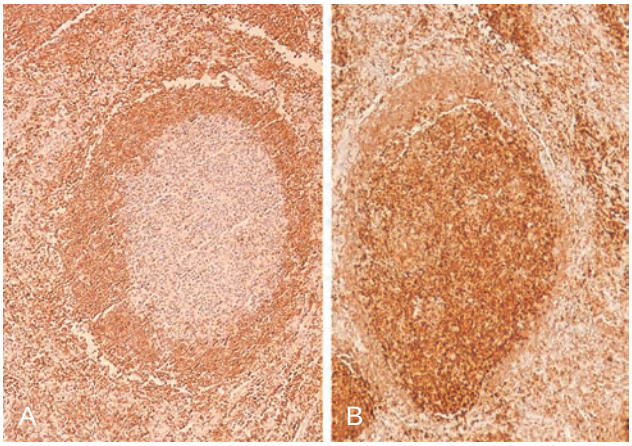

Figure 13-12 BCL2 expression in reactive and neoplastic follicles. BCL2 protein was detected by using an immunohistochemical technique that produces a brown stain. In reactive follicles **(A),** BCL2 is present in mantle zone cells but not follicular-center B cells, whereas follicular lymphoma cells **(B)** show strong BCL2 staining. (Courtesy Dr. Jeffrey Jorgenson, Department of Hematopathology, MD Anderson Cancer Center, Houston, Texas.)

predominance. The median patient age is about 60 years, but DLBCL also occurs in young adults and children.

Pathogenesis. Genetic, gene expression profiling, and immunohistochemical studies indicate that DLBCL is molecularly heterogeneous. One frequent pathogenic event is dysregulation of BCL6, a DNA-binding zinc-finger transcriptional repressor that is required for the formation of normal germinal centers. About 30% of DLBCLs contain various translocations that have in common a breakpoint in *BCL6* at chromosome 3q27. Acquired mutations in *BCL6* promoter sequences that abrogate *BCL6* autoregulation (an important negative-regulatory mechanism) are seen even more frequently. It is hypothesized that both types of lesions are inadvertent byproducts of somatic hypermutation that result in overexpression of *BCL6*, which has several important consequences. BCL6 represses the expression of factors that normally serve to promote germinal center B-cell differentiation, growth arrest, and apoptosis, and each of these effects is believed to contribute to the development of DLBCL. Mutations similar to those found in *BCL6* are also seen in multiple other oncogenes, including *MYC*, suggesting that somatic hypermutation in DLBCL cells is "mistargeted" to a wide variety of loci.

Another 10% to 20% of tumors are associated with the t(14;18) (discussed earlier under Follicular Lymphoma), which leads to the overexpression of the antiapoptotic protein BCL2. Tumors with *BCL2* rearrangements usually lack *BCL6* rearrangements, suggesting that these rearrangements define two distinct molecular classes of DLBCL. Some tumors with *BCL2* rearrangements may arise from unrecognized underlying follicular lymphomas, which frequently transform to DLBCL. Roughly 5% of DLBCLs are associated with translocations involving *MYC*; these tumors may have a distinctive biology and are discussed further under Burkitt Lymphoma (later). Finally, deep sequencing of DLBCL genomes has identified frequent mutations in genes encoding histone acetyltransferases such as p300 and CREBP, proteins that regulate gene expression by modifying histones and altering chromatin structure. This association has sparked interest in using drugs that target the epigenome as therapies for DLBCL.

MORPHOLOGY

The common features are a relatively **large cell size** (usually four to five times the diameter of a small lymphocyte) and a **diffuse pattern of growth** (Fig. 13-13). In other respects, substantial morphologic variation is seen. Most commonly, the tumor cells have a round or oval nucleus that appears vesicular due to margination of chromatin to the nuclear membrane, but large multilobated or cleaved nuclei are prominent in some cases. Nucleoli may be two to three in number and located adjacent to the nuclear membrane, or single and centrally placed. The cytoplasm is usually moderately abundant and may be pale or basophilic. More anaplastic tumors may even contain multinucleated cells with large inclusion-like nucleoli that resemble Reed-Sternberg cells (the malignant cell of Hodgkin lymphoma).

Immunophenotype. These mature B-cell tumors express CD19 and CD20 and show variable expression of germinal center B-cell markers such as CD10 and BCL6. Most have surface Ig.

Special Subtypes. Several subtypes of DLBCL are sufficiently distinctive to merit brief discussion.

- *Immunodeficiency-associated large B-cell lymphoma* occurs in the setting of severe T-cell immunodeficiency (e.g., advanced HIV infection and allogeneic bone marrow transplantation). The neoplastic B cells are usually infected with EBV, which plays a critical pathogenic role. Restoration of T-cell immunity may lead to regression of these proliferations.
- *Primary effusion lymphoma* presents as a malignant pleural or ascitic effusion, mostly in patients with advanced HIV infection or older adults. The tumor cells are often anaplastic in appearance and typically fail to express surface B- or T-cell markers, but have clonal IgH gene rearrangements. In all cases the tumor cells are infected with KSHV/HHV-8, which appears to have a causal role.

Clinical Features. DLBCL typically presents as a rapidly enlarging mass at a nodal or extranodal site. It can arise

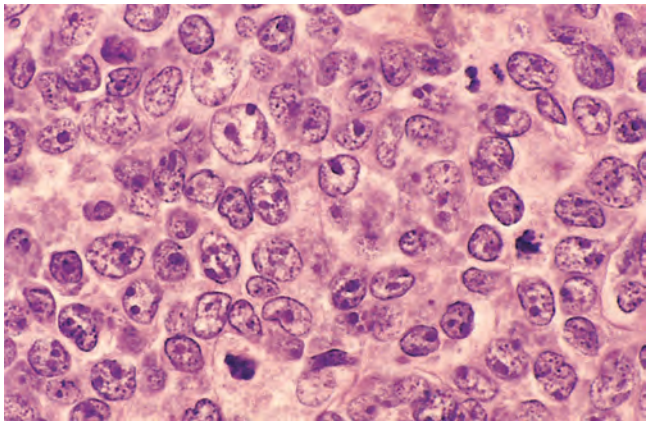

Figure 13-13 Diffuse large B-cell lymphoma. Tumor cells have large nuclei, open chromatin, and prominent nucleoli. (Courtesy Dr. Robert W. McKenna, Department of Pathology, University of Texas Southwestern Medical School, Dallas, Texas.)