Hematology

PATHOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number: **5**

Subject: **Polycythemia**

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Price:

Before we start ..

●This sheet was written according to the recording that belongs to section 3.

●This is the last lecture about RBCs pathology.

●You are required to study the sheets & Robbins Basic Pathology 9th ed., pages 408-425 and 447-448

●Information that are mentioned in this lecture but not written in your textbook are underlined.

I. Introduction.

● ***Polycythemia*** denotes an abnormally **high red cell count**, usually with a corresponding increase in the **hemoglobin level**.

- In polycythemia, these two criteria usually go side by side, so whenever you hear polycythemia, it means high RBC count as well as elevated hemoglobin level.
- While in anemia, the decrease in hemoglobin level not necessarily reflects low RBC Count. for example, in beta-thalassemia minor there's a normal or increased RBC count (Erytherocytosis) associated with low hemoglobin level.

●polycythemia is less common than anemia.

●Polycythemia may be **absolute** or **relative**.

II. Relative polycythemia

●Relative polycythemia occurs when **there's a decrease in plasma volume with no change on the total RBC mass.**

- It results from dehydration, such as occurs with diarrhea, vomiting or diuretic therapy.
- Remember the case of the pregnant woman that has low blood count as a result of fluid retention that leads to dilation of RBC concentration, but she doesn't have anemia. The same concept is applied here.

III. absolute polycythemia

●In **absolute polycythemia**, the increase of RBC count is due to **overproduction of RBCs in the bone marrow**.

- It's classified into **primary** and **secondary** absolute polycythemia
- It's described as **primary** when increased red blood cell mass **results from autonomous proliferation of erythroid progenitors.**
- While in **secondary**, this overproduction is **induced by erythropoietin**.

a) Secondary absolute polycythemia.

●As we just mentioned, secondary absolute polycythemia results from excess stimulation of erythroid progenitors by erythropoietin.

●But how does this occur? (See figure 1)

- Remember that erythropoietin is **produced certain cells in the kidne**y, as a result of hypoxia.
- In these cells there's a transcription factor called ***HIF (hypoxia induced factor)***, this factor is activated by hypoxia.
- In **high oxygen tension**, HIF will be destroyed and thus inactivated.
- While in hypoxia, this factor will be stabilized ,and therefore it will act as a transcriptional factor for many genes, one of them is the gene that codes for erythropoietin .
- Hypoxia is sensed by kidney cells.

●so, we conclude that any condition that leads to generalized hypoxia, can cause absolute polycythemia.

- Examples are smoking ***(Which is probably the most common cause of polycythemia in Jordan)***, High altitude and High affinity hemoglobins.

●If the hypoxia was localized to the kidney (like in Renal artery stenosis or polycystic kidney disease), the kidney will think that it's a generalized problem, producing more and more of erythropoietin.

- It's noteworthy that **any localized hypoxia in any tissue other than the kidney will not affect erythropoietin production**.

●Moreover, some tumors can secrete erythropoietin. examples are Wilms tumor ,

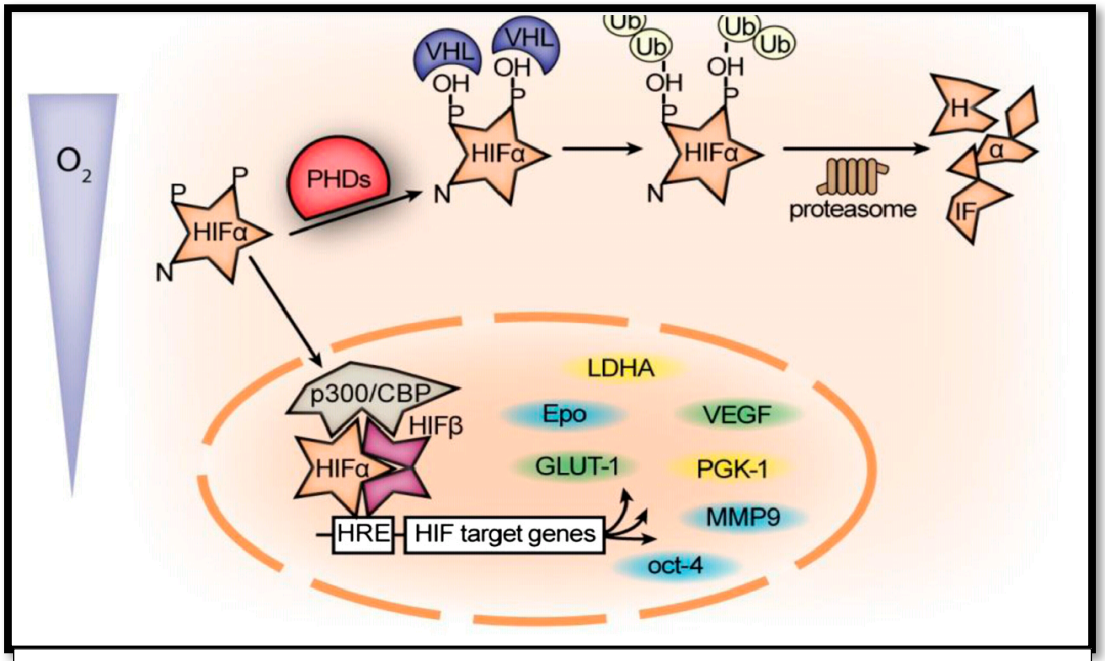

Figure 1: mechanism of erythropoietin gene stimulation.

Renal cell carcinoma, Celebellar hemangioma and Hepatocellular carcinoma.

b) *Primary absolute polycythemia*

● Primary absolute polycythemia, means that the increase in RBCs is not caused by any external factor, instead there's an **autonomous proliferation of erythroid progenitors**..

●The most common cause of Primary absolute polycythemia is ***polycythemia vera.***

● ***Polycythemia vera*** (PCV) is characterized by increased marrow production of red cells, granulocytes (including basophils), and platelets (panmyelosis),

- So It's a malignancy of bone marrow stem cells (*Chronic myeloproliferative disorder*)

- it causes overproduction of all myeloid derived cells.
- When we take a bone marrow biopsy, we will see **proliferation of all myeloid stem cells**. (While in chronic hemolytic anemia, only erythroid progenitors will be increased).
- But it is the **increase in red cells (polycythemia) that is responsible for most of the clinical symptoms .**

●PCV Is Strongly associated with **JAK2 mutation** .

- JAK2 is a down stream molecule in erythropoietin signaling pathway.
- The most common JAK2 mutation, is a Valine-to-phenylalanine substitution at residue 617.
- It's seen in over 90% of cases of PCV
- It's strongly associated with PCV, but it's not specific as it seen in 50% of cases of some other chronic myeloproliferative disorders, such as essential thrombocythemia and primary myelofibrosis.

●At first the patient will have **mild splenomegaly** (as a result of the congestion of the spleen) as well as **hypercellular bone marrow**.

- Late in the disease course, bone marrow fibrosis and significant organomegaly is present. PV carries a 2% risk for transforming to acute myeloid leukemia.

●Clinical features are:

- Pruritus, as a result of basophilia.
- Headache and dizziness, these are nonspecific symptoms, most probably due to due to hyperviscosity of the blood.
- Hyperuricemia and gout due to high cell turn over.
- Increased risk of both major bleeding and thrombotic episodes (what kills in PCV is the thrombosis not the neoplasm itself), examples :

  - ✓ Deep venous thrombosis
  - ✓ Stroke
  - ✓ Myocardial infarction
  - ✓ Bowel infarction
  - ✓ Budd-Chiari syndrome

- Bleeding tendency (due to dysfunctional platelets), it may lead to major hemorrhage and death in 10% of the patients.

●Treatment is Phlebotomy and JAK2 inhibitors:

- If you have high count of RBCs you have to donate them, as simple as that.
- And recently, JAK2 inhibitors have been developed.

●Criteria for PCV diagnosis according to WHO:

- **Major criteria :**

1. Haemoglobin >18.5 g/dL in men, 16.5g/dL in women. Or other evidence of increased red cell volume.
2. Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation.

- **Minor criteria :**

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic and megakaryocytic proliferation.
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro. (Not commonly used).

- To diagnose PCV, you have two observe two major and minor criteria, or the first major criterion with two minor criteria.
- The second major criterion is not sufficient, because JAK2 mutation is not specific for PCV.

●The Doctor's Questions:

1- Relative polycythemia occurs in the setting of:

A. Wilms tumor
B. Dehydration
C. Renal cell carcinoma
D. Polycythemia vera.
E. hypoxia

2- All of the following are examples of secondary absolute polycythemia, except:

A. Smokers
B. Renal artery stenosis
C. Polycystic kidney
D. Polycythemia vera
E. High altitude

3- The risk acute myeloid leukemia in polycythemia vera is:

A. 2%
B. 10%
C. 30%
D. 50%
E. 70%

4- One of the following is a major criterion for PCV

A. High hemoglobin
B. Hypercellular bone marrow
C. Low erythropoietin level
D. High erythropoietin level
E. Endogenous erythroid colony formation in vitro

5- a 21-years old male came to the ER as he suffers from severe chest pain. After doing CBC you suspected that he has anemia. By taking his history you knew that he has suffered from Salmonella osteomyelitis. your diagnosis is ?

A. Alpha-thalassemia
B. Beta-thalassemia major
C. PNH
D. Sickle cell anemia
E. Non of the above

Question	Answer
1	B. Dehydration
2	D. Polycythemia vera
3	A. 2%
4	A.High hemoglobin
5	D.Sickle cell anemia

●”you never know how strong you are, unless being strong is the only choice you have” .. be strong ;)

●Best wishes

●Mohammad Qussay Al-Sabbagh

☺ ☺ ☺ **THE END** ☺ ☺ ☺