The diagnosis of anaplastic large T/null-cell lymphoma is made when an expert hematopathologist recognizes the typical morphologic picture and a T-cell or null-cell immunophenotype with CD30 positivity. Documentation of the t(2;5) and/or overexpression of ALK protein confirm the diagnosis. Some diffuse large B-cell lymphomas can also have an anaplastic appearance but have the same clinical course or response to therapy as other diffuse large B-cell lymphomas. A small percentage of anaplastic lymphomas are ALK negative.

Patients with anaplastic large T/null-cell lymphoma are typically young (median age, 33 years) and male (~70%). Some 50% of patients present in stage I/II, and the remainder present with more extensive disease. Systemic symptoms and elevated LDH levels are seen in about one-half of patients. Bone marrow and the gastrointestinal tract are rarely involved, but skin involvement is frequent. Some patients with disease confined to the skin have a different and more indolent disorder that has been termed *cutaneous anaplastic large T/null-cell lymphoma* and might be related to lymphomatoid papulosis.

TREATMENT ANAPLASTIC LARGE T/NULL-CELL LYMPHOMA

Treatment regimens appropriate for other aggressive lymphomas, such as diffuse large B-cell lymphoma, should be used in patients with anaplastic large T/null-cell lymphoma, with the exception that the B-cell–specific antibody, rituximab, is omitted. Surprisingly, given the anaplastic appearance, this disorder has the best survival rate of any aggressive lymphoma. The 5-year survival is >75%. While traditional prognostic factors such as the IPI predict treatment outcome, overexpression of the ALK protein is an important prognostic factor, with patients overexpressing this protein having a superior treatment outcome. The ALK inhibitor crizotinib appears highly active as well. In addition, the CD30 immunotoxin, brentuximab vedotin, is active in the disease.

Peripheral T-Cell Lymphoma The peripheral T-cell lymphomas make up a heterogeneous morphologic group of aggressive neoplasms that share a mature T-cell immunophenotype. They represent ~7% of all cases of non-Hodgkin's lymphoma. A number of distinct clinical syndromes are included in this group of disorders. Table 134-10 shows the clinical characteristics of patients with peripheral T-cell lymphoma.

The diagnosis of peripheral T-cell lymphoma, or any of its specific subtypes, requires an expert hematopathologist, an adequate biopsy, and immunophenotyping. Most peripheral T-cell lymphomas are CD4+, but a few will be CD8+, both CD4+ and CD8+, or have an NK cell immunophenotype. No characteristic genetic abnormalities have yet been identified, but translocations involving the T-cell antigen receptor genes on chromosomes 7 or 14 may be detected. The differential diagnosis of patients suspected of having peripheral T-cell lymphoma includes reactive T-cell infiltrative processes. In some cases, demonstration of a monoclonal T-cell population using T-cell receptor gene rearrangement studies will be required to make a diagnosis.

The initial evaluation of a patient with a peripheral T-cell lymphoma should include the studies in Table 134-11 for staging patients with non-Hodgkin's lymphoma. Unfortunately, patients with peripheral T-cell lymphoma usually present with adverse prognostic factors, with >80% of patients having an IPI score ≥2 and >30% having an IPI score ≥4. As this would predict, peripheral T-cell lymphomas are associated with a poor outcome, and only 25% of the patients survive 5 years after diagnosis. Treatment regimens are the same as those used for diffuse large B-cell lymphoma (omitting rituximab), but patients with peripheral T-cell lymphoma have a poorer response to treatment. Because of this poor treatment outcome, hematopoietic stem cell transplantation is often considered early in the care of young patients.

A number of specific clinical syndromes are seen in the peripheral T-cell lymphomas. *Angioimmunoblastic T-cell lymphoma* is one of the more common subtypes, making up ~20% of T-cell lymphomas. These patients typically present with generalized lymphadenopathy, fever, weight loss, skin rash, and polyclonal hypergammaglobulinemia. In some cases, it is difficult to separate patients with a reactive disorder from those with true lymphoma.

Extranodal T/NK-cell lymphoma of nasal type has also been called *angiocentric lymphoma* and was previously termed *lethal midline granuloma*. This disorder is more frequent in Asia and South America than in the United States and Europe. EBV is thought to play an etiologic role. Although most frequent in the upper airway, it can involve other organs. The course is aggressive, and patients frequently have the hemophagocytic syndrome. When marrow and blood involvement occur, distinction between this disease and leukemia might be difficult. Some patients will respond to aggressive combination chemotherapy regimens, but the overall outlook is poor.

Enteropathy-type intestinal T-cell lymphoma is a rare disorder that occurs in patients with untreated gluten-sensitive enteropathy. Patients are frequently wasted and sometimes present with intestinal perforation. The prognosis is poor. *Hepatosplenic γδ T-cell lymphoma* is a systemic illness that presents with sinusoidal infiltration of the liver, spleen, and bone marrow by malignant T cells. Tumor masses generally do not occur. The disease is associated with systemic symptoms and is often difficult to diagnose. Treatment outcome is poor. *Subcutaneous panniculitis-like T-cell lymphoma* is a rare disorder that is often confused with panniculitis. Patients present with multiple subcutaneous nodules, which progress and can ulcerate. Hemophagocytic syndrome is common. Response to therapy is poor. The development of the hemophagocytic syndrome (profound anemia, ingestion of erythrocytes by monocytes and macrophages, elevated ferritin levels) in the course of any peripheral T-cell lymphoma is generally associated with a fatal outcome.

HODGKIN'S LYMPHOMA

Classical Hodgkin's Lymphoma Hodgkin's lymphoma occurs in 9000 patients in the United States each year, and the disease does not appear to be increasing in frequency. Most patients present with palpable lymphadenopathy that is nontender; in most patients, these lymph nodes are in the neck, supraclavicular area, and axilla. More than half the patients will have mediastinal adenopathy at diagnosis, and this is sometimes the initial manifestation. Subdiaphragmatic presentation of Hodgkin's lymphoma is unusual and more common in older males. One-third of patients present with fevers, night sweats, and/or weight loss—B symptoms in the Ann Arbor staging classification (Table 134-8). Occasionally, Hodgkin's lymphoma can present as a fever of unknown origin. This is more common in older patients who are found to have mixed-cellularity Hodgkin's lymphoma in an abdominal site. Rarely, the fevers persist for days to weeks, followed by afebrile intervals and then recurrence of the fever. This pattern is known as *Pel-Ebstein fever*. Hodgkin's lymphoma can occasionally present with unusual manifestations. These include severe and unexplained itching, cutaneous disorders such as erythema nodosum and ichthyosiform atrophy, paraneoplastic cerebellar degeneration and other distant effects on the CNS, nephrotic syndrome, immune hemolytic anemia and thrombocytopenia, hypercalcemia, and pain in lymph nodes on alcohol ingestion.

The diagnosis of Hodgkin's lymphoma is established by review of an adequate biopsy specimen by an expert hematopathologist. In the United States, most patients have nodular sclerosing Hodgkin's lymphoma, with a minority of patients having mixed-cellularity Hodgkin's lymphoma. Lymphocyte-predominant and lymphocyte-depleted Hodgkin's lymphoma are rare. Mixed-cellularity Hodgkin's lymphoma or lymphocyte-depletion Hodgkin's lymphoma are seen more frequently in patients infected by HIV (Fig. 134-11). Hodgkin's lymphoma is a tumor characterized by rare neoplastic cells of B-cell origin (immunoglobulin genes are rearranged but not expressed) in a tumor mass that is largely polyclonal inflammatory infiltrate, probably a reaction to cytokines produced by the tumor cells. The differential diagnosis of a lymph node biopsy suspicious for Hodgkin's lymphoma includes inflammatory processes, mononucleosis, non-Hodgkin's lymphoma, phenytoin-induced adenopathy, and nonlymphomatous malignancies.