Painful Skin Ulcers in a Hemodialysis Patient

Stuart M. Sprague

Summary
Calciphylaxis, also referred to as calcific uremic arteriolopathy, is a relatively rare but well described syndrome that occurs most commonly in patients with late stage CKD. It is characterized by very painful plaques or subcutaneous nodules and violaceous, mottled skin lesions that may progress to nonhealing ulcers, tissue necrosis, and gangrene with a 1-year mortality rate >50%. The pathogenesis of calciphylaxis is poorly understood. Risk factors include female sex, obesity, hyperphosphatemia, hypercalcemia, hyperparathyroidism, longer dialysis vintage, hypercoagulable states, and use of calcium-containing phosphate binders and warfarin. Treatment strategies for calciphylaxis are limited by inadequate understanding of its pathophysiology. Therapy is generally focused on correcting disturbances of calcium, phosphorus, and parathyroid hormone metabolism. Additional therapy focuses on decreasing inflammation and on dissolution of tissue calcium deposits with sodium thiosulfate. Additional strategies for calciphylaxis are limited by inadequate understanding of its pathophysiology. Therapy is generally focused on correcting disturbances of calcium, phosphorus, and parathyroid hormone metabolism. Additional therapy focuses on decreasing inflammation and on dissolution of tissue calcium deposits with sodium thiosulfate.

Case Description
Abhijit Naik, MD (Renal Fellow). A 54-year-old white man was referred from an outside dialysis clinic for evaluation of necrotic skin lesions. He had a 10-year history of diabetes and hypertension, with ESRD secondary to diabetes. His history was also significant for coronary artery disease, with two prior myocardial infarctions and atrial fibrillation. He had been undergoing thrice-weekly hemodialysis for 2 years with a Kt/V between 1.3–1.4. Three months before presentation he noticed several small firm and very painful nodules on both anterior thighs. He stated that after several weeks the lesions became much larger, black, and spread to the lateral thighs and buttocks. He was treated with mupirocin ointment and a vascular evaluation revealed normal blood flow in his legs. Aside from these painful lesions, he stated that he generally felt “ok.” Dialysis had been proceeding without problems. He denied chest pain, dyspnea, abdominal pain, or any gastrointestinal complaints. Review of systems was otherwise unremarkable. He never smoked and drank alcohol very infrequently. Medications included aspirin, amiodarone, simvastatin, famotidine, glipizide, clopidogrel, sevelamer carbonate, hydrocodone, and gabapentin. He had no known allergies.

On examination his vital signs were as follows: temperature, 98.8°F; heart rate, 80 beats per minute; BP, 94/60 mmHg, with no orthostatic changes; and respiratory rate, 20 breaths per minute. His BP was generally low, with systolic BP averaging between 90 and 100 mmHg. He was an ill appearing male in mild distress from extremity pain. His lungs were clear and a cardiovascular examination revealed a regular rate and rhythm with a 2/6 holosystolic murmur. His abdomen had normal bowel sounds and was mildly distended with some ascites, but was otherwise nontender and without appreciable masses or organomegaly. He had a normal appearing dialysis graft in his left arm. The patient’s lower extremities revealed multiple necrotic lesions of both thighs with smaller erythematous areas of the lower legs (Figure 1). The surrounding erythematous areas were extremely tender with subcutaneous firmness to palpation. He had lower extremity edema (2+) and palpable pulses in both feet. There were no other skin lesions. Pertinent laboratory data included the following: serum calcium, 8.8 mg/dl; phosphorus, 5.1 mg/dl; albumin, 3.2 g/dl; parathyroid hormone (PTH), 560 pg/ml; and alkaline phosphatase, 354 IU/L.

Discussion
In summary, this patient presented with a several month course of skin lesions progressing from small painful nodules to large necrotic lesions on both anterior thighs. The differential diagnosis of his presentation includes warfarin skin necrosis, peripheral vascular disease, vasculitis, cellulitis, and athereom-bolic disease (1). However, this case represents a rather classic presentation of calciphylaxis, otherwise known as calcific uremic arteriolopathy (CUA). CUA is a relatively rare but well described entity that occurs most commonly in patients with late stage CKD, ESRD, or after transplantation. Although the initial clinical description was likely in 1898 (2), it was not until 1961 when Selye and colleagues coined the term calciphylaxis after inducing an anaphylactic-like hypersensitivity response in rats that resulted in soft tissue calcification and cutaneous necrosis (3). Clinically, CUA is characterized by very painful placques or subcutaneous nodules, and violaceous, mottled skin lesions that may progress to nonhealing ulcers, tissue necrosis, and gangrene with a 1-year mortality rate >50%. The pathogenesis of calciphylaxis is poorly understood. Risk factors include female sex, obesity, hyperphosphatemia, hypercalcemia, hyperparathyroidism, longer dialysis vintage, hypercoagulable states, and use of calcium-containing phosphate binders and warfarin. Successful treatment generally results in improvement of pain and healing of the lesions within 2–4 weeks, but the disorder generally takes many months to completely resolve.


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Attending Rounds
necrosis, and gangrene. The clinical course may be complicated by surgical resections and amputations with a 1-year mortality rate >50%, with most deaths due to sepsis (4,5). Its pathology is significant for small vessel involvement and distal calcifications with intimal proliferation often accompanied by microthrombi. Although the pathogenesis of calciphylaxis is poorly understood, several factors appear to increase risk such as female sex, hyperphosphatemia, hypercalcemia, and hyperparathyroidism (5). Other factors associated with the development of calciphylaxis include obesity, longer dialysis vintage, hypercoagulable states, and the use of calcium-containing phosphate binders and warfarin (5-7). Risk factors in this patient included hyperparathyroidism and his long history of diabetes.

**Diagnosis**

CUA may develop in up to 4% of chronic dialysis patients (8,9). CUA can be very hard to diagnose clinically due to similar presentation of many other comorbid illnesses in CKD and dialysis patients. As previously mentioned, the differential diagnosis includes warfarin-induced skin necrosis, peripheral vascular disease, vasculitis, cellulitis, and atheroemboli (1). The absence of recent warfarin use rules out warfarin-induced skin necrosis. Peripheral vascular
disease generally presents with nonhealing distal painful ulcers in the legs and feet that are associated with decreased blood flow to the extremities with diminished pulses. Atheroembolic disease is part of a multisystem disorder with systemic manifestations. The cutaneous manifestations are the result of occlusion of small arterioles and present as blue toe syndrome or livedo reticularis (10). Cutaneous vasculitis frequently presents with petechiae, palpable purpura, hemorrhagic bullae, digital ulceration, or livedo reticularis, which can be easily differentiated from the classic firm subcutaneous nodules of CUA. Finally, cellulitis generally has noncalcium-containing radiolucent tissues but may be present in peripheral vascular disease tend to be distal. This is especially important because there is a high burden of peripheral vascular disease in dialysis patients.

Histopathologic features include circumferential wall calcification involving both the medial and intimal layers of small and medium size vessels. There is intimal hyperplasia with partial obliteration of the vessel lumen. Fibrin thrombi are often noted and are in close proximity to epidermal and dermal necrosis with necrosis frequently extending into the subcutaneous tissue (12).

A thorough clinical examination is the cornerstone of identifying these lesions early, especially when they are still nonulcerative (plaques), because they may represent potentially treatable disease (9). Tissue diagnosis is discouraged, first because it can initially be negative, but more importantly because performing biopsies may be associated with increased risk of progression of nonulcerative disease to ulcerative disease, infection, and mortality (9). Radiographic studies, including plain radiographs, high-resolution computed tomography scans, and mammographic techniques, can help distinguish calcium from surrounding noncalcium-containing radiolucent tissues but may be positive in <30% of patients with confirmed disease (9,13). Mammographic techniques are superior to computed tomography or plain films, although a significant limitation of mammographic imaging is that it can be quite painful, because it involves compressing the affected extremity between two plates (13). Bone scans may reveal increased technetium in affected areas in up to 97% of affected patients (8,9). The uptake is almost always subcutaneous. Given its noninvasive nature and high sensitivity, the bone scan could be the mode of choice to confirm a clinical suspicion of CUA. However, patients with florid and deep ulceration may have a negative scan due to complete denudation of subcutaneous tissue (9).

Risk Factors

Most information regarding risk factors for CUA is based on very small series and case reports, and thus should be interpreted with some caution. CUA rarely occurs in predialysis CKD patients and in the absence of renal failure (4,14) but most patients are undergoing dialysis. Peritoneal dialysis patients appear to have a slightly greater risk than hemodialysis patients (9,14,15). Most of the risk factors described point overwhelmingly to an altered calcium and phosphate milieu (Table 1), although CUA may occur in patients with serum calcium, phosphate and PTH concentrations in target ranges. Major risk factors for CUA include white race, younger age, elevated serum calcium or phosphate concentration, calcium×phosphate product and PTH concentrations (5), lower serum albumin, elevated serum alkaline phosphatase, and protein C and/or S deficiency (16–21). Local trauma, obesity (body mass index>30), liver disease, and use of systemic corticosteroids and warfarin have also been found to be independent risk factors (4,5,16–18). Warfarin likely promotes the development of CUA by reducing functional protein C levels and blocking vitamin K–dependent carboxylation of the matrix GLA protein, which is a local inhibitor of vascular calcification (22,23). Use of calcium supplements has been associated with increased risk of calciphylaxis in some (19,24), but not, all studies (7,17). Recent studies have suggested that parenteral iron may also be associated with development of CUA (25,26).

Risk factors in this patient included his being relatively young and white with a long history of diabetes and associated vascular disease. His laboratory data demonstrated mild hyperparathyroidism, although his PTH concentration was not especially elevated, nor were his serum phosphorus or calcium concentrations. He did have an elevated alkaline phosphatase and he was hypoalbuminemic. His dialysis vintage was not particularly long and he had not been exposed to warfarin.

Treatment and Outcome

Abhijit Naik, MD (Renal Fellow). A diagnosis of CUA was made and the patient was treated with daily dialysis with 25 g of sodium thiosulfate infused over the last hour of dialysis. His phosphate binder was switched from sevelamer carbonate to 2000 mg of lanthanum carbonate with meals. Daily wound care consisted of dressing changes, leaving the

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wounds dry with no debridement. After about 2 weeks, his pain was much improved and dialysis and sodium thiosulfate was decreased to thrice weekly. The dialysate calcium concentration was maintained at 2.5 mmol/L. He did not receive vitamin D receptor activator (VDRA) agents or cinacalcet for his hyperparathyroidism. Serum phosphate remained between 3.0 and 4.2 mg/dl and PTH between 350 and 500 pg/ml. He remained in the hospital for 3 weeks and was then transferred to a skilled nursing facility. He continued to improve over the next 6 weeks, but approximately 2 months after presentation he suffered a myocardial infarction and died.

Management

General Measures. Effective treatment options for CUA remain elusive. Treatment requires a multidisciplinary approach that may involve vascular and plastic surgeons, wound care experts, dieticians, and nephrologists. Early recognition is imperative to correct potential modifiable risk factors and initiate therapy that could prevent disease progression.

There is some evidence supporting the use of surgical debridement (4). However, most agree that debridement should be kept to a minimum because of poor wound healing with secondary infections and extension of the lesions (27). It is important to maintain a sterile environment with local wound care that should include gentle wound debridement while avoiding deep or wide surgical debridement and skin grafting. Appropriate sterile dressings should provide a moist environment while removing excessive exudates and should be easy to apply and remove in order to reduce surrounding skin trauma (4,27,28).

Warfarin should be discontinued, if possible (29). Alternatives such as heparin could be used for the short term if anticoagulation is necessary. The use of alternative anticoagulants, such as thrombin inhibitors, may have a role for patients needing long-term anticoagulation, although these agents have not been studied in calciphylaxis.

Tissues of patients with calciphylaxis have been shown to have low oxygen tension and hence hyperbaric oxygen is thought to have some utility (29–32). Hyperbaric oxygen therapy offers the ability to increase tissue oxygenation, improve angiogenesis, and enhance phagocytic activity and bactericidal action. Retrospective series have suggested that hyperbaric oxygen therapy reversed ulcerations in 8 of 11 (31) and 2 of 5 (32) patients with relatively well controlled hyperparathyroidism. Of note, among patients in whom tissue oxygenation was measured, those who failed hyperbaric therapy did not demonstrate an increase in tissue oxygenation (32). Favorable prognosis was associated with distal lesions and undergoing >20 sessions (31,32) Potential side effects include barotrauma, reversible myopia, and neurologic complications from oxygen toxicity (33).

Mineral Metabolism. The primary focus of therapy should be to optimize calcium and phosphate homeostasis. Avoidance of a positive calcium balance and preventing the development of hypercalcemia should be a high priority (Table 2). Limited clinical data are available suggesting that lowering calcium intake improves CUA (27,34). Thus, discontinuation of calcium-based phosphate binders, adjustment of hemodialysis or peritoneal dialysis dialysate, and minimizing the use of VDRAs should be considered as initial therapeutic steps. Depending on the serum calcium concentration, hemodialysate calcium concentration can be reduced, with appropriate monitoring of blood chemistries. Dialysate calcium concentrations as low as 0–1.0 mEq/L have been used effectively (34–37). I generally do not recommend using dialysate concentrations lower than 1.25 mEq/L, however, because of risk of hemodynamic instability or cardiac arrhythmias from transient hypocalcemia.

Hyperphosphatemia, with an associated increase in calcium×phosphate product, appears to be more important than calcium concentration alone in the pathophysiology of

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<td>Low calcium dialysate</td>
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<td>Decreasing calcium intake, including use of noncalcium-containing phosphate binders</td>
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<td>Increasing Kt/V</td>
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<td>Hyperbaric oxygen</td>
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<td>Bisphosphonates</td>
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PTH, parathyroid hormone.
CUA. Thus, aggressive control of hyperphosphatemia with noncalcium-based binders (e.g., sevelamer carbonate, lanthanum carbonate, or even aluminum) and dietary phosphate restriction should be initiated. Intensifying dialysis or changing from peritoneal to hemodialysis has been suggested to be beneficial in some studies (24). Decreasing serum phosphorous levels by increasing the duration and frequency of hemodialysis has been reported to be beneficial in the resolution of CUA by several investigators (27,34,36,38–41). Although there are no studies demonstrating the optimal duration of intensified dialysis, I strongly recommend a course of dialysis 5–7 days per week for the first couple weeks of treatment, with the duration of this intensified dialysis therapy depending on clinical response. The relationship of calciphylaxis with hyperparathyroidism is best seen in nonuremic patients (4,14,21,42). There are reports that parathyroidectomy may benefit wound healing (43–45) and increase survival (5,39,45), whereas other studies demonstrated no benefit to parathyroidectomy (4,46). In fact, Budisavljevic and colleagues reviewed 47 patients with CUA, 31 of whom underwent parathyroidectomy; 50% of these patients died within 9 weeks of surgery (47). Thus, the role of parathyroidectomy remains controversial (5,8,42,48–50). Parathyroidectomy is unlikely to be useful when PTH concentrations are not markedly elevated (1,5,41). I generally would not consider parathyroidectomy with PTH concentrations of <800–1000 pg/ml.

Medical management of hyperparathyroidism remains important and relies on intensified dialysis, as well as the use of noncalcium-based phosphate binders and cinacalcet. Cinacalcet has been successfully used in several patients with CUA (22,51–55). VDRAs increase the risk of developing hypercalcemia or hyperphosphatemia; however, they have been used successfully in combination with cinacalcet (54,56,57).

**Newer Therapies.** Several adjunctive therapies have recently been shown to have some success in the management of CUA (Table 2). Reports of sodium thiosulfate used to treat CUA first appeared in 2004 (51). There has since been numerous case reports and small series demonstrating effective treatment of CUA with the addition of sodium thiosulfate to the treatment regimen (22,38,52–55,58–61). Sodium thiosulfate is a chelating agent that has antioxidant activity and increases activity of endothelial nitric oxide synthetase (22); it has been used to treat cyanide toxicity, to reduce toxicity of cisplatin chemotherapy, and to chelate calcium in the treatment of nephro lithiasis (62–64). In CUA, sodium thiosulfate is believed to act by dissolving insoluble tissue calcium salts to form calcium thiosulfate, which is many thousand times more soluble than many other calcium salts (62).

There is no consensus as to the best dosing schedule for sodium thiosulfate (22,38,51–55,58–61). Intravenous doses have varied from 5 to 75 g after or during the last 30–60 minutes of hemodialysis. Sodium thiosulfate is predominantly metabolized by nonrenal mechanisms and is readily dialyzed. Serum concentrations drop quickly whether given before, during, or after dialysis, and more data are required to determine the optimal dosing schedule (65). The most commonly reported dose has been 25 g thrice weekly at the end of dialysis. In patients with more frequent dialysis, it is generally given after each dialysis session. Clinical improvement usually is noted within 2–3 weeks with a decrease in pain and stabilization of lesions. However, complete wound healing generally takes many months, and thus therapy may last for 6–12 months. Although it is generally well tolerated, adverse effects include nausea, emesis, and the development of a high anion gap metabolic acidosis. The acidosis is thought to occur through the generation of thiosulfuric acid when sodium thiosulfate is dissolved in aqueous solution (52) which can easily be managed by treating the patient with supplemental oral sodium bicarbonate or by altering the bicarbonate level of the dialysate. There are reports of a few patients undergoing successful intraperitoneal treatment with sodium thiosulfate (15,58), although it was thought to cause recurrent peritonitis in one patient (15). There is also a report of using oral sodium thiosulfate for prevention of recurrence in one patient (66) and as long-term maintenance therapy in four patients who had persistent skin lesions after 6 months of intravenous therapy (40). However, one of the four patients developed progression of disease, which was thought to be due to noncompliance.

Although there are no clear data as to the best treatment regimen, my standard protocol is to administer 25 g of sodium thiosulfate during the last hour of each dialysis session. Once there is a decrease in pain and stabilization of lesions, I generally decrease dialysis frequency and sodium thiosulfate dosage from 5–7 days weekly to thrice weekly, which generally occurs after 10–14 days. Once the patient becomes totally pain free and the lesions are clearly resolving, I then decrease the dose of sodium thiosulfate to 12.5 mg thrice weekly at the end of dialysis. This is generally 3–6 months into therapy. I also believe that it is easier to maintain more aggressive control of calcium and phosphate balance in patients with CUA with hemodialysis compared with peritoneal dialysis. Thus, I recommend that peritoneal dialysis patients be switched to hemodialysis and obtain intravenous sodium thiosulfate treatment.

Bisphosphonates are a class of antiresorptive drugs that inhibit osteoclastic activity and decrease bone turnover (67). There are several reports on the efficacy of bisphosphonate therapy in calciphylaxis (55,68–70). The potential mechanisms of bisphosphonate therapy likely include control of high bone resorption, an anti-inflammatory action (68), and an inhibition of calcification via inhibition of an NF-κB pathway (71). Unfortunately, bisphosphonates can have long-term adverse effects (and are typically contraindicated in patients with advanced CKD); thus, their role in treating calciphylaxis is unclear. Few data are available on the role of and the appropriate use of bisphosphonates in CUA. I suggest this therapy for those who have evidence of high bone turnover who are not responding to other therapies after 2–4 weeks.

**Questions**

Rebecca Seshasai, MD (Renal Fellow). Are dialysis patients who are successfully treated for calciphylaxis at increased risk for recurrence? If so, does the disease tend to recur in the same location? Do you have any recommendations for monitoring and treatment of recurrences?

The overall occurrence of CUA is relatively rare and sporadic with a relatively poor response to therapy. There are many patients who do not have complete recovery and
require long-term management. I would consider any patient who has developed CUA as being at increased risk of recurrence; however, there are no data available to assess risk of recurrence. In a review of 172 chronic hemodialysis patients who were treated with sodium thiosulfate, the long-term outcomes of 53 patients were obtained by a survey sent to the attending nephrologist. None of the patients were reported to have recurrence (61). As far as monitoring patients, I would recommend aggressive phosphate control, avoidance of hypercalcemia, avoidance of calcium-containing phosphate binders, as well as avoidance of agents that increase risk, such as warfarin, parenteral iron, and corticosteroids.

Suzanne Boyle, MD (Renal Fellow). Given that there are reports of calciphylaxis after transplant, can patients with a previous history of calciphylaxis receive a kidney transplant? Are they at increased risk for developing calciphylaxis again after transplantation?

Unfortunately, there are no data to assess the risk of calciphylaxis after transplantation, nor are there data reporting the outcome of patients who have had CUA and were subsequently transplanted. In my opinion, if a patient had CUA and has totally recovered, I would recommend that patient be evaluated and transplanted based upon the same criteria used for any other potential transplant candidate.

Matt Denker, MD (Renal Fellow). In an effort to prevent CUA, do you think we should have different target recommendations for serum calcium, phosphate, PTH, and choice of phosphate binder for patients who have multiple risk factors for CUA?

In terms of CKD-mineral bone disorder targets for patients at risk of CUA, I do not believe we should have different therapeutic targets. The primary focus should be on calcium and phosphate and we should aim to achieve normal values, as recommended by Kidney Disease Improving Global Outcomes guidelines (72). In regard to phosphate binders, it would be best to limit or avoid calcium-containing binders in those who are at increased risk for CUA.

In summary, calciphylaxis or CUA, is a relatively rare complication of CKD that results from disordered mineral metabolism, chronic inflammation, microvascular disease, and possibly a disordered coagulation system. It is critically important to correctly identify calciphylaxis due to its very high mortality rate of close to 50%. Therapy is multifactorial and includes aggressive management of calcium, phosphate, and PTH abnormalities, removal of potential inciting agents such as warfarin or calcium-containing drugs, and appropriate wound care. Most patients will require combined therapy that may include intensified dialysis, the early administration of sodium thiosulfate or possibly bisphosphonates, and the addition of cinacalcet or parathyroidectomy if severe hyperparathyroidism cannot be controlled.

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