM	• Atrophy • Thin physique
Precursor	Hyperplasia	Serous endometrial intraepithelial Cancer
Genetics	• PTEN Mutation (MC) • p53 (common mutation of Aggressive Cancer)	p53 gene mutation (sporadic)
Nature	Indolent	Aggressive
Spread	Lymphatic spread	• Lymphatic spread • Intra-peritoneal spread
Histological variant	Endometroid Cancer	Papillary serous cancer
Prognosis	Better prognosis	Poor prognosis

Previous Year's Questions

Q. Which of the following is the commonest genetic mutation in a 50 years old obese female presenting with postmenopausal bleeding and diagnosed with endometrial cancer? (JIPMER - May - 2018)

A. P53
B. PTEN
C. CHD4
D. Beta catenin

MYOMETRIAL DISORDERS

00:29:50

LEIOMYOMA

- Aka Fibroid
- Smooth muscle mass
- Benign in nature

Risk factors

- Chromosomal defects
  - MED 12 mutation (MC)
  - Chromosome 12q / 6p rearrangements
- Obesity
- Reproductive age group
- Hormone responsive (estrogen causes proliferation)

Sub types

- Sub-mucosal
- Intramural (MC variant)
- Sub-serosal

Clinical Features

- Asymptomatic mostly
- Menorrhagia
- ↓ Fertility
- Pressure Symptoms on bowel & bladder

Secondary changes

- Hyaline degeneration (MC)
- Red Degeneration: ↑ Vascularity → Seen in 2nd trimester of pregnancy
- Calcific Degeneration: Ca^{2+} deposition → White dystrophic calcification
  - Associated with "Womb Stone" appearance of fibroid
- Cystic Degeneration: 0.5% cases → Cancer

Atypical terms

- IV Leiomyomatosis: Tumor via IVC → right side of heart
- Disseminated peritoneal Leiomyomatosis: Multiple, small peritoneal nodules

Leiomyoma

Well differentiated smooth muscle cells

- Gross appearance: Well circumscribed; multiple mass with Greyish White Whorled appearance
- Microscopic appearance: well differentiated whorls of smooth muscle cells → spindle cells with cigar shaped nucleus

LEIOMYOSARCOMA

00:40:44

- Arises De Novo
- MC sarcoma of uterus
- Max incidence age group: 40-60yrs

- Malignant
  - Recurrence post-surgery
  - Metastasis to lungs, CNS, bones
- Morphology: Bulky tumor with hemorrhage & necrosis
- Differential diagnosis: Leiomyoma
- ≥ 10 mitosis/10 hpf, if tumor is well differentiated
- > 5 mitosis /10 hpf, if nuclear atypia, necrosis & large epithelioid cells are present

94 FEMALE GENITAL TRACT DISORDERS 3

- Ovaries are almond shaped with the size of 3cm X 3.5cm X 2.5cm

Ovarian tumors

- 1° ovarian tumors
  - Surface Epithelial tumors
  - Germ cell tumors
  - Sex cord stromal tumors
- 2° ovarian tumors
  - Metastatic involvement of ovaries (Stomach >> colon cancer)

Risk Factors 00:02:37

- Non genetic factors: contributed by epithelial injury due to longer chances of ovulation
  - Nulliparity
  - Early Menarche/late menopause
  - Asbestos
- Genetic factors
  - BRCA 1/2 mutation
  - K-RAS mutation
  - Lynch/Turner/PJ Syndrome
  - 1° Female relatives
- Protective factors
  - OCPs
  - Pregnancy

Clinical features

- Abdominal enlargement
- Abdominal pain
- Malignant ascites
  - Exfoliated tumor cells
  - ↑ CA-125 → useful to monitor disease progression
  - Osteopontin
- Palpable ovaries
- Pleural effusion (atypical presentation due to metastasis)

SURFACE EPITHELIAL TUMORS 00:15:53

- MC 1° ovarian tumors
- Can be either Benign/Borderline/malignant
- Variegated appearance: mixed solid/cystic areas

How to remember

- Subtypes of surface of epithelial tumors → My Servant Began Experiencing Cancer
  - My → Mucinous Tumor
  - Servant → Serous Tumor
  - Began → Brenner Tumor
  - Experiencing → Endometrioid tumor
  - Cancer → Clear cell tumor
- Epithelial stromal tumor: adenosarcoma/malignant mixed mullerian tumor

Molecular studies

Type I Tumor	Type II Tumor

• Low grade
• Associated with
  ○ Endometriosis
  ○ Boderline tumors
• Examples
  ○ Low grade serous tumor
  ○ Endometrioid tumor
  ○ Mucinous tumor
	• High grade
	• Associated with Serous intraepithelial Carcinoma
	• Example: High grade serous tumor

MUCINOUS TUMOR 00:18:15

- Cystic tumor → columnar non-ciliated epithelium (secretes mucus)
  - Benign: Mucinous cystadenoma
  - Malignant: Mucinous cystadenocarcinoma

Risk factors

- Smoking
- Genetic: K-RAS mutation

Clinical Features

- Middle aged female
- Unilateral ovarian enlargement with multiple cysts
- Mostly benign
- Pseudo Myxoma Peritonei/Mucinous Ascites
  - Overall MC cause: Appendecial Tumor

SEROUS TUMORS

00:21:48

- Cyst tumor (watery clear fluid) → lined with ciliated epithelium
- Benign >> Malignant (serous adenocarcinoma is MC 1° malignant ovarian tumor)
- Bilateral ovarian involvement with unilocular cyst
- Serous adenocarcinoma
  - BRCA 1 gene mutation
  - Psammoma body
- Prevention: prophylactic salphingo-oophorectomy

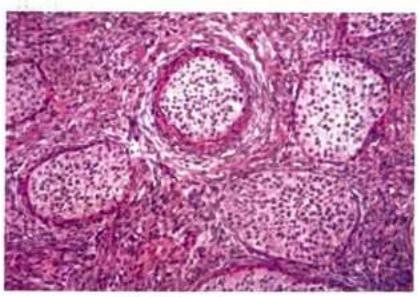
Important Information

Psamomma body

- Meningioma/mesothelioma
- Serous tumor of ovary
- Salivary gland papillary cancer
- Papillary cancer of thyroid
- Prolactinoma
- Glucagonoma

BRENNER TUMOR

- U/L mostly
- Benign in nature
- Rubbery tumor
- Epithelium similar to urothelium (Transitional Epithelium) of bladder
- Epithelial cells forms a collection → Walthard Nests
- On high power, Coffee bean nucleus is seen (also associated with theca cell tumor)
- Associated with Pseudo-meig syndrome



Walthard nests

Previous Year's Questions

Q. Which of the following ovarian tumors is derived from Walthard cell nests? (JIPMER – Dec - 2019)

A. Brennen tumor
B. Clear cell cancer
C. Serous cystadenoma
D. Yolk sac tumor

ENDOMETROID TUMOR

00:30:57

- Genetics: PTEN gene mutation
- Associated with Endometriosis
- Appear similar to endometrial adenocarcinoma

CLEAR CELL CANCER

- Variant of endometroid Cancer
- Clear cells → due to glycogen

GERM CELL TUMORS

DYSGERMINOMA

- Male counterpart → seminoma
- MC malignant GCT (100%)
- Radio Sensitive, chemo-sensitive
- U/L involvement mostly (85%)
- Non-functional tumor → hormones not secreted

Markers

- Transcription factors
  - OCT 3/4
  - NaNOg
  - KiT
- Enzymes
  - PLAP +ve
  - ↑↑ S. LDH
  - AFP – normal
  - ↑ ß HCG
- Associated with gonadal dysgenesis
- Microscopic appearance: Polyhedral cells, distinct cell membrane, pale nuclei with prominent nucleoli, watery cytoplasm (glycogen)

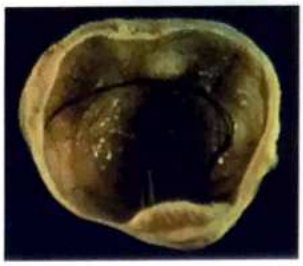
TERATOMA

00:36:49

- Presence of > 1 germ cell layer
- Cell origin: totipotent cells
- MC extra gonadal site: Mediastinum
- MC GCT

Subtypes

- Mature teratoma
  - MC subtype (90%)
  - Aka dermoid cyst
  - Young female → incidental finding
  - Paraneoplastic syndrome: inflammatory limbic encephalitis
  - Possible to undergo ovarian torsion
  - Components: Skin / hair / cartilage / Sebaceous gland
  - Karyotype study: 46XX (after first meiotic division)
  - Tumor containing skin → secondary malignancy → squamous cell carcinoma (MC)



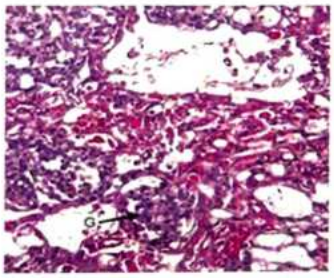
Teratoma

- Immature Teratoma
  - Seen in adolescent Females
  - Malignant in nature
  - Immature/Embryonic components

- Specialized teratoma
  - Mostly U/L
  - Struma Ovarii → presence of functional Thyroid tissue → hyperthyroidism
  - Carcinoid Syndrome → presence of cells secreting serotonin

YOLK SAC TUMOR

- Aka endodermal sinus tumor
- 2nd MC malignant GCT
- MC malignant ovarian tumor presenting in age group → < 4 yr
- Microscopic appearance: presence of Schiller Duval Body /Glomeruloid body
- Tumor markers: AFP, α_1 AT +ve



Schiller Duval Body

OVARIAN CHORIOCARCINOMA 00:48:24

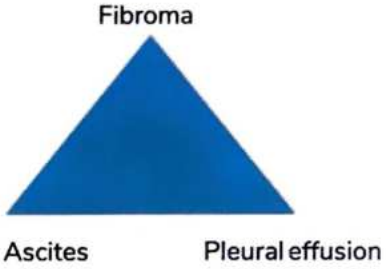
- Co-exists with other GCT
- Placental Origin → β HCG ↑↑↑ (marker)
- If it has ovarian origin: non responsive to chemotherapy → poor prognosis

SEX CORD STROMAL TUMORS 00:50:22

- Aka Functional Tumors

THECOMA - FIBROMA

- Theca cells: spindle shaped, secretes estrogen, oil red 'O' +ve
- Fibroma cells: spindle shaped, do not secrete estrogen, oil red 'O' -ve
- Mostly U/L involvement, benign in nature
- Clinical features: Pelvic mass (MC)
- Fibroma is associated with
  - Meig Syndrome



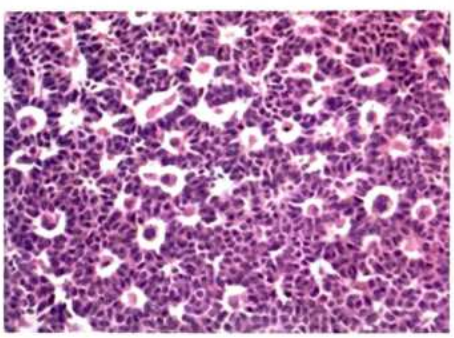
  - Basal Cell Nevus Syndrome: >6cm Fibroma

GRANULOSA - THECA CELL TUMORS

- Genetics: FOX L2 mutation
- Elderly female
- Functional tumor: Estrogen secretion
  - Precocious puberty
  - Endometrial hyperplasia
  - Endometrial malignancy
  - Post-menopausal bleeding (MC)

Microscopic appearance

- Call Exner Body: In centre acidophilic component Surrounded by arrangement of tumor cells with coffee bean nucleus
- Stain: Inhibin



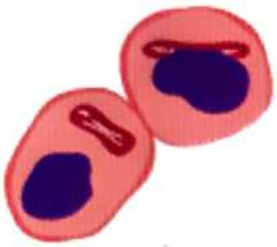
Call Exner Body

Previous Year's Questions

Q. Call-Exner bodies are seen in? (FMGE – Jun - 2018)
A. Theca all tumor
B. Yolk sac tumor
C. granulosa cell tumor
D. Fibroma of ovary

SERTOLI - LEYDIG CELL TUMOR

- Genetics: DICER 1 mutation (malfunction of RNA)
- Functional tumors: Androgen → masculinization
  - Oligomennorhea
  - Change in voice
  - Clitoral enlargement
  - Hirsutism
- Microscopic appearance: Presence of rod shaped eosinophilic nucleus → Reinke Crystals



Reinke Crystals

GONADOBLASTOMA / MIXED TUMOR

00:58:45

- Stroma + Germ cell = mixed tumor
- Abnormal sexual development → female Appearance (80%), male appearance (20%)
- Co-existence with dysgerminoma (50%)
- Treatment: Surgical excision → Good Prognosis

2° OVARIAN TUMORS

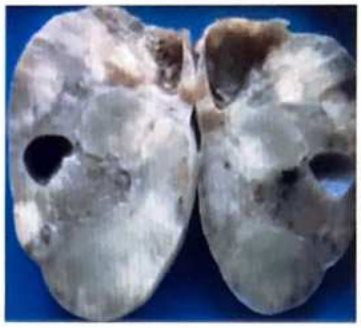
- Metastasis → mullerian tumor
  - uterus
  - Fallopian tube
  - opposite ovary
  - pelvic peritoneum
- Non mullerian origin
  - Stomach cancer
  - colon cancer
  - Breast cancer

KRUKERBERG TUMOR

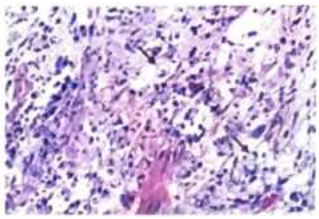
- B/L ovarian involvement by lymphatic spread
- Associated with
  - Stomach cancer (MC) → Diffuse variant
  - Breast cancer → lobular carcinoma
  - Colon cancer
  - Pancreatic cancer

Microscopic appearance

- Signet-Ring Appearance → mucinous vacuole pushing nucleoli



B/L ovarian involvement



Signet ting appearance

PSEUDO-MYXOMA PERITONEI

- Presence of mucus in ascetic fluid
- MC tumor: Appendiceal tumor

CLINICAL QUESTIONS

23-year-old boy with history of sickle cell anemia presents to the emergency department with a painful erection. The patient explains that the erection had started 3 hours ago. This condition is called as

A. Balanitis.
B. Hypospadias.
C. Peyronie disease.
D. Priapism.

Solution:

- Priapism is a persistent, often painful erection linked to illnesses including sickle cell anaemia, hypercoagulable states, spinal injuries, and certain medications
- Balanitis is caused by inflammation of the glans penis and is linked to inadequate hygiene.
- Hypospadias is a condition in which the urethral meatus opens on the penis' ventral side.
- Peyronie's disease is caused by a fibrosis of the dorsum of the penis under the skin.
- Phimosis is a condition in which the foreskin is excessively tight and difficult or impossible to retract over the glans penis.

Reference:

- Robbin's 10th Ed./page- 643

LEARNING OBJECTIVES

UNIT 18 ENDOCRINOLOGY

- **Parathyroid & thyroid disorders**
  - Hyperparathyroidism
  - Parathyroid Carcinoma
  - Hypoparathyroidism
  - Pseudo-Hypoparathyroidism
  - Pseudo-Pseudohypoparathyroidism
  - Thyroiditis
  - Hashimoto's Thyroiditis
  - De-Quervain's Thyroiditis
  - Sub-Acute Lymphocytic Thyroiditis
  - Grave's Disease
  - Malignant
  - Papillary Thyroid Cancer
  - Follicular Thyroid Cancer
  - Medullary Thyroid Cancer

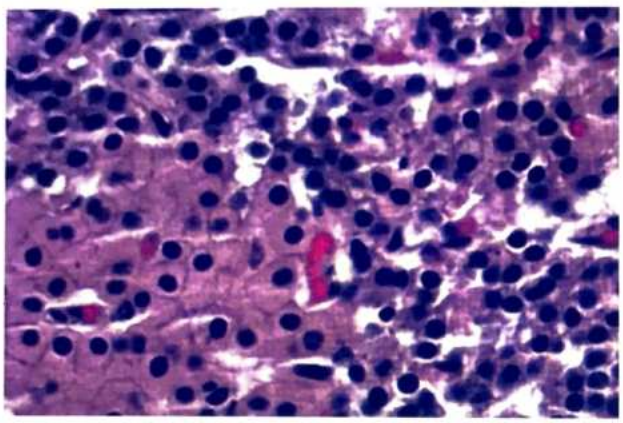
- **Adrenal gland disorders**
  - Pheochromocytoma; Clinical Features

95 THYROID & PARATHYROID DISORDERS

PARATHYROID GLANDS

Anatomy

- 2 pairs
  - Superior: 4th pharyngeal pouch
  - Inferior: 3rd pharyngeal pouch



Oxyphil cells Chief cells

Microscopic appearance

- 2 types of cells
  - Chief cells: secretary granules containing PTH, glycogen (water-clear cytoplasm)
  - Oxyphil cells: Acidophilic; Glycogen presence & tightly packed mitochondria

PTH

- Overall action: ↑ Ca^{2+}, ↓ PO_4^{3-}
- Kidneys → ↑ Ca^{2+} reabsorption, ↑ PO_4^{3-} excretion
- Bones → PTH acts on osteoblast → RANK-L → Osteoclast → ↑S.Ca^{2+}, ↑ S.Alkaline phosphatase
- ↑ Activity of 1 α-Hydroxylase → Active form of Vit D → Calcitriol → ↑ Ca^{2+}
- Parathyroid gland activity can be checked by Tc^{99} sestamibi scan

HYPERPARATHYROIDISM

00:06:12

PRIMARY HYPERPARATHYROIDISM

- Etiology: Parathyroid adenoma (MC) >> Parathyroid hyperplasia >> Parathyroid Carcinoma

Parathyroid Adenoma

- MC cause of 1° Hyperparathyroidism
- Solitary in nature
- Predilection area → Right Inferior parathyroid gland
- Microscopic appearance: ↑↑ cells (Sheets of cells) & no adipose tissue between them
- Variants: Sporadic >> familial

Sporadic	Familial
• Cyclin D_1 over activity (chromosome 11) → MC • MEN 1 gene under activity • CDC73 → associated with parafibromin secretion	• MEN 1/2/4 • FHH

Clinical features

Important Information

- Asymptomatic (↑↑ Ca^{2+}) → MC cause parathyroid adenoma
- Symptomatic (↑↑ Ca^{2+}) → metastasis (breast cancer)

- Kidneys: stones/nephrocalcinosis/polyuria
- Bones
  - Cortical bones >> medullary bones; involvement of skull/Vertebra/phalanges
  - Osteoporosis; micro-fractures → hemorrhage → osteitis fibrosa cystica (brown tumor/Von Recklinghausen disease)
  - Dissecting Osteitis: Medullary portion → osteoclastic activity on trabeculae → appears like dissection of trabeculae
- CNS: mood swings, depression, Psychic moans
- GIT: ↑ PUD (↑Ca^{2+} → ↑ Gastrin)/↑ Pancreatitis (phospholipase)/Constipation
- Joints: chondrocalcinosis → pseudo gout
- Diastolic HTN
- Eyes: calcium deposition at cornea-scleral junction (limbus) → band keratopathy

Diagnosis

- S.PTH → ↑↑
- S.Ca^{2+} → ↑↑
- S.Po_4^{3-} → ↓↓
- S.Alkaline phosphatase → ↑↑
- Tc^{99} sestamibi scan: ↑↑ Uptake of radio nucleotide material into affected area

Parathyroid hyperplasia

- All the 4 glands are affected
- ↑↑ Chief cells (WH hyperplasia)
- MEN/FHH
- Familial hypocalciruric hypercalcemia
  - AD condition
  - < 10yr child affected
  - CaSR gene defect → ↓ Ca^{2+} in urine and ↑ Ca^{2+} in blood → PTH (normal/↑)

Parathyroid Carcinoma 00:28:48

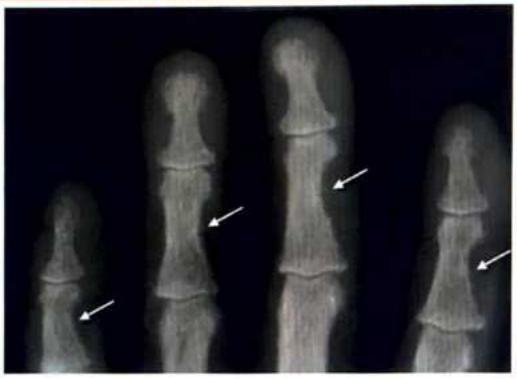
- Presence of invasion & Metastasis (differentiating factor from parathyroid adenoma)
- CDC73 gene → Parafibromin protein
  - Can also be associated with ↑ PTH/Jaw tumor syndrome

SECONDARY HYPERPARATHYROIDISM

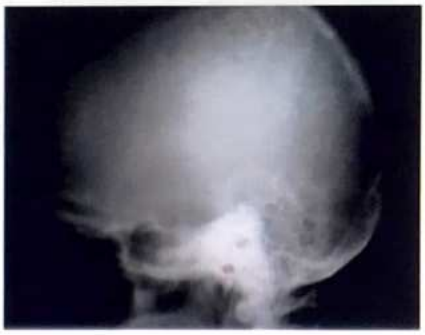
- CKD: ↓↓ Ca^{2+}/↑↑ PO_4^{3-} → ↑↑↑ PTH
- Vitamin D deficiency
- GI malabsorption
- Clinical symptoms appear due to 1° disease
- Calciphylaxis → narrowing of BV due to calcium deposition

Important Information

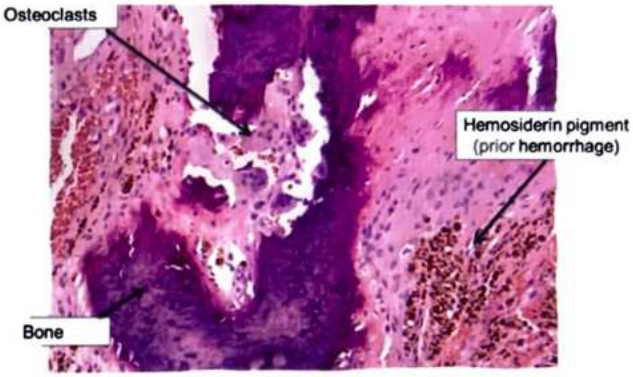
- 3° Hyperparathyroidism → autonomous activity PTH gland due to long standing 2° Hyperparathyroidism → ↑↑ Ca^{2+}



Radial aspect of phalanges affected



"Salt pepper" skull



Brown tumor

HYPOPARATHYROIDISM 00:38:42

Etiology

- Surgical Removal (MC) → Thyroid Surgery
  - Can be re-implanted in sternocleidomastoid, brachioradialis
- Autoimmune Disease(APS_1) → AIRE gene
  - Adrenal insufficiency
  - ↓ Parathyroid activity
  - Muco-cutaneous candidiasis
- Di-George Syndrome
  - ↓ Ca2+/↓ T-cell
  - Chromosome 22q11 deletion

Clinical features

- ↓↓ Ca^{2+} → Tetany
  - Carpo pedal Spasm
  - Chvostek sign
  - Trousseau sign
- ECG: ↑ QT interval
- Enamel hypoplasia
- ↑ Dental Caries
- Premature Cataract
- Basal Ganglia Calcification

Diagnosis

- S.Ca^{2+} ↓↓
- S.PTH ↓↓
- S.PO_4^{3-} ↑↑

- S.Alkaline phosphatase → Normal

PSEUDO-HYPOPARATHYROIDISM 00:47:21

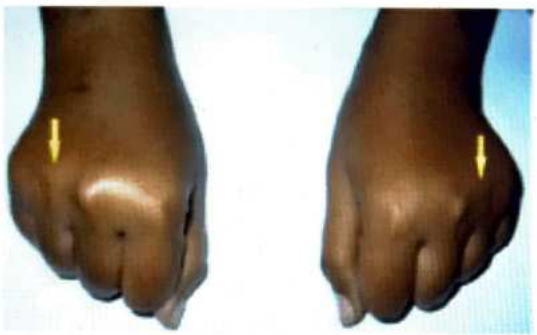
- End organ resistance to PTH
- PTH → Gs (+) → Action
- AD Condition → GNAS gene defect
- Associated with Maternal genomic Imprinting

Diagnosis

- S.Ca^{2+} ↓↓
- S.PO_4^{3-} ↑↑
- S.PTH ↑↑

Clinical features

- Tetany
- Mental Retardation
- Bone abnormality
- Short stature
- Archibald Sign: no knuckle in 4th/5th metacarpals, only dimple is present



Archibald Sign

- Gs subunit is also required for activity of FSH & LH → Hypogonadism
  - Compensatory FSH/LH ↑↑ → hyper-gonadotropic hypogonadism

PSEUDO-PSEUDOHYPOPARATHYROIDISM 00:54:07

- Presence of Paternal genomic Imprinting
- PTH unable to act at the level of bone
- S. Ca^{2+}
- S.PO_4^{3-} ↑↑
- S.PTH ↑↑

} normal

- Clinical features: MR/Obesity/Skeletal defects

THYROIDITIS 00:56:35

ACUTE THYROIDITIS

- Bacterial infection (Staphylococcus Aureus)

Clinical features

- Pain in thyroid
- Fever
- Malaise

Investigations

- S.T_3/T_4 ↑↑
- S.TSH ↓↓
- RAIU ↓↓

Treatment

- Antibiotics
- Anti-inflammatory drugs

HASHIMOTO'S THYROIDITIS 00:58:39

- Aka Struma Lymphomatosa/CLT
- Autoimmune disorder → ↓ self-tolerance → self-reactive CD_4/CD_8 T-Cells → damage to thyroid gland
- Genetics: TReg/PTPN-22/CTLA-4/IL2RA
- Auto-antibodies: anti-TSH receptor Ab, anti-TPO Ab
- Female >> male (45-55yrs)
- Associated with ↑ Risk of T1DM/Autoimmune adrenalitis/SLE/RA/MG/PA

Clinical features

- Middle aged female
- Gradually painless enlarging thyroid gland
- Hypothyroidism
- Hasimoto encephalopathy (emergency presentation)
- Hasitoxicosis

Important Information

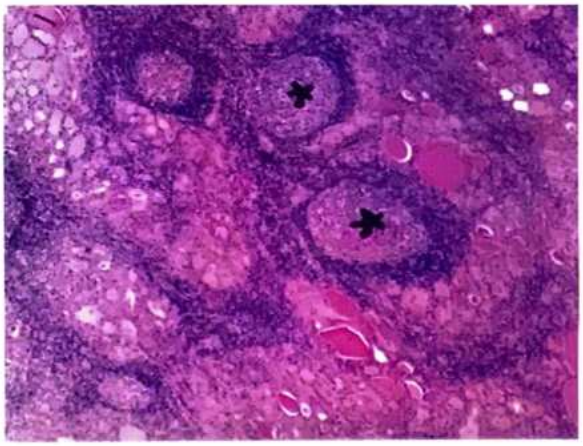
- MC Cause of hypothyroidism clinically
- MC Cause of hypothyroidism in iodine sufficient areas

Diagnosis

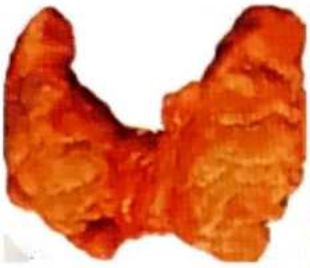
- ↑↑ TSH
- ↓↓ T_3/T_4
- ↓↓ RAIU
- Presence of auto-Ab
- Gross appearance: Gland is enlarged/ yellow tan cut surface

Microscopic appearance

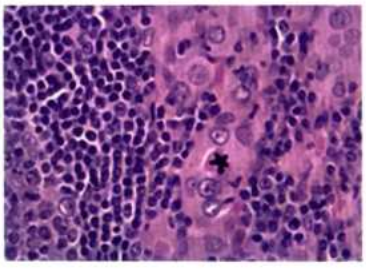
- Atrophy of follicles
- Lymphocytic Infiltration → Well-developed germinal centers
- Oncocytic metaplasia (eosinophilic/presence of granules)
  - Aka "Hurthle cells/Askanazy cells"
  - Can also be seen in follicular adenoma/carcinoma
- Deposition of fibrous tissue
- ↑ Risk For B-cell marginal lymphoma, papillary thyroid cancer



Lymphocytic infiltration



gross specimen



Hurthle cells

Treatment
- Thyroid supplementation
- Regular follow up

Previous Year's Questions

Q. A 30 years old came with complaints of thyroid swelling. On investigation her TSH levels were found to be elevated. Post-operative histopathological examination reports showed lymphocytic infiltration and hurthle cells. Which following is the most likely diagnosis? (JIPMER - Nov - 2020)

A. Graves' disease
B. Follicular carcinoma
C. Hashimoto thyroiditis
D. Medullary carcinoma thyroid

REIDEL'S THYROIDITIS
- IgG4 related disease
- Plasma cells → IgG4 → Fibrosis
- Associated with 1° sclerosing cholangitis, retroperitoneal fibrosis
- Presents in young females

Clinical features
- Fibrosis → wooden thyroid → Hypothyroidism
- Dysphagia
- Stridor/Dyspnea
- Mimics thyroid cancer→ seen in elderly patients

Diagnosis
- Hypothyroidism features
- Wedge Shaped Excision Biopsy

Treatment
- Rituximab
- Tamoxifen
- Steroids

DE-QUERVAIN'S THYROIDITIS

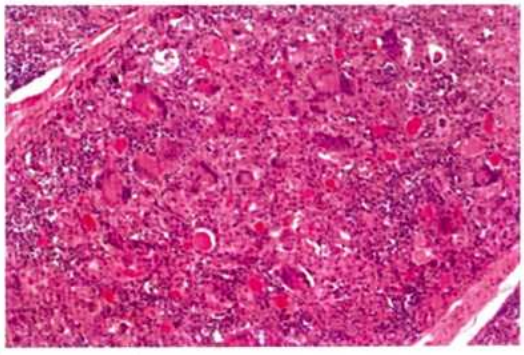
01:18:52

- Aka subacute granulomatous thyroiditis
- Associated with HLA-B5

Clinical features
- Young female with H/O Viral infection → inflammation
- Painful thyroid/ tender thyroid
- Hyperthyroidism like manifestations
- Fever
- Malaise
- Palpable cervical LN

Diagnosis
- S.T_4/T_3 ↑↑
- S. TSH ↓↓
- RAIU ↓↓

Microscopic appearance
- Presence of neutrophilic infiltration → lymphocytic infiltration (central colloid surrounded by giant cells)
- Presence of micro-abscess



Subacute granulomatous thyroiditis

Treatment
- NSAIDs
- Self-limiting condition → do not cause permanent hypothyroidism

SUB-ACUTE LYMPHOCYTIC THYROIDITIS 01:24:48

- Autoimmune Disease
- Postpartum thyroiditis
- Associated with HLA DR3/DR5
- Presence of lymphocytic infiltration → well developed germinal centers
- Painless thyroiditis
- No oncocytic metaplasia/fibrosis
- Seen in younger females

GRAVE'S DISEASE 01:27:24

- MC cause of Hyperthyroidism
- Auto Immune disease → HLA DR3/B8 → Auto Ab → TSH Receptor (TSIg)
- Also associated with Pernicious Anemia/Addison disease
- Female; 20-40yrs
- Triad of involvement
  - Thyroid
  - Skin: pre-tibial myxedema
  - Eye: proptosis

Clinical features

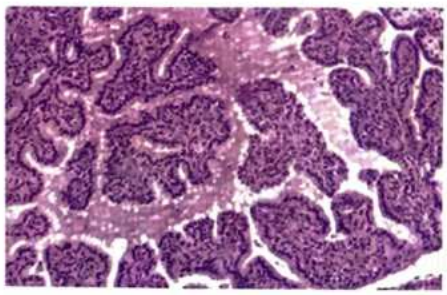
- Irregular menstruation
- Unable to gain weight (↑ metabolic rate)
- Palpitations (AF can also be seen)
- Heat Intolerance
- Thyroid Acropachy → clubbing of hands and feet

Diagnosis

- S.T_3/T_4 ↑↑
- S.TSH ↓↓
- RAIU ↑↑↑
- Morphologic appearance: hyper-vascular, beefy in size

Microscopic appearance

- Follicular hypertrophy & hyperplasia → T-Cell infiltration → presence of germinal centers
- Papilla Formation (no fibro-vascular core) → Scalloping Of Colloid



Scalloping of colloid

Treatment

- Anti-thyroid drugs
- Local radiotherapy
- Surgical decompression

THYROID TUMOR

Follicular Adenoma

- TSH → GPCR → ↑ epithelial proliferation
- Gain of function mutation in GPCR α-subunit
- MC benign thyroid tumor
- On FNAC → mimics follicular carcinoma (FNAC cannot be used for differentiation)

MALIGNANT 01:38:09

Risk Factors

- Environmental
  - Smoking
  - Radiation: Papillary Thyroid cancer
  - Goiter: Follicular Thyroid cancer
- Genetic
  - RET/PTC/BRAF gene, t(10;17): Papillary thyroid cancer
  - RAS; PAX-PPAR t(2;3): Follicular thyroid cancer
  - RET gene mutation: Medullary thyroid cancer
  - p53 gene mutation: Anaplastic thyroid cancer

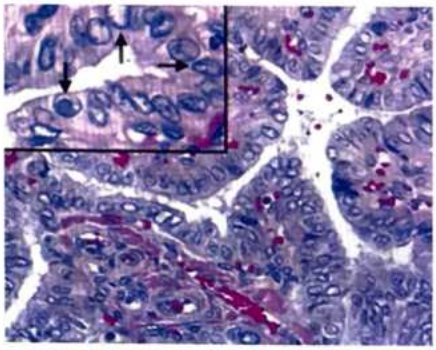
Clinical features

- Indolent growth
- Mass (cold nodule)
- Cervical LN enlargement

Diagnosis

- FNAC
- Biopsy

PAPILLARY THYROID CANCER 01:45:40



- MC type of thyroid cancer
- Associated with H/O Radiation exposure
- Genetics: BRAF >> RET-PTC
- Seen in young patients (20-40yrs)
- High chance of LN involvement → cervical lymphadenopathy

Diagnosis

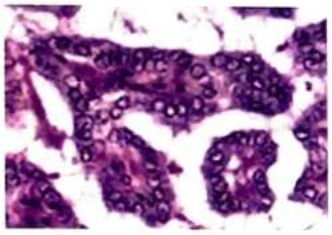
- Papillae formation (presence of fibro-vascular core)
- Psammoma bodies
- Nuclear findings → diagnostic
  - Empty looking appearance of nuclei: Orphan-Annie Eye nuclei
  - Cytoplasmic invagination → Pseudo-inclusions
  - Nuclear grooving

Subtypes

- Follicular variant (MC)
- Diffuse Sclerosing variant
- Tall cell variant → BRAF Mutation → more aggressive, extra-thyroidal extension (poor prognosis)
- Papillary micro carcinoma (< 1cm)

Previous Year's Questions

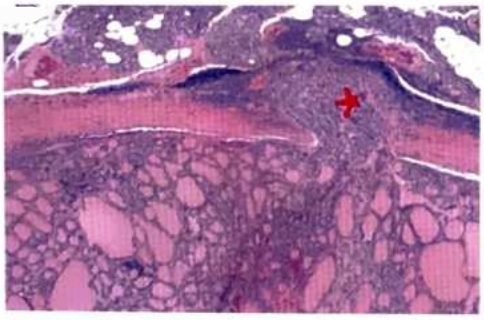
Q. A 25 years old male presented with a 2cm thyroid nodule. A thyroidectomy was done. The histology picture is given below. What could be the diagnosis? (NEET Jan 2020)



A. Papillary carcinoma thyroid
B. Follicular adenoma
C. Graves' disease
D. Adenomatous goiter

FOLLICULAR THYROID CANCER

01:55:26



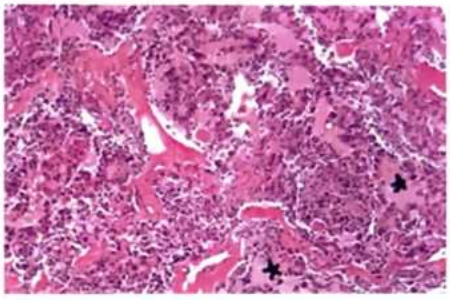
- Associated with RAS mutation/long standing goiter
- Age group: 40-50yrs; female
- Hematogenous Spread → Bones, Lungs, Liver
- FNAC not useful

Biopsy

- Involvement & erosion of thyroid capsule → metastasis
- Blood vessels in capsule is involved → capsular invasion/vascular invasion
- S.Thyroglobulin → marker of Recurrence
- Presence of Hurthle cells
  - If >50% → Hurthle cell carcinoma → poorer prognosis

MEDULLARY THYROID CANCER

01:59:47



- Arises from Para-Follicular cells/'C' cells → calcitonin (best tumor marker)
- S.calcium → not altered
- Tumor marker in calcitonin negative medullary cancer: CEA
- Associated with amyloid deposition
  - Polygonal cells
  - Amyloid in stroma
- Other secretions: ACTH/5-HT/VIPe

Sporadic variant	Familial variant
• Unilateral • Single mass	• Bilateral • Multicentric • Slow growth • Associated with MEN2A/2B, VHL syndrome

Previous Year's Questions

Q. A biopsy from a mass in the neck region reveals the presence of parafollicular cells. Which of the following is the best marker for follow up of this patient? (JIPMER – Nov - 2017)

A. Calcitonin
B. Thyroglobulin
C. T4
D. T3

ANAPLASTIC THYROID CANCER

- Papillary cancer → p53 mutation acquired
- Seen in Elderly
- Highly aggressive
- Firm thyroid gland → spread to extra-thyroidal structures
- Tumor marker: Thyroglobulin ⊖ ; Cytokeratin ⊕
- Worst prognosis

1° B-CELL LYMPHOMA

- Risk factor: Hashimoto's Thyroiditis
- Example of Marginal Zone Lymphoma

96 ADRENAL GLAND DISORDERS

- Chromaffin cell → neural crest derived cell
- Supporting cells → sustentacular cells

Chromaffin cell

- Responsible for secretion of catecholamine
  - Adrenaline → stress hormone
  - Nor-adrenaline
- Sites for adrenaline formation: adrenal medulla, organ of Zuckerkandl

$$NA \xrightarrow{N\text{-}MT} \text{Adrenaline}$$

Paraganglion system

- NE Cells
- Adrenal gland → Pheochromocytoma
- Extra-adrenal site → bladder, mediastinum, organ of Zuckerkandl (present at aortic bifurcation)

PHEOCHROMOCYTOMA

00:04:16

- Tumor arises from Adrenal medulla
- Seen in Adult

Rule of 10

- 10% - B/L Tumor
- 10% - malignant (metastasis is the most reliable sign of malignancy)
- 10% - children
- 10% - extra-adrenal (↑ risk of malignancy)
- 10% - without hypertension
- 25% - Germline mutation
  - Young, B/L involvement
  - Associated with
    - → VHL syndrome (3p)
    - → NF-1 syndrome (JMML; Pheochromocytoma)
    - → MEN II A/B → RET gene
    - → Succinate dehydrogenase (SDHB/SDHC/SDHD)

00:11:57

Clinical features

- Pounding Headache
- Episodic HTN
- Palpitations
- Chest pain
- Anxiety
- Diaphoresis
- Ileus

} essential HTN

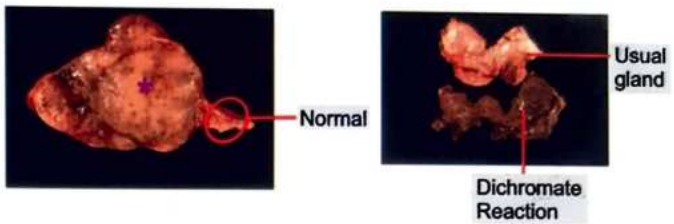
- Catecholamine induced cardiomyopathy

Diagnosis

- ↑ Glucose
- ↑ TLC

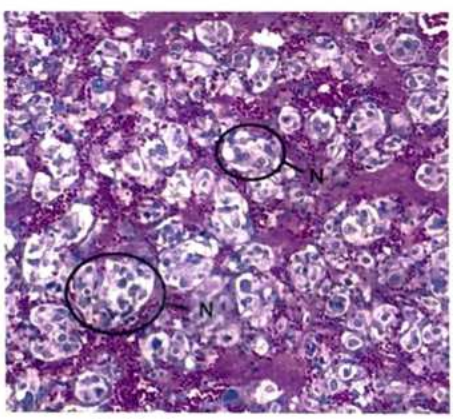
$$A/NA \xrightarrow{COMT} \text{Metanephrin/nor-metanephrine} \xrightarrow{MAO} VMA$$

- 24hr urinary metanephrine, VMA levels
- Radiology: MRI, MIBG Scan

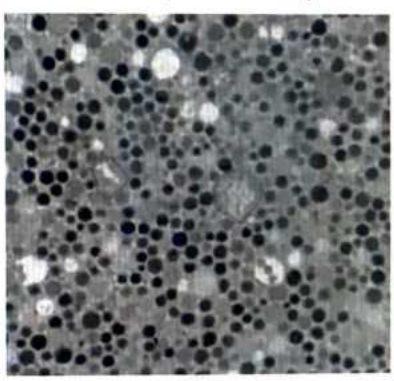


Gross appearance

- Yellowish appearance
- Presence of Hemorrhage & Necrosis
- Dichromate reaction: Potassium Dichromate application leads to Brown-Black appearance



Zellballen (nest of cells)



Neurosecretory granules

Microscopic appearance

- Group/cluster of tumor cells → Zellballen
- Nuclear appearance → salt & Pepper chromatin
- Tumor markers: chromogranin, Synaptophysin
- Sustentacular cells: S-100

Important Information

- Only reliable feature to differentiate malignant tumor from benign lesion is to demonstrate presence of metastasis

Treatment

- Surgery: definitive treatment
- Drugs: Labetalol (α+β#) to control BP

Previous Year's Questions

All of the following true about pheochromocytoma except? (JIPMER 2018)

A. 10% extra-renal
B. Increased urinary metanephrines is confirmatory for malignant tumor
C. Extra adrenal pheochromocytoma is mostly malignant
D. The usual extra adrenal site include organ of Zuckerkandl and carotid body

CLINICAL QUESTIONS

1) A 45-year-old woman complains of tingling in her hands and feet, 24 hours after removal of follicular thyroid carcinoma. Her symptoms rapidly progress to severe muscle cramps, laryngeal stridor, and convulsions. Which of the following laboratory findings would be expected in this patient prior to treatment?

A. Decreased serum calcium and decreased PTH
B. Decreased serum calcium and increased PTH
C. Increased serum calcium and decreased PTH
D. Increased serum calcium and increased PTH

Solution:

- Given clinical features point towards **hypocalcemia** resulted from **hypoparathyroidism**.
- **HYPOPARATHYROIDISM**
  - Most common cause is surgical resection of parathyroids as a complication of thyroidectomy.
  - Parathyroid levels falls→Hypocalcemia
  - Hypocalcemia→ ↑ Neuromuscular excitability → From mild tingling in hands & feet to severe muscle cramps, laryngeal stridor & convulsions.
  - Neuropsychiatric manifestations- Depression, Paranoia & Psychoses.
- Increased PTH in setting of parathyroid adenoma or paraneoplastic syndrome is associated with hypercalcemia **(choice D)**.

Reference:

- Robbins 10th edition, pg-1096

LEARNING OBJECTIVES

UNIT 19 CNS

- **CNS Disorders part 1**
  - Neurodegenerative Disorders
  - Findings of Alzheimer's Disease
  - Frontotemporal Lobe Degeneration
  - Parkinsonism
  - Huntington's Disease

- **CNS Disorders part 2**
  - General Features of CNS Tumors
  - Diffuse Astrocytic and Oligodendroglial Tumors
  - Oligodendroglioma
  - Meningioma
  - Schwannoma
  - Pilocytic Astrocytoma
  - Midline Glioma
  - Ependymoma
  - Primary CNS Lymphoma

97 CNS DISORDERS - 1

- 50% of cells are neurons and another 50% cells are glial cells.

Types

- Oligodendrocytes: Responsible formation of myelin in CNS

- Astrocytes
  - Responsible for blood-brain barrier
  - Associated with post-traumatic gliosis

- Ependymal cells: responsible for lining of ventricles
- Meningothelial cells: Responsible for covering /protection of brain.

- Microglia
  - Modified macrophages and are involved in process of phagocytosis.
  - In neuro-syphilis: "Rod cells"

NEURODEGENERATIVE DISORDERS 00:03:04

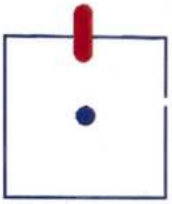
ALZHEIMER'S DISEASE

- MC cause of memory loss/dementia in humans

Variants

- Sporadic: Associated with ↑ Age
- Familial: Associated with Down syndrome
- Associated with early presentation
  - Presenilin 1 gene on chromosome 14
  - Presenlin 2 gene on chromosome 1
- Apo-lipoproteins
  - ApoE4 allele: ↑↑ risk
  - ApoE2 allele: ↓↓ risk

Pathophysiology



- APP (Amyloid Precursor Protein) present on chromosome 21
- Presenilin 1 & 2 gene contributes ↑ activity to β secretase

APP	
α secretase γ secretase ↓ Soluble fragment	β secretase γ secretase ↓ Insoluble fragment

Presentations

- Amyloid β plaque
  - Neuritic plaque: Central core of amyloid surrounded by neuritic plaques
  - Diffuse plaque: Central core of amyloid only without neuritic plaque.

- Tangles
  - Tau protein is responsible for stabilization of microtubules
  - Tau protein hyper-phosphorylation → loss of stability → Neurofibrillary tangles
  - ↑ Tangles is associated with ↑ dementia

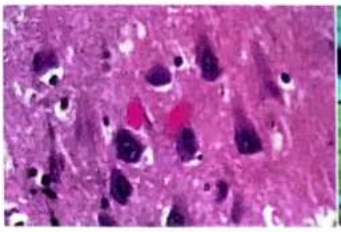
Findings 00:11:13

- Diffuse Cerebral Atrophy
  - Affects Frontal lobe, parietal lobe, Temporal lobe
  - Occipital lobe is involved in the last
  - Associated with involvement of Meyernet Nucleus

Important Information

- Neurofibrillary Tangles correlates with Severity of dementia and is best visualized by Silver Stain/Bielschowsky stain

- Neurofibrillary Tangles
- Aβ plaques
- HIRANO body: Actin aggregates
- Cerebral Amyloid Angiopathy: Aβ plaques around blood vessels → fragile blood vessel → ↑ Hemorrhage



HIRANO body

Bielschowsky stain

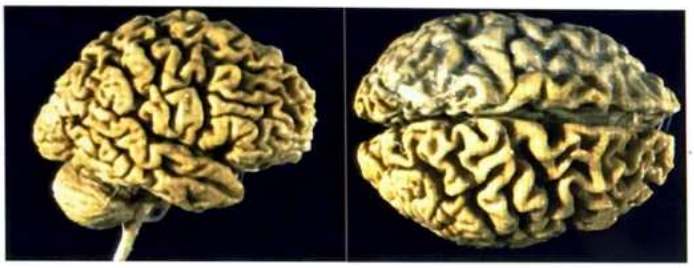
Previous Year's Questions

Q. Which of the following is not an alpha synucleinopathy? (AIIMS 2020)

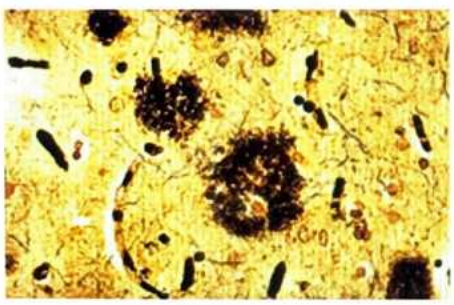
A. Parkinson's disease
B. Lewy body dementia
C. Alzheimer's disease
D. Multisystem atrophy

Clinical Features

- Short term memory
- Loss of smell
- Repeated infections: pneumonia (responsible for mortality)



Diffuse Cerebral Atrophy



Neuritic Plaque

Treatment

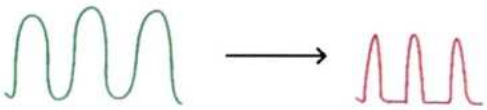
- Rivastigmine
- Donepezil
- Memantine

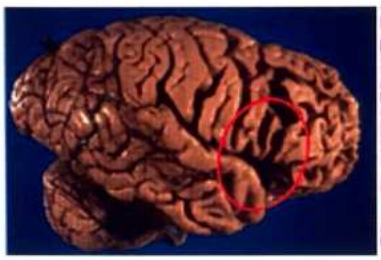
FRONTO TEMPORAL LOBE DEGENERATION 00:16:50

- Early
  - Frontal involvement: Behavioral defects
  - Temporal involvement: Language defects
- Late
  - Late Dementia

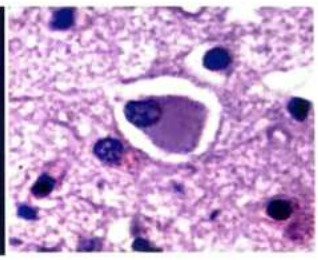
Variants

- FTLD: Tau / Pick's Disease (MC)
- FTLD: TDP
- RNA Protein TDP-43 present in nucleus, staining decrease

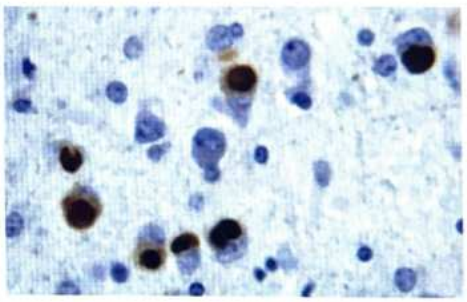




Whiffer thin gyri



Pick cell



Pick body (3R-TAU)

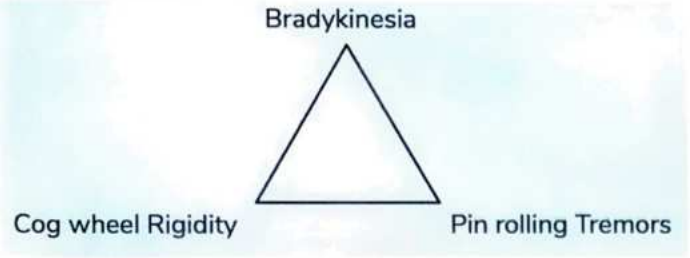
PARKINSONISM 00:19:26

- Dopaminergic pathway namely Nigrostrital pathway is involved.

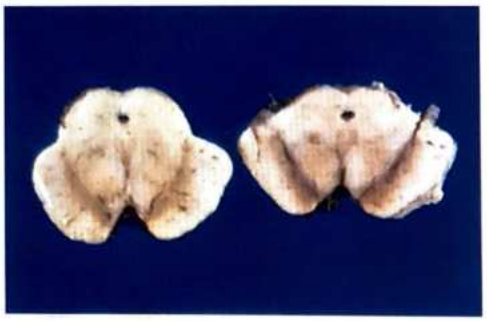
Risk Factors

- Age: Idiopathic (Parkinson's Disease)
- MPTP: Toxic byproduct of synthetic Meperidine
- Wilson disease
- CO poisoning
- Drugs (Typical antipsychotic drugs)

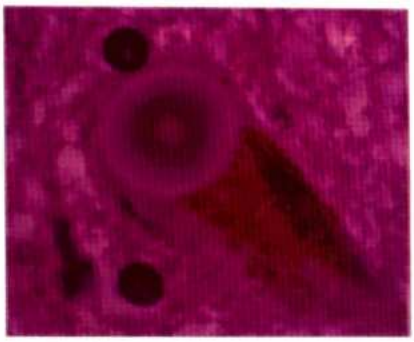
Clinical Features



- Festinating Gait
- Mask like Facies
- Stooping posture
- Drooling of saliva
- Seborrheic dermatitis



Loss of Dopaminergic Neurons



Lewy Body (α-synuclein)

HUNTINGTON'S DISEASE

00:23:57

Genetics

- Autosomal dominant inheritance
- CAG Repeats
- Chromosome 4
- Anticipation: Has paternal Transmission

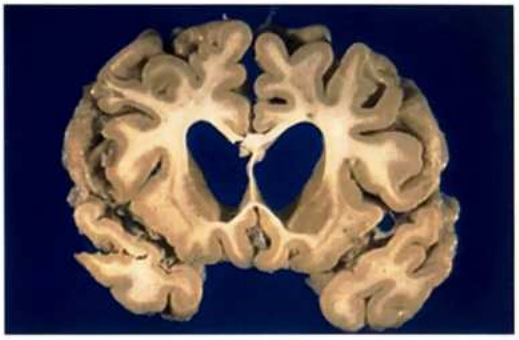
↑↑↑ CAG repeats with every Spermatogenesis

↓

Anticipation (early onset in next generation)

Clinical features

- Caudate Nucleus Atrophy → loss of inhibitory motor activity → ↑ activity
- Chorea/Athetosis
- Ocular manifestation
- Depression
- ↑ Infections (causes mortality)



Caudate atrophy

98 CNS DISORDERS - 2

CNS TUMORS

- 1° tumors
  - Solitary
- 2° Metastasis (MC)
  - Small cell lung cancer (MC metastasis)
  - Breast cancer: Leptomeningeal Metastasis, Spinal cord compression
  - Malignant melanoma
  - Renal cancer

Previous Year's Questions

Q. Most common site of intracranial metastasis is from primary carcinoma of? (FMGE 2018)

A. Breast
B. Lung
C. Stomach
D. Testes

GENERAL FEATURES OF CNS TUMORS 00:03:30

Clinical Features

- ↑ ICT
- Headache
- Nausea/vomiting
- Seizures

Diagnosis

- MRI: Gadolinium contrast

Risk Factors

- Smoking / Radiation
- Familial Syndromes
  - Turcot Syndrome: APC gene (↑ colorectal carcinoma)
  - Li - Fraumeni Syndrome: P53 gene
  - Gorlin Syndrome: PTCH gene
  - Cowden Syndrome: PTEN gene (BEST tumors)

Important Information

- Majority of adult brain tumors are supra-tentorial & infra-tentorial tumors are seen in pediatric age groups

WHO CLASSIFICATION 2016

- Based on Histology & molecular parameters
  - Atypical cells
  - Mitotic activity
  - Necrosis
  - Microvascular proliferation
- Molecular markers >>> histologic type
- GRADE I: Well-differentiated, Slow growth tumor with good prognosis
- Grade II: Anaplasia (+)
- Grade III: Anaplasia (+), high grade of mitosis
- GRADE IV: Highly Aggressive, poor prognosis (Grade III + Necrosis + endothelial cell proliferation)

Major Classes of CNS tumor

- Glial Tumors: Astrocytoma, oligodendroglioma, Ependymoma
- Neuronal Tumors: Ganglio-glioma, Dysembryoplastic Neuro-Epithelial Tumor, Central Neurocytoma
- Poorly Differentiated Tumor: Medulloblastoma, Atypical Teratoid/Rhabdoid Tumor
- Other Tumors: 1° CNS Lymphoma, Meningioma, Germ cell tumor

DIFFUSE ASTROCYTIC AND OLIGODENDROGLIAL TUMORS 00:14:56

- $IDH_{1/2}$ gene mutation

Astrocytoma

- Previously divided into:
  - Diffuse infiltrating Astrocytoma
  - Localized Astrocytoma: Pilocytic Astrocytoma
- Diffuse Infiltrating Astrocytoma
  - Grade II: Diffuse Astrocytoma
  - Grade III: Anaplastic Astrocytoma
  - Grade IV: Glioblastoma
- MC 1° malignant Brain tumor in adults
- Involvement of cerebral hemisphere
- Butterfly tumor: Crosses to the other hemisphere

GLIOBLASTOMA

Types

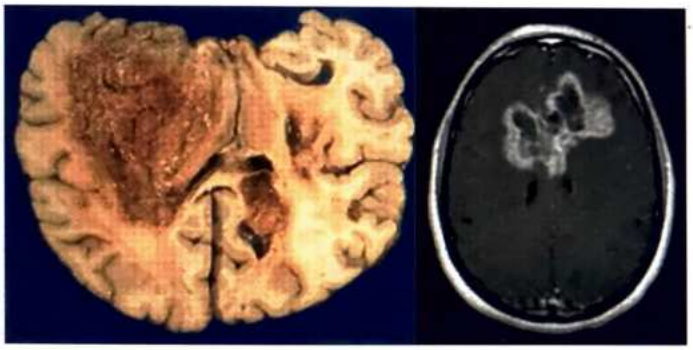
- Wild Type: No IDH mutation (MC)
- Mutant IDH glioblastoma: $IDH_{1/2}$ gene mutation is present
- Not otherwise specified

IDH_1 Wild Type Glioblastoma	IDH_1 Mutant Glioblastoma
• Denovo/1° GB • > 90% • Elderly patient • Supra-tentorial • TERT promoter/ EgFR amplification/ PTEN • Poor prognosis	• 2° GB • 10% • Younger patient • Frontal • P53/ ATRX • Good prognosis

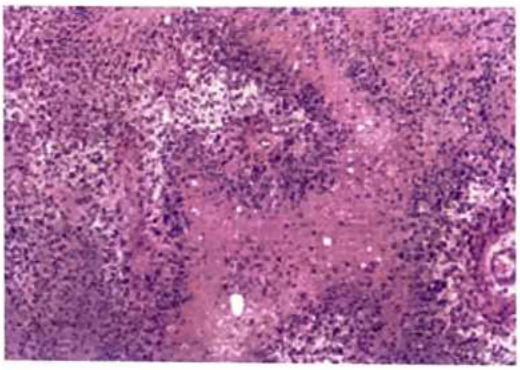
Diagnosis
- MRI

Microscopic Findings
- Pseudo-palisading: Serpentine necrosis with arrangement of tumor cells in fence like pattern
- Glomeruloid body: Excessive endothelial cell proliferation (minimum 2 layers)

Important Information
- True-palisading: Tumor cells arranged in fence like pattern without necrosis. It is seen in schwannoma



Glioblastoma Butterfly Tumor



Pseudo-palisading

Previous Year's Questions
Q. A 15 year old presents with a history of pain and swelling in the right thigh. Biopsy of mass demonstrate osteosarcoma. His mother was diagnosed with breast cancer 1 year age and his maternal grandmother died of breast cancer 10 year age. The patient has 3 younger siblings. The siblings have an increased risk of developing which of the following? (JIPMER May 2019)

A. Wilms
B. Neuroblastoma
C. Hepatoblastoma
D. Glioma

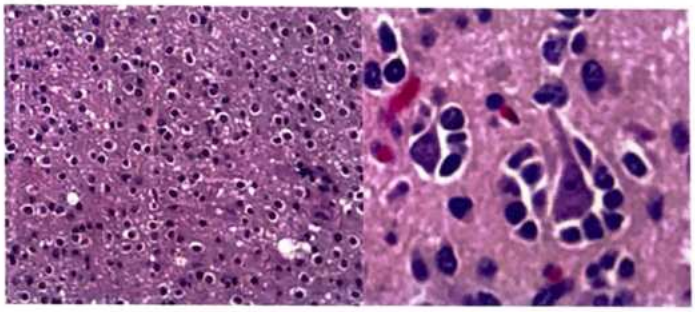
Gliomatosis cerebri
- New pattern of glioblastoma
- Highly aggressive in nature
- It arises from supra-tentorial area and it can grow into infra-tentorial area
- It involves >3 hemispheres

Treatment
- Surgical Resection
- Radiotherapy
- Temozolomide

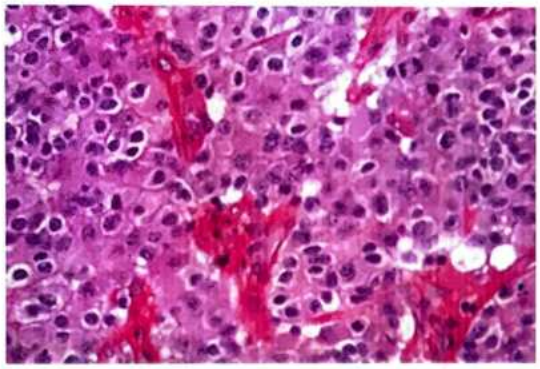
OLIGODENDROGLIOMA
00:28:50
- $IDH_{1/2}$ mutation + 1p/ 19q co-deletion
- Seen in 4th - 5th decade
- White matter involvement: Frontal lobe + calcification

Diagnosis
- MRI

Microscopic findings
- Fried Egg Appearance
- Peri-neuronal Satelittosis
- Chicken Wire Capillaries



Fried-egg appearance Peri-neuronal satellitosis



Chicken-wire capillaries

WHO 2016 update

- Oligodendroglioma: $IDH_{1/2}$ mutation + 1p/ 19q co-deletion, better prognosis
- Oligodendroglioma: IDH wild type; NOS
- Oligodendroglioma: NOS

Treatment

- Surgical resection
- Radiotherapy
- Chemotherapy

Malignancies of CNS with calcification

- Meningioma
- Oligodendroglioma
- Cranio-pharyngioma
  - Supra-sellar calcification
  - Arises from Rathke's pouch
  - Seen in children

MENINGIOMA

00:34:.08

- Arises from arachnoid meningothelial Cells
- MC 1° brain tumor of adults
- Benign tumor
- Sex predilection: F >>> M
- Progesterone receptor (+): ↑ in tumor Size during pregnancy

Risk Factors

- Radiation
- Gene mutation
  - NF 2 gene mutation due to deletion of Chromosome 22q12 [50-60%] → B/L meningioma
  - TRAF-7 gene mutation (low grade meningioma)

Clinical features

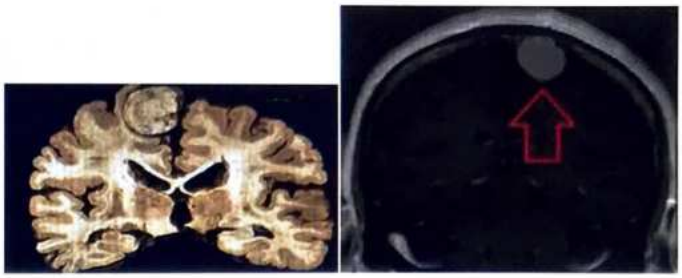
- Solitary tumor (exception: B/L tumor are seen in NF 2)
- Slow growth rate
- Headache, seizures
- Incidental finding

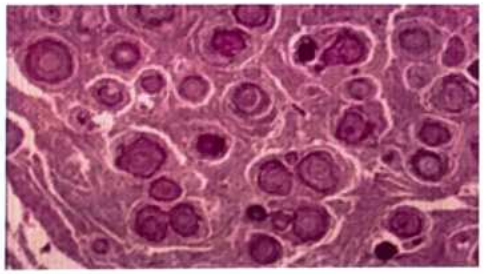
Diagnosis

- MRI (Dural Tail sign)

Microscopic features

- Concentric rings of calcification: Psammoma Body
- Immuno-histochemistry: EMA +ve (Epithelial membrane Antigen)





Psammoma Body

Subtypes

- Grade I: Meningioma → Fibroblastic/syncytical/secretory
  - Keratin/CEA +ve
- Grade II: Atypical meningioma
  - Brain invasion – single diagnostic criteria
- Grade III: Anaplastic meningioma

SCHWANNOMA

00:45:22

- Peripheral Nerve sheath tumor
- Benign Tumor
- It arises from Schwann cells of
  - Peripheral Nerves
  - Cranial nerves: 8^{th} >> 5^{th}

Pathogenesis

NF2 gene mutation
↓
↓ MERLIN
↓
↑EgFR
↓
↑ Cells

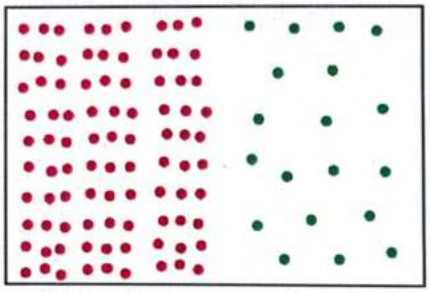
Acoustic Neuroma

- Vestibular part of 8^{th} CN
- Aka Vestibular schwannoma

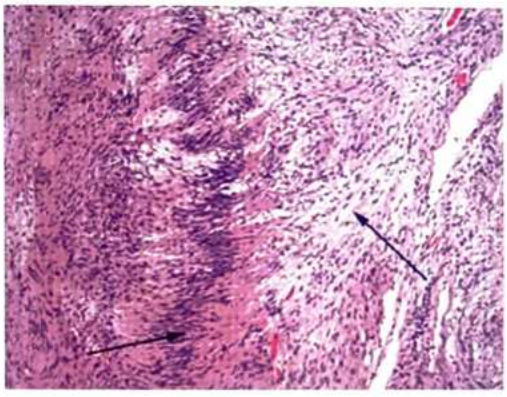
- Triad
  - Tinnitus
  - SNHL
  - ↓ corneal reflex

Diagnosis
- MRI: Gadolinium enhanced
- IHC: S-100 +VE

Microscopic findings
- Antony 'A' area: Hypercellular
- Antony 'B' area: ↓ cells



- Verocay Body: Nuclear free area
- Presence of true palisading



Previous Year's Questions

Q. A 20 year old present with swelling in the wrist joint for 2 year duration. Histopathological examination showed spindle shaped calls and verocay bodies. Which of the following is the diagnosis? (NEET Jan 2020)

A. Neurofibroma
B. Schwannoma
C. Lipoma
D. Dermoid cyst

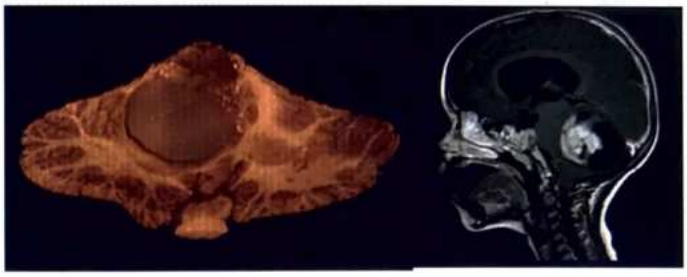
PEDIATRIC CNS TUMORS

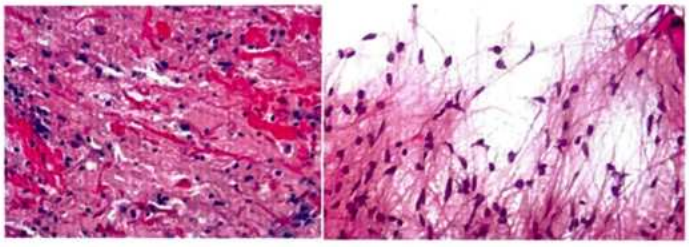
PILOCYTIC ASTROCYTOMA

00:52:01

"C"
- MC 1° benign brain tumor of children
- Grade I Astrocytoma
- NF-1, BRAF mutation
- Cerebellum >> 3rd ventricle
  Cystic mass

Microscopic findings
- Biphasic tumor: micro cystic + Fibrillary Area
- Bipolar cells: Hair like process with gFAP staining +ve
- Rosenthal Fibers (intra cytoplasmic Red-Pink inclusions)





Rosenthal fibers Bipolar Hair-like cells

MIDLINE GLIOMA

00:57:03

- Site: Pons > Spinal cord/Thalamus
- Associated with k27M mutation (+) in Histone H_3 gene

MEDULLOBLASTOMA

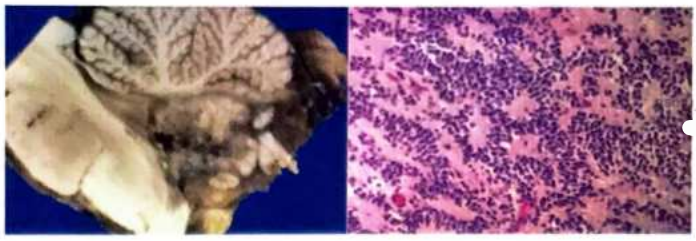
- MC 1° malignant brain tumor in children with midline origin
  - In adults it is lateral in location
- Arises in cerebellum
- Grade IV tumor

Important Information

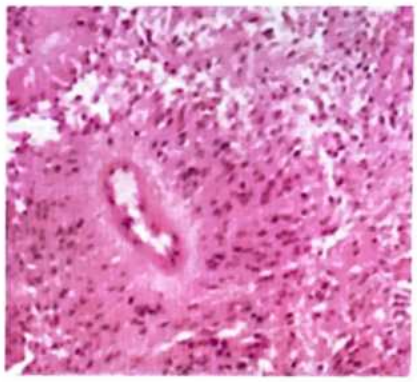
- Medulloblastoma arises from cerebellum and infiltrates distal sites with the help of CSF - Drop Metastasis

Microscopic Findings
- Sheet of anaplastic cells (small/round blue cells)

- Homer Wright Pseudo-Rosette: Flower like arrangement of tumor cells around the fibrillary core
- ↑ Mitosis: ki–67 +ve



Homer Wright Pseudo-rosette



Perivascular Pseudorosette

WHO classification 2016 update

- WNT TYPE
  - Associated with monosomy 6 & β catenin over activity
  - Best prognosis
- SHH TYPE
  - p53 mutant: High risk
  - p53 wild type: Low risk
  - Intermediate prognosis
- Group 3 Medulloblastoma
  - Over amplification MYC/presence of i17q
  - Worst prognosis
- Group 4 Medulloblastoma
  - i17q presence only
  - Intermediate prognosis

Treatment

- Radiosensitive tumor
- Surgery/Radiotherapy

EPENDYMOMA

01:06:31

- Malignant tumor
- Child: < 20yrs → 4th ventricle
  - Hydrocephalus
  - CSF spread
  - Poor prognosis
- Adult: spinal cord → NF-2 gene

Microscopic findings

- Perivascular Pseudo-rosette: Tumor cells surrounding a blood vessel with intervening area due to presence of ependymal processes
- gFAP +ve (Glial fibrillary Acidic Protein)
- Poor Prognosis

VARIANT OF EPENDYMOMA

Ependymoma Rela-fusion positive

- Seen in children
- Supra-tentorial location
- L1CAM expressed

Myxopapillary ependydoma

- Location: Filum Terminate of spinal cord
- Ependymoma-like cells
- Papillary elements in myxoid background (mucopolysachhride)

1° CNS LYMPHOMA

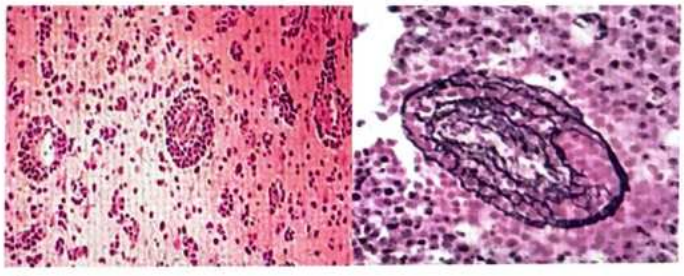
01:10:35

Etiology

- EBV infection: Immunosuppression
  - H/O AIDS
  - Post-transplant patients
- B-cell tumor (DLBCL)
- Multifocal tumor

Microscopic findings

- Hooping
  - Characteristic Finding (distinguishes from 2° CNS lymphoma)
  - Blood vessel surrounded by tumor cells Separated by reticulin or silver staining material



Hooping

CLINICAL QUESTIONS

A 44-year-old man presents with involuntary facial grimaces and movements of the fingers. His mother also had same symptoms started at approximately same age. Her disorder also had progressed from dancing movements, writhing of the arms and legs, and finally coma and death. His maternal grandfather also had a similar disorder but at an age older than the mother. Which of the following is most defining characteristic of this disease?

A. Degeneration of upper and lower motor neurons
B. Dopamine depletion and depigmentation of the substantia nigra
C. Increased number of trinucleotide repeats in a gene on chromosome 4
D. Neurofibrillary tangles and amyloid plaques in the cerebral cortex

Solution:

- This is a case of Huntington disease,
  - Autosomal Dominant,
  - Fatal, progressive degeneration and atrophy of the Striatum (Caudate nucleus and Putamen).
  - Characterized by an increased number of trinucleotide repeats(CAG) in huntingtin gene on the short arm of the chromosome 4.
- Degeneration of the upper and lower motor neurons is characteristic of ALS.
- Dopamine depletion and depigmentation of the substantia nigra is characteristic of Parkinson disease.
- Neurofibrillary tangles and amyloid plaques are found in Alzheimer disease.
- Pick bodies can be found in Pick disease, which clinically resembles Alzheimer disease

Reference:

- Robbins 10ed p1285

PREP NUGGETS

Prep Nuggets

Substance	Stain
Glycogen	_____
Lipids	_____
Amyloid	_____
Calcium	_____
Hemosiderin	_____
Connective tissue	Trichrome stain

Prep Nuggets

Antibody	Disease
Anti-Ro/La	_____
Anti-Sm Antigen	_____
Anti-CCP	_____
Anti-mitochondrial Ab (AMA)	_____

Prep Nuggets

Type of muscular dystrophy	Inheritance
Duchenne muscular dystrophy	_____
Emery-Dreifuss muscular dystrophy	_____
Myotonic dystrophy	_____
Becker muscular dystrophy	_____

Prep Nuggets

Disorder	Mutation/Translocation
Chronic myeloid leukemia	_____
Polycythemia vera	_____
Essential thrombocythemia/Primary myelofibrosis	_____
Systemic mastocytosis	_____
Chronic eosinophilic leukemia	_____
Chronic neutrophilic leukemia	_____