Multiple Myeloma

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Multiple myeloma (MM) is the most common hematologic malignancy. It is estimated that nearly 16,570 persons will be diagnosed with MM in the United States in 2006.[1] MM affects many organ systems, and its management requires a multidisciplinary approach. It is important for physicians from the multiple specialties involved in the management of these patients to have a clear understanding of MM. This article reviews the staging, diagnosis, and treatment of MM and the management of its complications.

TAKE HOME POINTS

- Multiple myeloma (MM) is one of the plasma cell dyscrasias, characterized by the proliferation of monoclonal plasma cells and end-organ damage.
- Monoclonal gammopathy of unknown significance (MGUS) transforms into a lymphoproliferative disorder, lymphoma or MM, at an average rate of 1% of cases per year.
- MM patients should be treated if they have symptomatic or advanced disease; early versus deferred therapy for asymptomatic MM has not been shown to provide any benefits.
- If therapy is needed, high-dose chemotherapy with hematopoietic stem cell rescue is the treatment of choice for patients with normal or near normal cardiac, renal, pulmonary, and hepatic function.
- Back pain in patients with MM warrants an immediate evaluation by magnetic resonance imaging. If spinal cord compression is detected, the patient should be started on dexamethasone while awaiting emergent neurosurgical evaluation.

DEFINITION

MM is a plasma cell dyscrasia. Plasma cell dyscrasias are disorders characterized by the proliferation of monoclonal plasma cells. They represent a spectrum of diseases that are classified according to the degree of plasma cell proliferation and the presence of end-organ damage. The continuum of disease begins with the mere presence of monoclonal protein (M-protein) in the serum, progressing through both asymptomatic and symptomatic forms of MM, and ending with the presence of monoclonal plasma cells in the peripheral blood.[2] Plasma cell dyscrasias can occur in any one of these forms, and they are capable of remaining stable or progressing further to more severe disease.

CLASSIFICATION OF PLASMA CELL DYSCRASIAS

The International Myeloma Working Group (IMWG)[2] summarized the criteria for classification of the plasma cell dyscrasias in 2003. The subcategories of plasma cell dyscrasias consist of monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma (SMM), solitary plasmacytomas, asymptomatic MM, symptomatic MM, and plasma cell leukemia (**Table 1**).[2–7] MGUS is the presence of a limited number of monoclonal lymphoid/plasma cells that has the potential to either remain stable over time or transform into a lymphoproliferative disorder, lymphoma or MM.[2,8] MGUS has been reported to transform into malignant disease at an average rate of 1% of cases per year.[3,4] The diagnostic criteria for MGUS include the presence of less than 3 g/dL of M-protein in the serum, percentage of plasma cells in bone marrow below 10%, no evidence of any other lymphoproliferative disease, and no end-organ damage. SMM is MM

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Table 1. Criteria for Diagnosis of Plasma Cell Dyscrasias

Plasma Cell Dyscrasia	M-Protein	Clonal Plasmacytosis	End-Organ Damage	Prognosis
MGUS	< 3 g/dL in serum	< 10% of bone marrow*	None	1% progress to MM per year[3,4]
Solitary plasmacytoma of bone or soft tissues	None or small	Single area in either bone or soft tissue, normal bone marrow	None	Bone: 50% 10-year survival rate; soft tissue: 15% progress to MM[2]
SMM	>3 g/dL in serum	> 10% of bone marrow	None	19.7% evolve to MM within 65 months[5]
MM	Present in serum or urine	In bone marrow or as a plasmacytoma	Yes	3% 10-year survival rate[6]
Plasma cell leukemia	Any†	Any†	Any†	Median survival of 2–6 months[7]

MGUS = monoclonal gammopathy of unknown significance; MM = multiple myeloma; SMM = smoldering multiple myeloma.

*Plus no evidence of other B-cell disorders.

†Presence of at least 2 x 10^9/L plasma cells in the peripheral blood and plasma cells comprise more than 20% of the cell differential.

Table 2. Evaluations for Multiple Myeloma

Reason	Test*
Initial diagnosis	Serum protein electrophoresis and immunofixation Urine protein electrophoresis (24 h) and immunofixation
End-organ complications	Complete blood count and metabolic profile Skeletal survey
Prognosis	C-reactive protein, lactate dehydrogenase, and beta-2 macroglobulin Bone marrow aspiration and biopsy, flow cytometry, and cytogenetics

*Abnormal tests should be repeated and followed during the course of treatment and remission.

without anemia, skeletal lesions, renal insufficiency, or hypercalcemia. Almost 20% of SMM cases evolve to symptomatic MM within 65 months.[5,9] Solitary plasmacytomas are plasma cell tumors of a single area of bone or soft tissue in a patient who has normal bone marrow, a normal skeletal survey, and no end-organ damage.

MM is defined by the presence of any characteristic end-organ damage (including bone pain, anemia, hyperviscosity, recurrent bacterial infections, renal insufficiency, amyloidosis, or hypercalcemia) in the presence of any amount of M-protein in the serum or urine and the presence of clonal plasma cells in the bone marrow. These criteria for MM were chosen by the IMWG in order to include the maximum number of patients with MM, because nearly all patients with MM have some M-protein in their serum or urine, yet a proportion of symptomatic patients have a percentage of plasma cells in their bone marrow below 10% and less than 3 g/dL of M-protein in their serum.[2]

In most cases, complete immunoglobulins (Ig) are secreted together with an excess of Ig fragments. When only Ig fragments occur, the condition is referred to as light chain disease or Bence Jones myeloma. Nonsecretory MM is a rare variant of MM in which M-protein is not detected in the serum or urine. Plasma cell leukemia is the most severe form of plasma cell dyscrasia and is characterized by the presence of at least 2 × 10^9/L plasma cells in the peripheral blood and plasma cells comprising more than 20% of the peripheral blood cell differential.[2]

CLINICAL PRESENTATION AND EVALUATIONS

MM is a disease of adults. Only 2% of patients are diagnosed before age 40 years.[10] Presenting symptoms include persistent bone pain, fatigue usually related to anemia, weight loss, paresthesias, and rarely fever due to MM. In up to one third of patients, a plasma cell proliferative process may be recognized before the diagnosis of MM.[10] With the wide use of blood tests, many asymptomatic patients present for evaluation after a laboratory abnormality such as anemia, renal dysfunction, increased serum globulins, or hypercalcemia is recognized.

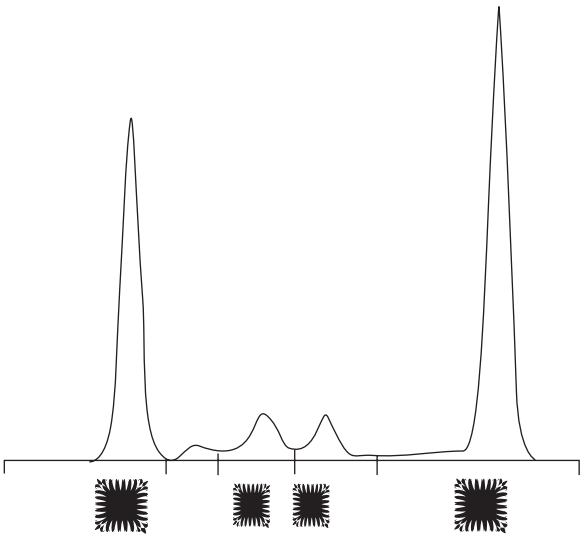
After a history and physical examination, the evaluation of patients in whom MM is suspected begins with complete blood count and differential (**Table 2**). A review of 1027 patients with newly diagnosed MM noted that 73% had a normochromic, normocytic anemia.[10] As the disease progresses, more patients will exhibit anemia. Serum chemistries might show hypercalcemia due to lytic bone lesions. It is important to monitor serum creatinine levels as a marker of renal failure, particularly in patients with high calcium levels.

A qualitative and quantitative assessment of the serum protein should be done next using serum protein electrophoresis (SPEP), which shows an M-protein peak in 82% of patients (**Figure 1**), a biclonal spike in 2%, and hypogammaglobulinemia in 10%.[11] The urine should be examined for abnormal proteins. Screening the urine with a dipstick is ineffective for finding M-proteins.[12] A collection of urine over 24 hours for protein electrophoresis (UPEP) should be used to calculate the daily amount of proteinuria, creatinine clearance, and M-protein excretion. UPEP reveals Bence Jones protein in most patients who do not have detectable levels of M-protein in the serum. Bence Jones protein has a molecular weight of approximately 25,000 and is excreted through the glomeruli. Consequently, levels in the serum are hard to detect due to the low concentration, even when immunoprecipitation studies are utilized. Light chain protein can be readily detected in the serum mainly when uremia or renal failure are present.

Immunofixation (from serum and urine) is needed to distinguish the specific Ig isotype. Immunofixation electrophoresis (IFE) is a 2-stage process combining agarose gel electrophoresis, UPEP or SPEP, with immunoprecipitation. Proteins are separated electrophoretically on several tracks on a gel, and antisera specific to individual classes of molecules are added to each track. If specific classes of light chain are present, insoluble complexes form with the antisera, which can then be stained and detected. This technique reveals a single distinct band with γ, μ, α, δ, or ε heavy chain sera, and a similar band with κ or λ light chain sera in a patient with a monoclonal gammopathy. Monoclonal Ig usually seen in MM patients are IgG (> 50% of patients), IgA (21%), free light chains (16%), nonsecretory (7%), IgD (2%), and IgM (0.5%).[10]

Several serum markers are useful to evaluate patients with MM. Beta-2 microglobulin (B2M) is the light chain component of human leukocyte antigen histocompatibility complexes found on the surface of plasma cells and all other nucleated cells. When elevated before treatment, B2M predicts survival and correlates with tumor burden and growth.[13–15] Levels of B2M are elevated during disease and fall during remission.[16] Serum albumin has been related to a patient's dietary status, performance status, and the velocity of MM growth.[1,6,17–19] Decreased serum albumin, when combined with increased B2M, provides a useful means to evaluate prognosis.[6,20]

A radiologic skeletal survey should be done to identify and evaluate bone lesions. In a large series of patients with MM at time of diagnosis, conventional radiographs



Total protein (g/dL): 11 (Reference range: 6.4–8.2 g/dL)
A/G ratio 0.39 (Reference range: 1.1–2.2)

Fractions	(g/dL)	Reference (g/dL)
Albumin	3.1	3.8–5.4
Alpha-1	0.2	0.1–0.3
Alpha-2	0.7	0.5–1.0
Beta	0.6	0.5–1.0
Gamma	6.5	0.5–14

Figure 1. Serum protein electrophoresis from a patient with multiple myeloma showing a monoclonal protein spike in the gamma region. A/G = albumin/globulin.

detected an abnormality in 79%, lytic bone lesions in 67%, osteoporosis in 23%, pathologic fractures in 26%, compression fractures in 22%, and no bone abnormalities in 21% (some patients had more than 1 defect).[10] Radiographic evaluation of the skeleton is more sensitive than technetium (Tc) 99 bone scans. Tc is preferentially taken up by osteoblasts during bone production and therefore is not absorbed by the lytic lesions. However, Tc scans may still be abnormal in the MM patient as the lytic lesions produce structural weak points that may lead to microfractures which heal via osteoblasts.

Bone marrow aspirate and biopsy provides information about the percentage and distribution of plasma cells in the marrow (**Figure 2**). Immunophenotyping by flow cytometry is done routinely at big centers to determine the proportion of abnormal cells and to determine the presence of plasmablastic cell markers.[21–26] Cytogenetics studies looking for chromosomal abnormalities should be done for added prognostic power, in particular, deletion of chromosome 13.

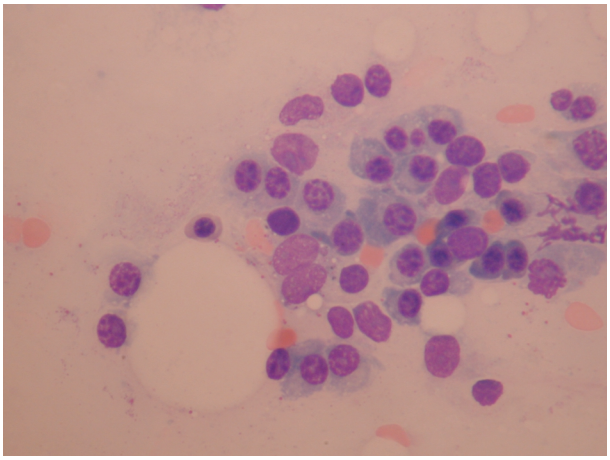


Figure 2. Plasma cells from a patient with multiple myeloma showing a basophilic cytoplasm with a perinuclear halo, an eccentric nucleus with coarse chromatin condensation, varying size, and a binucleate cell. Bone marrow examination revealed plasma cell infiltration in sheets and clumps.

Table 3. International Staging System for Multiple Myeloma

Stage	Beta 2-Microglobulin (µg/mL)	Serum Albumin (g/dL)	Median Survival (mo)
I	< 3.5	> 3.5	62
II	3.5–5.5	≥ 3.5	44
	< 3.5	< 3.5	—
III	> 5.5	Any	29

Data from Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma [published erratum appears in J Clin Oncol 2005;23:6281]. J Clin Oncol 2005;23:3412–20.

STAGING AND PROGNOSIS

The recently developed International Staging System (ISS) for MM can predict a patient's survival based on serum B2M and serum albumin (**Table 3**).[6] It separates patients into stages I, II, and III with corresponding median survival times of 62, 44, and 29 months, respectively.[6] The ISS has replaced the Durie-Salmon criteria due to its simplicity and ability to accurately predict survival.[6,17,27] Used to stage MM patients since 1975, the Durie-Salmon classification utilized bone marrow aspiration and biopsy, skeletal survey, serum electrophoresis, hemoglobin, and calcium levels to establish a patient's stage.[28] This staging system was complex, had multiple tests, and has not accurately correlated with prognosis.[28]

The percentage of plasma cells in the bone marrow, chromosomal abnormalities, and cell markers are also used for prognostication. If the percentage of plasma cells in the bone marrow is greater than 50%, the reported expected survival is 31 months, as opposed to 38 months for percentages below 50%.[1] The presence of a chromosome 13 deletion is associated with a poorer survival (34.9 versus 51 months) and poor response to therapy.[29] Plasmablastic cell markers have been related to poor prognosis. In one study, survival was reduced in patients with primarily plasmablastic cells compared to patients with more mature plasma cells (10 versus 35 months, respectively).[30]

Recently, fluorodeoxyglucose (FDG) positron emission tomography (PET) has been used to detect marrow involvement in patients with MM. This study may prove to be useful in the assessment of disease burden and may lead to more accurate staging and evaluation of therapeutic response. Further investigation of the role of FDG PET in MM is ongoing.[31]

INITIAL TREATMENT

Several treatment options are available for patients with MM. Deciding which to pursue depends upon the patient's overall health and stage of disease. Treatment is usually recommended for patients with symptomatic MM or advanced stage II or III disease. Early versus deferred therapy for SMM or asymptomatic MM has not been shown to provide any benefits.[32] In these patients, treatment might be considered if there is evidence of disease progression (**Figure 3**).

High-Dose Chemotherapy with Stem Cell Rescue

For patients requiring treatment, high-dose chemotherapy (HDC) with hematopoietic stem cell rescue (HSCR; formerly called autologous stem cell transplantation) has been shown to improve remission duration and, in some studies, increase survival.[33–35] Chronological age is less important than overall health when deciding between treatment options.[36] Ideally, patients should have normal or near normal cardiac, renal, pulmonary, and hepatic function; however, there are no stringent criteria to follow. Once the decision to proceed with HDC with HSCR is made, induction chemotherapy is started with either pulsed dexamethasone, vincristine-doxorubicin-dexamethasone (VAD), or dexamethasone-thalidomide.[37–39] Hematopoietic stem cells usually are harvested after at least 3 cycles of induction therapy. A melphalan-based preparative regimen is used 24 to 48 hours prior to reinfusion of stem cells.

The Intergroupe Français du Myélome[33] randomized 200 previously untreated MM patients under the age of 65 years to conventional chemotherapy for 18 cycles

(12 months) or conventional chemotherapy for 4 cycles followed by HDC (melphalan 140 mg/m^2 and total-body irradiation) and autologous HSCR. At 5 years, HDC with HSCR improved event-free survival (28% versus 10%; $P = 0.01$) and overall survival (52% versus 12%; $P = 0.03$) over conventional chemotherapy. The Medical Research Council Myeloma VII[34] trial demonstrated a complete response rate of 44% with HDC with HSCR versus 8% with standard chemotherapy. The overall survival and progression-free survival were prolonged by almost 1 year when compared to standard conventional-dose combination chemotherapy. Intergroup Trial S9321[35] enrolled 899 patients with newly diagnosed MM to receive chemotherapy induction for 4 cycles, followed by randomization to HDC with HSCR or further chemotherapy. Median progression-free survival was superior after HDC with HSCR (25 versus 21 months; $P = 0.05$), but overall survival was not (58 versus 53 months; $P = 0.8$). The equivalent survival seen in this study may relate to the fact that 52% of patients who failed conventional chemotherapy received salvage HDC with HSCR, with a post-relapse survival of 30 months versus 23 months without salvage HDC with HSCR ($P = 0.05$).[35] HDC with HSCR has a treatment-related mortality rate of 1% to 2 %.[33,35]

Research is ongoing to determine whether tandem or allogeneic transplantations offer better results in certain MM populations. In tandem transplantation, patients undergo a second HDC with HSCR once they have recovered from the first one.[40–46]

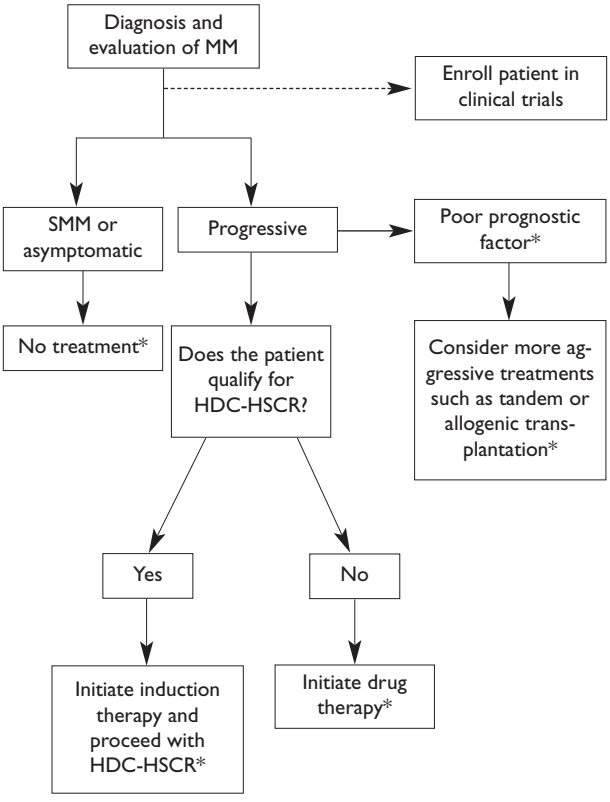


Figure 3. Therapeutic approach for the patient with multiple myeloma. HDC-HSCR = high-dose chemotherapy with hematopoietic stem cell rescue; MM = multiple myeloma. *Registration into an appropriate clinical trial should be considered at every decision point. It is of utmost importance to learn from each case of MM, at all stages.

Standard-Dose Therapy

For patients who are not eligible for HDC with HSCR, there are multiple treatment regimens with comparable benefits among them. The most commonly used therapies are melphalan plus prednisone (MP), high-dose dexamethasone, VAD, and thalidomide-dexamethasone.[37–39,47–49] The choice of chemotherapy depends on several factors, including the patient's performance status, age, renal function, cardiac function, desire for inpatient or outpatient therapy, and likelihood of receiving future stem cell transplantation.

All alkylating agents at standard doses and schedules have been shown to produce equivalent results.[47] The most commonly used is MP. MP is preferred in the elderly or in patients in whom stem cell transplantation is not possible in the future because of its ease of administration and low toxicity. MP is administered orally for 4 or 7 days every month. The bioavailability of oral melphalan is not always predictable, so the dose is adjusted to cause moderate leucopenia 2 weeks after administration of the drug. MP is a less desirable option if the patient has poor renal function or is in need of a faster response due to severe complications from MM.

In patients with renal failure or highly aggressive disease, VAD may be the treatment of choice because it can achieve a faster response and none of the drugs are renally excreted. The VAD regimen has produced responses in approximately 65% of previously treated and untreated patients.[38,50–52] VAD is administered intravenously as a continuous infusion for 4 days every 3 to 4 weeks. An alternative version of VAD that substitutes pegylated liposomal doxorubicin for doxorubicin eliminates the need for an infusion and produces comparable responses.[53,54] This regimen avoids early exposure to alkylating agents, thereby reducing future problems with stem cell collection, if needed, and decreasing the risk for myelodysplasia or secondary leukemia. Disadvantages include parenteral administration, cardiotoxicity, myelosuppression, and increased risk for thrombosis.

Thalidomide is an immunomodulatory agent with

antiangiogenic properties. Thalidomide is given orally on a daily basis, most commonly at doses between 50 mg and 200 mg, and has activity in patients who have and have not been previously treated for MM.[55–59] When combined with dexamethasone, thalidomide has shown 70% to 80% response rates in previously untreated patients, but long-term efficacy is not known.[34,56] Thalidomide's benefits include minimal hematologic toxic effects and oral administration. Common nonhematologic side effects of thalidomide include sedation, constipation, peripheral neuropathy, and deep venous thrombosis. Elderly patients may be unable to tolerate high doses, and corticosteroids increase its toxicity. Combinations of thalidomide, dexamethasone, and conventional chemotherapy are under evaluation.[60,61]

High-dose corticosteroid therapy consists of intermittent dexamethasone given orally at a dose of 40 mg for 4 consecutive days followed by 4 days of rest, 3 times every 4 weeks: days 1–4, 9–12, and 17–20 every 28 days.[37] A response rate of 43% in previously untreated patients has been reported, which is nearly as high as VAD but with fewer side effects.[37] The advantages of this regimen include ease of administration, lack of significant hematologic toxic effects, applicability for elderly patients and patients with poor performance status, and avoidance of alkylating agents or anthracycline chemotherapy.

Bortezomib is an inhibitor of the 26S proteasome, an intracellular ATP–dependent protease that is responsible for ubiquitin-mediated protein degradation. Bortezomib has been approved by the US Food and Drug Administration for the treatment of refractory MM.[62] The role of bortezomib in initial treatment is being evaluated.

Patient Monitoring

During therapy, patients with MM are monitored with monthly physical examination, complete blood count, and serum chemistry. In addition, any previously abnormal UPEP, SPEP, and B2M results should be followed with repeat testing every 2 months. Individuals who respond to therapy will often have a quick decline in bone pain, fewer infections, and improvement in hypercalcemia and anemia. A set timeline for treatment has not been established. Generally, therapy is continued until a plateau on SPEP, UPEP, and B2M has been achieved and maintained for at least 2 to 4 months. At that point, a chemotherapy holiday with close monthly monitoring can be safely considered. Treatment may restart when there is evidence of progression. If relapse occurs less than 6 to 12 months after conventional therapy, a different regimen is generally used. If relapse occurs 12 months after therapy, the original regimen might be reinstituted. Patients who relapse after HDC with HSCR and have cryopreserved stem cells might benefit from salvage HDC with repeat HSCR.[49]

Maintenance Therapy

Maintenance therapy relates to the use of a specific agent after a response has been achieved by conventional treatment. Maintenance strategies are controversial and are not widely used since they mostly have been shown to increase progression-free survival with minimal or no benefit in overall survival.[63] Maintenance therapy with interferon-alfa has been shown to prolong initial remission duration; however, its toxic effects make it difficult to use as maintenance.[63–65] Prednisone at 50 mg on alternate days improved progression-free and overall survival in responding patients after first-line VAD chemotherapy.[66] It is unclear whether these results can be generalized to patients with MM who are not treated with induction VAD, including HDC with HSCR. Novel approaches, including thalidomide maintenance, are under investigation.

COMPLICATIONS ASSOCIATED WITH MULTIPLE MYELOMA

Renal Disease

Renal disease occurs in up to 50% of patients with MM.[67] Although the etiology is typically multifactorial, patients who produce excessive Ig light chains are at higher risk of renal impairment. Renal disease caused by light chain formation usually presents as acute renal failure or nephrotic syndrome. Acute renal failure is seen in patients with myeloma kidney, which consists of tubular injury and obstruction from intratubular cast formation following filtration of toxic light chains. Nephrotic syndrome is found with primary amyloidosis and light chain deposition disease, both of which involve macrophage consumption and secretion of Ig light chains, leading to precipitate formation.[68] Type 1 cryoglobulinemia, which forms cryoprecipitate and leads to a membranoproliferative pattern, and plasma cell invasion are less common causes of renal disease associated with MM.

Treatment of renal disease is largely determined by presentation and can result in partial recovery of renal function in over 50% of cases.[69] Patients who present with nephrotic syndrome should be started on nonnephrotoxic chemotherapy aimed at the MM. Treatment for those presenting with acute renal failure is primarily directed toward aggressive hydration followed by chemotherapy. Loop diuretics might improve

hypercalcemia in patients who are adequately hydrated.[70] If renal function does not recover, a renal biopsy should be obtained. In patients with high plasma levels of light chains along with tubulointerstitial changes or minimal abnormalities, plasmapheresis along with chemotherapy has been shown to reduce the concentrations of nephrotoxic myeloma protein faster than chemotherapy alone.[71] Dialysis can be used as needed.

Avoidance of precipitating factors leading to the promotion of light chain filtration and cast formation is essential. MM patients should maintain a euvolemic to slightly overhydrated status and avoid nephrotoxic drugs and intravenous contrast dye. Chemotherapy can reduce light chain formation before the onset of impaired renal function. Trials are currently investigating the role of urine alkalinization and colchicine to reduce cast formation in myeloma kidney.

Although rarely associated with MM, uric acid nephropathy (UAN) can occur as a result of tubular uric acid precipitation following chemotherapy-induced cell lysis. UAN usually can be prevented by treating patients with allopurinol and aggressive hydration prior to chemotherapy.[72,73] When prophylaxis is not totally effective, therapy can consist of allopurinol (if not already given), loop diuretics and fluids aimed at washing out the uric acid crystals, and rasburicase. Rasburicase is a recombinant urate oxidase enzyme that is indicated for the management of elevated plasma uric acid levels following chemotherapy for leukemia, lymphoma, or any solid tumor malignancy in children. This drug is under investigation for prophylaxis against UAN with aggressive therapeutic modalities against MM.[74]

Hyperviscosity Syndrome

Elevated concentrations of abnormal polymers of IgA, IgG, and κ light chains in the serum increase the viscosity of blood and lead to microcirculation impairment. Symptoms may range from a simple headache to somnolence, hearing loss, or visual impairment. The appearance of these symptoms should prompt investigation of plasma viscosity. Due to distinct molecular characteristics, the degree of complications varies according to the type and concentration of the particular immunoglobulin. Although there is no specific threshold at which all patients become symptomatic, symptoms typically occur with an IgM concentration greater than 4 g/dL, IgG concentration greater than 5 g/dL, and IgA concentration greater than 7 g/dL, with most patients developing complications after levels exceed 10 g/dL regardless of type.[75] Daily plasma exchange and replacement with albumin solution until symptoms subside is the treatment of choice for hyperviscosity syndrome.[75] Hyperviscosity caused by smaller Ig, IgA, or IgG often requires more treatments than IgM-related disease because the smaller Ig are able to re-equilibrate from the extravascular to intravascular space.[76] Symptoms often demonstrate a corresponding improvement as serum viscosity is lowered; however, irreversible damage can occur.[75] Concurrent institution of chemotherapy is of utmost importance because plasmapheresis does not treat the underlying MM producing the excess Ig.[75]

Skeletal Consequences

Through a variety of proposed cytokinetic factors, MM tumor cells can increase osteoclast activity.[77–81] Consequently, the formation of lytic lesions and removal of calcium weaken the bones of individuals with MM, which can lead to pathological fractures and severe pain, usually located in the back and ribs. A randomized, double-blind study of patients with stage III MM showed a reduction of bone pain, pathological fractures, spinal cord compression, and the need for bone irradiation (skeletal-related events) in patients treated with pamidronate versus placebo (38% versus 51%, respectively) after 21 months of therapy.[82] Consequently, bisphosphonates are recommended for treatment of patients with MM who have osteopenia or lytic bone lesions.[83,84] Bisphosphonates can be used with radiation therapy and analgesics to minimize patient discomfort from osteolytic disease.[85] During therapy with bisphosphonates, patients should be monitored at least every 3 to 6 months for worsening renal function. If discovered, a change in dosage or temporary stoppage of bisphosphonates until renal function returns to baseline should be instituted. Surgical intervention is often needed for individuals with fractures or impending fractures.[84] Less invasive procedures (eg, kyphoplasty and vertebroplasty) have recently been shown to improve pain in up to 84% of patients with vertebral body fractures. This technique utilizes a radiologically guided percutaneous approach to inject bone cement into vertebral body fractures to stabilize vertebral bodies and, in the case of kyphoplasty, restore vertebral height.[86]

Spinal Cord Compression

Malignant infiltration of plasma cells into vertebrae or paraspinal tissues as well as bone fractures can result in spinal cord compression. Back pain in patients with MM must be treated seriously and warrants an immediate evaluation by magnetic resonance imaging. If spinal cord compression is detected, the patient should be started on dexamethasone while awaiting neurosurgical evaluation. Further management is based on the presence of spinal instability, in which case surgery is

indicated. If the spine is stable, radiotherapy is equally efficacious.[87]

Infection

Although the monoclonal Ig component is increased in patients with MM, their ability to fight infection is decreased due to immunoparesis, which is characterized by suppressed levels of Ig other than M-protein.[88] Quantitative deficits in CD4+ T cells and qualitative deficits in complement activation are also thought to contribute to the decreased immune effectiveness.[89–91] The most common infections found in patients with MM are pneumonia and pyelonephritis, which are thought to be a consequence of defects in complement clearance of encapsulated organisms such as *Streptococcus pneumococcus* and an increased susceptibility to *Escherichia coli* and other gram-negative bacteria after chemotherapy.[88–90] Individuals with MM should be immunized with pneumococcal and influenza vaccinations at the time of diagnosis.[87,91] Intravenous Ig may be considered in the setting of recurrent infections from encapsulated bacteria or common viral pathogens.[92]

Anemia

Either as a presenting symptom or consequence of disease progression, anemia is a common finding associated with MM. Patients can be treated with transfusion as needed and erythropoietin analogs (EPO). EPO can be started when the hemoglobin level falls below 11 g/dL to prevent symptoms from worsening anemia. Patients with symptomatic anemia who respond to chemotherapy often show improvement in quality of life and a decrease in the need for blood transfusions after EPO administration.[93–95] EPO should be stopped if no response is seen following 12 weeks of therapy or after a patient's hemoglobin reaches 12 to 13 g/dL or greater. In MM patients treated with EPO, polycythemia should be avoided and hypertension aggressively treated to prevent vascular complications.

CONCLUSION

Patients with MM can develop signs and symptoms involving multiple organ systems; therefore, it is essential that physicians of all disciplines be able to recognize its manifestations. A thorough understanding of the disease process will help guide physical examination and laboratory evaluation. MM therapy should be directed towards the primary disease along with treatment or palliation of the associated complications. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 26.

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