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Gout Affecting the Nail Unit: Report of Two Cases and Literature Review

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Tophaceous gout · Pseudocarcinomatous hyperplasia · Squamous cell carcinoma · Squamous cell carcinoma mimicker · Nail · Nail disorder

Abstract
Background: Gout is a depositional, inflammatory disorder that is rarely reported to affect the nail unit. Cases of gout involving the nail unit are likely underrecognized and therefore underreported. We present two cases of tophaceous gout affecting the nail unit and a literature review of the various presentations. ***Summary:*** Five cases of gout were identified to affect the nail unit. In all cases, these presented as white hyperkeratotic papulonodules with associated nail dystrophy. Chalky discharge was seen in three of the five cases. Nine cases were identified to have demonstrated pseudocarcinomatous changes that histopathologically mimic squamous cell carcinoma (SCC). Literature review highlights a range of findings including subclinical deposits of uric acid in the nail, onychoschizia, onychorrhexis, and Beau's line. ***Key Messages:*** Physicians should be aware of the subtle and nonspecific clinical findings of gout, which may be easily misconstrued for other pathological entities.

Introduction

Gout is caused by deposition of monosodium urate (MSU) crystals in articular and non-articular structures with a reported prevalence of 3.90% [1]. It is characterized by an asymptomatic phase of hyperuricemia followed by recurrent acute inflammatory arthritis intervening with pain-free periods between attacks known as intercritical gout. With long-standing gout, deposition of MSU crystals leads to formation of chronic foreign body granulomatous-like structures seen clinically as tophi [1].

While tophi are typically seen 10 or more years after initial gout flare, tophi have been reported to develop without an antecedent history of arthritic gout. In a recent case report and literature review by Bieber et al. [2], the authors identified 36 cases and analyzed another study investigating 65 additional patients who presented with tophi as the initial manifestation of the gout. While this corresponded to a prevalence of 4.4% in the review, a previous study demonstrated an even higher rate at 16.2% of their cohort of patients with gout of less than 10 years [2]. This same study found colchicine use, diuretic use, and decreased creatinine clearance to be risk factors for early development of tophi [2, 3]. Identification of tophi in these populations is of great importance as the clinical presence of tophi alone is associated with rapid decline in creatinine.

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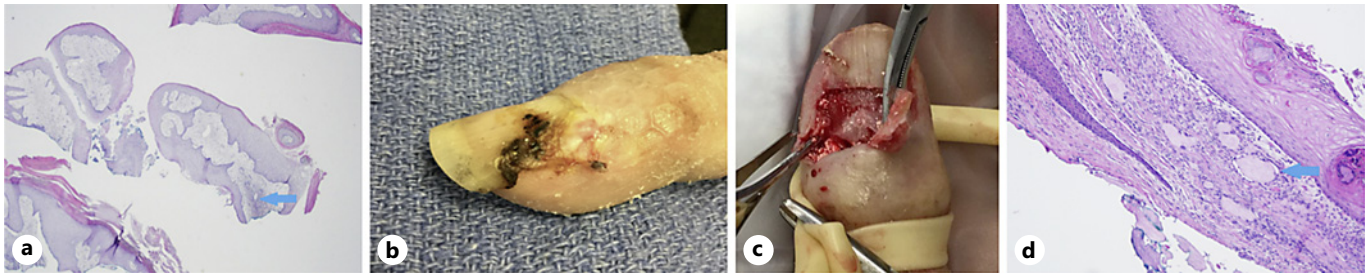

Fig. 1. a Case 1: Photomicrograph of shave biopsy of PNF interpreted at outside hospital as atypical squamous proliferation concerning for squamous cell carcinoma. Upon review at our institution, focally present was material suggestive but not diagnostic of gout (arrow) (hematoxylin-eosin ×20). **b** Case 1: Clinical appearance at presentation to nail clinic prior to nail unit exploration and matrix biopsy. A tender, white papule with associated swelling and hemorrhagic crusting of the PNF is present. **c** Case 1: Intraoperative appearance after wiping away copious amounts of thick, white chalky material typical of gouty tophus expressed spontaneously after incision of the PNF. **d** Case 1: Nail matrix biopsy showing amorphous eosinophilic material with a feathery appearance typical of monosodium urate crystals surrounded by granulomatous inflammation (arrow) representative of gout tophus and without pseudocarcinomatous hyperplasia nor squamous cell carcinoma (hematoxylin-eosin ×100).

Classically, tophi present as subcutaneous nodules that can range from pink, white, to cream-colored and can be tender. While tophi typically affect tendons, joints, and ears, they have also been found in a wide variety of unusual locations such as mitral valves, bronchus, breasts, finger pulps, and periungual area [4–6].

Tophaceous gout affecting the nail unit was first reported in 2002 by Dacko et al. [4] with only one additional case and clinical image being reported since then [6, 7]. In two of those three previously reported cases, the clinical differential diagnosis for the lesions included squamous cell carcinoma (SCC). Here, we present two cases of tophi affecting the nail unit, one of which was the patient's first presenting sign of gout. Additionally, we conducted a review of the literature for the various presentations of gout in the nails, highlighting the clinical and histopathologic features of this important presentation of a systemic diagnosis.

Methods

The literature review analyzed currently available English-language publications of gout with nail changes. An electronic search was conducted in PubMed (Medline), Google Scholars, and OVID databases ranging from 1969 to 2023. A combination of search input including the following keywords was utilized: "tophaceous gout," "gout," "tophi," "nail," and "nails." In addition, MeSH search conducted with the following terms: "gout" with "nails" and "gout" with "squamous cell carcinoma" yielded a total of two case reports, one correspondence article, and one clinical image publication describing cases of gout affecting the nail.

Cases

Case #1

A male in his 70s was sent in consultation from an outside institution for management of a lesion on the radial aspect of the right thumb proximal nail fold (PNF) causing onychodystrophy. This lesion had twice been shaved biopsied at an outside institution and signed out as an atypical squamous proliferation concerning for SCC. In this context, the outside slides were requested for review by dermatopathology prior to planned Mohs surgery. Sections showed a shave biopsy of PNF with epithelial hyperplasia and mild keratinocyte atypia in association with an infiltrate of lymphocytes and histiocytes forming multinucleated giant cells approximating infrequent tiny collections of pink amorphous material (shown in Fig. 1a).

These findings in this shallow specimen were not definitively diagnostic but were suggestive of pseudocarcinomatous hyperplasia (PCH) secondary to tophaceous gout though the patient had no history of gout. Subsequently, the patient was scheduled and seen in nail clinic and was noted to have persistence of a hyperkeratotic papule at the prior PNF shave biopsy site with associated hemorrhagic crusting and edema (shown in Fig. 1b). Given the aforementioned concerns, a repeat biopsy was planned, and an exploratory proximal nail avulsion was performed. During the procedure, incision of the PNF yielded copious amounts of thick, white chalky material (shown in Fig. 1c). Grossly, there was no neoplasm within the PNF; however, during nail unit exploration, a defect filled with this white material was observed within and deep to the matrix of unclear nature. Therefore, a tangential biopsy of the nail matrix was then performed. The biopsy demonstrated a relatively unremarkable matrix epithelium with onychodermal pink, amorphous, feathery material surrounded by granulomatous inflammation diagnostic of gout (shown in Fig. 1d). Subsequent analysis of the patient's uric acid levels demonstrated elevation (10.9 mg/dL) and a creatinine level of (2.37 mg/dL), and he was referred to rheumatology where he was treated with allopurinol.

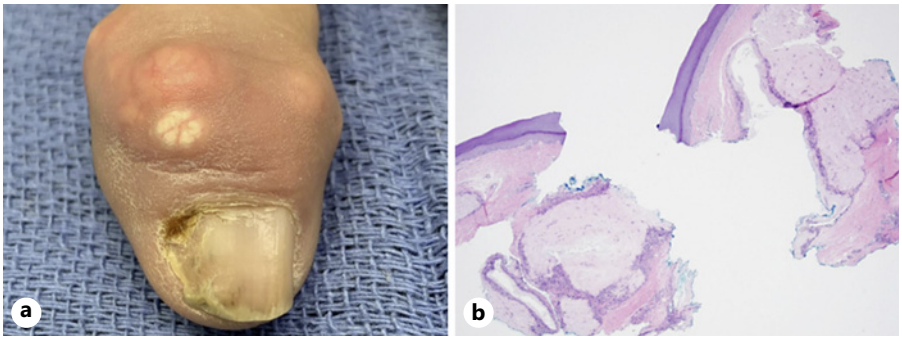

Fig. 2. a Case 2: Clinical image: multiple white-yellow tophi affecting the proximal nail fold causing a longitudinal groove in the nail. **b** Case 2: Biopsy demonstrating amorphous eosinophilic material consistent with tophaceous gout (hematoxylin-eosin; original magnification ×20).

Case #2

An 89-year-old male with a previous history of gout was sent to dermatology in consultation by his primary care physician for evaluation of a nontender growth on the left 2nd digit. The lesion had been present for years without causing any discomfort or discharge, but in the months prior to evaluation began to change prompting evaluation. Physical examination demonstrated white-yellow soft subcutaneous nodules overlying the PNF and distal interphalangeal joint of the left 2nd nail unit causing a longitudinal groove affecting the radial aspect of the nail (shown in Fig. 2a). Biopsy of a representative nodule revealed tophaceous gout (shown in Fig. 2b).

Discussion and Literature Review

Including our two cases, there have been five reported cases of tophaceous gout directly affecting the nail unit (Table 1). It is likely the rarity of reports is because tophaceous gout involving the nail is both underrecognized and underreported. This is suggested by a study examining the clinical appearance of patients with chronic tophaceous gout where more than 30% had clinical evidence of gouty tophi of the finger-pads, a previously presumed rare presentation [8].

In all five reported cases, there was an associated hyperkeratotic, white papulonodular periungual lesion. While most cases also had a known history of gout, our case in addition to one other previously reported case demonstrated nail unit tophi as the first presentation of gout. In three of the five cases, characteristic drainage of chalky fluid was also seen. These more distinctive findings may aid clinician in making the diagnosis of gout when it presents in the nail unit.

In the absence of more specific exam findings and historical clues, there is a broad differential for nail dystrophy with hyperkeratotic papulonodular lesions ranging from benign digital mucous cyst to malignancy such as SCC. Histologic evaluation may be necessary for making a definitive diagnosis.

PCH has been documented in specimens of non-nail unit tophi and may mimic SCC thus leading to unnecessary surgery. Within a shallow shave biopsy, tophi may not be present or small foci may be overlooked. An English language literature search of gouty tophi and SCC yielded an additional eight cases of tophaceous gout mimicking SCC both clinically and histologically (Table 2), the latter of which is attributed to presence of PCH [4–6, 9–11]. Five of the total nine cases involved lesions on the ears while the other four were reported to involve the finger pulp and the PNF. In one-third of the cases, the patients had no previously reported history of gout.

Gout was first described to impact the nail in Sequeira's Diseases of the Skin textbook and later that year expanded in a manuscript in the British Journal of Dermatology in 1969 [12, 13]. In the manuscript, 19 patients with elevated serum uric acid levels were described as having longitudinal ridging, called "reeding" and extreme brittleness and breakage of the nails. While the association was noted, it is not possible to know with certainty based on the lack of further documentation whether these nail changes were a direct result of gout nor whether they equate to onychoschizia possibly as an age-related change independent of gout in this population. Next in 1982, a patient was described to have multiple transverse grooves in the nail plate consistent with Beau's lines that were attributed to gout but confounded by his poorly controlled diabetes mellitus, a known cause of Beau's line [14, 15].

Importantly, the subclinical detection of elevated levels of uric acid in the nail plate has been documented as far back as 1953 when authors demonstrated elevated levels of uric acid via the uricase method in toenail specimens paired from cadavers with a history of renal insufficiency and gout compared to controls [16]. It was not until 2011, where another article described the presence of birefringent crystals on nail specimens

Table 1. Cases of gout affecting the nail unit reported in the literature

Study	Age	Sex	PCH	History of previous gout	Clinical exam findings	Other tophi on examination
Dacko et al. [4], 2002	84	M	Yes	Yes	Hyperkeratotic papule with nail dystrophy. Discharge of chalky material	Yes
Vela et al. [7], 2015	77	M	No	Yes	White periungual papule with nail dystrophy	Yes
Xu et al. [6] 2021	66	M	Yes	No	Hyperkeratotic nodule with longitudinal nail splitting. Discharge of chalky material	No
Hu (current cases)	77	M	Yes	No	White papule with hemorrhagic crusting and nail dystrophy. Discharge of chalky material	No
	89	M	N/A	Yes	White-yellow subcutaneous nodule with longitudinal groove	Yes

PCH, presence of pseudocarcinomatous hyperplasia; M, male; N/A, not available.

Table 2. Cases of gout with pseudocarcinomatous changes reported in the literature

Study	Age	Sex	Location	History of gout
Dacko et al. [4], 2002	84	M	Proximal nail fold	Yes
Morrissey et al. [9], 2014	51	M	Helix	Yes
	58	M	Helix	Yes
	85	M	Helix	No
Sutton and Parekh [10], 2016	70	M	Helix	Yes
Mueller et al. [5], 2021	92	F	Finger pad	Yes
Xu et al. [6], 2021	66	M	Proximal nail fold	No
Yousefian et al. [11], 2022	69	M	Helix	Yes
Hu (current cases)	77	M	Proximal nail fold	No

F, female; M, male.

from 2 patients with a history of gout that were presumed to have a diagnosis of onychomycosis [17]. More recently, the use of high-performance liquid chromatography with ultraviolet (HPLC-UV) as a novel technique has been used to quantify uric acid levels in fingernail specimens [18]. This distinction in levels between healthy volunteers and patients with gout were again delineated in a follow-up study that not only found that the level of urate of fingernail specimen correlated with volume of crystals measured by dual-energy CT, but also showed that reductions in urate levels in the nail could be detected 3 months after starting urate-lowering therapy [19]. Unfortunately, this technique is unavailable for commercial use and still requires further prospective trials to validate findings on a larger scale. Furthermore, HPLC-UV technique is expensive when compared to conventional serum analysis but represents a potential future non-invasive alternative to evaluating a patient's degree of MSU burden.

The aforementioned evidence provides crucial insights into the possible progression and clinical spectrum of nail changes associated with gout. Data suggest that deposition of uric acid occurs early in the course of disease. We postulate that accumulation of uric acid in the nail may lead to onychodystrophy in the form of onychoschizia and onychorrhexis as the initial signs of gouty involvement. In long-standing disease or in patients with risk factors for early development, tophi represent end-stage manifestation with associated mass-effect on the nail and pseudocarcinomatous changes that can mimic SCC both histologically and clinically.

Overall, there is a scarcity of information on the impact of gout on the nail. While subclinical levels of MSU deposition can be detected in nail plate, it is unclear what role this novel testing may serve in the future. However, our cases and review of the literature importantly demonstrate that nail unit gout may be subtle in its presentation and that MSU is present in

nails and skin long before it eventuates in tophi. The most common findings of gout affecting the nail are nonspecific onychodystrophy, and as such dermatopathologists should be aware that uric acid crystals are identifiable in nail plate clippings.

Gouty tophi present as a hyperkeratotic papulonodule of the nail fold. While features of chalky drainage, tophi on other parts of the physical exam, and history of gout are present in the majority of the cases, these are not a universal finding. Therefore, clinicians and dermatopathologists should also be aware that gout may present in the nail unit as tophi and mimic SCC due to the presence of PCH. By raising awareness of nail unit gout, we hope to enable clinicians to make this diagnosis, mitigate the progression of kidney disease in patients through prompt initiation of urate-lowering therapy and early referrals to appropriate specialists, and avoid unnecessary surgery in those that present with tophaceous gout.

Statement of Ethics

Written informed consent was obtained from all the patients for publication of the details of their medical cases and any accompanying images.

Conflict of Interest Statement

The authors declare that there is no conflict of interest.

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Author Contributions

Jeffery Z. Hu: investigation and writing of original draft. Nathaniel J. Jellinek: contribution to the conception and revision. Molly A. Hinshaw: reviewing, editing, critical revision, and supervision.

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