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A Comprehensive Approach to Management of Calciphylaxis: A Case Series

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Introduction

Uremic calciphylaxis is a rare condition most common in patients with end-stage renal disease who are on dialysis. While the exact pathophysiology is unknown, calciphylaxis is thought to be due to abnormal metabolism of phosphate and calcium, uremic toxins, hypercoagulability, and endothelial dysfunction. Calciphylaxis has a high mortality rate of forty to sixty percent. Risk factors include poorly controlled secondary hyperparathyroidism, diabetes mellitus, obesity, medications such as warfarin, calcium-based binders, and vitamin D analogues, hypercoagulable states and hypoalbuminemia. Histologically, there is a transformation of smooth muscle cells into osteoblast like cells. This causes calcification of arterioles in dermis and subcutaneous adipose tissues, which leads to skin ischemia and necrosis. Calciphylaxis most commonly looks like violaceous, plaque like subcutaneous nodules, indurations with eschars. Patients commonly present with severe pain in the involved skin areas. These wounds often becomes infected and can lead to sepsis and death.

Case 1

The patient is a 62-year-old female with history of end stage renal disease (ESRD) and kidney transplant in 2001. She presented with an anterior right leg wound on 11/4/22. She denied any trauma to the area and rated her pain as a 7/10. The wound was full thickness and measured 1.8 x 1.3 x 0.1cm. She was instructed to apply 0.1% Gentamycin ointment to the wound. Ankle brachial index and venous insufficiency studies were negative for peripheral arterial disease and positive for venous insufficiency of the common femoral vein. At her two week follow up appointment, the wound measured approximately six times larger. Due to the worsening presentation, two punch biopsies were performed. The results identified the wound as a venous stasis ulcer in the setting of chronic venous stasis and lipodermatosclerosis. The patient was hospitalized shortly after for pain control. Repeat biopsies were performed which again favored lipodermatosclerosis. However, due to increase in size of the wound, worsening clinical presentation, as well as high pain levels, clinical suspicion for calciphylaxis remained high. The patient began sodium thiosulfate infusions (STS) twice weekly in February 2023 which continued into June. Following initiation of infusion, her wound began to decrease in size, with less necrotic tissue and improved pain.



11/4/22

12/22/22

3/29/23

6/7/23

9/1/23

Case 2

The patient is a 61-year-old female with a past medical history of renal transplant, type 2 diabetes, and left lower extremity below knee amputation. Of note, the patient developed hypercalcemia and tertiary hyperparathyroidism after her renal transplant in 2001. She presented with a right medial lower leg wound measuring 3.0 x 2.2 x 0.2 cm in March 2021. The wound began as a scratch and developed worsening cellulitis. She was referred to the emergency department where her workup confirmed absence of deep vein thrombosis (DVT), abscess, or osteomyelitis. Additionally, her vascular studies did not suggest peripheral arterial disease (PAD). She was treated with vancomycin and piperacillin/tazobactam and was discharged on cephalexin and sulfamethoxazole-trimethoprim. The patient followed up in the comprehensive wound care clinic, where she received pulse lavage treatment as well as manual lymphatic drainage with occupational therapy to manage her lymphedema. The wound measured 8.0 x 8.5 x 0.3 cm with a largely mixed fibrotic and necrotic base. She was transitioned to topical wound care with an enzymatic debriding agent. Despite eight weeks of wound care, there was minimal demonstrated improvement.

A dermatology referral was placed for further evaluation. Here, a punch biopsy confirmed calciphylaxis. Following this official diagnosis, the patient was closely monitored by nephrology to help optimize her kidney function. Her renal function, serum calcium, tacrolimus levels and urinalysis were monitored on a quarterly basis and her parathyroid hormone (PTH) levels were monitored monthly. A negative parathyroid scan ruled out the possibility of primary hyperparathyroidism and her nephrologist advised against parathyroidectomy. Of note, the patient's dose of cinacalcet was increased from 30 mg to 60 mg to help regulate serum calcium.

Gradually, the wound demonstrated a decrease in nonviable necrotic tissue and an increase in granular tissue. As the wound improved, a human cadaveric graft was applied to the wound to optimize healing. Her first application was on July 21, 2022, at which time her wound measured 7.0 x 3.0 x 0.1 cm. She continued with graft applications every two weeks. After approximately four months, the patient had her last human cadaveric graft application in November 2022. Her wound measured 4.9 x 3.2 x 0.1 cm, a greater than 90 percent reduction in surface area



Discussion

Calciphylaxis is a rare disease that is difficult to diagnose. To date, there is no consensus on clinical practice guidelines for the prevention and treatment of calciphylaxis⁵ and much of the literature is limited to expert opinion. While an atypical appearance and poor healing may obscure a patient's presentation, calciphylaxis most often requires an early, high index of clinical suspicion. This in turn leads to a timely biopsy and expedites course of treatment.

Obtaining a tissue biopsy played a key role in establishing the appropriate diagnosis for the patients in these cases. However, acquiring a biopsy for suspected calciphylaxis is debated in the literature due to inherent risks associated with the biopsy itself, including ulceration, bleeding, infection, necrosis, and poor technical proficiency.³ If a sufficient sample is not obtained, it will not be useful for histopathologic analysis. In line with previous literature, we suggest performing a punch or telescoping biopsy using 4-5 mm biopsy needle and the sample should be obtained from the periphery of the lesion, avoiding necrotic areas.¹

As calciphylaxis may present secondary to abnormalities of calcium, phosphorus and PTH, certain lab markers can be ordered to assist in diagnosis. Specifically, a metabolic panel will provide the patient's calcium and phosphorus levels. Albumin and parathyroid hormone levels will help to determine appropriate functioning of the patient's thyroid.³ Partial thromboplastin time and International Normalized Ratio can help determine if a patient is in a hypercoagulable state. Lastly, for patients with calciphylaxis who are on hemodialysis, dialysis treatment needs to optimize serum levels of calcium and phosphorus. This may include increasing the duration and/or frequency of dialysis.³

Adjustment or elimination of certain medications can also help to prevent calciphylaxis. For example, calcium-based binders and vitamin D analogs should be avoided as they may increase the rate of vascular calcifications and tend to raise serum calcium and phosphorus.³ Calcium supplements and iron should be discontinued. Patients with poorly controlled hyperparathyroidism should be prescribed a calcimimetic agent, which suppresses PTH and lowers serum calcium.³ An example of such a medication adjustment is cinacalcet.³ This was exemplified by the patient in case two of this series, whose cinacalcet dose was increased upon diagnosis of calciphylaxis. However, patients with severe disease who are unresponsive to such changes in medication may consider a parathyroidectomy.

The patient in case one benefited from the use of STS as an adjunctive treatment and demonstrated complete healing of their respective wounds. Thiosulfate forms highly soluble complexes with calcium and decreases calcium-phosphate precipitation in the vascular wall.¹ It also possesses an antioxidant and vasodilatory effect, which helps to decrease tissue ischemia. Sodium thiosulfate is typically prescribed intravenously at a dose of 25 g three times weekly over 30-60 minutes during the last hour of hemodialysis. Patients not on dialysis receive treatment twice weekly.³ Most patients are treated for three months. Clinical improvement within 2-3 weeks may be a predictor of favorable response.

As is exemplified by this case series, calciphylaxis is best managed using a collaborative multi-disciplinary approach, including podiatry, dermatology, wound care, nephrology, vascular surgeons, nurse practitioners and pain management. The primary goals of treatment include appropriate wound care, management of infection and pain, and close monitoring.

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