An 85-year-old man with a medical history notable for monoclonal gammopathy of undetermined significance (MGUS), prostate cancer, bladder cancer, and squamous cell skin cancer presented to the emergency department with periodic epistaxis of 3 to 4 weeks’ duration. The bleeding was spontaneous without antecedent trauma. The episodes of epistaxis usually lasted for about an hour. Pressure to the nares would stop the bleeding. The patient noted prolonged bleeding of his gums after brushing his teeth. He denied easy bruising, petechiae, spontaneous hemarthrosis, or rashes. He had experienced fatigue during the past few months with an unintentional weight loss of about 10 kg even though his appetite was normal. He denied new bone or joint pain.

The patient’s medications included clonidine, hydrochlorothiazide, multivitamin, and a hyaluronic/glucosamine/chondroitin preparation. He denied any previous medication reactions or intolerances.

Physical examination revealed a blood pressure of 88/46 mm Hg and a heart rate of 58 beats/min. The patient was afebrile and appeared well nourished and alert. He had bilateral scattered ecchymoses of the lower extremities. The abdomen was soft and nontender, had normal bowel sounds, and showed dullness to percussion of Traube space with inspiration. Findings on pulmonary, cardiovascular, prostate, and lymph node examinations were normal.

1. Which one of the following is the most likely explanation for the findings on abdominal examination?
   a. Splenomegaly
   b. Pancreatic mass
   c. Hydronephrosis
   d. Ascites
   e. Periumbilical lymphadenopathy

   Traube space is a triangular space in the left lower anterior portion of the chest. It is bordered superiorly by the limits of cardiac dullness, inferiorly by the costal margin, and laterally by the mid-axillary line. Traube first described dullness to percussion in this space as indicative of pleural effusion. However, Parrino found dullness to percussion of Traube space with inspiration to be a sign of splenomegaly, with a sensitivity of 11% to 76% and a specificity of 63% to 95%. For experienced examiners, the positive likelihood ratio for dullness to percussion of Traube space indicating splenomegaly is 2.1. This patient, hepatomegaly secondary to amyloidosis is a possible but less likely explanation for dullness to percussion of Traube space.

   The pancreas is anatomically distant from Traube space, making a pancreatic mass an unlikely source for dullness to percussion in this area. Because the kidneys are a retroperitoneal organ, percussion is not typically a useful physical examination tool to assess their size. Ascites can be assessed by flank dullness with a sensitivity of 80% to 94% and a specificity of 29% to 69%. Periumbilical lymph nodes, known as Sister Mary Joseph nodes after a Mayo Clinic nurse, are often a sign of metastatic cancer.

   Laboratory studies (reference ranges in parentheses) were performed. A complete blood cell count (CBC) exhibited pancytopenia with a hemoglobin level of 8.3 g/dL (13.5-17.5 g/dL) compared to 13 g/dL 5 months earlier. The platelet count was 29,000 × 10⁹/L (150-450 × 10⁹/L), and leukocytes were 2 × 10⁹/L (3.5-10.5 × 10⁹/L).

   Review of the patient’s medical record revealed that MGUS had been diagnosed 1 year earlier. At that time, the patient had a normal CBC; serum protein electrophoresis (SPEP) showed an increased γ-globulin level of 2.1 g/dL (0.6-1.6 g/dL) and M-spike of 1.4 g/dL with immunofixation showing IgG of 1930 mg/dL (767-1590 mg/dL). At the patient’s most recent MGUS follow-up 5 months previously, the M-spike was stable at 1.8 mg/dL.

2. Which one of the following is correct regarding the patient’s yearly risk of developing multiple myeloma?
   a. 1%
   b. 5%
   c. 7%
   d. 10%
   e. 15%

   The risk of progression from MGUS to multiple myeloma is generally 1% per year. However, size (<1.5 g/dL has a lower rate of progression) and type (IgG has a lower rate...
of progression compared with IgM or IgA) of M-spike has been associated with progression.\textsuperscript{7} Additionally, an abnormal \textsuperscript{κ}/\textsuperscript{λ} free light chain ratio (<0.26 or >1.65) increases the risk of progression to myeloma.\textsuperscript{8} In patients with MGUS, the general recommended follow-up is 6 months and then annually, if stable.\textsuperscript{6,8} However, follow-up is tailored to the individual patient on the basis of the previously described predictors of progression.

Smoldering multiple myeloma, which is classified as a serum monoclonal protein of 3 g/dL or higher and/or 10% or greater bone marrow clonal plasma cells without end-organ damage (lytic lesions of bone, anemia, hypercalcemia, or renal insufficiency), portends a 10% risk per year of progression to overt multiple myeloma or amyloidosis in the first 5 years after diagnosis.\textsuperscript{9} Because smoldering multiple myeloma progresses much faster than MGUS, such patients require closer follow-up.

A bone marrow biopsy specimen from our patient revealed 30% to 40% monoclonal \textsuperscript{κ} plasma cells, hypercellular marrow with trilineage hematopoiesis with decreased granulopoiesis, and decreased megakaryocytes.

3. Given the biopsy information, which one of the following is most likely diagnosis in this patient?
   a. MGUS
   b. Multiple myeloma
   c. Waldenstrom macroglobulinemia
   d. Solitary plasmacytoma
   e. AL amyloidosis

The diagnostic requirement for MGUS is a serum M protein level less than 3 g/dL; bone marrow plasma cells less than 10%; no myeloma-related organ or tissue impairment including symptoms or bone lesions on skeletal imaging; and no evidence of other B-cell proliferative disorders or light chain–associated amyloidosis or other light chain, heavy chain, or immunoglobulin-associated tissue damage.\textsuperscript{10,11} Asymptomatic or smoldering myeloma is defined as a serum M protein level greater than 3 g/dL and/or bone marrow clonal plasma cells greater than 10% without myeloma-related organ or tissue impairment.\textsuperscript{9,11}

Symptomatic myeloma is defined as an M protein in serum and/or urine, bone marrow with clonal plasma cells or biopsy proven plasmacytoma, and any myeloma-related organ or tissue impairment including bone lesions on bone imaging.\textsuperscript{10,11} Myeloma-related organ or tissue impairment includes increased calcium levels, renal insufficiency attributable to myeloma, anemia, bone lesions (lytic lesions or osteoporosis with compression fractures), symptomatic hyperviscosity, amyloidosis, and recurrent bacterial infections (>2 episodes in 12 months).\textsuperscript{11}

Waldenstrom macroglobulinemia is diagnosed by demonstrating lymphoplasmacytic lymphoma in the bone marrow with an IgM monoclonal gammopathy on SPEP and immunofixation of blood.\textsuperscript{10,11} Splenomegaly and hyperviscosity are much more common in Waldenstrom macroglobulinemia.

A solitary plasmacytoma is a tumor composed of plasma cells identical to those seen in multiple myeloma. The criteria for diagnosing a solitary plasmacytoma include clonal plasma cells as noted on a bone or soft tissue biopsy specimen, bone marrow without evidence of clonal plasma cells, skeletal survey and magnetic resonance imaging of the spine and pelvis without lytic lesions besides the plasmacytoma, and absence of multiple myeloma–related end-organ damage.\textsuperscript{10,11} If clonal plasma cells are noted in the bone marrow with a concomitant solitary lesion of clonal plasma cells, stage I multiple myeloma is diagnosed.\textsuperscript{10,11}

Primary (AL) amyloidosis is defined as deposition of amyloid fibrils into tissues such as the heart, lungs, liver, intestines, and kidneys.\textsuperscript{12} Amyloid consists of precipitated monoclonal light chains produced by overproliferation of plasma cells. Primary amyloidosis can be caused by multiple myeloma; however, it causes end-organ damage, such as hepatic failure, heart failure, and nephrotic syndrome, that is not usually associated with multiple myeloma. Multiple myeloma rarely develops after amyloidosis (0.4%).\textsuperscript{12} Primary amyloidosis is diagnosed by biopsy proven amyloid deposition of involved tissue, such as abdominal fat, bone marrow, rectum, kidney, or myocardium.

Additional laboratory studies revealed the following: albumin, 3.2 g/dL (3.5-5.0 g/dL); plasma cell labeling index, 3.4% (low, 0.0-2%; intermediate, 0.3-0.99%; high, 1-2.99%; very high, >3%); creatinine, 0.9 mg/dL (0.8-1.3 mg/dL); and β-2 microglobulin, 6.67 μg/mL (0.70-1.80 μg/mL).

4. Which one of the following findings would predict a better prognosis for the patient's multiple myeloma?
   a. Platelet count of 29,000 x 10\textsuperscript{12}/L
   b. β-2 Microglobulin of 6.67 μg/mL
   c. Plasma cell labeling index of 3.4%
   d. Serum creatinine level of 0.9 mg/dL
   e. Age of 85 years

Factors that aid in predicting the prognosis of multiple myeloma have been described.\textsuperscript{13} Thrombocytopenia can indicate bone marrow infiltration or platelet consumption and is associated with a poor prognosis.\textsuperscript{11,13} β-2 Microglobulin is a component of the major histocompatibility complex found on nucleated blood cells. It is associated with increased blood cell proliferation, and high levels portend a poor prognosis in multiple myeloma.\textsuperscript{11,13} The plasma cell labeling index indicates the proliferation rate of plasma cells in the bone marrow. Higher plasma cell labeling index percentages are associated with a worse prognosis.\textsuperscript{11,13} Normal serum creatinine levels are associated with a better
prognosis in multiple myeloma because they can suggest no kidney involvement by the disease. Survival is better in patients with multiple myeloma who are younger than 70 years (median duration, 40.5 months) compared with those older than 70 years (median duration, 26.4 months).

Our patient’s advanced age is a poor prognostic indicator. Additional poor prognostic indicators include poor performance status and albumin levels lower than 3 g/dL.

The patient was seen by the otorhinolaryngology service in the hospital. They found a source of bleeding and successfully cauterized the area. The patient was discharged, with a follow-up appointment with a hematologist several days later.

5. Which one of the following should be the first-line treatment regimen for this patient’s multiple myeloma?
   a. Melphalan
   b. Paclitaxel
   c. Methotrexate
   d. Vincristine
   e. Doxorubicin

Melphalan was one of the earliest therapeutic regimens used for the treatment of multiple myeloma and currently is the initial regimen used. It is given in conjunction with a corticosteroid, such as prednisone. Methotrexate and paclitaxel are not used in the treatment of multiple myeloma. When stem cell transplant is anticipated, a regimen such as vincristine, doxorubicin, and dexamethasone can be used to achieve cytocrudation without compromising stem cell mobilization. Several studies have shown the superiority of the effect of autologous and allogeneic stem cell transplants on survival, but a large number of patients cannot undergo stem cell transplant because of older age (>70 years), poor performance status, or serious comorbid conditions. Thalidomide has been used for relapsed or refractory disease. Rituximab has also been investigated in the treatment of CD20+ multiple myeloma, but no current studies have shown a significant disease-free survival compared to or in combination with traditional therapies.

The patient received melphalan and prednisone chemotherapy for IgG multiple myeloma. His epistaxis continued periodically from diagnosis until his death several months later from sepsis, respiratory failure, and cardiomyopathy due to aspiration pneumonia in the setting of immunosuppression. His epistaxis was attributed to thrombocytopenia with concomitant serum light chain–associated platelet dysfunction.

DISCUSSION

Multiple myeloma accounts for approximately 1% to 2% of all malignancies and 10% to 15% of all hematologic malignancies. The annual incidence of multiple myeloma is 3.3 to 4.3 per 100,000 people in the United States, and it has nearly doubled during the past 60 years, likely because of an increase in diagnosis (ascertainment bias) rather than to an increased de novo occurrence. Certain chemical substances and ionizing radiation have been potentially implicated in occurrences of multiple myeloma. The median age of diagnosis for multiple myeloma is between 66 and 70 years. Myeloma is more common in African Americans compared with white persons, and less common in Asians. Men are more commonly affected than women. Most cases present de novo, although a minority evolves from MGUS. In one study, 20% of patients with multiple myeloma were recognized as having MGUS, and 9% were noted to have smoldering multiple myeloma before symptomatic multiple myeloma developed.

The classic clinical presentation of multiple myeloma is fatigue and malaise associated with a normocytic, normochromic anemia and/or hypercalcemia, back pain from lytic bone disease, and impaired renal function as indicated by elevated serum creatinine concentrations. Although weight loss is not usually included in this classic description of multiple myeloma, it has been described in nearly one-quarter of all cases. One study found bone pain at diagnosis in 58% of patients and fatigue in 32% of patients, usually associated with anemia. Anemia is present in nearly three-quarters of patients at diagnosis but is rarely severe.

Investigations for suspected myeloma include screening tests, establishing a diagnosis, estimating tumor burden and prognosis, assessing myeloma-related organ impairment, and special tests for certain patients. Screening tests include CBC, erythrocyte sedimentation rate, plasma viscosity, electrolyte panel, urea, creatinine, calcium, albumin, uric acid, radiography of symptomatic bony areas, SPEP, and urine protein electrophoresis. A full skeletal survey, immunofixation of serum and urine, and bone marrow aspiration are used to establish a diagnosis of suspected myeloma.

Thrombocytopenia is an uncommon finding at presentation of multiple myeloma. A study that reviewed 1027 patients with newly diagnosed multiple myeloma at Mayo Clinic found only 3 patients with platelet counts lower than 30 x 10^9/L. Of these 3 patients, 2 had idiopathic thrombocytopenic purpura, and 1 had sepsis. Thrombocytopenia and leukopenia in multiple myeloma are most commonly caused by bone marrow infiltration of plasma cells.

Although hypercalcemia and renal failure are known to be associated with multiple myeloma, only 48% and 28% of patients present with a creatinine level greater than 1.3 mg/dL and a calcium level greater than 10.1 mg/dL, respectively. Studies have shown that renal impairment
is present in 30% of patients at diagnosis and in 50% of patients at some time during their disease.\textsuperscript{11} Renal impairment is less common because only 3% to 12% of patients undergo dialysis.\textsuperscript{11}

**REFERENCES**
