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In Practice

Calciphylaxis: Risk Factors, Diagnosis, and Treatment

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Calciphylaxis is a rare but devastating condition that has continued to challenge the medical community since its early descriptions in the scientific literature many decades ago. It is predominantly seen in patients with chronic kidney failure treated with dialysis (uremic calciphylaxis) but is also described in patients with earlier stages of chronic kidney disease and with normal kidney function. In this review, we discuss the available medical literature regarding risk factors, diagnosis, and treatment of both uremic and nonuremic calciphylaxis. High-quality evidence for the evaluation and management of calciphylaxis is lacking at this time due to its rare incidence and poorly understood pathogenesis and the relative paucity of collaborative research efforts. We hereby provide a summary of recommendations developed by a multidisciplinary team for patients with calciphylaxis.

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CASE PRESENTATION

A 62-year-old obese white woman is evaluated for an extremely tender right thigh skin lesion. She has a long-standing history of end-stage renal disease from uncontrolled diabetes mellitus requiring long-term hemodialysis therapy. A skin biopsy demonstrated dermal arteriolar calcification and mural thrombosis associated with septal panniculitis consistent with a diagnosis of calciphylaxis. Her laboratory data are as follows: serum parathyroid hormone (PTH), 160 pg/mL (160 ng/L); serum calcium, 8.1 mg/dL (2.03 mmol/L); serum phosphorus, 3.9 mg/dL (1.26 mmol/L); and serum albumin, 3.2 g/dL (4.64 μmol/L). Which risk factors and treatment strategies should be considered for further evaluation and management?

INTRODUCTION

Calciphylaxis is a rare and highly morbid condition that has continued to challenge the medical community since its early descriptions.[1-4] Calciphylaxis predominantly affects patients with chronic kidney failure treated by dialysis.[5,6] However, calciphylaxis is not limited to patients treated by dialysis and also occurs in patients with normal kidney function and those with earlier stages of chronic kidney disease (CKD; referred to as nonuremic calciphylaxis).[7-10] Both uremic and nonuremic calciphylaxis are associated with significant morbidity and mortality. The morbidity is related to severe pain, nonhealing wounds, recurrent hospitalizations, and adverse effects of treatments. The 1-year mortality in patients with calciphylaxis is reported at 45% to 80%, with ulcerated lesions associated with higher mortality compared with nonulcerated lesions and sepsis being the leading cause of death.[11-13] Mortality rates in long-term hemodialysis patients with calciphylaxis were almost 3 times higher than for long-term hemodialysis patients without calciphylaxis in the US Renal Data System.[14] Some studies also report that the incidence of calciphylaxis is increasing in the dialysis population; however, whether this is truly an increase in incidence or enhanced awareness is unclear.[11,14,15]

Calciphylaxis clinically presents with severe painful skin lesions (livedo reticularis, reticulate purpura, violaceous plaques, or indurated nodules) that demonstrate poor healing and are frequently complicated by blistering and ulcerations with superimposed infections (Fig 1).[7,16,17] Ulcerated lesions commonly demonstrate black eschar. Although skin manifestations dominate the clinical presentation, patients have been reported to have vascular calcifications in skeletal muscle, brain, lungs, intestines, eyes, and mesentery.[18-24] In this regard, calciphylaxis can be considered as a continuum of a systemic process leading to arterial calcification in many vascular beds.[25] Histologically, calciphylaxis is characterized by calcification, microthrombosis, and fibrointimal hyperplasia of small dermal and subcutaneous arteries and arterioles, leading to ischemia and intense septal panniculitis (Fig 2).[26-28] Calcification most commonly

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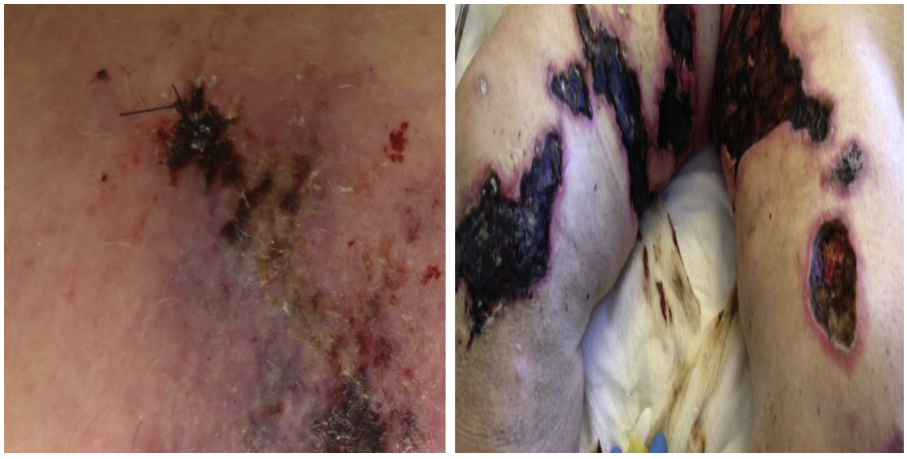

Figure 1. Morphology of calciphylaxis lesions. Reproduced from Allegretti et al[10] with permission of Elsevier.

involves the medial layer of small arteries and arterioles; however, involvement of the intimal layer and the interstitium of subcutaneous adipose tissue has been reported.[17] Calcification is considered to be an early and essential process in calciphylaxis plaque development, and it is hypothesized that the vascular calcification leads to vascular endothelial dysfunction and injury.[29-31] Despite the well-characterized clinical and histologic descriptions of calciphylaxis, its exact pathogenesis remains unclear and there are limited data regarding the diagnostic and therapeutic approaches for this devastating condition.

In this review, we discuss the available medical literature regarding risk factors, diagnosis, and treatment of calciphylaxis. We emphasize that the rare incidence of calciphylaxis combined with its poorly understood pathogenesis and relative paucity of collaborative research efforts have imposed significant limitations for the development of high-quality evidence for calciphylaxis. We provide a summary

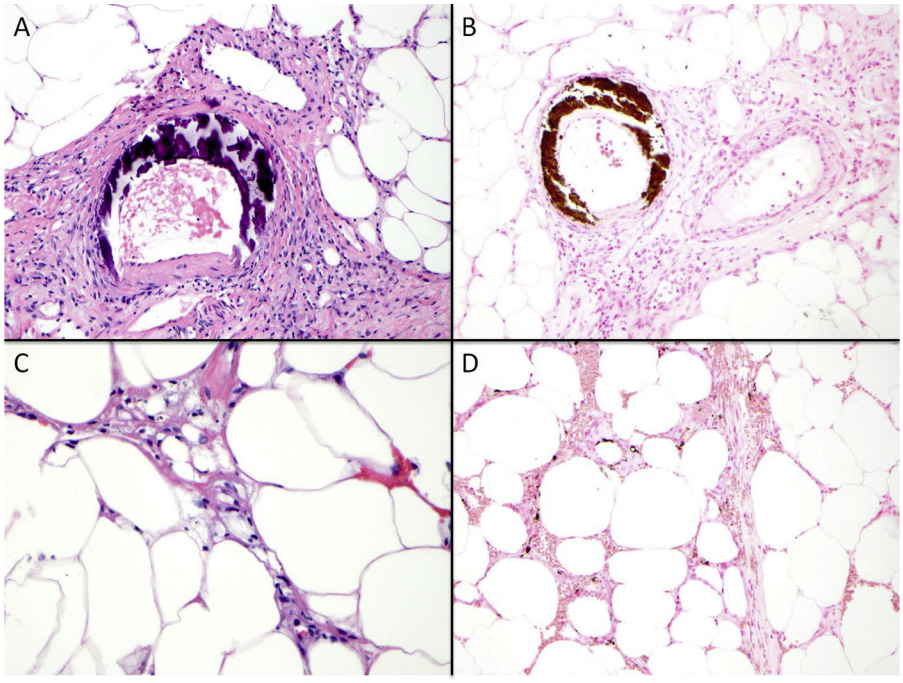

Figure 2. Histopathology of calciphylaxis. (A, B) Coarse basophilic medial calcification of small arteries as demonstrated by hematoxylin & eosin stain (original magnification, ×400) and highlighted by von Kossa histochemical stain (original magnification, ×200). (C) Septal panniculitis and subcutaneous fat necrosis with presence of subtle finely granular basophilic calcium deposits (hematoxylin & eosin; original magnification, ×400). (D) von Kossa histochemical stain aids in the detection of interstitial calcium deposits, which may not be identified on routine histologic sections (original magnification, ×200).