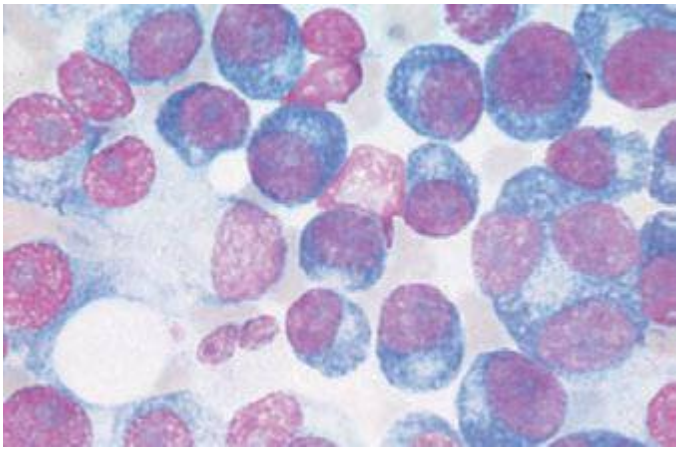

**FIGURE 136-3 Multiple myeloma (marrow).** The cells bear characteristic morphologic features of plasma cells, round or oval cells with an eccentric nucleus composed of coarsely clumped chromatin, a densely basophilic cytoplasm, and a perinuclear clear zone containing the Golgi apparatus. Binucleate and multinucleate malignant plasma cells can be seen.

## GLOBAL CONSIDERATIONS

The incidence of myeloma is highest in African Americans and Pacific Islanders; intermediate in Europeans and North American whites; and lowest in people from developing countries including Asia. The higher incidence in more developed countries may result from the combination of a longer life expectancy and more frequent medical surveillance. Incidence of multiple myeloma in other ethnic groups including native Hawaiians, female Hispanics, American Indians from New Mexico, and Alaskan natives is higher relative to U.S. whites in the same geographic area. Chinese and Japanese populations have a lower incidence than whites. Immunoproliferative small-intestinal disease with alpha heavy chain disease is most prevalent in the Mediterranean area. Despite these differences in prevalence, the characteristics, response to therapy, and prognosis of myeloma are similar worldwide.

## PATHOGENESIS AND CLINICAL MANIFESTATIONS

Multiple myeloma (MM) cells bind via cell-surface adhesion molecules to bone marrow stromal cells (BMSCs) and extracellular matrix (ECM), which triggers MM cell growth, survival, drug resistance, and migration in the bone marrow milieu (Fig. 136-4). These effects are due both to direct MM cell–BMSC binding and to induction of various cytokines, including IL-6, insulin-like growth factor type I (IGF-I), vascular endothelial growth factor (VEGF), and stromal cell–derived growth factor (SDF)-1α. Growth, drug resistance, and migration are mediated via Ras/Raf/mitogen-activated protein kinase, PI3K/Akt, and protein kinase C signaling cascades, respectively.

Bone pain is the most common symptom in myeloma, affecting nearly 70% of patients. Unlike the pain of metastatic carcinoma, which often is worse at night, the pain of myeloma is precipitated by movement. Persistent localized pain in a patient with myeloma usually signifies a pathologic fracture. The bone lesions of myeloma are caused by the proliferation of tumor cells, activation of osteoclasts that destroy bone, and suppression of osteoblasts that form new bone. The increased osteoclast activity is mediated by osteoclast activating factors (OAFs) made by the myeloma cells (OAF activity can be mediated by several cytokines, including IL-1, lymphotoxin, VEGF, receptor activator of NF-κB [RANK] ligand, macrophage inhibitory factor [MIP]-1α, and tumor necrosis factor [TNF]). The bone lesions are lytic in nature and are rarely associated with osteoblastic new bone formation due to their suppression by dickhoff-1 (DKK-1) produced by myeloma cells. Therefore, radioisotopic bone scanning is less useful in diagnosis than is plain radiography. The bony lysis results in substantial mobilization of calcium from bone, and serious acute and chronic complications of hypercalcemia may dominate the clinical picture (see below). Localized bone lesions may expand to the point that mass lesions may be palpated, especially on the skull (Fig. 136-5), clavicles, and sternum; and the collapse of vertebrae may lead to spinal cord compression. The next most common clinical problem in patients with myeloma is susceptibility to bacterial infections. The most common infections are pneumonias and pyelonephritis, and the most frequent pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* in the lungs and *Escherichia coli* and other gram-negative organisms in the urinary tract. In ~25% of patients, recurrent infections are the presenting features, and >75%



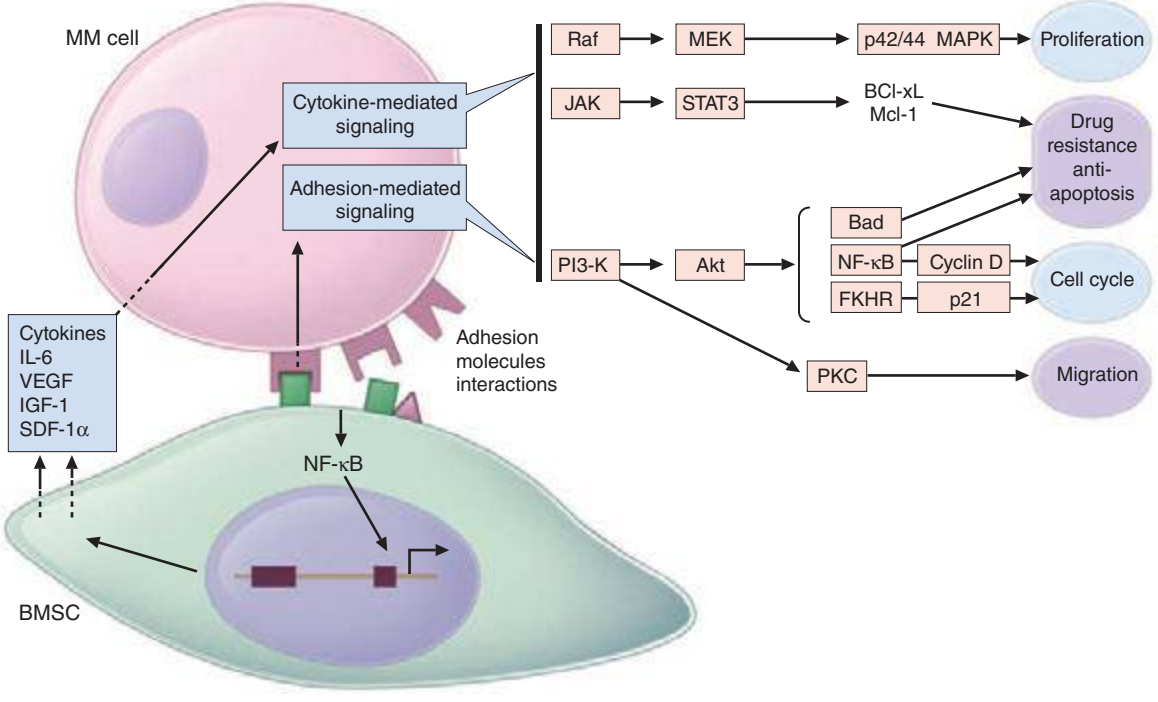


**FIGURE 136-4 Pathogenesis of multiple myeloma.** Multiple myeloma (MM) cells interact with bone marrow stromal cells (BMSCs) and extracellular matrix proteins via adhesion molecules, triggering adhesion-mediated signaling as well as cytokine production. This triggers cytokine-mediated signaling that provides growth, survival, and antiapoptotic effects as well as development of drug resistance.