Early diagnosis and intervention of calciphylaxis leading to rapid resolution

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INTRODUCTION

Calciphylaxis is a rare life-threatening disorder characterized by skin necrosis due to calcium deposition within small- and medium-sized vessels and subsequent thrombosis leading to tissue ischemia.[1,2] Though the exact pathogenesis of calciphylaxis is poorly understood, risk factors such as chronic kidney disease can promote calcium deposition and vascular calcification contributing to the disease process.[3] This condition presents with poor healing, painful skin lesions, which initially may be confused with mimickers, such as cellulitis; peripheral vascular disease, warfarin necrosis, or vasculitis.[4] While calciphylaxis is considered a rare disease predominantly affecting patients with chronic kidney disease on renal replacement therapy, there has been an increase in clinical awareness, which may be reflected in the increase in incidence.[4] Despite calciphylaxis having a high morbidity and 1-year mortality as high as 80% in some cases,[4] no randomized controlled trials examining longitudinal outcomes and treatment efficacy have been published.[4] This report discusses 3 cases of early calciphylaxis diagnosis and treatment leading to rapid resolution and survival, highlighting the impact of timely recognition and intervention.

Abbreviations used:

ED:	emergency department
ESRD:	end-stage renal disease
IV STS:	intravenous sodium thiosulfate

CASE DESCRIPTIONS

Case 1

A 74-year-old woman with a history of hypertension, end-stage renal disease (ESRD) on hemodialysis, prior cerebrovascular accident, type II diabetes mellitus, and warfarin use presented to the emergency department (ED) with swelling, pain, and redness in her lower portion of the left leg. Four weeks prior to presentation, the patient's daughter noticed bruising on the lower portion of the left leg in the absence of trauma. Within 2 days, the lower portion of the left leg became swollen, red, and tender, prompting the patient to escalate care. She was diagnosed with cellulitis and discharged on oral cephalexin with close outpatient follow up (Fig 1, *A*). The patient's symptoms persisted, and she received intravenous cefazolin and vancomycin during outpatient dialysis with no improvement. She represented to the ED, where dermatology was consulted. Physical examination revealed exquisitely painful retiform purpura of the left lower extremity with areas of induration and without warmth, characteristic of calciphylaxis (Fig 1, *B*).

A multidisciplinary team including dermatology, nephrology, wound care, and pain management immediately intervened in this patient's care. Her risk factors for calciphylaxis included female sex, ESRD, a history of hemodialysis, and warfarin, vitamin D, and calcium use.[4] Warfarin, calcium supplementation, vitamin D, and antibiotics were discontinued. The patient had a normal electrocardiogram and was initiated on intravenous sodium thiosulfate (IV STS) 25 g three times weekly at hemodialysis. The patient was initiated on pentoxifylline 400 mg and apixaban 2.5 mg twice daily, and a hypercoagulability workup was normal. Diligent

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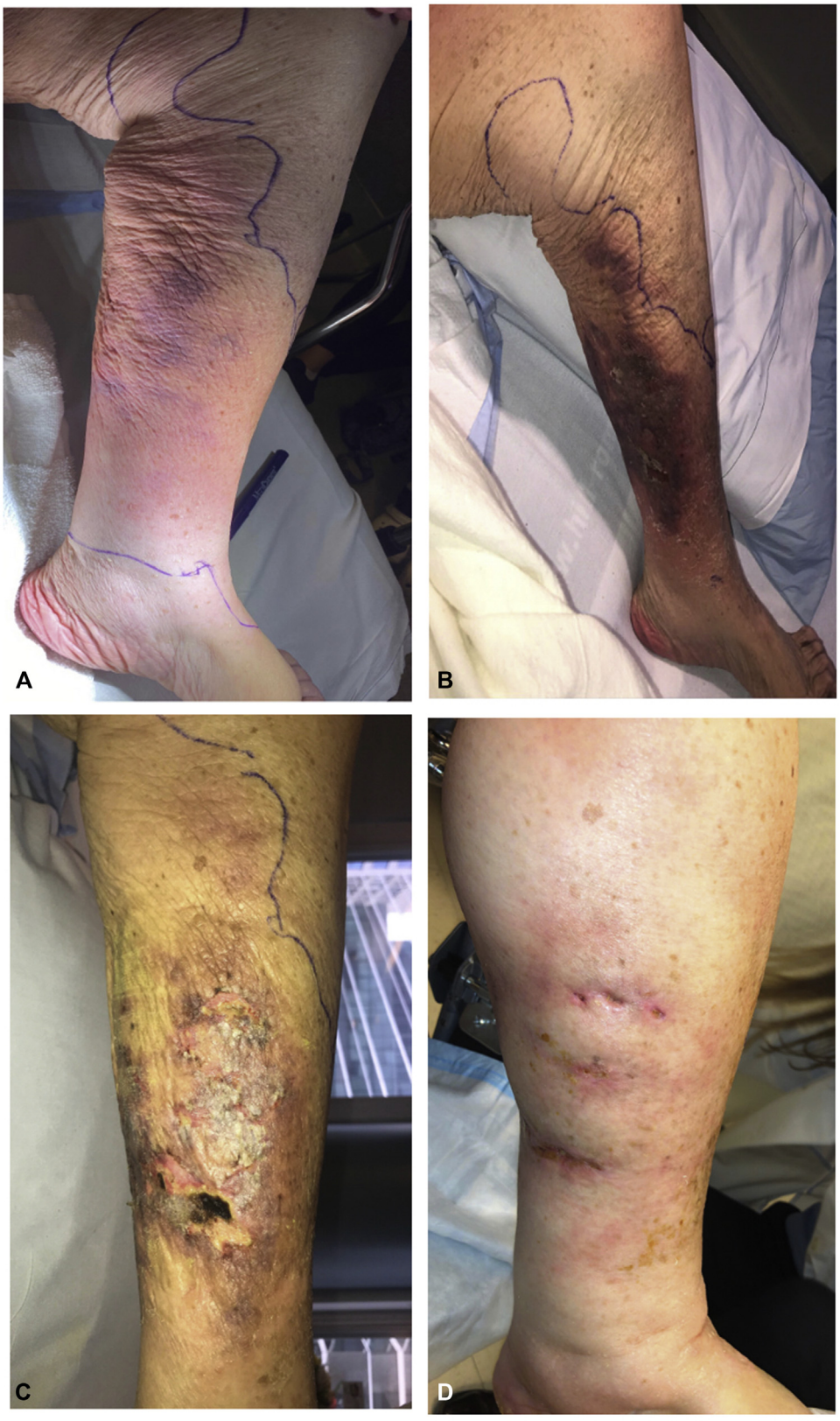

Fig 1. Photographs of left lower extremity calciphylaxis lesions for Case 1. **A**, Lower portion of the left leg erythema and early, central faint purpura at the first presentation. **B**, 4 weeks after initial presentation, lower portion of the left medial leg with nearly circumferential retiform purpura and early focal erosions. **C**, Resolution of purpura, superficial desquamation, and small superficial ulceration with small necrotic eschar. **D**, 4 months after discharge with atrophic scars at the sites of the previous ulcers with nearly resolved focal ulceration inferiorly.

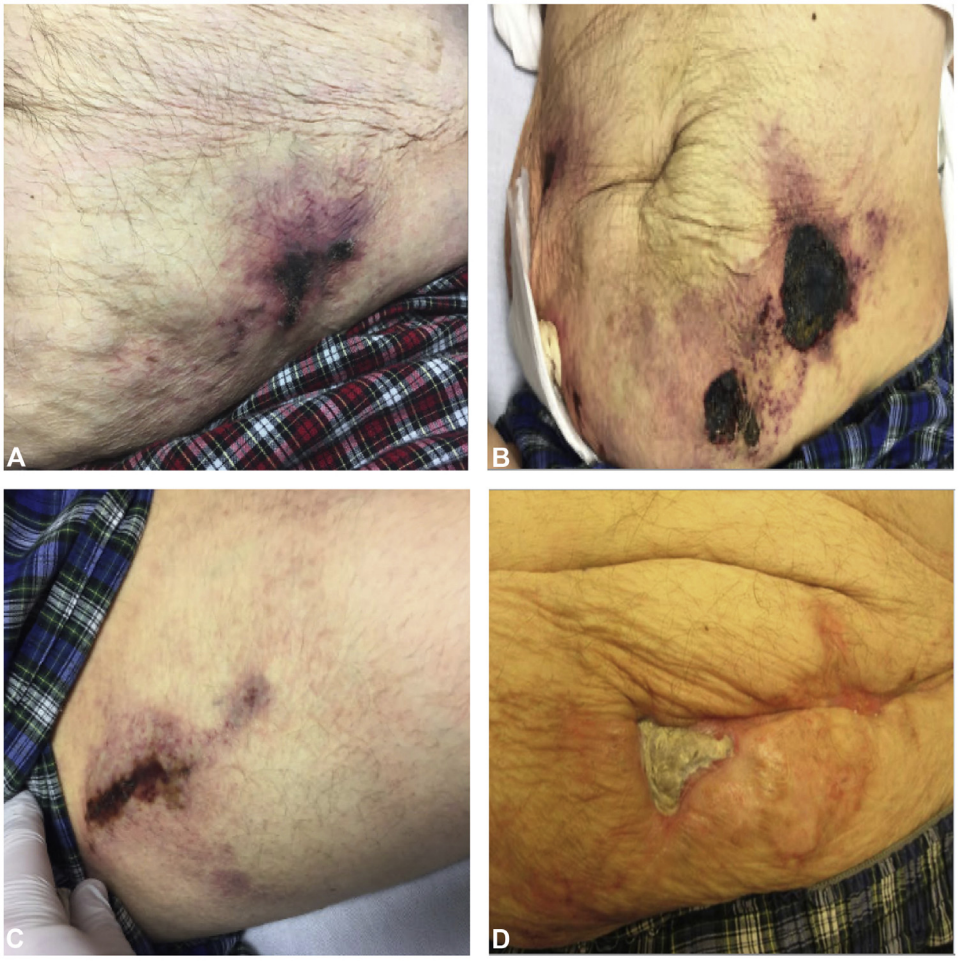

Fig 2. Photographs of abdominal and lower extremity calciphylaxis lesions for Case 2. **A**, Violaceous plaque with central necrosis on the left lower aspect of the abdomen at initial presentation. **B** and **C**, 1 month after initial presentation, retiform purpura with enlarged necrotic eschar and subcutaneous nodules along the abdomen and inner portion of the left thigh. **D**, Abdomen with superficial ulcerations and hypergranulation status after silver nitrate application.

wound care was conducted to minimize skin trauma and breaks with application of a hydrocolloidal suspension of *Leptospermum* honey covered by foam dressing and wraps. Her pain was managed with oral hydromorphone and a transdermal fentanyl patch.

Over the course of the subsequent 3 weeks, retiform purpura indicating active disease and pain associated with the lesions resolved (Fig 1, *C*). She completed a 3-month course of IV STS and a 4-month course of pentoxifylline. She continues taking apixaban as an alternative to warfarin,[5] due to her stroke history. Early intervention minimized the extent of ulceration, and she was nearly healed at her 4-month follow up with no recurrence of her disease activity over the subsequent 16 months (Fig 1, *D*).

Case 2

A 36-year-old man with a history of hypertension, type II diabetes mellitus, chronic kidney disease, thought to be due to autosomal dominant tubulointerstitial kidney disease, obesity, chronic liver disease, and a concern for hematological malignancy with a previously negative workup presented to the ED with painful abdominal erosions and nodules lasting for 2 months. Dermatology consultation raised suspicion for calciphylaxis versus panniculitis based on the clinical presentation (Fig 2, *A*). Plastic surgery conducted an excisional skin biopsy of an abdominal nodule, which revealed a focal area of fat necrosis and focal amyloid deposition in the subcutaneous tissue, suggestive of systemic amyloidosis. Further workup was inconclusive for a plasma cell

Table I. Patient clinical course and outcome

Patient presentation	Physical examination finding	Skin biopsy results	Time from lesion onset to treatment	Treatment	Outcome
Case 1| 74-year-old woman with hypertension, ESRD on hemodialysis, type II diabetes mellitus, prior stroke, and warfarin use presenting with left lower leg swelling, pain, and redness lasting for 1 month.	Exquisitely painful retiform purpura with areas of induration and without warmth on the left lower extremity.	n/a	Approximately 1 month	Discontinuation of warfarin, calcium supplementation, and vitamin D. Initiation of IV STS, pentoxifylline, and apixaban. Pain control with hydromorphone and a transdermal fentanyl patch.	Nearly healed disease activity within 4 months with complete resolution within 1 year. The patient is still alive.
Case 2| 36-year-old man with hypertension, type II diabetes mellitus, CKD due to autosomal dominant tubulointerstitial kidney disease versus amyloid deposition, obesity, and chronic liver disease presenting with new painful skin nodules lasting for 1 month.	Exquisitely painful retiform purpura along the abdomen, bilateral thighs, and right shin. Two large eschars along the abdomen with a smaller focus of eschar on the lower extremity.	Thrombotic vasculopathy with fibrin thrombi and stippled calcification of the subcutaneous vessels, highlighted by Von-Kossa stain, suggestive of calciphylaxis.	Approximately 1 month.	Initiation of IV STS, and rivaroxaban. Pain control with hydromorphone and oxycodone.	Disease resolved within 3 months with no active lesions. The patient continued to have complete resolution at the 4-year examination. The patient is still alive.
Case 3| 46-year-old woman with type II diabetes mellitus, ESRD on peritoneal dialysis, and paroxysmal atrial fibrillation on warfarin presenting with lower extremity pain lasting for 3 weeks.	Exquisitely painful, violaceous, indurated plaques on the bilateral thighs and flank with areas of skipped lesions.	Calcium deposition within subcutaneous capillaries and associated thrombotic vasculopathy highlighted by Von-Kossa stain consistent with calciphylaxis.	Approximately 3 weeks.	Discontinuation of warfarin. Initiation of IV STS and apixaban. Pain control with oxycodone and gabapentin.	Well healing wounds at 3-month follow up with no new lesions. Fully resolved lesions at 1-year follow up. Patient deceased 1.5 years later in the setting of a fall and femur fracture.

CKD, Chronic kidney disease; *ESRD*, end-stage renal disease; *IV STS*, intravenous sodium thiosulfate; *n/a*, not applicable.

malignancy, and the patient was ultimately discharged with hematology and rheumatology follow-up for treatment. He represented to the hospital 1 month later with new lesions of painful retiform purpura on the lower extremities (Fig 2, *B*), which were punch biopsied by dermatology and observed to be consistent with calciphylaxis (Table I). During this admission, he was initiated on IV STS 25 g 5 times per week, rivaroxaban 20 mg nightly, and hydromorphone and oxycodone for pain control. He completed a 10-week course of IV STS, and his calciphylaxis had nearly resolved within 3 months (Fig 2, *C*) with no recurrence of disease at his 4-year evaluation.

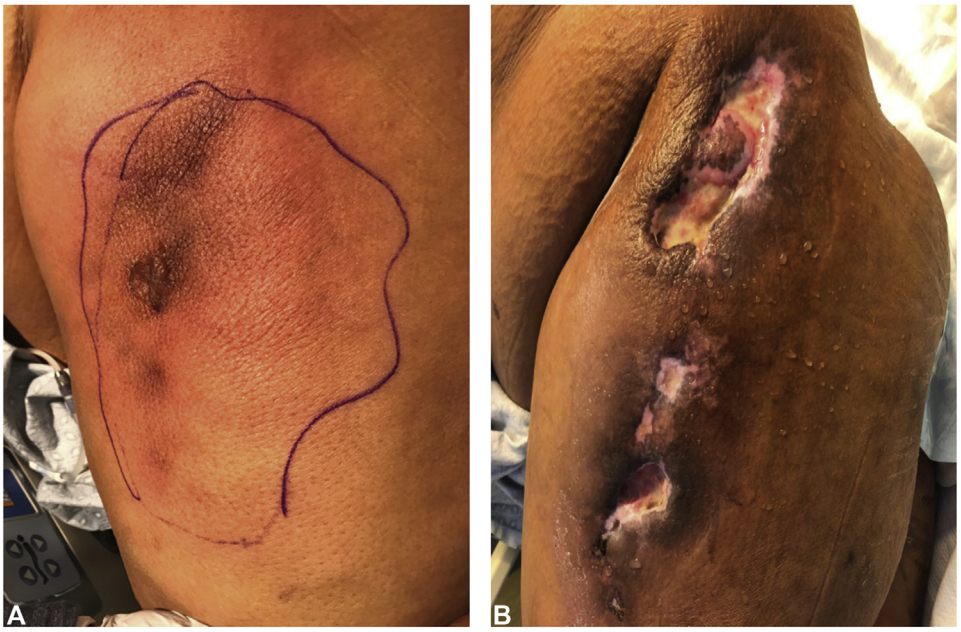

Fig 3. Photographs of left hip calciphylaxis lesions for Case 3. **A**, Exquisitely painful, violaceous, and indurated plaque on the left thigh and hip at initial presentation. **B**, 3 months after initial presentation, clean deep-based ulcer with minimal overlying fibrinous debride. The wound is healing well with no evidence of active calciphylaxis.

Case 3

A 46-year-old woman with a history of type II diabetes mellitus, ESRD on peritoneal dialysis, and paroxysmal atrial fibrillation on warfarin presented to the ED with lower extremity pain lasting for 3 weeks. Dermatology evaluation revealed exquisitely painful, indurated, and violaceus plaques on the bilateral thighs and flank (Fig 3, *A*) with a punch biopsy indicative of calciphylaxis. During the hospitalization, the patient's warfarin was discontinued, and the patient was initiated on apixaban 5 mg twice daily and IV STS 25 g 3 times per week for 3 months. At her 3-month follow up appointment, her wounds were healing well with no new lesions (Fig 3, *B*), and she exhibited fully resolved lesions at her 1-year follow-up visit.

DISCUSSION

Prompt recognition and diagnosis of calciphylaxis in these 3 patients led to rapid multi-disciplinary intervention with significant clinical improvement despite the patients' risk factors typically associated with a poor prognosis, including ESRD, cardiovascular disease, diabetes mellitus, and warfarin use.[6] Calciphylaxis has recently been reported to have a misdiagnosis rate as high as 73% with cellulitis being the most common misdiagnosis.[7] The clinical presentation of calciphylaxis may vary, and early lesions can be erythematous or violaceous, and painful. As vascular occlusion progresses, ischemic changes can present as livedo reticularis, retiform purpura, ulceration, and tissue necrosis.[3] Failure to improve with antibiotic treatment and severely painful and progressing skin lesions were important indicators of an alternative diagnosis in the first case, necessitating dermatological assessment. Furthermore, the second case presented an early diagnostic challenge with initial findings concerning for hematologic malignancy and excisional skin biopsy demonstrating amyloidosis. A skin biopsy can confirm the diagnosis of calciphylaxis in uncertain presentations. There are risks associated with skin biopsy, such as worsening pain, lesion progression, and false-positive and -negative histologic diagnosis.[8] A repeat punch biopsy 1 month after the first biopsy resulted in a confirmatory diagnosis of calciphylaxis, which led to immediate intervention.

While the specific interventions of IV STS, pentoxifylline, apixaban, and wound and pain management are mostly supported by smaller case series or retrospective studies,[4] they appear to be effective early interventions, although more research is conducted on the topic. Adjunctive treatments such as hyperbaric oxygen therapy and nutrition management may also be considered in these patients for further improvement.[4] Clinical indications of a rapid response to therapy included the prompt reduction in pain, decrease in lesion size and number,

resolution of purpura, cessation of ulcer propagation, and formation of new granulation tissue. While calciphylaxis is associated with high morbidity and mortality, early diagnosis and multidisciplinary treatment initiation is an important intervention, as more research on treatment is underway.

Conflicts of interest

None disclosed.

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