

A Rare Blood Malignancy in a Genetic Hematological Disorder: Polycythemia Vera (PV) in Sickle Cell Disease (SCD)

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Abstract

Objective: To delineate the etiology, symptomatology, and treatment of Polycythemia Vera in adults with Sickle Cell Disease. The current review contains a review of the 4 case reports that we found on the topic. To our knowledge, no other case reports exist.

Methods: We reviewed the scientific literature to discover case reports that included the topic of PV. We noted consistencies in presentation, evaluation, treatment, and clinical outcomes.

Results: We reviewed 4 case reports and a limited number of clinical papers on PV in SCD. We found and reported on consistencies in clinical presentation and the diversity of treatments. We reported hematological, bone marrow, and radiographic findings.

Conclusions: There is great variability in the evaluation and treatment of cases of PV in SCD. We advocate for more research and deconstructing the complicated relationship between these two comorbid disorders.

Keywords: Polycythemia Vera, Sickle Cell Disease, Case reports

Introduction

Polycythemia Vera (PV) is a rare blood cancer that manifests as a pathologically high concentration of hemoglobin secondary to the reduction of blood volume or hypererythropoiesis. PV can develop as a primary idiopathic disorder or a disease secondary to another disorder. PV typically develops slowly and results in hypercoagulability, which increases the risk of blood clots and circulatory vessel occlusions with tissue damage, thrombotic strokes, myocardial infarctions, and other organ and system's damage [1,2].

PV is most often associated with a mutation in the gene Janus Kinase 2 (JAK2) [3]. Normally, JAK2 coordinates the production of blood cells to maintain hemostatic balance. Approximately 95 percent of patients with PV demonstrate a JAK2 gene defect that causes abnormal red blood cell production [4]. The relationship of PV to JAK2 in the five percent of individuals without the gene defect has become increasingly of interest. PV occurs more often in men than women and is not usually diagnosed in people under 40.

History and Clinical Manifestations

PV is not a new clinical manifestation-- the symptoms were first described in a patient in 1892 by Louis Henri Vaquez [5]. "Myeloproliferative Disorder" (MPD) was the first term used to describe PV and similar disorders back in 1951. In 2008 the World Health Organization later changed the term from MPD to myeloproliferative neoplasms (MPN) to reflect the malignant nature of the blood disorders [6]. PV is classified as an MPN along with essential thrombocytosis (ET) and primary myelofibrosis (PMF).

PV can manifest with diverse presentations but with symptoms cohering around thrombotic complications [7]. These complications can be divided into two categories: microvascular and macrovascular complications. Symptoms associated with microvascular manifestations include cephalgia, vertigo, visual disturbances, erythromelalgia, paresthesia, and transient ischemic attacks (TIA). Symptoms associated with macrovascular manifestations are categorized as either arterial thrombotic or venous thrombotic events. Arterial thrombotic events include myocardial infarction, angina, stroke, cerebral vascular accidents, and peripheral arterial occlusion. Venous thrombotic events include deep vein thrombosis, pulmonary embolism, intra-abdominal vein thrombosis, and cerebral vein thrombosis [7]. Other symptoms that may be associated with an increase in inflammatory cytokines are fatigue, pruritus, and cognitive disturbances.

Genetics

Myeloproliferative neoplasm (MPN) is a group of rare hematologic diseases, characterized by an abnormal proliferation of hematopoietic stem and progenitor cells [5]. Polycythemia Vera (PV) is one of three MPN diseases, and can be distinguished by erythrocytosis, though white blood cell and platelet counts may also be elevated [6]. The increase in hemocytes results in the hyperviscosity of the blood, commonly leading to other complications [7]. Genetic testing methods have specified that PV can be predominantly attributed to a mutation in the Janus Kinase 2 (JAK2) protein-coding gene [8].

The JAK2 gene is involved in the portion of hematopoietic cytokine receptors in the cytoplasm, including erythropoietin, thrombopoietin, and granulocyte colony-stimulating-factor. Following ligand binding, JAK2 would normally activate intracellular signaling pathways [5]. Roughly 97% of JAK2 mutations are indicated by JAK2V617F, which becomes constitutively active [9]. The JAK2V617F mutation has been shown to lead to a significant reduction in the normal inhibitory role of the pseudokinase (JH2) domain on the active (JH1) kinase domain [9].

The mutation may also cause a direct activation of the JH1 domain by-way-of the SH2-JH2 linker. As a result, the stimulation of intracellular signaling pathways begins via signal transducer and activator of transcription (STAT) protein signaling [9]. The mitogen-activated protein kinase and phosphoinositide 3-kinase signaling pathways may also be implicated, though to a lesser extent. These processes, in sum, result in the excessive proliferation and differentiation of myeloid cells [9]. The JAK2V617F mutation is believed to be associated with stimulated erythropoiesis, lower platelet count, larger spleen size, higher incidence of splenomegaly and pruritus, and an increased need for cytoreductive therapy [5]. Additionally, this specific mutation may be significantly implicated in thrombotic complications.

Diagnostic Considerations

Diagnosing PV may be achieved through genetic testing to identify mutations in the JAK2, blood testing to determine excess erythrocytes, leukocytes, and thrombocytes, bone marrow biopsy, and an evaluation of erythropoietin levels. World Health Organization (WHO) criteria are most commonly used to confirm a diagnosis of PV (**Table 1**) [5]. However, diagnostic criteria for PV are also outlined by two other groups, the Polycythemia Vera Study Group (PVSG) (**Table 2**), and the British Committee for Standards in Hematology (BCSH) (**Table 3**) [6]. See **Table 4** for ICD-10 diagnostic codes for PV and

SCD. A key distinction between WHO and BCSH is that WHO (Hct) counts as part of their diagnostic criteria, whereas BCSH continues to include both hemoglobin (Hb) and hematocrit does not use hemoglobin.

Table 1. WHO (2016) diagnostic criteria for PV [7].	
Major Criteria	<ol style="list-style-type: none"> Hb >16.5 g/dL in men/ Hb >16.0 g/dL in women, or Hct >49% in men/ Hct >48% in women, or increased RCM; BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature, megakaryocytes (differences in size); Presence of JAK2V617F or JAK2 exon 12 mutation
Minor Criteria	Subnormal serum EPO level
Criteria Required for Diagnosis	All three major criteria or the first two major and the minor criterion
Abbreviations: Hb: Hemoglobin; Hct: Hematocrit; RCM: Red Cell Mass; BM: Bone Marrow; EPO: Erythropoietin	

Table 2. PVSG diagnostic criteria for PV [6].	
Category A	<ul style="list-style-type: none"> A1: Raised RCM, male ≥ 36 ml/kg/ female \geq ml/kg A2: Sats $\geq 92\%$ A3: Splenomegaly
Category B	<ul style="list-style-type: none"> B1: Platelets $>400 \times 10^9/L$ B2: WBC $>12 \times 10^9/L$ B3: Leukocyte alkaline phosphatase >100 B4: Serum B12 >900 pg/ml or unbound B12 binding capacity >220 pg/ml
Criteria Required for Diagnosis:	<ul style="list-style-type: none"> A1 + A2 + A3 A1 + A2 + two of category B
Abbreviations: RCM: Red Cell Mass; Sats: Oxygen Saturation; WBC: White Blood Cells	

Table 3. BCSH diagnostic criteria for PV [6].	
Category A	<ul style="list-style-type: none"> A1: Raised RCM or Hct, male ≥ 0.60/ female ≥ 0.56 A2: No secondary erythrocytosis A3: Palpable spleen A4: Abnormal karyotype
Category B	<ul style="list-style-type: none"> B1: Platelets $>400 \times 10^9/L$ B2: Neutrophils $>10 \times 10^9/L$ B3: Splenomegaly on ultrasound scanning B4: Low serum EPO or characteristic BFU-E growth
Criteria Required for Diagnosis	<p>A1 + A2 + A3 or A4</p> <p>A1 + A2 + two of category B</p>
Abbreviations: RCM: Red Cell Mass; EPO: Erythropoietin; BFU-E: Burst-Forming Unit-Erythroid	

Sickle Cell Disease

Sickle cell disease (SCD) is a group of hematological disorders representing the most commonly inherited blood disease characterized by abnormally shaped sickled hemoglobin [10]. The sickled shaped hemoglobin transforms the normally round and donut shaped red blood cells into a crescent moon shape cell. This process is called sickling [11]. Sickled red blood cells have increased cellular rigidity and can occlude small and even some medium sized vessels leading to stroke and other cerebral damages, ocular and joint problems, infections, and acute pain crises often transformed into chronic pains [12].

There are several types of SCD; the SCD genotype is contingent upon genes inherited from both parents. The most common types of SCD are the following; HbSS, HbSC, and HbS/ beta-thalassemia. Hemoglobin SS disease (HbSS) is the most common form of SCD and manifest when both parents contribute the SCD gene. This type is known as sickle cell anemia and is considered the most severe type of SCD. Hemoglobin Sickle C Disease is a milder form of SCD; individuals with this type of SCD inherit a hemoglobin "S" gene from one parent and abnormal gene hemoglobin "C" from the other parent. Individuals with hemoglobin beta thalassemia inherit a hemoglobin "S" gene from one parent and a gene for beta thalassemia from the other parent. Beta thalassemia has two forms: zero (HbS beta⁰) and plus (HbS beta⁺). Individuals with HbS beta⁰ typically have a more severe form of SCD, while those with HbS beta⁺ tend to have a milder SCD [13].

Sickle cell trait (SCT) is distinguished from SCD by the inheritance of a hemoglobin "S" gene from one parent and a normal hemoglobin "A" gene from the other parent. Those with (SCT) are often asymptomatic but because they carry the gene for SCD, can produce offspring with the disease. In unique cases, individuals with SCT experience SCD complications such as pain crises and, in extreme circumstances, sudden death [14].

PV can manifest as a rare complication within SCD.

Treatments for PV, SCD, and PV/SCD

PV

Treatment for PV is commonly guided by presenting symptomatology and an assessment of risk for further morbidity and or mortality. High-risk patients include those who are above the age of 60 and/or have a known history of thrombotic complications. Conversely, low-risk patients are those who are 60 years old or younger, and have no history of thrombotic complications [15]. Recommended treatments for low-risk patients can be as simple as the addition of a low dose aspirin regimen and whole blood reductions via phlebotomy, while treatment for high-risk patients can include cytoreductive therapies such as Hydroxyurea or Interferon or those that address bone marrow production of HCT like Ruxolitinib and Busulfan [15,16].

Therapeutic phlebotomy has been shown to be a reliable treatment for various hematologic diseases. PV is characterized by excessive proliferation of hematopoietic stem and progenitor stem cells, especially erythropoietic cells [5]. Consequently, individuals with PV have elevated hemoglobin and/or hematocrit levels and are at greater risk for thrombotic complications. Therapeutic phlebotomy is utilized as a means to reduce both of these problems in patients who are considered low risk. Studies have demonstrated that patients who received phlebotomy experienced a reduced incidence of hematomas and solid tumors [17]. Phlebotomy has been associated with the maintenance of target hematocrit levels at less than 45%, and a lower incidence of significant thrombotic diseases [17]. As noted above, phlebotomy is often used in conjunction with low-dose aspirin for low-risk patients (81 mg/day) [15].

Cytoreductive therapy is often recommended for high-risk patients with PV who have increasingly high blood counts, progressive splenomegaly, and/or are intolerant to phlebotomy [17]. The goal of cytoreductive therapy is to control total blood cell count, notably preventing erythrocytosis and thrombocytosis. These treatments are favorable over whole blood reduction as they prevent the fluctuation that occurs following phlebotomy.

Hydroxyurea (HU) is currently regarded as the first-line treatment for high-risk patients. However, recombinant interferon-alpha (IFN- α) has now been established to exert similar effects as HU, and is regarded as second-line cytoreductive therapy for individuals who may have developed intolerance to HU [15]. Cytoreductive therapy has been shown to be less effective at managing symptoms such as fatigue and splenomegaly [16]. HU also has the potential to cause toxicity that can result in ulcerations and excessive myelosuppression [16]. Alternatively, IFN- α may result in an elevation of liver function tests, autoimmune complications, fever, flu-like symptoms, and fatigue [16]. HU resistance and intolerance presents an opportunity for interferon, busulfan, and ruxolitinib to achieve similar outcomes [18].

SCD

Medical: Three disease-modifying therapies have been identified for the treatment of SCD, including HU, chronic blood transfusions, and genetic editing. Aside from its utility as a chemotherapy drug, HU was approved by the U.S. Food and Drug Administration (FDA) in 1998 (adults, 18 years and above) and in 2017 (pediatrics, 2 years and above) for the treatment of SCD. In the setting of SCD, HU promotes the production of fetal hemoglobin (HbF), which subsequently reduces the intracellular concentration of abnormal hemoglobin S (HbS). These processes ultimately reduce erythrocytic damage, such as sickling and cellular rigidity, thereby reducing vaso-occlusion and related complications [19]. In the setting of comorbid SCD and PV, HU may be a particularly beneficial treatment option for patients who are able to tolerate it, as it functions to treat both underlying conditions.

Blood transfusions are another supportive treatment method for patients with SCD. The goal of transfusions is to increase hemorheology and oxygenation to tissues, as well as increase the concentration of hemoglobin A (HbA) relative to the concentration of HbS [20]. Additionally, blood transfusions help reduce hemolytic anemia, thereby decreasing anemia-related complications such as acute chest syndrome (ACS) and organ damage. Long-term, repetitive use of simple or exchange transfusions have beneficial properties, including the reduction of HbS concentration to 30%-40%, thereby making it a critical, supportive component in many treatment plans.

Genetic editing is the only curative therapy for SCD and involves hematopoietic stem cell transplantation (HSCT). HSCT may be available for patients with sickle cell anemia (HbSS) and other SCD genotypes, however, this option involves potential short and long-term morbidity and mortality, increasing the importance of psychoeducation prior to the decision to move forward with the procedure. The process requires a matched sibling donor (MSD), with donor stem cells being most frequently acquired from bone marrow or umbilical cord blood [21]. Experimental and clinical trials are continuing to explore other possible donor sources for HSCT.

A hallmark complication in SCD is chronic episodes of vaso-occlusive crises (VOCs), which result in tissue ischemia, injury, and severe pain. Acute pain from VOCs is the most frequent cause of hospitalization in SCD patients. In nearly all of these cases, patients require pharmacological management for painful episodes. Successful pain management is mainly achieved by the use of short-acting and long-acting opioid analgesics and may be given intravenously during acute care at the emergency department or orally as part of home regimens. In the setting of chronic pain, gabapentinoids or serotonin-norepinephrine reuptake inhibitors (SNRIs) may be more effective for the alleviation of pain. During both acute and chronic pain episodes, non-opioid analgesics such as ibuprofen, aspirin, and non-steroidal anti-inflammatory drugs (NSAIDs) may be used to supplement primary pain medications [22,23].

PV and SCD: Interferon (INF) can be used as a first and second-line treatment for PV when it is tolerated [24,25]. The evaluation of INF using double-blind trials has not been conducted in SCD to the authors' knowledge. A few studies examined the use of PEG-INF among those with SCD with comorbid hepatitis C and indicated it was tolerated in this population [26-28].

Busulfan has been studied as a second-line option for treatment in HU resistant and intolerant older adults [29]. Busulfan has been used in those undergoing hematopoietic stem cell transplantation (HSCT) [30,31]. A small case-controlled study involving children indicated that busulfan clearance was not affected by SCD in terms of pharmacokinetics, but that other modifying factors such as organ pathologies and/or co-

administered medications may have a different effect in those with SCD [32]. This suggests that there would need to be some consideration given for the use of busulfan among those with comorbid PV and SCD. Another small study indicated that busulfan was well-tolerated in those undergoing HSCT given that the patients received an adequate dose [30].

Ruxolitinib, a JAK 1/2 inhibitor, has also been utilized in the treatment of PV in cases of HU resistance and intolerance [33]. Vannucchi and colleagues reported that ruxolitinib demonstrated improved hematocrit stability and significantly reduced spleen volume. There are limited studies on ruxolitinib among those with SCD. Studies are showing promising results for ruxolitinib among those undergoing HSCT that encounter steroid refractory graft-versus host disease [34]. Still, these findings are limited among those with SCD and often include younger populations. No studies were identified that examined the use of ruxolitinib among those with comorbid SCD and PV.

Behavioral Treatments in the Management of PV/SCD

As with many chronic diseases, those with PV and SCD may experience depression, anxiety, poor sleep, or engage in maladaptive health behaviors. Cognitive-behavioral therapies (CBT) can also be utilized as a treatment option to address depression, anxiety, pain management, smoking cessation, optimization of treatment utilization and compliance, and sleep quality [35-37]. It is important to consider this aspect of treatment as it is often safe, effective, and can assist with reducing the negative effects of maladaptive behaviors on both the cognitive and psychophysiological aspects of stress responses.

Psychosocial distress among those with SCD has been well-established [10]. Maladaptive coping strategies, limited coping capacity, and poorer social support have been associated with greater disability, pain perception, and poorer outcomes among those with SCD. CBT has been well-established for use among those with SCD, especially in treating SCD-related pain [38]. Reductions in pain intensity, negative thinking, and use of medications to manage pain were also observed in those with SCD after completing CBT. Those with SCD were additionally able to improve their use of adaptive coping strategies and exhibited greater self-regulation following CBT. Edwards and Edwards also found that there were many aspects of CBT that applied to those with SCD including psychoeducational programs, behavior modification, optimizing social support, and improving the self-management of one's own health [38].

There is a general paucity in research on cognitive and behavioral aspects of PV. Some studies have shown promise using CBT as possible a treatment option for pruritus and skin picking that has been associated with PV [39,40]. This includes techniques such as relaxation training, developing cognitive-strategies, and habit reversal techniques [40].

To the authors' knowledge, no studies were found examining CBT techniques in those with SCD and PV. Still, the clinical applications described for each condition above are expected to be relevant in comorbid cases but may need to be customized based on the clinical needs of each individual. CBT is also expected to be useful in addressing any aspects of depression and/or anxiety that may be present in these populations.

Case Reports

We review four published case reports of PV in female patients with SCD. We were unable to find additional case reports in men. Two of the four cases were referred to a hematologist for further analysis due to abnormal blood counts. The patients were presented with symptoms including dizziness, headaches, vertigo, and progressive pain. One of the cases presented with a disability from avascular necrosis of the left hip, while another case was asymptomatic. At time of admission, three of the four patients had a previous medical history of heterozygous β -thalassemia, and one patient was noted to have both SCD and beta-thalassemia. One of the four patients was also noted to have the JAK2V617F gene

mutation, while the remaining three reports did not specify if the JAK2V617F mutation was present. Results of RBC are provided in **Table 1** [41-44].

Presenting symptoms at the ED often included dizziness, headaches, dyspnea, and progressively increased pain (See **Table 5** for Medical History and Presenting Symptoms). During admission, laboratory tests were conducted on these patients with known SCD. ALP was only specified in one of the four patients and the reported value was 82. LDH was specified in one of the four patients and the reported value was 326 U/L (See **Table 6** for Hematological Outcomes). A bone marrow biopsy was conducted on three of the four patients. Results were as follows: one patient was compatible with MPN of the PV type without excessive fibrosis or increased numbers of immature cells; the second patient's results included hypercellularity with trilinear (erythroid, myeloid, and megakaryocytic) hyperplasia, which was compatible with MPN; the last patient's results indicated normocellular with increased megakaryocytes and a myeloid erythroid ratio of 0.8. See **Table 7** for Summary of hepatic enzyme levels and bone marrow biopsy results.

Table 4. ICD-10 codes for polycythemia vera, sickle cell disease, and beta-thalassemic disorders.

ICD-10 Code	Disorder
D45	Polycythemia Vera
D57.09	Hb-SS disease with other specified complication
D57.218	Sickle-cell/ Hb-C disease with other specified complication
D57.418	Sickle-cell thalassemia, unspecified, with other specified complication
D57.438	Sickle-cell thalassemia beta zero with other specified complication
D57.458	Sickle-cell thalassemia beta plus with other specified complication
D57.818	Other sickle-cell disorders with other specified complication
D56.1	Beta thalassemia major
D56.2	Delta-beta thalassemia
D56.3	Beta thalassemia minor/ Beta thalassemia trait
D56.5	Hemoglobin E-Beta thalassemia

Table 5. Medical history, presenting symptoms, hemoglobin, and hemoglobin A values.

Reference	History	Presenting Symptoms	Hemoglobin	Hemoglobin A2
Kottas et al., 2020 [41] 84-year-old, F	Hypercholesterolemia Hypothyroidism Depression Osteopenia HBT	Four week history: - Dizziness - Headaches - Vertigo	9-months prior to presentation: - 14 g/dL At presentation: - 3.8%	At presentation: - 3.8%

Lopes et al., 2011 [42] 75-year-old, F	Bilateral chronic venous insufficiency HBT	Asymptomatic	15.4 g/dL	4.3%
Thomas, 2001 [43] 71-year-old, F	Hypertension HBT Hyperlipidemia Three spontaneous abortions Anemia during pregnancies required blood transfusion therapy	One month prior to presentation: - Exertional chest pressure - Dyspnea	At hematology: - 15.6%	At hematology: - Slightly elevated
Castro, 1981 [44] 48-year-old, F	Malaria Occasional bone and joint pain during childhood Sickle cell beta-thalassemia	At initial presentation: - Progressive pain and disability from avascular necrosis of the left hip	At initial presentation: - 10.4 g/dL Follow-up value: - 13.6 g/dL	At initial presentation: - N/S Follow-up value: - 30%
Abbreviations: HBT: Heterozygous Beta-Thalassemia				

Table 6. RBC count, hematocrit, total RCV, MCV, EPO level, and platelet count.

Reference	RBC Count	Hct	Total RCV	MCV	EPO Level	Platelet Count
Kottas et al., 2020 [41] 84-year-old, F	9-months prior to presentation: - 6.13 X 10 ¹² /L At presentation: - 7.01 X 10 ¹² /L	9-months prior to presentation: - 45.6% At presentation: - 50.4%	N/S	At presentation: - 69 fL	At presentation: - 3.0 mU/mL	9-months prior to presentation: - Normal At presentation: - 236 X 10 ⁹ /L
Lopes et al., 2011[42] 75-year-old, F	At presentation: - 9.0 X 10 ¹² /L	At presentation: - 51.8%	At presentation: - 3,449 mL	At presentation: - 59.2 fL	At presentation: - 1.0 U/L	N/S
Thomas, 2001 [43] 71-year-old, F	N/S	At hematology: - 48.1%	At hematology: - 2,365 mL	At hematology: - 65 fL	At hematology: - Low	At hematology: - 486 X 10 ³ /mm ³
Castro, 1981 [44] 48-year-old, F	At initial presentation: - 5,740,000/ cu mm Follow-up value: - 5,980,000/ cu mm	At initial presentation: - 35% Follow-up value: - 42%	N/S	At initial presentation: - N/S Follow-up value: - 70 cu μ m	N/S	At initial presentation: - N/S Follow-up value: - 878,000/cu mm
Abbreviations: RBC: Red Blood Cell; Hct: Hematocrit; RCV: Red Cell Volume; MCV: Mean Corpuscular Volume; EPO: Erythropoietin						

Table 7. Relevant liver enzyme levels (ALP, LDH), results of bone marrow biopsy, presence of the JAK2V617F mutation, and treatment provided.

Reference	ALP	LDH	Results of Bone Marrow Biopsy	JAK2V617F mutation (Yes/No)	Treatment	Other Findings
Kottas et al., 2020 [41] 84-year-old, F	N/S	326 U/L	Compatible with MPN of the PV type without excessive fibrosis or increased numbers of immature cells	Yes	Low-dose aspirin Hydroxyurea	CT of brain showed ischemic leukoencephalopathy
Lopes et al., 2011[42] 75-year-old, F	82	N/S	Hypercellularity with trilinear (erythroid, myeloid, and megakaryocytic) hyperplasia, which was compatible with MPN	N/S	N/S	Mild splenomegaly
Thomas, 2001 [43] 71-year-old, F	N/S	N/S	N/S	N/S	At cardiologist: - Started on medical regimen for ischemic heart disease Treatment for PV: - Phlebotomy of 1 unit of blood to achieve a Hb concentration of 13 g/dL - After a total of 4 units of blood were removed over 1 month period, phlebotomy discontinued - Erythrocyte count began to rise, with a return of bilateral parietal headaches, chest pressure, and dyspnea - Phlebotomy was restarted, removing 2 units of blood over 6 weeks, 2 weeks apart, with an achieved Hb level of 15.0 g/dL	At cardiologist: - Electrocardiogram that showed an inferior infarct of undetermined age - Echocardiogram showed an ejection fraction of 60% and possible diastolic dysfunction - Cardiac catheterization which showed severe triple vessel disease, and arterial oxygen saturation of 96%, inferior wall hypokinesis, and an ejection fraction of 53%
Castro, 1981 [44] 48-year-old, F	- N/S	- N/S	At presentation: - normocellular with increased megakaryocytes and a myeloid erythroid ratio of 0.8	N/S	At initial presentation: - Busulfan 2 mg daily Treatment after follow-up: - Phlebotomy of 1 unit of blood was removed, then another 1 unit was removed again the following month Two years later: - Patient returned for follow-up and was treated with a 15-day course of uracil mustard 2 mg daily	Chest roentgenogram was normal

Abbreviations: ALP: Alkaline Phosphatase; LDH: Lactate Dehydrogenase; JAK2V617F: mutation frequently observed in cases of polycythemia vera; CT: Computed Tomography; MPN: Myeloproliferative Neoplasm; PV: Polycythemia Vera; Hb: Hemoglobin

Treatment options were mentioned in three of the cases but varied significantly in each case. In one of the four cases, the patient was administered Hydroxyurea and low-dose aspirin. Two of the four cases administered used phlebotomy. In these cases, one patient was administered phlebotomy of 1 unit of blood to obtain an Hb concentration of 13 g/dL and then restarted on phlebotomy to remove two units of blood over a six-week period with a two-week gap to achieve a Hb level of 15.0 g/dL, totaling to four units of blood removed over a one-month period of time. The second patient was administered phlebotomy twice to remove one unit of blood with a one-month gap between treatments. This same patient was also administered Busulfan 2 mg daily and two years later was administered a 15-day course of 2 mg daily of uracil mustard at follow up. Additional findings were mentioned in each case report that contributed to the treatments administered. One patient had a CT of the brain that showed ischemic leukoencephalopathy.

The second patient's results yielded a diagnosis of mild splenomegaly. The third patient had an electrocardiogram that showed an inferior infarct of undetermined age, an echocardiogram that showed an ejection fraction of 60% and possible diastolic dysfunction, and a cardiac catheterization which showed severe triple vessel disease and arterial oxygen saturation of 96%, inferior wall hypokinesis and an ejection fraction of 53%. The last patient had a chest roentgenogram, but results were normal [41-44].

Discussion

In consideration of the PRISMA guidelines that were updated in 2020, we began our exploration of papers related to PV for this review following a broader investigation of rare adult hematological manifestations in adults with SCD [45,46]. Our paper was based on reviews of papers from several databases to include Medline, Psychlit, PubMed, and google scholar. In the current review, we reported on all four published cases of the rare occurrence of PV in adults with SCD that we found but noticed immediately that all four patients were female.

It is unclear if adult females with SCD are at greater risk for the development of PV or if, simply, the co-occurrence of the two diseases are so rare that very little that is reliable can be inferred from the literature. Alternatively, cases could be epidemiologically present and just not documented by clinicians in the scientific literature. Independent of the preferred and most valid explanation for the status of the literature, it is clear that additional research is needed to better understand the seemingly complicated relations between PV and SCD. For example, if there is a genetic or neurohormonal susceptibility that increases risk for women compared to men, we need to identify and understand that mechanism through research. If the epidemiology of PV in adults with SCD is higher than is suggested by the current literature, then a review like ours becomes even more important as a call to action. Lastly,

if the rare nature of the combined disorder precludes easy identification followed by accurate diagnosis and treatment, then we must do better to educate clinicians and researchers about this important combination of disorders.

The development of malignancy in patients with sickle cell disease has been documented in multiple case reports and case series. But the types of cancer and the incidence of malignancy in patients with sickle cell disease is unknown. Large national databases like the National Cancer Database, North American Association of Central Cancer Registries, and SEER do not collect data on the presence of sickle cell disease. This has made it difficult to calculate the incidence of malignancy in this patient population. With the advent of hydroxyurea therapy, there is concern about increasing the cancer risk for patients with SCD.

The incidence of malignancy in sickle cell patients should be calculated in a larger population base. Further studies can be done to determine if a single type of sickle cell genotype increases the risk of malignancy. All the centers where sickle cell patients are followed should monitor the patients prospectively for the development of malignancy. PV and SCD both are genetic disorders and genetic disorders always have a probability of having more genetic mutations and the development of additional genetic disorders.

We envision the current review paper as an incremental but important step towards the development of standards to care for PV in adults with SCD by highlighting the significant variability in identification, evaluation, referral, and treatment procedures. We hope to promote a discussion about how best to use current diagnostic criteria for PV and SCD to reflect the autonomy of each disease or a shared etiological foundation that would best be noted by new ICD-10 codes.

We lastly recognize that little progress will be made on any front related to these comorbid diseases until more research is conducted. For example, with novel gene-based treatments for PV in clinical trials, some of which exploit the role of janus kinase 2 tyrosine kinase receptor (JAK2V617 F) inhibition, there appears to be reason for optimism about reducing morbidity and potentially mortality, and increase quality of life of patients with hydroxyurea refractory disease [47,48]. We believe that research must be continued, on a medical and psychosocial level, to disentangle the complicated relationship between these hematological and oncological disorders.

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