ANEMIA

Anemia is defined as decrease in the RBC mass

Clinically it is usually reflected by decrease in hemoglobin and hematocrit levels

Symptoms include:

•pale skin and pale conjunctiva due to decreased Hgb
•fatigue, dizziness, faintness, chest pain (MI in severe cases), and muscle weakness due to decreased oxygen delivery
•tachypnea and tachycardia. Some anemias may cause splenomegaly. These are related to compensatory mechanisms.
•symptoms related to the cause of anemia

WORK UP

- Iron indices (serum iron, serum iron-binding capacity, transferrin saturation, and serum ferritin concentrations)
- Plasma unconjugated bilirubin, haptoglobin, and lactate dehydrogenase levels
- Serum and red cell folate and vitamin B12 concentrations
- Hemoglobin electrophoresis, which is used to detect abnormal hemoglobins
- Coombs test, which is used to detect antibodies or complements

CLASSIFICATION

There are two classifications for anemia:

1. etiology (decreased production or increased peripheral removal) - differentiated by reiculoctye count (low means decreased production and high means peripheral removal)
2. size of RBCs (micro, normo and macro based on MCV).

ANEMIA OF DECREASED PRODUCTION

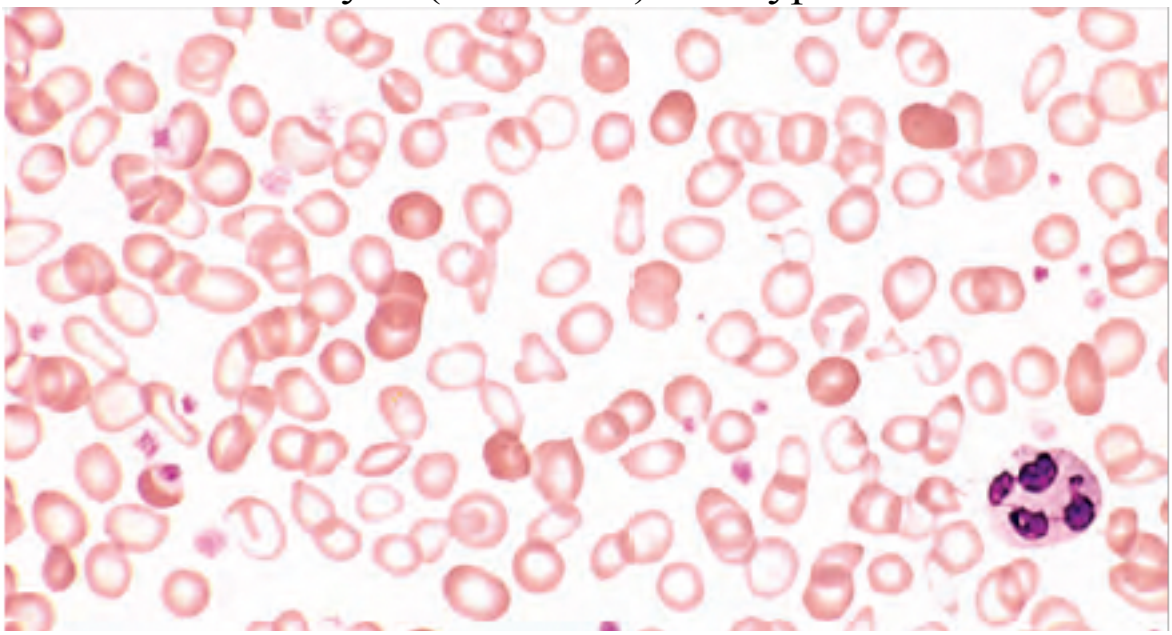
1. IRON DEFICIENCY ANEMIA

most common nutritional deficiency in the world

Causes include:
- Chronic blood loss (Western world) in GIT and the female genital tract
- Diet (developing world) - low intake and poor bioavailability
- Increased demands (pregnancy and infancy)
- Malabsorption in celiac disease or after gastrectomy.

Clinical findings:
- usually asymptomatic
- underlying cause symptoms
- symptoms of anemia
- spooning of the fingernails and pica

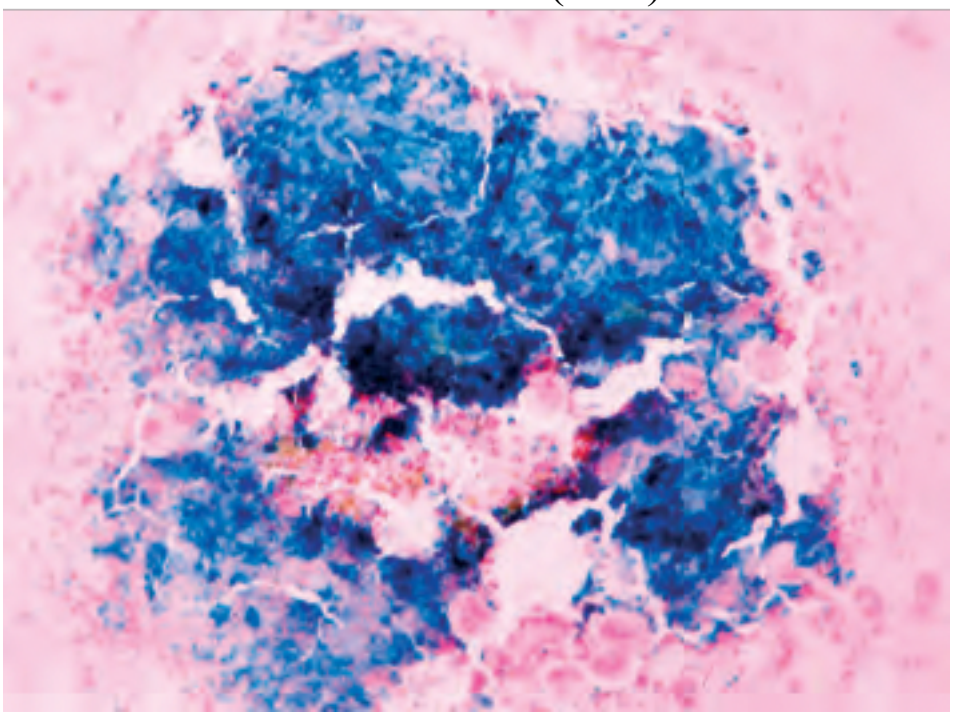
Laboratory findings:
RBCS are microcytic (low MCV) and hypochromic.



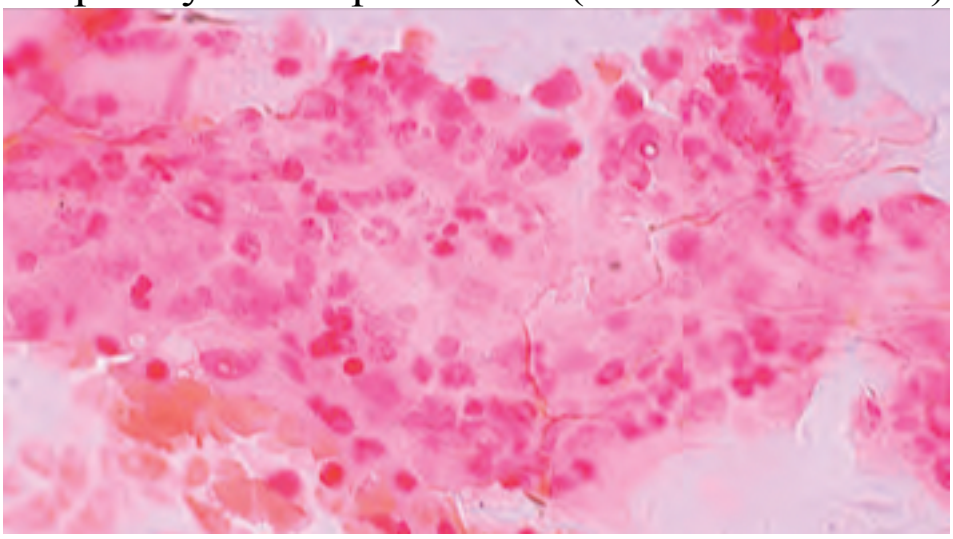
Diagnostic criteria include:

- low serum ferritin (sensitive to IDA)
- low iron levels
- low transferrin saturation
- increased total serum iron- binding capacity
- increased RDW
- platelet count often is elevated
- Erythropoietin levels are elevated but RBC count is low

BM with normal iron levels (blue)



completely iron depleted BM (no blue so no iron)



Treatment - iron replacement and treat underlying cause

2. ANEMIA OF CHRONIC INFLAMMATION/CHRONIC DISEASE

most common form of anemia in hospitalized patients

associated with sustained inflammation:
- Chronic microbial infections, such as osteomyelitis, bacterial endocarditis, and lung abscess
- Chronic immune disorders, such as rheumatoid arthritis and regional enteritis
- Neoplasms, such as Hodgkin lymphoma and carcinomas of the lung and breast

Pathogenesis: there is elevated hepcidin, which regulates absorbed iron. IL-6, due to systemic inflammation, increases hepcidin production, which decreases ferroportin and more iron is incorporated into cytoplasmic ferritin and is lost by excretion, causing iron deficiency. Additionally, chronic inflammation suppresses erythropoietin production by the kidneys.

High serum iron levels also increases hepcidin. In iron deficiency anemia hepcidin is low as compensation so less iron is lost.

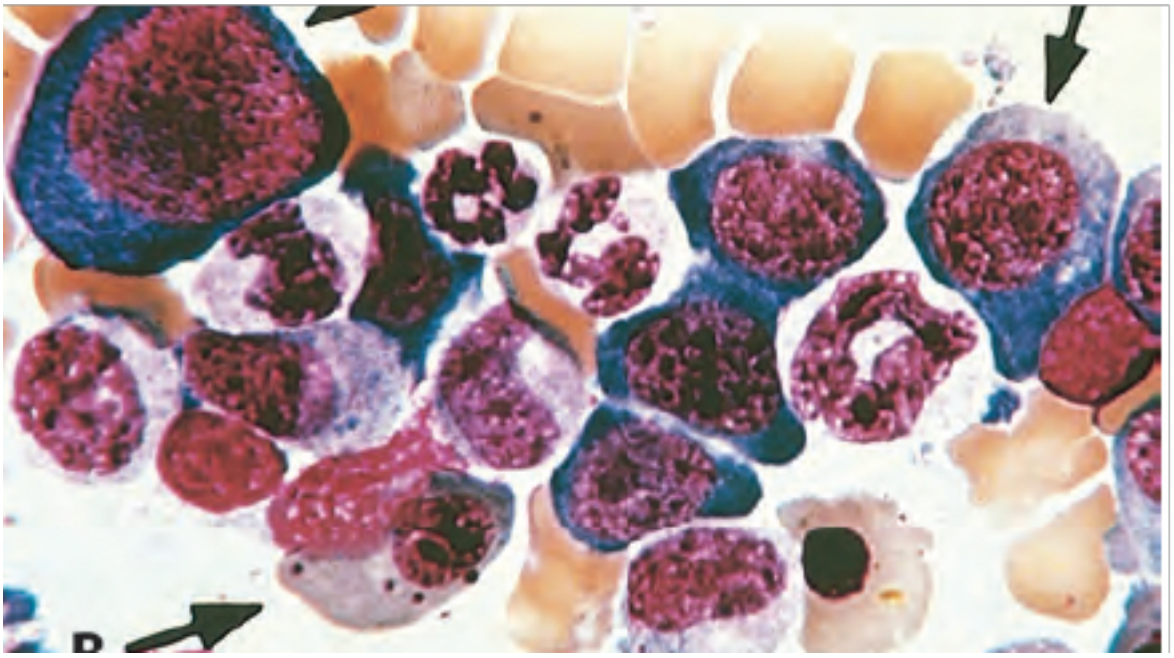
Clinical Features
- low serum iron levels
- RBCs slightly hypochromic and microcytic
- storage iron in the bone marrow increased
- serum ferritin increased
- total iron-binding capacity is reduced

Treatment
erythropoietin and iron administration to manage condition but only effective treatment of the underlying condition is curative

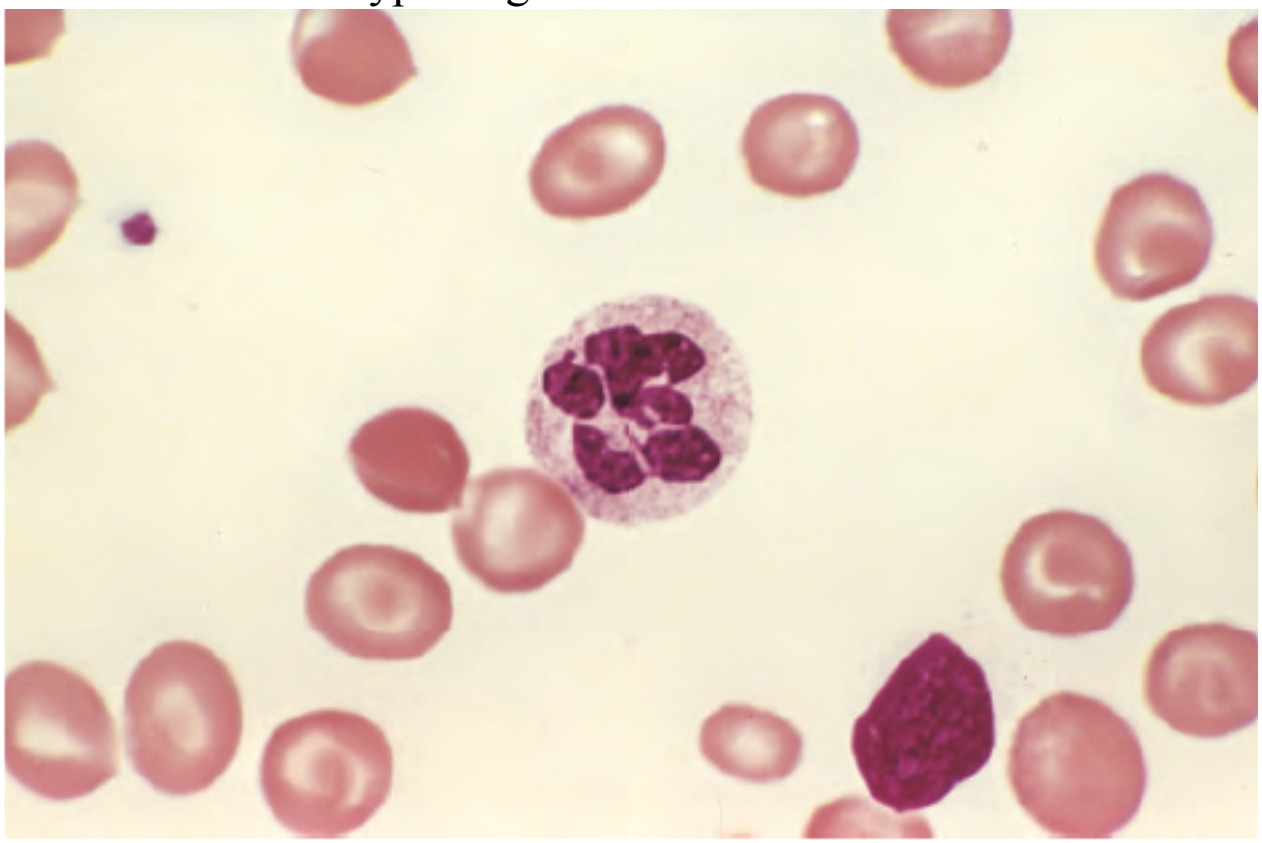
3. MEGALOBLASTIC ANEMIA

Megaloblastic anemia is caused by deficiency of vitamin B12 and/ or folate deficiency

Morphology
- large erythroid precursor cells
- nuclear-cytoplasmic asynchrony (immature nuclei but normal cytoplasm)
- hypersegmented neutrophils (nuclei with more than 4 segments)
- abnormally shaped platelets



centre cell shows hyper segmentation



- Increased apoptosis of erythroid precursors cells causes anemia
- Patients commonly present with pancytopenia
- RBCs are usually oval shaped and markedly macrocytic

NOTE ABOUT MACROCYTIC ANEMIA:

Macrocytic anemia is divided into two classes

- Megaloblastic anemia: caused by B12 and/or folate deficiency (discussed next)
- Nonmegaloblastic anemia: such as hypothyroidism, myeodysplastic anemia, and some cases of aplastic anemia (not discussed but important to know)

3A. Folate deficiency

results from:

- Diet (most common cause)
- Increased demands (pregnancy and infancy)
- Certain foods (acidic foods and beans)
- Drugs (phenytoin and methotrexate).
- Malabsorptive disorders (*celiac disease* and *tropical sprue)*

Clinical manifestations:

- asymptomatic or nonspecific, weakness, fatigue and shortness of breath if severe
- sore tongue can develop
- no neurological symptoms

diagnosis

- smears of peripheral blood and bone marrow (shows megaloblastic characteristics)
- low serum and RBC folate

3B. Vitamin B12 deficiency

For vitamin B12 to be absorbed we need intrinsic factor that is produced by gastric parietal cells. Deficiency occurs if this mechanism is disrupted
Dietary deficiency is an exceptionally rare (only in strict vegans)

Conditions that interfere with absorption:

- Pernicious anemia (most common cause)
- Gastrectomy
- Ileal resection
- Disorders that disrupt the function of the distal ileum (Crohn disease, tropical sprue, and Whipple disease).
- In older persons, gastric atrophy and achlorhydria (acid and pepsin are needed to release vitamin B12 from its bound form)

Clinical manifestations

- same nonspecific symptoms seen in folate deficiency
- neurological symptoms such as peripheral neuropathy, numbness, parasthesia, loss of position sense, ataxia. Neuropsychiatric manifestations, delusions, hallucinations, cognitive changes (like memory decline), depression, and dementia

diagnosis

- low serum vitamin B12 level
- normal or elevated serum folate level
- megaloblastic characteristics
- a dramatic reticulocytic response to administration of vit B12
- Pernicious anemia has additional serum antibodies to intrinsic factor.

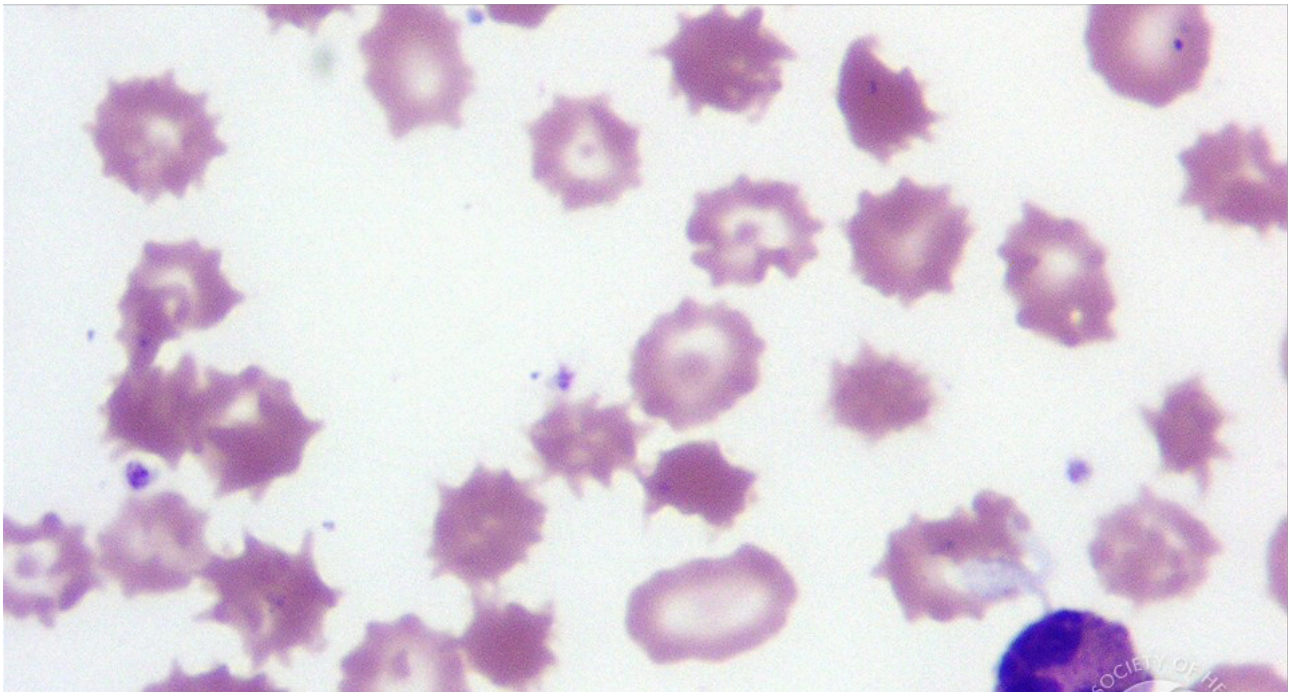
4. ANEMIA OF CHRONIC LIVER DISEASE

Anemia in the setting of chronic liver disease (eg. cirrhosis), results from several etiologies:

- Iron deficiency (most common)
- Hypersplenism
- Therapy related hemolytic anemia and suppression of EPO receptor
- Alcoholic-cirrhosis-induced folate deficiency

Morphology:

spur cells (or acanthocytes) which are large erythrocytes covered with spikelike projections that vary in width, length, and distribution.



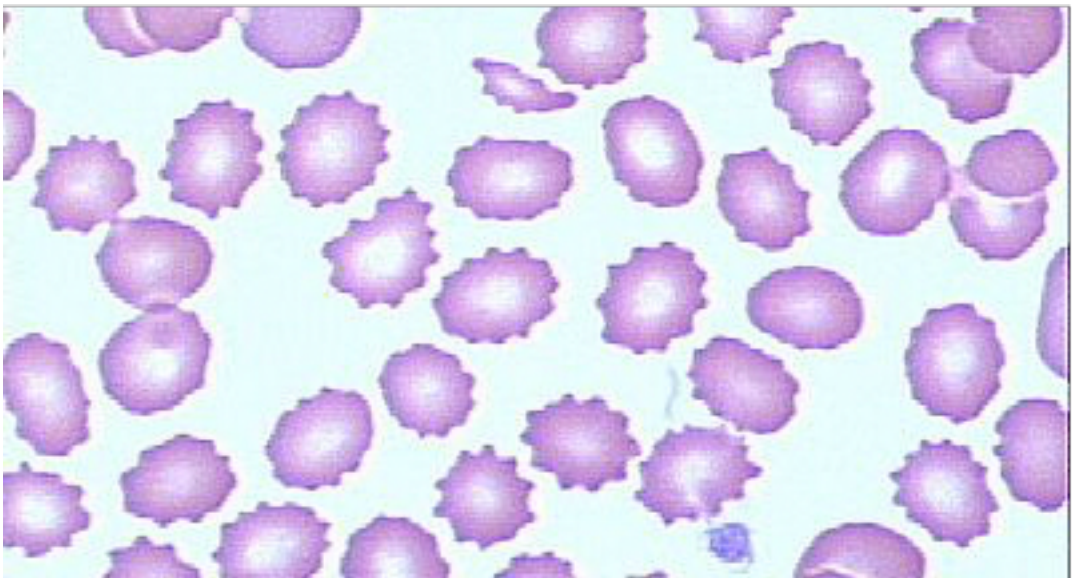
5. ANEMIA OF CHRONIC RENAL DISEASE

Anemia of chronic renal disease stems from several etiologies:

- Decrease EPO production by the damaged kidney.
- High levels of inflammatory cytokines
- Hemolysis
- Chronic bleeding
- Folate deficiency in patients on dialysis

Morphology:

ecchinocytes (also known as Burr cells) which are RBCs with circumferential short, wide-based membrane projections.



6. APLASTIC ANEMIA

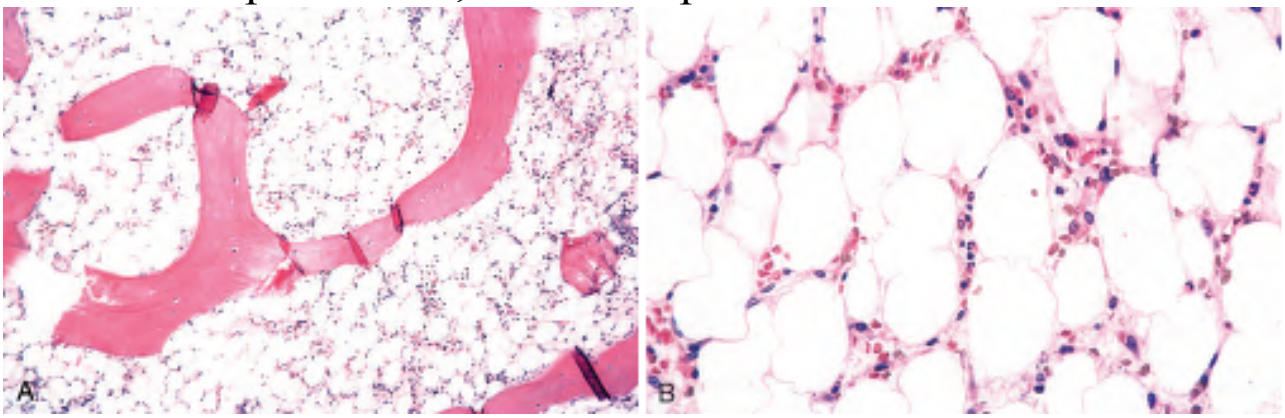
Is a syndrome of chronic primary hematopoietic failure

Etiology:
- mainly idiopathic
- some causes are drugs, chemical agents, infection, hereditary syndromes (eg Fanconi anemia)

PATHOGENESIS:
Two mechanisms:
- An immune attack against the multipotent stem cells by T lymphocytes
- Stem cells are unable to divide and differentiate

Clinical manifestations:
- bleeding
- increased risk of infections
- pancytopenia (anemia, neutropenia, and thrombocytopenia)
- no splenomegaly or gallbladder stones

BM with adipose tissue, no hematopoietic cells



Treatment:
- anti-T cell immune therapy
- bone marrow transplantation.

7. MYELOPHTHISIC ANEMIA

Caused by extensive infiltration of the marrow by tumors or other lesions.

Associated with:

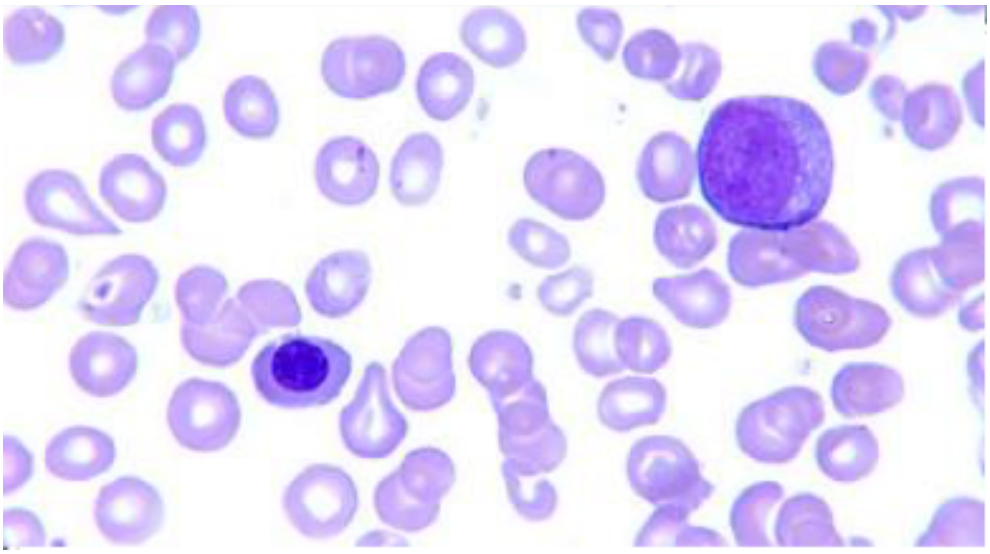
- metastatic breast, lung, or prostate cancer or other tumors
- advanced tuberculosis
- lipid storage disorders
- osteosclerosis

Clinical manifestations:

- anemia and thrombocytopenia
- mild leukocytosis

Morphology:

- Characteristically misshapen red cells (teardrops)
- Immature granulocytic and erythrocytic precursors *(leukoerythroblastosis)*



Treatment - treat underlying condition

ANEMIA OF PERIPHERAL REMOVAL

1. ANEMIA OF BLOOD LOSS

Causes**:**

- hemorrhage
- Acute blood loss
- Injury to the external arteries
- Internal bleeding (ruptured aneurism or ruptured intestine. accidents or stabbing wound)

These patients may be admitted to the hospital, important to treat their hypovolemia due to fluid loss. Anemia appears 2-3 days later

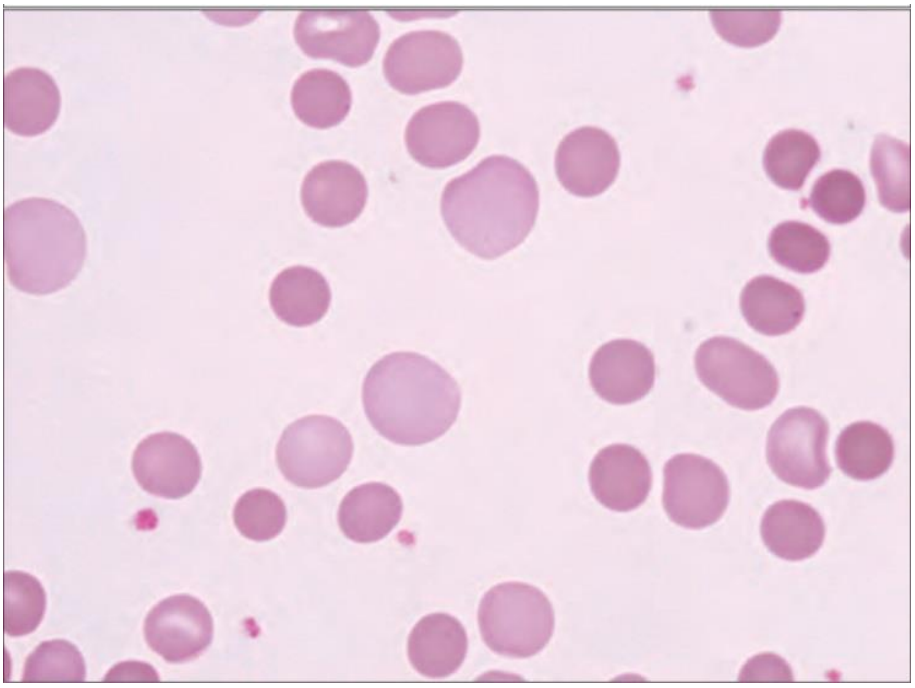
Clinical findings:

- Increased Erythropoietin level
- Increased reticulocyte count
- Leukocytosis but after recovery thrombocytosis
- Normocytic normochromic anemia or slightly macrocytic due to reticulocytes

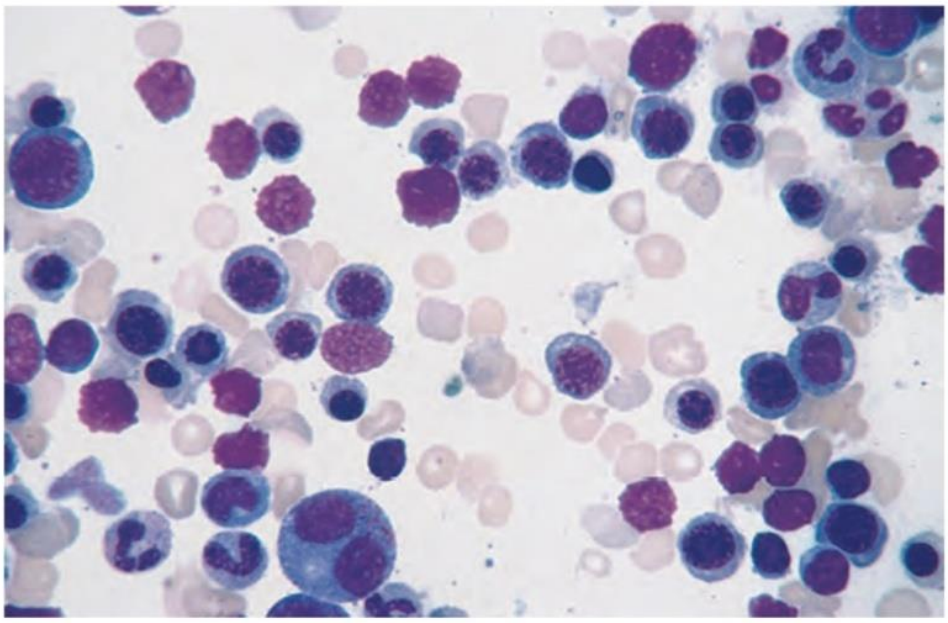
2. Anemia of Hemolysis

- Increase destruction of RBCs
- Elevated erythropoietin levels
- Accumulation of hemoglobin degradation products, bilirubin and iron.
- Erythroid precursor hyperplasia in the bone marrow and reticulocyte counts in the blood.

High reticulocyte Count in the blood



erythroid hyperplasia



Hemolysis can occur in two settings - Intra or extra vascular

Extra vascular means hemolysis occurred in the Spleen and intravascular means hemolysis occurred in the blood vessels

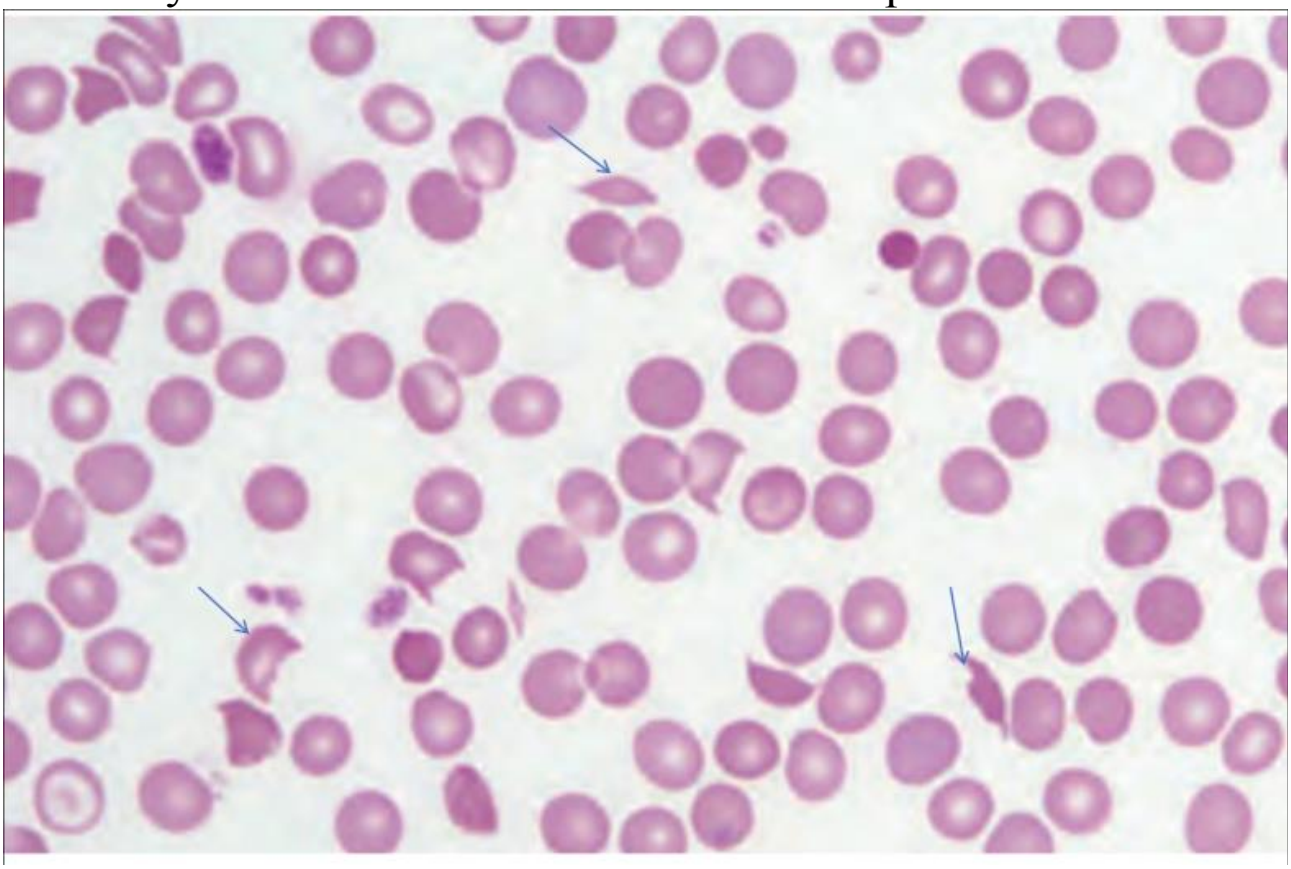
They have these shared clinical manifestations:

- Low haptoglobin
- High LDH (lactate dehydrogenase) - very nonspecific finding.
- Splenomegaly
- Jaundice

The difference between them:

Extravascular - No hemoglobinuria and no hemoglobinemia
Intravascular - there is hemoglobinemia and hemogloburia

Also, histologically we will find Schistoyctes in peripheral blood smears which are indicators of Intravascualr hemolysis only
Schistocytes is a torn RBCs with a helmet shape



Anemia of hemolysis can also be either extrinsic or intrinsic

extrinsic means there is something destroying the RBCs, there are 3 different causes:

A) Immune hemolytic anemia

autoimmune antibodies against RBCs of two types

A1) Warm antibodies (IgG) that bind to RBCs at 37C. Causes are idiopathic or associated with CLL, SLE and some medications. Present with mild anemia with splenomegaly.

A2) Cold antibodies (IgM) that bind RBCs at 33 – 34 C^{o} at the peripheral parts eg fingers. IgM is large so can block capillaries and cause ischemia in the periphery. This type can be either Acute (mycoplasma infection and EBV) or Chronic (lymphomas such as lymphoplasmastic lymphoma LPL)

As you can see the binding of antibodies (cold and warm) occurs within blood vessels (peripheral and central, respectively). After binding the complex goes to the spleen for destruction of RBCs so autoimmune hemolysis is extra vascular. It is the most common cause of extra vascular hemolysis.

Diagnosis: based on Coombs test to check antibodies are present. If positive then clot formation will occur.

B) Hemolysis of mechanical trauma : (intravascular)

Mechanical trauma to the RBCs causes its damage and hemolysis

Causes:

- Prosthetic heart valves
- Repeated physical activity; marathon racers.
- Microangipathic hemolytic anemia. This is a diseases in small blood vessels (capillaries) where there is narrowing so RBCs are damaged when they pass through and its causes include:
  - disseminated intra vascular coagulation, DIC (the most common)
  - Malignant hypertension
  - SLE
  - TTP ; thrombotic thrombocytopenic purpura
  - Hemolytic uremic syndrome Disseminated cancer.

C) Infection (intravascular)

- Parasites within the RBCs, rupture resulting in hemolysis and episodic symptoms, mainly Malaria but also babesia
- Hematin released from the RBCs results in brown pigmentation of the spleen, liver and bone marrow
- Massive splenomegaly and occasional hepatomegaly.
- Falciparum can cause cerebral malaria which can be fatal.

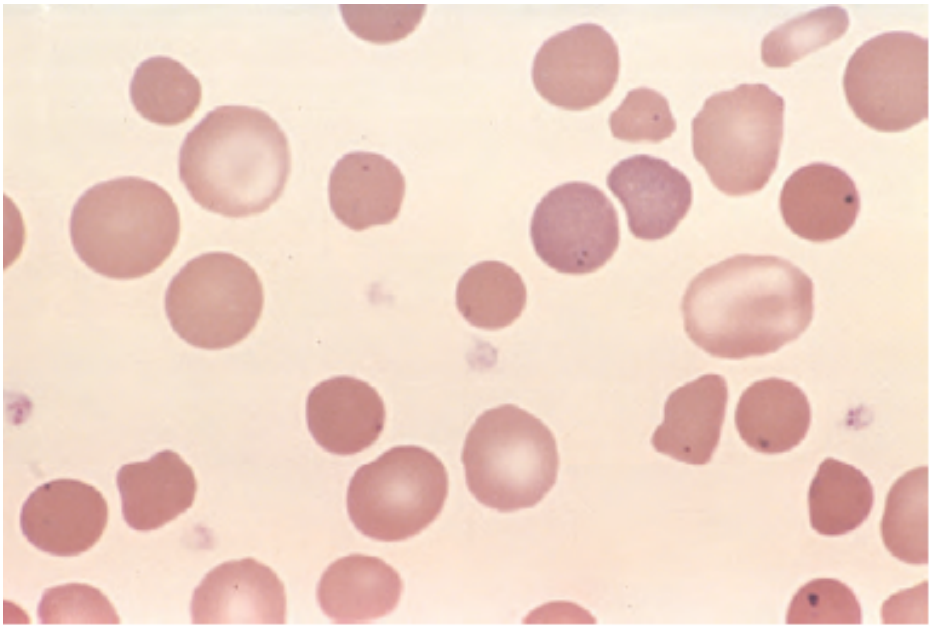
Hemolytic anemia of Intrinsic causes

Intrinsic (problem in RBCs) can be hereditary or acquired.
Hereditary causes are 3:

A) Hereditary spherocytosis
This is a membranopathy. A mutation in a membrane protein (either ankyrin, band 3, or spectrin) causes RBCs to be spherical

- Autosomal dominant
- Splenic trapping
- extravascular
- Can be complicated by aplastic crisis due to parvovirus B19 which causes temporary cessation of red cell production

Clinical manifestations:
- Anemia, jaundice, gallbladder stones, splenomegaly
- only anemia with high MCHC



Diagnosis - osmotic fragility test - In spherocytosis the rupture will appear in higher concentration (0.85) which is earlier than normal RBCs (0.5)
Treatment: symptomatic with splenectomy for patients above 5yrs

B) Hemoglobinopathies

here the issue is with the hemoglobin, there are two types - Sickle Cell Disease and Thalassemia.

B1. Sickle Cell anemia:

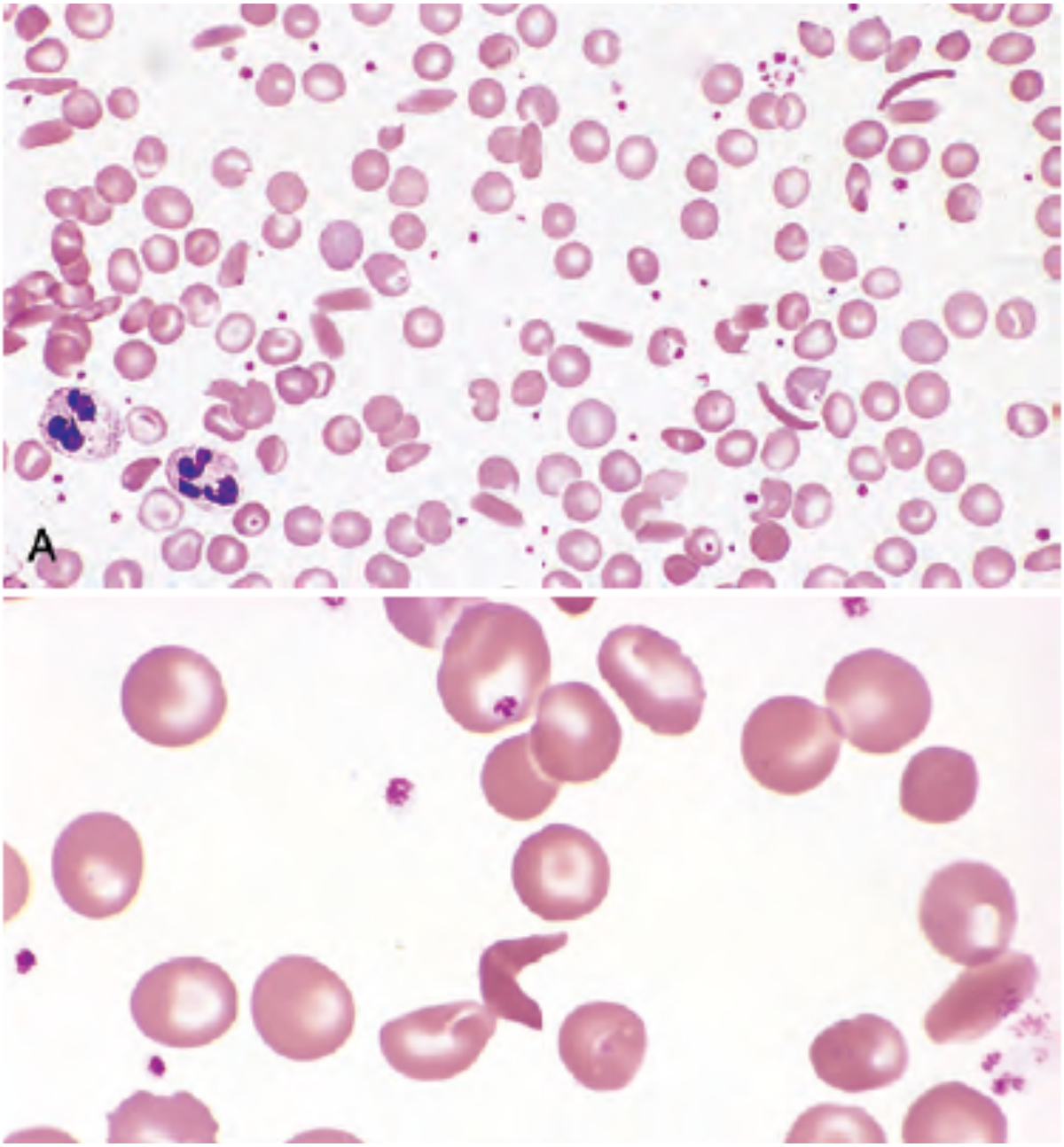
- mutation in the β chain
- addicted to analgesics
  related to deformities in the deoxygenized environment
- RBCs can't enter the capillaries, this causes ischemia which manifests as chronic pain.
- autosomal recessive

Clinical manifestations:

- Chronic hemolytic anemia.
- Fatty change in the heart, liver and renal tubules.
- Reticulocytosis and erythroid hyperplasia in bone marrow.
- Bone changes, prominent cheekbones and crew-cut skull
- Extramedullary hematopoiesis in liver and spleen (splenomegaly at first) but eventually we will have autosplenectomy. so no gallbladder stones or splenomegaly.
- Increase risk of infections, salmonella osteomyelitis.
- Vessel occlusion, bone pain, acute chest syndrome, stroke
- Aplastic crisis if they are affected by Parvo19 virus.

Diagnosis:
- Hemoglobin electrophoresis to demonstrate HbS
- Fetal DNA via amniocentesis or chorionic villi biopsy

Treatment:
- hydroxyurea
- bone marrow transplant



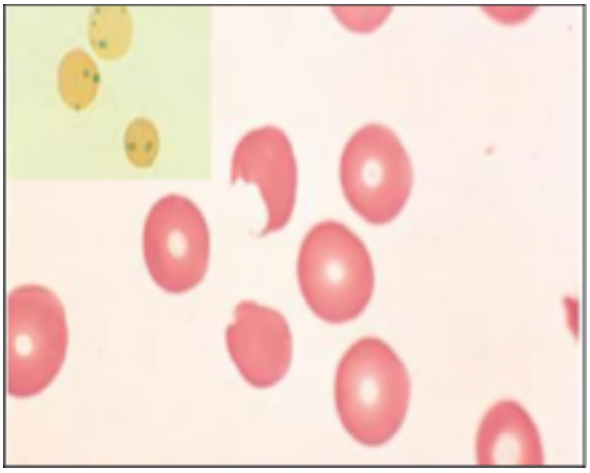
sickle cells

B2) Thalassemia:

In thalassemia there is no structural deformities but there is a decrease in the quantity of hemoglobin chains.

We have two type of thalassemia - α and β

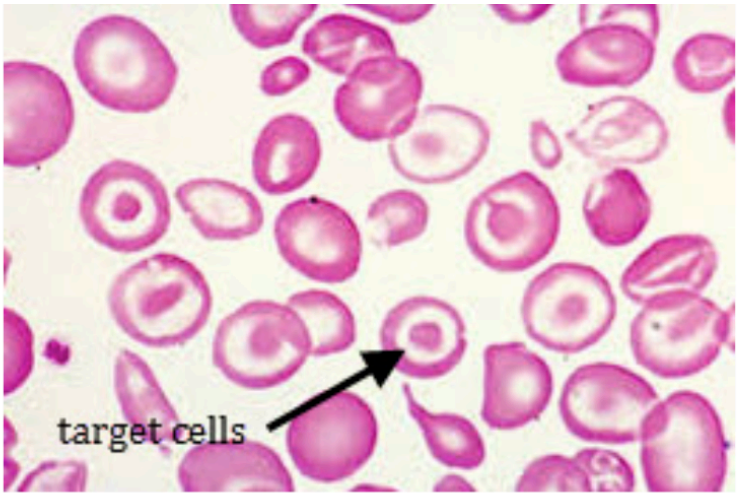
in β thalassemia:
- Decreased production and hemolysis both contribute to anemia
- there is an increase in α chains which aggregate in RBCs forming Heinz bodies. These are phagocytosed in the spleen creating “bite cells” or “blister cells” (figure)

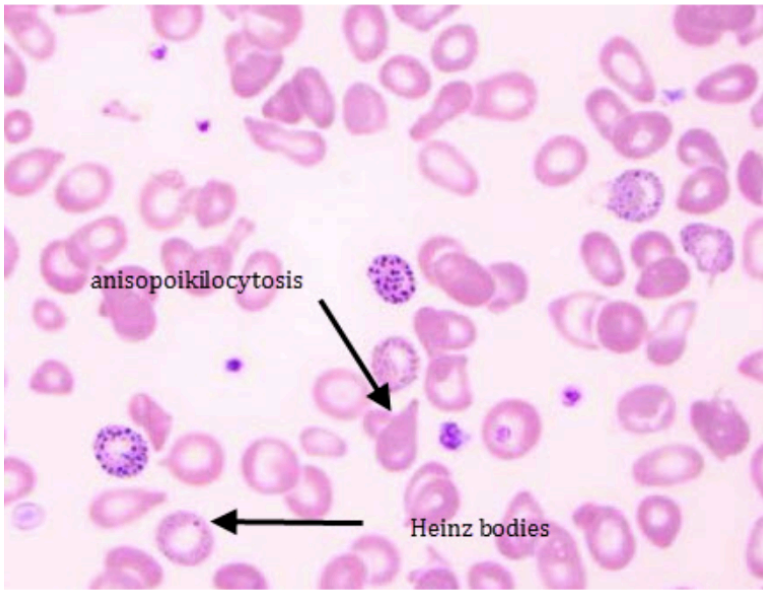


Clinical manifestations:
- tissue hypoxia, and red cell hemolysis
- Low hemoglobin 3-6g/dL
- very low MCV (micro)
- normal to low RDW

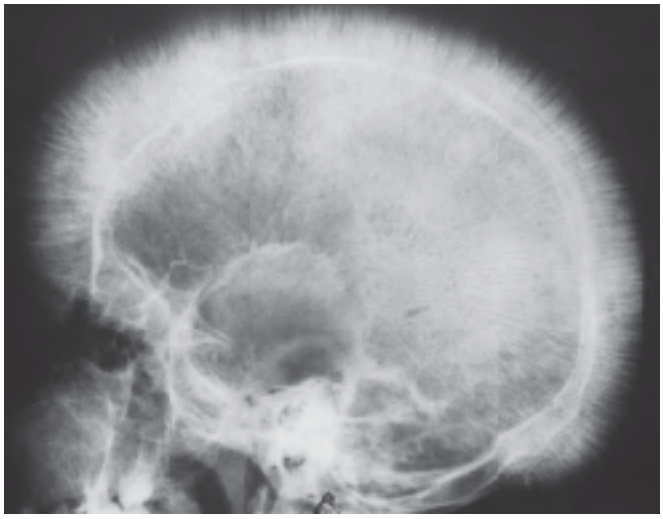
Diagnosis
- Elevated HbF and HbA2 (sensitive for beta thalassemia)

Morphology:
- No specific morphology
- Presence of target cells (not specific)





bone marrow expansion trying to compensate causes skeletal deformities, show on X-ray - perpendicular radiations resembling a crew-cut



Manifestations:
- Hepatosplenomegaly.
- Cardiac disease

Treatment:
- Transfusion dependent
- Stem cell transplantation is the only hope for cure

Beta thalassemia minor:

- Usually asymptomatic
- Increased erythropoietin and RBCs
- Bone marrow erythropoiesis progenitor hyperplasia
- Normal Hb
- Low MCV
- RDW is normal
- Elevated HbA2

C) Enzymopathies - G6PD deficiency

- the issue is with the G6PD enzyme so RBCs cannot handle oxidative stress
- X-linked disorder
- Hemolysis is acute and episodic caused by:
    - Infections: most common cause
    - Drugs: antimalarials, nitrofurantoin (old antibiotic for UTIs, especially in females
    - Certain foods: fava beans (least common)

New RBCs can handle oxidative stress caused by these episodes so only the old RBCs will die. So even if the episode continues the patient will be normal after the initial old RBCs are lost.

- Heinz bodies and bite cells are seen
- Hemolysis in G6PD can be either intra- or extravascular
- features related to chronic hemolysis (splenomegaly and gallbladder stones) are typically absent

Acquired hemolytic anemia of Intrinsic causes - Paroxysmal nocturnal hemoglobinuria (PNH)

- occurs when an acquired mutation occurs in the protein found on RBCs that protects it from the complement system
- PNH results from acquired mutations in the phosphatidylinositol glycan complementation group A gene (PIGA) enzyme that regulates complement system
- PIGA gene is present on the X chromosome.
- A mutation in PIGA gene will result in decreased production of PIGA protein so the cell will be more prone to complement fixation and hemolysis.
- only hemolytic anemia resulting from an acquired genetic mutation

Clinical manifestations

- Low level chronic hemolytic anemia.
- Nocturnal (at night) due to the slight decrease in blood pH during sleep
- has some association with aplastic anemia and thrombosis
- High incidence of bone marrow disorders like myelodysplastic syndrome and leukemia

Treatment

focused on targeting the complement system so this will increase the risk of Neisseria infections

finished anemia, now a new topic

Polycythemia

high RBC count and elevated hemoglobin level

Polycythemia may be absolute or relative.

Relative Polycythemia

Occurs when there's a decrease in plasma volume with no change in the total RBC mass.
It results from dehydration (diarrhea, vomiting or diuretic therapy)

Absolute Polycythemia

here there is an actual increase of RBC count due to overproduction of RBCs in the bone marrow

can be primary or secondary

In **secondary**, the overproduction of RBCs is induced by elevated erythropoietin. This occurs due to hypoxia which is sensed by kidney cells. This causes the transcriptional factor, HIF (hypoxia induced factor) to turn on the gene for erythropoietin, which increases RBC production

- there are two types of hypoxia
  Generalized hypoxia (smoking, High altitude and High affinity hemoglobins)
- Localized hypoxia (renal artery stenosis and polycystic kidney disease)

Some tumors can secrete erythropoietin. Eg. Wilms tumor, Renal cell carcinoma, Cerebellar hemangioma, Hepatocellular carcinoma.

Whereas, **Primary** is when there is autonomous proliferation of erythroid progenitors and low erythropoietin levels

The most common cause is polycythemia vera which is characterized by increased marrow production of red cells, granulocytes, and platelets (panmyelosis),

It's an acquired, clonal neoplasm of all bone marrow stem cells (Chronic myeloproliferative neoplasm).

PCV is Strongly associated with JAK2 mutation but it's not specific as its seen in other chronic myeloproliferative disorders (thrombocythemia and primary myelofibrosis)

- mild splenomegaly at first but then becomes more severe
- hypercellular bone marrow
- bone marrow fibrosis and significant organomegaly occurs in late stages
- 2% risk for transforming to acute myeloid leukemia.

Clinical Features:

- Pruritis.
- Headache; dizziness.
- Hyperuricemia and gout.
- Increased risk of both major bleeding and thrombotic episodes (fatal) includes: DVT, stroke, MI, Bowel infarction, Budd-Chiari syndrome, Epistaxis and bleeding gums.

Treatment:
- Phlebotomy
- administration of JAK2 inhibitors:

Criteria for PCV diagnosis according to WHO:
must have either both major and a minor OR 2 minor and first major

Major criteria:
1. Haemoglobin >18.5 g/dL in men, 16.5 g/dL in women. Or other evidence of increased red cell volume.
2. Presence of JAK2 mutation

Minor criteria:
1. Bone marrow biopsy showing hyper-cellularity
2. Low serum erythropoietin level
3. Endogenous erythroid colony formation in vitro. (Not commonly used).