Case Series

Calciphylaxis, A Case Series: The Importance of Early Detection

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Abstract

Introduction
Calciphylaxis is a rare disorder that involves the formation of cutaneous, subcutaneous, and vascular calcifications. Although it is predominantly seen in patients with end-stage renal disease (ESRD), it has also been reported in patients without chronic kidney disease. The presence of multiple risk factors, a poorly understood mechanism, high mortality, and the lack of standardized treatment make calciphylaxis an important subject.

Case Presentation
We describe the clinical presentation, disease course, and management of 3 patients with calciphylaxis and also provide a literature review. In all 3 patients, the diagnosis was confirmed histologically, and the management involved the continuation of renal replacement therapy, pain medication, wound debridement, and intravenous (IV) sodium thiosulphate.

Conclusion
Calciphylaxis should be suspected in ESRD patients presenting with painful areas of cutaneous induration, and the early recognition of these findings allows for prompt diagnosis and management.

Keywords
calciphylaxis; end-stage renal disease (ESRD); vascular calcification; calcific uraemic arteriolopathy; chronic kidney failure; renal failure; pain; skin ulcer

Introduction
Calciphylaxis, or calcific uremic arteriolopathy, is a multifactorial vasculopathy characterized by arterial calcification that primarily affects patients with end-stage renal disease (ESRD).[1, 2] A typical clinical presentation demonstrates painful, plaque-like, subcutaneous nodules that progress to ischemic, necrotic ulcers with overlying eschar that often becomes superinfected.[3] Most drug therapies remain controversial. In some cases, however, intravenous (IV) sodium thiosulphate has shown clinical improvement.[4] For all 3 of our patients, severe bilateral thigh pain was the chief complaint. Of note, physical examinations revealed tender indurated areas without ulceration on the medial thighs of these patients. After a histological diagnosis of calciphylaxis, each patient was prescribed IV sodium thiosulphate with every dialysis session, along with pain management and wound care.

Case Description
Case 1
A 62-year-old White male presented with 3-week bilateral thigh pain as well as an episode of fever and chills. The pain was localized to several indurated areas on his anteromedial thighs. His comorbidities included ESRD, which required hemodialysis via arteriovenous (AV) fistula, hypertension, type 2 diabetes, and coronary artery disease. Upon physical examination,

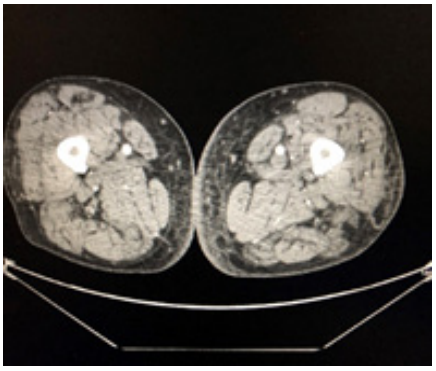

Figure 1. Subcutaneous fat stranding is seen on the bilateral thighs on a CT scan.

the medial aspect of both thighs were firm, warm, and tender to touch.

Although the patient had no skin ulcers, his history of ESRD and complaints of 10 out of 10 pain associated with indurated areas on his thighs (numerical pain scale 0-10, 0 = no pain and 10 = severe pain) put calciphylaxis high on the differential diagnosis. The patient's work-up included an ultrasound of the lower extremities that was negative for deep venous thrombosis (DVT). Computed tomography (CT) revealed subcutaneous fat stranding in both lower extremities, the left greater than the right (**Figure 1**). A skin biopsy of one of the indurated areas on the left medial thigh showed calcification of deep dermal blood vessels consistent with calciphylaxis (**Figures 2A and 2B**).

The patient was treated with 25 g of IV sodium thiosulphate, which was given with each dialysis session for pain management. After 1 month following his initial presentation, the patient reported much less pain, and the indurated sites on both medial thighs were improved. The skin biopsy site was well healed.

Case 2

A 49-year-old Hispanic male with a medical history significant for dialysis-dependent ESRD, hypertension, type 2 diabetes, obstructive sleep apnea, hyperlipidemia, and multiple toe amputations was admitted for lightheadedness and bilateral lower extremity pain. The patient reported the pain to be 10 out of 10 (numerical pain scale 0-10, 0 = no pain and 10 = severe pain). Upon physical examination, the patient had multiple tender papules on his hands and legs, non-tender papules on his abdomen, and 2 ulcers on his penis that were covered with yellowish slough. Multiple indurated areas were palpable on the medial aspect of both thighs and calves. The indurated areas were warm, slightly erythematous, and extremely tender to touch.

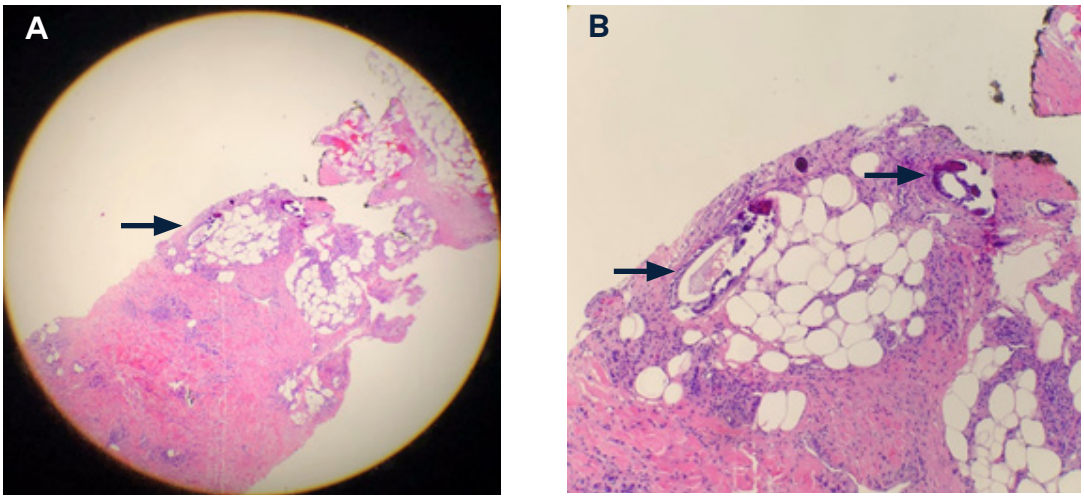

Figure 2. A. Low power magnification shows calcification of blood vessels (arrow). B. High power magnification shows calcification of deep dermal vessels and septal panniculitis with fat necrosis (arrows).

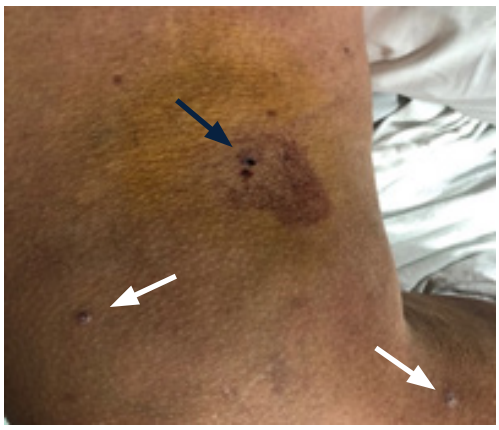

Figure 3: The skin punch biopsy site is shown in an indurated area on the medial aspect of the right thigh (black arrow) with multiple papules (white arrows).

A skin punch biopsy was performed on an indurated area on the right medial thigh (**Figure 3**). The pathology demonstrated blood vessel calcification of the tunica media, compatible with calciphylaxis (**Figures 4A and 4B**). The patient's management included IV sodium thiosulphate administered with each session of dialysis, wound care, and pain management.

Case 3

A 53-year-old White female was admitted to the hospital with a several-week history of body aches, multiple painful skin ulcers, and suicidal ideation due to the pain. She had a history of ESRD secondary to polycystic kidney disease, secondary hyperparathyroidism, mitral valve replacement, hypertension, anemia of ESRD, and major depressive disorder. Physical examination revealed tender, indurated, bilateral thigh nodules with ulceration (**Figure 5a**), skin and soft tissue ulcers of the left scapula and breast (**Figure 5b**), and a stage II sacral decubitus ulcer. The base of these ulcers had a predominantly yellowish slough except for the ulcer on the patient's left thigh, which had a black eschar (**Figure 5A**).

Following a working diagnosis of calciphylaxis, a skin punch biopsy was obtained from the left breast ulcer and subcutaneous nodules on the left medial thigh. The biopsy from the left thigh showed nonspecific inflammation, while the biopsy from the left breast ulcer showed multiple thrombosed vessels with fat necrosis and dystrophic calcification, consistent with calciphylaxis (**Figures 6A and 6B**).

In addition to the IV administration of sodium thiosulphate during dialysis, the patient under-

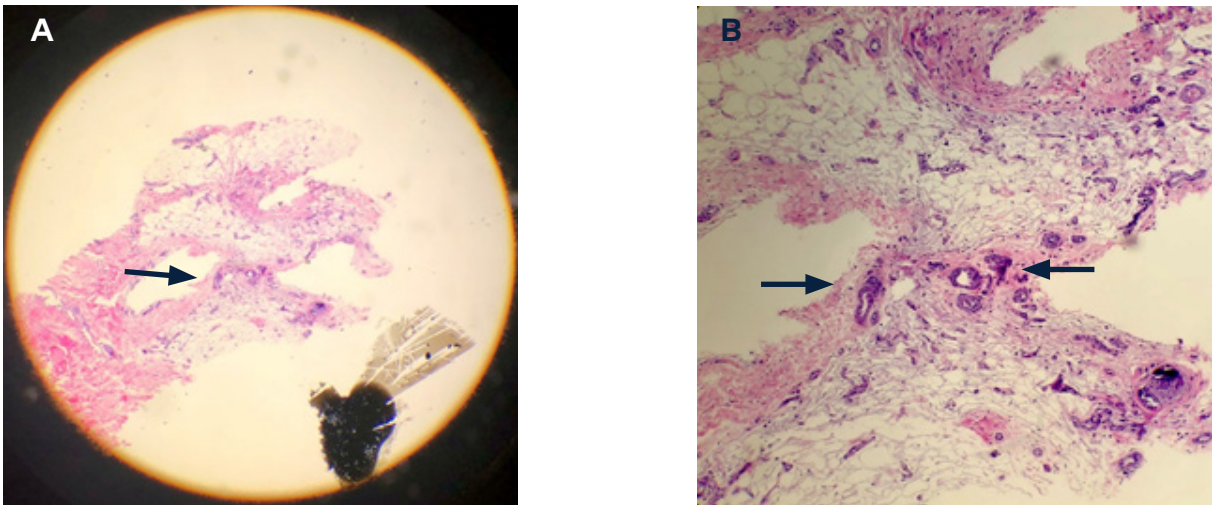

Figure 4. A. Low power magnification shows calcification of blood vessels (arrow). B. High power magnification shows mild panniculitis and rare blood vessels with calcification of tunica media (arrows).

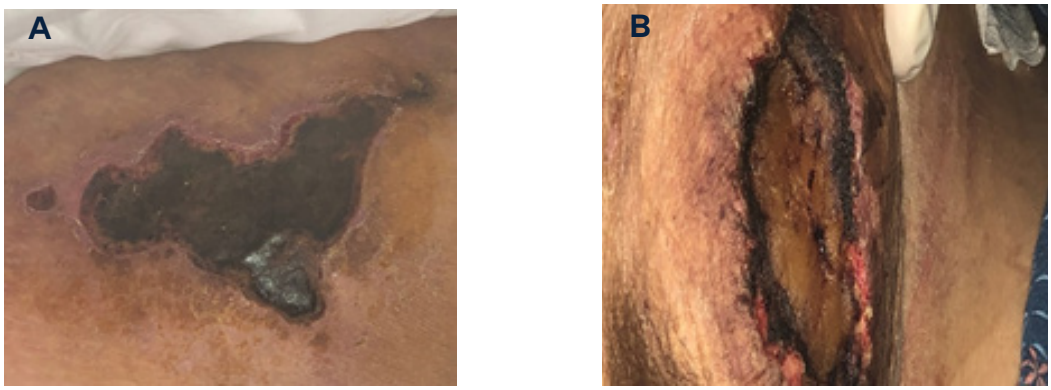

Figure 5. A. An ulcer is shown on the left thigh with a necrotic plaque. B. An ulcer is shown on the left breast with a necrotic edge.

went surgical debridement of the breast and thigh ulcers as well as wound vacuum-assisted closure (VAC) therapy for the ulcer on her left lateral thigh. Despite attempts to care for her ulcers and treat her pain, the patient's pain persisted, and her ulcers showed poor healing. She ultimately underwent a mastectomy of her left breast.

Discussion

Calciphylaxis is predominantly seen in patients with ESRD. Although the exact figure is unknown, recent data reports the incidence of calciphylaxis to be 3 new cases per 1000 patient-years among ESRD patients on chronic hemodialysis.[5] This incidence may be lower than the true incidence of calciphylaxis because of subclinical disease or misdiagnosis.[1] Hyperphosphatemia, hypoalbuminemia, obesity, female gender, liver disease, and vitamin K antagonist (warfarin) have also been implicated as risk factors.[5-7] All 3 patients in this case series had ESRD. Two of them had obesity and hypoalbuminemia, and 1 patient was on warfarin. The incidence rate has been higher for patients using warfarin (6.24 per 1000 patient-years) than those not on warfarin (3.41 per 1000 patient-years).[5] About 75% of patients complain of severe pain and cutaneous manifestations, including indurations, ulcerations, and erythema.[8] Skin lesions were localized in 71% of cases on the legs or gluteal region.[9]

A current diagnosis is based on clinical features and histological findings.[10] Histological findings include vascular calcification, intimal hyperplasia, and microthrombosis.[11] Dermal angioplasia, a potential marker of chronic low-grade ischemia,

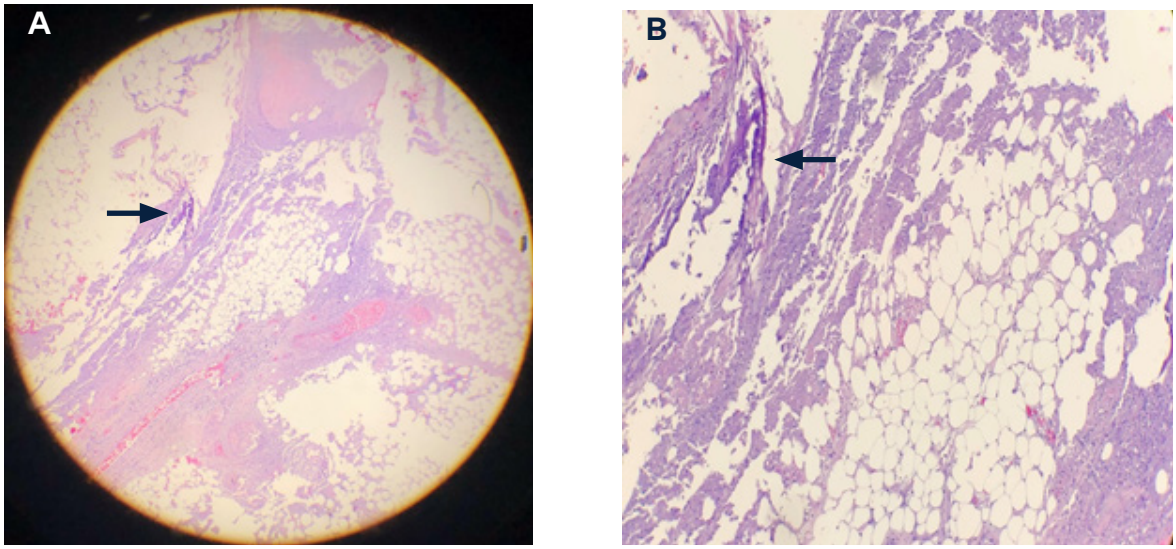

Figure 6. A. Low power magnification shows calcification of blood vessels (arrow).
B. High power magnification shows thrombosed blood vessels with subtle dystrophic calcification and fat necrosis (arrow).

is another frequent microscopic finding in calciphylaxis.[12] More recently, it has been debated whether histologic confirmation is necessary for typical cases of calciphylaxis because a biopsy creates an ulcer that has a high risk of not healing and subsequent infection, ultimately adding to the morbidity of the disease.[13]

Calciphylaxis has high mortality, and the most common cause of death is sepsis secondary to wound infection.[2] Mortality rates have been reported to be 27% at 6 months and 45% at 12 months after the diagnosis.[5] Mortality may be even higher for patients with cardiovascular disease and patients on warfarin.[14] Mortality associated with calciphylaxis is lower in patients without chronic kidney disease (CKD) or with CKD 3 or 4 as compared to patients with ESRD.[15]

Sodium thiosulphate, a calcium-ion chelator, slows down calcification; therefore, it has been used for the treatment of calciphylaxis.[14] Whenever possible, it has also been recommended to stop using contributing medications like warfarin and calcium supplements in patients with calciphylaxis.[16] Warfarin can cause vascular calcification by inhibiting vitamin K-dependent matrix protein, and it can cause thrombosis by reducing proteins C and S. Thus, cessation of warfarin is an essential step in management. Individualized wound care and debridement, optimization of dialysis, IV sodium thiosulphate, management of pain and nutrition, and modification of risk factors should be incorporated into the treatment plan.[11] Solanky et al. reported successful surgical treatment of severe calciphylaxis with staged debridement and a dermal regenerative graft.[17] A few patients with calciphylaxis have been treated successfully by kidney transplantation. However, some patients will develop calciphylaxis even after kidney transplantation.[18]

Calciphylaxis is an important but not widely recognized cause of abnormal vessel calcification. Therefore, many patients are misdiagnosed. Our patients' risk factors and clinical clues (**Table 1**) led to the timely consideration of calciphylaxis as a possible diagnosis, and further work-ups were performed with skin punch biopsies. Early detection of calciphylaxis is essential to initiate prompt treatment with sodium thiosulphate and the cessation of possible contributing medications.

Table 1. Features of 3 Patients with Calciphylaxis

	Case 1	**Case 2**	**Case 3**
Chief complaint	Pain on bilateral lower extremities	Pain on bilateral lower extremities	Pain on bilateral lower extremities
Pain scale	10/10	8/10	10/10
Indurations	Present	Present	Present
Ulcers	Absent	Penile ulcers present	Multiple ulcers on left breast, left scapular area, bilateral thighs
Risk factors			
ESRD on dialysis	Present	Present	Present
Obesity	Present	Present	Present
Female	No	No	Yes
Warfarin use	Present	Absent	Absent
Management	Sodium thiosulphate, pain management	Sodium thiosulphate, wound care, pain management	Wound debridement, wound vac therapy, left mastectomy, strict wound care, sodium thiosulphate, pain management

Differences can be observed between case 3, whose disease course rapidly progressed despite appropriate wound care, versus case 1, which benefitted from an early diagnosis in terms of the absence of ulcers or skin necrosis from diagnosis to follow-up.

Conclusion

As evidenced in the cases presented here and supported by a literature review, the pain experienced by patients with calciphylaxis is difficult to control, and the skin ulcers are notorious for poor healing. We recommend including a pain specialist in the multidisciplinary management of calciphylaxis. Close attention to subtle clinical clues is necessary for early diagnosis and prompt treatment of calciphylaxis to limit morbidity and prevent the rapid progression of skin ulcers, sepsis, and death.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Drs Sijapati, Mercado, and Myers are employees of HCA Florida St. Petersburg Hospital, a hospital affiliated with the journal's publisher.

Drs Hung Fong, Ansari, Misra, and Narasimha are employees of HCA Florida Brandon Hospital, a hospital affiliated with the journal's publisher.

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