Painful medial thigh ulcer

Angela Yen Moore, MD,[a,b,c] and Kara Hurley, BSA[c]

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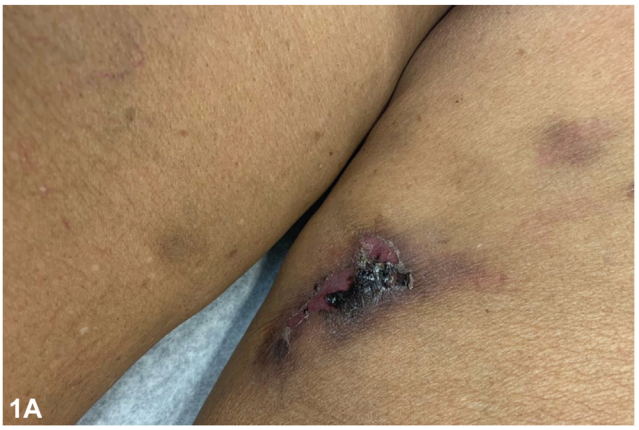

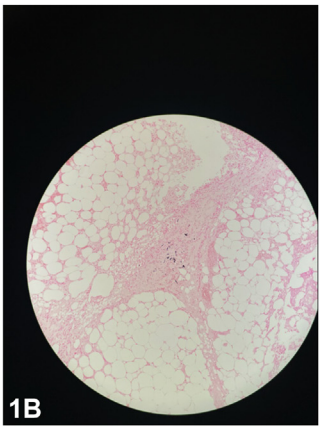

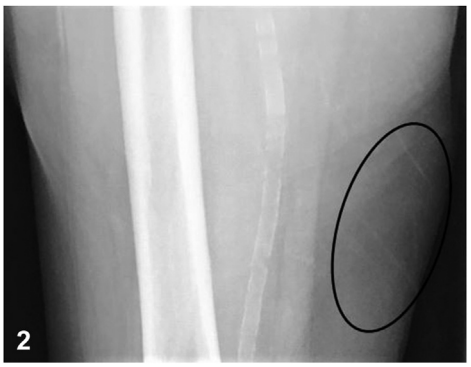

A 74-year-old female with a past medical history of type II diabetes mellitus and end-stage renal disease on hemodialysis and warfarin presented with a new, painful ulcer on her left inner thigh. Gross examination showed retiform purpura with central ulceration and black-brown crusting (Fig 1, *A*). A biopsy was performed, and histopathological examination of the lesion showed full-thickness ischemic necrosis with overlying ulceration and diffuse dermal angiomatosis with scattered calcification deposits around the subcutaneous vessels in the subcutaneous septae (Fig 1, *B*). Grocott methenamine silver and gram stains were negative for fungal or bacterial organisms.

From the Arlington Center for Dermatology, Arlington, Texas[a]; Department of Dermatology, Baylor University Medical Center, Dallas, Texas[b]; and University of North Texas Health Science Center Texas College of Osteopathic Medicine, Fort Worth, Texas.[c]

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Correspondence to: Angela Yen Moore, MD, Arlington Center for Dermatology, 711 East Lamar Blvd, Suite 200, Arlington, TX 76011. E-mail: acderm@acderm.com.

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Question 1: What is the most likely diagnosis?

A. Warfarin-induced skin necrosis

B. Polyarteritis nodosa

C. Calciphylaxis

D. Levamisole-induced vasculitis

E. Venous ulcer

Answer:

A. Warfarin-induced skin necrosis — Incorrect. Warfarin-induced skin necrosis is a condition characterized by a transient hypercoagulable state that causes thrombotic skin and subcutaneous tissue necrosis on dorsal or distal extremities within days of initiating warfarin.

B. Polyarteritis nodosa — Incorrect. Affecting the skin and kidneys, polyarteritis nodosa (PAN) is a systemic necrotizing vasculitis that often presents with asymmetric polyneuropathy and abdominal pain.

C. Calciphylaxis — Correct. Characterized by small- and medium-vessel calcification causing chronic, low-grade ischemia, calciphylaxis most often occurs in patients with end-stage renal disease, known as calcific uremic arteriolopathy. Calciphylaxis can also occur in the absence of renal disease (nonuremic calciphylaxis). Risk factors include elevated calcium and phosphate levels, female sex, obesity, diabetes mellitus, liver disease, high alkaline phosphatase, warfarin therapy, low serum albumin, and systemic corticosteroid use. Clinical manifestations include intense local pain with ulceration of the medial thighs from microthrombi causing local infarction with diffuse calcification of small capillaries in the subcutaneous tissue.[1]

D. Levamisole-induced vasculitis — Incorrect. Levamisole-induced vasculitis arises from cocaine that has been laced with levamisole, an anthelminthic drug that can be reduced to a fine white powder but has been discontinued for humans. Widespread ulcers often involve the ears and affect at least 10% total body surface area.[2]

E. Venous ulcer — Incorrect. While venous ulcers are the most common etiology of lower extremity ulceration, they are often shallow and present on calves and ankles.

Question 2: Besides biopsy, which test would be most diagnostic?

A. X-ray of the femur

B. Urine drug screen

C. Erythrocyte sedimentation rate

D. Protein C level

E. Venous duplex ultrasound

Answer:

A. X-ray of the femur — Correct. Diagnosis of calciphylaxis requires a high degree of clinical suspicion. In our case, the patient's laboratory test results showed elevated creatinine and decreased glomerular filtration rate. Hematology was significant for a normocytic anemia, lymphocytopenia, and neutropenia. While pathology is diagnostic for calciphylaxis lesions, imaging is a useful adjunctive tool if biopsy is contraindicated, inconclusive, or pathology interpretation is pending.[1] A fine, reticular, netlike pattern of calcification on radiograph has a specificity of 90%.[3] While the pathology results were pending in this case, X-ray of the femur showed atherosclerotic calcifications of the femoral artery and fine arteriole calcification (Fig 2).

B. Urine drug screen — Incorrect. Urine drug screen will aid in the diagnosis of levamisole-induced vasculitis if positive for cocaine.

C. Erythrocyte sedimentation rate — Incorrect. While the diagnosis of PAN is confirmed by biopsy, elevated erythrocyte sedimentation rate is sensitive for PAN but carries low specificity.

D. Protein C level — Incorrect. Patients with protein C deficiency are more likely to develop warfarin-induced skin necrosis. Protein C levels are not diagnostic for warfarin-induced skin necrosis, but known deficiency could aid in clinical diagnosis.

E. Venous duplex ultrasound — Incorrect. Venous duplex ultrasound would aid in the diagnosis of a venous stasis ulcer but has minimal diagnostic benefit in calciphylaxis.

Question 3: What is the most appropriate therapy?

A. Oral steroids

B. Drug cessation counseling

C. Compression stockings

D. Unfractionated heparin

E. Sodium thiosulfate

Answer:

A. Oral steroids — Incorrect. Oral glucocorticoids are the first-line treatment in patients with mild or moderate PAN without organ involvement or worsening neuropathy but no proven benefit in calciphylaxis. Intravenous glucocorticoids or cyclophosphamide can be used in severe PAN.

B. Drug cessation counseling — Incorrect. Cocaine cessation is the first-line treatment for levamisole-induced vasculitis along with wound care.

C. Compression stockings — Incorrect. Compression stockings increase lower extremity venous flow and decrease stasis ulcer recurrence. Compression therapy benefits comorbid conditions associated with calciphylaxis but has no benefit in specific therapy.

D. Unfractionated heparin — Incorrect. The management of warfarin-induced skin necrosis includes discontinuation of warfarin and administration of vitamin K, unfractionated heparin, and fresh frozen plasma or protein C concentrate.

E. Sodium thiosulfate — Correct. Intravenous sodium thiosulfate inhibits calcification of adipocytes and vascular smooth muscle cells.[1] Calciphylaxis treatment also focuses on infection prevention, management of comorbid conditions, and discontinuation of such medications as warfarin, vitamin D, iron, and calcium supplements that may contribute to calciphylaxis. Warfarin inhibits synthesis of the vitamin K-dependent matrix G1a protein, which prevents arterial calcium deposition.[4] This is thought to induce a distinct subgroup of nonuremic calciphylaxis, known as warfarin-induced calciphylaxis.[5] In our case, as the patient continued hemodialysis for end-stage renal disease, she became less compliant in taking warfarin. The calciphylaxis ulcers gradually resolved prior to intravenous sodium thiosulfate initiation, which likely implicates warfarin in calciphylaxis development in this patient.

Abbreviation used:

PAN: polyarteritis nodosa

Conflicts of interest

None disclosed.

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