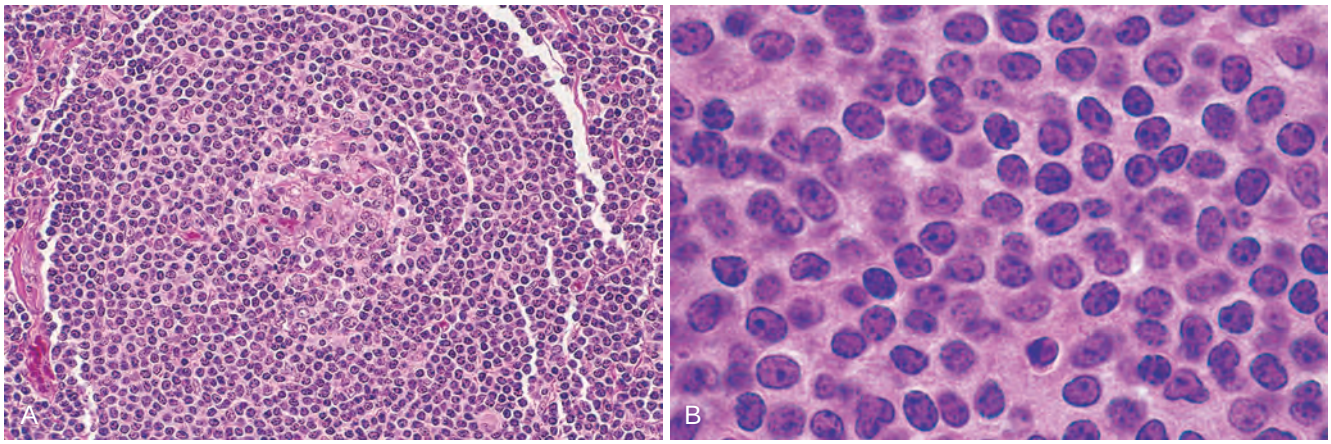

Figure 13-20 Mantle cell lymphoma. **A,** At low power, neoplastic lymphoid cells surround a small, atrophic germinal center, producing a mantle zone pattern of growth. **B,** High-power view shows a homogeneous population of small lymphoid cells with somewhat irregular nuclear outlines, condensed chromatin, and scant cytoplasm. Large cells resembling prolymphocytes (seen in chronic lymphocytic leukemia) and centroblasts (seen in follicular lymphoma) are absent.

Immunophenotype. Mantle cell lymphomas express high levels of cyclin D1. Most tumors are also express CD19, CD20, and moderately high levels of surface Ig (usually IgM and IgD with κ or λ light chain). It is usually CD5+ and CD23–, which help to distinguish it from CLL/SLL. The IgH genes lack somatic hypermutation, supporting an origin from a naive B cell.

Clinical Features. The most common presentation is painless lymphadenopathy. Symptoms related to involvement of the spleen (present in ~50% of cases) and gut are also common. The prognosis is poor; the median survival is only 3 to 4 years. This lymphoma is not curable with conventional chemotherapy, and most patients eventually succumb to organ dysfunction caused by tumor infiltration. The blastoid variant and a "proliferative" expression profiling signature are associated with even shorter survivals. Hematopoietic stem cell transplantation and proteasome inhibitors are newer therapeutic approaches that show some promise.

Marginal Zone Lymphomas

The category of marginal zone lymphoma encompasses a heterogeneous group of B-cell tumors that arise within lymph nodes, spleen, or extranodal tissues. The extranodal tumors were initially recognized at mucosal sites and are often referred to as mucosa-associated lymphoid tumors (or "MALTomas"). In most cases, the tumor cells show evidence of somatic hypermutation and are considered to be of memory B-cell origin.

Although all marginal zone lymphomas share certain features, those occurring at extranodal sites deserve special attention because of their unusual pathogenesis and three exceptional characteristics.

- They often arise within tissues involved by chronic inflammatory disorders of autoimmune or infectious etiology; examples include the salivary gland in Sjögren disease, the thyroid gland in Hashimoto thyroiditis, and the stomach in *Helicobacter* gastritis.
- They remain localized for prolonged periods, spreading systemically only late in their course.
- They may regress if the inciting agent (e.g., *Helicobacter pylori)* is eradicated.

These characteristics suggest that **extranodal marginal zone lymphomas arising in chronically inflamed tissues lie on a continuum between reactive lymphoid hyperplasia and full-blown lymphoma.** The disease begins as a polyclonal immune reaction. With the acquisition of still-unknown initiating mutations, a B-cell clone emerges that still depends on antigen-stimulated T-helper cells for signals that drive growth and survival. At this stage, withdrawal of the responsible antigen causes tumor involution. A clinically relevant example is found in gastric "MALToma," in which antibiotic therapy directed against *H. pylori* often leads to tumor regression (Chapter 17). With time, however, tumors may acquire additional mutations that render their growth and survival antigen-independent, such as the (11;18), (14;18), or (1;14) chromosomal translocations, which are relatively specific for extranodal marginal zone lymphomas. All of these translocations up-regulate the expression and function of BCL10 or MALT1, protein components of a signaling complex that activates NF-κB and promotes the growth and survival of B cells. With further clonal evolution, spread to distant sites and transformation to diffuse large B-cell lymphoma may occur. This theme of polyclonal to monoclonal transition during lymphomagenesis is also applicable to the pathogenesis of EBV-induced lymphoma and is discussed more fully in Chapter 7.

Hairy Cell Leukemia

This rare but distinctive B-cell neoplasm constitutes about 2% of all leukemias. It is predominantly a disease of middle-aged white males, with a median age of 55 and a male-to-female ratio of 5:1.

Pathogenesis. **Hairy cell leukemias are associated in more than 90% of cases with activating point mutations in the serine/threonine kinase BRAF,** which is positioned immediately downstream of RAS in the MAPK signaling cascade (Chapter 7). The specific mutation, a valine to glutamate substitution at residue 600, is also found in diverse other neoplasms, including many melanomas and Langerhans cell histiocytosis (discussed later).