The clinicopathologic diagnosis of multiple myeloma rests on radiographic and laboratory findings. It can be strongly suspected when the distinctive radiographic changes are present, but definitive diagnosis requires a bone marrow examination. Marrow involvement often gives rise to a normocytic normochromic anemia, sometimes accompanied by moderate leukopenia and thrombocytopenia.

The prognosis is variable, but has improved in recent years with new therapeutic approaches. The median survival is 4 to 7 years, and cures have yet to be achieved. Patients with multiple bony lesions, if untreated, rarely survive for more than 6 to 12 months, whereas patients with "smoldering myeloma" may be asymptomatic for many years. Translocations involving cyclin D1 are associated with a good outcome, whereas deletions of 13q, deletions of 17p, and the t(4;14) all portend a more aggressive course.

New therapies are bringing hope. Myeloma cells are sensitive to inhibitors of the proteasome, a cellular organelle that degrades unwanted and misfolded proteins. As discussed in Chapter 2, misfolded proteins activate apoptotic pathways. Myeloma cells are prone to the accumulation of misfolded, unpaired Ig chains. Proteasome inhibitors may induce cell death by exacerbating this inherent tendency, and also seem to retard bone resorption through effects on stromal cells. Thalidomide and related compounds such as lenalidomide also have activity against myeloma. Interestingly, this may also involve changes in protein degradation, as lenalidamide appears to activate ubiquitin ligases, thereby targeting proteins for proteolysis that are required for myeloma growth. Biphosphonates, drugs that inhibit bone resorption, reduce pathologic fractures and limit the hypercalcemia. Hematopoietic stem cell transplantation prolongs life but has not yet proven to be curative.

Solitary Myeloma (Plasmacytoma). About 3% to 5% of plasma cell neoplasms present as a solitary lesion of bone or soft tissue. The bone lesions tend to occur in the same locations as in multiple myeloma. Extraosseous lesions are often located in the lungs, oronasopharynx, or nasal sinuses. Modest elevations of M proteins in the blood or urine may be found in some patients. Solitary osseous plasmacytoma almost inevitably progresses to multiple myeloma, but this can take 10 to 20 years or longer. In contrast, extraosseous plasmacytomas, particularly those involving the upper respiratory tract, are frequently cured by local resection.

Smoldering Myeloma. This entity defines a middle ground between multiple myeloma and monoclonal gammopathy of uncertain significance. Plasma cells make up 10% to 30% of the marrow cellularity, and the serum M protein level is greater than 3 gm/dL, but patients are asymptomatic. About 75% of patients progress to multiple myeloma over a 15-year period.

Monoclonal Gammopathy of Uncertain Significance. MGUS is the most common plasma cell dyscrasia, occurring in about 3% of persons older than 50 years of age and in about 5% of individuals older than 70 years of age. By definition, patients are asymptomatic and the serum M protein level is less than 3 gm/dL. **Approximately 1% of patients with MGUS develop a symptomatic plasma cell neoplasm, usually multiple myeloma, per year**, a rate of conversion that remains roughly constant over time. The clonal plasma cells in MGUS contain many of the same chromosomal translocations and deletions that are found in full-blown multiple myeloma, indicating that MGUS is an early stage of myeloma development. As in patients with smoldering myeloma, progression to multiple myeloma is unpredictable; hence, periodic assessment of serum M component levels and Bence Jones proteinuria is warranted.

Lymphoplasmacytic Lymphoma. Lymphoplasmacytic lymphoma is a B-cell neoplasm of older adults that usually presents in the sixth or seventh decade of life. Although bearing a superficial resemblance to CLL/SLL, it differs in that a substantial fraction of the tumor cells undergo terminal differentiation to plasma cells. Most commonly, the plasma cell component secretes monoclonal IgM, often in amounts sufficient to cause a hyperviscosity syndrome known as *Waldenström macroglobulinemia*. Unlike multiple myeloma, complications stemming from the secretion of free light chains (e.g., renal failure and amyloidosis) are relatively rare and bone destruction does not occur.

Pathogenesis. Recent deep sequencing studies have shown that virtually all cases of lymphoplasmacytic lymphoma are associated with acquired mutations in *MYD88*. The *MYD88* gene encodes an adaptor protein that participates in signaling events that activate NF-κB and also augment signals downstream of the B-cell receptor (Ig) complex, both of which may promote the growth and survival of the tumor cells.

MORPHOLOGY

Typically, the marrow contains an infiltrate of lymphocytes, plasma cells, and plasmacytoid lymphocytes in varying proportions, often accompanied by mast cell hyperplasia (Fig. 13-19). Some tumors also contain a population of larger lymphoid cells with more vesicular nuclear chromatin and prominent nucleoli. Periodic acid-Schiff-positive inclusions containing Ig are frequently seen in the cytoplasm (**Russell bodies**) or the nucleus (**Dutcher bodies**) of some of the plasma cells. At diagnosis the tumor has usually disseminated to the lymph nodes, spleen, and liver. Infiltration of the nerve roots, meninges, and more rarely the brain can also occur with disease progression.

Immunophenotype. The lymphoid component expresses B-cell markers such as CD20 and surface Ig, whereas the plasma cell component secretes the same Ig that is expressed on the surface of the lymphoid cells. This is usually IgM but can also be IgG or IgA.

Clinical Features. The dominant presenting complaints are nonspecific and include weakness, fatigue, and weight loss. Approximately half the patients have *lymphadenopathy, hepatomegaly, and splenomegaly.* Anemia caused by marrow infiltration is common. About 10% of patients have *autoimmune hemolysis* caused by *cold agglutinins*, IgM antibodies that bind to red cells at temperatures of less than 37°C (Chapter 14).