Recalcitrant Ulcer on the Lower Leg

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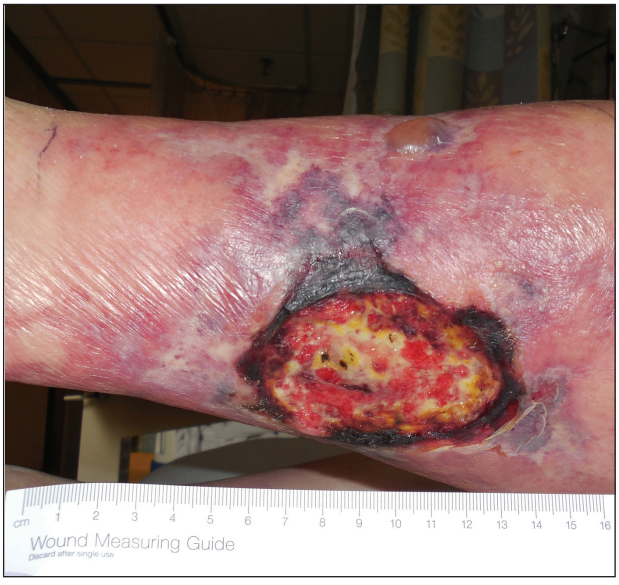

An 80-year-old woman with a medical history notable for obesity (body mass index, 31.2), type 2 diabetes mellitus, hypertension, and chronic atrial fibrillation treated with warfarin presented with a chronic painful wound on the left lower calf of 1 month's duration. A 7×7-cm ulcer on the posterior aspect of the left calf with necrotic debris was seen surrounded by skin of mottled purple discoloration. The edge of the ulcer was not undermined. There were tense nonhemorrhagic bullae on the medial aspect of the left leg and on bilateral anterior tibial areas. Two punch biopsy specimens were obtained from the anterior tibial bulla and the edge of the ulcer.

WHAT'S THE **DIAGNOSIS?**

a. Martorell hypertensive ischemic ulcer
b. necrobiosis lipoidica
c. nonuremic calciphylaxis
d. pyoderma gangrenosum
e. warfarin necrosis

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The authors report no conflict of interest.
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THE **DIAGNOSIS:** Nonuremic Calciphylaxis

Histopathologic findings revealed ischemic necrosis and a subepidermal blister (Figure 1) with arteriosclerotic changes and fat necrosis. Foci of calcification were noted within the fat lobules. Arterioles within the deeper dermis and subcutis showed thickened hyalinized walls, narrowed lumina, and medial calcification (Figure 2). Multiple sections did not reveal any granulomatous inflammation. Periodic acid–Schiff and Gram stains were negative for fungal and bacterial elements, respectively. No dense neutrophilic infiltrate was seen. Multifocal calcific deposits within fat lobules and vessel walls (endothelium highlighted by the CD31 stain) suggested calciphylaxis.

Laboratory test results revealed a normal white blood cell count, international normalized ratio level of 4 (on warfarin), and an elevated sedimentation rate at 72 mm/h (reference range, 0–20 mm/h). Serum creatinine was 1.1 mg/dL (reference range, 0.6–1.2 mg/dL) and the calcium-phosphorous product was 40.8 mg^2/dL (reference range, <55 mg^2/dL). Hemoglobin A_{1C} (glycated hemoglobin) was 8.2% (reference range, 4%–7%). Wound cultures grew *Proteus mirabilis* sensitive to cefazolin. Acid-fast bacilli and fungal cultures were negative. Computed tomography of the left lower leg without contrast showed no evidence of osteomyelitis. Of note, the popliteal arteries and distal vessels showed moderate vascular calcification.

Histopathology findings as well as a clinical picture of painful ulceration on the distal extremities and uncontrolled diabetes with normal renal function favored a diagnosis of nonuremic calciphylaxis (NUC). The patient was treated with intravenous infusions of sodium thiosulfate 25 mg 3 times weekly and oral cefazolin for superadded bacterial infection. Local wound care included collagenase dressings with light compression. Warfarin was discontinued, as it can worsen calciphylaxis. Complete reepithelialization of the ulcer along with substantial reduction in pain was noted within 4 weeks.

Ulceration of the lower legs is a relatively common condition in the Western world, the prevalence of which increases up to 5% in patients older than 65 years.[1] Of the myriad of causes that lead to ulceration of the distal aspect of the leg, NUC is a rare but known phenomenon. The pathogenesis of NUC is complicated based on theories of derangement of receptor activator of nuclear factor κβ, receptor activator of nuclear factor κβ ligand, and osteoprotegerin, leading to calcium deposits in the media of the arteries.[2] This deposition precipitates vascular occlusion coupled with ischemic necrosis of the subcutaneous tissue and skin.[3] Some of the more common causes of NUC are primary hyperparathyroidism,

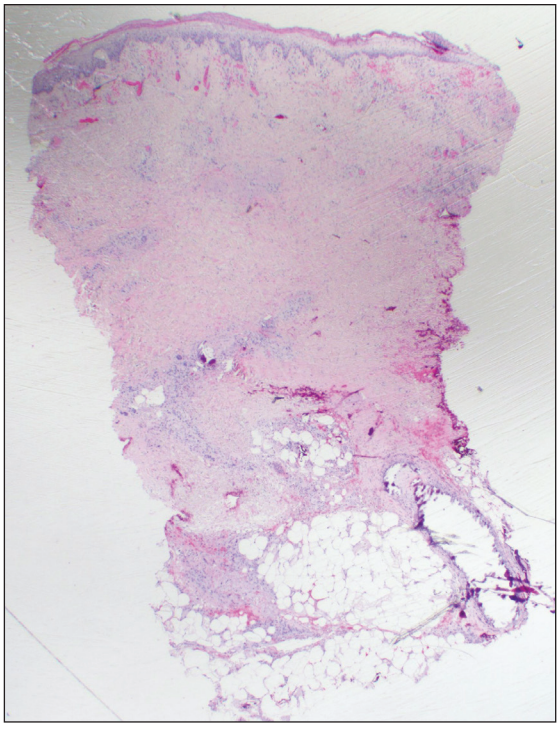

FIGURE 1. Ischemic necrosis and a subepidermal blister with arteriosclerotic changes and fat necrosis (H&E, original magnification ×10).

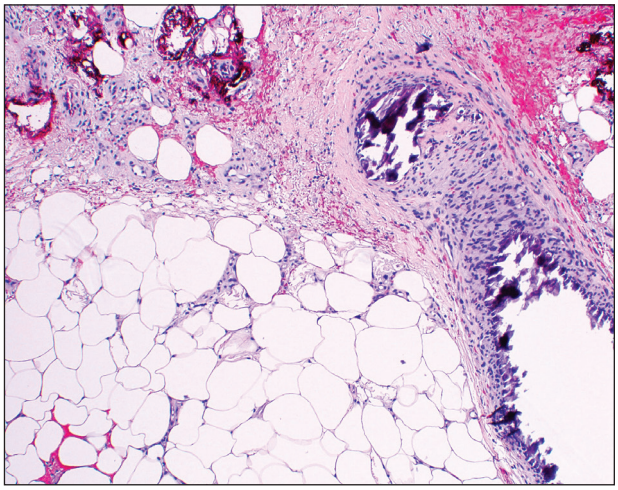

FIGURE 2. Arterioles within the deeper dermis and subcutis showed thickened hyalinized walls, narrowed lumina, and medial calcification (H&E, original magnification ×40).

malignancy, and rheumatoid arthritis. Type 2 diabetes mellitus is a less common cause but often is found in association with NUC, as noted by Nigwekar et al.[2] According to their study, the laboratory parameters commonly found in NUC included a calcium-phosphorous product greater than 50 mg^2/dL and serum creatinine of 1.2 mg/dL or less.[2]

Our patient displayed these laboratory findings. However, distinguishing NUC from other atypical lower extremity ulcers such as Martorell hypertensive ischemic ulcer, pyoderma gangrenosum, and warfarin necrosis can pose a challenge to the dermatologist. Martorell hypertensive ischemic ulcer is excruciatingly painful and occurs more frequently near the Achilles tendon, responding well to surgical debridement. Histopathologically, medial calcinosis and arteriosclerosis are seen.[4]

Pyoderma gangrenosum is a neutrophilic dermatosis wherein the classical ulcerative variant is painful. It occurs mostly on the pretibial area and worsens after debridement.[5] Clinically and histopathologically, it is a diagnosis of exclusion in which a dense neutrophilic to mixed lymphocytic infiltrate is seen with necrosis of dermal vessels.[6]

Warfarin necrosis is extremely rare, affecting 0.01% to 0.1% of patients on warfarin-derived anticoagulant therapy.[7] Necrosis occurs mostly on fat-bearing areas such as the breasts, abdomen, and thighs 3 to 5 days after initiating treatment. Histologically, fibrin deposits occlude dermal vessels without perivascular inflammation.[8]

Necrobiosis lipoidica is a rare cutaneous entity seen in 0.3% of diabetic patients.[9] The exact pathogenesis is unknown; however, microangiopathy in collaboration with cross-linking of abnormal collagen fibers play a role. These lesions appear as erythematous plaques with a slightly depressed to atrophic center, ultimately taking on a waxy porcelain appearance. Although most of these lesions either resolve or become chronically persistent, approximately 15% undergo ulceration, which can be painful. Histologically, with hematoxylin and eosin staining, areas of necrobiosis are seen surrounded by an inflammatory infiltrate comprised mainly of histiocytes along with lymphocytes and plasma cells.[9]

Nonuremic calciphylaxis can mimic the aforementioned conditions to a greater extent in female patients with obesity, diabetes mellitus, and hypertension. However, microscopic calcium deposition in the media of dermal arterioles, extravascular calcification within fat lobules, and cutaneous necrosis, along with remarkable response to intravenous sodium thiosulfate, confirmed a diagnosis of NUC in our patient. Sodium thiosulfate scavenges reactive oxygen species and promotes nitric oxygen generation, thereby reducing endothelial damage.[10] Although there are no randomized controlled trials to support its use, sodium thiosulfate has been successfully used to treat established cases of NUC.[11]

REFERENCES

1. Spentzouris G, Labropoulos N. The evaluation of lower-extremity ulcers. *Semin Intervent Radiol*. 2009;26:286-295.
2. Nigwekar SU, Wolf M, Sterns RH, et al. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol.* 2008;3:1139-1143.
3. Bardin T. Musculoskeletal manifestations of chronic renal failure. *Curr Opin Rheumatol.* 2003;15:48-54.
4. Hafner J, Nobbe S, Partsch H, et al. Martorell hypertensive ischemic leg ulcer: a model of ischemic subcutaneous arteriolosclerosis. *Arch Dermatol.* 2010;146:961-968.
5. Sedda S, Caruso R, Marafini I, et al. Pyoderma gangrenosum in refractory celiac disease: a case report. *BMC Gastroenterol.* 2013;13:162.
6. Su WP, Davis MD, Weenig RH, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. *Int J Dermatol.* 2004;43:790-800.
7. Breakey W, Hall C, Vann Jones S, et al. Warfarin-induced skin necrosis progressing to calciphylaxis. *J Plast Reconstr Aesthet Surg.* 2014; 67:244-246.
8. Kakagia DD, Papanas N, Karadimas E, et al. Warfarin-induced skin necrosis. *Ann Dermatol.* 2014;26:96-98.
9. Kota SK, Jammula S, Kota SK, et al. Necrobiosis lipoidica diabeticorum: a case-based review of literature. *Indian J Endocrinol Metab.* 2012;16:614-620.
10. Hayden MR, Goldsmith DJ. Sodium thiosulfate: new hope for the treatment of calciphylaxis. *Semin Dial*. 2010;23:258-262.
11. Ning MS, Dahir KM, Castellanos EH, et al. Sodium thiosulfate in the treatment of non-uremic calciphylaxis. *J Dermatol.* 2013;40:649-652.