

CASE REPORTS

Calciophylaxis (Calcific Uremic Arteriopathy) in a Patient With Chronic Kidney Disease

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Narrative Description

This Case Report reviews the presentation, the differential diagnosis and the treatment modalities used to treat calciophylaxis. It emphasizes the poor prognosis and that there is inadequate clinical experience to guide a physician as to what the most appropriate treatment is despite promising anecdotal reports about a variety of agents. The report demonstrates that intravenous sodium thiosulfate is tolerated.

Key Points

- Calciophylaxis occurs in 1 to 4% of patients with end stage renal failure.
- Two patterns of presentation are generally recognized—central and peripheral.
- Pain is a prominent symptom and eschar formation is usually present.
- The role of surgery is controversial.
- Several promising modalities for the treatment of this condition have been described in anecdotal reports.

Calciophylaxis is a rare condition. It is seen most frequently in patients with chronic kidney disease and can affect any part of the body.^{1–4} Calciophylaxis is increasingly being referred to as calcific uremic arteriopathy as this term more accurately reflects the histology of vascular calcification in small- and medium-sized arteries, intimal arterial hypertrophy, and small vessel thrombosis associated with panniculitis, dermal necrosis, and eschar formation.⁵ Pain is a prominent symptom. The most effective treatment for this condition remains uncertain.

Case Report

A 68-year-old female presented with an 8-month history of increasing lower extremity edema, and numerous large, painful, necrotic ulcers with an associated foul odor. She had a past medical history of type 2 diabetes mellitus, hypertension, end stage renal disease requiring hemodialysis 3 times a week for the previous 6 months, severe periph-

eral vascular disease, coronary artery disease for which she had previously undergone coronary artery bypass surgery, multiple myocardial infarctions, and congestive heart failure with an ejection fraction of 20%. She had also suffered from numerous infections including septicemia, endocarditis, and a sternal wound infection in the past with no current evidence of septicemia or endocarditis. The patient was not on calcium supplements, Vitamin D, warfarin or calcium-containing phosphate binders.

Eight months prior to admission she developed vesicles on the left thigh that slowly progressed to large, extremely painful, violaceous, indurated plaques with central ulceration and eschar (Figure 1). She subsequently developed several smaller lesions with similar morphology on her legs and feet and gangrene of her left big toe (Figure 2). A biopsy from the left thigh was consistent with calciophylaxis with associated necrosis of the deep dermis and subcutaneous tissues. The patient's lesions were aggressively debrided, broad spectrum antibiotics given, and the patient dialyzed with low calcium dialysates. Ultimately intravenous sodium thiosulfate (25 g intravenously, over 60 minutes), was given which she tolerated with no side effect. Sodium thiosulfate is thought to act by forming highly soluble calcium thiosulfate salts and therefore mobilizing tissue calcium.⁵ Hyperbaric oxygen was contraindicated because of the patient's left ventricular ejection fraction (LVEF) of 20% and previous history of congestive heart failure as this treatment modality may precipitate congestive heart failure in a patient with a low LVEF particularly with a past history of congestive heart failure. Her condition continued to deteriorate and she died a few days after initiation of intravenous sodium thiosulfate infusion secondary to a massive gastrointestinal bleed.

Discussion

The differential diagnosis for painful necrotic cutaneous ulcerations with eschar formation includes: calciophylaxis, cryoglobulinemia, cryofibrinogenemia, peripheral vascular disease, embolic phenomenon (endocarditis, septic,



FIGURE 1. Indurated, violaceous plaque with eschar formation and surrounding erythema and ulceration.

cholesterol), warfarin skin necrosis, brown recluse spider bites, hypercoagulable states, hyperoxaluria, and necrotizing vasculitis.¹⁻⁴

Calciphylaxis is a rare entity that affects approximately 1% to 4% of end stage renal failure patients.^{1,3} The typical patient is a morbidly obese, female with longstanding end stage renal disease, diabetes, hyperphosphatemia and an elevated calcium-phosphate product usually greater than 60 mg²/dL.^{1,3} It has also been described in patients with alcoholic cirrhosis and acute reversible renal failure,⁶ primary and secondary hyperparathyroidism,⁷ and metastatic breast cancer.⁸

Patients typically present with symmetric lesions that evolve from erythematous to violaceous, livedo-reticularis like patches or plaques with occasional bullae to painful, indurated, necrotic plaques that subsequently ulcerate. The ulcerations are slow to heal and covered with eschar.^{4,9}

There are 2 patterns of involvement. The central/proximal pattern involves the abdomen, gluteal region, and thighs while the peripheral/distal pattern involves the extremities distal to the elbows and knees.^{1,2,4} The central pattern tends to carry a worse prognosis,^{9,10} though this has not been validated in all reports and recent literature suggests that patients with both patterns have the worst prognosis.¹¹

A biopsy may be required to exclude other diagnoses. The histology demonstrates an obliterative vasculopathy secondary to the vascular intimal changes and endovascular fibrosis.¹² A suggestive finding is calcification of the medial wall of small- and medium-sized arteries and arterioles with associated intimal hyperplasia and fibrosis. Necrosis of the surrounding tissue, panniculitis, and soft tissue calcification are often present.^{9,13} The trauma of the biopsy can lead to worsening of the disease.

Secondary to its association with end stage renal disease, laboratory data often reveals elevated blood urea nitrogen (BUN), creatinine, parathyroid hormone, and calcium-phosphate product. Bone scans show increased uptake in the



FIGURE 2. Indurated plaque with eschar formation on the dorsum of the foot. Dry gangrene of the left big toe secondary to severe peripheral vascular disease. A pressure ulcer is seen on the lateral aspect of the heel.

subcutaneous calcified plaques.¹⁴ X-rays utilizing mammogram technique have demonstrated arteriolar calcification.¹⁵

Besides chronic kidney disease, other potential risk factors include protein C and S deficiencies, obesity, warfarin use, high calcium containing dialysates, liver disease, and systemic corticosteroids.^{4,9,11,16}

Calciphylaxis is a difficult disease to treat with a mortality of 60% to 70%⁹ and a 1-year survival rate of 45.8%.¹¹ There is no consistently effective treatment.⁵ Therapy therefore, is focused on symptom control, debridement, and treatment of infection. Mortality is most commonly due to wound infections and resulting septicemia. Meticulous wound care is important with any infection treated early and aggressively. Though trauma and surgical procedures have been known to precipitate ulcerations, given their high rate of infection early surgical debridement of wounds is often required and has been shown to improve mortality.^{11,17} Because of the poor healing of the involved tissues, wounds are often left to close by secondary intention or in some circumstances with vacuum assistance.²

As secondary hyperparathyroidism is common, attempts are often made to lower the calcium-phosphate product. This often requires parathyroidectomy.¹⁸ Calcium containing phosphate binders are avoided and low calcium dialysate used.¹⁹ However, the above interventions do not consistently improve mortality.^{5,11}

Other potential treatments include: hyperbaric oxygen therapy,²⁰ intravenous sodium thiosulfate,¹⁴ low-dose tissue plasminogen activator,²¹ cinacalcet,²² etidronate disodium,²³ and maggots.²⁴ Because of the rarity of the condition, most of the literature to date is anecdotal and based on case reports and small retrospective studies.

Conclusions

As the number of patients who develop chronic kidney disease and require hemodialysis increases, it is likely that the

number of patients who develop calciphylaxis will also increase. Hospitalists, besides nephrologists, should therefore become familiar with the presentation of this disease as it is possible, although unproven, that treatment in the early stage of the disease may result in a better response. Although several treatment modalities have been used to treat calcific uremic arteriopathy or calciphylaxis, it remains unclear what is the best treatment for these patients. Carefully done clinical trials using some of the treatment modalities mentioned will help physicians decide what the most appropriate treatment is for patients with this debilitating and often fatal disease.

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