Anemia summary

We will talk initially about the main classifications of anemia and their basic clinical features

According to cause

- Blood loss
  - acute
  - chronic
- Diminished RBC production
  - most common cause
- increased destruction
  - hemolytic anemia

Normal RBC production but they die early

- extrinsic
  - The problem is outside the RBC
- intrensic
  - Hereditary
  - acquired

According to morphology

size

- normcytic
  - → MCV 80-100 fl
- microcytic
  - → MCV < 80 fl
- macocytic
  - → MCV > 100 fl

color

- Normochromic
  - → central pale area about 30%
- hypochromic
  - → The pale area is larger than 30%
- Hyperchromic [we don't use this term]
  - → it's equal to macrocytic anemia

shape

- Anisopoikelocytosis
  - → variable shapes and sizes
  - we test it by RBC distribution width
    - → varient shapes = Large value
    - → same shapes = smaller value

Clinical features of anemia

- Dizziness
- Fatigue *tiss won't function optimally*
- Pallor *decreased vascularization in the superficial part of the skin, thus will appear brighter*
- Headache

Adaptive changes:

- Tachycardia
- Tachypnea *increasing respiratory rate to gain more oxygen*
- Increased red cell 2,3-diphosphoglycerate

If the patient has heart or lung diseases, symptoms will be worse

Anemia of blood loss

Type	Cause	Symptoms and complications	Morphology
Acute	Traumatic blood loss Internal bleeding GIT bleeding	Decreased intravascular volume Hypovolemic shock Death Dilutional anemia due to shifting fluid from interstitial to intravascular space Hypoxia	Normochromic normocytic with reticulocytes
Chronic	Rates of RBCs loss is exceeds regeneration GIT diseases Excessive Menstruation	IDA	Hypochromic / microcytic Low reticulocytes

Anemia of decreased production

→ Nutrienal Deficeincy
→ Chronic inflammation
→ Bone marrow failure

Type of anemia	Cause	Symptoms and complications	Morphology	Lab findings
Iron deficiency anemia	Chronic blood loss Diet Decreased absorption due to: 1. Gastrectomy 2. Hypochlorhyria 3. Intestinal diseases 4. Elderly Enzymatic deficiency Hypotransfrretinemia Increased demands: 1. Growing children 2. Myeloproliferative neoplasms 3. Pregnancy	General symptoms of anemia Pica Glossitis Stomitis Spooning of finger nails Restless leg syndrome Hair loss Blue sclera Weakened immunity Cognitive impairment	Hypochromic Microcytic Piokelcytosis Target cells Low reticulocytes Thrombocytosis due to the shifting in the progenitor cells to megakaryocytic	Low iron in bone marrow aspirate *Low serum ferritin level Low serum iron level High total iron binding capacity Low reticulocyte hemoglobin content Low MRV
Anemia of chronic inflammation	Chronic infections: High IL-6>> high hepcidin >> degrade ferroprotin on macrophages Chronic inflammation inhibit the synthesis of erythropoietin from kidneys Cancer Chronic immune diseases	Similar to IDA	normal morphology then Hypochromic microcytic	Low iron serum High serum ferritin level High bone marrow iron stores Low reticulocytes

* there are other factors that affect the serum ferritin level (other than iron). These include:

a) Inflammation (serum ferritin **increases**)
b) Fasting (serum ferritin **increases**)
c) Vitamin C deficiency (serum ferritin **decreases**)
d) Pregnancy (serum ferritin **decreases**), especially during the first trimester due to dilution (because of the increase of the fluids in pregnancy)

Serum ferritin is low in Iron deficiency anemia using this test.

Type of anemia	Cause	Symptoms and complications	Morphology	Lab findings
Megaloplastic anemia	Vitamin B12 or folate deficiency	General symptoms of anemia Glossitis Mild jaundice Pancytopenia in sever cases In class of Vitamine B 12 deficiency : Posterior and lateral degeneration of spinal cord Parenthesis (numbness) Loss of proprioception(balance) Peripheral neuropathy Neuropsychotic symptoms	Macroovalocyte Megaloblastoid cells : large sized RBCs with immature nucleus	Low B12 levels Low folate levels
Pernicious anemia	Autoimmune gastritis >> damage to parietal cells >> deficiency of intrinsic factor >> B12 deficiency Autoantibodies block. The binding of V B12 with the intrinsic factor >> inhibit B12 absorption	———	———	———

Causes of V B12 deficiency

Dietary deficiency occurs most commonly in vegetarians
More commonly: deficiency results from defective absorption
Pernicious anemia

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)

Causes of folate 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

Aplastic anemia

Damage to multi potent myeloid stem cell in bone marrow
Bone marrow becomes depleted of hematopoietic cells excepts for lymphocytes and what remains is fat

And we have to forms of aplastic anemia
1. Acquired
2. Inherited

	Acquired (60-70% of cases are idiopathic)	Inherited
Cause	Happens because of extrinsic factor antibodies raised against the extrinsic factor can also react with stem cells in the bone marrow in a process called antigen cross-reactivity. And this in turn activates T-lymphocytes to destroy stem cells Whereas associated factors like chloramphenicol, gold injections (used in rheumatoid arthritis), NSAIDs (as an idiosyncratic reaction* not allergic), pregnancy, and some hepatitis viruses, consist only 30% of the cases.	Caused by intrinsic factor 10% of aplastic anemia patients have inherited defects in telomerase thus stem cells die early due to mutations Or those genetically altered stem cells express additional abnormal antigen attracting T cells
Symptoms	Sever infections due to leukopenia Major bleeding due to thrombocytopenia	Sever infections due to leukopenia Major bleeding due to thrombocytopenia
Morphology	Normochromic or microcytic anemia	Normochromic or microcytic anemia
Lab findings	Peripheral blood: pancytopenia , low reticulocyte Bone marrow : decreased hematopoietic cells	Peripheral blood: pancytopenia , low reticulocyte Bone marrow : decreased hematopoietic cells

hemoglobinization problem ---> most probably microcytic anemia
stem cell problem ----> most probably Macrocytic anemia

Fanconi anemia :
Rare, inherited form of aplastic anemia
Defect in DNA repair proteins
Patients develop aplastic anemia and acute leukemia in early life

Pure red cell aplasia:
Only erythrocytes cells are absent in bone marrow can be :
1. Congenital :diamonds black fan anemia
2.acquired: autoimmune (SLE,RH ,parvovirus B19 infection)

We will continue with anemias

Type	Cause	Symptoms	Morphology	Lab findings
Myelophthisic anemia	Infiltration of bone marrow >> physical damage to hematopoietic cells Cancer: acute leukemia , advanced lymphoma ,metastatic cancer Granulomatous diseases >> physical damage by forming a mass	Insidious but accelerated symptoms of anemia Thrombocytopenia >> skin bleeding Neutropenia >> serious infection and death	Nucleated RBC Myelocytes Teardrop RBC Peripheral blood : leucoerthroblastic anemia (shift to the lift >> high levels of immature cells)	Peripheral blood : Immature granulocytic and erythrocytes precursors
Anemia of renal disease	Decreased erythropoietin production from kidneys No correlation between kidney function and severity of anemia	Decreased RBC production Normal count of platelets with abnormal function >> bleeding	Echinocytes appear (burr cells)	Low reticulocytes levels
Anemia of liver disease	We need multi factorial process to cause anemia : 1. Decreased synthesis of clothing factors 2. Bleeding from varices 3.decreased synthesis of transferrin	Abnormal metabolism of lipids >> abnormalities of plasma membranes of the RBCs >> abnormal morphology	Acanthocyte (spur cells)	
Anemia of hypothyroidisim	Thyroid Hormon stimulate erythropoiesis and erythropoietin production So any defect could affect the blood production process		Normocytic or macrocytic anemia	
Myelodysplastic syndrome	Disease of old age Mutations in BM stem cells >> prolonged survival and defective maturation Bone marrow full of cells but they are inactive	Anemia refractory to treatment (not responding to therapy)	Macrocytic anemia	

Hemolytic anemia
—> acceleration in RBC destruction >> hypoxia >> triggers erythropoietin release >> erythroid hyperplasia in BM

—> extra-medullary hematopoiesis in sever cases
Due to the destruction >> hemoglobin released from RBCs —-> converts to bilirubin >> jaundice
——> bind with heptaglobin

Hemolytic anemia classification

Main site of hemolysis

Extravascular
- spleen
- -patients have jaundice
- -Pigmented gallbladder stones
- -Spleenomegaly

Intravascular
- -inside blood stream
- -patients have hemoglobinemia (high Hb)
- -hemoglobinurea
- -hemosiderinurea
- -Iron deficiency

Cause of anemia

Extracellular
- Cause is from outside the cell

Intracellular
- Cause from inside the cell

THALASSEMIA

the most important hemolytic disease

- Group of inherited disorders that result in decrease production of either α/β chains
- Amount of synthesized Hg is below normal
- The deficiency in one of globin chains results in relative increase in the other one, excessive unpaired chains will cause instability and hemolysis
- Mode of inheritance: autosomal recessive — both parents are carrier
- Common in Middle East, Africa and South East Asia
- Resistant to infection by malaria falciparum
- Normal Hg types in adults: HgA, HgA2, HgF

1. HgA, accounting for 95% of the total red blood cell hemoglobin. Made of 2 α and 2 β chains. (mostly affected).
2. HgA2, made of 2 α and 2 δ. Important for diagnosis.
3. HgF, made of 2 α and 2 ɣ. least common one in adults.

Alpha thalassemia

encoded by 2 genes on chromosome 16

Mutation	Features
1 or 2 genes deletion	Silent carriers , asymptomatic
3 genes deletion	Hb H disease → extra β chains Bart disease → extra ɣ chains both have low affinity to oxygen → life long symptomatic anemia
4 genes deletion	Hydrops fetalis

encoded by one gene on chromosome 11

Beta thalassemia

genotype	Disease
β / β^+	silent carrier → mild anemia Thalassemia minor
β^+ / β^+	Thalassemia intermedia
β^0 / β^0	Thalassemia major Cooly anemia

β : normal production
β^+ : Decreased production
β^0 : no production

↑ α chains → hemolysis of RBC and their precursors → ineffective erythropoiesis

Morphology

In general	Thalassemia major	
	Bone marrow	Peripheral blood
Hypochromic mycrocytic anemia Target cells Basophilic stippling Reticulocytes	Normoblasts : filling the bone marrow and expanding into bone Hemosedrosis : accumulation of iron in organs	Piokelocytosis Nucleated RBCs

Causes of hemosiderosis:
1. As RBCs release iron when they are hemolyzed, the iron does not get excreted. Instead, it accumulates in tissues.
2. High erythropoietin levels inhibit hepcidin synthesis (a molecule that inhibits absorption of iron from the GIT) which means more absorption of iron from the gut.
3. The usual treatment for thalassemia major is blood transfusion, and this also supplies the body with even more iron.

CLINICAL SYMPTOMS

In the premarital test, we can detect the abnormality by doing the complete blood count (CBC) test and detect (the mean cell volume) if it below the normal then it may be iron deficiency anemia (common) OR thalassemia to know we do another test(next slide)

(carriers)

- Thalassemia traits are asymptomatic, normal life span, premarital test is important — the RBCs are hypochromic and microcytic but in a mild degree

- β Thalassemia major: symptoms begin after age of 6 months, persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion — fetal Hg (alpha-gamma)
  - Systemic hemochromatosis and related organ damage occurs in 2nd or 3rd decade of life → then death — heart \ endocrine system
- mild β Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion — 3 deletion

DIAGNOSIS

Although we have blood film and the clinical picture, the most important test is hemoglobin electrophoresis

- Hemoglobin electrophoresis test
  - In all types of β-thal, there is increase in HgA2 and HgF percentages — alpha-delta, alpha-gamma
    - The normal range of HbA2 is up to 3.5%, if it's more than that then the patients has β- thalassemia.
    - HgF level is not reliable as HgA2 test because there are normal variation between individuals (people might have a higher HbF percentage normally)
  - In β-thal major, HgA is absent or markedly decreased
  - In HgH disease, HgH and Hg Barts bands appear
  - In α-thal carrier and minor, no abnormality is found. Genetic testing is available
    - (Because there is a decrease in α-chains → there is an equal decrease in HbA, HbA2, and HbF → percentages stay the same)

But then, how do we diagnose alpha thalassemia carriers:
- mild hypochromia and mild microcytosis
- normal electrophoresis
- normal iron test (iron deficiency anemia is excluded)

→ we used to suspect α-thalassemia by exclusion. But nowadays we do a DNA genetic test