Nonuremic Calciphylaxis Triggered by Rapid Weight Loss and Hypotension

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PRACTICE **POINTS**

- Calciphylaxis is a potentially fatal disease caused by metastatic calcification of cutaneous small- and medium-sized blood vessels leading to ischemia and necrosis.
- Calciphylaxis most commonly is seen in patients with renal disease requiring dialysis, but it also may be triggered by nonuremic causes in patients with known risk factors for calciphylaxis.
- Risk factors for calciphylaxis include female gender, white race, obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, underlying malignancy, protein C or S deficiency, corticosteroid use, warfarin use, diabetes, iron or albumin infusions, and rapid weight loss.
- The term *calcific uremic arteriolopathy* should be disregarded, as nonuremic causes are being reported with increased frequency in the literature.

Calciphylaxis is a potentially fatal disease caused by metastatic calcification of the small- and medium-sized blood vessels of the dermis and subcutis. It most commonly is seen in patients with renal disease requiring dialysis, but it also may be triggered by nonuremic causes in patients with known risk factors for calciphylaxis. We report a case of nonuremic calciphylaxis (NUC) occurring in the setting of multiple risk factors, including chronic corticosteroid use, obesity, rapid weight loss, and hypotension. A review of the literature also is provided with an in-depth discussion of the known risk factors and triggers of NUC.

Cutis. 2020;105:E11-E14.

Calciphylaxis, otherwise known as calcific uremic arteriolopathy, is characterized by calcification of the tunica media of the small- to medium-sized blood vessels of the dermis and subcutis, leading to ischemia and necrosis.[1] It is a deadly disease with a 1-year mortality rate of more than 50%.[2] End-stage renal disease (ESRD) is the most common risk factor for calciphylaxis, with a prevalence of 1% to 4% of hemodialysis patients with calciphylaxis in the United States.[2-5] However, nonuremic calciphylaxis (NUC) has been increasingly reported in the literature and has risk factors other than ESRD, including but not limited to obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, and underlying malignancy.[3,6-9] Triggers for calciphylaxis in at-risk patients include use of corticosteroids or warfarin, iron or albumin infusions, and rapid weight loss.[3,6,9-11] We report an unusual case of NUC that most likely was triggered by rapid weight loss and hypotension in a patient with multiple risk factors for calciphylaxis.

Case Report

A 75-year-old white woman with history of morbid obesity (body mass index, 40 kg/m^2), unexplained weight loss of 70 lb over the last year, and polymyalgia rheumatica requiring chronic prednisone therapy presented with painful lesions on the thighs, buttocks, and right shoulder of 4 months' duration. She had multiple hospital admissions preceding the onset of lesions for severe infections resulting in sepsis with hypotension, including *Enterococcus faecalis* endocarditis, extended-spectrum beta-lactamase bacteremia, and *Pseudomonas aeruginosa* pneumonia. Physical examination revealed large well-demarcated ulcers and necrotic eschars with surrounding

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The authors report no conflict of interest.

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violaceous induration and stellate erythema on the anterior, medial, and posterior thighs and buttocks that were exquisitely tender (Figures 1 and 2).

Notable laboratory results included hypoalbuminemia (1.3 g/dL [reference range, 3.5–5.0 g/dL]) with normal renal function, a corrected calcium level of 9.7 mg/dL (reference range, 8.2–10.2 mg/dL), a serum phosphorus level of 3.5 mg/dL (reference range, 2.3–4.7 mg/dL), a calcium-phosphate product of 27.3 mg^2/dL^2 (reference range, <55 mg^2/dL^2), and a parathyroid hormone level of 49.3 pg/mL (reference range, 10–65 pg/mL). Antinuclear antibodies were negative. A hypercoagulability evaluation showed normal protein C and S levels, negative lupus anticoagulant, and negative anticardiolipin antibodies.

Telescoping punch biopsies of the indurated borders of the eschars showed prominent calcification of the small- and medium-sized vessels in the mid and deep dermis, intravascular thrombi, and necrosis of the epidermis and subcutaneous fat consistent with calciphylaxis (Figure 3).

After the diagnosis of calciphylaxis was made, the patient was treated with intravenous sodium thiosulfate 25 mg 3 times weekly and alendronate 70 mg weekly. Daily arterial blood gas studies did not detect metabolic acidosis during the patient's sodium thiosulfate therapy. The wounds were debrided, and we attempted to slowly taper the patient off the oral prednisone. Unfortunately, her condition slowly deteriorated secondary to sepsis, resulting in septic shock. The patient died 3 weeks after the diagnosis of calciphylaxis was made. At the time of diagnosis, the patient had a poor prognosis and notable risk for sepsis due to the large eschars on the thighs and abdomen as well as her relative immunosuppression due to chronic prednisone use.

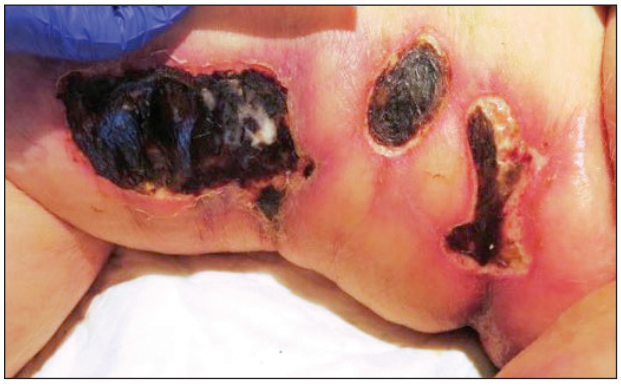


FIGURE 1. Necrotic eschars surrounded by erythema and livedo reticularis on the right medial thigh.

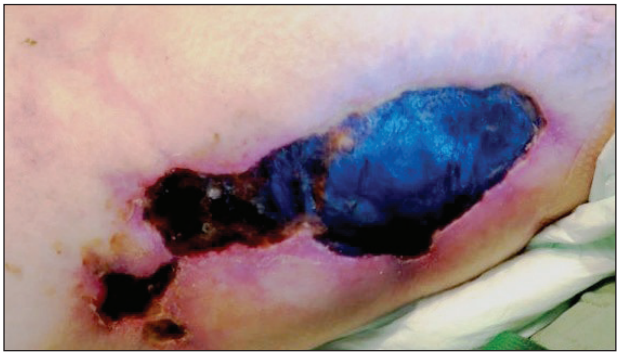
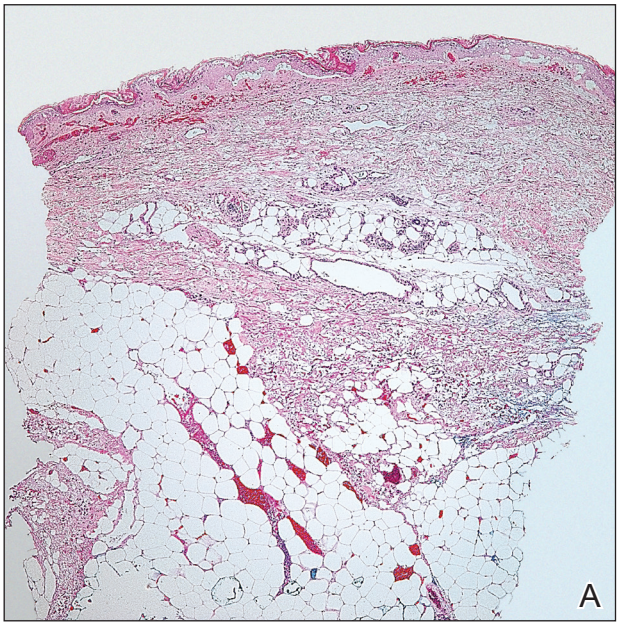


FIGURE 2. Eschar with a rolled erythematous border on the left lateral thigh.

Comment

Background on Calciphylaxis—Calciphylaxis is a rare but deadly disease that affects both ESRD patients receiving



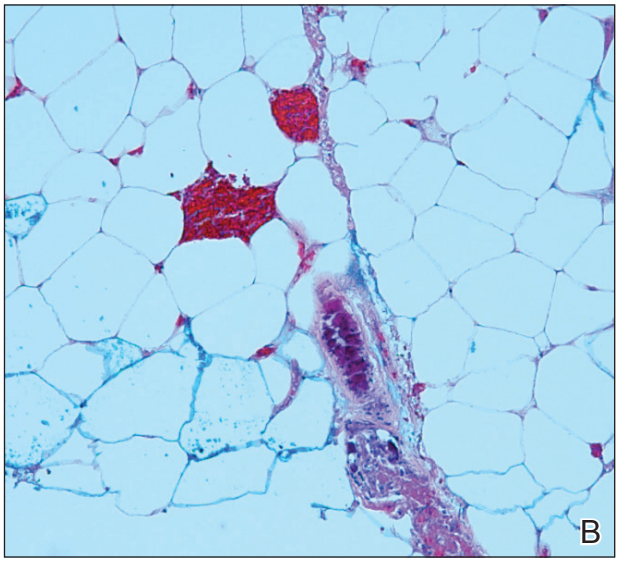


FIGURE 3. A, Epidermal necrosis, small- and medium-sized vessel calcification and thrombus, and underlying septal panniculitis with fat necrosis (H&E, original magnification ×100). B, High-power magnification of small vessel calcification in the subcutaneous fat (H&E, original magnification ×400).

dialysis and patients without ESRD who have known risk factors for calciphylaxis, including female gender, white race, obesity, alcoholic liver disease, primary hyperparathyroidism, connective tissue disease, underlying malignancy, protein C or S deficiency, corticosteroid use, warfarin use, diabetes, iron or albumin infusions, and rapid weight loss.[3,6-9,11] Although the molecular pathogenesis of calciphylaxis is not completely understood, it is believed to be caused by local deposition of calcium in the tunica media of small- to medium-sized arterioles and venules in the skin.[12] This deposition leads to intimal proliferation and progressive narrowing of the vessels with resultant thrombosis, ischemia, and necrosis. The cutaneous manifestations and histopathology of calciphylaxis classically follow its pathogenesis. Calciphylaxis typically presents with livedo reticularis as vessels narrow and then progresses to purpura, bullae, necrosis, and eschar formation with the onset of acute thrombosis and ischemia. Histopathology is characterized by small- and medium-sized vessel calcification and thrombus, dermal necrosis, and septal panniculitis, though the histology can be highly variable.[12] Unfortunately, the already poor prognosis for calciphylaxis worsens when lesions become either ulcerative or present on the proximal extremities and trunk.[4,13] Sepsis is the leading cause of death in calciphylaxis patients, affecting more than 50% of patients.[2,3,14] The differential diagnoses for calciphylactic-appearing lesions include warfarin-induced skin necrosis, disseminated intravascular coagulation, pyoderma gangrenosum, cholesterol emboli, and various vasculitides and coagulopathies.

Risk Factors—Our case demonstrates the importance of risk factor minimization, trigger avoidance, and early intervention due to the high mortality rate of calciphylaxis. Selye et al[15] coined the term *calciphylaxis* in 1961 based on experiments that induced calciphylaxis in rat models. Their research concluded that there were certain sensitizers (ie, risk factors) that predisposed patients to medial calcium deposition in blood vessels and other challengers (ie, triggers) that acted as inciting events to calcium deposition. Our patient presented with multiple known risk factors for calciphylaxis, including obesity (body mass index, 40 kg/m^2), female gender, white race, hypoalbuminemia, and chronic corticosteroid use.[16] In the presence of a milieu of risk factors, the patient's rapid weight loss and episodes of hypotension likely were triggers for calciphylaxis.

Other case reports in the literature have suggested weight loss as a trigger for NUC. One morbidly obese patient with inactive rheumatoid arthritis had onset of calciphylaxis lesions after unintentional weight loss of approximately 50% body weight in 1 year[17]; however, the weight loss does not have to be drastic to trigger calciphylaxis. Another study of 16 patients with uremic calciphylaxis found that 7 of 16 (44%) patients lost 10 to 50 kg in the 6 months prior to calciphylaxis onset.[14] One proposed mechanism by Munavalli et al[10] is that elevated levels of matrix metalloproteinases during catabolic weight loss states enhance the deposition of calcium into elastic fibers of small vessels. The authors found elevated serum levels of matrix metalloproteinases in their patients with NUC induced by rapid weight loss.[10]

A meta-analysis by Nigwekar et al[3] found a history of prior corticosteroid use in 61% (22/36) of NUC cases reviewed. However, it is unclear whether it is the use of corticosteroids or chronic inflammation that is implicated in NUC pathogenesis. Chronic inflammation causes downregulation of anticalcification signaling pathways.[18-20] The role of 2 vascular calcification inhibitors has been evaluated in the pathogenesis of calciphylaxis: fetuin-A and matrix gla protein (MGP).[21] The activity of these proteins is decreased not only in calciphylaxis but also in other inflammatory states and chronic renal failure.[18-20] One study found lower fetuin-A levels in 312 hemodialysis patients compared to healthy controls and an association between low fetuin-A levels and increased C-reactive protein levels.[22] Reduced fetuin-A and MGP levels may be the result of several calciphylaxis risk factors. Warfarin is believed to trigger calciphylaxis via inhibition of gamma-carboxylation of MGP, which is necessary for its anticalcification activity.[23] Hypoalbuminemia and alcoholic liver disease also are risk factors that may be explained by the fact that fetuin-A is synthesized in the liver.[24] Therefore, liver disease results in decreased production of fetuin-A that is permissive to vascular calcification in calciphylaxis patients.

There have been other reports of calciphylaxis patients who were originally hospitalized due to hypotension, which may serve as a trigger for calciphylaxis onset.[25] Because calciphylaxis lesions are more likely to occur in the fatty areas of the abdomen and proximal thighs where blood flow is slower, hypotension likely accentuates the slowing of blood flow and subsequent blood vessel calcification. This theory is supported by studies showing that established calciphylactic lesions worsen more quickly in the presence of systemic hypotension.[26] One patient with ESRD and calciphylaxis of the breasts had consistent systolic blood pressure readings in the high 60s to low 70s between dialysis sessions.[27] Due to this association, we recommend that patients with calciphylaxis have close blood pressure monitoring to aid in preventing disease progression.[28]

Management—Calciphylaxis treatment has not yet been standardized, as it is an uncommon disease whose pathogenesis is not fully understood. Current management strategies aim to normalize metabolic abnormalities such as hypercalcemia if they are present and remove inciting agents such as warfarin and corticosteroids.[29] Other medical treatments that have been successfully used include sodium thiosulfate, oral steroids, and adjunctive bisphosphonates.[29-31] Sodium thiosulfate is known to cause metabolic acidosis by generating thiosulfuric acid in vivo in patients with or without renal disease; therefore, patients on sodium thiosulfate therapy

should be monitored for development of metabolic acidosis and treated with oral sodium bicarbonate or dialysis as needed.[30,32] Wound care also is an important element of calciphylaxis treatment; however, the debridement of wounds is controversial. Some argue that dry intact eschars serve to protect against sepsis, which is the leading cause of death in calciphylaxis.[2,14,33] In contrast, a retrospective study of 63 calciphylaxis patients found a 1-year survival rate of 61.6% in 17 patients receiving wound debridement vs 27.4% in 46 patients who did not.[2] The current consensus is that debridement should be considered on a case-by-case basis, factoring in the presence of wound infection, size of wounds, stability of eschars, and treatment goals of the patient.[34] Future studies should be aimed at this issue, with special focus on how these factors and the decision to debride or not impact patient outcomes.

Conclusion

Calciphylaxis is a potentially fatal disease that impacts both patients with ESRD and those with nonuremic risk factors. The term *calcific uremic arteriolopathy* should be disregarded, as nonuremic causes are being reported with increased frequency in the literature. In such cases, patients often have multiple risk factors, including obesity, primary hyperparathyroidism, alcoholic liver disease, and underlying malignancy, among others. Certain triggers for onset of calciphylaxis should be avoided in at-risk patients, including the use of corticosteroids or warfarin; iron and albumin infusions; hypotension; and rapid weight loss. Our fatal case of NUC is a reminder to dermatologists treating at-risk patients to avoid these triggers and to keep calciphylaxis in the differential diagnosis when encountering early lesions such as livedo reticularis, as progression of these lesions has a 1-year mortality rate of more than 50% with the therapies being utilized at this time.

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