- *Heavy-chain disease* is a rare monoclonal gammopathy that is seen in association with a diverse group of disorders, including lymphoplasmacytic lymphoma and an unusual small bowel marginal zone lymphoma that occurs in malnourished populations (so-called *Mediterranean lymphoma*). The common feature is the synthesis and secretion of free heavy-chain fragments.
- *Primary or immunocyte-associated amyloidosis* results from a monoclonal proliferation of plasma cells secreting light chains (usually of λ isotype) that are deposited as amyloid. Some patients have overt multiple myeloma, but others have only a minor clonal population of plasma cells in the marrow.
- *Monoclonal gammopathy of undetermined significance (MGUS)* is applied to patients without signs or symptoms who have small to moderately large M components in their blood. MGUS is very common in older adults and has a low but constant rate of transformation to symptomatic monoclonal gammopathies, most often multiple myeloma.

With this background, we now turn to some of the specific clinicopathologic entities. Primary amyloidosis was discussed along with other disorders of the immune system in Chapter 6.

Multiple Myeloma. **Multiple myeloma is a plasma cell neoplasm commonly associated with lytic bone lesions, hypercalcemia, renal failure, and acquired immune abnormalities.** Although bony disease dominates, it can spread late in its course to lymph nodes and extranodal sites. Multiple myeloma causes 1% of all cancer deaths in Western countries. Its incidence is higher in men and people of African descent. It is chiefly a disease of older adults, with a peak age of incidence of 65 to 70 years.

Pathogenesis. Multiple myeloma is associated with frequent rearrangements involving the IgH locus and various proto-oncogenes. Included among the loci that are recurrently involved in translocations with the Ig heavy-chain gene on chromosome 14q32 are the cell cycle-regulatory genes cyclin D1 on chromosome 11q13 and cyclin D3 on chromosome 6p21. Deletions of chromosome 17p that involve the *TP53* tumor suppressor locus also occur and are associated with a poor outcome. Late-stage, highly aggressive forms of the disease such as plasma cell leukemia are associated with acquisition of rearrangements involving *MYC*. More recent deep sequencing of myeloma genomes has identified frequent mutations involving components of the NF-κB pathway, which supports B-cell survival. Based on these studies, it is evident that myeloma molecularly heterogeneous.

The proliferation and survival of myeloma cells are dependent on several cytokines, most notably IL-6. IL-6 is an important growth factor for plasma cells. It is produced by the tumor cells themselves and by resident marrow stromal cells. High serum levels of IL-6 are seen in patients with active disease and are associated with a poor prognosis. Myeloma cell growth and survival are also augmented by direct physical interactions with bone marrow stromal cells, which is a focus of new therapeutic approaches.

Factors produced by neoplastic plasma cells mediate bone destruction, the major pathologic feature of multiple myeloma. Of particular importance, myeloma-derived MIP1α up-regulates the expression of the receptor activator of NF-κB ligand (RANKL) by bone marrow stromal cells, which in turn activates osteoclasts. Other factors released from tumor cells, such as modulators of the Wnt pathway, are potent inhibitors of osteoblast function. The net effect is a marked increase in bone resorption, which leads to hypercalcemia and pathologic fractures.

MORPHOLOGY

Multiple myeloma usually presents as destructive plasma cell tumors (plasmacytomas) involving the axial skeleton. The bones most commonly affected (in descending order of frequency) are the vertebral column, ribs, skull, pelvis, femur, clavicle, and scapula. Lesions begin in the medullary cavity, erode cancellous bone, and progressively destroy the bony cortex, often leading to pathologic fractures; these are most common in the vertebral column, but may occur in any affected bone. **The bone lesions appear radiographically as punched-out defects, usually 1 to 4 cm in diameter** (Fig. 13-16), and consist of soft, gelatinous, red tumor masses. Less commonly, widespread myelomatous bone disease produces diffuse demineralization (osteopenia) rather than focal defects.

Even away from overt tumor masses, the marrow contains an increased number of plasma cells, which usually constitute more than 30% of the cellularity. The plasma cells may infiltrate the interstitium or be present in sheets that completely replace normal elements. Like their benign counterparts, malignant plasma cells have a perinuclear clearing due to a prominent Golgi apparatus and an eccentrically placed nucleus (Fig. 13-17). Relatively normal-appearing plasma cells, **plasmablasts** with vesicular nuclear chromatin and a prominent single nucleolus, or **bizarre, multinucleated cells** may predominate. Other cytologic variants stem from the dysregulated synthesis and secretion of Ig, which often leads to intracellular accumulation of intact or partially degraded protein. Such variants include **flame cells** with fiery red cytoplasm, **Mott cells** with multiple grapelike cytoplasmic droplets, and cells containing a variety of other inclusions, including **fibrils, crystalline rods, and globules**. The globular inclusions are referred to as **Russell bodies** (if cytoplasmic) or **Dutcher bodies** (if nuclear). In advanced disease, plasma cell infiltrates may be present in the spleen, liver, kidneys, lungs, lymph nodes, and other soft tissues.

Commonly, the high level of M proteins causes red cells in peripheral blood smears to stick to one another in linear arrays, a finding referred to as **rouleaux formation**. Rouleaux formation is characteristic but not specific, as it may be seen in other conditions in which Ig levels are elevated, such as lupus erythematosus and early HIV infection. Rarely, tumor cells flood the peripheral blood, giving rise to **plasma cell leukemia**.

Bence Jones proteins are excreted in the kidney and contribute to a form of renal disease called **myeloma kidney**. This important complication is discussed in detail in Chapter 20.

Immunophenotype. Plasma cell tumors are positive for CD138, an adhesion molecule also known as syndecan-1, and often express CD56, a feature that can be helpful in identifying small populations of neoplastic cells.

Clinical Features. The clinical features of multiple myeloma stem from (1) the effects of plasma cell growth in