Hematology

PATHOLOGY

■ Sheet ☐ Slide ☐ Handout

Number: 3

Subject: Anemia of Blood Loss {1}

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Date:

Price:

This Sheet's Sources

[1] Section 2 Record*[Sheet was not written in the same order of the lecture]*

[2] Robbins Basic Pathology – 9th Edition**[Pages 408-425] and pages 447 and 448 for polycythemia vera**

[3] Slides

The doctor reiterated that for the purpose of the test BOTH the lectures and the book are to be thoroughly studied.

Main Topics of the Lecture:

- Hemorrhagic Anemia
- Hemolytic Anemia-general
- Immunohemolytic Anemia
- Traumatic Anemia
- Infectious Anemia

Quick Revision

Anemia: Reduction in the oxygen-transporting capacity of blood, which stems [mainly caused] from a decrease in red blood cell mass to subnormal levels.

The following mechanisms serve as one basis for classifying anemia: {According to how RBC count is decreased}

[1] Blood Loss

A. hemorrhage

B. hemolysis (destruction of the red blood cells)

[2] Diminished Red Cell Production [Aregenerative Anemia]

1.Anemia of Blood Loss [Hemorrhage]

Divided into two main types {Acute & Chronic}

[A] Acute: **Trauma**

External -[Stab Wound, Car Accident, Gun Shot] or

Internal [Rupture of Aortic Aneurysm]

A healthy young patient can tolerate acute blood loss for up to 20% of the blood volume, which is around 1 Liter. However, if the blood loss **exceeds** 20% of blood volume [> 1 L] , the patient will face an immediate threat of a **hypovolemic shock** *rather than anemia*.

Hypovolemia: Is a state of decreased intravascular volume whether due to plasma loss (dehydration) or loss of all components of blood (RBCs and plasma as in hemorrhage)

If the patient survives the hypovolemic shock he will be carried to the hospital.

In cases of trauma, since the patient looses proportionate amounts of plasma and RBCs, anemia will not be evident, however, after the patient receives fluid, and when the fluid shifts from the interstitial compartment to the blood vessels diluting the RBCs, the full effect of anemia will be revealed, usually around 2-3 days.

[Q] Why is the RBC count low?

When trauma has occurred, RBCs have been leaked out of the patient's body.

[Q] When does anemia appear?

Couple of days after receiving fluid because shifting toward intravascular compartment takes 2-3 days.

The recovery from the ***blood loss anemia*** is enhanced by a compensatory rise in **erythropoietin** from the kidney.

In the *beginning*,acute hemorrhagic anemia is described as both **normocytic& normochromic** anemia.

And then the bone marrow reaponse will ensue, resulting in Reticulocytosis, and as you know, reticulocytes are larger than the mature RBCs, and hence the mean cell volume will increase, resulting in a slightly macrocytic anemia.

The doctor focused on that it is **slightly/mildly** macrocytic unlike megaloblastic anemia which is highly macrocytic.

Type of Anemia	**MCV [fL]**
No Anemia [Normal Healthy Person]	81-97
Acute Hemorrhagic	104-106 ***Slightly Macrocytic***
Megaloblastic	>120

Leukocytosis will occur in acute hemorrhagic anemia:

In acute hemorrhage, the stress hormones, adrenaline and cortisol are profusely [excessively] produced, causing the demargination in the blood vessels, and therefore leaking the WBC's into the circulation.

Also, in acute hemorrhagic anemia ***thrombocytosis*** upon recovery occurs.

[B] Chronic: Gastrointestinal Tract Lesions & Gynecologic Disturbances

It has been discussed with full details in the previous lecture so the following paragraph, quickly summarizing it, has been taken from Robbins.

With chronic blood loss, iron stores are gradually depleted. Iron is essential for hemoglobin synthesis and erythropoiesis, and its deficiency leads to chronic anemia of underproduction. Iron deficiency anemia can occur in other settings as well; it is described later along with other anemias caused by decreased cell production.

[Question] What is the name of anemia which results from chronic blood loss?

[Answer] iron deficiency anemia.

[Question] A compensatory rise in erythropoietin occurs in chronic blood hemorrhage?

True

False

[Answer] True; because rise in erythropoietin is found in all types of anemias except anemias caused by ***chronic renal disease or chronic inflammation***.

2. Hemolytic Anemia [Hemolysis]

Caused by accelerated red blood cells destruction resulting in the decreased life span, which is normally about 120 days.

In here, there is also a compensatory increase in the erythropoietin level.

Accumulation of hemoglobin degradation products, bilirubin and iron:

The globin "protein portion of hemoglobin" will be degraded into amino acids.

The protoporphyrin ring of heme will be converted into bilirubin, and then accumulated.

The iron of heme will not be converted, just accumulated.

The iron *turnover* is preserved, that means iron coming out from the hemolysed [destructed] RBC is the same used to produce more RBC's. This means that a patient having hemolytic anemia will **not** suffer from iron deficiency anemia.

In bone marrow, erythroid precursor hyperplasia occurs.

According to the destruction of red blood cells, hemolytic anemia can be divided into two main types [A] Extravascular [B] Intravascular

[A] **Extravascular** Hemolytic Anemia [More Common]:

- Destruction of the red blood cells can occur with the tissue macrophages of the spleen and the liver (outside the blood vessels).

- It is **not** associated with hemoglobinemia or hemoglobinuria, however it is associated with splenomegaly due to hyperplasia of macrophages.
- **Note:** hemoglobinemia means that free hemoglobin "not the hemoglobin which is present within the memebrane of RBCs" is high in the blood, while Hemoglobinuria means that free hemoglobin is high in urine.
- It is associated with low haptoglobin & high LDH (Lactate dehydrogenase).
- **Note:** Haptoglobin - in blood plasma- binds free hemoglobin released from erythrocytes with high affinity and thereby inhibits its oxidative activity. The haptoglobin-hemoglobin complex will then be removed by the reticuloendothelial system(mostly the spleen) thus decreasing the level of haptoglobin.

Question: How can you explain low haptoglobin in extravascular hemolysis though there is no hemoglobinemia " no free hemoglobin''?

Answer: excess hemolysis can release some hemoglobin causing haptoglobin levels to be decreased even the amount of free hemoglobin is not detected but when we do a test for haptoglobin, we can detect it because that little amount of hemoglobin is enough to bind haptoglobin to decrease its level.

Question: why do you find LDH high?

Answer: As a result of hemolysis , the content of RBCs will leak out and since LDH is founf inside RBCs; its level in blood will rise up.

- **Note:** Also in clinical practice patients -with cancer leukemia specifically and high blood cells count- treated with chemotherapy , their neoplastic cells are subjected to hemolysis thus LDH level will be high.

- It is associated with jaundice due to high bilirubin and possibly gallbladder stones**.**
- **Morphologically: we see polychromasia and spherocytes. In the bone marrow, erythroid cell hyperplasia is noted**

[B] **<u>Intravascular</u>** Hemolytic Anemia:

- Destruction of the red blood cells occurring within the vascular compartment.
- It can result from mechanical forces [turbulence created by a defective heart valve].
- or biochemical/physical agents causing damage to RBC membrane [toxins/heat].
- Intravascular Hemolytic Anemia leads to:

- Hemoglobinemia (because hemolysis occurs in the blood).
- Hemoglobinuria.
- Splenomegaly.

- **Morphologically: we see schistocytes.**

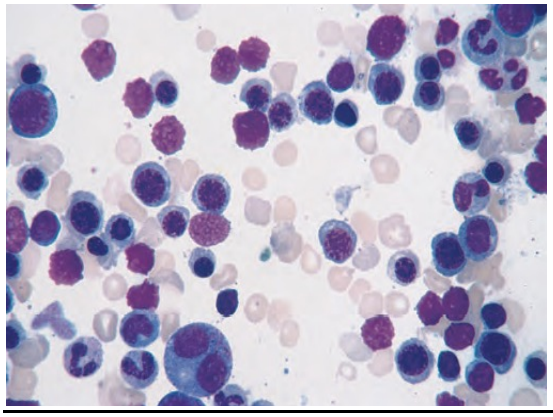
- Effect of Intravascular Hemolysis:

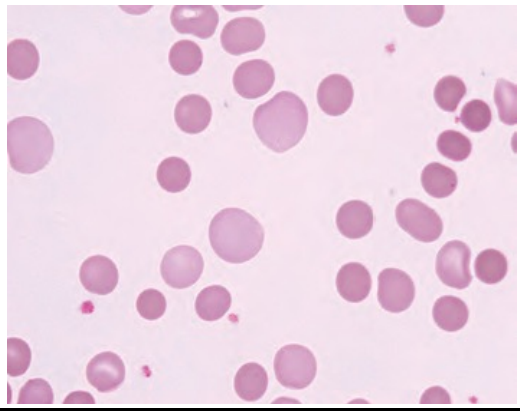
- Low Haptoglobin.
- High LDH [Lactate Dehydrogenase] – Normally found in RBC.

While hemolysis occurs, LDH that is found in the RBC will get into the free circulation, resulting in **high** amounts of LDH.

Both extravascular and intravascular hemolytic anemias will be associated with high bilirubin[hyperbilirubinemia] causing jaundice, and sometimes gallbladder stones.

Morphology of hemolytic anemia





According to the right picture, Notice the presence of mature RBCs (red and small cells) and the reticulocytes (polychromatic and large cells; these cells increase in

anemia of blood loss) , the polychromasia of reticulocytes results from presence of ribosomes remenants (RNA) giving the blue color and hemoglobin giving the red color.

According to the left picture, Notice the presence of blue abundant cells in bone marrow which they are erythroid precursor cells. Normally , these cells should not exceed 25% but in this condition they reach the 50% and this represents ***erythroid precursor hyperplasia.***

Another Classification for Hemolytic Anemias:

Destruction can be either – [1] Extrinsic OR [2] Intrinsic

{They are a complete different classification from Extra/Intra vascular}

[1] Extrinsic :

Factors from outside the RBC [extra corpuscular] affected the RBC.

It is usually acquired.

[2] Intrinsic :

Factors from the RBC itself [intra corpuscular] attacked the RBC.

It is usually inherited (except paroxysmal nocturnal hemoglobinuria).

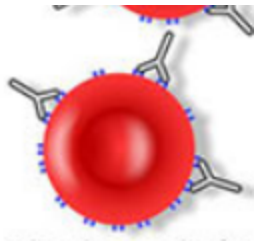
Intrinsic Factors arising from the RBC's:	Disease Caused
Membrane	Spherocytosis
Hemoglobin [Hb]	Sickle Cell & Thalassemia
Enzymes	G6PD Deficiency

Extrinsic:

1.Immune Hemolytic Anemia

Extrinsic hemolytic anemia

It is the RBC's destruction resulting in decreased life span, secondary to antibodies binding to the RBC's.



When the antibody binds to RBC; there are two possible cases:

[1] fixation of complement.

[2] The antibody acts as an opsonin; the spleen[macrophage] will think that this antibody is foreign, therefore consuming it.

In both cases the RBC will be lysed.

At what temperature will the antibody cause the problem?

This will classify "Immune Hemolytic Anemia" into two categories ;*warm & cold.*

- **Warm Immunohemolytic anemia:**
  Bind to cell membranes at normal body temperature [37 C].

  Commonly caused by ***IgG***, or rarely, ***IgA*** antibodies.

  In the majority of the cases [60%] we don't know the main cause/ route of pathogenesis, so it is termed as ***"idiopathic".***

  In the minority of cases, main cause be known, and they can result from:
- B-Cell Neoplasms [Chronic Lymphocytic Leukemia(CLL)]
- Autoimmune Disorders [Systemic Lupus Erythematosus(SLE)]
- Drugs [Alpha Methyldopa, Penicillin, Quinidine]

  Most patients have mild anemia [slightly anemic] with splenomegaly and require **no treatment**.
  CLL is the most common leukemia and stays with the patient around 10-15 years and ***suddenly*** anemia affects the patient so, you should think about immunohemolytic anemia(or iron deficiency anemia) and ***it is unlikely to be myelophthisic anemia(discussed in the previous lecture)*** since the patient is stable along these years.

- **Cold Immunohemolytic anemia:**
  Bind to cell membranes at temperatures below [30 C].

  Occurs in distal body parts such as ears, hands, and toes in cold weather.

  Caused by ***IgM antibody*** only.

  Divided into two types:
- Acute: Mycoplasma infection and infectious mononucleosis
- Chronic: Mainly idiopathic and sometimes secondary to B-Cell Lymphoid Neoplasms [Lymphoplasmacytic Lymphoma]

  Usually mild without clinical significance.

Mechanisms of Action of cold type:

1.In cold weather the IgM antibody will attach to the red blood cell's membrane resulting in a complement fix. The cell will proceed to the core body temperature which is 37, but hemolysis will not occur because IgM doesn't work in warm temperature.

The IgM will now detach from the RBC leaving the C3b attached there.

Recall; What is C3b?

It is an opsonin, polymorphic glycoprotein, and a component of complement fixation.

Now because C3b is an opsonin, the RBC's are phagocytosed by macrophages, mainly in **the spleen and liver**. The hemolysis is **extravascular.**

2.IgM binding is **pentavalent**, attaching each 5 antibodies to each other (in cold weather), then this large molecule goes to distal body parts blocking the capillaries there, and this called *Raynaud phenomenon*.

Immune Hemolytic Anemia can be diagnosed by Coombs test [Direct/Indirect]:

[1] Direct Coombs Test –Detects Antibodies on the **RBC and it is used to detect the presence of antibodies.** In this test, blood sample of patient -with immune mediated hemolytic anemia in which the antibodies bind to the antigens of RBCs- is incubated with antihuman antibodies (coombs reagent) which attack the

antibodies(here, they act as antigens) on the RBCs ; if the test gives positive result, that means RBCs agglutinate because antihuman antibodies form links between RBCs by binding to human antibodies on the RBCs.

[2] Indirect Coombs Test – Detects Antibodies of the **Serum and it is used to know the characterstic antigens.** In this test, Recipient serum is obtained by centrifugation containing antibodies (here , they are free antibodies in serum not bound to RBCs) then is added to donor's blood sample (obtained from a companies and the RBCs have a characterstic antigen). Recipient's antibodies that target the donor's RBCs form antibody-antigen complexes, after that antihuman antibodies (coombs reagent) are added to solution; if the test gives positive result, that means Agglutination of RBCs occurs, because human antibodies are attached to RBCs.

2.Traumatic Hemolytic Anemia

It is intravascular.

Abnormal mechanical forces result in red cell hemolysis.

[1] It can occur incidentally during any activity involving *repeated* physical blows or their equivalent [Marathon Race, Karate, Playing on Drums]. It is not severe, sometimes not even detected, and doesn't cause problems.

[2] Most significant mechanical hemolysis is produced by defective cardiac valves.

The cardiac valves are of two types; Biologic and Synthetic

Biologic: Taken from the hearts of any mammal.

Synthetic: Mechanical/ Metallic.

The synthetic [mechanical/metallic] are more likely to get defective causing turbulent blood flow, and then hemolytic anemia.

[3]Microangiopathic Hemolytic Anemia:

A disease causing the small vessels [capillaries/venules] to be partially obstructed or narrowed by lesions. The RBC's will try to squeeze itself through these obstructed/narrowed vessels → resulting in mechanical damage.

The most frequent cause of microangiopathic hemolysis is the intravascular deposition of *fibrin* known as disseminated intravascular coagulation [**DIC**]

Other causes of microangiopathic hemolysis include:

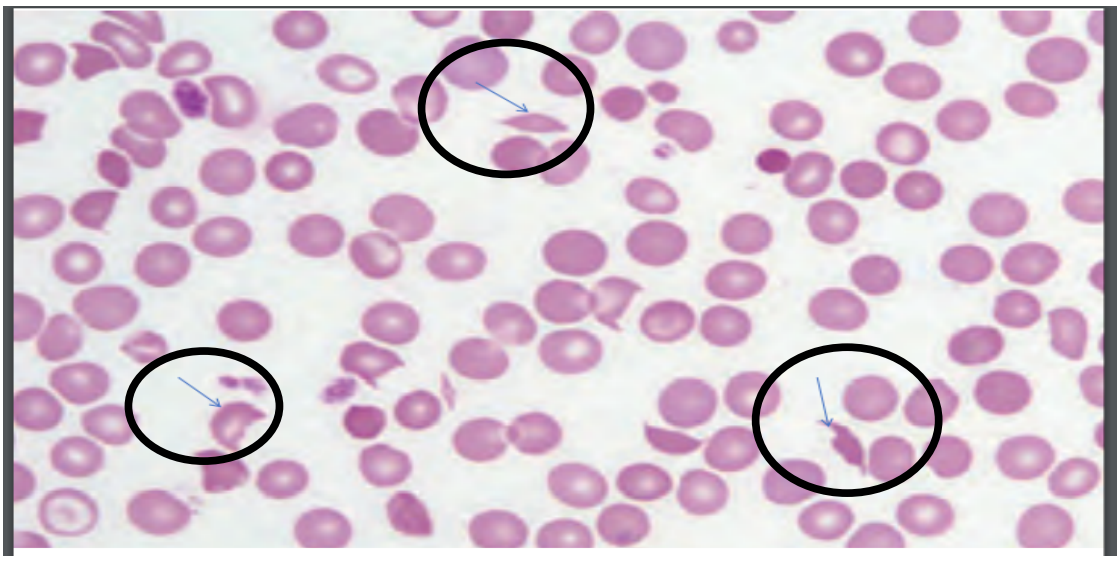
[Malignant hypertension , SLE ,Thrombotic thrombocytopenic purpura ,Hemolytic uremic syndrome [HUS] and Disseminated cancer]

All of them have a similar action which is obstructing the small blood vessels, obstructing the RBC's pathway, causing its hemolysis.

Microangiopathic hemolytic anemia is not, by itself, a serious disease, but it points to serious underlying disorders.[Like Disseminated Cancer for example]

In other words, while having microangiopathic hemolysis, anemia is of our **least** concern.

Morphology



The appearance of those burr/helmet/triangle pointed cells known as *schistocytes*.

They are specific for intravascular hemolysis, not for a certain disease.

3.Anemia caused by "Infections":-

- **Malaria**

P → Plasmodium

Caused by one of four types of protozoa
[P.*Falciparum*, P.Malariae, P.Vivax, P.Ovale].
The most important is the P.Falciparum which causes certian malaria [Celebral malaria] which is a serious disorder with a high fatality rate.

- The asexual phase is completed when the trophozoites give rise to new merozoites, which escape by lysing the RBCs.
- Malaria is associated with episodic symptoms.
- RBC, once lysed, will release hematin, resulting in brown pigmentation of the spleen, liver, & bone marrow.
- Massive spleen enlargement [splenomegaly]; and occasional hepatomegaly.

Normally the RBC is negatively charged and this prevents it's clotting on blood vessels, but when malaria[**P.Falciparum]** infects the patient, the RBC will turn into a positive charge , allowing the RBC to stick to the blood vessels of the brain →**Cerebral** Malaria → Death☹

The Doctor's Questions = [Solve them & the answers are in the next page]

1- Other than anemia, one of the following can be seen in the setting of anemia of hemorrhage:
   A. Leukocytopenia
   B. Neutropenia
   C. Leukocytosis
   D. Lymphocytopenia
   E. Thrombocytopenia

2- - Which one of the following is most helpful to differentiate between intravascular and extravascular hemolysis:
   A. LDH
   B. Haptoglobin
   C. Bilirubin
   D. Hemoglobinuria

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. malarie

Answers

Q	Answer
1	C
2	D
3	C
4	E
5	C

END OF LECTURE 3.

I really do apologize for any unintended mistake.

Best of Luck ☺

HasanSaimeh.