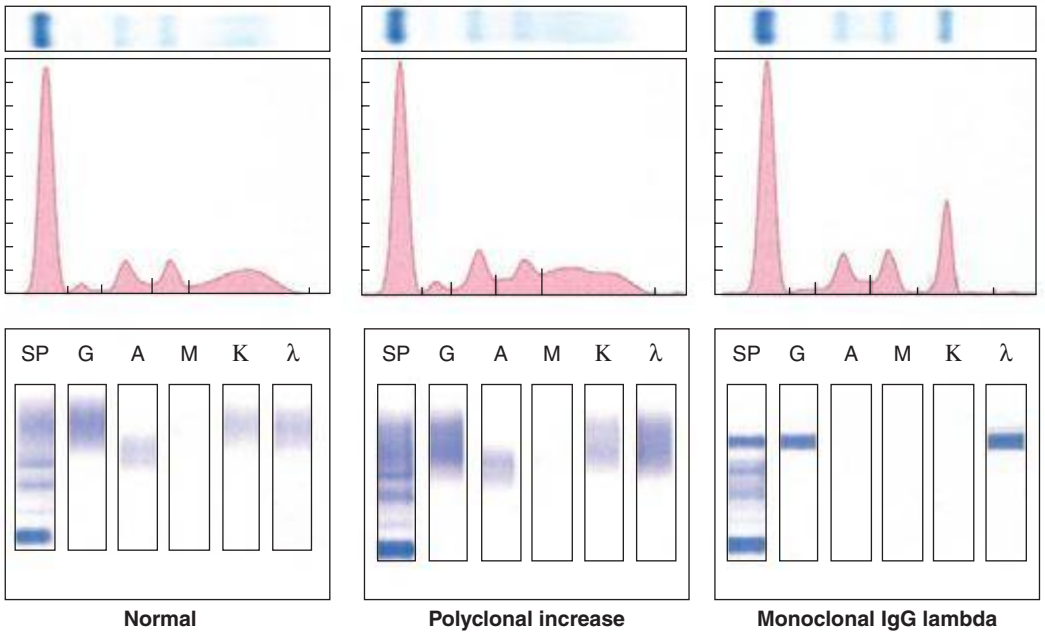

FIGURE 136-2 Representative patterns of serum electrophoresis and immunofixation. The *upper panels* represent agarose gel, middle panels are the densitometric tracing of the gel, and *lower panels* are immunofixation patterns. Panel on the *left* illustrates the normal pattern of serum protein on electrophoresis. Because there are many different immunoglobulins in the serum, their differing mobilities in an electric field produce a broad peak. In conditions associated with increases in polyclonal immunoglobulin, the broad peak is more prominent (*middle panel*). In monoclonal gammopathies, the predominance of a product of a single cell produces a "church spire" sharp peak, usually in the γ globulin region (*right panel*). The immunofixation (*lower panel*) identifies the type of immunoglobulin. For example, normal and polyclonal increase in immunoglobulins produce no distinct bands; however, the *right panel* shows distinct bands in IgG and lambda protein lanes, confirming the presence of IgG lambda monoclonal protein. *(Courtesy of Dr. Neal I. Lindeman; with permission.)*

cell disorders, M components may be detected in other lymphoid neoplasms such as chronic lymphocytic leukemia and lymphomas of B- or T-cell origin; nonlymphoid neoplasms such as chronic myeloid leukemia, breast cancer, and colon cancer; a variety of nonneoplastic conditions such as cirrhosis, sarcoidosis, parasitic diseases, Gaucher's disease, and pyoderma gangrenosum; and a number of autoimmune conditions, including rheumatoid arthritis, myasthenia gravis, and cold agglutinin disease. Monoclonal proteins are also observed in immunosuppressed patients after organ transplant and, rarely, allogeneic transplant. At least two very rare skin diseases—lichen myxedematosus (also known as papular mucinosis) and necrobiotic xanthogranuloma—are associated with a monoclonal gammopathy. In papular mucinosis, highly cationic IgG is deposited in the dermis of patients. This organ specificity may reflect the specificity of the antibody for some antigenic component of the dermis. Necrobiotic xanthogranuloma is a histiocytic infiltration of the skin, usually of the face, that produces red or yellow nodules that can enlarge to plaques. Approximately 10% progress to myeloma. Five percent of patients with sensory motor neuropathy also have a monoclonal paraprotein.

The nature of the M component is variable in plasma cell disorders. It may be an intact antibody molecule of any heavy chain subclass, or it may be an altered antibody or fragment. Isolated light or heavy chains may be produced. In some plasma cell tumors such as extramedullary or solitary bone plasmacytomas, less than one-third of patients will have an M component. In ~20% of myelomas, only light chains are produced and, in most cases, are secreted in the urine as Bence Jones proteins. The frequency of myelomas of a particular heavy chain class is roughly proportional to the serum concentration, and therefore, IgG myelomas are more common than IgA and IgD myelomas. In approximately 1% of patients with myeloma, biclonal or triclonal gammopathy is observed.

MULTIPLE MYELOMA

DEFINITION

Multiple myeloma represents a malignant proliferation of plasma cells derived from a single clone. The tumor, its products, and the host response to it result in a number of organ dysfunctions and symptoms, including bone pain or fracture, renal failure, susceptibility to infection, anemia, hypercalcemia, and occasionally clotting abnormalities, neurologic symptoms, and manifestations of hyperviscosity.

ETIOLOGY

The cause of myeloma is not known. Myeloma occurred with increased frequency in those exposed to the radiation of nuclear warheads in World War II after a 20-year latency. Myeloma has been seen more commonly than expected among farmers, wood workers, leather workers, and those exposed to petroleum products. A variety of chromosomal alterations have been found in patients with myeloma: hyperdiploidy, 13q14 deletions, translocations t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16), and 17p13 deletions. Evidence is strong that errors in switch recombination—the genetic mechanism to change antibody heavy chain isotype—participate in the transformation process. However, no common molecular pathogenetic pathway has yet emerged. Genome sequencing studies have failed to identify any recurrent mutation with frequency >20%; *N-ras*, *K-ras*, and *B-raf* mutations are most common and combined occur in over 40% of patients. There is also evidence of complex clusters of subclonal variants at diagnosis that acquire additional mutations over time, indicative of genomic evolution that may drive disease progression. The neoplastic event in myeloma may involve cells earlier in B-cell differentiation than the plasma cell. Interleukin (IL) 6 may play a role in driving myeloma cell proliferation. It remains difficult to distinguish benign from malignant plasma cells based on morphologic criteria in all but a few cases (Fig. 136-3).

INCIDENCE AND PREVALENCE

An estimated 24,050 new cases of myeloma were diagnosed in 2014, and 11,090 people died from the disease in the United States. Myeloma increases in incidence with age. The median age at diagnosis is 70 years; it is uncommon under age 40. Males are more commonly affected than females, and blacks have nearly twice the incidence of whites. Myeloma accounts for 1.3% of all malignancies in whites and 2% in blacks, and 13% of all hematologic cancers in whites and 33% in blacks.