MAYO CLINIC

61-Year-Old Man With Right Knee Pain and Chronic Anemia

Moritz Binder, MD, MPH; Hassan B. Alkhateeb, MD; and Ronald S. Go, MD

See end of article for correct answers to questions.

Resident in Internal Medicine, Mayo School of Graduate Medical Education, Rochester, MN (M.B., H.B.A.); Advisor to Residents and Consultant in Hematology, Mayo Clinic, Rochester, MN (R.S.G.).

A 61-year-old man presented to the emergency department with acute right knee pain after hyperflexion of the joint while lying in bed. His medical history was notable for obesity, hypertension, hyperlipidemia, and diabetes mellitus. The patient also reported that at age 40 years, mild microcytosis secondary to β-thalassemia minor was diagnosed, and he had noticed worsening frothy urine over the past year. He described the pain as severe, impairing his ability to bear weight and ambulate, and located both over the posterolateral aspect of his knee and the anterior aspect of his tibia. He reported an associated sensation of grinding and clicking in the joint. He denied any trauma to the joint, the involvement of other joints, constitutional symptoms, rashes, and exposure to ticks. His vital signs were within normal limits.

Physical examination revealed no redness, swelling, or instability of the joint. Radiography performed in the emergency department did not identify evidence of fractures and revealed a mild joint effusion, few osteochondral bodies posterior to the right knee, and stable sclerotic changes of the tibial metaphysis. The joint was immobilized, and the patient was discharged home with a scheduled analgesic regimen for symptomatic relief.

Because conservative management did not resolve his symptoms, the patient presented to his primary care physician 3 weeks later for further evaluation. His symptoms and findings on physical examination were unchanged. Magnetic resonance imaging (MRI) of the right knee revealed synovitis associated with a moderate joint effusion, extensive intrameniscal degeneration involving both the medial and lateral menisci with a tear of the posterior horn of the medial meniscus, widespread chondromalacia, and prominent red bone marrow in the distal femur, but all ligaments were intact. Specifically, the bone marrow appeared markedly hyperintense compared with muscle tissue on T1-weighted images and slightly hypointense on T2-weighted fat saturated sequences.

1. Which *one* of the following is the *most likely* explanation for the bone marrow abnormalities seen in the distal femur on MRI in this patient?

a. Motion artifact
b. Primary myelofibrosis
c. Gaucher disease
d. Normal variant
e. Plasma cell dyscrasia

The patient presented with right knee pain and was incidentally found to have signal abnormalities involving his bone marrow. Motion artifacts would likely distort the overall image and not affect only the bone marrow in a geographic distribution. Likewise, the geographic distribution of the findings would be unusual for primary myelofibrosis, and signal attenuation is more commonly seen than increases in signal intensity.[1] Storage diseases such as Gaucher disease would likely manifest signal attenuation on T1-weighted images and marked increases on T2-weighted sequences. Although mild red bone marrow hyperplasia can sometimes be seen in smokers and obese adults, the marked abnormalities in this patient are concerning for a pathologic process. The prominent appearance of the red bone marrow is most concerning for an infiltrative process such as a plasma cell dyscrasia.

The patient returned to his primary care physician and eventually received a corticosteroid injection in the affected joint for symptomatic relief. After discussion of the imaging findings, the decison was made to further investigate the underlying etiology.

2. To investigate the aforementioned imaging findings and history of frothy urine in this

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patient, which *one* of the following is the *most appropriate* initial diagnostic approach?

a. Repeat complete blood cell count in 3 months
b. Bone marrow biopsy, serum electrophoresis with immunofixation, and free light chain studies
c. Urine electrophoresis with immunofixation and free light chain studies
d. Positron emission tomography (PET) with computed tomography of the axial skeleton
e. Measurement of serum β_2-microglobulin and albumin concentrations

The patient presented with abnormal imaging findings and frothy urine, warranting further diagnostic testing for an underlying plasma cell dyscrasia. A repeated complete blood cell count would be unlikely to yield further information, and the possibility of an underlying infiltrative process warrants a timely work-up. Bone marrow biopsy is the diagnostic gold standard and is essential in confirming the diagnosis of a plasma cell dyscrasia. The initial screening also encompasses the combination of serum electrophoresis with immunofixation and free light chain studies, which are 93% sensitive. Although the addition of urine studies increases sensitivity by about 4%, they are more helpful in monitoring disease progression and response to therapy.[2] Imaging studies are helpful in delineating disease extent, but a conventional bone survey is usually sufficient. Serum β_2-microglobulin and albumin concentrations are of prognostic importance but have no role in establishing the diagnosis.

Laboratory studies revealed the following (reference ranges provided parenthetically): monoclonal IgGκ M spike of 1.6 g/dL on serum electrophoresis; IgA, 101 mg/dL (61-356 mg/dL); IgM, 28 mg/dL (37-286 mg/dL); IgG, 1630 mg/dL (767-1590 mg/dL); κ light chain, 184 mg/dL (0.33-1.94 mg/dL); and λ light chain, 0.91 mg/dL (0.57-2.63 mg/dL), translating into an abnormal free light chain ratio of 203 (0.26-1.65 mg/dL). Flow cytometry identified the presence of monotypic plasma cells expressing κ cytoplasmic immunoglobulin light chains, CD38, and CD138 (but not CD19 or CD45). The serum calcium level was 9.6 mg/dL (8.9-10.1 mg/dL), the creatinine concentration was 1.3 mg/dL (0.8-1.3 mg/dL), and the hemoglobin level was 11.5 g/dL (13.5-17.5 g/dL). No other imaging studies were available to assess for additional bone lesions. His β_2-microglobulin level was 2.97 μg/mL (1.21-2.70 μg/mL), his albumin concentration was 3.8 g/dL (3.5-5.0 g/dL), and his lactate dehydrogenase level was 137 U/L (122-222 U/L). Results of urine microscopy were normal, a 24-hour urine study yielded 556 mg of protein (<167 mg/24 h), and immunofixation revealed the presence of monoclonal κ and an IgGκ fragment. Bone marrow biopsy revealed increased plasma cells in large aggregates occupying approximately 10% of the bone marrow.

3. On the basis of the laboratory results, which *one* of the following is the *most likely* diagnosis in this patient?

a. Active multiple myeloma
b. Smoldering multiple myeloma
c. Monoclonal gammopathy of undetermined significance
d. Light chain (AL) amyloidosis
e. Schnitzler syndrome

The diagnosis of active multiple myeloma can be made on the basis of the free light chain ratio of 100 or higher, considered a myeloma-defining event (MDE), in this patient. The presence of an MDE precludes the diagnosis of smoldering multiple myeloma, and the extent of bone marrow involvement is beyond the range of monoclonal gammopathy of undetermined significance (<10%). In order to establish a diagnosis of systemic amyloidosis, tissue deposition of amyloid would need to be present in addition to a plasma cell dyscrasia. Although joint symptoms are common and monoclonal IgG can sometimes be seen in Schnitzler syndrome, the most prevalent heavy chain is IgM, and our patient lacks the characteristic skin involvement as well as fever, lymphadenopathy, and leukocytosis.

The patient had 10% plasma cells in his bone marrow, but none of the classic MDEs (end-organ damage attributable to the underlying plasma cell proliferation such as hypercalcemia, renal insufficiency, anemia, or lytic bone lesions) were present at the time of initial presentation. With the 2014 revision of the diagnostic criteria,[3] a bone marrow involvement of 60% or more, a serum free light chain ratio of

100 or higher (as long as the involved light chain is >100 mg/dL), or more than one focal lesion (≥5 mm) on MRI also qualify as MDEs. Fluorescence in situ hybridization of the clonal plasma cell population revealed a deletion of the short arm of chromosome 17 and the long arm of chromosome 13 as well as the presence of an additional chromosome 8. A skeletal survey revealed widespread osteopenia with scattered osteolytic lucencies in the clavicles and proximal humeri. Plain film chest radiography revealed a masslike opacity overlying the lower portion of the left lung with loss of visualization of the anterior sixth rib, findings concerning for a plasmacytoma. PET revealed a 6.5 × 4.5-cm intensely fludeoxyglucose-avid, malignant-appearing soft tissue mass destroying the distal end of the left sixth rib and 2 smaller similar-appearing lesions involving the posterior third and distal 11th rib.

After his primary care physician made the diagnosis and completed the initial work-up, the patient established care with our hematology department. He was educated on the natural history, therapy, and prognosis of multiple myeloma. After discussing the advantages and disadvantages of different approaches, recommendations for initial treatment were made.

4. With a new diagnosis of multiple myeloma, which *one* of the following is the *most appropriate* initial treatment strategy for this patient?

a. Bisphosphonate therapy and observation with close follow-up
b. Bisphosphonate therapy and single-agent chemotherapy
c. Bisphosphonate therapy and combination chemotherapy followed by allogeneic hematopoietic stem cell transplant (HSCT)
d. Bisphosphonate therapy and combination chemotherapy followed by autologous HSCT
e. Bisphosphonate therapy and combination chemotherapy followed by whole-body irradiation

The patient has multiple myeloma with a deletion of the gene coding for the tumor suppressor p53. Bisphosphonates play an important role in current treatment strategies but are used in combination with chemotherapy in newly diagnosed multiple myeloma. The addition of a bone-modifying agent is beneficial in the presence of lytic lesions. A 3-drug chemotherapy regimen is a reasonable approach in newly diagnosed disease, and single-agent chemotherapy is not recommended in younger patients with good performance status. Conferring an unfavorable prognosis, the presence of cytogenetic high-risk features warrants more aggressive treatment including early consideration of high-dose chemotherapy, HSCT, and maintenance therapy in eligible patients. Before the introduction of proteasome inhibitors, patients with the aforementioned deletion had a median overall survival of about 15 months after undergoing high-dose chemotherapy followed by autologous HSCT.[4] With current chemotherapy regimens, the prognosis of this patient population has almost doubled.[5] The role of allogeneic HSCT in multiple myeloma is not very well defined and therefore is rarely considered in a patient with newly diagnosed disease. Although localized radiation is used to treat plasmacytoma, whole-body irradiation is not commonly employed in patients with multiple myeloma.

The patient achieved a very good partial response after 4 cycles of chemotherapy with bortezomib, lenalidomide, and dexamethasone before proceeding with autologous HSCT. His posttransplant course was complicated by dehydration with symptomatic orthostasis leading to a brief hospitalization.

5. Which *one* of the following findings is *most important* in determining this patient's prognosis?

a. Serum lactate dehydrogenase level within normal limits
b. Serum albumin level higher than 3.5 g/dL
c. Serum β_2-microglobulin level less than 3.5 μg/mL
d. Deletion of the short arm of chromosome 17
e. Trisomy of chromosome 8

The normal lactate dehydrogenase, normal albumin, and low serum β_2-microglobulin levels alone would predict a 5-year overall survival of 82%.[6] However, our patient also has a deletion of the short arm of chromosome 17, which translates into a predicted 5-year overall survival of 40%[6] and has been associated with an unfavorable prognosis across different

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treatment approaches.[4,7,8] The aforementioned deletion as well as t(4;14), t(14;16), and t(14;20) are commonly seen high-risk cytogenetic features in multiple myeloma. Although the presence of trisomies of the odd-numbered chromosomes may ameliorate the effect of high-risk cytogenetic abnormalities,[9] the potential implications of an isolated trisomy of chromosome 8 are unknown.

One year later, the patient continues on bortezomib maintenance therapy and has ongoing response to treatment. His serum κ free light chain concentration has decreased by 95%, and he no longer has an M protein spike. His creatinine level has remained stable, and urine electrophoresis no longer reveals evidence of monoclonal protein. His total protein remains slightly elevated on repeated 24-hour urine studies. The patient has not had any infections and continues to work full-time.

DISCUSSION

We report the case of a 61-year-old man who presented with right knee pain and was found to have asymptomatic multiple myeloma with high-risk cytogenetic features. The patient received chemotherapy and underwent autologous HSCT 6 months after his initial presentation. He achieved a complete response and remains in good performance status several months later. This case emphasizes the importance of a comprehensive evaluation of common complaints, the challenges in establishing the diagnosis of multiple myeloma, and the recent changes in the diagnostic criteria for multiple myeloma.

With the recent addition of 3 new MDEs, close attention must be paid to serologic findings, bone marrow studies, and MRI studies in patients who would formerly have been classified as having smoldering multiple myeloma.[3] Asymptomatic patients with markedly increased bone marrow plasma cells, high serum free light chain ratios, or lesions on MRI are at imminent risk of progression to multiple myeloma[3,10,11] and do benefit from early treatment with novel chemotherapeutic agents.[12] These new MDEs help to identify a high-risk population of patients that is very likely to have subsequent end-organ damage (70%-90% in the following 2 years). This improved understanding of the process of disease progression from its premalignant state into multiple myeloma with its clinical manifestations and the availability of several novel chemotherapeutic agents has led to a change in the approach to treatment of patients with newly diagnosed disease.

Magnetic resonance imaging is more sensitive in detecting multiple myeloma lesions than standard plain film skeletal survey. PET has been shown to effectively identify the distribution of disease and the fludeoxyglucose uptake by multiple myeloma lesions that correspond to areas of bone lysis seen on computed tomography. Although it is not as sensitive as MRI, PET is able to differentiate active from inactive lesions, and disease activity at the time of diagnosis has prognostic importance.

With the introduction of novel agents in the treatment of multiple myeloma over the past decade, the outlook for patients with newly diagnosed disease has changed dramatically. Risk-adapted treatment strategies rely on cytogenetic evaluation at the time of diagnosis and have led to improved response rates and overall survival in subsets of patients with cytogenetic high-risk abnormalities, especially in those with t(4;14) translocation. Combination chemotherapy and early consideration of autologous HSCT remain important in younger patients with good performance status in order to achieve an optimal response.

Correspondence: Address to Ronald S. Go, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (go.ronald@mayo.edu).

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CORRECT ANSWERS: 1. e. 2. b. 3. a. 4. d. 5. d