

Weakness in an 88-Year-old Man

Mark Stellingworth, MD; Amy Broussard, MD; Vince Cataldo, MD;
J. Rene Morrissey, MD; Gary Lipscomb, MD; Fred A. Lopez, MD; and Perry Rigby, MD

Multiple myeloma is a malignant proliferation of plasma cells that typically occurs in older individuals and is characterized by anemia, renal failure, bone pain, lytic lesions, and a monoclonal gammopathy. This disease is associated with significant morbidity and mortality.

An 88-year-old African American man without any significant past medical history presented for evaluation after being “found down” at home. A neighbor alerted Emergency Medical Services after the patient failed to answer his phone for several days. Apparently the patient had passed out while fixing a window. He was unsure how long he had been down, but had been too weak to rise from the floor. In addition, he believed that “laser beams” had depleted his strength.

The patient denied any significant surgical history. He denied any use of alcohol, tobacco, or intravenous drugs. He lived alone. He was a former driver for the local bank and had been retired for over 25 years. He had no primary care physician. In fact, he had not been to a doctor for nearly 50 years.

On initial physical exam, he was noted to be alert and oriented to year, month, place, and person. He was in no apparent distress. His vital signs included a blood pres-

sure of 112/62 mm Hg, a pulse of 93 beats per minute, a respiratory rate of 12 breaths per minute, and a temperature of 36.8°C; pulse oximetry was 99% on room air. Further examination revealed poor dentition and temporal wasting. Cardiovascular exam demonstrated a prominent PMI located in the fifth intercostal space in the left mid-clavicular line. Auscultation revealed clear lung fields. The patient’s abdominal exam revealed no abnormalities. Extremity exam demonstrated 4/5 muscle strength throughout and equal carotid, radial, femoral and dorsalis pedis pulses bilaterally. The patient had no focal neurologic abnormalities. Stool exam did not reveal the presence of blood.

The patient’s laboratory test results were significant for a slightly increased serum sodium of 147 mmol/L (normal range, 135-146 mmol/L) as well as an increased chloride of 112 mmol/L (normal range, 96-107 mmol/L). His BUN was 45 mg/dL (normal range, 7-25 mg/dL) and the creatinine level was 1.9 mg/dL (normal range, of 0.8-1.6 mg/

CME INFORMATION

TARGET AUDIENCE

The March/April Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists, general practitioners, obstetricians-gynecologists, emergency medicine physicians, pediatricians, dermatologists, radiologists, psychiatrists, and neurologists.

EDUCATIONAL OBJECTIVES

After reading this article, physicians should be able to better identify and understand the pathophysiology, clinical presentation, diagnosis, and treatment of multiple myeloma.

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) hour of

category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

DISCLOSURE

Dr. Stellingworth has nothing to disclose.
Dr. Broussard has nothing to disclose.
Dr. Cataldo has nothing to disclose.
Dr. Morrissey has nothing to disclose.
Dr. Lipscomb has nothing to disclose.
Dr. Lopez discloses that he is a member of the LSMS *Journal* Board and the LSMS *Journal* Editorial Board.
Dr. Rigby has nothing to disclose.

ORIGINAL RELEASE DATE
4/30/2003

EXPIRATION DATE
4/30/2004

Estimated time to complete this activity is 1 hour.

dL). The patient's bicarbonate was decreased at 20 mmol/L (normal range, 24-32 mmol/L). A normocytic anemia with a hemoglobin of 11.6 gm/dL (normal range, 13.5-17.7 gm/dL) and hematocrit of 35.3% (normal range, 40%-51%) was also appreciated. The patient's total serum protein was elevated at 8.9 g/dL (normal range, 6.0-8.0 g/dL), serum globulin was increased at 5.6 g/dL (normal range, 2.3-3.5 g/dL), and albumin was decreased at 3.3 g/dL (normal range, 3.4-5.0 g/dL). The corrected serum calcium was 9.8 mg/dL (normal range, 8.4-10.3 mg/dL). The urinalysis revealed the presence of protein and ketones. A urine toxicology screen was negative.

The patient was admitted for further evaluation and management. A CT scan of the head revealed age-appropriate atrophy. There was no serologic evidence of syphilis or hepatitis A, B, or C infection. His serum TSH level was within the normal range. His family reported that the laser beam delusion had actually been present for at least 10 years. Psychiatric consultation and evaluation established a diagnosis of psychosis and a low dose of risperidone was recommended. After intravenous fluid hydration, repeat laboratory tests demonstrated resolution of the hypernatremia and an anion gap that had decreased to 5 mmol/L.

A paraproteinemia was suspected based on the elevated total protein, anemia, renal insufficiency, and the slightly decreased anion gap. Serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) with immunofixation were ordered (Figure 1). The SPEP demonstrated a prominent restriction in the gamma fraction. Gamma globulin was increased at 2.8 g/dL (normal range, 0.5-1.5 g/dL) and the M spike was 2.3 g/dL (normal, 0 g/dL). UPEP revealed an elevated IgG at 2380 mg/dL

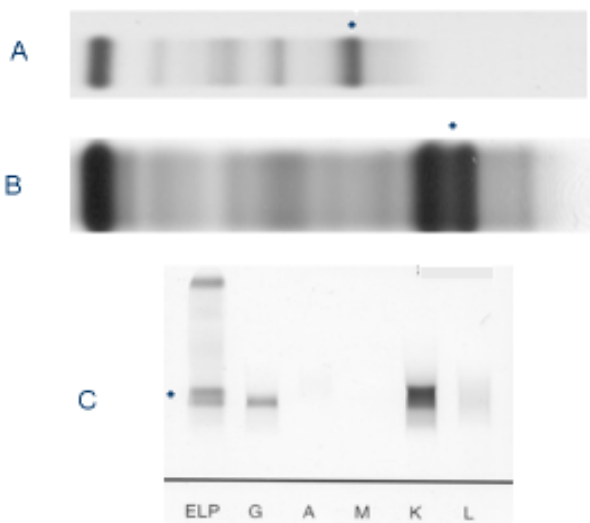


Figure 1. A—Serum protein electrophoresis showing abnormal band (*) in gamma region. B—Urine protein electrophoresis showing two abnormal bands (*) in gamma region. C—Urine immunofixation showing abnormal bands (*) of monoclonal IgG kappa and free kappa (Bence-Jones) light chains.

(normal range, 680-1530 mg/dL), and a reduced IgM at 35 mg/dL (normal range, 40-168 mg/dL). Serum and urine immunofixation were both significant for an IgG predominance. The patient's serum beta-2-microglobulin level was also elevated at 4.0 mg/mL (normal range, 1.0-1.7 mg/mL). The patient's bone marrow biopsy contained 15% plasma cells, a finding consistent with multiple myeloma (Figure 2). Lytic lesions were discovered on plain radiographs of the pelvis. Flow cytometry demonstrated plasma cells that stained positive for CD38 and CD138, a binding pattern also consistent with multiple myeloma. A chemotherapeutic regimen of melphalan and prednisone was offered but was declined.

The patient was discharged on hospital day 5 for follow-up in the Hematology/Oncology Clinic.

MONOCLONAL GAMMOPATHIES - AN OVERVIEW

While a polyclonal immunoglobulin excess represents a natural reactive or inflammatory process, monoclonal gammopathies usually represent an overproduction of immunoglobulins by clonal malignant plasma cells.¹ The protein produced may be a complete immunoglobulin molecule, a light chain component, or a heavy chain component. A broad spectrum of plasma cell dyscrasias are encountered clinically, which are related by their abnormalities in plasma cell proliferation and immunoglobulin production but differentiated by location, amount, and type of immunoglobulin production. Multiple myeloma, Waldenstrom's macroglobulinemia, osteoclastic myeloma, heavy chain disease, and light chain disease/primary amyloidosis are examples of plasma cell disorders.

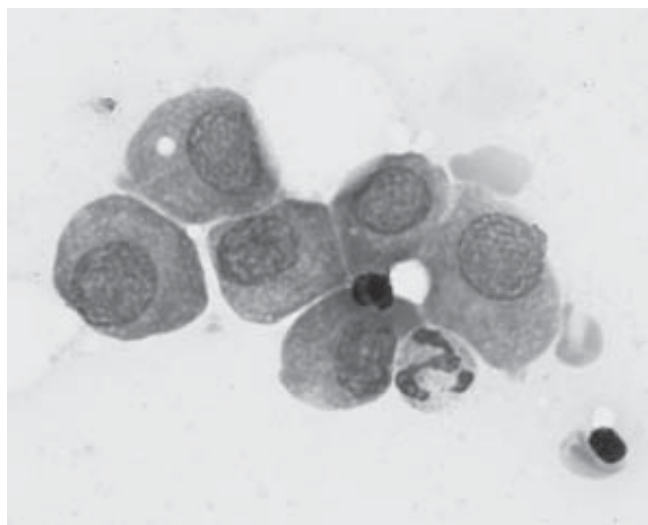


Figure 2. Cluster of abnormal plasma cells with a neutrophil from bone marrow aspirate.

Further clinical classification recognizes diseases that are not ready for therapeutic interventions and include monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).

Waldenström's macroglobulinemia, first described in 1944, is characterized by an oversecretion of IgM by abnormal lymphoid cells.² Organs that are characteristically infiltrated with these abnormal plasmacytoid lymphocytes include the bone marrow, spleen, liver, and lymph nodes. Patients may present with chronic bleeding (most commonly from the gums and nose) and anemia, visual disturbances and neuropathies, or Raynaud's phenomenon. Glomerular abnormalities may manifest as uremia, dehydration, and nonselective proteinuria. Pathogenesis appears dependent upon IgM reactivity with carbohydrate epitopes of myelin associated glycoprotein (MAG) or various gangliosides.

Osteoclastic myeloma is better known by the acronym POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes). Sclerotic skeletal lesions are a hallmark of this IgA gammopathy, and most patients will also have a chronic, demyelinating inflammatory polyneuropathy.³ Hepatosplenomegaly or lymphadenopathy may be present. Gynecomastia and testicular atrophy are common endocrinopathies associated with this disease.³ Typical dermatologic findings include hyperpigmentation, hypertrichosis, and angiomas.

Heavy or light chains may individually contribute to the development of disease. Heavy chain disease (HCD) is rare and involves three immunoglobulin classes: alpha-HCD is the most frequent, mu-HCD is rare, and gamma-HCD is of intermediate incidence.⁴ The demonstration of heavy chains by immunochemical methods in the absence of light chains is mandatory for the diagnosis of HCD.⁴ Alpha-HCD is commonly found in the small intestine, and it is speculated that the highly active lymphoid tissue in this organ results in the potentiation of a mutant clone.⁴ Patients commonly present with signs of malnutrition as well as clubbed fingers. While alpha-HCD is common in Mediterranean and Middle Eastern patients, there is no discernable epidemiologic pattern to gamma-HCD.⁴ This disease has no specific histologic pattern, and autoimmune disorders including rheumatoid arthritis, SLE, myasthenia gravis, thyroiditis, and Sjögren's syndrome frequently appear in these patients.⁴ Though only thirty documented cases of mu-HCD have been published over the last 30 years, it appears to be associated with chronic lymphocytic leukemia.⁴

The presence of light chains in either the urine or serum usually signals an aggressive neoplastic process. However, idiopathic light chain (Bence Jones) proteinuria may remain stable for years before degrading into either multiple myeloma or primary amyloidosis (PAL).⁵ Indeed, there is a direct link between abnormal light chains and PAL. The amyloid protein subunit is usually a lambda-class light chain fragment.⁶ Patients with PAL may present with macroglossia, congestive heart failure, nephrotic syn-

drome, gastrointestinal malabsorption, peripheral neuropathy and carpal tunnel syndrome.⁶

MULTIPLE MYELOMA

Epidemiology and Pathogenesis

Multiple myeloma represents 10% of hematologic malignancies and 1% of all cancers.⁷ The risk for disease increases with age and the median age at diagnosis is 65 to 70 years. Only 2% of all cases occur before the age of 40.⁸ Multiple myeloma is more common in African-Americans than Caucasians, and the male to female ratio for this diagnosis is approximately 2:1.⁹ The median survival rate is 2.5 years with a five-year survival rate of 25%.

A myriad of possible etiologies and associations for multiple myeloma have been reported in the literature. Occupational exposures are diverse and include low dose radiation, wood, textile, rubber metal, and even petroleum products.⁹ Research suggests that there may be a genetic predisposition to the disease. First-degree relatives of affected patients appear to have a higher incidence of the disease, and animal studies have demonstrated that specific strains of mice are more prone to the development of plasmacytomas following mineral oil injections.⁹ Cytogenetic studies have demonstrated that chromosomal abnormalities may contribute to the development of disease. The most common translocation associated with multiple myeloma involves the band 14q32, which codes for the immunoglobulin heavy chain locus. This region is frequently exchanged with chromosomes 11q13, 4p16 and 16q23, which encode for the cyclin D1 gene, fibroblast growth receptor 3 and c-maf oncogene, respectively.¹⁰ Deletions of chromosomes 13q and 17p are associated with a poor prognosis in multiple myeloma.¹⁰ More specifically, deletion of 17p results in the loss of the tumor suppressor gene-associated p53 and median survival in these patients is only 14 months. Conversely, trisomies of chromosomes 6, 7 and 9 are associated with an improved survival rate.¹⁰ Recent literature has suggested that the human herpes virus 8 may provide support for tumor growth in the bone marrow.¹¹ It is postulated that this virus infects nonmalignant dendritic cells and encodes a viral homologue of interleukin six that stimulates growth and prevents apoptosis of the malignant plasma cells.¹¹ No cause and effect relationship has been proven for this hypothesis of viral oncogenesis.

Unopposed osteoclast activity is responsible for two of the most common clinical findings in this disorder: bone pain and hypercalcemia. Tumor necrosis factor-alpha, IL-11, and macrophage inhibitory protein 1-alpha have been implicated in the potentiation of osteoclast-associated activity.¹²

CLINICAL PRESENTATION AND INITIAL DIAGNOSTIC STUDIES

Patients commonly present with bone pain and unexplained weakness. Bone pain is often acute in onset, se-

vere in intensity, and exacerbated with movement. It may be due to pathologic fractures involving the vertebra, ribs, or femoral neck. Vertebral compression fractures may result in spinal cord compression. Unexplained fatigue, weakness, and even dyspnea is often due to anemia. Renal insufficiency is present in more than one-half of patients and is usually due to tubular abnormalities caused by light-chain (ie, Bence-Jones) proteins. The development of hypercalcemia may result in numerous complications including dehydration, fatigue, nausea, vomiting, constipation, renal insufficiency, weakness, somnolence, confusion, and psychiatric disturbances. Impaired humoral-mediated immune function results in infections, usually due to encapsulated bacteria. Even a hyperviscosity syndrome may develop with resultant alterations in mental status, bleeding from mucous membranes, vestibular abnormalities, and nausea. This syndrome is more common in patients with an IgA paraproteinemia. Much as in our patient, a recent report has noted that 24% of patients with newly-diagnosed multiple myeloma have weight loss.¹³

Patients suspected of having multiple myeloma should have a complete history and physical exam, a CBC with peripheral smear, chemistries for serum calcium, creatinine, and albumin as well as a routine urinalysis (UIA) and metastatic bone survey. Laboratory studies and work-up may reveal hypercalcemia, anemia, an increased total serum protein, azotemia, and lytic bone lesions on roentograms. A narrowed anion gap may also be seen due to the presence of positively charged immunoglobulins. The anemia is multifactorial, a result of decreased erythrocyte production, increased destruction and myelophthisis.¹⁴ A peripheral smear may show red blood cell rouleaux (ie, "coin stacking") of the red blood cells. The patient may excrete large amounts of light chains, but a routine U/A may not reveal proteinuria because conventional dipsticks primarily detect albumin. The addition of sulfosalicylic acid to the urine may correct this problem.

Lytic bone lesions are best appreciated with plain bone radiographs of the axial skeleton. Bone scans in this setting are usually negative due to the lack of osteoblastic involvement.

Beta-2-microglobulin is a protein that is shed by B cells and corresponds to myeloma cell mass. Increased levels of beta-2-microglobulin as well as C-reactin protein and lactate dehydrogenase are associated with a worse prognosis.¹⁵ Serum and urine protein electrophoresis with immunofixation should also be performed. An IgG paraprotein is found in more than 50% of patients, an IgA paraprotein in 20%, and an IgD paraprotein in less than 2.5%; light chains alone are found in 16% of patients.¹³

A bone marrow aspirate and biopsy are essential components in the evaluation of multiple myeloma.^{14,15} The bone marrow is typically infiltrated by 10% or more plasma cells. Immunoperoxidase staining of the marrow permits the physician to distinguish monoclonal gammopathies from reactive plasmacytosis due to chronic liver diseases, metastatic cancer, and chronic infections including AIDS.

Only one light chain will stain positive in multiple myeloma. When both kappa and gamma chains are demonstrated, a polyclonal process is present. Flow cytometry characteristically demonstrates plasma cells that are positive for CD38, CD56, and CD138 and negative for CD19.¹⁰ The absence of CD56 may characterize a rare variant of multiple myeloma known as plasma cell leukemia. The bone marrow plasma cell labeling index is a double immunofluorescence technique, which helps to distinguish overt myeloma from monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. Fresh bone marrow is incubated with stains that identify active DNA synthesis and the presence of plasma cells. Increased levels of DNA synthesis in plasma cells is highly suggestive of symptomatic multiple myeloma.

Diagnostic Confirmation and Staging

In a patient with the usual clinical features of multiple myeloma (see above), the essential criteria for the diagnosis of multiple myeloma include a bone marrow containing at least 10% plasma cells and at least one of the following: a serum-associated monoclonal protein in the serum that is >3 g/dL, a monoclonal protein in the urine, or the presence of bone lesions that are lytic.¹⁴

The Durie-Salmon system is used for staging of multiple myeloma. The original system determined the tumor burden or myeloma cell mass by evaluating urine or serum-associated monoclonal protein levels; the number of lytic lesions; and clinically relevant factors such as anemia, hypercalcemia, and renal function.¹⁶ Recently, a modified staging system was developed that predicts prognosis and survival based only on serum concentrations of albumin and beta-2-microglobulin.¹⁷ For example, a beta-2-microglobulin level of less than 2.5 mg/L predicts a median survival of 58 months, while patients with a beta-2-microglobulin greater than 5.5 mg/L and an albumin level less than 3.0 mg/L have a median survival of only 16 months.

Clinicians must distinguish multiple myeloma from a differential diagnosis that includes monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). MGUS is characterized by an M protein spike <3 g/dL, <10% plasma cells in the bone marrow and less than 50 mg/day of Bence Jones (ie, light chain) proteins.^{5,14} In addition, there are typically no lytic lesions, no anemia, no hypercalcemia, and no renal failure. More common than multiple myeloma, MGUS is present in 3% of patients over the age of 70.⁵ Over a quarter of patients diagnosed with MGUS will go on to develop a malignant monoclonal gammopathy, usually multiple myeloma. In one study, the mean interval between diagnosis of MGUS and the development of malignancy was approximately 10 years.⁵ Unfortunately, no findings have been determined that allow for predicting which patients will progress to overt disease. Patients with MGUS should be followed at regular intervals to detect the development of serious disease.

SMM is found in asymptomatic patients with an M

protein >3g /dL and/or >10% bone marrow plasma cells.^{14,18} As in MGUS, patients with SMM have no lytic lesions, renal insufficiency, or hypercalcemia. The annual conversion rate from SMM to multiple myeloma appears to be approximately 3.3% per year. The presence of Bence Jones proteins in urine, >10% bone marrow plasma cells, and an IgA isotype predict a more rapid progression to overt disease.⁵

There are several other variants of multiple myeloma which warrant discussion. Patients with a solitary bone lesion and no other evidence of myeloma are diagnosed with a solitary plasmacytoma of bone.¹⁹ Biopsy of these bone lesions demonstrates plasma cells. The bone marrow examination typically reveals the absence of a monoclonal protein and less than 10% plasma cells and the skeletal survey is negative for additional bone lesions. Anemia, hypercalcemia, and renal insufficiency are characteristically absent.¹⁹ In contrast to multiple myeloma, uninvolved immunoglobulins are not suppressed. A low concentration of the monoclonal protein is present in either the urine or serum. Treatment usually involves radiotherapy. Although patients may be asymptomatic over a prolonged period, greater than two-thirds will eventually develop multiple myeloma.¹⁹

Extramedullary plasmacytoma is diagnosed when monoclonal plasma cell infiltrates are present outside of the bone marrow.¹⁹ These tumors are frequently found in the upper respiratory tract but can arise anywhere. Radiotherapy is the treatment of choice and the recurrence rate is less than 5%.¹⁹

Nonsecretory multiple myeloma is characterized by the inability of the abnormal plasma cells to secrete immunoglobulins. It comprises 1% to 5% of all multiple myelomas.³ Immunoperoxidase stains of bone marrow reveal the presence of light chains, usually the kappa class, in the plasma cell-associated cytoplasm.³ Despite the absence of an M protein in either the serum or urine, nonsecretory multiple myeloma has a similar clinical presentation to multiple myeloma, and bone marrow biopsy reveals 20% to 75% plasma cells.²⁰ Treatment and survival are very similar to classic multiple myeloma.³

Plasma cell leukemia accounts for approximately 3% of all cases of multiple myeloma, and is characterized by an absolute plasma cell count of greater than $2 \times 10^9/L$.³ Two variants of plasma cell leukemia exist. The primary form is more common and presents without evidence of previous multiple myeloma while the secondary form represents leukemic transformation of established disease.³ Plasma cells lack CD56 and also demonstrate an upregulation of the CD20 receptor. Prognosis is grim with a median survival of 7 months.³ Combination chemotherapy followed by stem cell rescue is optimal when age and clinical condition permit.³

Treatment

Symptomatic patients with advanced disease should be treated with chemotherapy and localized radiotherapy to

bone lesions when appropriate.¹⁵ Stem cell transplantation should be considered in patients less than 70 years old.¹⁵ Allogeneic transplants reduce the risk of relapse by utilizing cancer-free stem cells. However, nearly 90% of multiple myeloma patients are ineligible for this procedure due to lack of a donor, age, or poor functional status. The mortality rate associated with this type of procedure approaches 25%.¹² Autologous transplants have only a 1% to 2% mortality rate but there is an inherent risk of harvesting tumor cells.¹⁵

All patients over the age of seventy years and younger patients with contraindications to transplant typically receive melphalan and prednisone, a standard chemotherapeutic regimen for over a quarter century. The objective for therapy is palliation and control of disease rather than cure. The response rate is approximately 55% and is manifest by decreases in serum and urine monoclonal protein levels as well as improvement in complications of disease including bone pain and anemia.¹² While other combination chemotherapies have higher response rates, there may be little definitive benefit in survival.¹⁰ Interferon has been used to extend the plateau phase of disease, which is reflected by a stable decrease in monoclonal proteins. Extended courses of chemotherapy are associated with the development of myelodysplastic syndrome.

Not all patients respond to chemotherapy. There are several mechanisms for drug resistance in multiple myeloma. Relapsing or refractory disease may be due to upregulation of glycoprotein P-170 pump(s) that decrease the intracellular concentration of the chemotherapeutic agent.¹² Enhanced cellular repair, altered drug metabolism, and reduced drug efficacy due to alterations in drug targets may occur simultaneously and decrease the effectiveness of treatment regimens.¹² Relapsing or refractory disease is usually treated with vincristine, adriamycin, and dexamethasone (VAD) in either infusion or bolus form. In at least one trial, the combination of vincristine, carmustine, doxorubicin, and prednisone (VBMCP) was noted to produce a 4-month response rate of 56% in resistant patients, similar to the results achieved with VAD chemotherapy.²¹ Repeat stem cell transplants after relapse are of little benefit in most patients.¹²

The role of thalidomide in treatment of this disease is still evolving. This drug is known to inhibit angiogenesis and is postulated to directly inhibit malignant plasma cell proliferation.²² Single agent use of thalidomide has primarily been administered in patients with progressive and refractory disease.²³ This drug has the potential to cause severe side effects including neuropathy, thrombotic events, and severe birth defects.

The clinician needs to be able to address complications that may develop in their patients with multiple myeloma. Patients with renal failure should be vigorously hydrated with normal saline and urine output should be closely monitored. Plasmapheresis and hemodialysis may also be needed. Anemic patients may benefit from erythropoietin administration. Patients should receive influenza and S.

pneumoniae vaccination. Intravenous gamma globulin may also be used in patients whose recurrent infections are due to suboptimal humoral-mediated immune function. Bone pain typically responds to chemotherapy, but may benefit from radiotherapy if localized and refractory. Patients with bone pain, more than one lytic lesion, and/or hypercalcemia benefit from bisphosphonate therapy. The actions of bisphosphonates in multiple myeloma are not completely understood. It is speculated that these agents reduce osteoclast activity and induce apoptosis. In vitro studies demonstrate that bisphosphonates increase the activity of gamma delta T cells, which preferentially attack malignant plasma cells.¹² Clinical trials have demonstrated a reduction in skeletal complications when a monthly dose of pamidronate is administered with chemotherapy.²⁴

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CME QUESTIONS

To earn CME credit, read the preceding CME article and complete the registration, evaluation, and answer form on page 119. Mail or fax the registration, evaluation, and answer form to the Educational and Research Foundation. Answers must be postmarked or faxed prior to April 30, 2004. Participants must attain a minimum score of 75% to receive credit.

For each question, choose the one answer that is most correct.

- All of the following are common clinical manifestations of multiple myeloma except:
 - Osteolytic bone lesions
 - Anemia
 - Hypercalcemia
 - Increased total serum protein
 - Osteoblastic bone lesions
 - Renal dysfunction
- True or False. Standard urinalysis primarily detects albumin and not light chains as part of its protein detection.

3. True or False. Decreased levels of beta-2 microglobulin are associated with worse prognosis in multiple myeloma.
4. All of the following statements about multiple myeloma are true except:
 - a) Multiple myeloma represents 10% of all hematologic malignancies.
 - b) Chromosomal abnormalities appear to play a role in the pathogenesis of multiple myeloma.
 - c) Osteoclastic activity is responsible for bone pain and hypercalcemia in multiple myeloma.
 - d) The diagnosis of multiple myeloma requires an M protein spike of <3 g/dL, $<10\%$ plasma cells in the bone marrow, and <50 mg/day of Bence Jones proteins.
 - e) Melphalan and prednisone are used in the treatment of patients with multiple myeloma who are greater than 70 years of age or who have contraindications to bone marrow transplantation.