PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM – LECTURE 3

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APLASTIC ANEMIA

- Damage to multipotent myeloid stem cell in bone marrow
- Bone marrow becomes depleted of hematopoietic cells
- Peripheral blood pancytopenia
- Low reticulocytes

PATHOGENESIS

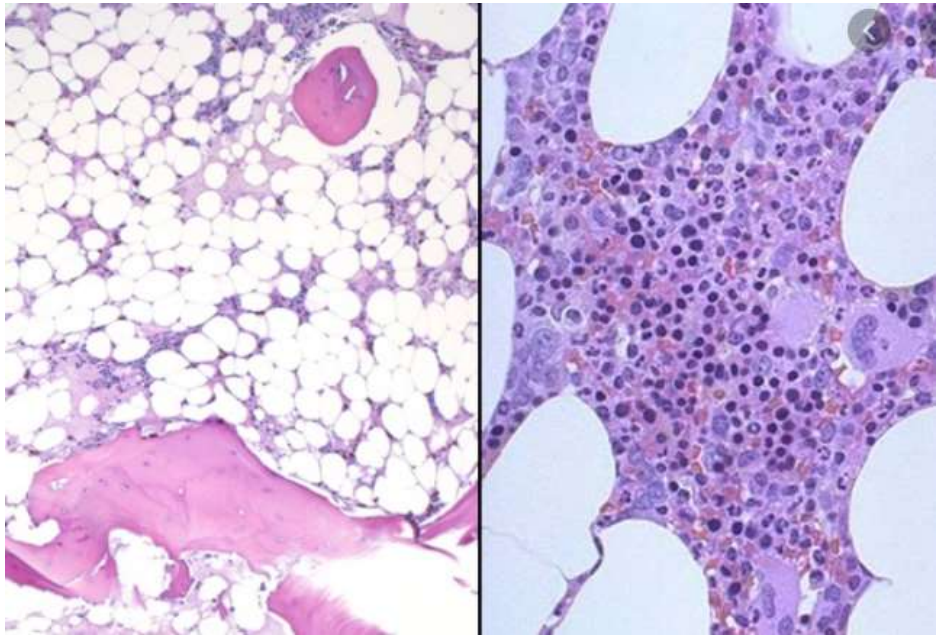
- Extrinsic factor
- Antigen cross reactivity with stem cells (drug, virus, environmental factor)
- Activated T-lymphocytes destroys stem cells
- Evidence: immunesuppressive drug restores bone marrow in 70% of cases
- Most cases are idiopathic
- Associated factors: chloramphenicol, gold injections, NSAID, pregnancy, some hepatitis viruses

PATHOGENESIS

- 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

LABORATORY FINDINGS

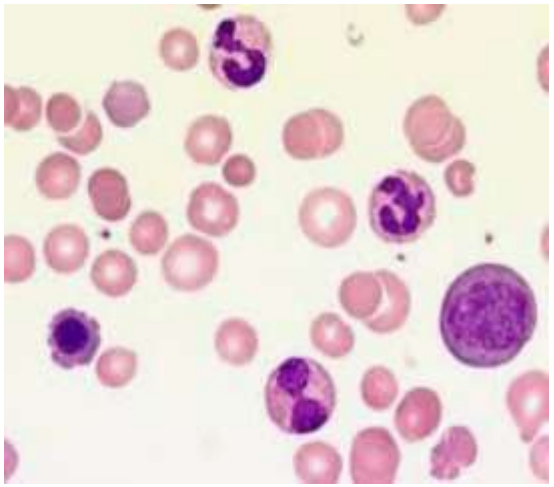
- Peripheral blood: pancytopenia, anemia is normochromic or macrocytic
- Bone marrow: decreased hematopoietic cells

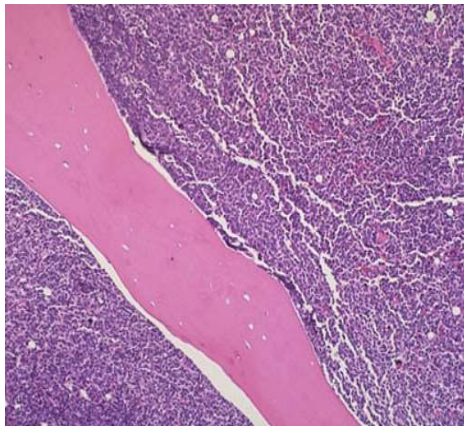


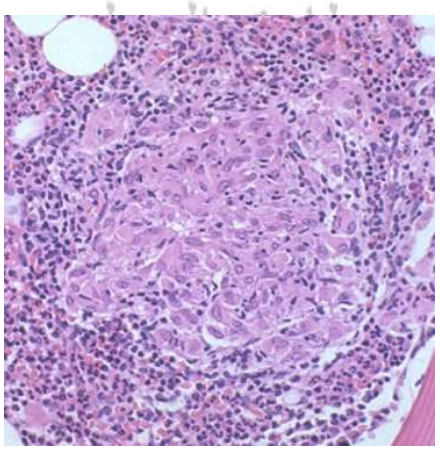
- Fanconi anemia: rare, inherited form of AA, defect in DNA repair proteins, patients develop AA and acute leukemia in early life
- Pure red cell aplasia: only erythroid cells are absent in bone marrow, can be congenital (Diamond-Blackfan anemia) or acquired (autoimmune, Parvovirus B19 infection)

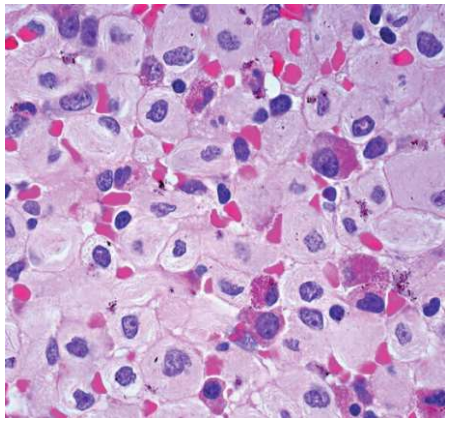
MYELOPHTHISIC ANEMIA

- Infiltration of bone marrow causing physical damage to hematopoietic cells
- Cancer: most commonly in acute leukemia, advanced lymphoma, metastatic cancer
- Granulomatous disease: TB
- Storage diseases: Gaucher
- Immature granulocytic and erythroid precursors commonly appear in peripheral blood









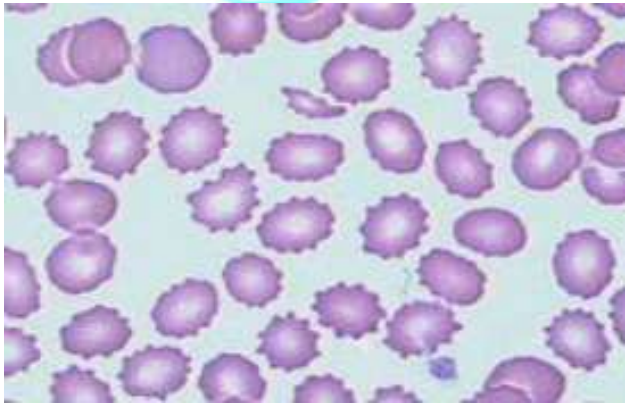
- Peripheral blood: leucoerythroblastic anemia (shift to left + nucleated RBCs)

SYMPTOMS

- Insidious but accelerated symptoms of anemia
- Thrombocytopenia manifests as skin bleeding
- Neutropenia may results in serious infections and death

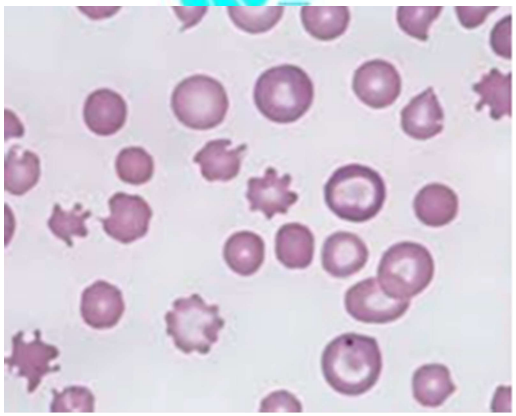
ANEMIA OF RENAL DISEASE

- Mainly results from decreased erythropoietin production from kidneys
- Does not correlate well with kidne finction (serum creatinine)
- Decreased RBC production (low retic count)
- Patients with uremia develop abnormal platelets function (bleeding), echinocytes (Burr cells) appear



ANEMIA OF LIVER DISEASE

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



ANEMIA OF HYPOTHRYOIDISM

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

MYELODYSPLASTIC SYNDROME

- Acquired, relatively common disease
- Primarily disease of old age
- Mutations in BM stem cell, results in prolonged survival and defective maturation
- Most patients have anemia, refractory to treatment
- RBCs are macrocytes

HEMOLYTIC ANEMIA

- RBC life span < 120 days
- Hypoxia triggers release of erythropoietin
- Erythroid hyperplasia in bone marrow
- Peripheral blood reticulocytosis
- Extramedullary hematopoiesis in severe cases
- Hemoglobin is released from damaged RBCs
- Serum haptoglobin: decreased (binds free Hg)

GENERAL CLASSIFICATION OF HEMOLYTIC ANEMIA

Main site of hemolysis:

- 1) Extravascular: occurs primarily in spleen (RBCs have abnormal shape or coated with antibodies, removed by macrophages, patients have jaundice, pigmented gall bladder stones, splenomegaly)
- 2) Intravascular: inside blood stream (sudden release of Hg, patients have hemoglobinemia, hemoglobinurea, hemosiderinurea, iron deficiency)

According to cause of hemolysis

- Extracorpuscular vs intracorpuscular

THALASSEMIA

- 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
- Common in Middle East, Africa and South East Asia
- Resistant to infection by malaria falciparum
- Normal Hg types in adults: HgA, HgA2, HgF

GENETICS

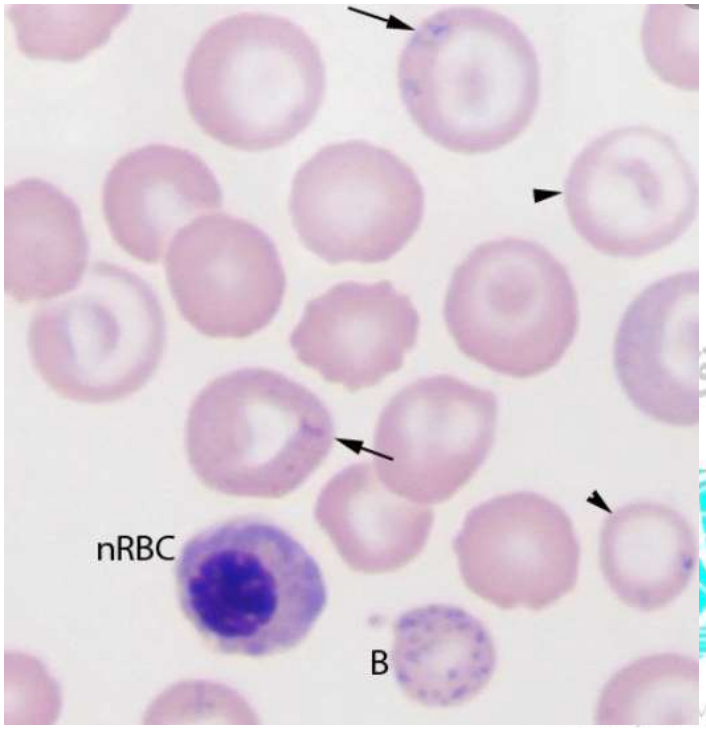
- α-chain is encoded by 2 genes on chromosome 16
- Most mutations in α-thalassemia are deletion
- Deletion in 1,2 gene(s) results in a silent carrier
- Deletion of 4 genes results in hydrops fetalis
- Deletion of 3 genes results in Hemoglobin H disease (extra β-chains binds each other to a tetramer called Hg-H, extra γ-chains form Hg-Barts). Both have high affinity to oxygen

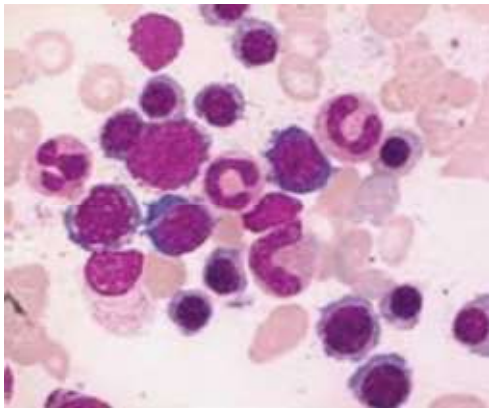
GENETICS

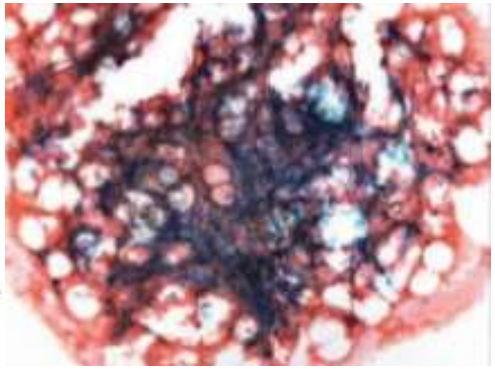
- B-chain is encoded by a single gene of chromosome 11
- Most mutations in β-thal are point mutations
- β^0: no production of β-chain
- β^+: decreased production of β-chain
- β/β^+:silent carrier or mild anemia (thal-minor)
- β^+/β^+: thalassemia intermedia
- β^0/β^0 or β^0/β^+: thalassemia major (Cooley anemia)
- Extra α-chains remain uncoupled, causing hemolysis of RBCs and precursors (ineffective erythropoiesis)

MORPHOLOGY

- Hypochromic microcytic anemia
- Target cells
- Basophilic stippling
- Reticulocytosis
- In thalassemia major:
- Peripheral blood: + poikelocytosis, nucleated RBCs
- Bone marrow: ↑↑ normoblasts, filling BM spaces and expanding into bone, hemosiderosis


nRBC
B





CLINICAL SYMPTOMS

- Thalassemia traits are asymptomatic, normal life span, premarital test is important
- Thalassemia major: symptoms begin after age of 6 months, persistent symptoms of anemia, growth retardation, skeletal abnormalities, both are ameliorated by regular blood transfusion
- Systemic hemochromatosis and related organ damage occurs in 2nd or 3rd decade of life
- Thalassemia intermedia and HgH disease have moderate anemia, do not require regular blood transfusion

DIAGNOSIS

- Hemoglobin electrophoresis test
- In all types of β-thal, there is increase in HgA2 and HgF percentages
- 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

ANALYTE ID	%	TIME	AREA
F	8.4	1.12	146914
P2	3.9	1.29	65767
P3	4.2	1.64	70198
Ao	77.9	2.37	1315634
A2	4.9	3.56	67100
Unknown 1	0.8	4.74	13136
	TOTAL AREA		1678749
F	8.4%	A2	4.9%