Why Does My Patient Have Thrombocytosis?

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KEYWORDS

• Thrombocytosis • Platelets • Gene mutation
• Molecular therapy

Thrombocytosis is defined as having excess platelets in the blood. The normal platelet count in adults ranges between 150,000 and 450,000/μL (mean ± 2 standard deviations), regardless of sex and ethnicity.[1,2] Based on the normal distribution, this implies that a platelet count exceeding 450,000/μL exists in about 2.5% of the population.

An increased platelet count usually has an acquired cause. It is rarely congenital. Congenital thrombocytosis results from gain-of-function mutations in either thrombopoietin (TPO) or its receptor (MpL).[3–5] The altered regulation is usually transmitted in an autosomal dominant fashion and often involves the 5′-untranslated region of the TPO mRNA (a donor splice site), resulting in increased translational efficiency.[5] Increases in serum TPO concentrations are noted in those patients with a TPO gene mutation.[4]

Acquired thrombocytosis may be either a primary or secondary process. Essential thrombocytosis (ET) is also known as primary thrombocytosis, essential thrombocythemia, and autonomous thrombocytosis. It is a disease of the bone marrow associated with myeloproliferative neoplasms that lead to an increase in platelets. This process may be growth factor independent or growth factor hypersensitive.[6] Acquired thrombocytosis may be reactive and secondary to an unrelated condition such as infection, chronic inflammation, hemolysis, iron deficiency anemia, or splenectomy, and is referred to as reactive thrombocytosis (RT).

REACTIVE THROMBOCYTOSIS (RT)

Prevalence and Relevance

RT refers to an increase in platelet count associated with conditions other than chronic myeloproliferative or myelodysplastic disorders. It is observed in a variety of conditions that may cause an acute, transient, or sustained increase in platelet counts (**Table 1**). It is generally accompanied by the signs and symptoms of the underlying disease and normalizes, or is expected to normalize, after resolution of this condition.[10] In routine clinical practice, RT accounts for more than 85% of cases

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Table 1
Causes of thrombocytosis (platelet count of 500 × 10^9/L or more) in unselected cohorts of consecutive patients (values are approximate percentages)

Condition	Adults (n = 777)[7]	Platelet Count of 1 Million/μL or More (n = 280)[8]	Children (n = 663)[9]
Infection	22	31	31
Rebound thrombocytosis	19	3	15
Tissue damage (eg, surgery)	18	14	15
Chronic inflammation	13	9	4
Malignancy	6	14	2
Renal disorders	5	NS	4
Hemolytic anemia	4	NS	19
After splenectomy	2	19	1
Blood loss	NS	6	NS
Primary thrombocythemia	3	14	0

Abbreviation: NS, not specified.

of thrombocytosis,[11] even in patients with extreme thrombocytosis (platelet count >1000 × 10^3/μL).[8,12]

It is important to distinguish between RT and ET because of their different clinical manifestations and treatment strategies. There is a well-established association of ET with vasomotor symptoms and thrombotic or bleeding complications.[13,14] In general, thromboembolic complications are rare in RT compared with ET, unless clinically provoked by underlying conditions such as malignancy or atherosclerosis.[10] More often, high-risk patients with ET require cytoreductive therapy to prevent catastrophic thrombohemorrhagic complications, whereas the prothrombotic potential of RT may be too low to even justify the use of platelet directed therapy,[8,15,16] even in the context of surgical procedures.[17] Because of the low likelihood of vascular complications, there is no evidence to support the use of cytoreductive agents in patients with RT.

Pathogenesis

A list of the causes of RT is shown in **Table 1**. Several cytokines and lymphokines are increased in the blood of patients with RT, especially those associated with infection, inflammation, malignancy, and tissue damage. These cytokines include interleukin (IL)-6, thrombopoietin, IL-1, IL-4, interferon γ, and tumor necrosis factor-α.[18,19] Of all the cytokines implicated, the most compelling evidence for their pathogenic role is noted with IL-6 and interferon γ. The administration of a transcription factor that mimics interferon γ led to the correction of thrombocytopenia in a genetic model.[20] IL-6 stimulates TPO production in the liver.[21–23] Thrombocytosis and induction of other acute phase reactants are noted with the administration of human recombinant IL-6 in patients with metastatic cancer.[24]

RT is a predictable finding after splenectomy, with an incidence approaching 50% in large series.[25] Thrombocytosis is commonly seen immediately after splenectomy and normalizes in most cases within several months, and rarely only after many years. Hyposplenism-associated RT may reflect platelet redistribution in the peripheral blood as well as altered metabolism of thrombopoietic cytokines.[26–28] Persistent thrombocytosis has been described in congenital and functional asplenia (celiac sprue,

amyloidosis). Whatever the cause, in the absence of a chronic myeloproliferative disorder (MPD), hyposplenic-associated thrombocytosis is rarely associated with an increased risk of thrombosis.[27]

Reactive Thrombocytosis Versus Essential Thrombocytosis (ET)

ET is a clonal proliferation process with subsequent increase in platelet counts. A thorough history and physical examination are the most important elements in differentiating RT from ET. Determining the duration of thrombocytosis is a key diagnostic step of the initial workup. If no obvious explanation is provided, longstanding and persistent thrombocytosis strongly suggests ET. A history of vasomotor symptoms, thrombohemorrhagic complications, and physical examination findings such as splenomegaly and acral erythema also strongly suggest ET. An increased platelet count in the presence of conditions associated with RT, as outlined in **Table 1**, may favor the diagnosis of RT. However, if thrombocytosis is noted in the absence of associated clinical conditions such as vasculitis and infection, then ET may be more likely.

Complete blood count with differential counts, red blood cell indices, and peripheral blood smear examination, as well as iron studies, provide additional information for differentiating ET from RT (**Fig. 1**). Laboratory findings that suggest RT include microcytosis, which may indicate iron deficiency anemia. Although a normal ferritin level may reduce the likelihood of iron deficiency anemia associated with RT, a low level does not necessarily eliminate the possibility of ET. Increased acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate,[29] plasma fibrinogen,[30] and

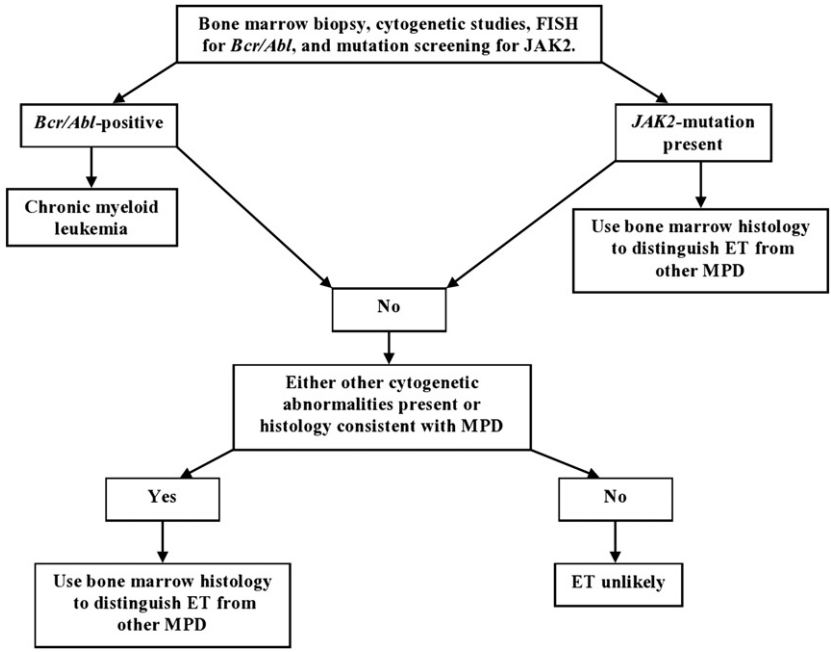

Fig. 1. A diagnostic algorithm for thrombocythemia that is clinically not consistent with reactive thrombocytosis. MPD, myeloproliferative disorder. (*Modified from* Tefferi A, Gilliland DG. The JAK2^{V617F} tyrosine kinase mutation in myeloproliferative disorders: status report and immediate implications for disease classification and diagnosis. Mayo Clin Proc 2005;80:954; with permission.)

IL-6[31] levels have been shown to be increased in RT. The presence of Howell-Jolly bodies on the peripheral blood smear suggests hyposplenism, supporting a diagnosis of RT, whereas a leukoerythroblastic smear suggests primary myelofibrosis (PMF) (also known as myelofibrosis with myeloid metaplasia).

It is difficult to discriminate between ET and RT based on the degree of thrombocytosis, regardless of how high the platelet counts might be.[8,32] There is no diagnostic usefulness of platelet indices (mean volume, size distribution width) in discriminating between ET and RT because of the considerable overlap in the measured values. Although abnormalities of platelet function as measured by prolonged bleeding time,[33] decreased adenosine triphosphate secretion,[34] and altered thromboxane generation are seen in ET,[35] these laboratory assays are not routinely used because they require substantial expertise to perform and interpret.

The presence of cytogenetic abnormalities, such as the Janus kinase 2 ($JAK2^{V617F}$) mutation, is strongly associated with MPDs.[36] This abnormality has not been detected in healthy controls or in patients with secondary erythrocytosis or RT,[37,38] thus making mutation screening an important part of the diagnostic workup (see **Fig. 1**).[39] Although clonal cytogenetic abnormalities can be detected and are diagnostic of ET, not all causes of ET have detectable cytogenetic abnormalities (<5% of patients with ET).

Consequently, bone marrow histology evaluation is still a critical part of the evaluation process. Although the bone marrow histology is normal in RT, it displays a wide variety of abnormalities in ET depending on the cause of the underlying chronic myeloproliferative disease (CMD). These abnormalities include aberrations in cellular morphology, increased numbers of megakaryocytes, presence of megakaryocyte clusters, and reticulin fibrosis.[40]

ESSENTIAL THROMBOCYTOSIS (ET) AND MYELOPROLIFERATIVE STATES

ET is a clonal expansion of a multipotential stem cell observed in the presence of a chronic MPD or myelodysplastic syndrome (MDS).[41] Clonal or autonomous thrombocytosis is part of ET and is seen in 50% of patients with polycythemia vera (PV).[42] It is also seen in about 35% of patients with chronic myeloid leukemia (CML).[43]

These disorders (MPD and MDS) may be classified as those that exhibit trilineage morphologic dysplasia (in MDS) and those that do not (in MPD). The classification of chronic myeloid disorders is shown in **Box 1**.[44] Although thrombocytosis in MDS has been associated with the presence of ringed sideroblasts and may be linked with certain cytogenetic abnormalities including trisomy 8,[45] 5q− syndrome,[31,46] and abnormalities of chromosome 3,[47] the underlying pathogenic connection between these defects and thrombocytosis is unclear. Except for a few atypical myelodysplasia states and CML, the molecular pathogenesis of the MPDs is also unclear.[48]

ET

Epidemiology

ET is a diagnosis of exclusion once other causes of thrombocytosis such as reactive conditions, MDS, and other myeloproliferative states have been eliminated (see **Table 1**). Among the classic MPDs, ET has the highest prevalence (about 24/100,000) and carries the best prognosis.[49] ET does not routinely occur in children.[50] The median age at diagnosis is 40 to 60 years.[51] There is a suggestion of a female preponderance.[52]

Distinction from Other Causes of ET

Because of MDS,[53] PMF, and CML[54,55] can all mimic ET in their presentation, it is important to clinically distinguish these separate entities when a working diagnosis

Box 1
A semimolecular classification of chronic myeloid disorders

1. MPS
2. MPDs
   a. Classic MPDs
      i. Molecularly defined
         1. CML (*Bcr/Abl*$^{+}$)
      ii. Clinicopathologically assigned (Bcr/Abl^{-} and frequently associated with JAK2^{V617F} mutation)
         1. Essential thrombocythemia
         2. PV
         3. Myelofibrosis with myeloid metaplasia
   b. Atypical MPDs
      i. Molecularly defined
         1. *PDGFRA*-rearranged eosinophilic/mast cell disorders (eg, *FIP1L1-PDGFRA*)
         2. *PDGFRB*-rearranged eosinophilic disorders (eg, *TEL/ETV6-PDGFRB*)
         3. Systemic mastocytosis associated with *c-kit* mutation (eg, *c-kit*^{D816V})
         4. *8p11* Myeloproliferative syndrome (eg, *ZNF198/FIM/RAMP-FGFR1*)
      ii. Clinicopathologically assigned
         1. Chronic neutrophilic leukemia
         2. Chronic eosinophilic leukemia, molecularly not defined
         3. Hypereosinophilic syndrome
         4. Chronic basophilic leukemia
         5. Chronic myelomonocytic leukemia
         6. Juvenile myelomonocytic leukemia (associated with recurrent mutations of RAS signaling pathway molecules including *PTPN11* and *NF1*)
         7. Systemic mastocytosis, molecularly not defined
         8. Unclassified MPD

Data From Tefferi A, Gilliland G. Classification of myeloproliferative disorders: from Dameshek toward a semi-molecular system. Best Pract Res Clin Haematol 2006;19(3):365–85.

of ET is considered. Workup should include exclusion of CML by conventional cytogenetics and fluorescence in situ hybridization (FISH) testing for BCR/ABL.[56] Bone marrow histology should be examined for features that suggest MDS and PMF, such as the presence of trilineage dysplasia and increased marrow cellularity with atypical megakaryocyte hyperplasia and myelofibrosis, respectively.

Pathophysiology

Before the discovery of the JAK2^{V617F} mutation, scant information existed regarding the molecular pathogenesis of ET. This new discovery has advanced knowledge of the pathophysiology of the condition, as well as the development of new therapeutic tools.[57] The JAK2^{V617F} mutation, which rarely exists in a homozygous state, is estimated to occur at a frequency of 23% to 60% in ET and 95% in PV.[58] JAK2^{V617F} is

part of the cytoplasmic protein tyrosine kinases. This mutation is an acquired G to T nucleotide shift at position 1849 in exon 12, which leads to a valine to phenylalanine substitution at codon 617 ($JAK2^{V617F}$).[58,59] This mutation is located in the pseudokinase domain (JH2) of the JAK2 protein and interferes with autoinhibitory function. Consequently, mutated JAK2 exists in a constitutively phosphorylated state.

$JAK2^{V617F}$ mutation has been associated with induction of erythropoietin hypersensitivity, a hallmark of PV and other classic MPDs.[58] In vivo, a retrovirus containing $JAK2^{V617F}$, when transduced into murine bone marrow, induced erythrocytosis in the transplanted mice.[60,61] These findings suggest some pathogenic relevance for this particular mutation in MPDs.

Clinical Features of ET

The diagnosis of ET is usually incidental.[62] Many patients with ET are asymptomatic at diagnosis and have a prolonged, stable, or uneventful clinical course. The signs and symptoms may be non–life threatening, such as the presence of vasomotor features (headaches, erythromelalgia, and lightheadedness), splenomegaly, or hypertension, or life threatening, such as thrombohemorrhagic complications.

Erythromelalgia

Erythromelalgia is a classic vasomotor symptom of essential thrombocythemia. It has been described even in patients with only marginal increase in platelet counts. It is defined as a burning sensation associated with a red discoloration of the hands or feet. This condition can be precipitated by heat or exercise.[63] The ensuing digital ischemic changes may be caused by arteriolar inflammation secondary to abnormal platelet-endothelium interaction.[64] Histopathologic studies in erythromelalgia have shown platelet-rich arteriolar microthrombi with endothelial inflammation and intimal proliferation. The prompt response of erythromelalgia to aspirin (40–325 mg/d) is consistent with a diagnosis of a vasomotor symptom as opposed to a thrombotic complication.[64]

Thrombosis

Age greater than 60 years, thrombotic history, leukocytosis greater than $11 \times 10^3/\mu L$, and presence of the $JAK2^{V617F}$ mutation are considered important factors in assessing the risk of thrombosis.[65,66] In general, thrombotic events are more frequent than bleeding episodes, with more arterial events than venous events. **Tables 2** and **3** list the incidence of thrombotic and hemorrhagic events in ET, respectively.[68] It is common to have both microcirculatory and large vessel involvement.[11] Abdominal large vessel occlusions and cerebral sinus thrombosis are potentially catastrophic events that occasionally occur in patients with ET.[69,70]

The pathogenesis of thrombosis in ET is complex. It centers around the combination of endothelial dysfunction, abnormal platelet shapes and function, and the presence of circulating platelet-leukocyte aggregates.[66] Potential risk factors include leukocytosis[66] and defects in arachidonic acid metabolism. These theories are strengthened by the beneficial clinical response associated with myelosuppressive therapy[71] and low-dose aspirin, respectively.[72]

Bleeding

Bleeding, including epistaxis, gingival bleeding, and mild gastrointestinal or genitourinary hemorrhage, occurs less frequently in ET than thrombosis.[62] Although thrombocytosis by itself may not be a risk factor for bleeding, the concurrent use of aspirin therapy may reveal the bleeding tendency in patients.[73] The pathogenesis of bleeding in ET is thought to arise from altered Von Willebrand factor (VWF) function, which is

Table 2
Thrombotic and hemorrhagic events in ET reported at diagnosis

	n	Platelet × 10^9/L (Median/Mean)	Asymptomatic (%)	Major Thrombosis (%)	Major Arterial Thrombosis[a] (%)	Major Venous Thrombosis[a] (%)	MVD (%)	Total Bleeds (%) (Major)
ET								
Bellucci et al,[105] 1986	94	1200	67	22	81	19	43	37 (3.2)
Fenaux et al,[51] 1990	147	1150	36	18	83	17	34	18 (4)
Cortelazzo et al,[52] 1990	100	1135	34	11	91	9	30	9 (3)
Colombi et al,[106] 1991	103	1200	73	23.3	87.5	12.5	33	3.6 (1.9)
Basses et al,[83] 1999	148	898	57	25	NA	NA	29	6.1 (NA)
Jensen et al,[67] 2000	96	1102	52	14	85	15	23	9 (5.2)

Abbreviations: IAVT, intra-abdominal venous thrombosis; MVD, microvascular disturbances; NA, not available.

[a] Percentage of total major thrombotic events.

Data from Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 2005;128:275–90.

Table 3
Thrombotic and hemorrhagic events in ET reported at follow-up

	n	Major Thrombosis (%)	Major Arterial Thrombosis (%)[a]	Major Venous Thrombosis (%)[a]	MVD (%)	Total Bleeds (%) (Major)	Percentage of Deaths From Hemorrhage (%)	Percentage of Deaths From Thrombosis (%)
ET								
Bellucci et al,[105] 1986	94	17	62.5	37.5	17	14 (3.2)	0	0
Fenaux et al,[51] 1990	147	13.6	86	14	4.1	NA (0.7)	0	25
Cortelazzo et al,[52] 1990	100	20	71	29	NA	NA (1)	0	100 (1 patient, IAVT)
Colombi et al,[106] 1991	103	10.6	91	9	33	8.7 (5.8)	0	27.3
Besses et al,[83] 1999	148	22.3	94	6	27.7	11.5 (4.1)	0	13.3
Jensen et al,[67] 2000	96	16.6	69	31	16.7	13.6 (7.3)	3.3	16.7

Abbreviations: IAVT, intra-abdominal venous thrombosis; MVD, microvascular disturbances; NA, not available.
[a] Percentage of total major thrombotic events.
Data from Elliott MA, Tefferi A. Thrombosis and haemorrhage in polycythaemia vera and essential thrombocythaemia. Br J Haematol 2005;128:275–90.

platelet dependent. In the presence of extreme thrombocytosis (platelet count >1 million/μL), the ADAMTS13 cleaving protease is activated, which leads to increased proteolysis of high-molecular-weight VWF.[74] Other potential causes of excessive bleeding in ET include platelet dysfunction. Platelet abnormalities such as storage pool deficiency, decreased adrenergic receptor expression, impaired response to epinephrine, and decreased membrane glycoprotein receptor expression have been described.[67,68]

Pregnancy complications

ET is the most common MPD among women of childbearing age and is associated with an increased risk of fetal and maternal complications. The most common complication is first trimester abortion caused by placental infarctions associated with platelet dysfunction.[75,76] Treatment recommendations depend on the risk stratification (**Table 4**). Aspirin is usually sufficient, but therapy with interferon α or low-molecular-weight heparin are indicated in high-risk individuals such as those with a prior history of thrombosis.[77]

Disease transformation

In the absence of leukemogenic therapy, conversion of ET to acute myeloid leukemia (AML) rarely occurs.[78] The 15-year cumulative risk of evolution into either AML or PMF is 2% and 4% respectively.[13,78,79] An increase in myelofibrosis transformation is seen as the disease progresses and with the use of anagrelide.[78]

Diagnosis

In establishing a diagnosis of ET, other causes of thrombocytosis must first be considered. This process includes eliminating the possibility of reactive thrombocytosis and CML with relevant laboratory work such as cytogenetic studies and FISH for the BCR/ABL gene rearrangement. In addition, mutation screening for $JAK2^{V617F}$ aids in distinguishing ET from RT, but not necessarily other MPDs (see **Fig. 1**). The second step in determining whether thrombocytosis is caused by ET involves histopathologic analysis of the bone marrow, which helps eliminate the possibility of other myeloid disorders.

Prognosis

ET is an indolent disorder. There are few valid prospective data regarding long-term survival in ET. Most data are gathered from retrospective studies.[80] Compared with the general population, a 2-fold decrease in survival is seen in patients with ET, starting from the first decade after diagnosis. Most deaths are associated with thrombotic events.[58]

Table 4
Risk stratification in essential thrombocythemia

Low risk	Age less than 60 y and No history of thrombosis, and Platelet count less than 1.5 million/μL, and Absence of cardiovascular risk factors (smoking, hypertension, hyperlipidemia, diabetes)
Indeterminate risk	Neither low risk nor high risk
High risk	Age 60 y or older, or a positive history of thrombosis

Treatment

Before considering treatment, affected individuals must be stratified based on their risk category (see **Table 4**).[52,81] A step-by-step approach is involved in management based on the defined goals of therapy, existing evidence that supports such an action, and the risk of the patient. Treatment involves the use of antiplatelet aggregating agents and cytoreductive therapy. In the low-risk individual, treatment with aspirin (40–325 mg daily) to reduce vasomotor symptoms may be sufficient once the possibility of clinically significant acquired Von Willebrand syndrome has been excluded in patients with extreme thrombocytosis.[68,82] Cytoreductive therapy is generally not indicated in low-risk individuals given the low risk of thrombosis,[51,52,69,83] but may be considered in the treatment of refractory symptoms.

The goal of therapy with the use of cytoreductive agents is to prevent thrombohemorrhagic events. As a result, we recommend cytoreductive therapy in high-risk patients (see **Table 4**).[84,85] Cytoreduction is also considered in patients with extreme thrombocytosis (platelet count >1.5 million/μL) in the setting of a bleeding diathesis or aspirin-resistant microvascular symptoms. The desired platelet count in this instance is the level that provides symptomatic relief or corrects the bleeding diathesis.

Although various cytoreductive agents have been used to treat thrombocytosis, hydroxyurea is currently the treatment of choice. Compared with anagrelide, both alone and in combination with aspirin, there was a significantly decreased number of thrombotic and bleeding events in the hydroxyurea treatment arm (36 vs 55 events in the anagrelide group). A dose of 500 to 1000 mg daily should result in decreased platelet numbers. The therapeutic goal in terms of platelet count, based on anecdotal evidence of optimal thrombosis control, is less than 400,000/μL.[86] Although there is concern about the leukemogenic effect of hydroxyurea, the presumed association has not been shown by large retrospective or prospective controlled trials. In addition, no association with leukemic transformation has been documented in other disease states treated with hydroxyurea.[84,87] However, leg ulcers are a complication associated with hydroxyurea.

In patients who are intolerant of hydroxyurea, anagrelide or interferon α has been used as a second-line cytoreductive agent. Anagrelide works by altering megakaryocyte maturation. It is associated with side effects such as headaches, palpitations, diarrhea, and fluid retention, which are intolerable to many patients. These symptoms are dose dependent and generally abate after 4 to 8 weeks of therapy. Interferon is commonly used at a dose of 3 million units 3 times a week and has an inhibitory effect on megakaryopoiesis. It is particularly safe to use in pregnancy and has been shown to induce a stable state of remission in about 80% to 90% of patients.[62] Although the addition of antiplatelet therapy has not yet been shown prospectively to reduce the incidence of thrombosis in ET, we recommend its use in combination with cytoreductive therapy in all high-risk patients (**Table 5**).[88]

$JAK2^{V617F}$ inhibitors have been shown to be tolerable, with benefits in alleviating symptoms such as fatigue. Although there are data showing control of myeloproliferation in patients with ET, information about effects on thrombosis and disease transformation into more aggressive states, such as leukemia, is currently lacking.[89] Additional studies on these potential therapeutic modalities need to be undertaken.

Plateletpheresis has been reserved for patients with extreme thrombocytosis with a platelet count greater than 1 million/μL and those with acute thrombotic or hemorrhagic complications. Because the benefits of plateletpheresis are not permanent, this should be followed with cytoreductive therapy. Patients most likely to benefit include those with severe organ dysfunction.[90]

Table 5
Treatment algorithm in ET

Risk Category	Age <60 y	Age ≥60 y	Women of Childbearing Age
Low risk	Low-dose aspirin[a]	Not applicable	Low-dose aspirin[a]
Indeterminate risk[b]	Low-dose aspirin[a]	Not applicable	Low-dose aspirin[a]
High risk	Hydroxyurea and low-dose aspirin	Hydroxyurea and Low-dose aspirin	Interferon α and low-dose aspirin

[a] In the absence of a contraindication including evidence for acquired Von Willebrand syndrome (ie, a ristocetin cofactor activity of <50%).
[b] The decision to use cytoreductive agents in indeterminate-risk patients should be made on an individual basis (see text for elaboration).

POLYCYTHEMIA VERA (PV)

PV is a disease often diagnosed by laboratory assessment that is ordered because of symptoms or signs such as headaches, visual changes, erythromelalgia, splenomegaly, and postbath pruritus. Diagnostic criteria include an increased hemoglobin level (>18.5 g/dL for men or 16.5 g/dL for women) and a $JAK2^{V617F}$ gene mutation.[91] Thrombocytosis is commonly a feature of PV.[92] Although the presence of a $JAK2^{V617F}$ or mutation involving MpL reduces the possibility that thrombocytosis is caused by a reactive process, it does not distinguish among the different types of myeloproliferative neoplasms. The presence of a $JAK2^{V617F}$ mutation and increased red cell mass is consistent with PV 95% of the time.[58,93]

The clinical course of PV, much like that of ET, is characterized primarily by thrombohemorrhagic complications, myelofibrosis, or leukemic transformation.[58] The presence of a $JAK2^{V617F}$ mutation status[78,94] and high allelic burden of greater than 75%[95,96] are associated with a high risk of thrombosis. Mortality is increased compared with the general population and is age dependent, with a 2-fold increase in patients more than 50 years old (1.6-fold vs 3.3-fold in patients >50 years old).[58,97]

Similar to the recommendations for ET, the treatment of PV depends on the classified risk status. Low-dose aspirin and repeated phlebotomies are sufficient for low-risk patients. In contrast, cytoreductive agents are necessary for patients considered high risk, such as those with a history of thrombotic events, or patients with massive splenomegaly and extreme leukocytosis or thrombocytosis. Treatment with hydroxyurea or interferon α is frequently used.[91]

CHRONIC MYELOGENOUS LEUKEMIA (CML)

CML is one of the myeloproliferative neoplasms and is characterized by the unregulated proliferation of mature and maturing granulocytes. The clinical picture of CML consists of leukocytosis, splenomegaly, and thrombocytosis.[10] An increased platelet count is seen in as many as 35% of patients with CML.[43] Diagnostic confirmation is accomplished with FISH or polymerase chain reaction analysis for the Philadelphia chromosome, BCR-ABL gene rearrangement, or the mRNA gene product. A low leukocyte alkaline phosphatase (LAP) score differentiates CML from PV, in which the LAP score is increased.[98] The use of tyrosine kinase inhibitors is now the mainstay of therapy, with cytogenetic remission observed in about 80% of patients.[91]

PRIMARY MYELOFIBROSIS

Primary myelofibrosis (PMF) is one of the least common myeloproliferative neoplasms, with an estimated incidence of 1.5 per 100,000 per year in Olmsted County, Minnesota.[85] It clinically presents with splenomegaly, hepatomegaly, and extramedullary hematopoiesis. Thrombocytosis occurs in about 13% to 50% of patients at diagnosis, with thrombocytopenia becoming apparent as the disease progresses.[43,99] Peripheral blood smear and histologic bone marrow findings such as the presence of tear drop–shaped cells and fibrosis, respectively, are key in distinguishing this disease entity from other causes of primary thrombocytosis. Unlike PV and ET, which have a good prognosis, patients with PMF have a median survival of less than 5 years.[100] Poor prognostic factors include the presence of circulating blasts (>3%) and platelet count less than 100,000/μL.

$JAK2^{V617F}$ mutations have been described in primary myelofibrosis and are estimated to occur in 43% to 57% of patients with PMF,[101] with apparent homozygosity in 13% of patients.[102] Although it is uncertain whether the clinical course differs based on the $JAK2^{V617F}$ mutation status,[39,103] in transplant patients, achievement of $JAK2^{V617F}$ negativity is linked to a decreased relapse rate.[101] Mutations involving MpL have been documented and are thought to be partially responsible for thrombocytosis observed in PMF.[104]

Treatment of PMF is targeted toward symptoms instead of the underlying molecular disorder.[103] For instance, splenectomy is indicated in patients with severe pain and red cell transfusions, with iron chelation therapy for those with symptomatic anemia. Drugs such as danazol and thalidomide have been used with good results to correct cytopenias and to halt splenomegaly.[100,103] Studies evaluating the therapeutic role of $JAK2^{V617F}$ kinase inhibitors in patients with PMF are currently underway.[91]

SUMMARY

Thrombocytosis is a common clinical problem frequently encountered during routine evaluation. The diagnostic workup entails a step-by-step approach, which allows for an accurate assessment of the underlying cause. A through clinical history and physical examination may help differentiate thrombocytosis secondary to a reactive process versus an underlying clonal proliferation process. Once ET is evident, relevant laboratory evaluation for an ongoing MPD is paramount. With the recent advances in $JAK2^{V617F}$ mutation analysis, more appropriate diagnostic conclusions may be achieved.

With regard to treatment, various modalities targeted toward correction of the underlying cause in the case of reactive thrombocytosis and, in the case of ET, the use of agents such as aspirin, hydroxyurea, anagrelide, and interferon (based on identified risk profiles) have all been proved to be beneficial. With further scientific investigation underway, molecular therapies targeted at identified $JAK2^{V617F}$ mutations may soon be cornerstones of therapy in ET.

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