HLS

SHEET NO. 3

PATHOLOGY

كتابة: Doctor 2021

تدقيق: فرح سائد

الدكتور: د. طارق

REMBER: in the previous lec we classified anemia into 3 types according to the cause:

1) Blood loss
2) Diminished RBC production (the topic of this lec)
3) Increased destruction

ANEMIA OF DECREASED PRODUCTION

- It is anemia of low production from the bone marrow and it is classified into three main categories / General causes:

1. Nutritional deficiency is the most common
2. Anemia of Chronic inflammation
3. Bone marrow failure

Let's start with MICROCYTIC ANEMIA

IRON DEFICIENCY ANEMIA (IDA)

Important especially in clinical practice

- Most common type of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries, so it is more common in low resources countries.

- Iron storage pool /stored in 2 forms:

1. iron is stored in **ferritin** which is (a small water soluble molecule)
2. iron is stored in **hemosiderin** (large, insoluble) presents in bone marrow, liver and spleen

Both (ferritin and hemosiderin) form 15-20% of total iron and the bulk remaining percentage present in the Hb.

- Hemosiderin consists of large iron particles (it is a combined of ferritin fragments) granular in shape, intracellular (mainly in the macrophages in the BM), and visible by light microscope.

- Serum ferritin is derived from stored ferritin, so it reflects its amount.

Serum iron is transported by transferrin in blood, **normally** only one third of transferrin is saturated by iron.

INDICATORS OF IRON STATUS

- Bone marrow aspirate (the best one and the most accurate) by inserting a needle in the bone marrow shows: earliest changes in the iron amount of BM, invasive procedure, painful, stained by Perl's Prussian blue stain a special iron stain appears in form of blue granular particles (**↓ in IDA** iron deficiency anemia)

- Serum ferritin level (↓ in IDA) * reflects hemosiderin in BM (low hemosiderin, low serum ferritin level) the problem in the ferritin that is an acute phase protein increases in the inflammatory conditions that masks iron deficiency results in normal ferritin level.

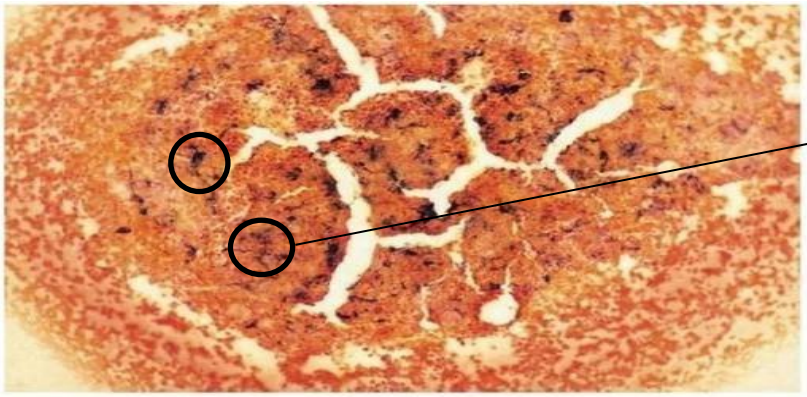
- Serum iron level (↓ in IDA) reflects transferrin and the transferrin saturation becomes lower than 1/3 which is abnormal

- Total iron binding capacity [TIBC] This is the opposite test of transferrin saturation, It is done by adding iron to the blood sample then if it takes a lot of iron this indicates the deficiency of iron (**↑ in IDA**)
  Note it's the only indicator that increases in IDA

- Reticulocyte hemoglobin content (CHr): (↓ in IDA)
- Mean reticulocyte volume (MRV): (↓ in IDA)

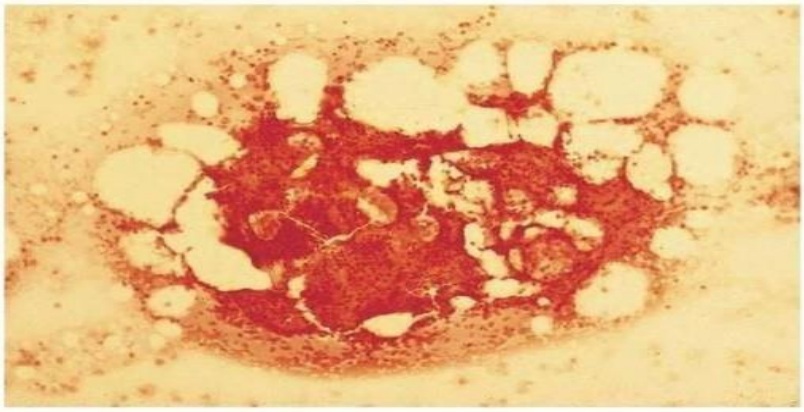
* Affected by inflammation (increased)

- Bone marrow examination of hemosiderin. it is stained with Perl's stain



- It has normal stores of iron in granular hemosiderin

Aspirate of normal marrow (BM): bluish-black i (haemosiderin) in macropha fragment. Perls' stain ×40.



- She\ he has iron deficiency because we don't see any blue parts

Aspirate of normal a fragment with no stainable Perls' stain ×40.

IRON HEMEOSTASIS

- Normal loss of body iron: is by shedding skin and mucosal epithelium (no normal way for iron excretion) because it is difficult to excrete iron from our body.
- Dietary iron is either hem (red meat) well absorbed or non-hem (inorganic, vegetarian) difficult to be absorbed.
- 20% of hem and 1% of non-hem iron are absorbed in the duodenum

  - Hepcidin: hormone (hep: secreted from the liver), normally inhibits iron absorption (degrade ferroportin on enterocytes in the small bowel)

Regulation of hepcidin:

- Hepcidin hormone is **positively** regulated by **HFE** High Ferrous **protein** on the Cell membrane of hepatocytes, which is activated when serum **iron level rises.**
- Hepcidin hormone is also **positively** regulated by **IL-6**, which increases in inflammation

- Hepcidin is **negatively** regulated to decrease or stop its secretion by **erythroferrone**, a hormone secreted by erythroblasts in bone marrow
- **We can see low hepcidin in 3 diseases:**

Low hepcidin:

1. **In iron deficiency**.

Very low hepcidin:

2. **thalassemia major** (high erythroferrone due to the large number of erythroblasts in BM)
3. **primary hemochromatosis** (defective HFE)

CAUSES OF IRON DEFICIENCY

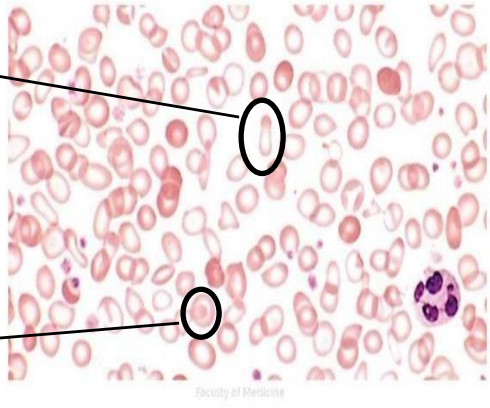
- Chronic blood loss because iron is difficult to control by the body, and there is a high tendency to lose it with Hb.
- Dietary: vegetarians, infants (low iron in the Breast milk), teenagers (fast food, menstrual cycle in females,,,,)
- Decreased absorption due to some diseases: like **gastrectomy, hypochlorhydria** (low stomach acid (HCL) that is important to ferrous conversion and absorption of iron), **intestinal diseases** like Inflammatory bowel disease and celiac disease that lead to inflammation so iron level will decrease, and **elderly** due to physiological atrophy of the stomach which decreases iron absorption.
- Increased demands: growing children, pregnancy, myeloproliferative neoplasms (in this case we have a high amount of WBC that takes up the iron instead of RBC)
- Hypotransferritinemia: decreased synthesis of transferrin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in the urine (nephrotic syndrome)
- Enzyme deficiency, a congenital disease, (rare but should be considered when the deficiency develops very early in life and it is difficult to treat)

MORPHOLOGY

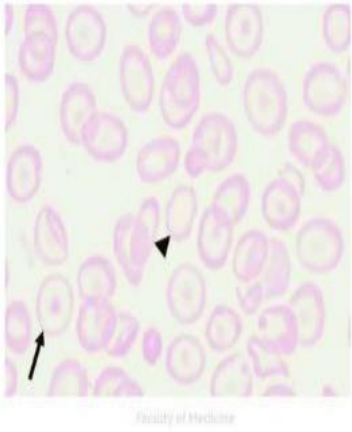
- RBCs appear small and empty (hypochromic microcytic). When there's not enough hemoglobin due to iron deficiency, red blood cells become smaller and dull in color
- Different and abnormal shapes of RBCs appear (poikelocytosis) like elongated and pencil shaped RBCs because Iron is important for the integrity of the cell membrane of RBCs, so they will have abnormal shapes
- Target cells: RBCs with a red dot in the middle appear in iron deficiency anemia, thalassemia and sickle cell anemia (abnormal Hb = Target cells)
- Low reticulocytes (Erythropoietin is high, but **ineffective** the BM can not produce RBCs due to Iron deficiency)
- **Thrombocytosis** is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid making more platelets)

poikelocytosis Small and elongated

Target cell has red dot in the middle



□IDA: note the hypochromia and poikelocytosis



□IDA: note the target cells (arrow)

SYMPTOMS

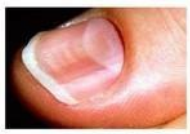
IDA is a chronic anemia (never comes quickly)

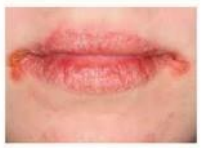
General symptoms of anemia Hypotension, dizziness, fatigue

Pica (special symptom, when patients have a strong desire to eat abnormal things like dirt, paint, and ice)

Glossitis, stomatitis bcz iron present in epithelial tissues

Spooning of fingernails wide and depressed





Restless leg syndrome moving the legs due to neurological condition

Hair loss

Blue sclera sclera become thin and transparent

Weakened immunity

Cognitive impairment lately and in severe cases

ANEMIA OF CHRONIC INFLAMMATION

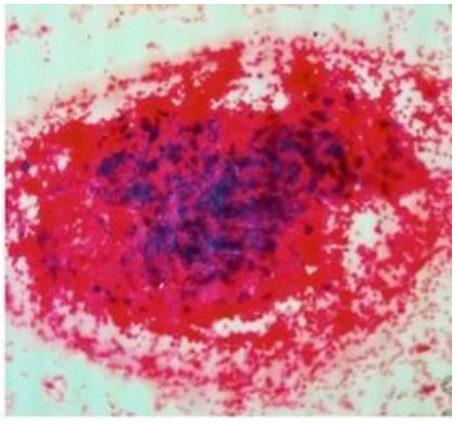
- Also called anemia of chronic disease (old name)
- Seen in chronic infections, cancer, chronic immune diseases

  - There are chronic non-inflammatory diseases such as Alzheimer's and Parkinson's disease, those patients do not suffer from anemia, so it appears in chronic inflammatory diseases not only chronic disease.

- Common in hospitalized patients
- High IL-6→high hepcidin →blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages this keeps the iron inside macrophages in the BM in the form of hemosiderin). Also suppress erythropoietin secretion from kidneys. (exception! Like renal anemia)

NOTE Hepcidin is the normal antagonist for erythropoietin.

LABORATORY FINDINGS



- Similar to IDA: serum iron is low
- RBCs: normal morphology, then hypochromic microcytic
- Reticulocytes ↓ due to low erythropoietin
  In contrast:
- Bone marrow iron stores ↑In certain theory: The benefit of this is that iron is stored in macrophages in the BM, preventing the iron from reaching harmful bacteria as a form of protection for the body
- Serum ferritin↑ one of the acute phase reactants

Let's start with MACROCYTIC ANEMIA!

MEGALOPLASTIC ANEMIA

- Caused by deficiency in vitamin B12 or folate
- Both are required for the synthesis of thymidine a nucleic acid in DNA, thus DNA replication is impaired and the cell dies by apoptosis
- Abnormalities occur in all rapidly dividing cells, but **hematopoietic cells** (erythroid cells) are most severely affected
- Maturation of RBC progenitors is deranged due to abnormalities in the nucleus of these cells, **many** undergo apoptosis **inside** bone marrow leads to ineffective erythropoiesis and mild hemolysis which is a side process, not the main one, as in hemolytic anemia, so it's not classified as a hemolytic anemia.
- Some Viable nucleated RBCs take a **longer time** to mature (Not all of them will undergo apoptosis), resulting in typical morphology as large cells due to the accumulation of more cytoplasm than normal over time because the cytoplasm doesn't need thymidine , so it continues growing
  (megaloblastoid ; mega: large , blastoid : immature nucleus)

FOLATE (B9) DEFICIENCY

- Normally, minimal amount of folate is stored in human body
- Folate is vastly present in food (green leaves), but it is destroyed by cooking
- Causes of deficiency:

1. Decreased dietary intake
2. Increased demands (pregnancy)it's the first supplement REMEMBER GIVE VITAMIN **B9** FOR THE **9 MONTHS** OF PREGNANCY) , chronic hemolytic anemia : high turnover , cells die and a lot of erythroblasts that proliferate so they need more folate , as a result they can develop a second anemia which is folate deficiency.
3. Intestinal diseases decrease absorption.
4. Beans, legume, alcohol, phenytoin (it is an anti-epileptic drug that inhibits the absorption of folic acid)
5. **Methotrexate** (chemotherapy agent): inhibits folate metabolism and cellular usage doesn't inhibit absorption

VITAMIN B12

- Mainly present in animal products (you can find it in eggs, meat, and milk,,)
- Resistant to cooking
- Synthesized by bacteria in the bowel
- Enormous stores in the liver. B12 takes 5 to 20 years to be completely depleted from its stores (a lot of time for the disease to develop and a lot of time for treatment)
- Dietary deficiency occurs most commonly in vegetarians
- More commonly: deficiency results from defective absorption

PERNICIOUS ANEMIA

(important cause of B12 deficiency)

- Autoimmune gastritis anemia starts in the stomach!!
- Autoreactive T-lymphocytes, causing injury to parietal cells (normally secrete HCL and intrinsic factors so both of them will decrease)
- Activates B-lymphocytes and plasma cells to synthesize and secrete autoantibodies that further damage parietal cells, and block the binding of vitamin B12 to intrinsic factors and iron deficiency anemia may occurs due to the decrease in HCl.

OTHER CAUSES OF VITAMIN B12 DEFICIENCY

- Gastrectomy As mentioned above, this leads to a decrease in intrinsic factors that are important for B12 absorption. REMEMBER THE INTRINSIC FACTORS ARE IMPORTANT FOR B12 ABSORPTION. AND HCL FOR NON-HEME IRON ABSORPTION.
- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- **Metformin that is used by diabetic patients** (inhibits absorption)

OTHER FUNCTONS OF VITAMIN B12

- Recycling of tetrahydrofolate to produce folate
- Synthesis of myelin sheath
- Synthesis of neurotransmitters (dopamine, serotonin)
- Metabolism of homocysteine (toxic to neurons)
- Degree of neuronal damage does not correlate with the degree of anemia

so patients end up with neuropathy which seen in B12 deficiency but not in folate deficiency.

MORPHOLOGY OF MEGALOPLASTIC ANEMIA

Big and elongated with high MCV> 110fL and it is hyperchromatic

Neutrophils: hypersegmetation of the nucleus more than 5 segments (appears as **earliest** Feature) bcz it takes long time to mature

□Macroovalocyte: characteristic of megaloblastic anemia

SYMPTOMS

- Chronic, general symptoms of anemia
- Glossitis (beefy tongue)
- Mild jaundice (Due to mild hemolysis and the excretion of bilirubin from the cells)
- In severe cases: pancytopenia (platelets and neutrophils production fails)

In vitamin B12 deficiency:

- Posterior and lateral columns degeneration of spinal cord which mainly leads to sensory problems (paresthesia, loss of proprioception which is position scenes)
- Peripheral neuropathy
- Neuropsychotic symptoms

APLASTIC ANEMIA (AA)

a: non, plasia: production, so it is a total bone marrow failure

Damage to multipotent stem cells in bone marrow

- Bone marrow becomes depleted of hematopoietic cells
- Peripheral blood pancytopenia (pan: all) even platelets and neutrophils become very low
- Low reticulocytes
- Affects all age groups, but it is more common in the young
- Patients develop life-threatening infections, bleeding and symptoms of anemia

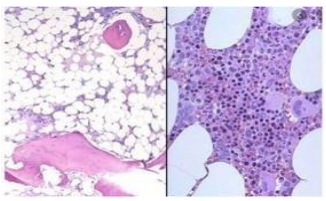
PATHOGENESIS

- **Extrinsic factor**
- Antigen cross reactivity with stem cells (drug, virus, environmental factor)
- Activated T-lymphocytes destroy stem cells
- Evidence: immunosuppressive drug restores bone marrow in 70% of cases
- Most cases are idiopathic
- Associated factors: **chloramphenicol** (antibiotic), gold injections to treat Rheumatism, NSAID, pregnancy, some hepatitis viruses
- **Intrinsic factor** (problem within stem cells)
- 10% of aplastic anemia patients have inherited defects in telomerase (stability of chromosomes) that is why Stem cells die early by apoptosis
- These genetically altered stem cells might express abnormal antigens This causes Attracting T- cells

LAPORATORY FINDINGS

Stem cells defect = macrocytic

- Peripheral blood: pancytopenia, anemia is **normochromic** or **macrocytic.**
- Bone marrow: decreased hematopoietic cells and predominance of fat.



SPECIAL TYPES OF BONE MARROW FAILURE

- **Fanconi anemia:** rare, inherited form of AA, defect in DNA repair proteins, patients develop AA and transform to acute leukemia in early life.

- **Pure red cell aplasia**: only erythroid cells are absent in bone marrow, can be *congenital* (Diamond-Blackfan anemia) or *acquired* affected people with (autoimmune diseases, or infection with Parvovirus B19 infection disrupts the immature cell and this causes the disappearance of the red blood cell)

MYELOPHTHISIC ANEMIA

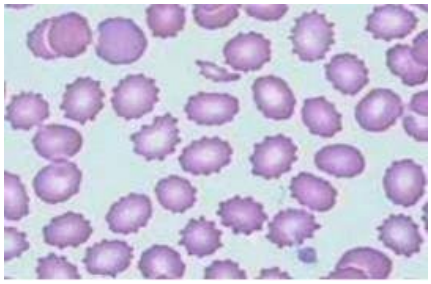
resembles aplastic anemia, patients come with pancytopenia but the mechanism differs. In myelophthisic anemia the bone marrow is fully infiltrated and destroyed by either cancer or infectious process.

- Myelo: bone marrow, phthesia: Infiltration of bone marrow causing physical damage to hematopoietic cells
- Cancer: most commonly in bone marrow tumors like acute leukemia, advanced lymphoma and myeloma, or metastatic cancer like breast cancer, colon cancer which are solid cancers that make metastasis and then destruction to the bone marrow
- Granulomatous dissease (inflammatory cells + physical mass in the tissue): TB
- Storage diseases inborn errors of metabolism, so the tissues in the body store either lipid, glycogen or sphingomyelin: most commonly is Gaucher
- Immature granulocytic and erythroid precursors commonly appear in peripheral blood

making pancytopenia, that is what makes it different from AA.

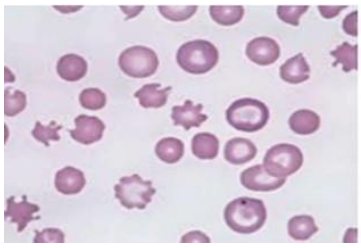
ANEMIA OF RENAL DISEASE

- Mainly results from decreased erythropoietin production from kidneys
- Does not correlate well with kidney function (serum creatinine). Mild renal injury may cause severe anemia and vice versa
- Decreased RBC production (low retic count)



- Patients with uremia (urine in the blood) develop abnormal platelets function leads to anemia of chronic disease (bleeding), **echinocytes** mean spiked cell membrane, and the SECOND NAME IS (***Burr cells***) appear

ANEMIA OF LIVER DISEASE



- Multiple factors causing anemia (multifactorial)
- Decreased synthesis of clotting factors (bleeding)
- Especially Bleeding from varices becomes anemia of chronic blood loss
- Decreased synthesis of transferrin thus develops iron deficiency
- Acanthocyte (spur cell) appears with longer spikes.

ANEMIA OF HYPOTHYROIDISM

- Thyroid hormones stimulate erythropoiesis
- Also stimulates erythropoietin production
- Anemia is most commonly normocytic, but can be macrocytic because maturation takes longer time due to decreased thyroid hormones

MYELODYSPLASTIC SYNDROME

Acquired neoplastic disease of bone marrow

- Primarily disease of old age
- Mutations in BM stem cells, result in prolonged survival and defective maturation same principle of **megaloblastic anemia** (take long time to mature abnormally)
- Mature blood cells do not exist bone marrow like in the normal way so the bone marrow fills with erythroid cells
- Patients commonly develop neutropenia and thrombocytopenia as well
- Anemia is refractory to treatment which means it is resistant to treatment because the problem in mutations of DNA can't be corrected
- RBCs are macrocytes