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anti-CD52 monoclonal antibody alemtuzumab are especially effec tive in younger MDS patients (<60 years old) with more favorable IPSS. In a consortium retrospective review, about 50% of patients with mainly refractory anemia responded to ATG, usually com bined with cyclosporine, particularly patients with hypocellular marrow.

HGFs can improve blood counts but, as in most other marrow failure states, have been most beneficial to patients with the least severe pancytopenia. EPO alone or in combination with G-CSF can improve hemoglobin levels, particularly in those with low serum EPO levels who have no or a modest need for transfusions. Sur vival is improved by EPO and its amelioration of anemia. G-CSF treatment alone failed to improve survival in a controlled trial. Thrombopoietin mimetics appear to improve platelet counts in some patients, but TPO agonists may increase the rate of leukemic progression in high-risk MDS. No clear evidence suggests that they increase leukemic transformation in low-risk MDS. Luspatercept, which affects transforming growth factor β–mediated suppression of erythropoiesis, has been approved by the FDA for anemia in low-risk MDS, particularly those with SF3B1 mutations. The FDA has approved ivosidenib, an IDH1 inhibitor, for MDS. Venetoclax, a BCL2 inhibitor, is FDA approved for patients with AML and has been used in combination with HMA in high-risk MDS; however, it remains investigational. PART 4 Oncology and Hematology Promising novel agents in trials include targeted therapies (i.e., TP53, splicing factor mutations), inflammation pathway inhibitors (including inflammasome and interleukin 1 receptor–associated kinase), and imetelstat, a telomerase inhibitor. Likely, HMA alone will be replaced with HMA combination therapies. The same principles of supportive care described for aplastic anemia apply to MDS. Many patients will be anemic for years. RBC transfusion support should be accompanied by iron chelation to prevent secondary hemochromatosis. MYELOPHTHISIC ANEMIAS Fibrosis of the bone marrow (see Fig. 65-19), usually accompanied by a characteristic blood smear picture called leukoerythroblastosis, can occur as a primary hematologic disease, called myelofibrosis or myeloid metaplasia (Chap. 108), and as a secondary process, called myelophthi sis. Myelophthisis, or secondary myelofibrosis, is reactive. Fibrosis can be a response to

invading tumor cells, usually an epithelial cancer of breast, lung, or prostate origin or neuroblastoma. Marrow fibrosis may occur with infection of mycobacteria (both Mycobacterium tuberculosis and Mycobacterium avium), fungi, or HIV and in sarcoidosis. Intracel lular lipid deposition in Gaucher disease and obliteration of the mar row space related to absence of osteoclast remodeling in congenital osteopetrosis also can produce fibrosis. Secondary myelofibrosis is a late consequence of radiation therapy or treatment with radiomimetic drugs. Usually the infectious or malignant underlying processes are obvious. Marrow fibrosis can also be a feature of a variety of hema tologic syndromes, especially chronic myeloid leukemia, multiple myeloma, lymphomas, myeloma, and hairy cell leukemia. The pathophysiology has three distinct features: proliferation of fibroblasts in the marrow space (myelofibrosis); the extension of hema topoiesis into the long bones and into extramedullary sites, usually the spleen, liver, and lymph nodes (myeloid metaplasia); and ineffective erythropoiesis. The etiology of the fibrosis is unknown but most likely involves dysregulated production of growth factors: platelet-derived growth factor and transforming growth factor β have been implicated. Abnormal regulation of other hematopoietins would lead to localiza tion of blood-producing cells in nonhematopoietic tissues and uncou pling of the usually balanced processes of stem cell proliferation and differentiation. Myelofibrosis is remarkable for pancytopenia despite very large numbers of circulating hematopoietic progenitor cells. Anemia is dominant in secondary myelofibrosis, usually normocytic and normochromic. The diagnosis is suggested by the characteristic leukoerythroblastic smear. Erythrocyte morphology is highly abnor mal, with circulating nucleated RBCs, teardrops, and shape distortions.

WBC numbers are often elevated, sometimes mimicking a leukemoid reaction, with circulating myelocytes, promyelocytes, and myeloblasts. Platelets may be abundant and are often of giant size. Inability to aspi rate the bone marrow, the characteristic “dry tap,” can allow a presump tive diagnosis in the appropriate setting before the biopsy is decalcified. The course of secondary myelofibrosis is determined by its etiology, usually a metastatic tumor or an advanced hematologic malignancy. Treatable causes must be excluded, especially tuberculosis and fungus. Transfusion support can relieve symptoms. ■ ■FURTHER READING Arber DA et al: International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical, and genomic data. Blood 140:1200, 2022. Bernard E et al: Molecular International Prognostic Scoring System for myelodysplastic syndromes. NEJM Evid 1:EVIDoa2200008, 2022. Cazzola M: Myelodysplastic syndromes. N Engl J Med 383:1358, 2020. DeFilipp Z et al: Hematopoietic cell transplantation in the manage ment of myelodysplastic syndrome: An evidence-based review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. Transplant Cell Ther 29:71, 2022. Gurnari C, Maciejewski JP: How I manage acquired pure red cell aplasia in adults. Blood 15;137:2001, 2021. Hellstrom-Lindberg ES et al: Clinical decision-making and treat ment of myelodysplastic syndromes. Blood 142:2268, 2023. Khoury JD et al: The 5th edition of the World Health Organization classification of haematolymphoid tumours: Myeloid and histiocytic/ dendritic neoplasms. Leukemia 36:1703, 2022. Mustjoki S, Young NS: Somatic mutations in “benign” disease. N Engl J Med 384:2039, 2021. Townsley DM et al: Eltrombopag added to standard immunosuppres sion for aplastic anemia. N Engl J Med 376:1540, 2017. Young NS: Aplastic anemia. N Engl J Med 379:1643, 2018. Jerry L. Spivak

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Other Myeloproliferative Neoplasms The World Health Organization (WHO) classification of the chronic myeloproliferative neoplasms (MPNs) includes eight disorders, some of which are rare or poorly characterized (Table 108-1) but all of which share an origin in a hematopoietic stem cell; overproduction of one or more of the formed elements of the blood without significant dysplasia; and a predilection to extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia. Within this broad TABLE 108-1 World Health Organization Classification of Chronic Myeloproliferative Neoplasms Chronic myeloid leukemia, BCR-ABL–positive Chronic neutrophilic leukemia Chronic eosinophilic leukemia, not otherwise specified Polycythemia vera Primary myelofibrosis Essential thrombocytosis Mastocytosis Myeloproliferative neoplasms, unclassifiable

classification, however, significant phenotypic heterogeneity exists. Some diseases such as chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), and chronic eosinophilic leukemia (CEL) express primarily a myeloid phenotype, whereas in other dis eases, such as polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocytosis (ET), erythroid or megakaryocytic hyperplasia predominates. The latter three disorders, in contrast to the former three, also appear capable of transforming into each other. Such phenotypic heterogeneity has a genetic basis; CML is the con sequence of the balanced translocation between chromosomes 9 and 22 (t[9;22][q34;11]); CNL has been associated with a mutation of CSF3R and a t(15;19) translocation; and CEL occurs with a deletion or bal anced translocations involving the PDGFRα usually with the FIP1L1, PDGFRβ, FGFR1, and PCM1-JAK2 genes. By contrast, PV, PMF, and ET are characterized by driver mutations that directly or indirectly constitutively activate JAK2, a tyrosine kinase essential for the function of the erythropoietin and thrombopoietin receptors and also utilized by the granulocyte colony-stimulating factor receptor. This important distinction is reflected in the natural histories of CML, CNL, and CEL, which are usually measured in years, with a high rate of leukemic trans formation. The natural histories of PV, PMF, and ET, by contrast, are usually measured in decades, and transformation to acute leukemia is uncommon in the absence of chemotherapy. This chapter focuses only on PV, PMF, and ET because their clinical features and driver mutation overlap are substantial, although their disease duration and clinical manifestations vary. The other chronic MPNs will be discussed in Chaps. 110 and 115. POLYCYTHEMIA VERA PV is a clonal hematopoietic stem cell disorder in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus. The most common of the MPNs, PV occurs in 2.5 per 100,000 persons, sparing no adult age group and increasing with age to rates >10/100,000. Familial transmission is infre quent, and women under age 50 predominate among sporadic cases. ■ ■ETIOLOGY Nonrandom chromosome abnormalities such as deletion 20q and deletion 13q or trisomy 9 occur in up to 30% of untreated PV patients, but unlike CML, no consistent cytogenetic abnormality has been asso ciated with the disorder. However, a mutation in the autoinhibitory pseudokinase domain of the tyrosine kinase JAK2 that replaces valine with phenylalanine (V617F), causing constitutive kinase activation, has a central role in PV pathogenesis. JAK2 is a member of an evolutionarily well-conserved, nonreceptor tyrosine kinase family and serves as the cognate tyrosine kinase for the erythropoietin and thrombopoietin receptors. It also functions as an obligate chaperone for these receptors in the Golgi apparatus and is responsible for their cell-surface expression. The conformational change induced in the erythropoietin and thrombopoietin receptors following binding to their respective cognate ligands, erythropoi etin or thrombopoietin, leads to JAK2 autophosphorylation, receptor phosphorylation, and phosphorylation of proteins involved in cell proliferation, differentiation, and resistance to

apoptosis. Transgenic animals lacking JAK2 die as embryos from severe anemia. Constitu tive activation of JAK2, on the other hand, explains the erythropoietin hypersensitivity, erythropoietin-independent erythroid colony forma tion, rapid terminal differentiation, increased Bcl-XL expression, and apoptosis resistance in the absence of erythropoietin that characterize the in vitro behavior of PV erythroid progenitor cells. More than 95% of PV patients express this mutation, as do ~50% of PMF and ET patients. Importantly, the JAK2 gene is located on the short arm of chromosome 9, and loss of heterozygosity on chromo some 9p involving the segment containing the JAK2 locus over time due to mitotic recombination (uniparental disomy) is the most com mon cytogenetic abnormality in PV. Loss of heterozygosity in this region leads to homozygosity for JAK2 V617F and occurs in ~60% of PV patients and to a lesser extent in PMF but is rare in ET. Most PV patients who do not express JAK2 V617F express a mutation in exon 12

of the gene and are not clinically different from those who do, with the exception of a higher frequency of isolated erythrocytosis, nor do JAK2 V617F heterozygotes differ clinically from homozygotes. Importantly, the predisposition to acquire JAK2 mutations 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 increased blood cell production and increased inflammatory cyto kine production; however, it cannot solely account for the entire PV phenotype and is probably not the initiating lesion in any of the MPNs. First, PV patients with the same phenotype and documented clonal disease can have mutations in LNK, a JAK2 inhibitor, or rarely, calre ticulin (CALR), an ER chaperone, since MPN driver mutations are not mutually exclusive. Second, ET and PMF patients have the same muta tions but different clinical phenotypes. Third, familial PV can occur without the mutation, even when other members of the same family express it. Finally, in some JAK2 V617F–positive PV or ET patients, acute leukemia can occur in a JAK2 V617F–negative progenitor cell, suggesting the presence of an ancestral precursor cell.

■ ■CLINICAL FEATURES Although PV is a panmyelopathy, isolated thrombocytosis, leukocy tosis, or splenomegaly can be its presenting manifestation, but most often, the disorder is first recognized by the incidental discovery of a high hemoglobin, hematocrit, or red cell count. With the exception of aquagenic pruritus or erythromelalgia, no symptoms distinguish PV from other causes of erythrocytosis. CHAPTER 108 Uncontrolled erythrocytosis causes hyperviscosity, leading to neu rologic symptoms such as vertigo, tinnitus, headache, visual distur bances, 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, and mesenteric vessels are most commonly involved. Hepatic venous thrombosis (BuddChiari syndrome) is particularly common in young women and may be catastrophic if sudden and complete obstruction of the hepatic vein occurs; portal vein thrombosis is more common in male PV patients. Indeed, PV should be suspected in any woman who develops hepatic vein thrombosis, since this is the only type of thrombosis associated with JAK2 V617F expression. Digital ischemia, easy bruising, epistaxis, acid-peptic disease, or gastrointestinal hemorrhage may occur due to vascular stasis or extreme thrombocytosis (>900,000/mL). In the lat ter instance, absorption and proteolysis of high-molecular-weight von Willebrand multimers by the large platelet mass cause acquired von Willebrand’s disease. Erythema, burning, and pain in the extremities, a symptom complex known as erythromelalgia, is another complication of thrombocytosis in 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. Polycythemia Vera and Other Myeloproliferative Neoplasms ■ ■DIAGNOSIS When PV presents with erythrocytosis in combination with leukocyto sis, thrombocytosis, or splenomegaly or any combination of these, the diagnosis is apparent. However, when patients present with an elevated hemoglobin, hematocrit, and red cell count alone, the diagnostic evalu ation is more complex because of the many diagnostic possibilities (Table 108-2). 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, particularly in women; thus, red cell mass and plasma volume determinations are necessary to establish the presence of an absolute erythrocytosis and distinguish this from relative erythrocyto sis due to a reduction in plasma volume alone (also known as stress or spurious erythrocytosis or Gaisböck's syndrome). Figure 66-18 illustrates a diagnostic algorithm for the evaluation of suspected erythrocytosis. While an assay for JAK2 or rarely LNK mutations in the presence of a normal arterial oxygen saturation appears to provide an alternative

TABLE 108-2 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 SGLT2 inhibitors Focal sclerosing or membranous glomerulonephritis Recombinant erythropoietin Familial (with normal hemoglobin function) Postrenal transplantation Renal cysts Erythropoietin receptor mutations PART 4 Oncology and Hematology Bartter's syndrome VHL mutations (Chuvash polycythemia) 2,3-BPG mutation PHD2 (EGLN1) and HIF2α (EPAS1) mutations LNK mutations Polycythemia vera Abbreviations: 2,3-BPG, 2,3-bisphosphoglycerate; VHL, von Hippel-Lindau. diagnostic approach to isolated erythrocytosis since red cell mass and plasma volume determinations are not usually available, isolated eryth rocytosis is uncommon as an initial manifestation of PV, and not every one expressing a low JAK2 V617F quantitative mutation allele burden (variant allele frequency [VAF] ≤5%) actually has a blood disease. In addition, a normal serum erythropoietin level does not exclude the presence of PV, but an elevated erythropoietin level is most consistent with a secondary cause for the erythrocytosis. 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 <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 usually normal, whereas with hypoxic erythrocytosis or PV, the RDW may be elevated due to associ ated iron deficiency. Today, however, the quantitative assay for JAK2 V617F or JAK2 exon 12 mutations using next-generation sequencing technology has superseded the other surrogate tests for establishing the diagnosis 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

inflammatory cytokine production. The latter also appears to be responsible for some of the constitutional symptoms in PV. 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 impede hematopoiesis and by itself has no prognostic significance in PV. In ~15% of patients, however, myelofi brosis is associated with hematopoietic stem cell failure, manifested by substantial extramedullary hematopoiesis in the liver and spleen and transfusion-dependent anemia. Organomegaly can cause significant mechanical discomfort, portal hypertension, and progressive cachexia. Although the incidence of acute myeloid leukemia is increased in PV, the incidence of acute leukemia in patients not exposed to chemo therapy or radiation therapy is very low. Interestingly, chemotherapy, including hydroxyurea, has been associated with acute leukemia in JAK2 V617F–negative hematopoietic stem cells (HSCs) in some PV patients. Erythromelalgia is a curious syndrome of unknown etiology associated with thrombocytosis, primarily involving the lower extremi ties and usually manifested by erythema, warmth, and pain of the affected appendage and occasionally digital infarction. It occurs with a variable frequency and is usually responsive to salicylates. Some of the central nervous system symptoms observed in patients with PV, such as ocular migraine, appear to represent a variant of erythromelalgia. Left uncontrolled, erythrocytosis can lead to thrombosis involving vital organs such as the liver, heart, brain, or lungs. Patients with mas sive splenomegaly are particularly prone to thrombotic events because the associated increase in plasma volume masks the true extent of the red cell mass elevation measured by the hematocrit or hemoglobin level. A “normal” hematocrit or hemoglobin level in a PV patient with massive splenomegaly should be considered indicative of an elevated red cell mass until proven otherwise. TREATMENT Polycythemia Vera PV is generally an indolent disorder, the clinical course of which is measured in decades, and its management should reflect its tempo. Thrombosis due to erythrocytosis is the most significant complication and often the presenting manifestation; maintenance of the hemoglobin level at ≤140 g/L (14 g/dL; hematocrit <45%) in men and ≤120 g/L (12 g/dL; hematocrit <42%) in women is mandatory to avoid thrombotic complications. Phlebotomy serves initially to reduce hyperviscosity by reducing the red cell mass to normal while further expanding the plasma volume. Periodic phlebotomies thereafter serve to maintain the red cell mass within the normal range and induce a state of iron deficiency that prevents accelerated reexpansion of the red cell mass. In most PV patients, once an iron-deficient state is achieved, phlebotomy is usually only required at 3-month intervals. Neither phlebotomy nor iron deficiency increases the platelet count relative to the effect of the disease itself, and neither thrombocytosis nor leukocytosis is cor related with thrombosis in PV, in contrast to the strong correlation between erythrocytosis and thrombosis. The use of salicylates to prevent thrombosis in PV patients is potentially harmful not only if the red cell mass is not controlled by phlebotomy, but also due to an increased incidence of bleeding, particularly in patients over age 60. Anticoagulation is indicated when a thrombosis has occurred, and the newer oral anticoagulants may be preferable to a vitamin K

antagonist since they do not require monitoring. Asymptomatic hyperuricemia (<10 mg/dL) requires no therapy, but allopurinol should be administered to avoid further elevation of the uric acid when chemotherapy is used to reduce splenomegaly or leukocytosis or to treat pruritus.

Generalized pruritus intractable to antihistamines or antidepressants such as doxepin can be a major problem in PV; the JAK1/2 inhibitor ruxolitinib, pegylated interferon α (IFN-α),

psoralens with ultraviolet light in the A range (PUVA) therapy, and hydroxyurea are other methods of palliation. Asymptomatic throm bocytosis requires no therapy unless the platelet count is sufficiently high to cause bleeding due to acquired von Willebrand's disease, but bleeding in this situation is not usually spontaneous and is responsive to tranexamic acid or ε-aminocaproic acid. Symptomatic splenomegaly can be treated with either ruxolitinib or pegylated

IFN-α. Both ruxolitinib and pegylated IFN-α target the involved HSCs in PV and are not mutagenic; hydroxyurea does not target the involved HSCs in PV and is mutagenic. Furthermore, pegylated IFN-α allows only biweekly administration and produced complete hematologic and molecular remissions in ~20% of PV patients. Anagrelide, a phosphodiesterase inhibitor, can reduce the platelet count and, if tolerated, is preferable to hydroxyurea because it lacks marrow toxicity and is also protective against venous thrombosis, whereas hydroxyurea is not. However, chronic anagrelide therapy is cardiotoxic and nephrotoxic, particularly in older PV patients. A reduction in platelet number may be necessary for the treat ment of erythromelalgia or ocular migraine if salicylates are not effective or if the platelet count is sufficiently high to increase the risk of hemorrhage but only to the degree that symptoms are alleviated. Alkylating agents and radioactive sodium phosphate (32P) are leuke mogenic in PV, and their use should be avoided. If a cytotoxic agent must be used, hydroxyurea is preferred, but this drug does not pre vent either thrombosis or myelofibrosis in PV, is itself leukemogenic, and should be considered as a short-duration therapy. Previously, PV patients with massive splenomegaly unresponsive to reduction by chemotherapy or IFN required splenectomy. However, with the introduction of the nonspecific JAK1/2 inhibitor ruxolitinib, it has been possible in the majority of patients with PV complicated by myelofibrosis and myeloid metaplasia to reduce spleen size while at the same time alleviating constitutional symptoms and pruritus due to cytokine release while reducing the phlebotomy requirement. However, in contrast to PMF, PV patients have a more chronic course; in contrast to other malignancies, PV patients have a low rate of mutation accumulation, and the acquisition of deleterious mutations such as TP53 mutations as detected by next-generation sequencing is usually associated with leukemic transformation. Since hydroxyurea antagonizes TP53 and also causes del17p, leading to TP53 haploinsufficiency, its chronic use should be constrained in PV. Ruxolitinib has also been demonstrated in a phase 3 clinical trial to be effective in PV patients without myelofibrosis who are intolerant or refractory to hydroxyurea or best available supportive therapy. Three other JAK2 inhibitors, fedratinib, pacritinib, and momelotinib, have been approved for treatment of PV patients with myelofibrosis in whom ruxolitinib treatment failed or who were intolerant to the drug. In some PV patients with end-stage disease, pulmonary hypertension may develop due to fibrosis or extramedullary hematopoiesis. A role for bone marrow transplanta tion, either allogeneic or haploidentical, in PV has not been defined. Most patients with PV can live long lives without functional impairment when their red cell mass is effectively managed with phlebotomy alone. Chemotherapy is never indicated to control the red cell mass in PV, but when venous access is an issue, ruxolitinib or pegylated IFN is the preferred therapy. Interestingly, hepcidin production is suppressed, but not absent in PV, and a hepcidin agonist has been shown to reduce phlebotomy requirements in PV. ■ ■PRIMARY MYELOFIBROSIS Chronic PMF (other designations include idiopathic myelofibrosis, agnogenic myeloid metaplasia, or myelofibrosis with myeloid metaplasia) is a clonal HSC disorder associated with mutations in JAK2, MPL, or CALR, and

characterized by marrow fibrosis, extramedullary hema topoiesis, variable suppression of hematopoiesis, and splenomegaly. PMF is the least common MPN, and establishing its diagnosis in the absence of a specific clonal marker is difficult because myelofibrosis and splenomegaly are also features of both PV and CML. Furthermore, myelofibrosis and splenomegaly also occur in a variety of benign and malignant disorders (Table 108-3), many of which are amenable to specific therapies not effective in PMF. In contrast to the other MPNs and so-called acute or malignant myelofibrosis, which can occur at any age, PMF primarily afflicts men in their sixth decade or later. ■ ■ETIOLOGY Nonrandom chromosome abnormalities such as 9p, 20q−, 13q−, trisomy 8 or 9, or partial trisomy 1q are common in PMF, but no

TABLE 108-3 Disorders Causing Myelofibrosis MALIGNANT NONMALIGNANT Acute leukemia (lymphocytic, myelogenous, megakaryocytic) HIV infection Hyperparathyroidism Renal osteodystrophy Systemic lupus erythematosus Tuberculosis Vitamin D deficiency Thorium dioxide exposure Gray platelet syndrome Chronic myeloid leukemia Hairy cell leukemia Hodgkin’s disease Primary myelofibrosis Lymphoma Multiple myeloma Myelodysplasia Metastatic carcinoma Polycythemia vera Systemic mastocytosis cytogenetic abnormality specific to the disease has been identified. JAK2 V617F is present in ~55% of PMF patients, and mutations in the thrombopoietin receptor, MPL, occur in ~4%. Most of the rest have mutations in the calreticulin gene (CALR) that alter the carboxyterminal portion of the protein, permitting it to bind and activate MPL while presenting it at the cell surface. The degree of myelofibrosis and the extent of extramedullary hematopoiesis are not related. Fibrosis in this disorder is associated with overproduction of transforming growth factor β and tissue inhibitors of metalloproteinases and thrombopoi etin, while osteosclerosis is associated with overproduction of osteo protegerin, an osteoclast inhibitor. Marrow angiogenesis occurs due to increased production of vascular endothelial growth factor. Impor tantly, fibroblasts in PMF are polyclonal and not part of the neoplastic clone but can be induced by it to produce inflammatory cytokines. CHAPTER 108 Polycythemia Vera and Other Myeloproliferative Neoplasms ■ ■CLINICAL FEATURES No signs or symptoms are specific for PMF. Many patients are asymp tomatic at presentation, and the disease is often detected by the dis covery of splenic enlargement and/or abnormal blood counts during a routine examination. In contrast to its companion MPN, night sweats, fatigue, and weight loss are common presenting complaints. A blood smear will show the characteristic features of extramedullary hemato poiesis: teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes; myeloblasts may also be present (Fig. 108-1). Anemia, usually mild initially, is common, whereas the leukocyte and platelet counts are either normal or increased, but either can be depressed. Mild hepatomegaly may accompany splenomegaly but is unusual in its FIGURE 108-1 Teardrop-shaped red blood cells indicative of membrane damage from passage through the spleen, a nucleated red blood cell, and immature myeloid cells indicative of extramedullary hematopoiesis are noted. This peripheral blood smear is related to any cause of extramedullary hematopoiesis.

FIGURE 108-2 This marrow section shows the marrow cavity replaced by fibrous tissue composed of reticulin fibers and collagen. When this fibrosis is due to a primary hematologic process, it is called myelofibrosis. When fibrosis is secondary to a tumor or a granulomatous process, it is called myelophthisis. PART 4 Oncology and Hematology absence; isolated lymphadenopathy should suggest another diagnosis. Both serum lactate dehydrogenase and alkaline phosphatase levels can be elevated. Marrow is usually inaspirable due to the myelofibrosis (Fig. 108-2), and bone x-rays may reveal osteosclerosis. Exuberant extramedullary hematopoiesis can cause ascites; portal,

pulmonary, or intracranial hypertension; intestinal or ureteral obstruction; pericardial tamponade; spinal cord compression; or skin nodules. Splenic enlarge ment can be sufficiently rapid to cause splenic infarction with fever and pleuritic chest pain. Hyperuricemia and secondary gout may ensue. ■ ■DIAGNOSIS While the clinical picture described above is characteristic of PMF, all of these clinical features can be observed in PV or CML. Massive splenomegaly commonly masks erythrocytosis in PV, and reports of intraabdominal thrombosis in PMF most likely represent instances of unrecognized PV. In some PMF patients, erythrocytosis has developed during the course of the disease. Importantly, because many other dis orders have features that overlap with PMF but respond to distinctly different therapies, the diagnosis of PMF is one of exclusion, which requires that the disorders listed in Table 108-3 be ruled out. The presence of teardrop-shaped red cells, nucleated red cells, myelocytes, and promyelocytes establishes the presence of extramedul lary hematopoiesis, while the presence of leukocytosis, thrombocytosis with large and bizarre platelets, and circulating myelocytes suggests the presence of an MPN as opposed to a secondary form of myelofibrosis (Table 108-3). Marrow is usually inaspirable due to increased marrow reticulin, but marrow biopsy will usually reveal a hypercellular mar row with trilineage hyperplasia and, in particular, increased numbers of megakaryocytes in clusters and with large, dysplastic nuclei. A small number of PMF patients with a low JAK2 V617F mutation allele burden (≤25%) have a faster time to anemia and leukopenia and a shortened survival. However, there are no specific bone marrow mor phologic abnormalities that distinguish PMF from the other MPNs. Splenomegaly due to extramedullary hematopoiesis may be sufficiently massive to cause portal hypertension and variceal formation. In some patients, exuberant extramedullary hematopoiesis dominates the clini cal picture. An intriguing feature of PMF is the occurrence of autoimmune abnormalities such as immune complexes, antinuclear antibodies, rheumatoid factor, or a positive Coombs' test. Whether these represent a host reaction to the disorder or are involved in its pathogenesis is unknown. Cytogenetic analysis of the blood is useful both to exclude CML and for prognostic purposes, because the development of com plex karyotype abnormalities portends a poor prognosis in PMF. It is thought that impaired expression of the cytokine CXCL4 is responsible for the markedly increased number of circulating CD34+ cells in PMF

TABLE 108-4 Three Current Scoring Systems for Estimating Prognosis in PMF Patients RISK FACTOR IPSS (2009)a DIPSS (2010)b DIPSS PLUS (2011)c Anemia (<10 g/dL) X X X Leukocytosis (>25,000/μL) X X X Peripheral blood blasts (≥1%) X X X Constitutional symptoms X X X Age (>65 years) X X X Unfavorable karyotype X Platelet count (<100,000/μL) X Transfusion dependence X aBlood 113:2895, 2009. bBlood 115:1703, 2010. cJ Clin Oncol 29:392, 2011. Note: The Dynamic International Prognostic Scoring System (DIPSS) was developed to determine if the International Prognostic Scoring System (IPSS) risk factors identified as important for survival at the time of primary myelofibrosis (PMF) diagnosis could also be used for risk stratification following their acquisition during the course of the disease. One point is assigned to each risk factor for IPSS scoring. For DIPSS, the same is true, but anemia is assigned 2 points. The DIPSS Plus scoring system represents recognition that the addition of unfavorable karyotype, thrombocytopenia, and transfusion dependence improved the DIPSS risk stratification system for which additional points are assigned (Table 108-5). More recent studies suggest that mutational analysis of the ASXL1, EZH2, SRSF2, and IDH1/2 genes further improves risk stratification for survival and leukemic transformation (Leukemia 27:1861, 2013), as can cytogenetic abnormalities (Leukemia 32:1631, 2018). These prognostic scoring systems are not accurate for risk assessment in polycythemia vera or essential thrombocytosis patients who have developed myelofibrosis (Haematologica 99:e55,

2014). (>15,000/μL) compared to PV patients, unless they too develop extra medullary hematopoiesis. Importantly, ~55% of PMF patients, like patients with its companion MPNs, express the JAK2 V617F mutation, often as homozygotes. Such patients are usually older and have higher hematocrits than patients with MPL (4%) or CALR (36%) mutations; PMF patients expressing an MPL mutation tend to be more anemic and have lower leukocyte counts than JAK2 V617F–positive patients. Somatic mutations (due to deletions [type 1] or insertions [type 2]) in exon 9 of CALR have been found in a majority of patients with PMF who lack mutations in either JAK2 or MPL. In some studies, type 1 mutations, the most common CALR mutation in PMF, had a survival advantage compared to JAK2 or MPL mutations but not with respect to leukemic transformation. PMF patients who lack a known MPN driver mutation (triple-negative) appear to have the worst prognosis. ■ ■COMPLICATIONS Survival in PMF varies according to specific risk factors at diagnosis (Tables 108-4 and 108-5) but is much shorter than in PV and ET patients. The natural history of PMF is one of increasing marrow fail ure with transfusion-dependent anemia and increasing organomegaly due to extramedullary hematopoiesis. As with CML, PMF can evolve from a chronic to an accelerated phase with constitutional symptoms and increasing marrow failure. About 10% of patients spontaneously transform to an aggressive form of acute leukemia for which therapy is usually ineffective. Additional important prognostic factors for disease acceleration during the course of PMF include the presence of complex TABLE 108-5 IPSS and DIPSS Risk Stratification Systems NUMBER OF RISK FACTORS RISK CATEGORIESa IPSS DIPSS DIPSS PLUS Low

Intermediate-1

1–2

Intermediate-2

3–4 2–3 High ≥3

> 4 4–6 aThe corresponding survival curves for each risk category can be found in the references cited in the footnotes of Table 108-4. Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System.

cytogenetic abnormalities, thrombocytopenia, and transfusion-dependent anemia. Mutations in the ASXL1, EZH2, SRSF2, and IDH1/2 genes have been identified as risk factors for early death or transformation to acute leukemia, as have complex cytogenetic abnormalities, and have proved to be more useful for PMF risk assessment than the clinical scoring systems. TREATMENT Primary Myelofibrosis No specific therapy exists for PMF. The causes for anemia are mul tifarious and include ineffective erythropoiesis uncompensated by splenic extramedullary hematopoiesis, hemodilution due to sple nomegaly, splenic sequestration, blood loss secondary to throm bocytopenia or portal hypertension, folic acid deficiency, systemic inflammation, and autoimmune hemolysis. Neither recombinant erythropoietin nor androgens such as danazol have proven to be consistently effective as therapy for anemia. Erythropoietin may worsen splenomegaly and will be ineffective if the serum erythro poietin level is >125 mU/L. Given the inflammatory milieu that

characterizes PMF, glucocorticoids can ameliorate anemia as well as constitutional symptoms such as fever, chills, night sweats, anorexia, and weight loss, and combining these with low-dose thalidomide has proved effective as well. Thrombocytopenia can be due to impaired marrow function, splenic sequestration, or autoimmune destruction and may also respond to low-dose thalidomide and prednisone. Splenomegaly is by far the most distressing and intractable prob lem for PMF patients, causing abdominal pain, portal hypertension, easy satiety, and cachexia, whereas surgical removal of a massive spleen is associated with significant postoperative complications including mesenteric venous thrombosis, hemorrhage, rebound leukocytosis and thrombocytosis, and hepatic extramedullary hematopoiesis with no amelioration of either anemia or thrombo cytopenia when present. For unexplained reasons, splenectomy also increases the risk of blastic transformation. Splenic irradiation is, at best, temporarily palliative and associ ated with a significant risk of neutropenia, infection, and subsequent operative hemorrhage if splenectomy is attempted. Allopurinol can control significant hyperuricemia, and bone pain can be alleviated by local irradiation. Pegylated IFN-α can ameliorate fibrosis in early PMF, but in advanced disease, it may exacerbate bone mar row failure. The JAK1/2 inhibitor ruxolitinib has proved effective in reducing splenomegaly and alleviating constitutional symptoms in a majority of advanced PMF patients while possibly prolonging survival, but in some patients, ruxolitinib is associated with RAS mutations. Although anemia and thrombocytopenia are its major side effects, these are dose-dependent, and with time, anemia stabilizes, and thrombocytopenia may improve. Fedratinib, a new tyrosine kinase inhibitor with anti-FLT3 activity, has proved useful in patients with disease refractory to ruxolitinib. Two other JAK2 inhibitors have been approved for PMF therapy, pacritinib, which is useful when thrombocytopenia is present, and momelotinib, which may be useful in improving red cell production. In some patients, hypomethylating agents such as azacytidine or decitabine in combination with high-dose ruxolitinib have been used to control the disease or prepare patients for bone marrow transplantation. Transformation to acute leukemia in PMF, like PV or ET, is usually refractory to treatment. Allogeneic bone marrow transplantation is the only curative treatment for PMF and should be considered in younger patients and older patients with high-risk disease; nonmyeloablative con ditioning regimens permit hematopoietic cell transplantation to be extended to older individuals. ESSENTIAL THROMBOCYTOSIS ET (other designations include essential thrombocythemia, idiopathic thrombocytosis, primary thrombocytosis, and hemorrhagic thrombocy themia) is a clonal hematopoietic stem cell disorder associated with

TABLE 108-6 Causes of Thrombocytosis Tissue inflammation: collagen vascular disease, inflammatory bowel disease Hemorrhage Malignancy Iron-deficiency anemia Infection Surgery Myeloproliferative disorders: polycythemia vera, primary myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia Rebound: Correction of vitamin B12 or folate deficiency, post-ethanol abuse, postsplenectomy Myelodysplastic disorders: 5q– syndrome, idiopathic refractory sideroblastic anemia Hemolysis Postsplenectomy or hyposplenism Familial: Thrombopoietin overproduction, JAK2, CALR, or MPL mutations mutations in JAK2 (V617F), MPL, or CALR and manifested clinically by overproduction of platelets without a definable cause. ET has an incidence of 1–2/100,000 and a distinct female predominance. Canonical MPN driver mutations distinguish 90% of ET patients from the more common nonclonal, reactive forms of thrombocytosis (Table 108-6); mutationnegative ET patients may have either uncommon MPL mutations, JAK2 V617F expression limited to the platelets, or a hereditary form of throm bocytosis. Once considered a disease of the elderly and responsible for significant morbidity due to hemorrhage or thrombosis, it

is now clear that ET can occur at any age in adults and often without symptoms or dis turbances of hemostasis. There is an unexplained female predominance in contrast to PMF or the reactive forms of thrombocytosis where no sex difference exists. Because no specific clonal marker is available, clinical and laboratory criteria have been proposed to distinguish ET from other MPNs, which may also present initially with isolated thrombocytosis but have differing prognoses and therapies (Table 108-6). These criteria are useful in identifying disorders such as CML, PV, PMF, or myelodysplasia, which can masquerade as ET. Furthermore, as with “idiopathic” erythro cytosis, nonclonal benign forms of thrombocytosis exist (e.g., hereditary overproduction of thrombopoietin and those with noncanonical JAK2 driver mutations) that are not widely recognized because we currently lack diagnostic assays. Approximately 50% of ET patients express JAK2 V617F, 30% CALR (both type 1 and type 2), and 8% MPL mutations. ET patients lacking a canonical MPN driver mutation usually have a benign prognosis. CHAPTER 108 Polycythemia Vera and Other Myeloproliferative Neoplasms ■ ■ETIOLOGY Megakaryocytopoiesis and platelet production depend on thrombo poietin 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 terminal development is also enhanced by the chemokine stromal cell-derived factor 1 (SDF-1). Interestingly, terminal megakaryocyte maturation and platelet production do not require thrombopoietin. Megakaryocytes are unique among hematopoietic progenitor cells because reduplication of their genome is endomitotic rather than mitotic and promoted by thrombopoietin. Unlike erythropoietin, thrombopoietin is produced only in the liver but has important func tions in the bone marrow where it functions to maintain hematopoi etic stem cells quiescent in their endosteal niches; once released from their niches, thrombopoietin promotes the proliferation of these cells in the sinusoidal niches. Like plasma erythropoietin and its target erythroblasts, an inverse correlation exists between the platelet count and plasma thrombopoietin. However, unlike erythropoietin, throm bopoietin is only constitutively produced and the plasma thrombopoi etin level is controlled by the size of the platelet and megakaryocyte progenitor cell pools. 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. Paradoxically, in the three MPNs,

expression of the thrombopoietin receptor, MPL, is impaired and plasma thrombopoietin is increased despite the increased number of megakaryocytes and platelets.

The clonal nature of ET was established by analysis of glucose-6-

phosphate dehydrogenase isoenzyme expression in patients hemizy gous for this gene. Although thrombocytosis is its principal manifesta tion, like the other MPNs, the hematopoietic stem 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 such kindreds. ■ ■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. 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 pres ent, 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 test tube artifact and not associated with electrocar diographic 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. PART 4 Oncology and Hematology The elevated platelet count may hinder marrow aspiration, but marrow biopsy usually reveals megakaryocyte hypertrophy and hyper plasia, 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 defi ciency 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 uncom mon, 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 108-6), in many of which inflammatory cytokine production 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 man datory to determine if the thrombocytosis is due to CML or a myelo dysplastic disorder such as the 5q– syndrome or sideroblastic anemia. Because the BCR-ABL translocation can be present in the absence of the Ph chromosome, and because the 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 (type 1 or type 2) are present in 30% and MPL mutations are present in 8% of ET patients who do not have a JAK2 mutation. Anemia and ringed sideroblasts are not features of ET, but they are features of idiopathic refractory sideroblastic anemia with the SF3B1 mutation, and in some of these patients, thrombocytosis occurs in association with expression of JAK2 V617F, CALR, or an MPL mutation. Significant

splenomegaly should suggest the presence of another MPN such as PV or PMF, because splenomegaly can mask the presence of erythrocyto sis. Importantly, what appears to be ET can evolve into PV (usually in women with JAK2 V617F) or PMF (usually in men with type 1 CALR mutations) after a period of many years due to clonal evolution or succession. There is sufficient overlap of the JAK2 V617F neutrophil allele burden between ET and PV that this test cannot be used as a dis tinguishing diagnostic feature with the exception that, in ET, the quan titative JAK2 V617F neutrophil allele is never greater than 50%, and importantly in this regard, 64% of JAK2 V617F–positive ET patients in one study actually were found to have PV when red cell mass and plasma volume determinations were performed. Claims that ET and PV form a biological continuum are unfounded as these disorders have different gene expression profiles and different natural histories. ■ ■COMPLICATIONS Perhaps no other condition in clinical medicine has caused

otherwise astute physicians to intervene inappropriately more often than throm bocytosis, particularly if the platelet count is >1 × 106/μL. It is com monly believed that a high platelet count causes 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 unrecog nized causes of hypercoagulability (Chaps. 121 and 122) make the older literature on the complications of thrombocytosis unreliable. TREATMENT Essential Thrombocytosis Survival of ET patients is not different than the general population regardless of their driver mutation. An elevated platelet count in an asymptomatic patient without cardiovascular risk factors or tobacco use requires no therapy. Indeed, before any therapy is initi ated in a patient with thrombocytosis, the cause of symptoms must be clearly identified as due to the elevated platelet count. When the platelet count rises above 1 × 106/μL, a substantial quantity of high-molecular-weight von Willebrand multimers are removed from the circulation and destroyed by the enlarged platelet mass, resulting in an acquired form of von Willebrand's disease. This can be identified by a reduction in ristocetin cofactor activity. In this situation, aspirin could promote hemorrhage. Bleeding in this situ ation is rarely spontaneous and usually responds to tranexamic acid or ε-aminocaproic acid, which can be given prophylactically before and after elective minor surgery. Plateletpheresis is at best a temporary and inefficient remedy that is rarely required. Importantly, ET patients treated with 32P or alkylating agents are at risk of developing acute leukemia without any proof of benefit; combining either therapy with hydroxyurea increases this risk. If platelet reduction is deemed necessary on the basis of symptoms refractory to salicylates alone, pegylated IFN-α, the quinazoline derivative anagrelide, or hydroxyurea can be used to reduce the platelet count, but none of these is uniformly effec tive or without significant side effects. Hydroxyurea and aspirin

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Revision #1
Created 2026-01-06 16:31:58 UTC by Omar Ayman
Updated 2026-01-06 16:31:58 UTC by Omar Ayman