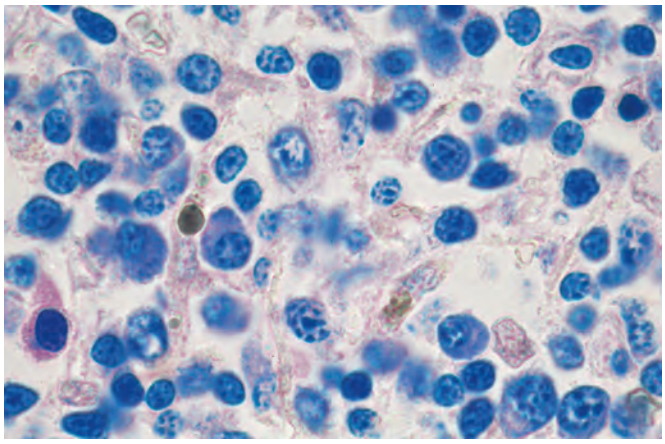

Figure 13-19 Lymphoplasmacytic lymphoma. Bone marrow biopsy shows a characteristic mixture of small lymphoid cells exhibiting various degrees of plasma cell differentiation. In addition, a mast cell with purplish red cytoplasmic granules is present at the left-hand side of the field.

Patients with IgM-secreting tumors have additional signs and symptoms stemming from the physicochemical properties of IgM. Because of its large size, at high concentrations IgM greatly increases the viscosity of the blood, giving rise to a *hyperviscosity syndrome* characterized by the following:

- *Visual impairment* associated with venous congestion, which is reflected by striking tortuosity and distention of retinal veins; retinal hemorrhages and exudates can also contribute to the visual problems
- *Neurologic problems* such as headaches, dizziness, deafness, and stupor, all stemming from sluggish blood flow and sludging
- *Bleeding* related to the formation of complexes between macroglobulins and clotting factors as well as interference with platelet functions
- *Cryoglobulinemia* resulting from the precipitation of macroglobulins at low temperatures, which produces symptoms such as Raynaud phenomenon and cold urticaria

Lymphoplasmacytic lymphoma is an incurable progressive disease. Because most IgM is intravascular, symptoms caused by the high IgM levels (e.g., hyperviscosity and hemolysis) can be alleviated by plasmapheresis. Tumor growth can be controlled for a time with low doses of chemotherapeutic drugs and immunotherapy with anti-CD20 antibody. Transformation to large-cell lymphoma occurs but is uncommon. Median survival is about 4 years.

KEY CONCEPTS

Plasma Cell Neoplasms

Multiple Myeloma

- Plasma cell tumor that manifests with multiple lytic bone lesions associated with pathologic fractures and hypercalcemia
- Neoplastic plasma cells suppress normal humoral immunity and secrete partial immunoglobulins that are nephrotoxic
- Associated with diverse translocations involving the IgH locus; frequent dysregulation and overexpression of D cyclins
- May be associated with AL amyloidosis (as may other neoplasms later)

Other Plasma Cell Neoplasms

- MGUS (monoclonal gammopathy of unknown significance): common in older adults, progresses to myeloma at a rate of 1% per year
- Smoldering myeloma: disseminated disease that pursues an unusually indolent course
- Solitary osseous plasmacytoma: solitary bone lesion identical to disseminated myeloma; most progress to myeloma within 7 to 10 years
- Extramedullary plasmacytoma: solitary mass, usually in the upper aerodigestive tract; rarely progresses to systemic disease
- Lymphoplasmacytic lymphoma: B cell lymphoma that exhibits plasmacytic differentiation; clinical symptoms dominated by hyperviscosity related to high levels of tumor-derived IgM; highly associated with mutations in the *MYD88* gene

Mantle Cell Lymphoma

Mantle cell lymphoma is an uncommon lymphoid neoplasm that makes up about 2.5% of NHL in the United States and 7% to 9% of NHL in Europe. It usually presents in the fifth to sixth decades of life and shows a male predominance. As the name implies, the tumor cells closely resemble the normal mantle zone B cells that surround germinal centers.

Pathogenesis. **Virtually all mantle cell lymphomas have an (11;14) translocation involving the IgH locus on chromosome 14 and the cyclin D1 locus on chromosome 11 that leads to overexpression of cyclin D1.** This translocation is detected in about 70% of cases by standard karyotyping and in virtually all tumors by fluorescence in situ hybridization. The resulting up-regulation of cyclin D1 promotes G1- to S-phase progression during the cell cycle, as was described in Chapter 7.

MORPHOLOGY

At diagnosis the majority of patients have generalized lymphadenopathy, and 20% to 40% have peripheral blood involvement. Frequent sites of extranodal involvement include the bone marrow, spleen, liver, and gut. Occasionally, mucosal involvement of the small bowel or colon produces polyp-like lesions (lymphomatoid polyposis); of all forms of NHL, mantle cell lymphoma is most likely to spread in this fashion.

Nodal tumor cells may surround reactive germinal centers to produce a nodular appearance at low power, or diffusely efface the node. **Typically, the proliferation consists of a homogeneous population of small lymphocytes with irregular to occasionally deeply clefted (cleaved) nuclear contours** (Fig. 13-20). Large cells resembling centroblasts and proliferation centers are absent, distinguishing mantle cell lymphoma from follicular lymphoma and CLL/SLL, respectively. In most cases the nuclear chromatin is condensed, nucleoli are inconspicuous, and the cytoplasm is scant. Occasionally, tumors composed of intermediate-sized cells with more open chromatin and a brisk mitotic rate are observed; immunophenotyping is necessary to distinguish these "blastoid" variants from ALL.