CLINICAL MANAGEMENT extra

Nonhealing Ulcers in Patients with Tophaceous Gout: A Systematic Review

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GENERAL PURPOSE:

To provide information from a review of the literature about chronic ulcers associated with tophaceous gout.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After participating in this educational activity, the participant should be better able to:

1. Identify the pathophysiology of tophaceous gout, its presentation, phases, and common comorbidities.

2. Evaluate the findings in this review regarding effectiveness of interventions for chronic tophaceous ulcers.

ABSTRACT

OBJECTIVE: Treating chronic ulcers associated with tophaceous gout is an uncommon but important clinical challenge. However, treatments vary greatly from topical therapies, to debridements, to free flap wound coverage. To the authors' knowledge, this is the first study to assemble and compare these different approaches in order to guide effective treatment.

DATA SOURCES: An electronic search of MEDLINE (PubMed) was conducted. Search terms included (gout and ulcer) not "peptic ulcer," and (gout, chronic wound) or (gout, nonhealing wound).

STUDY SELECTION: Studies that discussed the presentation, characterization, or treatment of gout-associated wounds were included. The literature search yielded 9 case reports and case series; there were no randomized controlled studies or reviews.

DATA EXTRACTION: Patient and wound characteristics, treatment approaches, and outcomes were noted.

DATA SYNTHESIS: The 82% of 22 patients were male, aged 36 to 95 years. Three patients had not been previously diagnosed with gout, whereas others had received a diagnosis 2 to 35 years prior to presentation with an ulcer. Many patients had comorbidities including diabetes and peripheral vascular disease. Most of the 43 total ulcers occurred on the feet. Treatments included topical 3% citric acid in petroleum jelly, allogeneic culture dermal substitute, silver-containing dressing and heterologous lyophilized collagen, debridements, and free flap coverage.

CONCLUSIONS: Chronic tophaceous wounds are a worldwide problem. Although physicians report some successes with different treatments, controlled studies are needed to determine the most effective approach and to identify risk factors and preventive strategies.

KEYWORDS: chronic wounds, foot ulcers, gout, tophaceous gout, tophi, urate crystals in wounds

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INTRODUCTION

Gout affects more than 8 million Americans (4% of US adults) and has a similarly high prevalence worldwide.[1,2] It is the most common type of inflammatory arthropathy and is caused by deposition of monosodium urate crystals in synovial fluid and other tissues.[3,4] Hyperuricemia, defined as a serum urate of 6.8 mg/dL (405 μmol/L) or more, is associated with the development of gout, because this level is the limit of urate solubility at physiologic temperature and pH.[3,4]

There are 2 clinical phases of gout. In the first phase, crystal deposition triggers an acute inflammatory response, resulting in acute attacks that typically resolve spontaneously after 7 to 10 days, with no symptoms in between attacks.[4] Patients with poorly controlled hyperuricemia can progress to the second phase, chronic gout. Chronic gout is characterized by polyarticular involvement, tophi formation, and the presence of symptoms between acute attacks.[4] Diagnosis of gout is typically made using the American College of Rheumatology criteria; the primary criteria are joint swelling/pain/tenderness, monosodium urate crystals in the synovial fluid, and presence of tophi.[3,5]

Gout tophi are subcutaneous accumulations of monosodium urate crystals in a matrix of lipids, protein, and mucopolysaccharides, surrounded by chronic mononuclear and giant cell inflammation.[2,3] The most common site of tophi formation is the first metatarsophalangeal joint.[3,6] Other typical sites of tophi formation include the finger and toe joints and around the knees, elbows, wrists, and ankles.[2,3] However, urate crystals can deposit in other locations throughout the body, including the vertebrae, soft tissues, and skin.[3,7]

Although the soft tissue overlying tophi might seem thinned or stretched and particularly vulnerable to trauma and breakdown, ulcers at these sites are surprisingly uncommon.[2,6] However, when breakdown does occur, chronic ulcers with persistent discharge can develop (Figure).[6] Ulcers on the feet at sites of joint deformity and weight bearing are especially prone to delayed healing.[6] To compound the problem, patients with gout are more likely to have other comorbidities that predispose them to impaired wound healing, including diabetes, obesity, and peripheral vascular disease.[8,9] Thus, treating these ulcers is an uncommon but important clinical challenge.

The goal of this study was to perform a systematic review of the literature pertaining to the management of patients with chronic ulcers associated with tophaceous gout, a task that to the authors' knowledge has not been previously undertaken.

METHODS

An electronic search of MEDLINE (PubMed) was conducted for English-language articles only, without any year limits. Search terms included (gout *and* ulcer), *not* "peptic ulcer," and (gout, chronic wound) *or* (gout, nonhealing wound). All articles mentioning ulcers or nonhealing wounds in patients with gout were examined. Those that focused on the presentation, characterization, or treatment of these ulcers were included in this study. Excluded from the study were 2 broad review articles on the surgical management of tophaceous gout and 1 article that described soft tissue shaving to reduce the size of tophi because they merely listed ulcers as an indication for surgery, without further discussion.[10–12] In addition, an article that described ulceration in 5 cases of intradermal tophi (vs the typical subcutaneous tophi) was excluded because the report focused on the unusual location of the tophi and did not report ulcer healing outcomes.[7] The reference listings of every included article were also examined to ensure all relevant studies were captured.

RESULTS

The literature search, after application of inclusion/exclusion criteria, yielded 9 articles for final analysis (Table 1). These were published between 2009 and 2014 and represented reports from 8 different countries. There were 3 case series and 6 case studies reporting lower quality evidence. Unfortunately, no randomized controlled studies or review articles were found in the search. Eight of the included articles reported on specific interventions performed to treat ulcers associated with tophaceous gout, whereas the remaining article by Rome et al[6] described the characteristics of these wounds without detailing an intervention.

Figure.

50-YEAR-OLD MAN PRESENTED WITH LEFT MEDIAL FOOT WOUND INFECTION SECONDARY TO GOUT. HE UNDERWENT WOUND DEBRIDEMENT, INTRAVENOUS ANTIBIOTICS, UNNA BOOT, AND OFFLOADING. THE WOUND HEALED IN 10 WEEKS. A) CLINICAL PRESENTATION. B) POST WOUND DEBRIDEMENT. C) POST WOUND CLOSURE.

These 9 case series and case reports included a total of 22 patients. Their ages ranged from 36 to 95 years, with a mean of 61 (excluding 4 patients, as Patel et al[2] did not report individual ages), and 82% (18/22) of them were male. Three of these patients did not have a previous diagnosis of gout prior to their presentation with an ulcer (age at presentation ranged from 74 to 84 years), whereas the other patients had received a diagnosis of gout 2 to 35 years prior (Table 2). Comorbidities were reported in 19 of 22 cases. The most common comorbidity was diabetes mellitus (n = 11), followed by hypertension (n = 9). Two patients had chronic venous insufficiency, and 1 patient had peripheral artery disease. Other comorbidities included hyperlipidemia, ischemic heart disease, cerebrovascular disease, and kidney disease.

Among these 22 patients, there were a total of 43 ulcers; the number of ulcers per patient ranged from 1 to 7. The vast majority of ulcers were located on the foot, especially over the toe joints, but they also occurred on the heel, thumb, and second finger. Two nonhealing ulcers occurred after procedures: 1 occurred over the lateral malleolus after the excision of a soft tissue mass (later determined to be bursitis with tophus), and the other occurred at the amputation site of the third and fourth toes (reason for amputation not reported).[6,13] One nonhealing ulcer developed after mild trauma (scraping the toe against the ground).[14]

On physical examination, chalky exudate and tophi were observed with most ulcers. Defect sizes ranged widely from 0.04 to 195 cm^2; however, the studies did not specify whether measurements were made before or after debridement. Tanabe et al[15] and Ou et al[16] reported tendon exposure after debridement, and Lin et al[17] reported both tendon and bone exposure after debridement.

The interventions varied greatly among the 8 studies. From least invasive to most invasive, they included the simple topical application of 3% citric acid in petroleum jelly,[13] 1-time debridement with or without subsequent topical treatments (ie, allogeneic culture dermal substitute or silver-containing dressing and heterologous lyophilized collagen),[14,15,18] gentle monthly debridements after using hydrogel to soften the tophus,[2] and free flap coverage of defects.[16,17,19] Many of these patients were also medically treated with allopurinol. All studies reported good healing outcomes with their respective interventions, except for 1 patient who died of an

Table 1.
CHARACTERISTICS OF INCLUDED STUDIES OF CHRONIC ULCERS IN PATIENTS WITH GOUT

Author	Country	N	Mean Age Range, y (avg) Gender	Intervention	Gout Medication	Complications	Wound Outcome
Simman et al,[14] 2009	United States	1	84/F	Debridement ×1	Allopurinol	None	Healed well
Ou et al,[16] 2010	Taiwan	1	46/M	Bilateral anterolateral thigh free flaps	Not reported	Right: dehiscence, requiring debridement; left: ulcer recurrence, requiring debridement and sequestrectomy	Healed well
Lee et al,[19] 2010	South Korea	1	62/M	Superficial peroneal nerve accessory artery perforator free flap	Allopurinol	None	Healed well
Patel et al,[2] 2010	United Kingdom	4	74–84 (78)/2 M, 2 F	Hydrogel to soften tophus, gentle debridement monthly	Allopurinol	None	3 healed well; 1 died of unrelated cause before healing
Tanabe et al,[15] 2010	Japan	1	52/M	Debridement ×1, allogeneic culture dermal substitute ×4 wk	Not described	None	Healed well
Falidas et al,[18] 2011	Greece	1	75/M	Debridement ×1, silver-containing dressing and topical heterologous lyophilized collagen ×33 d	Not described	None	Healed well
Lin et al,[17] 2011	Taiwan	6	36–72 (50)/6 M	Anterolateral thigh free flap (5/6) *or* medial sural free flap (1/6)	Not described	None	All healed well
Nagoba et al,[13] 2013	India	1	80/M	3% citric acid petroleum jelly ointment ×22 d	Allopurinol	None	Healed well
Rome et al,[6] 2014	New Zealand	6	41–95 (67)/5 M, 1 F	Report of wound characteristics only, intervention not described	Allopurinol +/− colchicine	Not reported	Not reported

unrelated cause before healing occurred. Time to healing was reported by 3 studies and ranged from 7 to 40 days.[14,15,18] Seven of the studies reported no complications. Ou et al[16] reported dehiscence and ulcer recurrence requiring further debridement after bilateral anterolateral thigh flaps, but this patient's ulcer ultimately healed well.[16]

DISCUSSION

Ulcers resulting from tophaceous gout are quite uncommon, which makes it challenging to develop high-quality studies on the management of these wounds. Yet, the fact that they have been treated and reported by physicians of 8 diverse countries, despite their low incidence, reflects the fact that

Table 2.
CHARACTERISTICS OF PATIENTS AND THEIR WOUNDS

Author	Age, y	Gender	History of Gout, y	Comorbidities	Ulcer Location	Defect Size, cm^2	Wound Description
Simman et al[14]	84	F	No	Diabetes, hypertension, congestive heart failure	Tip of 2nd toe	Not reported	"Erythematous, crusted"
Ou et al[16]	46	M	Yes (10)	Not reported	MTPJ 1st toe bilaterally	R 100, L 150	"Skin necrosis with drainage and tophi deposition"
Lee et al	62	M	Yes (13)	Hypertension, nephropathy	PIPJ 2nd finger	32	"Tender, enlarged subcutaneous nodules, and draining tophi"
Patel et al[2]	74–84 (78)[a]	M	Yes (30)	Diabetes, chronic venous insufficiency	MTPJ 1st toe	2.25[b]	"Hard gout tophus was palpable in the base of all, with no evidence of overlying granulation tissue formation"
	74–84 (78)[a]	F	No	Hypertension, peripheral vascular disease, ischemic heart disease, cerebrovascular disease	MTPJ 1st toe	0.04[b]	
	74–84 (78)[a]	F	Yes (2)	Hypertension, ischemic heart disease, chronic venous insufficiency	MTPJ 5th toe	0.04[b]	
	74–84 (78)[a]	M	Yes (20)	Diabetes, hypertension, hyperlipidemia	Heel	2	
Tanabe et al[15]	52	M	Yes (20)	Not reported	MTPJ ×2 1st toe, MTPJ 2nd toe	4[c]	"Chalky material on the surface" with tendon exposure after urate deposit debridement
Falidas et al[18]	75	M	Yes (unknown)	Not reported	MTPJ 1st toe, Tip of thumb, IPJ 1st toe	Not reported	"Grayish, voluminous and ulcerated nodule containing chalky material"
Lin et al[17]	46	M	Not reported	Hypertension	MTPJ 1st toe	195	"Purulent discharge" with tendon and bone exposure after debridement
	50	M	Not reported	Diabetes, hypertension	MTPJ 1st toe, MTPJ 2nd toe	112	
	36	M	Not reported	Hypertension	MTPJ 1st toe, MTPJ 2nd toe	112	
	39	M	Not reported	Diabetes	TMTJ 4th toe, TMTJ 5th toe	36	
	56	M	Not reported	Diabetes, hypertension	TMTJ 4th toe, TMTJ 5th toe	48	
	72	M	Not reported	Diabetes	TMTJ 4th toe, TMTJ 5th toe	50	
Nagoba et al[30]	80	M	No	None	Lateral malleolus	Not reported	Ulcer occurred after excision of painful soft tissue mass (determined to be bursitis with tophus)

(continues)

Table 2.
CHARACTERISTICS OF PATIENTS AND THEIR WOUNDS, CONTINUED

Author	Age, y	Gender	History of Gout, y	Comorbidities	Ulcer Location	Defect Size, cm^2	Wound Description
Rome et al[6]	95	M	Yes (35)	Ischemic heart disease, kidney disease	DIPJ 1st toe ×6, DIPJ 3rd toe	0.1–0.5	"The majority of patients presented with ulcers that had low levels of exudate," granulation tissue observed in 3 of 6 patients
	55	M	Yes (20)	Diabetes, hyperlipidemia, ischemic heart disease	MTPJ 1st toe ×2, DIPJ 1st toe ×2, 1st/2nd webspace, PIPJ 5th toe	0.2–5.0	
	59	M	Yes (25)	Diabetes, hyperlipidemia	Tip 3rd toe	Not reported	
	76	M	Yes (18)	Diabetes, hyperlipidemia	DIPJ 3rd toe	Not reported	
	74	F	Yes (20)	Ischemic heart disease, hyperlipidemia	DIPJ 3rd toe	0.5	
	41	M	Yes (16)	Diabetes, hyperlipidemia	Post amputation 3rd and 4th toes	0.2–1.0	

Abbreviations: DIPJ, distal interphalangeal joint; IPJ, interphalangeal joint; MTPJ, metatarsophalageal joint; PIPJ, proximal interphalangeal joint; TMTJ, tarsometatarsal joint.
[a]Age range and mean of case series; individual ages not reported.
[b]Area calculated from reported diameters: 1.5 and 0.2 cm, respectively.
[c]Size of largest ulcer, others not reported.

ulcerated gout is a worldwide problem that should be discussed and addressed to ensure prompt diagnosis and improve treatment practices.

It is well established that the prevalence of gout increases with age and is significantly higher in men.[1,20,21] This pattern holds true for ulcerated gout. Among the reported cases, the mean age was 61 years, and 82% were men. Nevertheless, the development of ulcers is not limited to older adult patients or to those who have had chronic gout for many years. At the time of presentation, 5 patients were in their 30s or 40s, and 3 patients had not previously received a diagnosis of gout. Others had a variable history, having received a diagnosis of gout anywhere from 2 to 35 years prior to presentation with an ulcer.

The variability in gout history may also be because patients did not seek medical attention until their wounds were quite advanced. Tophaceous gout tends to occur in patients with poorly controlled hyperuricemia, and nonhealing ulcers primarily develop over sites of tophi.[2,4] This suggests that patients who are at greater risk of developing chronic tophaceous ulcers are those who have limited access to healthcare or are noncompliant with medical recommendations.

There are other factors that may contribute to chronic ulcerated tophaceous gout. Multiple studies have demonstrated that patients with gout are more likely to have other comorbidities that impair wound healing, such as diabetes and vascular disease, and the patients in this study were no exception: they had diseases including diabetes, hypertension, chronic venous insufficiency, peripheral arterial disease, and ischemic heart disease.[8,9,20]

It is not surprising that the feet are the most common site of ulcerated tophaceous gout, not only because tophi frequently occur here, but also because they are subject to weight-bearing stress.[2,3,6] Rome et al[6] noted that 3 of their 6 patients frequently wore ill-fitting shoes such as slippers and flip-flops; these provided inadequate cushioning and support and may have contributed to delayed wound healing.

There is little consensus about the treatment of these ulcers. Patel et al[2] observed that none of the 4 patients in their case series (wound size 0.04–2.25 cm^2) formed granulation tissue prior to treatment. They proposed that tophi impair wound healing by inhibiting the formation of granulation tissue. Their solution was to apply hydrogel to soften the tophi to facilitate gentle monthly debridement.[2] Yet, Rome et al[6] observed granulation tissue in 3 of 6 patients in their study.

Other groups reported successes with topical treatments—allogeneic cultured dermal substitute, topical collagen, and citric acid gel—with and without prior debridement. Unfortunately, the literature on the use of allogeneic cultured dermal substitute,

as used by Tanabe et al,[15] is limited to case reports and case series, although they do report successes in promoting granulation tissue formation in patients with chronic leg ulcers associated with antiphospholipid syndrome, pyoderma gangrenosum, epidermolysis bullosa, and status post–tumor resection.[15,22–25] Similarly, although a few reports from the 1990s suggest that topical collagen promotes wound healing,[26,27] other studies have refuted the efficacy of topical collagen when compared with "topical hydrocolloid" and "no topical treatment" controls.[28,29] Falidas et al[18] reported effective healing in 1 patient after debridement, followed by application of antibacterial silver-containing dressings and topical collagen. However, topical collagen's role in the management of tophaceous ulcers remains unclear. The use of topical citric acid to improve wound healing is marginally better supported. Virtually all of the literature on this treatment comes from the same group, Nagoba et al.[13,30] They have published several other studies on the efficacy of citric acid to treat other wounds, including 1 study demonstrating improved burn wound healing after use of citric acid gel compared with conventional antibiotic therapy and dressings.[13,30] Proposed mechanisms of action of citric acid include antibacterial activity and improving wound vascularity.[13] Debridement and appropriate dressings certainly have a role in treating nonhealing ulcers associated with gout, but further study is required to determine the most effective regimen.

Patients with much larger wounds (32–195 cm^2) were treated with free flaps. Specifically, 3 of the included 9 articles described use of 6 anterolateral thigh, 1 medial sural, and 1 superficial peroneal nerve accessory artery perforator flaps to treat 7 patients (1 patient had bilateral ulcers and received 2 flaps).[16,17,19] Free flaps are frequently used to cover large traumatic defects, but their use to cover chronic wounds has been more limited. Small vessel disease associated with diabetes and vascular disease raises concerns for an increased risk of flap loss.[31,32] However, free tissue transfer is gaining acceptance as an alternative to amputation in the treatment of chronic wounds and has been shown to provide good outcomes in patients with peripheral arterial disease.[32] The cases included in this study also support its use in patients with large defects secondary to tophaceous gout.

One final treatment to consider is skin grafting. Lin et al[17] briefly mentioned 2 patients who did not require free flaps and were instead treated with debridement, vacuum-assisted closure, and split-thickness skin grafts. Because these patients were only discussed as exclusions from the authors' free flap case series, the details and outcomes of their presentation and management were not provided.[17]

The primary goal in treating ulcerated tophaceous gout is treating the underlying disease. Collaborating with the patient's primary care provider to optimize gout medications to decrease hyperuricemia and inflammation is fundamental to wound healing. Treating the whole patient and not only the ulcer reduces the likelihood of ulcer recurrence. In the included studies, improved medical management of the patients' gout and comorbidities may have played a role in promoting wound healing, but limited information was provided on medical management. This potential cofounder cannot be properly addressed without a controlled trial.

The primary weakness in this study is that the literature regarding the management of ulcerated tophaceous gout consists of case series and case reports that provide much lower quality evidence compared with randomized controlled trials. Also, Ou et al[16] reported 1 incidence of ulcer recurrence at 3 months following the initial treatment. Unfortunately, the duration of follow-up was varied and often not clearly reported, so the recurrence rate of ulcers after all these interventions remains undetermined. Future studies are needed to identify the risk factors that predispose patients with gout to developing ulcers and to define effective treatment protocols. A clearer understanding of gout wound formation and wound healing mechanisms could also be achieved by creating and studying an animal model.

CONCLUSIONS

Nonhealing ulcers associated with tophaceous gout are an uncommon but worldwide problem. They can be challenging to treat because of their tendency to develop on the feet, a high-stress weight-bearing area. The comorbidities seen among patients with gout, including diabetes and peripheral vascular disease, compound the difficulties. The reported approaches to ulcer management vary greatly from debridement with or without topical treatments to microvascular free flap coverage, with successful outcomes in case reports and case series. Unfortunately, no controlled studies exist to evaluate the risk factors for developing ulcerated tophaceous gout. The role of medical management and the benefits of these treatments need further study.

PRACTICE PEARLS

- Chronic tophaceous wounds are uncommon, but they affect patients worldwide and are challenging to treat.
- Small ulcers can be treated with standard wound care and debridement.
- Topical treatments, such as collagen and silver-containing dressings, may help but the clinical evidence is limited.
- Large ulcers may be successfully treated with flap coverage. However, patients with gout often have medical comorbidities such as diabetes, which may negatively impact free tissue transfer outcomes.
- Medical management of gout is a key component to treating chronic tophaceous wounds.

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Registration Deadline: May 31, 2019 (nurses); May 31, 2018 (physicians).

PAYMENT AND DISCOUNTS

- The registration fee for this test is $17.95 for nurses; $22 for physicians.