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The role of thrombocytapheresis in the contemporary management of hyperthrombocytosis in myeloproliferative neoplasms: A case-based review

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ABSTRACT

Extreme thrombocytosis induces an acquired thrombotic-hemorrhagic diathesis, and left uncontrolled is a harbinger of potentially fatal vascular complications. Currently, cytoreduction with medical therapy remains the mainstay of hyperthrombocytosis management. However, it offers a less-than-ideal option in situations where a rapid reduction in platelets is urgently needed, as in the presence of vital end-organ ischemia or to ameliorate of life-threatening hemorrhage. The role of thrombocytapheresis, or plateletpheresis, in hyperthrombocytosis has become increasingly obsolete given the proactive titration of cytoreductive therapies and early identification and correction of reversible causes of reactive thrombocytosis. Despite its narrowed indications, plateletpheresis continues to offer a valuable temporizing measure in platelet count reduction before cytoreductive agents exert their maximal effect. In this context, it is important for the treating physician to be aware of the symptoms and risks associated with hyperthrombocytosis to inform best clinical practices. In this review, we discuss the role of plateletpheresis in the modern-day management of hyperthrombocytosis in patients with myeloproliferative neoplasms through a case based review of the literature. It becomes apparent throughout the discussion that the decision to perform plateletpheresis should be individualized based upon the clinical scenario, degree of thrombocytosis, available infrastructure and every patient's risk profile.

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1. Introduction

Among the few hidden dangers in the indolent natural history of essential thrombocythemia (ET), a relatively benign myeloproliferative neoplasm (MPN), are episodes of extreme thrombocytosis which can cause hemorrhage and/or thrombosis. The term hyperthrombocytosis conveys an extreme form of thrombocytosis characterized by very high elevations in platelet counts. Previous authors had variably defined hyperthrombocytosis as platelet counts greater than 800×10^9/L – 1000×10^9/L [1–4]. While seemingly arbitrary, these cut-off points historically served as diagnostic aids in differentiating MPN from conditions associated with reactive thrombocytosis such as infections, trauma, hemorrhage, or burns among many others [1,5,6]. However, it has long since been realized that there exists a significant overlap in platelet count ranges between these etiologically disparate entities. It is worth noting here that, although not routinely performed, ancillary platelet indices demonstrating high platelet distribution widths and mean platelet volumes may facilitate distinction of MPN from reactive etiologies, especially in so-called triple negative (i.e., *JAK2*-, *MPL*-, and *CALR*-mutation negative) cases [6–8]. Hyperthrombocytosis is frequent phenomenon, reported in up to 50% of MPN patients along the course of their disease [9]. This condition also occurs in chronic myeloid leukemia (CML), albeit at a much lower incidence of about 5.5% [10].

Thrombocytosis occurs in response to a variety of stimuli, including systemic infections, inflammation, hemorrhage, trauma, burns, and malignancies [11,12]. Extreme thrombocytosis in CML occurs much more commonly in females and in disease with high to intermediate Sokal scores [10]. However, extreme thrombocytosis is much more commonly encountered in MPN and after splenectomy [12]. The spleen constitutes a major reservoir pool for platelets and plays an important role in platelet turnover. Irrespective of the underlying cause, splenectomy may cause a significant rise in peripheral platelet counts, peaking 1–3 weeks postoperatively [13]. Non-splenectomized patients experience a faster recovery in platelet numbers after plateletpheresis than post-splenectomy patients, primarily owing to rapid platelet mobilization from the splenic pool into the bloodstream [14,15]. Importantly, the spleen's role in regulating circulating platelet mass becomes especially significant in patients with MPN, who can experience a marked thrombocytosis after splenectomy with the attendant risk for hemorrhagic thrombocythemia [16,17]. Along similar lines, it is plausible that other more common non-malignant etiologies may contribute to acute rises in platelet count in MPN patients and the ensuing hemorrhagic/thrombotic risks.

In this review, we describe four patients with MPN who presented with extreme thrombocytosis in different clinical settings [Fig. 1]. A detailed report of each case will follow, illustrating the valuable temporizing role of plateletpheresis in the management of hyperthrombocytosis and its associated complications.

2. Case 1

A 76-year-old gentleman with a history of primary myelofibrosis (MF) presented to our clinic with a complaint of subacute alteration of mental status two weeks after sustaining a fall. His medical history was also significant for coronary artery disease, atrial fibrillation, hyperlipidemia, and prostate cancer treated with surgical resection. He had been diagnosed with MF four years prior and been managed with hydroxyurea and anagrelide. Six months before presentation, his course was complicated by splenic rupture, requiring urgent splenectomy. After recovering from surgery, he was referred to our clinic for persistent fatigue and malaise. A complete blood count (CBC) at the time of initial diagnosis showed a white blood cell (WBC) count of 50,000/μL, hemoglobin (Hgb) 8.5 g/dL and a platelet count of 1552×10^9/L. Initial bone marrow evaluation confirmed the diagnosis of MF with 6% blasts, and molecular testing was positive for *ASXL1* and *KRAS* mutations, and negative for *JAK2* and *MPL* mutations. Cytogenetic analysis revealed 46XY, del(13q), t(9; 12) in all 20 metaphases. The patient was initially treated with ruxolitinib at 20 mg twice daily along with low-dose aspirin. Ruxolitinib alone proved unsuccessful in controlling his rising counts, and he was subsequently enrolled in a clinical trial of ruxolitinib plus 5-azacytidine to manage the persisting leukocytosis and thrombocytosis. Other forms of cytoreduction were not allowed per study protocol. He presented for his regular follow-up visit at the end of the second cycle. CBC revealed a WBC 42,100/μL, hemoglobin 7.6 g/dL, and platelets 2420×10^9/L. On reviewing his history, the patient reported tripping and sustaining a fall after which he lost consciousness for a few minutes. This was followed by worsening gait imbalance, blurry vision and dizziness over the subsequent two weeks. He was transferred to the emergency department for further evaluation. A CT scan showed no evidence of intracranial abnormality. His subacute neurological symptoms were therefore felt to be related to hyperthrombocytosis, and therapeutic plateletpheresis was planned. While attempting a femoral catheter placement, an incidental deep vein thrombosis (confirmed on Doppler ultrasound) was found in the right proximal femoral vein. Apheresis was performed on days 1, 2 and 5 of his hospital stay. His platelets dropped to below 1500×10^3/μL after two rounds of apheresis. He was started simultaneously on hydroxyurea 2.5 g/day on day 1. His platelets dropped to below 1000×10^9/L over a week, after three sessions of apheresis and one week of hydroxyurea. The patient tolerated apheresis without experiencing any further adverse events, while also reporting resolution of his subacute neurological symptoms. Shortly thereafter, his MF evolved into biopsy-proven acute myeloid leukemia, from which he died 6 months later despite treatment.

3. Case 2

A 68-year-old man with *JAK2*-positive post-ET MF previously treated with multiple lines of therapy presented to the emergency department with new-onset gum bleeding. He had first been diagnosed with ET at an outside facility about 3 years prior and was taking hydroxyurea to manage his platelet counts. At our institution, he engaged in several clinical studies: two different JAK2 inhibitors, lasting 6 cycles each, then ruxolitinib plus azacytidine, and finally, the phosphatidylinositol-3-kinase (PI3 K) gamma delta inhibitor, duvelisib. His disease had progressed to accelerated MF with elevated blasts and he was restarted on ruxolitinib plus azacytidine. Bone marrow biopsy performed after 2 cycles showed persistent post-ET MF with modest reduction in blast percentage. However, over the subsequent weeks, he developed multiple infec-