**Anemia**

Anemia: is a reduction in the oxygen carrying capacity of blood.

Classification of anemia:

1. Etiological classification
2. Increase RBC loss (bleeding)
3. Increase red cell destruction (hemolysis)
4. Decrease red cell production
5. Morphological classification:
6. Cell size (normocytic, microcytic, macrocytic)
7. Degree of hemoglobinization reflected by the color of the cell (normochromic, hypochromic)
8. Shape of the cells: normal shape, spherocyte, sickle cell shape…

**Clinical features of patient with anemia**: it largely depend on the type of anemia and hemoglobin level.

General features include: pallor, tiredness, palpitation, change in skin, hair and fingers, decrease in concentration

Jaundice and change in color of urine and stool with loin pain = intravascular hemolytic anemia

Jaundice +special face character splenomegaly and signs of iron deposition= extravascular hemolytic anemia

**Investigations**

* **Complete blood count:** detect the number of each blood cell+ Hb + PCV +special indices of RBC
* **TSB: total serum bilirubin which include both indirect (unconjucated) and direct (conjucated) bilirubin. In hemolytic anemia there was indirect (unconjucated) hyperbilirubinemia.**
* **Blood film:** detect the shape and size of the blood cells
* **Hb electrophoresis** if hemoglobinopathies (thalassemia, sickle cell anemia, ….) suspected
* **Bone marrow:** state of bone marrow cellularity, examine blood cell precursors, iron store and any pathological abnormality.

**I-Anemia of blood loss**

1. **Acute blood loss (hemorrhage):** acute massive blood loss result in hypovolemic shock rather than anemia. Anemia in acute blood loss is normochromic normocytic. The body reacts by hemodilution and increase erythropoietin level which stimulates bone marrow to increase RBC production. The onset of marrow response is marked by reticulocytosis (reticulocyte is anew RBC)
2. **Chronic blood loss:** here the iron store gradually depleted, iron essential for hemoglobin synthesis and effective erythropoiesis. Anemia is hypochromic anemia (iron deficiency anemia) corrected by treating the cause and iron supplementation.

**II- Anemia of increase RBC destruction (hemolytic anemia):**

Normal RBCs have a life span of about 120 days. If RBC destructed earlier, hemolytic anemia will occur.

General features of all hemolytic anemias: all characterized by

1. Increase rate of RBC destruction
2. Compensatory increase in erythropoiesis result in reticulocytosis
3. Retention by the body products of red cell destruction e.g. iron overload in extravascular hemolytic anemia.
4. Almost invariably hemolytic anemia associated with erythroid hyperplasia in the bone marrow and increased retic count in the peripheral blood. In sever hemolytic anemia extramedullary hematopoiesis often develops eg in spleen liver and lymph nodes.

Site of RBC destruction

1. Intravascular RBC destruction: hemolysis occurs within blood vessels. It results from mechanical destruction of the RBC (prosthetic valve), physical agent (heat), chemical agent (bacterial toxin, drugs) , G6PD deficiency, microorganism (malaria), immunological (type II hypersensitivity reaction, ABO mismatch). Regardless the cause, the anemia characterized by the followings: hemoglobinemia, hemoglobinuria, unconjugated hyperbilirubinemia (jaundice) and Sever deficiency or absent haptoglobin from plasma (circulating protein that bind and clear Hb). Intravascular Hemolytic anemia may lead to acute tubular necrosis and renal failure.

The patient present with sudden attack of loin pain, change in color of urine and drop in Hb.

1. Extravascular RBC destruction: hemolysis takes place largely within the phagocytic cells of the spleen. The phagocytic cells remove abnormal RBCs from the circulation (spherocytosis, sickle cell anemia, thalassemia). Abnormal RBC shape makes their passage difficult through splenic sinusoids and leads to splenic sequestration followed by phagocytosis. Extravascular hemolysis characterized by:

Unconjucated hyperbilirubinemia (jaundice) with iron that released from Hb by phagocytic cells accumulated in tissues lead to secondary hemosiderosis. no hemoglobinemia, **no** hemoglobinuria. The spleen was enlarged in most cases and pigmented gall stone formed.

The patients usually presented with sever anemia, signs of multiple organs disfunctioning due to hemochromatosis and splenomegaly.

Common examples of hemolytic anemias:

**Hereditary spherocytosis (HS):** is characterized by autosomal dominant inherited defect in RBC membrane that renders the cells spheroidal less deformable and vulnerable to splenic sequestration and destruction (extravascular hemolysis).

**Sickle cell anemia:**

Normal infant RBC contains HbF (Fetal hemoglobin HbF α2γ2). Adult RBC contain 96% HbA (α2β2), 3% HbA2 (α2δ2) and 1% of HbF (α2γ2).

In Sickle cell anemia HbS will produced by substitution of valin for glutamic acid of β chain. In homozygotes all HbA is replaced by HbS, whereas in heterozygotes only about half is replaced. Upon deoxygenation HbS molecules undergo polymerization (crystallization) these polymers distort RBC which assume an elongated crescentic or sickle shape (sickling) and become sticky less deformable then destructed by splenic macrophages. Sickling initially reversible then with recurrent episodes it become irreversible. The hemolysis is extravascular hemolysis.

**Thalassemia**

Thalassemia is heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of α or β chains.

Adult Hb (HbA) is a tetramer composed of two α and two β chains (α2β2). The α chains are encoded by two α globin genes, while the β chains are encoded by a single β globin gene. If mutation in α globin gene, α thalassemia will occur. If mutation in β globin gene, β thalassemia will occur.

**β thalassemia**

β thalassemia resulted when the β globin gene was mutated. Individuals inheriting one abnormal gene (ie from one parent) have thalassemia minor, which is asymptomatic or mildly symptomatic. If individuals inheriting two mutated allele (ie from both parents) thalassemia major will occur.

In β thalassemia there is:

1. Reduced synthesis of β globin leads to inadequate HbA formation and the RBC will be hypochromic microcytic
2. Reduced synthesis of β globin leads to unbalance between α and β of globin chains. Unpaired α chain will form insoluble precipitate on the red cell membrane which leads to extravascular hemolysis.

**α thalassemia**

The molecular basis of α thalassemia is quite different from that of β thalassemia. Most of α thalassemia are caused by deletion that remove one or more of the α globin gene loci. The severity of the disease that result from these lesions is directly proportional to the number of α globin genes that are missing. For example the loss of single α globin gene is associated with a silent carrier state, whereas the deletion of all four α globin genes is associated with fetal death in utero.

Hemolytic anemia due to α thalassemia less severe than that of β thalassemia because excess β globin chains form relatively stable β4 tetramers (HbH) and γ4 tetramers (HbBart) that cause less membrane damage than do free α globin chains. But unfortunately both HbH and HbBart have an abnormal high affinity for oxygen, which renders them ineffective at delivering oxygen to the tissues

**Glucose 6 Phosphate Dehydrogenase Deficiency (G6PDD):**

 X-linked recessive inherited disorder, ie males affected and the females become carrier. This genetic disorder affects the enzymes glucose 6 phosphate dehydrogenase which required to convert NADP to NADPH which intern required for glutathione (GSH) production. GSH protect RBC membrane from oxidative stress. The prototype of these anemias associated with G6PD deficiency make the RBC vulnerable to hemolysis. The patients have no symptoms until the patient is exposed to oxidant stress which include:

1. Drug: antimalarial drug premaquine, sulfonamide, nitrofurantoin, aspirin, phenacetin.
2. Food especially broad beans.
3. infection and inflammation

oxidative stress will produce free radicles, these free radicles encountered by GSH. GSH is impaired in G6PDD red cells so the free radicles attack the red cells including and intravascular hemolysis will occure

Hemolysis is intravascular hemolysis.

 **Immunohemolytic anemia:**

 Antibodies recognize antigens on red cell membrane cause the uncommon form of hemolytic anemia. Example of immune hemolytic anemia:

1. Rh incompatability: mother with Rh –ve blood group bearing fetus with Rh +ve blood group. RBC will escape from the fetus to mother circulation lead to Ab formation against Rh antigen. In the following pregnancy, if the fetus with Rh +ve antigen, anti Rh antibody in the mother circulation that formed in the first pregnancy cross the placenta and attack the fetus RBC Rh antigen lead to hemolysis of fetal RBC.
2. ABO incompatabolity when the patient receive incompatable blood group. Antibodies in the recipient patient react with antigens of the incompatable donor blood and the vice versa e.g patient with blood group A which have anti B antibodies in his blood receive blood from group B donor which have antiA antibodies..
3. Blood transfusion reaction: her the blood is compatable but the patient have antibodies in his serum may react with the received compatable blood. This can commonly occur in multiparous women, patient with multiple blood transfusions. Cross match test will decrease the occurrence of this reaction.

 **Traumatic hemolytic anemia (microangiopathic hemolytic anemia)**

In this type of anemia there is a vascular lesion that predisposes the circulating red cells to mechanical injury (intravascular hemolysis)this include:

1. Prosthetic heart valve
2. Disseminated intravascular coagulopathy (DIC)
3. Malignant hypertension
4. Disseminated cancer

**Anemia due to diminished erythropoiesis:**

 This type include

1. Anemias caused by an inadequate dietary supply of substances that are needed for hemopoiesis particularly iron, folic acid, and vit B12
2. Disorders that suppress the bone marrow RBC production like that occur in aplastic anemia, leukemia and cancer metastasis .

**Iron deficiency anemia:**

It is the most common cause of anemia. It estimated to affect 10% of population in developed countries and 25 in developing countries.

Total body iron content is about 2gm for women and 6gm for men. Approximately 80% of functional body iron is found in Hb, with the remainder being found in myoglobin and iron containing enzymes e.g. catalase and cytochromes. Iron storage pool represented by **hemosiderin and ferritin**. Iron stored mainly in liver, spleen, bone marrow and skeletal muscles.

Iron transported in plasma by protein called **transferrin**. In normal persons, transferrin is about 33% saturated , serum iron about 120 µg/dl in men and 100 µg/dl in women.

Iron absorption occurs in small intestine. There is no regulated pathway for iron excretion, which is limited to 1-2 mg/day that lost by shedding of mucosal and skin epithelial cells

 Causes of iron deficiency anemia:

1. Low iron intake: malnutrition and vegetarian diet
2. Malabsorption syndroms including stomach and small intestine e.g. sprue and celiac disease.
3. Increase demands : pregnancy and infancy
4. Chronic blood loss: this is one of most important causes of iron deficiency anemia. Loss may occur from gastrointestinal tract (peptic ulcers, colonic cancer, hemorrhoids, hook worms).

Diagnostic criteria for iron deficiency anemia:

1. Hypochromic microcytic anemia
2. Low serum iron and low serum ferritin
3. Low transferrin saturation
4. Increase total iron binding capacity

Anemia of chronic disease:

This is the most common form of anemia in hospitalized patients. It superficially resembles the anemia of iron deficiency, but it come from inflammation-induced sequestration of iron within the mononuclear phagocytic (reticuloendothelial) system.

To differentiate anemia of chronic disease from iron deficiency anemia: iron store increase so there is high serum ferritin

 **Megaloblastic anemia:**

This type of anemia occurs due to deficiency of either folic acid and vit.B12 or both. These vitamins are required for DNA synthesis. The RBC size increase (macrocyte) the other blood cell precursors in the bone marrow are also affected.

Causes of folate deficiency:

1. Elderly and persons with poor diet
2. Increase metabolic needs (pregnant women and patients with chronic hemolytic anemia)
3. Patients on anti -epileptic drugs e.g. phenytoin and other drugs that inhibit folate absorption.
4. For vit B12 deficiency usually caused by autoimmune disease (pernicious anemia) in which there is anti-parietal cell antibodies (parietal cells are present in the gastric fundal mucosa responsible for intrinsic factor production) resulting in decrease in production of intrinsic factor which is essential for vitB12 absorption.

Pathogenesis of megaloblastic anemia:

The morphological hallmark of megaloblastic anemia is an enlargement of erythroid precursor (megaloblast) which gives rise to abnormally large red cells (macrocytes).

The underlying cellular enlargement is due to impairment in DNA synthesis, which results in delay in nuclear maturation and cell division. Because the synthesis of RNA and cytoplasmic elements precede at a normal rate the erythroid precursors (megaloblasts) show nuclear/cytoplasmic asynchrony.

Precursors of other blood cells in the bone marrow also affected and if the condition sever the bone marrow output for other cells (granulocytes, platelets) also diminished and the patient present with pancytopenia and hypersegmented neutrophiles.

Diagnostic features of megaloblastic anemia:

1. In both folate megaloblastic anemia and pernicious anemia the patient present with pallor and tiredness, palpitation, changes in hair and fingers
2. Decrease hemoglobin and MCV more than 90. There is decrease in number of platelets and granulocytes
3. On blood film there is macrocytic red cells and hypersegmented neutrophils
4. To differentiate folate deficiency from pernicious anemia (vit B12 deficiency) the patients with pernicious anemia have normal serum folate and decrease in vit B12 with anti-parietal cells and anti- intrinsic factor antibodies in their serum.

**Aplastic anemia AA:**

AA is a disorder in which multipotent bone marrow stem cells are suppressed leading to marrow failure and pancytopenia

Etiology and pathogenesis:

1. Primary (idiopathic) 50% of cases.
2. Secondary to bone marrow damaging agent e.g neoplastic drug (chemotherapy), benzene antibiotics like chloramphenicol. Viral infection also an important cause for AA : e.g EBV

Autoreactive T lymphocytes play an important role. Perhaps viral Ag, drug derived haptens and/or genetic damage creates neoantigens within myeloid stem cells that serve as target for t lymphocytes. 70-80% of cases of AA respond to immunosuppressive drugs against t lymphocytes.

Features for diagnosis

* Patient present with Anemia (low Hb ) and recurrent spontaneous subcutaneous bleeding (ecchymosis) due to thrombocytopenia
* CBC (complete blood count) and Blood film show pancytopenia except lymphocytes.
* Bone marrow biopsy is hypocellular except lymphocytes and plasma cells

Neoplastic proliferation of white blood cells:

Neoplastic disorders represent the most important white cell disorder. They can be divided to:

1. Lymphoma: it is neoplasia of lymphocytes (T lymphocytes &B lymphocytes) which called hodgkin and non- Hodgkin lymphoma.

LYMPHOMA

|  |  |
| --- | --- |
| Hodgkin lymphoma | Non Hodgkin lymphoma |
| Hodgkin lymphoma is marked by the presence of **Reed-Sternberg** cells, which are mature B cells that have become malignant | derived from B cells or T cells and no Reed-Sternberg cells |
| arise in the lymph nodes | Arise in the lymph nodes as well as other organs. |
| Less common | More common |
| Median age of occurrence 35  | The median age of occurrence is 60 |
| Hodgkin lymphoma tends to progress in an orderly fashion, moving from one group of lymph nodes to the next | non-Hodgkin lymphoma progress in non-order fashion |
| Considered one of the most treatable cancers, with more than 90 percent of patients surviving more than five years.  | Survival rates for patients with non-Hodgkin lymphoma tend to be lower |

1. Leukemia: it is neoplasia that arise from stem cells in the bone marrow that give rise to granulocytes, red cells and platelets (MYLOID LINEAGE) and stem cells that give rise to lymphocytes (LYMPHOID LINEAGE). It divided to acute lymphocytic leukemia ALL, chronic lumphocytic leukemia (CLL), acute mylocytic leukemia AML, chronic myelocytic leukemia CML. These types of malignancy shows an increase in blast cells in the bone marrow and peripheral blood.

**ALL (acute lymphocytic leukemia):**

The incidence of ALL is highest at 3-7 years old. 85% of cases are of B cell type (B-ALL) which has equal sex incidence. The patient present with anemia (pallor and lethargy) , neutropenia(recurrent infection), thrombocytopenia (ecchymosis, and easily bleeding gum). The bone marrow shows >20% immature blast cells and spillage of these cells to the peripheral blood (blast cells in the blood film).