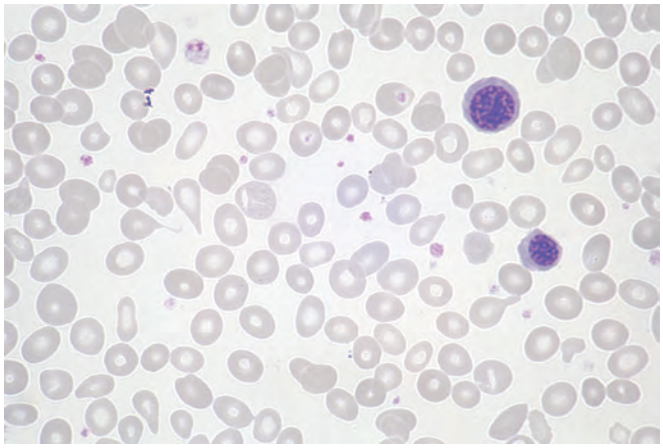

Figure 13-37 Primary myelofibrosis (peripheral blood smear). Two nucleated erythroid precursors and several teardrop-shaped red cells (dacryocytes) are evident. Immature myeloid cells were present in other fields. An identical picture can be seen in other diseases producing marrow distortion and fibrosis.

myelofibrosis, leukoerythroblastosis and teardrop red cells are seen in many infiltrative disorders of the marrow, including granulomatous diseases and metastatic tumors. Other common, albeit nonspecific, blood findings include abnormally large platelets and basophilia.

Clinical Features. Primary myelofibrosis is less common than PCV and ET and usually occurs in individuals older than 60 years of age. Except when preceded by another myeloproliferative disorder, it comes to attention because of progressive anemia and splenomegaly, which produces a sensation of fullness in the left upper quadrant. Nonspecific symptoms such as fatigue, weight loss, and night sweats result from an increase in metabolism associated with the expanding mass of hematopoietic cells. Hyperuricemia and secondary gout due to a high rate of cell turnover can complicate the picture.

Laboratory studies typically show a moderate to severe normochromic normocytic anemia accompanied by leukoerythroblastosis. The white cell count is usually normal or mildly reduced, but can be markedly elevated (80,000 to 100,000 cells/mm^3) early in the course. The platelet count is usually normal or elevated at the time of diagnosis, but thrombocytopenia may supervene as the disease progresses. These blood findings are not specific; bone marrow biopsy is essential for diagnosis.

Primary myelofibrosis is a much more difficult disease to treat than PCV or ET. The course is variable, but the median survival is in the range of 3 to 5 years. Threats to life include intercurrent infections, thrombotic episodes, bleeding related to platelet abnormalities, and transformation to AML, which occurs in 5% to 20% of cases. When myelofibrosis is extensive, AML sometimes arises at extramedullary sites, including lymph nodes and soft tissues. JAK2 inhibitors have recently been approved to treat this disease and are effective at decreasing the splenomegaly and constitutional symptoms. Hematopoietic stem cell transplantation offers some hope for cure in those young and fit enough to withstand the procedure.

KEY CONCEPTS

Myeloid Neoplasms

Myeloid tumors occur mainly in adults and fall into three major groups:

Acute myeloid leukemias (AMLs)

- Aggressive tumors comprised of immature myeloid lineage blasts, which replace the marrow and suppress normal hematopoiesis
- Associated with diverse acquired mutations that lead to expression of abnormal transcription factors, which interfere with myeloid differentiation
- Often also associated with mutations in genes encoding growth factor receptor signaling pathway components or regulators of the epigenome

Myeloproliferative disorders

- Myeloid tumors in which production of formed myeloid elements is initially increased, leading to high blood counts and extramedullary hematopoiesis
- Commonly associated with acquired mutations that lead to constitutive activation of tyrosine kinases, which mimic signals from normal growth factors. The most common pathogenic kinases are BCR-ABL (associated with CML) and mutated JAK2 (associated with polycythemia vera and primary myelofibrosis).
- All can transform to acute leukemia and to a spent phase of marrow fibrosis associated with anemia, thrombocytopenia, and splenomegaly.

Myelodysplastic Syndromes

- Poorly understood myeloid tumors characterized by disordered and ineffective hematopoiesis and dysmaturation
- Recently shown to frequently harbor mutations in splicing factors and epigenetic regulators
- Manifest with one or more cytopenias and progress in 10% to 40% of cases to AML

Langerhans Cell Histiocytosis

The term *histiocytosis* is an "umbrella" designation for a variety of proliferative disorders of dendritic cells or macrophages. Some, such as rare "histiocytic" lymphomas, are clearly malignant, whereas others, such as reactive proliferations of macrophages in lymph nodes, are clearly benign. Lying between these two extremes are the Langerhans cell histiocytoses, a spectrum of proliferations of a special type of immature dendritic cell called the Langerhans cell (Chapter 6).

The origin and nature of the proliferating cells in Langerhans cell histiocytosis has been controversial, leading to discussion of whether it is better considered a neoplasm or a reactive process. Recent sequencing has largely settled this score, as the majority of cases have mutations that are known to be oncogenic in other contexts. The most common mutation is an activating valine-to-glutamate substitution at residue 600 in BRAF, already discussed for its role in hairy cell leukemia, which is present in 55% to 60% of cases. Less common mutations have also been detected in TP53, RAS, and the tyrosine kinase MET. Thus, there seems no doubt that many of these proliferations are neoplastic in origin.