CASE REPORTS

Non-Uremic Calciphylaxis Without End-Stage Renal Disease: A Case Report

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Keywords: calciphylaxis, dermatology, renal, skin ulcer

Texas Family Medicine Research Journal

Vol. 1, Issue 2, 2025

Calciphylaxis is a rare but life-threatening disorder of medial arteriolar calcification with subsequent thrombosis, most often associated with end-stage renal disease (ESRD). Non-uremic calciphylaxis (NUC) – which occurs in the absence of ESRD— is even rarer, with limited literature describing its clinical course, management, and outcomes. We present the case of a 62-year-old female with rheumatoid arthritis and no history of ESRD who developed progressive bilateral lower extremity ulcerations complicated by recurrent infections. Her clinical course was characterized by treatment resistance, multiple hospitalizations, and poor wound healing, requiring a multidisciplinary approach including intravenous sodium thiosulfate, wound care, and hyperbaric oxygen therapy. This case highlights the diagnostic challenges of NUC, its high morbidity, the importance of early recognition, and combined therapeutic strategies.

BRIEF BACKGROUND

Calciphylaxis is an insidious, asymptomatic, progressive medial arteriolar calcification, resulting in clinical manifestations when vascular thrombosis occurs.[1] While classically associated with ESRD, calciphylaxis can also occur in the absence of severe renal dysfunction, termed non-uremic calciphylaxis (NUC). NUC is a rare potentially life-threatening condition and mortality estimates range from 50% to 80%, with most deaths attributable to sepsis from infected ulcers.[2,3] Limited literature is available on NUC but it has been associated with conditions such as obesity, hyperparathyroidism, alcoholic liver disease, history of transplant, connective tissues disease, malignancy, autoimmune disease, and certain medications such as glucocorticoids, teriparatide, and warfarin.[1,4-9] Early lesions of calciphylaxis often appear as indurated plaques with overlying mottling or livedoid pattern that progress to retiform purpura.[3] Purpuric lesions then evolve into black eschars. In later stages, necrotic, ulcerated, malodorous plaques or nodules are present, frequently complicated by infection. Prognosis is worse for patients with multiple risk factors such as autoimmune disease, hypercoagulability, corticosteroid use, and abnormalities of calcium-phosphate metabolism. Cutaneous biopsy is diagnostic and reveals characteristic findings like medial calcification of dermal and subdermal arterioles, fibrointimal hyperplasia, microthrombi, and vascular narrowing or occlusion.[10] Vascular calcification

results from active cellular processes involved in biomineralization and the NFkB pathway. Prothrombotic factors are additionally involved in the acute development of vascular occlusion. It usually presents as a painful skin lesion with a livedoid pattern progressing to necrosis, frequently with a black stellate eschar and surrounding purpura that heals poorly and frequently becomes infected.[3] Due to its rarity and overlap with other ulcerative dermatoses, diagnosis is often delayed, thereby worsening prognosis. However even with early diagnosis, many cases can still be fatal.[11] Here we report a case of NUC in a patient with rheumatoid arthritis and multiple comorbidities, the diagnostic process, hospital course, and therapeutic challenges.

CASE REPORT

A 62-year-old Caucasian female with a past medical history of rheumatoid arthritis, hypertension, and osteoporosis presented with worsening bilateral lower extremity ulcerations. Three months prior to presentation she had what was suspected to be a spider bite on her right lower extremity which grew and worsened in pain at which point she began seeing outpatient wound care. Wound cultures had grown *Pseudomonas aeruginosa*, *methicillin resistant Staphylococcus aureus (MRSA)*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Serratia marcescens*. A venous doppler at that time ruled out deep venous thrombosis and peripheral arterial disease. During this time she underwent multiple rounds of oral antibiotics including bactrim and levaquin, as well as steroids out of concern for vasculitis. Despite treatment with antibiotics, the periwounds continued to remain erythematous and the wound began developing black eschar. One month prior to hospital presentation, a new wound was found on her left lower extremity that started as a laceration. This wound grew to become another large ulcerated wound. Purplish discoloration of the legs was noted. Her wounds unfortunately did not improve and she then transitioned to being seen multiple times by dermatology as an outpatient and was started on ciprofloxacin when wound cultures grew pan-sensitive *Pseudomonas aeruginosa*.

She was functionally independent and worked full time running a family business. Of note, she did not possess any further risk factors including obesity, smoking, liver disease, cancer, kidney disease, or medication usage that could precipitate abnormal calcium-phosphate metabolism including glucocorticoids.

On presentation, lower extremity exam revealed bilateral eschars and ulcerated plaques with surrounding erythema (Figures 1 and 2). Lesions demonstrated retiform borders with stellate black eschars, consistent with late stage calciphylaxis. An extensive laboratory evaluation was suggestive of chronic inflammation, but was negative for rheumatologic etiologies (Table 1). Laboratory studies for cryoglobulinemia, viral hepatitis (which can cause

Table 1. Initial lab results and interpretation

Test	Result	Reference Range	Interpretation
WBC (initial)	11.18 x10^3/μL	4.0–10.0 x10^3/μL	Infected ulcers
WBC (during stay)	Remained <10 starting on hospital day 2	4.0–10.0 x10^3/μL	Response to IV cefepime
ESR	56 mm/hr	<20 mm/hr	Non-specific inflammation present
CRP	70.6 mg/L	<10 mg/L	Non-specific inflammation present
Rheumatoid Factor	21 IU/mL	<14 IU/mL	Unknown baseline prior to admission, likely reflective of ongoing inflammation versus ongoing rheumatoid arthritis
PTH	48.9 pg/mL	18.4–80.1 pg/mL	Ruled out hyperparathyroidism as an etiology for calciphylaxis
C3	192 mg/dL	88–201 mg/dL	Ruled out immune complex diseases
C4	25 mg/dL	15–45 mg/dL	Ruled out immune complex diseases
Cryoglobulins	Negative	—	Excluded cryoglobulinemia
Hepatitis Panel	Negative	—	Excluded viral hepatitis
Protein C / S	Normal	—	Excluded deficiency
Factor V Leiden	Negative	—	Excluded thrombophilia
Lupus Anticoagulant	Negative	—	Excluded antiphospholipid syndrome
Anti-CCP	Negative	—	Excluded antibody-mediated RA activity
Cardiolipin Antibodies	Negative	—	Excluded antiphospholipid syndrome

WBC = white blood cells
ESR = Erythrocyte sedimentation rate
CRP = C-reactive protein
PTH = parathyroid hormone
C3 = Complement C3
C4 = Complement C4
Anti-CCP = Anti-cyclic citrullinated peptide

mixed cryoglobulinemia), protein C/S deficiency (causes skin necrosis), and antiphospholipid syndrome were also obtained given these conditions have skin findings similar to calciphylaxis.

Imaging included a lower extremity venous doppler that was negative for deep vein thrombosis. Radiographs of the bilateral tibias also showed no evidence of acute osteomyelitis but did show soft tissue irregularities and subcutaneous edema along the bilateral calves consistent with the patient's known ulcerations. Lower extremity computed tomography showed irregular ulceration and edema of the mid to distal lower legs bilaterally. There was no organized fluid collection, subcutaneous emphysema, or evidence of acute osteomyelitis. Histopathology from an outside skin biopsy showed ulcers with an underlying mixed dermal inflammatory infiltrate, vascular thrombosis and focal dystrophic calcifications in a vessel wall most consistent with calciphylaxis.

The patient was started on intravenous cefepime with resolution of leukocytosis. Her hospital course was complicated by medication-related reactions: her condition worsened due to ciprofloxacin associated tendonitis, and allergic reactions to silver sulfadiazine and neomycin-containing topicals. Her ulcerations did, however, partially respond to topical mupirocin.

The dermatology, hyperbaric wound, rheumatology, and wound care teams were consulted. Per dermatology the patient was started on intravenous sodium thiosulfate 25 mg IV 3 times weekly, which she received a total of four doses during her hospital stay. Wound care regimen included topical mupirocin ointment to ulcers, non-adherent dressing such as Telfa, gauze, and Kerlix. Hyperbaric oxygen therapy was arranged for outpatient management. She was ultimately discharged with a peripherally inserted central catheter (PICC) for outpatient sodium thiosulfate infusions.

She has since undergone multiple wound debridements and sodium thiosulfate infusions. Her infusions were temporarily halted for one month due to her specialty pharmacy closing and subsequent insurance coverage issues. Her rheumatoid arthritis medication (Enbrel) was held due to concerns about impaired wound healing. Calciphylaxis is known to be an extremely painful condition and her pain control proved to be challenging as she failed multiple outpatient pain medications. She was ultimately referred to a pain management clinic for daily pain management and during wound debridements requiring a multi-modal pain regiment and long term opioids to to help with pain control. Despite these interventions, she required three additional hospitalizations (between the time of her discharge and the writing of this case report, roughly one year) for recurrent lower extremity cellulitis and acute-on-chronic ulcer exacerbations. This further underscores the refractory nature of NUC.

DISCUSSION

NUC is a rare condition that mimics infectious, autoimmune, and vascular etiologies. Differential diagnoses for this condition include:

- Antiphospholipid syndrome (hypercoagulable state)
- Atherosclerosis (peripheral vascular disease)
- Calcinosis cutis
- Cellulitis
- Cholesterol embolism
- Hematoma
- Infectious ulcer
- Livedoid vasculopathy

- Martorell hypertensive ischemic ulcer
- Pyoderma gangrenosum
- Small- to medium-vessel vasculitis
- Venous stasis ulcer.[12]

The pathogenesis for NUC specifically involves a combination of vascular calcification, thrombosis, and inflammation. Patients typically present with exquisitely painful lesions progressing to necrosis and ulceration, as seen in this patient. However, some patients will report pain before lesions appear.[13]

Early lesions present as painful nodules or indurated plaques, sometimes with mottling. These progress from livedo reticularis to livedo racemosa and then to retiform purpura, later evolving into black eschars and then necrosis (Figure 3).[2] This patient's presentation was typical of calciphylaxis including her most recent lesion that was caused by a laceration. It is important to be aware of the Koebner phenomenon which occurs when trauma at a specific site triggers the disease's development in that area, even if the patient has no pre-existing calciphylaxis, or triggers new lesions in already affected patients. Ulcers are predisposed to recurrent superimposed bacterial infection, leading to sepsis—the primary cause of death in calciphylaxis. While ESRD is absent in NUC, comorbid conditions such as autoimmune diseases (e.g., rheumatoid arthritis), corticosteroid therapy, warfarin use and systemic inflammation may contribute.[13] This patient's history of rheumatoid arthritis, elevated ESR and/CRP, and prior recurrent infections likely predisposed her to NUC.

There is no established cure for NUC, but standard of care is a multi-disciplinary and multi-interventional approach focusing on managing symptoms and preventing complications. If a family practice provider suspects NUC, urgent referral to dermatology for diagnostic biopsy is recommended. As trauma can be a trigger for progression of lesions, the risks and benefits must be weighed when NUC is in the differential diagnosis. In cases of patients with ESRD and painful necrotic ulcers, diagnosis can often be clinical. However in NUC, patients do not have ESRD and oftentimes biopsy provides the diagnostic confirmation in these uncertain cases. When biopsy is necessary, it is important to refer to a specialist who can perform a deep punch biopsy at the periphery of the lesion to include subcutaneous tissue and avoid necrotic areas.

Sodium thiosulfate infusions remain the first-line therapy as it is theorized to act via antioxidant, vasodilatory, and calcium-chelating mechanisms.[8,12] Other therapies include wound care with non-adherent dressings to reduce infection risk, pain management (which is crucial given severe nociceptive burden), and addressing underlying risk factors. Careful surgical or chemical

debridement of the lesions, to remove eschar, bacterial biofilms and inflamed adipose tissue, is also recommended. Other reported therapeutic alternatives are associated with positive outcomes but are largely extrapolated from uremic calciphylaxis cases.[3] These comprise hyperbaric oxygen therapy (HOT), lanthanum carbonate, statins, bisphosphonates, cinacalcet and sevelamer (to control parathyroid hormone levels and subsequently calcium-phosphate balance).[3,8] In selected cases, tissue plasminogen activator therapy to address the thrombotic component of the disease may be beneficial. To our knowledge, there has not been any reported differences in presentation, treatment, or outcomes between NUC and calciphylaxis associated with ESRD, although there still remains little literature on NUC. The most recommended strategy is to combine treatments to address both vascular calcification and thrombosis.

Patient information to promote better self-care and lower risk of re-infections from calciphylaxis is largely supportive wound care: keeping wounds clean and dry; monitoring for signs of infection such as redness, warmth, and drainage; and overall keeping a healthy lifestyle. If patients are undergoing sodium thiosulfate infusions, consistent PICC line care is crucial to minimize line complications and treatment delay. As mentioned prior, risk factors include obesity, smoking, liver disease, cancer, kidney disease, or medication usage that could precipitate abnormal calcium-phosphate metabolism including glucocorticoids.

This case underscores the importance of recognizing non-uremic calciphylaxis in patients presenting with painful ulcerative skin lesions and risk factors. As family medicine providers, we are regularly asked to evaluate a wide variety of ulcers and skin findings. It is important to distinguish whether to have NUC on the differential given a patient's history, progression of ulcers, and risk factors. Early biopsy is essential for diagnosis, as clinical features can mimic numerous other ulcerative dermatoses.[9] Multidisciplinary management—including prompt referral to dermatology for diagnostic biopsy, sodium thiosulfate therapy, wound care, hyperbaric oxygen therapy, and infection control—is required, though outcomes remain poor. Recovery is further complicated by poor quality of life as patients experience chronic pain, depression, poor nutrition, and insomnia.[2] Increased awareness and reporting of NUC cases are necessary to improve understanding of its pathophysiology and to guide future therapeutic strategies.

Submitted: October 04, 2025 CST. Accepted: November 05, 2025 CST. Published: December 22, 2025 CST.

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