Importantly, the *JAK2* gene is located on the short arm of chromosome 9, and loss of heterozygosity on chromosome 9p due to mitotic recombination is the most common cytogenetic abnormality in PV. The segment of 9p involved contains the *JAK2* locus, and loss of heterozygosity in this region leads to homozygosity for *JAK2* V617F. More than 95% of PV patients express this mutation, as do approximately 50% of PMF and ET patients. Homozygosity for the mutation occurs in approximately 30% of PV patients and 60% of PMF patients but is rare in ET. Over time, a portion of PV *JAK2* V617F heterozygotes become homozygotes due to mitotic recombination, but usually not after 10 years of the disease. Most PV patients who do not express *JAK2* V617F express a mutation in exon 12 of the kinase and are not clinically different from those who do, nor do *JAK2* V617F heterozygotes differ clinically from homozygotes. Interestingly, the predisposition to acquire mutations in *JAK2* appears to be associated with a specific *JAK2* gene haplotype, GGCC. *JAK2* V617F is the basis for many of the phenotypic and biochemical characteristics of PV such as elevation of the leukocyte alkaline phosphatase (LAP) score; however, it cannot solely account for the entire PV phenotype and is probably not the initiating lesion in the three MPNs. First, PV patients with the same phenotype and documented clonal disease lack any mutation of *JAK2*. Second, ET and PMF patients have the same mutation but different clinical phenotypes. Third, familial PV can occur without the mutation, even when other members of the same family express it. Fourth, not all the cells of the malignant clone express *JAK2* V617F. Fifth, *JAK2* V617F has been observed in patients with long-standing idiopathic erythrocytosis. Sixth, in some patients, *JAK2* V617F appears to be acquired after another mutation. Finally, in some *JAK2* V617F–positive PV or ET patients, acute leukemia can occur in a *JAK2* V617F–negative progenitor cell. However, although *JAK2* V617F alone may not be sufficient to cause PV, it appears essential for the transformation of ET to PV, although not for its transformation to PMF.

CLINICAL FEATURES

Although isolated thrombocytosis, leukocytosis, or splenomegaly may be the initial presenting manifestation of PV, most often the disorder is first recognized by the incidental discovery of a high hemoglobin or hematocrit. With the exception of aquagenic pruritus, no symptoms distinguish PV from other causes of erythrocytosis.

Uncontrolled erythrocytosis causes hyperviscosity, leading to neurologic symptoms such as vertigo, tinnitus, headache, visual disturbances, and transient ischemic attacks (TIAs). Systolic hypertension is also a feature of the red cell mass elevation. In some patients, venous or arterial thrombosis may be the presenting manifestation of PV. Any vessel can be affected; but cerebral, cardiac, or mesenteric vessels are most commonly involved. Intraabdominal venous thrombosis is particularly common in young women and may be catastrophic if a sudden and complete obstruction of the hepatic vein occurs. Indeed, PV should be suspected in any patient who develops hepatic vein thrombosis. Digital ischemia, easy bruising, epistaxis, acid-peptic disease, or gastrointestinal hemorrhage may occur due to vascular stasis or thrombocytosis. Erythema, burning, and pain in the extremities, a symptom complex known as erythromelalgia, are other complications of the thrombocytosis of PV due to increased platelet stickiness. Given the large turnover of hematopoietic cells, hyperuricemia with secondary gout, uric acid stones, and symptoms due to hypermetabolism can also complicate the disorder.

DIAGNOSIS

When PV presents with erythrocytosis in combination with leukocytosis, thrombocytosis, or splenomegaly or a combination of these, the diagnosis is apparent. However, when patients present with an elevated hemoglobin or hematocrit alone, the diagnostic evaluation is more complex because of the many diagnostic possibilities (Table 131-2). Furthermore, unless the hemoglobin level is ≥20 g/dL (hematocrit ≥60%), it is not possible to distinguish true erythrocytosis from disorders causing plasma volume contraction. This is because uniquely in PV, in contrast to other causes of true erythrocytosis, there is expansion of the plasma volume, which can mask the elevated red cell mass; thus, red cell mass and plasma volume determinations are necessary to establish the presence of an absolute erythrocytosis and to distinguish this from relative erythrocytosis due to a reduction in plasma volume alone (also known as *stress* or *spurious erythrocytosis* or *Gaisböck's syndrome*). Figure 77-18 illustrates a diagnostic algorithm for the evaluation of suspected erythrocytosis. Assay for *JAK2* mutations in the presence of a normal arterial oxygen saturation provides an alternative diagnostic approach to erythrocytosis when red cell mass and plasma volume determinations are not available; a normal serum erythropoietin level does not exclude the presence of PV, but an elevated erythropoietin level is more consistent with a secondary cause for the erythrocytosis.

TABLE 131-2 CAUSES OF ERYTHROCYTOSIS

Relative Erythrocytosis	
Hemoconcentration secondary to dehydration, diuretics, ethanol abuse, androgens, or tobacco abuse	
Absolute Erythrocytosis	
Hypoxia	**Tumors**
Carbon monoxide intoxication	Hypernephroma
High-oxygen-affinity hemoglobin	Hepatoma
High altitude	Cerebellar hemangioblastoma
Pulmonary disease	Uterine myoma
Right to left cardiac or vascular shunts	Adrenal tumors
Sleep apnea syndrome	Meningioma
Hepatopulmonary syndrome	Pheochromocytoma
Renal Disease	**Drugs**
Renal artery stenosis	Androgens
Focal sclerosing or membranous glomerulonephritis	Recombinant erythropoietin
Postrenal transplantation	**Familial (with normal hemoglobin function)**
Renal cysts	Erythropoietin receptor mutation
Bartter's syndrome	*VHL* mutations (Chuvash polycythemia)
	2,3-BPG mutation
	Polycythemia vera

Abbreviations: 2,3-BPG, 2,3-bisphosphoglycerate; VHL, von Hippel-Lindau.

Other laboratory studies that may aid in diagnosis include the red cell count, mean corpuscular volume, and red cell distribution width (RDW), particularly when the hematocrit or hemoglobin levels are less than 60% or 20 g/dL, respectively. Only three situations cause microcytic erythrocytosis: β thalassemia trait, hypoxic erythrocytosis, and PV. With β thalassemia trait, the RDW is normal, whereas with hypoxic erythrocytosis and PV, the RDW may be elevated due to associated iron deficiency. Today, however, the assay for *JAK2* V617F has superseded other tests for establishing the diagnosis of PV. Of course, in patients with associated acid-peptic disease, occult gastrointestinal bleeding may lead to a presentation with hypochromic, microcytic anemia, masking the presence of PV.

A bone marrow aspirate and biopsy provide no specific diagnostic information because these may be normal or indistinguishable from ET or PMF. Similarly, no specific cytogenetic abnormality is associated with the disease, and the absence of a cytogenetic marker does not exclude the diagnosis.

COMPLICATIONS

Many of the clinical complications of PV relate directly to the increase in blood viscosity associated with red cell mass elevation and indirectly to the increased turnover of red cells, leukocytes, and platelets with the attendant increase in uric acid and cytokine production. The latter appears to be responsible for constitutional symptoms. Peptic ulcer disease can also be due to *Helicobacter pylori* infection, the incidence of which is increased in PV, while the pruritus associated with this disorder may be a consequence of mast cell activation by *JAK2* V617F. A sudden increase in spleen size can be associated with painful splenic infarction. Myelofibrosis appears to be part of the natural history of the disease but is a reactive, reversible process that does not itself