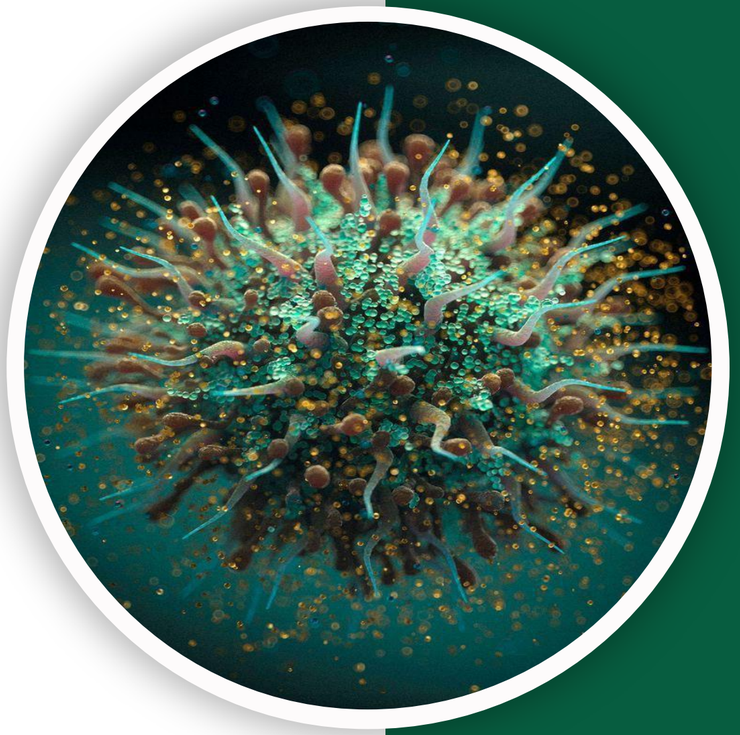
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HLS Pathology | FINAL 1

Polycythemia



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POLYCYTHEMIA

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DEFINITION

- Polycythemia: Increase in total RBC **mass (not number)** above normal range, and is defined by a numerical value, not by symptoms.
- Erythrocytosis: increased RBC s number (above the normal limit).
- *Note:* In very few conditions, the bone marrow produces a large number of RBCs, but these cells are empty (lack enough hemoglobin). Thus, total RBC mass does not increase above normal, and it does not reach true polycythemia.
- In most cases, erythrocytosis will lead to polycythemia.
- Polycythemia can be either absolute or relative:

1) Relative polycythemia: secondary to decreased plasma volume (seen in cases of water deprivation, severe diarrhea, vomiting, and excessive use of diuretics); a decrease in plasma volume (fluid part of the blood) leads to a high concentration of RBCs and hemoglobin, and hence polycythemia.

Normal RBC number but low plasma volume = high RBC concentration

ABSOLUTE POLYCYTHEMIA

Erythropoietin: a hormone produced by the kidney that stimulates bone marrow to produce RBCs.

2) Absolute (true) polycythemia: true increase in RBC mass (and concentration), secondary to increased RBC production by bone marrow rather than a decrease in plasma volume.

- Normal plasma volume but increase in RBC production = high RBC concentration
- Can be primary (no obvious cause for polycythemia, and the problem is within the bone marrow itself) or secondary (another obvious factor is causing polycythemia):
  - Primary: autonomous, high RBC production by a bone marrow neoplasm that arose from a mutation. Polycythemia resulting from a bone marrow neoplasm is termed **polycythemia vera**, and is characterized by low erythropoietin as a result of the negative feedback response created by high numbers of RBCs.
  - Secondary: caused by systemic hypoxia, which is sensed by the kidneys → kidneys secrete high amounts of erythropoietin → increased erythropoiesis. Therefore, unlike primary absolute polycythemia (polycythemia vera), secondary polycythemia is characterized by high erythropoietin. More on secondary polycythemia is on the next slide.

SECONDARY POLYCYTHEMIA

Causes of secondary polycythemia can be:

- Adaptive (a physiological response to hypoxia) : living in high altitude (where atmospheric oxygen levels tend to be lower), cyanotic heart disease (congenital heart defects that prevent the heart from pumping enough blood, leading to systemic hypoxia), and chronic pulmonary diseases including sleep apnea.
- Paraneoplastic: renal cancer, liver cancer which may secrete erythropoietin and lead to polycythemia. Recall that paraneoplastic syndrome is when a tumor, whether benign or malignant, secretes a hormone. This hormone could be endogenous to the organ from which the tumor originated, or belonging to a completely different gland (ectopic secretion).

SECONDARY POLYCYTHEMIA

Causes of secondary polycythemia can be:

- Surreptitious (meaning hidden, also known as blood doping): endurance athletes who take erythropoietin or even blood units to improve their athletic performance. This enhances oxygen delivery to skeletal muscles, which is particularly useful for long distance runners. These athletes exhibit high hemoglobin levels (polycythemia).
- Alcohol which causes both relative and secondary absolute polycythemia by different mechanisms: frequent urination (causing relative polycythemia because of fluid loss and leading to a high hemoglobin concentration), and depressed respiration (especially during sleep, leading to hypoxia).
- Smoking which causes hypoxia.
- In secondary polycythemia, regardless of the cause, you will see: high erythropoietin, no splenomegaly (*Important:* Unlike Polycythemia Vera, the spleen size is completely normal (no splenomegaly) in all causes of secondary polycythemia)

Explanation on next page

POLYCYTHEMIA VERA

- The most important cause of primary polycythemia
- Myeloproliferative neoplasm. Myelo : bone marrow, proliferative = production of a large number of cells (neoplastic).
- Mutation in tyrosine kinase JAK2 in bone marrow stem cells

The *JAK2* mutation makes the signaling pathway **constitutively active** (permanently active without needing erythropoietin), making hematopoietic cells independent of growth factors.

- Normally acts in the signaling pathway of erythropoietin receptor and other growth factor receptors
- Hematopoietic cells become less dependent on growth factors
- Excessive proliferation of erythroid, myeloid cells and megakaryocytes (panmyelosis)
- Not only increase in RBCs but WBCs and other blood cells, although Erythrocytosis is most prominent, results in polycythemia
- Splenomegaly is common with all myeloproliferative diseases, including polycythemia vera (a primary polycythemia), but is not seen in secondary polycythemia.

POLYCYTHEMIA VERA

As mentioned on slide 4, polycythemia vera is a type of primary polycythemia caused by a neoplasm. It is caused by a mutation in tyrosine kinase JAK2 in bone marrow stem cells, which is important in the signaling pathway of the erythropoietin receptor. This mutation results in the permanent activation of the erythropoietin receptor (the signaling pathway proceeds even in the absence of erythropoietin). When hematopoietic stem cells are affected by this mutation, all types of blood cells are produced in large numbers (panmyelosis), with RBCs being produced the most. As previously mentioned, low erythropoietin is a characteristic of polycythemia vera.

Key words to look for with polycythemia vera: neoplasm, panmyelosis, low erythropoietin, splenomegaly, primary polycythemia, JAK2.

SYMPTOMS OF POLYCYTHEMIA

Whether primary or secondary

Increased redness of the skin, especially in the face.

- Plethora (red skin) / cyanosis (blue skin because of hypoxia that cannot be resolved, e.g. in patients with heart disease)

Chronic hypoxia, especially in children with congenital heart disease (CHD), can cause increased cyanosis due to increased deoxygenated hemoglobin.

- Headache and dizziness (from hypertension resulting from the high RBC mass)
- Slow circulation (especially in small circulation and delicate organs like the retina because of the crowdedness of RBCs) and hyperviscosity cause cyanosis, blurred vision, tissue ischemia and necrosis
- Thrombosis, or bleeding (disturbed function of vWF; high numbers of RBCs may also interfere with the function of platelets and the coagulation system)

In polycythemia vera: similar symptoms plus:

- Pruritus (aquagenic, meaning itching when exposed to hot water). Recall that polycythemia vera causes panmyelosis, so WBCs are also produced in large amounts. Basophils in particular cause a variety of symptoms as they secrete histamine, one of which is pruritus.

SYMPTOMS OF POLYCYTHEMIA

In polycythemia vera: additional findings:

- Peptic ulcer as histamines produced by basophils also increase stomach acidity.
- Secondary gout, which is associated with neoplasms of the bone marrow as the high turnover rate of RBCs produces high levels of uric acid (recall nucleotide metabolism) which precipitate in joints and soft tissue (arthritis, kidney stones, tophi). Secondary Gout Increases in severity overtime.
- Occurs in old adults as do most tumors ⟶ Because of repeated damage
- Chronic disease (cancer is always chronic)
- Treated using phlebotomy (drawing blood from a vein) to decrease the patient's hemoglobin concentration.

Polycythemia Vera Phases:

In polycythemia vera: there are 2 Phases:

- Spent phase: a phase that occurs after an interval of 10 years of symptoms, hematopoietic cells die and bone marrow becomes fibrotic, hematopoiesis shifts to spleen and splenomegaly exacerbates.

- Rarely and after a long time some patients enter the blast phase/crisis, where the accumulation of more mutations over time leads to the transformation from polycythemia vera into acute myeloid leukemia, which is a much more aggressive disease. It is classified as high grade with visible myeloblasts (very immature).

LABORATORY FINDINGS OF POLYCYTHEMIA

- High hemoglobin concentration (>16.5 g/dL in men, 16 in women) and high hematocrit (>49% in men, 48% in women). These numbers must be persistent in order to diagnose the patient with polycythemia vera. However, slightly lower values may be accepted if the patient has iron deficiency.
- High RBCs count (erythrocytosis!)

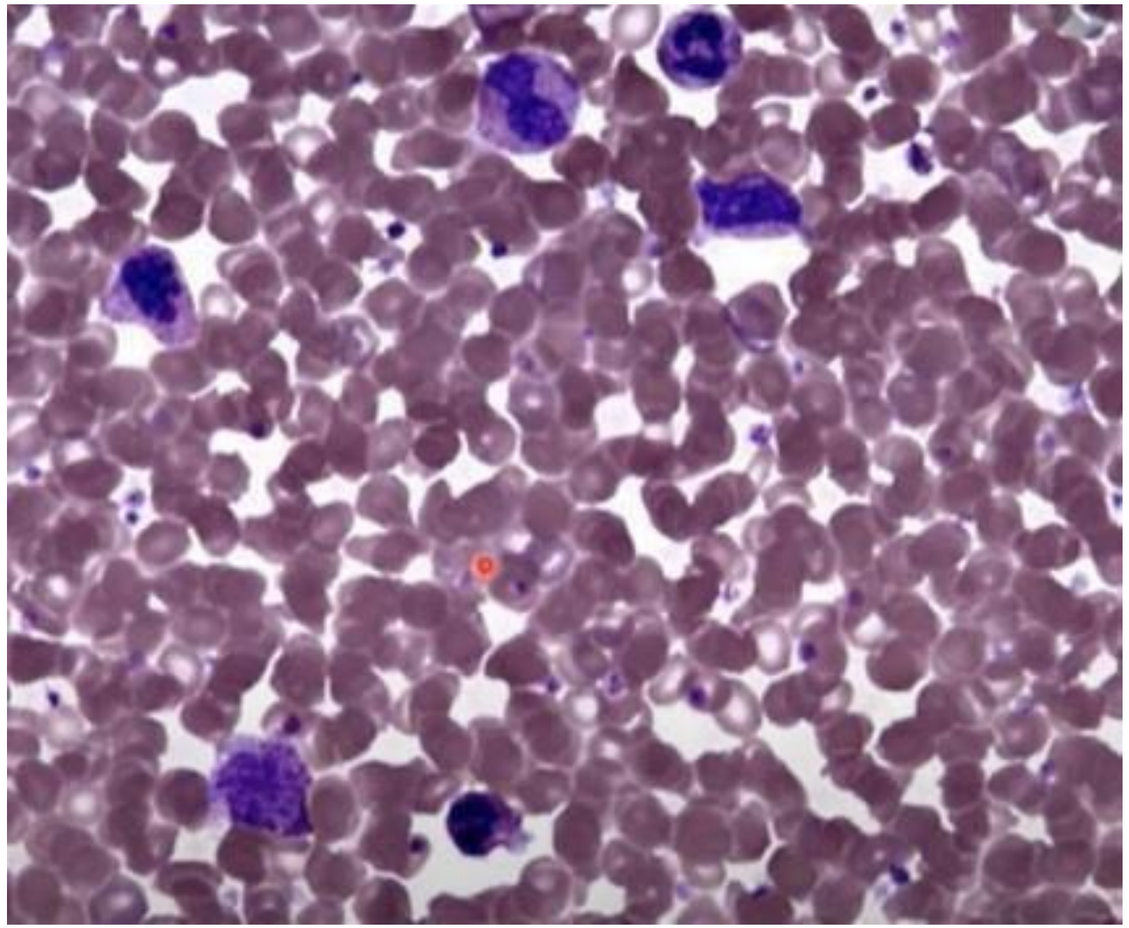
We get an exception if patients develop both diseases (Polycythemia & Iron Deficiency) at the same time.
A patient with Hemo concentration 16 and also have iron deficiency is considered Polycythemic; this is an exception.

- These tests might be masked if iron deficiency develops, high RBC number but low iron thus low Hb content in each RBC, masking laboratory tests NOT symptoms

In polycythemia vera: additional findings:

- Leukocytosis (including basophils, as previously mentioned) and thrombocytosis are common
- JAK2 gene mutation: positive. This mutation occurs in almost all patients with polycythemia vera. Although it is also found in other diseases, it is most common in polycythemia vera.
- Low erythropoietin level
- Hypercellular bone marrow with panmyelosis

Pan: all



Compact, crowded, dense RBCs. A single RBC’s contouring and biconcave shape cannot be seen.

- Peripheral blood smear in polycythemia: packed RBCs, boundaries can’t be seen

Pathoma Summary For Polycythemia Vera

A. **Neoplastic proliferation** of **mature myeloid cells**, especially **RBCs**
   1. **Granulocytes and platelets are also increased.**

B. Associated with **JAK2 kinase mutation.**

C. Clinical symptoms are mostly due to **hyperviscosity of blood.**
   1. **Blurry vision and headache**
   2. Increased risk of **venous thrombosis** (e.g., hepatic vein, portal vein, and duralsinus)
   3. **Flushed face due to congestion (plethora) – Red Skin**
   4. **Itching**, especially **after bathing – Aqagenic** (due to **histamine** release from increased **mastcells and basophils**), Also Called **Pruritus (aquagenic) happen due to increased basophils → Histamine release → Pruritus**
   5. **peptic ulcer caused by histamine release by basophils and mast cells**
   6. **Secondary gout (Arthritis, Kidney stones, tophi).**
   7. **Pruritus + peptic ulcer.**
   8. **(itching)**
   9. **Usually because of vascular complications.**
   10. **Increased risk of secondary gout due to large numbers of Hematopoietic cells that are dying and releasing uric acid.**

Pathoma Summary For Polycythemia Vera

D. Treatment is **phlebotomy; second-line therapy is hydroxyurea**.
   1. Without treatment, death usually occurs within one year, usually because of vascular complications.

E. **PV** must be **distinguished** from **reactive polycythemia**.
   1. In PV, *erythropoietin (EPO) levels are decreased, and Sao2 is normal.*
   2. In reactive polycythemia due to high altitude or lung disease, *Sao2 is low, and EPO is increased.*
   3. In reactive polycythemia due to ectopic EPO production from renal cell carcinoma, *EPO is high, and Sao2 is normal.*

USMLE Table for Laboratory finding regarding every type of Polycythemia

Polycythemia

	PLASMA VOLUME	RBC MASS	O_2 SATURATION	EPO LEVELS	ASSOCIATIONS
Relative	↓	–	–	–	Dehydration, burns.
Appropriate absolute	–	↑	↓	↑	Lung disease, congenital heart disease, high altitude, obstructive sleep apnea.
Inappropriate absolute	–	↑	–	↑	Exogenous EPO (athlete misuse, also called "blood doping"), androgen supplementation. Inappropriate EPO secretion: malignancy (eg, RCC, HCC).
Polycythemia vera	↑	↑↑	–	↓	EPO ↓ in PCV due to negative feedback suppressing renal EPO production.

↑↓ = 1° disturbance

Myeloproliferative neoplasms — Malignant hematopoietic neoplasms with varying impacts on WBCs and myeloid cell lines.

Polycythemia vera — Primary polycythemia. Disorder of ↑ RBCs, usually due to acquired *JAK2* mutation. May present as intense itching after shower (aquagenic pruritus). Rare but classic symptom is erythromelalgia (severe, burning pain and red-blue coloration) due to episodic blood clots in vessels of the extremities A. Associated with hyperviscosity and thrombosis (eg, PE, DVT, Budd-Chiari syndrome).

↓ EPO (vs 2° polycythemia, which presents with endogenous or artificially ↑ EPO).

Treatment: phlebotomy, hydroxyurea, ruxolitinib (JAK1/2 inhibitor).

Quiz

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Corrections from previous versions:

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