CASE REPORT

Gout, Have We Met before? No, Not Like This. . .

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LEARNING OBJECTIVES: Extra-articular symptoms could be the first manifestation of gouty arthritis (GA); polyarticular GA can mimic an infectious arthritis; infection can complicate GA.

CASE: A 66-year-old male with a history of gout presented with high fever and excruciating bilateral calf pain for 1 day. Examination revealed chronic knee effusions; range of motion in both knees was limited by calf pain. Joint aspiration showed negatively birefringent intracellular crystals and normal gram stain.

HOSPITAL COURSE: While receiving empiric antibiotics fever continued and he developed bilateral knee, right ankle, and shoulder pain. After demonstration of urate crystals and exclusion of infection, antibiotics were discontinued and steroids initiated. Fever, calf pain, and polyarthritis quickly resolved.

DISCUSSION: Polyarticular gouty attack is an uncommon presentation of gout, and can mimic several other conditions. An exceptional presentation of this entity is excruciating calf pain, probably caused by tenosynovitis or referred pain preceding an acute polyarticular gouty attack.

KEY WORDS: gout; polyarticular; calf pain.

DOI: 10.1111/j.1525-1497.2006.00606.x

J GEN INTERN MED 2006; 21:C5-C7.

Calf pain can be a presenting symptom of many medical conditions; however, to our knowledge it has not been described as presenting symptom of polyarticular gouty attack. This condition requires high degree of suspicion and diligent work up to rule out more life or joint-threatening disease processes. We present a case of polyarticular gouty arthritis (GA) that provided diagnostic and therapeutic challenges.

CASE

A 66-year-old male presented to the Emergency Department complaining of bilateral calf pain of 1-day duration without preceding lower extremity trauma or strain. The pain was exacerbated with ambulation with no alleviating factors. He had been well until 1 day before admission, when he suddenly developed unremitting, excruciating, bilateral calf pain that precluded weight bearing. He subsequently developed temperature of 40.0 °C, and was limited to bed rest due to unremitting symptoms. He denied prior calf pain; shortness of breath chest, back, hip, knee, or ankle pain associated with this episode.

His past medical history included medical nonadherence, hypertension, metabolic syndrome, coronary artery disease,

obstructive sleep apnea, gout, erectile dysfunction, mild mitral regurgitation, myopathy that was not otherwise specified, but associated with multiple falls due to weakness, and recent upper gastrointestinal bleeding necessitating discontinuation of aspirin and ibuprofen. He has been taking pantoprazole, lisinopril, amlodipine, sildenafil, allopurinol, and metoprolol as prescribed. He had no significant family history; was unemployed and never used illicit drugs. He discontinued smoking 1 year ago and drank 2 to 5 beers a day for over 20 years and follows no particular diet. Review of systems was remarkable for 15-year history of gout; he was started on allopurinol 300 mg a day at diagnosis, and has remained in the same dose. However, patient never followed up with his primary care provider regarding this issue. He had 3 to 4 episodes of acute GA annually, and most were monoarticular, involving his lower extremities. Over the last 2 years he had 1 to 2 episodes polyarticular attacks a year. These episodes typically started with foot involvement and progressed to involve knee, or shoulder, or both. He never had calf pain with gouty attacks.

The patient was obese, and acutely ill appearing. Vital signs were 115/53, 114, 40.1 °C, 28. Cardiovascular examination was remarkable for a 2/6 late-systolic murmur over apex. Skin without erythema, rash, or tophi. Extremities had mild nonpitting edema up to and including knees, normal muscle strength and tone, mild bilateral knee effusions with positive bulge sign, with absence of warmth or tenderness. However, the popliteal fossae bilaterally were tender. There was thickening of the synovium over the first metatarsophalangeal joints. No evidence of acute inflammation in any joints. Range of motion at the knees was severely restricted secondary to exquisite pain. Specifically, calf examination showed no erythema, swelling, or tenderness. The remainder of the physical examination was unremarkable.

On laboratory evaluation the amount of hemoglobin (Hgb) was 10.1 g/dL, MCV 87.8 fL, red blood cells distribution width 16.8%, white cell count $10.2 \times 10^9/L$ with $8.48 \times 10^9/L$ neutrophils, $0.93 \times 10^9/L$ monocytes and $0.71 \times 10^9/L$ lymphocytes, erythrocyte sedimentation rate was 46, platelets $162 \times 10^9/L$. Creatinine was 1.2 mg/dL, calcium 8.2 mg/dL; uric acid 5.0 mg/dL, aspartate transaminase 19, lactate dehydrogenase (LDH) 222; aldolase 11.9 U/L, creatinine kinase 633 U/L (normal 52 to 336) close to his baseline, C-reactive protein was 35.7. Urinalysis was unrevealing. Bilateral knee aspirates showed 12.0 to $15.0 \times 10^9/L$ white cells with negatively birefringent intracellular needle-shaped crystals, Gram stain was negative. Blood and knee aspirate bacterial cultures remained negative. When the knees were re-aspirated 48

No conflicts of interest to declare.

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Manuscript received January 7, 2006

Initial editorial decision March 2, 2006

Final acceptance July 3, 2006

hours later, white cell count was in 37.0 to $38.0 \times 10(9)/L$ range. Studies also included normal bilateral lower extremity compression ultrasonography, shin and knee films, and computed tomography pulmonary angiogram.

HOSPITAL COURSE

While awaiting results of studies he was treated with vancomycin and ceftriaxone for 48 hours. Over this period of time his fevers worsened, he developed bilateral knee, right shoulder, and ankle disabling pain that was stereotypical for his previously described gouty attacks. His shoulder and bilateral ankle examination revealed nonerythematous, warm, tender joints with pain-limited range of motion. At 48-hour re-aspiration, both knees were injected with 40 mg of methylprednisolone, and oral prednisone was started at 10 mg 3 times a day. Within 24 hours there was complete resolution of symptoms, and within 48 hours there was return of range of motion in all joints back to baseline.

Differential diagnosis at initial presentation included tendonitis, myositis, muscle strain or tear, superficial or deep venous thrombosis, shin splint syndrome, medial tibial stress syndrome, Baker's cyst rupture, septic arthritis or GA, and less likely radiculopathy, peripheral neuropathy, shingles, hemarthrosis, stress fracture, tibial or fibular fractures, compartment syndrome.

Myositis and muscle strain or tear would reveal muscle tenderness and would not evolve to include joints, this patient had nontender calves. While venous thrombosis often manifests as calf pain, typically it is unilateral pain even if patients have bilateral thrombosis and this diagnosis was ruled out by compressive ultrasonography and pulmonary computer tomography angiogram. Ruptured Baker's cyst is usually unilateral process, and was ruled out at the same time with negative ultrasonography; characteristically hypochoic space is seen

behind the calf muscles.¹ Splint syndrome and stress fractures typically seen in patients who have increased their level of activity. In splint syndrome one has diffuse tenderness over the middle to distal third of the medial tibial border and no discrete bone tenderness seen in stress fractures. Tibial or fibular fractures were ruled out by x-rays.

Radiculopathy and peripheral neuropathy are less likely given fever, absence of a dermatomyotomal distribution. Shingles classically evolves to a vesicular rash in a dermatomal distribution, and this was not observed in our patient. Compartment syndrome is usually unilateral manifesting as tender calves with distal neurovascular compromise.

Given the clinical presentation, progression, results of arthrocentesis, and response to steroids, a final diagnosis of atypical presentation of acute polyarticular GAWas made with possible tendonitis as a presenting symptom (Table 1).

DISCUSSION

Gout is the most common inflammatory arthritis in older patients due to decline in renal function with age and renal insufficiency, as well as widespread use of diuretics for treatment of hypertension. In the Framingham study, the mean age of the gout patient cohort was 58; and a 2-year incidence of gout was 0.32% in men and 0.05% in women.² Another study using self-reported data estimated a prevalence of 0.84% for all ages.³ The prevalence of gout in patients over the age 65 was 2.9%, 4.4% for men and 1.8% for women.

The plasma urate concentration is the most important feature for determining the risk of developing gout,⁴ but often is normal during the attack. Plasma urate concentration varies with age, sex, weather, physical activity, diet, body mass index, renal function, and ingestion of alcohol and drugs. Hyperuricemia is defined as the plasma urate concentration greater than 7.0mg/dL in males and 6.0mg/dL in premenopausal females.⁴ Above this limit, supersaturation of monosodium urate ensues, and the patient is at risk for development of gout. The risk of developing gout appears to be similar in men and women for a particular serum urate concentration. While hyperuricemia is the biochemical abnormality and gout its clinical expression, the majority of individuals with hyperuricemia never develop gout.² An elevated body uric acid pool is therefore the necessary, but not sufficient, metabolic abnormality for development of gout. About 40% of patients presenting with acute gout have normal uric acid levels.^{5,6}

The classic presentation of GA includes severe pain, erythema, swelling, and disability. At least 80% of initial attacks involve a single joint, typically in the lower extremity, and about half of these affect the first metatarsophalangeal joint (known as podagra), with the knee affected less frequently. Occasionally the shoulders, sternoclavicular joints, hips, and even the spine, or sacroiliac joints may become involved and cause diagnostic dilemma. Maximal severity of an attack is reached over several hours, and with most monoarticular attacks patients have minimal systemic symptoms. The signs of inflammation related to GA sometimes extend beyond the boundaries of the joint and may even give the suspicion of arthritis in several contiguous joints, dactylitis,⁷ tenosynovitis,⁸ or cellulites.⁹ Even so, acute excruciating bilateral calf pain and high fever without primary joint pain, to our knowledge has not been previously described in the literature.

Table 1. Differential Diagnosis of Calf Pain

Clinical entity	Typical features
Radiculopathy or peripheral neuropathy	Typically unilateral, specific dermatomyotomal distribution
Muscle strain or tear, myositis	History, muscle tenderness, elevated muscle enzymes
Tendonitis, synovitis	Limited range of motion, localized tenderness
Superficial or deep venous thrombosis	Symptoms usually unilateral, ultrasound positive
Shin splint syndrome	History of increased level of physical activity; diffuse tenderness over the middle to distal third of the medial tibial border and no discrete bone tenderness
Stress fracture	History of increased level of physical activity and discrete bone tenderness
Compartment syndrome	History of trauma; unilateral; distal neurovascular signs, and symptoms
Tibial or fibular fractures	History of trauma or bone disease, typically seen on x-rays
Baker's cyst rupture	History; unilateral, typically seen on ultrasonography
Shingles	History; unilateral, typical blistering rash
Arthritis, hemarthrosis	Extraarticular involvement seen with joint inflammation, however, rather secondary symptom
Claudication	History of exertional pain resolving with rest
Pseudoclaudication	History of pain with standing, resolves with bending forward

Acute polyarticular GA, although seen as an initial manifestation in less than 20% of instances, occurs with increasing frequency in later recurrences. It is known to cause low-grade fever and leukocytosis and often has to be differentiated from a septic process. It affects males and females equally, while monoarticular is much more common in males. Usually polyarticular GA is more of smoldering onset and reflects chronic, poorly controlled gout.¹⁰ Its presentation can be confused with septic polyarthritis,^{11,12} or rheumatoid arthritis.¹³ This form of gout is a frequent masquerader,¹³ and high level of clinical suspicion might be needed for diagnosis.

One prospective study, conducted to describe the clinical features of polyarticular GA, evaluated 106 consecutive patients with GA, 42 (40%) had articular inflammation at 2 or more joints.¹⁰ A comparison of these 2 groups revealed that polyarticular gout represents one end of a predictable spectrum of GA, reflecting chronicity associated with medical non-adherence; suboptimal management; attacks of more smoldering onset and increasing duration, with ascending asymmetric joint involvement; difference between the site (or sites) of patient's chief complaint and clinically involved joints on careful physical examination. No single laboratory or synovial fluid study meaningfully differentiated patients with polyarticular from those with monoarticular GA.

In order to prevent gouty attacks dietary changes, abstinence from alcohol, and use of nondiuretic therapies for hypertension are advised as the initial therapeutic strategy. Purine-rich foods, including red meat¹⁴ and fish, and alcohol¹⁵ are associated with increased risk of gout. Current recommendations are to titrate antihyperuricemic therapy to a serum urate concentration below 5 to 6 mg/dL (297 to 357 μ mol/L), lowering the level by no more than 0.6 mg/dL/mo (Grade 2C). Low dose prophylactic colchicine (0.6 mg twice daily for patients with normal renal function) during the initiation of antihyperuricemic therapy (Grade 1A). Alternatively, nonsteroidal anti-inflammatory drugs (NSAIDs) may be used prophylactically in patients who can not tolerate colchicine (Grade 2C).

In treatment of acute GA, NSAIDs are the first line of therapy, corticosteroids or subcutaneous injections of corticotropin are additional alternatives. Colchicine is generally not used as first line of therapy due to lesser effectiveness and tolerability. Urate-lowering therapy, such as allopurinol or probenecid, are not instituted during the acute attack, as these agents can exacerbate the attack.

Medical management of gout includes not only termination of acute attacks, but also prevention of future attacks and complications and treatment of associated conditions such as obesity, hypertension, hypertriglyceridemia, and alcoholism.¹⁶ The presence of tophi, recurrent gouty attacks, or urate overproduction warrants long-term uric acid-lowering therapy. Allopurinol and potent uricosuric agents such as probenecid are equally acceptable as first-line drugs in the absence of documented urate overproduction or renal failure.¹⁷

Septic arthritis is included in the differential diagnosis of both mono and polyarticular gout and could coexist with it in acute gouty attack. In addition, patients with septic arthritis complicating GA will have intracellular urate crystals making differentiation more complicated. Certainly, in many cases a presumption of septic arthritis is made until it can safely be

excluded. If differentiation between the 2 conditions is not obvious concurrent treatment for both processes may be necessary.

Our patient had hypertension, mild chronic renal insufficiency, obesity, metabolic syndrome, chronic gout that been poorly controlled secondary to his noncompliance with non-pharmacologic as well as pharmacologic recommendations, all contributing to chronic polyarticular GA development. This attack was probably provoked by his dietary overindulgence, alcohol consumption, chronic poorly controlled gout, the recent massive gastrointestinal bleeding, blood transfusions, and stopping NSAIDs. In addition, trauma, surgery, starvation, and antihyperuricemic agents themselves can incite an attack.

This presentation was unusual, as the patient had atypical location of pain, namely in the calves with no joint pain. One explanation for this could be acute tenosynovitis versus referred pain as primary presenting symptom that evolved into classic polyarticular gouty attack. Independent of etiology, ruling out life and limb/joint threatening conditions is often necessary in confusing cases such as this. This is a rare manifestation of a common condition, with the final diagnosis being made after careful evaluation and exclusion of other sinister etiologies for this presentation.

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