Distinguishing patients with stable, nonprogressive MGUS from patients in whom multiple myeloma will eventually develop is difficult. The risk of progression is greater among patients with IgA- or IgM-type M proteins, in patients with initial concentrations of M protein in excess of 1.5 g/dL, and in patients with an abnormal free κ-to-λ light-chain ratio. Although no definitive evidence has been found that monitoring patients with the diagnosis of MGUS improves survival, it is recommended that patients undergo annual evaluation, including serum electrophoresis, to detect progression to multiple myeloma before the onset of overt symptoms or complications.

M proteins can be found in benign and malignant conditions other than the plasma cell dyscrasias (Table 49-5). About 10% of patients with CLL have detectable levels of monoclonal IgG or IgM in their sera. M proteins can also be detected in a variety of autoreactive or infectious disorders.

TABLE 49-5 CLASSIFICATION OF DISORDERS ASSOCIATED WITH MONOCLONAL IMMUNOGLOBULIN (M PROTEIN) SECRETION

DISORDER	M PROTEIN PATTERN
PLASMA CELL NEOPLASMS	
Multiple myeloma	IgG > IgA > IgD; ± free light chain or light chain alone (κ > λ)
Solitary myeloma of bone	IgG > IgA > IgD; ± free light chain or light chain alone (κ > λ)
Extramedullary plasmacytoma	IgA > IgG > IgD; ± free light chain or light chain alone (κ > λ)
Waldenström macroglobulinemia	IgM ± free light chain (κ > λ)
Heavy-chain disease	γ, α, or μ heavy chain or fragment
Primary amyloidosis	Free light chain (λ > κ)
Monoclonal gammopathy of unknown significance	IgG > IgM > IgA, usually without urinary light-chain secretion
OTHER B-CELL NEOPLASMS	
Chronic lymphocytic leukemia	M protein occasionally secreted; IgM > IgG
B-cell non-Hodgkin's lymphomas; Hodgkin's disease	M protein occasionally secreted; IgM > IgG
NONLYMPHOID NEOPLASMS	
Chronic myelogenous leukemia	No consistent patterns
Carcinomas (e.g., colon, breast, prostate)	No consistent patterns
AUTOIMMUNE OR AUTOREACTIVE DISORDERS	
Cold agglutinin disease	IgM κ most common
Mixed cryoglobulinemia	IgM or IgA
Sjögren syndrome	IgM
MISCELLANEOUS INFLAMMATORY, STORAGE, OR INFECTIOUS DISORDERS	
Lichen myxedematosus	IgG λ
Gaucher's disease	IgG
Cirrhosis, sarcoid, parasitic diseases, renal acidosis	No consistent pattern

Modified from Salmon SE: Plasma cell disorders. In Wyngaarden JB, Smith LH Jr, editors: Cecil textbook of medicine, ed 18, Philadelphia, 1988, WB Saunders, p 1026.
Ig, Immunoglobulin.

Multiple Myeloma

Definition and Epidemiology

Multiple myeloma is a malignant plasma cell disorder characterized by neoplastic infiltration of the bone marrow and bone and by monoclonal immunoglobulin or light chains in the serum or urine. The cause of myeloma is uncertain.

The disease is more common in men than women and in American backs than whites. Myeloma risk increases with age, with a median age of 69 years at diagnosis (SEER data). Myeloma risk is increased for patients with first-degree relatives with a plasma cell dyscrasia. Associations have been described with occupational exposures to organic solvents, pesticides, petroleum products, and ionizing radiation, but these risk factors are rarely seen in affected individuals.

Pathology

The tumor cell of these disorders exhibits features of a differentiated plasma cell that is adapted to synthesize and secrete immunoglobulin at a high rate. Biopsies of bone marrow or targeted bone biopsies of tumor sites reveal infiltration by plasma cells with light-chain restriction, defining clonality. Cell surface markers useful in identifying and enumerating plasma cells include CD38, CD 138, and immunoglobulin light chains; the B-cell marker CD20 is typically absent and aids in distinguishing other lymphoproliferative disorders from myeloma.

Genetic aberrations are détectable in most patients with myeloma if adequately sensitive tests are applied. Standard karyotyping and FISH are perfomed routinely on marrow samples to determine abnormalities of prognostic significance, including translocations involving the immunoglobulin heavy-chain locus on chromosome 14, hyperploidy, or délétions of chromosomes 1, 13, or 17.

Diagnosis and Differential Diagnosis

Myeloma must be distinguished from related disorders, including MGUS and plasmacytoma. The diagnosis of multiple myeloma is made by identifying some combination of an increase (>10%) in the number of plasma cells in the bone marrow, a serum M protein other than IgM exceeding 3 g/dL, or a clonal protein in the urine. Asymptomatic myeloma (i.e., stage I myeloma or "smoldering myeloma") is diagnosed when clonal plasma cells are found in more than 10% of the bone marrow or monoclonal protein occurs in an amount greater than 3 g/dL in the absence of end-organ–related injury, or both.

Patients with disease-related organ dysfunction (e.g., anemia, lytic bone lesions, hypercalcemia, renal dysfunction) are considered to have symptomatic myeloma, for which therapy is indicated. Recurrent infection with hypogammaglobulinemia is also considered a criterion for symptomatic myeloma. Solitary plasmacytoma is diagnosed when a single clonal plasma cell tumor is identified in bone or soft tissue in the absence of bone marrow involvement or other end organ–related injury.

Evaluation of the patient with suspected myeloma includes bone marrow biopsy; measurement of hemoglobin, calcium, renal function, and the serum free κ-to-λ light-chain ratio; serum or urine protein electrophoresis; immunoelectrophoresisimmunoelectrophoresis; and a skeletal survey.