Immunophenotype. Because it can be difficult to distinguish myeloblasts and lymphoblasts morphologically, the diagnosis of AML is confirmed by performing stains for myeloid-specific antigens (Fig. 13-29*B,C*).

Cytogenetics. Cytogenetic analysis has a central role in the classification of AML. Karyotypic aberrations are detected in 50% to 70% of cases with standard techniques and in approximately 90% of cases using special high-resolution banding. Particular chromosomal abnormalities correlate with certain clinical features. AMLs arising de novo in younger adults are commonly associated with balanced chromosomal translocations, particularly t(8;21), inv(16), and t(15;17). In contrast, AMLs following myelodysplastic syndromes or exposure to DNA-damaging agents (such as chemotherapy or radiation therapy) often have deletions or monosomies involving chromosomes 5 and 7 and usually lack chromosomal translocations. The exception to this rule is AML occurring after treatment with topoisomerase II inhibitors, which is strongly associated with translocations involving the *MLL* gene on chromosome 11q23. AML in older adults is also more likely to be associated with "bad" aberrations, such as deletions of chromosomes 5q and 7q.

Clinical Features. Most patients present within weeks or a few months of the onset of symptoms with complaints related to *anemia, neutropenia, and thrombocytopenia,* most notably fatigue, fever, and spontaneous mucosal and cutaneous bleeding. You will remember that these findings are very similar to those produced by ALL. Thrombocytopenia results in a bleeding diathesis, which is often prominent. Cutaneous petechiae and ecchymoses, serosal hemorrhages into the linings of the body cavities and viscera, and mucosal hemorrhages into the gingivae and urinary tract are common. Procoagulants and fibrinolytic factors released by leukemic cells, especially in AML with the t(15;17), exacerbate the bleeding tendency. Infections are frequent, particularly in the oral cavity, skin, lungs, kidneys, urinary bladder, and colon, and are often caused by opportunists such as fungi, *Pseudomonas*, and commensals.

Signs and symptoms related to involvement of tissues other than the marrow are usually less striking in AML than in ALL, but tumors with monocytic differentiation often infiltrate the skin (leukemia cutis) and the gingiva; this probably reflects the normal tendency of monocytes to extravasate into tissues. Central nervous system spread is less common than in ALL. AML occasionally presents as a localized soft-tissue mass known variously as a myeloblastoma, granulocytic sarcoma, or chloroma. Without systemic treatment, such tumors inevitably progress to full-blown AML over time.

Prognosis. AML is generally a difficult disease to treat; about 60% of patients achieve complete remission with chemotherapy, but only 15% to 30% remain free of disease for 5 years. However, the outcome varies markedly among different molecular subtypes. With targeted therapy using all-trans retinoic acid and arsenic salts (described in Chapter 7), AMLs with the t(15;17) now have the best prognosis of any type, being curable in more than 80% of patients. AMLs with t(8;21) or inv(16) have a relatively good prognosis with conventional chemotherapy, particularly in the absence of *KIT* mutations. In contrast, the prognosis is dismal for AMLs that follow MDS or genotoxic therapy, or that occur in older adults, possibly because in these contexts the disease arises out of a background of hematopoietic stem cell damage or depletion. These "high-risk" forms of AML (as well as relapsed AML of all types) are treated with hematopoietic stem cell transplantation when possible.

Sequencing of AML genomes has recently revealed new molecular predictors of outcome. It is certain that insights gained from DNA sequencing will have an increasingly important role in selecting therapy and stratifying patients in clinical trials of new therapeutics, such as drugs that target the tumor epigenome.

Myelodysplastic Syndromes

The term "myelodysplastic syndrome" (MDS) refers to a group of clonal stem cell disorders characterized by maturation defects that are associated with ineffective hematopoiesis and a high risk of transformation to AML. In MDS the bone marrow is partly or wholly replaced by the clonal progeny of a neoplastic multipotent stem cell that retains the capacity to differentiate but does so in an ineffective and disordered fashion. These abnormal cells stay within the bone marrow and hence the patients have peripheral blood cytopenias.

MDS may be either primary (idiopathic) or secondary to previous genotoxic drug or radiation therapy (t-MDS). t-MDS usually appears from 2 to 8 years after the genotoxic exposure. All forms of MDS can transform to AML, but transformation occurs with highest frequency and most rapidly in t-MDS. Although characteristic morphologic changes are typically seen in the marrow and the peripheral blood, the diagnosis frequently requires correlation with other laboratory tests. Cytogenetic analysis is particularly helpful, since certain chromosomal aberrations (discussed later) are often observed.

Pathogenesis. The pathogenesis of MDS is poorly understood, but important new insights have come from recent deep sequencing of MDS genomes, which has identified a number of recurrently mutated genes. These genes can be lumped into three major functional categories, as follows:

- *Epigenetic factors*. Frequent mutations are seen involving many of the same epigenetic factors that are mutated in AML, including factors that regulate DNA methylation and histone modifications; thus, like AML, dysregulation of the epigenome appears to be important in the genesis of MDS.
- *RNA splicing factors*. A subset of tumors has mutations involving components of the 3′ end of the RNA splicing machinery. The impact of these mutations on RNA splicing and other nuclear functions is not yet known.
- *Transcription factors*. These mutations affect transcription factors that are are required for normal myelopoiesis and may contribute to the deranged differentiation that characterizes MDS.

In addition, roughly 10% of MDS cases have loss-of-function mutations in the tumor suppressor gene *TP53*, which correlate with the presence of a complex karyotype and particularly poor clinical outcomes. Both primary MDS and t-MDS are associated with similar recurrent