CLINICAL VIGNETTE

Calciphylaxis in a Renal Transplant Patient

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Introduction

A 53-year-old female with a history of end-stage renal disease secondary to Type 2 diabetes mellitus status, post-deceased donor renal transplant (DDRT) 15 months ago presented to the hospital with non-healing ulcers for the past few months.

The ulcers originally began as small scratches from her dog but became larger and more painful as the months progressed. She had been going to the wound care clinic for the past three months for wound debridement with no improvement.

One month ago, she was hospitalized for cryptococcal pneumonia and treated with a course of cephalexin for a presumed diagnosis of cellulitis of her ulcers, also without any improvement.

Past medical history is relevant for a deceased donor kidney transplant with no episodes of rejection, Type 2 diabetes mellitus, paroxysmal atrial fibrillation, and both cryptococcal and aspergillus pneumonia.

Her medications included voriconazole, metoprolol, amiodarone, and warfarin.

Family history was significant for renal failure secondary to diabetes in her mother. She denied any tobacco, alcohol, or recreational drug usage. She denied any recent travel or sick contacts.

Her review of systems is significant only for constipation but negative for fevers, chills, weight loss, or joint pains.

Initial presentation showed a temperature of 36.9°C, pulse of 60, blood pressure of 138/61, a respiratory rate of 18/minute, and an oxygen saturation of 99% on room air.

Physical exam was significant for several necrotic ulcers with violaceous borders and eschar development on the bilateral lower extremities extremely tender to palpation *(Figure 1)* with a similar 1-2 cm lesion on the dorsal aspect of the right ulnar hand as well. Her lower extremities had strong pedal pulses with brisk capillary refill.

Initial laboratory evaluation revealed the following:

- Normal complete blood count (CBC);
- Normal creatinine of 0.9;
- Elevated calcium level of 11;
- Elevated erythrocyte sedimentation rate (ESR) of 74;
- Elevated C-reactive protein (CRP) of 3; and
- Elevated parathyroid hormone (PTH) at 156.

A nuclear medicine parathyroid scan showed a left and possibly right inferior parathyroid adenoma.

The patient was admitted to the medical service for expedited work up of her leg ulcers. Dermatology obtained three biopsies of the leg lesions, one of which was significant for calcium deposition in two medium-sized arterioles in the subcutis consistent with calciphylaxis. There were mild fibrinoid changes inconsistent with primary vasculitis with staining negative for Cryptococcus and other microorganisms. Bacterial and fungal cultures of both shin tissue and blood were negative as well.

The biopsy results solidified the clinical diagnosis of calciphylaxis. The patient was started on cinacalcet to lower her calcium levels, intravenous sodium thiosulfate therapy three times/week, and daily hyperbaric oxygen therapy.

The patient's ulcers showed some improvement, and she was discharged home with daily hyperbaric oxygen therapy without sodium thiosulfate.

Epidemiology

Calciphylaxis was a previously rare condition, but with the increasing population of patients on dialysis awaiting renal transplant, the number of reported cases have risen substantially.

The reported incidence is between 1-4% of patients with ESRD.[1] In addition to chronic kidney disease (CKD), other risk factors include obesity, female gender, Caucasian race, diabetes, and other metabolic disorders.[1]

Pathogenesis

Calciphylaxis is due to deposits of calcium-rich vesicles in the extracellular matrix. Hypophosphatemia associated with ESRD is known to be a precipitating event that causes formation of the calcium-phosphate product (CPP) that leads to increased matrix mineralization.[2] A CPP of greater than 70 mg^2/dL^2 is associated with a higher risk for calciphylaxis. Hans Selye performed the initial investigation of calciphylaxis in the 1960s,[3,4] in which he used a series of rat models to identify two classes of substances–"challengers" and "sensitizers"–required to cause calcification.

In general, sensitizing agents needed to be introduced 1 to 2 days prior to the challenging agent for calciphylaxis to occur. In patients with ESRD, increased PTH levels, calcium, and phosphorous serve as the sensitizing agent.

Obesity is also a known risk factor for calciphylaxis, possibly due to the increased tension placed on the arterioles by excess adipose tissue.[5]

Clinical Manifestations

Patients with calciphylaxis will typically present with livedo reticularis due to ischemia in the subcutaneous arterioles. Over time, these skin findings develop into extremely painful subcutaneous plaques and eventually into necrotic ulcers with eschar formation.[6]

The lesions are most commonly found on the lower extremities and the abdomen and occasionally found on the digits.[7,8] Calciphylaxis can often be differentiated from peripheral vascular disease by the diffuse bilateral location of the lesions as well as intact peripheral pulses. A non-skin finding that may be present is proximal muscle weakness due to ischemic myopathy.[9]

Diagnosis

Calciphylaxis is diagnosed clinically with the characteristic lesions of ischemic necrosis developing in areas of high adipose tissues (abdomen, buttocks, and thighs). In a large retrospective study of 172 patients, the legs were involved in 60% of cases, abdomen in 23%, and the buttocks in 9%.[8]

Definitive diagnosis can be made with biopsy of the lesion. Pathology will reveal calcification of the small and medium-sized vessels with thickening of the intima and smooth muscle atrophy surrounding the vessels.[10]

Management

There are no established calciphylaxis treatment guidelines for patients with normal renal function or with renal transplants, and only retrospective studies evaluating therapies in patients with ESRD. Thus in patients presenting with calciphylaxis, wound and pain management are paramount.

Surgery is controversial since local tissue trauma often exacerbates the lesions. However, one retrospective analysis shows that patients undergoing surgical debridement had greater than a 30% increased survival rate compared those who did not undergo debridement.[6] Debridement is likely most helpful to prevent further spread of infection after the ulcers have become primarily infected.

Intravenous sodium thiosulfate is increasingly being utilized as therapy for calciphylaxis, although the mechanism is unknown. One retrospective study examined 53 hemodialysis patients with calcific uremic arteriolopathy and found improvement in 73% of patients taking sodium thiosulfate.

A 35% mortality rate was found in this study compared to the previously reported rate of around 50%. However, the absence of a control group in the study limits the measure of the true efficacy of this therapy.

Oxygen therapy is also frequently used for calciphylaxis, although the data supporting its use are sparse. The largest study found that 8 of 9 patients treated with hyperbaric oxygen therapy had resolution of their lesions. Again the data were limited by the absence of a control group.[11]

The last tenet of calciphylaxis management is control of calcium, phosphorus, and PTH levels. Small studies and case reports have shown some benefit in using phosphate binders like sevelamer carbonate to lower phosphate levels and cinacalcet to lower PTH and calcium levels.[12,13,14,15]

The calcium phosphorus product should be maintained ideally below 55 mg^2/dL.[2,16] In patients with PTH > 300 pg/mL, parathyroidectomy for calciphylaxis reduces serum calcium, phosphate, and parathyroid hormone values and improves clinical response and overall survival.[17]

Discontinuing medications such as vitamin D, calcium supplements, and warfarin that may be associated with calciphylaxis development may also be of benefit.

Prognosis

Calciphylaxis is a disease associated with poor survival rates. Estimated one year mortality rate hovers around 50% in several retrospective studies.[6,17] Calciphylaxis complicated by skin ulceration increases the mortality rate up to 80%.[18] Response to therapeutic regimens is generally poor, and patients often succumb to infections of their lesions.

Discussion

Despite studies showing higher rates of calciphylaxis than previously thought in patients with end-stage renal disease on dialysis, there are very little data suggesting the presence of calciphylaxis in patients with functioning renal grafts.

Physicians must maintain a high level of suspicion for calciphylaxis when confronted with a patient with renal disease and high serum calcium levels. Initial tissue biopsies may not be sensitive, so it is imperative to obtain repeat biopsies to look for calcium deposition in the arterioles.

Given the rarity of this condition, there is very little data-guiding treatment of this serious disease. At this point, a

multi-interventional strategy with a focus on maximizing wound healing to prevent bacterial infection is most effective.

Sodium thiosulfate therapy, hyperbaric oxygen therapy, and controlling calcium and PTH levels play an integral role as well. With our patient, given the lack of evidence on the effectiveness of sodium thiosulfate combined with the challenges of scheduling regular sodium thiosulfate intravenous administration, we discharged her home with daily hyperbaric oxygen therapy.

Figures

Figure 1: Extremity on admission

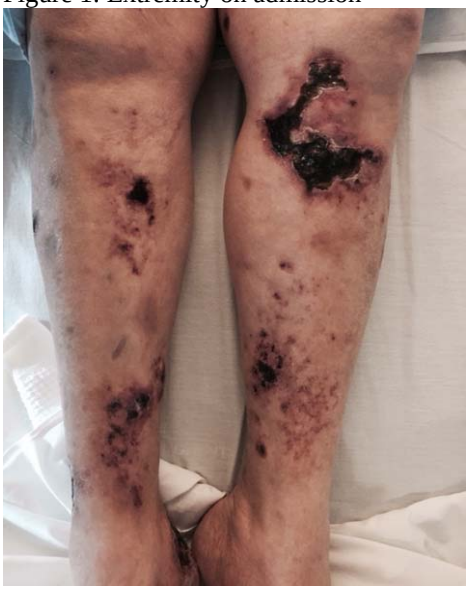
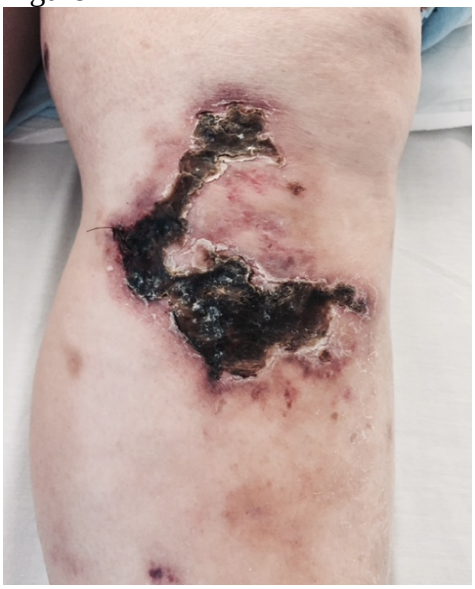


Figure 2



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