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Polycythemia Vera: A Case Study and Treatment Exploration

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ABSTRACT

Polycythemia Vera is a myeloproliferative neoplasm characterized by stark overproduction of erythrocytes despite a lack of physiological signals. Increased erythrocyte levels become risk factors for thrombosis and infarctions, causing the creation of strict treatment plans to keep hematocrit low. Standard treatment plans include phlebotomy as the primary course of action, but various cytoreductive therapies have recently received Food and Drug Administration approval. PV results from a gain of function Janus Kinase 2 (JAK2) mutation, which results in excessive hematopoiesis. While initial symptoms can be mild, and PV can often remain undiagnosed for years, phlebotomy and other hematocrit-reducing agents can introduce negative symptoms that decrease quality of life. Maintenance of a low iron and hematocrit level can introduce symptoms such as bruising, pallor, headaches, dizziness, and chronic fatigue from iron deficiency anemia. Popular cytoreductive treatments include hydroxyurea and ruxolitinib, both proving to be effective treatments for the disorder despite incidences of resistance or intolerance in specific populations. Phlebotomy is also a primary treatment plan, though strict hematocrit maintenance does lead to hyperviscosity in patients, which introduces additional negative symptoms. A case study of a female PV patient analyzed different complete blood count (CBC) and comprehensive metabolic panel (CMP) test levels and found trends in declining erythrocyte levels regardless of the treatment plan. In addition to hematocrit decline, administration of ruxolitinib also presented increased iron levels and decreased platelet levels while maintaining a stable, healthy hematocrit.

Keywords

Polycythemia Vera, Treatment, Transfusion.

Abbreviations

ATP: Adenosine Triphosphate, BMI: Body Mass Index, CBC: Complete Blood Count, CMP: Comprehensive Metabolic Panel, EPO: Erythropoietin, ET: Essential Thrombocytosis, JAK2: Janus Kinase 2, PF: Primary Myelofibrosis, PV: Polycythemia Vera, STAT: Signal Transducer and Activator of Transcription.

Introduction

A myeloproliferative disorder is characterized by the overproduction of blood cells within the bone marrow of a patient [1]. Under the umbrella of myeloproliferation are three disorders, Primary Myelofibrosis (PF), Essential Thrombocytosis (ET) and Polycythemia Vera (PV). Specifically, PV is a myeloproliferative chronic disorder caused by increased red blood cell production from the JAK2 mutation located on the small arm of Chromosome 9 [2,3]. Though the disorder has been discussed since the 1980s, very little has been known until recent years, as seen in the recency of most articles pertaining to the condition. Of all myeloproliferative disorders, PV does present with the highest incidence of thromboembolic issues and can often present with leukocytosis, erythrocytosis, thrombocytosis or a mix of multiple [3]. Though the JAK2 mutation is commonly found to coincide with PV, there have been documented cases of JAK2 mutation-negative PV patients, leading many researchers to explore other avenues of causation. Another study indicated additional loci of interest, such as areas on chromosomes 13q, 5q and 20q, which could lead to the PV phenotype [4]. However, JAK2 gain of function mutations are still found in over 95% of PV patients, and the same mutation can also be found in patients with other

related myeloproliferative neoplasms [5]. This somatic stem cell mutation leads to clonal myeloid hyperproliferation, resulting in excess erythrocytes. PV presents explicitly with fatigue and pruritus but can progress to more severe disorders if left untreated, such as myelofibrosis or leukemia. Untreated PV patients also face more significant risks of arterial and venous clotting, which can lead to strokes and aneurysms [1]. Current medical opinions recommend phlebotomy as a treatment for the disorder, as blood removal facilitates a lower hematocrit due to loss of erythrocytes. However, especially in older patients, repetitive large needle gauge blood draws can increase the risk for venous collapse or rupture, increasing the use of ports to maintain phlebotomy treatment. Over time, the progression of PV can cause lessened phlebotomy effectiveness, so other options have been explored in recent years. Though cytoreductive treatments such as ruxolitinib or hydroxyurea are available to improve quality of life and prevent thrombosis risk, there is no complete cure for the disorder nor a guaranteed medication to prevent the progression of PV into a more severe disorder [1,2]. Depending on clinical scenarios, risk factors and physician preferences, cytoreductive chemotherapy treatments are allocated case-by-case. Investigations are also being conducted into the long-term effects of the disorder, as well as the effects of commonly administered medications such as hydroxyurea.

Even though PV is known to result commonly from somatic cell mutations, the presence of JAK2 mutation-negative PV cases does imply additional causes of the disorder. Consequently, genetic factors are being considered, especially regarding the potential for familial inheritance. Though no statistically significant connection has been officially identified, speculation continues as to whether PV can present as an inherited condition.

Discussion

There is a plethora of side effects to be associated with the overproduction of erythrocytes. Primary symptoms can be debilitating, including chronic fatigue, bone pain, weight loss, night sweats and insomnia [6], which leads to a sharp downturn in overall quality of life. In addition to physical symptoms, risk factors also increase with untreated PV, including those for thrombosis and cardiovascular events [7]. Decreasing risk factors comes at the cost of rigid hematocrit maintenance, usually in the form of phlebotomy. However, the cost of a stable hematocrit level in some cases outweighs the decreased cardiovascular risk, especially as the low hematocrit and consequential iron levels in PV patients cause worsened symptoms. As hematocrit levels stabilize due to phlebotomy, worsened fatigue is standard, as are dizziness, pruritus, concentration issues and more severe insomnia [6].

For many polycythemia patients, the physical toll of adequate treatment is no better than the risk factors that unregulated patients face. Harsh symptoms can push patients to ask physicians to pursue other treatment methods, which include ruxolitinib, hydroxyurea and interferon. Lack of stable hematocrit can also cause a negative toll on quality of life, especially as blood shifts from hyperviscous to hypoviscous from treatment. Hyperviscosity can pose risk of clotting, tissue damage due to hypoxia, and vertigo, while hypoviscosity could cause fainting and dehydration. Despite outward symptoms reported by PV patients, blood smears are also highly telling of the dangers this disorder presents.

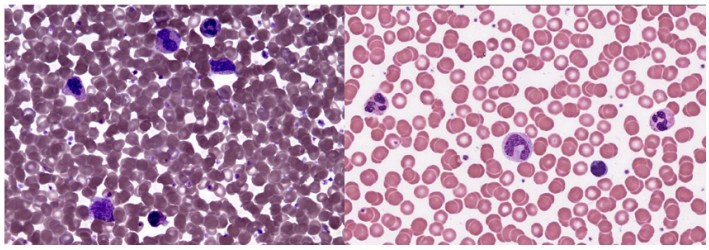

Figure 1: A comparison of 40x blood smears from a PV patient (left) and a healthy patient (right) [8].

Figure one shows a strong comparison between a healthy blood smear and a blood smear from a PV patient. The healthy smear illustrates normal hematocrit levels, where erythrocyte levels are present but not overwhelming. In the PV smear, dangerous levels of red blood cells can be found due to extensive hematopoiesis due to a lack of physiological factors [9], leaving very little open space in the smear. A high level of erythrocytes can lead to typical PV symptoms and increase the risk for thrombosis, stroke, and clotting [2]. In the early stages, treatment consists of regular phlebotomy appointments, where quantities of blood are removed to decrease overall erythrocyte levels. However, repetitive punctures with large gauge needles can cause vein damage over time, especially in older patients [10]. In many patients, implantation of a port is often recommended, which ensures easier vein access without risking damage to blood vessels.

In addition to an increase in erythrocytes, PV patients also face a smaller volume of plasma, which can cause bleeding complications and bruising. Though plasma levels can be decreased due to erythrocyte production, the tendency of PV to present with thrombocytosis causes overwhelming platelet levels also to be found in the blood. Excessive platelet activation can cause bleeding problems but also presents additional factors that must be considered when considering treatment plans for a patient. PV and thrombocytosis combined can become a very dangerous condition, as overproduction of erythrocytes and thrombocytes can easily lead to thrombosis. As more red blood cells are available, and clotting factors are more common, it is easier for blood clots to form in the brain, hands, feet, or other tissues [11]. In addition, small clots in the blood can lead to a lack of clotting factors for the rest of the body, which can lead to more severe bleeding issues. It is also important to differentiate between thrombocythemia and thrombocytosis. Thrombocythemia is an abnormally high platelet count due to a genetic mutation or other source, which presents as an independent condition. No other disorder is responsible for platelet levels. When another blood altering condition is present, and in turn creates excessive platelets, the disorder is termed thrombocytosis instead, indicating that the high platelet levels are

the fault of another condition that patient has.

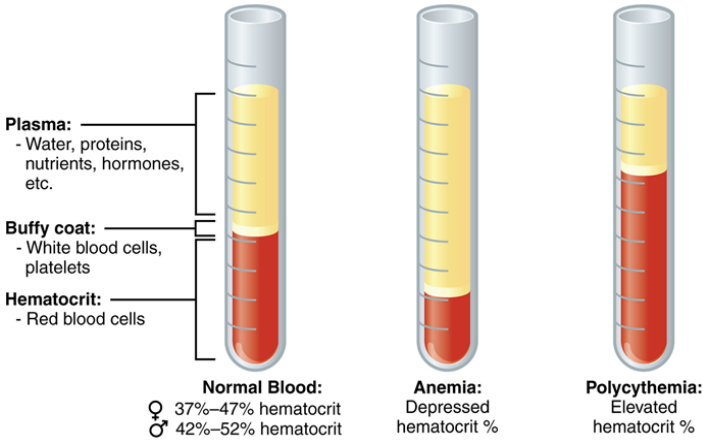

Figure 2: Visual depicting blood samples from normal, anemic and polycythemia patients [12].

Image two provides a visual of the differences between a polycythemic patient and a healthy patient regarding their hematocrit and plasma levels. Contrasted with anemic patients, who present with low red blood cell levels, polycythemic patients present with overwhelming erythrocyte populations, which replace potential plasma volume. When high erythrocyte levels are paired with high levels of thrombocytes, additional complications can occur, such as bleeding conditions and clot formations.

	Hemoglobin (<g/dL)	Hematocrit (<%)
Male	14-18	42-52
Female	12-16	37-47
Child	11-16	31-43
Infant	10-15	30-40
Newborn	14-24	44-64

Table 1: Average hematocrit and hemoglobin values for males and females, children, infants, and newborns [13].

As Table 1 demonstrates, different hematocrit values are expected depending on the gender and age of the patient. In general, PV patients of all genders are recommended to maintain a hematocrit level of 45% or less for strict guidance to decrease the potential risk of thrombosis and other cardiovascular issues [9]. Lenient guidance consisted of a hematocrit between 45% and 50%, though PV hematocrit levels could significantly exceed these guidelines. Phlebotomy is recommended to adhere to the guidelines, but more drastic treatment plans are available to ensure decreased hematocrit. Though phlebotomy can be a taxing treatment plan for a patient, other plans are available. Many patients who begin phlebotomy treatments are often moved to different potential solutions, most notably cytoreductive chemotherapy. Including hydroxyurea and ruxolitinib, these treatments operate on a cellular level to prevent erythrocyte overproduction [14]. In general, hydroxyurea is administered as a primary solution, but ruxolitinib can be substituted for those who present with hydroxyurea intolerance. Ruxolitinib works as a JAK2 inhibitor to improve quality of life and prevent splenomegaly and thrombosis. In a 2019 study, 49% of patients treated with ruxolitinib reported their symptoms improved by over 50%, and 62% reported improvements in splenomegaly [14]. Along with improvements in primary symptoms, patients also discussed better work concentration and performance. In study conclusions, 67% of ruxolitinib patients reported that their quality of life had greatly improved, as opposed to only 13% of patients receiving standard phlebotomy treatments.

The figure below further explores the results of the study. Despite the overall effectiveness of ruxolitinib, the long-term effects are still unknown, as is the relationship between ruxolitinib and intolerant or resistant patients [15]. The study discussed the commonality of ruxolitinib resistance, which seems prevalent with specific demographics. However, the robust method of action does make the treatment very effective in suitable populations. Working as a kinase inhibitor, ruxolitinib inhibits the JAK1/2-Signal Transducer and Activator of Transcription (STAT) pathways. Such inhibition decreases cytokine prevalence, which in turn decreases cell growth signals and stimulates a downturn in overall hematopoiesis.

In healthy cells, the JAK1/2 STAT pathway is essential to cell proliferation, working as a cytokine-activation signal transduction pathway. In addition to cell growth, the pathway also involves hematopoiesis, tissue repair, immune function, and apoptosis [16]. JAK proteins are responsible for recruitment of STAT proteins, which then dimerize and diffuse into the nucleus. Once in the nucleus, STAT proteins facilitate gene expression for the cell mechanisms. In specifics, the JAK2 complex has massive effects on hematopoiesis, to the extent where JAK2 knockout mice in an experiment were deceased just 12 days after gestation due to lack of essential hematocrit. In PV patients, JAK2 is affected with a gain-of-function mutation, which causes overactivation of the STAT group and excess gene expression for hematopoietic sequences. Specifically, regarding the JAK2 V617F mutation, which is found in over 95% of PV patients, the inhibitory pseudokinase JH2 is inactivated, leading to uncontrolled activation of JAK2 and STAT. JAK2 V617F also leads to a lack of megakaryocytes, which can further encourage the development of a myeloproliferative neoplasm such as PV. Despite the commonality of JAK2 mutations in PV patients, the overexpression can cause a plethora of other disorders as well, including Hodgkin lymphoma, Atopic Dermatitis and Rheumatoid Arthritis [16]. JAK mutations can also lead to cytokine overproduction, which in turn creases excessive inflammation within the tissues.

Treatment of PV with medications such as ruxolitinib can be effective due to the nature of the medication, which serves as a JAK inhibitor. This medication in specific is competitive with adenosine triphosphate (ATP), targeting multiple active JAK proteins to decrease overexpression. Though ruxolitinib is not specific to the JAK2 V617F mutation, it still effectively reduces the activation of the JAK1/2 STAT pathway, therefore decreasing the levels of

hematopoiesis in bone marrow. Negative effects of ruxolitinib do include severe discontinuation syndrome, where symptoms quickly worsen when the medication is stopped [16]. Therefore, the medication is only recommended for patients with a high level of commitment and trust with their physician. Figure three below provides a simplified visual representation of the pathway, showing the dimerization of the receptor following cytokine ligand binding, as well as the phosphorylation and subsequent activation of the STAT group. As STAT enters the nucleus, it encouraged gene expression for a wide range of sequences, but most notably those involved with the hematopoiesis process.

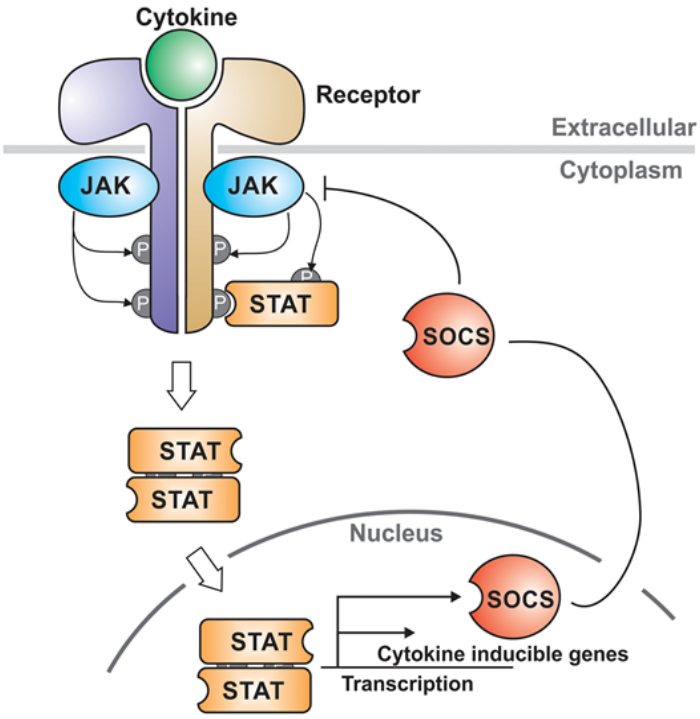

Figure 3: JAK1/2 STAT Pathway [17].

Though the JAK2 mutation is common in most PV patients, not every documented case of the disordered featured the specific mutation. Therefore, additional research is required into the other causes, and if those cases could help provide a cure. Current literature provides hypotheses of a genetic inheritance variable, or perhaps a mutation in other steps of the hematopoiesis process.

Due to both the cost and potential insensitivity to ruxolitinib, hydroxyurea remains the primary cytoreductive treatment plan for PV patients. However, patients do report lower success rates than those taking ruxolitinib. In the graph below, three of the most popular treatment plans are compared, namely ruxolitinib, hydroxyurea, and standard phlebotomy treatment. By far, ruxolitinib resulted in the highest proportion of symptom reduction and the highest number of patients who expressed they "very much improved."

Despite the promising treatments currently on the market to treat PV, there were not always such solutions for the disorder. Previous treatment plans included alkylating agents and radioactive phosphorus, which have since been proven to lead to leukemia and cancers within the gastrointestinal tract [18]. Though hydroxyurea is a better option than previous treatments, there is still suspicion that hydroxyurea is also a mutagenic agent. In previous studies, radioactive phosphorus increased leukemia risk by 13-14%, while hydroxyurea presents a 5.9% risk [19]. Overall, the literature reviewed many current treatments on the market for PV, and many had promising results for patients. Ruxolitinib presented with the highest positive response rate, especially in terms of symptom reductions for PV patients. Standard phlebotomy treatments provided much lower levels of positive responses, which could be attributed to the side effects the treatment is known to cause [14].

In addition to the mystery of a cure, genetic predisposition is another source of curiosity in the medical community. Currently, there is no verified answer as to how PV is connected to inheritance or if it is connected at all. Hypotheses have been made in previous years, especially due to the occasional tendency of PV to cluster over multiple generations in a family. A 2003 study hypothesized that the mode of inheritance is autosomal dominant but with incomplete penetrance. Though there is still the possibility that multiple PV cases in a family occur by chance, the study found that many families with a PV-affected parent ended up with two or more affected children [4]. However, other studies in the current era seem to contradict these results, instead arguing that there is no true genetic component of inheritance to be investigated. Other warning signs, such as mutations in erythropoietin (EPO) or other steps of the hematopoiesis pathway could be attributed to the familial clustering.

Another study also reviewed genetic inheritance and found an association between a disomy of chromosome 9 and PV diagnosis. The disomy is acquired via genetic inheritance, which proposes another hypothesis in favor of the passing of PV through families. However, the mutation mentioned is different from the more common JAK2 mutation found in 95% of current patients [20]. Loss of heterozygosity in the 9p chromosome region led to additional stem cell cloning, which can lead to PV. Additional studies explore new mutations, such as those in alternative splicing, which are not inherited by progeny [21]. Literature is divided over the true cause of PV, and how it relates to familial inheritance.

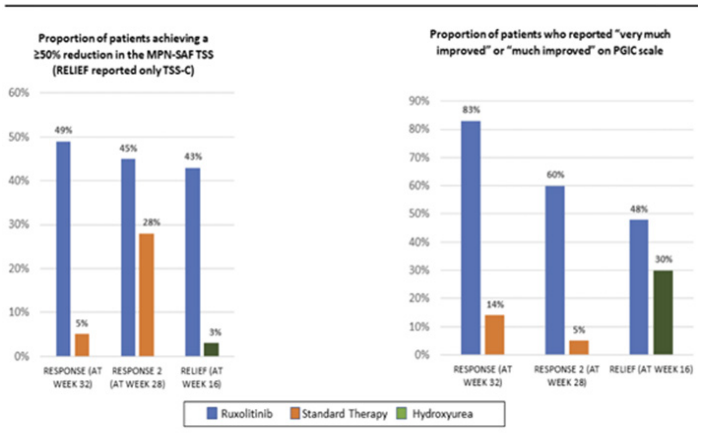

Figure 4: Comparison of various PV treatment plans [14].

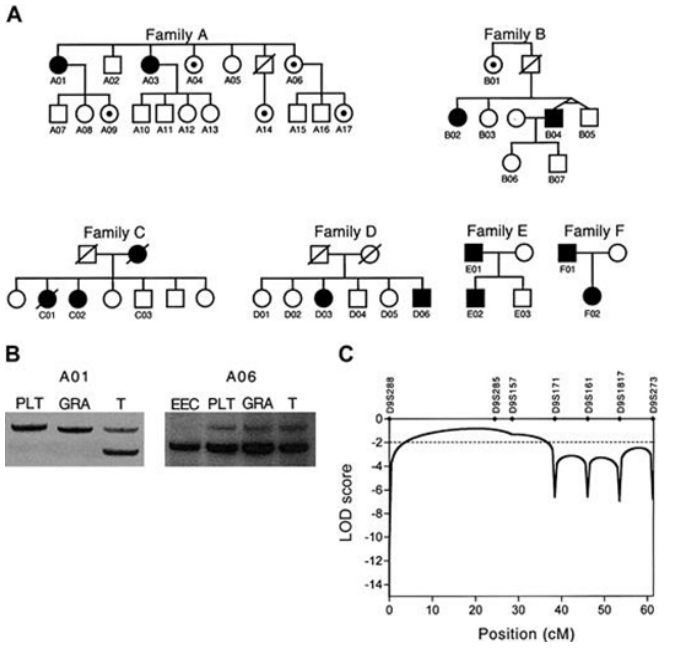

Figure 5: Pedigrees of Familial PV Inheritance [4].

The pedigrees shown in Figure five are utilized in a study to illustrate the potential genetic inheritance of PV. In all but one of the family pedigrees, children presented with PV genes. In three of these cases, a parent was also diagnosed with the disorder. Pedigree A resulted in no inheritance, while Pedigrees B and D showed affected children without parental involvement. Overall, the study suggested that there is some element of PV that relies on inheritance, at least in cases that present with the JAK2 mutation [4].

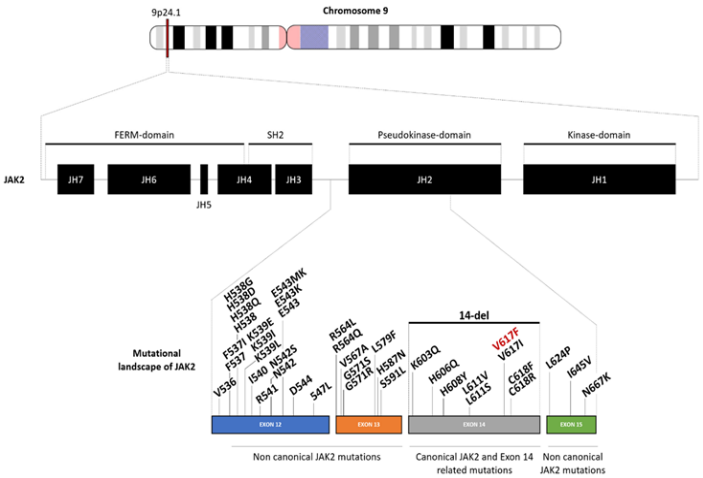

Figure 6: Expansion of the JAK2 mutation, a full view of the genetic landscape [21].

Figure six provides a unique view of the complexities of the JAK2 mutation, namely the exon relations and additional small mutations that can be seen in PV patients. As noted, the mutation is much more expansive than sometimes mentioned, and though the V617F mutation is the most common, many other mutations can be seen to coincide with the mutation or instead of it entirely [21].

Case Study

Patient One is a 58-year-old Caucasian woman diagnosed with PV in November of 2012 following a positive bone marrow aspiration. She is nonsmoking and nondiabetic, has a healthy body mass index (BMI), and is the mother of two children, who she had at 39 and 41. The diagnosis resulted from an unrelated *Mycobacterium marinum* infection, during which abnormally high hematocrit and platelet levels were detected. The patient's mother was diagnosed with Lupus in years past, leading the patient to be exceptionally watchful of blood test results. Following the infection, high platelet levels were discovered, among other abnormalities, foreshadowing the diagnosis. Since then, the patient has received multiple years of phlebotomy beginning in September 2015 and began chemotherapy in September 2023 via 10 mg of ruxolitinib (common name Jakafi) twice daily. Neither hydroxyurea nor interferon were ever prescribed as treatment; due to the physician's medical inclinations the patient was moved directly to ruxolitinib. Initial symptoms before diagnosis were not significant but appeared shortly after phlebotomy began. Overall, symptoms resulting from phlebotomy treatment excluded fatigue, increased susceptibility to migraines, clotting issues, contusions, and concentration issues. Side effects of the patient's treatment plan did seem to worsen over time, as did the risk for venous damage. Regardless of physical condition, the patient maintained excellent emotional and mental responses. Positivity for treatment and adherence to treatment plans were essential for the patient's success in maintaining hematocrit levels. Initial diagnosis was hypothesized following the bacterial infection, but confirmed after an erythropoietin test was conducted in conjunction with the bone marrow aspiration.

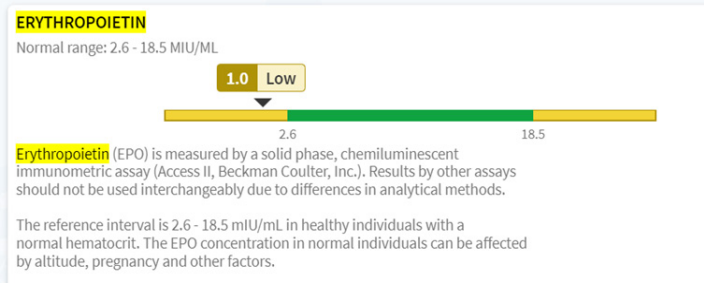

Figure 7: Erythropoietin levels of the patient. Low EPO supported the hypothesis of a polycythemia diagnosis. (Data reproduced with patient consent).

All information within the case study was reproduced with patient consent. Reproduced data is found in the forms of graphs, with each circle point representing a CBC. Circles in green indicate a healthy value in terms of the patient's physician, while a yellow circle represents a value that is either too high or too low regarding the goal range.

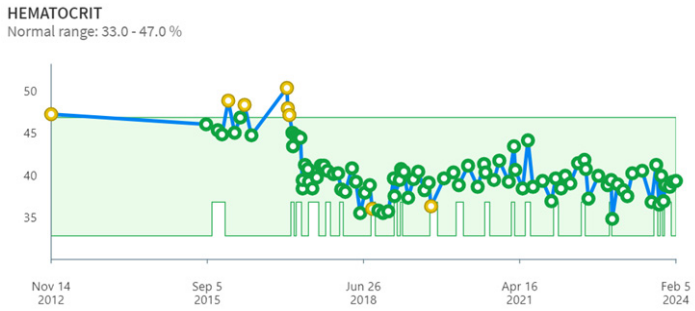

Figure 8: Hematocrit levels from diagnosis to current (Data reproduced with patient consent).

Figure eight reviews overall hematocrit levels from diagnosis to current treatment. Upon diagnosis, Patient One consistently presented with higher-than-average hematocrit levels, sharply decreasing with consistent phlebotomy. Since the beginning of treatment, hematocrit levels have remained below critical levels. However, the patient reported extensive fatigue and dizziness around times of especially low hematocrit levels. In addition, maintenance of low hematocrit levels was necessary to decrease the frequency of phlebotomy treatment, causing the patient to maintain minimal iron levels perpetually. As a result of extensive periods of low iron, the patient often reported cold hands and feet, brittle nails and hair, fatigue, and pallor.

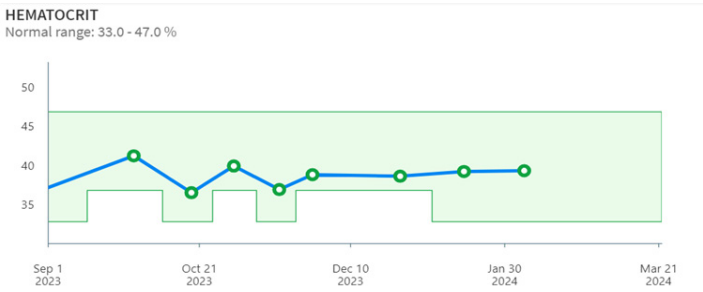

Figure 9: Hematocrit levels following administration of Jakafi. (Data reproduced with patient consent).

Figure 9 reviews hematocrit levels from Patient One, beginning with the first dose of ruxolitinib in September and continuing to the present day. It is noted from previous literature that ruxolitinib usually takes three months to begin consistent effect, which is noted in the stabilizing trend seen in the December blood test and onwards. Since beginning chemotherapy, hematocrit levels have stabilized, and no additional phlebotomy or other treatment has been needed. In addition, stable hematocrit levels have greatly improved the patient's quality of life, as many adverse side effects are now obsolete. Though there are emotional aspects to consider when discussing chemotherapy, especially for a chronic condition such as PV, the lack of physical side effects does outweigh the mental toll.

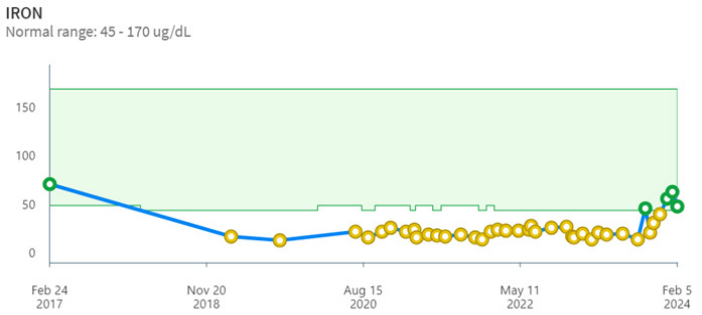

Figure 10: Iron levels following a PV patient through treatment. (Data reproduced with patient consent).

Iron levels (Figure 10) persisted at normal levels throughout many of the early years of diagnosis. However, to maintain phlebotomy effectiveness, the patient was advised to avoid iron-rich foods to keep iron and hematocrit levels low. Prolonged periods of lacking iron caused numerous adverse side effects in the patient, which encouraged her to pursue other treatment options. In addition, frequent phlebotomy treatments did cause an increased risk of collapsed veins. The patient strongly avoided a Port and was not interested in implantation. It is essential to note the increase in iron levels beginning after the onset of chemotherapy. As ruxolitinib provided more vigorous hematocrit maintenance, low iron was not required for the patient to avoid treatment as she had when undergone phlebotomy. Increasing iron levels alleviated many more severe reported symptoms, such as fatigue, bruising, brittle nails and fair, and migraines. Though the patient expressed an emotional toll associated with the new treatment plan, the benefits have greatly outweighed the initial fear of chemotherapy, and adverse side effects have been avoided. The ability to increase iron was a turning point for the patient's condition, and hematocrit has maintained safe levels even with higher iron. In addition to the cessation of side effects, maintaining healthy iron levels also allowed the patient more autonomy regarding diet. Following years of rigid diet restrictions, such as avoidance of iron-rich foods and red meat, the ability to finally tolerate such foods was very welcomed. Loss of food restrictions can significantly increase the quality of life in patients, especially if they have preferences for foods that were previously deemed risky.

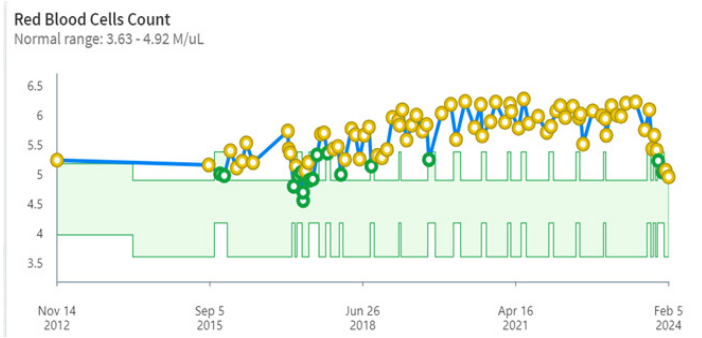

Figure 11: Erythrocyte levels in Case Study Patient. (Data reproduced with patient consent).

Figure 11 outlines the erythrocyte levels in the case study patient. As seen in the early years of the table, erythrocyte levels were sporadic and often shifted depending on the frequency of phlebotomy. Consistent phlebotomy saw periods of lower erythrocyte levels, some achieving marks in the healthy range, but a slow upward trend was seen in the later years of phlebotomy treatment. The beginning of chemotherapy marked a sharp downturn in erythrocyte levels, which have since stabilized with ongoing treatment. The upward trend in red blood cell count could spark an interesting avenue of exploration, reviewing whether prolonged phlebotomy treatment leads to a loss in effectiveness over time.

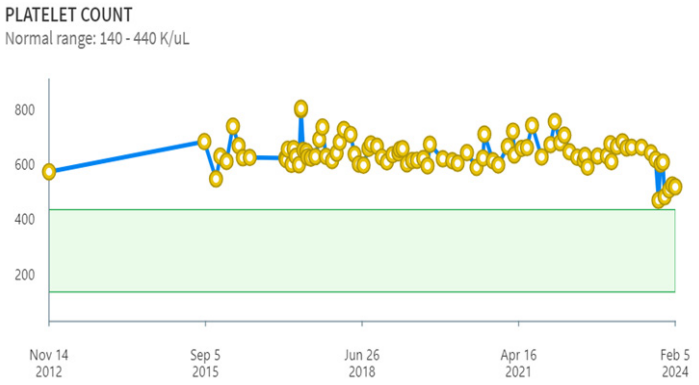

Figure 12: Platelet Values (Data reproduced with patient consent).

Figure 12 provides a graphical representation of platelet counts in the patient over the term of her diagnosis. Since diagnosis, the patient has presented with extremely high platelet levels, with a mild downturn around the start of ruxolitinib administration. Previous studies have shown that PV often presents with over enhanced platelet activation, which can increase chances of thrombosis [22]. Above average platelet levels can also cause bleeding complications and contribute other adverse side effects. Many PV patients are prescribed baby aspirin to help with overwhelming levels of both erythrocytes and thrombocytes, which can help decrease the chance of side effects or cardiac events. Regardless, the patient did start presenting with lower levels of platelets once ruxolitinib was added to her treatment plan.

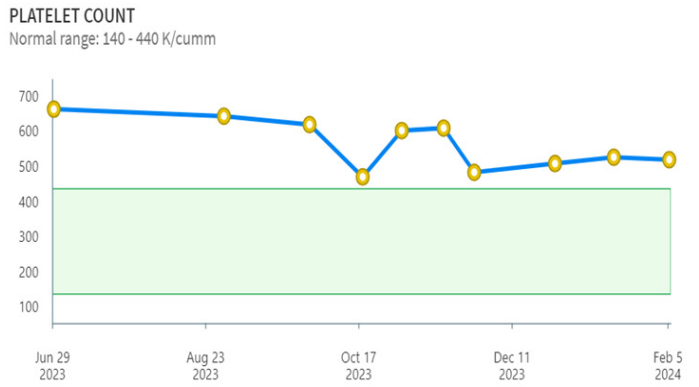

Figure 13: Platelet values following Ruxolitinib administration (Data reproduced with patient consent).

In Figure thirteen, platelet levels following chemotherapy can be compared to the previous figure, which details platelet levels overall. Ruxolitinib was added to the patient's treatment plan in August, and since the medication was prescribed platelet levels have slowly decreased. Literature does not confirm whether there is statistical significance between ruxolitinib and lowered platelet levels, but the patient does seem to present with healthier levels in recent months. Regardless of testing levels and changing blood cell concentrations, the patient is serving as a model patient for ruxolitinib administration. As a mother of two, wife and a self-employed artist, quality of life was of utmost importance. A love for travel and passion for exploring resulted in additional negative side effects, which further pushed her oncology physician to review other potential treatment options.

Cytoreductive chemotherapy has greatly improved fatigue, stress levels and many other phlebotomy effects, and has allowed the patient to pursue a higher quality of life. Increased iron levels ad decreased platelet levels further improve the patient's condition, allowing further diet autonomy and decreased risk for disease progression. Though cytoreductive therapy could have been offered at an earlier treatment stage, the patient reported severe apprehension in terms of a chronic treatment. Despite adverse side effects associated with phlebotomy, the patient still preferred her current treatment due to the avoidance of a long-term chemotherapy plan.

Summary and Conclusions

PV is a vastly complex disorder, characterized by a plethora of symptoms that significantly decreases a patient's quality of life. Despite various treatment plans, a cure has not been developed, and all major treatments revolve around improving quality of life and preventing the disorder from developing into a more severe diagnosis. As of late, phlebotomy persists as the primary course of action, though strict hematocrit control does greatly impact patient quality of life [9]. Though other options are available, such as cytoreductive therapy, they can be costly, and many populations demonstrate resistance to the medication. These drugs often act as kinase inhibitors, which work to stop excessive hematopoiesis in the JAK1/2-STAT pathway. Chemotherapy does hold its own set of side effects, though many patients report a better quality of life than when they were treated with phlebotomy. In addition, occasional cases have reported stabilizing hematocrit in the absence of medication after the patient had been taking it for many years.

Though cytoreductive therapy does have promising results, there are emotional conflicts that many patients report. As PV is a chronic disorder, chemotherapy would have to be taken for the rest of a patient's life, which can be viewed as a very negative prognosis. Many patients, especially those struggling to cope with a chronic disease often have trouble when their treatment plan is changed from phlebotomy to chemotherapy. Regardless, current treatment plans are very successful, and often significantly improve quality of life while decreasing the risk of leukemia transformation.

Moving forward, it is essential that physicians understand the fear of cytoreductive therapy that many patients face but also recognize the struggles that phlebotomy can impose. Fear of chronic treatment should not limit the quality of life for patients, and it is the responsibility of the physician to properly inform patients of the benefits that more advanced treatment can have. There is a right to fear the future but also a duty to enjoy the present, and physicians must ensure that the treatments they recommend respect both ideas. Cytoreductive therapy, though new, poses a quality of life for patients that other treatment plans cannot rival, and despite negative views held by patients, it is the job of the physician to properly educate and help patients understand that long-term treatment does lead to long-term health. Proper management of PV can make it a very manageable condition, with minimal risk of transformation or cardiac events. Despite the existing treatments for the disease, a cure is still needed to stop myeloproliferative neoplasms. In addition, more extensive research into the long-term effects of all treatment methods will help doctors see a bigger picture when recommending plans of action for their patients, but also allow patients to fully understand their options. Outside of the treatment for PV, the genetic component of diagnosis also requires additional exploration. Genetic inheritance of the disorder is still wildly unknown, and present literature often presents conflicting ideas of causation. Gathering a complete understanding of the genetic risks of PV could help prevent future cases and provide additional information to find a cure.

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