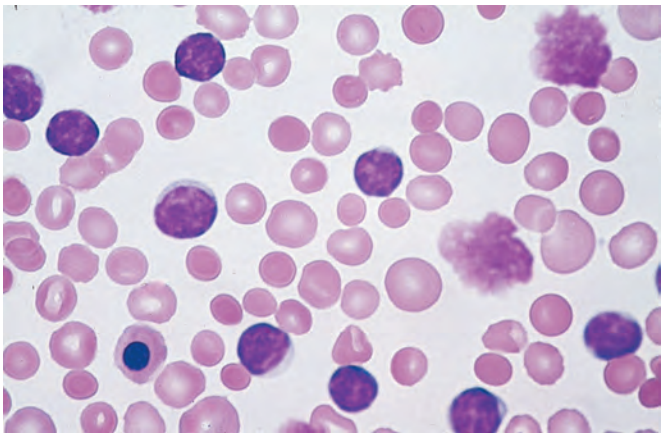

Figure 13-8 Chronic lymphocytic leukemia. This peripheral blood smear is flooded with small lymphocytes with condensed chromatin and scant cytoplasm. A characteristic finding is the presence of disrupted tumor cells (smudge cells), two of which are present in this smear. A coexistent autoimmune hemolytic anemia (Chapter 14) explains the presence of spherocytes (hyperchromatic, round erythrocytes). A nucleated erythroid cell is present in the lower left-hand corner of the field. In this setting, circulating nucleated red cells could stem from premature release of progenitors in the face of severe anemia, marrow infiltration by tumor (leukoerythroblastosis), or both.

Immunophenotype. CLL/SLL has a distinctive immunophenotype. The tumor cells express the pan B-cell markers CD19 and CD20, as well as CD23 and CD5, the latter a marker that is found on a small subset of normal B cells. Low-level expression of surface Ig (usually IgM or IgM and IgD) is also typical.

Clinical Features. Patients are often asymptomatic at diagnosis. When symptoms appear, they are nonspecific and include easy fatigability, weight loss, and anorexia. Generalized lymphadenopathy and hepatosplenomegaly are present in 50% to 60% of symptomatic patients. The leukocyte count is highly variable; leukopenia can be seen in individuals with SLL and marrow involvement, while counts in excess of 200,000/mm^3 are sometimes seen in CLL patients with heavy tumor burdens. A small monoclonal Ig "spike" is present in the blood of some patients.

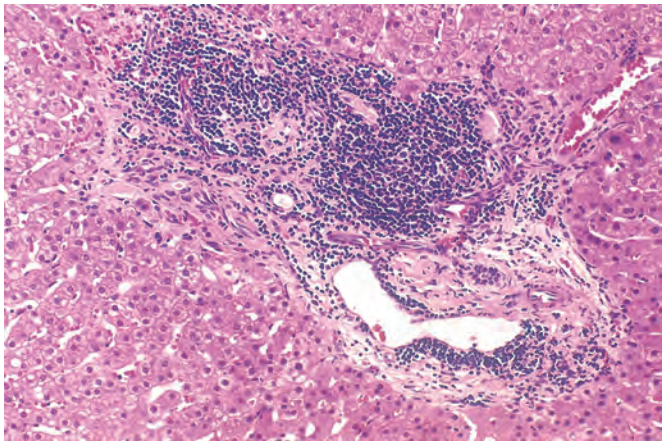

Figure 13-9 Small lymphocytic lymphoma/chronic lymphocytic leukemia involving the liver. Low-power view of a typical periportal lymphocytic infiltrate. (Courtesy Dr. Mark Fleming, Department of Pathology, Children's Hospital, Boston, Mass.)

At the other end of the spectrum are asymptomatic patients with monoclonal B cells in their peripheral blood but in numbers that are too few to merit the diagnosis of CLL. These abnormal B cells often have some of the same genetic aberrations that are seen in CLL, such as 13q deletions and trisomy 12, yet only about 1% of such patients progress to symptomatic CLL per year, presumably due to acquisition of additional genetic lesions.

CLL/SLL disrupts normal immune function through uncertain mechanisms. Hypogammaglobulinemia is common and contributes to an increased susceptibility to infections, particularly those caused by bacteria. Conversely, 10% to 15% of patients develop hemolytic anemia or thrombocytopenia due to autoantibodies made by non-neoplastic B cells.

The course and prognosis are extremely variable and depend primarily on the clinical stage. Overall median survival is 4 to 6 years, but is more than 10 years in individuals with minimal tumor burdens at diagnosis. Other variables that correlate with a worse outcome include (1) the presence of deletions of 11q and 17p, (2) a lack of somatic hypermutation, (3) the expression of ZAP-70, a protein that augments signals produced by the Ig receptor, and (4) the presence of *NOTCH1* mutations. Symptomatic patients are generally treated with "gentle" chemotherapy and immunotherapy with antibodies against proteins found on the surface of CLL/SLL cells, particularly CD20. Hematopoietic stem cell transplantation is being offered to the relatively young. The most promising new therapy is BTK inhibitors, described earlier.

Another factor that impacts patient survival is the tendency of CLL/SLL to transform to a more aggressive tumor. Most commonly this takes the form of a transformation to diffuse large B-cell lymphoma, so-called *Richter syndrome* (approximately 5% to 10% of patients). Transformation to diffuse large B-cell lymphoma is often heralded by the development of a rapidly enlarging mass within a lymph node or the spleen. Transformation probably stems from the acquisition of additional, still mutations that increase growth. Large-cell transformation is an ominous event, with most patients surviving less than 1 year.

Follicular Lymphoma

Follicular lymphoma is the most common form of indolent NHL in the United States, affecting 15,000 to 20,000 individuals per year. It usually presents in middle age and afflicts males and females equally. It is less common in Europe and rare in Asian populations.

Pathogenesis. **Follicular lymphoma likely arises from germinal center B cells and is strongly associated with chromosomal translocations involving *BCL2*.** Its hallmark is a (14;18) translocation that juxtaposes the *IGH* locus on chromosome 14 and the *BCL2* locus on chromosome 18. The t(14;18) is seen in up to 90% of follicular lymphomas, and leads to overexpression of BCL2 (see Fig. 13-12). BCL2 antagonizes apoptosis (Chapter 7) and promotes the survival of follicular lymphoma cells. Notably, while normal germinal centers contain numerous B cells undergoing apoptosis, follicular lymphoma is characteristically devoid of apoptotic cells. Deep sequencing of follicular lymphoma genomes have identified mutations in the *MLL2* gene in about 90% of cases as well. *MLL2* encodes a histone