Case Reports

A Unique Case of Calciphylaxis in a Non-ESRD Patient

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Abstract

Introduction

Calciphylaxis is a rare and serious medical condition that involves calcification of arterioles, microthrombosis, and resulting subcutaneous ischemic necrosis. It is most often seen in patients with "end-stage renal disease (ESRD) on dialysis; however, occasionally, it is seen in patients without chronic renal disease. Other associated conditions include obesity, hyperparathyroidism, malignancy, protein C and S deficiencies, alcoholic liver disease, and iatrogenesis with medications including glucocorticoids, warfarin, and vitamin D supplements. The pathogenesis is not well-understood, but new research points to an active cellular process as opposed to passive precipitation of calcium-phosphate crystals. Mortality ranges from 45-80%, and treatment focuses on preventing further calcification, pain management, and prevention of life threatening infection. Presented is a case of calciphylaxis in an obese non-ESRD female on chronic high dose vitamin D supplementation.

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Case Presentation

A 74-year-old morbidly obese woman with hypertension and obstructive sleep apnea presented to the Wake Forest Baptist Dermatology clinic with a chief complaint of painful “knots” on her lower abdomen for five months. She states they began with a bruise-like appearance, and progressed to hard knots with severe burning pain. She had two prior biopsies taken at a community hospital, and pathology was reviewed by another tertiary care center. The differential diagnosis suggested by the pathologist at that time included diffuse eruptive angiolipomas and traumatic panniculitis. She was treated with doxycycline and lidocaine/prilocaine cream without improvement.

On presentation to Wake Forest Dermatology, the patient’s physical examination revealed indurated dermal plaques of the pannus with overlying ulceration and necrosis (Figure 1). Another biopsy was performed which was consistent with calciphylaxis. She was referred to nephrology. Her labs revealed slightly elevated total calcium, a high ionized calcium, and low parathyroid hormone (PTH) (Tables 1 & 2). She was admitted to the hospital for treatment with sodium thiosulfate. On further history and workup, the patient’s only risk factors for calciphylaxis were obesity and vitamin D supplementation. She had been taking 50,000 IU of vitamin D weekly for 4 years.

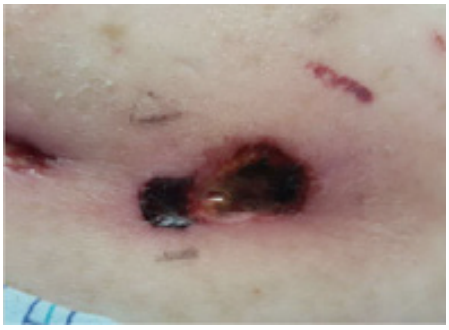

Figure 1: Abdominal wound with necrotic tissue/eschar in patient with calciphylaxis

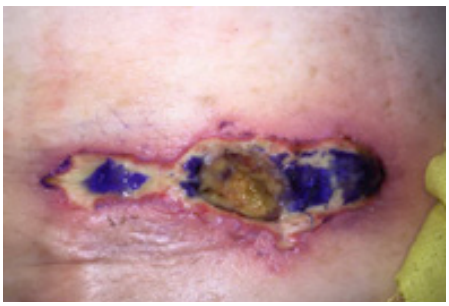

Figure 2: Abdominal wound in patient with calciphylaxis. Purple is crystal violet, used by wound care for infection prophylaxis.

Discussion

Calciphylaxis is a rare condition that involves calcification and microthrombosis of small arteries in the dermis. The prevalence has previously been reported as 4% in patients on chronic hemodialysis.[1] It occurs less often in patients with kidney disease not on dialysis, and in patients without kidney disease, although the incidence and prevalence in these populations is unknown. It is associated with high morbidity and mortality. The one year mortality rate ranges from 45-80%, and patients on hemodialysis who develop calciphylaxis are almost 3 times as likely to die as those who don't have calciphylaxis.[2,3]

Many potential risk factors have been cited. They include end stage renal disease and chronic hemodialysis, obesity, hyperparathyroidism, malignancy, elevated serum aluminum levels, alcoholic liver disease, Protein C and S deficiency, and medication use including calcium, vitamin D, glucocorticoids, and warfarin.[2,10-13] Although high serum calcium is often observed, it is not a requirement. A calcium-phosphate product > 70 mg2/dL^2 may suggest an increased risk of calciphylaxis; however, many patients with calciphylaxis do not have an increased calcium-phosphate product.[9]

The clinical presentation usually involves painful skin lesions that start as purpuric-like lesions or hard indurations in the dermis.[4] They can affect any area but often occur on the lower extremities or trunk.[6] The lesions will often progress to form a necrotic eschar, and superimposed infection often ensues. Sepsis secondary to wound infection is the leading cause of death in these patients, accounting for 41% of the deaths in one retrospective study.[5,6] The necrotic lesions can be large and unusually shaped, and they are excruciatingly painful. Biopsy reveals medial calcification of the small arteries and arterioles, microthrombi, and subintimal fibrosis.[4-6]

The pathophysiology of calciphylaxis is not well-understood. It was commonly believed to be secondary to passive precipitation of calcium-phosphate crystals into blood vessel walls. Research now points to a much more active cellular process as the cause, rather than passive mineralization. The vascular calcification in calciphylaxis begins with

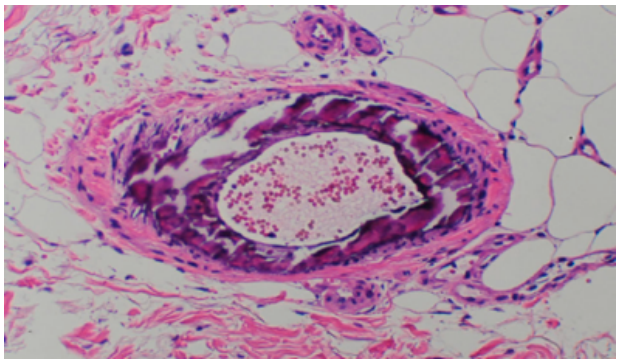

Figure 3: Example of calciphylaxis histology [20]. Arterial border is irregular and heavy staining in intima is calcium holding onto stain. Gaps in intima is slicing artifact during slide preparation due to vessel being calcified.

Sodium	130 (L)	135-146 MMOL/L
Potassium	4.4	3.5-5.3 MMOL/L
Chloride	91 (L)	98-110 MMOL/L
CO2	32	21 - 33 MMOL/L
Glucose	97	70 - 99 MG/DL
BUN	8	8.0 - 24.0 MG/DL
Creatinine	0.87	0.5 - 1.5 MG/DL
Calcium	10.8 (H)	8.5 - 10.5 MG/DL
Total Protein	6.4	6.0 - 8.3 G/DL
Albumin	4.4	3.5 - 5.0 G/DL
Magnesium	1.6	1.8 - 2.4 MG/DL
Phosphorus	4.1	2.5 - 4.5 MG/DL

Table 1: BMP/Electrolyte Lab results

Vit D, Total	43	--- NG/ML
Vit D, D2	41	--- NG/ML
Vit D, D3	2	--- NG/ML
Ionized Calcium	5.3 (H)	1.2-1.32 MMOL/L
Intact PTH	11 (L)	12-72 PG/ML
Protein C&S	Within Normal Limits	
Serum Protein Electrophoresis	Within Normal Limits	

Table 2: Other Lab Results

vascular smooth muscle differentiating into chondrocyte and osteoblast phenotypes.[7-9] Subsequently, a process similar to bone modeling ensues within the vessel wall. The complex factors and steps leading to this process are still being explored. Implicated in the pathogenesis are receptors (RANK), hormones (PTH, estrogen, leptin), inflammatory cytokines (TNF-a, IL-6), reactive oxygen species, and other proteins (MGP, Fetuin-A).[7,9] With continued advances in our understanding of calciphylaxis at a molecular level, new targeted therapies will be possible.

Treatment for calciphylaxis focuses on preventing further calcification, pain management, and prevention of life threatening infection. If patients are on associated medications or supplements, these should be stopped if possible. If it appears hypercalcemia is a contributing factor, then treating the underlying cause of the hypercalcemia is important. In dialysis patients, increasing the frequency of dialysis and using low calcium baths may be beneficial. Other agents such as bisphosphonates and cinacalcet have been used with varying results.[1,4] Finally, in the presented patient, sodium thiosulfate was used. Sodium thiosulfate is a calcium chelating agent and also has anti-oxidant effects. It improves patients' wounds and associated pain; however, it did not decrease the mortality associated with calciphylaxis.[4,14,15]

Finally, this case brings awareness to the fact that all supplements have risk. This patient was on vitamin D supplementation, 50,000 IU weekly for the past 4 years. It is likely that this contributed to the patient developing calciphylaxis, as vitamin D supplementation has previously been associated with calciphylaxis. There is conflicting evidence regarding the benefits of vitamin D supplementation. The Institute of Medicine's Recommended Daily Intake of vitamin D for patients >71 years old is 800 IU/d, with an upper limit of 4,000 IU/day.[16] The upper limit indicates the level above which there is risk of adverse events. Although some studies suggest higher doses are safe for most people, the use of 50,000 IU as a chronic form of supplementation has not been studied, and its safety profile is unknown.[17-19]

Vitamin D was discontinued, her calcium levels decreased, and she continued treatment with sodium thiosulfate infusions. She followed with the wound care clinic, and her wounds were treated with a combination of Santyl collagenase, silver/collagen dressings, and Dakin's wet to dry dressings. The wounds slowly improved over months.

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