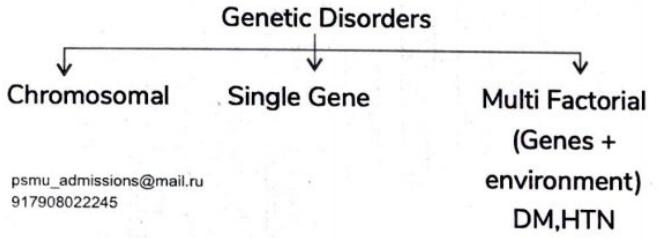
25 INTRODUCTION TO GENETICS

- 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%



psmu_admissions@mail.ru
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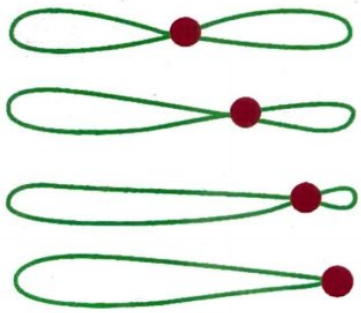
CHROMOSOMAL DISORDERS

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

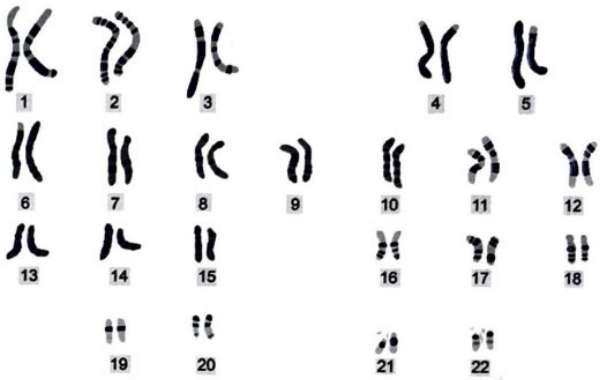


  - Metacentric: centromere present in the middle
  - Sub-metacentric: centromere present slightly on one side of middle (example: X chromosome)
  - Acro-Centric: centromere present towards one end (example: Y/13/ 14/15/ 21/22 chromosome)
  - Telocentric: centromere present right at the tip (not seen in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

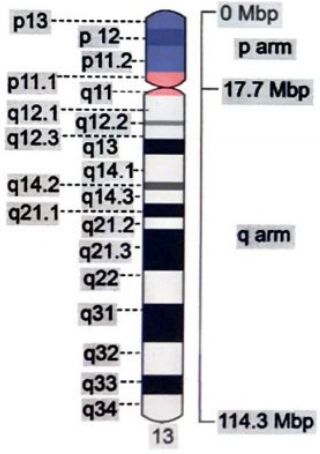
Karyotyping

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

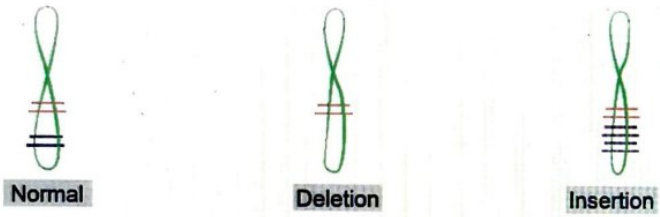
Important Information

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

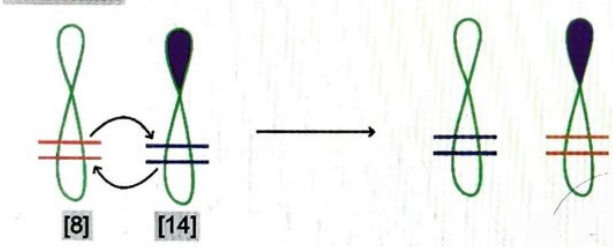
STRUCTURAL DEFECTS

00:16:37

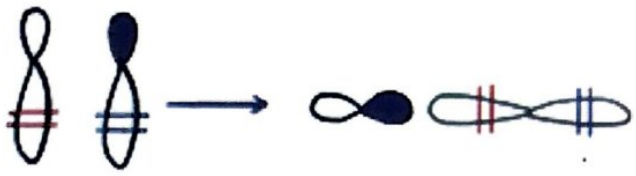
- Change in number of genes



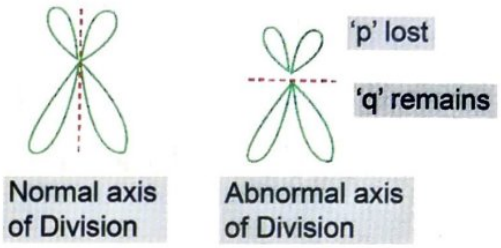
  - Change in position of genes: Inversion
  - Example: inversion (16) → AML-M4



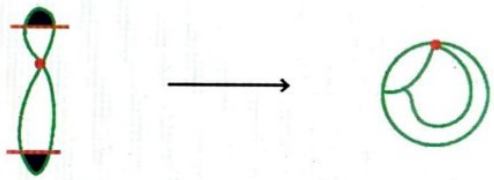
- Balanced Translocation
  - Equal amount of genetic material is exchanged
  - No loss of genetic material
  - t(8; 14) → Burkitt's Lymphoma



- 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

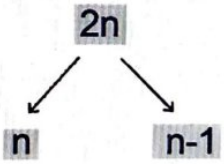


  - Defect at the edge of chromosome → loss of genetic material → 2 ends will fuse with each other
  - Example: Turner Syndrome → 46xy(x)

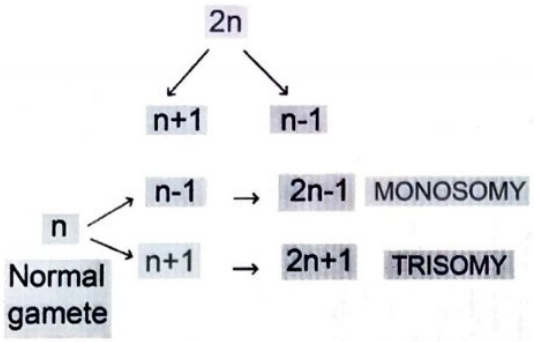
Aneuploidy

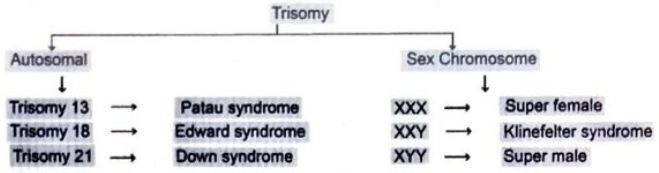
00:28:49

- Anaphase lag

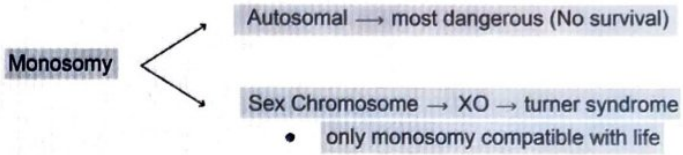


- Meiotic Non–Disjunction (unequal distribution of chromosome)





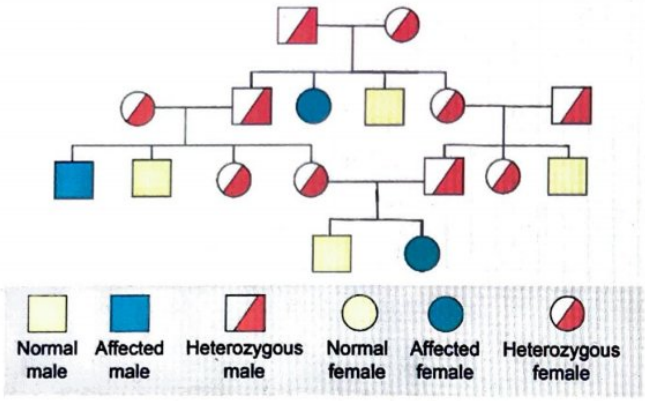
- MC Trisomy 16



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

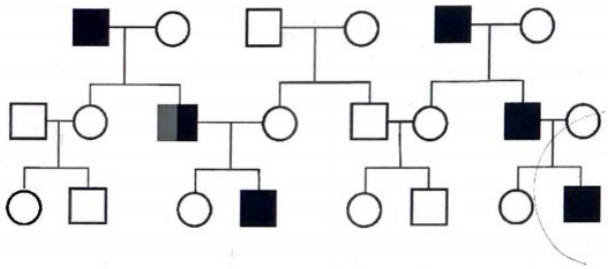
SEX LINKED INHERITANCE

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'**

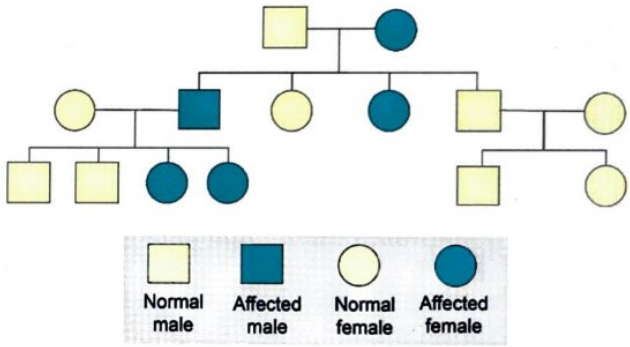
X Linked Recessive Disorders

- 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

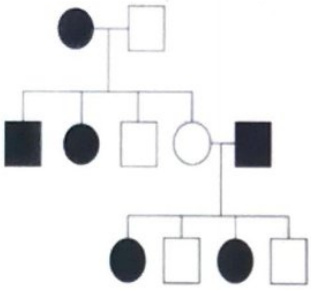
00:36:08



- 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)



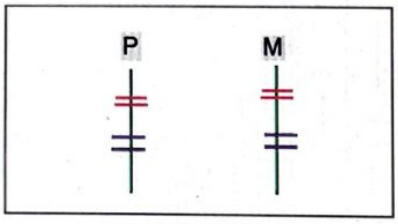
A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X-linked recessive

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



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

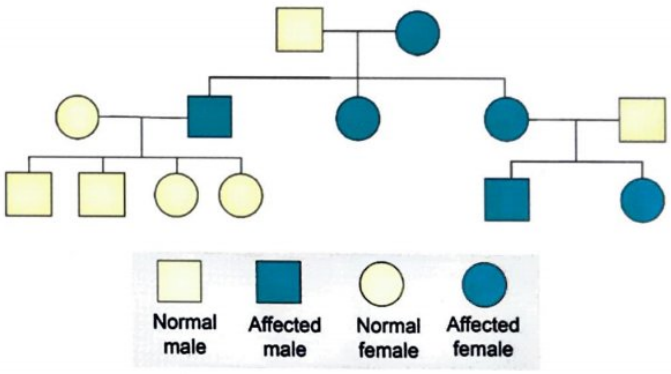
Genomic Imprinting

- 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

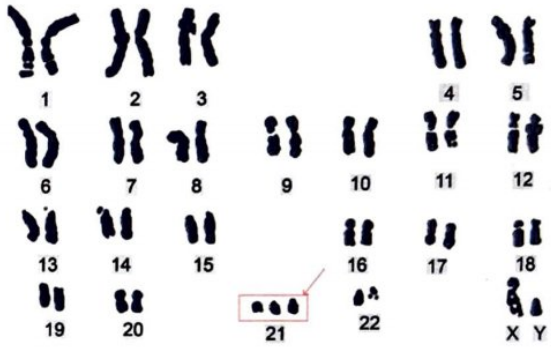
Clinical features

- 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
  - 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
- Familial Down syndrome → Robertsonian translocation



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

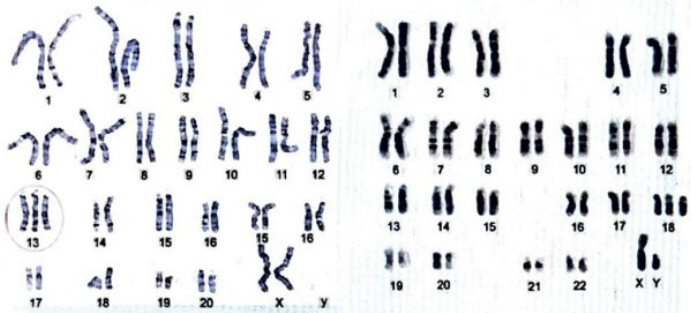
FEATURES OF OTHER TRISOMIES (13/18)

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



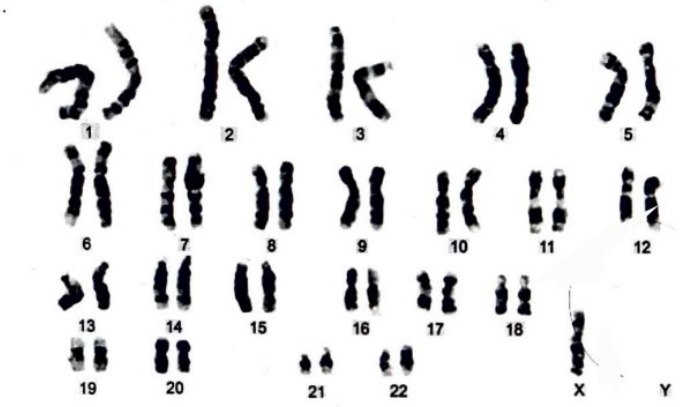
TURNER SYNDROME

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

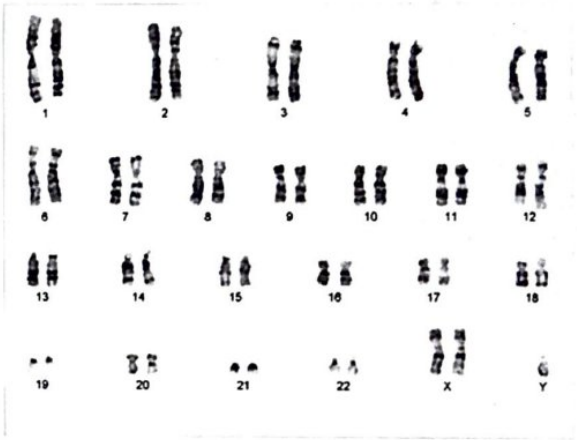
KLINEFELTER SYNDROME

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

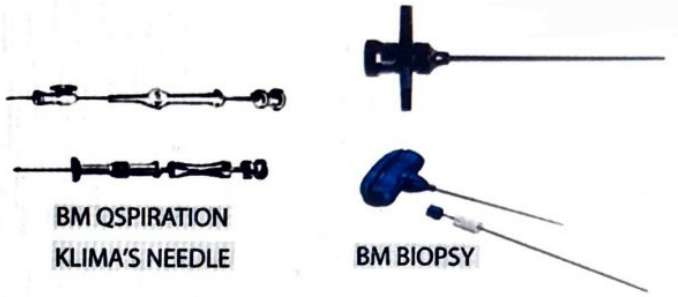
HSC
↓
MSC

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

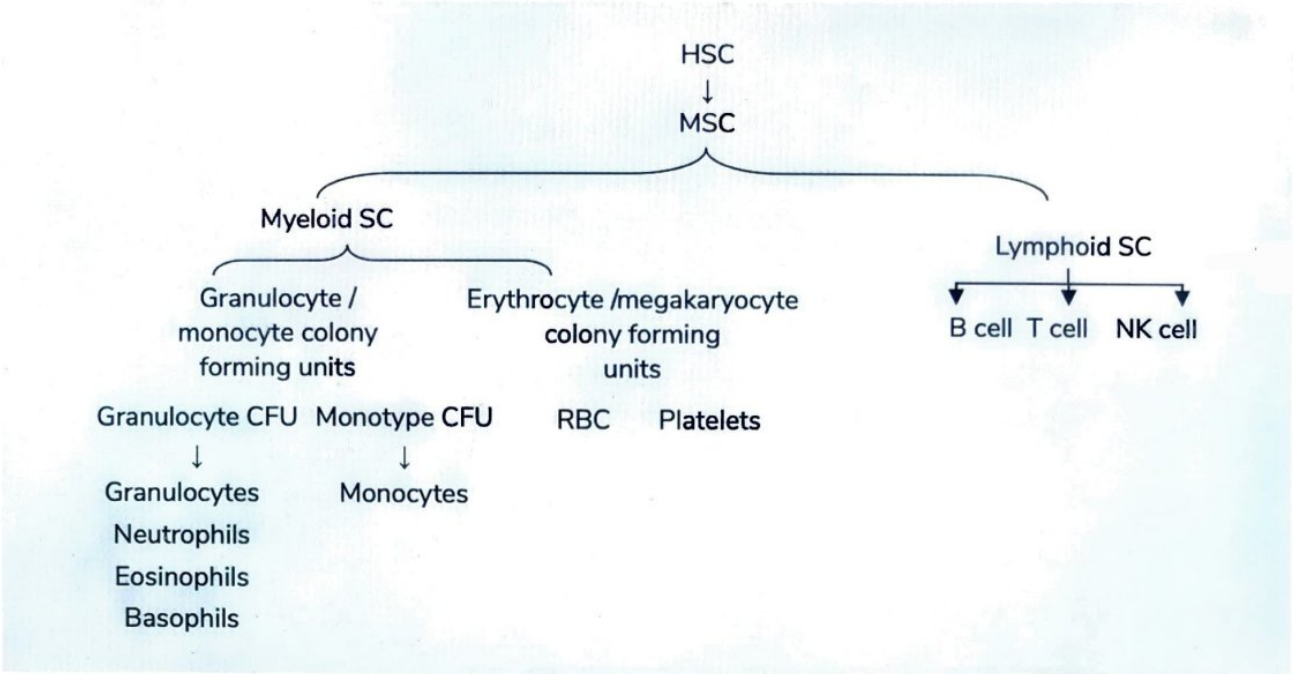
BM Examination 00:06:35



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]

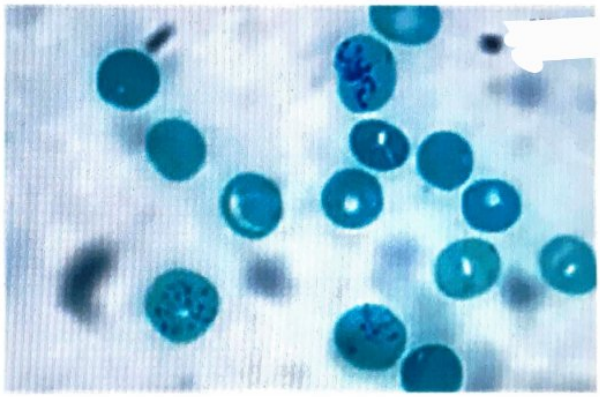
Normoblast
- Early: has a bluish cytoplasm so K/a Basophilic Normoblast
- Intermediate: Aka Polychromatophilic Normoblast, Hb can be detected by routine staining
- Late: Aka Ortho chromatophilic Normoblast

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

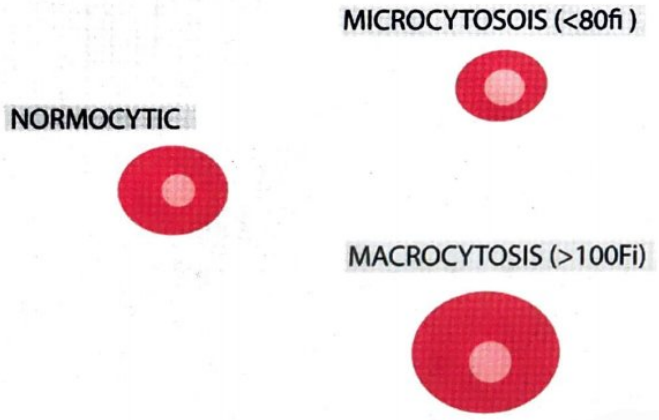
- Reticulocyte count Estimation gives Bm Activity aka 'Poor Man's Bm Aspiration'
- RPI <2.5 indicates: Decreased proliferation/ Decreased Maturation
- RPI > 2.5 indicates: hemolytic anemia
- Increased Reticulocyte count
  - Hemolytic anemia
  - Fe/FA/B12 Supplementation
- Decreased Reticulocyte count
  - 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	$\frac{\text{MCH}}{\text{MCV}}$



- $\text{MCV} = \frac{\text{Hematocrit} \times 10}{\text{RBC count}}$
- 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

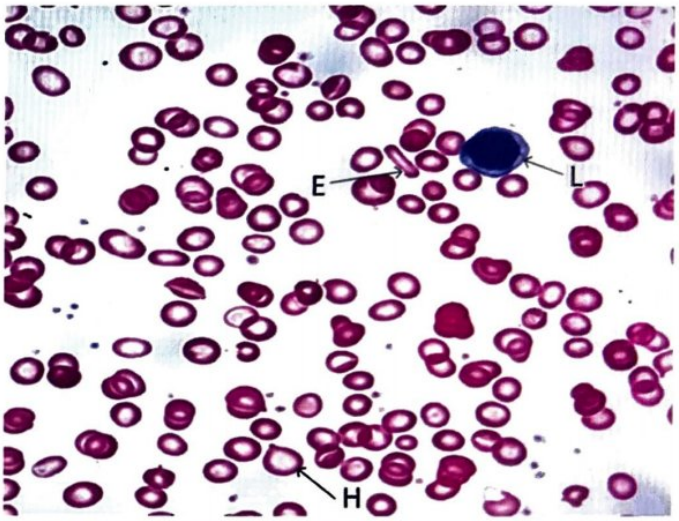
Q. Which of the following interfere with iron absorption? (FMGE June 2019)
A. Vitamin C
B. Phytates
C. Oxalate
D. Myoglobin

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

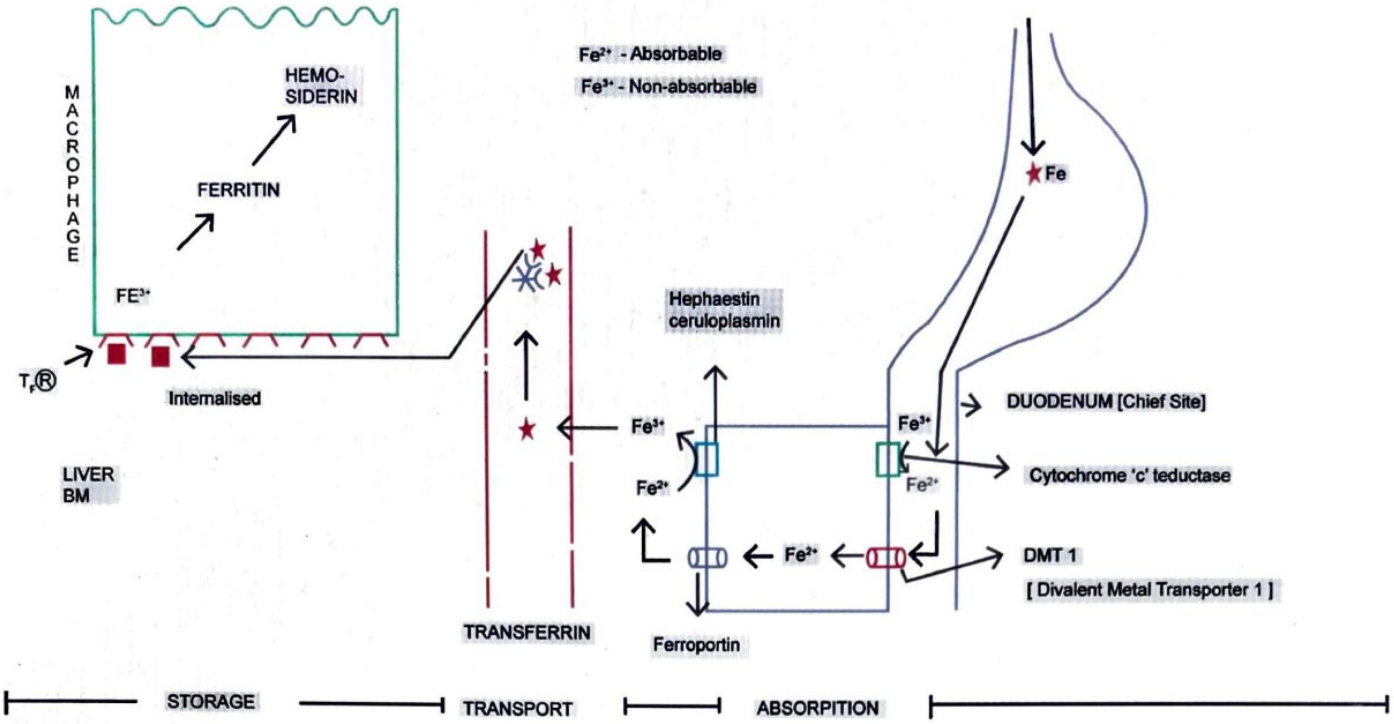
- SITA

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



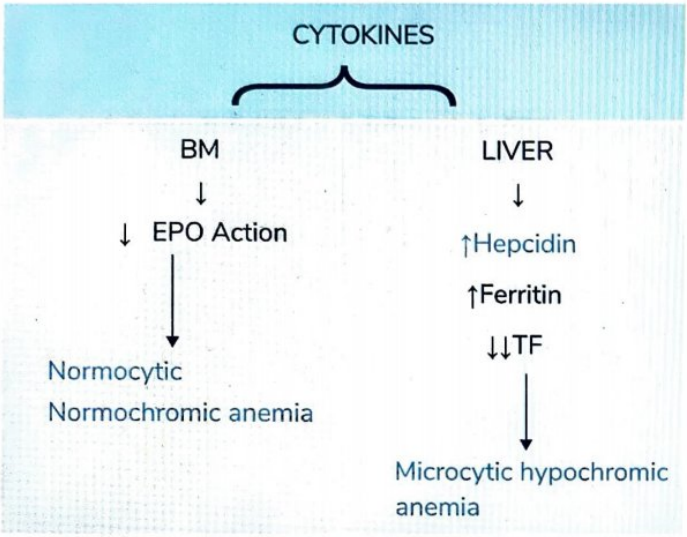
32 MICROCYTIC ANEMIA PART-2

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

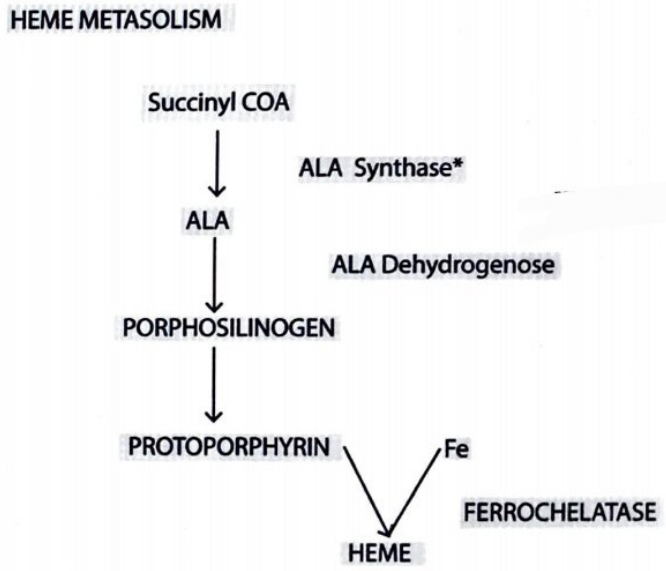
Treatment

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

SIDEROBLASTIC ANAEMIA

00:12:16

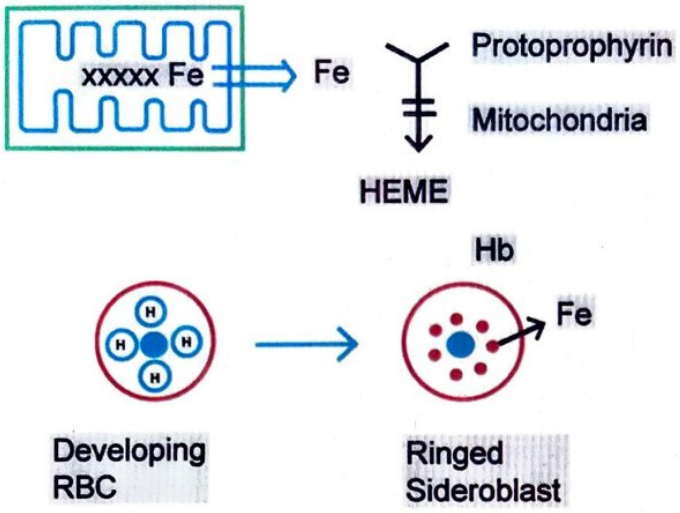
Heme Metabolism



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

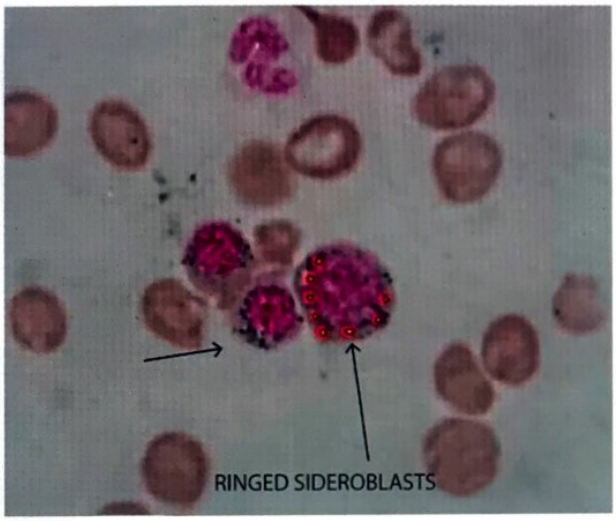


- Fe → damage to RBC Precursor→ Leakage of Iron → Iron Overload
- On BM examination Ringed sideroblasts can be seen
- Ringed sideroblast are seen in
  - Sideroblastic anemia
  - Myelodysplastic syndrome
  - Thalassemia
  - Megaloblastic anemia (B_{12}/ Folic acid deficiency)
  - Hemolytic anemias

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

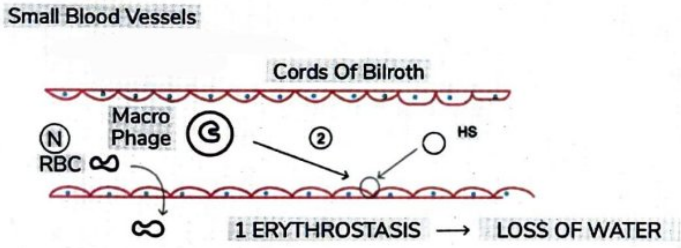
HEREDITARY SPHEROCYTOSIS

00:00:23

- Autosomal dominant

Normal Physiology of the RBC

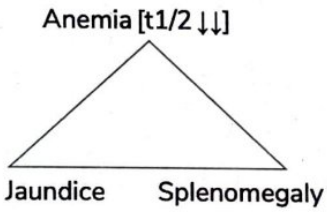
- Shape is Biconcave
- Biconcavity is due to membrane proteins
  - Spectrin: Most important membrane protein contributing to shape of the RBC
  - Ankyrin
  - Band 3
  - Band 4.1
  - Glycophorin: most abundant
- Size: 7 to 8 microns
- Normal lifespan: 100 – 120 days
- Most important membrane proteins 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

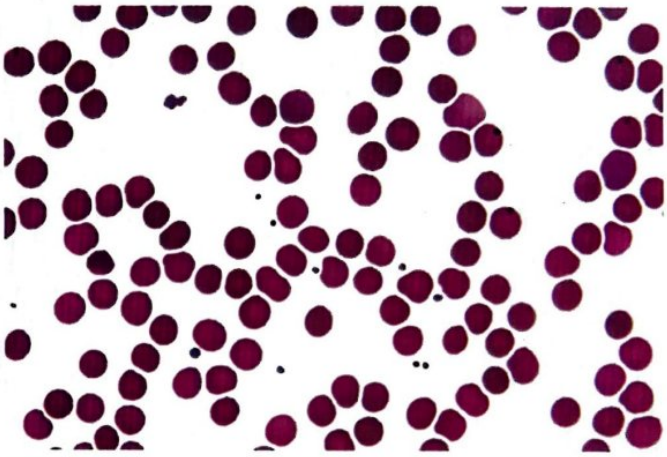
- Extravascular hemolytic anemia
- Splenomegaly
- Jaundice



Diagnosis

00:07:43

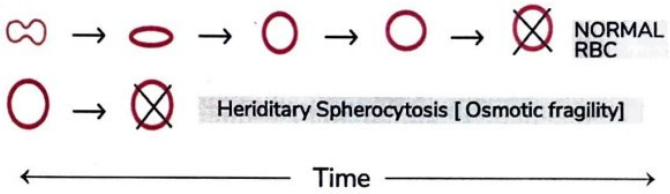
1. BM Examination → ↑ Cells / ↑ reticulocytes
2. Blood
   - ↓ Hb / ↑ LDH / ↓ S. Haptoglobin
   - MCH → (N)
   - MCV → ↓
   - MCHC → ↑↑↑ $\left[\frac{MCH}{MCV}\right]$
   - P/SMEAR Shows Spherocytes [no central pallor]



Important Information

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

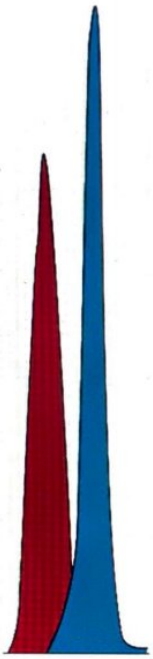
3. Osmotic Fragility Test/ Pink test [RBC in hypotonic solution]



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

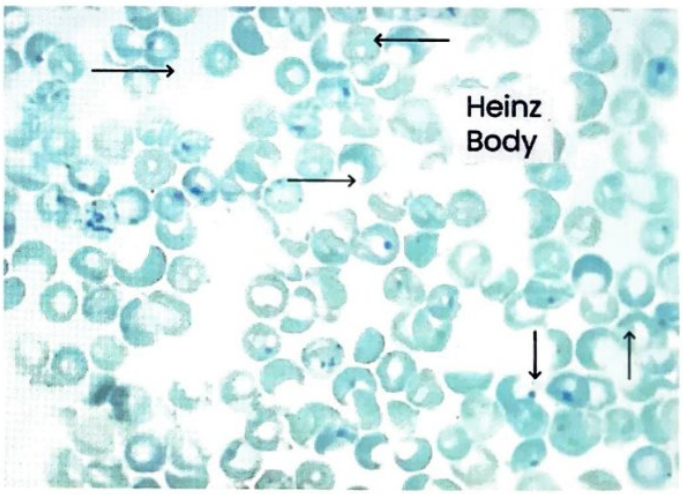
G6PD DEFICIENCY 00:21:57

- 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

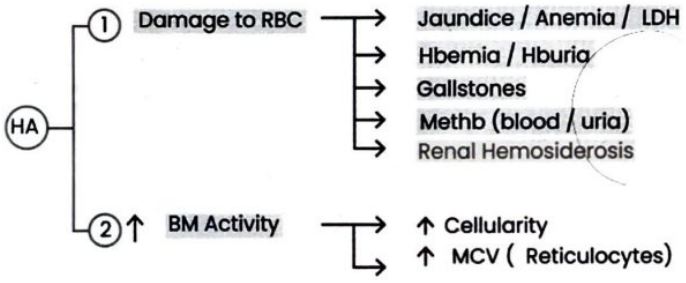
Refer Image 34.1

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 valve of Heptoglobin is seen with Bile duct obstruction

Causes of HA 00:16:27

Refer Table 34.1

Image 34.1

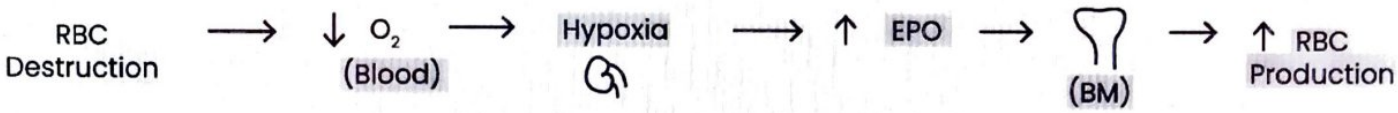


Table 34.1

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

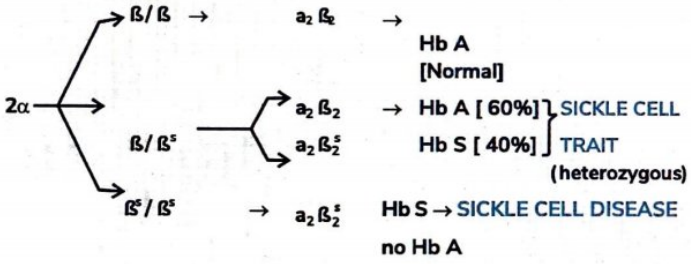
- Point mutation →
  - Glutamic Acid [Norma] (β) Polar AA
  - β6 AMINO Acid: Valine [Sickle cell anemia] (β^s) Neutral AA

How to remember

- Glutamic acid Goes and valine velcomes

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

→ 2ß → Hb F $\alpha_2\gamma_2$

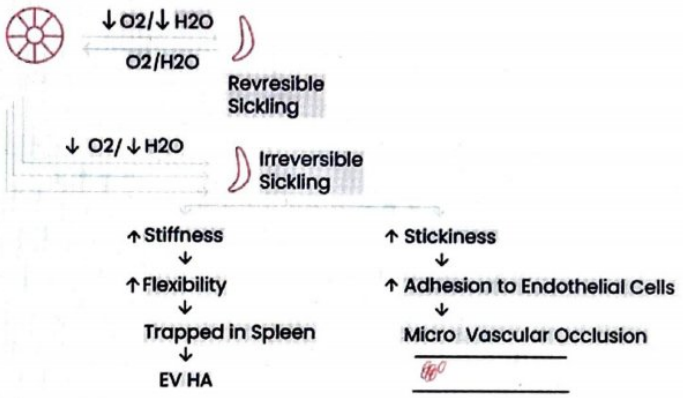


Important Information

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

Hemoglobin S

00:03:20



Clinical Features

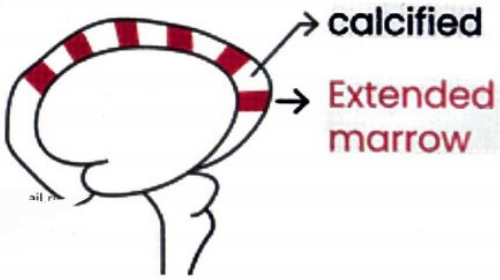
00:04:25

- 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



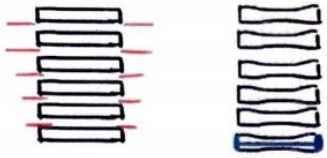
Calcified area

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)

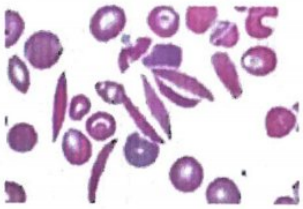
Previous Year's Questions

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

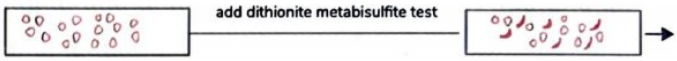
DIAGNOSIS 00:09:42

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



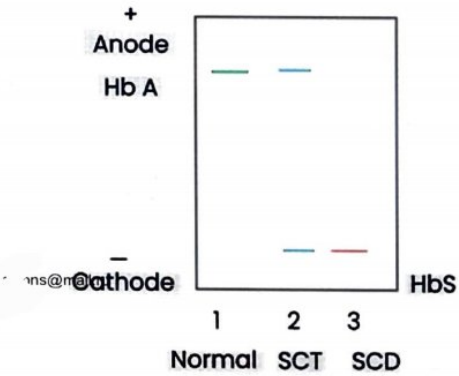
Drepanocyte

- 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]



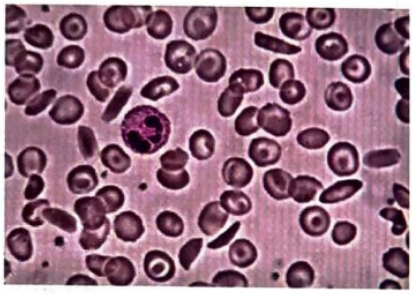
  - Limitation: Require expertise
- Genetic analysis - IOC
- HPLC - HIGH PERFORMANCE LIQUID CHROMATOGRAPHY
  - Can differentiate the types of Hb
  - Quantity of Hb S can be known
  - IOC (If genetic analysis is not in option)

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

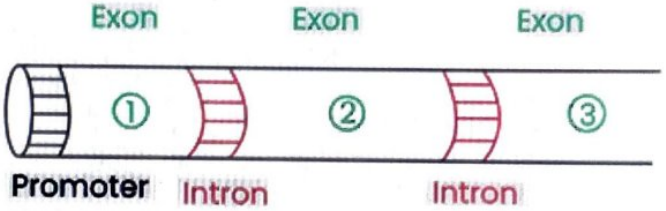
- Sickle cell of RBC – due to the amount of Hb S present in the RBC

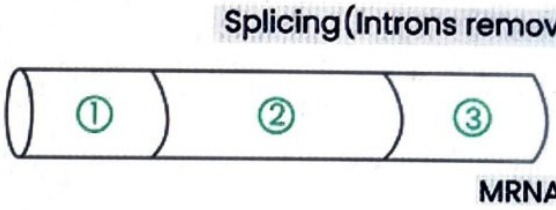
THALASSEMIA 00:18:20

- 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 ($\alpha_{2\gamma2}$) (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
- β°/β° 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

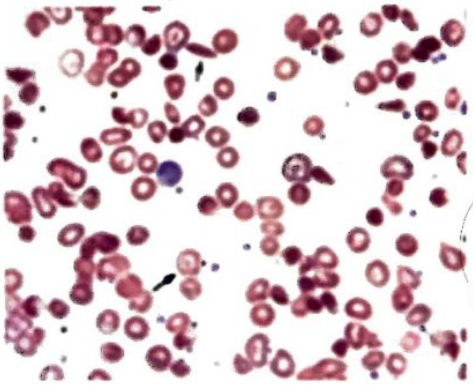
- Erythroferrone - Hormone acting on the liver to suppress Hepcidin
- Hepcidin acts negatively Iron regulator
- I° hemochromatosis – genetic defect at the level of iron
- 2° hemochromatosis – Extra amount of iron because of other causes

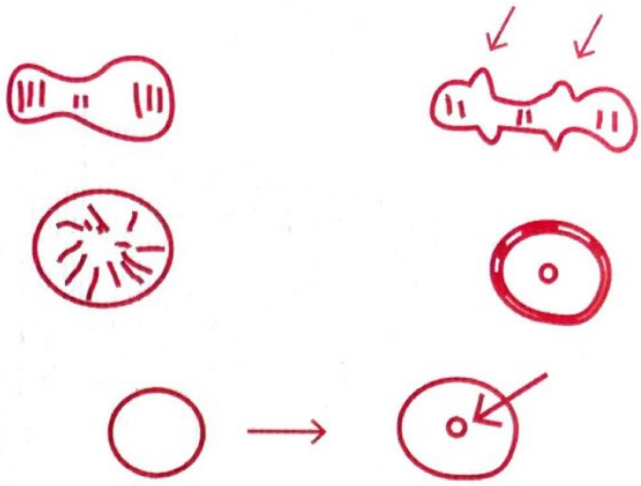
DIAGNOSIS 00:44:00

- 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

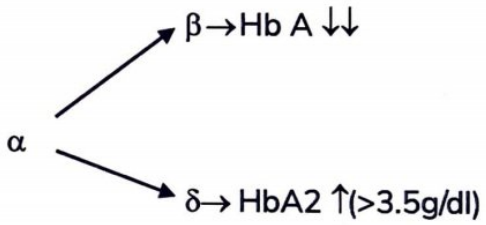
- NEST ROF TEST
  - NE – Naked eye
  - ST – Single tube
  - R – Red cell
  - OF – Osmotic Fragility
  - TEST
- OSMOTIC fragility → ↓
- Procedure
  - Mix Hypotonic Saline [5 ml] with 0.2 ml Blood
  - Wait for 30 minutes

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.

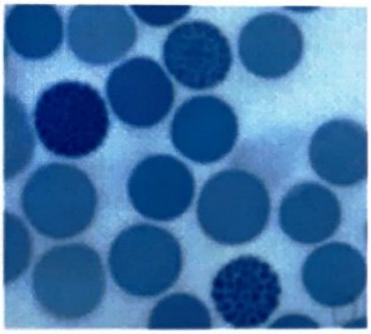
ALPHA THALASSEMIA

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]

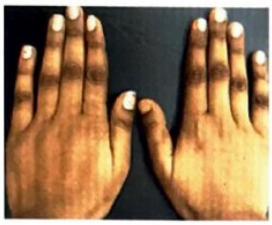
- Basophilic Stippling+[Abnormal RBC precursor]
- Howell Jolly bodies +
- Cabot ring +
- Hypersegmented neutrophils

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

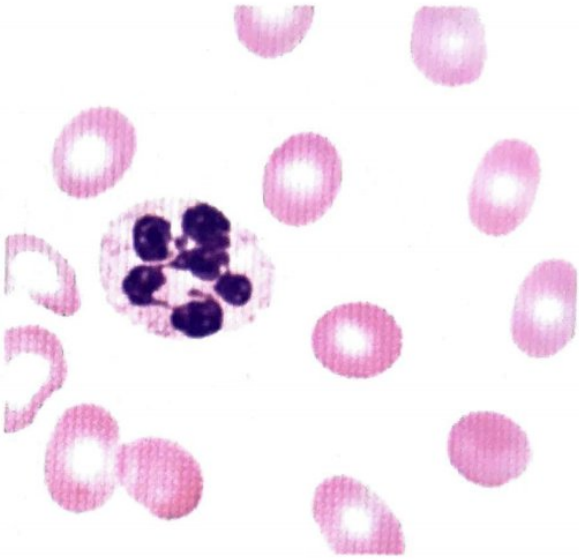
Important Information

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

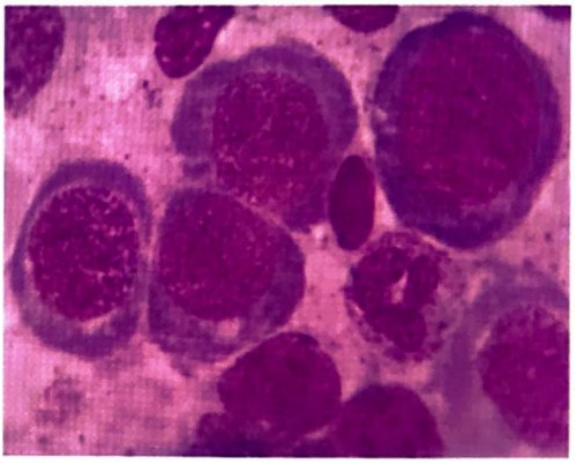
Previous Year's Questions

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)

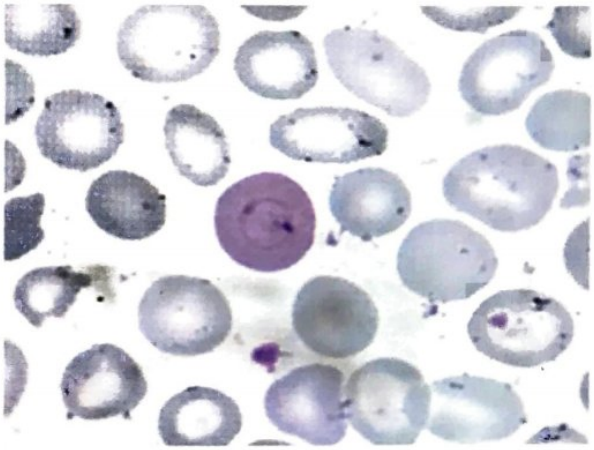
A. Folate not absorbed
B. Folic acid deficiency unmasked pyridoxin deficiency
C. Deficiency of folate reductase in CNS
D. Folate therapy cause rapid use of B12 stores aggravating symptom



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

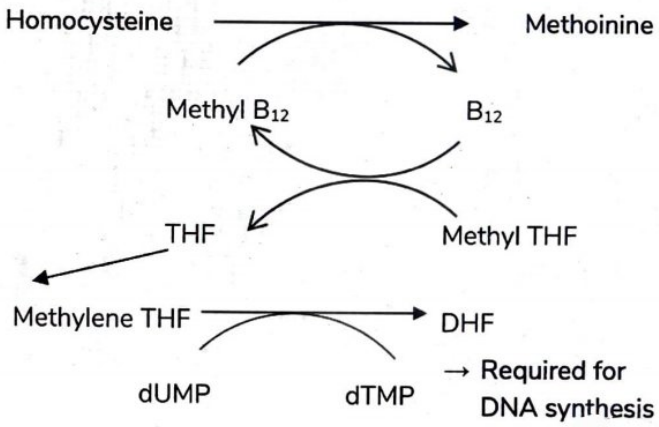
- B12 Supplementation
  - In pernicious anemia:Life time
  - In other causes: For Specific period
  - In treatment with B12 : Reversal
  - Blood picture: Reversal
  - neurological C/F: no further aggravation / no reversal
  - Cancer:higher than normal

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

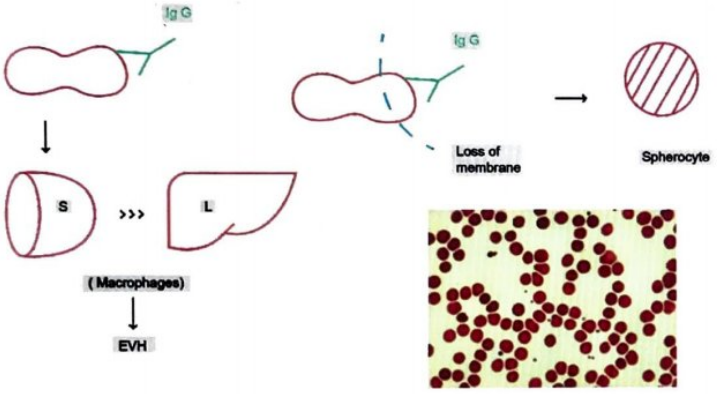
WARM AIHA

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"

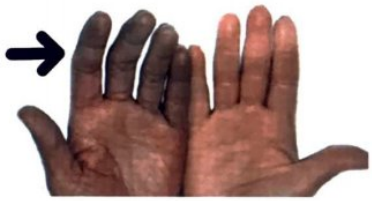
COLD AIHA

00:20:57

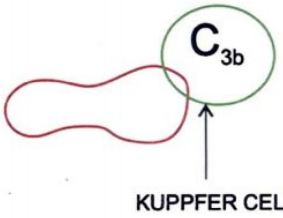
- Antibodies attach at lower temperatures (<37°C)
- It has 2 variants

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

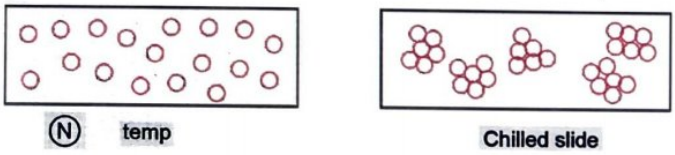
Previous Year's Questions

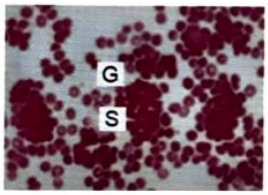
Q. Cold agglutinin are directed against which of the following RBC antigens?

(JIPMER 2019)

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

Diagnosis
- Cold slide test

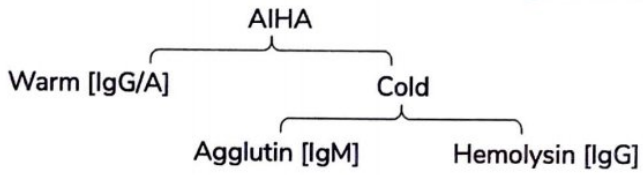




COLD HEMOLYSIN TYPE
- Formation of IgG → 'P' antigen of RBC
- Binds at lower temperature at 4°C → complement activation at 37°C → MAC formation → destruction of RBC (Intravascular hemolysis) → Hburia

- 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

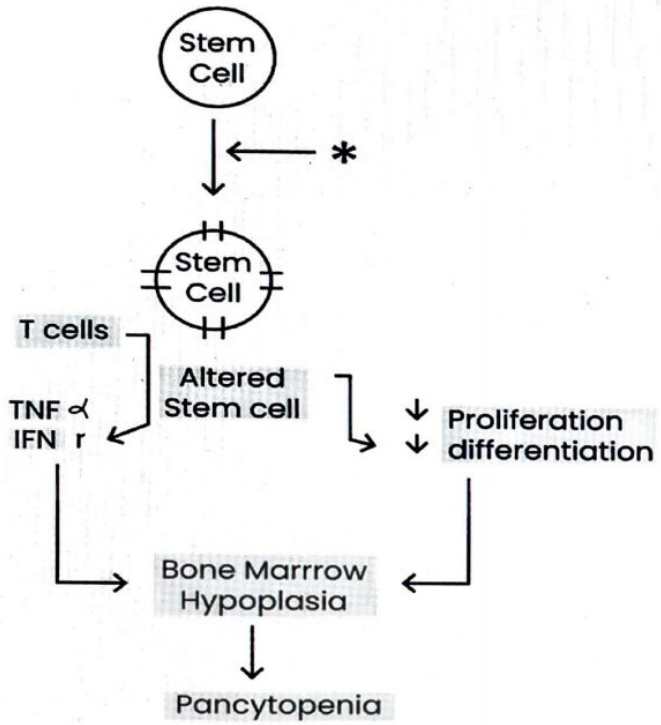
38 MISCELLANEOUS DISORDERS

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

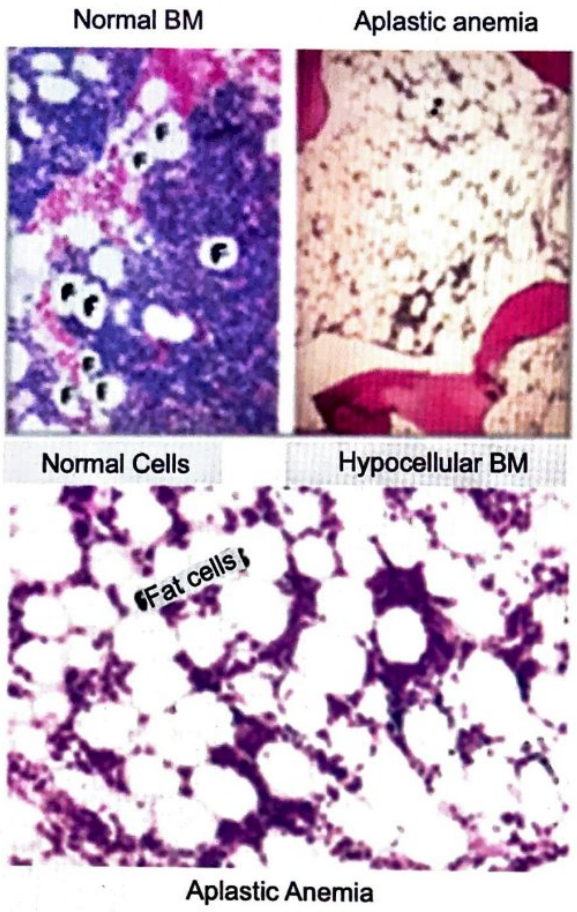
00:13:05

- 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



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

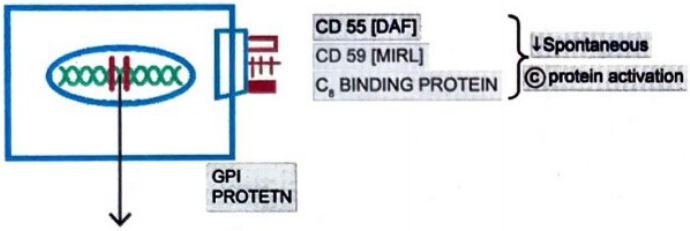
D. Absolute neutrophil count < 1500/mm^3

39 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA [PNH]

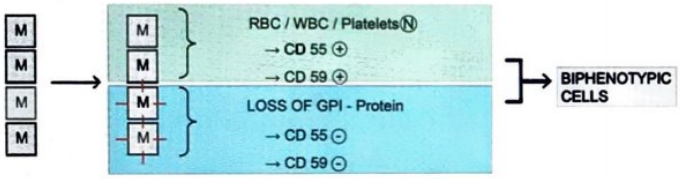
Paroxysmal Nocturnal Hemoglobinuria

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]

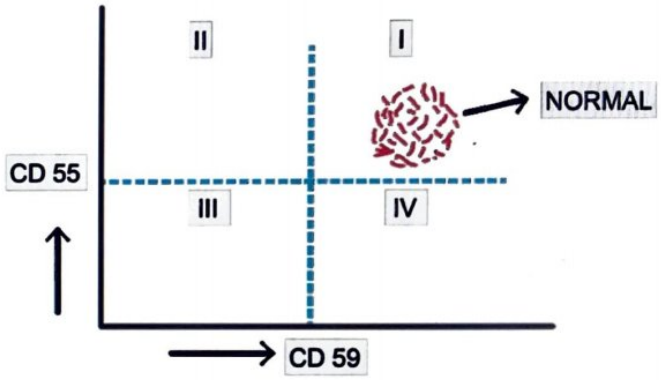
C System
↓
RBC Damage
↓
IV HEMOLYSIS
↓ Hb URIA
[altered color of Urine]

- 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

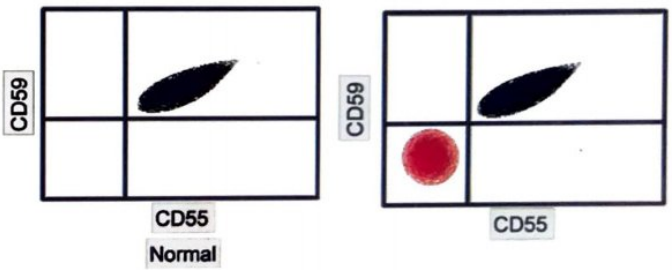
- Blood sample: Pancytopemia
- Screening Test
  (I) Ham's acidified serum Test
  - Blood + Acid → RBC destruction
  (ii) Sucrose Lysis Test
  - Blood + Sugar → RBC destruction
- I-Normal person [CD59, CD55 ⊕]
- III –Abnormal low level of CD59, Cd55



FLAER- FLOW CYTOMETRY [IOC]

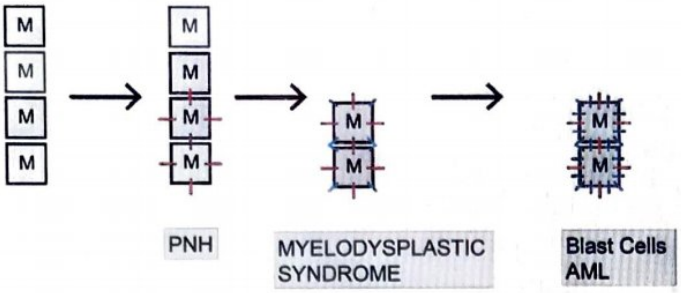
00:18:30

- 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

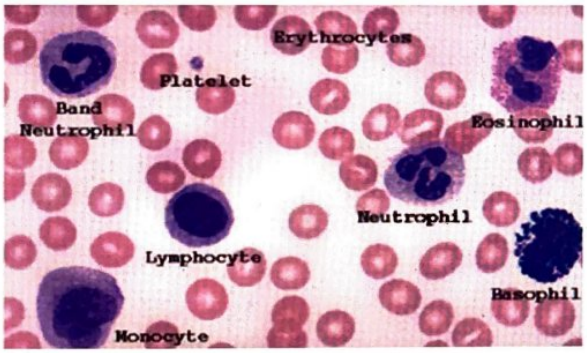
- **Introduction to WBC disorders**
  - Differential leukocyte count
  - WHO classification of lymphoid neoplasm & myeloid leukemia
  - Acute leukemia
- **Acute leukemias: ALL and AML**
  - Acute Myelogenous Leukemia
  - Classifications of AML
  - Acute Lymphoblastic Leukemia
  - Provisional Entities 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"

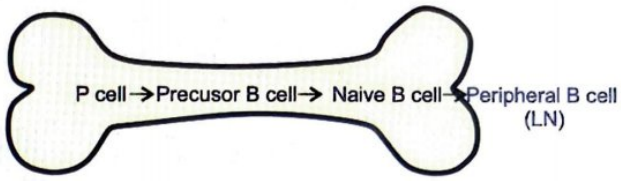


Wright staining smear

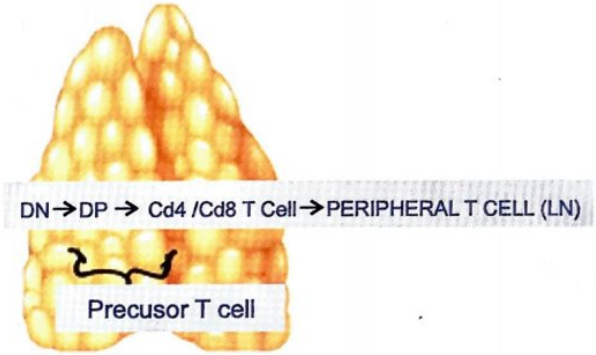
↑ WBC

- 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)

↓ ↓

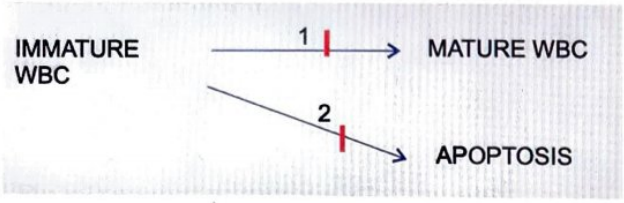
Acute leukemia chronic leukemia

ACUTE LEUKEMIA

Risk factors

- Ionizing radiation

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



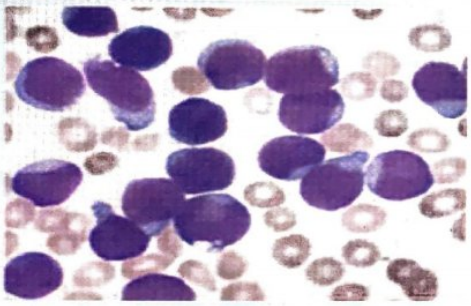
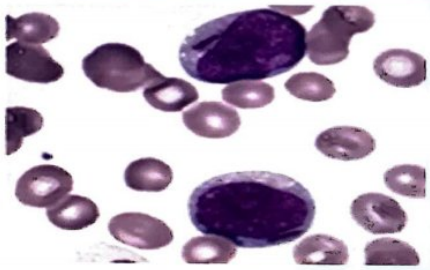
- BM examination
- Immunophenotyping/flow cytometry → Best method for diagnosis
- Cytogenetic analysis
- Molecular analysis

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

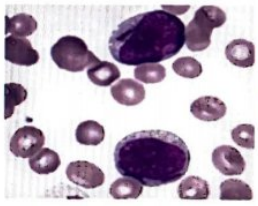
Important Information

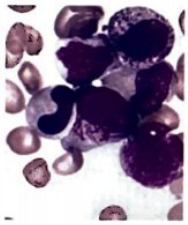
- Myeloblasts with Auer rods (azurophilic granules) is seen maximally in M_3 (acute promyelocytic leukemia)
- Group of Auer rods: Faggot cells

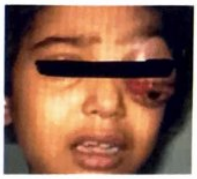
WHO CLASSIFICATION

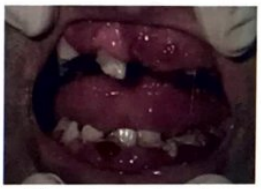
00:08:49

- 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?

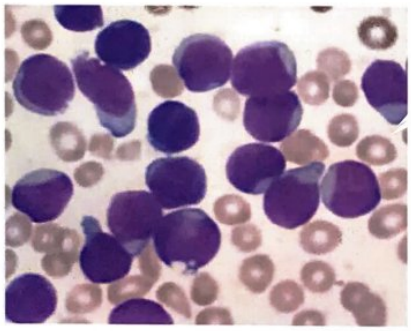
(FMGE 2020)

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

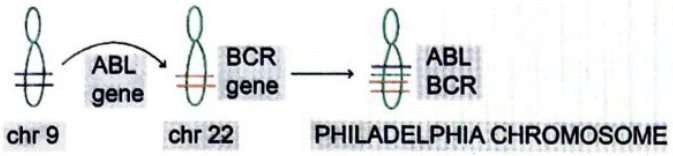
- B-cell ALL with iAMP 21
  - Seen in children
  - ≥ 5 copies of RUNX1 gene

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

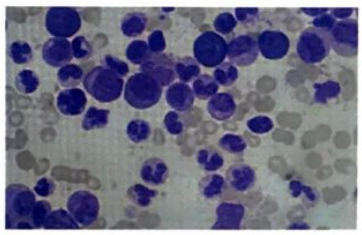
- ↑↑ TLC: DLC, Peripheral smear
  - ↑ Eosinophils
  - ↑↑↑ Basophils

Important Information

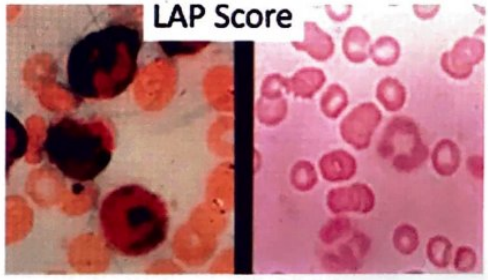
Leukemoid Reaction

- **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

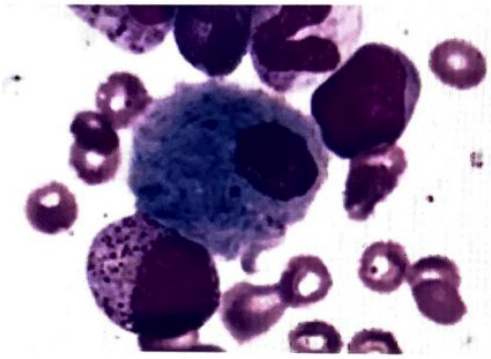


"College girl" appearance



BM Examination

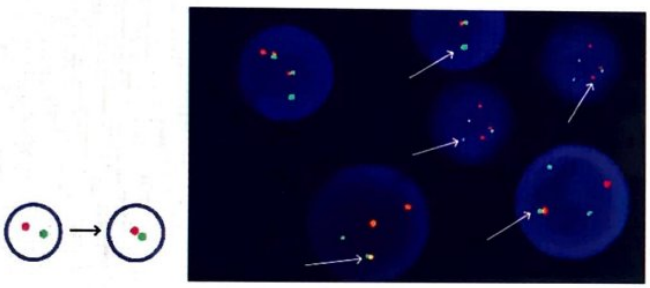
- ↑ Cellularity
- Reticulin +++
- Sea-blue histiocyte
- Pseudo - Gaucher Cells (seen in CML/ MM/ ALL/ MD/ Thalassemia)
  - No cytoplasmic inclusions
  - No iron staining



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
  - ITP (Auto Immune Thrombocytopenia)

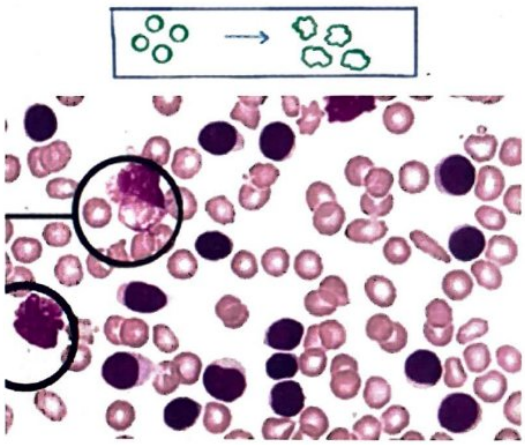
Clinical Features 00:09:35

- 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



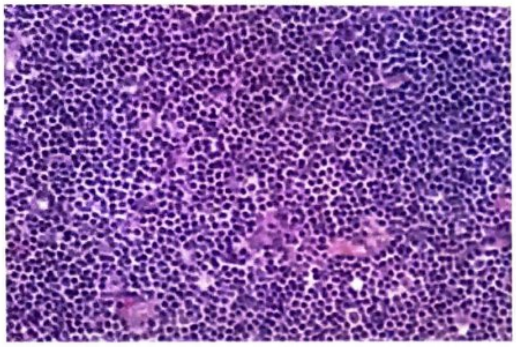
Smudge cells/Basket cells/Parachute cells

BM examination

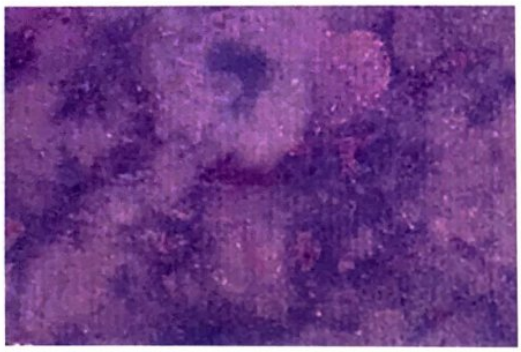
- Hypercellular
  - ↓ Myeloid cells
  - ↓ Erythroid cells
  - ↑ Lymphoid cells

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

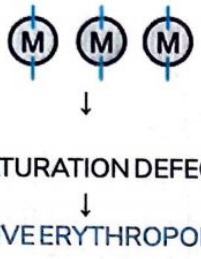
- Fludarabine (DOC)
- Rituximab (Anti CD20)
- Ibrutinib (B-Cell tyrosine Kinase enzyme)

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 $\xrightarrow{2\text{-}8\text{yrs}}$ 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

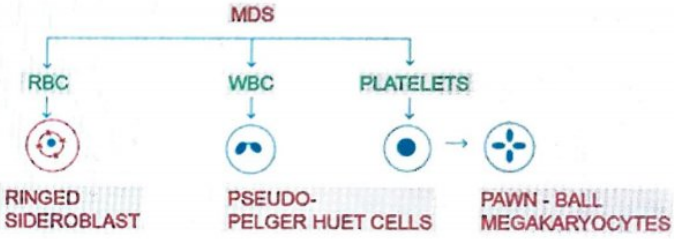
00:09:09

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

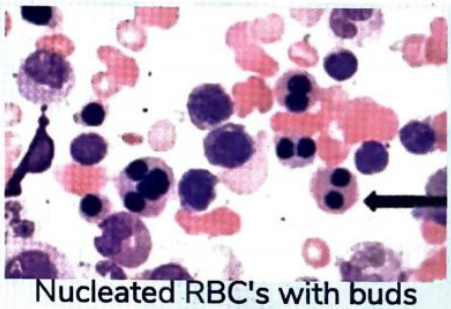
DIAGNOSIS

00:10:25

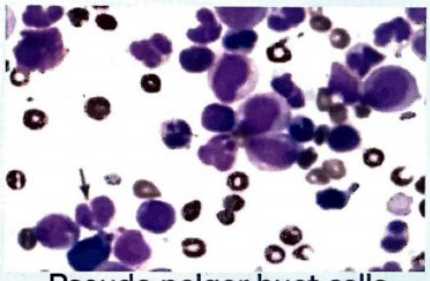
- Bone Marrow EXAMINATION
  - Hyper cellularity
  - Megaloblastic RBC
  - Nuclear budding anomaly
  - Ringed Sideroblasts
  - Pseudo pelger huet cells – MDS/AML/CML
  - Pawn - ball megakaryocytes



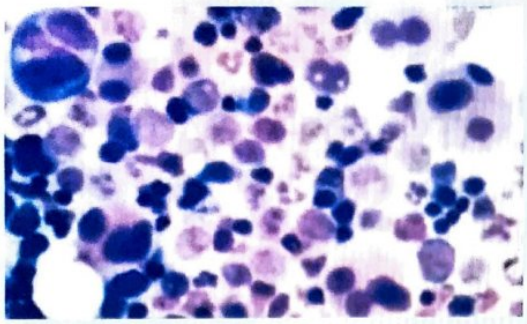
- PERIPHERAL SMEAR → Pancytopenia & abnormal cells



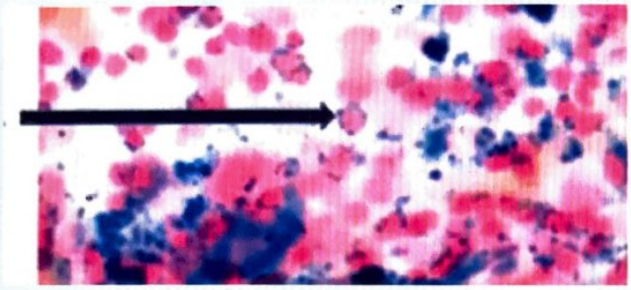
Nucleated RBC's with buds



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

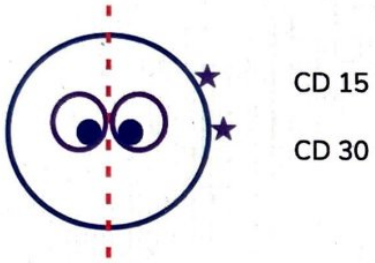
45 LYMPHOMAS: HL & NHL

HODGKIN LYMPHOMA

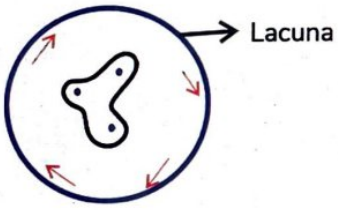
00:00:19

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

Reed Sternberg Cell

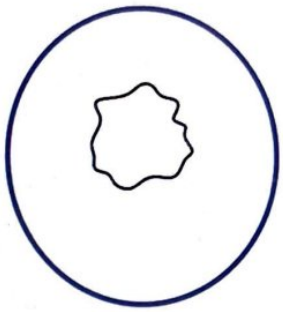


- Size: 15-45μ
- Owl-Eye Appearance
- Molecules expressed: CD15/30/45, PAX-5
  - Best marker: Cd30
- Variants of RS Cell
  - Non-classical RS cell → CD15/30 ⊖ & CD20/BCL-6 ⊕
  - Lacunar RS Cell: Presence of empty area (lacuna) around the nucleus caused by cytoplasm retracts



  - 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

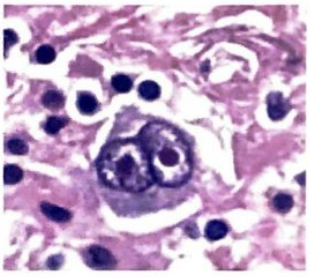
- Seen in Elderly individuals
- H/O HIV infection & strongly associated with EBV
- Bad prognosis
- Presence of Atypical Histiocytes → Hodgkin Cells

Lymphocyte Rich HL

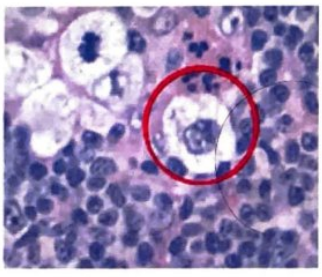
- Seen in Elderly
- Presence of mononuclear RS cells
- Can also be associated with EBV

Lymphocyte Predominant HL

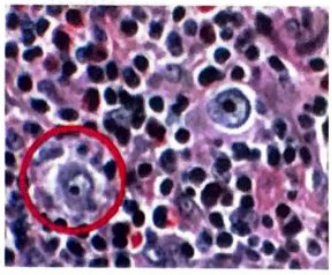
- No association with EBV
- Early presentation → overall best prognosis
- RS Cells → CD20 ⊕
- Aka lympho-histiocytic cell/popcorn cell



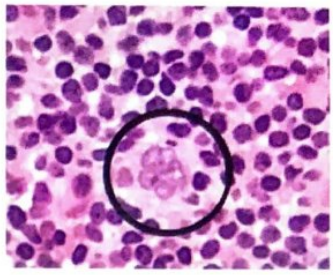
RS Cell



Lacunar cell



Mononuclear RS cell



Non-classical RS cell

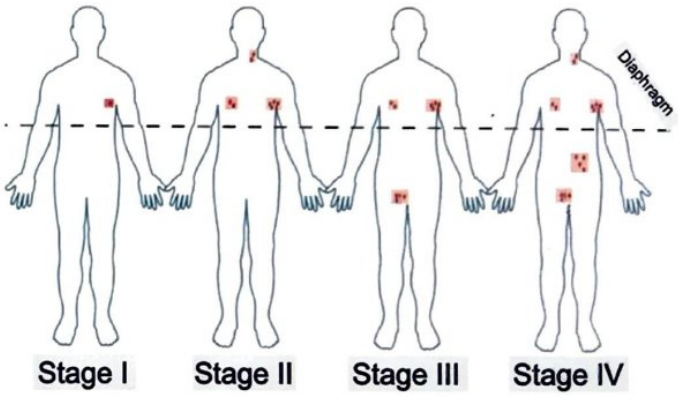
- Metastasis: Nodal disease >> Spleen

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



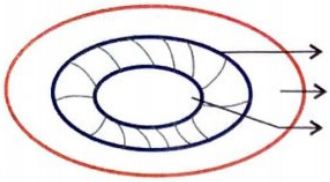
- Stage I: 1 LN or 1 extra lymphatic site
- Stage II: 2 or more LN on one side of diaphragm
- Stage III: Both the sides of diaphragm are involved
- Stage IV: Diffuse involvement

Treatment

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

NON-HODGKIN LYMPHOMA

00:29:42



- MANTLE ZONE
- MARGINAL ZONE
- GERMINAL CENTRE
  - → FOLLICULAR LYMPHOMA
  - → DLBCL
  - → BURKITT'S LYMPHOMA

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

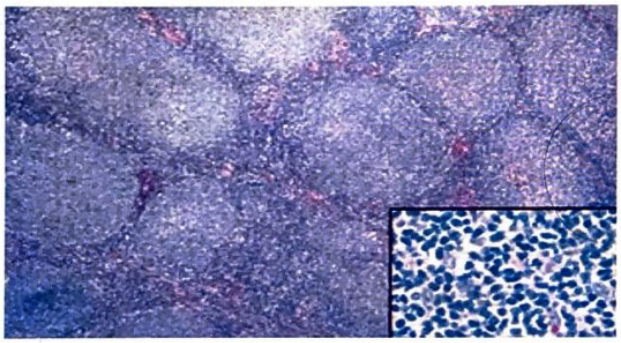
- Cell-origin: naive B-cells
- Associated with t(11;14) → → ↑↑↑ bcl-1 (Cyclin D_1) → diffuse lymphadenopathy
  - Chromosome 14 contains Ig gene
  - Chromosome 11 contains Cyclin D1 gene
- Flow cytometry
  - CD19/20/ Cyclin D1 ⊕
  - CD5 ⊕/CD 23 ⊖ → differentiates from CLL
  - New marker: SOX-11→best marker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

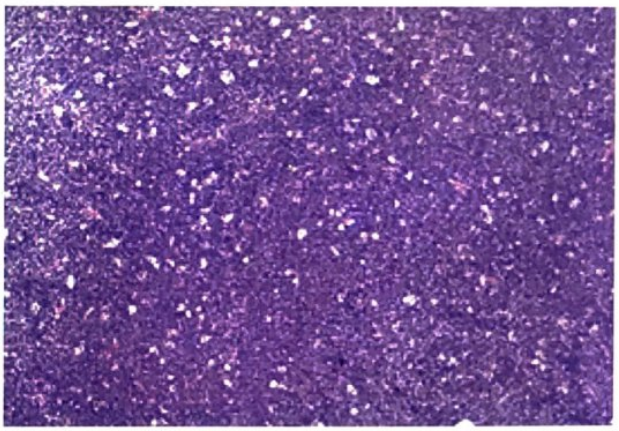
00:40:23

- 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

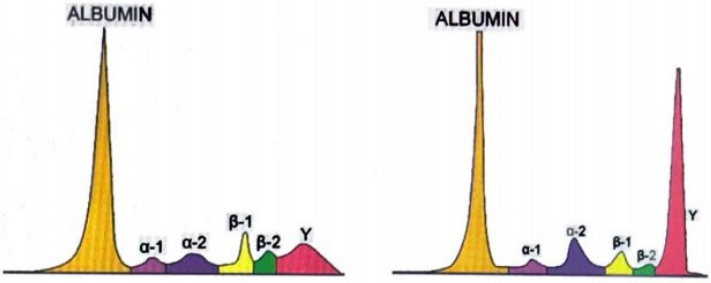
CUTANEOUS T-CELL LYMPHOMA

00:54:08

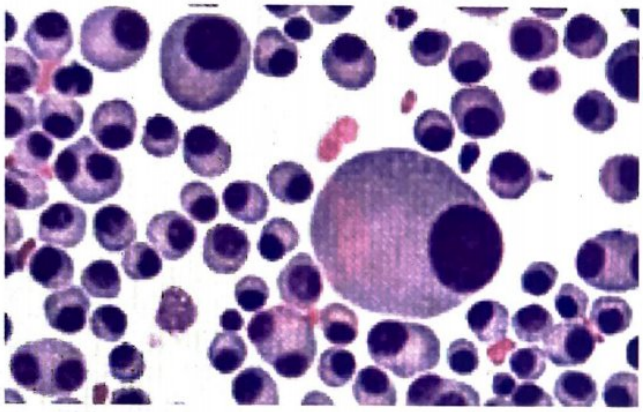
- Origin: CD_4 T-cell
- Predilection of Skin involvement → epidermotropism
- Blood involvement: SEZARY Syndrome
- Skin involvement: Pautrier's Microabscess/mycosis fungoides
- Presence of cerebriform nuclei
- Hallmark cells: horseshoe nucleus (anaplastic large cell lymphoma)
  - Associated with ALK gene 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

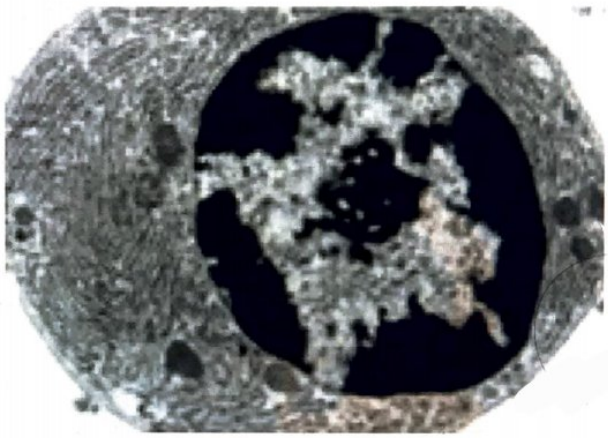


Normal 'M' spike pattern



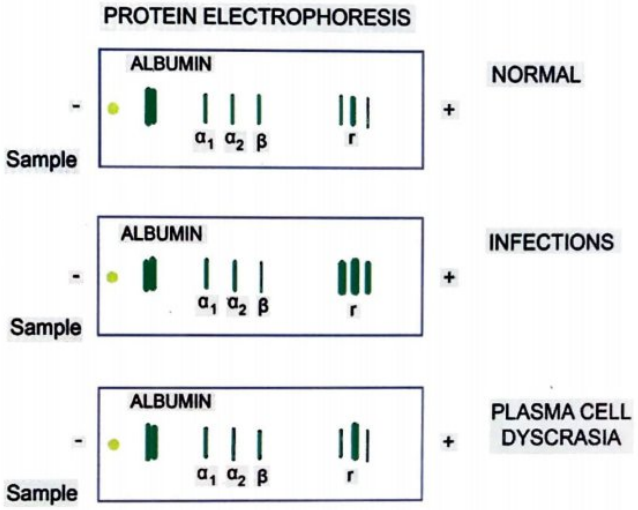
Normal Bone Marrow – Plasma cell

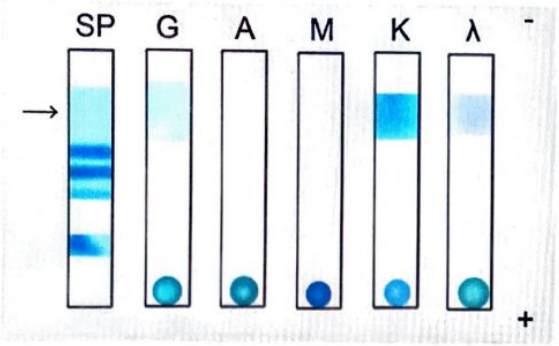
- Plasma cell has eccentric nucleus
- Peri nuclear 'Hof' around the nucleus is due to the presence of golgi apparatus.
- Basophilic cytoplasm is due to RER.



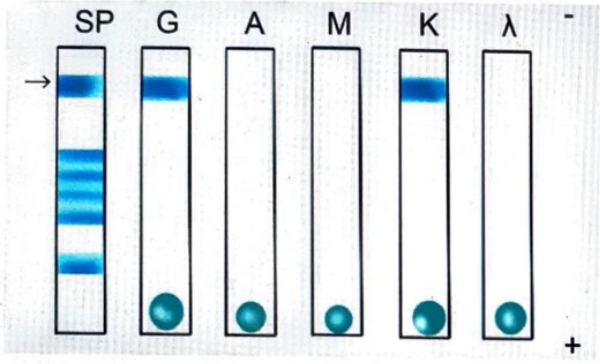
Cartwheel nucleus/clock face nucleus

- 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_6/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

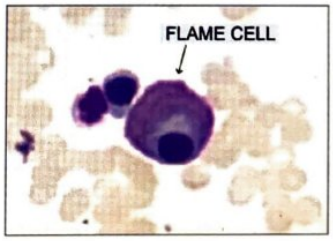
+

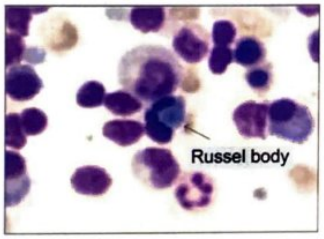
Any one of Myeloma defining events

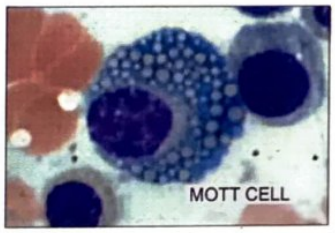
- Related organ/ tissue impairment
  - **C**alcium ↑↑ (>11mg/dl)
  - **R**enal Insufficiency (s.creatinine > 2mg/dl)
  - **A**nemia (< 10gm/ dl)
  - **B**ony lesions (≥1 osteolytic lesion)
- Biomarkers
  - **S** - Sixty (≥ 60% clonal BM cells)
  - **Li** - Light chain (involved: uninvolved → ≥ 100)
  - **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

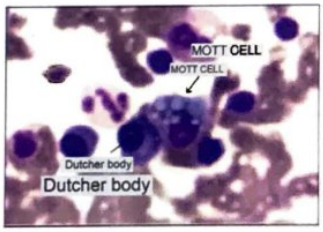
Mott cells

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)

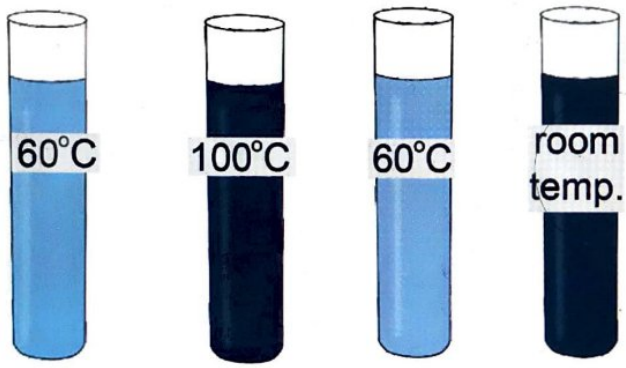
Previous Year's Questions

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.

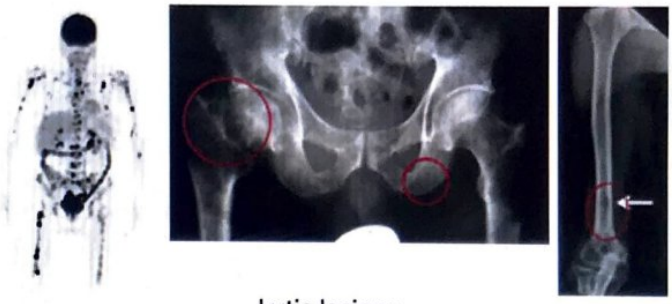
Urine

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

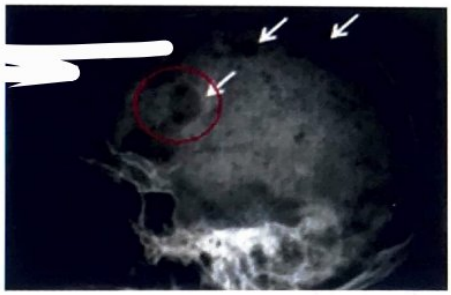


Radiological

- 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

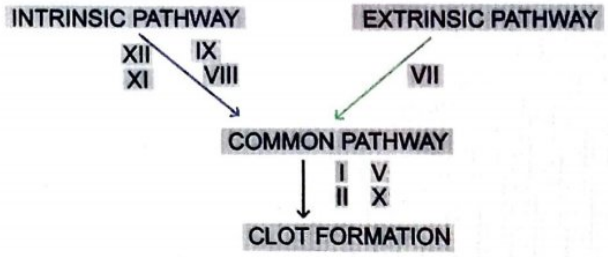
- Robbins & Cotran Pathologic Basis of Disease 10th ed pgs 596, 597

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

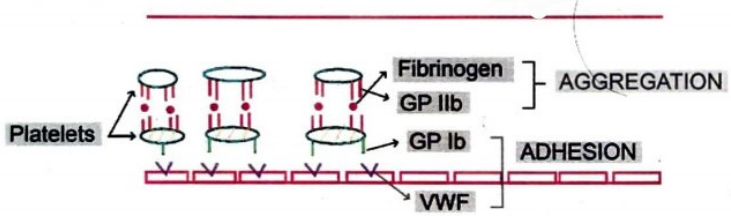
48 CONCEPT OF BLEEDING DISORDERS



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.



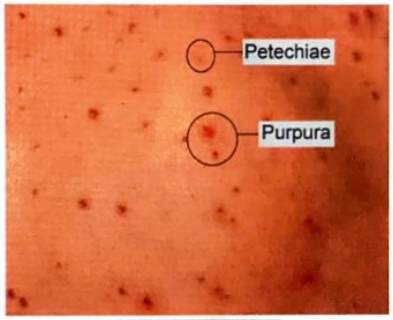
PLATELET BLEEDING DISORDER
- ↓ Platelet count - Thrombocytopenia disorder
  - Normal Platelet count: 150,000 – 450,000 per cubic mm
- Functional platelet disorder

FUNCTIONAL PLATELET DISORDERS 00:12:49

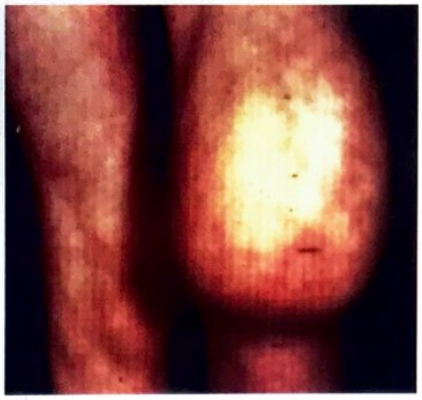
Important Information
- **Adhesion: VWF, GP-Ib**
- **Activation: TxA_2, ADP**
- **Aggregation: GP-IIb, Fibrinogen**

- 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

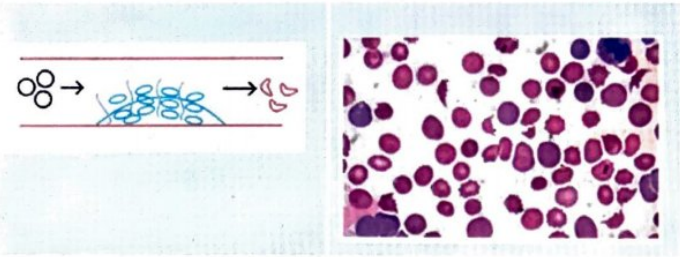
00:08:36

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

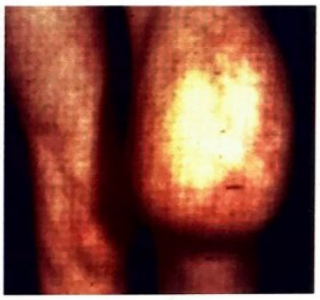
Sub Types

- 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 ↓ Normal aPTT → ↑↑ 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 [Q]	+ 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

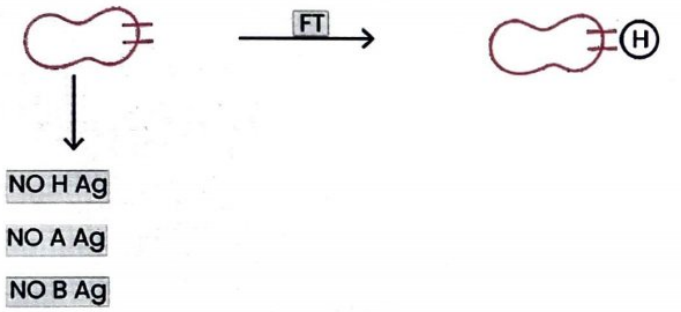
- Secretors [80%]
  - Saliva | Sweat / Plasma / Semen

- 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



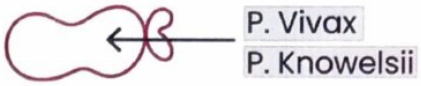
- Fucosyltransferases enzyme defect
- Discovered by BHENDE[Q]
- Rare blood group
- Anti A/B/H Ab in plasma
- Even 'O' can't be given to these patients
- Safest for transfusion for these patient → Bombay blood
- Detected by Reverse Grouping: detection of Ab in plasma

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

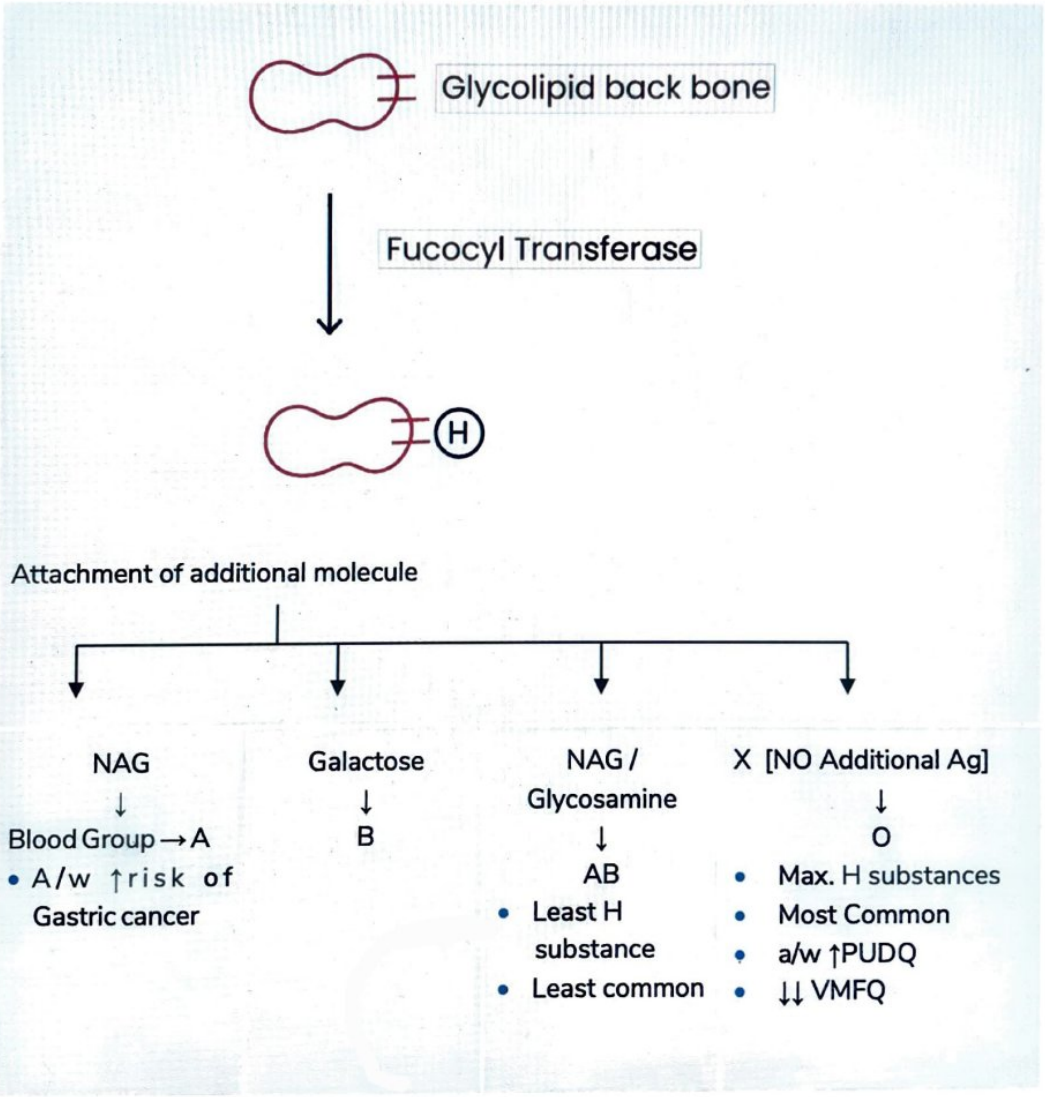
- KELL Ag + Kx Ag
- Deficiency of Kx protein causes McLeod Phenotype
  - ↓ RBC life Span
  - Cardiac defects ⊕
  - Muscular dystrophy ⊕
  - Acanthocytes ⊕

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

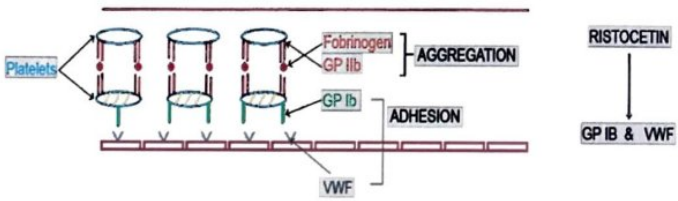
Acquired form of Von Willebrand Disease
- L.P.D (Lymphoproliferative Disorders): **MGUS** /Monoclonal gammopathy of undetermined significance (MC Plasma cell dyscrasia)♀
- **HEYDE Syndrome:** valvular defect (AS) + GI bleeding

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

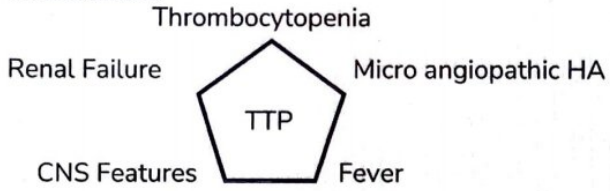
1. Deficiency of Adam Ts 13 K/a Upshaw - Schulman Syndrome
2. Ab formation against ADAM TS 13 M/c

- 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

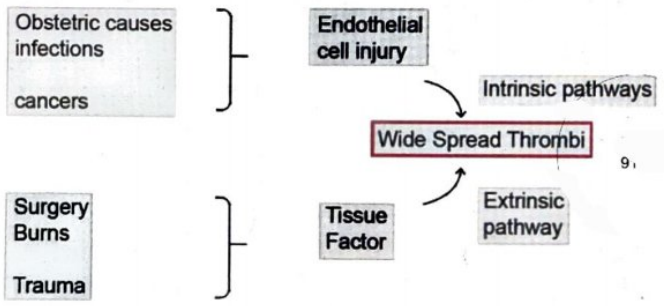
Definition

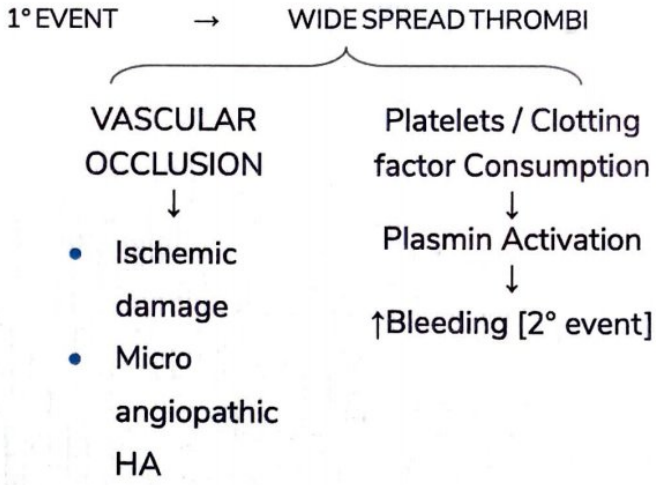
- Thrombo - Hemorrhagic disorder
- Acute | Sub acute | Chronic disorder

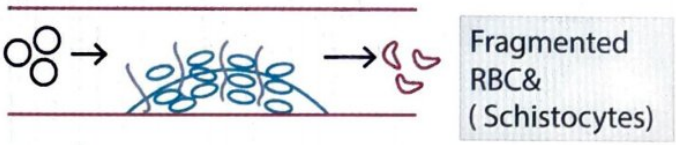
RISK FACTORS 00:38:20

- 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

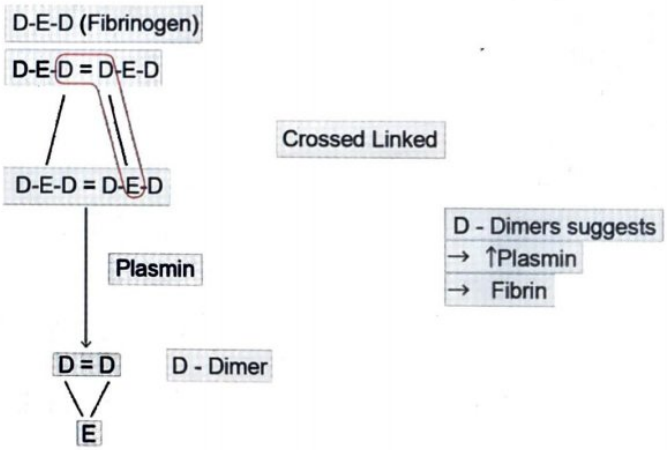






DIAGNOSIS 00:54:48

- ↓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.

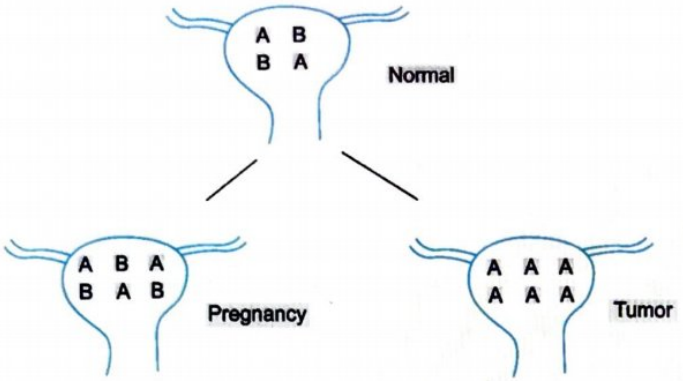
Reference

- Robbins & Cotran Pathologic Basis of Disease 10th ed pg 127

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

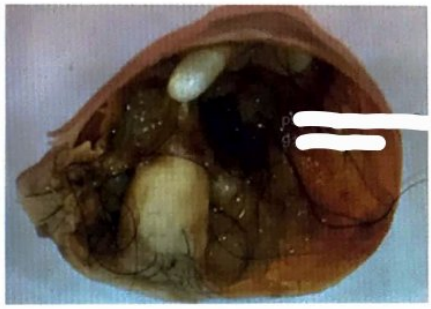
Important Information

- 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

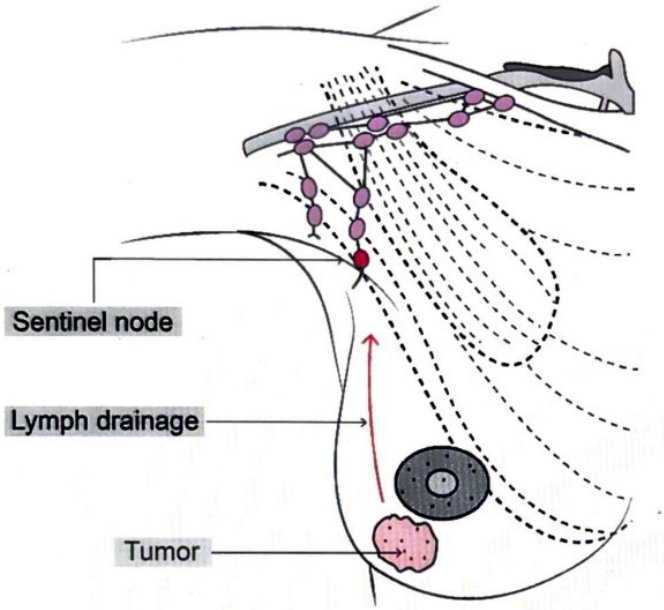
Previous Year's Questions

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.

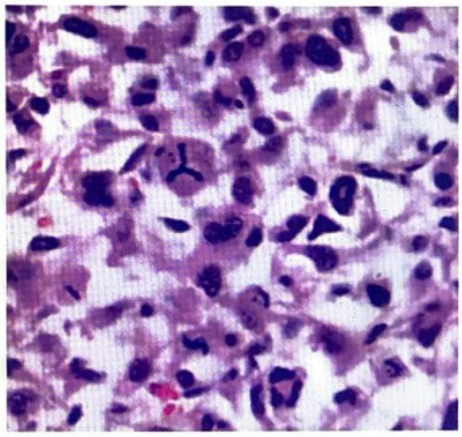
ANAPLASIA

- Hallmark feature of malignant transformation.

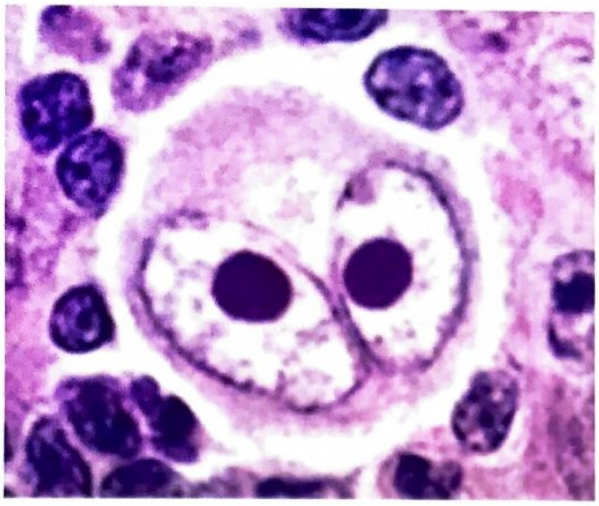
$$normal\ cell \xrightarrow{injury} metaplasia\ (benign, reversible) \rightarrow dysplasia \rightarrow anaplasia$$

Dysplasia

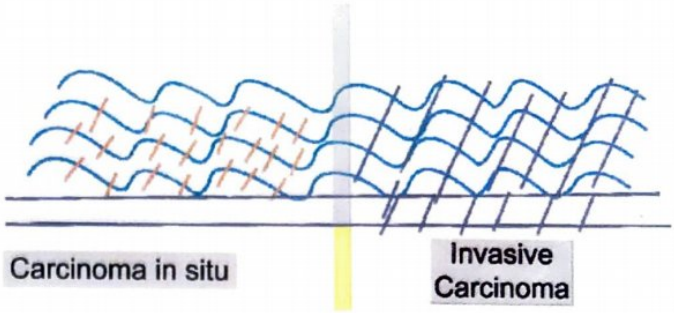
- Increase in nuclear cytoplasmic ratio
- Pleomorphism
- Reversible at initial stage (partially reversible stage)
  - Example: cervix → HPV → cervical cancer
- Associated with abnormal giant cells → RS cells in Hodgkin's lymphoma



Tri-polar mitotic spindle



RS cell

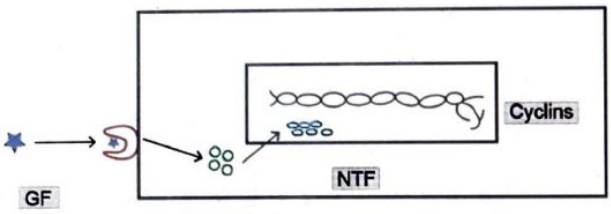


- Basement membrane is not affected in carcinoma in situ
- Basement membrane is affected in Invasive carcinoma

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

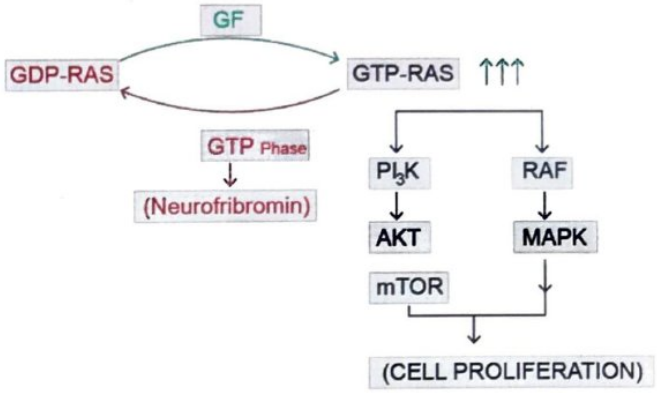
- PDGF (SiS) → glioma
- HGF → hepatocellular carcinoma

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

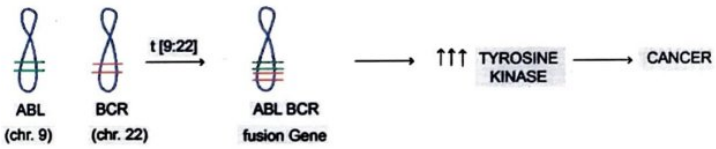
SIGNAL TRANSDUCTION PROTEINS 00:08:38

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

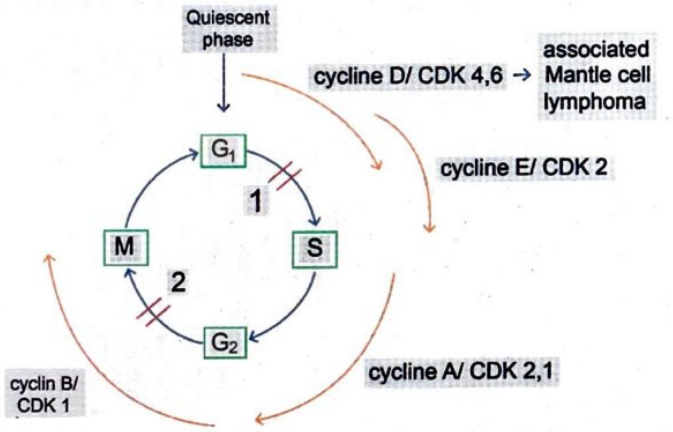
- Master regulator of cell proliferation
- C-MYC: Burkitt's lymphoma
- N-MYC: Neuroblastoma
- L-MYC: Lung cancer (small cell lung cancer)
- Hedgehog pathway (↑ MYC activity) → medulloblastoma

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

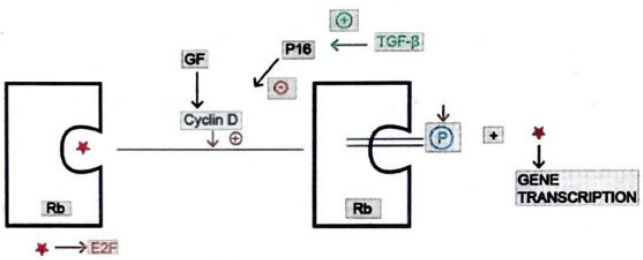
- Tumor Suppressor genes → ↓ hallmark of cancer
- Double-hit hypothesis
  - Both the alleles are underactive
  - It was proposed by Knudson: Rb gene

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

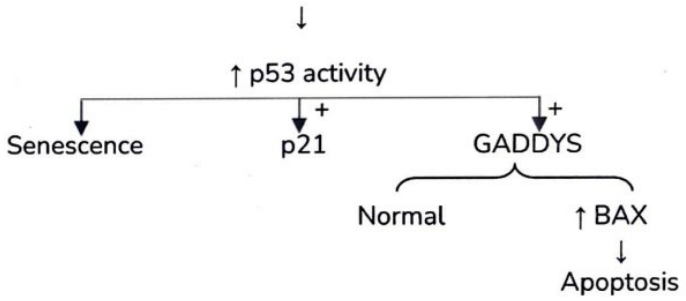
Important Information

- 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

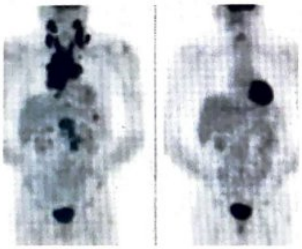
CHD_1 gene

- 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

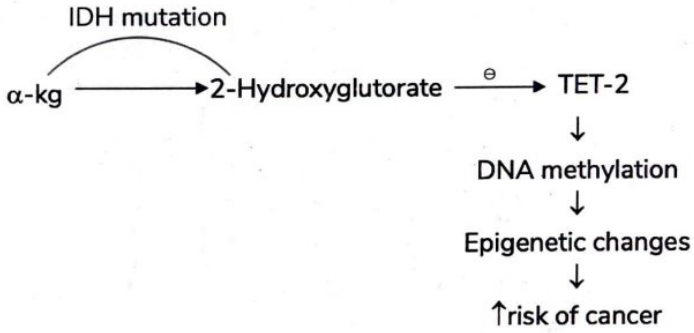


PET scan → ^{18}FDG

- 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

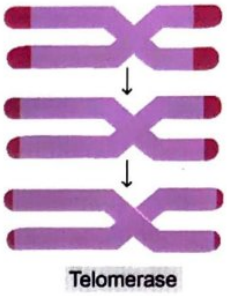
- IDH (Isocitrate Dehydrogenase)



- 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)

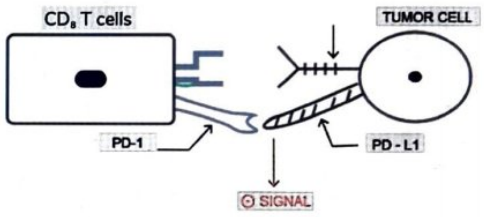
A. Basal cell carcinoma
B. Squamous cell carcinoma
C. Malignant melanoma
D. Merkel cell carcinoma

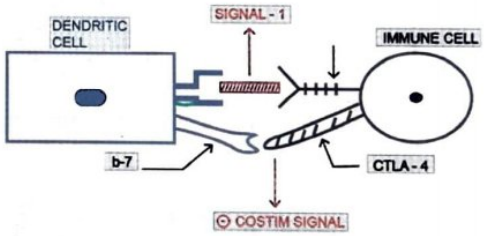
EVASION OF IMMUNE SURVEILLANCE 01:13:56

- Concept proposed by Lewis Thomas & M.Burnett
- Cytotoxic T-cells, NK cells, macrophages, TH_1 cells → important for destruction of tumor cells

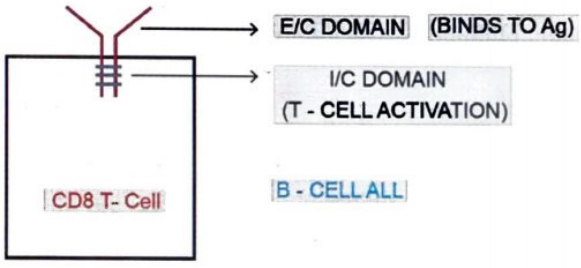
Cancer Immuno-editing

- 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

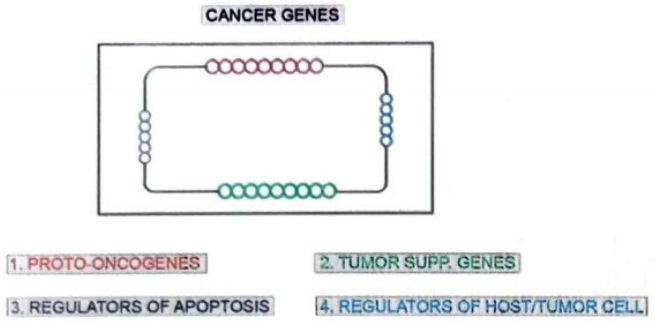
B-Cell —Ag Exposure→ AiD gene

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 $\xrightarrow{CYP1A1}$ 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

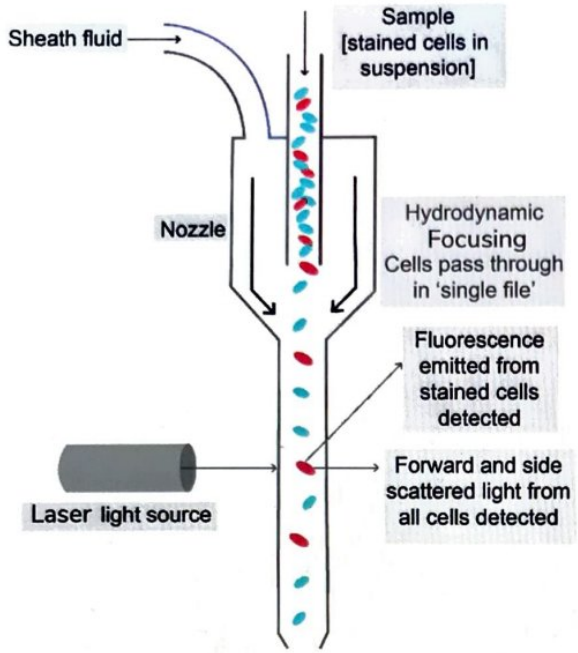
FLOWCYTOMETRY

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)

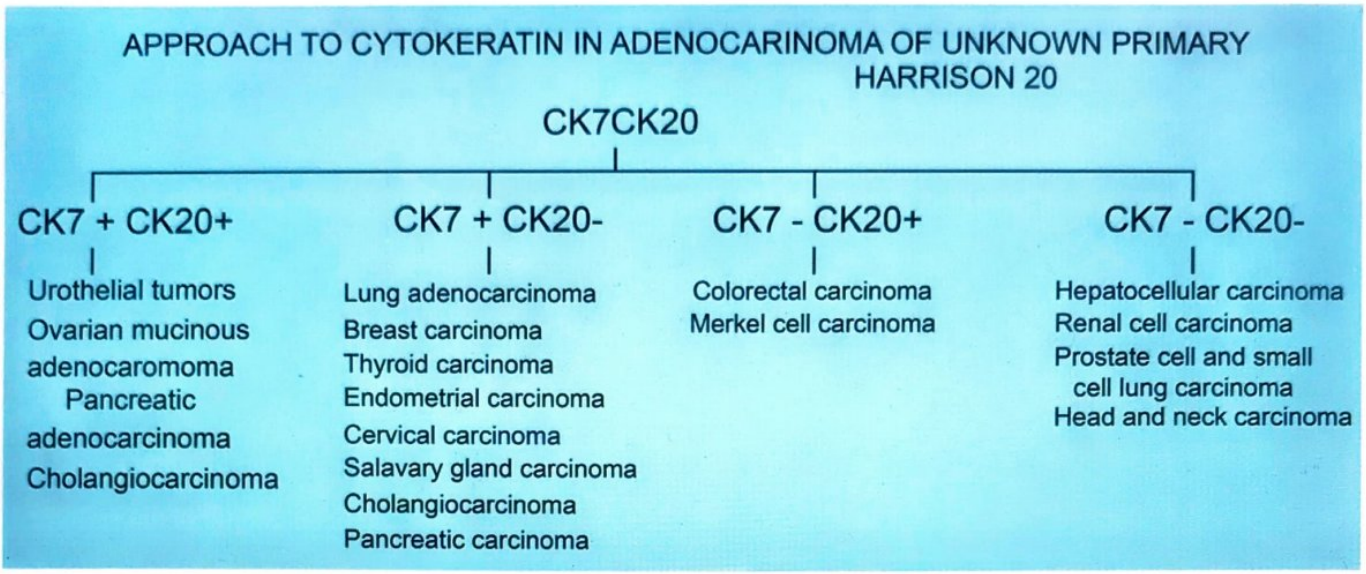
Previous Year's Questions

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

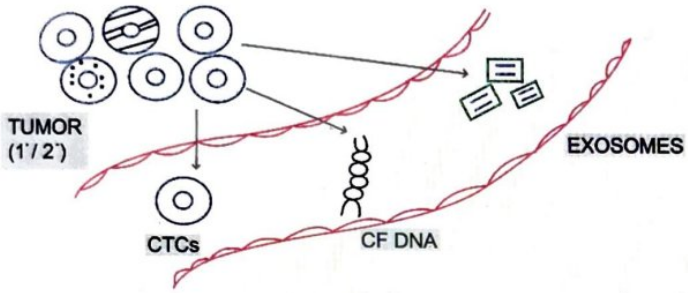
CUP: Carcinoma of Unknown Primary CK7/CK20 is used in assessment



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

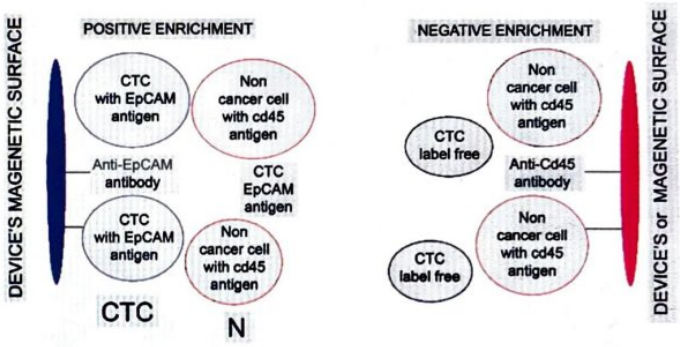
TYPES OF BIOMARKERS



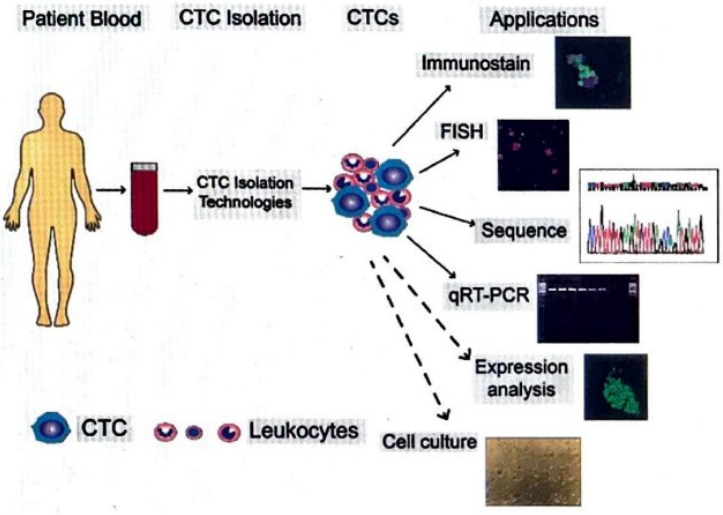
Standard tissue biopsy	Liquid biopsy
• Time intensive procedure	• Quick
• Localized sampling of tissues	• Comprehensive tissue profile
• Invasive & more complications	• Minimally invasive & less complications
• Not viable if tumor has been resected or can't be detected by imaging	• Allows for evaluation 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



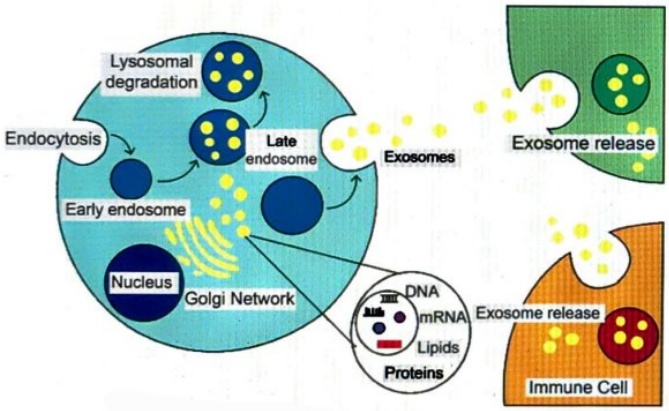
Cell free DNA (CfDNA)

- 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

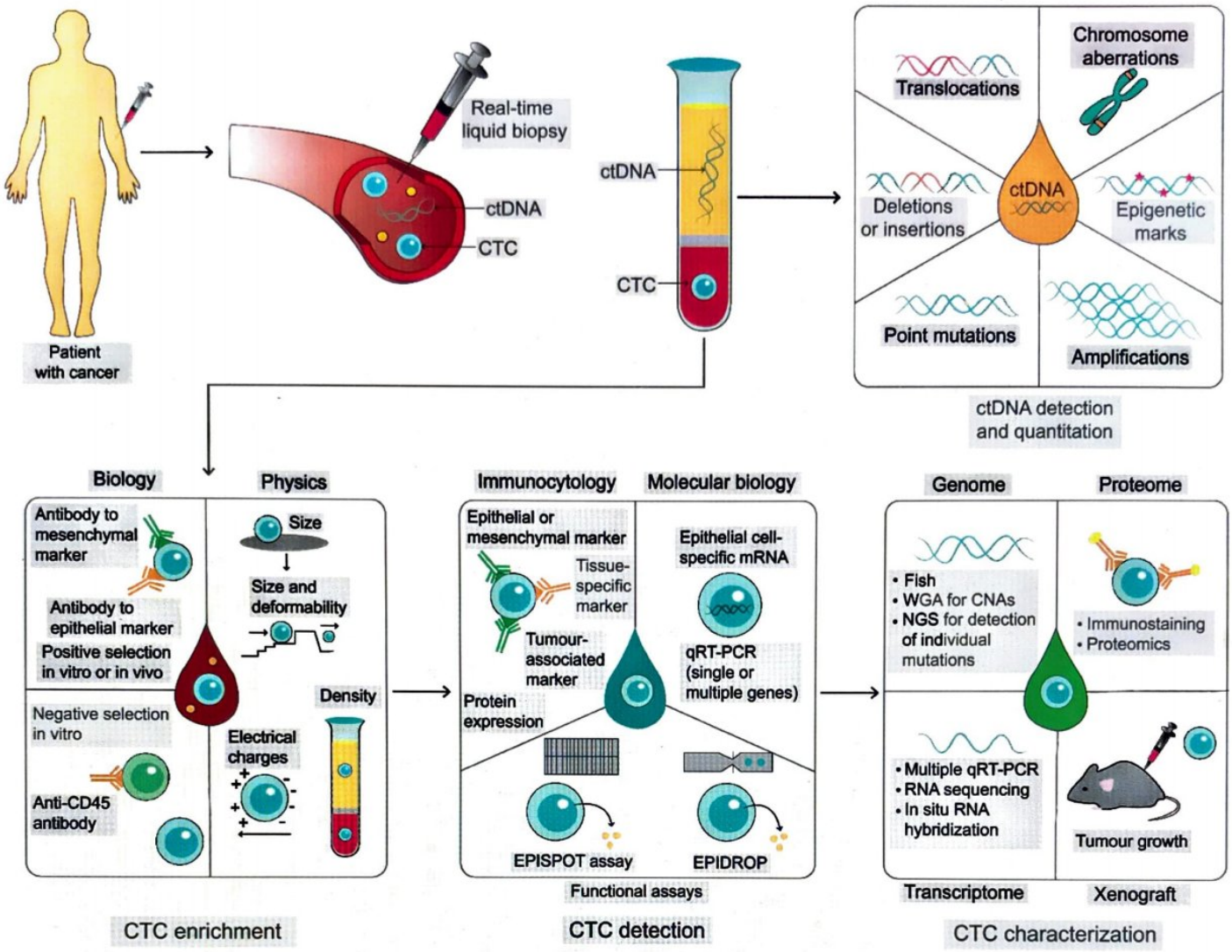
- PDGF → Secreted by platelets, responsible for epithelial mesenchymal transformation
- Involved in tumor invasion, angiogenesis
- RNA sequencing used to differentiate between normal platelets & tumor educated platelets

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



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

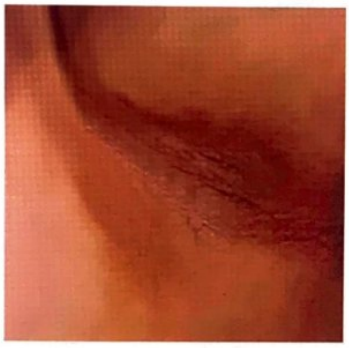
00:13:53

- 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

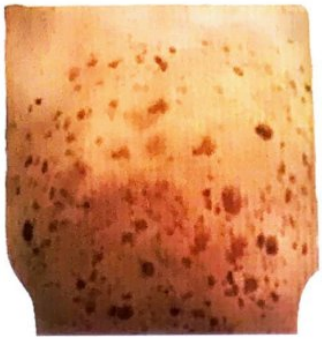
DERMATOLOGICAL

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