Anemia

General Info

Reduction of oxygen carrying capacity secondary to decrease in red cell mass (Not number).
(Yes, the number of RBCs is positively related to its mass but this is not always the case.)
As we sometimes have a large number of RBCs but they are empty, not functional.
RBC mass is also tied to Hb as Hb makes up around 30pg (MCH). Anemia causes hypoxia

Diagnosis: measured by hemoglobin concentration and hematocrit (RBC to overall blood %)
Before Hematocrit, PCV (packed cell volume) was used, it takes more time as the sample has to sit for a few days, not very practical.

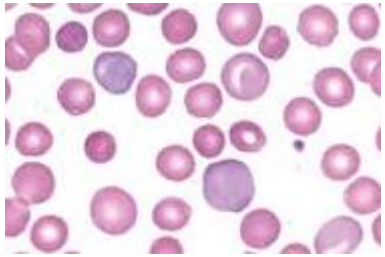
Physiology: (of Erythropoietin)
Anemia triggers production of erythropoietin from the kidneys (stimulates erythropoiesis) causing compensatory erythroid hyperplasia in bone marrow. This hyperplasia may be 5x folds more than the healthy person in cases of acute anemia.
In severe cases, erythropoietin causes extramedullary hematopoiesis (blood formation in sites outside the bone marrow) in secondary hematopoietic organs (these organs are liver and spleen, the blood makers during fetal life)
Exception: the erythropoietin mechanism is impaired in renal failure anemia and chronic inflammation anemia

Types: (Etiology based)
1) Blood Loss Anemia
2) Diminished RBC production Anemia (most common)
Includes following anemias (first 3 most common): Iron deficiency, Chronic inflammation, Megaloblastic, Aplastic, Pure red cell, Myelophthisic, Myelodysplastic Syndrome, Renal failure, Hypothyroidism anemias.
3) Hemolytic Anemia
-Extrinsic (not within the RBC): infections, autoantibodies, mechanical problems
-Intrinsic: Hereditary (abnormalities in membrane, enzyme, or hemoglobin) > more common or Acquired (Paroxysmal nocturnal hematouria)

Types: (Morphology based)
Size: Normocytic, Microcytic, Macrocytic (normal, smaller, larger respectively)
By MCV (normal range is 80-100 fL)
Color: Normo, Hyperchromic (in spherocytes), Hypochromic (larger central white/pallor area due to iron/Hb loss) by MCH
Target cells appear in abnormal hemoglobinization
Shape: An-Iso-Poikelocytosis (spherocytes, sickle, schistocytes) by RBC distribution width (RDW: the higher the RDW the more likely anisopoikelocytosis exists)

The size and color usually get along. Ex: Hypochromic Microcytic Anemia (reflects impaired Hb synthesis → sickle cell anemia or thalassemia) Macrocytic anemia → Reflects stem cell disease and its maturation

RBC measurements differ between labs, areas (higher in high altitudes), sex (higher in males), age (highest in newborns, O_2 taken from mother. Lower in elderly), ethnicity (lower in africans), activity.



Reticulocytes: are fresh immature red cells produced by the bone marrow, it appears larger and more bluish than the RBCs due to the DNA remnants. They do appear in blood but in low numbers (0.5-1.5% of entire RBC population) their presence in blood = polychromasia

Reticulocyte count: important to differentiate anemia of hemolytic anemia (their numbers will be more prominent)

Clinical features: (general)
Dizziness, headache, fatigue, Pallor, blood pressure decreases (hypotension)
As compensation: Tachycardia (heart beats fast), Tachypnea (increased respiration), 2,3-biphosphoglycerate (2,3BPG) increases (binds Hb for oxygen to dissociate for its release to tissues). Symptoms are worse in heart or lung diseases patients
In chronic hemolytic anemia: Jaundice, gallbladder pigmented stones (due to high unconjugated bilirubin), red urine
In extramedullary hematopoiesis: Splenomegaly, Hepatomegaly
Thalassemia major and sickle cell anemia: Growth retardation, bone deformity, secondary hemochromatosis (damage to heart, endocrine glands)

Anemia of acute blood loss:
Sudden decrease of intravascular volumes = Shock (organs stop functioning)
If loss is >20%of blood volume, might lead to hypovolemic shock and death
If amount is <20%, body responds by shifting fluids from interstitial to intravascular space, will cause dilutional anemia (worse) and gives worse hypoxia which will last 2-3days. If survived these days, they will live. Next, erythropoietin secretion is stimulated, activating bone marrow erythropoiesis (needs 5-7days to be effective).
In internal hemorrhage, the iron is restored to be used in erythropoiesis
In external and GI hemorrhage, iron is lost which complicates anemia to iron def anemia
This anemia is normochromic, normocytic (problem not in RBCs) with reticulocytosis (due to increased hematopoietin)

Anemia of chronic blood loss:
Occurs when RBC loss rate exceeds regeneration.
Mostly occurs in GI diseases (PUD, Hemorrhoids, colon cancer in elderly) or in excessive menstruation (gynaecologic diseases may occur as a follow up)
Almost always associated with iron loss. Iron is hard to retain and regain. It takes time.
Persistent loss of iron = iron deficiency anemia in manifestations and blood tests
RBCs appear small and pale (hypochromic, microcytic, low reticulocytes due to decreased regeneration from bone marrow)

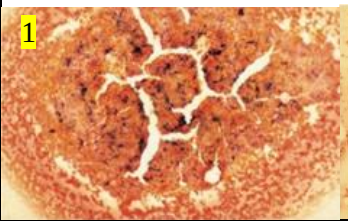
Iron Deficiency Anemia (IDA)

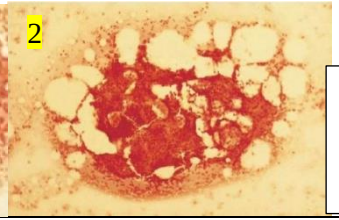
Diminished RBC Production Anemia

Most common type of anemia (community based/outside hospital)
Affects 10% in developed countries and 25-50% in developing countries

Physiology:
Iron is stored in ferritin (small and soluble, can't be seen as it is dissolved in cytoplasm)
And in hemosiderin (large and insoluble) present in bone marrow, liver and spleen
20% of iron is stored, while most of it is inside our RBCs
Hemosiderin is basically a large cluster of ferritin but with different characteristics as it has additional minerals, it looks granular in shape, present in the cytoplasm of macrophages.
Serum ferritin is derived from stored ferritin
Iron is normally lost in the body from shedding skin and mucosa (not by excretion)
Dietary iron is either of hem (red meat) which 20% is absorbed in duodenum
or of non-hem (inorganic, vegetarian) which 1% is absorbed in duodenum
Iron is only absorbed according to the body needs. Hepcidin is a hormone secreted from the liver which inhibits iron absorption (degrades ferroportin on enterocytes)
Hepcidin increases in high serum iron or in inflammations (IL6)
Hepcidin decreases in iron deficiency, very low in thalassemia major, primary hemochromatosis

Diagnosis:
-Most accurate one is **bone marrow aspirate** and stain it with Perl's Prussian blue
It detects earliest changes (any iron decrease effect starts from the bm) Con: invasive,expensive,needle stuck to bone. Will be low in IDA
-**Serum ferritin level**. Con: inflammation & fasting increase it, vitamin C deficiency and pregnancy decrease it. (in pregnancy due to increased fluid = dilution) low ferritin = decreased iron storage in the bone marrow = iron def anemia
-**Serum iron level** usually bound to transferrin (not an early change, takes longer time as the decrease starts from bone marrow to serum, may give FN) low transferrin = low iron=IDA
-**Transferrin saturation**. 30% is normal. Less than that will be deficiency = IDA
-**Total iron binding capacity**, old test, reliable. We take the blood, add artificial iron and see how much binds. If it increases = iron deficiency (IDA)
-**Serum transferrin and transferrin receptors**. Synthesized by the liver so the liver tries to compensate them by expressing them in anemia, so it will be overexpressed in IDA
-**Reticulocyte hemoglobin content (CHr)**, it will be decreased in iron def anemia (IDA)
-**Mean Reticulocyte Volume (MRV),** will be low in IDA
Remember all parameters in IDA decreased except the 1) Total iron binding capacity and 2)Serum transferrin and transferrin receptors





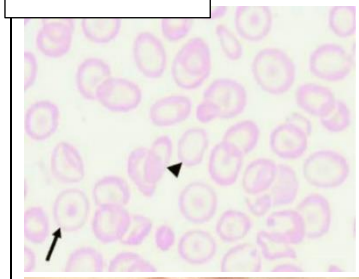
1) Normal Bone marrow aspirate shows bluish-black (hemosiderin) in macrophages
2) IDA Bone marrow aspirate with no stainable iron

Causes: (of iron deficiency)
-Chronic blood loss (GI diseases, excessive menstruation)
-Dietary: vegetarians, infants (human milk is poor in iron), teenagers (junk food)
-Decreased absorption of iron due to GI problems (Gastrectomy, hypochlorhydria, intestinal diseases like celiac, elderly (decreased function and possibly other comorbidities)
-Increased demand of iron (pregnancy, growing children, myeloproliferative neoplasms
-Less common: Hypotransferritinemia: decrease in transferritin secondary to liver disease or protein deficiency (diet, malabsorption) or nephrotic syndrome (loss in urine)
-Rare, appears early in life: enzyme deficiency (cannot absorb iron)

Morphology:
RBCs appear small and empty (Hypochromic microcytic)
Commonly Different shapes of RBCs (poikilocytosis) measured by RDW
Target cells (appearance of red dot in the center of the pallor) appears in any abnormal hemoglobinization
Low reticulocytes (although erythropoietin is low, it is not effective)
Thrombocytosis (increased platelets) in the bone marrow when the medium is low in iron, the progenitor/stem cells are shifted from erythroid to megakaryocytic.
So, remember thrombocytosis is a feature of IDA

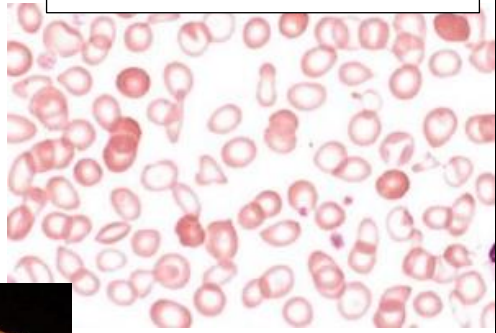
Symptoms:
-IDA is chronic (meaning it doesn't develop over hours or days, its treatment persists too)
-General symptoms of anemia (fatigue palor etc)
-Pica (craving/eating of abnormal things most commonly ice, dirt or paint)
-Glossitis and stomatitis (inflammation of tongue and lips specifically the corners) unknown reason but thought to be because iron is important for stabilization of the epithelial cells
-Spooning of finger nails
-Restless leg syndrome (moving leg constantly when sitting)
-Hair loss
-Blue sclera (epithelium thins)
-Weakened immunity (iron is imp for immune system, macrophages utilize iron)
-Cognitive impairment if severe (iron present in CNS)

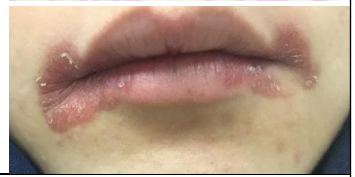
Target Cells



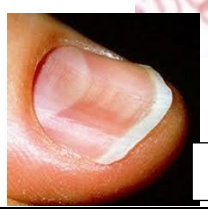
Blue Sclera

Poikilocytosis and hypochromia





Stomatitis



Spooning

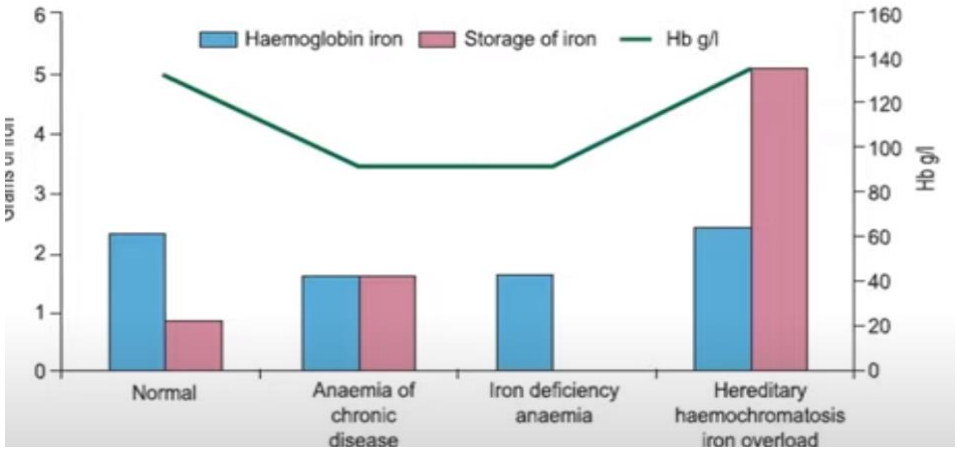
Anemia Of Chronic Inflammation

Diminished RBC Production Anemia

Most common anemia in inpatients (not the community)
Also called anemia of chronic disease
Seen in all chronic infections (TB, Brucella, HIV),
chronic immune diseases (RA, systemic lupus), cancers (their damage causes inflammation)

Pathogenesis:
Chronic inflammation inhibits synthesis of erythropoietin from kidneys.
Increased IL6 due to inflammation which increases hepcidin which blocks iron absorption and blocks transfer of iron from macrophages to RBCs
Theory: Macrophages keep iron for themselves and don't give out iron so microbes don't take it which is why the liver is not compensating transferrin

Diagnosis/Laboratory Findings:
Similar to IDA: Serum iron is low (retained in bone marrow macrophages), transferrin saturation is low due to low iron levels. RBCs are normal at first but develops to Hypochromic Microcytic, Low Reticulocytes due to low iron.
In contrast to IDA: bone marrow iron stores increase
Serum ferritin increases (it increases in inflammation)
Serum transferrin low (due to low iron. No compensatory liver overexpression)
Total iron binding capacity low (due to low transferrin)
Transferrin receptors are normal
Transferrin saturation is normal (because both iron and transferrin are equally low)



Aplastic Anemia (AA)

Diminished RBC Production Anemia

Aplasia = no production
Damage to multipotent myeloid stem cells in BM (multipotent means all 3 cell lines: myeloid, erythroid, megakaryocyte) so we have the lymphoid undamaged
So, the bone marrow becomes depleted of hematopoietic cells and what remains is the fat = peripheral blood pancytopenia, low reticulocytes

Pathogenesis:
Extrinsic factor:
-Antigen cross reactivity with stem cells (drug, virus, environmental factors)
Thus, activated T lymphocytes destroy stem cells. However, most cases are idiopathic
evidence: immunosuppressive drugs restore 70% of cases
-Associated factors (disease comes after an obvious incident):
Chloramphenicol (Antibiotic)
Gold injections (previously used in RA)
NSAIDs (In special people, idiosyncratic in a minority)
Pregnancy
Some viral hepatitis

Aplastic: Autoimmune, Pregnancy

Anemia: NSAIDS, Idiopathic

Can: Chloramphenicol

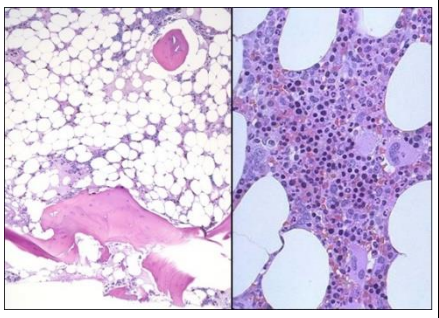
Get: Gold injections

Tough: Telomerase inherited genetic mutation, Hepatitis (viral)

Intrinsic factor: 10% of aplastic anemia there's an inherited defect in telomerase (chromosome stability) thus, stem cells die early. The autoimmune response in these genetically altered cells occurs due to their expression of abnormal antigens that attract T cells

Laboratory findings:
Peripheral blood: pancytopenia leukopenia, thrombocytopenia, normochromic anemia, sometimes macrocytic (remember problems related to stem cells give large cells)
Bone marrow: decreased hematopoietic cells and only residual fat, very minor hematopoietic cells which mostly are the lymphatic cells (see comparison pic)

Special subtypes:
Fanconi anemia: inherited form of aplastic anemia, defect in DNA repair proteins, patients develop aplastic anemia and leukemia in early life
Pure red cell aplasia: absence of only erythroid cells in BM, can be congenital (Diamond Blackfan Anemia) or more commonly, acquired (autoimmune or after parvovirus B19 infection which targets the earliest normoblast)



Symptoms:
Insidious but can be accelerated (symptoms of anemia)
Thrombocytopenia manifests as skin bleeding
Neutropenia may result in serious infections and death

Megaloblastic Anemia

Diminished RBC Production Anemia

Pathogenesis:
Caused by deficiency of either vitamin B12 or Folate, both which are required for synthesis of thymidine, thus DNA replication is impaired. Abnormalities occur in all rapidly dividing cells but hematopoietic cells are mostly affected as they directly use these compounds plus they are rapidly dividing.
Maturation of RBC progenitors is impaired as they have insufficient and incomplete DNA in their nucleus, many undergo apoptosis inside the bone marrow (Ineffective Erythropoiesis) with mild hemolysis INSIDE the bone marrow
Progenitor RBCs take longer time to mature (to synthesize adequate DNA), resulting in megaloblasts. Megaly = enlarged, blasts =immature cells (immature nucleus)

Folate: is stored in our body in minimal amounts, it is present food (green leaves) but it is destroyed by cooking.
Folate Deficiency:
Decreased dietary intake (common)
Increased demand (pregnancy, chronic hemolytic anemia due to damaged RBCs)
Intestinal diseases
Beans, legume, alcohol, phenytoin (all inhibit absorption)
Methotrexate (inhibits folate metabolism, even if supplemented there's no use)

Vitamin B12:
Large stores in the liver
Mainly present in animal products, resistant to cooking
Synthesized by bacteria in bowel
Dietary deficiency (most common in vegetarians)
More commonly: deficiency due to defective absorption

Morphology:
RBC maturation and synthesis is slowed down. However, the hemoglobin synthesis is normal, therefore each cell will be overFILLED with hemoglobin, making cells macrocytic
Macrocytic cells give high MCV
Anemia means low hemoglobin. So here, although we have each RBC overfilled with Hb, we have very low number of RBCs, so in total, we have a decreased number of Hb
Tendency of cells to turn oval (Macroovalocyte)
Neutrophils nucleus lobes will segment more (7 lobes) and they enlarge too because cells take longer to develop and have more time to segment

Symptoms:
Chronic with general symptoms of anemia
Glossitis (beefy tongue) (tongue epithelial cells cant regenerate when cells are scrapped off)
Very Mild jaundice (due to mild hemolysis)
In severe cases: Pancytopenia
In B12 deficiency: (neural effects due to myelin sheath degeneration = slower impulses)
Posterior and lateral columns degeneration of spinal cord due to myelin sheath loss = paresthesia (numbness in peripheries0 and loss of proprioception (sense of self position)
Peripheral neuropathy
Neuropsychotic symptoms

Pernicious Anemia

Diminished RBC Production Anemia – A Type Of Megaloblastic Anemia

B12 deficiency. Autoimmune disease:
Autoimmune gastritis where parietal cells that produce the intrinsic factor are destroyed, intrinsic factor deficiency will cause vitamin B12 deficiency.
Even if intrinsic factor supplementation was given, it will be destroyed due to formed antibodies by the activated B cells and plasma cells
It causes megaloblastic anemia

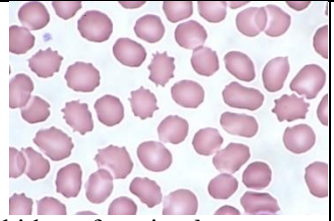
Other causes of B12 deficiency: (besides pernicious anemia)
Gastrectomy, small bowel diseases, elderly people (decreased gastric acids and pepsin = decreased digestion and release of vB12 from food),
Metformin known as Glucophage (inhibits absorption)

Other functions of B12:
Myelin sheath synthesis (nerves will be easily injured)
Recycling tetrahydrofolate (B12 deficiency can affect folate recycling)
Synthesis of neurotransmitter (dopamine, serotonin)
Metabolism of homocysteine (with B12 def, homocysteine will rise, which is toxic to neurons and heart)
Degree of neuronal damage does not correlate with the degree of anemia
Someone could still not manifest anemia but have the neuronal damage

Remember pernicious anemia is a type of megaloblastic anemia with just a different cause (autoimmune) thus the morphology and symptoms can be similar
It is called pernicious because it affects all rapidly dividing cells and it affects, the heart and brain too.

Anemia Of Renal Disease

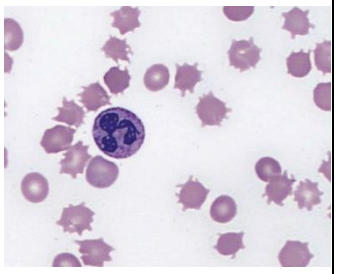
Diminished RBC Production Anemia



In renal disease, erythropoietin production will decrease = decreased RBC production (low reticulocytes)
Usually there's no correlation between erythropoietin amount and kidney function because serum creatinine could be only slightly high but have severe anemia (no correlation)
Serum creatinine level: if it's increased it means that erythropoietin won't be excreted and we have renal failure
Patients with uremia (renal disease) develop abnormal platelets function (bleeding) but with normal count, Echinocytes (Burr cells, cells appear spiked) secondary to increased uremia

Anemia Of Liver Disease

Diminished RBC Production Anemia



Patients with liver disease commonly have anemia (the anemia is multifactorial)
Decreased synthesis of clotting factors (bleeding), Bleeding from varices too
Decreased synthesis of transferrin (iron transporter) all which cause anemia
Sometimes Acanthocytes appear (Spur cells, spiked cells but with longer projections) not known why they appear but theory: abnormal metabolism of lipids on Plasma membrane

Anemia Of Hypothyroidism

Diminished RBC Production Anemia

Thyroid hormones stimulate erythropoiesis and also stimulate erythropoietin production
Anemia is most commonly normocytic but can be macrocytic (one of the causes of macrocytic anemia is hypothyroidism)→(in megaloblastic and can be seen in AA too)

Myelodysplastic Syndrome (MDS)

Diminished RBC Production Anemia

Acquired, relatively common. Primarily disease of old age.
Neoplastic disease. Multiple mutations in BM stem cells, cells have prolonged survival by abnormal maturation, so they can't function well = Most Patients will have Anemia
Refractory to treatment, meaning no use of it, no use of iron, folate, erythropoietin supply because the stem cells themselves are mutant. RBCs are macrocytes (stem cell problem)
Dysplastic = abnormality in growth

Hemolytic Anemia

General Info

Problem is in the survival of RBC (<120 days)
Hypoxia will occur which triggers erythropoietin release causing erythroid hyperplasia in bone marrow and peripheral blood reticulocytosis (high percent)
Remember if erythropoietin is very high and persistent for a long time, the patient will develop extramedullary hematopoiesis in severe cases (from spleen and liver which will cause hepatosplenomegaly)
Hemoglobin will be released from lysed RBCs which will cause jaundice

Diagnosis: Haptoglobin level decreases (because it is now bound to free hemoglobin) this is a liver protein which protects us from fee Hb which is toxic

General classification: (according to main site of hemolysis)
1) Extravascular: (most common) occurs primarily in spleen where RBCs are destroyed by macrophages, this occurs if the RBCs have abnormal shapes or are coated by antibodies
2) Intravascular: sudden hemolysis and sudden release of hemoglobin inside the blood vessels. Patients will have hemoglobinemia (the haptoglobin might not be enough), hemoglobinuria (Hb in urine = Red urine), hemosiderinuria all leading to iron deficiency
This type is more acute and critical, haptoglobin is almost absent because it occurs inside vessels
General classification: (according to cause)
Extracorpuscular: Outside RBC such as malaria, antibodies
Intracorpuscular: Enzymatic deficiency, thalassemia etc

Thalassemia

Hemolytic Anemias – Inherited

Most important hemolytic disease. It's a group of disease with either decreased production in alpha or beta chains of hemoglobin thus amount of hemoglobin is lower than normal. In addition, there will be one type of dominant chain which will be left unpaired and might cause damage inside the RBC and thus cause hemolysis.
It is an autosomal recessive disease. Common in middle east, Africa, south east asia
Resistant to malaria falciparum infection
Normal types of Hb in adults: HbA (α2,β2), HbA2 (α2,δ2), HbF (α2,γ2)

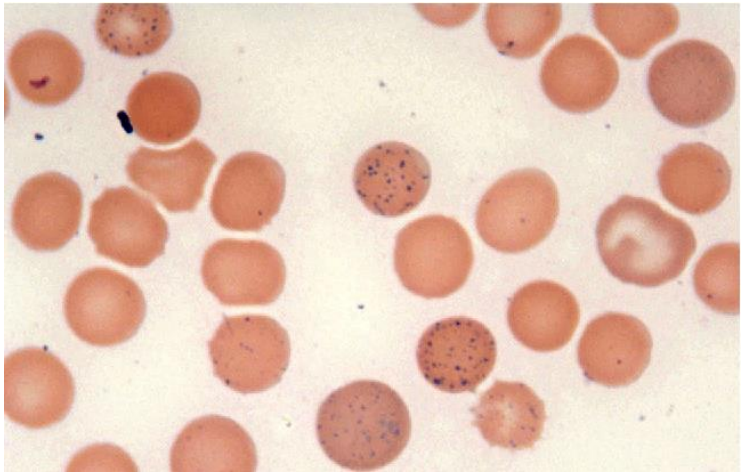
Genes: Alpha chain is encoded by two genes on chromosome 16 so in total we have 4 genes.
Most mutations in alpha chains are deletions (of the entire alpha gene).
If one gene is deleted → silent carrier
If 2 genes are deleted → silent carrier (thalassemia trait/thalassemia minor + mild anemia)
If 3 genes are deleted →HbH disease. HbH is a tetramer of beta chains causes with high affinity (thalassemia major)
If 4 genes are deleted → Hydrops fetalis (stillbirth or death shortly after birth) there will be Hb Bart (gamma tetramer) *Bart = Apart, dead*

Genes: Beta chain is encoded by one gene on chromosome 11 so in total we have 2 genes.
Most mutations in beta chains are point mutations (we have >100 mutations of beta chain)
β0: no production of beta chain
β+: decreased production beta chain
β/β+: silent carrier or mild anemia (thalassemia minor)
β+/β+: thalassemia intermedia
β0/β0: thalassemia major (Cooley Anemia)
extra remaining alpha chains cannot bind each other form a tetramer such as HbH disease, causing RBC hemolysis. Thus, Beta thalassemia is worse

Morphology:
Hypochromic microcytic anemia (due to low Hb, just like IDA)
Target cells (due to abnormal hemoglobinization)
Basophilic stippling (small blue dots which are remnants of ribosomes or DNAs from the precursor nucleated cells. They appear in thalassemia)
Reticulocytosis (unlike IDA due to erythropoietin)
In thalassemia major:
-poikilocytosis and nucleated RBCs in peripheral blood
-In the bone marrow, very high normoblasts (nucleated RBCs) so in histology we will see the nucleated normoblast cells dominant over the myeloid cells (it should be the opposite) due to erythropoietin, the normoblasts and iron fill BM spaces and expanding into bone forming abnormal bone growth, hemosiderosis (hemolysis will release iron, also iron will always be absorbed because erythropoietin inhibits hepcidin causing hemosidrosis in BM, if not treated will accumulate in all organs and this is fatal).

Clinical Features:
Thalassemia traits (carriers) are asymptomatic, normal life span, premarital test is important
Thalassemia major B: symptoms begin after 6 months of age, persistent symptoms of anemia, growth retardation, skeletal abnormalities are ameliorated (decreased) under regular blood transfusion but the problem is iron will accumulate, so systemic hemochromatosis will occur in 2nd or 3rd decade of life and die
Thalassemia intermedia and HbH disease have moderate anemia and do not need blood transfusion

Diagnosis: Blood film, clinical picture but most importantly the hemoglobin electrophoresis.
In all types of beta thalassemia HbA2 and HbF percentages increase
In B thal major: HbA is absent or markedly decreased
In HbH disease, HbH and Hb Bart bands appear
Alpha thalassemia carrier and minor are undetectable except in genetic testing.
Why? Because there's a decrease in alpha chains, there will be an equal decease in HbA, HbA2, HbF. We diagnose them when a patient has mild hypochromia and microcytosis with electrophoresis and normal iron so we suspect a-thal so we do a genetic test



Sickle Cell Anemia (SSA)

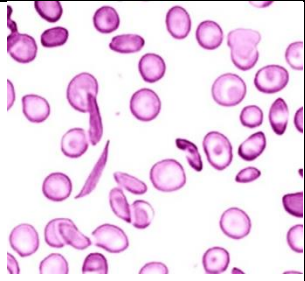
Hemolytic Anemias – Inherited

Most common familial hemolytic anemia, more common than thalassemia
Common in the old world. Autosomal recessive. Diseased people are resistant to malaria
Gene: single amino acid substitution in beta chain (glutamic acid (hydrophilic) to valine (hydrophobic)). Heterozygous genes = sickle cell carrier, Carries both HbA and HbS

Pathogenesis:
-When deoxygenated, HbS polymerizes, changing the shape of RBC to sickles.
This change is reversible once re-oxygenation occurs. However, with repeated sickling, the cell membrane is damaged and hemolysis occurs.
-Increased HbS concentration in the RBC promotes sickling especially in cases of dehydration or acidosis which occur in infections.
-Acidosis promotes deoxygenation (Bohr Effect) where the H ions stabilize the T state, it shifts the oxygen dissociation curve to the right
-Dehydration causes electrolyte disturbances
-People with alpha thalassemia have decreased sickling due to the already decreased Hb
-The presence of HbA in carriers or HbF in newborns inhibits the HbS polymerization. Newborns experience symptoms after 6th mo
-Sickle shaped RBCs may adhere to endothelial cells, forming a thrombus. They also take longer time to pass through the capillaries especially in the spleen where they are removed by monitoring macrophages (extravascular hemolysis)

Clinical features:
-Chronic moderate-severe anemia, with repeated sudden attacks of worsening anemia.
-Manifests at the age of 6mo when HbF is switched to HbA (which contains beta chain)
-Vaso-occlusive crisis can occur (thrombus formation) independent of sickle cell fractions. It results in organ infarction. This crisis is commonly associated in systemic infection, inflammation, dehydration, acidosis
-Hand-foot syndrome present if digits of the hand and foot are affected by ischemia. There will be deformities because as a growing child there will be multiple infarctions
-Acute chest syndrome, affects lungs and rib bones which might give breathing problems and further worsening the hypoxia
-Stroke, myocardial infarction → shorter life expectancy
-Retinopathy: thrombus formation or hypoxia which may trigger the formation of new blood vessels which may block the passage of light and worsen the symptoms
-Autosplenectomy: with the hemolytic anemia, splenomegaly will occur. But with the repeated infarctions, the spleen will become fibrosed and infarcted, so these patients will have no spleen when they grow up
-Aplastic crisis: can occur secondary to BM infarction, or to parvovirus B19 infection causing worsening anemia symptoms only in chronic anemia patients (such as in SSA or thalassemia. while in normal adults it cannot form a major symptom). Infection is self-limited. pure red cell aplasia may occur.
-Susceptibility for encapsulated bacteria after autosplenectomy (pneumococcus, salmonella)
-You can see that the complications come from infarction at different sites

Diagnosis: Routine blood smear (presence of sickle cells: RDW high) or target cells
Sickling test: adding hypoxic agent to RBCs to promote sickling (can be seen in diseased and carrier state)
Hemoglobin electrophoresis (differentiates carrier from diseased)
DNA testing
MCHC increases (MCV + MCH)



Hereditary Spherocytosis

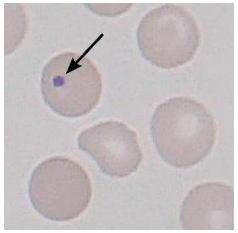
Hemolytic Anemias – Inherited

Autosomal Dominant, sometimes autosomal recessive.
Gene: Mutation in RBC membrane skeleton (commonly affects ankyrin, band 3, spectrin)
Cell membrane is unstable, keeps losing parts of it as RBCs age. Little cytoplasm is lost.
With decreasing surface area, the RBC loses its biconcave shape and becomes a smaller sphere

Pathogenesis:
Spherocytes are nondeformable, so they take longer time to move.
They are identified by the spleen and undergo extravascular hemolysis
If spleen is removed, spherocytes persist in peripheral blood and thus anemia is corrected (spherocytes are functional). Degree of anemia is variable (depends on mutation)
Some patients are asymptomatic, others have severe hemolysis
Treatment: Splenectomy

Diagnosis: spherocytes seen in blood film,
Low MCV since spherocytes are small in size
Little cytoplasm is lost (Hb) so we have normal MCH (mean cell hemoglobin) =normocytic
Taking MCV and MCH, the MCHC is increased.
Spherocytes show increased fragility when put in hypotonic solution (osmotic fragility test)
Which is nonspecific. Family history is important

Photo: RBCs are spherical with no central pallor. Also, we can see Howell Jolly bodies which are DNA remnants that appear as small black dots seen after splenectomy



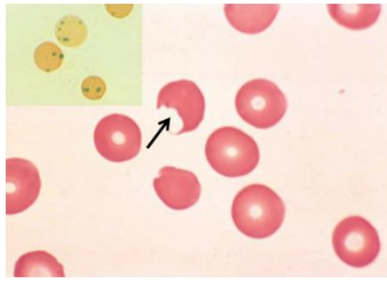
G6PD Deficiency

Hemolytic Anemias – Inherited

Known as favism, fava bean anemia,التفول, انيميا الفول, نقص الخميرا
Glucose-6-phosphate dehydrogenase deficiency. X linked recessive inheritance.
Meaning males are commonly affected (females will have another healthy X chromosome to override the diseased gene)

The G6PD enzyme is important in reducing NADP+ to NADPH which maintains the level of glutathione (glutathione is protective. it neutralizes ROS to avoid tissue damage, glutathione reduces ROS by giving them H- from NADPH)
The deficiency will cause recurrent, transient episodes of intravascular hemolysis.
RBCs are very prone for this deficiency
You can't have complete absence of the enzyme because, you'd be dead in utero

TRIGGERS:
Infections (WBC generate a lot of ROS)
Drug (Their metabolites consume large amounts of glutathione): sulfonamides, nitrofurantoin, large dose of aspirin, vitamin K, primaquine (used for malaria + RA)
Fava beans فول (vicine and convicine are antioxidants that consume glutathione)
Naphthalene (used in toilets as insect repellent, can be ingested by kids)
Certain food coloring (aniline dyes)



Overall, all these triggers produce large amounts of oxidants in which glutathione can't neutralize, causing hemoglobin denaturation which precipitates as Heinz Bodies making the cell less deformable (less flexible), also cell membrane is damaged causing massive hemolysis of RBCs, 2-3 days after exposure to trigger
Since RBCs lose their deformability, they are <u>partially</u> phagocytosed (to bite off the Heinz bodies part) inside the spleen forming bite cells

Diagnosis: blood film shows bite cells. If you do the supravital stain, you can see Heinz Bodies. Enzyme assay

Clinical features:
Anemia only shows as recurrent attacks (intravascular hemolysis). Patients will complain of general anemia symptoms. They will have dark urine (Hb directly goes to urine)
G6PD-A type: decreased amount of G6PD so bone marrow compensates by producing RBC
G6PD-Mediterranian: enzyme is present but has a qualitative defect (low functioning). More severe symptoms in this one because even in new RBC formation, there's no compensation
Females: can have symptoms if random inactivation affects the normal X chromosome
Generally, 10% of patients are females

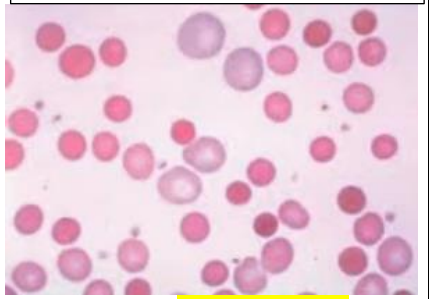
Immune Hemolytic Anemia (IHA)

Hemolytic Anemias – Acquired (extrinsic)

Or autoimmune hemolytic anemia (AIHA). Presence of auto-antibody against RBC membrane protein. The antibodies can be detected by Coomb's test.

Diagnosis:
Direct Coomb's test: RBCs are incubated with antibodies that target the autoimmune antibodies (normal antibodies) bound to the RBCs. Many antibodies will be bound and cause agglutination.
Indirect Coomb's test: Patients serum is taken and added to test RBCs that have certain known surface proteins. If disease is present, Agglutination will form

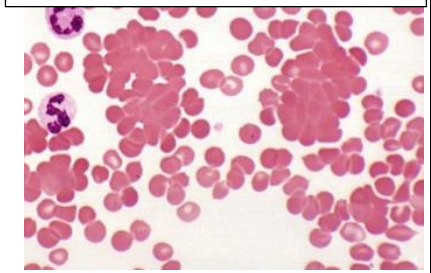
RBCs are sphere with no central pallor. Reticulocytes (purple) are abundant due to compensation



Warm Type
-High affinity autoantibody (mostly IgG type)
-Binding occurs in core circulation (37C)
-Macrophages in spleen remove the autoantibody from the RBCs by pinching the RBCs, eventually spherocytes will develop which are then destroyed by spleen (Extravascular hemolysis)
-60% are idiopathic, 25% associated with systemic lupus erythematosus, 15% by drugs (alpha-methyldopa, penicillin) because penicillin is deposited on RBCs, it can initiate an immune response
-Severity of anemia is variable, most patients have mild chronic anemia, reticulocytosis (because it's an extravascular hemolysis) and splenomegaly

Cold Type
-Low affinity autoantibody (IgM) ← can bind to 5 RBCs at once
-Binding occurs in peripheral areas of the body (digits, nose, ears) (<30C)
-After IgM binding, C3b proteins (complement system) bind to RBC's membrane
-When RBCs return to the core circulation, the temperature rises and IgM (low affinity) dissociates. However, the C3b stays, which is removed by splenic macrophages leaving us with spherocytes just like the Warm Type and are then destroyed
-Since IgM can bind 5 RBCs, it creates in vivo agglutination, might block small capillaries in fingers and toes causing Rayhaud Phenomenon
-Can be acute or chronic. (the warm type is chronic mild)
-The acute transient form, occurs in recovery of infections of mycoplasma pneumonia or by EBV (mononucleosis) → (mild, self-limited)
-Chronic persistent form, occurs in B-cell lymphoma (produces large amounts of Ab) or idiopathic
Reticulocytosis occurs here too since it's a type of hemolytic anemia

Sphere RBCs with no central pallor. Clumped together



Paroxysmal Nocturnal Hemoglobinuria (PNH)

Hemolytic Anemias – Acquired (intrinsic)

Paroxysmal = sudden, Nocturnal = at night.
Rare, acquired genetic disease

Acquired mutation in PIGA gene in stem cells of the bone marrow in which these mutated stem cells pass the mutation to all its descendant cells (WBCs, RBCs, and platelets are all affected). This mutation results in phosphatidylinositol glycan (PIG) deficiency. PIG is a structural protein present on cell membranes and anchors many proteins (CD55, CD59)
Mutations occur in bone marrow stem cells. The Gene is present on X chromosome

Pathogenesis:
Normally, CD55 and CD59 membrane proteins are attached to PIG in order to protect the cells from the activated complement system (C5b-C9) which are circulating proteins that form pores in bacterial cell walls. RBCs are the most affected cells by this PIG anchoring protein deficiency. Sudden hemolysis will occur in RBCs, to a lesser extent WBCs and platelets can be affected (depending on which cell lines are mutated)
If platelets are lysed, they release their contents causing thrombosis (common). So, although we have thrombocytopenia, we have thrombosis instead of bleeding (most common and serious symptom, can be fatal)
During sleep, there's more CO2, so blood is more acidic, which activates the complement system more, so the chances of hemolysis are more common during sleep

Diagnosis:
Flow cytometry: we test the presence of CD55 and CD59 on cell membranes.
PNH patients will be negative for CD55 and CD59.
One of the stem cells becomes mutant resulting in the entire progeny becoming mutant too.
Sometimes all the BM stem cells are mutated, but most commonly only partial stem cells are mutated

Traumatic Hemolysis

Causes:
Direct physical force or turbulence causing lysis of RBCs.
Prosthetic heart valves
Repetitive physical pounding (marathon, boxing, pounding, marching)
Disseminated thrombi (RBCs will be damaged as they pass by the thrombi.ex: microangiopathic hemolytic anemia)

Hallmark of traumatic hemolysis: Schistocytes (fragmented RBCs with different irregular shapes)

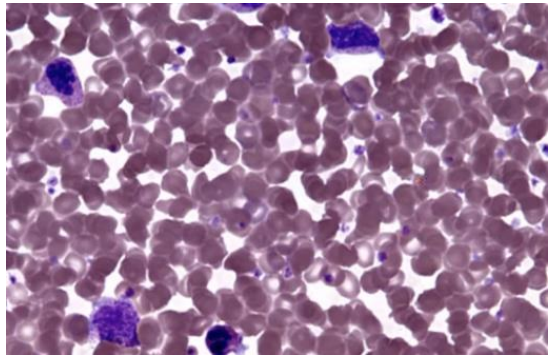
Will be discussed soon.

Polycythemia

Polycythemia: Increase in total RBC mass
Erythrocytosis: Increase in RBC number

Relative polycythemia: RBC count is normal but plasma volume is decreased (water deprivation, severe diarrhea, diuretics)
Absolute polycythemia: true increase in RBC mass, secondary to increased BM production due to chronic hypoxia. ← Secondary is the most common
Primary (Polycythemia Vera): no obvious problem, we have a neoplasm of RBC in the bone marrow. Characterized by low erythropoietin, splenomegaly (because it's a neoplasm)

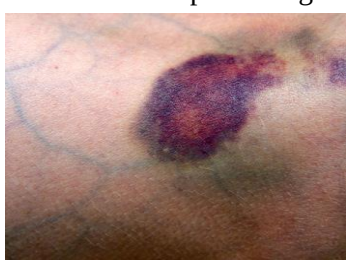
In the secondary form, the erythropoietin is high (hypoxia) and there's no splenomegaly.
Causes: (of secondary)
Adaptive (high altitudes, Cyanotic heart disease — congenital)
Alcoholism (Acidosis, hypoxia, sleep a lot)
Smoking
Paraneoplastic syndrome (production of more erythropoietin by renal or hepatic cancers)
Surreptitious polycythemia (means hidden) occurs in athletes who take hormones.

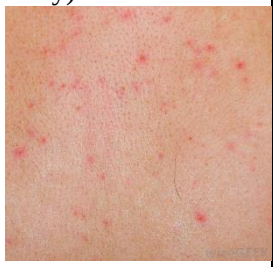


Bleeding Disorders

General Info

Pathologic bleeding occurs spontaneously or after trauma (prolonged bleeding)
Caused by defect in either: (all of these are needed to stop bleeding normally)
Clotting factors
Platelets
Blood vessels
Endothelium





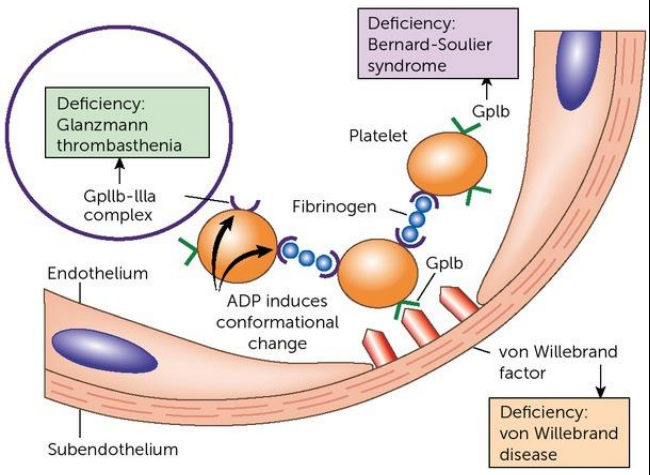
Blood vessels related bleeding:
Connective tissue diseases
Chronic steroid intake (weakens blood vessels, risk of rupture)
Systemic amyloidosis (amyloid protein can infiltrate through any organ causing damage)
Vasculitis infections (like spirochetes or fungus, causing rupture and bleeding)
Vitamin C deficiency (scurvy) (important for collagen in vessels. less common nowadays)
Patients will manifest spontaneous superficial bleeding in the skin and mucous membranes: Petechiae (small area) and ecchymosis (large bruise)

Platelets related bleeding:
Thrombocytopenia (ITP, AIDS) ITP= immune thrombocytopenic purpura (thrombocytopenia can occur in anemias: AA, PNH)
Thrombocytosis (platelets are large but dysfunctional. Common in myeloproliferative neoplasms)
Platelets function tests:
1) Bleeding time (obsolete: rarely used these days) we make a small superficial cut like in the ear and count time)
2) Platelet aggregation test
3) Von Willebrand factor test
The von Willebrand factor is essential for platelets function so we do both tests (2&3):
Ristocetin Agglutination test: Ristocetin (antibiotic) can cause artificial platelets aggregation by activating VWF to bind to glycoprotein Ib (on surface of platelets) causing platelets to clump, so if we add it and platelets do not aggregate, we know either VWF or the platelets are abnormal

Clotting factors related bleeding: (Coagulation disorders)
Inherited or more commonly acquired
Vitamin K deficiency: decreased synthesis of clotting factors related to vitamin K:
II (prothrombin), VII, IX, X *1972* (causes can be due to drugs more commonly -warfarin-,or dietary (rich in green leaves like spinach)
Liver disease (site of clotting factors synthesis)
DIC (Disseminated intravascular coagulation)
Warfarin, Autoantibodies (binds to single or multiple clotting factors, there will be no true deficiency but there will be less functionality)

Glanzmann Thrombasthenia

Platelets Related Bleeding



Asthenia = weakness
Rare autosomal recessive
Autoimmune Acquired
Deficiency/Blockage of platelets' fibrinogen receptors:
glycoproteins IIb-IIIa (CD41/CD61)
so fibrinogen cannot bind to platelets = Prolonged or spontaneous hemorrhage (gums, nose, bruising)
Diagnosis: Flow cytometry

Bernard Soulier Syndrome

Platelets Related Bleeding

Very rare, autosomal recessive.
Deficiency in platelets' VWF receptor: glycoprotein Ib (CD42b), which binds VWF.
Prolonged hemorrhage
Structural abnormalities: Platelets are large, can show thrombocytopenia
Diagnosis: Flow cytometry (check slides for diagram results from flow cytometry)

The VWF is located under the endothelial cells, it is exposed when the endothelium is damaged and removed (see diagram).

Heparin Induced Thrombocytopenia

Platelets Related Bleeding

Occurs in 5% of patients receiving unfractionated heparin (used as anticoagulant) where IgG antibody develops, against platelet factor 4 on platelet's cell membrane (in a heparin dependent matter) causing platelets aggregation = thrombosis
The patient has thrombocytopenia with thrombosis (like PNH)

Can also develop inn low-molecular weight heparin (fractionated) but less common

Immune Thrombocytopenic Purpura (ITP)

Platelets Related Bleeding

Purpura = skin bleeding. Immune system destroys platelets = thrombocytopenia
Patients have isolated thrombocytopenia (sometimes anemia of blood loss)
Most bleeding occurs in skin, mucosal surfaces (petechiae and ecchymosis), GI, urinary tract, CNS.

Acute ITP: affects children, commonly follows viral infection, self -limited
Chronic ITP: affects middle age adults (F>M)
IgG auto-antibodies against platelets membrane glycoprotein IIb/IIIa (chronic ITP)
Splenomegaly is not always present but patients benefit from splenectomy
Peripheral blood shows large platelets. Bone marrow shows increased number of megakaryocytes, spleen shows large aggregates of B cells and plasma cells

Thrombotic Microangiopathies

Platelets Related Bleeding

Microangiopathy: disease occurs in small blood vessels, slows down blood flow, bleeds
Two main diseases that cause this syndrome: Thrombotic Thrombocytopenic Purpura (TTP)
Hemolytic Uremic Syndrome (HUS)

TTP: we have thrombosis all over the body which results in thrombocytopenia because the platelets are consumed. Fever, microangiopathic hemolytic anemia, neurologic deficits and renal failure (5 symptoms, memorize)

HUS: similar symptoms as TTP but most dominantly is renal failure, no neurologic symptoms, common in children

In both diseases, the small circulation in the body is filled with platelets rich microthrombi, without activation of clotting factors (PT and PTT are normal, these are clotting factors)

Pathogenesis:
TTP: deficiency in ADAMTS13, a plasma protein required for VWF formation. It converts the precursor of VWF to the actual VWF. So, if this enzyme is absent we will only have the VWF precursor which is a very large multimer (short half-life), it is capable of binding so many platelets together forming aggregations = spontaneous thrombus

HUS: caused by EHEC (e. coli) infection in the gut that produces shiga-toxin, which reaches the kidneys causing endothelial damage and promotes thrombosis

Blood film in both diseases: schistocytes (direct physical damage of RBCs= Traumati) this damage is caused by passing through the thrombi, thrombocytopenia

Coagulation Disorders

Clotting Factors Related Bleeding

Diagnosis: How to test clotting factors:
Prothrombin time (PT): assesses extrinsic factors (V, VII) and common pathways (X, prothrombin or fibrinogen)
Partial thromboplastin time (PTT): assesses intrinsic factors (XII, XI, IX, VIII, V) and common pathways

In addition to the possible deficiencies mentioned above, an autoantibody (inhibitor) can interfere with the function of clotting factors.

Mixing study: adding an extrinsic normal serum to the patients serum and repeating the PT and PTT tests. If they are corrected, the patient has a true deficiency. If not corrected, the patient has an inhibitor antibody

Von Willebrand Disease

Clotting Factors + Platelets Related Bleeding

Most common clotting factors related bleeding, most common inherited bleeding disorder (1% of population). Autosomal dominant
Spontaneous bleeding from mucous membranes, wounds and menorrhagia (excessive menses). Remember VWF is important for platelets function

VWF circulates the plasma and carries factor VIII. VWF is synthesized inside the endothelium (Weibel-Palade bodies), also present beneath endothelium and inside platelets

After endothelial damage, the subendothelial VWF binds platelets through glycoprotein Ib, forming platelets plug

Diagnosis: Ristocetin agglutination test

In VWD (D-disease): there is a compound defect: non-functional platelets and deficiency in factor VIII (the deficiency occurs in severe cases)

Symptoms are mainly related to platelets defects, (meaning there will be superficial bleeding) except in homozygous state which is severe and causes VIII deficiency (resembles hemophilia A where bleeding occurs in body cavities not superficially, prolonged PTT)
Type1 VWD: Most common, decreased levels of serum VWF
Type IIA: absent high molecular weight multimers of VWF (precursor)
Type IIB: the high molecular weight multimers are present but have abnormal function (hyperfunctional with shorter half-life) which they consume platelets so Patients have mild chronic thrombocytopenia (same as TTB but TBB was more severe and widespread) but with no thrombi formation

Hemophilia A

Clotting Factors Related Bleeding

Or classic hemophilia
The second most common inherited bleeding disorder
X-linked inheritance. Can affect females (random inactivation of X normal chromosome)
70% are familial. 30% are sporadic with new mutations

Reduced factor VIII
Usually if there's mild deficiency, results in excessive bleeding AFTER trauma (esp in major surgery, or in circumcision of newborn males)
Severe life-threatening bleeding occurs if level drops <1% of normal level
10% have normal level but non-functioning factor

Characteristic: Bleeding tends to occur in deep tissues with mechanical stress (Muscles, joints, body cavities.. not superficially). As a growing child, repetitive bleeding will develop deformity in joints. Skin petechiae is absent.
Prolonged PTT (VIII def), corrected by mixing study
Specific assay test is available

Hemophilia B

Clotting Factors Related Bleeding

or Christmas disease
Deficiency in factor IX. X linked
Much less common than Hemophilia A
Clinically similar to Hemophilia A
If mild deficiency, bleeding occurs after trauma. If severely deficient, life-threatening bleeding may occur (like hemophilia A)
Prolonged PTT, corrected by mixing study
Factor assay test is available (to differentiate from Hemophilia A)

Disseminated Intravascular Coagulation

Endothelial Related Bleeding

Endothelial related bleeding.
Normally when forming a clot, there's an equilibrium between the formationof the new clot and the lysis of this clot (fibrinolysis is needed to stop the clot from getting too big and to get rid of it when the time is right)

Pathogenesis:
In DIC, there's an unbalance between the two mechanisms, so we have a favor in formation of new clots. This occurs secondary to sepsis, malignancy, trauma, obstetric complications (pregnancy complications), or intravascular hemolysis all which release a procoagulant/prothrombic agent (like tissue factors, LPS from bacteria, or enzymes) causing widespread endothelial damage and DIC. Rapid consumption of clotting factors (prolonged PTT, PT) and platelets, exceeding replacement process. So we have disseminated clots which will cause thrombocytopenia so in the other end, we have bleeding, the patients develop life-threatening bleeding.
Peripheral blood shows schistocytes, anemia and thrombocytopenia

Causes of DIC:
Endothelial damage: septicemia, viremia, snake venom, complicated labour (placenta produces tissue factor which forms thrombi. So, the tissue factor not only comes from the endothelium), advanced cancer (leukemia or epithelial cancers containing mucin), severe trauma, severe inflammation (acute pancreatitis)

WBC Disorders

General Info

-Deficiency of WBC = leukopenia
-Increased WBC in peripheral blood = leukocytosis
-Benign leukocytosis is called Reactive leukocytosis
-Leukemia: increased WBC in peripheral blood secondary to neoplasm
-Leukocytosis is much more common than leukopenia
-Reactive leukocytosis is more common than leukemia

Neutropenia (Agranulocytosis)

Agranulocytosis = absence of granulocytes production, most common cell is the neutrophil.
Patients become susceptible to infections (mainly bacteria and fungi)
If neutrophil count drops below 500 cells per microlitre = susceptibility to infections even by the normal flora (severe form)

Causes:
Decreased production: Aplastic Anemia, Myelophthisic anemia, Myelodysplastic syndrome, PNH, advanced megaloblastic anemia, chemotherapy (BM suppression), drugs (anti-epileptic, anti-hyperthyroidism)
Increased destruction: Immune mediated, Splenomegaly, overwhelming infections (bacterial, fungal, rickettsial)

Reactive Leukocytosis

Very common. Most people have developed it at some point in life.
Most common occurs in Neutrophils:
Neutrophilia: Due to infections (liquefactive necrosis) or inflammation (coagulative necrosis due to ischemia).
Necrosis always causes inflammation.

Lymphocytosis: common in viral infections, Bordetella pertussis (bacteria), chronic infections (TB, Brucellosis)
Monocytosis: Acute and Chronic infections (more predominant in chronic), rheumatologic diseases and inflammatory bowel disease (IBD)
Eosinophilia: Asthma, Allergic diseases, Drug sensitivity, Parasitic infections, some tumors like Hodgkin Lymphoma
Basophilia: Rare, seen in myeloproliferative neoplasms

Reactive Lymphadenitis

Reactive = Benign. Lymphadenitis = Lymph node inflammation.
Antigen in lymph nodes stimulates the proliferation of the lymphocytes causing the enlargement of lymph node (lymphadenopathy). Can be localized or generalized.

Acute Non-Specific Lymphadenitis

Very common. Inflammation secondary to bacteria and virus
Swollen, rapidly enlarged lymph nodes that stretch nerves causing painfulness
Overlying skin is red and may develop a sinus tract (pus can be formed)
The germinal centres are enlarged and infiltrated by neutrophils. With severe infection, liquefactive necrosis develops and may enlarge to form an abscess

Chronic Non-Specific Lymphadenitis

Chronic enlargement of lymph nodes, painless
Follicular Hyperplasia: Chronic proliferation of B cells, seen in rheumatologic diseases, toxoplasmosis, HIV. Benign. We see numerous follicles.
Paracortical Hyperplasia: T cells proliferation seen in viral infections (like in EBV), post vaccination or as a drug reaction. We see a diffuse solid area and less/smaller follicles
Sinus Histiocytes: Proliferation of macrophages in lymph node sinuses, seen in adjacent cancer *Histiocytes = macrophages* Least common one.

Cat-Scratch Disease

Bartonella infection. Transmitted from cats (bites, scratch, infected saliva)
Most common in children. Causes acute lymphadenitis in neck/axilla area
Symptoms appear after two weeks of infection
Bacteria causes liquefactive necrosis and necrotizing granulomas in LN
Mostly self -limited in 2-4mo, rarely disseminates to visceral organs

Hemophagocytic Lymphohistiocytosis (HLH)

Rare disease, critical, Fatal if not diagnosed or treated properly
Commonly follows a viral infection or sometimes associated with inflammatory diseases.
These agents activate macrophages (histiocytes) throughout the body to engulf normal blood cells and their precursors in bone marrow

Gene: defective genes related to the function of CD8 T cells and NK cells. Which makes these cells too engaged with their target cells (viral infected) for a long period of time which releases excess interferon gamma that activates macrophages

Activated macrophages release TNF and IL-6 that causes systemic symptoms of inflammations (systemic inflammatory response syndrome SIRS) = very severe symptoms of inflammation

HLH types:
1) Infants and young children:
Homozygous defects in PRF1 gene that encodes perfortin, an essential enzyme in cytotoxic T cells and NK cells

2) Adolescents and Adults:
Associated with X-linked lymphoproliferative disorder (more commonly in males):
Defective SLAM- associated protein *SLAM= Signalling lymphocyte activation molecule*
Increased susceptibility to EBV, T cells are unable to kill B cells that are infected with EBV, which ends up activating macrophages. no life-long immunity

3) may be associated with systemic inflammatory disorders (like rheumatologic diseases)
Patients have heterozygous genetic defects in essential genes for CD8 cells

4) T-cell lymphomas
Malignant neoplasms produce abnormal cytokines which dysregulates (function defective) the normal cytotoxic T cells

Symptoms:
Severe systemic inflammation (fever)
Splenomegaly (filled with macrophages)
Pancytopenia (macrophages engulf RBCs, platelets, granulocytes inside BM)
High ferritn (severe inflammation)
High triglyceridemia (increases in acute phase reactants)
High level of IL-2
Low level of blood CD8 and NK cells

WBC Neoplasms

General Info

Mostly considered as malignant (cancers), they are fluid tumors (no masses formed)
Varies in biologic behavior, from indolent to very aggressive cancers
In general, hematolymphoid cancers are common in adults, and in pediatrics they are (#1)
Our current classification system is by WHO for Hematolymphoid neoplasms
Classified according to lineage (myeloid or lymphoid (B or T)) etc., based on morphology, protein and molecular tests

Lymphoma

Cancer

Cancer of lymphoid lineage cells.
Always malignant. If affects bone marrow or peripheral blood → called lymphoid leukemia.
If affects lymph nodes or solid organs → called lymphoma (most common)
Classified into Hodgkin or non-Hodgkin lymphoma
Non-Hodgkin lymphomas are classified into B and T cell lymphomas (B cells are more common as they involve immunoglobulins genes, which is a more dynamic genetic system)

Malignancy can be of low grade (indolent) which persists for a long time and causes damage or high grade (aggressive) which is fatal if not treated

Immunodeficiency (HIV, Transplant patients) is a risk factor for lymphoma and Lymphoma is a risk for immunodeficiency

Diagnosis: Biopsy:
1) Morphologic assessment of tissue
2) Immunophenotype (B or T cell) done by immunohistochemistry or flow cytometry
The flow cytometry deals with fluids (from bone marrow or peripheral blood)
Further tests for mutations can be done for further classification

Immunophenotypes tests:
CD45 (common leukocyte antigen): present on cell membrane of all WBC
B cells express CD19, CD20, CD22
T cells express CD2, CD3, CD5, CD7
Germinal center lymphocytes express CD10 and BCL6 (B cells in follicle germinal center)
Plasma cells express CD138
T helper lymphocytes express CD4
Cytotoxic lymphocytes express CD8
Blasts express CD34 (most immature cells. For both myeloblast and lymphoblast)
Lymphoblasts express TDT (terminal deoxynucleotidyl transferase) and CD10

Hodgkin Lymphoma (HL)

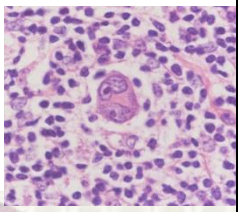
Hodgkin Lymphomas (HL) – (Cancer)

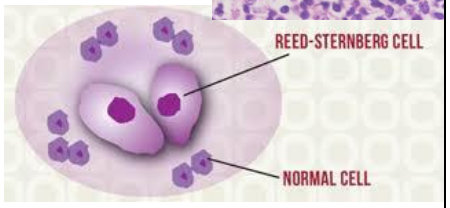
30-40% of all lymphomas. Most common lymphoma in Jordan, in children and young adults
Subtypes are similar to each other (unlike non-Hodgkin lymphomas which vary)

Morphology:
The neoplastic cells are giants (remember lymphocytes are usually the smallest nucleated cells in the body), different in morphology and immunophenotype, number of neoplastic cells are vey low (<10% of tumor mass) very low and dispersed. What makes up the tumor volume are the normal inflammatory cells.
Bimodal age distribution (first peak in children, then in old age groups)
B-symptoms: fever, night sweats, and weight loss

Reed-Sternberg Cells: Bi or Multi-nucleated giant cell with prominent nucleoli and abundant neoplasm (RS cells), eosinophilic in color compared to normal basophilic lymphocytes
Hodgkin cells: similar to RS but are Mononuclear giant cells. Both cell types can be seen
Both express CD30 and CD15 and negative for CD20, CD3 and CD45

Site: Arises primarily in a localized area of lymph nodes (neck, axilla, mediastinum), then spreads to adjacent lymph nodes. Mesenteric and Waldeyer ring are rarely involved
In this cancer, the sites are thankfully, very predictable.

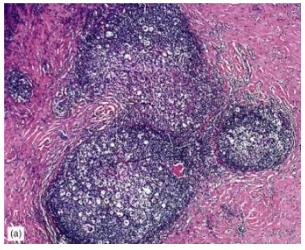


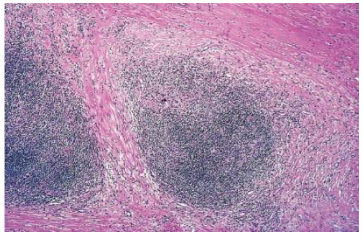


Classification:
-Classic Hodgkin Lymphoma: (95%) from most common to least
1) Nodular sclerosis
2) Mixed cellularity
(Bulk of the tumor formed by all WBCs in the background)
3) Lymphocyte-rich
4) Lymphocyte-depleted
-Non-classic Hodgkin: (5%)
5) Nodular lymphocyte-predominant (Nodular LP)

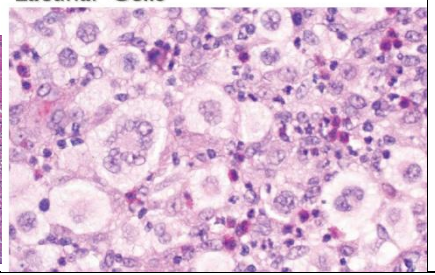
1) Nodular Sclerosis HL

Most common. Lymph nodes become nodular with dense sclerosis/fibrosis (pink) separating nodules (blue). Common in children and young adults
RS cells show clear cytoplasm as an artifcat = lacunar cells
10% EBV positive

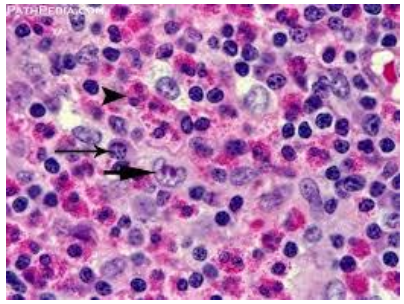




Lacunar Cells



2) Mixed Cellularity HL



Common in old people, no fibrous bands, just diffuse area in the lymph node, numerous RS cells, strongly associated to EBV (90% EBV positive)
Background: mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes

Notice all the mixed cells around, while the number of RS or Hodgkin cells are less

5) Lymphocyte-Predominant (non-classic HL)

Or nodular lymphocyte predominant.
Malignant cells are called lymphohistiocytes (L&H – old naming), variant RS or Lymphocyte-predominant (LP cells – newer name).
They resemble popcorns (popcorn cells)
Giant cell with multilobulated vesicular nuclear lobes and small blue nucleoli (opposite to RS cells which were multinucleated (not lobulated) and had large nucleoli)
Express normal B cell markers (CD45, CD20), negative for (CD15, CD30) whivh were the classic HL markers
Background of lymphocytes only. Arranged in nodules without the fibrous septa
Excellent prognosis (better than the classic)

Pathogenesis: (of HL)
Originate from germinal center B-cells, frequent association with EBV
RS cells secrete IL5 which attracts eosinophils into the tissue. In severe cases eosinophilia in the whole body.
RS cells also secrete IL13 and transforming growth factor beta (TGF-B) which activates themselves and other RS cells (autocrine)
RS cells express programmed death (PD) ligands on their cell membranes which binds to T cells, antagonizing them and inducing apoptosis, escaping immune surveillance
Prognosis is generally good

Treatment: Right now, a therapy is used where antibodies against PD are made which binds to it so lymphocytes can bind to RS cells and destroy them

Diffuse Large B-Cell Lymphoma (DLBCL)

Non-Hodgkin Lymphomas (NHL) – (Cancer)

Cancer of B cells
Most common (NHL). Their subtypes are very diverse and different. Remember, they are Mainly divided to B and T lymphomas with B as the most common one.
Predominantly in adults and old age
High grade (rapidly growing mass) remember they are diffuse and large, they are fatal

Site: Most common extra-nodal lymphoma (non-cutaneous. The skin usually has its own lymphomas). Most commonly appears in the GI (unlike HL)
Gene: Heterogenous (different mutational pathways):

1) 2/3 of cases have a mutation in B-cell lymphoma 6 promotor gene (Bcl6), which is an important regulator of gene expression for B cells proliferation in germinal centers

2) 30% of cases we have translocation between chromosomes 14 and 18.
Chromosome 14 contains the IgH immunoglobulin which is very active in B cells.
Chromosome 18 contains Bcl2 gene which fuses with chromosome 14.
So now with every IgH expression we have Bcl2 coming along, resulting in over expression pf Bcl2 (antiapoptotic protein)

3) Few cases have mutations in MYC gene (activates cell cycle)

Morphology:
Tissue architecture effacement (gone), no follicles or sinuses seen, cells are large and diffuse (3x larger than normal lymphocytes), irregular nuclei, small prominent nucleoli, a lot of mitosis and apoptosis, positive for CD20

DLBCL Subtypes:
Most cases develop de novo (from the start), a few arise as a complication from previous low-grade B cell lymphoma (secondary)
Primary mediastinal large B cell lymphoma: arises from thymic B cells, most patients are middle aged women, spreads to CNS and visceral organs (has special mutations)
EBV-associated DLBCL: Arise in immune suppressed patients and in elderly, begin as polyclonal B cell proliferation (as an infection then more mutations will be added) bad prognosis
Human Herpes virus 8: Rare but causes DLCBL in pleural cavity, encodes cyclin D1 mimicker protein, seen in immune suppressed patients. (the same virus causes Kaposi sarcoma)

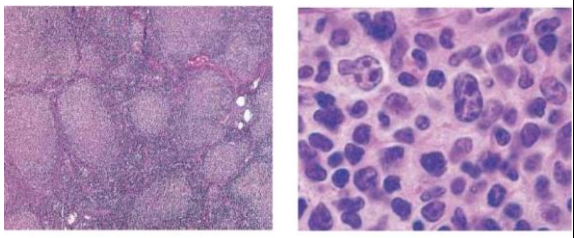
Follicular Lymphoma

Non-Hodgkin Lymphomas (NHL) – (Cancer)

Cancer of B cells
Second most common NHL. Common in the west. Mainly affects >50yrs old. M > F
Lymphomas usually affect men more than females. Except in mediastinal DLBCL.
Patients usually present with generalized lymphadenopathy in most of the body
Commonly disseminates to BM, liver and spleen (80%)
It is a low-grade lymphoma although it disseminates (it takes time till they destroy something)

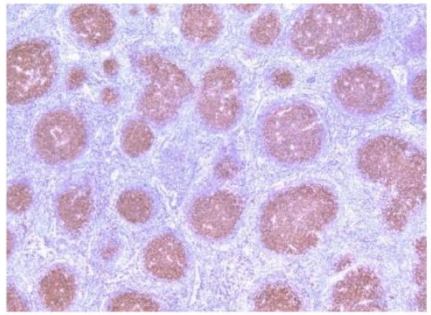
Gene: t(14;18) (Bcl2 → IgH) = prolonged survival of lymphoma cells
Just like DLCBL but here we have this mutation in all cases
1/3 of patients have an additional epigenetic mutation (not in the nucleotides) in genes encoding histone-modifying proteins (epigenetic change)

Morphology:
The normal architecture of lymph node is effaced by nodular proliferation (follicles)
The follicles are composed of 2 cell populations:
1) small, dark (mature), irregular shaped, called centrocyte (previously called cleaved lymphocytes)
2) large lymphocytes, they have vesicular nuclei and small nucleoli (centroblasts) immature



- Morphology of FL, left: nodular (follicular growth of neoplastic cells effacing the entire lymph node architecture. Right: most cells in this field are centrocytes, appear as small fark cells with cleaved nuclei. There are few large cells with multiple nucleoli, corresponding to centroblasts

Centroblasts are more proliferative than centrocytes
In most cases, the centrocytes predominate (low-grade). But with time, centroblasts increase (high-grade) so they become similar to DLBCL
Cells express CD20, Bcl2, Bcl6. (the presence of Bcl2 determines the malignancy and that the follicular hyperplasia is not reactive)



- Bcl2 immunohistochemical stain is positive in follicles in follicular lymphoma

Prognosis:
Indolent course (low-grade)
Overall median survival is 10yrs
40% develop transformation to DLBCL (worse than de novo DLBCL). = very bad prognosis
Treatment: Conventional chemotherapy is ineffective (they are slowly proliferating, as the mitosis is low). Chemotherapy is given when the disease accelerates to high-grade, to symptomatic patients, with bulky tumors and transformation
Cytotoxic chemotherapy, anti-CD20, Anti-Bcl2 are given

Burkitt Lymphoma (BL)

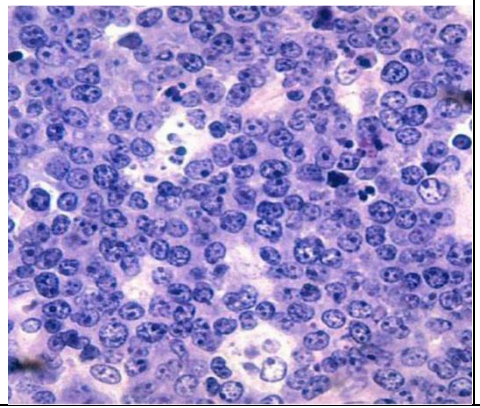
Non-Hodgkin Lymphomas (NHL) – (Cancer)

Cancer of B cells of germinal centre
Most common NHL in children
Three types:
1) Endemic in parts of Africa (100% EBV)
2) Sporadic in the rest of the world (20% EBV)
3) Immunodeficiency associated BL

Site: It's an extranodal lymphoma:
Occurs in the Jaw, causing disfigurement in the face (in endemic type)
Terminal ileum, retroperitoneum, ovary, CNS (sporadic + immunodeficiency type)
Sometimes leukemic

Gene/Pathogenesis:
t(8;14) MYC → IgH.
Overexpression of MYC transcription factor each time IgH is expressed in B cells, it is a potent regulator of Warburg metabolism (alternative to aerobic glycolysis) (cancer cells need energy)
Neoplastic lymphocytes are B cells of germinal center origin (CD20, bcl6)
Aggressive, but responsive to chemotherapy

Morphology:
Intermediate size cells (different than other NHL which are usually small or large cells)
Monomorphic (cells are similar to each other)
Round or oval, multiple small nucleoli
Lipid vacuoles in cytoplasm
Very high mitosis (BL is the fastest growing human cancer), and many apoptosis so macrophages come and clean: tangible body macrophages (appear pale with dark debris ingested) engulfing nuclear debris
Neoplastic lymphocytes are monotonous and uniform, multiple small nucleoli, brisk mitosis
The tissue gives starry sky appearance due to the pale macrophages immersed in dark area



Extranodal Marginal Zone Lymphoma

Non-Hodgkin Lymphomas (NHL) – (Cancer)

Indolent (slow growing) B-cell lymphoma, cells are more mature since they are marginal zone cells, which is located after the germinal center
Second most common lymphoma in extranodal sites in adults (DLBCL is first)
Arises in setting of chronic inflammation
Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjorgen)
Can complicate Helicobacter Pylori chronic gastritis
Infiltrate the epithelium and causes destruction

Mantle Cell Lymphoma

Non-Hodgkin Lymphomas (NHL) – (Cancer)

Rare NHL, arises from naïve B cells in mantle zone
Moe common in older men

Gene/Pathogenesis:
t(11;14) that fuses cyclin D1 gene to IgH locus
Overexpression of cyclin D, promotes progression of cell cycle
Site: Affects lymph nodes, Waldeyer ring
Commonly affects BM, or blood in 20%, or GI (appears as submucosal multiple nodules) → called lymphomatoid polyposis

Morphology:
Small centrocytes (cleaved cells like follicular lymphoma)
But they don't form follicles, they are diffuse
They are negative for CD10 and Bcl6 (because they are not of follicle origin)

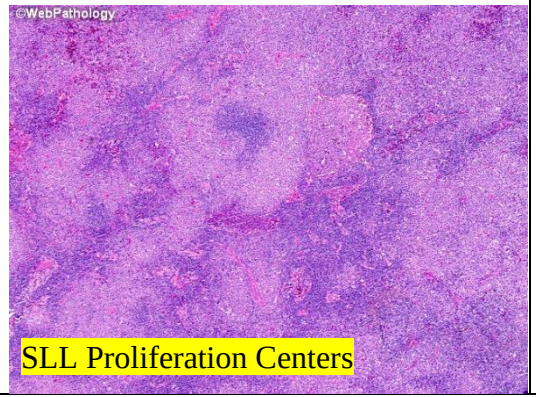
Small Lymphocytic Lymphoma (SLL) OR Chronic Lymphocytic Leukemia (CLL)

Non-Hodgkin Lymphomas (NHL) – (Cancer)

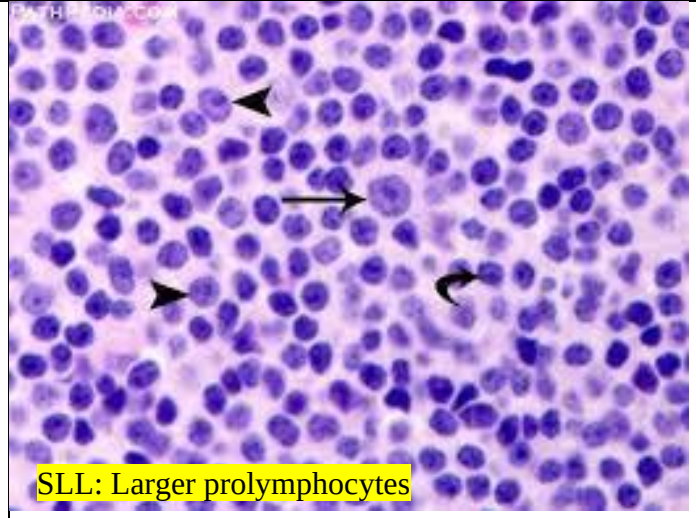
Called lymphocytic because they are mature cells. B cells have a prolonged life.
A single disease but with two faces.
If occurs in LN and solid tissue → SLL (only 4% of NHL)
If occurs in BM and peripheral blood → CLL (most common leukemia in adults)
Low grade B cell neoplasm, affects elderly
Not common in Asia. Common in western countries

Pathogenesis:
Chromosomal translocation is rare (exception to B cell lymphomas)
Pathway1: Increased Bcl2 production, due to deletion mutation in the genes that counteract Bcl2 (genes encoding micro-RNAs), so Bcl2 becomes more predominant. Bcl2 inhibits apoptosis = prolonged cell life
Pathway2: mutated immunoglobulin (BCR), it becomes autonomously activated which activates another protein: Bruton Tyrosine kinase (BTK) which activates genes that promote cell survival
Lymphoma cells express CD20, Bcl2 and CD5 (T cell marker)
When both CD 19 and CD5 are coexpressed = CLL
But if only CD5 = just a normal T cell
If only CD19 = normal B cell

Morphology: (of SLL)
It is diffuse, causes effacement of the LN architecture (no follicles)
Most of neoplastic cells are small in size, round
Slightly pale areas can be seen called Proliferation Centres : they are focal areas containing prolymphocytes and high mitosis. (it appears pale because mitotic cells are slightly larger)
Two populations of cells:
The lymphocytes: small, round, dark cells
The prolymphocyte: Large cells, prominent nucleoli
The lymphocytes are dominant in early disease but some patients with advanced progression have the prolymphocytes dominant

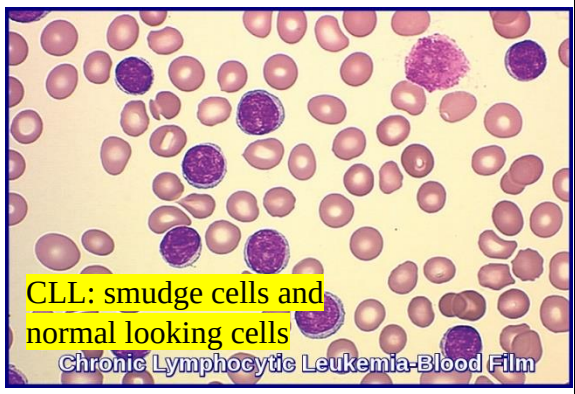


SLL Proliferation Centers


SLL: Larger prolymphocytes

Morphology: of (CLL)
Leukemic cells appear similar to lymphocytes but in large numbers
Prolymphocytes seen occasionally
Smudge cells are seen (dead broken lymphocytes)

Clinical features:
Many patients are asymptomatic
Leukocytosis can reach very high levels (>200,000)
50% have generalized lymphadenopathy and hepatosplenomegaly
Common to cause immune dysfunction by suppressing normal B cells, resulting in hypogammaglobulinemia (in 50% of patients)
Anemia: 15% of patients develop autoantibodies against RBCs and platelets (Cold type), secreted by normal B cells
Platelets attacked (Similar to ITP)
Variable outcome: some patients have normal survival while others have a bad prognosis (P53 mutation)
Richter transformation: in 10% of patients the diseases becomes accelerated, predominance of large cells. We only see the large cells, not a mixture (prolymphocytes), patients survive <1year)



CLL: smudge cells and normal looking cells

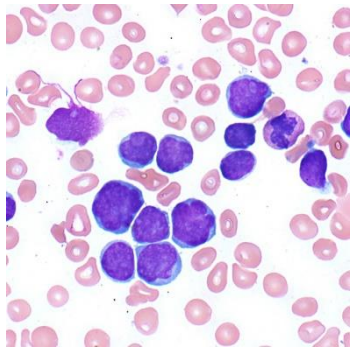
Precursor B and T cell neoplasms

Precursor = immature (blasts). Neoplastic cells are lymphoblasts, the most immature lymphoid cells, so they are aggressive. They express CD34, TDT
Lymphoblastic lymphoma: when occurs in solid tissues
Acute lymphoblastic leukemia: when occurs in bone marrow and peripheral blood (B>T)

B-ALL is the most common childhood malignancy
B-ALL commonly disseminates to solid organs (brain, testis, spleen) because T cells normally circulate the body, so the neoplasm mimics this behavior.
T-ALL is less common, presents in adolescents, more common in boys, arises in thymus

Pathogenesis:
Mutations in transcription factors for genes responsible for maturation of blasts (blast maturation is blocked) Additional mutations: in RAS signaling and tyrosine kinase proteins promoting cell survival
Genes:
In B-LL, mutation in PAX5 gene
Most childhood B-ALL have hyperdiploidy (>50 chromosomes) and t(12;21), involving ETV6 and RUNX1 genes, creating new transcription factors for cell proliferation
Adult B-ALL exhibits t(9;22) between ABL and BCR genes, similar to chronic myeloid leukemia, creating a new functional tyrosine kinase protein that promotes proliferation.
There is an antibody drug that can target TK (imatinib).
Imatinib is used in adult B-ALL and CML
In T-LL: 70% have mutations in NOTCH1 gene
T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

Morphology:
- Blasts are large, very high N/C ratio
- High in number
- Nucleus appears lighter than in mature cells
- Chromatin is open (pale)
- Nucleolus sometimes present
- Cytoplasm is not granular (opposite to myeloblasts)
- CD22,19 (B cell markers), TdT/CD34 (immature), CD10 (immature)



Clinical features:
Commonly: Anemia, thrombocytopenia secondary to bone marrow destruction
Damage to solid organs secondary to leukemic infiltration
- **Favorable prognostic factors in B-ALL**: hyperdiploidy, low WBC count, age between 2-10 years
- **Poor prognostic factors in B-ALL**: age < 2 years or age in adolescents or adults or if WBC count >100k

Flow cytometry reveals the type of cell and CD markers (view slides)

Plasma Cell Myeloma (Multiple Myeloma)

Cancer of plasma cells
Multiple myeloma =meaning it causes bone disease in multiple sites in the body
Common neoplasm, commonly in elderly, more common in men, African origin
Malignant plasma cells secrete monoclonal protein (M protein) meaning it's the same immunoglobulin because it comes from a malignant cell (normally it is polyclonal)
Most commonly: IgG (60%), then IgA (20-25%), followed by other types.
Sometimes only light chain (kappa or lambda),
can be detected in urine (Bence Jones proteins)

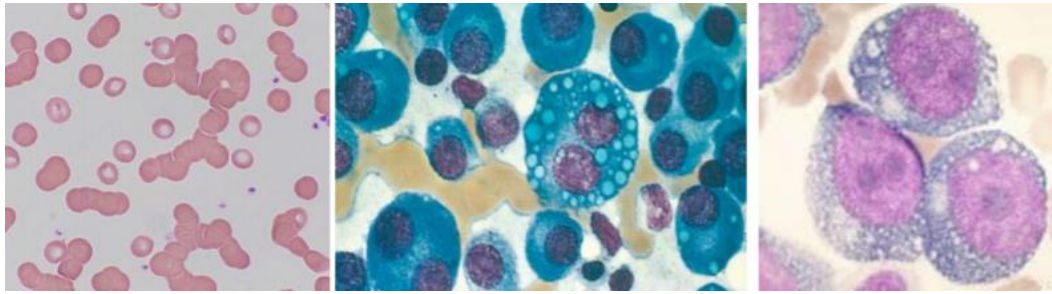
Pathogenesis:
- t(11;14) IgH-cyclinD1 and sometimes cyclinD3 (similar to Mantle cell lymphoma)

MYC gene mutation occurs late in disease (similar to BL)
- IL-6 is important is plasma cell survival, secreted from BM macrophages and fibroblasts
- Malignant plasma cells activate expression of receptor activator of NF-kB ligand (RANKL), that activates osteoclasts, causing bone resorption/erosion = bone pain

Other products inhibit osteoblast function (hypercalcemia meaning that Ca exits the bone matrix causing pathologic fracture) hypercalcemia affects brain and heart function + kidney stones
- Suppression of normal B-cell function
- Directly inhibits erythropoiesis (early onset anemia. very common.
- Renal failure: obstruction to distal collecting tubules by proteinaceous cast (Bence Jones protein, immunoglobulin, albumin).

Hypercalcemia produces kidney stones, causing further obstruction and renal infection (especially due to B-cell suppression)

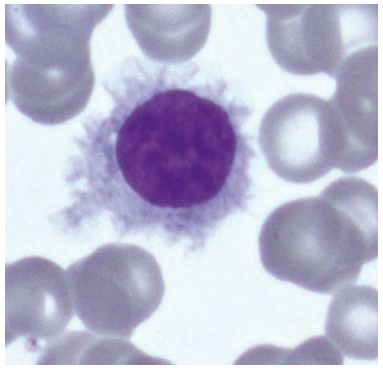
Morphology:
Peripheral blood: RBCs show rouleaux formation
Bone Marrow: increased number of plasma cells (>10% of bone marrow cells). Plasma cells stay in bone marrow, they rarely go to peripheral blood
Morphologically might resemble normal plasma cells, or
become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles filled with Ig, we can't see the cartwheel characteristic nucleus anymore. Instead we see nucleoli)



Clinical features:
C: hypercalcemia (Neuronal and cardiac symptoms, arrythmia)
R: renal failure
A: anemia (direct, early onset, normochromic normocytic)
B: bone fracture (bone lytic lesions, especially in skull)
-Very high ESR (erythrocytes sedimentation rate) due to the heavy rouleux
-Amyloidosis: occurs in few patients, secondary to deposition of light chain (lambda and kappa) called AL-amyloid, only seen in multiple myeloma. L stands for light chain
-In advanced disease: pancytopenia, plasma cell leukemia,
visceral damage

Treatment:
-Slowly growing, so its not curable with conventional chemotherapy, we use immunomodulators that change the cell biology instead.
-Lenalidomide: inhibits oncogenic proteins
-Proteasome inhibitors: inhibit degradation of misfolded proteins.
When misfolded proteins accumulate, apoptosis in plasma cells will occur

Hairy Cell Leukemia (HCL)



Uncommon low-grade B-cell leukemia
Affects older patients, more common in men, smokers.
Very indolent and sensitive to chemotherapy

Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis, similar to aplastic anemia where the bone marrow is empty

Site: Bone marrow and spleen (not LN). LN involvement is very rare
Gene: Mutation in serine/threonine kinase (BRAF gene)

Morphology:
Leukemic cells are few in number
have prominent cytoplasmic projections
Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen)

Peripheral T-Cell Lymphoma

Most common MATURE T-cell lymphoma (negative for TdT)
Aggressive, poor prognosis. T cell lymphomas in general are more aggressive than B
Neoplastic cells secrete inflammatory cytokines, causing severe inflammation
Patients are severely ill due to the severe inflammation that occurs even if the tumor volume was low.

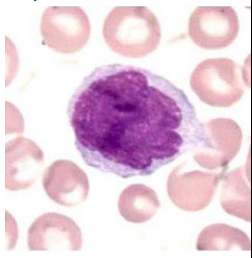
Site: in lymph node or extranodal
Positive for CD2, CD3, CD5, CD7

Mycosis Fungoides & Sezary Syndrome

Cutaneous cancer of CD4+ T-cells, that home to skin
Patients present with long history of erythema, progressive to plaque (thick area of skin) then tumor. Neoplastic lymphocytes have irregular nuclear membrane (cerebriform)

Site: Affects epidermis and dermis (most commonly the junction in between).
With disease progression, lymphoma disseminates to LNs and viscera (fatal)

Sezary syndrome: a variant of MF, patients present initially with widespread erythema over the entire body and we can see leukemia in the blood (Sezary cells, same as the skin ones)



Adult T-Cell Leukemia/Lymphoma

Neoplastic CD4+ T-lymphocyte
Caused by a retrovirus; human T-cell leukemia virus 1 (HTLV-1)
Endemic in Japan, Caribbean basin, West Africa and some parts of South America
Sporadic everywhere
Virus is transmitted through body fluids (blood, breastfeeding, sexual intercourse)
5% of carrier develop neoplasm, after a latent period of 40-60 years

Pathogenesis:
Tax protein is essential for viral mRNA transcription, also interacts with PI3 kinase and cyclin D, represses expression of CDK inhibitors, and activates NF- kB,
All promote cell survival. Tax also causes genomic instability, inhibiting DNA-repair

Clinical features:
Patients present with skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly and hypercalcemia, Poor prognosis
Neoplastic cells express CD25 (IL-2 receptor)

Myeloid Neoplasms

General Info

Cancer of hematopoietic progenitor stem cells
Neoplastic cells proliferate and efface normal hematopoietic cells
Divided into:
1.Acute myeloid leukemia (AML): impaired maturation, increased proliferation (myeloblast)
2.Myelodysplastic syndrome (MDS): abnormal maturation, normal proliferation
3.Myeloproliferative neoplasms (MPN): normal maturation, increased proliferation
MPN and MDS can transform to AML
BM is abnormally hypercellular looking in all myeloid neoplasms
Clonal hematopoiesis of indeterminant prognosis (CHIP): the fluid neoplasm version of 'carcinoma in situ'. represents a first precursor for AML and MDS neoplasm, patient has normal cell count despite the presence of a clone with a Mutation

Acute Myeloid Leukemia (AML)

Myeloid Neoplasms (1)

One of the worst human neoplasms, occur at all age groups, but more common in elderly
Heterogenous disease, we have many types, diagnosis is made by morphologic, immunophenotypic and karyotype studies (mutations)
Prognosis depends most importantly on type of mutations (molecular and cytogenetic studies (karyotypic)

Clinical features:
Symptoms are accelerated, become significant within few weeks, = death if not treated
Symptoms are related to anemia, thrombocytopenia and neutropenia
Meaning they will have severe infections and significant bleeding
Involvement of LN, spleen and solid organs is rare. When occurs, it is called myeloid sarcoma (acute monoblastic leukemia), remember the involvement of solid organs was common in acute B lymphoblastic leukemia

Gene: Mutations in genes of transcription factors required for maturation and differentiation of myeloblasts
Additional mutations in tyrosine kinase pathways (RAS) → prolonged survival
Epigenetic mutation is common (20%); mutation in isocitrate dehydrogenase (IDH) produces an abnormal oncometabolite that blocks enzyme of epigenome and interferes with myeloblast differentiation.

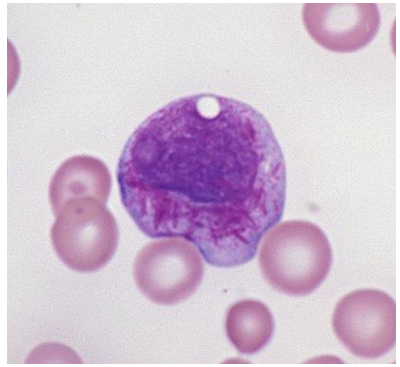
WHO-classification
-First, check if there's a history of chemotherapy or radiotherapy → Therapy related AML
-If not, we test cytogenetic mutations → AML with recurrent cytogenetic mutation, depending on the present mutation, the disease is named
-If not, we check for the presence of abnormal cell shapes (myelodysplasia) → AML with myelodysplasia: occurs de novo or complicates MDS
-Otherwise, classified as AML-not otherwise specified (AML-NOS)

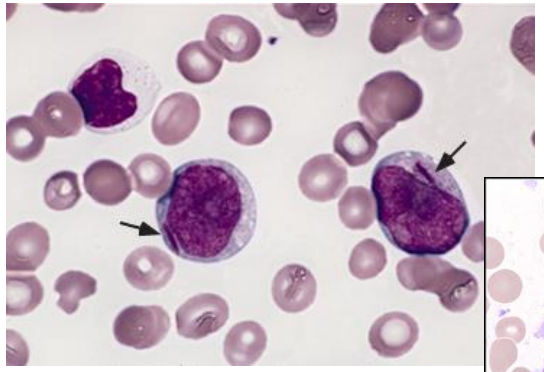
Diagnosis: of all types of AML:
We have to have 20% blasts in peripheral blood or bone marrow (of nucleated cells)

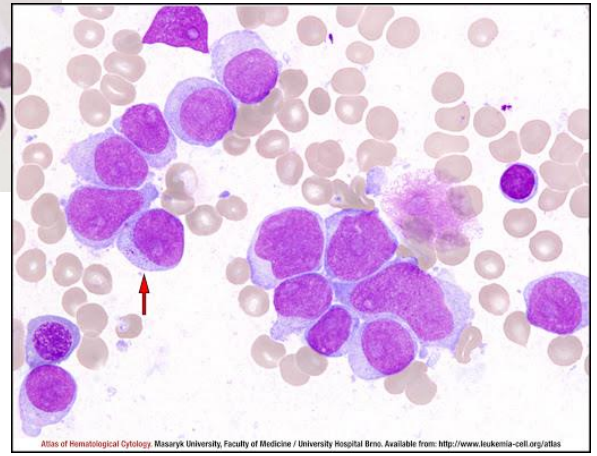
Morphology: large cells, high N/C ration, fine chromatin (pale, inactive), prominent nucleoli
cytoplasm more prominent than in lymphocytes
Fine granules in cytoplasm (not seen in lymphocytes),
Auer rods: (rare) small pink rods present in cytoplasm, represent peroxidase enzyme accumulation
Myeloblasts express CD34, (similar to lymphoblasts but lack TdT and CD10), myeloperoxidase (MPO), CD13, CD33
Sometimes: monoblast, erythroblast, megakaryoblast

Prognosis:
Generally poor, <30% responds to chemotherapy
High recurrence rate
Worse than ALL
P53 mutation: worse outcome

IDH inhibitors are new promising drugs







Acute Promyelocytic Leukemia

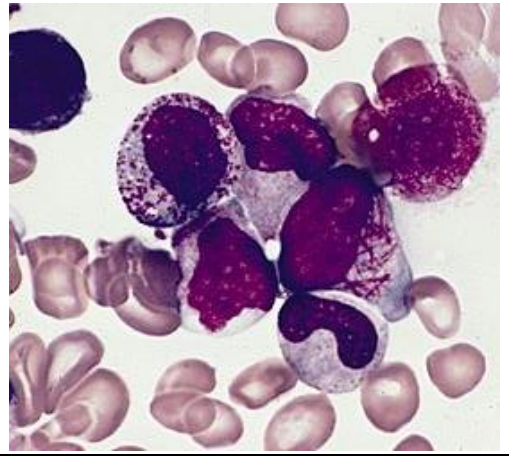
Subtype of AML (Myeloid Neoplasms)

Also called AML-M3
Maturation is arrested at promyelocyte stage by blocking the action of retinoic acid
(Vitamin A analogue)

Morphology:
Leukemic cells appear similar to promyelocytes (heavy cytoplasmic granules, numerous Auer rods
(negative for CD34)
malignant promyelocytes show numerous cytoplasmic granules and Auer rods.
The nuclei are commonly cleaved (figure of 8)

Gene: Carry recurrent mutation: t(15;17) fusion between PML gene (chrom 15) with alpha retinoic acid receptor (RARA) on chromosome 17. This himeric fusion gene produces a
protein that blocks promyelocyte maturation by inhibiting the action of retinoic acid.
Treatment: All trans-retinoic acid (ATRA), a vitamin A analogue, overcomes this block. Effect is synergistic with arsenic trioxide (degrades oncoprotein) treats 80% of cases
It does so by making the neutrophils have a short life-span

Malignant promyelocyte secrete tissue factor, causing DIC. It has a high tendency for DIC as this tissue factor activates both intrinsic and extrinsic pathways, forming disseminated coagulation = enough cause of death

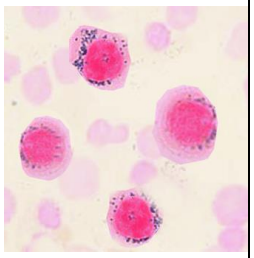


Myelodysplastic Syndrome (MDS)

Myeloid Neoplasms (2)

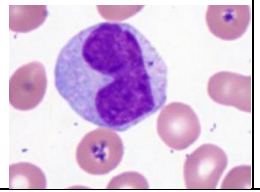
Main feature is defective maturation, ineffective hematopoiesis, the cells die in the BM,
high risk for transformation to AML
BM is replaced by a clonal progeny of transformed stem cell that has a capacity to
differentiate into 3 cell lines but with abnormal morphology and function
Hallmark of MDS: hypercellular BM, peripheral cytopenia and morphologic dysplasia
Tendency for accumulating more mutations and transform to AML
Most cases are idiopathic, rarely secondary to chemo or radiotherapy (therapy related)
Most patients are old

Genes:
-Chromosomal aberration in 50% of cases: monosomy 5, monosomy 7, deletions of
5q, 7q, 20q, trisomy 8
-Mutations in epigenetic factors that regulate DNA methylation and histone modifications
-RNA splicing factors: abnormal RNA processing → ring sideroblasts
-Transcription factors
-10% have P53 mutation



Morphology:
Erythroid: macrocytic anemia (stem cell related), megaloblastoid nuclei, ring sideroblasts (cells are round, iron accumulation inside mitochondria)
Myeloid: decreased granulation, hyposegmented nuclei of neutrophils
Megakaryocytes: small, hypolobated nuclei
Myeloblasts: can be increased, but <20% of nucleated cells

Refractory anemia, thrombocytopenia, neutropenia
Survival 9-29 months



Myeloproliferative Neoplasms (MPN)

Myeloid Neoplasms (3)

Maturation is normal, but proliferation is high
Permanently active tyrosine kinase pathway, independent from growth factors, cells can keep dividing without the need of growth factors so BM is hypercellular, peripheral blood shows cytosis

Neoplastic stem cells in MPN often seeds to spleen, liver and occasionally LNs, causing extramedullary hematopoiesis and thus hepatosplenomegaly (very common)
Tendency to transform to AML

Chronic Myeloid Leukemia

Subtype of MPN (Myeloid Neoplasms)

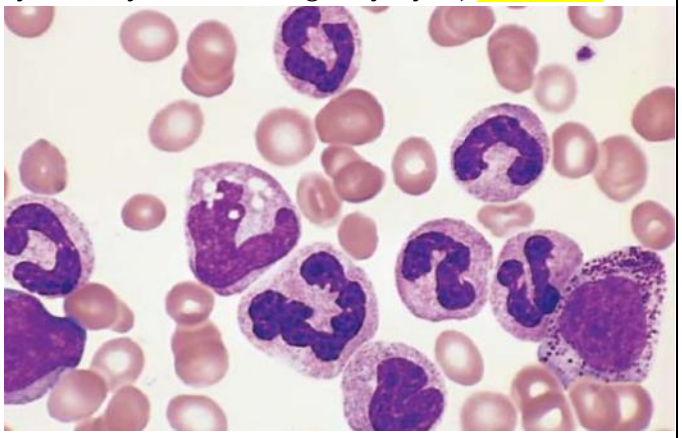
Most common MPN
Harbor t(9;22) □ Philadelphia chromosome, results in fusion of Bcr/Abl genes and
production of a tyrosine kinase that results in prolonged cell survival
Mutation is present in all BM cells (myeloid, erythroid and megs)
Affects adults 25-60 years □ Symptoms: non-specific: fatigue, heavy abdomen, weight loss
Imatinib: tyrosine kinase inhibitor, specific for bcr/abl mutation
Accelerated phase: worsening of symptoms, higher WBC count, thrombocytopenia,
resistance to imatinib
Blast crisis: transformation to acute leukemia (AML>ALL)

Chronic Myeloid Leukemia (CML)

Subtype of MPN (Myeloid Neoplasms)

'Chronic' both clinically and maturation wise:
1) The disease occurs over a long period of time
2) Cells appear mature, not blasts

Most common MPN
Gene: t(9;22) Philadelphia chromosome, results in fusion of Bcr/Abl genes and production of a tyrosine kinase that results in prolonged cell survival
Philadelphia chromosome is the new chromosome shape obtained after 9;22 chromosomes transfusion
Mutation is present in all BM cells (myeloid, erythroid and megakaryocytes) sometimes even lymphoid.
However, the myeloid lineage is the most affected of course.



Treatment:
Imatinib: tyrosine kinase inhibitor, specific for bcr/abl mutation

Clinical features:
Affects adults 25-60 years
non-specific: fatigue, heavy abdomen, weight loss

starts chronically, but with time, patients can undergo **Accelerated phase**: worsening of symptoms, higher WBC count, thrombocytopenia, resistance to imatinib.
Accelerated phase can occur whether on imatinib treatment or not.
Next, **Blast crisis** can occur: transformation to acute myeloid leukemia (AML>ALL)

Morphology:
Leukocytosis, can be >100K
Shift to left (=Myeloid precursors in peripheral blood)
Basophilia, eosinophilia
Thrombocytosis
Anemia (common. IDA type due to consumed iron by WBCs)
BM: increased myeloid and megakaryocyte (Hypercellular)
Spleen: EMH (extramedullary hematopoiesis)
Blasts: low (<20%)
Leukemoid reaction: high WBC and shift to left, occurs in severe inflammation
Leukemoid: looks like CML (Leukemia) but it is benign and reversible

How to differentiate leukemoid reaction?
It doesn't have basophilia or eosinophilia, no thrombocytosis. We test for Bcr/Abl mutation

Polycythemia Vera

Subtype of MPN (Myeloid Neoplasms)

Gene: Mutation in tyrosine kinase (JAK2), normally acts in the signalling pathway of erythropoietin receptor and other growth factor receptors. If mutated, remains permanently active, Hematopoietic cells become less dependent on growth factors
Excessive proliferation of erythroid, megalokryocytes and myeloid (panmyelosis)
Erythrocytosis is most prominent, results in polycythemia (low erythropoietin level)

Clinical features:
Insidious onset of symptoms, middle age
plethora (erythema all over the body), sometimes cyanosis
Cyanosis is the presence of deoxygenated hemoglobin leading to red/blue colored skin
headache, dizziness, peptic ulcer
pruritis (especially after a shower, due to activated basophils)
Thrombosis (due to increased platelets and slow viscous circulation) leads to tissue infarction
Bleeding is also common (GIT) because platelets have an impaired function
Gout (due to high numbers of hematopoietic cells, we have excessive secretion of uric acid)
After a chronic long period of no symptoms, patients develop spent phase
Spent phase: occurs after an interval of 10 years of disease course, BM becomes fibrotic, hematopoiesis shifts to spleen causing spleen enlargement although there is splenomegaly already (splenomegaly is a characteristic of all MPNs)
Blast crisis: transformation to AML (rare)

Treatment: phlebotomy, JAK2 inhibitor

Laboratory findings:
High RBC count
Hematocrit 60% of more
Leukocytosis is common
Basophilia
Thrombocytosis is common

Primary Myelofibrosis

Subtype of MPN (Myeloid Neoplasms)

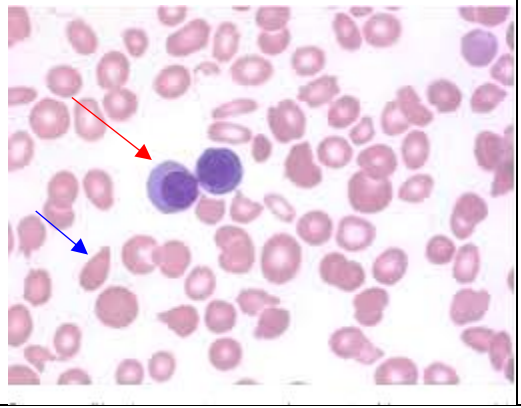
Primary= the problem is in the BM itself
Overt/severe BM fibrosis, reducing capacity for hematopoiesis, leads eventually to cytopenia and massive EMH
The disease starts with hypercellular BM but ends with hypocellular BM (fibrotic, not fatty)

Gene: JAK-STAT signalling pathway is active in all cases
50% have mutation in JAK2, 5% in MPL gene (thrombopoietin receptor)
Neoplastic megakaryocytes secrete TGF-B, which activates fibroblasts in BM to deposit reticulin and collagen fibres which effaces the BM, also causes angiogenesis
RBC production is impaired, RBCs appear as tear-drop, patients always have anemia

Morphology:
Peripheral blood: leucoerythroblastic anemia:
1.tear-drop cells
2.nucleated RBCs
3.shift to left (precursor cells are seen)
WBC: can be normal or increased
Platelets: normal or increased, then low due to fibrosis
BM: early: hypercellular and focal fibrosis
Late: hypocellular and extensive fibrosis.
Megakaryocytes are increased and form clusters

Clinical features:
The worst type of MPN
Non-specific symptoms, weight loss, anemia, massive splenomegaly (massive, reaches other side of abdomen), gout,
Bleeding
Infection
Worse outcome than CML and P Vera. 4-5 years survival
Frequent transformation to AML (5-20%)

Treatment: JAK2 inhibitor: decreases splenomegaly and symptoms



Essential Thrombocythemia

Subtype of MPN (Myeloid Neoplasms)

Cythemia = cytosis. Uncommon disease
Predominantly thrombocytosis (occasional leukocytosis)
JAK2 mutation is sometimes positive, but NO bone marrow fibrosis (so NO leucoerythroblastic anemia), Splenomegaly is positive in 50%, Good outcome

Langerhans Cell Histiocytes (LCH)

Histiocytic Cancers

Neoplasm of dendritic cells
- Langerhans cells express CD1a and Langerin
- Langerin is a transmembrane protein, attached to Birbeck granules (tennis ricket shape under electron microscope in cytoplasm)
- Proliferating Langerhans cells appear large and vacuolated, similar to macrophages. It occurs in tissues, its not a leukemia

Gene: acquired mutation in serin/threonine kinase BRAF, leads to hyperactivity of this kinase

Multisystemic LCH

Histiocytic Cancers

Occurs mostly in children less than 2 years, affects multiple organs
- Multiple cutaneous lesions, composed of LCs
- Hepatosplenomegaly and lymphadenopathy
- Pulmonary lesions (common, bad symptoms)
- Osteolytic lesions (proliferate in bone)
- Extensive bone marrow infiltration leads to pancytopenia
- Treated with chemotherapy

Unisystemic LCH

Histiocytic Cancers

AKA eosinophilic granuloma
Affects a single organ, most commonly bone, then skin, lung, stomach
Can be unifocal or multifocal. Unifocal is commonly asymptomatic, and can cause pain. Multifocal unisystem disease presents in children, commonly affects calvaria bone (skull) extends to pituitary gland causing diabetes insipidus, exophthalmos (rare, called HandSchuller-Christian triad). *Triad refers to osteolytic lesions, DI, exophthalmos*
Proliferating LCs are mixed with numerous eosinophils, lymphocytes, plasma cells and neutrophils
Treatment: unifocal: surgical excision, multifocal: chemotherapy,
Sometimes spontaneous regression (rare phenomenon in cancer)

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