Pathology : Anemia

Definition:

- Reduction of total RBC **MASS** below average levels.

- Reduction of oxygen carrying capacity of the blood.

- Leads to tissue hypoxia.

- Practically, measured by **Hemoglobin concentration**, and **Hematocrit** (ratio of packed RBCs to total blood volume**)/** *Both are good for diagnosis!*

Classification of anemia according to causes:

1)Blood Loss : might be acute or chronic!

2) Increased destruction (Hemolytic anemia) ***Bone marrow is very active***

- ➔ Extrinsic factors (Infection, antibody, mechanical)
- ➔ Intrinsic RBC abnromalities:

1. Hereditary (Cell membrane, enzyme, Hb abnormalities)
2. Acquired (Paroxysmal Nocturnal Hematuria)

3) Diminished RBC production ***Defect in the bone marrow***

-Iron deficiency anemia.
-Megaloblastic anemia.
-Aplastic anemia.
-Pure red cell aplasia.
-Myelophthisic anemia
-Myelodysplastic anemia

Classification of anemia according to morphology:

- *Size:* Normocytic , microcytic, macrocyticytic
- *Color:* Normochyromic, hypochromic (Increased central pallor)
- *Shape:* anisopoikelocytosis (spherocytes, sickle, schistiocytes)
- Hypochromic microcytic anemia usually reflects impaired Hb synthesis (No enough Hb)
- Macrocytic anemia reflects stem cell disease and maturation

RBC Indices:

-Slight variation is present between labs/ geographic areas.

-Sex, age, rate and mobility status have effect!!

RBC Count (RCC) : **Male:** 5.5 million/microliter **Female:** 4.8 million/microliter

Number of cells/ L

RBC Mass (Hb Concentration) : **Male**: 16g/dL (±2) **Female:** 14g/dL (±2)

Hematocrit (HCT) : **Male**: 46% **Female:** 42%

Volume % of RBCs in blood

Mean Cell Volume (MVC) : 80 - 100fL

(Average size in femoliter)

Mean Cell Hb (MCH) : 26 - 34

(Avergae mass of Hb in one RBC in pictograms)

Mean Cell Hb Concentration (MCHc) : 32 – 36 %

(Average concentration of Hb in a given volume of packed RBCs, only important in spherocytes; which are microcytic (Small MVC) and hyperchromic (High MCH), so MCHc in such cells is relatively high!

According to Dr. Tareq, we use MCH to determine the color of RBCs, not MCHc!

Reticulocyte Index (Retic Count) : 0.5 – 1.5%

-high reticulocytes → Hemolytic anemia

-Low reticulocytes → Anemia related to bone marrow diseases

Red Cell Distribution Width (RDW):

The coefficient of variation in red cell volume (differences in shape + size)

Clinical features of Anemia:

Dizziness | Fatigue | Pallor | Headache |Hypotension | Tachycardia | Tachyspnea.

Special types: Jaundice, bone and joint pain, growth retardation, aplenomegaly.

1. BLOOD LOSS

ANEMIA OF ACUTE BLOOD LOSS:

-Symptoms are related to decreased intravascular volume, might cause cardiovascular shock and death.

-Body responds by shifting fluid from interstitial to intravascular space, causing **dilutional anemia** and hypoxia

-Erythropoietin secretion is stimulated, activating BM erythropoiesis.

-Mature RBCs as well as Reticulocytes appear in blood after 5 days.

-In internal hemorrhage, iron is restored from extravasated RBCs and used again in erythropoiesis.

-In external and GIT hemorrhage, iron is lost, which complicated anemia

-The anemia is **normochromic normocytic**, with reticulocytosis.

(If then followed by Iron deficiency it appears as microcytic hypochromic)

-Leukocytosis (secondary to stress)

-Thrombocytosis (secondary to high erythropoietin); Megakaryocytes have receptors for erythropoietin!

Number of platelets commonly increases with anemia!

ANEMIA OF CHRONIC BLOOD LOSS:

-Occurs when the rate of RBC loss exceeds regeneration.

-Mostly associated with Iron deficiency anemia.

2. Increased Destruction (Hemolytic Anemia)

- Normally RBCs age is around 120 days, aged RBCs are engulfed by phagocytic cells in spleen, liver, BM!

- In hemolytic anemia→ premature destruction of RBCs→ Short life span!

- Accumulation of Hb degradation products (Free Hb!)

-Secondary increased erythropoiesis (High RBCs count in the BM)

- Retic count is increased

Hemolytic anemia is classified into:

1.Extravascular Hemolysis: Occurs in the spleen due to increased phagocytic activity.

It takes a long time. Patients usually have chronic diseases!

- Generally caused when the RBC is less deformable or having abnormal shape.

-Abnormal RBC shape prevents its normal movement in splenic sinusoids.

-Prolonged time of RBCs passage attracts histiocytes to engulf them.

-Free Hb from destructed RBCs binds Haptoglobin in serum. (low haptoglobin in the serum).

-Hb within phagocytes is converted to bilirubin and thus leads to Juandice!

The triad of extravascular HA is: Anemia, splenomegaly and jaundice.

-Increased erythropoiesis .

- High level of reticulocytes (high retic count).

-Lactate Dehydrogenase (LDH) level is elevated .

2.Intravascular Hemolysis: Occurs in blood vessels.

It attacks like a bomb! It occurs suddenly. It's more dangerous but less common!

-Caused by mechanical damage, complement fixation, microorganism, exogenous toxins.

-Large amount of free Hb:

1.It will bind to haptoglobin so haptoglobin is cleared from the serum

2.Free Hb in the serum is oxidized to Methemoglobin. (high level of metHb)

3.Free Hb and MetHb are excreted in the urine (Hemoglobinuria) causing dark urine

4. It might go to the kidney causing Renal hemosiderosis!

-No Splenomegaly. No Jaundice!

Lecture 2:

***All hemolytic anemias are hereditary except for one!**

1) Hereditary Spherocytosis (Extravascular hemolytic anemia)

-This inherited disorder is caused by intrinsic defects in the red cell membrane skeleton, so any small strike will destroy the membrane. (Absence of Spectrin and Ankyrin)

Spectrin is the major internal membrane protein, the tail of Spectrin binds with Actin. Spectrin-Actincomplex is connected by Ankyrinand (transmembraneprotein) making RBCs durable and elastic.

-The prevalence of HS is highest in **Northern Europe.**

-AD inheritance pattern.

-Frameshift mutations, resulting in absent protein.

-RBC Life span is dropped to less than 20 days.

Normal Hemoglobin content = Oxygen carrying capacity is normal! So, What's the problem!

-Because of the abnormal shape of RBCs, they will be phagosytosed by splenic macrophages, as spleen kills any abnormal RBC!

→ **Treatment: Splenectomy!**

They leave the bone marrow as normal RBCs, but during their movement & due to absence of such proteins, their size will be decreased as the cell membrane will be destroyed→ Spehrocytes.

Clinical features:

- Congestion of RBCs in the spleen causes splenomegaly and anemia
- High level of bilirubin →Jaundice
- Pigmented gall bladder stones
- High level of Lactate dehydrogenase (LDH)
- High level of erythropoietin.
- Reticulocytosis, erythropoiesis
- MCV= low (Microcytic)
- MCH= normal (Normal Hb content)
- Increased MCHC (Hyperchromic) [The only case where MHC doesn't correlate with MCHC!]
- **Abnormal osmotic fragility test**

Spherocytes are weak and easily fragile, so they are less **susceptible to hypotonic solution!**

Morphology:

Blood film:

- Spherocytic RBCs are round and small = Microcytic.

-No visible central pallor = Hyperchromic.

-Normal Hb content.

- Spherocytic RBCs becomes less deformable than normal ones, rigid and easily fragile (any minor strike can destroy the membrane)

- They are and vulnerable to splenic sequestration and destruction → become trapped in the splenic cords & phagocytosed by macrophages.

-"**Howell-Jolly**" bodies are seen in post splenectomy. A fragment of chromosome which is detached and left in the cytoplasm after the extrusion of the nucleus, secondary to accelerated erythropoiesis.
(*Appears as 1 or 2 eccentric dots)*.

2) Glucose-6-Phosphate Dehydrogenase Deficiency (Extravascular & Intravascular hemolytic anemia)

- G6PD presents in all cells.

- G6PD reduces NADP to NADPH while oxidizing Glucose-6-phosphate

- NADPH then provides reducing equivalents needed which protects against oxidant injury by catalyzing the breakdown of compounds such as H2O2. (NADPH antagonizes its action)

- G6PD deficiency is a recessive X-linked trait, placing males at higher risk for symptomatic disease.

No G6PD → No NADPH → Excess H2O2 → Physical damage!

-Several hundred G6PD genetic variants are known, but most are harmless.

-The normal enzyme is G6PD-B.

-Only two variants, designated **G6PD-African** (quantitative) and **G6PD-Mediterranean** (qualitative), cause most of the clinically significant hemolytic anemias.

-G6PD-Ais present in about 10% of American blacks; G6PD Mediterranean is prevalent in the Middle East.

-Because mature red cells do not synthesize new proteins, G6PD-A or G6PD Mediterranean enzyme activities fall quickly to levels inadequate to protect against oxidant stress as red cells age. Thus, older red cells are much more prone to hemolysis than younger ones.

- Oxidants cause both intravascular and extravascular hemolysis in G6PD-deficient individuals

-Exposure of G6PD-deficient red cells to high levels of oxidants causes the cross-linking of reactive sulfhydryl groups on globin chains, which become denatured and form membrane-bound precipitates known as *Heinz bodies (Insoluble globin chains form aggregates under the cell membrane)*

- These bodies are present beneath the cell membrane. They are seen as dark inclusions within red cells stained with Supravital stain **(crystal violet)**. Heinz bodies can damage the membrane sufficiently to cause intravascular hemolysis.

-Splenic macrophages identify Heinz bodies and pluck them out resulting in indentation. The remaining RBC is known as "**bite cells**" .
(Spleen only bites RBCs, it doesn't get rid of them)

-Normocytic Normochromic anemia!

Causes of hemolytic crisis

Hemolysis happens upon exposure to oxidant stress.

1. **Infections**
   The most common triggers are infections, in which oxygen-derived free radicals are produced by activated leukocytes.

2. **Drugs**
   Antimalarials (primaquineand/ chloroquine), some antibiotics (sulfonamides, nitrofurantoins)

3. **Food**
   Favabean (Favism)

4. **Unknown**
   Uncommonly, G6PD deficiency presents as neonatal jaundice or a chronic low-grade hemolytic anemia in the absence of infection or known environmental triggers.

Clinical features:

?Majority of patients are asymptomatic, anemia develops when the enzyme level drops <20% of normal activity.

?Hemolytic crisis appear 2-3 days after exposure to oxidant (It takes time).

?Only old RBCs hemolize, HB level drops,!

?patients have bone pain

•Chronic hemolysis (splenomegaly and GB stones) are absent→ BECAUSE mainly it's intravascular hemolysis!

?G6PD-A usually is self-limited

?G6PD-Mediterranian has more severe crisis, might need blood transfusion

?Recovery is associated with reticulocytosis

?Dx**: enzyme assay** (measure conversion to NAPDH), either we measure the quality or quantity.

3) Pyrovate kinase deficiency (Extravascular hemolytic anemia)

-AR inheritance

-PK is an enzyme in the anaerobic glycolysis pathway (main pathway in RBCs)

-PK deficiency causes **decreased ATP level** which is essential for cell membrane pumps (Na/K pump), intracellular Na accumulates, causing swelling of RBCs and rigidity.

PK deficiency →Low ATP in RBCs → Na\K pump is failing → Swelling→ Abnormal shaped RBCs (different shapes & sizes)

-Spleen clears abnormal shaped RBCs.

-2,3 diphosphoglycerate(DPG) level increases inside RBCs, facilitating O2 release, ameliorating the anemia & hypoxia.

Clinical features:
-Splenomegaly/ Jaundice/ GB stones.

-Anemia is exacerbated by stress

-Blood film shows Normocytic Normochromic anemia, variable reticulocytosis, **anisopoikelocytosis**

-Diagnosis: enzyme assay

-Treatment: splenectomy

4) Paroxysmal Nocturnal Hematuria (Intravascular hemolytic anemia)

- The **only acquired** hemolytic anemia.

- In PNH, GPI and their normally anchored proteins are absent

-Because the causative mutations occur in a hematopoietic stem cell, all of its clonal progeny (RBCs, WBCs and platelets) are deficient in
GPI-linked proteins that regulate complement activity: **CD55/ CD59**; which are potent inhibitors of C3 convertase that prevents the spontaneous activation of the alternative complement pathway.

-Normal individuals harbor small numbers of bone marrow cells with *PIGA* mutations

-In PNH, autoimmune reaction occurs against normal clones resulting in predominance of GPI-deficient clone

Clinical features:
Red cells, platelets, and granulocytes deficient in these GPI-linked factors are abnormally susceptible to lysis or injury by complement .

-Anemia : Acute hemolysis is rare (occurs In only 25% of cases). It appears as severs intravascular, paroxysmal and nocturnal hemolysis. chronic hemolysis without dramatic hemoglobinuria is more common!

-The tendency for red cells to lyse at night is explained by a slight decrease in blood pH during sleep, which increases the activity of complement.

- **Thrombocytopenia** BUT **Thrombosis is common**!

- **Neutropenia** (WBCs are least affected)

-In severe cases, pancytopenia develops (total failure of Bone marrow)

-About 5% to 10% of patients eventually develop acute myeloid leukemia or a myelodysplastic syndrome, possibly because hematopoietic stem cells have suffered some type of genetic damage.

Diagnosis:
Flow Cytometry (Measure CD55 + CD59 found on RBCs)
LDH level
Retic count

Lecture 3:

5) Autoimmune hemolytic anemia

" Abnormal antibodies circulating in the blood targeting RBCs' antigens"

- A group of anemias in which an abnormal immunoglobulin is attached to RBC membrane causing damage and lysis.

- **Coombs test:** The patient's RBCs are mixed with serum containing antibodies that are specific for human immunoglobulins. If the autoantibody is present, agglutination of RBCs occurs!

1. Warm Type

- It occurs in the core of the body where the temperature is high 37 C.
- 70% of immunohemolytic anemia.
- 50% are idiopathic (primary); the others are related to a predisposing condition or exposure to a drug.
- Most causative antibodies are of the **IgG** class; less commonly, IgA antibodies.
- A common target is the **Rh antigen** on RBCs
- The red cell hemolysis is mostly **extravascular**.

Pathogenesis:
RBCs have antibodies on their surface! The (Fc portion) will bind to splenic macrophages, and red cell membrane will be removed during "partial" phagocytosis. As in hereditary spherocytosis, the loss of membrane converts the red cells to spherocytes, which are sequestered and removed in the spleen. Moderate splenomegaly due to hyperplasia of splenic phagocytes is usually seen!

Drug induced hemolytic anemia

Antigenic drugs:
- In this setting hemolysis usually follows large, intravenous doses of the offending drug.
- Occurs 1 to 2 weeks after therapy is initiated.
- Penicillin, cephalosporins, anti-malarias drugs.
- These drugs bind to the red cell membrane.
- The responsible antibodies sometimes fix complement and cause intravascular hemolysis, but more often they act as opsonins that promote extravascular hemolysis within phagocytes

Tolerance-breaking drugs:
- Against red cell antigens, particularly the Rh antigens.
- α-methyldopa.

2. Cold Type

- This form is caused by IgM antibodies that bind with RBCs at low temperatures (0°-4°C), activating C3b!
- It is less common than warm antibody immunohemolytic anemia, accounting for 30% of cases.

Acute→ Self limited and the antibodies rarely induce clinically important hemolysis.! It appears transiently following certain infections, such as with *Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus, influenza virus, and HIV.
Chronic → Occurs in association with certain B-lymphomas! (severe).

Clinical symptoms: result from binding of IgM to red cells in vascular beds where the temperature may fall below 30°C, such as in exposed fingers, toes, and ears.

IgM binding agglutinates red cells and fixes complement rapidly.
As the blood recirculates and warms again, IgM is released, usually before complement-mediated hemolysis can occur (No hemolysis in peripheral organs where the temperature is low, because the amount is not enough for complement fixation)However, the transient interaction with IgM is sufficient to deposit sublytic quantities of C3b, an excellent opsonin, which leads to the removal of affected red cells by phagocytes in the spleen, liver, and bone marrow.
(Extravascular anemia)

-Unlike worm type, antibodies doesn't reach the spleen, as they will be released once the blood warms again)

Hemolytic Anemia Resulting from Trauma to Red Cells

Physical damage to RBCs :
1) Cardiac valve prosthesis

2) Vigorous exercise

3)Microangiopathic disease
- Disseminated Intravascular Coagulation (DIC).
- Thrombotic Thrombocytopenic Purpura (TTP).
- Hemolytic-Uremic Syndrome (HUS).

} aggregation of fibrin and platelets causing damage to RBCs!

- ➔ Severe activation of coagulation factors : Thrombosis everywhere!
- ➔ Activation of anti-coagulant factors : Bleeding.

RBCs appear as fragments (schistocytes).

Presence of schistocytes + Thrombocytopenia = Microangiopathic disease

Hemoglobinopathies:

Thalassemia

- The Thalassemia syndromes are a heterogeneous group of disorders caused by inherited mutations that decrease the synthesis of adult hemoglobin, **HgA** ($\alpha_2\beta_2$)
- Endemic in Middle East, tropical Africa, India, Asia

-β-Thalassemia is caused by deficient synthesis of β chains, whereas α-thalassemia is caused by deficient synthesis of α chains → decrease Hb synthesis (low Hb content!) → leads to Hypoxia.

-The hematologic consequences of diminished synthesis of one globin chain stem not only from hemoglobin deficiency but also from a relative excess of the other globin chain, particularly in β-thalassemia

β-Thalassemias

- Caused by mutations that diminish the synthesis of β-globin chains
- β^0 *mutations*, associated with absent β-globin synthesis
- β^+ *mutations*, characterized by reduced (but detectable) β-globin synthesis
- 100 different causative mutations, mostly consisting of point mutations

Pathophysiology:

-The deficit in HgA synthesis produces "underhemoglobinized" hypochromic microcytic red cells with subnormal oxygen transport capacity

- Diminished survival of red cells and their precursors, which results from the imbalance in α- and β-globin synthesis. Unpaired α chains precipitate within red cell precursors, forming insoluble inclusions, which damage cell membrane and results in cell death in RBC **precursors** (Ineffective erythropoiesis)
hemolysis starts early in the bone marrow!

- Those red cells that are released from the marrow also bear inclusions and membrane damage and are prone to splenic sequestration and extravascular hemolysis

- In severe β-thalassemia, uncompensated anemia leads to massive erythroid hyperplasia in the marrow and extensive **extramedullary hematopoiesis** in spleen, liver → hepatosplenomegaly!
Splenomegaly due to extravascular hemolysis and extramedullary hematopoiesis!

- The expanding mass of red cell precursors **erodes** the bony cortex, impairs bone growth, and produces skeletal abnormalities → Bone deformity!

- High level of Erythropoietin suppresses the circulating levels of Hepcidin, a critical negative regulator of iron absorption. Low levels of hepcidin → severe **iron overload**.

Clinical syndromes:

1. β-thalassemia Minor (β-thalassemia trait):
- One allele is affected!
- Heterozygotes (β^+/β or β^0/β).
- Mild asymptomatic microcytic hypochromic anemia.

2. β-thalassemia Intermedia
- Both alleles are affected!
-Moderate stable anemia.

3. β-thalassemia Major
- Both alleles are affected!
- Severe, transfusion-dependent anemia.

α-thalassemias

- Normally, there are four α-globin genes, and the severity of α-thalassemia depends on how many α-globin genes are affected.

- As in β-thalassemias, the anemia occurs both from inadequate hemoglobin synthesis and the effects of excess unpaired non-α chains (β, γ, and δ)

- Since free β and γ chains are more soluble than free α chains, hemolysis and ineffective erythropoiesis are less severe than in β-thalassemias.

- Gene deletion is the most common cause of reduced α-chain synthesis.

- In newborns with α-thalassemia, excess unpaired γ-globin chains form γ_4 tetramers known as **hemoglobin Barts**, whereas in older children and adults excess β-globin chains form β_4 tetramers known as **HgH**.

Clinical features:

- **Silent carrier**: a single gene deletion, patients have microcytosis but no anemia, asymptomatic.
- **α-Thalassemia Trait:** deletion of two genes, clinically identical to β-thalassemia minor: microcytosis, minimal or no anemia, and no abnormal physical signs.
- **Hemoglobin H Disease**: deletion of 3 genes, common in Asia, clinically resembles β-thalassemia intermedia, HgH has very high affinity to oxygen, leading to tissue hypoxia. It also precipitates within the RBC which results in extravascular hemolysis.
- **Hydrops fetalis**: deletion of 4 genes. Patients die in utero unless transfused.

Diagnosis:

Blood film**:**
- Hypochromic Microcytic anemia
- Target cells (codocytes): abnormal hemoglobinized RBCs).
- Basophilic stippling: Aggregates of ribosomes!

Hg electrophoresis**:** Different globin chains have different electrical charges.
Hg is separated on gel and an electrical current is applied. Each type of Hg migrate a specific distance and hence can be recognized.

HbA2 is increased in β-thalassemias!

Sickle Cell Anemia

- Hereditary hemoglobinopathy that occurs primarily in individuals of African descent.

- Sickle cell disease is caused by a **point mutation** in the sixth codon of **β-globin** that leads to the replacement of a **glutamate** residue with a **valine** residue

- The abnormal physiochemical properties of the resulting sickle hemoglobin (HbS) are responsible for the disease

Clinical features:

1. Sickle Cell Trait:
One defective gene | Heterozygosity of HgS| Silent carriers | Asymptomatic | Electrophoresis: HgS ≈ 40%

2. Sickle Cell Disease:
Two defective genes | Homozygosity of HbS | Symptomatic | Electrophoresis: HgS ≈ 90%

Both types of Hg are resistant to Malaria.

Pathophysiology :

- HbS molecules undergo polymerization when deoxygenated. Initially the red cell cytosol converts from a freely flowing liquid to a viscous gel as HbS aggregates form. With continued deoxygenation aggregated HbS molecules assemble into long needle-like fibers within red cells, producing a distorted sickle shape (2 sickle cells will aggregate).

- This causes damage to cell membrane. Ca^{+2} enters the cell and causes protein cross-linking. K^{+} and H_2O moves out of the cell from damaged membrane. With repeated sickling, more damage happens until the cell shape is irreversibly changed even if oxygenated again.

- HgC is a variant of Beta chain. It tends to cause dehydration in RBC. Thus, if it was combined with HgS (HgSC disease), sickling takes place

- Sickle cells are fragile, leading to **intravascular hemolysis**.

- Sickle cells are removed by macrophages, leading to **extravascular hemolysis** too.

The presence of HbS underlies the major pathologic manifestations:
(1) chronic hemolysis
(2) microvascular occlusions
(3) tissue damage

Interaction of HgS with the other types of hemoglobin :

-In heterozygotes with sickle cell trait: HgA interferes with HbS polymerization. As a result, red cells in heterozygous individuals do not sickle except under conditions of profound hypoxia

-HgF inhibits the polymerization of HbS even more than HgA; hence, infants do not become symptomatic until they reach 5 or 6 months of age, when the level of HgF normally falls

Blood morphology in sickle cell crisis:

-peripheral blood demonstrates variable numbers of irreversibly sickled cells, reticulocytosis, and target cells, which result from red cell dehydration
-The bone marrow is hyperplastic as a result of a compensatory erythroid hyperplasia
-Expansion of the marrow leads to bone resorption and secondary new bone formation, resulting in prominent cheekbones and changes in the skull that resemble a crew-cut in x-rays .
-Extramedullary hematopoiesis can also appear.
-The increased breakdown of hemoglobin can cause pigment gallstones and hyperbilirubinemia.

Splenic changes:

-In early childhood, the spleen is enlarged up to 500 gm by red pulp congestion, which is caused by the trapping of sickled red cells in the cords and sinuses . With time, however, the chronic erythrostasis leads to **splenic infarction**, fibrosis, and progressive shrinkage, so that by adolescence or early adulthood only a small residual splenic tissue is left; this process is called **autosplenectomy.**

-Howell-Jolly bodies (small nuclear remnants) are also present in some red cells due to the asplenia.

-Slpenomegaly - hypovalemia

Vaso-occlusive crisis :

- Also called pain crises, are episodes of hypoxic injury and infarction that cause severe pain in the affected region

Thrombosis | Tissue Infraction (Lungs) | Myocardial Infraction | Acute Chest Syndrome | Penis Priapism | Bone and joints pain | Skin Leg Ulcers

Aplastic crises :

-Acute event
-Infection of red cell progenitors by **parvovirus B19**, which causes a transient cessation of erythropoiesis and a sudden worsening of the anemia (it destroys erythroid precursors)

Diagnosis:

-Blood film (Sickle cells, Target cells, Howell-Jolly bodies)
-Sickling test: application of oxygen-consuming reagent to blood.
-Hemoglobin electrophoresis is also used to demonstrate the presence of HbS.

Lecture 4:

Anemias of diminished erythropoiesis (Inadequate RBC production)

1. Iron deficiency anemia

- The most common anemia worldwide.

- Only 10% of ingested iron is absorbed (Bioavailable iron).

- Most dietary iron occurs in red meat products.

- Iron absorption occurs in the duodenum.

- Stored iron is found in **hemosiderin** and **ferritin**.

-Store in **ferritin** in ferric status and transported by **transferrin** in ferrous status.

Causes:

-Decreased dietary intake (Vegetarians).

-Impaired absorption (GI disease).

-Increased demand (Pregnancy) .

-Chronic blood loss (GI bleeding/ Menorrhagia)

*<u>People at increase risk of anemia</u>: Infants, teenagers, elderly, low socioeconomic class!

Pathogenesis:

-Chronic disease. Insidious course.

- Iron stores in the bone marrow deplete first→ **Serum ferritin** decreases → Serum iron decreases!

Serum ferritin is derived from the storage pool of body iron, hence, it correlated well with body iron. However, Serum iron level does not reflect the actual status of total body iron.

- Serum transferrin increases.

-High level of erythropoietin but the marrow response is blunted by the iron deficiency → low erythropoiesis!

- Bone marrow cellularity is low and only slightly increased.

-The capacity to synthesize hemoglobin is diminished (low amount of Hb in RBCs).

-Low count of RBCs.

Clinical features:

- RBCs appear as microcytic and hypochromic.

- Target cells.

- **Poikilocytosis** (differences in shape and size) *measured by Red cell Distribution Width*.

- Thrombocytosis (because erythropoietin has receptors on megakaryocytes).

2. Megaloblastic Anemia

-Nutritional anemia.

- Large immature erythroid precursors.

-Two types: Vitamin B12 deficiency and folate deficiency.

- Both are coenzymes required for synthesis of Thymidine.

<u>Causes of Vit B12 deficiency:</u>

- Low intake (vegans).

- Impaired GI absorption (intrinsic factor deficiency, malabsorption disease, gastrectomy.

- Loss of storage takes a long time (Up to 1 year)

-B12 is important for neuronal functions!

<u>Causes of folate deficiency:</u>

- Low intake (inadequate diet, infancy).

- Impaired absorption (malabsorption, chronic alcoholism, anti-convulsants, oral contraceptives)

- Increased loss (especially in people with dialysis)

- Impaired utilization (methotrexate, Vit B12 deficiency)

3. Pernicious Anemia

Special type of megaloblastic anemia!

-Autoimmune disease! Both T-cells and B-cells are involved.

-Abnormal autoreactive T-cell response initiates direct gastric mucosal injury, also triggers formation of autoantibodies.

Type 1 antibody: blocks Vit B12 from binding to intrinsic receptors.

Type 2 antibody: blocks Vit B12-intrinsic factor complex to its ileal receptor.

Type 3 antibody: blocks Proton pumps on parietal cells (not specific).

- With time, anemia develops, gastric glands become atrophic.

- Neurologic symptoms develop secondary to spinal cord demyelination.

Morphology:

- Bone marrow : hypercellular! The cellularity is initially high, but with time it decreases→ Low count of RBCs!

- Erythroid precursors are large with immature nuclear chromatid due to absence of Thymidine! (Megablastoid cells).

- RBCs are oval, macrocytic and hyperchromic (No central pallor).

- Granylocytes: Hypersegmented neutroplhils (>4 lobes) , glantmetamyelocytes!

- Megakaryocytes : Large with hyperlobated nuclei.

- Increased erythropoietic level as well as impaired DNA synthesis leads to increased apoptosis in nucleated RBCs and hemolysis**.**

In this type of anemia, hemolysis in the bone marrow will occur, so just like the hemolytic anemias, we will find high levels of LDH in the serum!

4. Anemia of Chronic Disease

- Most common anemia in hospitalized people

- Associated with Chronic diseases with persistent inflammation (Rheumatoid arthritis or Cancer).

Pathogenesis:

- High level of IL-6

-Activates Hepcidin.

- Increased iron absorbtion.

- Increased iron storage.

- Blocks iron transfer from stores to RBCs.

-Use of iron by macrophages.

- The red cells can be normocytic and normochromic **or** hypochromic and microcytic (as in anemia of iron def.)

-There is increased storage iron in marrow macrophages, high serum ferritin level, and reduced total iron-binding capacity.

*Aplastic Anemia

A syndrome of chronic primary bone marrow failure (hematopoietic failure).

-Defect in stem cells proliferation→ A shortage of all types of blood cells (pancytopenia)

- In the majority of patients, autoimmune mechanisms are suspected.

-In some, genetic mutations, overlap with PNH can be inherited (Fanconi) or acquired.

Causes:

-Majority of the cases are idiopathic (No known cause can be identified).

-Less commonly associated with Rh diseases.

-Idiosyncratic drug reaction (Chloramphenicol, gold)

-Some viral hepatitis.

Morphology:

-Bone marrow is hypocellular (empty bone marrow).

-Largely devoid of hematopoietic cells (pancytopenia).

-BM is composed of adipose tissues (most cells become fat).

-Low retic count (Reticulocytopenia).

-No Splenomegaly!

*Myelophthisic anemia

-Infiltrative disease that destroys bone marrow cells.

-Common in cancer (Acute leukemia, Plasma cell lymphoma, metastasis, less commonly by granuloma).

-Leads to pancytopenia.

-No Splenomegaly!

*Hypothyroidism

-Causes decrease in cell metabolism.

-Results in mild Normochromic Normocytic anemia.

*Chronic Renal Failure

-This anemia tends to be roughly proportional to the severity of the **Uremia**

Caused by:

1) Diminished synthesis of erythropoietin by the damage kidneys. Which leads to inadequate red cell production.

2) Iron deficiency due to platelet dysfunction and increased bleeding, which is often encountered in uremia.

-Uremia causes a change in RBC membrane shape, known as **Echinocytes** (small projections)

*Chronic Liver Disease

-Bleeding is common (defects in coagulation factors).

-Folate and iron deficiencies caused by poor nutrition and excessive bleeding often exacerbate anemia in this setting.

-The anemia is slightly microcytic.

-Characteristic shape of **Acanthocytes** (Long projections)