Although most chromosomal aberrations in ALL alter the function of transcription factors, the t(9;22) instead creates a fusion gene that encodes a constitutively active BCR-ABL tyrosine kinase (described in more detail under chronic myelogenous leukemia). In B-ALL, the BCR-ABL protein is usually 190 kDa in size and has stronger tyrosine kinase activity than the form of BCR-ABL that is found in chronic myelogenous leukemia, in which a BCR-ABL protein of 210 kDa in size is usually seen. Treatment of t(9;22)-positive ALLs with BCR-ABL kinase inhibitors in combination with conventional chemotherapy is highly effective and has greatly improved the outcome for this molecular subtype of B-ALL in children. The outlook for adults with ALL remains more guarded, in part because of differences in the molecular pathogenesis of adult and childhood ALL, but also because older adults cannot tolerate the very intensive chemotherapy regimens that are curative in children.

Peripheral B-Cell Neoplasms

Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) differ only in the degree of peripheral blood lymphocytosis. Most affected patients have sufficient lymphocytosis to fulfill the diagnostic requirement for CLL (absolute lymphocyte count > 5000 per mm^3). **CLL is the most common leukemia of adults in the Western world.** There are about 15,000 new cases of CLL each year in the United States. The median age at diagnosis is 60 years, and there is a 2:1 male predominance. In contrast, SLL constitutes only 4% of NHLs. CLL/SLL is much less common in Japan and other Asian countries than in the West.

Pathogenesis. Unlike most other lymphoid malignancies, chromosomal translocations are rare in CLL/SLL. **The most common genetic anomalies are deletions of 13q14.3, 11q, and 17p, and trisomy 12q.** Molecular characterization of the region deleted on chromosome 13 has implicated two microRNAs, miR-15a and miR-16-1, as possible tumor suppressor genes. DNA sequencing has revealed that the Ig genes of some CLL/SLL are somatically hypermutated, whereas others are not, suggesting that the cell of origin may be either a postgerminal center memory B cell or a naive B cell. For unclear reasons, tumors with unmutated Ig segments (those putatively of naive B-cell origin) pursue a more aggressive course. Deep sequencing of CLL genomes has also revealed gain-of-function mutations involving the NOTCH1 receptor in 10% to 18% of tumors, as well as frequent mutations in genes that regulate RNA splicing.

The growth of CLL/SLL cells is largely confined to proliferation centers (described below), where tumor cells receive critical cues from the microenvironment. Stromal cells in proliferation centers seem to express a variety of factors that stimulate the activity of the transcription factor NF-κB, which promotes cell growth and survival. In addition, experimental models of CLL suggest that tumor cells rely on signals generated by the B-cell receptor (membrane bound immunoglobulin) for growth and survival. These signals are transduced by a cascade of kinases that include the Bruton tyrosine kinase (BTK), which is defective in patients with congenital X-linked agammaglobulinemia (Chapter 6). Of note, BTK inhibitors now being tested in clinical trials have produced sustained responses in a high fraction of CLL patients, indicating that human CLL cells are also dependent on this signaling pathway.

MORPHOLOGY

Lymph nodes are diffusely effaced by an infiltrate of predominantly small lymphocytes 6 to 12 μm in diameter with round to slightly irregular nuclei, condensed chromatin, and scant cytoplasm (Fig. 13-7). Admixed are variable numbers of larger activated lymphocytes that often gather in loose aggregates referred to as **proliferation centers**, which contain mitotically active cells. When present, **proliferation centers are pathognomonic for CLL/SLL**. The blood contains large numbers of small round lymphocytes with scant cytoplasm (Fig. 13-8). Some of these cells are usually disrupted in the process of making smears, producing so-called **smudge cells**. The bone marrow is almost always involved by interstitial infiltrates or aggregates of tumor cells. Infiltrates are also virtually always seen in the splenic white and red pulp and the hepatic portal tracts (Fig. 13-9).

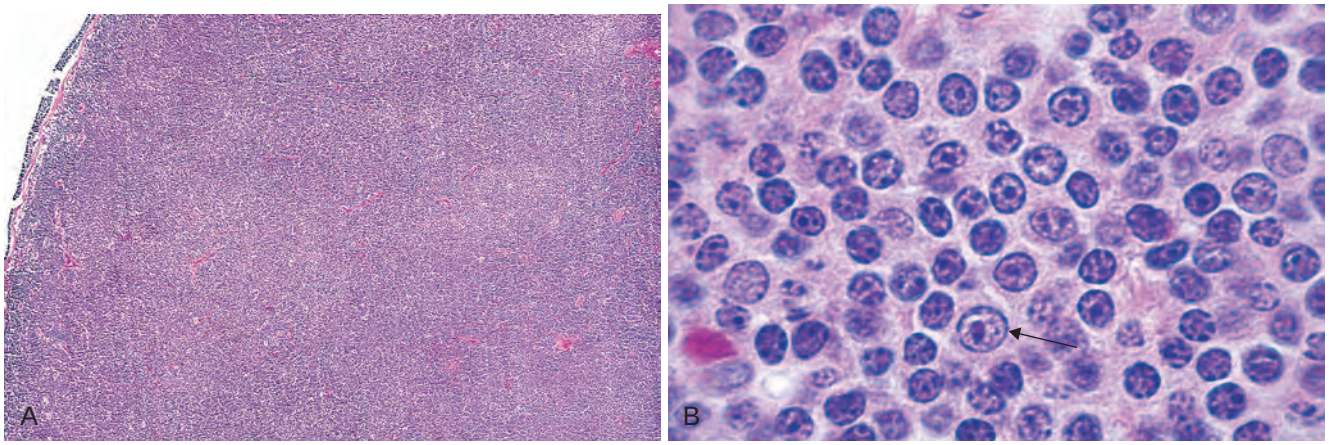

Figure 13-7 Small lymphocytic lymphoma/chronic lymphocytic leukemia (lymph node). **A,** Low-power view shows diffuse effacement of nodal architecture. **B,** At high power the majority of the tumor cells are small round lymphocytes. A "prolymphocyte," a larger cell with a centrally placed nucleolus, is also present in this field *(arrow)*. (**A,** Courtesy Dr. José Hernandez, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)