TABLE 136-1 DIAGNOSTIC CRITERIA FOR MULTIPLE MYELOMA, MYELOMA VARIANTS, AND MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Monoclonal Gammopathy of Undetermined Significance (MGUS)
M protein in serum <30 g/L
Bone marrow clonal plasma cells <10%
No evidence of other B cell proliferative disorders
No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a]
Smoldering Multiple Myeloma (Asymptomatic Myeloma)
M protein in serum ≥30 g/L *and/or*
Bone marrow clonal plasma cells ≥10%
No myeloma-related organ or tissue impairment (no end organ damage, including bone lesions)[a] or symptoms
Symptomatic Multiple Myeloma
M protein in serum and/or urine
Bone marrow (clonal) plasma cells[b] or plasmacytoma
Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)
Nonsecretory Myeloma
No M protein in serum and/or urine with immunofixation
Bone marrow clonal plasmacytosis ≥10% or plasmacytoma
Myeloma-related organ or tissue impairment (end organ damage, including bone lesions)[a]
Solitary Plasmacytoma of Bone
No M protein in serum and/or urine[c]
Single area of bone destruction due to clonal plasma cells
Bone marrow not consistent with multiple myeloma
Normal skeletal survey (and magnetic resonance imaging of spine and pelvis if done)
No related organ or tissue impairment (no end organ damage other than solitary bone lesion)[a]
POEMS Syndrome
All of the following four criteria must be met:
1. Polyneuropathy
2. Monoclonal plasma cell proliferative disorder
3. Any one of the following: (a) sclerotic bone lesions; (b) Castleman's disease; (c) elevated levels of vascular endothelial growth factor (VEGF)
4. Any one of the following: (a) organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy); (b) extravascular volume overload (edema, pleural effusion, or ascites); (c) endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic); (d) skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, and white nails); (e) papilledema; (f) thrombocytosis/polycythemia[d]

[a]Myeloma-related organ or tissue impairment (end organ damage): calcium levels increased: serum calcium >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L; renal insufficiency: creatinine >173 mmol/L; anemia: hemoglobin 2 g/dL below the lower limit of normal or hemoglobin <10 g/dL; bone lesions: lytic lesions or osteoporosis with compression fractures (magnetic resonance imaging or computed tomography may clarify); other: symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (>2 episodes in 12 months). [b]If flow cytometry is performed, most plasma cells (>90%) will show a "neoplastic" phenotype. [c]A small M component may sometimes be present. [d]These features should have no attributable other causes and have temporal relation with each other.

Abbreviation: POEMS, polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes.

myeloma is preceded by MGUS. Non-IgG subtype, abnormal kappa/lambda free light chain ratio, and serum M protein >15 g/L (1.5 g/dL) are associated with higher incidence of progression of MGUS to myeloma. Absence of all three features predicts a 5% chance of progression, whereas higher risk MGUS with the presence of all three features predicts a 60% chance of progression over 20 years. The features responsible for higher risk of progression from SMM to MM are bone marrow plasmacytosis >10%, abnormal kappa/lambda free light chain ratio, and serum M protein >30 g/L (3 g/dL). Patients with only one of these three features have a 25% chance of progression to MM in 5 years, whereas patients with high-risk SMM with all three features have a 76% chance of progression. There are two important variants of myeloma—solitary bone plasmacytoma and solitary extramedullary plasmacytoma. These lesions are associated with an M component in <30% of the cases, they may affect younger individuals, and both are associated with median survivals of ≥10 years. Solitary bone plasmacytoma is a single lytic bone lesion without marrow plasmacytosis. Extramedullary plasmacytomas usually involve the submucosal lymphoid tissue of the nasopharynx or paranasal sinuses without marrow plasmacytosis. Both tumors are highly responsive to local radiation therapy. If an M component is present, it should disappear after treatment. Solitary bone plasmacytomas may recur in other bony sites or evolve into myeloma. Extramedullary plasmacytomas rarely recur or progress.

The clinical evaluation of patients with myeloma includes a careful physical examination searching for tender bones and masses. Chest and bone radiographs may reveal lytic lesions or diffuse osteopenia. Magnetic resonance imaging (MRI) offers a sensitive means to document extent of bone marrow infiltration and cord or root compression in patients with pain syndromes. A complete blood count with differential may reveal anemia. Erythrocyte sedimentation rate is elevated. Rare patients (~1%) may have plasma cell leukemia with >2000 plasma cells/μL. This may be seen in disproportionate frequency in IgD (12%) and IgE (25%) myelomas. Serum calcium, urea nitrogen, creatinine, and uric acid levels may be elevated. Protein electrophoresis and measurement of serum immunoglobulins and free light chains are useful for detecting and characterizing M spikes, supplemented by immunoelectrophoresis, which is especially sensitive for identifying low concentrations of M components not detectable by protein electrophoresis. A 24-h urine specimen is necessary to quantitate Bence Jones protein excretion. Serum alkaline phosphatase is usually normal even with extensive bone involvement because of the absence of osteoblastic activity. It is also important to quantitate serum β_2-microglobulin and albumin (see below).

The serum M component will be IgG in 53% of patients, IgA in 25%, and IgD in 1%; 20% of patients will have only light chains in serum and urine. Dipsticks for detecting proteinuria are not reliable at identifying light chains, and the heat test for detecting Bence Jones protein is falsely negative in ~50% of patients with light chain myeloma. Fewer than 1% of patients have no identifiable M component; these patients usually have light chain myeloma in which renal catabolism has made the light chains undetectable in the urine. In most of these patients, light chains can now be detected by serum free light chain assay. IgD myeloma may also present with light chain disease. About two-thirds of patients with serum M components also have urinary light chains. The light chain isotype may have an impact on survival. Patients secreting lambda light chains have a significantly shorter overall survival than those secreting kappa light chains. Whether this is due to some genetically important determinant of cell proliferation or because lambda light chains are more likely to cause renal damage and form amyloid than are kappa light chains is unclear. The heavy chain isotype may have an impact on patient management as well. About half of patients with IgM paraproteins develop hyperviscosity compared with only 2–4% of patients with IgA and IgG M components. Among IgG myelomas, it is the IgG3 subclass that has the highest tendency to form both concentration- and temperature-dependent aggregates, leading to hyperviscosity and cold agglutination at lower serum concentrations.

PROGNOSIS

Serum β_2-microglobulin is the single most powerful predictor of survival and can substitute for staging. β_2-Microglobulin is a protein of 11,000 mol wt with homologies to the constant region of immunoglobulins that is the light chain of the class I major histocompatibility antigens (HLA-A, -B, -C) on the surface of every cell. Patients with β_2-microglobulin levels <0.004 g/L have a median survival of 43 months, and those with levels >0.004 g/L have a survival of only 12 months. Combination of serum β_2-microglobulin and albumin levels forms the basis for a three-stage International Staging System (ISS) (Table 136-2) that predicts survival. With the use of high-dose therapy and the newer agents, the