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The Role of Blood Component Removal in Essential and Reactive Thrombocytosis

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Abstract: An elevated platelet count is now a common finding in both hospitalized and ambulatory patients with the advent of automated complete blood cell counters. Clinicians may be called upon to make a distinction between a reactive process and a primary hematologic disorder as the cause of a thrombocytosis and to determine whether treatment is indicated. Essential thrombocythemia and other myeloproliferative disorders may present with marked increases in the platelet counts and may be associated with thrombohemorrhagic complications. Reactive thrombocytosis can be caused by iron deficiency and a variety of inflammatory conditions, infections, malignancy, bleeding or hemolysis, splenectomy, and drugs. Acute therapy for all of these disorders has included blood component removal, specifically plateletpheresis. The role of plateletpheresis in current management of thrombocytosis is considered, based on current knowledge of pathophysiology and a review of the literature. **Key Words:** Essential thrombocythemia—Reactive thrombocytosis—Plateletpheresis.

Essential thrombocytosis (thrombocythemia; ET) was first described in 1934 as "hemorrhagic thrombocythemia" (1), but it was not until 1960 that it was accepted as a distinct clinical entity (2,3). At this stage, patients were only considered for a diagnosis of ET if their platelet count exceeded $1{,}000 \times 10^9$/L, but this has since been lowered to $>600 \times 10^9$/L (4) and, most recently, to $>400 \times 10^9$/L (5,6). As well as being present in abnormally high numbers, the platelets in ET are also both morphologically and functionally abnormal (7). They vary in size, shape, and granular content, and may be hypo- or hyperaggregable, possibly as a result of surface membrane and receptor abnormalities (e.g., loss of the alpha-adrenergic receptor, increased Fc receptors, and reduced prostaglandin D_2[PGD_2] receptors) (7). One of the major difficulties in managing patients with ET is that neither the degree of thrombocytosis nor the platelet abnormalities observed consistently correlates with the clinical presentation (7–9).

CLINICAL FEATURES

More than half of the patients with ET are completely asymptomatic and are identified coincidentally. In symptomatic patients with ET, the characteristic clinical features are tendencies to hemorrhage and thrombosis which may occur separately or simultaneously (7). Bleeding typically occurs on mucocutaneous surfaces (including the nose and the gastrointestinal and genitourinary tracts) with rare cases of bleeding into the joints or the retroperitoneum. The major life-threatening complications of ET, however, are acute thrombotic events which may occur in both arteries and veins. Although arterial thrombi are usually microvascular, large arteries can be affected, including those in the brain and heart, with potentially disastrous effects. Deep vein thromboses, pulmonary embolism, and Budd-Chiari syndrome may also occur. Even at the microvascular level, the effects can be distressing, including a painful burning sensation in the extremities, particularly the palms and soles, known as erythromelalgia. In fact, this is the presenting feature in over 50% of ET patients (7). The arteriolar platelet thrombi thought to be responsible for erythromelalgia also can lead to peripheral necrosis and gangrene. Cerebral vasomotor symptoms are also common at presentation, including headache, dizziness, paresthesias, and seizures (7,10).

ET also has an adverse effect on pregnancy outcome with recurrent spontaneous abortions, abruptio placentae, fetal growth retardation, and premature delivery (11–13). In 1 retrospective study of 43

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pregnancies in 29 women with ET at a single U.S. institution, 3 were terminated deliberately (1 ectopic pregnancy and 2 elective abortions) (12). Among the remaining 40 pregnancies, there were 16 (40%) spontaneous abortions in the first trimester, 1 stillbirth (at 22 weeks), and 1 abruptio placentae (at 33 weeks) (12). It was not possible to predict these events from history of symptoms or the presence or absence of specific treatments during pregnancy. A review of the literature on pregnancy in ET identified 106 pregnancies in 57 women with ET (14). A similar spontaneous abortion rate of 36% was found (38/106) as well as intrauterine death and stillbirth after the 28th week in 5%, premature delivery in 8%, pre-eclampsia in 4%, and fetal growth retardation in 4%. In cases of in utero fetal death or growth retardation, chronic infarction of the placental surface has been reported (13–15).

Some patients with very high platelet counts may develop acquired von Willebrand disease (von Willebrand factor [vWF] deficiency) with an associated increased risk of bleeding, not only in ET but also in other myeloproliferative disorders (MPDs) (16). The pathogenesis of this condition is uncertain, but evidence suggests that it is the actual platelet numbers rather than their abnormal function that results in a deficiency of vWF, particularly large molecular weight vWF multimers (16). A similar multimeric pattern has been seen in reactive (secondary) thrombocytosis (RT), but without bleeding complications.

DIAGNOSIS

A patient is diagnosed with ET by exclusion of other MPDs (chronic myelogenous leukemia [CML], polycythemia vera, agnogenic myeloid metaplasia, and myelodysplastic syndrome [MDS]), and exclusion of factors that could be responsible for RT (17). The original set of diagnostic criteria provided by the Polycythemia Vera Study Group (Table 1) (4) have been revised to include patients with lower platelet counts (>400 × 10^9/L) and a number of additional laboratory investigations, recently shown to be useful for refining the diagnosis (Table 2) (5,6).

RT can be caused by a wide range of phenomena, including inflammatory diseases, infections, drugs, and even exercise (Table 3) (7). The relatively high frequency with which extreme thrombocytosis is encountered as a reactive phenomenon in a general acute care hospital population indicates the need for caution before making a diagnosis of ET. Platelet counts in the range of 450 to 600 × 10^9/L are not uncommon in conditions associated with bleeding or in those associated with thrombosis when there is also necrosis and/or inflammation (18).

ET usually can be differentiated from RT by utilization of a careful medical history and laboratory data to exclude underlying disorders. In many cases, the development of RT is believed to be related to high levels of interleukin-6 which are known to occur in a variety of infectious or inflammatory conditions (11). There is also a positive correlation between interleukin-6 and C-reactive protein, and either or both of these have been shown to be increased in 81% of patients with RT, but not in patients with uncomplicated ET (11). Spontaneous in vitro megakaryocyte and erythroid colony formation on culture of blood or bone marrow progenitor cells also confirms the diagnosis of ET as it is not seen in tissues from patients with RT (19–21). However, it does not occur in all ET patients and cannot, therefore, be used as a sole diagnostic criterion. Similarly, while thrombopoietin (TPO) levels, which are inversely correlated with platelet and megakaryocyte mass in healthy subjects, may be within the normal range or even slightly raised in ET, despite the increased megakaryocyte mass (22), this feature is not unique

TABLE 1. *Diagnostic criteria for essential thrombocytosis*[a]

I	Platelet count >600 × 10^9/L
II	Hemoglobin ≤13 g/100 ml or normal red cell mass (males <36 ml/kg, females <32 ml/kg)
III	Stainable iron in marrow or failure of iron trial (<1 g/100 ml rise in hemoglobin after 1 month of iron therapy)
IV	No Philadelphia chromosome
V	Collagen fibrosis of marrow
A	Absent, or
B	<⅓ biopsy area without both splenomegaly and leukoerythroblastic reaction
VI	No known cause for reactive thrombocytosis

[a] From the Polycythemia Vera Study Group, 1982 (4).

TABLE 2. *Revised diagnostic criteria for essential thrombocytosis*[a]

A1	Platelet count >400 × 10^9/L and no known cause of reactive thrombocytosis
A2	Increase in and clustering of mature giant megakaryocytes with hyperploid nuclei
A3	No preceding or allied other subtype of myeloproliferative disorder or myelodysplastic syndrome
B1	Normal or elevated LAP score, normal ESR, no fever
B2	Normal or slightly increased cellularity and no or minimal reticulin fibrosis
B3	Splenomegaly on palpation or spleen length >11 cm on diagnostic imaging procedure
B4	Spontaneous erythroid colony and/or spontaneous megakaryocyte colony formation on bone marrow culture

[a] A criteria are diagnostic; B criteria are confirmative. From the Polycythemia Vera Study Group, 1999 (5,6).

LAP: leukocyte alkaline phosphatase, ESR: erythrocyte sedimentation rate.

TABLE 3. *Causes of reactive thrombocytosis*[a]

I	Chronic blood loss—iron deficiency
II	Acute blood loss
III	Hemolytic anemia
IV	Chronic inflammatory diseases—vasculitis
V	Acute and chronic infections
V	Drugs—vinca alkaloids, epinephrine
VI	Asplenic states and splenectomy
VII	Malignancies
VIII	Rebound thrombocytosis—recovery from chemotherapy or ITP
IX	Exercise
IX	Myelodysplastic states—$5q^-$ syndrome

[a] From Mitus and Schafer, 1990 (7).
ITP: immune thrombocytopenia

to ET (17). The increased levels of TPO may result from the marked reduction in TPO receptor (c-Mpl) expression in platelets and megakaryocytes seen in ET (23,24), but, again, low c-Mpl expression is not specific to ET (17).

CLONALITY IN ESSENTIAL THROMBOCYTOSIS

ET was originally believed to be a clonal MPD resulting in clonal expansion of the megakaryocyte population. However, the use of a novel investigative technique (the X chromosome inactivation process) has revealed the existence of both monoclonal and polyclonal forms of ET (25). Tefferi has proposed a number of potential explanations for polyclonal ET: megakaryocyte lineage restriction of the clonal population, dilution of a clonal process by a predominantly polyclonal population, and truly polyclonal myeloproliferation mediated by aberrant cytokine production (17). Elsewhere, it has been suggested that molecular abnormalities in the TPO gene, found in several families with an autosomal dominant form of hereditary ET, may be one mechanism for the occurrence of nonclonal ET (26).

EPIDEMIOLOGY

The published incidence of ET ranges from 0.1 to 2.5 per 100,000 population (6,27,28). It is not known why there is such a variation in the reported rates, but it may reflect differences in age distribution of the study populations, diagnostic procedures, and racial/ethnic differences (29). It is also possible that the incidence of ET is underestimated since so many patients remain asymptomatic. While the median age at diagnosis is 60 years, ET also is known to occur in younger adults and even, though rarely, in children (17). There is a slightly higher incidence in females than males with a ratio around 1.5:1 although this female preponderance actually may be limited to patients in the age range of 30 to 50 years (30).

RISK ASSESSMENT AND PROGNOSIS

The lack of correlation between platelet counts and the incidence of thrombohemorrhagic events in patients with thrombocytosis, whether primary or secondary, makes risk assessment difficult. Attempts to use clinical laboratory tests such as platelet aggregation studies or bleeding time to predict which patients with thrombocytosis are more at risk of bleeding or thrombosis have been largely unsuccessful (9). It is possible that many patients have complex and multiple platelet defects and that the circulating population of platelets may change with treatment or with the natural progression of the disease, making correlation between platelet function and past clinical events unpredictable (9).

Approximately half of all patients with ET are asymptomatic at diagnosis while the rest present with a variety of vasomotor, thrombotic, or hemorrhagic complications as illustrated in a retrospective analysis of 148 patients with ET (Table 4) (31). In a small proportion of patients, ET may evolve into another MPD or into frank leukemia either as a part of the natural course of the disease or as a result of treatment with cytoreductive therapy (7). However, because thrombohemorrhagic complications are fatal in less than 5% of cases, and the development of other MPDs or acute leukemia is also relatively uncommon (also less than 5%), life expectancy in ET is generally considered to be more or less normal (7,17). A similar rate of transformation to acute leukemia also was reported in a review of 42 pediatric cases of ET (age range 6 weeks to 18 years) (32). In this study, 2 (5%) of the children developed acute myeloblastic leukemia after 3 and 6.5 years of follow-up, respectively, at the ages of 15 and 20 years (32). Both had been treated with potentially leukemogenic drugs (radiophosphorus in 1 and thiotepa plus busulfan in the other). Two other children developed idiopathic myelofibrosis. Four (9.5%) chil-

TABLE 4. *Incidence of symptoms at presentation in a retrospective analysis of 148 patients with ET*[a]

Symptoms at presentation[a]	% Patients
None	57
Vasomotor	29
Hemorrhagic	6
Thrombotic	12

[a] Data from Besses et al., 1999 (31).
Eighteen percent of patients had a history of thrombosis prior to diagnosis.

dren died of complications related to ET, 2 shortly after being diagnosed with acute leukemia and 2 of severe thrombotic events (32).

In the retrospective study referred to in Table 4, multivariate analysis of risk factors during a 6 year follow-up period revealed that age >60 years, a history of thrombosis, and hypercholesterolemia were each independent risk factors for complications of ET (31). The probability of having a major vascular event was 35.6% for patients over 60, compared to 21.4% in patients under 60, and only 1 of 36 patients younger than 45 years having such an event (31). However, in a separate review of 42 children with ET, 6 of 30 (20%) who were asymptomatic at diagnosis developed symptoms (bleeding or thrombotic events) during a follow-up period ranging from 9 months to 10 years (32). On the other hand, in a prospective controlled study of 65 low-risk ET patients (i.e., under 60 years of age, asymptomatic, and with no risk factors for thrombosis or hemorrhage) who remained untreated and were followed up for a mean of 4.1 years, the incidence of thrombosis was comparable to that in a healthy age- and sex-matched control population (33). Elsewhere, only patients aged >60 years and those with a history of thrombosis have been consistently reported as having an increased risk; the annual risk of thrombosis in these 2 populations has been reported as 30% and 15%, respectively (34).

In the retrospective analysis (31), as in other studies (34), there was no significant correlation between platelet counts and risk of thrombosis. However, extremely high platelet counts (1 to $2{,}000 \times 10^9$/L) have been associated with an increased risk of gastrointestinal bleeding, possibly as a result of acquired von Willebrand disease with loss of large molecular weight multimers (17,29). In a study of patients with extreme thrombocytosis, there was a significantly higher incidence of vaso-occlusive and/or bleeding symptoms in patients with MPD than in those with RT (32% versus 4%, respectively, $p = 0.0001$) (35). Nevertheless, there was a notable lack of documented cerebral or myocardial infarctions, thrombophlebitis, or peripheral arterial ischemia, despite the presence of extreme thrombocytosis that persisted, in some patients, for weeks or months. Patients who had symptoms of transient cerebral or myocardial ischemia were typically in the age range in which atherosclerotic disease might be expected.

Interestingly, there is also some evidence for a higher risk of thrombotic complications among patients with monoclonal ET compared to those with polyclonal disease (25,36). Furthermore, the presence of spontaneous megakaryocyte colony formation has been associated with an increased risk of thromboembolic or hemorrhagic problems, particularly in patients under 40 years of age, compared to patients without spontaneous colony formation (19).

In RT, the great majority of patients are asymptomatic. In a series of 280 patients with extreme thrombocytosis (platelet counts $\geq 1{,}000 \times 10^9$/L), only 4% of the 231 patients with RT had symptoms. Seven had bleeding (6 with iron deficiency anemia), and 3 had vaso-occlusive symptoms (18). In fact, bleeding was the cause rather than the result of thrombocytosis in these patients, and the platelet count returned to normal once the bleeding and/or iron deficiency resolved. Of the 3 patients with vaso-occlusive symptoms, 2 had evidence of peripheral vascular disease while the other had advanced unresectable lung cancer and had a cerebrovascular accident (CVA) 2 days after her platelet count peaked at $1{,}058 \times 10^9$/L. There are currently no reliable means by which risk of thrombotic events can be predicted in RT nor to determine whether treatment with drugs that inhibit platelet function is indicated.

TREATMENT

For patients with RT, the primary goal is to treat the underlying cause of the thrombocytosis. Earlier reports of sometimes fatal thrombotic complications in patients with postsplenectomy thrombocytosis prompted recommendations for the use of prophylactic anticoagulants or antiplatelet drugs in this setting (9). However, larger studies and more critical evaluation have not shown an excessive incidence of thromboembolism in postsplenectomy patients compared to other postoperative groups (9). Furthermore, when it does occur, there does not appear to be a clear correlation with the absolute platelet counts even when it exceeds $1{,}000 \times 10^9$/L. One possible exception is the persistence of thrombocytosis following splenectomy for hemolytic anemias or hemoglobinopathies in which the anemia does not resolve after the splenectomy. On the other hand, it has been observed that patients with hemolytic anemia are at increased risk of thrombosis, irrespective of splenectomy. In general, patients with secondary thrombocytosis of various etiologies are not at excessive risk for hemostatic complications and have normal platelet function.

For patients with ET, many of whom are asymptomatic, choice of treatment strategy largely is determined by weighing the risks of treatment (e.g., the leukemogenic potential of cytoreductive therapy) with its potential benefit in terms of preventing

thrombotic and/or hemorrhagic complications. Older patients, especially those with a history of thrombosis, are at greater risk of recurrent thrombosis, and it may be particularly important to lower the platelet counts in these patients (9).

Both ET and, less commonly, RT patients have been reported to benefit from plateletpheresis for management of an acute bleeding or thrombotic episode. However, no randomized controlled trials have addressed this controversial issue.

Prevention of complications in essential thrombocytosis

Tefferi has recently presented a risk stratifications chart for patients with ET, based on reported observations of clinical risk factors, which he used to devise a treatment algorithm (17). In high-risk patients (those age 60 years or more and/or with a history of thrombosis), cytoreductive therapy should be aimed at maintaining platelet levels below 400×10^9/L (11). Long-term treatment with cytoreductive agents is considered inappropriate in low-risk patients (29) particularly children (32) although low-dose aspirin (50 to 150 mg/day) may help to alleviate vasomotor symptoms and is particularly effective for erythromelalgia (29). Because of the potentially increased bleeding risk with very high platelet counts, aspirin is not recommended in patients with platelet counts $\geq 1{,}500 \times 10^9$/L (17). Anagrelide is a platelet-lowering agent that also has an antiaggregating effect, and it may be a useful alternative to aspirin in such cases.

Although the treatment algorithm devised by Tefferi refers only to hydroxyurea, anagrelide, and interferon-alfa, other platelet-lowering agents have been used for long-term management in high-risk patients with ET including busulfan, radiophosphorus, and pipobroman. However, only hydroxyurea has been shown to achieve significant reductions in the incidence of thrombosis in a randomized, controlled study in high-risk patients (37). As with other cytoreductive agents, there is a potential risk of leukemic transformation with hydroxyurea. Long-term follow-up of the controlled study for a mean of 6.1 years revealed a 7% incidence of MDS or leukemia among hydroxyurea-treated patients compared to 0% among controls (38). Anagrelide is a possible alternative to hydroxyurea, reducing platelet counts effectively in about 90% of patients treated (39). However, anagrelide is associated with a high frequency of side effects with about 20% of patients discontinuing treatment for one reason or another. It should be used only with caution in the elderly and is not recommended in patients with heart disease since it has been shown to have a vasodilator effect and positive inotropic activity, causing fluid retention and palpitation (29,39). In a few patients, initiation of anagrelide therapy was followed rapidly by the development of congestive heart failure (39).

As with alkylating agents, long-term treatment (>5 years) with radiophosphorus has been linked with the development of acute leukemia, but it may represent a useful alternative in elderly patients (>70 years). It has the advantage of simplifying their medical management as repeat administration may not be necessary for intervals of up to 6 months (17,29).

Among all these agents, only interferon-alfa is considered probably safe for use in pregnancy or women of child-bearing potential since it does not cross the placenta (13). It is also potentially nonleukemogenic and has been shown to achieve and maintain normal platelet counts in around 50% of patients treated with low doses (1 to 3 MU/day or every other day) (29). There have been reports of its successful use in a number of pregnancies (14,40). However, long-term studies are needed to determine its impact on thrombotic complications and survival. In a review of 106 pregnancies in women with ET, aspirin was the most frequently used drug in 47 of 93 recorded cases (57%) (14), and the live birth rate was higher among women treated with aspirin (12/16 [75%]) compared to untreated women (9/21 [41%]).

Plateletpheresis for acute events

Since drug therapy usually takes several days and sometimes weeks to reduce platelet counts effectively, therapeutic plateletpheresis is indicated in patients with ET when a rapid reduction in platelet counts is necessary (41,42). Patients considered most likely to benefit are those with life-threatening organ dysfunction, particularly neurologic or pulmonary (41). In the two distinct clinical syndromes of microvascular thrombosis, manifested either by digital ischemia or cerebrovascular ischemia, rapid lowering of the platelet counts by plateletpheresis may result in a dramatic clinical improvement (9).

Patients with very high platelet counts and acquired von Willebrand disease have an increased risk of bleeding. Aspirin is considered inadvisable in such cases, and since anagrelide or hydroxyurea may not have a sufficiently rapid onset of action, plateletpheresis is effective alternative therapy for the management of acute symptoms in this situation (16). Because the beneficial effect of plateletpheresis is generally quite brief and repeat procedures are often necessary, it is recommended also that cytoreductive

therapy be started as soon as possible for long-term control of the platelet count (41,42).

The earliest report of plateletpheresis for the management of symptomatic thrombocytosis was published by Colman et al. in 1966, who successfully performed manual pheresis in 3 patients with MPD (43). In 1971, Miller and colleagues published the first report of an automated continuous flow cell separator for rapid plateletpheresis in 2 patients with hemorrhagic thrombocytosis (44). In 1975, there were two reports of discontinuous flow centrifugation in patients with thrombocytosis, either to allow semi-urgent surgical procedures to be carried out (in 2 patients) (45) or to control gastrointestinal (GI) hemorrhage and neurological symptoms (in 1 patient) (46).

In 1977, Taft and colleagues reported the use of discontinuous flow (Haemonetics model) and continuous flow (Aminco Celltrifuge) centrifugation for plateletpheresis in 5 patients with acute complications of thrombocytosis: cerebrovascular events in a woman with polycythemia vera (PV), pulmonary embolism in a man with thrombocytosis secondary to splenectomy, painful extremities and headache in a female splenectomy patient, cardiovascular symptoms and GI bleeding in a man with PV, and sensory deficit and paresis in a woman with thrombocythemia (type not specified) (42). In each case, the treatment was effective in preventing additional morbidity and relieving symptoms. The authors commented that their aim was to reduce platelet counts to $<500 \times 10^9$/L with each procedure which usually required processing of 2 blood volumes over 3 to 4.5 h. Most patients required 2 or 3 procedures for adequate control of their platelet counts. They concluded that a temporary external arteriovenous shunt could simplify the procedure in patients without adequate venous access.

Several other case reports of successful plateletpheresis for the management of acute thrombotic or hemorrhagic events associated with thrombocytosis have been published since (47–49). In one, the investigators analyzed the size of the platelets being removed during pheresis with a Haemonetics discontinuous flow model (48). They determined that a greater percentage of abnormally large platelets had been removed selectively which they considered might have contributed to the efficacy of the procedure (48).

In the largest review published, Adami reported on 132 patients treated during a 15 year plateletpheresis program in Italy (50). Several different types of discontinuous flow processors were used (Haemonetics Model 30, VSO, and Dideco Progress) and 1 model of a continuous flow processor (Dideco Vivacell). Thrombocytosis was associated with various MPDs in most patients with splenectomy in 5 and unidentified diagnoses in 8 (Table 5). In most cases, plateletpheresis was carried out to relieve thrombotic or hemorrhagic complications, but asymptomatic patients were also treated if their platelet counts were $\geq 1{,}000 \times 10^9$/L. He analyzed their platelet counts in relation to symptoms and found that patients with platelet counts $\geq 1{,}500 \times 10^9$/L were more likely to be symptomatic than those with lower platelet counts, and this reached statistical significance in the ET population (Table 6). The types of symptoms were not specified. However, as a result of these findings, cytoreduction by pheresis in asymptomatic patients was only recommended for a platelet count of $\geq 1{,}500 \times 10^9$/L.

Plateletpheresis in pregnancy

Plateletpheresis has been used for the management of ET in pregnancy in a small number of patients because of the increased risk of first-trimester spontaneous abortions (11,15,35). However, other patients with similar platelet counts have been able to carry pregnancies to term without any therapy (11).

Falconer and colleagues reported on the managing of a woman with ET who had spontaneous abortions

TABLE 5. *Patients treated with plateletpheresis in a 15 year Italian program*[a]

Diagnosis	Symptomatic			Asymptomatic		
	No. of patients	No. of procedures	P/P	No. of patients	No. of procedures	P/P
ET	28	347	12.3	20	98	4.9
CML	18	591	32.8	7	89	12.7
PV	17	104	6.1	5	26	4.3
Postsplenectomy	5	13	2.6	14	42	3.0
Unidentified diagnosis	8	90	11.2	9	20	2.2

[a] From Adami, 1993 (50).

P/P: rate of procedures/patient, ET: essential thrombocytosis, CML: chronic myelogenous leukemia, PV: polycythemia vera.

TABLE 6. *Number of symptomatic patients out of number of treated patients in relation to platelet count in a 15 year Italian program*[a]

Diagnosis	Platelet count $\times 10^9$/L		
	>1,500	<1,499 >1,000	<999
	SP/TP	SP/TP	SP/TP
ET	14/16[b]	9/20[c]	5/12[d]
CML	10/12	4/6	4/7
PV	3/3	7/9	7/11
Postsplenectomy	2/7	3/9	0/3
Unidentified diagnosis	4/6	1/4	3/7

[a] From Adami, 1993 (50).
[b] versus [c] versus [d] $p < 0.05$; [b] versus [c] + [d] $p < 0.007$.
SP: no. of symptomatic patients; TP: no. of treated patients, ET: essential thrombocytosis, CML: chronic myelogenous leukemia, PV: polycythemia vera.

in 4 previous pregnancies, all in the first trimester (35). She had been treated with busulfan and aspirin for a short time after the initial diagnosis of ET, some years previously, but had refused further treatment. In her fifth pregnancy, they attempted to reduce the platelet count with regular plateletpheresis which was performed on 4 occasions. Unfortunately, the reductions in the platelet count were modest and short lived, there were difficulties with venous access, and the patient refused any further treatments. Intrauterine growth retardation was documented at 34 weeks, and the patient developed pre-eclampsia shortly afterward and underwent a cesarean section. The infant, a male, was very underweight at delivery (1,185 g), but his subsequent hospital course was uneventful.

More encouraging results were reported by Beard et al. in a series of 9 pregnancies in 6 patients with ET (51). They suggested that plateletpheresis may be useful for decreasing platelet counts for short periods of time, such as immediately before delivery (51). Tefferi et al. reported that 1 patient successfully underwent plateletpheresis during her first delivery, but also had an uneventful second delivery without intervention (11).

Perioperative plateletpheresis

The use of plateletpheresis for perioperative prophylaxis has been described also (52,53). One case involved a woman with ET and a history of angina who had developed an extensive femoral hematoma during coronary angiography (52). The patient was treated with pre-and postoperative plateletphereses, plasma transfusions, and platelet concentrates to reduce the bleeding risk during subsequent coronary artery bypass surgery. Surgery was carried out successfully, and during a 12 month follow-up period, there were no bleeding or thrombotic episodes nor any recurrence of angina. In another report, plateletpheresis was used to reduce the platelet counts during microsurgical free-tissue transfer in a patient with thrombocytosis secondary to splenectomy (53).

Long-term plateletpheresis

The use of plateletpheresis (Haemonetics discontinuous flow model) for more prolonged platelet lowering in 2 patients unable to receive chemotherapy was reported in 1979 by Panlilio and Reiss (54). One of these patients was a 58-year-old man with ET who was treated with repeated plateletpheresis over 3 months because of frequent syncopal episodes. His platelet count prior to starting pheresis was $2,800 \times 10^9$/L. He refused chemotherapy, and he underwent plateletpheresis 3 times a week for 4 weeks. His platelet count fell to $<1,000 \times 10^9$/L, and he became completely asymptomatic. Treatment was continued but reduced to twice weekly and then once weekly procedures over the next 2 months, which maintained his platelet counts at about the same level after which he agreed to start chemotherapy. The other patient was a 23-year-old woman with thrombocytosis secondary to splenectomy (due to splenic abscess associated with chronic peritonitis of unknown etiology) who was treated with plateletpheresis after a CVA when her platelet count was 820×10^9/L. Two days later, a second CVA occurred, and she was started on aspirin therapy and plateletpheresis. She underwent 6 procedures over a 22 day period with adequate control of her thrombocytosis until her underlying inflammatory process resolved.

The attempted use of plateletpheresis as sole therapy for ET in a patient who developed rapid leukopenia on chemotherapy was reported in 1978 by Goldfinger and colleagues (55). Although intensive plateletpheresis (4 to 5 procedures per week) achieved rapid lowering of the platelet counts, subsequent treatment with a more acceptable schedule of 2 to 3 procedures per week could not maintain platelet levels below $1,400 \times 10^9$/L. They, therefore, considered such treatment unsuccessful.

CONCLUSIONS

Approximately half of all ET patients are asymptomatic at diagnosis while the rest present with a variety of vasomotor, thrombotic, or hemorrhagic complications. Neither the degree of the thrombocytosis nor the platelet function abnormalities consistently correlates with the clinical presentations. An increased risk of thrombosis has been associated with age greater than 60 years and prior thrombosis. The risk of hemorrhage may increase with extreme thrombocytosis ($>2,000 \times 10^9$/L). Recent advances in

medical therapy have resulted in the availability of cytoreductive agents with fewer long-term side effects and, in particular, with a decreased risk of leukemic transformation.

Plateletpheresis is generally a well-tolerated procedure. Risks include potential complications of catheter placement such as bleeding, thrombosis around the catheter, and infection. Other risks are arrhythmias, hypotension, and citrate toxicity. Also, this remains a costly and time-consuming therapy with only short-term benefits. A decision to perform plateletpheresis in a patient with a MPD should be individualized based on his or her symptoms. There are no controlled trials establishing efficacy of pheresis for an asymptomatic patient even if their platelet count exceeds $1{,}000 \times 10^9$/L. In these instances, institution of platelet-lowering drugs with gradual reduction in the platelet count appears to be adequate treatment.

There is no evidence that women benefit from plateletpheresis during pregnancy and/or delivery. Low-dose aspirin is a consideration, and if cytoreductive therapy is required, then interferon-alfa is the treatment of choice.

There is usually no reason to perform plateletpheresis in patients with RT even those with extreme thrombocytosis. If there are vaso-occlusive symptoms, then antiplatelet agents can be considered. However, it is likely that there will be other factors contributing to the symptoms such as atherosclerosis, preexisting hypercoagulable states, underlying inflammation, or malignancy that cause activation of clotting by other mechanisms. Hemorrhage is usually the cause, rather than the consequence, of elevated platelet counts. Establishing hemostasis and treating coexisting iron deficiency almost always will resolve the thrombocytosis.

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