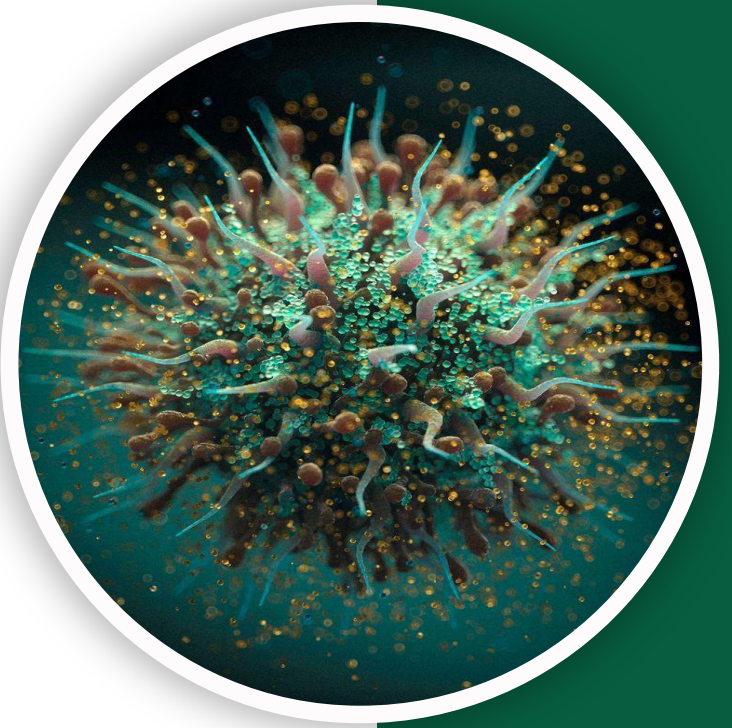
بسم الله الرحمـٰن الرحيم

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Pathology | Final 4

Anemias of Low production



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Anemia of Low Production

General causes:

- Nutritional deficiency (lacking raw materials such as iron, vitamin B12 and folate)
- Chronic inflammation (inflammatory signals 'hide' iron and reduce erythropoietin)
- Bone marrow failure

Iron Deficiency Anemia

- The most common type of anemia worldwide and among the subtypes of anemia
- Affects 10% of people in developed countries and 25-50% of people in developing countries (from the general population).
- Iron storage pool: iron is stored in ferritin, a small water-soluble molecule and hemosiderin, a large insoluble molecule, in bone marrow, liver, and spleen, both storage pools forming 15-20% of total iron, and the remaining bulk of iron is present in the hemoglobin.
- Hemosiderin consists of large iron particles, they are large fragment of ferritin combined, granular in shape, intracellular, mainly inside the macrophages, and visible by the light microscope.
- Serum ferritin is derived from stored ferritin, and it reflects the stored iron.
- Serum iron is transported by transferrin; normally, only one-third of transferrin is saturated by iron. 30% of transferrin is saturated with iron.

Indicators of Iron Status

IDA: IRON DEFICINCY ANEMIA

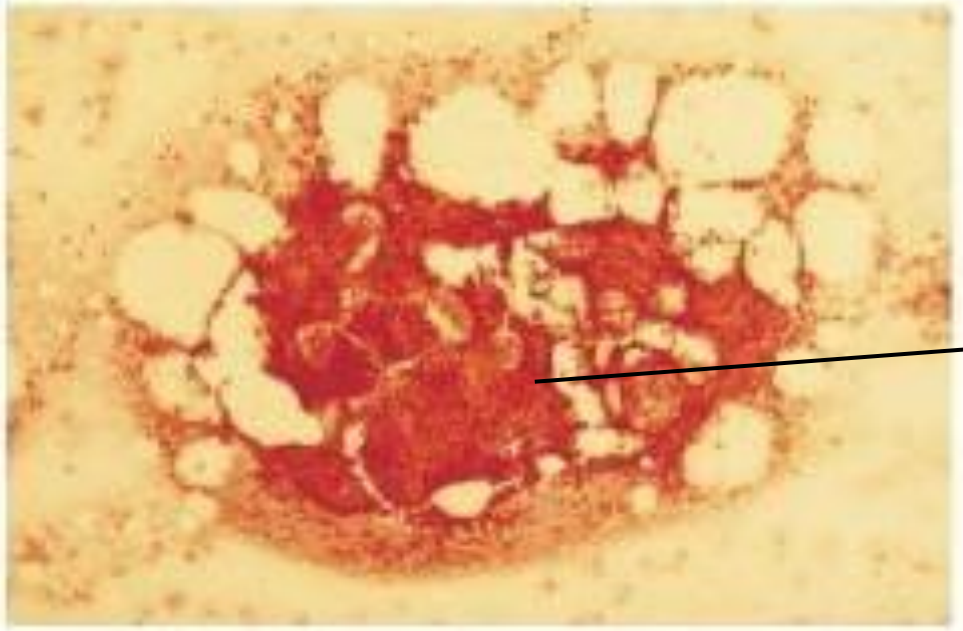
The most accurate way to determine the amount of iron stored—whether it is increased or decreased—is by examining the bone marrow directly through bone marrow aspiration.

- Bone marrow aspirate: _we will detect the earliest changes in hemosiderin storage_, an invasive procedure, and we use Perl's Prussian blue stain (↓ in IDA) .
- Serum ferritin level (↓ in IDA). The problem with serum ferritin is that it is an acute-phase protein. Therefore, if a patient has inflammation or infection, the ferritin level will rise, which can mask an underlying iron deficiency.
- Serum iron level (↓ in IDA). Serum iron level reflects transferrin saturation. In cases of iron deficiency anemia, the serum iron level decreases, and the transferrin saturation falls below the normal value that is about one-third of the total binding capacity.
- Total iron binding capacity (↑ in IDA), it's the opposite of serum iron level and the only indicator that will be increased. More empty transferrin available to bind iron and more transferrin is made to 'catch' as much iron as possible.
- Reticulocyte hemoglobin content (CHr): (↓ in IDA).
- Mean reticulocyte volume (MRV): (↓ in IDA).



Aspirate of normal bone marrow (BM): bluish-black iron (haemosiderin) in macrophages in a fragment. Perls' stain ×40.

These black dots represent normal hemosiderin levels in the bone marrow aspirate, which is stained using the Prussian blue stain.



Aspirate of normal BM: a fragment with no stainable iron. Perls' stain ×40.

In this picture, the absence of the black dots—which represent hemosiderin—indicates a severe iron deficiency.

Iron Homeostasis

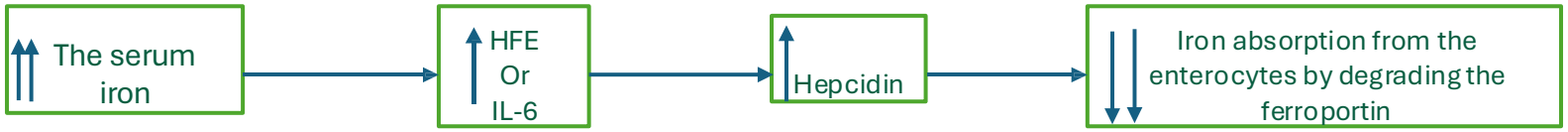
- Normal loss of body iron: shedding skin and mucosal epithelium (no mechanism of excretion).
- Dietary iron is either hem (red meat) or non-hem (inorganic, vegetarian).
- 20% of hem and 1 % of non-hem iron are absorbed in the duodenum. Therefore, you should ask the patient whether they are a vegetarian or not.

Iron Homeostasis

- Hepcidin: hormone secreted from the liver, inhibits iron absorption (degrades ferroportin on enterocytes)
- Hepcidin hormone is positively regulated by HFE protein (Heriditary Ferrochromatosis Protein) on hepatocytes, which is activated when serum iron level rises.
- Hepcidin hormone is also positively regulated by IL-6, an inflammatory mediator, which increases in inflammation, so I expect to see low Iron serum levels during the inflammation.
- Hepcidin is negatively regulated by erythroferrone, a hormone secreted by erythroblasts in bone marrow
- Low hepcidin: iron deficiency.
- Very low hepcidin:

1) Thalassemia major, very high erythroblast in the bone marrow, resulting in high erythroferrone.

2) primary hemochromatosis, defective HFE protein results in very low hepcidin level.

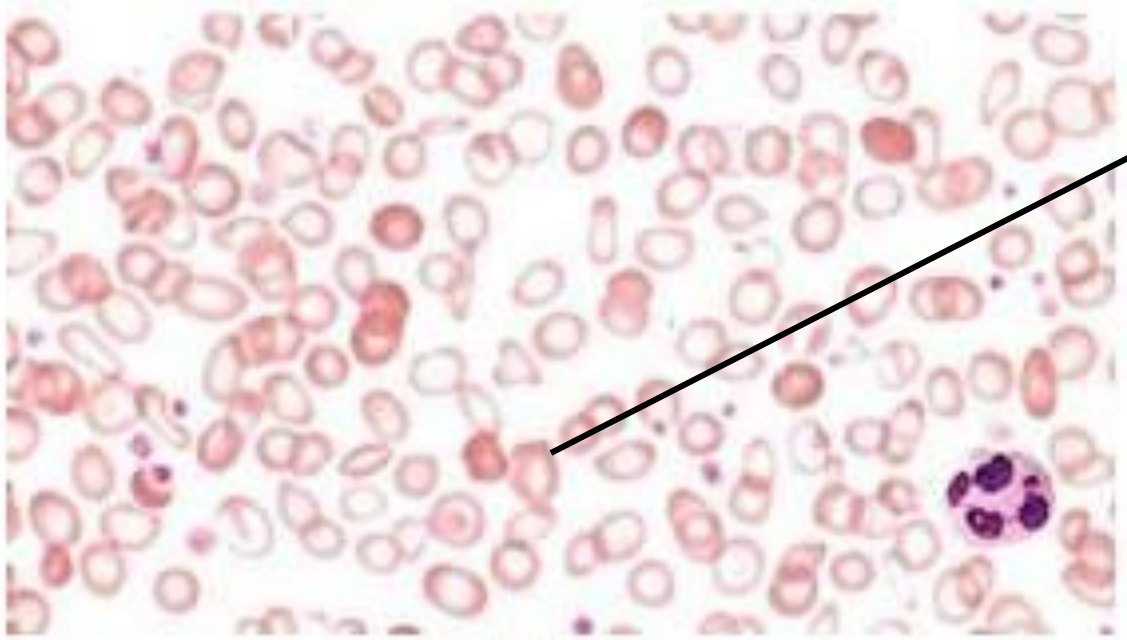


Causes of Iron Deficiency

- Chronic blood loss leads to iron loss as well. (GI disease, excessive menstruation)
- Dietary: vegetarians, infants, as the breastfeeding milk has a low amount of iron, and teenagers, as they prefer junk food over nutritional rich food.
- Decreased the absorption: gastrectomy, hypochlorhydria, intestinal diseases, elderly, as they have a physiologic atrophy in the stomach.
- Increased demands: growing children, pregnancy, myeloproliferative neoplasms
- Hypotransferritinemia: decreased synthesis of transferritin, secondary to liver disease, protein deficiency (diet, malabsorption), or loss in urine (nephrotic syndrome). Iron cant be transported to bone marrow
- Enzymatic deficiency, congenital diseases that appear early in life, they are usually non- correctable; they could affect iron absorption, metabolism, or transport.

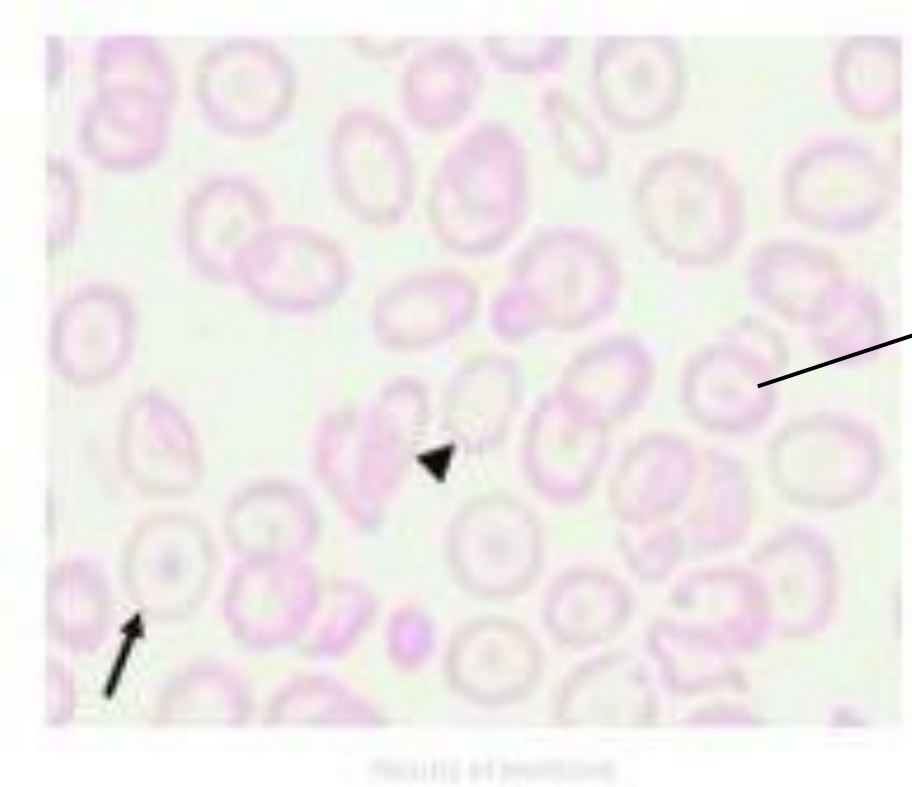
Morphology

- RBCs appear small and empty (hypochromic microcytic).
- Different shapes of RBCs appear (poikilocytosis).
- Target cells, red dot in the center of RBC, it also appears in thalassemia and sickle cell anemia.
- Low reticulocytes (Erythropoietin is high, but ineffective).
- Thrombocytosis is common (low iron medium in bone marrow shifts progenitor cells to megakaryocytic lineage instead of erythroid lineage).

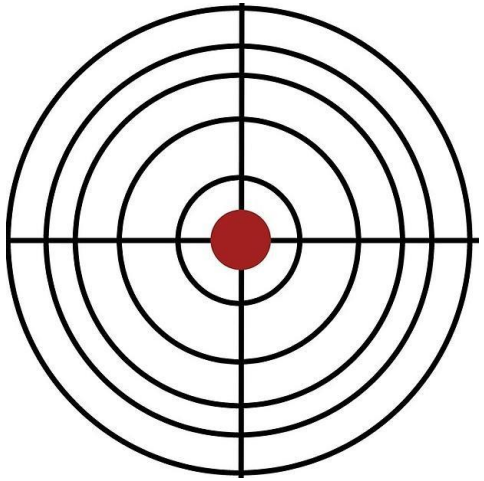


Here, RBCs are microcytic and hypochromic, with central pallor exceeding one-third of the cell diameter, notice also the existence of abnormal RBCs shapes which is known as poikilocytosis.

IDA: note the hypochromia and poikelocytosis



Target cells



- IDA: note the target cells (arrow)

Symptoms

- IDA is a chronic anemia (never comes quickly)
- General symptoms of anemia
- Pica, compulsive eating of non-food substances.
- Glossitis, stomatitis
- Spooning of fingernails
- Restless leg syndrome (due to iron being needed for brain dopamine synthesis)
- Hair loss
- Blue sclera (due to less collagen synthesis, as iron is a cofactor, so the sclera is thin, and the blue underneath is seen)
- Weakened immunity
- Cognitive impairment, occurs in late and severe cases.







Anemia of Chronic Inflammation

- Also called anemia of chronic disease
- Seen in chronic infections, cancer, and chronic immune diseases
- Common in hospitalized patients
- High IL-6 → high hepcidin → blocks iron transfer from macrophages to RBC precursors in bone marrow (degrades ferroportin on macrophages). Also suppresses erythropoietin, because it acts as an inhibitor of erythropoietin secretion from the kidneys

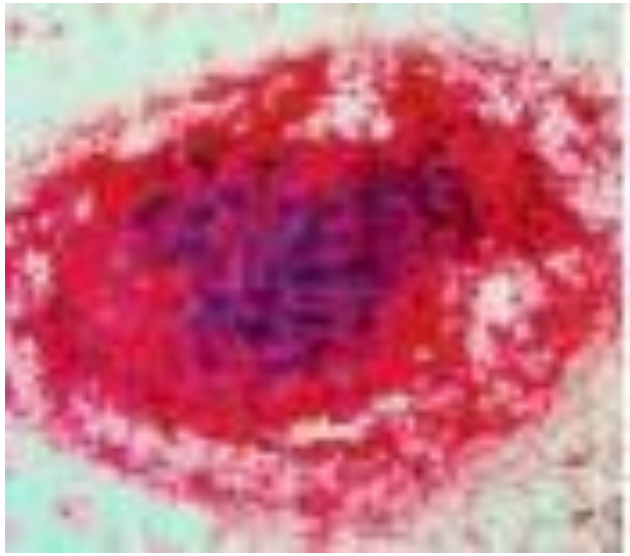
Laboratory Findings

- Similar to IDA: serum iron is low
- RBCs: normal morphology, then hypochromic microcytic
- Reticulocytes ↓ (due to low erythropoietin)

In contrast to IDA:

- Bone marrow iron stores ↑
- Serum ferritin↑

During infection, inflammatory mediators such as IL-6 that leads to increased hepcidin production mainly by the liver as part of the innate immune response. Hepcidin binds to ferroportin, the iron exporter on enterocytes, macrophages, and hepatocytes, causing its internalization and degradation. This traps iron inside the cells reducing serum iron levels (hypoferremia), thus limiting the iron availability for the invading pathogens that require iron for their proliferation.
When this inflammation becomes chronic it could lead to anemia of chronic inflammation as iron is not transported to supply the demands of erythropoiesis.



Bone marrow aspirate shows markedly increased iron stores, which can be identified using Prussian blue stain.

Megaloblastic Anemia

- Caused by a deficiency in vitamin B12 or folate
- Both are required for the synthesis of thymidine; thus, DNA replication is impaired, which results in abnormal and delayed DNA synthesis.
- Abnormalities occur in all rapidly dividing cells, but hematopoietic cells are most severely affected.
- Maturation of RBC progenitors is deranged, many undergo apoptosis inside the bone marrow (ineffective erythropoiesis, mild hemolysis). This is not classified as hemolytic anemia
- Viable nucleated RBCs take a longer time to mature, resulting in typical morphology (megaloblastoid). The cells take a longer time until they mature, accompanied by cytoplasmic buildup resulting in large cells, that's why they are called megaloblastoids, which means large immature cells.

Folate Deficiency

- Normally, a minimal amount of folate is stored in the human body
- Folate is vastly present in food (green leaves), but it is destroyed by cooking

Causes of deficiency:

- Decreased dietary intake
- Increased demands (pregnancy, chronic hemolytic anemia, premature destruction of RBCs increase red cell turnover. This stimulates erythropoiesis, which markedly raises the demand for folic acid required for DNA synthesis. Over time, the folate stores become depleted, leading to a secondary folate deficiency, resulting in megaloblastic anemia.)

Chronic hemolysis → ↑ RBC turnover → ↑ folate demand → folate depletion → **secondary megaloblastic**

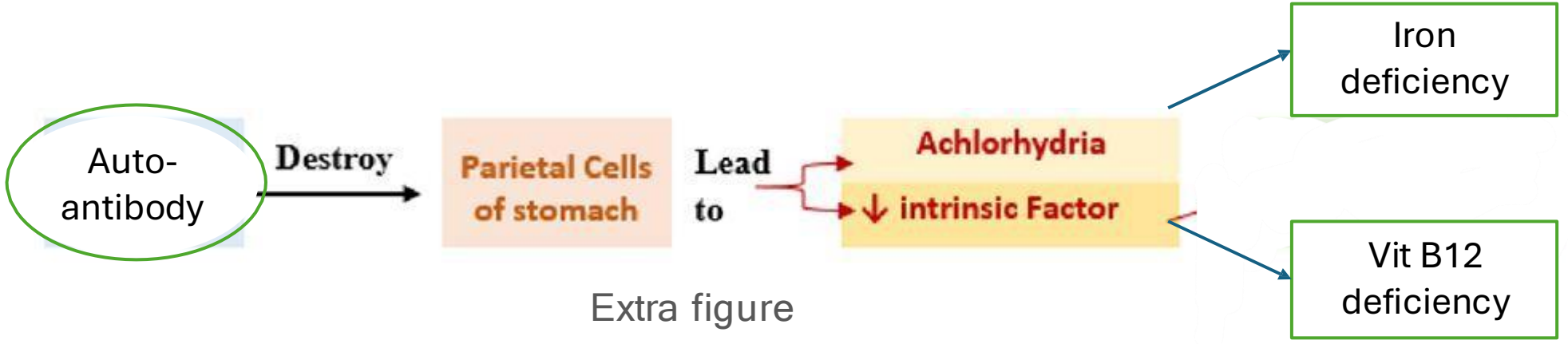
- Intestinal diseases affect the absorption.
- Beans, legumes, alcohol, phenytoin (inhibit absorption)
- Methotrexate: inhibits folate metabolism and cellular usage

Vitamin B_{12}

- Mainly present in animal products: meat, milk, eggs.
- Resistant to cooking.
- Synthesized by bacteria in the bowel.
- Enormous stores in the liver, so it may take 5 to 20 years for these stores to become totally depleted and for symptoms to appear.
- Dietary deficiency occurs most commonly in vegetarians.
- More commonly: deficiency results from defective absorption.

Pernicious Anemia

- Autoimmune gastritis.
- Autoreactive T-lymphocytes, causing injury to parietal cells.
- Activates B-lymphocytes and plasma cells to synthesize and secrete autoantibodies that further damage parietal cells, and blocks the binding of vitamin B12 to intrinsic factors.



Extra figure

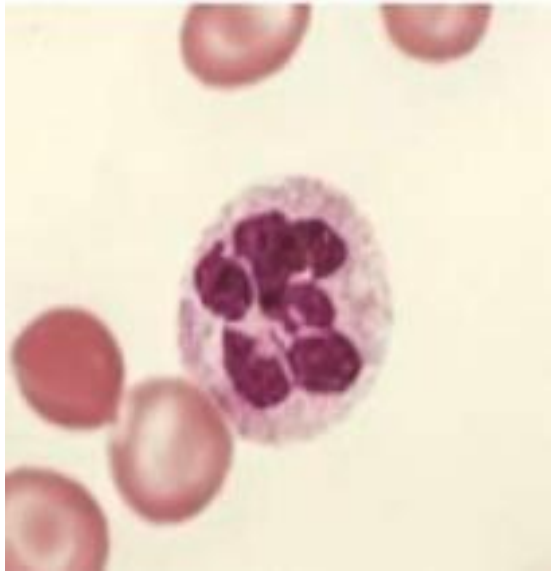
Other Causes of Vit B_{12} Difeciency

- Gastrectomy
- Small bowel diseases (malabsorption)
- Elderly people are susceptible (decreased gastric acids and pepsin, thus decreased release of vitamin B12 from food)
- Metformin (inhibits absorption) is very important because it is widely used.

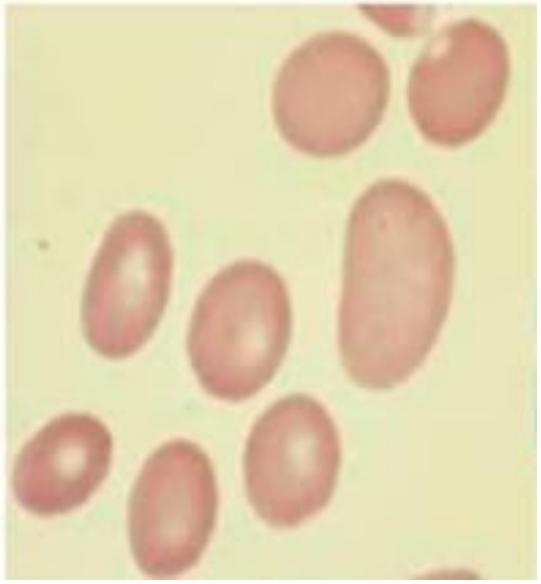
Other Functions of Vit B_{12}

- Recycling of tetrahydrofolate.
- Synthesis of myelin sheath.
- Synthesis of neurotransmitters (dopamine, serotonin).
- Metabolism of homocysteine (toxic to neurons).
- In case of vitamin B_{12} deficiency, the patient will also suffer from neuropathy, and this is **not seen** in folate deficiency.
- Degree of neuronal damage does not correlate with the degree of anemia. patients with mild vitamin B_{12} deficiency anemia could develop serious neuropathy and vice versa.

Morphology of megaloblastic anemia

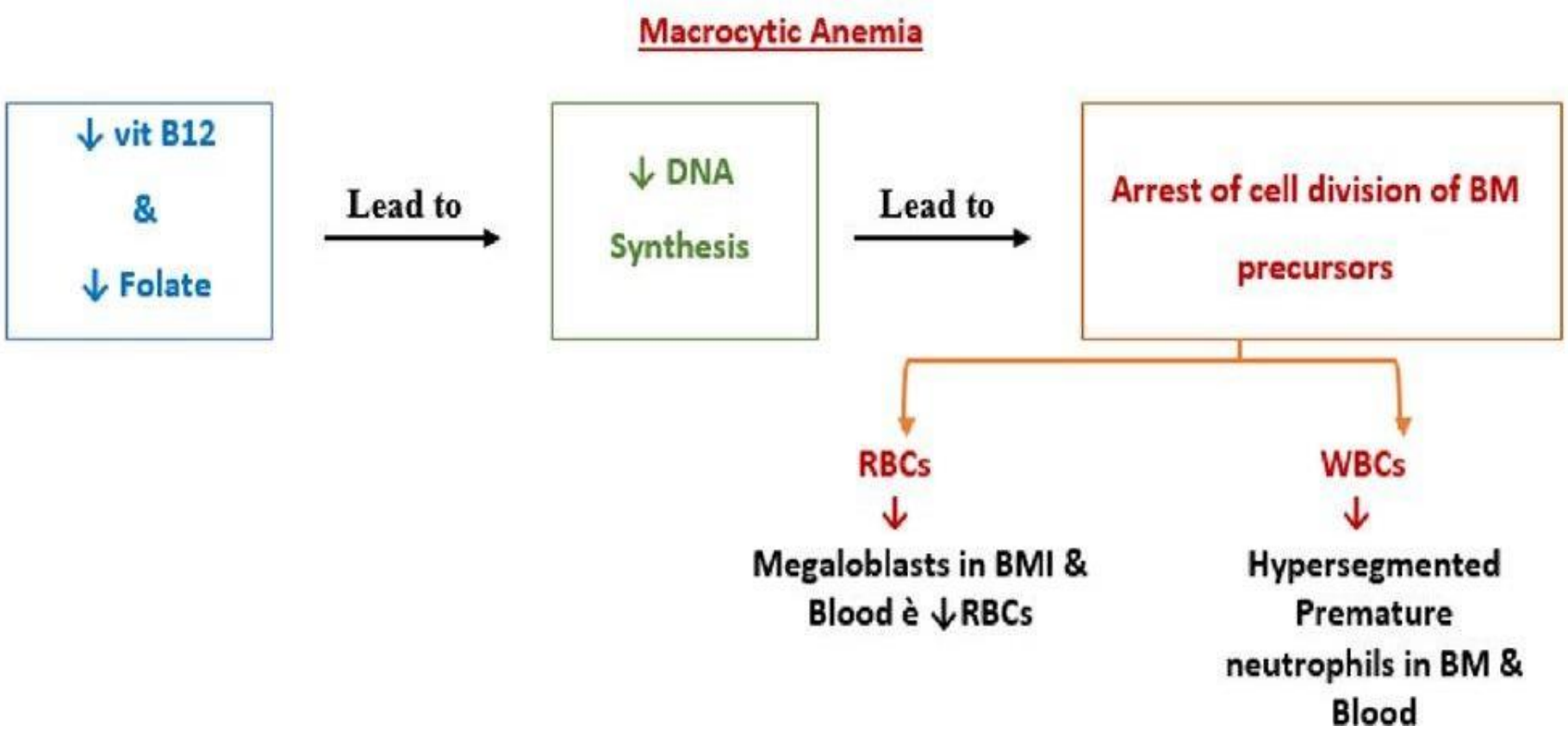


Hyper-segmented neutrophils > 5→ the earliest sign of megaloblastic anemia (seen in vitamin B12 or folate deficiency) due to delayed nuclear maturation.



Macro-ovalocytes: large, elongated RBCs; MCV >110 fL; hyperchromatic → typical of megaloblastic anemia.

Extra figure on megaloblastic anemia



Symptoms

- Chronic, general symptoms of anemia.
- Glossitis (beefy tongue).
- Mild jaundice.
- In severe cases: pancytopenia.

In vitamin B12 deficiency:

- Posterior and lateral columns degeneration of the spinal cord.
- (paresthesia, loss of proprioception: **position sense**).
- Peripheral neuropathy.
- Neuropsychotic symptoms.

Aplastic Anemia

- Damage to multipotent stem cell in bone marrow, they are no longer capable of surviving or undergoing mitosis.
- Bone marrow becomes depleted of hematopoietic cells.
- Peripheral blood pancytopenia. All blood cells gets affected. No WBCs and platelets.
- Low reticulocytes.
- Affects all age groups, it is more common among young age groups.
- Patients develop life-threatening infections due to neutropenia, bleeding and symptoms of anemia.

Pathogenesis

Extrinsic factors, problem is not in the cell itself.

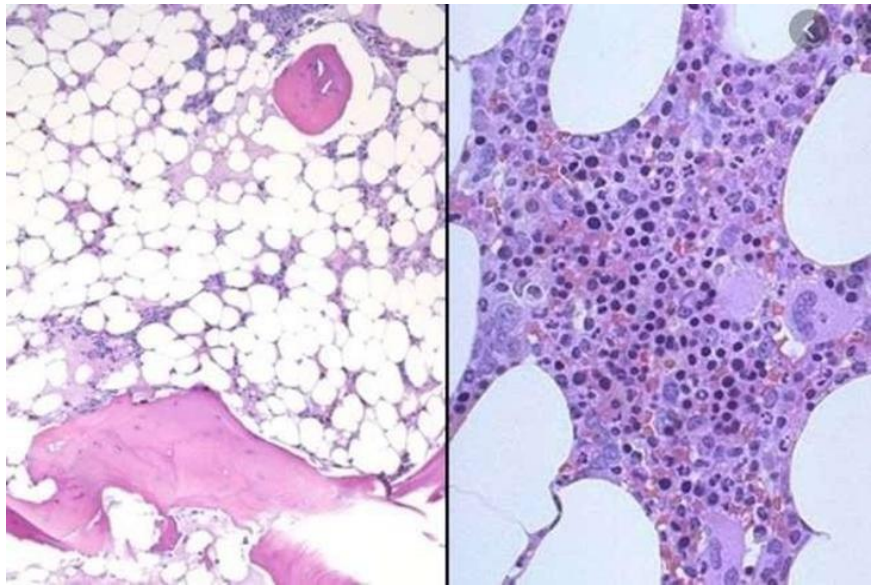
- Antigen cross reactivity with stem cells (drug, virus, environmental factor).
- Activated T-lymphocytes destroys stem cells.
- Evidence: immunosuppressive drugs restores bone marrow in 70% of cases.
- Most cases are idiopathic; these patients has no previous history of viral infection or drug exposure.
- Associated factors: **chloramphenicol** an antibiotic that became rarely used in medicine, gold injections that were used for rheumatoid arthritis, NSAIDs, rarley cause the disease, pregnancy, with no known cause, and some hepatitis viruses.

Intrinsic factors, the problem is within the stem cell.

- 10% of aplastic anemia patients have inherited defects in telomerase, this decreases the stability of the chromosomes, and the cells undergo apoptosis early.
- Stem cells die early.
- They can benefit from immunosuppressive drugs, theories suggest that these genetically altered stem cells might express abnormal antigen, attracting T-cells.

Laboratory Findings

- Peripheral blood: pancytopenia, anemia is normochromic or macrocytic, as stem cell defects produce macrocytes, same with the cells of megaloblatic anemia.
- Bone marrow: decreased hematopoietic cells and predominance of fat.



Normally (in the figure to the right) the bone morrow has a mixture of fat cells and stem cells, in condition of aplastic anemia, predominance of fat cells (the figure to the left) occurs in the bone morrow.

Special types of bone morrow failure

- Fanconi anemia: rare, inherited form of aplastic anemia, defect in DNA repair proteins, patients develop aplastic anemia, mutations accumulation leads to acute leukemia in early life.

- Pure red cell aplasia: only erythroid cells are absent in the bone morrow, myeloid stem cells and megakaryocytes stem cells are not affected, can be congenital (Diamond-Blackfan anemia) or acquired (autoimmune disease, Parvovirus B19 that infects immature erythroid cells and destroy them).

Myelophthisic Anemia

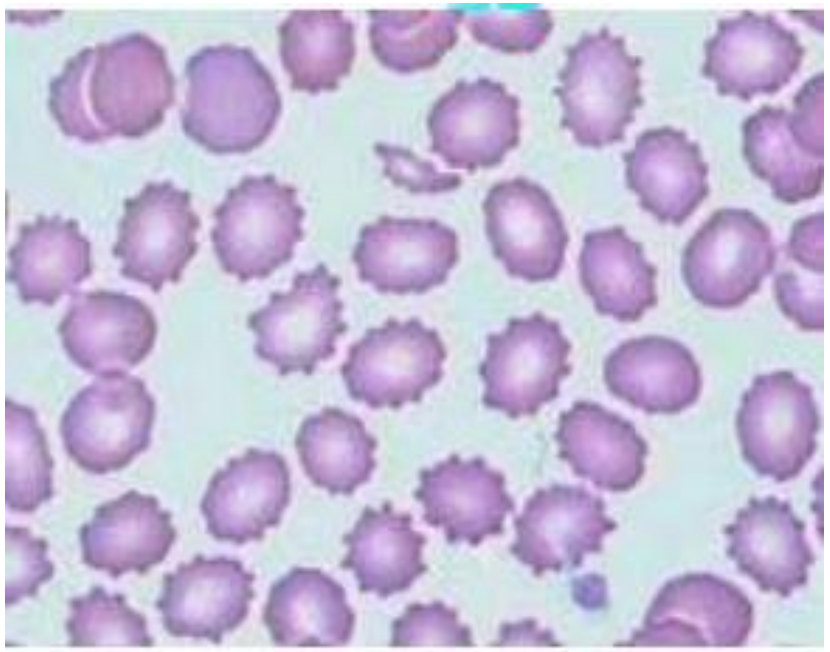
Myelo: bone morrow, Phthisis: infiltration

Infiltration of bone marrow causing physical damage to hematopoietic stem cells, causes include:

- Cancer: most commonly in acute leukemia, advanced lymphoma, and myeloma, also it could be caused by solid metastatic cancers such as breast and colon cancers.
  - Granulomatous disease: most commonly caused by TB granulomatous reaction that includes the formation of physical masses that destroy the bone tissue.
  - Storage diseases: the most common one is Gaucher's Disease, patients has inborn metabolism defects, tissues store excess material of lipids or glycogen, this leads to the proliferation of macrophages that engulf these materials, these macrophages will occupy the spaces of the bone morrow and destroy the surrounding tissue.
  - Immature granulocytic and erythroid precursors commonly appear in peripheral blood because they are displaced from the bone morrow, this feature help to differentiate myelophthisic anemia from aplastic anemia.

Anemia of renal disease

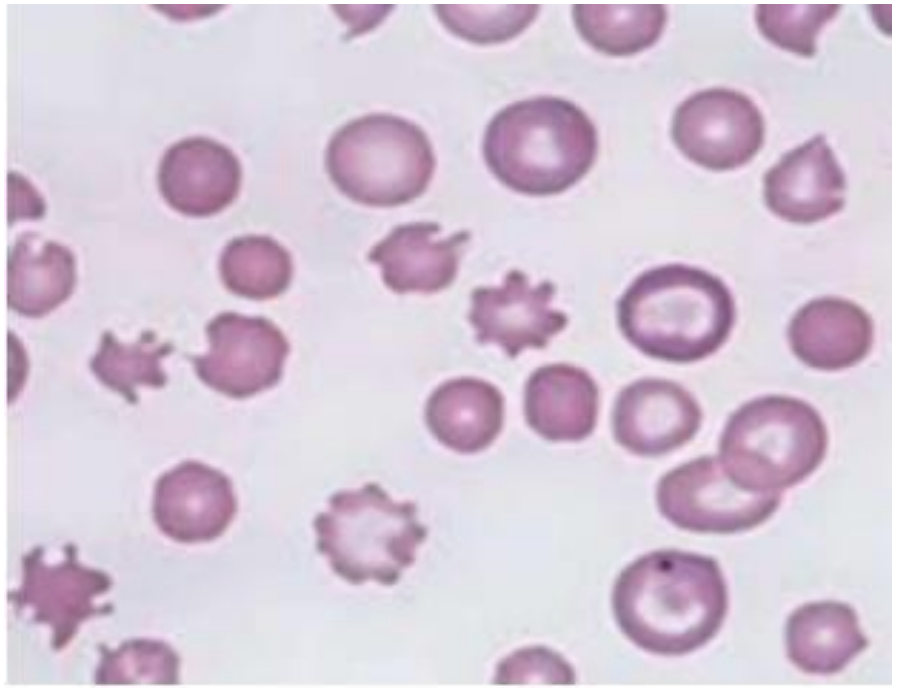
- Mainly results from decreased erythropoietin production from the kidneys
- Does not correlate well with kidney function (serum creatinine), patients with mild renal injury could develop serious anemia and vice versa.
- Decreased RBC production (low retic count).
- Patients with uremia develop abnormal platelet function (bleeding), nitrogen compound such as urea has toxic effects on platelets.
- RBCs shape gets affected, echinocytes (Burr cells) appear; small spines appear all around the surface of the cell.



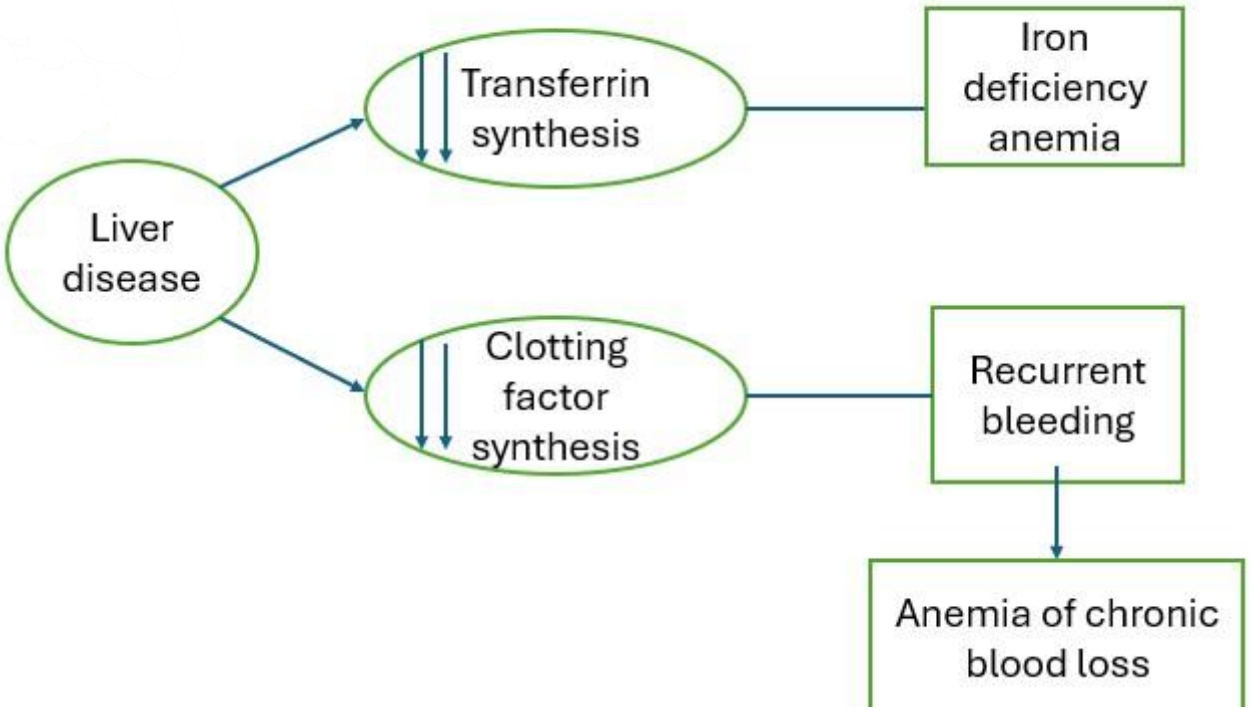
Anemia of liver disease

Multiple factors causing anemia

- Decreased synthesis of clotting factors (bleeding).
- Bleeding from varices.
- Decreased synthesis of transferrin.
- Acanthocyte (spur cell) appears. Here, the spikes are taller than those seen in anemia of renal disease, and it's difficult to distinguish between them so we depend on the history of the patient.



Extra figure on anemia of liver diseases



Anemia of hypothyroidism

- Thyroid hormones stimulate erythropoiesis and are essential for erythroid cells maturation, deficient thyroid hormones makes the maturation process slower leading to macrocytic anemia.
- Also stimulates erythropoietin production.
- Anemia is most commonly normocytic, but can be marcocytic, contrary to what is said in the slides, the doctor said that it is commonly macrocytic.

Myelodysplastic syndrome

- Acquired neoplastic disease of bone marrow.
- Primarily disease of old age.
- Mutations in the bone morrow stem cells result in prolonged survival and defective maturation. Thus, they will appear similar morphologically to megaloblastic anemia.
- Mature blood cells do not exist bone marrow like in the normal way.
- Patients commonly develop neutropenia and thrombocytopenia as well.
- Anemia is refractory to treatment; it resists the treatments because there is a problem in the DNA.
- RBCs are macrocytes.

Pathology Quiz 4



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HLS Pathology By Haneen

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			