Evolution of gout: "malignant" change over time?

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ABSTRACT

Gout is a common entity; yet it is such a great mimicker in its imaging features that it can confuse clinicians and radiologists alike, sometimes leading to unnecessary investigations and treatment. We present a case of a 52 year old male renal transplant patient who presented with a slow growing mass in his left shin. The initial radiograph demonstrated a non-aggressive looking calcified lesion. A fine needle aspiration demonstrated this lesion to be gout deposition. The lesion was unchanged in the following eight years until the patient reported a sudden growth in size. Imaging showed features of an aggressive lesion with disruption of the previous calcification as well as enhancement on magnetic resonance imaging. Surgical excision biopsy was performed in view of the worrisome features on imaging and the histology showed tophaceous gout. Following description of our case, we reviewed the clinical and imaging features of gout and discussed its differential diagnoses.

CASE REPORT

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A 52-year-old male patient with a history of dual cadaveric renal transplant presented nine years ago with a slow growing, painless mass in his left shin over 3 months. He was not known to have gout prior to this presentation.

Radiographs of the left tibia and fibula in anterior-posterior and lateral views demonstrated a well-defined mass with a calcified rim in the anterior compartment of the left mid shin (Fig. 1). This was initial thought to represent myositis ossificans or calcific myonecrosis. Further evaluation with computed topography showed a well-circumscribed mass predominantly confined in the anterior compartment with internal and rim calcification as well as ground-glass matrix (Fig. 2). It measured 3.7 x 3.0 x 16.8cm (Antero-posterior x medial-lateral x cranio-caudal). The mass did not involve the underlying bone. This was again interpreted to represent a non-aggressive lesion such as myositis ossificans or calcific myonecrosis. The clinician decided to perform a fine needle aspiration which showed the mass to be tophaceous gout (Fig. 3).

The mass remained stable in size for a period of eight years with rare interval radiograph performed demonstrating no significant change in the lesion (Fig. 4).

Eight years later, the patient presented once again with interval development of a smooth, flesh-colored lump at the anterior aspect of his left shin which was increasing in size. This was in the same region as the previously known mass (Fig. 5). Radiographs of the left tibia and fibula revealed disruption of calcification in the anterior aspect of the previously well-circumscribed calcified mass (Fig. 6). Suspicion of a new aggressive pathology such as a sarcoma occurring in this region was raised by the reporting radiologist.

CT confirmed the lesion had increased in size, now measuring 6.7 x 5.1 x 17.4cm (Antero-posterior x medial-lateral x cranio-caudal) with the lobulated anterior aspect of the mass having few scattered areas of calcification (Fig. 7). There was also a reduction in internal matrix and increase in periosteal reaction along the fibula shaft.

MRI was performed which demonstrated the complex nature of the mass, which was predominantly T1W isointense, heterogeneous T2W signal with internal calcification and avid enhancement particularly in its periphery (Fig. 8, Fig. 9). The signal characteristics and enhancement raised the possible diagnosis of a sarcoma.

A Technetium-99m methylene diphosphonate bone scan was also performed, which showed a non-osseous mass in the left shin with mild peripheral radiotracer uptake on the delayed images with central photopenia. No suspicious focus of abnormal tracer uptake is detected in the rest of the skeleton (Fig. 10). The findings rendered the diagnosis of osteosarcoma unlikely.

Nonetheless, in view of the suspicious features on the CT and MRI, decision was made to perform an excision biopsy of this mass to obtain a histological diagnosis. Histology showed features of chronic tophaceous gout, with numerous uric acid crystals seen on polarised light microscopy of the accompanying fluid sample (Fig. 11).The patient was thus once again reassured of the benign nature of the mass and was provided with medical management of his underlying gout.

DISCUSSION

Etiology & Demographics

"People wish their enemies dead, but I do not; I say give them the gout, give them the stone!" The words by English aristocrat Lady Mary Wortley Montagu (1689 - 1762) captured vividly the affliction of gout over many for more than two millennia, long before the pathophysiology of the monosodium urate crystal deposition disease was elucidated. The prevalence of gout is increasing and is mainly seen in developed countries [1]. Men are much more likely to be affected than women (10:1) and gout before young adulthood is exceedingly rare unless in patients with a specific enzyme defect [2]. It is estimated to affect 3.9% of adults in the United States of America [3]. As an inflammatory arthritis associated with hyperuricemia, gout is more common in patients with impaired excretion of uric acid or increased production of uric acid. Other risk factors include increasing age, obesity, a high protein diet, high alcohol consumption, combined hyperlipidemia, diabetes mellitus, ischemic heart disease, hypertension and family history of gout.

Clinical & Imaging findings of gout

The clinical manifestations of hyperuricemia may include: [4]

- Recurrent attacks of acute inflammatory mono-articular arthritic flares, classically in the unilateral first metatarsophalangeal joint (also known as podagra)
- Chronic polyarticular gout
- Chronic tophaceous gout where solid sodium urate forms smooth white deposits called tophi in skin and around joints, classically on the ear, the fingers or the Achilles tendon, which may ulcerate to reveal the chalky material
- Uric acid nephrolithiasis

Diagnosis of gout is often based on the clinical picture; demonstration of negatively birefringent crystals in the joint aspiration fluid is the gold standard [5] but is not always performed. Imaging of the affected joint may be performed to distinguish from other causes of joint pain.

The radiographic findings classically describe sharply marginated, juxta-articular erosions with sclerotic borders resulting in overhanging edges also known as "rat-bitten" or "punched out" appearances. The joint space is preserved until late in the course of the disease and there is no periarticular osteopenia. In the surrounding soft tissue, there may be collections of urate crystals called tophi. These tophi are usually a late finding and are more radio-opaque than the unaffected surrounding soft tissue and may also calcify [6].

Conventional CT does not usually provide additional information compared to conventional radiographs for the diagnosis of gout apart from higher sensitivity of detection of erosions and tophus, with the tophus demonstrating high density (170 Hounsfield units) compared to the surrounding tissue. Dual energy CT, however, has been shown to be able to differentiate between urate crystal deposition and calcium. This may have applications in quantifying the amount of crystal deposition and can in essence be used to monitor progression of disease [7].

Although findings are not specific for the diagnosis of gout, MRI allows early detection of tophi and bone erosion in patients with gout. MRI is useful to examine the extent of gout involving a joint as well as detection of associated tendon tears. The bony erosions in gout usually show relatively absence of marrow edema. Tophi generally demonstrate homogenous iso-to-hypointense T1W signal and iso-to-hyperintense T2W signal with avid peripheral enhancement seen.

Ultrasound is also able to detect erosions, joint effusion, synovitis, increased vascularity as well as urate crystal deposition in gout. The characteristic appearance of a soft tophus is described as an anechoic halo with hyperechoic heterogeneous center. Calcified, hard tophi results in an intensely hyperechoic foci with posterior acoustic shadowing and does not allow imaging of structures below it. Deposition of urate crystals over hyaline cartilage may also produce an irregular echogenic line called the "double contour" sign. Hyperechoic foci within synovial fluid, thought to represent microtophi, may give rise to a "snow-storm" or "urate-sand" appearance [8].

Differential Diagnosis

The diagnosis of gout in a patient presenting with first episode of mono-articular joint pain can be challenging. As there may be little to no erosive bony changes on radiological examination or associated tophus, it is imperative to consider

septic arthritis as a differential diagnosis. Other differential diagnoses of a mono-articular arthritis include trauma, calcium pyrophosphate crystal disease (CPPD), reactive arthritis, monoarticular osteoarthritis and seronegative spondyloarthropathies [9].

In the later phases, there may be erosive arthropathy changes on imaging, which have many differential diagnoses including rheumatoid arthritis, erosive arthritis and psoriatic arthritis. During this later phase, gout is easier to differentiate from the other causes of erosive arthropathy. The juxta-articular, sharply marginated erosions with preservation of joint space and bone density are key factors in diagnosing gout. In contrast, there is joint space narrowing and periarticular osteopenia in rheumatoid arthritis. Central erosions with joint space narrowing are seen in erosive osteoarthritis compared to the juxta-articular erosions and joint space preservation typical in gout. In psoriasis, the erosions, combined with bone proliferation and other distinct features such as dactylitis and acroosteolysis, help to differentiate between this entity and gout. These are summarized in Table 1.

In the chronic phase, urate crystal deposition may predominate the clinical picture and this may result in unusual soft tissue calcifications. On imaging, these tophaceous deposits can give rise to worrying imaging appearances that mimic malignancy, especially if they are found in unusual locations. Causes such as myositis ossificans and synovial sarcomas may have similar appearing heterogeneous calcifications and are difficult to conclusively differentiate based on imaging alone. If they occur near joints, well-defined bony erosions typically seen in gout may lead to the diagnosis. Other causes of soft tissue calcifications include venous malformations, in which case the phleboliths are usually ovoid with central lucencies, and dermatomyositis, which is accompanied by a rash and has more sheet-like appearing calcifications. These causes of soft tissue calcifications are further discussed in Table 2.

Treatment & Prognosis

The tenets of management of gout are symptomatic relief during an acute gouty flare and the prevention of further gouty attacks or progression of disease. The use of NSAIDs combined with colchicine is very effective in rapidly reducing the pain and swelling during an acute episode. In patients where these medications are contraindicated, therapeutic joint aspiration and intra-articular corticosteroid may be considered [10].

Lifestyle modification including reduction in alcohol intake, low purine diet and weight loss are paramount in preventing recurrent gouty attacks. In selected patients, uric acid lowering agents such as allopurinol and febuxostat, which are xanthine oxidase inhibitors, should be considered to achieve a serum urate target [11].

In a small group of patients, surgical management may be warranted. Gouty tophaceous deposits may be drained, surgically excised or shaved to improve cosmesis, alleviate pain, treat infection or restore function [12,13]. However, surgery for tophaceous gout is often associated with a relatively high rate of complication [14]. It has been suggested that earlier operations for gouty arthritis can reduce the technical difficulties and improve the functional outcomes [15].

TEACHING POINT

Gout is a common entity which may form soft tissue calcification anywhere in the musculoskeletal system. As its imaging features may evolve over time and mimic aggressive lesions on various imaging modalities, being aware of these pitfalls may avert the need for unnecessary investigations and treatment for patients.

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FIGURES

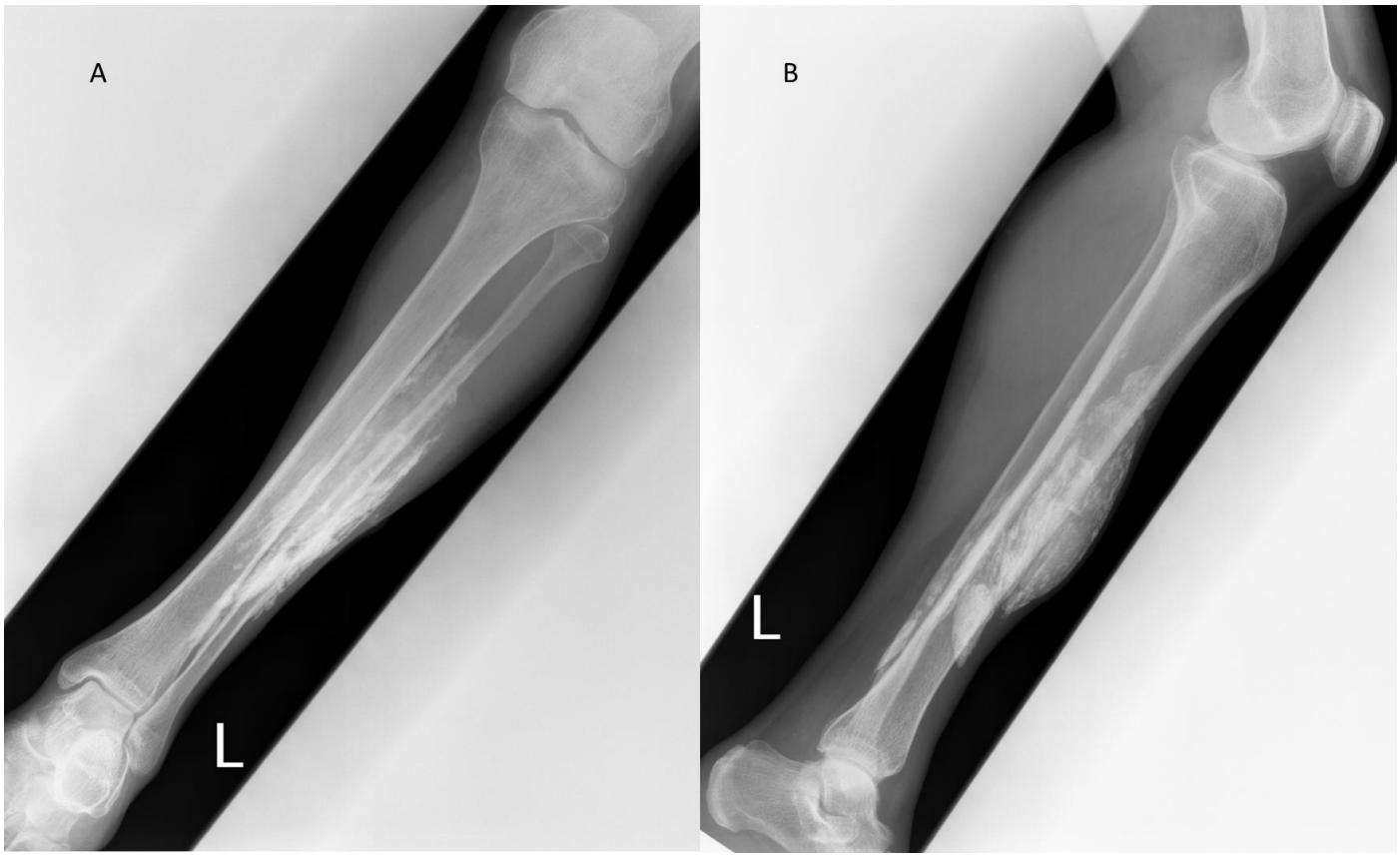

Figure 1: A 52-year-old male with chronic tophaceous gout. Anterior-posterior (A) and lateral (B) views of the radiograph of the left lower limb performed nine years ago. Well-defined calcification is seen centered at the anterior compartment of the left leg with no involvement of the underlying bone. Technique: Radiography.

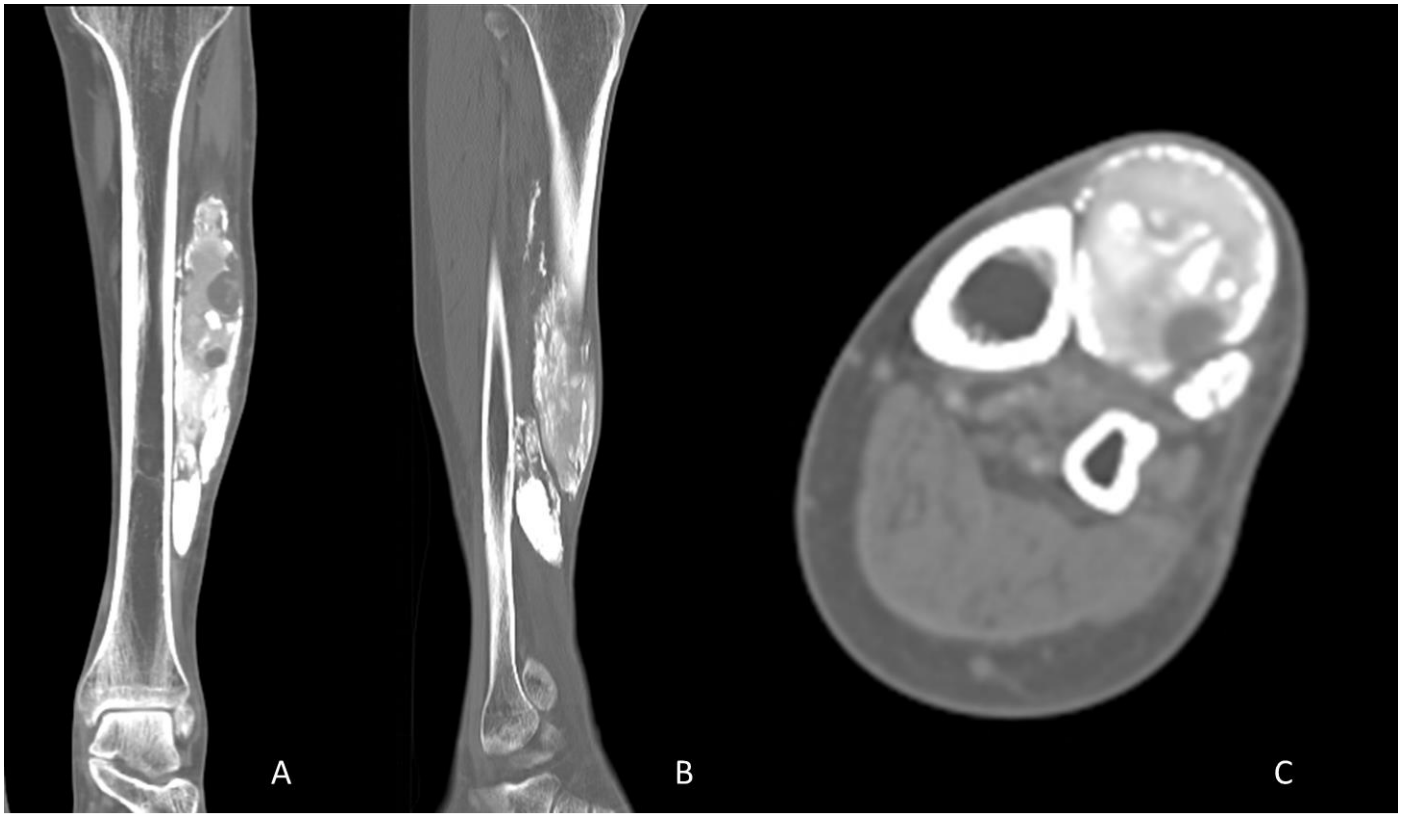

Figure 2: A 52-year-old male with chronic tophaceous gout. Coronal (A), sagittal (B) and axial (c) unenhanced CT images of the left leg performed nine years ago. Well-defined, rim calcified mass in the anterior compartment of the leg with internal ground-glass matrix. Though the mass comes into close proximity with the tibia, there were no changes detected in the underlying bones. Technical parameters: Siemens CT scanner, tube voltage 120kVp, tube current 40mA, slice thickness 3mm.

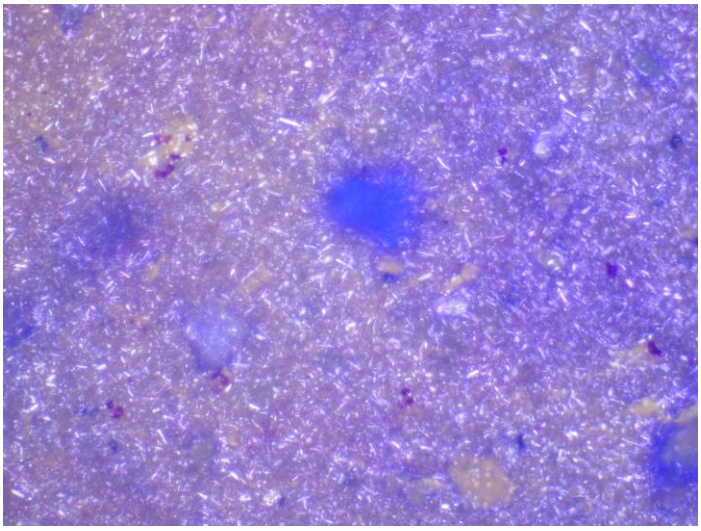

Figure 3: A 52-year-old male with chronic tophaceous gout. Polarized light microscopy of fine needle aspirate from the calcified left shin mass. The sample shows blue-stained calcified material and numerous urate crystals. Technical parameters: Hemacolor stain, original magnification x200.

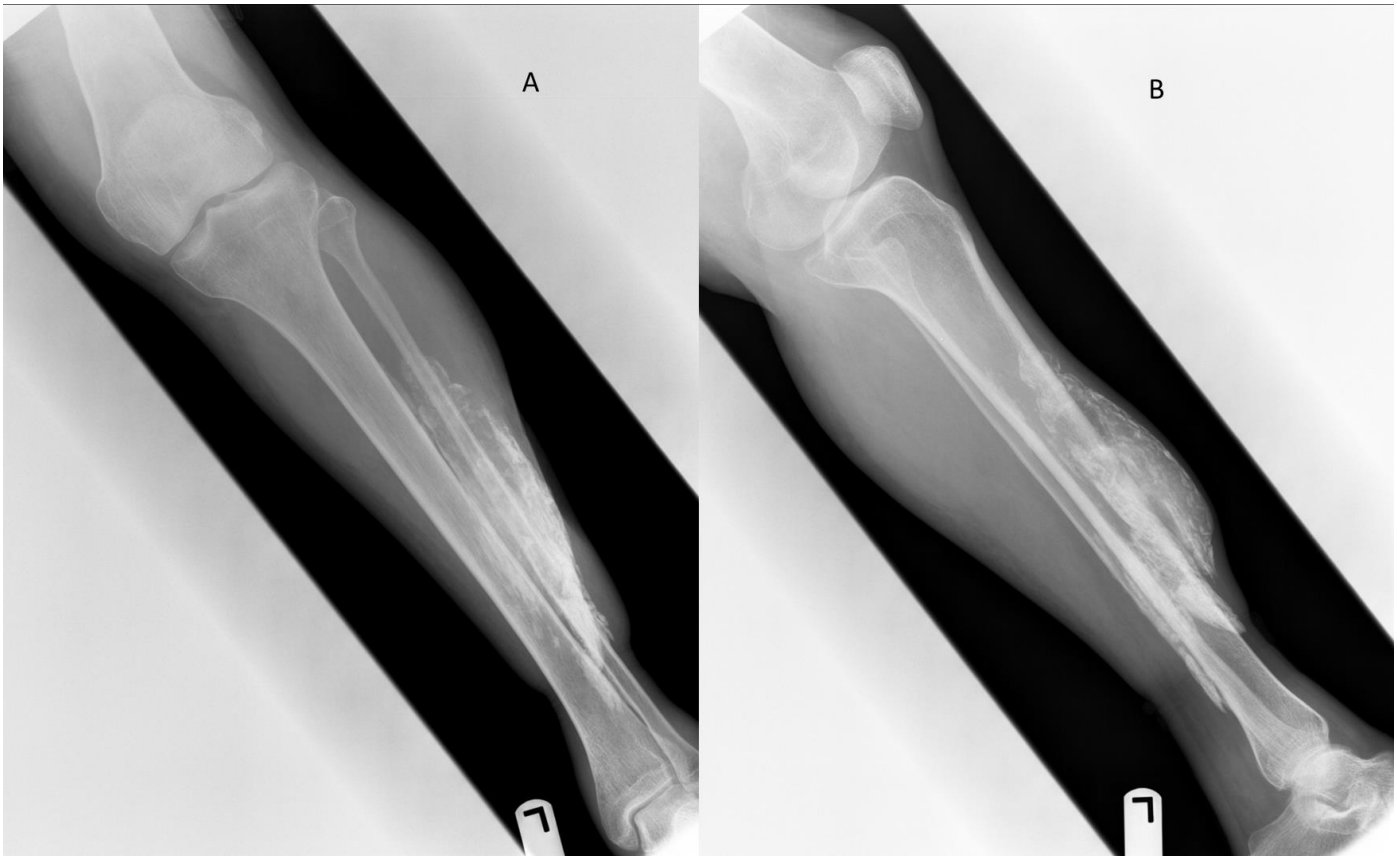

Figure 4: A 52-year-old male with chronic tophaceous gout. Anterior-posterior (A) and lateral (B) radiograph views of the left lower limb performed 7 years ago. The calcified mass in the left leg remains stable in appearance and does not show any interval change. Technique: Radiography.

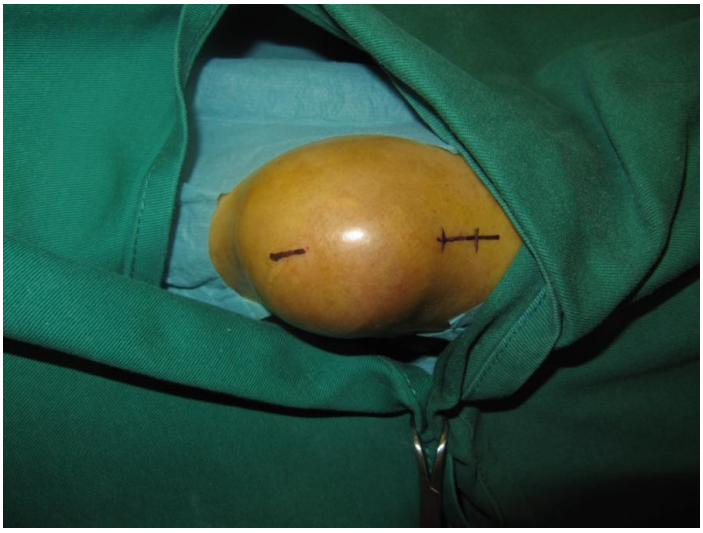

Figure 5: A 52-year-old male with chronic tophaceous gout. Gross appearance of the flesh colored lump along the anterior aspect of the patient's shin (photograph taken just prior to excision biopsy). Note the lack of classic chalky appearance expected in large chronic tophaceous gout.

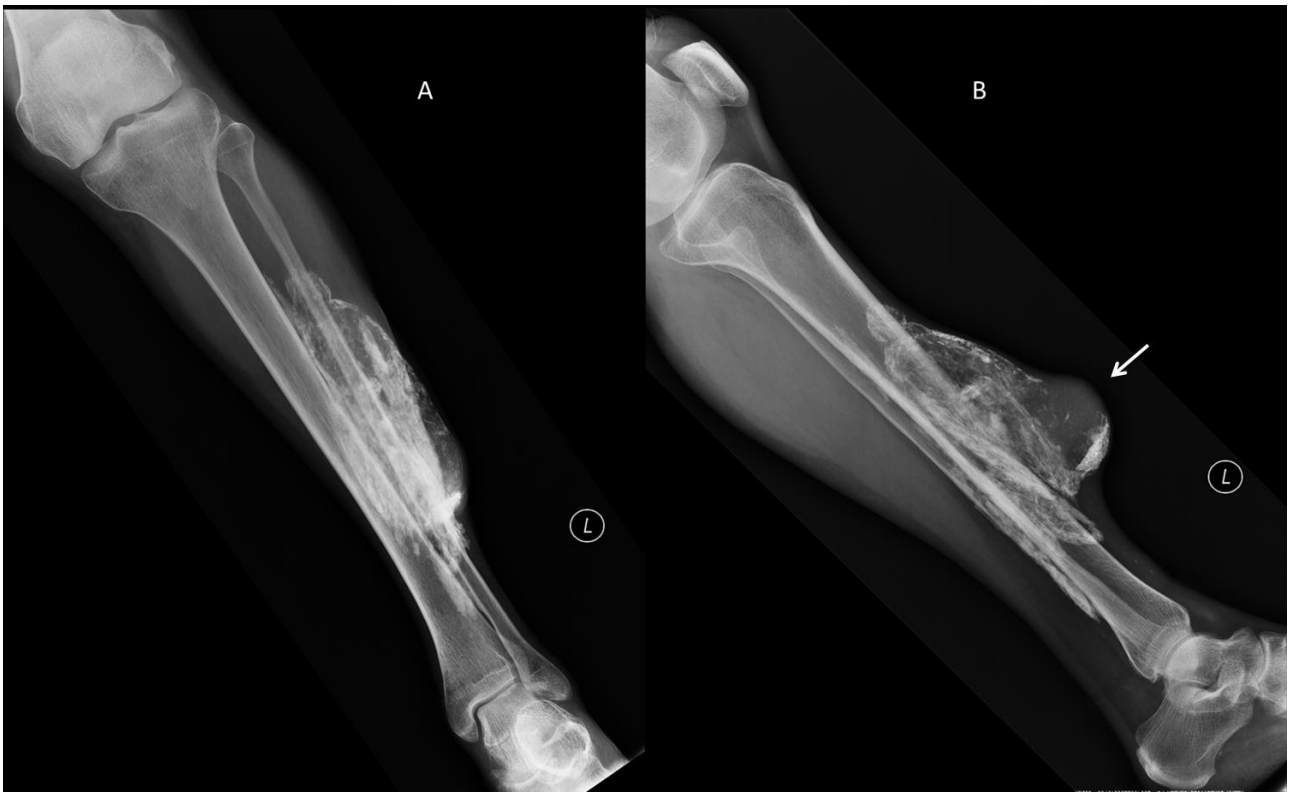

Figure 6: A 52-year-old male with chronic tophaceous gout. Anterior-posterior (A) and lateral (B) radiograph views of the left lower limb performed last year. There is now disruption of the calcification along its anterior aspect (arrow) of the previously well circumscribed calcified mass. The suspicion of possible neoplastic change was raised. Technique: Radiography.

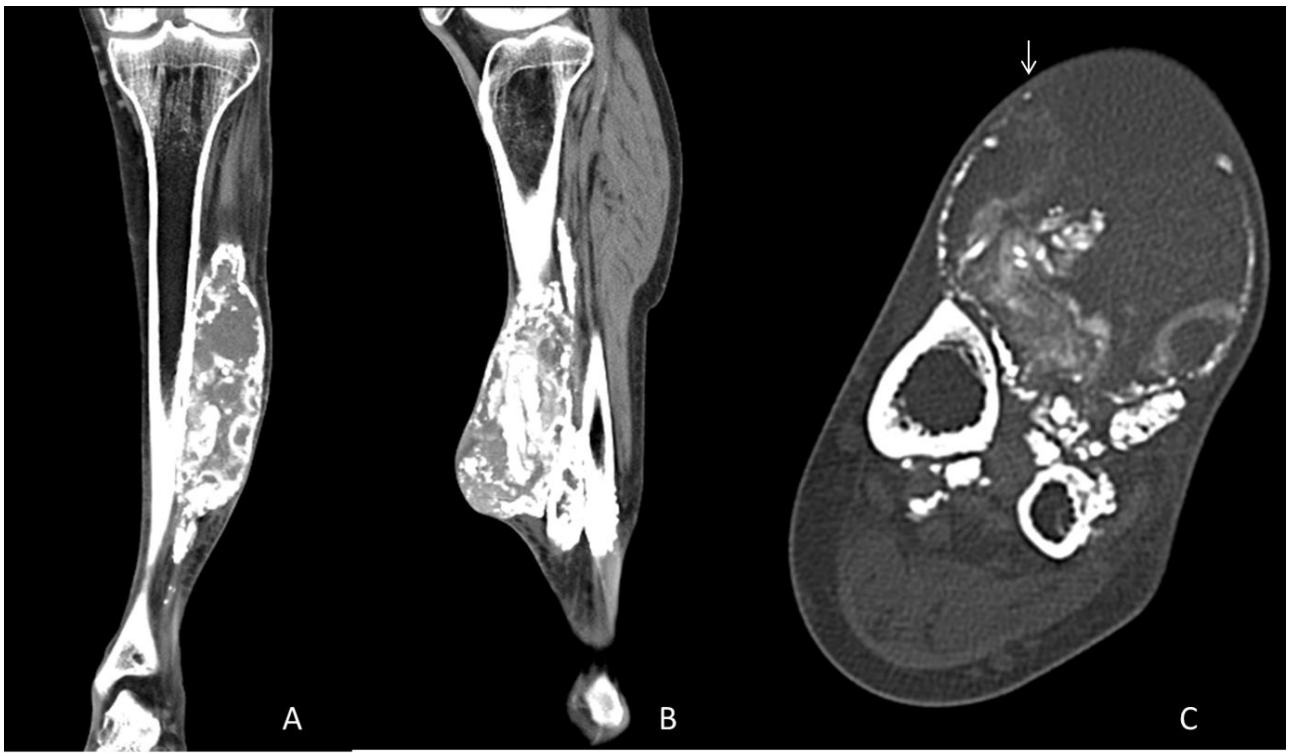

Figure 7: A 52-year-old male with chronic tophaceous gout. Coronal (A), sagittal (B) and axial (C) unenhanced CT images of the left leg performed last year. Compared to the previous CT study, the calcified mass in the anterior compartment of the leg shows interval decrease in its internal ground-glass matrix with disruption of its calcific rim anteriorly (arrow). New areas of calcification are also seen along the posterior aspect of the tibial shaft and there is now thick periosteal reaction noted along the fibula. Technical parameters: Siemens Sensation 64 CT scanner, tube voltage 120kVp, tube current 35mA, slice thickness 3mm.

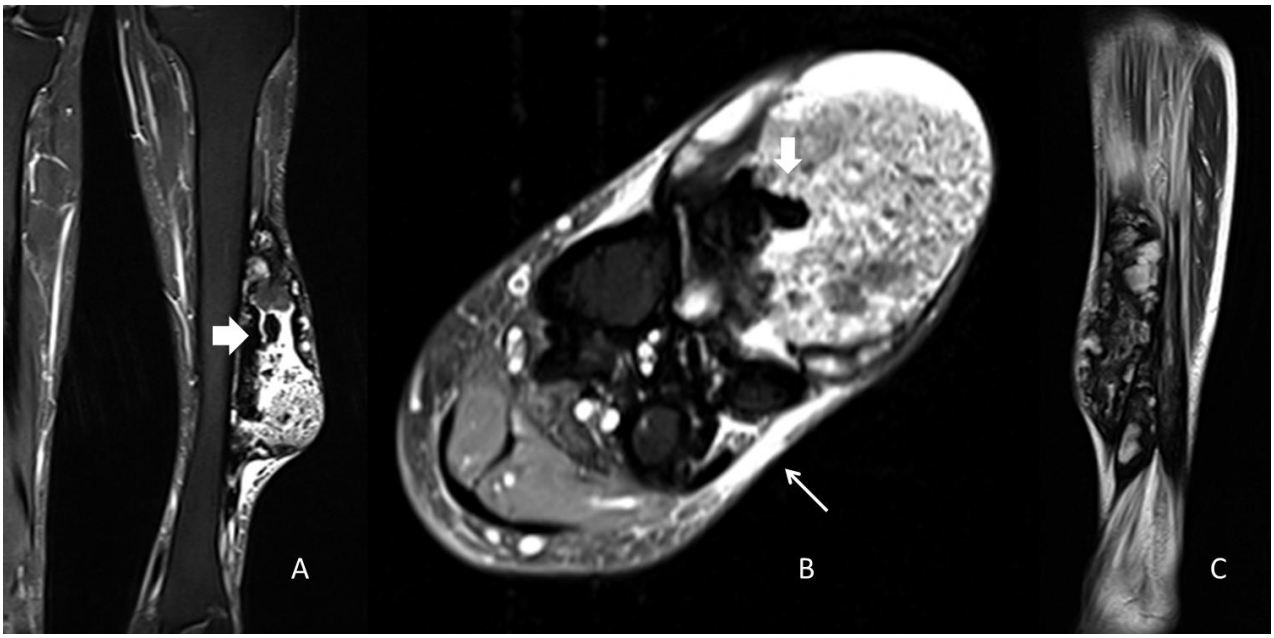

Figure 8: A 52-year-old male with chronic tophaceous gout. Short tau inversion recovery coronal (A) and axial (B) magnetic resonance sequences. T2-weighted sagittal image (C). The mass is heterogeneous with low intensity foci likely to represent the calcified components (thick arrow). Edema is seen along the adjacent margins of the mass (thin arrow). Technical parameters: Siemens AERA 1.5T, short tau inversion recovery coronal image (TR=3990; TE=60) and axial image (TR=3950; TE=12); T2-weighted sagittal image (TR=3230; TE=77).

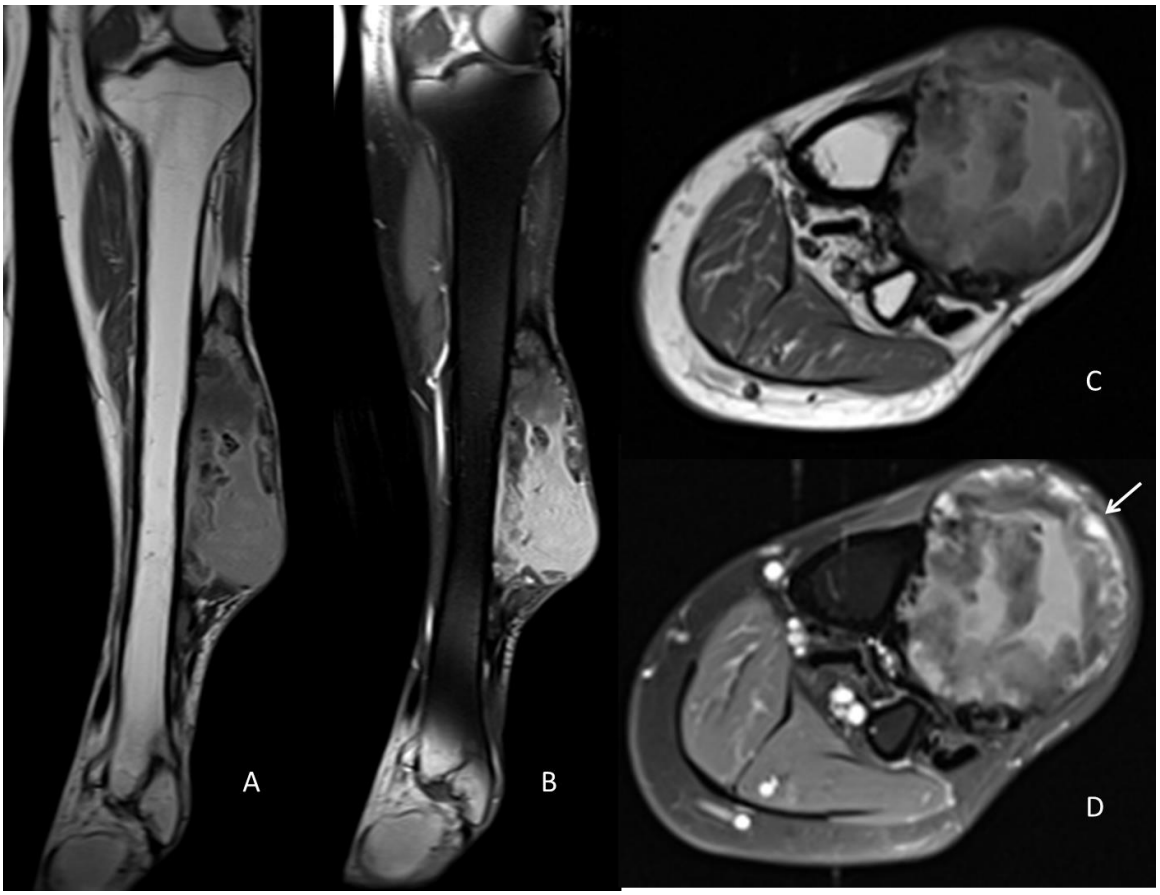

Figure 9: A 52-year-old male with chronic tophaceous gout. T1-weighted coronal (A) and axial (C) magnetic resonance sequences. T1-weighted fat-saturated post-contrast coronal (B) and axial (D) magnetic resonance sequences. The mass is heterogeneously iso to hypointense with patchy enhancement seen along its margins (arrow). This peripheral enhancement can be seen in cases of gout. Technical parameters: Siemens AERA 1.5T, T1-weighted coronal image (TR=516; TE=9); T1-weighted axial image (TR=520; TE=11); T1-weighted fat-saturated post-contrast coronal image (TR=532; TE=9) and axial image (TR=699; TE=11), Dotarem 12ml.

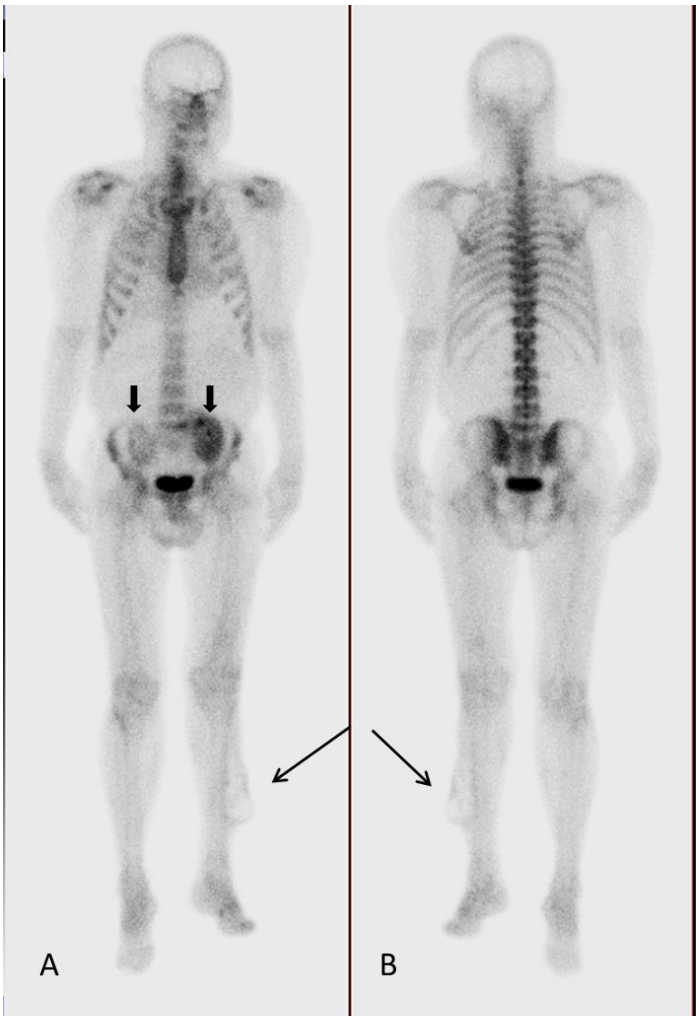

Figure 10: A 52-year-old male with chronic tophaceous gout. Anterior (A) and posterior (B) delayed whole body bone scan was performed. The mass in the left lower leg shows mild peripheral radiotracer uptake with central photopenia (thin arrows). Note the radiotracer uptake in the dual transplanted kidneys in bilateral iliac fossae (thick arrows). The native kidneys show no uptake of radiotracer. Technical parameters: 555 megabecquerel of Tc-99 MDP.

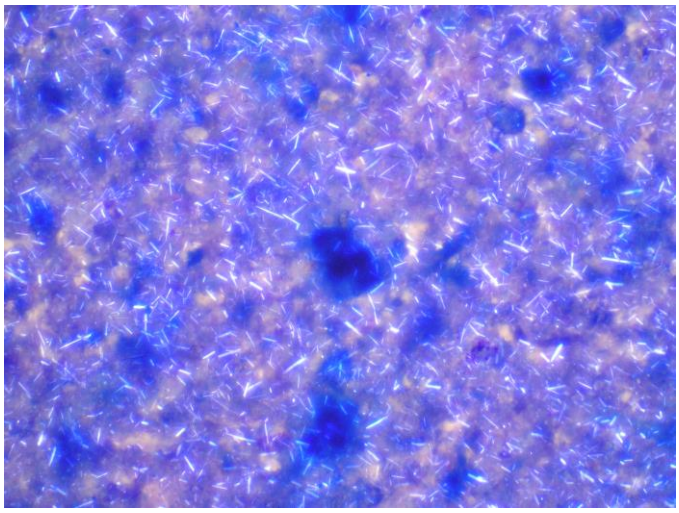

Figure 11: A 52-year-old male with chronic tophaceous gout. Sample from the excision biopsy of the calcified left shin mass shows very similar features from previously with blue-stained calcified material and numerous urate crystal. No malignant cell was detected. Technical parameters: Hemacolor stain, original magnification x200.

	Crystal deposition (gout and pseudogout)	**Septic arthritis**	**Rheumatoid arthritis**	**Erosive osteoarthritis**	**Psoriatic arthritis**
Age of onset	30-60yrs; M>F	Any age; M=F	30-50yrs; F>M	>70yrs; F>M	15-30yrs; M=F
History	• Previous history of gout. • Sudden onset of pain, swelling and erythema	• Constitutional symptoms (fever) • Monoarthritis • Swelling, erythema, pain, warmth	• Constitutional symptoms (fever, fatigue, malaise) • Polyarthritis occurring over long course (weeks or months)	• Pain related to use • No swelling or erythema	• Dactilitis • Back pain. • Family history of psoriasis • Skin changes
Distribution	• Small joints>large joints, 1st MTPJ most common • May be polyarticular • Asymmetrical	• Monoarthritis	• Proximal small joints • Symmetrical	• Hands (DIPJ, PIPJ and 1st CMCJ) • Symmetrical	• Variable (symmetric polyarthritis, asymmetric oligoarthritis)
Radiographic findings	• Normal bone density • Joint space preserved • Juxta-articular and intra-articular erosions with overhanging edges • Adjacent tophus which may or may not be calcified	• Joint effusion • Bony destruction on both sides of the joint	• Juxta-articular osteopenia • Joint space narrowing • Marginal erosions	• Joint space narrowing • Central erosions • Normal bone density	• Enthesis • Periostitis • Marginal to aggressive bone erosions • Bone resorption at tufts (Acroosteolysis) • Sacroilitis • Ankylosis • Normal bone density • Soft tissue swelling (sausage digit)
MR findings	• Tophus has • T1W: Intermediate • T2W: Heterogeneous • T1W +C: Tophus enhances	• T1W: Low signal marrow edema • T2W: High signal perisynovial and joint effusion • T1W +C: Synovial and marrow enhancement • Rim enhancing abscesses	• T1W: Low signal synovium, erosions and subchondral cysts • T2W: High signal synovium, marrow edema, erosions and subchondral cysts • T1W +C: Avid enhancement of synovium	• T1W: Low signal marrow edema • T2W: High signal marrow edema	• T1W: Low signal marrow edema • T2W: High signal enthesis, effusion and synovitis • T1W +C: Marrow and synovium may enhance

Table 1: Differential Table for Erosive Arthropathy

	Tophaceous gout	**Myositis ossificans**	**Venous malformations**	**Synovial sarcoma**	**Dermatomyositis**
Age	30-60yrs	Any age	Any age	15-40yrs	Bimodal distribution. Peak 50yrs
Presentation	• Previous history of gout.	• Usually after trauma • May be painful	• Usually long history • May be painful	• Slow growing mass • May be painless or painful	• Rash. • Proximal muscle weakness. • Fatigue.
Distribution	• On extensor surfaces • Near joints, bursa or tendons	• Within muscle but may be within fat, tendon or fascia	• Any location	• Within soft tissue near large joints or tendon sheaths	• Classically within the anterior compartment of the thigh
Radiographic findings	• Calcification, if present, usually cloudy and amorphous	• Early stages: Soft tissue swelling with minimal amorphous calcification • Late stages: Peripheral rim calcification with lucent center	• Soft tissue density mass containing small ovoid rim calcified foci with lucent centers (phleboliths)	• Soft tissue density mass. • Calcification in 1/3; usually peripheral or eccentric. • May cause pressure erosion or periosteal reaction in the underlying bone.	• Sheet like calcification
MRI findings	• <u>Tophus has</u> • T1W: Intermediate. • T2W: Heterogeneous. • T1W +C: Tophus enhances.	• <u>Early stages:</u> • T1W: Intermediate • T2W: Central and peripheral high signal due to edema, may have fluid levels • T1W +C: Enhances. • <u>Late stages:</u> • T1W: Peripheral low signal. • Central intermediate to high signal. • T2W: Peripheral low signal. • Central intermediate to high signal. • T1W +C: No enhancement.	• T1W: Intermediate. • Phleboliths may be low signal. • Subacute hemorrhage may have high signal. • T2W: Fluid levels. • Serpentine low signal flow voids. • T1W +C: Avid enhancement.	• T1W: Homogenous or heterogeneous signal which is iso/hypointense to muscle. • Intermuscular location results in "split fat" sign. • T2W: Fluid levels. • Calcification, necrosis, hemorrhage and soft tissue components result in the "triple" sign. • T1W +C: Diffuse, peripheral or heterogeneous enhancement.	• T1W: Nonspecific. • T2W: Hyperintense signal throughout affected muscle. • May have perimuscular and subcutaneous high signal from edema. • T1W +C: Enhances.

Table 2: Differential Table for Soft Tissue Calcification

Etiology	Hyperuricemia results in deposition of urate crystals in joints, soft tissues and bones inciting an inflammatory response.
Incidence	Approximately 3% of the population
Gender ratio	10 : 1 (Male : Female)
Age predilection	30 – 60 years old
Risk factors	• Age • Gender • Ethnicity • Family history of gout • Obesity • Hypertension • Hyperlipidemia • Ischemic cardiovascular disease • Diabetes mellitus • Chronic kidney disease • Dietary factors such as high protein diet • Alcohol • Medications altering urate balance
Treatment	Symptomatic relief during an acute gouty flare with NSAIDS and colchicine. Prevention of further gouty attacks or progression of disease with lifestyle modification and uric acid lowering agents such as allopurinol.
Prognosis	Good prognosis with adequate lifestyle modifications.
Findings on imaging	*Radiograph finding:* juxta-articular and intra-articular erosions with overhanging edges. Bone density and joint space are preserved. Adjacent tophus may or may not be calcified. *Ultrasound finding:* soft tophus appears as an anechoic halo with hyperechoic heterogeneous center. Calcified, hard tophi results in an intensely hyperechoic foci with posterior acoustic shadowing. Deposition of urate crystals over hyaline cartilage produces an irregular echogenic line ("double contour" sign). Hyperechoic foci within synovial fluid gives a "snow-storm" or "urate-sand" appearance. *Dual energy CT finding:* tophus demonstrates high density (170 Hounsfield units). *MR finding:* tophus demonstrates homogenous iso-to-hypointense T1W signal, iso-to-hyperintense T2W signal and avid peripheral enhancement.

Table 3: Summary Table for Gout

ABBREVIATIONS

CT = computed topography
DIPJ = distal interphalangeal joint
PIPJ = proximal interphalangeal joint
MRI = magnetic resonance imaging
MTPJ = metatarsal-phalangeal joint

KEYWORDS

Gout; soft tissue tumor; soft tissue calcification; malignant transformation; magnetic resonance imaging

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