DOI: 10.52544/2642-7184(1)4002

MedJEM

Review

Can Ultrasound Aid in the Diagnosis of Gout and Septic Arthritis in the Setting of Monoarticular Joint Pain?

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Abstract

Monoarticular joint pain is commonly encountered in the emergency department (ED) with a broad differential diagnosis. Septic arthritis represents a "can't miss" diagnosis while gout represents a chronic, painful arthropathy. Traditionally these diagnoses are made with arthrocentesis in addition to history, physical exam, imaging and laboratory studies. Ultrasound (US) represents a novel modality that may aid in the diagnosis of gout without requiring arthrocentesis. Furthermore, the sonographic features of gout may exclude the diagnosis of septic arthritis. Additional research is required in the ED setting to better clarify the role of US in these two disease states.

INTRODUCTION

Monoarticular joint pain or arthritis, is a commonly encountered clinical entity in the ED and musculoskeletal injuries account for anywhere from 8.7% to 15% of all ED visits.[1,2] Gout, a crystal arthropathy, is a common cause of joint pain affecting up to 3 percent of adults in the US.[3] The incidence of gout is increasing as are ED visits related to acute gout flares.[4,5] Gout is expensive with total costs to the healthcare system exceeding $6 billion[6] and has significant detrimental effects on the working age population including a decline in physical activity, work presenteeism, and productivity.[7] Septic arthritis represents the most serious and life-threatening cause of monoarticular joint pain and is a medical emergency requiring immediate evaluation. The incidence is approximately 6 cases per 100,000 individuals in modern nations and the mortality rate is as high as 11%.[8,9] In 2012, there were 16,000 EDs visits and 13,700 hospitalizations associated with septic arthritis and more than 80% of patients with septic arthritis require admission to the hospital.[10] In patients presenting with monoarticular joint pain and an effusion, diagnosing gout and septic arthritis presents a challenging clinical scenario. Ultrasound represents a novel modality that may aid in diagnosis and management.

Keywords: arthritis; sepsis; ultrasound; joint; gout; musculoskeletal

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PATHOPHYSIOLOGY AND NATURAL HISTORY

Gout is caused by monosodium urate (MSU) crystal deposition in the synovial fluid of joints secondary to elevated uric acid. Acute gout attacks cause significant morbidity, and increase in frequency and severity if hyperuricemia is left untreated. Gout risk is increased by non-modifiable risk factors (male gender, increased age, family history) and modifiable risk factors (diet, alcohol consumption and physical inactivity).[11,12] Gout is associated with multiple comorbidities including chronic kidney disease, hypertension, cardiovascular disease, obesity and type 2 diabetes and in some cases, the presence of gout may contribute to these diseases.[13,14] Septic arthritis represents invasion of the joint space by infectious organisms, most commonly staphylococcus aureus, followed by streptococci and gram negative organisms. Risk

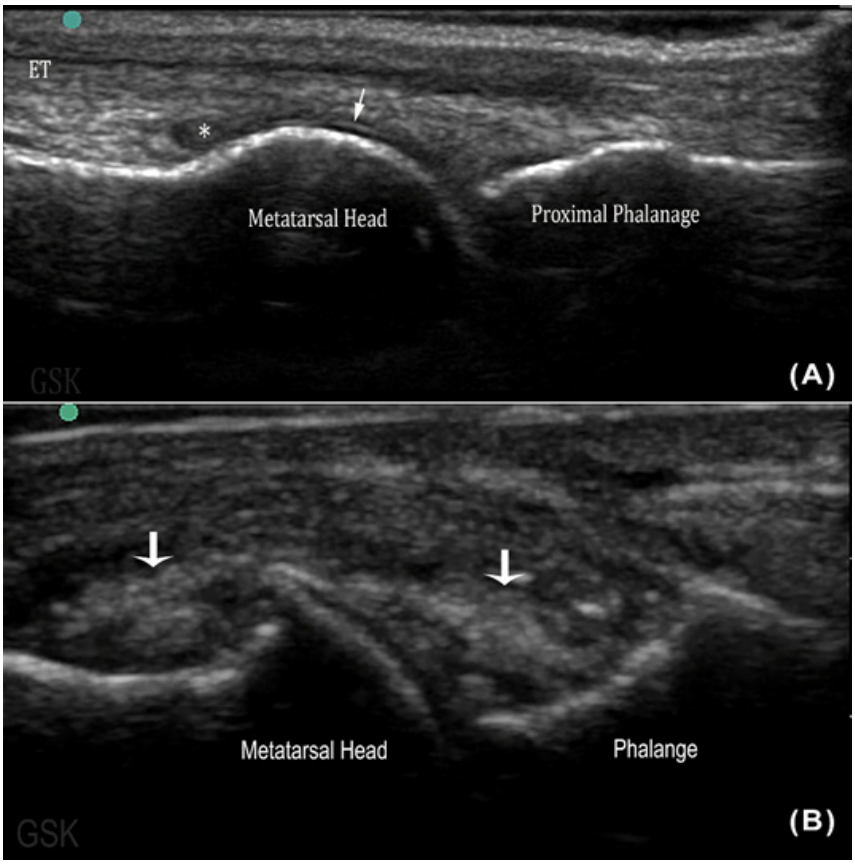

Figure 1 Long axis view of the first metatarsophalangeal joint. A: Left is proximal, right is distal. Small, physiologic effusion is seen in the dorsal recess (star), and an interface line (arrow) can be observed superior to the anechoic cartilage. B: Intrasynovial hypoechoic hetrogeneous material (arrows) with hyperchoic dots consistent with tophaceous deposits.
ET: extensor tendon

factors for septic arthritis include recent bacteremia, rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus, immunodeficiency, recent joint surgery, prosthetic joints and age extremes. Of note, disseminated gonococcal disease presents with a triad of dermatitis, tenosynovitis and arthritis.[15]

CLINICAL PRESENTATION

The initial presentation of a gout "flare" or attack in men typically affects the first metatarsophalangeal (MTP) joint (referred to as podagra) or the knee. Classically, a patient presenting with gout will be an obese, middle-aged male, with multiple comorbidities, a poor diet and consumer of alcohol. Although most gout flares are mono-articular affecting the knee and MTP joint, gout flares can involve other joints and can be polyarticular in up to 20% of patients.[16] Flares typically peak in 12-24 hours, lasting between 7-10 days. Chronic arthropathy or tophaceous gout is characterized by chronic inflammation and hyperuricemia with subsequent deposition of MSU crystals in joints, bursa and tendons and can occur in a variety of extra-articular soft tissues.[17] This leads to erosive changes in the joints as well as tendinopathy in affected tendons.

In patients with suspected septic arthritis, the classic triad is fever, joint pain and loss of range of motion. Patients are likely to report onset of fever, malaise, and local findings of pain, warmth, swelling, and decreased range of motion in the involved joint.[18] Absence of fever, localized heat or erythema surrounding the joint does not exclude the disease. The most commonly affected joints are knee (50%) and hip (20%), followed by shoulder (8%), ankle (7%), and wrists (7%) and more than 90% of non-gonococcal cases are monoarticular.[19]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of atraumatic monoarticular joint pain is broad and includes rheumatoid arthritis, familial Mediterranean fever which can mimic septic arthritis, crystal arthropathy including both gout and pseudogout, osteoarthritis, and septic arthritis.[20] At times, there may be clinical uncertainty whether the chief complaint of joint pain truly involves the joint or is referring to surrounding soft tissue structures. In patients who also present with warmth, swelling, and/or erythema overlying or including a joint, the differential can be expanded. This broader differential includes cellulitis, abscess, septic bursitis, venous thromboembolism, necrotizing fasciitis, flexor tenosynovitis, toxic shock syndrome, and erysipelas.[21] Other painful

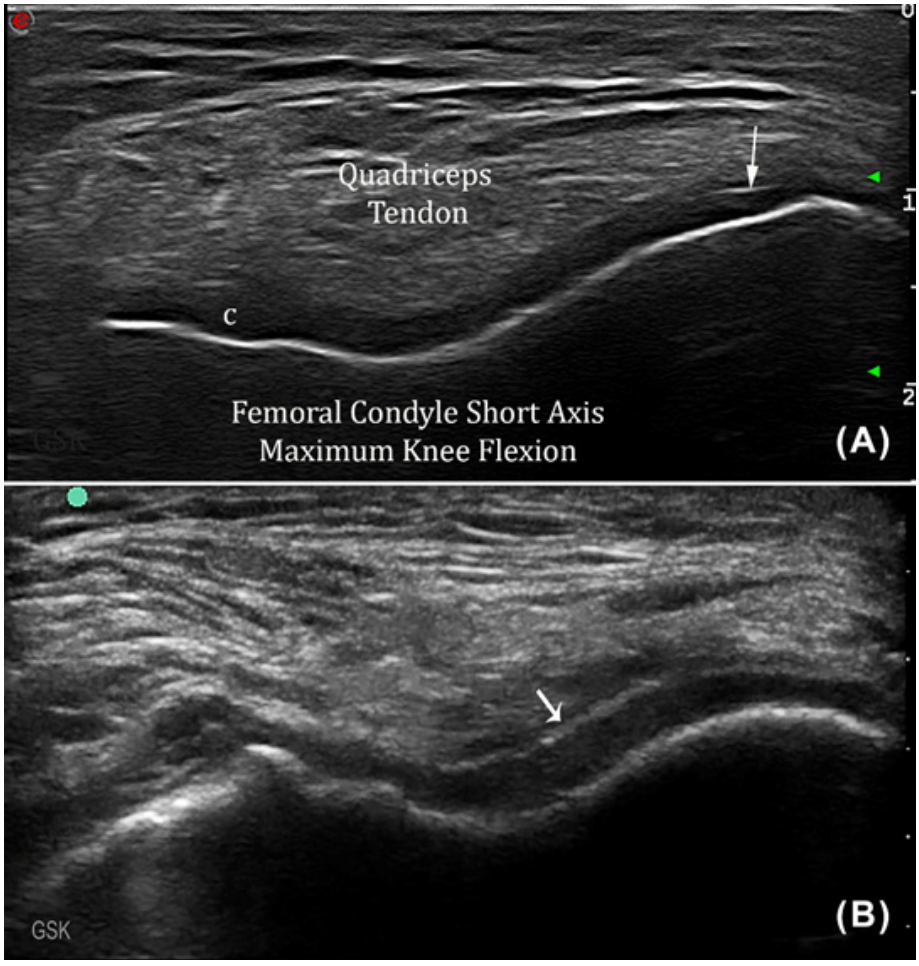

Figure 2 Short axis view of the femoral condyle with the knee in maximum flexion. A: Cartilage (C) is seen as an anechoic band. Note the typical interface sign (arrow), which is depicted as a sharp white line directly perpendicular to the angle of insonation. B: Arrow head indicates an irregular hyperechoic chondrosynovial layer consistent with urate deposition – the ”double contour sign”.

conditions would include bursopathies, muscle tendinopathies, ligament sprain, synovial cysts, chondromalacia and degenerative joint disease.

Hematologic evaluation. Most cases of monoarticular joint pain due not require laboratory evaluation. In patients with suspected crystal arthritis or septic arthritis, consideration should be made for both serum and synovial fluid evaluation. In serum studies, elevations in white blood cell count, with or without a neutrophil predominance, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly seen, although not specific to either disease.

Arthrocentesis. Arthrocentesis of the affected joint is recommended in the initial presentation of a painful, swollen joint in which the diagnosis is uncertain and crystal arthropathy or septic arthritis is a consideration. When possible, US should be

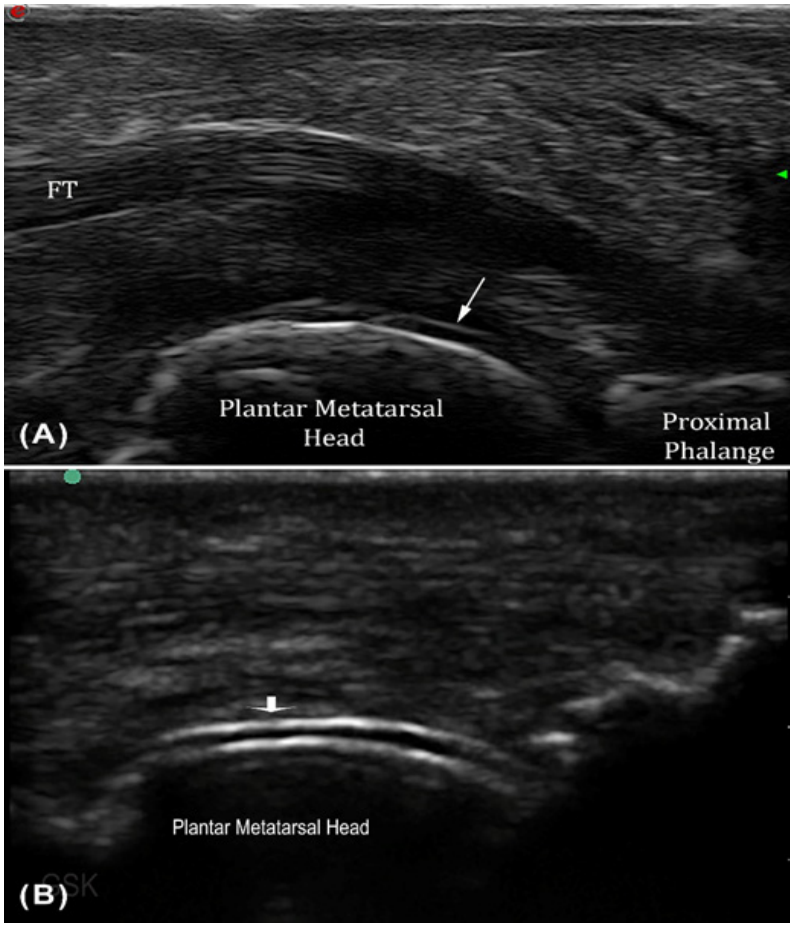

Figure 3 Long axis scan of the plantar aspect of the first metatarsophalangeal joint. (A): healthy joint in which the flexor hallus longus tendon (FT) is seen superficial to the metatarsal head. An interface line (arrow) is depicted superficial to the anechoic cartilage. (B): Diseased joint; arrow points to the double contour sign consistent with urate deposition.

used to evaluate the effusion and is superior to a landmark based approach.[22] Synovial fluid analysis should include cell count, gram stain, glucose, protein, crystal analysis, lactate and culture. In the case of inflammatory and septic arthropathies, there can be significant overlap of laboratory evaluation of synovial fluid which makes diagnosis challenging.

In patients presenting with gout or pseudogout, synovial fluid analysis will most commonly identify crystals under microscopy. Patients who have gout as their underlying etiology will demonstrate the presence of MSU crystals which appear needle shaped and negatively birefringent under a microscope. The presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus is sufficient for the diagnosis of gout.[23] During the intercritical period, synovial fluid analysis can still demonstrate MSU crystals and confirm the diagnosis.[24] Calcium pyrophosphate dihydrate (CPPD) crystals, seen in pseudogout, are rhomboidal and positively birefringent. Sensitivity is higher in MUS crystal detection (80 –95%) than that for CPPD (65– 80%).[25,26] Both MSU crystals and CPPD crystals can be seen in the same joint, further clouding the picture.[27] Other components of synovial fluid in patients with gout will usually include a yellow-cloudy appearance, 2,000-50,000 white blood cells with >50% polymorphonuclear neutrophils (PMN), glucose of 80-100% of predicted value, and protein > 4.0.[28].

In patients with septic arthritis, synovial fluid analysis will classically demonstrate a leukocytosis greater than 50,000/mm^3. A white blood cell count less than 50,000/mm3 decreased the likelihood of septic arthritis. However, Coutlakis et al found that those with synovial fluid WCCs of >50,000/mm^3 and >70,000/mm^3 had a diagnosis of septic arthritis in 47% and 77% of patients, respectively.[29]

A synovial white count >100,000 appears to be more specific with a positive likelihood ratio of 28.[30] Synovial PMN cells greater than 90% does not significantly increase or decrease the probability of septic arthritis.[31] Although glucose and protein are commonly measured, they do not reliably include or exclude the disease. A synovial lactate greater than 10 mmol/L is reportedly highly sensitive for septic arthritis, although this remains unclear in the literature and cannot be definitively stated.[32]

Diagnosis is typically confirmed by culture. Note that culture is more sensitive than microscopy alone, as synovial fluid gram staining is positive in only 50% of cases.[33] Cultures are more reliable for non-gonococcal etiologies, which grow out 95% of the time, while gonococcal is less than 50%.[28]

NON-ULTRASOUND RADIOGRAPHIC EVALUATION

There is no best imaging modality for gout or septic arthritis and they are generally adjunct to history, exam, hematologic and synovial studies. Radiographs can be normal but may also show joint effusion, 'punched out' erosive changes. Soft tissue shadowing may suggest tophi. No gout classification or guidelines currently exist that rely solely on advanced imaging techniques. Computed Tomography (CT) findings are similar to radiographs. For gout, a 2015 meta-analysis reviewed the published literature concerning the diagnostic performance of plain film radiography, Magnetic Resonance Imaging (MRI), US, conventional CT and dual energy CT (DECT).[34] Of the best available studies, the investigators found US and dual energy CT to show the most diagnostic promise. Gruber et al found US and DECT to have similar sensitivity, however the authors acknowledged false negative findings with DECT.[35] MRI can be useful to evaluate cartilage and bone involvement and evaluate for other diseases including osteomyelitis, myositis, abscess and multifocal infection.

SONOGRAPHIC EVALUATION

Point-of-care ultrasound (POCUS) in the ED has become increasingly popular for evaluation of skin and soft tissue and musculoskeletal injuries. The use of POCUS is associated with reduced use of advanced imaging[15], length of stay[36], and improved ED throughput[37] when compared to the use of traditional imaging modalities. Additional advantages compared to other imaging modalities include absence of radiation, improved patient safety, real-time image acquisition, and relatively low cost of imaging.[38] POCUS can aid in evaluation of a wide range of both skin and soft tissue as well as musculoskeletal pathologies, especially distinguishing arthritis from overlying bursitis. This includes bony injuries including fractures and dislocations[39], extremity tendon injuries[40], foreign body identification, especially in materials that are radiolucent[41], skin and soft tissue infections, especially where the clinical diagnosis is uncertain.[42] Clinicians using point of care US can yield diagnostic accuracy similar to other imaging modalities. For long bone fractures, POCUS is 90% sensitive and 96% specific[43] and for tendon injuries, 100% sensitive and 95% specific.[40] In patients undergoing incision and drainage for abscess, POCUS decreases the likelihood of clinical failure.[44] Finally, US guided arthrocentesis is superior to palpation guided aspiration of the knee, and can aid in arthrocentesis where a palpation guided approach is not feasible, such as the hip.[45,46]

The use of US in the ED represents a novel approach for the diagnosis and management of gout. Rheumatologists have been using US to aid in the evaluation of gout for nearly 20 years. However, to date, there is no research or literature investigating the use of US to evaluate gout in the ED. There are several specific sonographic findings suggestive of gout. Deposition of MSU crystals makes some sonographic features of gout unique. Tophaceous changes can be readily identified on US (Figure 1). The majority of tophi are hyperechoic, heterogeneous ('snowstorm' appearance) with or without hyperechoic areas (Figure 1). Tophi may have an anechoic border and can range from sonolucent to sono-opaque in appearance.[47] The 'double contour' sign, representing deposition of MSU crystals on the cartilage surface, is characterized by an irregular, echogenic line on the outer surface of the joint cartilage. This sonographic finding is the most studied, is specific to gout and is a component of the ACR gout classification criteria (Figures 2,3). Synovial effusion, hypertrophy, color

flow and doppler signal can be seen with gout. US can also evaluate cortical erosions of the bone.

There is compelling research in the rheumatology literature to support the use of US in the evaluation of gout. In a 2013 systematic review of patients evaluated in rheumatology clinics, Chowalloor et al found US was very good for assessing tophi, double contour and erosions.[48] They found the double contour sign to be specific but not sensitive. For cortical erosions, ultrasound was superior to radiographs but inferior to MRI. In 2018, Zhang et al published a second systematic review. In this study, the double contour sign was found to be 66% sensitive and 92% specific, the presence of tophi 56% sensitive and 94% specific, and snowstorm sign 31% sensitive and 91% specific.[49] In summary, the absence of these sonographic features does not exclude gout as a diagnosis. When all 3 signs are pooled together, the sensitivity improves to 80%. They found the presence of these findings correlated with serum uric acid level. Zhu et al found that combining hyperechoic aggregates and the double-contour sign improves specificity to 97%.[50] Shock wave elastography, a novel modality similar to color doppler, may aid in distinguishing acute gout flares from the intercritical phase.[51]

US has additional roles in managing patients with gout. In the patient with known gout, US can be used to trend a decrease in tophi after initiation of urate lowering therapy which correlates with serum uric acid level.[52,53] US may also aid in the evaluation of patients with musculoskeletal complaints in which the presentation is atypical for classic gout by demonstrating "silent" precipitation of MSU crystals.[54] In MSU confirmed cases of gout, crystal deposition can be identified in asymptomatic joints by US.[55] Despite being an intra-articular disease, tendons are the most frequent anatomical location of MSU crystal depositions (Figure 4B,D).[56] US may be useful to distinguish between gout and CPPD based on the characteristics of crystal aggregates and their preferential localization in different anatomical areas.[57]

Although there are no pathognomonic sonographic findings in septic arthritis, US can be used to confirm an effusion. In cadaver studies, it is estimated that only 5-10 mL is usually required to diagnose an effusion in large joints.[58] Compared to MRI, US is 81.3% sensitive and 100% specific for evaluating knee effusions and 96.3% sensitive and 80% specific for evaluating hip effusions.[59,60] It has been suggested, but not proven, that the absence of an effusion on US can exclude the diagnosis of septic arthritis. In children with hip pain, a presentation where septic arthritis and transient synovitis can be difficult to distinguish, US was only 86.4% sensitive for effusion.[61] The authors concluded that US cannot be used to safely distinguish between the two diseases. Doppler does not appear to increase diagnostic yield.[62] US can be used to guide synovial biopsy and arthrocentesis, which can aid in diagnosis of septic arthritis.[63]

MANAGEMENT

Management of acute gout flares involves three main categories of oral medications: colchicine, NSAIDS and corticosteroids. Intra-articular corticosteroid injections are a consideration in large joint involvement. Newer medications including Interleukin-1 inhibitors may play a role in acute gout attack management in the future. NSAID use should be avoided in patients with high risk comorbidities. In renal impairment and polypharmacy, colchicine should be avoided and strong consideration made for corticosteroids. Long term gout management requires preventative rather than abortive therapy. Patients with tophaceous gout need urate lowering therapy to lower uric acid to below 6. Xanthine oxidase inhibitors allopurinol or febuxistat are most commonly used. Additional options include uriscosurics (probenecid) and pegloticase. There is consistent evidence linking sustained control of serum uric acid levels to < 6 mg/dl with good long-term clinical outcomes, and eventually complete remission from symptoms.[64]

Management of septic arthritis generally revolves around irrigation and drainage of the joint and antibiotic therapy. In most cases, arthrocentesis is inadequate and the affected joint requires surgical irrigation and debridement. In one study, 62% of cases required a single surgical debridement, while the rest of the cases required more than one.[65] Choice of antibiotic is driven by history, i.e. suspicion for gonococcal arthritis, and findings on synovial fluid analysis. If initial gram stain demonstrates gram positive cocci, then the patient should be

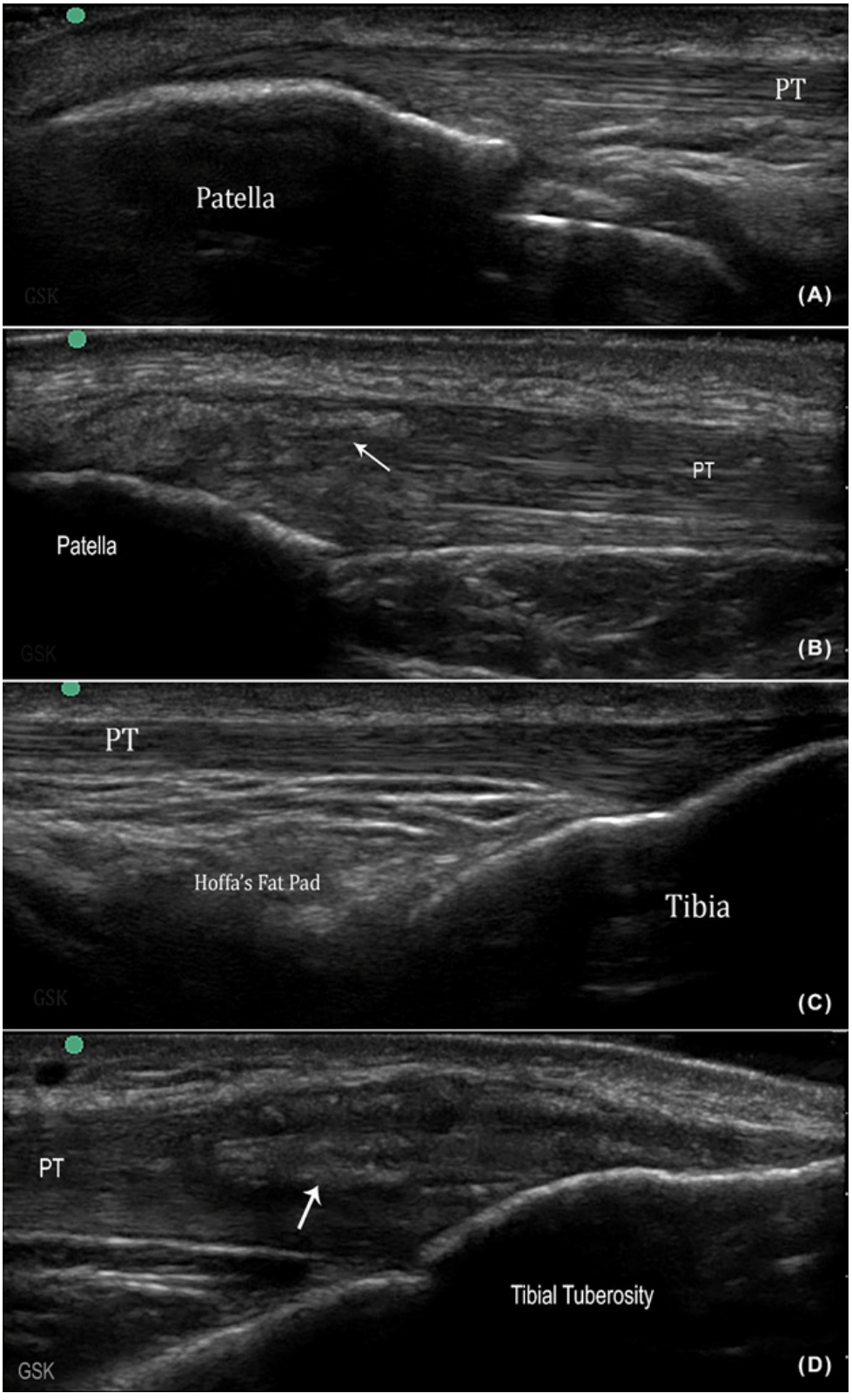

Figure 4 Long axis scan of patellar tendons (PT). A: proximal PT with normal fibrillar echotexture of the normal proximal patellar tendon at the inferior pole of the patella; B: diseased proximal PT appearance; C: distal PT with normal fibrillar echotexture of distal patellar tendon seen as it inserts into the tibial tuberosity; D: diseased distal PT appearance. Note heterogeneous hypoechoic deposits suggestive of gout indicated by arrows in B and D.

treated empirically with vancomycin.[66] This can subsequently be tapered down depending on whether the culture grows out methicillin-susceptible S. aureus or methicillin-resistant S. aureus. If the initial gram stain reveals a gram-negative bacilli, then 3rd or 4th generation cephalosporins should be started empirically. If the initial gram stain is negative, but the clinical picture remains suspicious for septic arthritis then the patient should be started on broad spectrum coverage. Patients with disseminated gonococcal septic arthritis should be treated with ceftriaxone. There are no clear guidelines for duration of therapy. One proposed timeline is 14 days of parenteral antibiotics followed by 14 days of oral antibiotics.[67]

SUMMARY

Undifferentiated atraumatic monoarticular joint pain is commonly seen in the ED. The majority of cases can be managed conservatively based upon symptoms. In cases where gout or septic arthritis are a consideration, arthrocentesis should be performed. In patients with suspected gout, point-of-care US represents a novel approach to aid in the rapid diagnosis and management. Use of US may represent an opportunity to decrease the number of painful, risky arthrocentesis performed, decrease resource utilization and time in the ED. To date, there are no large investigations evaluating POCUS use in the ED to diagnose and manage gout. Ultrasound may also represent an opportunity to improve ED evaluation of septic arthritis. There are no head-to-head studies investigating the use of ultrasound to distinguish gout from septic arthritis in the ED. Because gout has multiple sonographically unique features, their presence may aid in the diagnosis of gout and exclusion of septic arthritis as a cause of monoarticular joint pain. Additional research is required to evaluate the utility and cost effectiveness of US in gout and septic arthritis management in the ED and improved patient outcomes.

Conflicts of Interest: The authors declare no conflicts of interest or sources of funding.

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