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Thrombocytapheresis for Severe Post-Splenectomy Thrombocytosis and Dural Sinus Thrombosis in a Patient with Accelerated Phase Polycythemia Vera

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Abstract

Thrombocytapheresis involves the removal of excess platelets via an automated centrifugal apheresis machine. Evidence is scarce for the clinical efficacy of this procedure, as controlled trials have not been done. We present a case of thrombocytapheresis that was followed by rapid platelet reduction and clinical improvement in a female in her seventies with severe post-splenectomy thrombocytosis and dural sinus thrombosis in the setting of accelerated phase polycythemia vera.

Keywords: ***Thrombocytapheresis; Platelet reduction; Post-splenectomy; Thrombocytosis; Polycythemia vera; Myeloproliferative neoplasm***

1. Introduction

Thrombocytosis is defined as a circulating platelet count greater than 450 × 10^9 /L [1]. Thrombocytosis is most commonly a reactive process (secondary thrombocytosis) in response to infection inflammation, anemia, asplenia, and/or malignancy [1]. Primary thrombocytosis is less commonly implicated in cases of increased platelet count but can be seen in MPNs such as essential thrombocythemia (ET), polycythemia vera (PV), chronic myeloid leukemia (CML), pre-fibrotic primary myelofibrosis (PMF), and myelodysplastic syndrome [1].

Primary thrombocytosis is associated with increased risk of thrombosis and bleeding and impacts overall morbidity and mortality [2]. The current standard of care for primary thrombocytosis secondary to a MPN includes daily low dose aspirin and a cytoreductive therapy such as hydroxyurea [1]. Currently, limited data exists regarding the efficacy of thrombocytapheresis in the management of thrombocytosis. However, in select patients with acute complications such as bleeding and thrombosis, thrombocytapheresis may be effective intervention for rapid cytoreduction in the acute setting [2,3].

ET is characterized by autonomous overproduction of platelets [1]. The majority of Philadelphia chromosome negative primary thrombocythemia patients express a somatic mutation in JAK2, causing a constitutively active JAK2-STAT signaling pathway, resulting in hematopoietic progenitor cells to be hypersensitive to cytokines [3]. Other mutations implicated in the development of acquired thrombocytosis include BCR-ABL in the setting of chronic myeloid leukemia, MPL, or calreticulin (CALR) [1,3]. Inherited thrombocytosis is often accompanied by mutations in MPL, TPO, and MPL Baltimore genes [3].

In the setting of secondary thrombocytosis, patients do not exhibit an increased risk of thrombosis or hemorrhagic phenomenon due to the elevated levels of functionally normal platelets [1]. However, primary thrombocytosis due to clonal proliferation typically involves dysfunctional platelets and confers a 1%-3% risk of thromboembolism per patient-year [1]. Thromboembolic events can be present in arterial or venous systems and include microvascular thrombosis, stroke, transient ischemic attacks, myocardial infarction, venous thromboembolism, and first trimester pregnancy loss [1]. Patient risk factors for thromboembolism include older age, JAK2 mutation, history of thrombosis, or cardiovascular risk factors [1]. In addition to an increased risk for thromboembolism, there is an increased risk of bleeding due to dysfunctional platelet. Bleeding typically involved mucocutaneous sites and affects between 1%-30% of patients [1].

Treatment options are variable depending on patient specific risk factors. In low-risk patients, daily low-dose aspirin is indicated for thromboprophylaxis and has been effective in reducing symptoms such as headache, tinnitus, ocular disturbances, and erythromelalgia [1]. Cytoreductive therapy with hydroxyurea is indicated for high-risk patients [1]. Potential alternative treatment therapies include interferon-alpha and anagrelide, but these approaches have been associated with an increased risk of myelofibrosis [1].

In patients with severe thrombocytosis and hemorrhage, medical therapy and/or thrombocytapheresis may be utilized [1,4]. Thrombocytapheresis has also been used for prophylaxis and treatment of acute thromboembolism or hemorrhage in patients with extreme thrombocytosis and has been associated with reduced complications and rapid improvement in symptoms [1]. Thrombocytapheresis is rarely used, but it often leads to a rapid platelet decrease, especially in combination with medical cytoreduction [5]. To our knowledge, controlled trials have not investigated this question, and data is limited to uncontrolled observational reports.

2. Case Report

A female in her seventies at the time of thrombocytapheresis was diagnosed with polycythemia vera (JAK2 mutation positive) 18 years prior to presentation. She was treated with intermittent therapeutic phlebotomy and hydroxyurea since that time. The patient remained stable and established with care at our institution one year prior to thrombocytapheresis. Bone marrow biopsy

obtained at that time revealed hypercellular marrow with trilineage hematopoiesis, 3% blasts, and megaloblastic changes in addition to neutrophilia and thrombocytosis on peripheral blood smear.

The patient underwent splenectomy nine months prior to thrombocytapheresis. Pathologic examination of the spleen revealed red pulp hyperplasia and extramedullary hematopoiesis. Follow-up bone marrow biopsy revealed the hypercellular bone marrow with slight erythroid and megakaryocytic hyperplasia, marked granulocytic hyperplasia, dysplastic megakaryocytes, grade 1 myelofibrosis, and approximately 10% myeloblasts. The bone marrow biopsy was consistent with the accelerated phase of polycythemia vera. The patient continued to receive hydroxyurea 3000mg daily and intermittent therapeutic phlebotomy.

On the day of thrombocytapheresis, the patient presented to an outside facility with chief complaint of sudden onset severe headache and associated vomiting. Initial workup revealed a platelet count greater than 2.5 million/uL. A CT of the head without contrast revealed no acute intracranial hemorrhage. However, a CT venogram revealed left transverse and sigmoid dural venous sinus thrombosis. While her underlying condition of the accelerated phase of polycythemia may have also contributed to her thrombocytosis, we speculated that the most likely cause of her thrombocytosis was her post-splenectomy state.

Given the patient's condition, she was transferred to our hospital for further evaluation and treatment. Upon presentation, her platelet count was 1,762 K/uL, WBC count was 2.5 K/uL, and hemoglobin was 7.1 g/dL. She was started on a therapeutic heparin drip and aspirin 325 mg daily while hydroxyurea was held.

Given the patient's profound thrombocytosis and evidence of thrombosis, she underwent emergent thrombocytapheresis via an automated centrifugal apheresis machine with 1.5 total blood volumes (TBVs) processed. Her platelets went from 1.762 million/uL pre-procedure to 1.086 million/uL post-procedure. The goal was a platelet count of less than 500,000/uL. Thus, the following day the patient underwent repeat thrombocytapheresis with an increase to 2.0 TBVs processed. Her platelet count went from 1.086 million/uL pre-procedure to 333 K/uL post-procedure.

Given the patient's lack of response to suppressive therapies and the evidence of an accelerated phase, the patient was started on Azacitidine C1D1 for a 7-day course. Three days after thrombocytapheresis 1, her platelet count rebounded to 610 K/uL. Four days after thrombocytapheresis 1, her platelet count decreased mildly to 563 k/uL following initiation of Azacitidine C1D1.

Five days after thrombocytapheresis 1, CT angiogram of the head was done and revealed no evidence of interval complication from dural venous sinus thrombosis, an incidental vascular malformation at the left parapharyngeal space, but no other acute findings.

Her platelet count stabilized between 600 K/uL and 800 K/uL. She was transitioned to apixaban for further anticoagulation and treatment of dural sinus thrombus. She was discharged to home in stable condition with appointments scheduled with hematology/oncology for further management of polycythemia vera with thrombocytosis and with neurosurgery for evaluation of vascular malformation.

3. Discussion

3.1 Literature review highlights

Data regarding the use and efficacy of therapeutic thrombocytapheresis is limited. According to the 2019 AFSA guidelines there have been between 100 and 300 reported patients receiving thrombocytapheresis for thrombocytosis [1]. Per the guidelines, thrombocytapheresis carries a Grade 2C for the treatment of symptomatic or prophylactic thrombocytosis [1]. The therapeutic mechanism behind thrombocytapheresis is not well defined, but it is hypothesized that rapid reduction in platelet count can decrease prothrombotic factors associated with dysfunctional platelet [1]. It can also selectively remove larger dysfunctional platelets and normalize morphological and functional platelet properties [6]. Additionally, it may restore the short half-life of von Willebrand factor multimers associated with essential thrombocytosis [1].

A review was published by Boddu, et al, in 2017 that analyzed several case reports of thrombocytapheresis in the setting of thrombocytosis [4]. The review summarized 10 cases under varying clinical settings that included the use of thrombocytapheresis in four cases. Case #1 described thrombocytapheresis in a 76-year-old male with primary myelofibrosis with neurologic symptoms secondary to microcirculatory disturbances from severe thrombocytosis. The patient received three thrombocytapheresis procedures and was treated with hydroxyurea with a decrease in platelet count to below 1000×10^9/L [4].

Case #2 described a 68-year-old male with JAK2-positive essential thrombocytosis and myelofibrosis treated with numerous medical therapies [4]. Similar to our patient, this patient progressed to accelerated phase MF with elevated blasts and elevated platelet count despite hydroxyurea treatment [4]. The patient's platelet count was found to be $2,043 \times 10^9$/L and was treated with emergent thrombocytapheresis and elevated doses of hydroxyurea with a decrease in platelet count to less than 1000×10^9/L [4].

Case #3 described a 79-year-old female with a history of refractory MF treated intermittently with hydroxyurea and Anagrelide [4]. Thrombocytapheresis was considered for prophylactic measures to reduce counts to a range eligible for an investigational protocol. Despite the treatment, her platelet count increased from 2,200 to $5,00 \times 10^9$/L [4]. The patient received two apheresis sessions which decreased her platelet counts to $1,050 \times 10^9$/L [4].

Case #4 described a 61-year-old male with recurrent renal cell carcinoma and marked thrombocytosis of 1.548×10^9/L complicated by ischemic left third and fifth toes secondary to micro-thrombotic disease [4]. Due to concern for a MPN, the patient was started on cytoreduction with hydroxyurea 1 g daily, but the patient's platelet counts only decreased by less than 200×10^9/L [4]. The patient's condition was further complicated by hyper vascularized duodenal mass with actively bleeding ulcers [4].

Given the patient's ischemic toes and active bleeding, the patient was started on thrombocytapheresis with a reduction to $1,050 \times 10^9$/L [4]. Although the evidence is limited, a number of case reports (as described in the Boddu case-based review) show the potential efficacy of thrombocytapheresis for rapid reduction in platelet count and clinical improvement.

3.2 Risk of thrombosis and bleeding in MPNs

MPNs, including polycythemia vera, essential thrombocythemia, and primary myelofibrosis, confer an increased risk for both bleeding and thrombosis. The etiologies underlying both bleeding and thrombosis are unclear and most likely multifactorial. Proposed etiologies leading to thrombosis include vascular disturbances, platelet activation, endothelial damage, and microparticle-induced coagulation [2]. Hypothesized etiologies contributing to increased risk of bleeding include platelet dysfunction, thrombocytopenia, changes to vascular endothelium, and acquired von Willebrand syndrome [2].

One study reported that thrombotic complications associated with MPNs are a common occurrence and observed in more than 30% of patients [2]. Similarly, MPNs are associated with bleeding complications. Approximately 3%-18% of patients with ET experience abnormal bleeding at initial presentation. About 4% of patients with a MPN will experience a hemorrhagic event within the first 10 years following diagnosis. The overall prevalence of bleeding complications in patients with ET is approximately 9% [2]. Thrombosis and bleeding confer a significant risk of both morbidity and mortality in patients with MPNs [2]. This phenomenon further highlights the potential importance of rapid platelet reduction in the acute setting.

3.3 Technical aspects of thrombocytapheresis

Our patient exhibited a rapid reduction in platelet count following two thrombocytapheresis procedures. Notably, the TBVs processed appeared to have a significant impact on the magnitude of platelet reduction. Day 1 thrombocytapheresis processed 1.5 TBVs and resulted in a 41% reduction in platelet count, while day 2 thrombocytapheresis processed 2.0 TBVs resulted in a 69% reduction in platelet count. Typically, 1.5 to 2 TBVs processed appear to be the most common endpoints in therapeutic thrombocytapheresis [1]. Studies have shown that this typically results in a platelet decrease between 30%-60% [1].

Notably, thrombocytapheresis is typically associated with a greater reduction in patients who have not undergone splenectomy. This may be due to more platelet mobilization from a functioning spleen that results in more platelets that can be removed by thrombocytapheresis [1]. As demonstrated in this case report, despite the patient having undergone splenectomy, there was still a 69% reduction in platelet count when 2.0 TBVs were processed during thrombocytapheresis 2. One factor may have been the increased volume processed, while another factor may have been the fact that it was the second procedure performed and platelet rebound via mobilization may have occurred between procedure 1 and procedure 2 on the next day.

3.4 Etiologies of this patient's thrombocytosis

We speculate that the two most likely causes for her thrombocytosis were her post-splenectomy state and her underlying condition of the accelerated phase of polycythemia vera. On the one hand, thrombocytosis can be seen following splenectomy [7]. On the other hand, the phenomenon typically lasts days rather than weeks, as the platelet count usually peaks around day 8-10 to a level of around 600-800 $\times 10^9$/L [7]. Thus, we cannot say with certainty that this patient's significantly more severe and more sustained thrombocytosis was primarily due to her post-splenectomy state.

Similarly, her underlying condition could have contributed to her severe and sustained thrombocytosis, but we cannot be certain. On the one hand, severe thrombocytosis has been reported in a small but significant percentage of patients with accelerated phase PV [8]. Moreover, she had moderate thrombocytosis before her splenectomy. On the other hand, she had a

dramatic increase in her platelet count after splenectomy. That is, there appeared to be a clear temporal association with splenectomy over and above the increase associated with her accelerated phase PV that preceded splenectomy by several months. Thus, we speculate that these two factors (accelerated phase PV initially followed by splenectomy) both contributed to her severe thrombocytosis, and we further hypothesize that her MPN was the single biggest contributing factor for a thrombocytosis of this magnitude and duration.

4. Conclusion

In light of scarce data about the clinical utility of thrombocytapheresis, we share this report that indicates the potential efficacy of thrombocytapheresis for a patient with severe post-splenectomy thrombocytosis and dural venous sinus thrombosis in the setting of accelerated phase polycythemia vera.

5. Conflicts of Interest

The authors report no conflicts of interest.

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