MAYO CLINIC



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

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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**

**See end of article for correct answers to questions.**

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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 $\beta_2$-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 $\beta_2$-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 $\beta_2$-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


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