Case Report

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Pathology Section

Tophaceous Gout Presenting with Normouricaemia: A Diagnostic Challenge

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ABSTRACT

Tophaceous gout is a chronic manifestation of gouty arthritis characterised by the deposition of Monosodium Urate (MSU) crystals in soft tissues. Although hyperuricaemia is the usual finding, uncommon cases may present with normal Serum Uric Acid (SUA) levels (3.4-7 mg/dL), which can make diagnosis challenging. We report a case of a 60-year-old non-diabetic, non-alcoholic hypertensive male with a long-standing nodular lesion over the left lateral malleolus. The patient's Complete Blood Count (CBC), Liver Function Test (LFT), and Renal Function Test (RFT) were within normal limits. The SUA level was 5.4 mg/dL. The Anti-Nuclear Antibody (ANA) profile and Rheumatoid Arthritis (RA) factor were negative. Radiology indicated a soft tissue lesion with calcific bodies near the lateral malleolus. Fine Needle Aspiration (FNA) showed inflammatory pathology and crystalline deposits that was indistinguishable from calcification. Histopathology revealed abundant MSU crystal deposition with a foreign body giant cell reaction, even after formalin fixation, suggestive of tophaceous gout. Raised SUA level is the basis for gout. A clinical diagnosis of gout is considered when a patient presents with SUA levels more than 7 mg/dL with the characteristic arthritis. However, some patients with gouty tophus have normal SUA levels, especially noted in cases of diabetes and alcoholism. Rarely, tophi may occur in patients with normal uric acid levels due to fluctuations in serum concentration, previous treatment, or renal excretion abnormalities. Histological recognition of MSU deposits is critical in these atypical cases. This case underscores the importance of histopathological examination in chronic joint lesions and highlights that normouricaemia does not exclude the diagnosis of tophaceous gout.

Keywords: Histopathology, Malleolar lesion, Monosodium urate crystals, Normouricaemia, Tophaceous gout

CASE REPORT

A 60-year-old male presented with chief complaints of a nodular lesion over the left ankle for about 13 years. It was gradual in onset. The lesion was painless and progressively increased in size. The patient had a history of hypertension that was under control by anti-hypertensive medications for the last eight years. There was no history of diabetes mellitus, tuberculosis, asthma, or any trauma. The patient was a vegetarian and his personal history was negative for alcoholism or any other addiction.

Clinical Findings

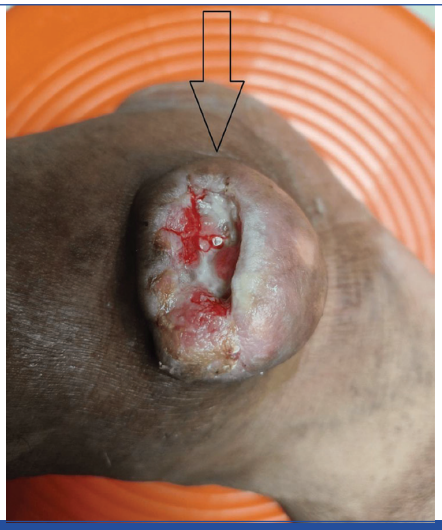
Local examination revealed a palpable nodule of size 3.5×3.2 cm present over the left lateral malleolus. It was firm, non-tender, and fixed to the underlying tissue. The overlying skin showed ulceration. The patient developed ulceration over the last three months. There was infrequent, slight bleeding, but no discharge or local rise in temperature. The systemic examination was within normal limits. It was clinically suspected to be a bony or soft tissue neoplasm, as the swelling was fixed and non-mobile.

Timeline of the Current Episode

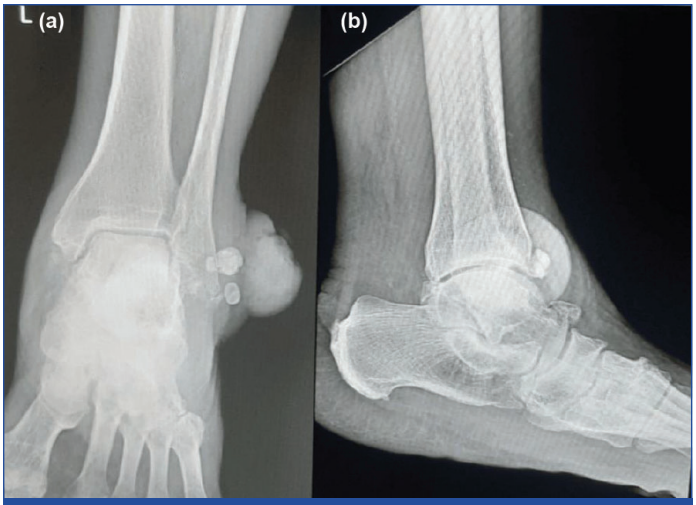
The patient had been complaining of a nodular, slowly progressive lesion on the left side of the ankle for the last 13 years. This was later associated with restricted mobility and stiffness of the left ankle joint. The patient denied noticing any acute flare-ups during the course of his disease. His C-Reactive Protein (CRP) levels were raised on a few occasions (four times over the past three years), ranging from 8-23 mg/L (normal range of CRP is <5 mg/L). His ANA profile (<1:40 titre) and RA factor (< 15 IU/mL) had been negative. The kidney function tests, including uric acid levels, were also seen within normal range (normal SUA levels: 3.4-7 mg/dL), on multiple occasions. An ulcerated area developed over the nodule 3 months ago, which prompted the patient to consult a surgeon.

Diagnostic Assessment

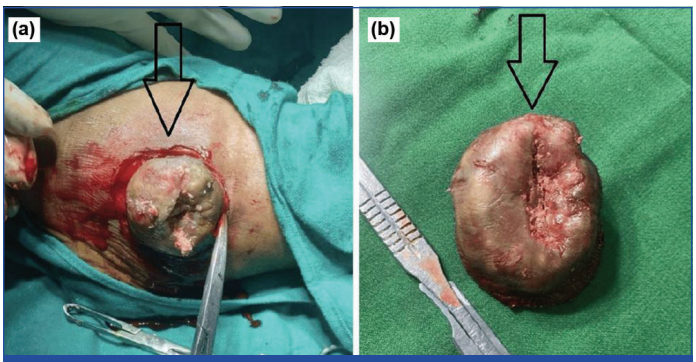
The patient presented to our diagnostic centre with a chronic, firm, nodular swelling over the left lateral malleolus [Table/Fig-1]. The patient's CBC, LFT, RFT and blood glucose levels were within normal limits. The serum analysis of uric acid was found to be 5.4 mg/dL (within normal range: 3.4-7 mg/dL). X-ray showed a soft-tissue lesion with calcific bodies adjacent to the lateral malleolus [Table/Fig-2]. The rest of the bones showed degenerative changes. FNA revealed inflammatory pathology with crystalline deposits, which could not be differentiated from calcification. The patient subsequently underwent surgery ([Table/Fig-3a] and the excised lesion [Table/Fig-3b]) was submitted for routine histopathological evaluation.



[Table/Fig-1]: A well-defined, firm, nodular swelling measuring approximately 3.5 × 3.2 cm, present over the lateral aspect of the ankle. The lesion showed areas of surface ulceration with exposed yellow-white, chalky material. The ulcer base appeared irregular and erythematous, with surrounding indurated margins. The overlying skin demonstrated thinning, focal crusting, and mild hyperpigmentation. There is no surrounding cellulitis or purulent discharge.



[Table/Fig-2]: (a) X-ray anteroposterior view of the left ankle demonstrates soft-tissue swelling with multiple rounded radio-opacities adjacent to the lateral malleolus. Marginal erosions seen at the lower end of the fibula; (b) X-ray lateral view of the left ankle reveals a large soft-tissue swelling overlying the lateral malleolus with internal calcifications. The adjacent bone shows erosive changes and cortical irregularity.



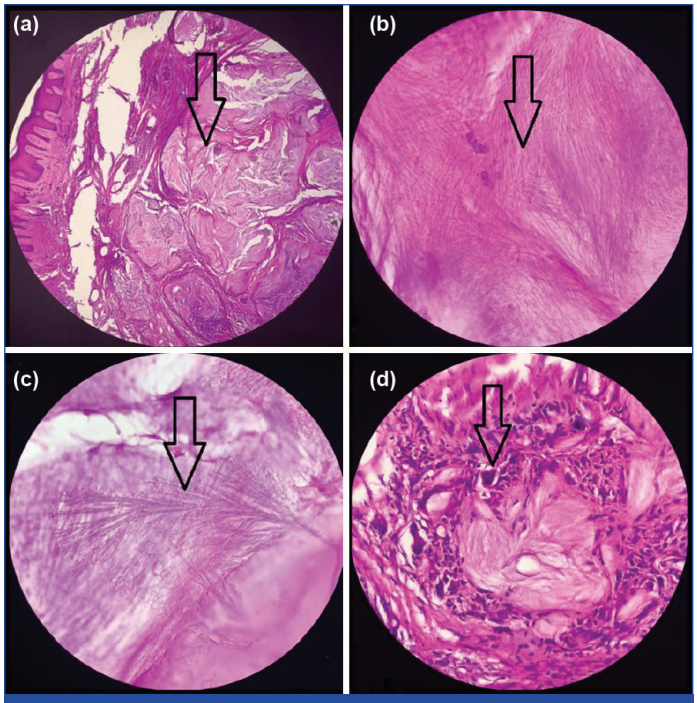
[Table/Fig-3]: (a) Intraoperative image of the lesion; and (b) Firm, nodular and ulcerated mass measuring 3.5 cm in greatest dimension.

On gross examination, the specimen was a firm, pale-tan to whitish nodule, 3.5 cm in greatest dimension. The cut section revealed chalky white areas. Formalin-Fixed Paraffin-Embedded (FFPE) sections were stained with haematoxylin and eosin. Multiple sections were examined under microscopy to assess the extent and morphology of deposits. Polarised light microscopy was later used to confirm the presence of MSU crystals.

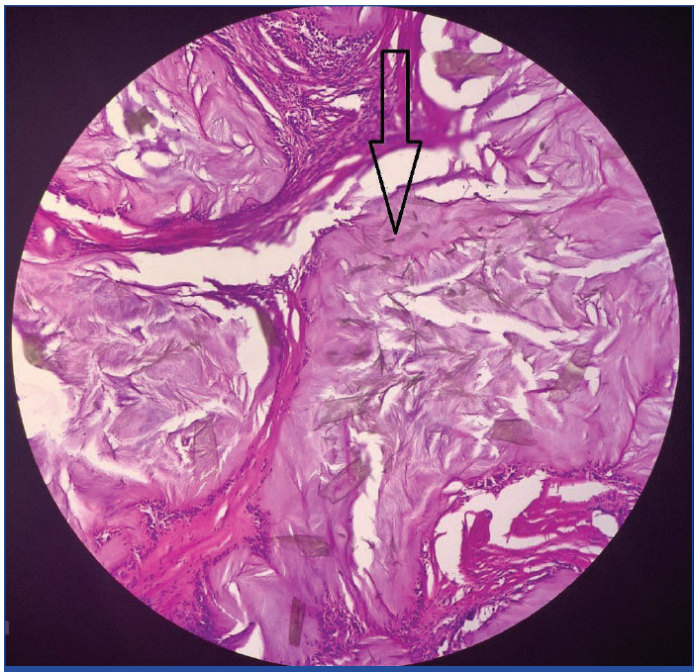
Diagnosis: Histopathological evaluation revealed amorphous, granular deposits [Table/Fig-4,5] surrounded by palisading histiocytes and multinucleated foreign body-type giant cells [Table/Fig-4d]. The deposits exhibited a feathery and acicular morphology suggestive of urate crystals. Remarkably, many crystalline areas remained intact despite formalin fixation. Polarised microscopy confirmed negatively birefringent crystals consistent with MSU [Table/Fig-6]. There was no evidence of neoplasia or infection. The final diagnosis was tophaceous gout with abundant MSU crystals, despite normal Serum Uric Acid (SUA) levels.

Follow-up and treatment: The postoperative period was uneventful. Although the patient's SUA levels were within normal limits, Urate-Lowering Therapy (ULT) was initiated to prevent recurrence, considering the histopathological confirmation of abundant MSU crystals. The patient was started on allopurinol 100 mg/day, with gradual titration planned based on follow-up labs and renal function.

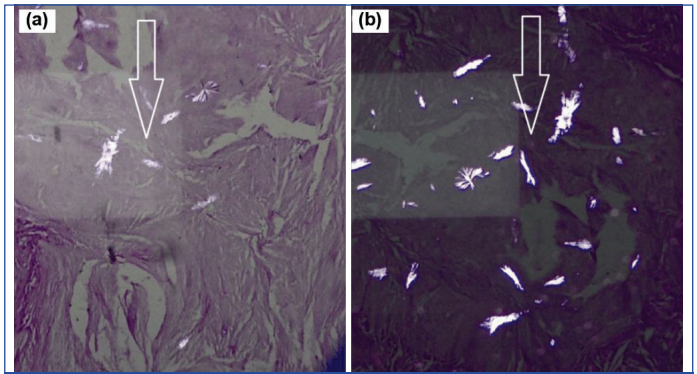
At the 3-month follow-up, the surgical site had healed well with no evidence of residual or recurrent tophus. The patient remained asymptomatic, and no new nodular lesions were noted. At six months, the patient continued to be stable on maintenance ULT with periodic monitoring and counselling regarding hydration and dietary modification.



[Table/Fig-4]: a) Haematoxylin & Eosin stain; 10x view showing subcutaneous aggregates of amorphous, eosinophilic tophaceous material, covered by superficial dermis and intact epidermis (left); (b,c) Haematoxylin & Eosin; 100x view showing the numerous slender, brownish needle-shaped MSU crystals that have resisted formalin dissolution; (d) Haematoxylin & Eosin stain; 40x view showing amorphous tophaceous material bordered by foreign-body giant cell and fibrovascular reaction.



[Table/Fig-5]: Haematoxylin & Eosin stain; 40x view showing abundant, acicular Monosodium Urate (MSU) crystals embedded within amorphous, eosinophilic tophaceous deposits.



[Table/Fig-6]: (a,b) Polarised light microscopy demonstrating strong negative birefringence of the MSU crystals (arrow), appearing as bright needle-shaped structures.

DISCUSSION

Normouricaemia in such presentations may be related to transient fluctuations in serum urate during inflammatory phases or increased renal excretion mediated by cytokine-driven pathways, mechanisms well-described in normouricaemic gout cases [1]. Additionally, long-standing crystal accumulation within tophi may persist independently of current serum urate levels, explaining the discordance between tissue diagnosis and biochemical values [2].

Gout is characterised by repeated episodes of inflammatory arthritis due to a metabolic disorder of uric acid [3]. MSU monohydrate crystals accumulate in soft tissues, causing dysarthrosis. Erosive polyarthritis and chronic tophaceous forms are seen in some patients in whom hyperuricaemia has been longstanding [4]. Deficient renal function or inborn abnormalities in purine metabolism cause primary gout. Conditions with high cell turnover or acquired renal illness are the causes of secondary gout. Gout can manifest as acute arthritis, silent arthritis, nephrolithiasis, or gouty tophi [2]. Hyperuricaemia is regarded as a significant risk factor for developing gouty tophi. However, doctors should be aware that tophi can occur even with normal SUA levels, especially in diabetics and alcoholics [5]. The cardinal sign for advanced gout is tophus, which is an organised chronic foreign body granulomatous inflammatory reaction to MSU crystals [6].

Gout is a disease of metabolism. The most common presentation is with acute flare-ups of arthritis that go away on their own and are effectively treated with medicine. Gouty tophi are chalky masses that can form from urate deposits over an extended period of time [7]. Recent literature indicates that many patients with tophaceous gout do indeed have elevated baseline SUA, though reported averages vary: for example, a large primary-care cohort in Malaysia found a mean SUA of ~10.5 mg/dL in tophus-positive patients [8].

Several case reports have documented tophaceous gout in patients with normal SUA ("normouricaemia"), similar to our patient. For instance, Song Y et al., described multiple tophi in the head and neck region in a patient with normal SUA [9]. Kimura et al. reported a gouty tophus in the foot of a 66-year-old man without hyperuricaemia, which was successfully removed surgically [10]. In another report, a 39-year-old man with a firm swelling at the medial malleolus and normal urate was initially misdiagnosed; FNA revealed MSU crystals, confirming gout [11]. On the histopathology front, preservation of MSU crystals after formalin fixation is challenging, since urate dissolves in many routine processing methods [12]. However, recently modified staining protocols (e.g., Gomori methenamine silver) can help retain and visualise these crystals [13]. Regarding management, prior surgical resections of tophi in normouricaemic patients have shown favourable outcomes without recurrence, reinforcing the utility of excision in symptomatic cases [14].

While most literature-reported normouricemic tophi are located in unusual sites (e.g., head/neck) [9] or diagnosed via imaging (e.g., dual-energy CT) [10], our case involves a more typical peri-malleolar soft-tissue lesion, which nonetheless mimicked calcific lesions on radiology. Importantly, histopathology in our case revealed abundant MSU crystals despite formalin fixation- a feature that is often lost in routine processing but was preserved here, highlighting the diagnostic value of polarising microscopy.

In our non-diabetic, non-alcoholic patient, alternative mechanisms likely underlie MSU crystal deposition. First, intermittent fluctuations in SUA- for example, earlier unrecognised hyperuricaemia can permit crystal seeding that persists after apparent normalisation. Second, local tissue factors, such as lower temperature in peripheral sites, microtrauma, and pH variations, may create a milieu favourable to MSU precipitation and stability despite normalised systemic SUA. Third, renal urate handling may not be straightforward: genetic variability and regulation of transporters such as Urate Transporter-1; SLC22A12 (URAT1) and Glucose Transporter-9; SLC2A9 (GLUT9) influence urate reabsorption and secretion, potentially leading to crystal deposition even when measured SUA is normal. Genetic variants in these transporters have been strongly associated with differences in urate homeostasis and gout risk [15,16]. Fourth, intestinal uric acid excretion via ATP-Binding Cassette Sub-family G Member 2 (ABCG2) has emerged as a significant regulator of systemic urate: inflammation can upregulate ABCG2 expression in intestinal epithelium, enhancing urate secretion and transiently lowering SUA during acute phases, which may mask underlying tissue deposition [17,18].

Recent genetic and molecular insights further support these mechanisms. A trans-ethnic Genome-Wide Association Meta-Analysis (GWAS) has identified novel loci associated with serum urate regulation beyond the classic transporter genes, suggesting a complex genetic architecture underlying urate balance [19]. Moreover, dysfunctional variants in URAT1 have been shown to strongly modulate gout risk, highlighting the importance of urate reabsorption control [20].

These observations help explain why normouricaemia does not reliably exclude tophaceous gout, and they underscore the critical role of histopathological confirmation, particularly by polarised-light microscopy, in diagnosing atypical presentations.

MSU crystal accumulation in and around soft tissues and joints results in masses known as tophi, which are typically believed to be a late cutaneous symptom of gout. Tophi typically manifest as fusiform swellings or firm pink nodules. The skin on top could be ulcerated, erythematous, or yellow. The lesions may discharge a thick, chalky substance or a clear fluid with urate particles. Pain, soft-tissue injury and deformity, joint deterioration, and nerve compression disorders like carpal tunnel syndrome are all consequences of tophi. They appear roughly 10 years after the initial gout episode and are the pathognomonic signature of the illness. Foreign body granulomas made of mono- and multinucleated macrophages containing deposits of MSU crystals are the histological hallmark of gout tophi. It is best to demonstrate MSU crystals in the synovial fluid or perform a biopsy in order to make a clear diagnosis of gout. SUA measurement is inefficient for diagnosing gout. In reality, the levels in certain individuals with gout may be low or normal. Diabetics may have lower serum urate levels due to the uricosuric effects of high blood glucose [21].

Only over half of people with SUA concentrations of ≥10 mg/dL had the development of clinically noticeable gout over a 15-year period. In a 2021 review, Zhang W-Z reports suggest that pathogenic pathways in gout formation include overproduction of chemotactic cytokines, cell proliferation and inflammation, and internalisation of SUA-induced pro-apoptotic and inflammatory effects. Hyperuricaemia is a key factor in the formation of MSU crystals, but other factors such as temperature, pH, ion concentrations, proteins, connective tissue conditions, and secondary nucleation formation can also contribute to gout flares. White Blood Cell (WBC) count in synovial fluid is strongly linked to MSU crystal formation [22].

Tissues should be fixed in formal-saline for as little time as possible to avoid the removal of urate deposits. It's preferable to fix it with absolute alcohol. Fixation in alcohol is essential for the preservation of sodium urate monohydrate deposits, which appear as needle-shaped, doubly refractile crystals. In this case, we preserved the sample in formalin because we had no knowledge of the clinical prediagnosis; yet we were able to demonstrate the crystals as they were in abundance, which was further confirmed by the negative birefringence of these crystals using polarised microscopy. During ordinary staining of histological sections, water-soluble crystals are typically removed; nevertheless, inspection of unstained sections with polarised light generally reveals the crystalline nature of the deposits. Again, despite our staining with haematoxylin and eosin, there were numerous visible areas of properly preserved crystalline structures.

MSU crystals are otherwise frequently lost following formalin fixation and during histological processing [21]. The case findings reaffirm the diagnostic utility of histopathology in distinguishing tophi from other chronic inflammatory lesions. This case is unique not only for the crystal preservation but also for its normouricaemic state, which challenges the reliance on SUA levels for diagnosis. A high index of suspicion and histopathological confirmation remain the cornerstones in such ambiguous presentations.

CONCLUSION(S)

This case highlights that tophaceous gout can occur even in non-diabetic, non-alcoholic and normouricaemic individuals, with histopathology playing a crucial role in diagnosis, especially when crystal preservation allows direct visualisation. Also, although persistent MSU crystals post-formalin fixation are rare but when present in abundance, they can be visualised readily. Clinicians and pathologists must consider tophaceous gout in chronic nodular lesions of the extremities, even in the absence of hyperuricaemia.

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