MORPHOLOGY

Hairy cell leukemia derives its picturesque name from the appearance of the leukemic cells, which have **fine hairlike projections** that are best recognized under the phase-contrast microscope (Fig. 13-21). On routine peripheral blood smears, hairy cells have round, oblong, or reniform nuclei and moderate amounts of pale blue cytoplasm with threadlike or bleblike extensions. The number of circulating cells is highly variable. The marrow is involved by a diffuse interstitial infiltrate of cells with oblong or reniform nuclei, condensed chromatin, and pale cytoplasm. Because these cells are enmeshed in an extracellular matrix composed of reticulin fibrils, they usually cannot be aspirated (a clinical difficulty referred to as a "dry tap") and are only seen in marrow biopsies. The splenic red pulp is usually heavily infiltrated, leading to obliteration of white pulp and a beefy red gross appearance. Hepatic portal triads are also involved frequently.

Immunophenotype. Hairy cell leukemias typically express the pan-B-cell markers CD19 and CD20, surface Ig (usually IgG), and certain relatively distinctive markers, such as CD11c, CD25, CD103, and annexin A1.

Clinical Features. Clinical manifestations result largely from infiltration of the bone marrow, liver, and spleen. *Splenomegaly*, often massive, is the most common and sometimes the only abnormal physical finding. *Hepatomegaly* is less common and not as marked; lymphadenopathy is rare. *Pancytopenia* resulting from marrow involvement and splenic sequestration is seen in more than half the cases. About one third of those affected present with *infections*. There is an increased incidence of atypical mycobacterial infections, possibly related to frequent unexplained monocytopenia.

Hairy cell leukemia follows an indolent course. For unclear reasons, this tumor is exceptionally sensitive to "gentle" chemotherapeutic regimens, which produce long-lasting remissions. Tumors often relapse after 5 or more years, yet generally respond well when retreated with the same agents, a feature that is highly unusual among human cancers. BRAF inhibitors appear to produce excellent responses in tumors that have failed conventional chemotherapy. The overall prognosis is excellent.

Peripheral T-Cell and NK-Cell Neoplasms

These categories include a heterogeneous group of neoplasms having phenotypes resembling mature T cells or NK cells. Peripheral T-cell tumors make up about 5% to 10% of NHLs in the United States and Europe, while NK cell tumors are rare. By contrast, for unknown reasons both T cell and NK cell tumors are relatively more common in the Far East. Only the most common diagnoses and those of particular pathogenetic interest will be discussed.

Peripheral T-Cell Lymphoma, Unspecified

Although the WHO classification includes a number of distinct peripheral T-cell neoplasms, many of these lymphomas are not easily categorized and are lumped into a "wastebasket" diagnosis, *peripheral T-cell lymphoma, unspecified*. As might be expected, no morphologic feature is pathognomonic, but certain findings are characteristic. These tumors efface lymph nodes diffusely and are typically composed of a pleomorphic mixture of variably sized malignant T cells (Fig. 13-22). There is often a prominent infiltrate of reactive cells, such as eosinophils and macrophages, probably attracted by tumor-derived cytokines. Brisk neoangiogenesis may also be seen.

By definition, all peripheral T-cell lymphomas are derived from mature T cells. They usually express CD2, CD3, CD5, and either αβ or γδ T-cell receptors. Some also express CD4 or CD8; such tumors are taken to be of helper or cytotoxic T-cell origin, respectively. However, many tumors have phenotypes that do not resemble any known normal T cell. In difficult cases where the differential diagnosis lies between lymphoma and a florid reactive process, DNA analysis is used to confirm the presence of clonal T-cell receptor rearrangements.

Most patients present with generalized lymphadenopathy, sometimes accompanied by eosinophilia, pruritus, fever, and weight loss. Although cures of peripheral T-cell lymphoma have been reported, these tumors have a significantly worse prognosis than comparably aggressive mature B-cell neoplasms (e.g., diffuse large B-cell lymphoma).

Anaplastic Large-Cell Lymphoma (ALK Positive)

This uncommon entity is defined by the presence of rearrangements in the *ALK* gene on chromosome 2p23. These

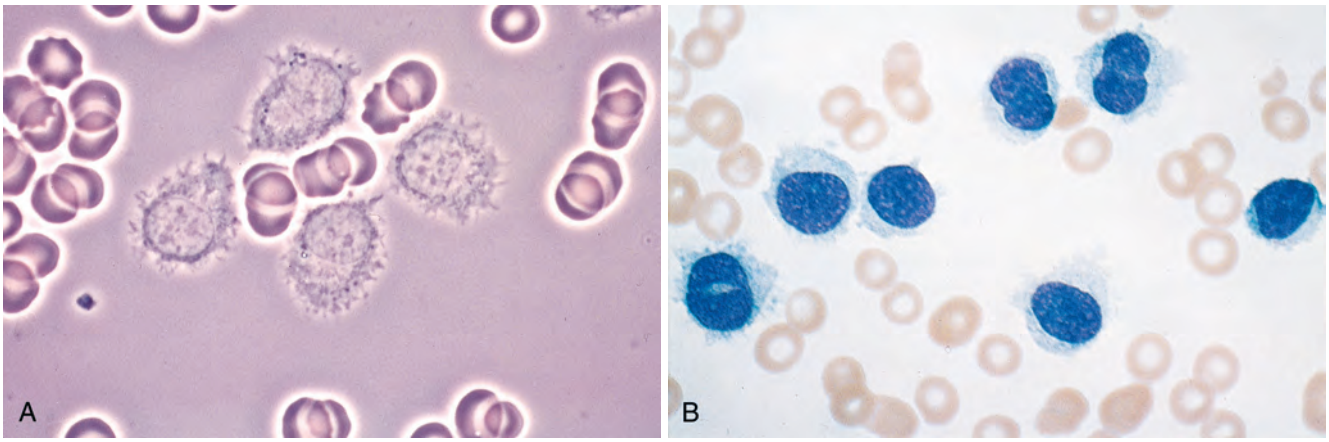

Figure 13-21 Hairy cell leukemia (peripheral blood smear). **A,** Phase-contrast microscopy shows tumor cells with fine hairlike cytoplasmic projections. **B,** In stained smears, these cells have round or folded nuclei and modest amounts of pale blue, agranular cytoplasm.