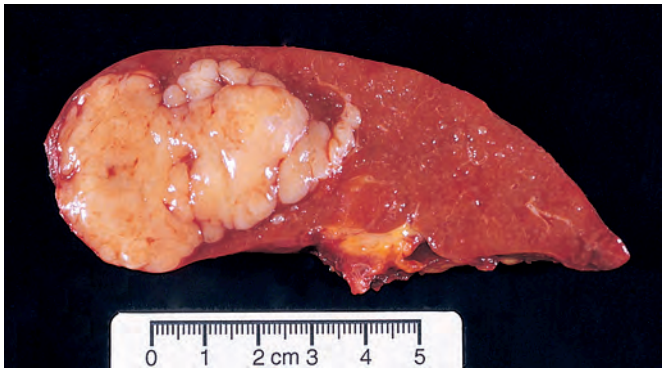

Figure 13-14 Diffuse large B-cell lymphoma involving the spleen. The isolated large mass is typical. In contrast, indolent B-cell lymphomas usually produce multifocal expansion of white pulp (see Fig. 13-11). (Courtesy Dr. Mark Fleming, Department of Pathology, Children's Hospital, Boston, Mass.)

virtually anywhere in the body. Waldeyer ring, the oropharyngeal lymphoid tissue that includes the tonsils and adenoids, is involved commonly. Primary or secondary involvement of the liver and spleen may take the form of large destructive masses (Fig. 13-14). Extranodal sites include the gastrointestinal tract, skin, bone, brain, and other tissues. Bone marrow involvement is relatively uncommon and usually occurs late in the course. Rarely, a leukemic picture emerges.

DLBCLs are aggressive tumors that are rapidly fatal without treatment. With intensive combination chemotherapy, 60% to 80% of patients achieve a complete remission, and 40% to 50% are cured. Adjuvant therapy with anti-CD20 antibody improves both the initial response and the overall outcome. Individuals with limited disease fare better than those with widespread disease or bulky tumor masses. Expression profiling has identified distinct molecular subtypes with differing clinical outcomes and has provided the rationale for new therapies directed at inhibiting the NF-κB and B cell receptor signaling pathways. Of note, about 5% of DLBCLs have *MYC* translocations, and these cases of DLBCL may be difficult to distinguish from Burkitt lymphoma (described later) by conventional diagnostic tests. In fact, recent data suggest that DLBCLs with *MYC* translocations have a worse prognosis than those without and may be better treated with chemotherapy regimens that are now standard for Burkitt lymphoma.

Burkitt Lymphoma

Within the category of Burkitt Lymphoma fall (1) African (endemic) Burkitt lymphoma, (2) sporadic (nonendemic) Burkitt lymphoma, and (3) a subset of aggressive lymphomas occurring in individuals infected with HIV. Burkitt lymphomas occurring in each of these settings are histologically identical but differ in some clinical, genotypic, and virologic characteristics.

Pathogenesis. **All forms of Burkitt lymphoma are highly associated with translocations of the *MYC* gene on chromosome 8 that lead to increased MYC protein levels.** MYC is a master transcriptional regulator that increases the expression of genes that are required for aerobic glycolysis, the so-called Warburg effect (Chapter 7). When nutrients such as glucose and glutamine are available, Warburg metabolism allow cells to biosynthesize all of the building blocks—nucleotides, lipids, proteins—that are needed for growth and cell division. Consequently, Burkitt lymphoma is believed to be the fastest growing human tumor. The translocation partner for *MYC* is usually the IgH locus [t(8;14)] but may also be the Ig κ [t(2;8)] or λ [t(8;22)] light chain loci. The breakpoints in the IgH locus in sporadic Burkitt lymphoma are usually found in the class switch regions, whereas the breakpoints in endemic Burkitt lymphoma tend to lie within more 5′ V(D)J sequences. The basis for this subtle molecular distinction is not known, but both types of translocations can be induced in germinal center B cells by AID, a specialized DNA-modifying enzyme required for both Ig class switching and somatic hypermutation (see earlier). The net effect of these translocations is similar; the *MYC* coding sequence is repositioned adjacent to strong Ig promoter and enhancer elements, which drive increased *MYC* expression. In addition, the translocated *MYC* allele often harbors point mutations that further increase its activity.

Essentially all endemic Burkitt lymphomas are latently infected with EBV, which is also present in about 25% of HIV-associated tumors and 15% to 20% of sporadic cases. The configuration of the EBV DNA is identical in all tumor cells within individual cases, indicating that infection precedes transformation. Although this places EBV at the "scene of the crime," its precise role in the genesis of Burkitt lymphoma remains poorly understood.

MORPHOLOGY

Involved tissues are effaced by a diffuse infiltrate of intermediate-sized lymphoid cells 10 to 25 μm in diameter with round or oval nuclei, coarse chromatin, several nucleoli, and a moderate amount of cytoplasm (Fig. 13-15). **The tumor exhibits a high mitotic index and contains numerous apoptotic cells**, the nuclear remnants of which are phagocytosed by interspersed benign macrophages. These phagocytes have abundant clear cytoplasm, creating a characteristic **"starry sky" pattern**. When the bone marrow is involved, aspirates reveal tumor cells with slightly clumped nuclear chromatin, two to five distinct nucleoli, and **royal blue cytoplasm containing clear cytoplasmic vacuoles**.

Immunophenotype. These are tumors of mature B cells that express surface IgM, CD19, CD20, CD10, and BCL6, a phenotype consistent with a germinal center B-cell origin. Unlike other tumors of germinal center origin, Burkitt lymphoma almost always fails to express the antiapoptotic protein BCL2.

Clinical Features. Both endemic and sporadic Burkitt lymphomas are found mainly in children or young adults; overall, it accounts for about 30% of childhood NHLs in the United States. Most tumors manifest at extranodal sites. Endemic Burkitt lymphoma often presents as a mass involving the mandible and shows an unusual predilection for involvement of abdominal viscera, particularly the kidneys, ovaries, and adrenal glands. In contrast, sporadic Burkitt lymphoma most often appears as a mass involving the ileocecum and peritoneum. Involvement of the bone marrow and peripheral blood is uncommon, especially in endemic cases.

Burkitt lymphoma is very aggressive but responds well to intensive chemotherapy. Most children and young adults can be cured. The outcome is more guarded in older adults.