SKIN

BRIEF ARTICLE

The Non-Healing Wound: An Early Clue to Calciphylaxis

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ABSTRACT

Calciphylaxis, also known as calcific uremic arteriolopathy (CUA), is a rare disease that presents as painful, necrotic lesions. While calciphylaxis is most commonly associated with renal insufficiency, calciphylaxis can occur in those without renal impairment. A case of non-uremic calciphylaxis occurring at a below-knee amputation site presenting as a single non-healing wound is provided; this presentation stands in stark contrast to the multiple, exquisitely painful lesions that are typical of calciphylaxis.

CASE REPORT

A 66-year-old female with a medical history of hypertension and diabetes presented to the hospital for a non-healing wound to the left lower extremity (**Figure 1**). Biopsy results at that time demonstrated nonspecific findings of ulceration with diffuse and chronic inflammation. Infliximab and steroids were initiated for presumed pyoderma gangrenosum. Left lower extremity x-ray noted calcification of posterior and anterior superficial vessels. Patient underwent sharp excisional debridement of the left lower extremity at which time repeat biopsies were obtained and showed osteomyelitis. Patient ultimately underwent below knee amputation (BKA).

Patient later returned to the hospital for wound infection of her BKA. The pain was worsened by falling on the wound which had dehisced. Dermatology was consulted by the primary team, and given the lack of improvement with systemic steroids, dry eschar formation on the lower aspect of the wound, and lack of pathergy after debridement performed during the initial hospitalization, pyoderma gangrenosum was not favored (**Figure 2**). Alternative diagnoses included arterial or venous ulceration, calciphylaxis, and Martorell hypertensive ulceration.

Biopsies from her BKA wound were obtained and demonstrated calciphylaxis (**Figure 3**). Because the patient did not have end-stage renal disease with a creatinine of 0.46, it was determined that the patient had non-uremic calciphylaxis. Treatment was initiated with 50 mL injections of sodium thiosulfate twice a week.

DISCUSSION

The diagnosis of non-uremic calciphylaxis (NUC) was made with a biopsy from a BKA stump that demonstrated calciphylaxis. The

Figure 1. Left lower extremity wound demonstrating sharply demarcated ulceration, significant pus, eschar formation, and tendon exposure.

Figure 2. Below knee amputation wound with erythematous border, pus formation, protruding bone, and dry eschar formation.

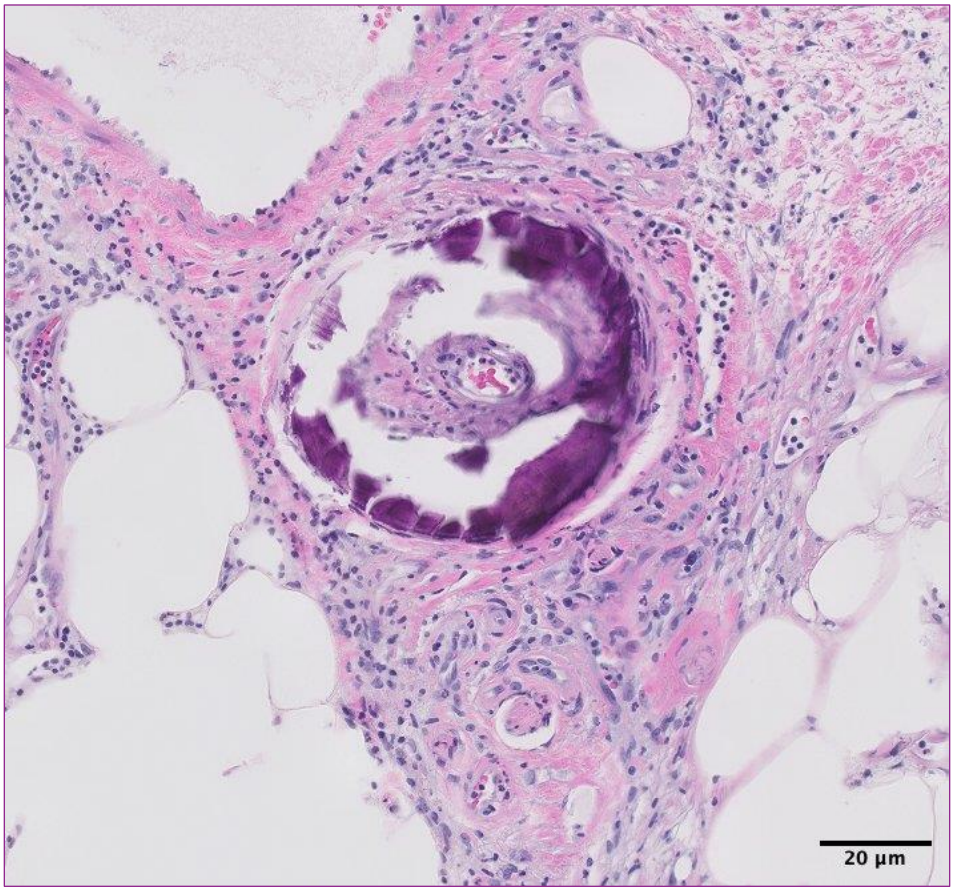

Figure 3. Biopsy from below knee amputation site demonstrating calcium deposition within the wall of the vessel, typical of calciphylaxis. Hematoxylin and eosin stain, magnification 400x.

patient had three biopsies taken at various times for identification of the cause of the wound. Only after the patient had a BKA did a biopsy come back positive for calciphylaxis. One explanation for the previously negative biopsies could be that the calciphylaxis was diagnosed at an earlier stage than normally encountered and thus poor wound healing was the primary manifestation. Typical calciphylaxis presents as multiple, painful ulcerations. One explanation for why calciphylaxis was confined to the BKA site could be that amputation prophylactically curtailed the development of numerous ulcerations.

This case highlights the importance of including calciphylaxis within the differential of a non-healing wound, even in patients without renal disease, due to its rapid progression and high mortality rate. The 1-year mortality rate for NUC ranges between 25 to 40 percent, whereas for uremic calciphylaxis it is 45 to 80 percent.[1] The high mortality associated with calciphylaxis may be related to the diagnosis being made late in the course of the disease. Diagnosis requires a high degree of suspicion to exclude differential diagnoses such as pyoderma gangrenosum, necrotizing vasculitis, and cholesterol embolism.

The patient had evidence suggestive of a calcification process well before biopsy-proven calciphylaxis was made with a left lower extremity x-ray scan demonstrating calcification of vessels, but due to the clinical appearance at that time, the patient continued to receive high-dose steroids for pyoderma gangrenosum. It is possible that

prolonged steroid use played a role in the development of calciphylaxis, as steroids are a risk factor for calciphylaxis.[1] If biopsy results are inconclusive, radiographic imaging should be obtained before calciphylaxis is ruled out, as imaging has a resolution comparable to histopathology and can visualize microvascular complications which are present before cutaneous manifestations appear.[2]

The patient had a single lesion with biopsy-proven calciphylaxis which is of particular importance, as only one case of non-uremic calciphylaxis localized to a single site has been described in the literature in which a patient had NUC at the distal tip of the penis.[2] A case of NUC was described in a patient who had calciphylaxis manifesting as gangrene of the bilateral toes and left-hand digits, all located most distally.[3] Likewise, our patient's calciphylaxis was localized to the most distal part of an extremity.

Not as much is known about the therapeutic options for non-uremic calciphylaxis in comparison to uremic calciphylaxis. One case describes non-uremic calciphylaxis that positively responded to intravenous pamidronate administered over three months in the outpatient setting, with skin lesions demonstrating regression over five months.[1] A treatment commonly utilized for uremic calciphylaxis is sodium thiosulfate (STS). STS for treatment of NUC is an off-label indication, as there are currently no FDA approved treatments for calciphylaxis.[3] Studies have shown that successful management of NUC can be achieved using intravenous STS, pain control, and wound hygiene as exemplified in a case study that examined three patients with NUC.[4] These results stand in stark comparison to a meta-analysis that examined results of STS treatment in patients with uremic calciphylaxis. This study concluded that there was no association between intravenous STS and skin lesion improvement or survival benefits compared with non-STS groups.[5] A meta-analysis comparing the efficacy of STS in cases of NUC has not been done. Due to the off-label use of STS for NUC, it is difficult to say whether earlier identification and treatment would have saved our patient's leg. Without biopsy-proven calciphylaxis, initiating STS based on suspicion only would be a medical dilemma. Diagnosis of calciphylaxis requires a high degree of suspicion due to its many appearance presentations, high mortality, and numerous risk factors that are common to patients both with and without end-stage renal disease. Studies have shown varying reports of effectiveness in using STS to treat calciphylaxis; these results may be due to the time treatment was initiated and when the diagnosis was made. Despite prompt wound care as well as infectious and pain control, mortality remains high for both uremic and non-uremic calciphylaxis and more efficient therapeutic measures and evidence-based recommendations are needed.

Conflict of Interest Disclosures: Robert T. Brodell is a principal investigator for clinical trials (Novartis and Sanofi), the Corevitas psoriasis biologic registry and owns stock in Veradermics, Inc. Carlie Reeves, MS4 has no conflicts of interest.

Funding: None

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