ANEMIA OF LOW PRODUCTION

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ANEMIA OF DECREASED PRODUCTION

General causes:

- Nutritional deficiency Most common
- Chronic inflammation
- Bone marrow failure

IRON DEFICIENCY ANEMIA

- Most common type of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries
- Iron storage pool: iron is stored in ferritin (soluble) and hemosiderin (insoluble) in bone marrow, liver and spleen, forming 15-20% of total iron The bulk remaining of iron is inside Hb
- Hemosiderin consists of large iron particles, granular in shape, intracellular, visible by light microscope

Mainly macrophages in BM

- Serum ferritin is derived from stored ferritin Comes from hemosiderin so its reflects the amount of total iron
- Serum iron is transported by transferrin, normally only one third of transferrin is saturated by iron

INDICATORS OF IRON STATUS

- Bone marrow aspirate: earliest changes, invasive procedure, Perl's Prussian blue stain (↓ in IDA)
- Serum ferritin level (↓ in IDA)*
- Serum iron level (↓ in IDA)
- Total iron binding capacity (↑ in IDA)
- Reticulocyte hemoglobin content (CHr): (↓ in IDA)
- Mean reticulocyte volume (MRV): (↓ in IDA)

Hb content inside the reticulocyte is low in IDA

* *Affected by inflammation (increased)*

Further explanation of the previous slide :

Bone marrow aspirate : Depletion of hemosiderin in BM reflects iron deficiency anemia

Serum ferritin level : The problem is that its an acute phase protein so if the patient has infection or inflammation for any reason this will raise the ferritin so it will mask the (IDA)

Serum iron level : Its a reflection for transferrin so it will be decreased along with decrease in saturation

Total iron binding capacity test : the opposite test for transferrin saturation . We take blood from the patient and we add manually iron if it takes (consumes) a lot of iron . Then the patient has IDA

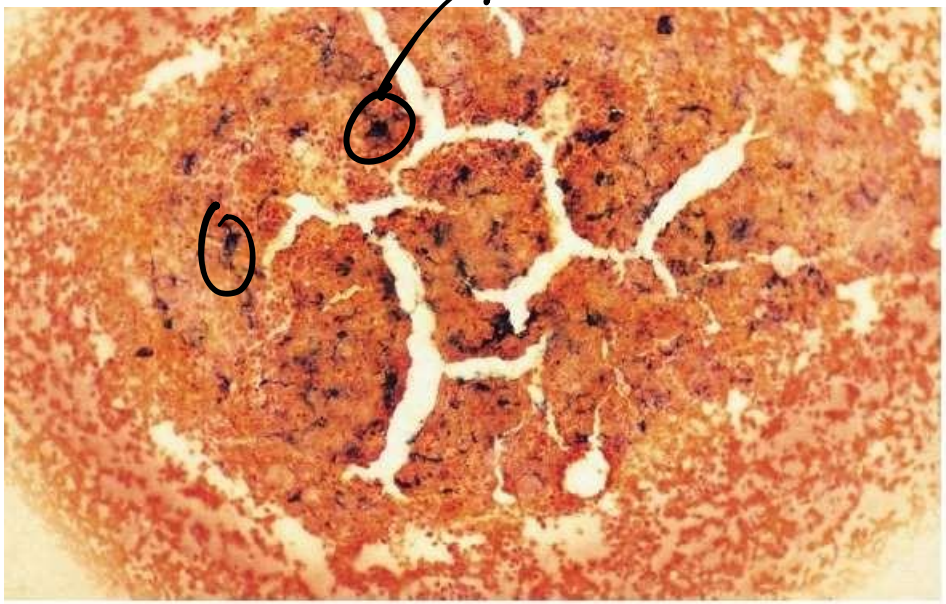
Reticulocyte hemoglobin content CHr :The average amount of Hb in newly produced RBCs (reticulocytes) to detect early Iron deficiency even before anemia appears

MCH : The average amount of Hb per mature RBC .

MRV : The size of new RBCs (reticulocytes)

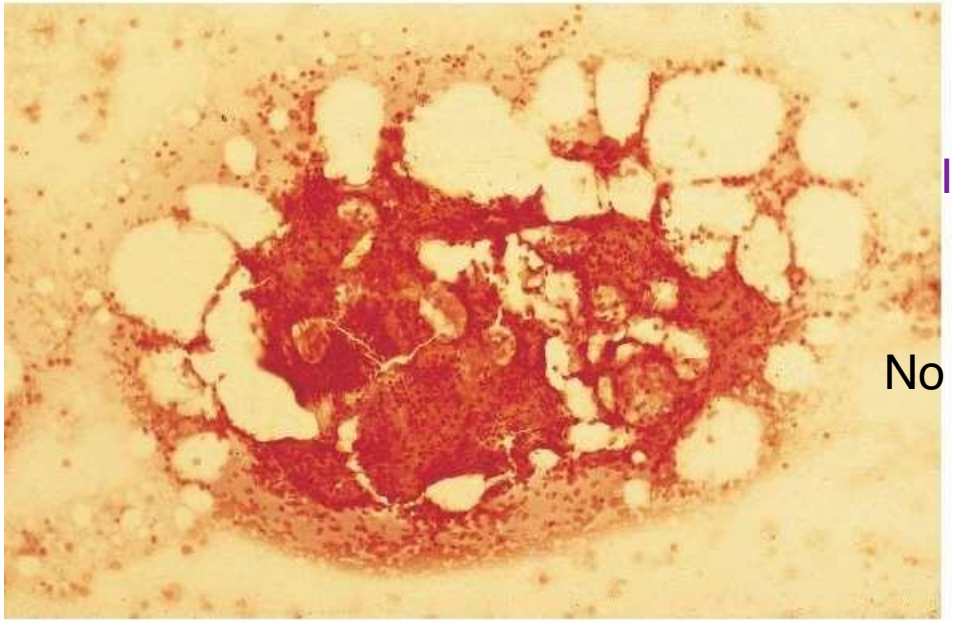
MCV : the size of RBCs

Hemosiderin



Normal Person

Aspirate of normal bone marrow (BM): bluish-black iron (haemosiderin) in macrophages in a fragment. Perls' stain ×40.



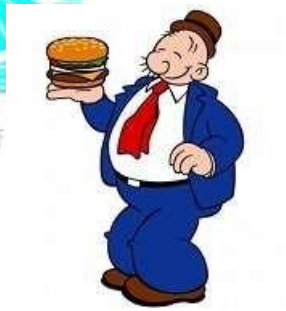
IDA patient

No hemosiderin

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

IRON HOMEOSTASIS

- Normal loss of body iron: shedding skin and mucosal epithelium (no excretion)
- Dietary iron is either hem (red meat) or non-hem (inorganic, vegetarian)
- 20% of hem and 1% of non-hem iron are absorbed in duodenum



You need to ask the patient if he is eating red meat or vegetables in order to assess the intake of iron

IRON HOMEOSTASIS

- Hepcidin: hormone secreted from liver, inhibits iron absorption (degradeferroportin on enterocytes)
- Hepcidin hormone is positively regulated by HFE protein on 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 by erythroferrone, a hormone secreted by erythroblasts in bone marrow
- Low hepcidin: iron deficiency. Very low: thalassemia major (high erythroferrone), primary hemochromatosis (defective HFE)

Ferroportin is a protein that allows the absorption of iron

High iron in the blood —> activates HFE —> activates hepcidin —> inhibits ferroportin —> Blocks absorption

Inflammation ———-—> IL-6 ———> activates hepcidin —-> inhibits ferroportin —> Blocks absorption

BM erthroblasts Normally —> erthroferrone —> inhibits hepcidin —-> normal ferroportin —-> normal iron absorption

In IDA . As a response from the body to increase iron absorption we will have a very low hepcidin

CAUSES OF IRON DEFICIENCY

- Chronic blood loss
- Dietary: vegetarians, infants, teenagers

Iron amount in breastmilk is very low

- Decreased absorption: gastrectomy, hypochlorhydria, intestinal diseases, elderly

Low HCL which converts Fe+3 into Fe+2

- Increased demands: growing children, pregnancy, myeloproliferative neoplasms

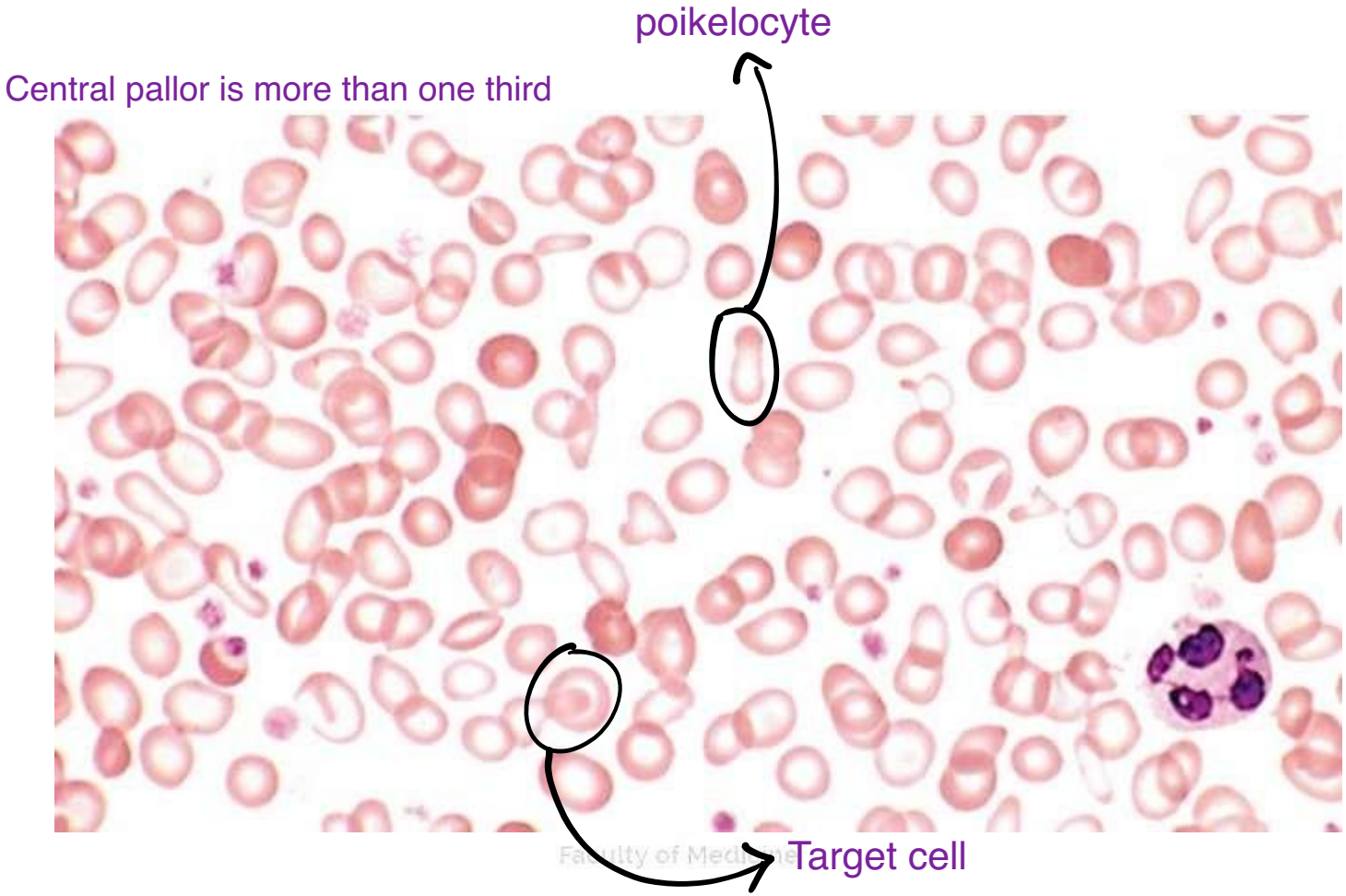
: Large numbers of WBC so they take the iron instead of RBCs

- Hypotransferritinemia: decreased synthesis of transferritin, secondary to liver disease, protein deficiency (diet, malabsorption) or loss in urine (nephrotic syndrome)
- Enzymatic deficiency

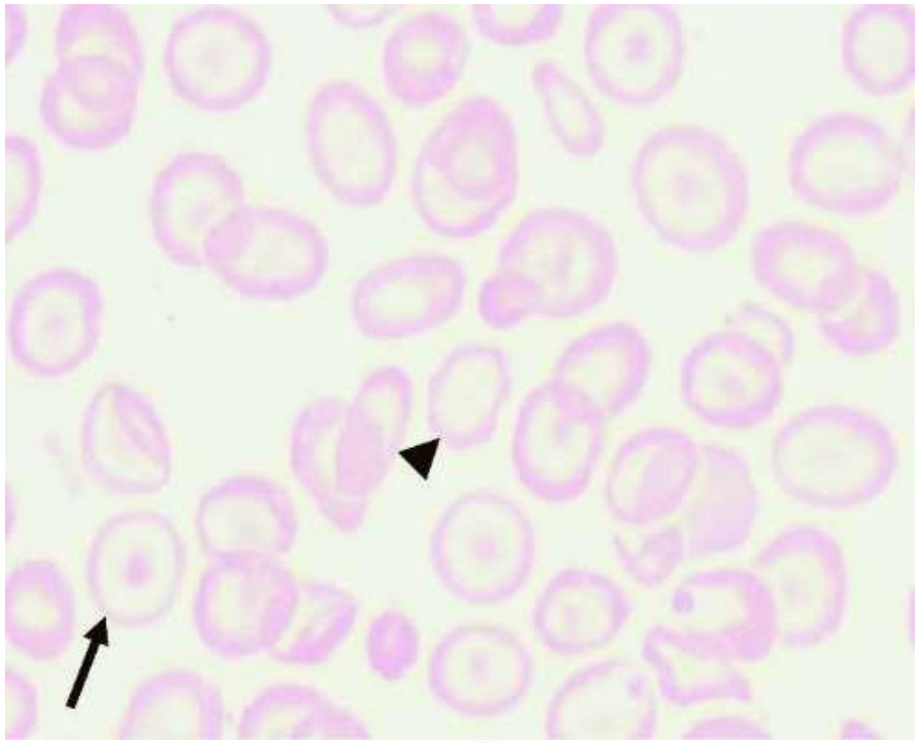
Inherited diseases very early in life and difficult to treat . (Rare)

MORPHOLOGY

- RBCs appear small and empty (hypochromic microcytic) No enough amounts of Hb
- Different shapes of RBCs appear (poikelocytosis) Iron is important for the integrity of RBCs
- Target cells Red dot in the center of the RBCs . (inside the central pale area) appears also in thalassemia and Sickle cell anemia . Caused by abnormal Hb distribution
- Low reticulocytes (Erythropoietin is high, but ineffective) Because we don't have iron to form new RBCs
- Thrombocytosis is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid)



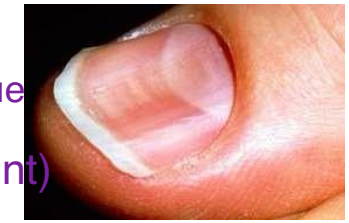
- IDA: note the hypochromia and poikelocytosis



- IDA: note the target cells (arrow)

SYMPTOMS

- IDA is a chronic anemia
- General symptoms of anemia Dizziness , hypotension , fatigue

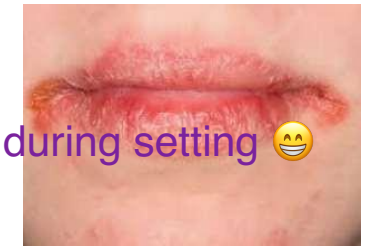


Special symptoms

- Pica: Abnormal craving to eat non-dietary things such as (ice,paint)
- Glossitis, stomatitis

Tongue inflammation

- Spooning of fingernails White
- Restless leg syndrome : Moving the legs repeatedly during setting 😄
- Hair loss
- Blue sclera Thin
- Weakened immunity
- Cognitive impairment In severe cases



Pica and leg syndrome is only statistically associated with IDA .

ANEMIA OF CHRONIC INFLAMMATION

- Also called anemia of chronic disease
- Seen in chronic infections, cancer, chronic immune diseases
- Common in hospitalized patients
- High IL-6 → high hepcidin → blocks iron transfer from macrophages to RBC precursors in bone marrow (degrade ferroportin on macrophages). Also suppress erythropoietin secretion from kidneys

Normally macrophages inside the BM transfers iron to RBCs from their intracellular hemosidern stores .
. hepcidin is a normal antagonist for erthropoietin

~ Non-inflammatory chronic diseases is not associated with anemia .

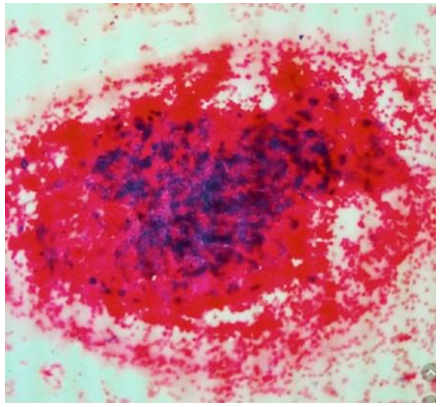
~ Erthropoietin is low in Anemia of chronic inflammation and anemia of kidney disease.

LABORATORY FINDINGS

- Similar to IDA: serum iron is low
- RBCs: normal (Early) morphology, then hypochromic microcytic
- Reticulocytes ↓

In contrast:

- Bone marrow iron stores ↑
- Serum ferritin ↑



The major difference with IDA is that iron stores (hemosidren) is markedly increased (theory : because some bacteria needs iron for survival and the body protect itself by retaining the iron away in cases of chronic infections).

MEGALOBLASTIC ANEMIA

- Caused by deficiency in vitamin B12 or folate
- Both are required for synthesis of thymidine, thus DNA replication is impaired More prominent in continuously dividing cells like enterocytes but it is more prominent in hematopoietic stem cells and erthryoid cells
- Abnormalities occur in all rapidly dividing cells, but hematopoietic cells are most severely affected
- Maturation of RBC progenitors is deranged, many undergo apoptosis inside bone marrow (ineffective erythropoiesis, mild hemolysis) But you can't classify it as hemolytic anemia because here its only a side process not the main feature .
- Viable nucleated RBCs take a longer time to mature, resulting in typical morphology (megaloblastoid) Large immature cells .

Even the neutrophils and platelets become larger than normal .

FOLATE DEFICIENCY

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

Causes of deficiency:

- Decreased dietary intake
- Increased demands (pregnancy, chronic hemolytic anemia)
- Intestinal diseases
- Beans, legume, alcohol, phenytoin (inhibit absorption)
- Methotrexate: inhibits folate metabolism and cellular usage
  - Chemotherapy that does not affect the absorption but affects the metabolism so the cells cant utilize the folate

High turn over of RBCs requires more folate . So they could develop a second anemia.

VITAMIN B12

- Mainly present in animal products Meat,eggs,milk .
- Resistant to cooking
- Synthesized by bacteria in bowel
- Enormous stores in the liver It takes 5-20 years until symptoms develop
- Dietary deficiency occurs most commonly in vegetarians
- More commonly: deficiency results from defective absorption

PERNICIOUS ANEMIA

The main pathology starts in the stomach

- Autoimmune gastritis
- Autoreactive T-lymphocytes, causing injury to parietal cells

Which secrets HCL and intrinsic factor

- Activates B-lymphocytes and plasma cells to synthesize and secrete auto antibodies that further damage parietal cells, and blocks binding of vitamin B12 to intrinsic factors

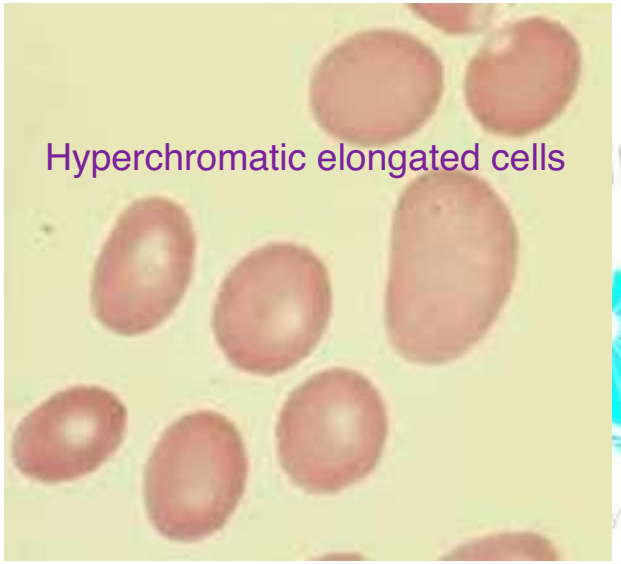
OTHER CAUSES OF VITAMIN B12 DEFICIENCY

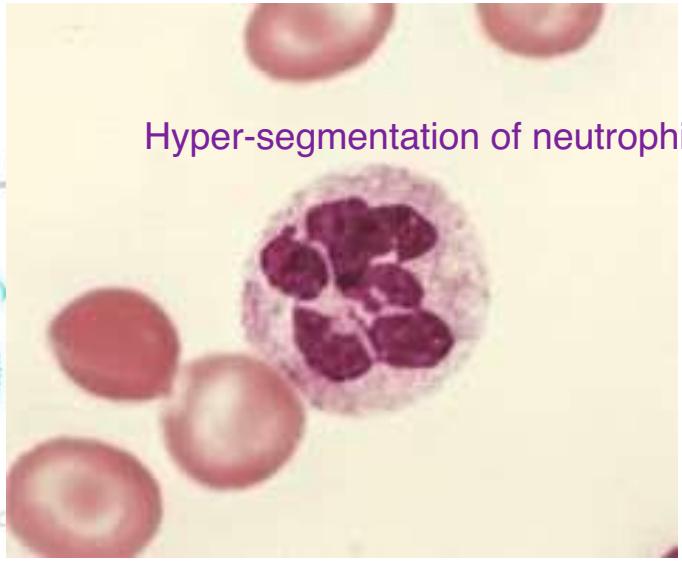
- Gastrectomy
- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- Metformin (inhibits absorption)
  - Widely used drug to treat diabetes .

OTHER FUNCTIONS OF VITAMIN B12

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

MORPHOLOGY OR MEGALOBLASTIC ANEMIA





- Macroovalocyte: characteristic of megaloblastic anemia
  - MCV is high

SYMPTOMS

- Chronic, general symptoms of anemia
- Glossitis (beefy tongue) Because folate and B12 are important for the epithelial cells
- Mild jaundice Because of mild hemolysis
- In severe cases: pancytopenia Production of another WBCs and platelets falls in severe cases .

<u>In vitamin B12 deficiency:</u>

- Posterior and lateral columns degeneration of spinal cord (paresthesia, loss of proprioception)
  (النمنمة) Position sense
- Peripheral neuropathy
- Neuropsychotic symptoms

Aplastic Anemia BM failure

- Damage to multipotent stem cell in bone marrow
- Bone marrow becomes depleted of hematopoietic cells
- Peripheral blood pancytopenia Common
- Low reticulocytes
- Affects all age groups But its more common in the young
- Patients develop life-threatening infections, bleeding and symptoms of anemia

Because of neutropenia

Because of thrombocytopenia

Pathogenesis

Non-completely known two theories :

- **Extrinsic factor**: Because some of the patients have previous history of viral infections or exposure to drugs .
- Antigen cross reactivity with stem cells (drug, virus, environmental factor)
- Activated T-lymphocytes destroys stem cells
- Evidence: immunesuppressive drug restores bone marrow in 70% of cases
- Most cases are idiopathic
- Associated factors: chloramphenicol, gold injections, NSAID, pregnancy, some hepatitis viruses

Was used to treat rheumatism

Limited used antibiotic

Rarely

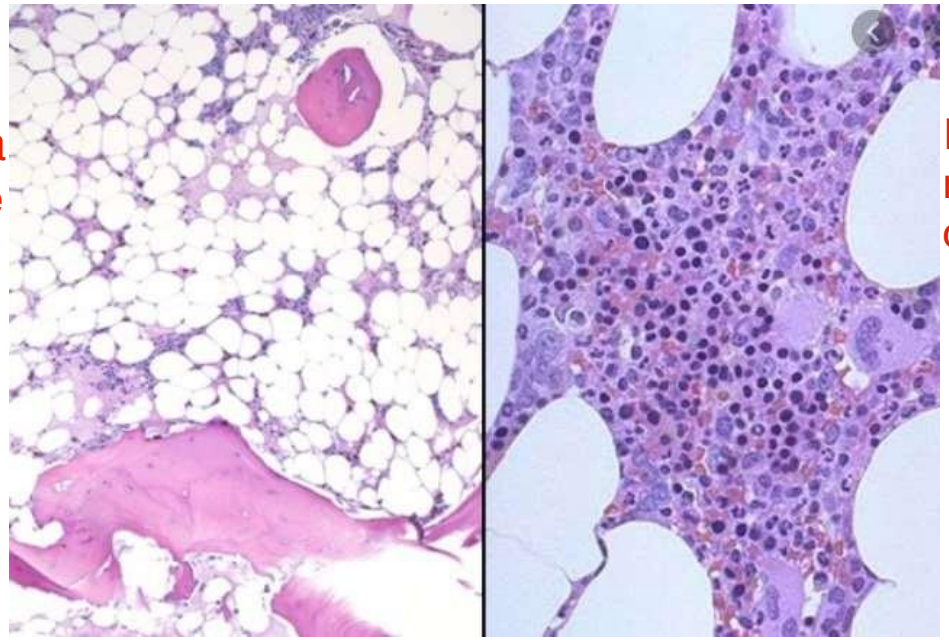
- **Intrinsic factor**
- 10% of aplastic anemia patients have inherited defects in telomerase (stability of chromosomes)
- Stem cells die early
- These genetically altered stem cells might express abnormal antigen?? Attracting T-cells

Still they can benefits from immunosuppression Unknown how. Maybe because these abnormal stem cells attracts T-lymphocytes .

Laboratory Findings

- Peripheral blood: pancytopenia, anemia is normochromic or macrocytic: Because we have stem cells Defects .
- Bone marrow: decreased hematopoietic cells and predominance of fat

In Aplastic anemia
Fat predominance



In normal person : A mixture of hematopoietic cells and fat .

Special types of bone marrow failure

- Fanconi anemia: rare, inherited form of AA, defect in DNA repair proteins, patients develop AA and 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 (autoimmune, Parvovirus B19 infection)

Attack the immature erythroid cells

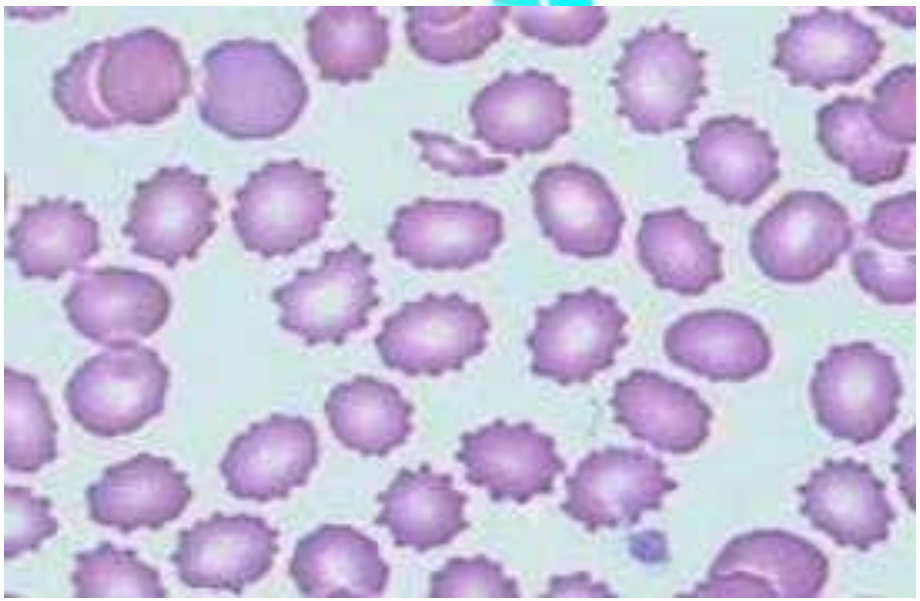
Myelophthisic Anemia

Like AA but here the BM is fully infiltrated and destroyed by cancer or infectious disease.

- Infiltration of bone marrow causing physical damage to hematopoietic cells
- Cancer: most commonly in acute leukemia, advanced lymphoma, metastatic cancer
- Granulomatous disease: TB : Because it cause a physical mass in the tissue
- Storage diseases: Gaucher
- Immature granulocytic and erythroid precursors commonly appear in peripheral blood : This is different from AA

Anemia of renal disease

- Mainly results from decreased erythropoietin production from kidneys
- Does not correlate well with kidney function (serum creatinine): The patient could have a mild renal injury with severe anemia or vice versa .
- Decreased RBC production (low retic count) Reticulocytes
- Urea in the blood
- Patients with uremia develop abnormal platelets function (bleeding), echinocytes (Burr cells) appear As a result of Uremia

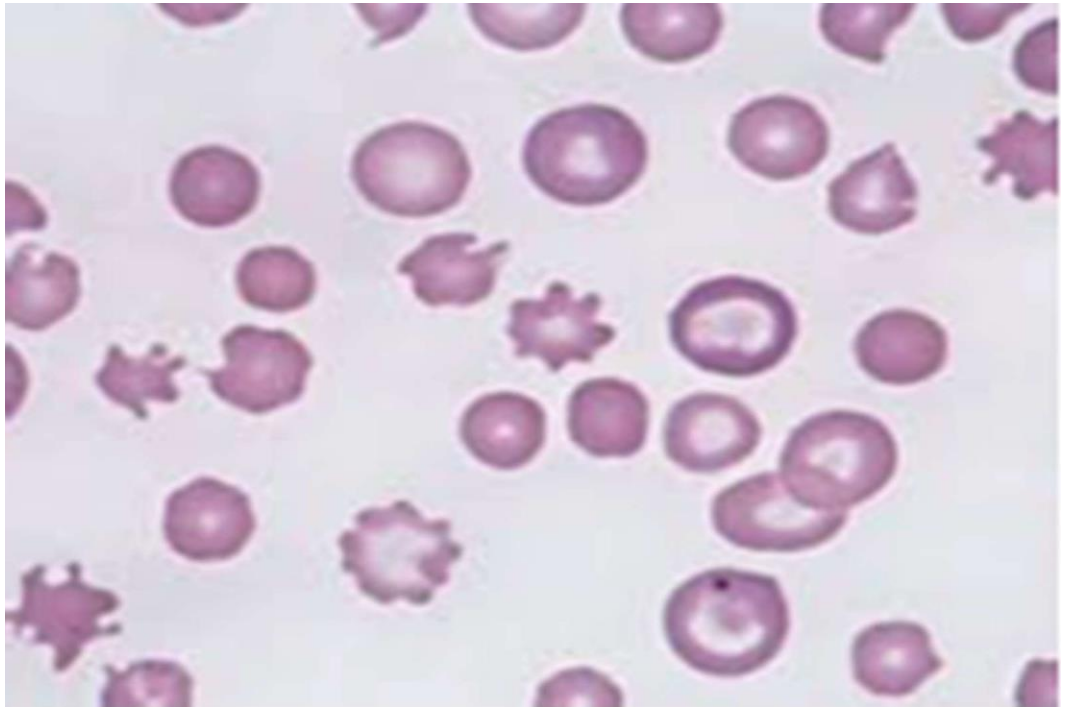


Anemia of liver disease

Patient history is important

- Multiple factors causing anemia
- Decreased synthesis of clotting factors (bleeding)
- Bleeding from varices
- Decreased synthesis of transferrin
- Acanthocyte (spur cell) appears

Spikes .



Anemia of hypothyroidism

- Thyroid hormones stimulate erythropoiesis
- Also stimulates erythropoietin production
- Anemia is most commonly normocytic, but can be marcocytic

Myelodysplastic syndrome

This disease looks as megaloblastic anemia very much . But its a neoplastic disease

- Acquired neoplastic disease of bone marrow
- Primarily disease of old age
- Mutations in BM stem cell, results in prolonged survival and defective maturation

Taking a lot of time to mature . But they don't mature normally

- Mature blood cells do not exist bone marrow like in the normal way
- Patients commonly develop neutropenia and thrombocytopenia as well
- Anemia is refractory to treatment
- RBCs are macrocytes