Hematology

PATHOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number: 2

Subject: Anemia of diminished production

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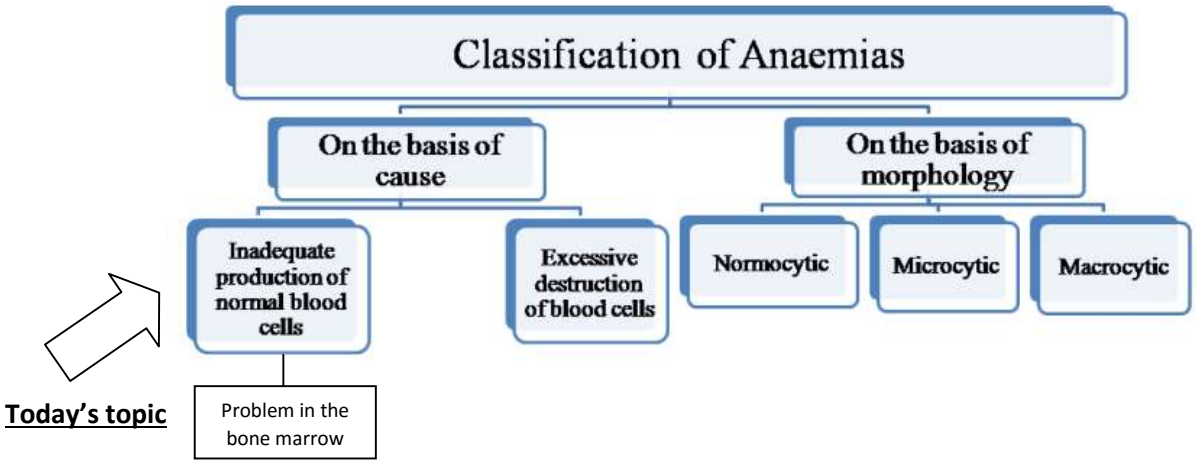
Anemia of diminished production

Lecture 2 - Objectives covered in this sheet:

- **Iron deficiency anemia**
- **Anemia of chronic disease**
- **Megaloblastic anemia**
- **Others…** (Anemia in liver disease / Anemia in renal disease / Aplastic anemia / Myelophthisic anemia)



- ✓ *Note) If only anemia is seen then it might be due to bone marrow problem (diminished production) or due to increased consumption of cells.*
- ✓ *Note) If there are multiple cytopenias like anemia, thrombocytopenia, & leukopenia then it's definitely a bone marrow problem.*

❖ Iron deficiency anemia

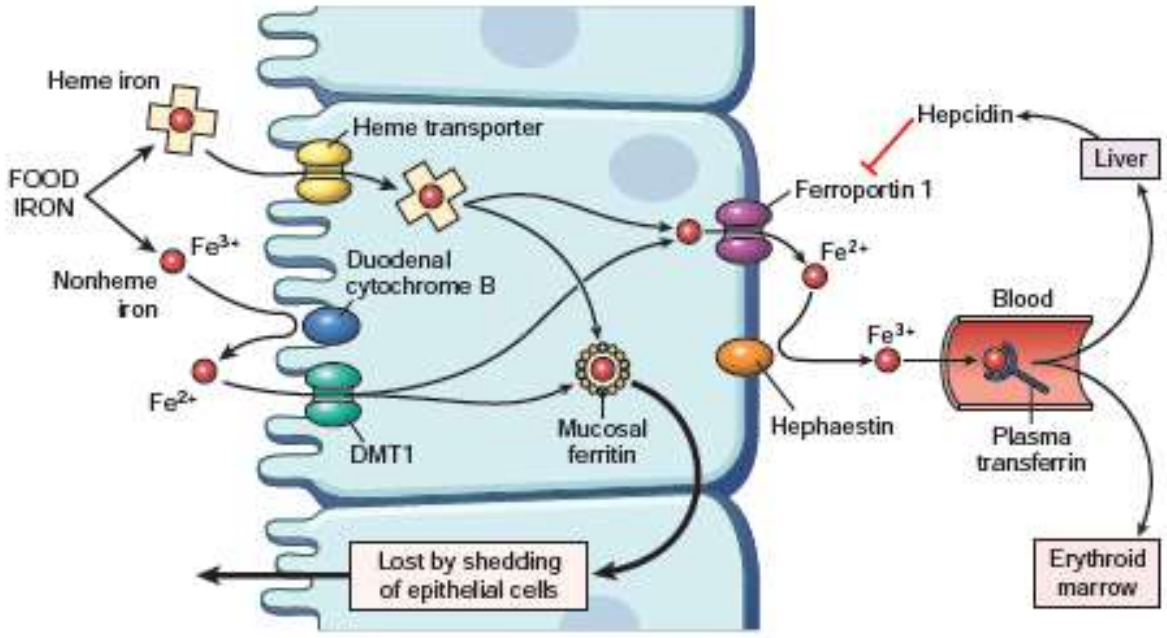
Before talking about Iron deficiency anemia & Anemia of chronic disease, let's talk a little about iron metabolism in the body.

- Normally, iron (Fe) is resent in 2 compartments of the body:
  - Storage compartment (~30%) ➔ bound to proteins (**transferrin** & **ferritin**)
  - Functional compartment (~70%) ➔ majority in **hemoglobin** then myoglobin
- Transferrin transfers iron within the blood, Ferritin is intracellular.
- Iron is interchangeable between the two compartments via **transferrin**.

- Transferrin is the major transport protein in plasma & is normally occupied by 1/3
- Ferritin in the ***plasma*** is derived from the storage pool of body iron; If you find plasma ferritin, this indicates an increase in the total body iron and vice versa.
- Total amount of iron in our body depends on the absorption, NOT on the secretion. (There is no mechanism in our body that can control secretion of iron when needed)
  → Secretion of iron is constant (1-2 mg/day) and happens by shedding of mucosal cells of the GI & skin.
- Dietary intake of iron is mostly from organic sources (meaty products) & to a lesser extent from inorganic sources (vegetarian sources)
- Absorption of iron from organic sources (Ferrous Fe^{2+}) is more efficient than absorption of iron from inorganic sources (Ferric Fe^{3+}).

Mechanism of absorption: (picture below)

- Iron enters from the GI tract to the cell through the receptor "DMT1" & inside the cell, it will either bind to ferritin **or** go to the blood (depending on the body need)
- Iron enters from the cell to the blood through the receptor "Ferroportin 1"
- When iron is in excess, hepcidin will increase, inhibiting Ferroportin 1, thus iron will remain bound to ferritin inside the cells.
- When iron is deficient, hepcidin will decrease, allowing iron to go to the blood from cells. *(REMEMBER: NO MECHANISM TO CONTROL SECRETION)*



- Iron deficiency is the <u>most common nutrition deficiency</u> in the world. The most common symptoms are non-specific symptoms of anemia & there also might be some others.

  Iron deficiency can result from:

  - Chronic blood loss (haemorrhage) ➔ MOST COMMON.
  - Impaired absorption
  - Increased requirement
  - Dietary

  (It is logical that chronic blood loss is the most common cause of iron deficiency, great example to indicate this is the menstrual cycle of females.)

  - Which clinical scenario is **<u>more serious:</u>**
    - A 19 year old lady, with sever menorrhagia (sever menstruation) presenting with shortness of breath on exertion, fatigue, pallor and a hemoglobin of 7.6g/dl (*very low*), low MCV
    - A 79 year old asymptomatic gentleman who, on routine checkup, was found to have a hemoglobin of 11g/dl (*little low*) and low MCV

  - The 79 year old asymptomatic man's case is more serious! because in the lady's case we know the underlying cause of that hemoglobin drop (anemia) which is heavy menstruation, while in the man's case we don't know the underlying cause of that little hemoglobin drop. It could be cancer or something serious that needs early intervention!

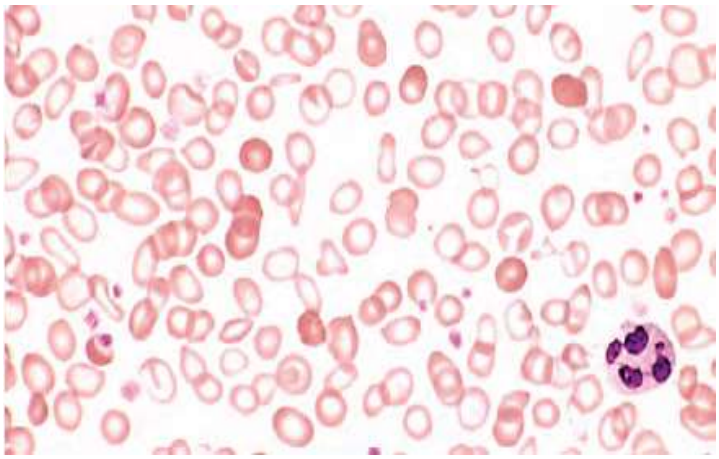
<u>Pathogenesis of iron deficiency</u>

- There will be a negative iron balance (secretion more than absorption/intake), secondary to any reason
- Iron stores that are present in mainly in the bone marrow (mainly <u>macrophages</u>) will shift it's pool to the periphery/blood circulation to support RBCs with iron
- The deficiency is continued until the storage pool is depleted ➔ Anemia develops.
- Iron deficiency anemic patients will have low ferritin & transferrin saturation.

Morphology of iron deficiency anemia

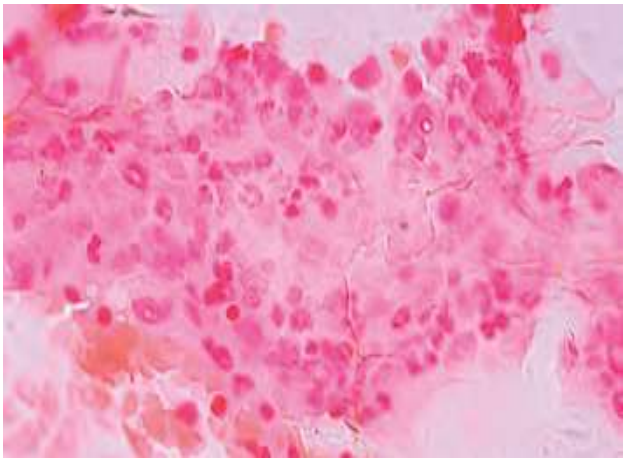
It is NOT specific but characteristic;

- **High RDW**; noticeable variation in cell sizes; some are normal, some are smaller ➔ microcytosis
- **Pallor centres** of some blood cells; due to hemoglobin deficiency
  ➔ hypochromia
  (Normally, that pale centre should not exceed 1/3 of the cell)
- **Elliptocytosis** (oval shape of RBCs)

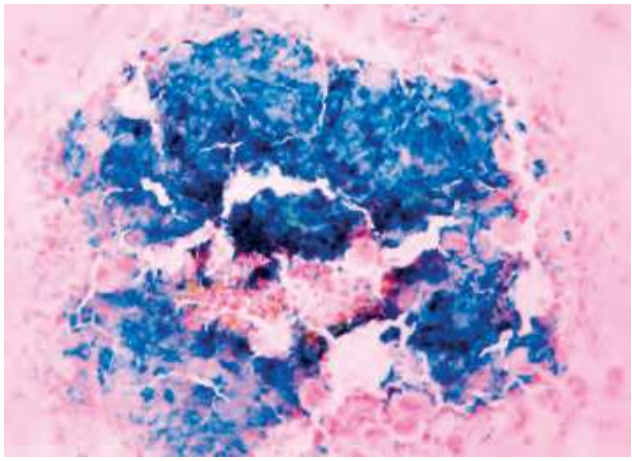


The gold standard for testing iron deficiency is examination of the **bone marrow.**
(Although is not being done anymore due to the presence of lab tests)

We add iron stain to the bone marrow biopsy, if iron is present then it will stain blue.



Bone marrow with iron deficiency



Normal bone marrow

Clinical presentation of iron deficiency anemia

There are signs and symptoms that are present in all anemias & other signs that are specific for iron deficiency anemia patients like:

- Tongue abnormalities (flattening of the villi)
- Pica
- Nails spooning (Koilonychia)
- Esophageal webs

Lab findings of iron deficiency anemia

- ✓ Low hemoglobin & hematocrit (because it's anemia)
- ✓ Low MCV & MCH (because it's hypochromic microcytic)
- ✓ Low ferritin & transferrin saturation
- ✓ Low hepcidin
- ✓ High TIBC (Total Iron-Binding Capacity)
- ✓ High RDW

TIBC: It indicates the affinity of the body to bind more iron.

➔ When iron is deficient, there will be high total iron-binding capacity and vice versa.

hence from its name, (capacity)

TIBC is opposite to transferrin saturation.

➢ Treatment by iron supplementation & treating the underlying cause.

❖ Anemia of chronic disease

It involves diminished red cell production secondary to a chronic disease like an inflammation, autoimmune reaction, malignancy, etc…

➢ The most common anemia in hospitalized patients.
(Remember: the most common anemia in general is iron deficiency anemia)

Pathogenesis

- When there is chronic infection, malignancy, etc… there will be an increase in proinflammatory cytokines, one of them is **IL-6 (Interleukin-6)**.
- IL-6 will increase the production of hepcidin
- Hepcidin will result in iron deficiency by 3 mechanisms:

1) Impairs absorption of dietary iron to blood by inhibiting "Ferroportin 1"

2) Starves the EP (Erythoid precursor) cells from iron by inhibiting the release of iron from macrophages that are inside the bone marrow; (If we examine the bone marrow, it will be profusely stained due to excess iron in macrophages)

3) Inhibits erythropoietin release from kidneys ➔ decreases EP proliferation

(Hepcidin has an immunologic role that starves the bacteria/any other pathogen causing the problem from iron, so it's a faulty process and doesn't always work well.)

Clinical manifestations of anemia of chronic disease

- Symptoms are mostly due to the underlying cause, not to the anemia itself.
- Anemia is mild (hemoglobin doesn't go below 10 g/dL)

Lab findings

- ✓ Low hemoglobin & hematocrit
- ✓ Hypochromic microcytic or normochromic normocytic (low or normal MCV/MCH)
- ✓ High ferritin (ferritin increases in inflammation
- ✓ Low TIBC

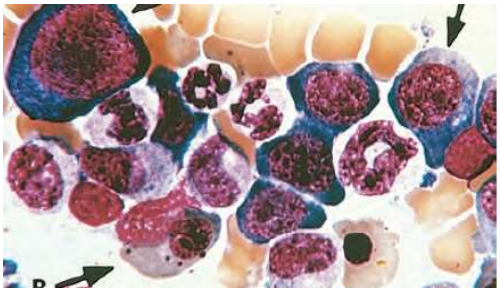
(Opposite to iron deficiency anemia)

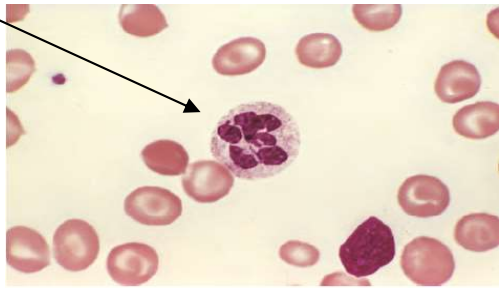
❖ Megaloblastic anemia

- It results from Vitamin B12/Folate deficiency
- In RBC precursors: - Slowly maturing nucleus & - Normal maturing cytoplasm (Asynchrony)
  - One of the 2 functions of Vitamin B12 is being a coenzyme for the production of Tetrahydrofolate (THF) which is responsible for DNA synthesis
  - When DNA synthesis is impaired/slowed down, nucleus will maturate slower than normal & cytoplasm will remain maturing normally because it has ribosomal RNA & proteins that are independent of nuclear DNA.

Morphology

- General enlargement of all the cells in the bone marrow, especially EP cells & enlargement of mature RBCs in the blood are bigger than usual.
  (hence the name –megaly-)
- Less dark nucleus with open chromatin
- Hypersegmentation of neutrophil nuclei (it will show >=5 segments)

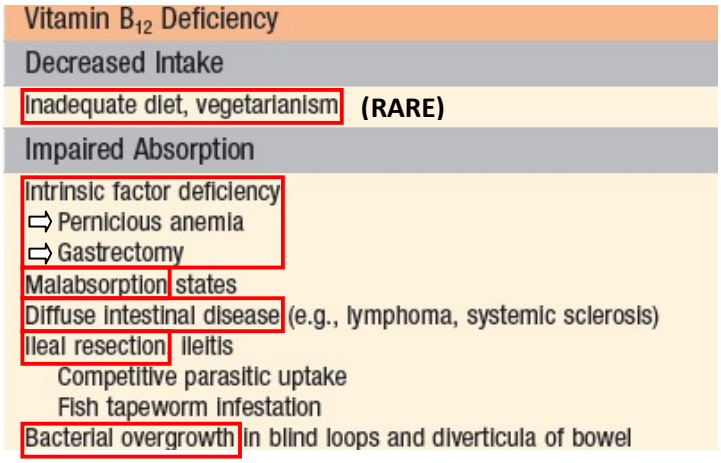




Absorption of Vitamin B12 **&** Vitamin B12 deficiency

- We consume most of the Vitamin B12 from animal products
- In the mouth's saliva, it is attached to a molecule called "haptocorrin"
- The stomach secretes an important factor called "intrinsic factor (IF)"
- In the duodenum, pancreatic enzymes will dissociate the Haptocorin-B12 complex and attach the Vitamin B12 to the intrinsic factor
- IF-B12 complex will travel to the terminal ileum & bind an IF receptor "cubulin" and then B12 will leave the complex
- Vitamin B12 is then transferred to the body via binding to "transcobalamin".

(Distortion at any of those steps will lead to Vitamin B12 deficiency)



- Nutritional deficiency of Vitamin B12 is exceptionally rare because the body store of Vitamin B12 can be enough for at least 5 years.
  (you have to be strictly vegan for that to happen)

- Most common cause of Vitamin B12 deficiency is disruption of absorption at the level of the **stomach**; (intrinsic factor will not attach to Vitamin B12)

- Bacterial growth interferes with the mechanism of Vitamin B12.

Pernicious anemia *(Subtype of Megaloblastic anemia)*

- It is an autoimmune disease
- It has 3 subtypes of antibodies at the level of gastric mucosa:
  - Antibodies that attack cells that produce intrinsic factor, mainly Parietal cells
  - Blocking antibodies; block IF-B12 complex from attaching to cubulin at ileum
  - Antibodies that directly attack the IF-B12 complex

Folate deficiency

- Like Vitamin B12, it is involved in production of THF and thus, DNA synthesis.
- Unlike Vitamin B12, nutritional deficiency of folate is common!
  (Body store of folate is enough for few months to maximally 1 year)

  ➔ During pregnancy, the mother must take folate supplementation due to the needs of the child, if the baby doesn't receive enough folate he will develop neural manifestations called "neural tube defects"
- Due to the effects on GI epithelium lining, GI symptoms will develop.

Clinical manifestations of megaloblastic anemia

- Non-specific signs of anemia (weakness, fatigue, shortness of breath, etc...)
- Signs of macrocytic anemia (large cells)
- Leukopenia
- Hypersegmented nucleus in neutrophils
- **In folate deficiency:**
  GI symptoms
- **Only in Vitamin B12 deficiency:**
  Neurologic symptoms (Numbness, Unsteady gate, Loss of position state)
- **Only in pernicious anemia:**
  Increased risk of malignancies

❖ Anemia in liver disease

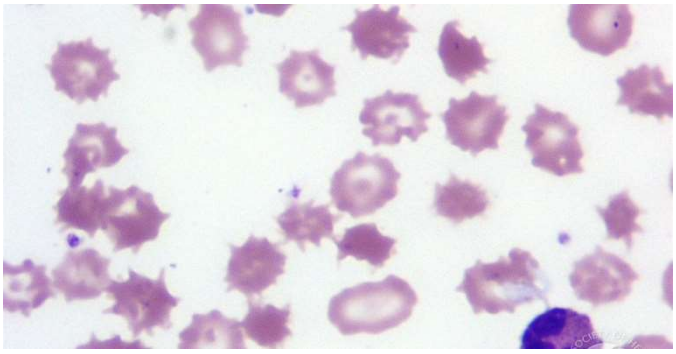
The patient who got liver disease might develop anemia due to several causes, including:

- Iron deficiency (MOST COMMON)
- Hypersplenism (hyperactive spleen results in rapid death of blood cells in it)
- Therapy-related haemolytic anemia
- EPO (erythropoietin) receptor suppression
- Alcoholic-cirrhosis-induced folate deficiency

Morphology

RBCs will have long & narrow projections on its surface

- This structure is called "**Spur cells**" (Acanthocytes)



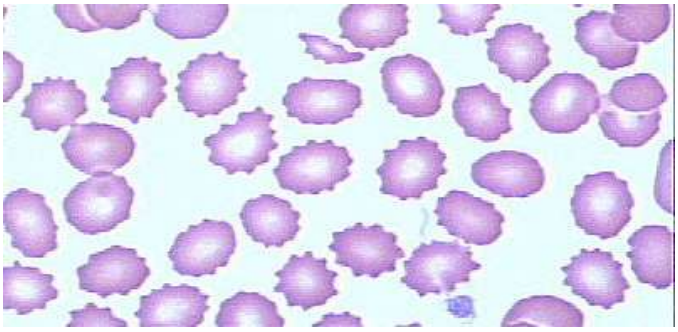
❖ Anemia in renal disease

- Most commonly a normochromic normocytic anemia
- It is related to impaired erythropoietin production by the damaged kidney
- Damaged kidney can cause multiple factors that might result in anemia, including:
  - High levels of inflammatory cytokines → high hepcidin.
  - Haemolysis
  - Chronic bleeding
  - Folate deficiency (in dialysis patients)

Morphology

RBCs will have short & wide projections on its surface

- This structure are called "**Ecchinocytes**"



❖ Aplastic anemia

- It results from **primary hematopoietic failure** & attendant **pancytopenia** (anemia, neutropenia & thrombopenia)
- 50% of the cases are idiopathic (most commonly)
- It increases the risk of developing malignant leukemias
- Other causes include:
  - Drugs
  - Viral infections
  - Radiation
  - Inherited (Fanconi anemia & Telomerase defects)

Fanconi anemia

- Autosomal recessive genetic disease
- More common in Eastern Europeans & Ashkenazi Jews
- It results in:
  - Low-set ears
  - Deafness
  - Strabismus
  - Abnormal thumbs
  - **Aplastic anemia**

Pathogenesis of aplastic anemia

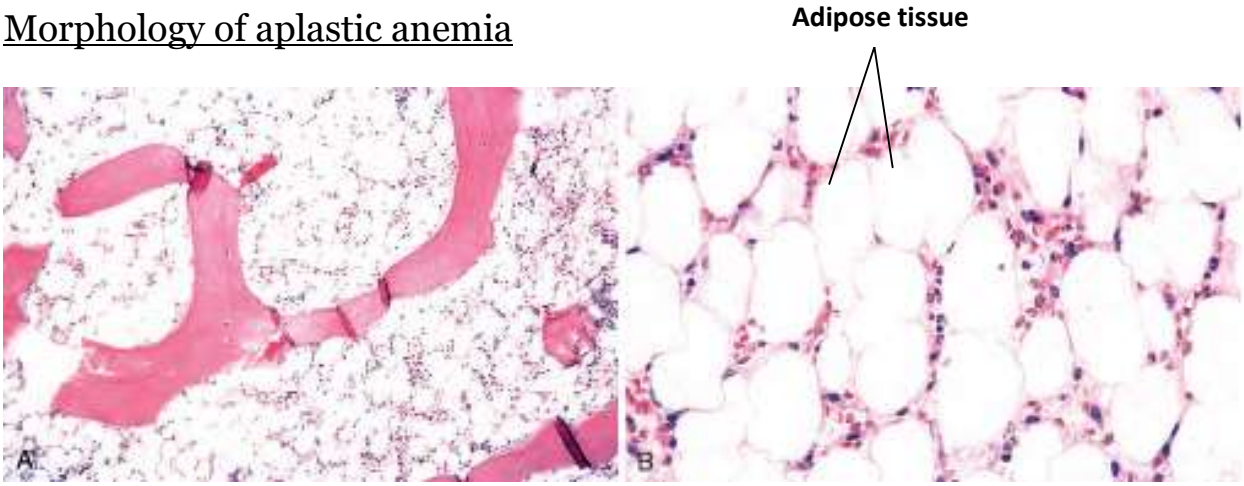
It is idiopathic but there are 2 expected theories due to environmental changes on stem cells, these environmental changes cause in altering the stem cell DNA, resulting in either:

- Reduced proliferative and differentiative capacity **OR**
- Expressing new antigens, making them susceptible for immune attacks

Clinical manifestations of aplastic anemia

- No gender predilection (can occur at any age)
- Stigmata of pancytopenia; (susceptibility to infections due to leukopenia, bleeding tendency due to thrombocytopenia)
- Mostly normocytic, sometimes macrocytic
- No splenomegaly
- No increased reticulocyte count

Morphology of aplastic anemia



Bone marrow affected by aplastic anemia (low power in the left, higher power on the right)

⇨ *Extremely hypocellular bone marrow; the majority of bone marrow spaces are occupied by **adipose tissue (fat)**. Also few numbers of lymphocytes & plasma cells are noted, but the normal haematopoiesis is severely diminished.*

- Bone marrow examination is a must for diagnosis
- Treatment of aplastic anemia by:
  - Immunosuppressive therapy **OR**
  - Bone marrow transplant (treatment of choice with 5-year survival of >75%)

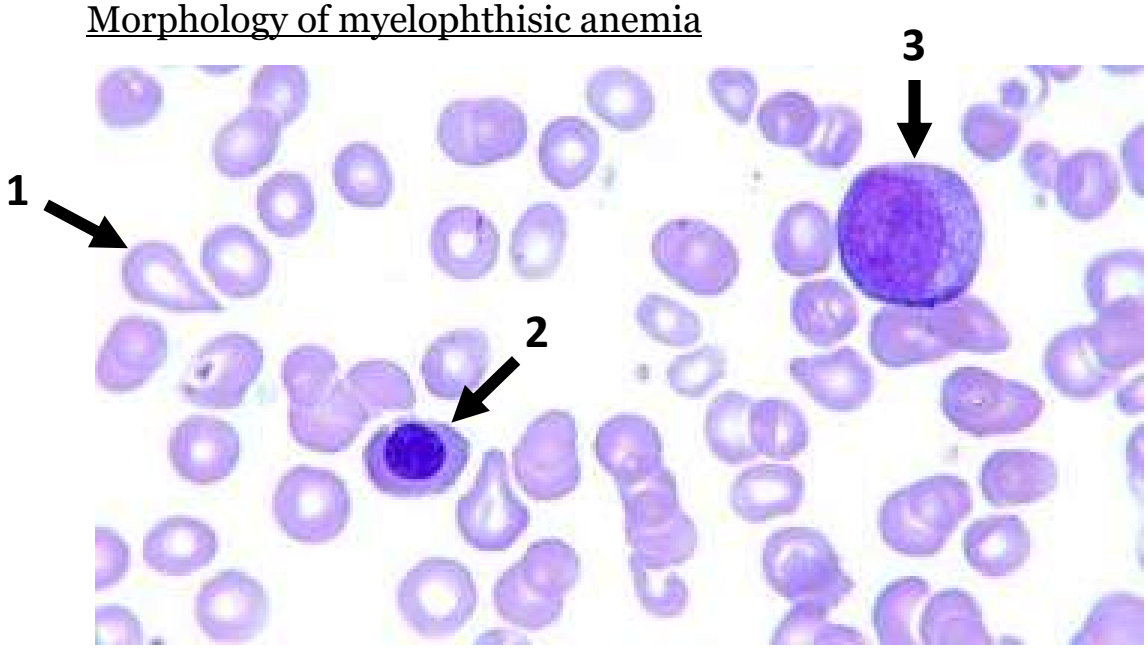
❖ Myelophthisic anemia

Extensive infiltration of the bone marrow space by molecules of the underlying cause that are responsible of the anemia, these could be:

- Infections (e.g. Tuberculosis)
- Malignancy (e.g. lung, breast, prostate cancers)
- Lipid storage disorders
- Osteosclerosis

- It involves a leukoerythroblastic reaction on the peripheral blood; (abnormal presence of RBC/WBC precursors in the peripheral blood)

Morphology of myelophthisic anemia



1) Tear drop mature RBC
2) Immature RBC precursor (EP cell)
3) Immature WBC precursor (immature myeloid)

→ **Leukoerythroblastic reaction**

- Bone marrow examination is a must for diagnosis
- Patient will have anemia & thrombocytopenia
  - ➔ WBC are less affected (normal count)
- Treatment by treating the underlying etiology (underlying cause)

Doctor's questions of lecture 2

1. All of the following can be found in iron deficiency anemia, except:

A. Low ferritin
B. Low serum iron
C. Low TIBC
D. Low transferrin saturation
E. Low MCV

2. Anemia of chronic disease is caused by elevated levels of:

A. Hepcidin
B. Iron
C. Ferritin
D. B12
E. Neutrophils

3. All of the following are true regarding megaloblastic anemia, except:

A. Defective DNA synthesis, resulting in nuclear immaturity
B. Macrocytic anemia
C. Can be seen in the setting of pernicious anemia
D. Most common cause is nutritional deficiency of B12
E. Can be associated with neurological symptoms in the case of B12 deficiency.

4. The most common cause of anemia in patients with liver disease is:

A. Iron deficiency
B. Hypersplenism
C. Therapy related hemolytic anemia
D. Therapy related suppression of EPO receptor
E. Alcoholic-cirrhosis-induced folate deficiency

5. One of the following can cause myelophthisic anemia:

A. Tuberculosis
B. B12 deficiency
C. Folate deficiency
D. Iron deficiency
E. Anemia of chronic disease.

GOOD LUCK <3