



Literature Review on Polycythemia vera Diagnostic and Management Approach

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ABSTRACT

Polycythemia vera (PV) is a condition that originates from stem cells and this disorder is affiliated with chronic myeloproliferative neoplasms (MPNs). It is highlighted by malignant neoplastic proliferation of the trilineage elements of bone marrow. Even though it is insufficient of establishing a definitive diagnosis, it is distinguished from other myeloproliferative neoplasms by increased red blood cell mass. Since the course of this disease is insidious and usually picked up incidentally, prompt diagnosis and proper management reduce the risks of fatal sequelae. The goal of this study is to review the literature and enhance the understanding and awareness of polycythemia. We reviewed the literature for polycythemia; clinical manifestations and approach to diagnosis. Articles were chosen from the PubMed database, and selected studies were subjected to a thorough review. Because of its gradual onset, polycythemia Vera is difficult to diagnose, however, it should be suspected in people having an increased red blood cell mass. Abnormally high hemoglobin or hematocrit, combined with a clinical presentation like splenomegaly, thrombocytosis, and leukocytosis, highly suggests it. As quickly as possible, a referral to a hematologist for bone marrow aspiration and therapy should be arranged. Consequently, with correct therapy and monitoring, the risk of thromboembolism can be reduced.

Keywords: Polycythemia, Aquagenic pruritus, Erythromelalgia, JAK2

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Received: 01 October 2021

Accepted: 12 December 2021

INTRODUCTION

Polycythemia Vera (PV) is a condition from stem cell disorders that fall under the umbrella of chronic myeloproliferative neoplasms (MPNs). It is characterized by malignant, neoplastic, and pan- hyperplastic proliferation of bone marrow's myeloid cells. The myeloproliferative neoplasms are classified according to the predominance of the myeloid element implicated in the disease development. Although it is inadequate for establishing a clear-cut diagnosis, PV is differentiated clinically from other entities of MPNs by elevated red blood cell mass. Early recognition of clinical features and identification of the specific cause of PV is crucial for the appropriate treatment of the patient (Arber *et al.*, 2016). In this review, we focus on the clinical features and diagnostic approach of polycythemia vera.

MATERIALS AND METHODS

WPubMed database platform was used for fetching relevant articles, henceforth mesh was used using the following

keywords ((“Polycythemia”[Mesh]) AND (“Clinical Features”[Mesh]) AND “Diagnosis”[Mesh])). The inclusion criteria included articles selected based on the following: polycythemia's clinical features and diagnosis. Exclusion criteria were all other articles that did not have one of the criteria of inclusion criteria results in their topic.

Review

Epidemiology

Polycythemia vera is most common between the ages of 50 and 70 (Tefferi *et al.*, 2013). However, this disorder can affect people of all ages, including early adulthood and children, but it is uncommon (Cario *et al.*, 2008). Males have a somewhat higher incidence of this disorder than females, according to most reports. PV affects approximately 44 to 57 per 100,000 people in the USA (Ma *et al.*, 2008). One systematic review reported the annual incidence rates of PV in the general population to be ranging between 0.01 and 2.61 per 100,000. Nevertheless, it was concluded that this result is not reliable to accentuate worldwide due to limited studies in the literature (Mouillard *et al.*, 2014).

Clinical presentation

The majority of people with PV are detected by chance when a complete blood count is taken for another reason and increased hemoglobin or hematocrit is found. Others show signs of disease (headache, dizziness, visual abnormalities, pruritus, early satiety, splenomegaly, etc.) or complication (e.g., thrombosis, bleeding) (Tefferi *et al.*, 2013).

Pruritus

Aquagenic pruritus is a type of pruritus that occurs after a warm bath or shower and is characterized by strong skin sensations without apparent changes in the skin. It is frequently the primary complaint of a PV patient and might manifest years before a diagnosis of PV is established. In most patients, it is described as itching, stinging, or burning to occur within less than ten minutes after water contact. The most typically implicated symptomatic areas were shown to be the chest, back, medial side of the arms, and ventral side of the legs (Steinman & Greaves, 1985; Saini *et al.*, 2010; Siegel *et al.*, 2013). Moreover, this symptom is worse with warm water. In PV, the reason for pruritus is unknown. Mast cell degranulation, with the production of histamine, fibrinolytic, prostaglandins, or interleukin-31, has been postulated to play a role (Jackson *et al.*, 1987; Steinman *et al.*, 1987). Another theory is that when the skin is cooled down, the production of adenosine diphosphate from red cells or catecholamines from adrenergic vasoconstrictor nerves causes platelet aggregation in skin blood vessels, resulting in the regional release of pruritogenic substances such as prostaglandins. The fact that aspirin can reduce pruritus in some patients is consistent with prostaglandins playing a significant role (Fjellner & Hägermark, 1979; Batarseh *et al.*, 2022).

Erythromelalgia

This feature of PV is highlighted by a burning sensation that can be found on the hand and feet along with redness, paleness, or cyanosis, in the presence of palpable pulses (Tefferi *et al.*, 2013). In PV and essential thrombocythemia, erythromelalgia and the concomitant symptom of acral paresthesia, both of which can be regarded forms of dysesthesia, are deemed pathognomonic microvascular thrombotic sequelae and are associated with platelet counts of >400,000/microL (Van Genderen & Michiels, 1997). Low-dose aspirin or low-dose myelosuppressive drugs reduces these symptoms considerably (Michiels, 1997; Zahid & Khan, 2022).

Bleeding and thrombosis

It is very common in PV patients to suffer from bleeding and thrombotic events, such as cerebrovascular accidents, MI, superficial thrombophlebitis, deep vein thrombosis, and pulmonary embolism (Tefferi *et al.*, 2013). Although the processes behind this hypercoagulable condition are unknown, blood viscosity, platelets, and leukocytes have all been linked (Landolfi *et al.*, 2008).

Visual disturbances

Transient ocular blindness called amaurosis fugax, scotoma, and ophthalmic migraine can manifest transiently in patients

with PV, like those implicated in individuals with essential thrombocythemia (Michiels *et al.*, 1996).

Gastrointestinal disturbances

PV patients frequently experience gastrointestinal problems, including epigastric pain, peptic ulcer disease, and gastroduodenal erosions on upper endoscopy. Alterations in the blood flow of mucous in the stomach which can cause changes in the blood viscosity and enhance secretion of histamine from tissue basophils have been attributed (Torgano *et al.*, 2002; Mathew *et al.*, 2022).

Laboratory features

The majority of people with PV are detected by chance when a full blood count is taken for another reason and increased hemoglobin or hematocrit is found. The following laboratory findings are implicated in most PV patients:

Peripheral blood smear

The results of peripheral blood tests vary depending on the stage of illness at the time of diagnosis. Peripheral blood normally exhibits an excess of normochromic, normocytic red blood cells during the prepolycythemic and overt polycythemic stages. On the other hand, if there is an iron deficit, hypochromic, microcytic red cells may be found. Thrombocytosis is frequent with a range of 70 to 2,370,000/microL, mimicking essential thrombocytosis. Leukocytosis is also a frequent finding in peripheral blood smears. However, because neutrophils are distinctly elevated in PV, the total WBC count may not correctly indicate disease activity. While immature cells can be observed, blasts are rarely a common occurrence (Tefferi *et al.*, 2013).

Bone marrow examination

Aspirate of the bone marrow classically exhibits hypercellularity for age and hyperproliferation of the trilineage elements: erythrocytes, granulocytes, and megakaryocytes. As the disease progresses, the observations on bone marrow examination change, from a pre-polycythemia stage with mild erythrocytosis to a conspicuous polycythemic phase with expanded red cell mass, to post-polycythemic myelofibrosis with cytopenias, ineffectual erythropoiesis, fibrosis, extramedullary hematopoiesis, and hypersplenism (Arber *et al.*, 2016).

Moreover, bone marrow examination can be performed to uncover clonal markers linked to PV. Concernedly, the JAK2 gene, which has a somatic point mutation in practically all PV patients, is located on chromosome 9p24. Roughly 96% and 3% of patients are showing somatic point mutations in exon 14 and exon 12 of JAK2, respectively (Najfeld *et al.*, 2002; Tefferi & Spivak, 2005; Spivak, 2010). Furthermore, it has been found that the mutation of exon 14 of the JAK2 gene that is implicated in most PV patients is not found in normal individuals in addition to those with secondary polycythemia. Hence, it can differentiate between primary PV from secondary polycythemia (Tefferi & Spivak, 2005).

Increased red blood cell mass

Isotope dilution methods can be used to directly quantify red blood cell mass, although this method is no longer available in

many places. For that reason, estimation of the red blood mass such that a hemoglobin >18.5 g/dL in men or >16.5 g/dL in women has replaced the former methods and has been used by most clinicians for measuring increased red blood mass (Fairbanks, 1999; Sirhan et al., 2005).

Serum erythropoietin

Low serum erythropoietin (EPO) values are common in PV patients. Although low EPO levels are very specific for PV, higher levels are uncommon and indicate secondary erythrocytosis (Cotes et al., 1986).

Diagnosis

Index of suspicion

Any patient with an elevated red blood cell mass increased hemoglobin/hematocrit, and arterial oxygen saturation of more than 92% should be suspected of PV. Men ought to have a hemoglobin value of at least 16.5 g/dL or a hematocrit level of 49%, while women ought to have a hemoglobin value of at least 16 g/dL or a hematocrit level of 48% to be regarded for the diagnosis. In addition, clinical features such as splenomegaly, thrombocytosis and/or leukocytosis, thrombotic sequelae, erythromelalgia, aquagenic pruritus, and microvascular symptoms support the diagnosis of PV (Silver et al., 2013).

Diagnostic criteria

World Health Organization (WHO) developed criteria for diagnosis of PV that has evolved over the years. PV diagnostic criteria comprise the following:

Major criteria

- Elevated hemoglobin value (>16.5 g/dL in men or >16.0 g/dL in women), hematocrit (>49% in men or >48% in women), or other findings of increased red blood cell mass.
- Bone marrow exhibiting hypercellularity for age and hyperproliferation of the trilineage elements: erythrocytes, granulocytes, and megakaryocytes with pleomorphic, mature megakaryocytes
- JAK2 exon 14 or JAK2 exon 12 mutations.

Minor criterion

- Low serum erythropoietin level.

The presence of all three major criteria, or the first two major criteria plus the minor criterion, is required for the diagnosis of PV. These diagnostic criteria are only applicable in individuals who have had a proper diagnostic assessment to rule out secondary causes of polycythemia (Silver et al., 2013; Barbui et al., 2014).

CONCLUSION

Polycythemia vera is difficult to diagnose because of its gradual onset, however, it should be put under assumption in people who have an increased red blood cell mass. It is strongly suggested by excessively high hemoglobin or hematocrit combined with diagnostic characteristics such as thrombocytosis, splenomegaly, and leukocytosis. A referral to a

hematologist for bone marrow aspiration and therapy should be made as soon as possible. Subsequently, thromboembolism risk can be decreased with proper therapy and monitoring.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

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