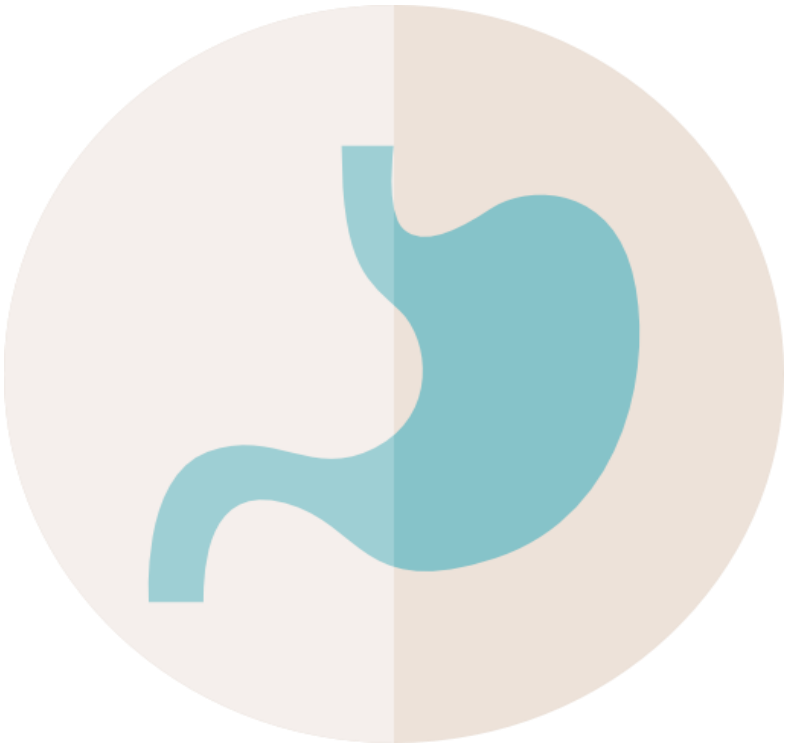
HAEMATOLOGY 436

MEDICINE
KING SAUD UNIVERSITY



Revision File

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Good Luck!

Lecture 4- Approach to bleeding disorders:

- platelets defects or vessels wall defects will lead to superficial bleeding (Mucocutaneous Bleeding)
- Clotting factors defect will lead to deep bleeding (in muscles called Haematomas, in joints called Haemarthrosis)

- platelets formed from cytoplasm of Megakaryocyte
- Normal platelets life span: 7-10 Days

- Platelets components: احفظ مكونات الـدينس والالفا بتكون الباقي

1. Dense granules: contains:-
- Nucleotides (ADP), Ca2 & Serotonin.

2. alpha granules.

- Glycoproteins in the platelets membrane:-
- **GP(Ib,IIb,IIIa):** aggregate and adheres to vessels subendothelium indirectly by Von-Willebrand's factor.
- **GPIa:** adheres to subendothelium directly

- Hereditary platelets disorders:-

1- Glanzmann's disease: lack of GP IIb & IIIa.
- platelets are normal in number & morphology.

2- Bernard-Souiler disease: lack of GP Ib.
- increase platelets size (Giant platelets) and reduction of count.

3- Storage pool diseases: Defective in alpha or dense granules.

- **Thrombocytopenia:** reduction of platelets count **due to:-**
- Bone marrow failure of platelets production (Amegakaryocitic aplasia).
- increased consumption due to immune diseases like : Immune thrombocytopenic purpura (ITP).
- Heparin.
- Abnormal platelets distribution: splenomegaly.

Cont'd Lecture 4- Approach to bleeding disorders:

- **ITP (Immune thrombocytopenic purpura):-**

- reduction in platelets count lead to Mucocutaneous Bleeding, if it less than 10,000 it may lead to CNS&GI Bleeding.
- Acute ITP most common before age of 10 after common childhood viral infection.

ITP characterized by:-
- petechiae & bruising.
- Thrombocytopenia with increased number of large platelets.
- Megakaryocytes are increased in number & size.
- Elevated level of IgG & IgM that associates to platelets (Anti-platelets antibodies).

Remember: aspirin affect the function of platelets while heparin reduce the number.

Lecture 5- Megaloblastic anemia

- Macrocytic anemia may be:-

1- Megaloblastic: we will talk about it later

2- Normoblastic: Normal appearance of RBCs maturation, but may still associated with a macrocytosis in peripheral blood (it is not associated with vit.B12 or folate deficiencies), they may be due to:-
a- Pregnancy or newborn (physiological)
b- Alcohol.

- **Megaloblastic anemia:**

- abnormal RBCs development characterized by Dissociation between the nuclear and cytoplasmic development in erythroblasts, it arise from disorders in DNA synthesis.

Causes of Megaloblastic anemia:-
1- Vit.B12 (Cobalamin) deficiency
2- Folate Deficiency
3- Antifolate drugs like: Methotrexate
(We need Vit.B12 & Folate to synthesize DNA)

Cont'd Lecture 5- Megaloblastic anemia

- Vit.B12:
- Source: Animal.
- Stores in: Liver.
- Develop anemia in absence of intake or absorption: After 2-10 Years.
- Requirements for absorption: Intrinsic factor.
- Absorbed in: Terminal ileum.

- Vit.B12 deficiency: due to
- Veganism.
- Gastrectomy.
- Congenital intrinsic factor deficiency.

- Folate:
- Source: Most foods.
- Stores in : Liver.
- Develop anemia in absence of intake or absorption: After 5 months.
- Absorbed in: Duodenum & Jejunum.

- Folate deficiency: due to
- Inadequate intake.
- increased requirement like in pregnancy.

- **Pernicious Anemia: مهم**
- Megaloblastic anemia due to autoimmune attack on the gastric mucosa leading to atrophy which will cause absence of intrinsic factor secretion that will lead to absent serum Vit.B12.

- Clinical Features of Megaloblastic Anemia:-
- Common Anemia features.
- Mild jaundice, Angular cheilosis.
- Melanin pigmentation.

- Complications of Megaloblastic anemia:-
- **Neuropathies:** due to accumulation of S-adenosyl homocysteine & due to Vit.B12 deficiency.
- **Neural tube defect:** Due to folate or Vit.B12 deficiency in the mother.

Cont'd Lecture 5- Megaloblastic anemia

- **Hematological findings in Megaloblastic anemia:-**

a- Peripheral blood:-

- Hypersegmented neutrophils.
- Leucopenia & Thrombocytopenia.

b- Bone marrow:-

- Dissociation between the nuclear and cytoplasmic development in erythroblasts.
- Hypercellular BM.
- Increased stainable iron.
- Metamyelocytes.
- Mitosis & dying cells.

- **Laboratory abnormalities:-**

- Increased indirect bilirubin.
- increased LDH & Serum iron.
- Reduced haptoglobins.

Lectures 6&7- Acute Leukemia:-

- **Acute Leukemias:**

- it is malignant hematopoietic disorders characterized by accumulation of abnormal blasts in bone marrow (more than 20%).
- There is block of differentiation, increased proliferation & decreased apoptosis.

- **Features:-**

1- Light Microscope:

- Blast count is More than 20% of total cells in bone marrow.
- Myeloblasts are characterized by presences of Auer rods. (Auer rods=AML).

2- Markers:

- Stem cell (blasts) markers (indicate Acute Leukemia) : CD34 & TDT.
- Myeloid marker: MPO.
- T-Lymphoid marker: CD3.
- B-Lymphoid marker: you have to find 2 markers one is CD19 and the another is one of these (CD10, CD79a or CD22).

Cont'd Lectures 6&7- Acute Leukemia:-

Acute Leukemia divided into:-

1- Acute Myeloid Leukemia (AML): CD34,TDT & MPO are +ve & Auer rods in microscope

2- Acute Lymphoblastic Leukemia (ALL):

-If T-Lymphoid: CD34,TDT & CD3 are +ve.

-If B-Lymphoid: CD34,TDT & CD19 with one of (CD10, CD22 & CD79a) are +ve.

1. Acute myeloid Leukemia (AML):

- it is hematopoietic neoplasm caused by proliferation of malignant myeloid blasts in BM & Blood.
- blasts 20% or more , or t(8;21), t(16;16) or t(15;17).

• Classifications:-

1- FAP: based on morphology:-

- **M2:** t(8;21).
- **M3:** (Promyelocytic Leukemia): t(15;17) & Associated with DIC.
- **M4:** t or inv(16;16).
- **M5:** t(9;11) .
- Gum hypertrophy is associated with M4&M5.

2- WHO: based mainly on Genetic.

• Clinical features:

1- Pancytopenia (Every thing decreased)
2- hepatosplenomegaly
3- Gum hypertrophy & Myeloid sarcoma are associated with Acute Monoblastic Leukemia (M4&M5)
4- DIC Associated with Acute Promyelocytic Leukemia (M3).

2- Acute Lymphoblastic Leukemia (ALL):

- it is hematopoietic neoplasm caused by proliferation of malignant lymphoid blasts in BM & Blood.
- Better than AML.

Classified into:

1- B-ALL: 80% of the cases better prognosis than T-ALL

2- T-ALL: Characterized by Mediastinal mass

Lecture 8- Chronic Leukemia:

• Chronic Leukemias:

- Uncontrolled proliferation and decreased apoptosis with variable degrees of differentiation (blasts are less than 20%)

• Myeloproliferative Neoplasms (MPN):-

- It is malignant proliferation of myeloid cells (maturing cells) in blood & BM.

MPN Features:- مهم

- Cytosis.
- Organomegaly (mainly spleen).
- Hyper cellular BM.
- High uric acid.
- May progress to AML.

• Chronic Myeloid Leukemia (CML):

- it is type of MPN.
- Associated with BCR-ABL1 Fusion gene located in Philadelphia (Ph) chromosome which results from t(9;22) which will lead to increase Tyrosine kinase that will cause uncontrolled proliferation.
- Myelocytes & Neutrophils are highly increased in CML.
- NAP score will be Low.

Clinical presentation of CML:-

- 20%-40% asymptotic.
- Massive splenomegaly.
- Abdominal discomfort due to splenomegaly.

How to differentiate between CML & other diseases?

1- Chronic MyeloMonocytic Leukemia (CMML): it will have Monocytosis & -ve BCR-ABL.

2- Leukemoid reaction:

- it is leukocytosis due to infection or stress.
- it will have increased bands cells (while in CML there will be increase of Myelocytes & Neutrophils) and it will be -ve BCR-ABL & High NAP score

Cont'd Lecture 8- Chronic Leukemia:

- **Myelodysplastic Syndrome (MDS):-**

- it is Group of myeloid neoplasms characterized by increased proliferation (in the bone marrow) with increased apoptosis (in peripheral blood) that will lead to :-
- Hypercellular marrow
- Peripheral cytopenia (decreased cells in peripheral blood)

These 2 features together give me what called Ineffective hematopoiesis

- **Chronic MyeloMonocytic Leukemia (CMML):**

- it is an MDS/MPN Disease that characterized by proliferation of Monocytes & Neutrophils.
- Philadelphia chromosome and BCR-ABL1 Must be –ve.
- Blasts must be less than 20%.
- MDS/MPN Disease: it the disease that has both:

a) Features of MDS (Dysplasia & Enhanced apoptosis).
b) Features of MPN (Marked proliferation).

Lecture 9- Polycythemia:-

- **JAK-2:** it is like ON/OFF Button of cellular proliferation, By activation of STATs system

- When there is point mutation at codon 617 in JH2, JAK-2 Will loss its auto inhibitory control and it will be always in active state ((Proliferation Always ON)

1- Polycythemia: divided into 3 types:-

a. **Relative (Stress) Polycythemia:** due to sever dehydration
b. **Secondary Polycythemia:** increased RBCs due to high Erythropoietin in case of hypoxia

c. Polycythemia vera:

- It is a type of MPN (Check MPN features in previous lecture) characterized by increased RBCs count due to JAK-2 mutation.

When do we say that this patient has PV? Important!

- When he has 3 Major criteria or First 2 Major and the Minor criteria.

- Major criteria
1. Hb> 16.5 g/dl in men or Hb>16.0 g/dl in women
Or Hematocrit > 49% in men or >48% in women
Or Increased Red Cells Mass (RCM).
2. Bone Marrow biopsy shows (panmyelosis).
3. Presence of JAK2V617 or JAK2 exon12 Mutation.

- Minor criteria
- Subnormal serum erythropoietin level.

Features:-

- Increased Hb.
- Increased blood viscosity.
- Thrombosis.
- Splenomegaly (70%) & Hepatomegaly (40%).
- Normocytic Normochromic RBCs.
- Hypercellular Bone marrow.

Cont'd Lecture 9- Polycythemia:-

2- Essential Thrombocythemia (ET):

- It is a type of MPN That involved mainly Megakaryocytic lineage characterized by thrombocytosis.

- Cause: due to JAK-2 or CALR Mutations.

- Features:-
- Hypercellular BM with megakaryocytic proliferation.
- Thrombosis (due to increased platelets number).
- Bleeding (due to deficiency of ingredients in the platelets).

3- Primary Myelofibrosis:-

- It is a type of MPN Characterized by proliferation of Megakaryocytes & Granulocytes

- Cause: JAK2 & CALR Mutations

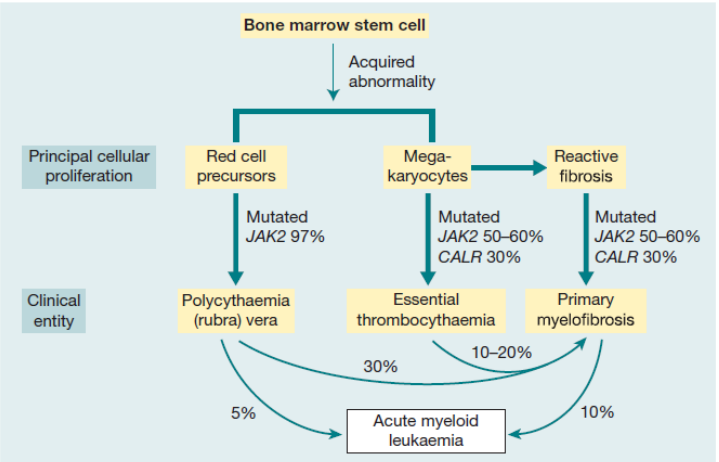
- Features:-
- Leucoerythroblastic Blood Picture under microscope.

- **Stages of Primary Myelofibrosis:-**

- Pre-fibrotic stage: We will find Leukocytosis & Thrombocytosis.

- Fibrotic stage: we will find :-

a) Anemia.
b) Leukopenia.
c) Thrombocytopenia.
d) Extramedullary Hematopoiesis.



Lecture 10- Approach to Haemolysis:

- **Hemolysis:** premature distruction of RBCs
- Clinical features of hemolysis:-
- Jaundice.
- Bone deformity.
- Leg ulcers.
- Dark urine.

- **Types of hemolysis:-**

1- Intravascular hemolysis: breakdown of RBCs in circulation.
- Laboratory features of intravascular hemolysis:
- Haemoglobinaemia & Haemoglobinuria

2- Extravascular hemolysis: breakdown of RBCs in the Spleen & Liver

- **Hemoglobin C disease:**
- it is congenital hemolytic anemia due to abnormal hemoglobin caused by mutation affect Amino acid number 6 in beta chain (will convert it from Glu (Glutamate) to Lys (lysine)).

- **Sickle cell anemia:**
- it is congenital hemolytic anemia due to abnormal hemoglobin caused by mutation affect Amino acid number 6 in beta chain (will convert it from Glu (Glutamate) to Val (Valine)).

- Clinical manifestations of sickle anemia:-
- Hand-foot syndrome.
- Bones and joints pain.
- Leg ulceration.

- Sickle cell might be:-

1- Sickle cell trait (AS)
2- Homozygous Sickle cell disease (SS) = Sickle cell anemia
3- double heterozygous Sickle cell disease:
a. Sickle cell & Hemoglobin C disease
b. Sickle cell & Thalassemia

- Factors increase sickling:-
- low O2.
- Low pH.

Cont'd Lecture 10- Approach to Haemolysis:

- Factors precipitating crises in sickle cell disease:
- Dehydration.
- Pregnancy.
- Infection especially malaria.

- Laboratory diagnosis of Sickle cell disease:-
- Sickle Solubility Test.
- Hb Electrophoresis.
- Genetic study.

Lecture 11- Lymphoproliferative disorder

- **Chronic Lymphocytic Leukemia (CLL):-**
- Cell: Naive B-cells
- Lymphocyte > 5,000
- Morphology: Soccer ball & Smudge cells
- Markers: CD5&23, IgM,IgD

- **Burkitt lymphoma:-**
- Cell: GC blast.
- Mutation: t(8;14) C-myc.
- Morphology: starry sky appearance.

- **Follicular lymphoma:-**
- Cell: Centrocyte.
- Mutation: t(14;18) Bcl2.
- Markers: CD10&20.

- **Multiple myeloma:**
- Associated with lytic bone lesions and may cause bone pain & fractuers.
- Cell: Plasma cells.

Hodgkin lymphoma:-
- involving cervical lymph nodes.
- Morphology: binucleated cells (Reed–Sternberg cells).
- Markers: CD30&15.

Lecture 12- Bleeding disorders:

- Normal Coagulation mechanism needs Ca2 & tissue factor (TF)

- Fibrinolytic mechanism: it is the enzymatic lysis of clot by dissolution of Fibrin into Fibrin-degradation products (FDPs), FDPs carried by plasmin

Tests of clotting defects:- مهم

1- APTT: estimates the activity of intrinsic system (XII,XI,IX,VIII,X,V,II&Fibrinogen)
Prolonged in: Hemophilia A&B, Von-Willebrand's disease.

2- PT: estimates the activity of extrinsic system (VII,X,V,II&Fibrinogen)

- **both of them (APTT& PT) Will prolonged in The Defect in common pathway.**

3- Thrombin Time (T.T): detect the deficiency of Fibrinogen

- **All of them (APTT, PT& TT) Will prolonged in the DIC!**

4- Bleeding Time: Prolonged only in Von Willebrand's disease & palates diseases

1- Congenital coagulation disorders:-

a. Hemophilia A: VIII Factor deficiency
b. Hemophilia B: IX Factor deficiency
} sex-linked diseases (X-chromosome)
c. Von Willebrand's disease: Von Willebrand Factor deficiency, Autosomal disorder (ch12)

a- Hemophilia A&B

- Prolonged deep hemorrhage (joints & muscles).
- Intracranial bleeding is most common cause of death.
- **If coagulation factors activity:-**

1. Less than 1% : severe disease, Joints deformity and crippling & Frequent spontaneous bleeding episodes
2. 1%-5%: Moderate disease, Post-traumatic bleeding
3. 5%-20%: Mild Disease, Post-traumatic bleeding.

Cont'd Lecture 12- Bleeding disorders:

b- Von-Willebrand Disease

- Abnormal bleeding time.
- Deficiency of Factor VIII Activity (because Von-Willebrabd factor is the carrier of factor VIII).
- Abnormal platelets aggregation.

2- Acquired Coagulation Disorders

- DIC
- Liver diseases

• Disseminated Intravascular Coagulation (DIC):

- Generalized activation of clotting system followed by marked activation of fibrinolytic system leads to consumption of Clotting factors & Platelets and increased FDPs.

• Caused by:

- Infections.
- Malignancies: especially Acute Promyelocytic Leukemia (M3).
- Snake bites.

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