CLINICAL IMAGE

PERIPHERAL WHITE NODULES

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CASE REPORT

A 92-year-old female presented with white nodules on her toes. Her nodules appeared approximately 3 weeks prior and had been slowly increasing in size. They were associated with pressure sensation but no other symptoms. She denied having skin lesions in other areas of her body. She also denied having fever, fatigue, myalgias, joint swelling, abdominal pain, and nausea. She had a past medical history of atrial fibrillation, hyperlipidemia, hypertensive chronic kidney disease, hypothyroidism, and pulmonary hypertension. Medications included amlodipine, apixaban, ferrous sulfate, levothyroxine, metoprolol tartrate, simvastatin, and vitamin D3.

Examination revealed multiple chalky-white subcutaneous nodules located on her second distal interphalangeal (DIP) joints of her bilateral toes (Figure 1). Her left second DIP toe lesion was ulcerated with chalky-white discharge (Figure 2). No other skin lesions and no acute joint findings were observed. A basic metabolic panel and uric acid level were obtained. Her glomerular filtration rate was

FIGURE 1:

The patient's toes at presentation.

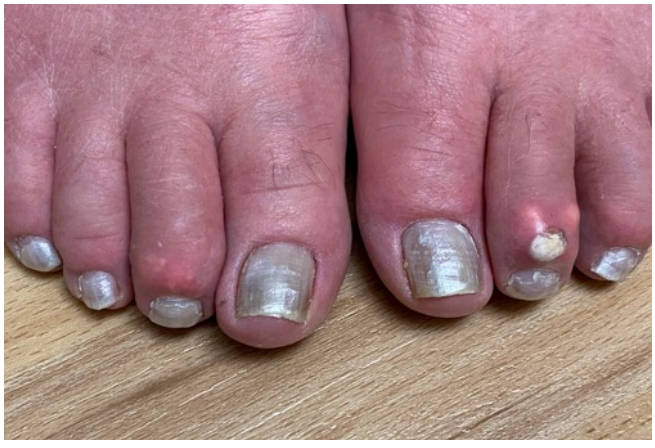

FIGURE 2:

Ulcerated lesion with chalky-white discharge.

QUESTIONS

1. Which of the following tests is required for diagnosis of gouty tophi?

a. Serum uric acid greater than 7.0 mg/dL in men or 6.0 mg/dL in women

b. Joint aspirate revealing negatively birefringent uric acid crystals

c. Characteristic imaging findings (eg, erosions on X-ray or ultrasound)

d. Tests are not required; gouty tophi can be diagnosed clinically

2. In a patient taking allopurinol for treatment of chronic tophaceous gout, what is the recommended target for serum uric acid?

a. Less than 4.0 mg/dL

b. Less than 5.0 mg/dL

c. Less than 6.0 mg/dL

d. Serum uric acid is not a useful treatment target, and treatment should be aimed at clinical resolution of symptoms

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3. Susan is a 76-year-old female with a medical history of gout, hyperlipidemia, hypertensive chronic kidney disease, hypothyroidism, and chronic low back pain. She had a recent gout flare and wonders whether any of her medications may be leading to her gout flares. Which of Susan's medications is most likely to increase serum uric acid and trigger a gout flare?

a. Amlodipine 10 mg PO daily for hypertension

b. Simvastatin 20 mg PO daily for hyperlipidemia

c. Aspirin 325 mg PO TID as needed for low back pain

d. Levothyroxine 125 mcg PO daily for hypothyroidism

ANSWERS

1. Which of the following tests is required for diagnosis of gouty tophi?

Correct Answer:

d. Tests are not required; gouty tophi can be diagnosed clinically

Gouty tophi can be diagnosed clinically based on the presence of white chalky cysts or nodules. Laboratory and imaging can also provide evidence to support the diagnosis. Elevated serum urate can be present in patients with gout, but is not considered diagnostic as patients with hyperuricemia can be asymptomatic and serum urate can be normal during an acute flare. Radiography and ultrasound can provide characteristic findings of tophaceous gout and may be helpful in supporting the diagnosis. A combination of diagnostic criteria can help estimate the likelihood of gout without aspiration. Tophi aspiration is confirmatory and should be considered if the diagnosis remains unclear.

2. In a patient taking allopurinol for treatment of chronic tophaceous gout, what is the recommended target for serum urate?

Correct Answer:

c. Less than 6.0 mg/dL

Treatment target of serum urate <6.0 mg/dL is strongly recommended as it leads to increased urate lowering therapy compliance, tophi reduction, and decreased acute flare frequency. More stringent uric acid targets have been suggested for patients with a heavier disease burden, and may facilitate resolution of tophi. However, there is a lack of study data to routinely recommend lower serum uric acid levels.

3. Susan is a 76-year-old female with a medical history of gout, hyperlipidemia, hypertensive chronic kidney disease, hypothyroidism, and chronic low back pain. She had a recent gout flare and wonders whether any of her medications may be leading to her gout flares. Which of Susan's medications is most likely to increase serum uric acid and trigger a gout flare?

Correct Answer:

c. Aspirin 325 mg PO TID as needed for low back pain

Aspirin is a hyperuricemic medication and can increase her risk of gout. Practical alternatives to aspirin include acetaminophen, naproxen, and ibuprofen. Losartan, simvastatin, and metformin are not known to cause hyperuricemia.

DISCUSSION

Gout is the most common type of inflammatory arthritis and affects up to 3.9% of adults in the United States.[1,2] Gout is closely linked to comorbid conditions including chronic kidney disease, hyperlipidemia, hypertension, insulin resistance, and obesity.[2,3] Tophi are estimated to be present in 12% to 35% of patients with gout.[4,5] A cross-sectional survey of US and EU patients with gout found that tophi have been associated with adverse effects on health care–related quality of life, employment productivity, and utilization of health care resources.[4]

Hyperuricemia is the precursor of gout, and it results from overproduction and/or underexcretion of uric acid. Urates are the ionized form of uric acid, with monosodium urate (MSU) being the most prevalent form at pH 7.4. When the serum urate concentration exceeds 6.8 mg/dL, urate crystals precipitate, which results in hyperuricemia.[6] Long-standing hyperuricemia leads to chronic gout, which classically manifests as tophi. Tophi form from the combination of proinflammatory and anti-inflammatory processes. They contain a center of MSU crystals surrounded by chronic granulomatous deposition of macrophages with overlying connective tissue.[7-10]

Tophi typically present as white chalky cysts or nodules that are firm and nontender. They can manifest either subcutaneously or intra-articularly.[3,7] Observed locations of tophi include the olecranon bursa, wrist, carpal tunnel, interphalangeal joint, metacarpophalangeal joint, spine, talus, metatarsophalangeal joint, hallux, ear, larynx, and cardiac valve.[3,11-13] Tophi can enlarge and emerge superficially, and can result in exudation of white discharge. Complications of tophi include impaired joint function, necrotic ulceration, neuropathy, radiculopathy, and bony erosion.[3,14-16] Tophi can occur even in the absence of gouty arthritis, as in the above patient. This tends to occur in patients who are older, female, take anti-inflammatory drugs or diuretics, or have kidney disease.[11,13,17]

While the diagnosis of tophi can be made clinically, laboratory and imaging evaluation can provide supportive findings.[11,18] Serum urate is typically increased in patients with gout, but it is not diagnostic. Hyperuricemia can be present in asymptomatic patients, and serum urate can be normal in the setting of an acute attack.[18,19] A combination of diagnostic criteria can help estimate the likelihood of gout without aspiration. Criteria include male gender, previous arthritic flare, onset within 1 day, joint erythema, involvement of first metatarsophalangeal joint (MTP1), presence of hypertension or other cardiovascular disease, and serum urate >5.88 mg/dL.[20] Aspiration of tophi provides confirmatory evidence by showing the presence of MSU crystals, and should be utilized when diagnosis is unclear. Aspiration helps exclude the presence of other etiologies, especially septic arthritis.[3,13,18,19]

Plain radiography has higher utility during later stages of chronic gout. Findings include bony erosion, MSU deposition in cartilaginous areas, articular or periarticular soft tissue nodularities, and joint space narrowing.[19,21] Computed tomography (CT) can provide more specific imaging of tophi as compared to ultrasound (US) and magnetic resonance imaging (MRI). CT has been effective in identifying bony erosion and tophi.[21] Dual-energy CT directly visualizes urate deposition with volume measurement, which aids diagnosis and disease monitoring.[22] MRI can help identify tophi in atypical locations, such as the axial spine,[19] and evaluate for complications, such as reduced knee mobility, in the setting of tophaceous deposition.[23] However, MRI is limited by its lower specificity and high cost.[19,20] US can diagnose tophi based on characteristic features such as MSU deposition in cartilaginous areas and identification of tophaceous material and presence of erosion.[24,25] Moreover, US has been validated in the measurement of tophi, which can be used to monitor response to therapy.[20,26]

MANAGEMENT

Starting urate-lowering therapy (ULT) is recommended when patients present with at least one subcutaneous tophus, radiographic evidence of bone erosion attributable to tophi, or have two or more gout flares in a year.[1] ULT facilitates tophi resolution by reducing serum urate concentration.[27,28] Treatment target of serum urate <6.0 mg/dL is strongly recommended as it leads to increased ULT compliance, tophi reduction, and decreased acute flare frequency. It is strongly recommended to use ULT with concurrent anti-inflammatory prophylaxis for 3 to 6 months.[1]

Allopurinol and febuxostat are xanthine oxidase inhibitors (XOIs) and are firstline ULT agents for most patients, including patients with chronic kidney disease stage ≥3. Allopurinol is recommended above febuxostat.[1] The use of febuxostat is limited by increased cost and higher risk of adverse cardiovascular events.[29] Switching to an alternative XOI may be considered if a patient is on maximum dose of the initial agent and has serum urate levels >6 mg/dL, recurrent flares, or persistent tophi.

Probenecid is a uricosuric agent that can be added to XOI therapy if a patient has limited serum urate improvement.[1] Pegloticase is a recombinant uricase that is recommended for patients who have serum urate above treatment goal and persistent tophi despite the use of XOI, uricosuric agents, and other treatments.[1,12,28] Lesinurad is a uric acid transporter 1 inhibitor that has been studied in combination with allopurinol and febuxostat. Lesinurad has mixed evidence supporting its efficacy in managing tophi, and has been withdrawn in the United States. Additional randomized controlled trials are needed for other ULTs.[1,12]

Colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and prednisone are firstline medications in acute flare management. Initiating ULT during an acute flare may be conditionally considered. ULT can increase patient compliance and has not been shown to adversely affect duration or severity of acute flare.[1] Surgical intervention for tophi is indicated in the setting of severe complications including infection, entrapment neuropathy, and irreversible joint destruction.[16]

Hyperuricemia medications can increase the risk of gout flares. Examples include aspirin, cyclosporine, tacrolimus, and loop and thiazide diuretics. Medication changes can be considered if the benefit of reduced serum urate is greater than the risk of potential changes.[1,30] The discontinuation of low-dose aspirin, when taken for appropriate indications, is conditionally not recommended due to the lack of alternatives.[1] Thiazides at daily doses of 25 mg or greater have been associated with increased risk of gout.[31] For patients who take hyperuricemia medications, sufficient hydration and symptom and serum urate monitoring are recommended.[30] Additionally, dietary factors including alcohol intake, high-fructose corn syrup, and a high-purine diet have been linked to elevated serum urate levels and increased gout flares. Therefore, dietary recommendations along with weight loss should be advised.[1,3]

CONCLUSION

Gout, with or without tophi, is a relatively common clinical diagnosis in US adults that primary care providers often encounter. Tophi can present subcutaneously or intra-articularly in many parts of the body, and often are found as firm cysts or nodules. Hyperuricemia, either from overproduction or inadequate urate excretion, is the principal etiology for the precipitation of urate crystals that leads to gouty arthritis and tophi. ULT, often with allopurinol as firstline therapy, can help improve hyperuricemia and reduce symptoms.

The patient was started on allopurinol 100 mg daily. After 2 months, her uric acid level decreased to 5.0 mg/dL which met the goal of ULT. Her nodular lesions also improved clinically.

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