exist (such as hereditary overproduction of thrombopoietin) that are not widely recognized because we currently lack adequate diagnostic tools. Approximately 50% of ET patients carry the *JAK2* V617F mutation, but its absence does not exclude the disorder.

ETIOLOGY

Megakaryocytopoiesis and platelet production depend on thrombopoietin and its receptor *Mpl*. As in the case of early erythroid and myeloid progenitor cells, early megakaryocytic progenitors require the presence of interleukin 3 (IL-3) and stem cell factor for optimal proliferation in addition to thrombopoietin. Their subsequent development is also enhanced by the chemokine stromal cell-derived factor 1 (SDF-1). However, megakaryocyte maturation requires thrombopoietin.

Megakaryocytes are unique among hematopoietic progenitor cells because reduplication of their genome is endomitotic rather than mitotic. In the absence of thrombopoietin, endomitotic megakaryocytic reduplication and, by extension, the cytoplasmic development necessary for platelet production are impaired. Like erythropoietin, thrombopoietin is produced in both the liver and the kidneys, and an inverse correlation exists between the platelet count and plasma thrombopoietic activity. Unlike erythropoietin, thrombopoietin is only constitutively produced, and the plasma thrombopoietin level is controlled by the size of its progenitor cell pool. Also, in contrast to erythropoietin, but like its myeloid counterparts, granulocyte and granulocyte-macrophage colony-stimulating factors, thrombopoietin not only enhances the proliferation of its target cells but also enhances the reactivity of their end-stage product, the platelet. In addition to its role in thrombopoiesis, thrombopoietin also enhances the survival of multipotent hematopoietic stem cells and their bone marrow residence.

The clonal nature of ET was established by analysis of glucose-6-phosphate dehydrogenase isoenzyme expression in patients hemizygous for this gene, by analysis of X-linked DNA polymorphisms in informative female patients, and by the expression in patients of nonrandom, though variable, cytogenetic abnormalities. Although thrombocytosis is its principal manifestation, like the other chronic MPNs, a multipotent hematopoietic progenitor cell is involved in ET. Furthermore, a number of families have been described in which ET was inherited, in one instance as an autosomal dominant trait. In addition to ET, PMF and PV have also been observed in some kindreds. Like PMF, most patients who do not have *JAK2* mutations have *CALR* mutations.

CLINICAL FEATURES

Clinically, ET is most often identified incidentally when a platelet count is obtained during the course of a routine medical evaluation. Occasionally, review of previous blood counts will reveal that an elevated platelet count was present but overlooked for many years. No symptoms or signs are specific for ET, but these patients can have hemorrhagic and thrombotic tendencies expressed as easy bruising for the former and microvascular occlusive events for the latter such as erythromelalgia, ocular migraine, or a TIA. Physical examination is generally unremarkable except occasionally for mild splenomegaly. Splenomegaly is indicative of another MPN, in particular PV, PMF, or CML.

Anemia is unusual, but a mild neutrophilic leukocytosis is not. The blood smear is most remarkable for the number of platelets present, some of which may be very large. The large mass of circulating platelets may prevent the accurate measurement of serum potassium due to release of platelet potassium upon blood clotting. This type of hyperkalemia is a laboratory artifact and not associated with electrocardiographic abnormalities. Similarly, arterial oxygen measurements can be inaccurate unless thrombocythemic blood is collected on ice. The prothrombin and partial thromboplastin times are normal, whereas abnormalities of platelet function such as a prolonged bleeding time and impaired platelet aggregation can be present. However, despite much study, no platelet function abnormality is characteristic of ET, and no platelet function test predicts the risk of clinically significant bleeding or thrombosis.

The elevated platelet count may hinder marrow aspiration, but marrow biopsy usually reveals megakaryocyte hypertrophy and hyperplasia, as well as an overall increase in marrow cellularity. If marrow reticulin is increased, another diagnosis should be considered. The absence of stainable iron demands an explanation because iron deficiency alone can cause thrombocytosis, and absent marrow iron in the presence of marrow hypercellularity is a feature of PV.

Nonrandom cytogenetic abnormalities occur in ET but are uncommon, and no specific or consistent abnormality is notable, even those involving chromosomes 3 and 1, where the genes for thrombopoietin and its receptor *Mpl*, respectively, are located.

DIAGNOSIS

Thrombocytosis is encountered in a broad variety of clinical disorders (Table 131-6), in many of which production of cytokines is increased. The absolute level of the platelet count is not a useful diagnostic aid for distinguishing between benign and clonal causes of thrombocytosis. About 50% of ET patients express the *JAK2* V617F mutation. When *JAK2* V617F is absent, cytogenetic evaluation is mandatory to determine if the thrombocytosis is due to CML or a myelodysplastic disorder such as the 5q− syndrome. Because the bcr-abl translocation can be present in the absence of the Ph chromosome, and because bcr-abl reverse transcriptase polymerase chain reaction is associated with false-positive results, fluorescence in situ hybridization (FISH) analysis for bcr-abl is the preferred assay in patients with thrombocytosis in whom a cytogenetic study for the Ph chromosome is negative. *CALR* mutations are present in most patients who do not have *JAK2* mutations, but diagnostic tools to detect these mutations are not yet widespread. Anemia and ringed sideroblasts are not features of ET, but they are features of idiopathic refractory sideroblastic anemia, and in some of these patients, the thrombocytosis occurs in association with *JAK2* V617F expression. Splenomegaly should suggest the presence of another MPN, and in this setting, a red cell mass determination should be performed because splenomegaly can mask the presence of erythrocytosis. Importantly, what appears to be ET can evolve into PV or PMF after a period of many years, revealing the true nature of the underlying MPN. There is sufficient overlap of the *JAK2* V617F neutrophil allele burden between ET and PV that this cannot be used as a distinguishing diagnostic feature; only a red cell mass and plasma volume determination can distinguish PV from ET, and importantly in this regard, 64% of *JAK2* V617F–positive ET patients actually were found to have PV when red cell mass and plasma volume determinations were performed.

COMPLICATIONS

Perhaps no other condition in clinical medicine has caused otherwise astute physicians to intervene inappropriately more often than thrombocytosis, particularly if the platelet count is $>1 \times 10^6/\mu L$. It is commonly believed that a high platelet count causes intravascular stasis and thrombosis; however, no controlled clinical study has ever established this association, and in patients younger than age 60 years, the incidence of thrombosis was not greater in patients with thrombocytosis than in age-matched controls, and tobacco use appears to be the most important risk factor for thrombosis in ET patients.

To the contrary, very high platelet counts are associated primarily with hemorrhage due to acquired von Willebrand's disease. This is not meant to imply that an elevated platelet count cannot cause symptoms in an ET patient, but rather that the focus should be on the patient, not the platelet count. For example, some of the most dramatic neurologic problems in ET are migraine-related and respond only to lowering of the platelet count, whereas other symptoms such as erythromelalgia respond simply to platelet cyclooxygenase-1 inhibitors such as aspirin or ibuprofen, without a reduction in platelet number. Still others may represent an interaction between an atherosclerotic vascular system and a high platelet count, and others may have no relationship to the platelet count whatsoever. Recognition that PV can present with thrombocytosis alone as well as the discovery of previously unrecognized causes of hypercoagulability (Chap. 142) make the older literature on the complications of thrombocytosis unreliable.