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From Diagnosis to Health Practice: Polycythemia Vera. A Literature Review

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Abstract:

Introduction and purpose: Polycythemia vera (PV) is a chronic myeloproliferative neoplasm, part of the group of Philadelphia-negative neoplasms alongside essential thrombocythemia and myelofibrosis. It is characterized by elevated red blood cell mass, frequently accompanied by leukocytosis and thrombocytosis. A JAK2 mutation is present in about 95% of cases, typically with low erythropoietin levels. This study aims to review the current understanding of PV, including its pathophysiology, diagnostic criteria, treatment options, and emerging therapies.

A brief description of the state of knowledge: PV is rare, with an incidence of 0.01–4 cases per 100,000 annually, and is usually diagnosed between the ages of 60 and 65. Symptoms stem from increased blood viscosity and include headaches, aquagenic pruritus, thrombosis,

and splenomegaly. Diagnosis relies on elevated hemoglobin/hematocrit, bone marrow findings, and JAK2 mutation. According to ICC and WHO criteria, diagnosis can sometimes be made without bone marrow biopsy. Standard treatment includes low-dose aspirin and phlebotomy, with cytoreductive therapy (hydroxyurea or pegylated interferon) based on thrombotic risk. New drugs such as rusfertide, idasanutlin, and givinostat show promise in symptom control and potential disease modification.

Summary: While current therapies effectively manage hematocrit and thrombotic risk, they do not address the root cause of PV. Novel treatments targeting molecular mechanisms may improve quality of life and reduce the risk of progression to myelofibrosis or acute leukemia. Further research is needed to develop curative strategies.

Key words: polycythemia vera, JAK2, phlebothomy

Introduction and purpose:

Polycythemia vera (PV) is one of three chronic myeloproliferative neoplasms. Together with essential thrombocythemia (ET) and myelofibrosis (MF), it constitutes the so-called Philadelphia-negative myeloproliferative neoplasms. Laboratory findings in PV are characterized by increased hemoglobin levels in the blood (males >16.5 g/dL, females >16 g/dL) and elevated hematocrit (females >48%, males >49%). The vast majority of patients (95% [1]) also harbor a mutation in the *JAK2* gene, along with suboptimal erythropoietin (EPO) levels (in 85% of patients). Clinically, patients report a variety of symptoms associated with microvascular disturbances, pruritus, splenic discomfort associated with splenomegaly, superficial thrombophlebitis, minor mucocutaneous bleeding, or overt thrombotic or hemorrhagic events. Currently, PV has a median overall survival of approximately 15 years, with this duration extending in patients diagnosed before the age of 40-50 years. The treatment of polycythemia vera focuses on preventing thrombotic complications; phlebotomy and low-dose aspirin remain the standard of care. Currently, for some patients, first-line treatment options also include hydroxyurea (HU) and interferon-alpha. Second-line treatment options include busulfan and rituximab. PV has a tendency to transform into the myelofibrosis and acute myeloid leukemia (AML), which occurs in approximately 2,3%-14,4% of cases

[2–4]. The aim of our work is to analyze the latest available literature describing the causes, diagnostic pathways, and management of PV, as well as future therapeutic possibilities.

In order to create this article on 01.05.2025 we conducted a review of literature using PubMed, Google Scholar and Elsevier. Two independent authors (B.R. and K.S.) performed a search using term: “polycythemia vera”. Any disagreements about inclusion were solved by discussion and consultation with third person (N.K.). Additional references were identified using bibliographies of chosen articles.

Description of state of knowledge:

Epidemiology

Polycythemia vera (PV) is a rare, chronic blood cancer classified as a myeloproliferative neoplasm. It is characterized by the overproduction of red blood cells, and sometimes white blood cells and platelets. Based on various registry data, the annual incidence of PV ranges from 0.01 to 4.0 cases per 100,000 people, with prevalence estimates (total number of people living with the disease) ranging between 0.49 and 46.88 per 100,000 [5–7]. In the United States, PV affects approximately 65,000 people [6], and prevalence is thought to be higher there and in Europe compared to countries like Japan [8]. The median age at diagnosis is between 61 and 64 years, though PV can present at any age, from young adults (as early as 19 years old) to the elderly (up to 95 years) [9]. Up to 25% of cases are diagnosed before the age of 50 [1], and about 10% are diagnosed before age 40 [10]. Although earlier studies suggested that younger women might be at higher risk, more recent evidence shows that PV is more common in men across all age groups [11]. There are both non-modifiable and modifiable risk factors for PV. Non-modifiable factors include older age, male sex, White race, and European ancestry [5]. In contrast, modifiable risk factors include smoking, obesity, high blood pressure, diabetes, and high cholesterol, all of which may contribute to increased risk. [12] While PV often has a relatively indolent course, especially in younger patients (with median survival exceeding 35 years), it can be interrupted by serious complications [13]. These include blood clots (thrombosis), bone marrow fibrosis, and transformation to acute myeloid leukemia (AML) - with 20-year risk estimates of 26% for thrombosis, 16% for fibrosis, and 4% for AML [14]. Although life expectancy in PV is generally modestly reduced compared to the general population, many patients live for decades. This long-term survival contributes to its relatively high prevalence despite its low incidence.

Etiology and pathophysiology

The underlying cause of polycythemia vera (PV) is a type of abnormal, cancer-like cell growth (neoplastic proliferation). This occurs due to a defect in cell signaling, which causes blood-forming cells to respond inappropriately to growth signals. As a result, a group of abnormal stem cells (a clone) interferes with the development of normal blood cells. In about 90% of PV cases, there is a mutation in the JAK2 gene, which plays a key role in how cells respond to signals that control growth [15]. This mutation, known as JAK2 V617F, changes the gene's structure and causes it to stay "switched on," even without external signals. This leads to constant stimulation of cell growth, especially for red blood cells and platelets [16].

Bone marrow in PV contains both normal and abnormal (clonal) blood-forming stem cells. However, the abnormal clone tends to dominate, suppressing normal cell production. This uncontrolled growth across multiple blood cell lines - red cells, white cells, and platelets - is called panmyelosis. At the time of diagnosis, about 20% of patients show chromosomal abnormalities (cytogenetic changes) in their blood-forming cells. This number increases with time, affecting over 80% of patients after 10 years of disease. The JAK2 V617F mutation is also found in 50–60% of patients with primary myelofibrosis and in about half of those with essential thrombocythemia, highlighting its key role in several related blood disorders [15,17]. The increased blood cell production caused by this mutation contributes to complications like blood clots (thrombosis) and bleeding.

Symptoms

The clinical presentation of Polycythemia Vera is heterogeneous. A significant proportion of patients, potentially up to 40-50%, are asymptomatic at the time of diagnosis, with the condition being discovered incidentally during routine complete blood count (CBC) examinations performed for other reasons [18]. When symptoms do occur, they are often related to the increased red blood cell mass and consequent hyperviscosity of the blood, microcirculatory disturbances, an enlarged spleen, or the systemic effects of pro-inflammatory cytokines released by the clonal cells and the reactive bone marrow microenvironment [19]. Patients may experience a wide array of symptoms that can significantly impact their quality of life. These include:

- Constitutional symptoms: Fatigue is one of the most prevalent and debilitating symptoms, reported by a large majority of patients. Other constitutional symptoms include night sweats, unexplained weight loss, and low-grade fevers [20].
- Hyperviscosity-related symptoms: These arise from the thickened blood impairing oxygen delivery and flow. They include headaches, dizziness or vertigo, tinnitus (ringing in the ears), visual disturbances such as blurred vision, scotomata (blind spots), or transient visual changes (amaurosis fugax), and occasionally, symptoms of impaired concentration or "brain fog" [9,10,21].
- Microcirculatory symptoms: Erythromelalgia, characterized by intense burning pain, warmth, and redness, typically in the extremities (hands and feet), is a relatively specific symptom. Paresthesias (numbness or tingling) can also occur [22].
- Pruritus: Itching, particularly aquagenic pruritus (itching triggered or worsened by contact with water, especially warm water), is a classic and often distressing symptom of PV, affecting a substantial number of patients. This is thought to be related to mast cell degranulation and histamine release. According to studies, this symptom occurs in about 40% of patients [23,24].
- Splenomegaly-related symptoms: An enlarged spleen can cause abdominal discomfort or pain, typically in the left upper quadrant, a feeling of fullness, or early satiety.
- Other symptoms: Gastritis, peptic ulcer disease (potentially due to increased histamine from basophils and altered gastrointestinal blood flow), claudication, insomnia, and bone pain have also been reported. Shortness of breath, especially when lying down, can also occur.

The significant symptom burden, even in patients traditionally classified as "low-risk" for thrombosis, underscores the need for comprehensive patient assessment that goes beyond mere hematocrit control. Many of these symptoms are non-specific, which can contribute to delays in diagnosis if PV is not considered in the differential.

Diagnosis

The diagnosis of Polycythemia Vera (PV) is based on a combination of clinical findings, blood tests, bone marrow examination, and genetic analysis. A diagnosis of polycythemia vera can be considered when a JAK2 mutation is found along with high hemoglobin or hematocrit levels—above 16.5 g/dL or 49% in men, and above 16 g/dL or 48% in women [10]. Although examining the bone marrow can help confirm the diagnosis, it is not always required. Over 95% of people with polycythemia vera (PV) have a change (mutation)

in the JAK2 gene. This genetic mutation helps doctors tell PV apart from other conditions that cause high red blood cell levels, like smoking or sleep apnea [6].

For diagnosing polycythemia vera (PV), the International Consensus Classification (ICC) includes three main criteria and one minor criterion:

Major criteria:

1. High hemoglobin or hematocrit levels: More than 16.5 g/dL or 49% in men, and more than 16 g/dL or 48% in women. Alternatively, a red cell mass over 25% above the normal predicted value.
2. Bone marrow findings: The bone marrow should be more cellular than expected for the patient's age and show increased production of all three blood cell lines - red blood cells, white cells, and platelets (panmyelosis). There should also be an increase in mature, variable-sized megakaryocytes (platelet-producing cells), without abnormal features.
3. JAK2 mutation: Either the JAK2V617F mutation or a JAK2 exon 12 mutation must be present. The test must be sensitive enough to detect very low levels (<1%) of the mutation.

Minor criterion:

1. Subnormal erythropoietin (Epo) level in the blood.

To diagnose PV using the ICC system, a patient must meet either all three major criteria, or the first two major criteria plus the minor one [25]. If the JAK2 mutation is present at very low levels (<1%), it should be confirmed with a second test, and the doctor should also consider the clinical context and Epo level. Bone marrow biopsy can be skipped in some cases. Specifically, if a patient has a JAK2 mutation and very high hemoglobin or hematocrit levels - above 18.5 g/dL or 55.5% in men, and 16.5 g/dL or 49.5% in women - a diagnosis may be made without bone marrow examination. However, examining the bone marrow is still helpful. Around 14 - 48% of PV patients already have some level of bone marrow fibrosis (scarring) at diagnosis. This is usually mild (grade 1), but it may be linked to a larger spleen and a higher chance of progressing to post-PV myelofibrosis (MF), though with a lower risk of blood clots. If PV patients meet all diagnostic criteria, they should still be classified as having PV, even if mild fibrosis is present in the bone marrow at diagnosis [26,27]. Bone marrow examination also helps detect chromosomal abnormalities, which have been linked to worse survival outcomes in PV [28].

The diagnostic criteria for polycythemia vera (PV) are slightly different between the World Health Organization (WHO) 2022 guidelines and the International Consensus Classification

(ICC) 2022, but the main principles are the same. Both systems focus on key features like high hemoglobin or hematocrit levels, bone marrow findings, and the presence of a JAK2 mutation. However, the WHO no longer requires a red cell mass (RCM) measurement to make the diagnosis [29], which is a small change from the ICC criteria.

Treatment

In the most recent clinical guidelines, all patients diagnosed with polycythemia vera are recommended to receive low-dose aspirin, typically at a dose ranging from 40 to 100 mg once daily, along with periodic phlebotomy aimed at maintaining the hematocrit level below 45 percent. Further therapeutic decisions are guided by the patient's risk category, which is determined by age and history of thrombosis [10].

In patients classified as low-risk - defined by the absence of prior thrombotic events and age below 60 years - treatment may involve intensification of antiplatelet therapy to twice-daily aspirin in selected individuals [30]. This approach is considered when additional risk factors are present, including cardiovascular comorbidities, leukocytosis, or microvascular symptoms such as erythromelalgia or neurological disturbances. The introduction of pegylated interferon-alpha should be considered in low-risk patients who require frequent phlebotomies or who suffer from severe aquagenic pruritus, symptomatic splenomegaly, or persistent disease-related symptoms that impair quality of life.

In contrast, high-risk patients—those over 60 years of age or with a history of thrombotic complications, excluding women of reproductive age, who are managed according to the low-risk algorithm—are recommended to initiate cytoreductive therapy with hydroxyurea, starting at a dose of 500 mg twice daily. In cases of intolerance, resistance, or patient preference against hydroxyurea, pegylated interferon-alpha represents the preferred alternative. In elderly patients, busulfan may be considered, whereas JAK2 inhibitors are favored when patients exhibit symptoms suggestive of evolving post-polycythemia vera myelofibrosis. Among high-risk patients with a history of arterial thrombosis, escalation to twice-daily aspirin is advised, while those with prior venous thromboembolism should receive concurrent anticoagulation in addition to standard therapy.

Several new drugs are currently being studied in clinical trials for polycythemia vera (PV), including rusfertide (PTG-300), idasanutlin, and givinostat.

- **Rusfertide**, a synthetic version of the natural hormone hepcidin, is given as a subcutaneous injection. It regulates iron availability without fully depleting iron stores and has been shown to significantly reduce the need for phlebotomy in many patients,

along with symptom improvement. However, because hematocrit can already be well controlled using standard treatments—phlebotomy and pegylated interferon (peg-IFN) in low-risk patients, or hydroxyurea (HU) and peg-IFN in high-risk patients—the long-term role of rusfertide in PV therapy is still uncertain. Additionally, unlike rusfertide, cytoreductive drugs like peg-IFN help manage other disease features such as high platelet and white cell counts, enlarged spleen, itching, and general symptoms [30].

- **Idasanutlin**, an oral drug that blocks the interaction between MDM2 and TP53 (helping to stabilize TP53 activity), has shown effectiveness in 30–60% of PV patients, improving hematocrit, symptoms, and spleen size. It also led to a decrease in the JAK2 mutant allele burden. However, its development is challenged by significant gastrointestinal side effects [31].
- **Givinostat**, a histone deacetylase inhibitor that targets JAK2-mutated cells, has also been effective in controlling hematocrit and symptoms. It reduced the JAK2 mutant allele burden but had limited effect on spleen size. Treatment with givinostat was associated with several side effects, including prolonged QT interval on ECG, low platelet counts, diarrhea, altered taste, and headaches [32].

Conclusions:

Currently, the goals of treatment in polycythemia vera (PV) are to reduce the risk of thrombotic events, alleviate symptoms, prevent disease progression, and improve overall survival and quality of life. However, the underlying cause of the disease remains unaddressed by current therapies, highlighting the need for a deeper focus on disease-modifying and potentially curative approaches.

Disclosure:

Authors' contribution

Conceptualization: KS and BR;

Methodology: KS and JMM;

Software: WK and KS;

Check: AD, BR and JMM;

Formal analysis: KS;

Investigation: BR and KS;

Resources: MJ and NK;

Data curation: MJ;
Writing - rough preparation: BR and KS;
Writing - review and editing: MJ, NK and JMM;
Visualization: MJ and WK;
Supervision: BR;
Project administration: KS;
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