Update on Calciphylaxis Etiopathogenesis, Diagnosis, and Management

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PRACTICE **POINTS**

- Maintain a high index of suspicion for calciphylaxis in patients with end-stage renal disease on chronic dialysis presenting with severely painful livedoid plaques or retiform purpura, particularly in fat-rich body sites.
- Skin biopsies may be limited by biopsy site, inadequate biopsy depth, missed areas of microcalcification, and absence of definitive histologic criteria. Special calcium stains and review by an experienced dermatopathologist may lower the rate of false-negative biopsies.
- In cases where the most likely clinical diagnosis is calciphylaxis, treatment should be initiated even if definitive histopathology findings are lacking.
- Treatment should be multimodal, including elimination of risk factors, intravenous sodium thiosulfate, agents addressing calcium-phosphate metabolism, and surgical debridement, if indicated.

Calciphylaxis is a rare painful skin condition classically seen in patients with end-stage renal disease (ESRD), particularly those on chronic dialysis; however, it also has been increasingly reported in patients with normal renal function. Calciphylaxis is associated with high mortality rates, and excruciating pain and nonhealing ulcers often lead to recurrent hospitalizations and infectious complications. It is critical for dermatologists to recognize the clinical features of calciphylaxis to ensure accurate and timely diagnosis and proper management. In this article, we provide an update on calciphylaxis etiopathogenesis, diagnosis, and management, and we highlight the challenges faced in managing this potentially fatal condition.

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Calciphylaxis, also known as calcific uremic arteriolopathy, is a painful skin condition classically seen in patients with end-stage renal disease (ESRD), particularly those on chronic dialysis.[1,2] It also has increasingly been reported in patients with normal renal function and calcium and phosphate homeostasis.[3,4] Effective diagnosis and management of calciphylaxis remains challenging for physicians.[2,5] The condition is characterized by tissue ischemia caused by calcification of cutaneous arteriolar vessels. As a result, calciphylaxis is associated with high mortality rates, ranging from 60% to 80%.[5,6] Excruciating pain and nonhealing ulcers often lead to recurrent hospitalizations and infectious complications,[7] and poor nutritional status, chronic pain, depression, and

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insomnia can further complicate recovery and lead to poor quality of life.[8]

We provide an update on calciphylaxis etiopathogenesis, diagnosis, and management. We also highlight some challenges faced in managing this potentially fatal condition.

Epidemiology

Calciphylaxis is considered a rare dermatosis with an estimated annual incidence of 1% to 4% in ESRD patients on dialysis. Recent data suggest that incidence of calciphylaxis is rising,[5,7,9] which may stem from an increased use of calcium-based phosphate binders, an actual rise in disease incidence, and/or increased recognition of the disease.[5] It is difficult to estimate the exact disease burden of calciphylaxis because the diagnostic criteria are not well defined, often leading to missed or delayed diagnosis.[3,10] Furthermore, there is no centralized registry for calciphylaxis cases.[3]

Etiology and Pathogenesis

Calciphylaxis is thought to have a multifactorial etiology with the exact cause or trigger unknown.[7] A long list of risk factors and triggers is associated with the condition (Table 1). Calciphylaxis primarily affects small arteries (40–600 μm in diameter) that become calcified due to an imbalance between inhibitors and promoters of calcification.[2,11] Fetuin-A and matrix Gla protein inhibit vascular calcification and are downregulated in calciphylaxis.[12,13] Dysfunctional calcium, phosphate, and parathyroid hormone regulatory pathways provide an increased substrate for the process of calcification, which causes endothelial damage and microthrombosis, resulting in tissue ischemia and infarction.[14,15] Notably, there is growing interest in the role of vitamin K in the pathogenesis of calciphylaxis. Vitamin K inhibits vascular calcification, possibly by increasing the circulating levels of carboxylated matrix Gla protein.[16]

Clinical Features

Calciphylaxis is most commonly seen on the legs, abdomen, and buttocks.[2] Patients with ESRD commonly develop proximal lesions affecting adipose-rich sites and have a poor prognosis. Distal lesions are more common in patients with nonuremic calciphylaxis, and mortality rates are lower in this population.[2]

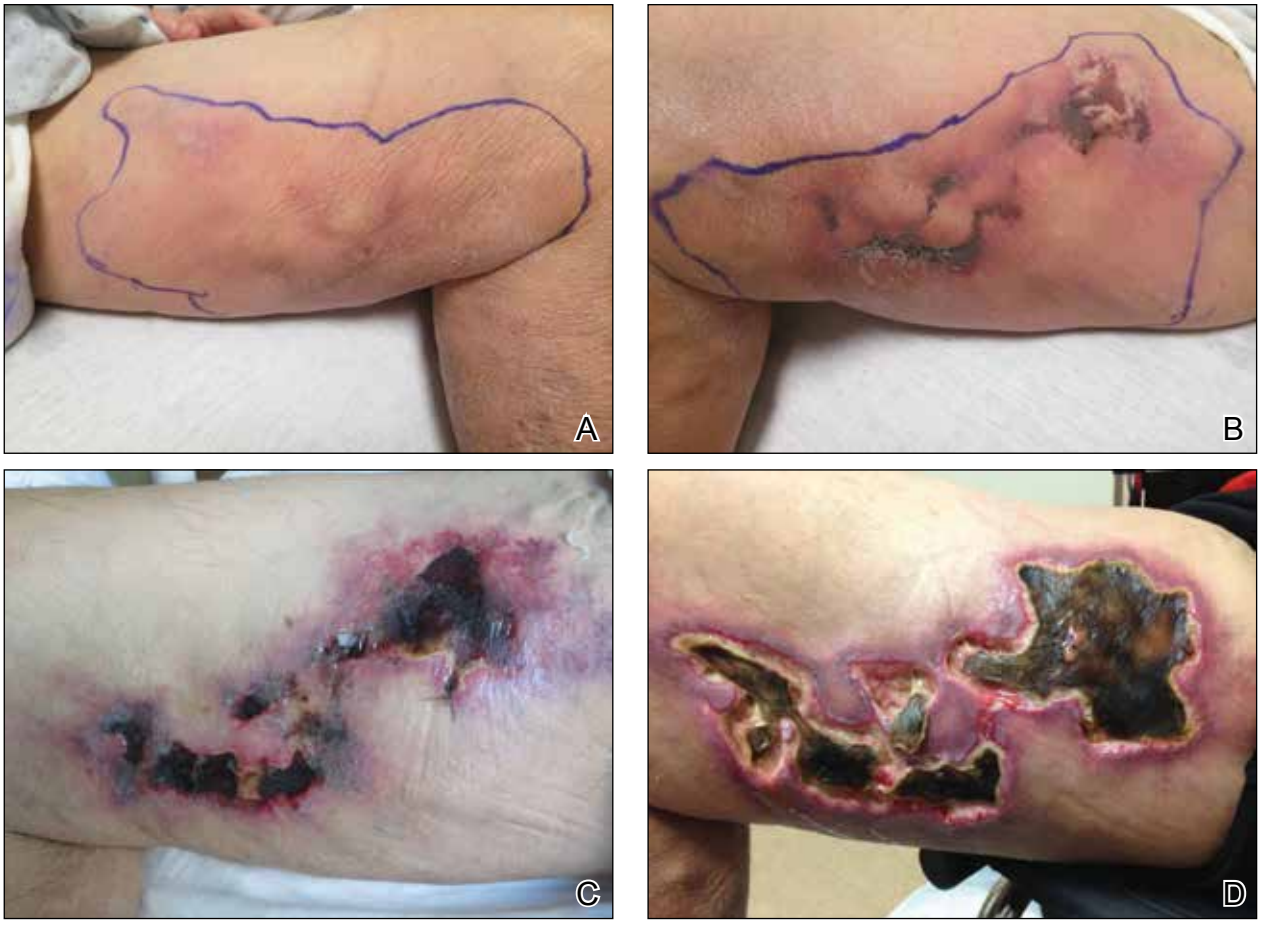
Early lesions present as painful skin nodules or indurated plaques that often are rock-hard or firm to palpation with overlying mottling or a livedoid pattern (Figure, A). Early lesions progress from livedo reticularis to livedo racemosa and then to retiform purpura (Figure, B). Purpuric lesions later evolve into black eschars (Figure, C), then to necrotic, ulcerated, malodorous plaques or nodules in later stages of the disease (Figure, D). Lesions also may develop a gangrenous sclerotic appearance.[2,5]

Although most patients with calciphylaxis have ESRD, nonuremic patients also can develop the disease. Those with calciphylaxis who do not have renal dysfunction frequently have other risk factors for the disease and often

TABLE 1. Calciphylaxis Risk Factors and Triggers

Autoimmune disease: systemic lupus erythematosus
Coagulation disorders: antithrombin III deficiency, lupus anticoagulant, protein C deficiency
Disturbed calcium/phosphate homeostasis: ESRD, hypercalcemia, hyperphosphatemia, secondary hyperparathyroidism
Environmental factors: exposure to heavy metals (eg, aluminum) and UV light
Ethnicity: white
Gender: female
Genetic polymorphisms: CD73 (rs4431401, rs9444348), FGF23 and vitamin D receptor (rs7310492, rs11063118, rs13312747, and rs17882106)
Hypoalbuminemia
Malignancy: Metastatic cancer (eg, colon, lungs), POEMS syndrome
Medications: Calcium-containing medications (eg, phosphate binders), corticosteroids, iron supplements, recombinant human parathyroid hormone, warfarin, vitamins D and E
Metabolic diseases: diabetes, ESRD (especially dependence on dialysis for >2 years, recent transition onto dialysis, or insufficient dialysis [ie, missed sessions])
Nutritional disorders: gastric bypass surgery, malnutrition, obesity
Skin trauma: skin biopsy, subcutaneous insulin or heparin injection, other direct trauma to the skin

Abbreviations: ESRD, end-stage renal disease; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes.



Early lesions of calciphylaxis often appear as indurated plaques with overlying mottling or livedoid pattern (A) that progress to retiform purpura (B). Purpuric lesions then evolve into black eschars (C). In later stages, necrotic, ulcerated, malodorous plaques or nodules are present (D).

report another notable health problem in the weeks or months prior to presentation.[4] More than half of patients with calciphylaxis become bedridden or require use of a wheelchair.[17] Pain is characteristically severe throughout the course of the disease; it may even precede the appearance of the skin lesions.[18] Because the pain is associated with ischemia, it tends to be relatively refractory to treatment with opioids. Rare extracutaneous vascular calcifications may lead to visual impairment, gastrointestinal tract bleeding, and myopathy.[5,9,19,20]

Diagnosis

Considering the high morbidity and mortality associated with calciphylaxis, it is important to provide accurate and timely diagnosis; however, there currently are no validated diagnostic criteria for calciphylaxis. Careful correlation of clinical and histologic findings is required. Calciphylaxis biopsies have demonstrated medial calcification and proliferation of the intima of small- to medium-sized arteries.[21] Lobular and septal panniculitis and extravascular soft-tissue calcification, particularly stippled calcification of the eccrine sweat glands, also has been seen.[2,22] Special calcium stains (eg, von Kossa, Alizarin red) increase the sensitivity of biopsy by highlighting subtle areas of intravascular and extravascular calcification.[5,23] Sufficient sampling of subcutaneous tissue and specimen evaluation by an experienced dermatopathologist are necessary to ensure proper interpretation of the histologic findings.

Despite these measures, skin biopsies may be nondiagnostic or falsely negative; therefore, when there is high clinical suspicion, it may be appropriate to move forward with a presumptive diagnosis of calciphylaxis even if the histologic findings are nondiagnostic.[1,9,24] It also is worth noting that localized progression and ulceration may occur following skin biopsy, such that biopsy may even be contraindicated in certain cases (eg, penile calciphylaxis).

Standard laboratory workup for calciphylaxis includes evaluation for associated risk factors as well as exclusion of other conditions in the differential diagnosis (Table 2). Blood tests to evaluate for risk factors include liver and renal function tests, a complete metabolic panel, parathyroid hormone level, and serum albumin level.[5] Elevated calcium and phosphate levels may signal disturbed

TABLE 2. Calciphylaxis Differential Diagnoses

Antiphospholipid syndrome (or other hypercoagulable state)
Atherosclerosis (peripheral vascular disease)
Calcinosis cutis
Cellulitis
Cholesterol embolism
Hematoma
Infectious ulcer
Livedoid vasculopathy
Martorell hypertensive ischemic ulcer
Pyoderma gangrenosum
Small- to medium-vessel vasculitis
Venous stasis ulcer

TABLE 3. Calciphylaxis Treatment Options

Medical Treatments
Anticoagulants (excluding warfarin)
Becaplermin (recombinant platelet-derived growth factor)
Bisphosphonates (eg, pamidronate, alendronate)*
Cinacalcet (in the setting of elevated parathyroid hormone)[a]
Discontinue medications (if possible) that may contribute to calciphylaxis (eg, warfarin, steroids)[a]
Intralesional sodium thiosulfate
Intravenous sodium thiosulfate[a]
Non–calcium-containing phosphate binders (eg, sevelamer)[a]
Pentoxifylline
Prostaglandins
Vitamin K supplementation
Surgical Treatments
Debridement (in appropriate candidates)
Dermal regenerative template
Parathyroidectomy
Renal transplantation
Miscellaneous
Hyperbaric oxygen therapy
Local wound care[a]
Pain management[a]

[a]Therapies most frequently employed by the authors.

calcium and phosphate homeostasis but are neither sensitive nor specific for the diagnosis.[25] Complete blood cell count, blood cultures, thorough hypercoagulability workup (including but not limited to antiphospholipid antibodies, proteins C and S, factor V Leiden, antithrombin III, homocysteine, methylenetetrahydrofolate reductase mutation, and cryoglobulins), rheumatoid factor, antineutrophil cytoplasmic antibodies, and antinuclear antibody testing may be relevant to help identify contributing factors or mimickers of calciphylaxis.[5] Various imaging modalities also have been used to evaluate for the presence of soft-tissue calcification in areas of suspected calciphylaxis, including radiography, mammography, computed tomography, ultrasonography, nuclear bone scintigraphy, and spectroscopy.[2,26,27] Unfortunately, there currently is no standardized reproducible imaging modality for reliable diagnosis of calciphylaxis. Ultimately, histologic and radiographic findings should always be interpreted in the context of relevant clinical findings.[2,9]

Prevention

Reduction of the net calcium phosphorus product may help reduce the risk of calciphylaxis in ESRD patients, which can be accomplished by using non–calcium-phosphate binders, adequate dialysis, and restricting use of vitamin D and vitamin K antagonists.[2,5] There are limited data regarding the benefits of using bisphosphonates and cinacalcet in ESRD patients on dialysis to prevent calciphylaxis.[28,29]

Management

Management of calciphylaxis is multifactorial. Besides dermatology and nephrology, specialists in pain management, wound care, plastic surgery, and nutrition are critical partners in management.[1,5,9,30] Nephrologists can help optimize calcium and phosphate balance and ensure adequate dialysis. Pain specialists can aid in creating aggressive multiagent pain regimens that target the neuropathic/ischemic and physical aspects of calciphylaxis pain. When appropriate, nutrition specialists can help establish high-protein, low-phosphorus diets, and wound specialists can provide access to advanced wound dressings and adjunctive hyperbaric oxygen therapy. Plastic surgeons can provide conservative debridement procedures in a subset of patients, usually those with distal stable disease.

The limited understanding of the etiopathogenesis of calciphylaxis and the lack of data on its management are reflected in the limited treatment options for the disease (Table 3).[2,5,9] There are no formal algorithms for the treatment of calciphylaxis. Therapeutic trials are scarce, and most of the current treatment recommendations are based on small retrospective reports or case series. Sodium thiosulfate has been the most widely used

TABLE 4. Clinical Trials for the Treatment of Calciphylaxis

Phase	Clinicaltrials.gov Identifier	Methods	Description
III	NCT03150420	Multicenter, randomized, double-blind, placebo-controlled clinical trial	CALISTA trial: evaluate the safety and efficacy of intravenous sodium thiosulfate injection for treatment of acute calciphylaxis–associated pain in hemodialysis patients
II	NCT02790073	Multicenter, open-label clinical trial	Evaluate the effect of SNF472 (hexasodium phytate) in addition to standard of care for promoting wound healing and therapeutic response in hemodialysis patients with calciphylaxis
I	NCT01289626	Single center, open-label clinical trial	Evaluate the efficacy of lanthanum carbonate for remission of skin lesions and reduction of phosphate levels in ESRD patients with calciphylaxis
NA	NCT02278692	Single center, randomized, parallel assignment trial	Evaluate the effects of oral vitamin K supplementation on anticalcification factor (carboxylated matrix Gla protein) levels and clinical outcomes in calciphylaxis
NA	NCT03319914	Multicenter observational study	Observational follow-up study of patients from the ST-001 CALISTA study
NA	NCT03146793	Single center observational, retrospective cohort study	Evaluate whether early administration of sodium thiosulfate reduces mortality in dialysis patients with calciphylaxis

Abbreviations: ESRD, end-stage renal disease; NA, not applicable.

treatment option since 2004, when its use in calciphylaxis was first reported.[31] Sodium thiosulfate chelates calcium and is thought to have antioxidant and vasodilatory properties.[32] There are a few promising clinical trials and large-scale studies (Table 4) that aim to evaluate the efficacy of existing treatments (eg, sodium thiosulfate) as well as novel treatment options such as lanthanum carbonate, SNF472 (hexasodium phytate), and vitamin K.[33-36]

Prognosis

Calciphylaxis is a potentially fatal condition with a poor prognosis and a median survival rate of approximately 1 year following the appearance of skin lesions.[37-39] Patients with proximal lesions and those on peritoneal dialysis (as opposed to hemodialysis) have a worse prognosis.[40] Mortality rates are estimated to be 30% at 6 months, 50% at 12 months, and 80% at 2 years, with sepsis secondary to infection of cutaneous ulcers being the leading cause of death.[37-39] The impact of calciphylaxis on patient quality of life and activities of daily living is severe.[8,17]

Future Directions

Multi-institution cohort studies and collaborative registries are needed to provide updated information related to the epidemiology, diagnosis, treatment, morbidity, and mortality associated with calciphylaxis and to help formulate evidence-based diagnostic criteria. Radiographic and histologic studies, as well as other tools for early and accurate diagnosis of calciphylaxis, should be studied for feasibility, accuracy, and reproducibility. The incidence of nonuremic calciphylaxis points toward pathogenic pathways besides those based on the bone-mineral axis. Basic science research directed at improving understanding of the pathophysiology of calciphylaxis would be helpful in devising new treatment strategies targeting these pathways. Establishment of a collaborative, multi-institutional calciphylaxis working group would enable experts to formulate therapeutic guidelines based on current evidence. Such a group could facilitate initiation of large prospective studies to establish the efficacy of existing and new treatment modalities for calciphylaxis. A working group within the Society for Dermatology Hospitalists has been tasked with addressing these issues and is currently establishing a multicenter calciphylaxis database.

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