Diagnosis and Treatment of Gout and Pseudogout for Everyday Practice

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KEYWORDS

- Crystalline arthropathy • Gout • Arthritis • Pseudogout
- Calcium pyrophosphate deposition disease • Monoarthritis • Polyarthritis
- Urate-lowering therapy

KEY POINTS

- The clinical recognition and differentiation of gout and pseudogout from other causes of inflammatory arthritis is key in rendering appropriate and timely treatment.
- Nonsteroidal antiinflammatory drugs, colchicine, and corticosteroids can control acute gout symptoms; allopurinol and febuxostat are the first-line urate-lowering therapies to definitively treat gout.
- Medication noncompliance is the most common reason for "treatment-resistant" gout.
- Aside from treatment of acute arthritis in pseudogout, there is no proven therapy to prevent recurrence or result in long-term remission.

INTRODUCTION

The crystalline arthropathies, gout and pseudogout, are often successfully managed by the primary care provider. It is essential that primary care clinicians understand the underlying pathophysiology of these diseases, differentiate them from other forms of inflammatory arthritis, know the guidelines for treatment and monitoring, and understand indications for referral to a rheumatologist. A basic knowledge of more advanced medications used in these diseases is important, especially the potential side effects and medication interactions. In this article we present gout and pseudogout from diagnosis to treatment for everyday practice.

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GOUT

Gout incidence is increasing—doubling between the 1970s and 1990s.[1] Hyperuricemia, regardless of the etiology, is the primary cause of this disease. Needle-shaped monosodium urate (MSU) crystals deposit and precipitate within the synovium, ultimately triggering an intense inflammatory response through activation of the innate immune system.

PATHOPHYSIOLOGY

Pathophysiology of Hyperuricemia

Uric acid is a byproduct of purine metabolism. Purines are required for DNA, RNA, adenosine triphosphate, diphosphate, and monophosphate, cyclic adenosine monophosphate, and many other integral molecules. Hyperuricemia results from urate overproduction, underexcretion through the renal tubules, or a combination thereof.

During purine metabolism, uric acid is synthesized via multiple intermediaries, including hypoxanthine and guanine, which converge at the common substrate xanthine (**Fig. 1**). The enzyme xanthine oxidase (XO) then converts xanthine into uric acid. In humans, purine metabolism ends with uric acid. In almost all animals except humans and primates, the enzyme uricase converts uric acid into allantoic acid, a soluble compound that can be degraded into urea and excreted. In addition to de novo synthesis, the purine salvage pathway works through hypoxanthine guanine phosphoribosyl transferase and is responsible for resynthesizing the purines inosine 5'-monophosphate and guanosine monophosphate from hypoxanthine and guanine. The loss of hypoxanthine guanine phosphoribosyl transferase activity results in hyperuricemia. Once serum urate reaches a certain threshold, urate crystals are deposited in synovium. Secondary causes of urate overproduction include increased cell turnover causing increased purine generation (**Box 1**).

Hyperuricemia may also occur as a result of decreased uric acid excretion. Approximately 65% of uric acid is excreted through the renal system.[2] The gastrointestinal tract also excretes uric acid and in chronic kidney disease, may increase its excretion.[3] In the kidneys, uric acid secretion and resorption occur across the proximal tubule epithelium. Important transporters for excretion of uric acid include URAT1, GLUT9, OAT4, and others[4] (**Fig. 2**). URAT1, on the apical tubule surface, transfers tubule lumen urate into the cytosolic environment of the epithelial cell and is the target for some urate lowering therapies. Renal insufficiency and metabolic acidosis, regardless of the cause, promote urate underexcretion, and involve a complex process beginning with a decrease in filtered volume past the glomerulus. Drugs that may promote hyperuricemia include thiazide and loop diuretics and salicylates.

Pathophysiology of Acute and Chronic Gouty Arthritis

Under the appropriate conditions, MSU crystals can activate the NLRP3 inflammasome, a multiprotein cytosolic complex that activates caspase-1.[5] The caspase-1 enzyme cleaves pro-interleukin (IL)-1β to the active IL-1β protein, which is central to the subsequent acute inflammatory response. MSU crystals also induce many other inflammatory cytokines and chemokines, including complement activation. Large amounts of neutrophils are recruited to the joint during an acute gout attack and play a crucial role in the intense inflammation in gout. Neutrophils also release serine proteases that further activate IL-1β, contributing to a positive inflammatory feedback loop.[6]

The tophus is the cardinal feature of chronic gout. A granuloma-like response results in large collections of MSU crystals and inflammatory cells. The tophus produces a persistent inflammatory response in adjacent bone along with reduced osteoblast

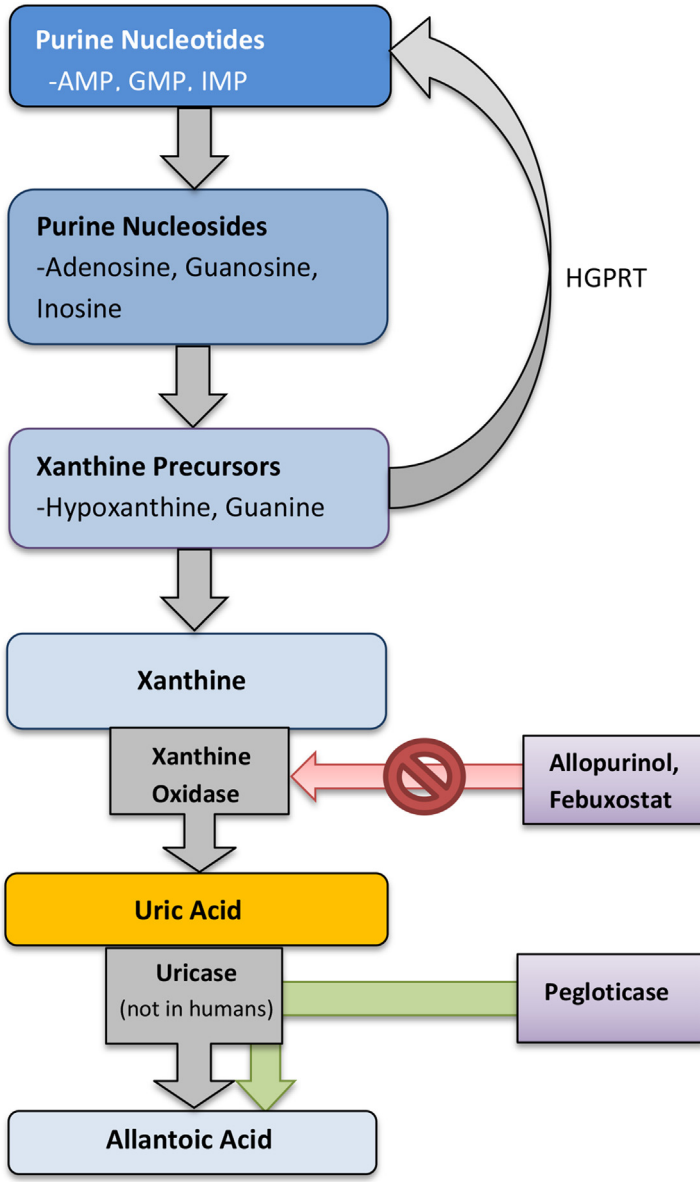

Fig. 1. Purine degradation pathway leading to production of uric acid. Purine nucleotides are degraded into urate precursors, and ultimately into uric acid. The xanthine oxidase inhibitors, allopurinol and febuxostat, inhibit this final step of uric acid production. Pegloticase is recombinant uricase and degrades uric acid into allantoic acid, a soluble metabolite readily excreted by the kidneys. Intermediaries and enzymes not pertinent to the pathophysiology and medications discussed are omitted for simplicity. AMP, adenosine monophosphate; GMP, guanosine monophosphate; HGPRT, hypoxanthine guanine phosphoribosyl transferase; IMP, inosine 5′-monophosphate; XMP, xanthosine 5′-monophosphate.

Box 1
Causes of hyperuricemia

Overproduction
- Acute leukemia and lymphoma
- Tumor lysis syndrome
- Solid organ malignancy
- Hemolytic anemia
- Multiple myeloma, Waldenstrom's macroglobulinemia
- Thalassemia and sickle cell disease
- Myelodysplastic syndrome
- Psoriasis
- Sarcoidosis
- Metabolic and mitochondrial myopathies

Underexcretion
- Renal insufficiency
- Volume depletion
- Medications (diuretics)

Mixed
- Sepsis
- Myocardial infarction and congestive heart failure

Metabolic
- Hypothyroidism and hyperthyroidism
- Hypoparathyroidism and hyperparathyroidism
- Obesity

differentiation and increased osteoclastic activity, which leads to bone resorption and erosions.[7]

EPIDEMIOLOGY

Gout is primarily a disease of males and postmenopausal females, with an increasing incidence seen with advancing age. In 2007 and 2008, the prevalence was estimated at 3.9% of all U.S. adults, and upwards of 9.3% in adults over the age of 60.[1] The incidence of gout was estimated to be 20.2 per 100,000 in 1977, and was noted to have doubled to 45.9 per 100,000 in 1995.[8]

Risk Factors

Risk factors for gout include factors that contribute to hyperuricemia. Male gender alone increases risk for gout compared with premenopausal women given a gender-associated 1 mg/dL higher uric acid at baseline. The etiology likely lies in estrogen effects on uric acid clearance, and this difference is lost in the postmenopausal state.[9] Comorbid renal disease in advanced age likely contributes to the higher rate of hyperuricemia seen in the elderly.[9] Ethnic influences on risk include African American ethnicity with higher serum uric acid levels than Caucasians at baseline.[10] Rare X-linked inborn errors of metabolism, such as Lesch-Nyhan syndrome (hypoxanthine guanine phosphoribosyl transferase enzyme deficiency), are associated with hyperuricemia and gout. Metabolic comorbidities, such as obesity, hypertension, hyperlipidemia, and the metabolic syndrome, are also associated with hyperuricemia and gout.[11,12] Endocrine abnormalities including hyperparathyroidism and hypoparathyroidism, and hyperthyroidism and hypothyroidism, are known to influence kidney function, but the effect on serum urate levels and risk of developing clinical gout is less clear.[13]

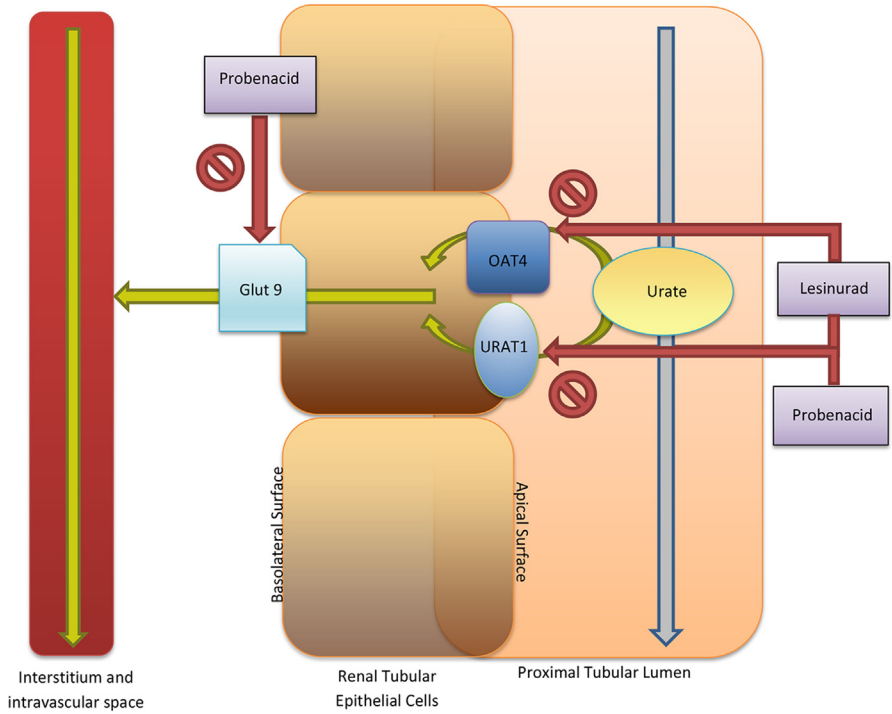

Fig. 2. Renal urate handling. Urate in the renal tubular lumen is ultimately reabsorbed into the intravascular space via action of URAT1 and OAT4/10 on the apical surface, and Glut9 on the basolateral surface of the tubule epithelium. Activity of these transporters is inhibited by the uricosurics probenecid and lesinurad. For simplicity, not all transporters are shown.

Acute Attack Triggers

Repetitive joint microtrauma or severe macrotrauma, purine-rich foods, critical illness, infection, and surgery are associated with attack onset. Medications that increase serum uric acid include diuretics, beta-blockers, low-dose aspirin (<1 g/d) and cyclosporine; initiation or dose changes can precipitate an acute attack.

CLINICAL PRESENTATION

The clinical spectrum of gout spans asymptomatic hyperuricemia to chronic polyarthritis with tophaceous deposits.

Acute Gout

Acute gout typically presents as monoarticular arthritis and is characterized by intense erythema, warmth, swelling, and pain with peak symptoms developing within 24 hours of onset. The most commonly affected joint is the first metatarsophalangeal joint. Other frequently affected joints include the insteps of the feet, heels, ankles, and knees. Less commonly affected joints include the wrists, elbows, and even small joints of the fingers. Acute bursitis, tendinitis, or tenosynovitis can also occur. The hips, shoulders, and spine are almost never affected. Accompanying systemic symptoms are more likely in the setting of polyarticular attacks and may include low-grade fevers, chills, and malaise. If untreated, an

acute attack usually resolves within 5 to 14 days. The differential diagnosis of monoarthritis (**Box 2**) or polyarthritis (**Box 3**) should be thoughtfully considered. The coexistence of gout and septic arthritis has been well-described, making it even more important for the clinician to approach the diagnosis with an appropriate level of suspicion.[14]

Intercritical Period

The intercritical period represents the time after the initial attack that is symptom free before the next attack. For some patients, this period may last years. During this period, crystals can still be found in synovial fluid from asymptomatic joints.[15] Ultrasound examination may also reveal a double-contour sign or presence of tophi, which can strongly support a diagnosis of gout.[16]

Chronic Gout

Chronic gout is characterized by chronic arthritis with persistent low-grade inflammation, bone erosions, and tophaceous deposits in joints and soft tissues. This variant is classically a late feature and is also associated with high levels of hyperuricemia as well as concomitant diuretic use or renal disease.[17] From the time of the first gout attack, tophi typically take longer than 10 years to develop, although they may occur earlier in those with more symptomatic disease and decreased creatinine clearance.[17]

DIAGNOSIS

Most patients with hyperuricemia never develop clinical gout.[1] Furthermore, up to 42% of patients may actually have normal serum urate levels during an acute attack.[18] Therefore, the diagnosis of gout should not be based on serum hyperuricemia alone.

Arthrocentesis of the affected joint with visualization of needle-like negatively birefringent MSU crystals remains the gold standard for diagnosis (**Fig. 3**). Because gout is commonly diagnosed by primary care providers in outpatient clinics, arthrocentesis and polarizing light microscopy may not be feasible. The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) published clinical classification criteria in 2015 to enable standardized enrollment of individuals with gout into studies[19] (**Table 1**). The criteria were not intended for use in making a diagnosis in a clinical setting. Nonetheless, they can serve as a helpful guide for practitioners who are unable to perform a joint aspiration. In addition to MSU crystals, synovial fluid analysis during an acute gout attack may demonstrate white blood cell counts as high as 50,000 to 100,000. Other useful studies include gram stain and culture, to rule out septic arthritis.

Box 2
Differential diagnosis of acute monoarthritis

- Septic arthritis
- Hemarthrosis
- Trauma
- Crystalline arthritis (gout, pseudogout)
- Autoimmune disease (spondyloarthropathy, rheumatoid arthritis, sarcoidosis)
- Leukemia

Box 3
Differential diagnosis of acute polyarthritis

Crystalline arthritis (gout, pseudogout)

Disseminated *Neisseria* infection

Lyme disease

Autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, spondyloarthropathy)

Ancillary Studies

Plain radiographs

Radiographic changes indicate chronicity of disease and may not be apparent for 5 to 10 years after the initial gout attack.[20] Chronic tophi in the soft tissues can erode adjacent periarticular bone and produce well-defined erosions with sclerotic borders and a "punched out" appearance with overhanging edges (**Fig. 4**). The joint space is classically preserved until late in the disease.[20,21] The only radiographic changes during an acute gout attack may be nonspecific soft tissue swelling and effusions.

Ultrasound imaging

Musculoskeletal ultrasound imaging is increasingly being used for establishing a diagnosis of gout. In fact, the 2015 ACR-EULAR classification criteria include ultrasound evidence of urate deposition in a joint or bursa.[19] Highly specific ultrasound features of gout include the double-contour sign (**Fig. 5**), a hyperechoic irregular linear density over the surface of the hyaline cartilage, hyperechoic aggregates (**Fig. 6**) within the joint space indicative of tophus, and the "snowstorm" appearance of floating hyperechoic foci suggesting MSU crystals in synovial fluid.[16] There are several generic signs of inflammation associated with gout as well, including synovial hypertrophy, bony erosions, and increased power Doppler signal during acute gout attacks.

Dual-energy computed tomography

Dual-energy computed tomography (DECT) is a new imaging technique used to help diagnose gout. This imaging modality is able to analyze the chemical composition of

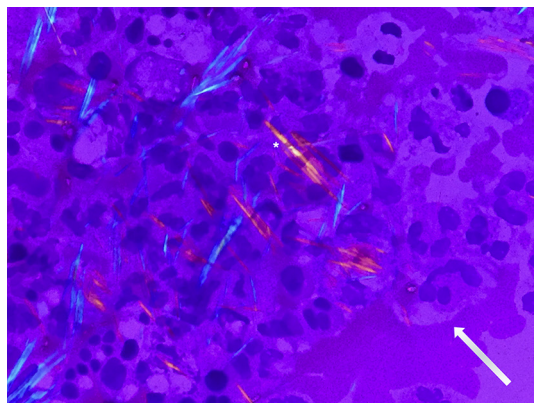

Fig. 3. Polarizing microscopy at an original magnification of x 100 demonstrating negatively birefringent needle-like monosodium urate crystals within milieu of neutrophils consistent with gout (*asterisk*). The polarizer is directed in the upward-left direction as indicated by the white arrow. (*Courtesy of* Jordan M. Hall, MD, Dept of Pathology, BAMC, San Antonio, TX.)

Table 1
The American College of Rheumatology/European League Against Rheumatism gout classification criteria

Criteria	Definitions/Considerations	Score
Entry criterion	Must have ≥1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	Needed for entry into criteria
Sufficient for diagnosis	Tophus or MSU crystals present within symptomatic joint/bursa	Diagnostic of gout If negative, use below criteria
Criteria with scoring (if sufficiency criterion not met above)		
Pattern of joint/bursa involvement during episodes	Distribution of involvement	MTP1: 2 Ankle/midfoot without MTP1: 1 Any other joint: 0
Characteristics of symptomatic episodes	Presence of (1) difficulty with walking or inability to use joint, (2) inability to bear touch/pressure, (3) erythema overlying the affected joint	Three characteristics: 3 Two characteristics: 2 One characteristic: 1 No characteristics: 0
Time course	Typical episode: presence of >2 of the following: time to maximal pain <24 h, resolution ≤14 d, complete resolution between episodes	Recurrent typical episodes: 2 One typical episode: 1 No typical episodes: 0
Clinical evidence of tophus	Present/absent	Present: 4 Absent: 0
Serum urate cut-offs	<4 mg/dL 4–6 mg/dL 6–<8 mg/dL 8–<10 mg/dL ≥10 mg/dL	−4 0 2 3 4
Synovial fluid analysis	MSU negative or not performed (MSU positive is sufficient on its own)	Not performed: 0 MSU negative: −2
Imaging evidence of urate deposition	Ultrasound/DECT presence or absence Presence of gout-related erosions or absence	Present: 4 (either modality) Absent: 0 Present: 4 Absent: 0

A web based calculator can be accessed at http://goutclassificationcalculator.auckland.ac.nz. Synovial fluid positive for monosodium urate crystals immediately classifies a patient as having gout. Otherwise, a score of 8 or higher allows for gout classification.

Adapted from Neogi T, Jansen TL, Dalbeth N, et al. Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2015;74(10):1795; with permission.

uric acid compared with other materials, such as calcium, in musculoskeletal tissue. DECT characterizes the composition of the material using different colors.[22] MSU crystals can also be visualized in the tendons, ligaments, and soft tissues using this technique (Fig. 7). DECT is especially helpful in cases where there is a high clinical

suspicion of gout but aspiration is negative for MSU crystals or in asymptomatic patients during the intercritical period. A recent metaanalysis found DECT to have a high diagnostic accuracy with 84.7% sensitivity and 93.7% specificity.[22] The sensitivity is related to tophaceous burden, with very high sensitivity in joints with tophaceous gout, and lower sensitivity in nontophaceous gout.[22–24] Therefore, false negatives are more likely in patients with recent onset disease.

TREATMENT

If treated properly, gout is a disease from which a patient can enjoy sustained remission. There are published treatment guidelines from multiple organizations including the ACR, American College of Physicians (ACP), and EULAR.[25–27] Although similar in many regards, these guidelines differ in some areas, especially regarding chronic treatment (**Table 2**).

Acute Treatment

The goal of acute gouty arthritis treatment is to quell the intense inflammation. In addition to antiinflammatory medication, all patients should receive appropriate analgesics during this period.

Colchicine

Colchicine is a tricyclic alkaloid that inhibits multiple pathways involved in the inflammatory cascade. In gout, it suppresses the activation of caspase-1, which prevents IL-

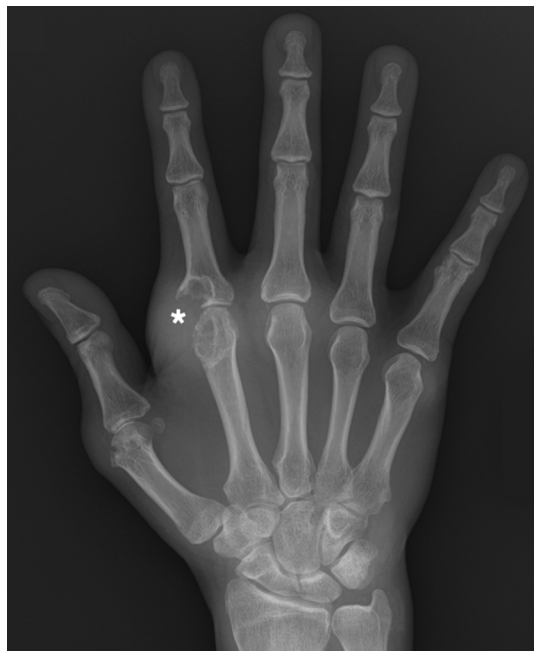

Fig. 4. Plain anteroposterior right hand radiograph demonstrating a punched out lesion with an overhanging edge and sclerosis consistent with gouty erosion (asterisk). Note the presence of adjacent soft tissue swelling.

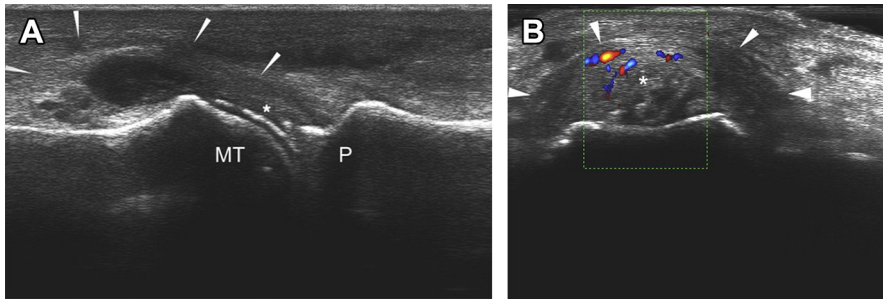

Fig. 5. (*A*) Ultrasound image of a first metatarsophalangeal joint with double-contour sign (*asterisk*). White arrows outline the synovial lining. MT, metatarsal head; P, phalangeal head. (*B*) Ultrasound image of a metatarsophalangeal joint in transverse orientation with hyperechoic tophi and increased Doppler signal indicating active inflammation (asterisk). Arrows outline the synovial lining.

1β generation and inflammasome activation. It also prevents neutrophil migration and activity, which causes gout symptoms.[5,28]

Oral colchicine is most effective when given early during the acute flare, that is, within the first 36 hours of symptom onset.[29] The recommended dosing regimen in

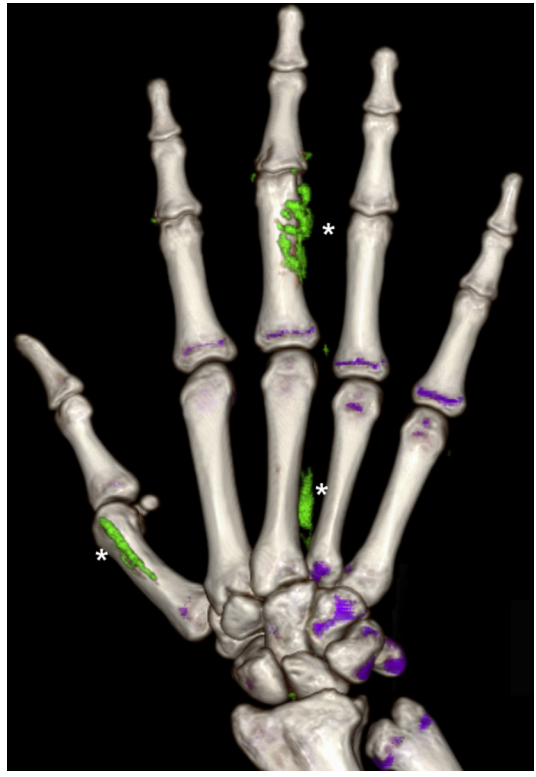

Fig. 6. Dual energy computed tomography depicting multiple dense collections of monosodium urate crystals (*asterisks*) consistent with tophaceous gout. Green is indicative of monosodium urate crystals.

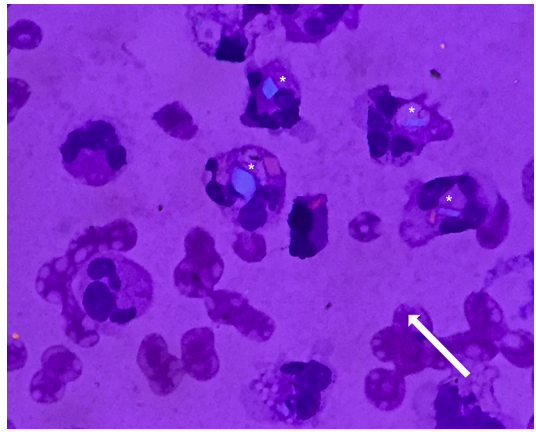

Fig. 7. Polarizing microscopy at an original magnification of x100 demonstrating positively birefringent rhomboid-shaped calcium pyrophosphate crystals present within neutrophils (*asterisks*). Polarizer is directed in the upward-left direction as indicated by the white arrow. (*Courtesy of* Jordan M. Hall, MD, Dept of Pathology, BAMC, San Antonio, TX)

an acute episode is 1.2 mg as a single dose followed 1 hour later by a single 0.6-mg dose.[30] This regimen is typically followed by colchicine 0.6 mg twice daily until symptoms resolve. Gastrointestinal toxicity, including diarrhea and severe nausea, is the most common dose-limiting side effect. Because colchicine is metabolized and eliminated by P-glycoprotein and cytochrome P4503A4, combining it with medications such as clarithromycin, erythromycin, verapamil extended release, diltiazem extended release, and cyclosporine, can result in severe toxicity.[31] The concomitant use of statins increases the risk of myopathy and rhabdomyolysis. Colchicine clearance is decreased in patients with impaired renal function. Low-dose colchicine should be reduced by at least 50% for patients with stage III chronic kidney disease or worse, and the treating clinician should exercise increased caution when considering this treatment in those with more advanced renal disease.[29]

Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit prostaglandin synthesis and reduce inflammation and pain in an acute gout flare. No specific NSAID is recommended over another. Prescribing at the full-strength dose until the acute gout attack has resolved is recommended regardless of the NSAID chosen.[29] Unfortunately, oral NSAID use is limited and complicated by conditions including gastropathy, nephropathy, liver dysfunction, and platelet dysfunction.

A study with initial results made recently available examined the use of naproxen compared with colchicine as the first-choice treatment.[32] Findings from this study suggest that both naproxen and low-dose colchicine are effective in the treatment of acute gout, but there were less side effects with naproxen and possibly greater analgesic effect. This is in line the ACR 2012 guidelines that recommend equally considering an NSAID, oral colchicine, or systemic corticosteroids[29] (**Table 3**).

Systemic Corticosteroids

Corticosteroids reduce the activation, proliferation, and survival of a variety of inflammatory cells. They decrease migration of neutrophils, inhibit prostaglandins and

Table 2
Comparison of the ACR, ACP, and EULAR recommendations for acute and chronic gout management

	ACR	ACP	EULAR
Acute Attack management	Colchicine and NSAIDs as first line, alone or in combination in refractory cases; intraarticular corticosteroid can be considered in cases of 1–2 large joints involved	Steroids first line, can consider colchicine or NSAIDs	Colchicine and/or NSAIDs, oral corticosteroid, or intraarticular corticosteroid
Acute attack management in NPO patient	Intraarticular corticosteroids vs IV/IM methylprednisolone 0.5–2.0 mg/kg	Not addressed	Not addressed
Indication for ULT	Tophi on clinical examination or imaging study, frequency ≥2 attacks per year, CKD stage 2 or worse, past urolithiasis	Not after first attack or <2 attacks per year; use in ≥2 attacks per year or gouty tophi, CKD, or urolithiasis	Recurrent flares, tophi, urate arthropathy and/or renal stones, young age (<40) or very high serum urate (>8 mg/dL) and/or comorbidities (renal disease, HTN, ischemic heart disease, heart failure)
Initial ULT	Allopurinol (starting dose 100 mg/d) or febuxostat 40mg/d	Allopurinol or febuxostat	Allopurinol at 100 mg/d in those with normal renal function, and increase by 100 mg increments every 2–4 wk
Prophylaxis with concomitant ULT	Low-dose NSAID or low-dose colchicine; continue for ≥6 mo; or 3 mo after achieving target serum urate in patients with no tophi or 6 mo after achieving target serum urate in patients with tophi	Low-dose colchicine or low-dose NSAIDs for ≥8 wk while initiating ULT	Prophylaxis with low-dose colchicine for first 6 mo of ULT; if colchicine not tolerated/contraindicated consider low-dose NSAID
Gout flare during ULT	Continue ULT, treat for acute attack	Not addressed	Not addressed
ULT strategy	Treat to target uric acid goal <6 mg/dL at minimum, and in select cases <5 mg/dL; titrate ULT every 2–5 wk to obtain serum urate goal	Treat to avoidance of gout attacks	Goal serum urate <6 mg/dL, or <5 mg/dL in those with severe gout

Abbreviations: ACP, American College of Physicians; ACR, American College of Rheumatology; CKD, chronic kidney disease; EULAR, European League Against Rheumatism; HTN, hypertension; IV/IM, intravenous/intramuscular; NSAID, nonsteroidal antiinflammatory drug; ULT, urate-lowering therapy.
Data from Refs.[26,27,37]

proinflammatory cytokines such as IL-1β.[33] Although there are no placebo-controlled trials examining the efficacy of oral corticosteroids, multiple studies have assessed the effectiveness of corticosteroids against NSAIDs. Both treatment modalities demonstrated similarity in time to symptom resolution and pain reduction, although NSAIDs[34] demonstrated increased gastrointestinal and other NSAID-associated adverse events. A single dose of intramuscular (IM) corticosteroids, such as triamcinolone acetonide or methylprednisolone acetate, is also efficacious in the treatment of acute gout[34,35] (see **Table 3**). Systemic corticosteroids are particularly useful if the acute attack is severe and polyarticular. High doses of corticosteroids are typically required, with starting doses of prednisone typically 0.5 mg to 1 mg/kg tapered over 7 to 14 days.[29]

Intraarticular Steroids

Intraarticular steroid injection is useful in patients with severe attacks involving 1 or 2 joints, especially in large weight-bearing joints. Additionally, this is a useful treatment modality in such patients where NSAIDs and colchicine are contraindicated. One study evaluated intraarticular triamcinolone acetonide 10 mg, which resulted in pain relief within 48 hours in all 19 study patients with no significant side effects or rebound attacks, and no additional treatment needed for the given attack.[36] Dosage of corticosteroid should be adjusted to the size of the joint.

Interleukin-1 Inhibition

IL-1β is activated by the initial inflammasome response to the MSU crystals, and then further propagates the inflammatory reaction. Thus, there are high levels of interest in blocking this pathway with anti–IL-1 agents, including anakinra (IL-1 receptor antagonist) and canakinumab (anti–IL-1β monoclonal antibody). Canakinumab is approved for acute gout in Europe.[37] These agents offer effective treatment for patients in whom first-line acute therapies provided an inadequate response or are contraindicated. Both canakinumab and anakinra are injected subcutaneously at the first sign of an acute gout attack. Current infection is a contraindication to the use of IL-1 blockers.

Table 3
Common dosing and frequency for antiinflammatory medications used in acute gout

Nonsteroidal Antiinflammatory	Dosage and Frequency
Ibuprofen	600–800 mg 3 times daily
Naproxen	500 mg twice daily
Indomethacin	50 mg 3 times daily
Others	
Colchicine	Acute: 1.2 mg followed by 0.6 mg 1 hour later, then 0.6 mg twice daily
Corticosteroids	
IM methylprednisolone	0.5-2.0 mg/kg IV or IM
Prednisone	0.5 mg/kg for 5–10 d then discontinue vs 0.5 mg/kg/day for 2-5 days then taper for 7-10 days
Intraarticular corticosteroid	Dosed based on joint size

Abbreviation: IV/IM, intravenous/intramuscular.
Data from Refs.[27,29,37]

Chronic Urate-Lowering Therapy

The mainstay of treatment in gout is the use of urate-lowering therapy (ULT) to prevent acute flares and ultimately to prevent erosive, destructive, and debilitating joint disease. Aside from obvious functional improvements related to the avoidance of attacks, joint destruction, and tophaceous disease, a recent study found that allopurinol use was associated with decreased acute cardiovascular events in patients with comorbid gout and diabetes.[25] The urate-lowering agents work in various ways to either prevent the production of urate or enhance its excretion.

The treating clinician should consider several factors when deciding whether to initiate long-term ULT. After the initial acute gout attack, the asymptomatic intercritical period may last years in some patients. For this reason, the ACR, EULAR, and ACP guidelines agree that chronic ULT does not need to be started immediately after the first attack in the absence of tophi, nephrolithiasis, chronic kidney disease, or multiple prior attacks ($\geq$2 per year).[29,37] The risk–benefit ratio of starting any lifelong ULT should be discussed individually with a patient. Once initiated, ULT should be continued during any subsequent gout flares and the acute flare should be treated appropriately.

The ACR and EULAR recommend treating to a target serum urate level given that there is decreased uric acid precipitation when serum levels are less than 6 mg/dL.[26] Furthermore, both the ACR and EULAR recognize that for severe disease with tophi, chronic gouty arthritis, or frequent attacks, a lower serum urate target (<5 mg/dL) may be necessary to speed dissolution of crystals. In contrast, the ACP recommends using a "treat to avoid symptoms" approach.[27] This recommendation is based primarily on the relative lack of studies looking specifically at the efficacy of uric acid targets. The primary concern of most rheumatologists is that, even in the absence of acute attacks, MSU crystals continue to deposit in the joints and tissues, and cause cartilage damage and bone erosion.

For many years, it was thought that ULT initiation during an acute episode would prolong the painful gout attack. However, there are 2 high-quality randomized controlled trials that found that initiating allopurinol during an acute gout attack does not adversely affect the resolution of the acute attack, as long as effective acute management has been instituted.[38,39] This finding supports the ACR recommendation that pharmacologic ULT can be started during an acute attack.

Prophylaxis of Acute Gout During Urate-Lowering Therapy

It is well-documented that the initiation of serum ULT is associated with an increased frequency of acute gout flares.[40] Acute gouty attacks during the first months of ULT contribute to decreased adherence.[40,41] All 3 guidelines from the ACR, EULAR, and ACP agree that patients starting ULT should concomitantly receive daily prophylaxis for acute gout. The first-line agents are either low-dose colchicine (0.6 mg twice daily, adjusted for creatinine clearance or drug interactions) or low-dose NSAIDs (naproxen 250 mg twice a day). Prophylaxis should generally be continued for at least 3 months after achieving the target serum urate levels and 6 months after achieving target urate levels in patients with tophi.[26,27,37] For patients who have contraindications to colchicine or NSAIDs, low-dose corticosteroids (prednisone <10 mg) may be considered. There are also data supporting the possibility of using IL-1 inhibitors (anakinra, canakinumab, rilonacept), but none of them are approved for prophylactic treatment yet.[42]

Xanthine Oxidase Inhibition

XO inhibitors are recommended as first-line ULT by the ACR, ACP, and EULAR. XO inhibition is effective regardless of whether the hyperuricemia is due to overproduction or underexcretion. Therefore, it is not necessary to order a 24-hour urine uric acid in all patients before beginning ULT.

Allopurinol

The first XO inhibitor to be used for chronic ULT was allopurinol. The recommended starting dose is 100 mg/d.[26,37] In patients with a glomerular filtration rate of less than 30 mL/min, the initial dose should be no higher than 50 mg/d.[43] Upward titration of the starting dose can occur every 2 to 5 weeks in intervals of 100 mg in normal individuals, and by 50 mg every 2 to 5 weeks in those with a glomerular filtration rate of less than 30 mL/min.[44] Following these guidelines, allopurinol can be safely increased to achieve target serum urate, including in those with a reduced glomerular filtration rate.[44] Most patients will require doses greater than 300 mg/d. The maximum US Food and Drug Administration–approved dose of allopurinol is 800 mg/d.

Allopurinol is generally well-tolerated, although side effects include nausea, diarrhea, and transaminase elevation. The dreaded complication is the allopurinol hypersensitivity syndrome (AHS), characterized by Stevens-Johnson syndrome and toxic epidermal necrolysis, eosinophilia, leukocytosis, fever, hepatitis, and renal failure.[43] The AHS occurs in only 0.1% of patients but it is associated with high mortality and there is no proven treatment, other than allopurinol withdrawal.[44] Risk factors for the AHS include a higher starting dose of allopurinol, increased age, renal impairment, diuretic use, and some ethnic groups. The HLA-B*5801 genotype is associated with an increased risk of AHS.[45,46] The ACR recommends that patients of Han Chinese, Korean, or Thai descent should be screened for the HLA-B*5801 allele and that those with a positive test should not receive allopurinol.[46] It is generally recommended that allopurinol should be stopped at the first sign of a rash. The AHS almost always begins within the first 8 weeks after initiating allopurinol.[45]

Medications to avoid concomitantly with allopurinol include azathioprine, 6-mercaptopurine, and theophylline, because the inhibition of XO can result in severe toxicity of these medications with slowed metabolism and toxic effects.

Febuxostat

Febuxostat is started at a dose of 40 mg/d, and can be increased to 80 mg/d if uric acid does not reach goal after 2 to 4 weeks. Studies have demonstrated that the 40-mg dose of febuxostat is comparable with 300 mg allopurinol dosing for patients with normal renal function. Febuxostat is also safe for use in those with chronic kidney disease stages II and III.[47]

Febuxostat can be used in cases of allopurinol intolerance or inadequate uric acid response to allopurinol. It does not have known cross-reactivity with allopurinol, given that it has a different molecular structure. Because of this, febuxostat is safe to use in patients who have experienced a severe allopurinol adverse reaction, including the AHS.[48] The most common side effects include diarrhea and elevation of liver transaminase enzymes. However, because febuxostat inhibits XO, there are still major potential drug interactions with concomitant use of azathioprine, 6-mercaptopurine, and theophylline.

Treatment of Refractory Gout

Multiple studies have suggested medication nonadherence in gout patients. A systematic review revealed that the proportion of medication-compliant patients with

gout is only 10% to 46%.[49] Thus, for those not responding to XO inhibitors, a discussion of mediation compliance and its rationale may provide therapeutic benefits.

Uricosurics

Uricosuric agents increase renal uric acid excretion. The multiple contraindications to uricosuric ULT and drug interactions are the reason they are not considered first-line ULT treatment by any of the major societies. However, they may be useful in cases where XO inhibitors are contraindicated or when an additional urate-lowering effect is needed.

A history of nephrolithiasis presents an important contraindication to uricosurics. Elevated urinary uric acid levels are also a contraindication to uricosuric ULT because this finding indicates uric acid overproduction.[26] Furthermore, they are ineffective in the setting of renal insufficiency with a creatinine clearance of less than 50 mL/min. Uricosurics are also associated with many different drug interactions, resulting in either altered levels of the uricosuric agent or the urinary excretion of other drugs. Medication classes that should be avoided in combination with uricosurics include penicillins, cephalosporins, nitrofurantoin, and NSAIDs, including indomethacin, ketorolac, zidovudine, and methotrexate.

Probenecid

Probenecid is a uricosuric agent that inhibits urate anion reabsorption in the proximal renal tubule (see **Fig. 2**). It is approved for monotherapy but it can also be used in combination with XO inhibitors. Typically, this medication is started at 250 mg twice daily and titrated up to 1000 mg twice daily.

Lesinurad

Lesinurad is another uricosuric agent that decreases uric acid reabsorption in the proximal renal tubule (see **Fig. 2**). A recent double-blind randomized controlled trial found that lesinurad 200 and 400 mg/d in combination with allopurinol 300 mg/d were associated with 52% and 59% of subjects, respectively, achieving a urate level of less than 6 mg/dL at 6 months, as opposed to only 27.9% in the allopurinol-only group.[50] A study is currently underway to evaluate lesinurad as monotherapy (clinicaltrials.gov identifier NCT01508702).

Lowering Urate as a Side Effect

Multiple medications may provide ancillary benefit to traditional ULT. Calcium channel blockers, fenofibrate, and losartan have been found to have modest uricosuric effects and can be added to other ULT.[51]

Uricase

Pegloticase is a recombinant porcine–baboon uricase that converts uric acid to allantoin, which is a more soluble compound that can be easily excreted in the urine (see **Fig. 2**). Pegloticase has been proven to rapidly reduce serum urate levels, which can lead to more rapid resolution of gout attacks and tophi.[52] Severe infusion-related reactions can occur. Preinfusion serum urate levels are monitored, because a loss of response is indicative of drug antibody development. Patients should also be screened for G6PD deficiency before use. This medication is only recommended in severe refractory cases in which other standard treatments are contraindicated.[29,53]

Dietary Modification

Data on the impact of dietary intake generally suggests that purine-rich foods, especially red meat, organ meat, shellfish, high-fructose and glycemic index foods, and

alcohol, particularly beers and ales, contribute to hyperuricemia.[54] However, other purine-rich foods such as legumes, fruits, and vegetables do not increase the risk of gout. There is an inverse relationship between increased dairy consumption and serum urate.[55] Additionally, vitamin C may have a mild urate-lowering effect and the consumption of cherries may reduce the risk of recurrent gout attacks.[54] Generally, avoiding excess calorie consumption and decreasing body mass index seems to reduce the risk of gout.[54,56] Although dietary modification and fitness are recommended by both the ACR and EULAR, strict lifestyle modification alone is unlikely to reduce serum urate levels by more than 10% to 18%.[26,53,56] Therefore, most patients will also require pharmacologic ULT.

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE

Pseudogout is clinically similar to gout, but is due to the presence of calcium pyrophosphate (CPP) and not MSU crystals.[57] In this section, we discuss the pathophysiology, epidemiology, clinical presentation and diagnosis, risk factors, and management of pseudogout.

Nomenclature

It is impossible to address "pseudogout" without also addressing the confusing nomenclature. Originally coined as pseudogout, this disease has also been known by several other terms. In 2011, the EULAR recommended a more consistent naming pattern, with the use of CPP crystals to refer to the crystals themselves and CPP deposition (CPPD) as an umbrella term to refer to all occurrences of CPP crystals.[58] The term chondrocalcinosis refers to the radiographic findings consistent with CPPD.

Pathophysiology of Calcium Pyrophosphate Deposition and Inflammation

CPPD is characterized by the deposition of CPP crystals in the articular hyaline and fibrocartilage. The pathogenesis of CPPD is not as clearly defined as gout, but it is known that the first step includes an overproduction of inorganic pyrophosphate anions by chondrocytes. Ultimately, the formation of CPP crystals within the joint cartilage matrix is due to the interaction of the cation, calcium, and the anion, inorganic pyrophosphate.[59] These crystals result in inflammatory-mediated damage by activation of the innate immune system, just as discussed in gout.

Although the articular cartilage is specialized to avoid calcification, the degenerative changes to chondrocytes and cartilage as seen in osteoarthritis, and even normal aging, predisposes to pathologic crystal deposition. Conditions including hyperparathyroidism, hypophosphatasia, hypomagnesemia, and hemochromatosis may predispose to crystal deposition owing to increased inorganic pyrophosphate levels in the synovium.[59–61] Upon generation of CPP crystals, the NLRP3 inflammasome complex is activated, as in gout, to secrete the inflammatory cytokine IL-1β. Additionally, neutrophils are activated and a prolonged neutrophilic inflammatory response is observed in patients with acute CPPD arthritis.[62] Although less well-understood, the long-term presence of these CPP deposits within the synovium results in chronic changes similar to that in osteoarthritis.

Epidemiology and Risk Factors

CPPD is usually found in patients over the age of 60 and there is a strong association with advancing age.[63,64] The prevalence of chondrocalcinosis depends on the joint imaged. Radiographic chondrocalcinosis affects up to 7% to 8% of the middle-aged to elderly adult European and US populations and has been reported

in up to 44% of patients over the age of 84 years.[64] However, a definitive diagnosis of CPPD arthritis requires positive identification of CPP crystals on synovial fluid analysis. Radiographic chondrocalcinosis is often asymptomatic and does not always lead to clinical CPPD, making the true estimation of clinical disease uncertain. Conversely, chondrocalcinosis may be difficult to visualize by conventional radiography in some joints despite identification of CPP crystals from the joint. Chondrocalcinosis likely only identifies 40% of those with clinical CPPD disease.[65]

Advancing age is the primary risk factor for developing CPPD. In addition, multiple metabolic conditions increase the risk for development of CPPD, including primary hyperparathyroidism, hemochromatosis, hypomagnesemia, hypophosphatemia, and osteoarthritis in the affected joint[66] (**Table 4**). Acute cases may be associated with trauma or even in acute systemic illness. Of note, there are no particular dietary associations with CPPD development.

Clinical Presentation

Acute arthritis

The most common presentation of acute CPPD arthritis is monoarthritis affecting large joints, most often the knee or wrist, and less frequently the elbow. Analogous to the presentation of acute gout, patients may have severe and sudden inflammation with painful swelling. Attacks typically last as long as 10 days, but unlike typical gout attacks, can linger for weeks. CPPD can cause an oligoarthritis, polyarthritis, or even migratory or additive acute arthritis. In some patients, acute episodes may present similar to rheumatoid arthritis, with inflammation of multiple small joints that can include the metacarpophalangeal joints while also affecting the large joints. In elderly patients, a positive rheumatoid factor may create diagnostic confusion.[60,67] Concomitant fevers and malaise may raise suspicion for septic arthritis given the similarity in presentation and elevated erythrocyte sedimentation rate and C-reactive protein.

Axial disease

CPPD can occur in the axial skeleton, including the atlantoaxial junction, facet and intervertebral joints, and discs. The crowned dens syndrome is due to CPPD at the atlantoaxial junction with calcifications around the dens. Acute attacks may present with severe neck pain, neck rigidity, and fever, and could be misdiagnosed as

Table 4
Comorbidities associated with CPPD and their associated laboratory evaluation

Comorbidity	OR for CPPD[63]	Testing
Hyperparathyroidism	3.35	PTH and calcium increased
Osteoarthritis	2.26	Clinical, radiography
Hemochromatosis	1.87	Ferritin elevated, serum transferrin elevated
Hypomagnesemia	1.23	Low magnesium
Calcium supplementation	1.15	n/a
Chronic kidney disease	1.12	Creatinine, glomerular filtration rate

Abbreviations: CPPD, calcium pyrophosphate deposition; n/a, not applicable; OR, odds ratio; PTH, parathyroid hormone.

From Kleiber Balderrama C, Rosenthal AK, Lans D, et al. Calcium pyrophosphate deposition disease and associated medical co-morbidities: a national cross-sectional study of US veterans. Arthritis Care Res (Hoboken) 2017;69(9):1400–6.

meningitis, polymyalgia rheumatica, or temporal arteritis.[68] Chronic instability of the atlantoaxial joint can result in a severe myelopathy and death.

Chronic Osteoarthritis-Like Calcium Pyrophosphate Deposition

This clinical phenotype resembles osteoarthritis. However, joints such as the shoulder (glenohumoral joint), metacarpophalangeal joints, wrists and elbows, which are not typical of primary osteoarthritis, are often involved. Also, unlike typical osteoarthritis, patients will have flares of inflammatory arthritis.

Diagnosis

CPPD is an underdiagnosed condition. The gold standard lies in obtaining positively birefringent, rhomboid-shaped crystals from synovial fluid of an affected joint (**Fig. 8**). The synovial fluid is typically highly inflammatory with elevated leukocyte counts during an acute attack. Ancillary testing includes radiography with chondrocalcinosis, the radiographic appearance of CPP crystals. CPP crystal deposition appears as heavy rounded calcifications within the fibrocartilage (eg, knee meniscus and triangular fibrocartilage of the wrist), or hyaline (articular) cartilage. Ultrasound examination is a useful tool to detect CPP crystal deposition in cartilage, particularly in the knee.[69] Ultrasound imaging can also distinguish chondrocalcinosis from MSU deposition. CPPD is identified as hyperechoic rounded deposits with in the substance of the cartilage, as opposed to MSU crystals, which appear more linear and deposit on the surface of the cartilage.[70] More advanced imaging modalities include DECT scanning for detection of calcium-containing crystals.

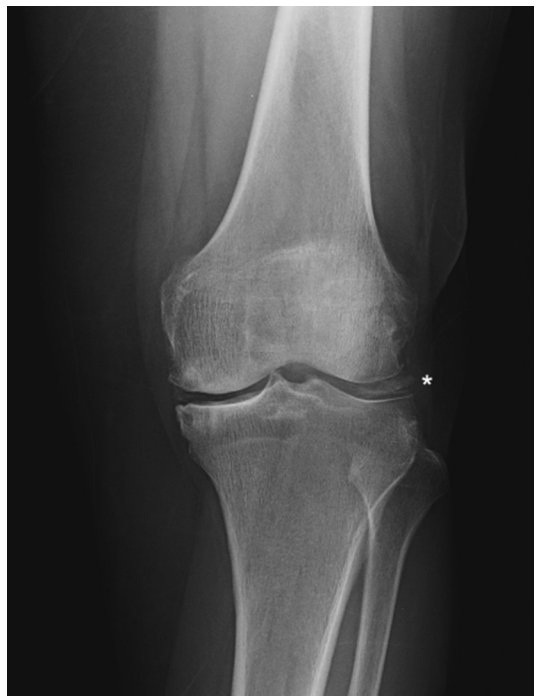

Fig. 8. Weight-bearing knee radiograph depicting chondrocalcinosis within the fibrocartilage (asterisk) and medial compartment joint-space narrowing and subchondral sclerosis (adjacent to asterisk) consistent with concomitant osteoarthritis.

TREATMENT

Acute calcium pyrophosphate deposition arthritis

The acute arthritis owing to CPPD is highly inflammatory and involves activation of the innate immune system and many of the same inflammatory mechanisms as gout. Therefore, the treatment for acute CPPD arthritis is similar to the treatment for acute gouty arthritis. CPPD may respond well to intraarticular corticosteroid injection.[53] However, in patients with a polyarticular flare in which injection of each individual joint is not practical, systemic corticosteroid dosing with prednisone or IM injection of triamcinolone or methylprednisolone can be used.[55] NSAIDs at a full-strength dose and even colchicine, dosed as used in gout, may also relieve inflammation and pain in the acute period.[54]

Chronic calcium pyrophosphate deposition

The approach to chronic CPPD arthritis is problematic given that there is frequently comorbid degenerative joint disease. There are no well-studied, evidence-based chronic suppressive treatment regimens or definitive strategies to lower CPP levels. Rather, there are case reports and small case series reporting the use of colchicine,[71] IL-1 inhibition,[53] and hydroxychloroquine[72] with varying success. A small randomized placebo-controlled trial recently evaluated methotrexate efficacy in chronic or recurrent CPPD arthritis. Unfortunately, the results indicated that methotrexate did not provide a significant benefit.[73] Aside from low-dose colchicine, we would recommend treating only in consultation with a rheumatologist with any of these other DMARD or biologic treatments given the risks and side effect profiles.

REFERRAL TO A RHEUMATOLOGIST FOR GOUT OR PSEUDOGOUT

Ultimately, the time to refer a patient to a rheumatologist relies on a shared decision between the provider and patient. Recalcitrant disease warrants referral for evaluation of other potential etiologies and use of less traditional therapies. Patients with comorbidities that portend a more difficult treatment course owing to contraindications to use of traditional gout medications, such as posttransplant patients taking cyclosporine or azathioprine, warrant specialty consultation.

SUMMARY

Gout and pseudogout represent entities that present commonly to primary care clinics. Upon recognition, gout may be effectively treated in both the acute and chronic stages. Patient medication noncompliance is a common cause of recurrent gout. Pseudogout should be differentiated from gout, because the chronic therapies used in gout will not provide benefit. However, acute CPPD arthritis can be effectively managed using many of the same therapies.

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