A 60-year-old woman with a medical history significant for gout, chronic kidney disease (stage 3), breast cancer, and anthracycline-induced dilated cardiomyopathy with heart failure (with recent ejection fraction of 25%) presented to her primary care physician because of an acute-onset of left knee pain. She had been diagnosed with gout during the previous year, and this was managed with febuxostat that was initiated 3 months prior; she was not on colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids. Her heart failure was managed with carvedilol, losartan, eplerenone, and furosemide. In clinic, she stated that she first noticed her knee pain the previous day after spending much of the day in a dental chair with her leg extended while undergoing a root canal procedure. The pain was significant both with activity and rest. A review of systems was unremarkable; she denied fevers, chills, and malaise. She denied any preceding trauma to her knee.

On physical examination, the patient was afebrile with a blood pressure of 89/55 mm Hg (near her baseline) and heart rate of 78 beats/min with a regular rhythm. She appeared to be in mild distress with an antalgic gait. Her left knee was mildly swollen, erythematous, and warm. Her knee was most tender along the anterior aspect, just superior to the patella. Knee flexion (both active and passive) exacerbated her pain and was limited to 60 degrees due to pain. Knee extension was full and less painful. No tophi were noted on exam.

Three weeks earlier, she had undergone laboratory testing that had shown a serum uric acid level of 5.2 mg/dL (reference range: 2.4 to 6.0 mg/dL). Before initiating febuxostat, her uric acid level had been 10.6 mg/dL.

1. Which one of the following is the most likely cause of this patient’s knee pain?
   a. Cellulitis
   b. Septic arthritis
   c. Prepatellar bursitis
   d. Reactive arthritis
   e. Crystalline arthropathy

The patient’s clinical presentation and examination findings are concerning for an inflammatory process involving the knee, with the initial evaluation focused on differentiating between infectious versus noninfectious etiologies, intra-articular versus extra-articular processes, and systemic versus localized disease.

Given the patient’s severe pain with movement of the knee joint, an overlying cellulitis is less probable compared to a joint-related process. Cellulitis is also less likely to present with abrupt onset and with no preceding wound or ulceration.

Septic arthritis is a possibility as it frequently affects the knee with symptoms of swelling, warmth, and pain, as observed in our patient. In addition, this patient has risk factors for septic arthritis, including recent dental work, which can lead to transient bacteremia and hematogenous seeding. However, this diagnosis would be somewhat less likely in the absence of systemic symptoms, such as fever or malaise.

Prepatellar bursitis is possible as it commonly presents as an acute onset of knee pain, and patients are often unable to flex at the knee due to pain. This diagnosis is less likely, however, given her physical exam, as her knee was most tender superior to the patella; in the case of prepatellar bursitis, tenderness would be most pronounced anterior to the patella. In addition, pain would be less pronounced with rest,
and there might be a history of frequent kneeling or recent trauma to the knee.

Reactive arthritis is less likely as it typically presents as an oligoarthritis most commonly in patients aged 20 to 40 years in days-to-weeks following an inciting enteric or genitourinary infection, which our patient did not have.

Altogether, this patient’s presentation is most consistent with a flare of crystalline arthritis, specifically gout, with rapid presentation and maximal symptomatic severity typically reached within a day of onset, in addition to significant inflammation on exam with minimal systemic symptoms. Her prior episodes of gout and other risk factors including post-menopausal status, chronic kidney disease, and furosemide therapy also increase the likelihood of this representing a flare. While her recent uric acid level was normal, gout flares can occur despite normouricemia or even hypouricemia. In addition, although long-term treatment with urate-lowering therapy can significantly reduce gout flares, it is very common for patients to continue to have flares during the year or so following initiation of therapy. Given this, the 2020 American College of Rheumatology Guideline for the Management of Gout strongly recommends administering concomitant anti-inflammatory prophylaxis therapy (eg, colchicine, NSAIDs, or prednisone/prednisolone) to lower the risk of acute gout flares during the first months of antihyperuricemic therapy. In this patient’s case, she had only been taking febuxostat for approximately 3 months before this episode, and she had unfortunately not been on prophylactic therapy due to colchicine intolerance and was avoiding NSAIDs and systemic steroids given her chronic kidney disease and heart failure.

2. What is the best next step in diagnosis and management of this patient’s knee pain?
   a. Plain radiographs
   b. Magnetic resonance imaging
   c. Dual-energy computed tomography (DECT)
   d. Diagnostic arthrocentesis
   e. Ultrasound

Plain radiographs would be helpful if there were suspicion for acute fracture or bony abnormality. However, other than potentially showing subcortical bone cysts without erosions or the classic juxtaarticular “rat bite” lesions, plain radiographs are not typically helpful in diagnosing crystalline arthropathy. These radiographic findings are also associated with chronic gout and so are less likely to be seen in a patient with a relatively short history of gout.

Magnetic resonance imaging is sensitive in showing soft-tissue and osseous abnormalities, but findings observed in crystalline arthritis are not specific.

Dual-energy computed tomography can detect monosodium urate (MSU) crystal deposition within joints and soft tissues and is particularly useful for joints that are not amenable to aspiration or in cases in which there remains high suspicion for crystalline arthropathy despite negative aspiration. Dual-energy computed tomography can be falsely negative in patients with a first episode of gout and fewer than 6 weeks of symptoms. However, the gold standard for gout diagnosis is joint arthrocentesis with polarized light microscopy to identify uric acid crystals within white blood cells. A further benefit of joint arthrocentesis is that aspirated synovial fluid can be sent for total nucleated cell count with differential as well as cultures if there remains a suspicion for coincident infection.

Ultrasound is useful to determine if a joint effusion is present that would be amenable to aspiration and to guide diagnostic arthrocentesis; however, it is not the gold standard for diagnosis of crystalline arthropathy.

One year before this patient’s current episode of acute knee pain, she had the onset of left mid-foot pain and was found to have a serum uric acid level of 11.2 mg/dL. In the weeks before the onset of her foot pain, she was having difficulty with episodes of congestive heart failure in the setting of her chemotherapy-induced cardiomyopathy. She had her medications adjusted on two occasions with improvement in heart failure symptoms. In evaluation of her foot pain,
she underwent diagnostic arthrocentesis of the second tarsometatarsal joint with polarized light microscopy demonstrating intracellular uric acid crystals consistent with acute gout. Careful review and reconsideration of cardiac medications is important following a new diagnosis of gout. At the time of this initial gout flare, our patient was taking losartan, furosemide, spironolactone, and carvedilol. She had been placed on losartan after developing a persistent cough while taking lisinopril.

3. Which antihypertensive is most helpful to reduce gout exacerbations in this patient?
   a. Lisinopril
   b. Losartan
   c. Furosemide
   d. Spironolactone
   e. Carvedilol

   A large nested case-control study performed in the United Kingdom (involving more than 24,000 cases of incident gout in patients with hypertension and 50,000 matched controls) provided data showing the relative risk of incident gout with various antihypertensive drugs. Based on this data, the use of angiotensin-converting enzyme inhibitors including lisinopril is associated with an increased risk of incident gout (relative risk 1.25). In contrast, the angiotensin receptor blocker losartan is associated with fewer gout exacerbations (relative risk [RR]: 0.81). Losartan reduces serum uric acid levels by producing a uricosuric effect that is not observed in non-losartan angiotensin receptor blockers. Diuretics as a group have the strongest increased risk of incident gout (relative risk 2.36). However, this risk differs among diuretics. Both thiazide and loop diuretics are known to increase serum uric acid and the risk of gout attacks by increasing renal urate reabsorption. In contrast, potassium-sparing diuretics appear to not significantly increase risk of incipient gout. αβ-blockers such as carvedilol are associated with increased gout flares (RR: 1.48) as well as increased serum urate; however, the mechanism remains unclear.

   Thus, among the antihypertensives with which our patient had been treated, losartan would have provided the most benefit. Although she was taking carvedilol and furosemide, which both would have increased her risk for gout, it was not believed that her medications could be changed given her significant cardiomyopathy.

   The gout in our patient’s foot was initially treated with a short course of oral prednisone with symptomatic resolution. Subsequently, she started on allopurinol 100 mg daily in combination with colchicine 0.6 mg daily. Two weeks after initiating these medications, she developed a rash, fever, and diarrhea with an elevated C-reactive protein 26.7 mg/L (<10 mg/L). Allopurinol was discontinued due to suspicion of a mild drug reaction. Colchicine was also discontinued given concern it was contributing to her diarrhea. After a few months off of therapy, she was started on febuxostat.

4. Which of the following represents this patient’s greatest risk factor for a severe allopurinol hypersensitivity reaction?
   a. Chronic kidney disease
   b. Age 60 years or older
   c. Female sex
   d. Initial allopurinol dose less than or equal to 100 mg
   e. Caucasian ethnicity

   A large study using US Medicaid data involving 400,401 allopurinol initiators identified 203 hospitalizations as a result of severe allopurinol hypersensitivity. Chronic kidney disease (RR: 2.3), age 60 years or older (RR: 1.7), female sex (RR: 2.5), and initial allopurinol dose greater than 100 mg (RR: 1.9) were all identified as independent risk factors. Asians, blacks, and Native Hawaiian/Pacific Islanders were also shown to be at greater risk of allopurinol hypersensitivity reactions, with RRs of 3.0, 3.0, and 6.7, respectively, compared with whites and Hispanics. This is explained by the higher prevalence of the HLA-B*5801 allele in those ethnic groups. An important caveat to this study was that stages of chronic kidney disease were not separated, and it is possible...
that most of the patients in this study had earlier-stage kidney disease than our patient. Patients with more advanced kidney disease and lower glomerular filtration rate are significantly more likely to have severe hypersensitivity when the starting dose of allopurinol is not appropriately adjusted. Although this patient’s chronic kidney disease, age, and sex all increased her risk for a severe allopurinol hypersensitivity reaction, given her low allopurinol starting dose, her risk was likely increased the most by her sex. Some would advocate starting an even lower dose (100 mg alternating every other day with 50 mg) to further minimize any renal-related risk with her estimated glomerular filtration rate that was just below 60 mL/min per 1.73 m².7

To evaluate our patient’s current episode of left knee pain, she underwent diagnostic arthrocentesis. An ultrasound exam of the left knee was performed before the procedure.

5. Which of the following ultrasound findings is most specific for gout in this patient?
   a. Double contour sign
   b. Synovitis
   c. Joint effusion
   d. Bone proliferation
   e. Juxta-articular erosion

The “double contour sign” is considered a highly specific ultrasound finding for gout, defined as an abnormal hyperechoic band over the superficial margin of the articular hyaline cartilage, independent of the angle of insonation, and which may be irregular or regular, continuous, or intermittent and can be distinguished from the cartilage interface sign. In a large international multicenter study, the presence of the double contour sign was 91.4% specific and had an 87.7% positive predictive value with a 69.3% negative predictive value. In contrast, synovitis, edema within the synovium, and increased flow on Doppler ultrasound are less specific findings typically associated with an inflammatory arthritis. Joint effusion, seen on ultrasound by observing fluid in the joint space that is pushed away when compression is applied, and bone proliferation are nonspecific findings seen in a variety of arthropathies, both inflammatory and non-inflammatory. “Rat bite” or juxta-articular erosions are frequently seen in gout, though this is typically a radiographic as opposed to sonographic finding.9

The patient’s left knee ultrasound showed no knee intra-articular effusion, minimal synovitis, and no double contour sign. No fluid could be aspirated from the joint. During the ultrasound exam there was significant point tenderness just above the patella. Images of the left quadriceps tendon/patellar enthesis (the site of attachment of the tendon to bone) showed hyper-echoic crystalline deposits. Power Doppler of the same area showed extensive hyperemia. Ultrasound findings were consistent with uric acid deposition and acute inflammation of the quadriceps tendon/patellar enthesis.

Based on the ultrasound findings and the clinical presentation, our patient was diagnosed with gout enthesitis. Gout enthesitis could be treated with systemic glucocorticoids or NSAIDs. However, given this patient’s cardiomyopathy and frequent heart failure episodes, an ultrasound-guided peri-tendinous glucocorticoid injection was performed. Ultrasound guidance is important as inadvertent intratendinous injection could increase the risk of rupture. It is our experience that intra-articular glucocorticoid injection does not relieve symptoms of quadriceps enthesitis. Were ultrasound-guided corticosteroid injection not available, use of oral dexamethasone could have been considered, as this steroid has minimal mineralocorticoid activity and thus fewer issues with volume retention.

Following the ultrasound-guided injection of methylprednisolone and lidocaine around the site of the quadriceps enthesis, our patient experienced immediate relief (lidocaine effect) and could fully flex her knee without pain. She continued to enjoy sustained relief of her knee pain at a visit 2 weeks later and has experienced no further episodes.

DISCUSSION

Gout is the most common form of inflammatory arthritis in the United States with a
prevalence of 1% to 4% in the adult population (1% to 2% in women, 3% to 6% in men). Deposition of MSU crystals in the tissues, especially the joints and peri-articular tissues, can cause an acute inflammatory response. While hyperuricemia must be present for MSU crystals to form, uric acid levels fluctuate and are often normal during gouty attacks. When gout is suspected, synovial fluid or tophi aspirate should be obtained and studied for crystals. When this is not possible, the American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria provide an approach to diagnosis, although these are not diagnostic criteria but rather guidelines that are primarily intended for facilitating enrollment in studies. Without treatment, chronic tophaceous gout may develop, with extensive joint destruction and deformity.

Our patient developed gout enthesitis, which is one of the known extra-articular manifestations of gout. In individuals with gout, urate deposition can be seen in a variety of locations within the soft tissue of the musculoskeletal system, including the tendons, ligaments, bursae, and entheses. Enthesitis is often difficult to diagnose because pain at enthesal sites often presents as arthralgia, and swelling is typically absent. Awareness of this condition, especially in patients in whom gout flares are suspected but seemingly unresponsive to intra-articular steroid injection, can substantially improve management.

Once suspected, diagnosis of gout enthesitis is either based on clinical findings or may be assisted by imaging, particularly ultrasound or DECT. Although there are clinical guidelines to direct treatment of gout arthropathy, there are no such guidelines for gout enthesitis; thus, treatment of this condition is typically based on recommendations for gout arthropathy. Given that this is a relatively common but greatly underdiagnosed condition, it is hoped that with increased recognition and treatment, specific guidelines for extra-articular gout will be developed.

Potential Competing Interests: The authors report no competing interests.

Correspondence: Address to Laura S. Greenlund, MD, PhD, Division of Community Internal Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (greenlund.laura@mayo.edu).

ORCID
Gregory J. Challener: https://orcid.org/0000-0002-2844-4661; Laura S. Greenlund: https://orcid.org/0000-0002-9040-920X

REFERENCES

Correct Answers: 1. e. 2. d. 3. b. 4. c. 5. a.