HEMATOLOGY
&LYMPH SYSTEM

Pathology sheet

Number	3
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The arrangement of this sheet differs from that of the record.

Anemia of peripheral removal in which we are losing hemoglobin and RBCs mass and the two major Causes are:

- **Anemia of blood loss, Hemorrhage**
- **Hemolysis**

And we rule out chronic blood loss such as iron deficiency anemia (IDA) because it is an anemia of decreased production in which we are losing iron not losing hemoglobin or RBCs; when we are taking about hemorrhage in **anemia of peripheral removal** we mean **acute hemorrhage** a case like a stab wound patient that comes to ER.

❖ Anemia of blood loss, hemorrhage:

Acute blood loss causes loss of RBC mass either by:

- Injury to the external arteries and cause hemorrhage.
- Internal bleeding such as ruptured aneurism or ruptured intestine.

Hemorrhage might be for many reasons ; internal, accidents or stabbing wound.

*exam question : which of the following causes of anemia has elevated reticulocyte count?

a) Anemia of acute hemorrhage
b) Chronic hemorrhage
c) A plastic anemia
d) Myelophlistic anemia

In anemia of blood loss or hemorrhage, the problem is not anemia in its self but **Hypovolemia** which is a loss of blood that exceed 20% of the whole blood volume and this lead to hypovolemic shock because of this huge loss in the fluids that can't be compensated by the body mechanisms.

*when a patient comes to you to ER you should follow "ABC"

A >> open the **A**irways

B>> check for **B**reathing

C>> check for **C**irculation

If the patient airways are open and his breathing is not compromised you have to check his circulation by measuring the blood pressure and if it is not okay you first treat him with fluids to restore the plasma and thus the blood pressure but we can't restore RBCs count so when you now do CBC the

patient he will be anemic but if you do the CBC before the administration of fluids the patient will not be anemic because he lost a proportional amount of RBCs and plasma.

*the full effect of anemia starts after 2 to 3 days , there will be shift of fluids from intracellular to extracellular and then the anemia will appear very clear.

Clinical findings:

1. Increase Erythropoietin level; to increase the production of RBCs
2. Increase reticulocyte count
3. Leukocytosis at first and when the patient starts recovery he will develop thrombocytosis
4. Normocytic normochromic anemia or slightly macrocytic because of high level of reticulocyte which is a larger cell than a mature RBC that increase MCV.

❖ Anemia of hemolysis :

It divided into :

- **Extrinsic** causes: here the RBC is functioning very well but it receives insult from outside that cause its hemolysis ; it could be :
  1. **Immune hemolytic** >> we have auto immune antibodies that attack RBCs and cause their destruction.
  2. Hemolytic anemia that result from **mechanical Trauma**; such as patients that have problem in heart e.g. Prosthetic heart valves or microangiopathic hemolytic anemia.
  3. **Infections**; malaria.

- **Intrinsic** causes ; (the doctor will discuss them in the next sheet) but In brief the problem is in the RBCs itself and it is either :
  - ✓ Genetic ;
    1. Defect in membrane >> hereditary spherocytosis
    2. Modified hemoglobin >> sickle cell anemia, thalassemia.. etc.
    3. Deficiency in enzymes >> G6PD deficiency
  - ✓ Acquired; intrinsic proximal nocturnal hemoglobinuria.

Try not to be confused with:

- Intrinsic and extrinsic hemolysis >> the problem either in the RBCs itself or from outside.
- Intra/extra vascular hemolysis :

- Intra vascular >> hemolysis occurs inside the blood vessels; in the blood stream.
- Extra vascular >> hemolysis occurs in the spleen.

In anemia of hemolysis we have **destruction of RBCs** so there **life span** will **decrease** from the normal 120 days so there will be **decrease in oxygen delivery** to the kidney which will respond by **increase** secretion of **Erythropoietin** to increase the hematocrit, the **bone marrow** will respond to high erythropoietin level and **try to compensate the loss of RBCs by increasing their production which lead to a condition of <u>erythroid precursor cells hyperplasia</u> and yields high reticulocyte count in the blood.**

- Massive destruction of RBCs will lead to the production of a byproducts;
  - Remember that hemoglobin is composed of globin chain (it is a protein that will by catalyzed into amino acids), heme ring (which will be converted to bilirubin) and iron which will go the iron stores.

00:00 – 10:00

Where the hemolysis happens?

❖ Extra vascular hemolysis :

Happens outside the blood vessels, in the **spleen** by the act of reticuloendothelial system (macrophages)

<u>Clinical findings</u>:

1. No hemoglobinuria ; no free hemoglobin in the urine
2. No hemoglobinemia ; no free hemoglobin in the blood
3. Low haptoglobin ?
   >> haptoglobin is a plasma protein with not really known function but what it does here is; in case of hemolysis there is amount of free hemoglobin in the blood that binds haptoglobin decreasing its level.
   But how come that we say extra vascular hemolysis outside the blood vessel and then we say low haptoglobin due to free hemoglobin in the blood that binds to it ? -_-
   Again , how extra vascular hemolysis is associated with low haptoglobin even though there is no hemoglobinemia ???
   Finally the answer is >> even if there is extra vascular hemolysis in the spleen , a small amount of free hemoglobin will go to the serum and binds haptoglobin and decrease its level

This small amount of free hemoglobin that reached the blood is **enough to cause low haptoglobin level but it is not enough to cause hemoglobinemia and hemoglobinuria**.

4. High LDH (lactate dehydrogenase) a protein that existed in most of the cells and when any cells rupture it will cause its level in the blood to increase >> very nonspecific finding.
5. Splenomegaly >> enlargement of the spleen due to hyperplasia of the macrophages within it.
6. Jaundice >> high bilirubin level.

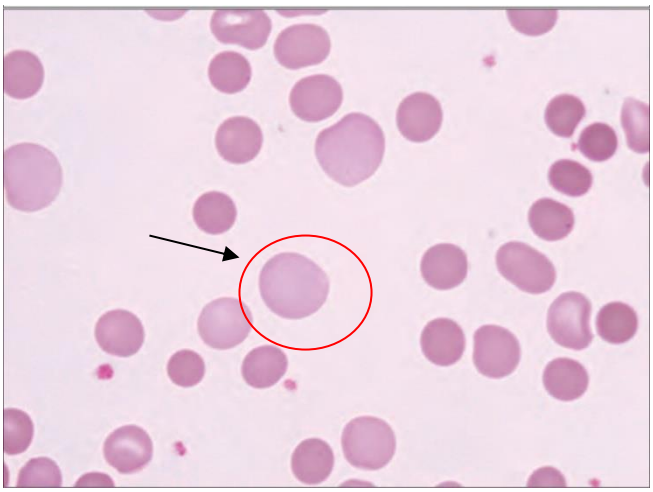
❖ **Intravascular hemolysis :**

Hemolysis inside the blood vessels, the clinical findings are pretty the same to extra vascular except we have hemoglobinemia and hemoglibinurea:

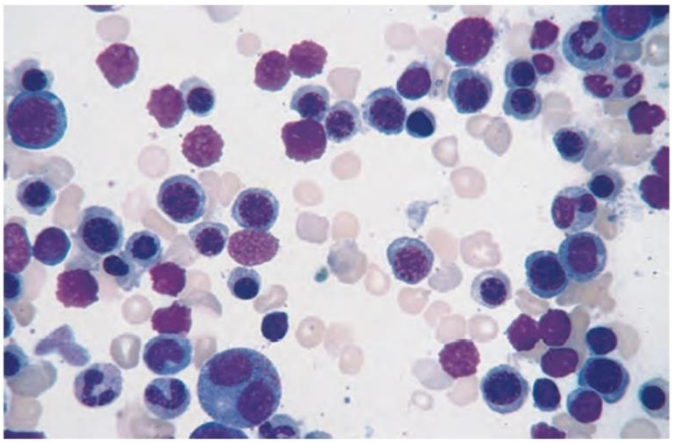
1. Hemoglobinemia
2. Hemogloburia
3. Low haptoglobin
4. High LDH
5. Splenomegaly
6. jaundice

Now what you will see in the peripheral blood in case of hemolysis?

❖ High reticulocyte
Count in the blood
A large cell its color
Is slightly blue due to
Remnant of RNA
And because it's
Large it increases
MCV a little bit.



❖ Erythroid precursor cells
Its normal level should
Not exceed 20% but here
It is 40 -50 %
>> erythroid hyperplasia



❖ Immune hemolytic anemia:

It is an extrinsic cause of hemolysis where we have autoimmune antibodies that attack RBCs and cause their destruction and those antibodies are of two types:

- Warm antibodies >> are of IgG type (and rarely IgA) antibodies bind RBCs at temperature of 37 C^o, 50 – 60 % of cases are idiopathic, sometimes associated with CLL, and SLE and some medications might induce warm auto immune hemolytic anemia >> mild anemia with splenomegaly.

- Cold antibodies>> are of IgM type, antibodies bind RBCs at 33 – 34 C^o at the peripheral parts of the body where the temperature are below 37 such as fingers, has two types :

    - Acute; as in cases of mycoplasma infection and EBV (infectious mononucleosis), usually resolves shortly after the infection is resolved and does not persist for long.
    - Chronic; in some lymphomas such as LPL (lymphoplasmastic lymphoma and it is the only type of lymphoma that routinely produces IgM).

Both of warm and cold auto immune hemolysis is extra vascular and happens in the spleen but the binding of antibodies to RBCs occur in the vessels and according to the temperature warm 37 or cold 33-34.

IgM : is a pentavalant molecule that can form penatmers (a large molecule composed of five IgM molecules) at once this binding is enough to block small capillaries of the periphery and shut the blood supply to the distal parts of the finger and cause ischemia and necrosis so patients are advise not to be exposed to severe cold temperature.

Coombs test :

this test is used to reveal if there is antibodies in the blood and it is of two types:

- Direct coombs test >> used to reveal antibodies that are binding to RBCs.
- Indirect coombs test >> used to reveal antibodies in the blood.

Direct coombs test :

we have an RBCs of a patient that we suspect of auto immune hemolytic anemia and then we add artificial antibodies to the RBCs and mix them together,

these artificial antibodies are designed in a way that will make them recognize the binding auto antibodies as an antigen and then binds to it and causes aggregate of blood cells and then form a clot >> positive direct comb's test.

Indirect comb's test:

We bring the serum of a patient whom suspected with free auto antibodies and then we add RBCs from outside and wait a little bit that if we have auto immune antibodies they will bind to the added RBCs, then next we add our artificial antibodies and continues as if it was direct . at last if a clot forms it means positive indirect comb's test .

Again ;

Direct >> reveal auto immune antibodies binding to RBCs.

Indirect >> reveal auto immune antibodies free in the serum.

❖ Hemolysis of mechanical trauma :

Mechanical trauma to the RBCs causes its damage and hemolysis .

Causes of trauma to RBCs:

1. Cardiac valve disease where there is a replacement of the diseased valve with a prosthetic one either from animal or metal; this prosthetic valve is not as smooth as the normal one thus result in a trauma to RBCs and causes it to breakdown.
2. Repeated physical activity; marathon racers.
3. Microangipathic hemolytic anemia" pathologic formation of fibrin micro thrombi in small vessels, RBCs are sheared (مقصوص) resulting in hemolytic anemia with schistocytes." Pathoma.
   Doctor said there is narrowing of the capillaries in which RBCs can't smoothly pass through so they break.
   Causes of Microangiopathic hemolytic anemia:
   a. DIC ; (disseminated intra vascular coagulation) the most common.
   b. Malignant hypertension
   c. SLE
   d. TTP ; thrombotic thrombocytopenic purpura
   e. Hemolytic uremic syndrome
   f. Disseminated cancer.

The common thing between all the causes of RBCs trauma is : Schistocytes.

Please remember that the Schistocyte is a marker of intravascular hemolysis and is not specific for a single cause of hemolysis

Schistocytes is a torn RBCs with a helmet shape, and it's associated with some parasitic infection in the RBCs such as Malaria and babesia.

❖ Infection

• Malaria:

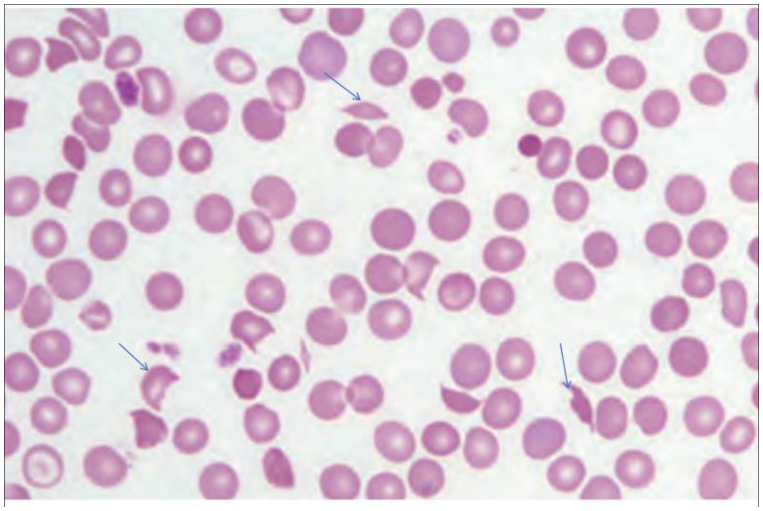
• Parasites within the RBCs, rupture resulting in hemolysis and episodic symptoms

• Hematin released from the RBCs results in brown pigmentation of the spleen, liver and bone marrow.

• Massive splenomegaly and occasional hepatomegaly.

• Falciparum can cause cerebral malaria which can be fatal.

Schistocytes



Now try to answer Dr.'s questions :

1. Other than anemia, one of the following can be seen in the setting of anemia of hemorrhage:

   A. Leukocytopenia1
   B. Neutropenia
   C. Leukocytosis
   D. Lymphocytopenia
   E. Thrombocytopenia

2. Which one of the following is most helpful to differentiate between intravacular and extravscular hemolysis:

   A. LDH
   B. Haptoglobin
   C. Bilirubin
   D. Hemoglobiuria

3. Warm antibody immune hemolytic anemia is most commonly caused by:

   A. IgM
   B. IgA
   C. IgG
   D. IgD
   E. IgE

4. Which one of the following is a characteristic finding in microangiopathic hemolytic anemia:

   A. Target cells
   B. Sickle cells
   C. Spur cells
   D. Ecchinocytes
   E. Schistocytes

5. Which one of the following can cause Cerebral malaria:

   A. P.vivax
   B. P. ovale
   C. P. falciparum
   D. P. malaria

Answers are : 1.c / 2.d / 3.c / 4.e / 5.c