A Case of Nonhealing Skin Ulcers in a Patient with Nonuremic Calciphylaxis

Dear Editor,

Calciphylaxis is a rare and serious condition that typically presents with painful purpuric plaques and nodules, ultimately progressing to necrotic ulcers that frequently become superinfected, and have a dismal prognosis. It is typically diagnosed in patients with end-stage renal disease (ESRD) on dialysis.[1] When it develops in patients without ESRD, it is called nonuremic calciphylaxis (NUC).

A 47-year-old female was transferred to our hospital for painful, nonhealing, escharotic skin lesions present over her right ankle [Figure 1a], bilateral flanks, right arm [Figure 1b], and bilateral forearms. The patient reported that the lesions started as erythematous, tender nodules over her right ankle and bilateral flanks 3 weeks before presentation and progressed to open ulcerative lesions with irregular borders, erythematous edges, and subsequently to dry necrosis with eschar.

She had long-standing erosive rheumatoid arthritis, for which she was on 10 mg of daily prednisone for the past 7 years. She also suffered from stage 3 chronic kidney disease (CKD) of unknown etiology, Sjogren syndrome, and Hashimoto thyroiditis. Vitals signs were normal, and infectious workup was negative. Laboratory investigations revealed the following: creatinine (2.2 mg/dl), glomerular filtration rate (GFR; 25 ml/min/1.73 m^2), C-reactive protein (CRP; 0.7 mg/dl), and erythrocyte sedimentation rate (ESR; 102/mm). Further evaluation showed highly elevated rheumatoid factor (RF) levels and normal anti-nuclear antibody (ANA), anti-dsDNA, anti-anti-Sjögren's-syndrome-related antigen A (SS-A) and -Sjögren's-syndrome-related antigen B (SS-B) antibody levels. Hypercoagulable workup was performed with protein C and S, antithrombin III, homocysteine, factor VIII, anti-cardiolipin, and lupus anticoagulant antibody, and all were found to be within normal limits.

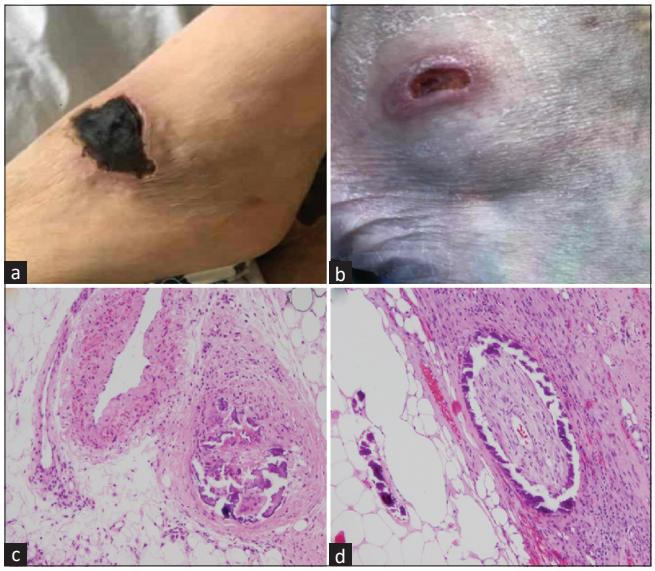

Figure 1: (a) An irregular (6.5 × 3.5 cm) eschar on the medial surface of the right arm. (b) An ulcerated (1.5 × 2.5 cm) lesion on the lateral surface on the right ankle. (c) Histologic examination of skin and subcutaneous tissue samples. H and E staining, original magnification ×200, showing focal interstitial and intimal calcium deposition. (d) Histologic examination of skin and subcutaneous tissue samples. H and E staining, original magnification × 400, showing focal interstitial and intimal calcium deposition. H&E = Hematoxylin and eosin

Full-thickness skin biopsy including subcutaneous tissue was performed. Histopathology revealed focal fat necrosis and focal interstitial and intimal calcium deposition with focal septal chronic panniculitis. Direct immunofluorescence (DIF) studies failed to show deposition with IgG, IgM, IgA, C3, C1q, and fibrinogen. Definitive diagnosis of NUC was made based on histopathology findings [Figure 1c and d].

The patient was followed by rheumatology, wound care, and general surgery during admission. She was continued on appropriate dressings and infection control, along with opioids for analgesia. In consultation with nephrology, the patient was started on sodium thiosulfate with initial pretreatment serum chemistry and electrocardiogram (ECG) performed to establish baseline and then before every dose. She tolerated therapy well without any complications. She was then transferred to a short-term nursing care facility for continued wound care and sodium thiosulfate administration. At 1-month follow-up, the patient's lesions improved with decrease in size, and improvement in pain was also reported.

Calciphylaxis is a rare, usually fatal, vasculopathic disorder characterized by cutaneous ischemia and necrosis due to calcification, intimal fibroplasia, and thrombosis of pannicular arterioles.[1] It is a condition with high morbidity and mortality, with studies showing mortality up to 52%.[1] NUC is diagnosed when histopathology is consistent with calciphylaxis in the absence of end-stage kidney disease, renal transplantation, or acute kidney injury requiring renal replacement therapy. Etiology is multifactorial, with primary hyperparathyroidism, connective tissue disorders, malignancy, and alcoholic liver disease having the most consistent association. Systematic reviews have also found a strong association between NUC and connective tissue disorders, especially when patients are on treatment with glucocorticoids. These can manifest in patients with only mild CKD,

with creatinine level as low as 1.2 mg/dl and even with a normal estimated GFR.[2] Lesions generally develop in areas of high adiposity, which include proximal and distal lower and upper extremities and flanks. Clinical mimics of calciphylaxis include cutaneous vasculitis, warfarin-induced skin necrosis, purpura fulminans, and oxalate vasculopathy, and therefore, it requires a high index of suspicion for diagnosis.[1] Even after the right diagnosis, NUC remains a therapeutic challenge lacking effective treatment options. Treatment generally comprises good supportive measures like aggressive wound care, analgesia, and control of infection and risk factors. Medications such as sodium thiosulfate, lanthanum carbonate, bisphosphonates, statins, sevelamer, and calcimimetics are frequently used, but their efficacy remains low.[3] Antibiotic threshold should be low to prevent sepsis, which is responsible for 50% of the deaths in these patients, most of them occurring within 1 year after diagnosis.[1] Our case reiterates the need to maintain a high index of suspicion for NUC while evaluating skin lesions in patients with these underlying conditions even in the absence of end-stage kidney disease.

Declaration of patient consent

Informed consent was obtained from the patient.

Acknowledgements

None.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Access this article online	
Quick Response Code:	Website: https://journals.lww.com/ijon
	DOI: 10.4103/ijn.IJN_85_21

How to cite this article: Agarwal S, Ozluk E, Boparai S. A case of nonhealing skin ulcers in a patient with nonuremic calciphylaxis. Indian J Nephrol 2023;33:75-6.

Received: 26-02-2021; **Accepted:** 08-07-2021; **Published:** 22-11-2022.