myelophthisis. 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. Intracellular lipid deposition in Gaucher's disease and obliteration of the marrow 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 hematologic 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 hematopoiesis 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 localization of blood-producing cells in nonhematopoietic tissues and uncoupling 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 **(see Fig. 129-1)**. Erythrocyte morphology is highly abnormal, 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 aspirate the bone marrow, the characteristic "dry tap," can allow a presumptive 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.

131 Polycythemia Vera and Other Myeloproliferative Neoplasms

Jerry L. Spivak

The World Health Organization (WHO) classification of the chronic myeloproliferative neoplasms (MPNs) includes eight disorders, some of which are rare or poorly characterized **(Table 131-1)** but all of which share an origin in a multipotent hematopoietic progenitor 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 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 diseases, 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.

TABLE 131-1 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

Such phenotypic heterogeneity has a genetic basis; CML is the consequence of the balanced translocation between chromosomes 9 and 22 [t(9;22)(q34;11)]; CNL has been associated with a t(15;19) translocation; and CEL occurs with a deletion or balanced translocations involving the *PDGFRα* gene. By contrast, to a greater or lesser extent, PV, PMF, and ET are characterized by a mutation, V617F, that causes constitutive activation of JAK2, a tyrosine kinase essential for the function of the erythropoietin and thrombopoietin receptors but not the granulocyte colony-stimulating factor receptor. This important distinction is also reflected in the natural histories of CML, CNL, and CEL, which are usually measured in years, and their high rate of leukemic transformation. By contrast, the natural history of PV, PMF, and ET is usually measured in decades, and transformation to acute leukemia is uncommon in PV and ET in the absence of exposure to mutagenic drugs. This chapter, therefore, will focus only on PV, PMF, and ET, because their clinical and genetic overlap is substantial even though their clinical courses are distinctly different.

The other chronic myeloproliferative neoplasms will be discussed in Chaps. 133 and 135e.

POLYCYTHEMIA VERA

PV is a clonal disorder involving a multipotent hematopoietic progenitor cell in which phenotypically normal red cells, granulocytes, and platelets accumulate in the absence of a recognizable physiologic stimulus. The most common of the chronic MPNs, PV occurs in 2.5 per 100,000 persons, sparing no adult age group and increasing with age to rates over 10/100,000. Familial transmission is infrequent, and women predominate among sporadic cases.

ETIOLOGY

The etiology of PV is unknown. Although nonrandom chromosome abnormalities such as deletion 20q and trisomy 8 and 9 have been documented in up to 30% of untreated PV patients, unlike CML, no consistent cytogenetic abnormality has been associated 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—appears to have a central role in the pathogenesis of PV.

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, erythropoietin 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. Constitutive activation of JAK2, on the other hand, explains the erythropoietin hypersensitivity, erythropoietin-independent erythroid colony formation, rapid terminal differentiation, increase in Bcl-X_L expression, and apoptosis resistance in the absence of erythropoietin that characterize the in vitro behavior of PV erythroid progenitor cells.