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Case Report

A Positive Outcome in a Patient with Bilateral Leg Calciphylaxis: A Case Report

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Abstract

Calciphylaxis is a rare but serious condition characterized by calcification of small blood vessels, which causes thrombosis and tissue necrosis. Most patients who are diagnosed with calciphylaxis have End-Stage Renal Disease (ESRD) and are on dialysis therapy. The one-year mortality rate is as high as 50%, with the cause of death usually related to complications from wound infections. Treatment consists of wound cares, control of serum calcium concentrations, aggressive dialysis, and time.

In this case report we present a 70 y/o male with ESRD on dialysis who presented with severe bilateral calciphylaxis encompassing both legs from the knees to the ankles. Amputation was considered, but after multimodal treatment consisting of wound cares, pharmacotherapy with sodium thiosulfate and cincalcet, and consistent dialysis, he eventually recovered after about 1 year of therapy. This case report demonstrates the significance of multidisciplinary treatment of this disease and can act as a valuable guide for clinicians who are treating patients with calciphylaxis.

Keywords: Calciphylaxis; Calcific Uremic Arteriolopathy; End-Stage Renal Disease; Dialysis; Wound Cares; Calcium; Sodium Thiosulfate; Cincalcet

Abbreviations

ESRD; End-Stage Renal Disease; PTH; Parathyroid Hormone

Body Text

The patient is a 70-year-old male with a past medical history of ESRD who had been undergoing routine hemodialysis 3 days a week via a left upper extremity arteriovenous fistula for the past 5 years. He presented to a hospital in the Midwest U.S. with a chief complaint of left leg pain and redness. He was very concerned about the possibility of bug bites as the cause of his symptoms. He was initially followed closely as an outpatient, but the erythema and tenderness increased over the next month, and he was briefly treated with doxycycline for a suspected cellulitis. Eventually his right leg started becoming affected as well. He started developing black eschars on both shins, and the legs became increasingly scaly and dry.

He came to the emergency department about 3 months after the onset of symptoms. He described a "crawling" sensation on both legs, still convinced he was suffering from multiple bug bites. On exam his legs were erythematous, extremely tender, edematous, and warm from the ankles to the knees. Labs were notable for an elevated serum C-reactive peptide of 131 mg/dL, but his total serum calcium was 8.8 mg/dL and his other labs were within normal limits as well. Doppler studies showed normal arterial function bilaterally. One of the eschars was noted to resemble calciphylaxis, so a skin biopsy was performed and confirmed to be calciphylaxis.

The patient was started on sodium thiosulfate and wound care specialists were consulted. A few weeks later he was started on cincalcet. By about 2 months following the initial diagnosis, he had developed circumferential black eschars, and the patient described his wounds as "very hot water being poured down my legs." Vascular surgery was consulted to discuss amputation. Representative photographs of his legs at this time are depicted in (Figure 1).

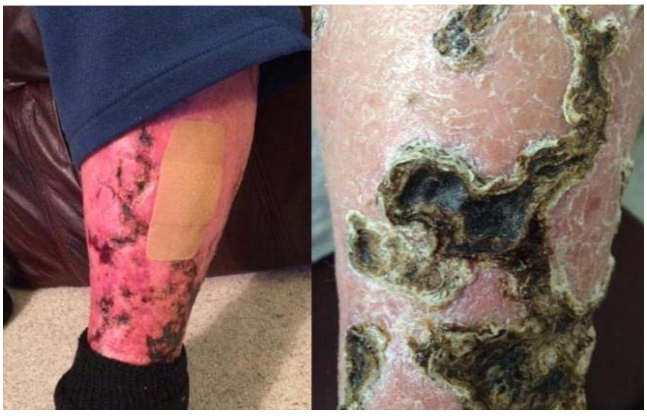

Figure 1: Representative images of patient's left lower extremity calciphylaxis at peak severity. Photographs taken and submitted with patient permission.

The decision was made to hold off on surgical intervention and continue current cares. About a month later the eschars started contracting and becoming malodorous, with yellow discharge at the edges. The patient also had a mild fever and a leukocytosis. The patient was started on empiric moxifloxacin and was later switched to doxycycline. A few days later an eschar on the left calf sloughed off. Surgery was re-consulted and stayed on board permanently to help with wound management. Aggressive wound cares continued daily. Antibiotics were able to be discontinued around month 4, and the patient started being able to walk again with the help of physical

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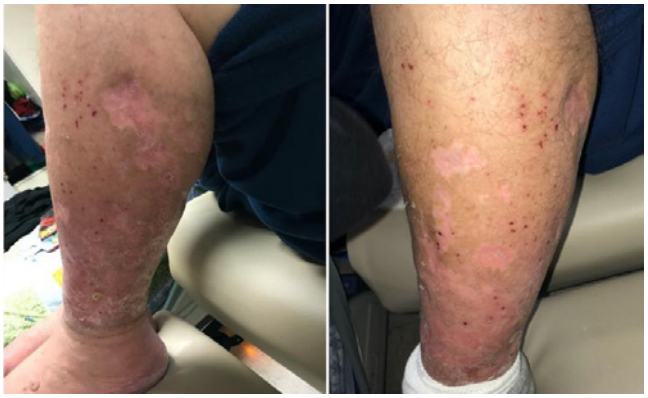

Figure 2: Representative images of patient's left lower extremity calciphylaxis after 10 months of treatment. Photographs taken and submitted with patient permission.

therapy. He was tolerating daily showers and was no longer having pain during the application of topical antibiotic ointments and wound dressings.

For this entire time the patient continued hemodialysis 3 times a week, and his calcium and phosphate levels stayed within normal limits. He never developed any additional wound complications and continued to improve each week. Representative photographs of his healing legs are depicted in (Figure 2).

Discussion

Definition: Calciphylaxis is a syndrome where the small blood vessels become calcified and thrombotic, leading to tissue necrosis and significant morbidity and mortality. Some authors state that "calciphylaxis" is a misnomer because the suffix "-phylaxis" means "protection against" and there is no evidence that calciphylaxis has any protective value in clinical settings [1]. The term was developed by Hans Selye, who first performed experiments in rats and felt that cutaneous calcification in these animals was an adaptive, or protective response [2]. An alternative, more descriptive term proposed by some authors is "calcific uremic arteriolopathy", [3] but this term limits itself only to uremic patients, and calciphylaxis can develop in non-uremic patients [4]. Calciphylaxis is the most commonly understood term to describe this condition and is the term used in this article. Another descriptive term is "metastatic calcification, describing the passive deposition of calcium in the small arterioles of the skin [5].

Epidemiology: Calciphylaxis is rare. It is most often seen in patients with end stage renal disease on dialysis, with a prevalence of about 4% in one 1997 study [6]. End stage renal disease, hypercalcemia, and hyperphosphatemia are the strongest risk factors. Other risk factors are diabetes mellitus, obesity, autoimmune conditions, hypercoagulable states, hypoalbuminemia, and reliance on dialysis for longer than about 6-7 years. It has a 2:1 female predominance [4]. There is growing suspicion that warfarin use is somehow associated with the development of calciphylaxis [7], which is why warfarin was discontinued in our patient.

Pathophysiology: The true mechanism underlying the development of calciphylaxis is not completely understood. Vascular calcification is a ubiquitous finding in patients who do not get calciphylaxis – atherosclerosis and arteriosclerosis show vascular calcification - so there must be a more complicated mechanism driving this disease process. One attractive explanation is a "2-hit model" where the preexistence of calcified vessels must be followed by a thrombus formation before ischemia and tissue necrosis is able to set in [8, 9].

Diagnosis: The diagnosis of calciphylaxis is a clinical one, relying on a collective consideration of several factors. There is no simple blood test that can prove the existence of calciphylaxis. Skin biopsy can definitively diagnose the disease, but unfortunately the act of performing the biopsy can create a nidus for the calciphylactic process at the site of the biopsy, making matters worse [10, 11]. An experienced clinician can often make the diagnosis based on the appearance of the lesions alone. This is how our patient first received his diagnosis; biopsy was performed later in hopes of ruling it out.

Often the first sign of calciphylaxis is a livedo reticularis pattern [4, 9, 12]. Symptoms usually include superficial pain similar to that of zoster neuralgia, which is often included in the initial differential diagnosis [9]. Our patient repeatedly described the symptom of formication – the sensation of bugs crawling under the skin – but similar descriptions of this symptom are not easily found in the literature. The location of the lesions is variable. It is commonly seen on the trunk and legs [10], but there are reports of calciphylaxis showing up on the dorsal hands [13], vulva [14], and face [15].

Oddly, high serum calcium and phosphate concentrations are not sensitive diagnostic markers. In one study, patients who had calcium x phosphate products of 70 or more had a highly specific (95%) association with calciphylaxis, but the sensitivity was low (21%); more than 50% of patients diagnosed with calciphylaxis had a calcium-phosphate product less than 50 [5]. Our patient maintained normal calcium and phosphate levels essentially throughout his entire course.

When skin biopsies are obtained, a triad of descriptors is typical in the pathology report: medial calcification of cutaneous arterioles, intimal hyperplasia, and adipose tissue necrosis [9].

Treatment: Treatment of calciphylaxis is multimodal, consisting of local wound cares with the goal of avoiding infection, and regulation of serum calcium and phosphate concentrations to prevent worsening vascular calcification. The most frequent cause of death in these patients is sepsis from wound complications. Therefore, preventing wound infections is a critical component of treatment.

Sodium thiosulfate is an antioxidant used to treat cyanide poisoning, but it can also be used off-label to treat calciphylaxis [16]. A meta-analysis of the drug showed that sodium thiosulfate was effective in 84.4% of case reports and 67.0% of multi-case reports [17].

Cincalcet is a calcium-mimicking drug that has also shown efficacy in case reports [18]. This medicine increases the sensitivity of the calcium-sensing receptor on the parathyroid glands, which leads to decrease PTH levels and subsequent reduction in calcium concentrations [19].

Cessation of warfarin is also a wise treatment decision in patients who are taking the anticoagulant for other indications. There is an association between warfarin and the development of calciphylaxis, but the mechanism is not yet known [7].

Prognosis: The prognosis is notoriously poor, with most studies and reports showing a one-year survival rate of around 50%. One study showed a 1 year survival rate of 61.6% for patients who underwent surgical debridement compared with 27.4% survival after 1 year in patients who did not undergo debridement [5].

Summary and Future Directions: In this brief case report we present a positive outcome in a patient with calciphylaxis. Our patient had several risks factors and demonstrated the classic signs and symptoms of calciphylaxis. He did well because we employed a multimodal treatment approach, patience while the patient slowly recovered over several months, and an interdisciplinary team of surgeons, wound care nursing specialists, infectious disease physicians, and nephrologists working with the patient every day.

As the prevalence of chronic kidney disease increases, more patients will be requiring dialysis in the future. Many of these future patients might find themselves still on dialysis after several years, and many of these patients might develop this unfortunate syndrome. As the awareness of calciphylaxis increases, more diagnoses will be made, more research will be undertaken, and hopefully our ability to treat these patients will continue to improve.

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