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A 71-Year-Old Female with Myocardial Infarction and Long-Standing Ulcers on the Thigh

Eduardo De Flammineis a  Patrick M. Mulvaney b  Stefan Kraft c  
Martin C. Mihm Jr. e  Shinjita Das d  Daniela Kroshinsky d

a Department of Dermatology, San Raffaele Hospital, Milan, Italy; b Harvard Combined Dermatology Residency Program, Departments of c Pathology and d Dermatology, Massachusetts General Hospital, and e Department of Dermatology and Pathology, Brigham and Women’s Hospital, Boston, MA, USA

Keywords
Calciphylaxis · Nonuremic calciphylaxis

Abstract
Calciphylaxis is most commonly encountered in patients with end-stage renal disease; however, it is increasingly observed in nonuremic patients as well. It is important to consider and diagnose nonuremic calciphylaxis early, as prompt treatment and mitigation of associated risk factors is essential to improve long-term outcomes for these patients. Here, we present the case of a 71-year-old woman with atrial fibrillation on warfarin, but without renal disease, who presented with two long-standing ulcers on her thigh and was diagnosed with the aid of biopsy with calciphylaxis. We review the existing literature on the subject and offer this case as a representative report of a clinicopathologic correlation for this disorder.
vessel disease; however, due to the complex anatomy, she was deemed a poor candidate for repeat intervention and was managed medically.

The dermatology inpatient service was consulted when the primary team incidentally noted two ulcers on the patient’s left thigh. The patient explained that the lesions had developed several years prior without any preceding trauma and had not recently changed. She denied having pain, tenderness, or drainage.

Examination of the left thigh revealed two nontender, pink, indurated plaques with central shallow ulcerations measuring 1.0 × 2.0 and 1.0 × 0.5 cm (Fig. 1). The ulcers had fibrinous debris at the base but no eschar, and there was no surrounding retiform purpura. Mild edema of the legs extended up to the thighs, and there was background chronic stasis dermatitis on the pretibiae. A skin biopsy of the skin and subcutaneous fat was performed for evaluation.

**Diagnosis and Clinical Course**

The histologic examination of the skin lesions revealed dermal and subcutaneous small vessel calcification, subintimal fibrosis, stasis changes, mixed inflammation, focal subcutaneous necrosis with vascular thrombosis, and interstitial and focal vascular calcium deposition (Fig. 2a, b). A von Kossa stain showed marked interstitial calcium deposition and focal calcium deposition in the walls of small subcutaneous vessels, consistent with a diagnosis of calciphylaxis (Fig. 2c). No organisms were seen on PAS and Gram stains. The patient’s serum calcium (8.7 mg/dL; normal 8.5–10.5), creatinine (0.89 mg/dL; normal 0.6–1.5), and albumin (3.8 g/dL; normal 3.3–5.0) levels were all within normal limits. The parathyroid hormone level was slightly elevated (70 pg/mL; normal 10–60).

A bone scan was performed and showed diffuse, nonfocal radiotracer activity involving the soft tissue of both lower thighs and legs. Wound care was started with honey-based gel followed by Mepilex® dressings. For anticoagulation, she was transitioned from warfarin to apixaban. Treatment also included compression stockings for edema management along with emollients and mid-potency topical steroids for stasis dermatitis. The ulcers healed without further consequence.

**Discussion**

Calciphylaxis, or calcific uremic arteriolopathy, is a rare disease that most frequently affects patients on dialysis for end-stage renal disease and is associated with high morbidity and mortality. The 1-year mortality rate for calciphylaxis in general is estimated at 45–80%, with sepsis being the leading cause of death [1]. Despite the classic association with renal disease, calciphylaxis is increasingly observed in patients with preserved renal function.
There are numerous risk factors and associated comorbidities for calciphylaxis. Genetic predispositions include Caucasian race [2] and female sex [3]. Comorbidities include obesity, diabetes mellitus [3], liver disease [2], antiphospholipid syndrome [4], autoimmune conditions [5], thrombophilic disorders, and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) [6]. Calciphylaxis can be associated with laboratory abnormalities, including elevated calcium-phosphorus product [2], alkaline phosphatase [7], parathyroid hormone [6], and erythrocyte sedimentation rate [2], as well as decreased levels of albumin [8] and protein C and S [9, 10]. Calciphylaxis has also been associated with administration of systemic corticosteroids [2], vitamin K antagonists (warfarin), teriparatide [6], vitamin D [2], calcium supplements [6], calcium-based binders [11], and iron [12]. In addition, nonuremic calciphylaxis has been reported in patients with rapid weight loss [13] and vitamin D deficiency [14].

The exact pathogenesis of calciphylaxis is not fully understood. In 1962, Selye and colleagues proposed a two-hit model for calciphylaxis, whereby initial exposure to a “sensitizer” (e.g., elevated calcium-phosphate product) followed by exposure to a “challenger” triggers the disease. This process results in medial vessel calcification, vascular endothelial injury, cutaneous arteriolar narrowing, and, finally, thrombosis resulting in tissue infarction [15–17]. Given the presence of calciphylaxis in patients without clinically detectable altered calcium-phosphate metabolism, the common histopathologic pattern of tissue injury in both calciphylaxis and nonuremic calciphylaxis is likely caused by a variety of heterogeneous insults [17]. Derangements of receptor activator of NF-κB (RANK), which is involved in regulation of extraskeletal mineralization, has been noted as a final common pathway in uremic and nonuremic calciphylaxis [18]. Some of the factors that predispose to nonuremic calciphylaxis (parathyroid hormone, corticosteroids, and liver disease) are known to play a role in RANK activity [19–21]. Another known contributing factor is the use of warfarin, which may act by inhibiting vitamin K-dependent carboxylation of the calcification inhibitor matrix Gla protein [22]. In case of weight loss-related calciphylaxis, increased levels of systemic matrix metalloproteinases may act as triggers [23].

Clinically, calciphylaxis is characterized by areas of excruciatingly painful ischemic skin necrosis. Lesions commonly develop in areas with the greatest adiposity, including the thighs, abdomen, breast, and buttocks [24]. Early ischemic changes may present as painful erythematous patches mimicking cellulitis or livedo reticularis owing to alterations in blood flow [25, 26]. Characteristic lesions are painful retiform patches with underlying subcutaneous nodules, which often extend beyond the edge of the apparent superficial lesion [16, 26]. Progression to ulcers with eschars occurs once vascular thrombosis has advanced [16]. The ulcers can become superinfected [24], and gangrene may ensue [26]. Ischemic myopathy, presenting as painful proximal muscle weakness, is a less frequent manifestation that can occur without skin necrosis [27]. Vascular calcifications in the brain, lungs, heart, pancreas,
intestines, eyes, tongue, penis, and mesentery have been observed among calciphylaxis patients [1, 8]. Nonuremic calciphylaxis presents with skin lesions of similar morphology and distribution to those of uremic calciphylaxis [1].

Histologic examination of the skin lesions reveals dermal arteriolar calcification, subintimal fibrosis, and thrombotic occlusion [1, 2, 28, 29]. Primary vasculitis is absent. Calcification most commonly involves the medial layer of small arteries and arterioles; however, involvement of the intimal layer and the interstitium of subcutaneous adipose tissue has also been reported [30]. Detection of microcalcification often requires special stains, such as von Kossa or alizarin red [31].

Treatment for calciphylaxis is challenging, and varying degrees of success have been reported with the available treatments [32]. Appropriate care aims to address the underlying process, metabolic derangements, risk factors, wound healing, and pain management, and, given the complexity of needs, is best served by multidisciplinary teams [1]. Nonuremic calciphylaxis treatment approaches are modeled after therapies for calciphylaxis in patients with renal disease [33] with intravenous sodium thiosulfate (STS) treatment as the most common first-line therapy for both types of calciphylaxis [1, 34–42]. STS was originally believed to reverse the disease via calcium-chelating properties [43], but its mechanism of action is still not precisely understood. Recent in vitro investigations have shown that the effects of thiosulfate may not be explained by actions on ionized calcium, calcium phosphate solubility, pH, oxidative stress, or hydroxyapatite formation [44]. Studies on the actions of STS have noted direct vascular calcification inhibition, reduction in oxidative stress, and vasodilatory properties [44–46]. Other therapeutic options include intralesional STS, hyperbaric oxygen [1], bisphosphonates [47], cinacalcet [48, 49], tissue plasminogen activator [50], sterile maggot therapy [51], vitamin K supplementation [52], low-density lipoprotein apheresis [53], and kidney transplantation [54]. Case reports suggest a benefit from treating abnormalities of calcium and phosphorus [55–58] and elevated parathyroid hormone [49, 59, 60]. If possible, all medications that may contribute to calciphylaxis or decrease wound healing should be stopped, and known aggravating conditions should be addressed [33, 61]. Aggressive wound care and pain control are critical. Wound care should be administered and adjusted according to the daily status of the ulcers. Management includes a combination of exudate control along with proper selection of wound dressing and chemical debridement agents [2, 62]. Daily gentle enzymatic debridement of eschars [34] and atraumatic resection of necrotic skin [48] can facilitate wound healing. Surgical debridement can be performed for infected wounds but should always be done judiciously, since local tissue injury can aggravate calciphylaxis [1, 34].

Our patient presented with erythematous ulcerated plaques on her left thigh that were consistent with calciphylaxis by pathologic examination. Her risk factors for calciphylaxis included female sex, obesity, diabetes, supplemental vitamin D use, and atrial fibrillation necessitating warfarin [17]. Atypical features included the lack of eschar, cutaneous pain, retiform and/or stellate shape, and hemodialysis requirement, as well as normal levels of calcium, albumin, and creatinine. Given the improvement of the ulcers with risk factor modification and good wound care, STS therapy was deferred.

**Statement of Ethics**

The manuscript was prepared in compliance with all ethical and confidentiality guidelines and principles.
Disclosure Statement

The authors have no conflicts of interest to disclose.

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