Thrombocytosis

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THROMBOCYTOSIS IS TYPICALLY DISCOVERED AS AN INCIDENTAL LABORATORY ABNORMALITY when the complete blood count is obtained for some unrelated reason. When found, however, it creates an important diagnostic challenge. Thrombocytosis generally either is a reactive process (secondary thrombocytosis) or is caused by a clonal bone marrow (myeloproliferative) disorder; the latter category includes essential thrombocythemia. It is often exceedingly difficult to differentiate between the reactive and clonal types of thrombocytosis on the basis of clinical findings or laboratory test results. Yet there are fundamental differences between them in terms of cause, pathophysiological features, and clinical implications.

MECHANISMS OF THROMBOCYTOSIS

Thrombopoietin is the key hormone in the regulation of megakaryocyte differentiation and proliferation, although various cytokines (e.g., interleukin-6 and interleukin-11) may play an accessory role in the process.\(^1\) Megakaryocytes and their platelet progeny have receptors for thrombopoietin (referred to as c-Mpl receptors). Thrombopoietin in plasma binds to c-Mpl on the surfaces of circulating platelets; the remaining, unbound thrombopoietin in plasma is available to promote megakaryocyte proliferation. Thus, when the platelet count drops, increased plasma levels of free thrombopoietin stimulate megakaryocytopoiesis; conversely, when the platelet count rises, reduced levels of free thrombopoietin slow megakaryocytopoiesis. In this way, the total mass of platelets (and megakaryocytes) can regulate platelet production and maintain it at a steady state (Fig. 1A). In some cases of reactive thrombocytosis, an underlying inflammatory stimulus may up-regulate the production of thrombopoietin by the liver.\(^2\)

Plasma levels of thrombopoietin are high or inappropriately normal in reactive (secondary) thrombocytosis.\(^3,4\) In cases of acute inflammation, this elevation precedes an increase in the platelet count.\(^5,6\) Plasma levels of interleukin-6 are also elevated in reactive thrombocytosis: this interleukin, which plays a prominent role in the acute-phase response of inflammatory and neoplastic diseases, up-regulates the expression of thrombopoietin messenger RNA (mRNA) in the liver.\(^7\) Thus, interleukin-6 may be a key mediator of the increased synthesis of thrombopoietin and the consequent reactive thrombocytosis (Fig. 1B).

Thrombopoietin levels are also elevated or inappropriately normal in clonal thrombocytosis, but in this case the mechanism involves abnormalities in the regulation of c-Mpl receptor-mediated uptake of constitutively synthesized thrombopoietin (Fig. 1C). In essential thrombocythemia, a clonal defect in platelet and megakaryocyte expression of c-Mpl causes impaired binding of thrombopoietin and leads to higher-than-expected levels of plasma free thrombopoietin.\(^8-11\) This situation contrasts with that in other myeloproliferative disorders, in which clonal proliferation of a hematopoietic lineage leads, by a physiological feedback mechanism, to the suppression of the specific growth factors that normally control the differentiation and proliferation of individual hematopoietic progenitors.
etnic lineages: for example, there are decreased levels of serum erythropoietin in polycythemia vera and decreased levels of granulocyte colony-stimulating factor in chronic myelogenous leukemia. In myeloproliferative disorders, there is reduced binding of thrombopoietin to megakaryocytes because of the decreased number and function of thrombopoietin receptors, but in essential thrombocytemia, these progenitors are also markedly hypersensitive to the action of the hormone. This leads to the increased megakaryocyte proliferation and platelet production seen in essential thrombocytemia.

FAMILIAL THROMBOCYTOSIS
Rare cases of familial thrombocytosis were initially described as an autosomal dominant disorder in which gain-of-function mutations in the thrombopoietin gene lead to overproduction of thrombopoietin and marked elevation of its plasma levels. These forms of familial thrombocytosis are an example of a recently described genetic mechanism of disease, one that involves loss of translational repression, which leads to increased efficiency of mRNA translation. However, other modes of inheritance, ones in which thrombopoietin levels are normal, are now also recognized, so familial thrombocytosis is a genetically heterogeneous disorder. Furthermore, since these patients may have thrombotic and vascular complications, it is possible that some cases of apparently sporadic essential thrombocytemia may in fact prove to be familial forms.

MAJOR CAUSES OF THROMBOCYTOSIS

REACTIVE (SECONDARY) THROMBOCYTOSIS
By far the most common cause of thrombocytosis in general medical populations is a reactive, or secondary, process. The degree of elevation in the platelet count does not clearly differentiate clonal from reactive thrombocytosis. In a series of 732 medical and surgical patients with platelet counts of 500,000 per cubic millimeter or higher, 643 (88 percent) had secondary thrombocytosis; the most frequent underlying causes were tissue damage due to major surgery, infection, cancer, and chronic inflammation. Similarly, in a series of 280 consecutive hospitalized patients with platelet counts of 1 million per cubic millimeter or higher, 231 (82 percent) had reactive thrombocytosis, 11 (4 percent) had thrombocytosis of uncertain cause, and only 38 (14 percent) had a myeloproliferative disorder.

Reactive thrombocytosis is driven by elevated endogenous levels of thrombopoietin, interleukin-6, other cytokines, or catecholamines that may be produced in inflammatory, infectious, or neoplastic conditions or in situations of stress. The most common causes of secondary thrombocytosis are listed in Table 1. In most patients, there are clinically apparent symptoms of an active, underlying systemic disease. In others, however, subclinical disorders (e.g., occult cancers) may be responsible for the secondary thrombocytosis. It is the latter group of patients that presents the more vexing diagnostic challenge for the clinician. Before ascribing thrombocytosis to a clonal (myeloproliferative) disorder, which is largely a diagnosis of exclusion and has very different therapeutic implications (see below), the clinician must be confident that the elevated platelet count is not due to an inapparent, but potentially treatable, underlying disease.

CLONAL THROMBOCYTOSIS
Essential thrombocythemia is one of the chronic myeloproliferative disorders, a group of related disorders of the hematopoietic stem cells. Other myeloproliferative disorders include polycythemia vera, chronic myelogenous leukemia, and myeloid metaplasia with or without myelofibrosis. Thrombocytosis does not occur exclusively in essential thrombocytemia; it may also occur in the other myeloproliferative disorders, particularly polycythemia vera. Furthermore, some apparent cases of essential thrombocytemia actually represent the recently recognized entity of prefibrotic myelofibrosis, which evolves into overt myelofibrosis. Thrombocytosis may also be associated with the myelodysplastic 5q– syndrome, which is characterized by deletion of the long arm of chromosome 5 and is one of the so-called “mixed myelodysplastic and myeloproliferative syndromes.” The elevated platelet count in essential thrombocytemia and other myeloproliferative disorders is referred to as clonal thrombocytosis.

Clonality
Clonality in these disorders has been demonstrated by several approaches based on X-linked polymorphic markers in female patients. Recent studies have suggested that essential thrombocytemia may not always be clonal. These findings raise the possibility that a nonclonal disease can progress to clonal disease, that clonality is restricted in some patients to the megakaryocytic lineage, or that essential thrombocytemia is a heterogeneous disorder.
Because of substantial pitfalls in the interpretation of clonality assays, these tests are not yet clinically applicable for diagnostic purposes.

**Clinical Complications**

Essential thrombocythemia remains largely a diagnosis of exclusion of secondary (reactive) causes of thrombocytosis. Clinical findings that may distinguish between these two categories of thrombocytosis are listed in Table 2. Bleeding and thrombotic complications are major causes of illness and death in patients with essential thrombocythemia and other myeloproliferative disorders, particularly older patients who have associated risk factors. These hemostatic problems do not occur in secondary thrombocytosis, regardless of the degree of elevation in the platelet count, unless the underlying systemic disorder predisposes patients to them. Their absence in secondary thrombocytosis is presumably due to the fact that the interaction of platelets with the vessel wall remains qualitatively normal. In clonal thrombocytosis, bleeding complications tend to be of the “platelet type,” involving spontaneous hemorrhage at superficial sites (e.g., the skin or mucous membranes of the gastrointestinal, respiratory, or genitourinary tracts). Although it may seem counterintuitive, patients with essential thrombocythemia who have extreme thrombocytosis (platelet count, ≥1.5 million per cubic millimeter) are at increased risk for bleeding, as are those who take aspirin and other antiplatelet drugs.

In a series of 187 consecutive patients with essential thrombocythemia who were followed at a
single institution, 50 percent had at least one thrombotic episode within nine years after diagnosis. Microvascular ischemia of the digits is characteristic of essential thrombocythemia. It may be associated with the syndrome of erythromelalgia, which is characterized by intense burning or throbbing pain in a patchy distribution in the hands and feet, particularly the plantar surfaces. Physical findings may be entirely absent or may include warmth, dusksiness, and mottled erythema of the involved areas. Because platelet occlusion typically involves only the microvasculature, the peripheral pulses may remain palpable. Left untreated, digital ischemia in essential thrombocythemia may progress to limb-threatening gangrene.

Neurologic complications in clonal thrombocythosis are presumably caused by platelet-mediated cerebrovascular ischemia. They occur in about 25 percent of patients with essential thrombocythemia and may be manifested as nonspecific symptoms, such as chronic headache or dizziness, or as focal neurologic signs. Large-vessel arterial or venous thrombosis may also complicate the course of clonal thrombocythosis. Deep-vein thrombosis and pulmonary embolism are the most common forms of venous thrombosis in clonal thrombocythemia. However, intraabdominal thrombotic complications, such as hepatic-vein thrombosis (the Budd–Chiari syndrome) and portal-vein thrombosis, are characteristic of the myeloproliferative disorders. Recurrent spontaneous abortion and fetal growth retardation affect about 50 percent of pregnancies in women with essential thrombocythemia. These complications are characterized by multiple placental infarctions caused by platelet thrombosis.

Although the degree of elevation in the platelet count does not correlate with the risk of thrombosis, control of the platelet count by cyto reduction does reduce the frequency of thrombosis in some patients. Qualitative platelet abnormalities and leukocyte or endothelial dysfunction may also contribute to the hemostatic complications of myeloproliferative disorders.

**Natural History**

Although earlier analysis of actuarial survival among patients with essential thrombocythemia indicated no significant decrease in their life expectancy, the more recent, population-based Olmsted County Study suggested that survival among patients with essential thrombocythemia was significantly worse than that among age- and sex-matched healthy control subjects.

Thrombotic and vascular complications are the chief causes of death in patients with essential thrombocythemia; however, in a few patients (who have not received leukemogenic treatment) the disease terminates by converting to acute leukemia or myelodysplasia or may evolve into myelofibrosis.

There are presently no diagnostic findings that can definitively distinguish between clonal and secondary (reactive) thrombocytosis (Table 2). As discussed above, patients with secondary thrombocythosis typically have clinically apparent, coexisting, underlying systemic diseases that account for the elevated platelet count. Unlike patients with secondary thrombocythosis, those with clonal thrombocythosis have thrombotic, vascular, and bleeding complications. Splenomegaly is found in about 40 percent of patients with essential thrombocythemia, but it may also occur in some patients with secondary thrombocythosis, particularly when the enlarged spleen is detected by imaging studies.

Laboratory tests likewise do not offer clear-cut distinctions. Giant platelets are often found on the
Peripheral-blood smear in clonal thrombocytosis but not in secondary thrombocytosis (Fig. 2A). A variety of platelet-function abnormalities also have been described in the clonal but not the secondary form of thrombocytosis. These abnormalities may include acquired von Willebrand syndrome and the absence of epinephrine-induced platelet aggregation. Examination of bone marrow aspirate and biopsy specimens (Fig. 2B) reveals increased numbers of megakaryocytes in both forms of thrombocytosis, but there may be relatively subtle differences in their morphologic features. Megakaryocytes in secondary thrombocytosis appear normal, but in clonal thrombocytosis they may assume giant, dysplastic forms with increased ploidy and may be associated with large masses of platelet debris (“platelet drifts”). Therefore, bone marrow examination is a useful ancillary test for clonal thrombocytosis, albeit a nondiagnostic one.

Neither form of thrombocytosis involves diagnostic cytogenetic abnormalities. However, some patients with essential thrombocythemia have a Philadelphia chromosome or the BCR-ABL rearrangement, even in the absence of leukocytosis or other features of chronic myelogenous leukemia. Although the clinical implications of this finding are not entirely clear, at least some patients with such findings who may appear to have essential thrombocythemia (with isolated thrombocytosis) may actually have a variant of chronic myelogenous leukemia. Although such tests are not yet clinically applicable, continued development of clonality assays and tests for c-Mpl expression in megakaryocytes and platelets promises to provide diagnostic tools to differentiate clonal from secondary thrombocytosis.

**TREATMENT CONSIDERATIONS**

The challenge of correctly identifying the cause of thrombocytosis in an individual patient becomes particularly critical when the clinician is confronted with treatment decisions. Figure 3 outlines an approach to the management of thrombocytosis. Patients with secondary (reactive) thrombocytosis do not require platelet-lowering or antiplatelet treatment because their abnormal platelet count itself does not place them at risk for hemostatic or vascular events. It is crucial, however, to identify the cause of their secondary thrombocytosis, even when it is clinically inapparent, so that treatment can be directed to the underlying disease. A normal erythrocyte sedimentation rate and a normal level of C-reactive protein may help to rule out an underlying inflammatory disorder. The search for occult cancer should involve a thorough physical examination, including examination of stool specimens for occult blood, chest radiography, and further testing as indicated by systemic and localizing symptoms and signs.

In clonal thrombocytosis, in contrast, it may indeed be necessary to lower the platelet count. The prophylactic efficacy of platelet-lowering therapy in asymptomatic, low-risk patients with essential thrombocythemia, irrespective of the degree of thrombocytosis, remains untested. Patients are at high risk for thrombotic and vascular events if they have a history of thrombosis or bleeding, have associated cardiovascular risk factors, or are more than 60 years old. One prospective, randomized controlled trial has shown that platelet-cytoreductive therapy with hydroxyurea offers benefit to high-risk patients with essential thrombocythemia; those who were treated with hydroxyurea had sustained and significant increases in the rates of thrombosis-free survival.

### Table 2. Clinical Findings That May Distinguish between Clonal and Secondary (Reactive) Thrombocytosis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>Clonal Thrombocytosis</th>
<th>Secondary (Reactive) Thrombocytosis</th>
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</thead>
<tbody>
<tr>
<td>Underlying systemic disease</td>
<td>No</td>
<td>Often clinically apparent</td>
</tr>
<tr>
<td>Digital or cerebrovascular ischemia</td>
<td>Characteristic</td>
<td>No</td>
</tr>
<tr>
<td>Large-vessel arterial or venous thrombosis</td>
<td>Increased risk</td>
<td>No</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>Increased risk</td>
<td>No</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Yes, in about 40% of patients</td>
<td>No</td>
</tr>
<tr>
<td>Peripheral-blood smear</td>
<td>Giant platelets</td>
<td>Normal platelets</td>
</tr>
<tr>
<td>Platelet function</td>
<td>May be abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Bone marrow megakaryocytes</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Morphologic features</td>
<td>Giant, dysplastic forms with increased ploidy, associated with large masses of platelet debris</td>
<td>Normal</td>
</tr>
</tbody>
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* Clonal thrombocytosis includes essential thrombocythemia and other myelo-proliferative disorders.
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sively with platelet-cytoreductive agents. Plateletapheresis is reserved for patients with acute cerebrovascular complications or digital ischemia, since rapid reduction of the platelet count and symptomatic relief are required.

Except in some older patients who cannot tolerate other drugs, alkylating agents are no longer used for platelet reduction because they can cause acute leukemia. Until recently, hydroxyurea, a nonalkylating agent, was the platelet-lowering agent of choice because of its ease of use. However, some studies have raised concern about its leukemogenic potential as well, particularly after prolonged use, in combination with other drugs, or in patients with essential thrombocytosis who have a deletion of the short arm of chromosome 17.39-42

Anagrelide, an orally administered quinazoline derivative that inhibits megakaryocyte proliferation and differentiation,43 has now been established as alternative first-line therapy to reduce the platelet count, when indicated, in clonal thrombocytosis. Anagrelide is nonleukemogenic and is therefore a particularly reasonable initial option in young patients with essential thrombocytosis who require long-term platelet-count control. The starting dose of the oral formulation is usually 2 mg per day (given in two or four divided doses) and can be increased by 0.5 mg per day every seven days to attain the target platelet count, up to a maximal dose of 10 mg per day. Almost 30 percent of patients cannot tolerate anagrelide because of its vasodilatory and positive inotropic properties; its side effects include fluid retention, palpitations and arrhythmias, heart failure, and headaches, and hence its use requires particular caution in elderly patients or those with heart disease. The side effects of anagrelide decrease over time, but progressive anemia develops in many patients.44

Interferon alfa is an effective, nonmutagenic platelet-lowering agent, the use of which is limited by severe side effects that make it intolerable for about 20 percent of patients. In women at high risk who are contemplating pregnancy, interferon alfa is the treatment of choice, since hydroxyurea is teratogenic and since anagrelide crosses the placenta (with unknown safety implications). Hematopoietic stem-cell transplantation can be considered for highly selected younger patients with clonal thrombocytosis who have advanced, complicated disease.45

Aspirin may be a highly effective adjunctive therapy in patients with essential thrombocytosis who have recurrent thrombotic complications, particularly those with digital or cerebrovascular ischemia, in conjunction with platelet-lowering treatment. However, aspirin must be used with caution in other patients with clonal thrombocytosis because it can cause serious bleeding.46 A recent double-blind, placebo-controlled, randomized trial in patients

*Figure 2. Histologic Features of Essential Thrombocytopenia.*

In Panel A, a peripheral-blood smear from a patient with essential thrombocytopenia contains an increased number of platelets, including giant platelets (arrow; Wright's stain, x100). In Panel B, a specimen of bone marrow from a patient with essential thrombocytopenia contains an increased number of megakaryocytes (hematoxylin and eosin, x100). (Courtesy of Dr. Scott Murphy, American Red Cross Blood Services, Penn–Jersey Region, Philadelphia.)
with polycythemia vera who did not have contraindications to aspirin therapy showed that low-dose aspirin (100 mg per day) is effective in preventing thrombotic complications without increasing the risk of major bleeding.\textsuperscript{47} There are few published data concerning the use of newer antiplatelet agents (e.g., clopidogrel) in patients with clonal thrombocytosis.

Differentiating clonal from secondary causes of thrombocytosis can be extremely difficult, yet the distinction has important therapeutic implications. Secondary thrombocytosis per se does not result in vascular or hemostatic problems, but its underlying cause must be identified and treated, if possible. In contrast, clonal thrombocytosis (essential thrombocythemia and the other, related chronic myeloproliferative disorders) is associated with thrombotic and bleeding complications. Patients at high risk for vascular events should receive prophylactic platelet-lowering therapy, as well as aspirin if it is not contraindicated. Patients with essential thrombocythemia who have active cerebrovascular or digital ischemia should be treated promptly with a platelet-cytoreductive agent and aspirin. The development of new, clinically applicable clonality assays should help provide a rational basis for the diagnosis and management of thrombocytosis.

**CONCLUSIONS**

Differentiating clonal from secondary causes of thrombocytosis can be extremely difficult, yet the distinction has important therapeutic implications. Secondary thrombocytosis per se does not result in vascular or hemostatic problems, but its underlying cause must be identified and treated, if possible. In contrast, clonal thrombocytosis (essential thrombocythemia and the other, related chronic myeloproliferative disorders) is associated with thrombotic and bleeding complications. Patients at high risk for vascular events should receive prophylactic platelet-lowering therapy, as well as aspirin if it is not contraindicated. Patients with essential thrombocythemia who have active cerebrovascular or digital ischemia should be treated promptly with a platelet-cytoreductive agent and aspirin. The development of new, clinically applicable clonality assays should help provide a rational basis for the diagnosis and management of thrombocytosis.
REFERENCES


