CLINICAL VIGNETTE

Polycythemia Vera

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Polycythemia vera (PV) is a rare clonal disorder of hematopoietic cells that leads to erythropoietin (Epo) independent erythrocytosis as well as a variable degree of leukocytosis and thrombocytosis. PV shares several similarities with other diseases, such as essential thrombocythemia (ET) and primary myelofibrosis (PMF), all which are characterized as myeloproliferative neoplasms (MPNs). PV is a chronic disease arising from a point mutation on the JAK2 gene in a hematopoietic progenitor cell and must be differentiated from secondary polycythemia. Symptoms of PV include non-specific vascular disturbances or major thrombosis. Diagnosis relies on laboratory and molecular criteria including screening for the JAK2 mutation. Thrombotic complications are the main cause of morbidity and mortality; treatment is tailored toward reducing this risk. Therapy includes low-dose aspirin and phlebotomy for all patients with the addition of myelosuppressive drugs such as hydroxyurea (HU) for those with high thrombotic risk. We describe a patient who presented with nonspecific symptoms of hyperviscosity and was eventually diagnosed to have PV.

Case Report

A 72-year-old female with no significant past medical history was brought to the hospital by ambulance after an episode of severe dizziness and feeling like she "was going to pass out". There was no loss of consciousness. However, she reported mild shortness of breath, and her friend called the ambulance. The patient did not have routine medical care and denied headache, pruritus, and pain in the extremities. She did note facial erythema but no other rash. She had no history of stroke, heart attack, or venous thrombosis. Upon arrival at the emergency department, her vital signs were blood pressure 128/80 mmHg, heart rate 78 beats per minute, temperature 97.9°F, respiratory rate 18 breaths per minute, and oxygen saturation 98% on ambient air. Physical exam was normal; the patient was given intravenous fluids and felt much improved. Routine blood tests were done, and the patient was admitted to the hospital because of blood test abnormalities. Specifically, complete blood count (CBC) showed a white blood cell count (WBC) $23.9x10^3/\mu L$, hemoglobin (Hgb) 19.0 g/dL, hematocrit (HCT) 53.9%, and platelet count $595x310^3/\mu L$. Differential showed an absolute neutrophil count of $20.2x10^3/\mu L$ and mean corpuscular volume of 75.1 fL. Peripheral smear revealed pancytosis with microcytic red blood cells. Of note, previous CBC done three years prior showed WBC $10.8x10^3/\mu L$, Hgb 13.2 g/dL, HCT 38.6%, and platelet count $380x10^3/\mu L$. Basic metabolic panel was unremarkable. No infection was identified. The patient had no obvious cause of secondary polycythemia. PV was suspected and further testing was done that showed a low Epo level 2.0 mIU/mL (range 3.6 - 24.0) and positive JAK2V617F mutation confirming the diagnosis of PV. There was no increase in myeloblasts on flow cytometry, and the BCR-ABL1 fusion transcription was not detected. Based on these results, the patient was diagnosed with PV and hematology consultation was obtained. The patient was started on low-dose aspirin and referred for phlebotomy and close outpatient hematologic follow-up for further treatment.

Discussion

In 1895, a French physician, Henri Vaquez, reported a disease characterized by cyanosis, dizziness, liver and spleen enlargement, and marked erythrocytosis leading to death.[1] In 1908, Osler described PV as a new disease distinct from secondary erythrocytosis.[2] More recently, in 2005, a major breakthrough that has changed the understanding, diagnosis, and treatment of PV was made with the description of the JAK2 mutation, and the discovery that > 95% of patients with PV harbor this mutation.[3,4] It is now known that PV is a MPN that arises from the mutation of a single hematopoietic progenitor cell and is characterized by trilineage expansion of morphologically normal red cells, white cells, and platelets without significant bone marrow fibrosis.[5,6] The mutation leads to progenitor cells that are able to proliferate independent of the physiological growth factor Epo and distinguishes PV from the many acquired causes of secondary polycythemia.[7,8] Early studies in untreated PV patients found a high incidence of thrombotic events and a life expectancy of about 18 months after diagnosis. Cytoreductive treatment of blood hyperviscosity with either phlebotomy or cytotoxic drugs in addition to the use of low-dose aspirin has dramatically reduced the incidence of thrombosis. Since thrombosis is the main cause of morbidity and mortality in PV patients, current treatment is adapted for the expected thrombotic risk of the patient and is largely based on expert consensus. With proper treatment, the life expectancy of PV patients is only moderately reduced.[6,9]

PV is a rare disease with an incidence slightly higher in men than women (highest for men aged 70-79 years). Patients with PV often report nonspecific complaints attributable to microcirculatory disturbances such as headache, dizziness, hearing and visual disturbances, weakness, excessive sweating, pruritus, and erythromelalgia. Pruritus, especially following a bath or a shower, is often the main complaint and has been attributed to hypersensitivity in basophil mast cell degranulation with release of histamine and other cytokines.[5,7] Erythromelalgia manifests with burning pain in the extremities with local redness that is followed by cyanosis that may progress to ischemia and necrosis. These attacks are caused by platelet thrombi in dermal arteries and by an intense inflammatory reaction. Gastrointestinal symptoms such as dyspepsia or peptic ulcer disease are also common in PV.

In around a third of patients, PV presents with a major thrombotic event (2/3 of these are arterial) such as an ischemic stroke (CVA) or transient ischemic attack (TIA), acute myocardial infarction (AMI), deep vein thrombosis (DVT), or pulmonary embolism (PE).[10] Bleeding events are relatively rare in PV. DVT in unusual sites such as splanchnic veins (including Budd-Chiari syndrome and obstruction of the portal, mesenteric, and splenic systems) or cerebral veins (dural vein) are often associated with PV and should prompt a workup for MPN.[11] In fact, a MPN can be diagnosed in about 65% of patients with abdominal vein thrombosis and in about 80% of those with Budd-Chiari syndrome. This presentation often occurs in younger women and diagnosis can be difficult in these patients as blood counts are often normal.

PV is diagnosed incidentally in some patients when an elevated hematocrit is noted on routine testing. In these cases, physicians must first rule out secondary polycythemia. Secondary polycythemia in adults is most commonly due to acquired causes such as chronic lung disease, smoking, and renal disease (**Table 1**). In these conditions, there are circulating plasma factors, usually an oxygen-sensitive Epo response to hypoxia, that stimulate erythropoiesis. Relative polycythemia from loss of body fluids from burn injuries, dehydration, and stress should also be ruled out.[7]

The pathogenesis of PV was elucidated in 2005 when different groups reported the molecular basis of >95% of cases of PV represented by a point mutation in JAK2 exon 14. This mutation causes a single amino acid substitution at position 617 (valine replaced by phenylalanine, represented as JAK2V617F) and results in a gain-of function of JAK2 that activates downstream signaling pathways.[3,4] This mutation leads to activation of several biochemical pathways implicated in erythropoietin receptor signaling leading eventually to erythrocytosis and PV. Interestingly, a significant proportion of patients with other MPNs (ET or PMF) also have the JAK2 mutation. The discovery of this mutation had a major impact on the diagnostic approach to PV and screening for this mutation is now standard as part of the initial evaluation of all patients with suspected PV.[6] In addition, the JAK2 mutation is positive in over 50% of patients with Budd-Chiari syndrome and over 35% of patients with portal vein thrombosis. It is now recommended in all patients with abdominal vein thrombosis to rule out PV.[11-13]

The diagnosis of PV is based on both clinical and laboratory variables according to World Health Organization (WHO) criteria (**Table 2**).[14] The diagnostic criteria for PV have changed considerably in recent years due to the discovery of the JAK2 mutation. More than 95% of patients with PV have the classical mutation (JAK2V617F), which is absent in normal subjects as well as those with secondary polycythemia.[3,4] When PV is suspected, the diagnostic algorithm begins with peripheral blood mutation screening for the JAK2 mutation. This mutation is highly sensitive (97% sensitivity) and virtually 100% specific for distinguishing PV from other causes of increased hematocrit.[5] Concomitant measurement of serum Epo level is important and is subnormal in more that 85% of patients with PV. The presence of the JAK2 mutation confirms the diagnosis of PV and its absence, combined with normal or increased serum Epo level, excludes the diagnosis.[14]

If the classic JAK2V617F mutation is absent and the Epo level is subnormal, then additional mutational analysis for the JAK2 exon 12 mutation, which account for about 3% of PV patients is indicated. Bone marrow examination is not essential for PV patients if a JAK2 mutation is present. However, bone marrow biopsy is necessary in JAK2 negative cases. When evaluating thrombocytosis, it is important to remember that the JAK2 mutation is not specific for PV, since it is also present in at least half of patients with ET and PMF.[5] Presence of the JAK2V617F mutation in this circumstance confirms the presence of an underlying MPN, but its absence doesn't rule it out, as up to 40% of ET patients will not have the mutation. The 2008 World Health Organization (WHO) diagnostic criteria for PV and other MPNs allow one to distinguish between these related diseases.[14]

The clinical course of PV is marked by a high incidence of thrombotic complicaitons.[5-7] Earlier studies in untreated patients showed a high incidence of thrombotic events (reported to range from 12-39%) and a life expectancy of about 18 months after diagnosis.[8,11] The life expectancy of well-treated PV patients is only moderately reduced, with a 15-year survival of 65%.[7] Arterial thrombosis accounts for 60-70% of events and includes ischemic stroke (CVA) (30-40% of all thrombotic events), acute myocardial infarction (AMI), and peripheral arterial occlusion. Venous thrombosis constitutes approximately one-third of total events and includes DVT of the lower extremities, PE, intraabdominal/splachnic, and cerebral vein thrombosis.[11]

In the largest and most recent epidemiologic study of PV patients, 1,638 patients were followed for a median of 2.8

years.[10] In comparison to the general Italian population, there was an excess of mortality of PV patients of 2.1 times. Cardiovascular mortality (AMI, CVA) accounted over 40% of all deaths. Hematological transformation (mainly AML) and major bleeding were responsible for 13% and 4% of deaths, respectively. In a study of recurrent thrombosis in PV and ET patients, cytoreductive treatments (discussed below) halved the probability of both arterial and venous recurrences and is now recommended for all patients with acute vascular events.[6] Also, as a result of the increased risk of cardiovascular mortality, aggressive risk reduction including strict control of historical risk factors such as hyperlipidemia and diabetes as well as smoking cessation is strongly recommended.[6,9]

In patients with PV, known risk factors for shortened survival include advanced age, a history of thrombosis and leukocytosis. Increasing age (>60-65 years) and history of thrombosis have consistently proven to be independent predictors of thrombosis in patients with PV. These are the two risk factors used to risk stratify patients into low (no risk factors) and high (1-2 risk factors) risk groups.[5,6,11] Reducing thrombotic risk is the cornerstone of PV treatment and recommendations are tailored to each patient's risk group. Leukocytosis is also an independent risk factor for thrombosis. However, no study to date has demonstrated a significant correlation between platelet number and thrombosis.[6] One study showed a median survival of 23 years in PV patients in the absence of advance age and leukocytosis versus 9 years if both of these factors were present.[5]

The pathogenesis of the hypercoagulable state leading to thrombosis in PV is complex and multifactorial. Several factors are involved including abnormalities of erythrocytes, platelets, and leukocytes arising from the clonal hematopoietic progenitor cells making them prothrombotic as well as an inflammatory response of vascular endothelial cells to cytokines and other mediators released by malignant cells.[11] Blood hyperviscosity not only rises from quantitative changes in the number of circulating cells but also qualitative changes that lead to the expression of procoagulant factors and subsequent thrombophilia. Abnormalities of the vascular endothelium also occur leading to expression of higher levels of adhesion molecules on their surface. Taken together, these changes can trigger systemic hypercoagulation and ultimately thrombosis in PV patients. A progressively higher hematocrit corresponds to an increased thrombotic risk especially in the cerebral circulation.[11] While absolute number of platelets is not correlated with thrombosis, platelet activation is thought key to the thrombophilia in PV. In support of this, the oral anticoagulant warfarin is ineffective whereas control of platelet function with low-dose aspirin significantly reduces thrombotic events.[10,11] In contrast to the increased risk of thrombosis, bleeding is uncommon in PV. Extreme thrombocytosis (platelet count >1,000 x 10^9/L) can be associated with acquired von Willebrand syndrome and increased risk of bleeding. Major bleeding usually is a result of gastrointestinal hemorrhage. Due to this risk, patients with extreme thrombocytosis are treated differently.[5]

A feared complication of PV is evolution to myelofibrosis or AML. Evolution to myelofibrosis is rare, and generally occurs after many years. The 10-year risk of leukemic/fibrotic transformation is <3%/10% in PV while the risk of thrombosis exceeds 20%.[5] The development of AML is an ominous complication of PV. AML typically manifests with a sudden increase or reduction of white count, anemia, and thrombocytopenia. Fever and bleeding are commonly seen. Such 'secondary' leukemias are generally refractory to chemotherapy and are frequently associated with unfavorable cytogenetic abnormalities such as deletions of chromosomes 5, 7, and 17. The risk of leukemic transformation is rare, but advanced age and use of certain chemotherapeutic agents are associated with an increase risk.[6]

Currently, recommendations for treatment of PV are adapted to the risk of thrombosis and are largely based on the consensus of experts.[6,8,9,11] 'High-risk' for thrombosis is defined by age >60 years or a history of thrombosis and 'low-risk' is defined by the absence of both of these two risk factors. Low-dose aspirin and phlebotomy are recommended in all patients, whereas the addition of cytotoxic therapy is indicated in patients at high-risk for thrombosis. Controlled studies have shown that low-dose aspirin helps prevent thrombosis among all risk categories. In high-risk patients, hydroxyurea (HU) is typically the drug of choice because of its efficacy in preventing thrombosis and low leukemogenicity.[6,9] Interferon-alpha (IFN-α) or busulphan are usually effective if HU fails.[5]

Blood hyperviscosity from erythrocytosis and expansion of other myeloid cell lines is a major cause of vascular disturbances that severely impacts morbidity and mortality in PV.[9] As a result, in patients newly diagnosed with PV, phlebotomy is used to obtain a normal or acceptable hematocrit level. Phlebotomy is recommended for all patients with PV as it is associated with improved survival and is typically the only cytoreductive treatment needed in patients at low-risk for vascular complications. The exact target HCT remains controversial and currently investigators are conducting a prospective, randomized clinical trial addressing this issue.[7,9] Phlebotomy is started by withdrawing ~350 mL of blood daily or every other day until a HCT of 40-45% is obtained. In the elderly, or those with a history of cardiovascular disease, blood should be drawn twice weekly. Blood counts are then checked every 4-8 weeks to establish the frequency of future phlebotomies. Supplemental iron therapy should not be given.[6,9]

Historically, the use of aspirin in PV was discouraged because it was thought to increase the hemorrhage risk. This was based on early trials where 'high-dose' aspirin (300 mg orally three times per day) and pyrimadole were used. A more

recent study evaluated the anti-thrombotic efficacy of low-dose aspirin (100 mg daily) was assessed in a multicenter randomized European trial.[10] In this study, 518 PV patients were randomized to treatment with low-dose aspirin or placebo. Aspirin significantly lowered the combined risk of cardiovascular death, nonfatal AMI, nonfatal CVA, PE, or major venous thrombosis. There were no significant differences between aspirin and placebo in the rates of major or minor bleeding. Given these results, low-dose aspirin is recommended in all PV patients without a history of major bleeding, gastric intolerance, or extreme thrombocytosis.[5,8,10] Low-dose aspirin therapy has also been shown to be effective in alleviating vasomotor (microvascular) disturbances (e.g., headaches, lightheadedness, tinnitus, and erythromelalgia) associated with PV.[15]

For patients at high thrombotic risk, many myelosuppressive drugs are available, and HU is recommended as first line therapy for most patients. Cytotoxic drugs reduce the rate of thrombosis, but there is concern about their leukemogenicity. As stated previously, cytoreductive treatments were shown to halve the probability of recurrence of vascular events in patients with PV or ET.[6] Use of chemotherapy leads to reduction of the hematocrit as well as leukocyte and platelet counts. In PV patients treated with phlebotomy alone, platelet counts may reach very high values. In patients with high risk of thrombosis, it is recommended to keep platelet and leukocyte counts below 400 x 10^9/L and 10 x 10^9/L, respectively. However, there is no consensus on the safest and most effective strategies. Early studies (1970s) favored phlebotomy alone as chemotherapy drugs led to an increased risk of leukemic transformation and secondary cancers.[5] Currently, the choice of myelosuppressive agent depends on age with HU considered the agent of choice in young patients. Busulfan or pipobroman is often used in older patients.[6]

HU is an antimetabolite that prevents DNA synthesis by inhibiting the enzyme ribonucleotide reductase and is recommended as first line therapy for high-risk PV patients. HU is highly effective in preventing thrombosis.[8,9] Supplemental phlebotomy should be performed if needed to keep HCT at target levels. The main side effects of HU are neutropenia and macrocytic anemia. Less frequently, it can cause oral and leg ulcers. Theoretically, HU may increase the risk of leukemic transformation, but no controlled studies have implicated this drug as being leukemogenic to date. Also, there is additional evidence from long-term studies of patients receiving hydroxyurea for sickle cell disease that do not support the concerns about leukemia.[9] However, caution is warranted as studies have shown that the risk of leukemic transformation is increased when HU is given to patients previously treated with other myelosuppressive drugs or those carrying certain cytogenetic abnormalities.[7]

IFN-α suppresses the proliferation of hematopoietic progenitors and is effective in controlling erythrocytosis, reducing spleen size, and reducing symptoms such as pruritus in the majority of PV patients.[9] The main drawback of IFN-α is severe side effects such as flu-like symptoms with fever, nausea, and vomiting. Toxicity is reduced by using pegylated IFN-α. Pegylated IFN-α leads to hematologic remission in ~80% of patients and even leads to undetectable JAK2 levels (molecular complete remission) in 5-10% of patients. IFN-α is more expensive and less tolerated than HU however. In studies of pegylated IFN-α, 96% of patients reported side effects and 22% discontinued treatment.[5] Busulfan is a cell cycle non-specific alkylating agent that can produce long-term control of hematologic parameters in patients with PV when used at low doses. The leukemogenic risk associated with low-dose busulphan is thought to be small, and many experts recommend intermittent use of this drug in elderly patients.[9]

To summarize, experts recommend that in addition to low-dose aspirin and phlebotomy to control hematocrit, high-risk patients with PV should also be treated with HU (starting dose 500 mg BID) as a first line agent to minimize their thrombotic risk. The dose of HU is titrated to keep the platelet count in the normal range and the leukocyte count >2x 10^9/L. In patients who are intolerant or resistant to HU, INF-α (pegylated) or busulfan are often effective. Most advocate IFN-α for patients younger than 65 years and busulfan in the older age group because of the potential leukemogenicity. There is no controlled evidence regarding second line therapy.[5,8] A number of new drugs that selectively target JAK2 kinase are currently under investigation. It is still unknown whether this targeted treatment approach can have a significant impact on long-term PV prognosis.[9]

Pruritus occurs in the majority of patients with PV and is often exacerbated by a hot bath or shower. The precise etiology of pruritus in PV is uncertain and treatment response to antihistamines is variable. Recent studies have shown a greater than 50% response rate in PV-associated pruritus treated with paroxetine (20 mg/day).[16] Low-dose aspirin or non-steroidal anti-inflammatory agents inhibit platelet prostaglandin and are very effective in reversing the erythromelalgic attack.[7]

Patients with PV or other MPNs also have an increased risk of morbidity and mortality when undergoing surgical procedures. One study showed major thrombosis and major hemorrhage both occurring in 5-10% of patients within 3 months of the surgical procedure. There are no controlled trials to guide optimal management, but optimal control of erythrocytosis and thrombocytosis with phlebotomy and/or myelosuppression in recommended. Aspirin should be held for at least a week before surgery. These patients should be followed carefully as they are paradoxically at-risk for both bleeding and thrombotic perioperative complications.[6]

In conclusion, PV is a rare clonal disorder of hematopoietic cells arising from a well-characterized mutation (JAK2) that leads to Epo independent red blood cell expansion. Symptoms

are a result of hyperviscosity and thrombophilia leading to microvascular disturbances and major thrombosis. Diagnosis relies on the clinical, laboratory, and molecular abnormalities that characterize this disease. Treatment is aimed at reducing the risk of thrombosis. With proper treatment, PV patients can live a near normal lifespan and symptoms can be controlled. The patient we described was prescribed low-dose aspirin and immediately referred for hematologic consultation and phlebotomy and hydroxyurea were initiated.

Tables

Table 1. **Selected causes of Secondary Polycythemia***

- **A. Congenital**
  - a. Epo receptor mediated
  - b. High oxygen-affinity hemoglobin
- **B. Acquired (mediated by Epo release)**
  - a. Chronic lung disease
  - b. Carbon monoxide poisoning
  - c. Cigarette smoking
  - d. Hypoventilation syndromes including sleep apnea and high-altitude living
  - e. Right-to-left cardiopulmonary vascular shunts
  - f. Renal causes (renal artery stenosis, end stage renal disease, polycystic kidney disease, renal cell cancer, post-renal transplant)
  - g. Androgen treatment
- **C. Idiopathic erythrocytosis**

*Adapted from Landolfi R, Nicolazzi MA, Porfidia A, Di Gennaro L. Polycythemia vera. Intern Emerg Med. 2010:5:375-84.

Table 2. WHO Diagnostic Criteria for PV*

Diagnosis requires both major criteria and one minor criterion or the first major criterion and two minor criteria.

- **A. Major Criteria**
  - a. Hgb > 18.5 g/dL in men, 16.5 f/dL in women (or other less commonly used criteria for increased red cell mass)
  - b. Presence of JAK2V617F mutation (>95% of patients) or other functionally similar mutation
- **B. Minor Criteria**
  - a. Bone marrow biopsy showing trilineage myeloproliferation (erythroid, granulocytic, and megakaryocytic proliferation)
  - b. Serum Epo level below normal
  - c. Endogenous erythroid colony formation in vitro

*Adapted from Tefferi A, Bardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization criteria and point-of-care diagnostic algorithms. Leukemia. 2008;22:14-22.

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