after hydroxyurea failure. This agent is associated with acute side effects (e.g., fluid retention, palpitations), hemorrhage (i.e., with concomitant aspirin use), and an increased risk of transformation to myelofibrosis. Both agents are known teratogens and therefore cannot be used in the significant fraction of patients with ET who are young women of childbearing age. Because patients with ET have a high incidence of fetal wastage, interferon-α (i.e., cytokine that alters the biologic mechanisms of the malignant clone but does not cross the placenta) with heparin or aspirin has been recommended to improve pregnancy outcomes in these patients.

PRIMARY MYELOFIBROSIS

Definition and Epidemiology

PMF (i.e., idiopathic myelofibrosis or agnogenic myeloid metaplasia) is a clonal stem cell disorder characterized by abnormal excessive marrow fibrosis leading to marrow failure. PMF is a rare chronic disease that usually is seen in elderly persons. The annual incidence of PMF is 0.5 cases per 100,000 people.

Pathology

An abnormal myeloid precursor is thought to give rise to dysplastic megakaryocytes that produce increased levels of angiogenic and fibroblast growth factors. These cytokines act on normal fibroblasts and other stromal cells, a process that stimulates excessive proliferation and collagen deposition. Over time, increasing fibrosis of the bone marrow leads to premature release of multipotent hematopoietic precursors into the periphery. These cells then migrate and reestablish themselves in other sites, thereby shifting hematopoiesis out of the bone marrow and into other tissues, especially the spleen and liver. This process is called *extramedullary hematopoiesis.*

Diagnosis and Differential Diagnosis

Early in the disease, patients may be asymptomatic, with incidental findings of abnormal blood counts on routine laboratory tests. Although low blood counts may occur, overall platelet and red blood cell numbers at diagnosis may be increased or normal depending on the degree of compensatory extramedullary hematopoiesis. Review of the peripheral blood profile commonly reveals leukoerythroblastic changes characterized by teardrop-shaped erythrocytes, giant platelets, and nonleukemic immature myeloid, erythroid, and leukocyte cells.

Diagnosis of PMF is made by demonstration of bone marrow fibrosis with markedly increased reticulin or collagen fibers (see E-Fig. 46-1) or increased marrow cellularity. Other underlying causes of neoplastic and non-neoplastic bone marrow fibrosis (Table 46-5) should be ruled out. Testing for *JAK2*, *BCR/ABL*, or other diagnostic mutations and cytogenetic markers should be performed before a diagnosis of PMF is made (Table 46-6).

Clinical Presentation

Although many patients are asymptomatic at diagnosis, most complain over time of progressive fatigue and dyspnea related to anemia or early satiety and left upper quadrant pain associated with splenomegaly and splenic infarction. More than one half of these patients develop massive hepatosplenomegaly due to extramedullary hematopoiesis. Patients with more advanced disease may have constitutional symptoms such as fever, weight loss, night sweats, cachexia, pruritis, and bone pain.

As bone marrow failure evolves, complications of neutropenia, thrombocytopenia, and anemia develop as a result of ineffective hematopoiesis. Bleeding from occult disseminated intravascular coagulation is a risk. Extramedullary hematopoiesis in the peritoneal and pleural cavities and in the central nervous system (CNS) may also cause symptoms.

Treatment and Prognosis

Median survival of patients with PMF is poor, ranging from 2 to 5 years after diagnosis. The most commonly accepted adverse prognostic factors at onset include age greater than 65 years, hemoglobin concentration of less than 10 g/dL, leukocyte count of more than 25×10^9/L, a high percentage of circulating blasts (≥1%), and constitutional symptoms. Other important clinical factors are leukopenia, thrombocytopenia (platelets $<100 \times 10^9$/L), massive hepatosplenomegaly, red cell transfusion needs, and unfavorable cytogenetic abnormalities.

TABLE 46-5 CAUSES OF BONE MARROW FIBROSIS

I. Neoplastic causes
   a. Chronic myeloproliferative disorders: chronic idiopathic myelofibrosis, chronic myelogenous leukemia, polycythemia vera
   b. Acute megakaryoblastic leukemia (FAB M7)
   c. Myelodysplasia with myelofibrosis
   d. Hairy cell leukemia
   e. Acute lymphoblastic leukemia
   f. Multiple myeloma
   g. Metastatic carcinoma
   h. Systemic mastocytosis
II. Non-neoplastic causes
   a. Granulomatous diseases: mycobacterial infections, fungal infections, sarcoidosis
   b. Paget's disease of bone
   c. Hypoparathyroidism or hyperparathyroidism
   d. Renal osteodystrophy
   e. Osteoporosis
   f. Vitamin D deficiency
   g. Autoimmune diseases: systemic lupus erythematosus, systemic sclerosis

FAB M7, French-American-British acute myeloid leukemia classification subtype 7.

TABLE 46-6 WORLD HEALTH ORGANIZATION 2008 DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS MAJOR CRITERIA

Major criteria*
1. Megakaryocyte proliferation and atypia accompanied by reticulin and/or collagen fibrosis, *or* in the absence of reticulin fibrosis, the megakaryocytic changes must be accompanied by increased marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis (i.e., prefibrotic primary myelofibrosis)
2. Not meeting World Health Organization criteria for chronic myelogenous leukemia, polycythemia vera, myelodysplastic syndrome, or other myeloid neoplasm
3. Demonstration of *JAK2* V617F mutation or other clonal marker or no evidence of reactive marrow fibrosis

Minor criteria
1. Leukoerythroblastosis
2. Increased serum lactate dehydrogenase level
3. Anemia
4. Palpable splenomegaly

*Diagnosis of primary myelofibrosis requires meeting all three major criteria and two minor criteria.