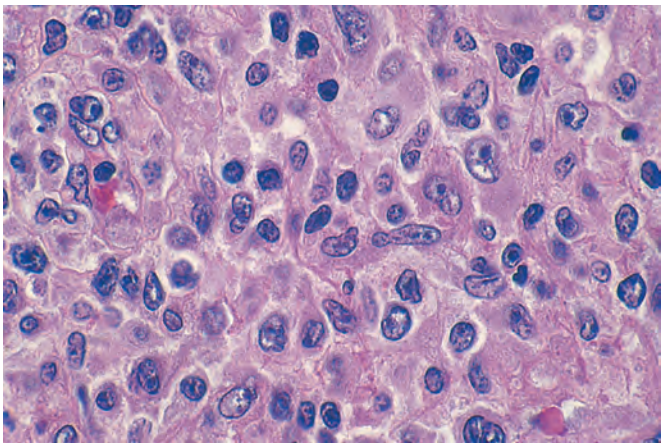

Figure 13-22 Peripheral T-cell lymphoma, unspecified (lymph node). A spectrum of small, intermediate, and large lymphoid cells, many with irregular nuclear contours, is visible.

rearrangements break the *ALK* locus and lead to the formation of chimeric genes encoding ALK fusion proteins, constitutively active tyrosine kinases that trigger the RAS and JAK/STAT signaling pathways.

As the name implies, this tumor is typically composed of large anaplastic cells, some containing horseshoe-shaped nuclei and voluminous cytoplasm (so-called *hallmark cells*) (Fig. 13-23*A*). The tumor cells often cluster about venules and infiltrate lymphoid sinuses, mimicking the appearance of metastatic carcinoma. ALK is not expressed in normal lymphocytes; thus, the detection of ALK protein in tumor cells (Fig. 13-23*B*) is a reliable indicator of an *ALK* gene rearrangement.

T-cell lymphomas with *ALK* rearrangements tend to occur in children or young adults, frequently involve soft tissues, and carry a very good prognosis (unlike other aggressive peripheral T-cell neoplasms). The cure rate with chemotherapy is 75% to 80%. Inhibitors of ALK have been developed and are being evaluated as a form of selective, targeted therapy. Morphologically similar tumors lacking *ALK* rearrangements occur in older adults and have a substantially worse prognosis. Both the ALK+ and ALK- tumors usually express CD30, a member of the TNF receptor family; of note, recombinant antibodies that bind and kill CD30-expressing cells have produced promising responses in patients with anaplastic large cell lymphoma and Hodgkin lymphoma, another CD30+ tumor (described later).

Adult T-Cell Leukemia/Lymphoma

This neoplasm of CD4+ T cells is only observed in adults infected by human T-cell leukemia retrovirus type 1 (HTLV-1), which was discussed in Chapter 7. It occurs mainly in regions where HTLV-1 is endemic, namely southern Japan, West Africa, and the Caribbean basin. Common findings include skin lesions, generalized lymphadenopathy, hepatosplenomegaly, peripheral blood lymphocytosis, and hypercalcemia. The appearance of the tumor cells varies, but cells with multilobated nuclei ("cloverleaf" or "flower" cells) are frequently observed. The tumor cells contain clonal HTLV-1 provirus, which is believed to play a critical pathogenic role. Notably, HTLV-1 encodes a protein called Tax that is a potent activator of NF-κB, which, as previously discussed, enhances lymphocyte growth and survival.

Most patients present with rapidly progressive disease that is fatal within months to 1 year despite aggressive chemotherapy. Less commonly, the tumor involves only the skin and follows a much more indolent course, like that of mycosis fungoides (described below). It should be noted that in addition to adult T-cell leukemia/lymphoma, HTLV-1 infection sometimes gives rise to a progressive demyelinating disease of the central nervous system and spinal cord (Chapter 28).

Mycosis Fungoides/Sézary Syndrome

Mycosis fungoides and Sézary syndrome are different manifestations of a tumor of CD4+ helper T cells that home to the skin. Clinically, the cutaneous lesions of *mycosis fungoides* typically progress through three somewhat distinct stages, an inflammatory *premycotic phase*, a *plaque phase*, and a *tumor phase* (Chapter 25). Histologically,

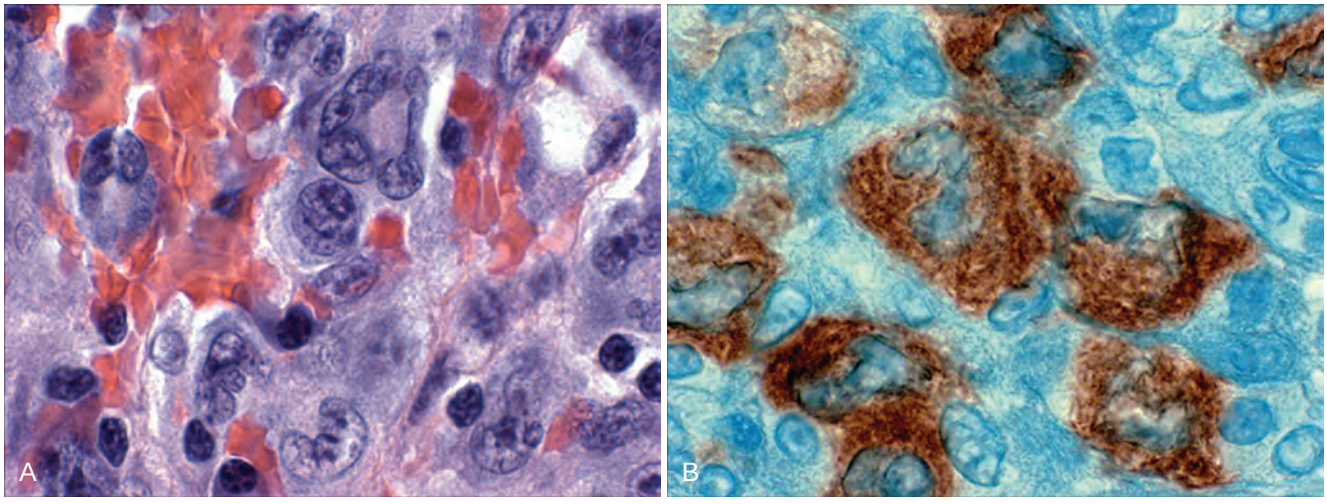

Figure 13-23 Anaplastic large-cell lymphoma. **A,** Several "hallmark" cells with horseshoe-like or "embryoid" nuclei and abundant cytoplasm lie near the center of the field. **B,** Immunohistochemical stain demonstrating the presence of ALK fusion protein. (Courtesy Dr. Jeffrey Kutok, Department of Pathology, Brigham and Women's Hospital, Boston, Mass.)