the epidermis and upper dermis are infiltrated by neoplastic T cells, which often have a cerebriform appearance due to marked infolding of the nuclear membrane. Late disease progression is characterized by extracutaneous spread, most commonly to lymph nodes and bone marrow.

Sézary syndrome is a variant in which skin involvement is manifested as a *generalized exfoliative erythroderma*. In contrast to mycosis fungoides, the skin lesions rarely proceed to tumefaction, and there is an associated leukemia of "Sézary" cells with characteristic cerebriform nuclei.

The tumor cells express the adhesion molecule cutaneous leukocyte antigen (CLA) and the chemokine receptors CCR4 and CCR10, all of which contribute to the homing of normal CD4+ T cells to the skin. Although cutaneous disease dominates the clinical picture, sensitive molecular analyses have shown that the tumor cells circulate through the blood, marrow, and lymph nodes even early in the course. Nevertheless, these are indolent tumors, with a median survival of 8 to 9 years. Transformation to aggressive T-cell lymphoma occurs occasionally as a terminal event.

Large Granular Lymphocytic Leukemia

T-cell and NK-cell variants of this rare neoplasm are recognized, both of which occur mainly in adults. Individuals with T-cell disease usually present with mild to moderate lymphocytosis and splenomegaly. Lymphadenopathy and hepatomegaly are usually absent. NK-cell disease often presents in an even more subtle fashion, with little or no lymphocytosis or splenomegaly.

Recent work has shown that 30% to 40% of large granular lymphocytic leukemias have acquired mutations in the transcription factor STAT3, which functions downstream of cytokine receptors. These mutations occur in both T-cell and NK-cell forms of the disease and appear to result in cytokine-independent activation of STAT3, which is now postulated to have a major role in the pathogenesis of these heretofore mysterious proliferations.

The tumor cells are large lymphocytes with abundant blue cytoplasm and a few coarse azurophilic granules, best seen in peripheral blood smears. The marrow usually contains sparse interstitial lymphocytic infiltrates, which can be difficult to appreciate without immunohistochemical stains. Infiltrates are also usually present in the spleen and liver. As might be expected, T-cell variants are CD3+, whereas NK-cell large granular lymphocytic leukemias are CD3–, CD56+.

Despite the relative paucity of marrow infiltration, ***neutropenia* and *anemia* dominate the clinical picture**. Neutropenia is often accompanied by a striking decrease in late myeloid forms in the marrow. Rarely, *pure red cell aplasia* is seen. There is also an increased incidence of rheumatologic disorders. Some patients with *Felty syndrome*, a triad of rheumatoid arthritis, splenomegaly, and neutropenia, have this disorder as an underlying cause. The basis for these varied clinical abnormalities is unknown, but autoimmunity, provoked in some way by the tumor, seems likely.

The course is variable, being largely dependent on the severity of the cytopenias and their responsiveness to low-dose chemotherapy or steroids. In general, tumors of T-cell origin pursue an indolent course, whereas NK-cell tumors behave more aggressively.

Extranodal NK/T-Cell Lymphoma

This neoplasm is rare in the United States and Europe, but constitutes as many as 3% of NHLs in Asia. It presents most commonly as a destructive nasopharyngeal mass; less common sites of presentation include the testis and the skin. The tumor cell infiltrate typically surrounds and invades small vessels, leading to extensive *ischemic necrosis*. In touch preparations, *large azurophilic granules* are seen in the cytoplasm of the tumor cells that resemble those found in normal NK cells.

Extranodal NK/T-cell lymphoma is highly associated with EBV. Within individual patients, all of the tumor cells contain identical EBV episomes, indicating that the tumor originates from a single EBV-infected cell. How EBV gains entry is uncertain, since the tumor cells do not express CD21, the surface protein that serves as the B-cell EBV receptor. Most tumors are CD3– and lack T-cell receptor rearrangements and express NK-cell markers, supporting an NK-cell origin. No consistent chromosome aberration has been described.

Most extranodal NK/T-cell lymphomas are highly aggressive neoplasms that respond well to radiation therapy but are resistant to chemotherapy. Thus, the prognosis is poor in patients with advanced disease.

KEY CONCEPTS

Uncommon Lymphoid Neoplasms

Mantle cell lymphoma: Tumor of naive B cells that pursues a moderately aggressive course and is highly associated with translocations involving the cyclin D1 gene

Marginal zone lymphoma: Indolent tumors of antigen-primed B cells that arise at sites of chronic immune stimulation and often remain localized for long periods of time

Hairy cell leukemia: Morphologically distinct, very indolent tumor of mature B cells that is highly associated with mutations in the BRAF serine/threonine kinase

Peripheral NK/T cell lymphomas and leukemias

- Anaplastic large cell lymphoma: Aggressive T cell tumor, associated in a subset with activating mutations in the ALK tyrosine kinase
- Adult T cell leukemia/lymphoma: Aggressive tumor of CD4+ T cells that is uniformly associated with HTLV-1 infection
- Large granular lymphocytic leukemia: Indolent tumor of cytotoxic T cells or NK cells that is associated with mutations in the transcription factor STAT3 and with autoimmune phenomena and cytopenias
- Extranodal NK/T cell lymphoma: Aggressive tumor, usually derived from NK cells, that is strongly associated with EBV infection

Hodgkin Lymphoma

Hodgkin lymphoma (HL) encompasses a group of lymphoid neoplasms that differ from NHL in several respects (Table 13-7). While NHLs frequently occur at extranodal sites and spread in an unpredictable fashion, **HL arises in a single node or chain of nodes and spreads first to**