POLYCYTHEMIA VERA

TERM DEFINITION

A chronic myeloproliferative neoplasm (MPN) associated with elevated red cell mass and Hb/Hct and increased risk of thrombosis and disease progression to myelofibrosis or acute leukemia.

MPN CLASSIFICATION

PHILADELPHIA CHROMOSOME

POSITIVE

Driven by Philadelphia chromosome (BCR-ABL+)

NEGATIVE

- **Polycythemia vera**
- Primary myelofibrosis
- Essential thrombocythemia
- Chronic neutrophilic leukemia
- Chronic eosinophilic leukemia

CLINICAL PEARLS

Aquagenic Pruritis

Aquagenic pruritis may predate diagnosis by years; present in one-third of patients at diagnosis.

Clots

Patients may present with thrombosis in unusual sites in both arteries and veins.

Von Willebrand Disease

Patients may develop acquired von Willebrand disease and have paradoxical bleeding.

Iron Deficiency

Patients often present with iron deficiency from chronic gastrointestinal blood loss.

Stem Cell

Polycythemia vera is a stem cell disorder, hence the frequent elevation of white cells and platelets.

Macrocytosis

Patients often have elevated mean cell volume (MCV) from use of hydroxyurea to treat the disease.

PRESENTATION

SYMPTOMS

CONSTITUTIONAL:
- Fatigue
- Night sweats
- Fever

AQUAGENIC PRURITIS:
Intense itching within 30 minutes of exposure to (typically warm) water.

VASOMOTOR:
- Erythromelalgia
- Headache
- Dizziness
- Tinnitus
- Visual disturbances
- TIA

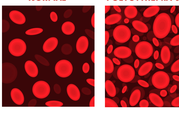
SYMPTOMS OF IRON DEFICIENCY:
- Pica
- Restless legs
- Headache
- Hair loss
- Brittle nails

HISTORY OF THROMBOSIS OR BLEEDING:
- Arterial thrombi
- Venous thrombi

TIA, transient ischemia attack

SIGNS

- Hypertension
- Plethora
- Cyanosis
- Splenomegaly (one-third of patients)



Typical CBC from patient with plocythemia vera and iron deficiency:

WBC	RBC	Hgb	Hct	MCV	MCH	MCHC	RDW	RDWSD	Plt Ct
7.7	4.96	16.3	37.3	75	21.2	28.2	22.5	58.0	455

HEMATOLOGY LABS:
- Elevated Hb/Hct
- Thrombocytosis in some
- Leukocytosis in some

JAK2* SEQUENCING → V617F mutation in 95% of cases

** JAK2 is also known as Janus protein tyrosine kinas*
Jak2 V617F is also present in many other MPNs

LDH → Elevated in 50%

SERUM ERYTHROPIETIN → Low level

IRON INDICES:
In those presenting with iron deficiency:
- Low serum iron
- High TIBC (surrogate for transferrin level)
- Low ferritin (marker of iron stores)

CBC, complete blood count; TIBC, total iron binding capacity

DIAGNOSIS

MAJOR CRITERIA*
- Hb > 16.5 g/dL or Hct >49% in men; Hb > 16 g/dL or Hct > 48% in women.
- Characteristic findings in bone marrow biopsy.
- *JAK2* V617F or *JAK2* exon 12 mutation.

MINOR CRITERION
- Low serum erythropoietin level.

** Diagnosis of PV requires either all 3 major criteria or the first 2 major criteria and the minor criterion*

DIFFERENTIAL DIAGNOSIS

Causes of **secondary polycythemia** including*:
- Sleep apnea
- Testosterone supplements
- Hypoxic pulmonary disease
- Hepatoma
- Leiomyomatoma
- Cerebellar hemangioblastoma
- Congenital erythrocytosis

** None of these conditions is associated with JAK2 V617F*

THERAPEUTIC PRINCIPLES

Removal of blood to lower the Hct to < 45%:
- Therapeutic phlebotomy

Cytoreduction:
- Typically with hydroxyurea
- Interferon an alternative

Antiplatelet agents:
- Low-dose aspirin

COMPARATIVE PHYSIOLOGY

Polycythemia vera (also referred to as primary erythrocytosis in the veterinary literature) is rarely reported in animals. Recently the V617F genetic mutation in JAK2 was identified in dogs with the condition! Polycythemia vera is usually a diagnosis of elimination, ruling out other causes of secondary erythrocytosis or a relative increase in Hct.

PROXIMATE MECHANISMS

JAK2 V617F is an acquired somatic gain-of-function mutation that results in **constitutive activation of the JAK-STAT signaling pathway**, allowing the cells to bypass their growth-control mechanisms and conferring a growth advantage to the mutated cells.

The ruddy complexion (red facies) observed in patients with polycythemia is caused not so much by the thicker blood (higher Hb) but rather by vasodilation of subcutaneous blood vessels. If we consider **Poiseuille's law**, we can see that this is an adaptive response:

$$\Delta p = \frac{8\mu LQ}{\pi R^4}$$

According to Poiseuille's law, a change in radius of a blood vessels counteracts the effect of viscosity (u) on blood pressure (delta P) by the fourth power... big bang for the buck!

EVOLUTIONARY MECHANISMS

Evolutionary mechanisms may be viewed through 2 prisms:

The **first** deals with evolution of organisms within an ecosystem. Why are humans so vulnerable to cancer, or clonal conditions such as polycythemia vera? The answer lies, in part, in the fact that we have lots of fast growing, self-renewing cell types in our bodies and the more cell divisions, the more opportunity for mutations to creep in. When signaling pathways are affected, a growth advantage may occur. This is the cost of renewing our cell populations.

A **second** view is that of cancer, or clonal disorders such as polycythemia vera as a Darwinian process in and of itself. According to this hypothesis, first proposed in 1976, cancer evolution is governed by the interplay between generation of heritable variation and the Darwinian selection of certain cells based on their relative fitness advantage. In polycythemia vera, the initial mutation in JAK2 initiates the condition, while additional mutations lead to transformation to AML and MF in some patients.

HISTORY OF MEDICINE

Polycythemia vera was first described by a physician named Vaquez in 1892, and it was named "Vaquez's disease" for several decades after. Writing for the British Medical Journal in 1913, a physician lamented that "no factor could be ascertained in the case described here which seemed to throw any light on the etiology of the condition". It would some 90 years later (2005) when 2 groups discovered the V617F mutation in patients with polycythema vera.

NOTES

ATTRIBUTIONS
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The Blood Project
ENCYCLOPEDIA OF BLOOD