Anemia of Decreased production

Microcytic Anemia

Nutritional Deficiency (Iron Deficiency anemia) (IDA)

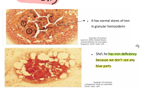
- Most common type
- affects → 10% of people in developed countries
  - ↳ 25-50% of people in developing countries

iron storage pool

- Ferritin (soluble)
  - stored ferritin ↓ serum ferritin
  - * serum iron transported by Transferrin
  - *Normal saturation = 1/3 (transferrin saturated by iron)
- Hemosiderin (insoluble) in → BM, liver, spleen
  - 15-26% of total iron
  - *consist of: large iron particles; granular in shape; intracellular ↓ Mainly in Macrophages in the BM; visible in LM

Indicators of iron status

- BM aspirate (Best one and the Most accurate)
  - show earliest changes
  - invasive procedure
  - expensive
  - painful
  - stained by Perl's prussian blue stain (a special iron stain appears in form of blue granular particles)
  - (↓ in IDA)
- Serum ferritin level (↓ in IDA)
  - *problem: Ferritin is an acute phase protein that ↑ in the inflammatory conditions (that Masks ID results in Normal Ferritin level)
- Serum iron level (↓ in IDA) ↓ Become less than 1/3
- Total iron binding capacity (TIBC) — opposite test of transferrin saturation
  - *Done By: adding iron to blood sample → if it takes a lot of iron → indicate Iron Deficiency
  - (↑ in IDA) → the only indicator that increases in IDA
- Reticulocyte Hemoglobin content (CHr) (↓ in IDA)
- Mean reticulocyte volume (MRV) (↓ in IDA)



Anemia of chronic inflammation (anemia of chronic Disease) → old name

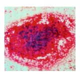
Must be chronic inflammatory, not only chronic

- Seen in
  - chronic infections
  - Cancer
  - chronic immune diseases
- * common in Hospitalized pts
- ↑IL-6 → ↑Hepcidin
  - Blocks iron transfer from Macrophages to RBC precursors in BM
    - *Degrade ferroportin on Macrophages → this keeps the iron inside Macrophages → this Keep the iron inside Macrophages in the BM in the form of hemosiderin
  - Suppress EPO Secretion from Kidneys

Note: Hepcidin is the Normal antagonist for EPO

Laboratory findings

- Similar to IDA (serum iron is low)
- RBCs – Normal Morphology ⇓ then Hypochromic Microcytic
- ↓ Reticulocytes — Due to low EPO
- In contrast (result) — Differ from IDA:
  - Bone Marrow iron stores ↑ — iron is stored in Macrophages in the BM → preventing the iron from reaching harmful bacteria (as a form of protection for the body)
  - Serum ferritin ↑ — one of the acute phase reactants



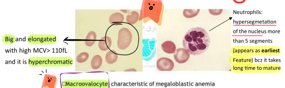
physio — *Iron Hemeostasis*

- Normal Loss of Body iron
  - Shedding skin & mucosal epithelium
  - (No normal way for iron excretion as its difficult)
- Dietary iron
  - Hem (red Meat) – well absorbed
  - non-hem (inorganic, vegetarian) difficult to be absorbed
  - 20% ← iron absorbed in duodenum → 1%
- Hepcidin (secreted from liver)
  - *Normally ⊖ iron absorption (degrade ferroportin on enterocytes in the small bowel)
  - *Regulation of Hepcidin*
    - +ve regulation
      - High ferrous protein (HFP) (on the cell membrane of hepatocytes): ↑iron ⊕→ HFE ↓⊕ Hepcidin → ↓iron
      - IL-6: inflammation → ↑IL-6 ↓⊕ Hepcidin ↓ ↓iron
    - -ve regulation (*to ↓ or stop secretion)
      - Erythroferrone (hormone): Erythroblasts in BM ↓ secrete Erythroferrone ↓⊖ Hepcidin → ↑iron
- → *Hepcidin levels*
  - Low ↓ iron deficiency
  - very Low
    - Thalassemia Major – High erythroferrone *Due to large # of erythroblasts in BM
    - primary Hemochromatosis (Defective HFE) ∴ very low Hepcidin

Megaloplastic Anemia

- Caused by: Deficiency in vitamin B12 or Folate
  - required for synthesis of thymidine (nucleic acid in DNA)
  - ⇓ Thus DNA replication is impaired and the cell dies by Apoptosis
- *Abnormalities occur in all rapidly dividing cells, But hematopoitic cells (erythroid cells) Are Most severely affected
- Maturation of RBC progenitors is deranged (Due to abnormalities in the nucleus of these cells)
- Many undergo Apoptosis inside bone Marrow
  - Lead to → ineffective erythropoiesis & Mild hemolysis (side process Not Main one)
- Not all of them will undergo apoptosis (Some Viable nucleated RBCs take a longer time to Mature) ⇓ resulting in
- Typical Morphology Megaloblastoid (large, immature nucleus)
- large cell due to the accumulation of More cytoplasm than normal over time because cytoplasm doesn't need thymidine ↓ So it continues growing

Morphology: Hyperchromatic ← → Big & elongated



Symptoms (in severe cases)

- chronic general symptoms of Anemia
- Glossitis (beefy tongue)
- Mild jaundice — Due to Mild hemolysis & the excretion of bilirubin from the cells
- Pancytopenia — platelets & neutrophils production fails

Aplastic Anemia (AA)

- total bone Marrow Failure
- *Damage to Multipotent Stem cells in BM
- BM becomes → Depleted of Hematopoietic cells
- peripheral blood pancytopenia (*even platelets & neutrophils become very low)
- Low reticulocytes
- *affects all age groups (but More common in young)
- Pts develop life-threatening infections, bleeding & symptoms of Anemia

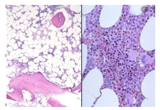
pathogenesis

- Extrinsic factors
  - Antigen cross reactivity with stem cells — Drug-virus — environmental factor
  - Activated T-lymphocytes destroy stem cells ⇓ Evidence: Immunosupressive Drug restores BM in 70% of cases
  - *Most cases are idiopathic
  - associated factors: chloramphenicol (antibiotic); gold injections *to treat rheumatism; NSAID; pregnancy; Some Hepatitis viruses
- Intrinsic factors (problem within stem cells)
  - 10% of aplastic Anemia pts have inherited defects in telomerase (stability of chromosomes) ⇓ that's why stem cells Die early by Apoptosis
  - these genetically altered stem cells might express abnormal antigens will causes attracting T-cells

Stem cells defect = Macrocytic

Laboratory findings

- peripheral Blood
  - pancytopenia
  - anemia is normochromic or Macrocytic
- Bone Marrow
  - ↓ Hematopoietic cells and predominance of fat
  - Hematopoitic → Adipose



special types of Bone Marrow Failure

- Fanconi Anemia
  - rare, inherited form of AA (Aplastic Anemia)
  - Defect in DNA repair proteins
  - *pts develop AA & transform to ↓ Acute leukemia in early life
- pure red cell aplasia
  - *only erythroid cells are absent in BM
  - *can be*: congenital (Diamond-blackfan Anemia) or Aquired — affected people with: Autoimmune diseases or infection with parvovirus B19 infection

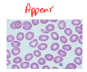
Myelophthisic Anemia

- *infiltration of BM causing physical damage to Hematopoietic cells
- *resembles AA → pts come with pancytopenia (But different Mechanism)
- ↓ Differ in: The BM is fully infiltrated & destroyed By cancer or infectious process.
- *disrupts the immature cell → will causes The Disappearance of the RBC
- * can be caused by*:
  - Cancer — *Most commonly in Bone Marrow tumors like Acute Leukemia, Advanced Lymphoma & Myeloma; or Metastatic Cancer – breast cancer – colon cancer (Make Metastasis & then destruction to the BM)
  - Granulomatous Disease (TB) (inflammatory cells + physical mass in the tissue)
  - Storage Diseases (inborn errors of Metabolism) — the tissue in the body stores either lipid – glycogen or – sphingomyelin
    - Most commonly is Gaucher
    - Gaucher Disease: The most common storage disease that affects the bone marrow. It results from the accumulation of glucocerebroside, a type of lipid, due to a deficiency in the enzyme glucocerebrosidase. This accumulation disrupts normal bone marrow function, affecting blood cell production.
  - immature granulocytic & Erythroid precursors commonly appear in peripheral blood ↓ Making pancytopenia (that's what Makes it different from AA)

Macrocytic anemia

Anemia of Renal Disease

- Mainly result from ↓EPO production from Kidneys
- *Doesn't correlate with well with Kidney function (serum creatinine)
  - Mild renal injury — May cause Severe anemia (vice versa)
- ↓RBC production (Low retic count)
- Pts with uremia (urin in the blood)
  - ① Develop abnormal platelets function ↓ lead to Anemia of chronic Disease (Bleeding)
  - ② Echinocytes (Burr cells) (spiked cell membrane) Appear

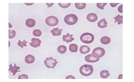


Anemia of Liver Disease

Multiple factors causing Anemia

- ↓ synthesis of clotting factors (Bleeding) — Especially Bleeding from varices ↓ Becomes Anemia of chronic blood Loss
- ↓ synthesis of transferrin ↓ so Develops iron deficiency

*Acanthocyte (spur cell) appears with Longer spikes



Myelodysplastic Syndrome

- * Aquired neoplastic disease of BM
- * primarly disease of old age
- * Mutation in BM stem cells result in
  - prolonged Survival & defective Maturation (same principle of Megaloblastic Anemia (take long time to Mature abnormally))
- *Mature Blood cells Do not exit bone Marrow in normal way so The BM fills with erythroid cells
- *Pts commonly develop: Neutropenia & thrombocytopenia
- Anemia is refractory to treatment (resistant) ⇒ as the problem in mutations of DNA can't be corrected yet
- RBCs are Macrocytes

Anemia of Hypothyroidism

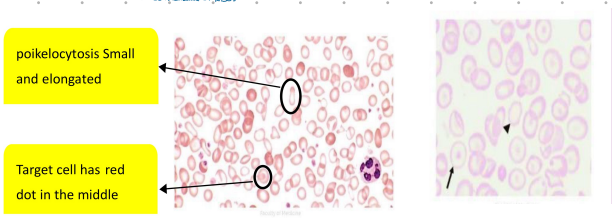
- *Thyroid Hormones —stimulate→ Erythropoiesis; —stimulate→ EPO production
- *Anemia is Most commonly Normocytic but it can be Macrocytic
  - ↓ Because Maturation takes longer time due to Decreased thyroid hormones

* causes of iron deficiency *

- Chronic Blood loss
  - iron is difficult to control by the body
  - there is a slight tendency to lose it with Hb
- Dietary
  - vegetarians
  - infants
    - iron in breast milk
    - first fruit
  - teenagers
    - Menstrual cycle in females
- ↓ absorption
  - Due to some diseases like:
  - gastrectomy
  - Hypochlorhydria
    - low stomach acid (HCl) that is important to
      - Ferrous conversion
      - & absorption of iron
  - intestinal diseases
    - inflammatory bowel disease
    - celiac disease
    - Lead to inflammation
    - iron level will ↓
  - Elderly
    - due to physiological atrophy of the stomach which ↓ iron absorption
- increased Demands
  - Growing children
  - pregnancy
  - Myeloproliferative neoplasms
    - in these cases we have high amounts of WBC that fasten up the iron instead of RBC
- Hepatransferritinemia
  - Decreased synthesis of transferrin
  - 2° to
    - liver disease
    - protein deficiency
      - by
        - Diet
        - Malabsorption
    - loss in the Urine (Nephrotic syndrome)
- Enzyme deficiency
  - a congenital disease
  - rare but should be considered when the deficiency develops very early in life
  - Difficult to treat

* Morphology *

- RBCs appear empty & small (Hypochromic Microcytic)
  - Small in color
  - * No enough Hb due to iron deficiency
- Different & abnormal shapes of RBCs (poikelocytosis)
  - elongated & pencil shaped RBCs
  - * Because iron is important for the integrity of the cell membrane of RBCs
- Target cells
  - RBCs with red dot in the Middle
  - * Appear in
    - thalassemia
    - sickle cell anemia
  - iron deficiency Anemia
  - abnormal Hb = Target cells
- low reticulocytes
  - * High EPO but ineffective
  - * BM can't produce RBCs due to iron deficiency
- Thrombocytosis
  - common (low iron Medium in BM shifts progenitor cells to Mega Karyocytic linage instead of erythroid => Making More platelets



* IDA is a chronic anemia (Never comes quickly)

* Symptoms *

- General symptoms of Anemia
  - Hypotension
  - dizziness
  - fatigue
- Spicial Symptoms
  - Pica
    - * Pts have a strong desire to eat abnormal things like: dirt, paint & ice
- glossitis & stomatitis
  - * Bcz iron present in epithelial tissues

- Spooning of fingernails
  - wide & depressed

- Restless leg Syndrome
  - Moving the legs due to neurological condition
- Hair loss
- Blue Sclera
  - * Become thin & transparent

- weakened immunity
- cognitive impairment
  - lately & severe cases

* Folate (B9) deficiency *

- Normally: Minimal amount is stored in body
- Vastly present in Food (green leaves), But destroyed by cooking

* Causes *

- ↓ Dietary intake
- increased demands
  - pregnancy
    - * the 1st supplement given for pregnant for the 4 months
  - & chronic hemolytic Anemia
    - High turnover
    - Lots cells die and a lot of erythroblasts but poikilocyte
    - So they need More Folate & result
    - Can develop a 2nd anemia (Folate deficiency)
- intestinal diseases (↓ absorption)
- Beans, legume, alcohol & phenytoin
  - (Anti-epileptic drug that inhibits the absorption of folic acid)
- Methotrexate (chemotherapy agent)
  - inhibits Folate Metabolism & cellular usage
  - * Doesn't inhibit absorption *

* Vitamin B12 *

- Mainly in animal products
- resistant to cooking
- Synthesized by bacteria in the bowel
- Enormous stores in the liver
  - * B12 takes 5-20 years to be completely depleted from its stores (about time for Disease Development & treatment)
  - * Dietary deficiency occurs Most commonly in vegetarians
  - * Deficiency results from defective absorption ← More commonly

* Functions of Vitamin B12 *

- Recycling of tetrahydrofolate
  - to produce folate
- synthesis of Myelin Sheath
- Synthesis of neurotransmitters
  - Dopamine
  - Serotonin
- Metabolism of Homocysteine
  - (toxic to neurons)

* Degree of neuronal damage does not correlate with the degree of anemia *

- So pts end up with neuropathy but seen in B12 deficiency but not in Folate deficiency

* Causes of VB_{12} deficiency *

- Pernicious Anemia (important cause)
  - Autoimmune gastritis (anemia starts in the Stomach)
  - Autoreactive T-lymphocytes
    - causing injury to parietal cells
      - HCl → important for non-heme iron absorption
      - Normally secrete & intrinsic factors (important for B12 absorption)
      - So both of them will decrease
      - Iron deficiency anemia May occurs due to the decrease in HCl
  - Activates → B-lymphocytes
    - plasma cells
      - to → synthesize
      - secrete → Autoantibodies
        - Block the binding of VB_{12} to intrinsic Factors
        - Hurt further damage parietal cells
- Gastrectomy (Usually ↓ in intrinsic factors)
- small bowel Disease (Malabsorption)
- Elderly people are susceptible
  - ↓ gastric acids & pepsin
  - ↓ release of VB_{12} from Food
- Metformin
  - used by diabetic Pts
  - (inhibits absorption)

* Symptoms in Vitamin B12 deficiency *

- posterior & lateral columns degeneration of spinal cord
  - (Mainly in the sensory problems)
  - Paresthesia
  - Loss of proprioception (position sense)
- peripheral Neuropathy
- Neuropsychiatric Symptoms