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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.

Keywords

plateletpheresis; thrombocytapheresis; hyperthrombocytosis; essential thrombocythemia; myeloproliferative neoplasms; hydroxyurea; anagrelide; interferon; myelofibrosis; reactive

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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 $800 \times 10^9/L$ - $1000 \times 10^9/L$ [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 [figure 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.

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/ μ L, hemoglobin (Hgb) 8.5 g/dL and a platelet count of $1,552 \times 10^9$ /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/ μ L, hemoglobin 7.6 g/dL, and platelets $2,420 \times 10^9$ /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 / μ L after two rounds of apheresis. He was started simultaneously on hydroxyurea 2.5 grams/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.

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 (PI3K) 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 infectious complications and progressively rising platelet counts (to over $2,000 \times 10^9$ /L) despite intervening treatment with hydroxyurea.

On presentation to the emergency department, the patient reported two days of unremitting retromolar gum bleeding. Labs performed at that time were remarkable for a WBC count of $2.3 \times 10^9/L$, with 19% blasts, hemoglobin 9.2 g/dL, and platelets $2,043 \times 10^9/L$; coagulation parameters were normal. A detailed diagnostic workup entailed evaluation for acquired von-Willebrand disease with vWF function studies including ristocetin cofactor activity. Meanwhile, he was given aminocaproic acid mouthwashes to control his oral bleeding, and aspirin was held. In addition, he was emergently treated with a session of plateletpheresis and continued on hydroxyurea at a higher dose of 3 grams daily. His platelets dropped to $1,400 \times 10^9/L$ within a day of undergoing apheresis. The platelet counts continued to drop further on the higher dose of hydroxyurea, and no further sessions of apheresis were required. Hydroxyurea was de-escalated gradually over the next few weeks to maintain a platelet count below $1,000 \times 10^9/L$. He did not suffer any further bleeding complications after these interventions. He was instructed to continue on the same outpatient regimen. During this time, his vWD panel studies returned normal. He received an additional 11 cycles of azacitidine and ruxolitinib before progressing to fatal acute myeloid leukemia.

CASE 3

A 79-year-old woman with a history of refractory MF presented to our clinic for regular follow up. Her history dated back 24 years prior when she was first diagnosed with polycythemia vera. She was started on low-dose aspirin and hydroxyurea. Six years later the hydroxyurea was discontinued due to leg ulcers, and she was maintained on intermittent phlebotomies with gradual resolution of the leg ulcers. During this time, however, her platelet counts started to rise steadily and she was restarted on hydroxyurea. Despite recurrence of her leg ulcers, she was maintained on hydroxyurea along with anagrelide. At her initial evaluation in our clinic, a CBC showed WBC $34.9 \times 10^9/L$ with 1% blasts, hemoglobin 11.2 g/dL, and platelets $2,200 \times 10^9/L$. A bone marrow evaluation revealed grade-1 MF with 2% blasts. Anagrelide was increased to 2 grams daily while the patient was being screened for enrollment on a clinical trial. Plateletpheresis was instituted as a prophylactic measure and to help reduce counts to within the range defined by eligibility criteria for an investigational protocol. Over the subsequent two weeks, her platelet count had risen from 2,200 to $5,000 \times 10^9/L$. Therefore, the patient was referred for plateletpheresis and proceeded to receive two apheresis sessions, which successfully decreased her platelet counts to $1,050 \times 10^9/L$. She was discharged uneventfully. Unfortunately, after discharge, her clinical condition continued to deteriorate, and she refused further therapy and was transitioned to hospice. She passed away from sepsis a month later.

CASE 4

A 61-year-old man was referred to the hematology clinic for progressive thrombocytosis and a 6-week history of painful, discolored toes bilaterally. His medical history was significant for renal cell carcinoma (RCC), clear cell type, diagnosed 25 years prior and treated with right radical nephrectomy. Four years earlier, he presented again with progressive weakness and was found to be markedly anemic. Imaging revealed lesions in duodenum, liver, pancreas, and lungs. Duodenal biopsy confirmed recurrent RCC. The patient was treated

with multiple different agents, including interleukin-2, pazopanib, everolimus and, most recently, sorafenib.

The day prior to his consultation with us, the patient was found to have a new heart murmur and marked thrombocytosis. On further questioning, he reported intermittent episodes of melena over the previous several months. Examination revealed warm extremities with grade 2+ radial and dorsalis pedis pulses bilaterally. The right fifth toe showed black discoloration and ulceration, while the left third and fifth toe were erythematous with desquamation of the skin. A vascular surgery consultation was ordered, and peripheral arterial duplex ultrasound was normal. The toe ischemia was felt to be secondary to micro-thrombotic disease. A CBC at that time revealed a WBC count of $19.5 \times 10^9/L$, hemoglobin of 6.7g/dL, and platelets of $1.548 \times 10^9/L$. Upon reviewing the initial peripheral smear, numerous, large platelets were observed, raising concern for MPN. However, bone marrow evaluation did not confirm this hypothesis; further, *JAK2* was not mutated, although *MPL* and *CALR* testing were not performed. Cytoreduction with hydroxyurea at a dose of 1 g daily was initiated, but the platelet count only decreased by less than $200 \times 10^9/L$ in two days. Meanwhile, a diagnostic endoscopy revealed a hypervascularized duodenal mass with actively bleeding ulcers. Plateletpheresis was instituted to rapidly decrease the platelets in the setting of simultaneous bleeding and ischemia of the toes. After one session, the platelets decreased to $1,050 \times 10^9/L$, and no additional sessions were planned. His ulcerated gastric lesions were endoscopically clipped, and he was discharged after his platelets dropped further on continued therapy with hydroxyurea. Over the next several months, his toe ulcers also healed and he had no residual pain. The patient was eventually transitioned to hospice due to progressive metastatic RCC and passed away from the disease.

DISCUSSION

Complications of hyperthrombocytosis

Hyperthrombocytosis may be discovered incidentally or present with thrombocytosis-related symptoms and complications. Symptoms are predominantly vasomotor and may include headaches, dizziness, blurring of vision, syncope and erythromelalgia [18, 19]. In addition, patients with hyperthrombocytosis are at increased risk for major thrombotic and hemorrhagic complications. Regardless of the cause, thrombocytosis results in a pro-aggregatory effect. Although thrombosis typically occurs in patients with very high platelet counts, there does not exist a good correlation between the degree of thrombocytosis and the incremental risk of thrombosis [20]. Thrombosis can occur at any location in the arterial or venous vasculature, causing a wide range of complications, such as stroke, coronary artery ischemia, pulmonary embolism, digital ischemia, deep vein thrombosis, and visceral/splanchnic vein thrombosis, [21]. On the other hand, it is very well established that bleeding diathesis associates significantly with very high platelet counts due to acquired von Willebrand factor deficiency [18, 22, 23]. The risk of bleeding increases proportionally with platelet counts of above $1000 \times 10^9/L$ [24]. MPN-related hyperthrombocytosis causes pronounced quantitative and qualitative abnormalities in the larger von-Willebrand multimers, decreases ristocetin cofactor activity (vWF: RCo), and prolongs bleeding time, thereby inducing an acquired hemorrhagic diathesis [24, 25]. Platelets in patients with MPN

exhibit important qualitative differences (such as increased aggregatory activity and surface activation response) compared with platelets in secondary thrombocytosis [26].

Rationale and indications for plateletpheresis

Assessment of hyperthrombocytosis requires evaluating whether elevated counts are due to a primary proliferative process or a reactive response to an inciting condition [27].

Asymptomatic patients with secondary thrombocytosis do not require platelet reduction since they are not placed at an increased risk of hemorrhagic or thrombotic events. In contrast, patients with ET who have additional cardiovascular and/or thrombotic risk factors, or who have active ongoing complications should be treated [28]. Age >60 years, prior thrombohaemorrhagic event and platelet counts $>1500 \times 10^9/L$ confer a high risk for thrombo-hemorrhagic events in ET, and patients meeting any of these criteria should receive cytoreductive treatment [29]. The choice and intensity of cytoreduction depends on the severity of thrombocytosis and impending risk for ischemic/hemorrhagic events.

Hydroxyurea and the more platelet-selective anagrelide offer effective cytoreductive options that should be instituted promptly [30]. The two agents have proven equally effective in preventing additional thrombotic complications in ET patients when counts are maintained below $600 \times 10^9/L$ [31–34]. Of note, higher initial doses of anagrelide (1 gm BID) can elicit faster responses, reducing platelets $< 400 \times 10^9/L$ within 2 weeks [35]. The combination of hydroxyurea and anagrelide may better reduce platelets in patients with unsatisfactory responses to monotherapy [36]. In all scenarios, pharmacologic cytoreduction is not immediate, and in selected cases, plateletpheresis may be the only viable option to achieve rapid platelet count reduction during the first critical days, thus providing symptomatic relief and preventing new or worsening major vascular complications. On the other hand, since plateletpheresis only offers a short term solution and does not treat the etiology of hyperthrombocytosis, cytoreductive agents, with or without other treatments, are to be instituted and titrated simultaneously [37]. While the use of plateletpheresis in the therapeutic and prophylactic setting has been described in the context of CML-related hyperthrombocytosis, prompt institution of tyrosine kinase inhibitor therapy offers the only option for definitive, long term platelet count reduction [10, 38]. Plateletpheresis is currently a category II [i.e., second-line therapy] American Society for Apheresis (ASFA) recommendation in symptomatic primary thrombocytosis and category III [optimum role not established, decision individualized] in the prophylactic high-risk ET or secondary thrombocytosis setting [39]. It may provide symptom relief through cytoreduction, thereby alleviating pain during active ischemia [40, 41]. Cases illustrating its role as a prophylactic measure to prevent untoward consequences in patients at high risk for occlusive or hemorrhagic events have been described [41, 42]. Plateletpheresis has been used prior to emergent surgery as a means to rapidly reduce platelet counts and thereby avert hemorrhagic complications during and after surgical procedures in patients with hyperthrombocytosis [43, 44]. While it has been employed as a prophylactic measure during pregnancy in high-risk patients with ET, its benefits in this setting are not clear [45]. Its value as a maintenance therapy in high-risk pregnancy is hampered by the rapid compensatory rise in platelet counts to pre-apheresis levels, thereby requiring frequent sessions to maintain counts within desirable ranges [45]. Current guidelines recommend interferon therapy as a first line therapy in pregnant ET patients [46]. However, the therapy, while successful, is poorly

tolerated by most patients, with drug discontinuation observed in more than 60% patients in a case series [47]. While pegylated interferon may prove to be a more efficacious, better tolerated alternative to traditional interferon therapy [48], elective plateletpheresis can provide an effective means of rapid cytoreduction in patients intolerant to interferon or in whom there exists a high risk of an impending thrombohemorrhagic event [49].

Effects on platelet function and coagulation parameters

Plateletpheresis has effects on coagulation parameters by decreasing pro-thrombotic FVIII, fibrinogen, anti-thrombin, protein C and protein S levels, albeit maintaining them within acceptable ranges [50, 51]. While von-Willebrand multimeric structures remain unchanged, von Willebrand levels can drop by up to 15% as a result of dilution and replacement of plasma by anticoagulant during apheresis [52]. Platelet sizing data suggest that the efficacy of plateletpheresis is partly related to its selective removal of the larger, dysfunctional platelet populations [53]. Apheresis has also been demonstrated to normalize morphological and functional platelet properties from a pro-aggregatory to a normo-aggregatory state [54]. The procedure causes leukocyte activation, inducing an increase in plasma tumor necrosis factor (TNF)-alpha levels; however, this has not been shown to impair endothelial cell function [55]. In addition, platelets become activated during apheresis and have been shown to interact with leukocytes [56]. Contact of platelets with artificial surfaces induces transient increases in platelet-derived soluble growth factors [57]. Cases of central retinal vein and axillary vein thrombosis occurring immediately after apheresis have been rarely reported, suggesting that the anti-thrombin reduction and platelet activation induced by plateletpheresis may have clinical effects [58, 59]. However, transient platelet activation likely does not have clinical implications in determining the optimum safe interval between apheresis sessions [60]. One of the shortcomings of apheresis is that it induces a transient, yet pronounced, increase in hematopoietic stem cell growth factors, including thrombopoietin, as a coordinated homeostatic response to rapid platelet count reduction, leading to a rapid, compensatory platelet overproduction after apheresis [61, 62].

Technical aspects

Modern intermittent-flow and continuous-flow automated centrifugation systems are effective means of rapidly and effectively reducing platelet counts [63–65]. Currently used systems for platelet apheresis include COBE® Spectra, Terumo® Trima and Fenwal Amicus®. COBE® spectra and Spectra Optia are currently the only one approved for therapeutic plateletpheresis [66, 67]. Single needle access procedures are equivalent in efficacy and quality to dual needle plateletpheresis protocols [67]. Total of 1.5-2 times the total blood volume is generally processed, which can reduce platelet counts by as much as 30–60%. Notably, plateletpheresis yields are higher in non-splenectomized patients when compared with post-splenectomy patients due to active platelet mobilization from a functional spleen, in response to circulating platelet removal, resulting in a larger available platelet fraction accessible to withdrawal by apheresis [15]. The anticoagulant to whole blood ratio is maintained at around 1:6–12 to prevent platelet activation and clumping. Medical therapy often requires 2–3 weeks to control platelet counts, during which time up to 2–3 sessions of platelet apheresis may be required to achieve control [68]. Apheresis sessions should be continued until platelet counts drop to below $600 \times 10^9/L$ or until symptom

alleviation and resolution of clinical indications for treatment. Symptomatic ET/MPN patients generally require more sessions than asymptomatic ones given the additional need for symptom resolution beyond achieving cytorreduction [69].

Adverse events

Plateletpheresis is a relatively safe procedure and is associated with few side effects [37]. Some of the more commonly observed adverse events include hemodynamic complications such as vasovagal syncope and citrate-related complications, including hypocalcemia and citrate toxicity [37, 70]. Women are more affected by hypotension than men [71]. Other factors influencing the risk of hypotension include height of the individual, model of apheresis machine, and mode of plasma collection [72]. Allergic reactions previously seen with apheretic procedures have decreased considerably with the use of more biocompatible polymer systems.

Summary

In case # 1, plateletpheresis was initiated due to neurological symptoms that were deemed secondary to microcirculatory disturbances versus a transient thromboembolic episode resulting from hyperthrombocytosis. Platelet counts were successfully reduced to appropriate limits after three sessions of plateletpheresis. In case # 2, plateletpheresis was instituted due to concern for hyperthrombocytosis-related acquired von Willebrand disease. Counts were successfully decreased with apheresis and the patient was resumed on his previous treatment regimen. In case # 3, the patient was required to undergo plateletpheresis as a prophylactic measure and to help reduce counts to within the range defined by eligibility criteria for an investigational protocol. In case # 4, although the etiology of hyperthrombocytosis was unclear, the patient received apheresis to obtain symptomatic relief in the context of an ischemic toe and simultaneously, a bleeding diathesis. In all cases platelet counts were successfully decreased within 1–3 sessions without any complications. None of the patients suffered major adverse events.

Conclusions

We emphasize that MPN-related thrombocytosis is occasionally punctuated by episodes of extreme thrombocytosis, which are potentially precipitated by concomitant reactive processes. Clinicians should closely assess the response of hyperthrombocytosis to cytoreductive agents and titrate proactively, if required, to prevent emergence of hyperthrombocytosis. A recently published survey of physicians suggested that contemporary management of extreme thrombocytosis and target platelet counts on cytorreduction seem to be weighted heavily upon the physician's years of experience, and not necessarily by a physician's interest in MPN or the volume of their MPN practice [73]. Plateletpheresis as an option for cytorreduction was favored in cases of extreme thrombocytosis complicated by a thrombohemorrhagic event or when requiring rapid reduction prior to emergent surgery. Data on the clinical utility of plateletpheresis is largely based on anecdotal experience, and the current AFSA guidelines are not supported by randomized controlled trials.

While current guidelines do not specify a platelet count threshold at which to perform apheresis in asymptomatic ET patients, patients with counts above $1500 \times 10^9/L$ are often symptomatic patients who are at an increased risk of hemorrhage from acquired von Willebrand deficiency [69]. Plateletpheresis should be considered with relative urgency in patients with platelet counts above this range and an increased risk of major hemorrhage, especially in settings where cytoreductive agents are contraindicated or less desirable due to their relatively slow onset of action [39]. In conclusion, the decision to perform plateletpheresis should be individualized based on the clinical scenario (symptoms and/or signs of vascular complications), degree of thrombocytosis, and an individual's risk factor profile [table 1]. The prophylactic use of plateletpheresis may be considered when a rapid reduction in platelet counts is required, such as perioperatively and after splenectomy, or when cytoreductive agents are contraindicated or not tolerated, such as in pregnancy.

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highlights

- Pheresis use should be based upon degree of thrombocytosis and patient's risk profile
- Current AFSA guidelines on plateletpheresis are not supported by randomized trials
- Pheresis is favored in extreme thrombocytosis complicated by thrombohemorrhagic event
- One may consider prophylactic use in settings where rapid count reduction is required

Figure 1.
Figure illustrating the clinical course of each case before and after plateletpheresis.

Case reports of MPN patients treated with plateletpheresis, highlighting the clinical utility of this procedure under varied clinical settings

Table 1

Ref	Clinical condition	Age	Platelet counts before plateletpheresis ($\times 10^9/L$)	Other cytoreductives including aspirin prior to pheresis	Indication for platelet pheresis	Duration of platelet pheresis	Outcomes	Comments
[45]	ET, pregnancy; h/o TIAs and abortion	31	1500–2000	None. Aspirin was discontinued at the time of pregnancy due to h/o TIAs and hemorrhages	Subcutaneous hemorrhages, to prevent first trimester abortion	Throughout pregnancy. 1 session per week to maintain counts below 1500.	Resolution of hemorrhages with counts maintained. Reappearance of hemorrhages on discontinuing pheresis each time. Hence, required to receive pheresis throughout pregnancy	Valuable option providing rapid cytoreduction in high risk conditions, such as pregnancy, where other cytoreductive agents are associated with serious adverse effects. May require continued sessions to maintain counts within reasonably safe limits
[74]	Post-splenectomy thrombocytosis; h/o portal hypertension	42	1580	Failed response to a month of hydroxyurea (started soon after splenectomy)	Abdominal pain, with mesocaval shunt thrombosis, a month after splenectomy	3 sessions over three days	Platelets dropped to $950 \times 10^9/L$ after three sessions and patient's symptoms were relieved	Provides rapid temporization in situations of active thrombocytosis especially when standard cytoreductive agents fail to control platelet levels
[44]	Essential thrombocytosis; traumatic femoral fracture	68	601	none	Prevention of post-operative thrombosis after intramedullary nail fixation	1 session	Physician elected to proceed to surgery after drop in platelets to $500 \times 10^9/L$	Role of pheresis in preventing surgery related thrombocytosis complications are unclear; however, the procedure is safe and effective and should be considered in a high-risk ET patient.
[75]	MF, h/o MF related pulmonary HTN	43	Not reported	Not reported	Dyspnea correlating with rising platelet counts	Intermittent sessions to drop counts	Marked alleviation of dyspnea with plateletpheresis	High activated generation may contribute to worsening dyspnea in patients with low pulmonary vascular reserve
[76]	ET, h/o Raynaud's syndrome	34	800–1034	Aspirin and hydroxyurea	Worsening cyanosis and tenderness of fingers and toes despite 5 days of hydra	2 sessions dropping counts to $348 \times 10^9/L$	Resolution of toe ischemia; however, finger ischemia had already progressed to gangrene	Degree of platelet count probability of thrombotic episode [77]. Therapeutic cytoreduction should aim for symptom relief and not predetermined platelet counts in the setting of active symptoms.
[14]	ET	58	1160	None	Dizziness and faintness	Five sessions over 16 days	Reported feeling well following the procedures; received sessions once or twice a week and remained symptom free on that	Effective option in rapidly alleviating neurological symptoms secondary to hyperthrombocytosis.

Ref	Clinical condition	Age	Platelet counts before plateletpheresis (x 10 ⁹ /L)	Other cytoreductives including aspirin prior to pheresis	Indication for platelet pheresis	Duration of platelet pheresis	Outcomes	Comments
[14]	Post-splenectomy thrombocytosis; splenectomy for splenic abscess	23	820	none	Cerebrovascular accident two days after splenectomy	Sessions to maintain platelet counts below 1,000x10 ⁹ /L. aspirin started simultaneously	No further cardiovascular events. Required sessions far less frequent than prior case	Kinetics of rise in platelets post procedure slower than in patients with intact spleen (due to mobilization from spleen after procedure). May avert a potentially life-threatening secondary event in patients who have experienced a major thrombotic event.
[43]	Primary thrombocythemia; subdural hematoma with motor weakness	62	1090	none	Pre-surgery to avoid hemorrhagic complication during surgery	A session before surgery and two after surgery along with chemotherapy	Uneventful post-operative course, with resolution of neurological symptoms after surgical evacuation	Provides rapid cytoreduction in primary thrombocythemic patients who are at high risk for hemorrhage or who have had a hemorrhagic event, preventing further hemorrhagic complications.
[38]	Chronic myelogenous leukemia (CML), sudden onset digital cyanosis	52	1553	none	sudden onset digital cyanosis with drop in along with giddiness, headache and malaise	Two sessions platelet count from 1553 → 513 x 10 ⁹ /L. on aspirin simultaneously	Resolution of all symptoms except cyanosis on the tip, which progressed to gangrene	Symptomatic hyperthrombotic episodes rare in CML. Patient treated with a goal of dropping platelets to 500 10 ⁹ /L. While the primary goal end-point is primarily symptom alleviation irrespective of platelet count, further sessions may be given to bring platelets to 500 x 10 ⁹ /L if symptoms do not resolve
[42]	Idiopathic thrombocythemia vs. polycythemia vera	68	3055	none	asymptomatic	Four sessions dropping platelet count from 3055 → 500 x 10 ⁹ /L	Nocomplications from procedure. Successful drop in platelet count	Prophylactic use of this procedure should be limited to patients at high risk of hemorrhage. Not advocated for treating only the 'numbers'