The onset is insidious. Mild-to-moderate anemia and hypermetabolism due to increased cell turnover lead to fatigability, weakness, weight loss, and anorexia. Sometimes the first symptom is a dragging sensation in the abdomen caused by splenomegaly, or the acute onset of left upper quadrant pain due to splenic infarction. CML is best differentiated from other myeloproliferative disorders by detection of the *BCR-ABL* fusion gene through either chromosomal analysis or PCR-based tests.

The natural history is one of slow progression; even without treatment, the median survival is about 3 years. After a variable period averaging 3 years, about 50% of patients enter an "accelerated phase" marked by increasing anemia and thrombocytopenia, sometimes accompanied by a rise in the number of basophils in the blood. Additional clonal cytogenetic abnormalities, such as trisomy 8, isochromosome 17q, or duplication of the Ph chromosome, often appear. Within 6 to 12 months, the accelerated phase terminates in a picture resembling acute leukemia (*blast crisis*). In the other 50% of patients, blast crises occur abruptly without an accelerated phase. In 70% of crises, the blasts are of myeloid origin (myeloid blast crisis), whereas in most of the remainder the blasts are of pre–B cell origin (lymphoid blast crisis). This is taken as evidence that CML originates from a pluripotent stem cell with both myeloid and lymphoid potential.

Given that we have seen that acute leukemias often stem from complementary mutations involving a transcription factor and a tyosine kinase, it might be predicted that blast crisis would be caused by an acquired mutation in a key transcriptional regulator. This prediction has been realized in lymphoid blast crisis, in which 85% of cases are associated with mutations that interfere with the activity of Ikaros, a transcription factor that regulates the differentiation of hematopoietic progenitors. The same types of Ikaros mutations are also seen in BCR-ABL-positive B-ALL, suggesting that these two varieties of aggressive leukemia have a similar pathogenic basis.

Understanding of the pathogenesis of CML has led to the use of drugs that target BCR-ABL. Treatment with BCR-ABL inhibitors results in sustained hematologic remissions in greater than 90% of patients, with generally tolerable side effects. These inhibitors markedly decrease the number of BCR-ABL-positive cells in the marrow and elsewhere, but do not extinguish the CML "stem cell," which persists at low levels. As a result, it is not clear if BCR-ABL inhibitors are ever truly curative. However, this form of targeted therapy controls blood counts and substantially decreases the risk of transformation to the accelerated phase and blast crisis, which is the greatest threat to the patient. It may be that by lowering the proliferative drive of the BCR-ABL-positive progenitors, BCR-ABL inhibitors decrease the rate at which these cells acquire mutations that lead to disease progression.

The other major threat to the patient is the emergence of resistance to first generation BCR-ABL inhibitors, which in about 50% of cases stems from mutations in BCR-ABL and in the remaining cases mutations in other kinases. This problem has been overcome in part by development of second and third generation kinase inhibitors that are active against mutated forms of BCR-ABL. For relatively young patients, hematopoietic stem cell transplantation performed in the stable phase is curative in about 75% of cases. The outlook is less favorable once the accelerated phase or blast crisis supervenes, as transplantation and treatment with BCR-ABL inhibitors are both less effective in these settings.

Polycythemia Vera

Polycythemia vera is strongly associated with activating point mutations in the tyrosine kinase JAK2. Polycythemia vera (PCV) is characterized by increased marrow production of red cells, granulocytes, and platelets (panmyelosis), but it is the increase in red cells (polycythemia) that is responsible for most of the clinical symptoms. PCV must be differentiated from relative polycythemia resulting from hemoconcentration and other causes of absolute polycythemia (Chapter 14).

Pathogenesis. **JAK2 participates in the JAK/ STAT pathway, which lies downstream of multiple hematopoietic growth factor receptors, including the erythropoietin receptor.** In PCV the transformed progenitor cells have markedly decreased requirements for erythropoietin and other hematopoietic growth factors due to constitutive JAK2 signaling. Accordingly, serum erythropoietin levels in PCV are low, whereas secondary forms of polycythemia have high erythropoietin levels. The elevated hematocrit leads to increased blood viscosity and sludging. These hemodynamic factors, together with thrombocytosis and abnormal platelet function, make patients with PCV prone to both thrombosis and bleeding.

More than 97% of cases are associated with a mutation in *JAK2* that results in a valine-to-phenylalanine substitution at residue 617; other *JAK2* mutations are found in most (and perhaps all) of the remaining cases. The mutated forms of JAK2 found in PCV render hematopoietic cell lines growth factor-independent, and when expressed in murine bone marrow progenitors cause a PCV-like syndrome that is associated with marrow fibrosis. In 25% to 30% of cases the tumor cells contain two mutated copies of *JAK2*, a genotype that is associated with higher white cell counts, more significant splenomegaly, symptomatic pruritus, and a greater rate of progression to the spent phase.

The proliferative drive in PCV (and other myeloproliferative disorders associated with JAK2 mutations) is less than in CML, which is associated with more pronounced marrow hypercellularity, leukocytosis, and splenomegaly. Presumably, JAK2 signals are quantitatively weaker or qualitatively different from those produced by BCR-ABL (Fig. 13-32).

MORPHOLOGY

The marrow is hypercellular, but some residual fat is usually present. **The increase in red cell progenitors is subtle and usually accompanied by an increase in granulocytic precursors and megakaryocytes as well.** At diagnosis, a moderate to marked increase in reticulin fibers is seen in about 10% of marrows. Mild organomegaly is common, being caused early in the course largely by congestion; at this stage extramedullary hematopoiesis is minimal. The peripheral blood often contains increased numbers of basophils and abnormally large platelets.