

An Unusual Presentation of Calciphylaxis

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PRACTICE POINTS

- Calciphylaxis is a rare microvascular occlusion syndrome characterized by cutaneous ischemia and necrosis secondary to calcification.
- Clinically, lesions present with severely painful, violaceous, retiform patches and plaques, and less commonly bullae that progress to necrotic ulcers on the buttocks, legs, or abdomen, which is most often associated with end-stage renal disease and hyperparathyroidism.
- The diagnosis is made through deep wedge or excisional biopsy and shows calcification of medium-sized vessels in the deep dermis and subcutaneous fat. Treatment requires a multidisciplinary approach, but morbidity and mortality remain high.

To the Editor:

Calciphylaxis (also known as calcific uremic arteriopathy and calcifying panniculitis) is a rare vasculopathy affecting the small vessels.¹ It is characterized by cutaneous ischemia and necrosis secondary to calcification. It is most commonly seen in patients with end-stage renal disease (ESRD) and hyperparathyroidism.¹⁻³ Histopathologic features that are consistent with the diagnosis of calciphylaxis include calcification of medium-sized vessels in the deep dermis or subcutaneous fat as well as smaller distal vessels that supply the papillary dermis and epidermis.^{4,5} Although it commonly presents as well-demarcated, painful, purplish lesions that evolve into necrotic eschars,

calciphylaxis rarely can present with hemorrhagic or serous bullous lesions followed by ulceration, as was seen in our patient.^{1,5,6} We report this uncommon presentation to highlight the variety in clinical appearance of calciphylaxis and the importance of early diagnosis.

A 43-year-old woman presented to the emergency department for evaluation of chest and abdominal pain that began 1 day prior to presentation. She had a history of systemic lupus erythematosus and ESRD secondary to poststreptococcal glomerulonephritis and was currently on peritoneal dialysis. The patient was admitted for peritonitis and treated with broad-spectrum antibiotics. At the time of admission, the patient also was noted to have several painful bullae on the legs. Her medical history also was remarkable for cerebral infarction, fibromyalgia, cerebral artery occlusion with cerebral infarction, sciatica, hyperlipidemia, deep vein thrombosis, and seizures. She had no history of herpes simplex virus. Surgical history was remarkable for tubal ligation, nephrectomy and kidney transplant, parathyroidectomy, and cholecystectomy. The patient's medications included sevelamer carbonate, prednisone, epogen, calcium carbonate, esomeprazole, ondansetron, topical gentamicin, and atorvastatin.

Skin examination was performed by the inpatient dermatology service and revealed several tense, 1- to 5-cm, nonhemorrhagic bullae on the thighs and lower legs, some that had ruptured. The lesions were notably tender to palpation. No surrounding erythema, ecchymosis, or warmth was appreciated. The Nikolsky sign was negative. The patient also was noted to have at least grade 2 to 3+ pitting edema of the bilateral legs. The oral and conjunctival mucosae were unremarkable.

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Antinuclear antibody, double-stranded DNA, and anti-Smith antibody levels were negative. A punch biopsy of the left lateral thigh revealed intraepidermal vesicular dermatitis with dermal edema suggestive of edema bullae and direct immunofluorescence was negative for immune complex and complement deposition.

Conservative therapy with wound care was recommended. The patient continued to report persistent severe skin pain and developed a subcutaneous nodule on the right inner thigh 1 week later, prompting a second biopsy. Results of the excisional biopsy were nondiagnostic but were suggestive of calciphylaxis, revealing subepidermal bullae with epidermal necrosis, a scant perivascular lymphocytic infiltrate, and extravasated erythrocytes. No evidence of calcification was seen within the vessels. The patient was then started on sodium thiosulfate with hemodialysis for treatment of presumed calciphylaxis.

Despite meticulous wound care and treatment with sodium thiosulfate, the patient developed ulcerations with necrotic eschars on the bilateral buttocks, hips, and thighs 1 month later (Figure 1). She subsequently worsened over the next few weeks. She developed sepsis and was transferred to the intensive care unit. A third biopsy was performed, finally confirming the diagnosis of calciphylaxis. Histopathology revealed small blood vessels with basophilic granular deposits in the walls consistent with calcium in the subcutaneous tissue (highlighted with the von Kossa stain), as well as thrombi in the lumens of some vessels; early fat necrosis; focal epidermal necrosis with underlying congested blood vessels with deposits in their walls; a perivascular infiltrate predominately of lymphocytes and neutrophils with scattered nuclear dust; and thick, hyalinized, closely crowded collagen bundles in the reticular dermis and in a widened subcutaneous septum (Figures 2 and 3).

Supportive care and pain control were continued, but the overall prognosis was determined to be very poor, and the patient eventually was discharged to hospice and died.

Although calciphylaxis is commonly seen in patients with ESRD and hyperparathyroidism, patients without renal disease also may develop the condition.^{2,3} Prior epidemiologic studies have shown a prevalence of 1% in patients with chronic kidney disease and up to

4% in those receiving dialysis.²⁻⁵ The average age at presentation is 48 years.^{6,7} Although calciphylaxis has been noted to affect males and females equally, some studies have suggested a female predominance.⁵⁻⁸

The etiology of calciphylaxis is unknown, but ESRD requiring dialysis, primary or secondary hyperparathyroidism, obesity, diabetes mellitus, skin trauma, and/or a hypercoagulable state may put patients at increased risk for developing this disease.^{2,3} Other risk factors include systemic corticosteroids, liver disease, increased serum aluminum, and increased erythrocyte sedimentation rate. Although high calcium-phosphate product has been noted as a risk factor in prior studies, one retrospective study found that it does not reliably confirm or exclude a diagnosis of calciphylaxis.⁸

The pathogenesis of calciphylaxis is not well understood; however, some researchers suggest that an imbalance in calcium-phosphate homeostasis may lead to calciphylaxis; that is, elevated calcium and phosphate levels exceed their solubility and deposit in the walls of small- and medium-sized arteries, which consequently leads to ischemic necrosis and gangrene of the surrounding tissue.⁹

Clinically, calciphylaxis has an indolent onset and usually presents as well-demarcated, painful, purplish, mottled lesions that evolve into necrotic gray-black eschars and gangrene in adjacent tissues.^{1,5,6} The ischemic process may even extend to the muscle layer.⁵ Other common presentations include mild erythematous patches; livedo reticularis; painful nodules; necrotic ulcerating lesions; and more rarely flaccid, hemorrhagic, or serous bullous lesions followed by ulceration, as was seen in our patient.^{6,9,10} Lesions usually begin at sites of trauma and seem to be distributed symmetrically.^{5,6} The most commonly affected locations are the legs, specifically the medial thighs, as well as the abdomen and buttocks, but lesions also can be found at more distal sites such as the breasts, tongue, vulva, penis, fingers, and toes.^{5,6,10} The head and neck region rarely is affected. Although uncommon, calciphylaxis may affect other organs, including the lungs, stomach, kidneys, and adrenal glands.⁵ The accompanying systemic symptoms and findings may include muscle weakness, tenderness, or myositis with

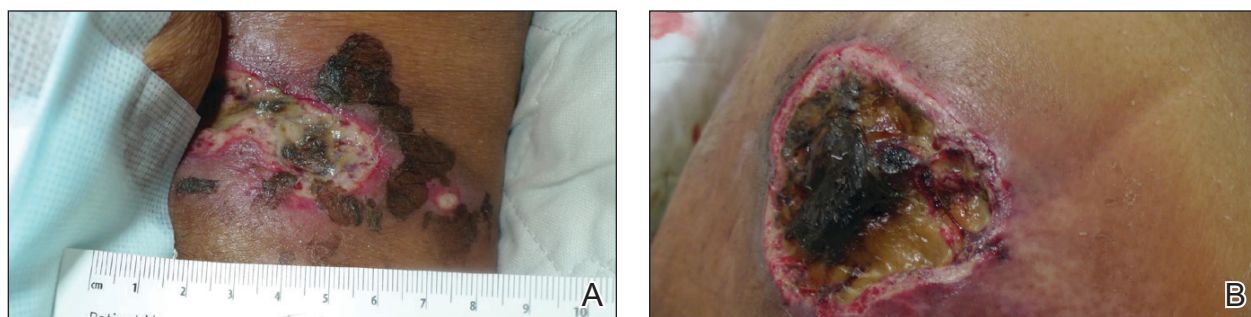


FIGURE 1. A and B, Rupture of nonhemorrhagic bullae on the left leg that evolved into ulcerations and necrotic eschars with surrounding purpura.

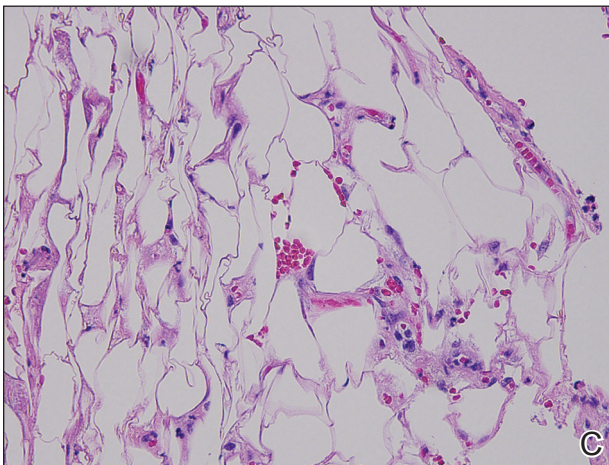
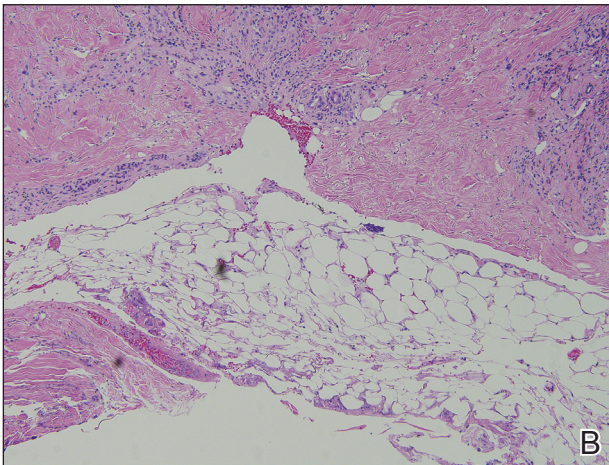
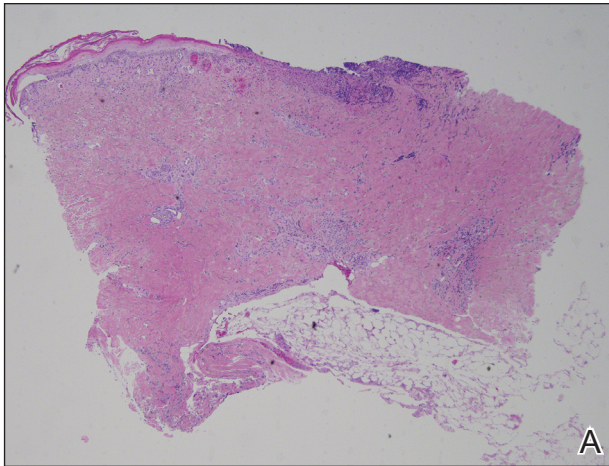


FIGURE 2. A–C, A biopsy from the left lateral thigh revealed focal epidermal necrosis with underlying congested blood vessels with fibrin and basophilic granular deposits in the walls. Some of the vessels had thrombi in the lumens. There was a perivascular infiltrate predominantly of lymphocytes and neutrophils with scattered nuclear dust. There was early fat necrosis. In the reticular dermis and in the widened subcutaneous septum, there were thick, hyalinized, closely crowded collagen bundles (H&E; original magnifications $\times 4$, $\times 10$, and $\times 40$, respectively).

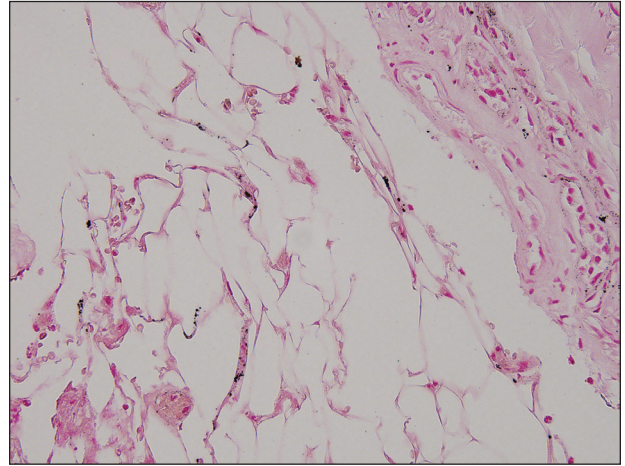


FIGURE 3. Calcium deposits were highlighted in the vessel walls (von Kossa, original magnification $\times 40$).

rhabdomyolysis; calcific cerebral embolism; dementia and infarction of the central nervous system; acute respiratory failure; heart disease; atrioventricular block; and calcification of the cardiac conduction system.⁶ Unlike other forms of peripheral vascular disease, distal pulses are present in calciphylaxis, as blood flow usually is preserved distal and deep to the areas of necrosis.^{5,6}

A careful history and thorough physical examination are important first steps in the diagnosis of this condition.^{2,10} Although there are no definitive laboratory tests, elevated serum calcium, phosphorous, and calcium-phosphate product levels, as well as parathyroid hormone level, may be suggestive of calciphylaxis.^{2,5} Leukocytosis may occur if an infection is present.⁵

The most accurate method to confirm the diagnosis is a deep incisional biopsy from an erythematous, slightly purpuric area adjacent to the necrotic lesion.^{2,10,11} The histopathologic features used to make the diagnosis include calcification of medium-sized vessels, particularly the intimal or medial layers, in the deep dermis and subcutaneous fat in addition to lobular capillaries of the subcutaneous fat.^{5,10} These vessels, including the smaller distal vessels that supply the papillary dermis and epidermis, also may be thrombosed due to calcification, leading to vascular occlusion and subsequently ischemic necrosis of the overlying epidermis.¹⁰ Other findings may include pseudoxanthoma elasticum changes, panniculitis, and subcutaneous fat necrosis.^{4,10}

The differential diagnosis for calciphylaxis includes peripheral vascular disease, vasculitis, juvenile dermatomyositis, proteins C and S deficiencies, cryofibrinogenemia, calcinosis cutis, and tumoral calcinosis.² Polyarteritis nodosa, Sjögren syndrome, atherosclerotic peripheral vascular disease, pyoderma gangrenosum, systemic lupus erythematosus, necrotizing fasciitis, septic embolism, and necrosis secondary to warfarin and heparin may mimic calciphylaxis.⁵

Treatment of calciphylaxis is multidimensional but primarily is supportive.^{6,11} Controlling calcium and phosphate levels and secondary hyperparathyroidism through diet and phosphate binders (eg, sevelamer hydrochloride) has been shown to be effective.⁶ Pamidronate, a bisphosphonate, inhibits arterial calcification in animal models and has been reported to treat calciphylaxis, resulting in marked pain reduction and ulcer healing.^{4,6} Cinacalcet, which functions as a calcimimetic, has been implicated in the treatment of calciphylaxis. It has been used to treat primary and secondary hyperparathyroidism and to normalize serum calcium levels; it also may be used as an alternative to parathyroidectomy.^{4,6} Intravenous administration of sodium thiosulfate, a potent antioxidant and chelator of calcium, has been helpful in reversing signs and symptoms of calciphylaxis.^{6,12} It also has been shown to effectively remove extra calcium during peritoneal dialysis.⁶ Parathyroidectomy has been useful in patients with markedly elevated parathyroid hormone levels, as it suppresses or eliminates the sensitizing agent causing hypercalcemia, elevated calcium-phosphate product, and hyperparathyroidism.^{1,2,6,13}

Wound care and prevention of sepsis are essential in the treatment of calciphylaxis. Management options include surgical debridement, hydrocolloid and biologic dressings, skin grafts, systemic antibiotics, oral pentoxifylline combined with maggot therapy, nutritional support, hyperbaric oxygen therapy, and revascularization and amputation when other interventions have failed. Pain control with analgesics and correction of thrombosis in the skin and blood vessels via anticoagulation therapy also are important complementary treatments.⁶

The clinical outcome of calciphylaxis is dependent on early diagnosis, antimicrobial therapy, and wound management,⁹ but overall, the prognosis usually is poor and has a high mortality rate. The most common causes of death are infection and sepsis.^{1,9} A study of 7 cases reported 100% mortality,¹⁴ but other studies have suggested a mortality rate of 60% to 80%.^{4,10} Female sex and obesity are poor prognostic indicators.² A better prognosis has been appreciated in cases in which lesions occur at distal sites (eg, lower legs, hands) compared to more proximal sites (eg, abdomen), where 25% and 75% mortalities have been noted, respectively.^{10,14,15} In one study, the overall mortality rate was 45% in patients with calciphylaxis at 1 year.⁶ The rate was 41% in patients

with plaques only and 67% in those who presented with ulceration. Patients who survive often experience a high degree of morbidity and prolonged hospitalization; these patients often are severely debilitated, especially in the case of limb amputation.⁶

Our report of calciphylaxis demonstrates the diversity in clinical presentation and emphasizes the importance of early and accurate diagnosis in reducing morbidity and mortality. In our case, the patient presented with skin pain and tense nonhemorrhagic bullae without underlying ecchymotic or erythematous lesions as the earliest sign of calciphylaxis. Physicians should have a high degree of suspicion in the setting of dialysis-dependent ESRD patients with bullae, extreme pain, and continuous decline. We hope that this case will help increase awareness of the varying presentations of this condition.

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