

Tender Nonhealing Lesion on the Leg

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A 50-year-old woman presented to our dermatology clinic with an exquisitely tender, nonhealing lesion on the left leg of 2 weeks' duration that began as a small red-purplish spot. She applied a triple antibiotic ointment and wrapped the area with gauze daily but reported that it continued to enlarge and darken in color before forming a "scab." She noted occasional seropurulent discharge and denied any trauma or new exposures to the area. She was seen at a local emergency department 3 days prior to presentation and was prescribed oral clindamycin for suspected cellulitis, but she denied any improvement with the initiation of antibiotics.

Her medical history was notable for obesity, depression, hypothyroidism, and liver disease secondary to alcohol use disorder. She reported that she drank a pint of vodka daily. Her medications included pantoprazole, spironolactone, bumetanide, citalopram, levothyroxine, naltrexone, tramadol, and a multivitamin. Physical examination revealed violaceous mottling with areas of superficial erythema and ulceration with necrotic eschars on the proximal left thigh that were extremely painful. A biopsy was obtained for confirmation of diagnosis, but the patient died before the results were returned.

WHAT'S YOUR DIAGNOSIS?

- calciphylaxis
- ecthyma gangrenosum
- Hughes syndrome
- idiopathic purpura fulminans
- necrotizing fasciitis

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The authors report no conflict of interest.

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doi:10.12788/cutis.0624

THE DIAGNOSIS: Calciophylaxis

Calciophylaxis is a rare life-threatening condition that most often is seen in patients with end-stage renal disease at a rate of 35 per 10,000 chronic dialysis patients.¹ It less commonly has been described in nonuremic patients. The exact incidence of nonuremic calciophylaxis is unknown, but multiple risk factors have been identified, such as alcoholic liver disease, primary hyperparathyroidism, connective tissue diseases, and underlying malignancies. Other less common risk factors include type 2 diabetes mellitus, hypercoagulable disorders, obesity, hypoalbuminemia, and warfarin/corticosteroid use.² However, most often no obvious triggers are identified.¹

Regardless of the etiology, calciophylaxis is characterized by the calcification of blood vessels and connective tissues, leading to vessel injury, intimal fibrosis, and thrombosis, followed by ischemic necrosis of the skin and soft tissue. It is postulated that microvascular calcification occurs as an active cell-mediated process that depends on the balance between the promoters and inhibitors of calcification.¹ In our patient, liver disease likely predisposed formation of calcification through the creation of an environment susceptible to vascular injury via decreased synthesis of proteins C and S.³ Synthesis of fetuin-A, a protein that acts as a circulating inhibitor of vascular ossification/calcification, also is decreased in calcification. Another inhibitor of calcification, matrix Gla protein, is unable to undergo activation through vitamin K–dependent carboxylation secondary to liver disease–induced vitamin K deficiency.³ Microvascular calcification without calciophylaxis may occur in other conditions such as type 2 diabetes mellitus. Therefore, clinicopathologic correlation is important in determining the diagnosis.

Calciophylaxis has a variety of clinical presentations depending on the stage of disease. It begins as a fixed, indurated, livedo reticularis–like plaque. The lesions become increasingly violaceous with intermixed areas of light blanching secondary to ischemia and then develop retiform pupura.⁴ Eventually, affected sites can become bullous and ulcerate or form a necrotic eschar. Severe pain is a cardinal feature throughout all stages.⁴ Lesions in nonuremic calciophylaxis most commonly are located in the central and/or proximal areas of the body.²

Clinical suspicion is essential for diagnosis. Skin biopsy is the standard method for confirmation in unclear cases. The classic histologic features include intravascular and extravascular calcification, microthrombosis, and fibrointimal hyperplasia of the small dermal and subcutaneous arteries and arterioles, leading to ischemia and intense septal panniculitis.¹ Von Kossa immunostaining is used to increase the detection of calcium deposits

(Figure 1).¹ In addition to the classic changes, our case demonstrated a rare histologic variant with pseudoxanthoma elasticum (PXE)–like changes (Figure 2), which are thought to occur secondary to pathologic elastin fibrogenesis or increased proteolytic activity resulting in abnormal remodeling of the extracellular matrix in the setting of increased calcification of elastin fibers.⁵ Detection of PXE-like changes may be a helpful clue when specimens lack other characteristic signs.

Wound care, pain control, and addressing underlying causes are mainstays of therapy. Sodium thiosulfate, an antioxidant with vasodilatory properties that also inhibits

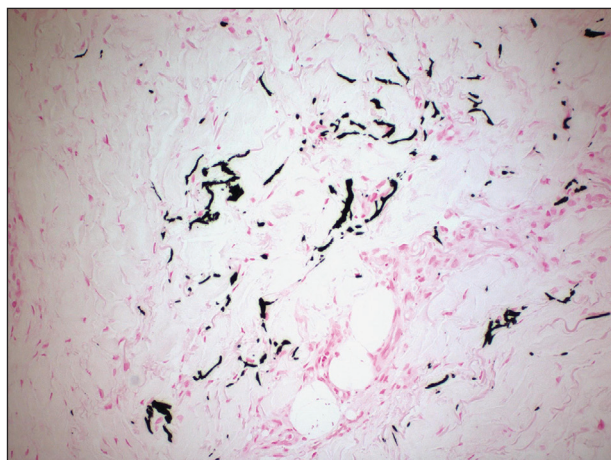


FIGURE 1. Von Kossa immunostaining showed calcifications in the subcutis that appeared black (original magnification $\times 200$).

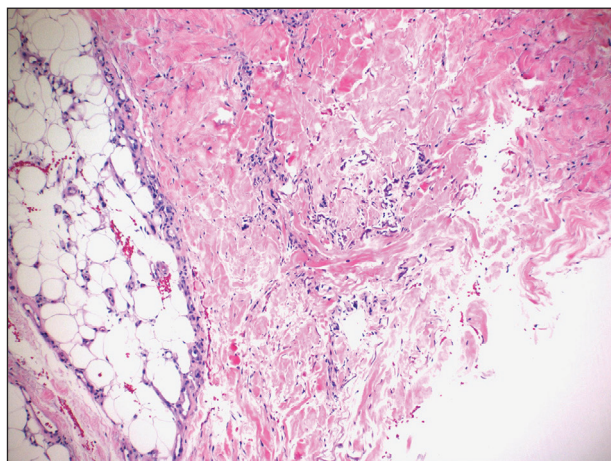


FIGURE 2. Scattered purple calcifications were interspersed in both dermal collagen and subcutaneous adipose tissue with pseudoxanthoma elasticum–like changes (H&E, original magnification $\times 100$).

adipocyte calcification and blocks the ability of adipocytes to induce calcification of vascular smooth-muscle cells, also is useful. Antibiotic prophylaxis is not indicated.¹

Even with treatment, both uremic and nonuremic calciphylaxis have a dismal prognosis; 1-year mortality is approximately 50% to 60% and rises to 80% at 2 years.⁴ Lesion location affects prognosis, and more proximal lesions portend worse outcomes. In patients with both proximal and distal lesions, there is a 90% mortality rate within 1 year. Ulceration also portends worse outcomes, as the wounds often are resistant to healing and act as nidus for infection.⁴ Septicemia is the most common cause of death.¹

Ecthyma gangrenosum is a cutaneous manifestation secondary to an infection most commonly associated with *Pseudomonas aeruginosa*.⁶ It often presents in immunocompromised patients with an underlying gram-negative septicemia.⁷ The clinical presentation initially begins with painless macules that rapidly progress into necrotic ulcers, usually accompanied by associated systemic symptoms such as fever, chills, and hypotension. Histopathology reveals numerous gram-negative rods around necrotic vessels.⁷

Idiopathic purpura fulminans is the rarest form of purpura fulminans. It is caused by autoantibody formation against protein S, resulting in protein S depletion and subsequent hypercoagulability.⁸ It usually occurs 7 to 10 days after the onset of a precipitating infection. Lesions begin as erythematous macules that progress within hours to painful, sharply defined areas of purpura and hemorrhagic cutaneous necrosis that may extend to deeper tissues.⁸ Secondary infection of gangrenous tissue may occur. Distribution usually is diffuse and signs of septic shock and disseminated intravascular coagulation usually are present.

Hughes syndrome, also known as antiphospholipid syndrome, is an acquired autoimmune disorder that manifests clinically as recurrent arterial or venous thrombosis.⁹ Cutaneous manifestations consist of livedo reticularis, arterial and venous ulcers, and superficial thrombophlebitis.¹⁰ Laboratory testing for antiphospholipid antibodies and obtaining a detailed history of the patient's cardiovascular health are crucial for diagnosis.⁹

Necrotizing fasciitis typically begins as an inconspicuous superficial cutaneous infection that rapidly

is transmitted to the fascia. Infection can spread along fascial planes for several days without affecting the overlying skin, leading to delayed diagnosis.¹¹ The first signs to appear are disproportionate pain and a change in skin color to reddish-purple or bluish-gray. Next, the skin will become indurated, swollen, shiny, and more painful.¹¹ Skin breakdown will begin in 3 to 5 days and is accompanied by bullae and cutaneous gangrene. The involved area becomes painless due to thrombosis of the small vessels that supply the superficial nerves.¹² Septic shock ultimately will develop if untreated.

We present a rare case of nonuremic calciphylaxis. We encourage dermatologists to include calciphylaxis in the differential when evaluating any patient with a painful retiform rash or ulcerated eschar, even in the absence of renal disease.

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