***“Anemia of diminished erythropoiesis” part -2-***

***Folic acid & vitamin B12 deficiency anemia (megaloblastic anemia):***

**General features:**

1. The morphologic hallmark of megaloblastic anemia is the presence of megaloblasts **(** enlarged erythroid precursor that give rise to abnormally large red cells(macrocytes)**)** granulocytes precursor are also increased in size. The reason for this cellular gigantism is the defective DNA synthesis that impairs nuclear maturation and cell division.
2. Because the synthesis of RNA and cytoplasmic elements is within normal rate ,whereas the synthesis of DNA (nucleus) the hematopoietic precursors show nuclear-cytoplasmic asynchrony.
3. Many megaloblasts are so defective in DNA synthesis that they undergo apoptosis in the bone marrow (ineffective hematopoiesis).
4. Platelets and granulocytes are also affected and most patients present with pancytopenia (anemia/ thrombocytopenia / granulocytopenia)
5. Morphologic features:
* Hyper cellularity of the bone marrow with megaloblastic erythroid precursor.

In the bone marrow

* Megaloblasts are larger than normal erythroid progenitors and have delicate, finely reticulated nuclear chromatin (indicative of nuclear immaturity)
* The granulocyte precursor also demonstrate nuclear-cytoplasmic asynchrony, yielding giant metamyelocytes.
* Appearance of hypersegmented neutrophils (lobules >5) before the onset of anemia.

In the blood

* Red cells are large, egg- shaped macro-ovalocytes (MCV>110) ,although macrocytes appear hyperchromic but MCHC is normal.

**First: folic acid deficiency anemia:**

1. Sources of folic acid: fresh uncooked vegetables and fruits.
2. Site of absorption: upper third of the small intestines.
3. Function: DNA synthesis.
4. Causes:
* Poor diet
* Increased demands (pregnancy, patients with chronic hemolytic anemia)
* Substances such as: phenytoin, acidic food and substances found in beans which inhibit folate absorption / methotrexate which inhibits folate metabolism.
* Malabsorption: celiac disease and tropical sprue.
1. Folate deficiency anemia symptoms and manifestations:
* Insidious with nonspecific symptoms (weakness/ fatigue) duo to anemia.
* Because GI tract cells have a high turnover rate they will also affected by folate deficiency and symptoms like sore tongue are common.
1. Diagnosis:
* Serum and red cell folate and B12 levels to distinguish between the 2 types of anemia.
* smears from peripheral blood and the bone marrow.

**Second: vitamin B12 deficiency anemia:**

1. Sources: food derived from animals.
2. Site of absorption: distal ileum.
3. Function: required for recycling of tetrahydrofolate, the form of folate that is required for DNA synthesis/ myelination of nerves (especially posterior and lateral columns of spinal cord)
4. Causes:
5. defects involving intrinsic factor: autoimmune reaction against parietal cells and intrinsic factor, which produces gastric mucosal atrophy.(pernicious anemia) Evidences of autoimmune reaction against parietal cells and intrinsic factor are:
6. Presence of autoantibodies in the gastric juice and serum of most patients. These antibodies include( parietal canalicular antibodies against parietal cells/ blocking antibodies which disrupt the binding of B12 to intrinsic factor/ intrinsic factor-B12 complex anti bodies which prevent the complex from binding to its receptor in the distal ileum (cubulin)
7. this anemia often occurs with other autoimmune diseases (Hashimoto thyroiditis /Addison disease/ diabetes mellitus type 1)
8. Patients with other autoimmune disease often have serum antibodies against intrinsic factor.
9. Poor diet: confined to strict vegans because once B12 is absorbed , it is stored in the liver which contains reserves sufficient to support bodily needs for 5to 20 years (rare)
10. Malabsorption: after gastrectomy / ileal resection/ disorders that disrupt the function of the distal ileum (Crohn disease/ Whipple disease/ tropical spru).
11. Gastric atrophy and achlorohydria (decrease in HCl secretion) in old people which disturb the production of pepsin and acid required to release B12 from its bound form in food.
12. B12 deficiency anemia symptoms and manifestations :
* Pallor, fatigue, in severe cases dyspnea and congestive heart failure.
* Similar GI tract symptoms to folate deficiency =sore tongue.
* Mild jaundice due to ineffective erythropoiesis.
* Spinal cord disease (symmetric numbness/tingling/ burning in feet or hand/ unsteadiness of gait / loss of position sense especially in the toes)
1. Diagnosis (of pernicious anemia):
* Low serum B12 & normal or high folate levels
* Serum antibodies against intrinsic factor
* Megaloblastic anemia
* Leukopenia with hypersegmented granulocytes.

important

* Dramatic response (reticulocytosis) to B12 administration.
1. Note: B12 deficiency anemia is reversed with administration of folate. By contrast, folate administration doesn’t prevent and may worsen the neurologic symptoms.

***Aplastic anemia:***

A disorder in which multipotent myeloid stem cells are suppressed ,leading to bone marrow failure , it must be distinguished from pure red cell aplasia in which only erythroid progenitors are affected and anemia is the only manifestation.

Causes:

1. Idiopathic (unknown) in more than 50% of the cases.
2. Exposure to a known myelotoxic agent (drug /chemical) .the damage can be:
* Predictable, dose related, and reversible: antineoplastic drugs, benzene, and chloramphenicol.
* Unpredictable, not dose related, and may be duo to hypersensitivity to small unmyelotoxic doses: chloramphenicol, sulfonamides.
1. After certain viral infections (e.g. Community acquired viral hepatitis in which the specific virus responsible is not known)
2. Genetic damage: defects in telomerase which may lead to premature senescence of hematopoietic stem cells. the evidence of genetic damage in aplastic anemia is supported by the development of bone marrow aplasia in children with Fanconi anemia (an inherited disorder of DNA repair)

 These agents seem to trigger T cells to attack the bone marrow (the formation of autoreactive T cells that attack the bone marrow)

Morphology:

1. The bone marrow is hypocellular (but there is a minimal presence of few lymphocytes and plasma cells) with 90% of the spaces being occupied by fat.
2. Anemia causes fatty change in the liver

Manifestations and symptoms: it is important to separate aplastic anemia from anemias caused by marrow infiltration (myelophthisic anemia) , aleukemic leukemia ,and granulomatous diseases which have similar manifestations but easily distinguished on bone marrow examination.

1. Thrombocytopenia and granulocytopenia results in hemorrhages (petechiae and ecchmoses) and bacterial infections respectively.
2. Doesn’t cause splenomegaly
3. Anemia,The red cells are normochromic and normocytic or slightly macrocytic

Treatment:

1. Blood transfusion which may lead to hemosiderosis
2. Withdrawal of offending agent (.e.g. drugs) sometimes leads to remission but not always
3. Immunosuppressive therapy in patients >40 years
4. Bone marrow transplantation + immunosuppressive therapy is curative in patients <40

***Myelophthisic anemia:***

Extensive infiltration of the bone marrow by tumor or other lesions.

Causes:

1. Metastatic breast, lung , or prostate cancer.
2. Advanced tuberculosis
3. Lipid storage disorder
4. Osteosclerosis

Symptoms and manifestations:

* Anemia with misshapen RBCs some resembling teardrops)
* Thrombocytopenia
* Appearance of early erythroid and granulocytic precursors (leukoerythroblastosis)

***Done by: Fekra…..Good luck!!!***