CLINICAL VIGNETTE

Calciphylaxis in a Patient with Multiple Risk Factors

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Introduction

Calciphylaxis, also known as calcific uremic arteriolopathy, is a rare disease with a high morbidity and mortality. In calciphylaxis there is calcification, fibrosis, and thrombosis of the small vessels of the body. The resultant processes result in intensely, painful cutaneous lesions.[1] Calciphylaxis typically occurs in patients with chronic kidney disease (CKD), called uremic calciphylaxis, particularly occurring in those with end-stage renal disease on dialysis. However, calciphylaxis can also occur in patients with normal renal function and those with less advanced forms of CKD, called non-uremic calciphylaxis, though at a lower incidence.[1,2] Calciphylaxis typically presents as painful lesions, involving the adipose tissue, that typically occur on the thighs and abdomen.[3] Skin biopsy is the gold standard for the diagnosis of calciphylaxis. Treatment of the disease typically requires a multi-disciplinary team approach. Though, treatment of calciphylaxis is unclear, intravenous sodium thiosulfate is the most commonly used medication. The one-year mortality of calciphylaxis is 45-80% with sepsis the primary cause of death.[1]

We present calciphylaxis in a woman with alcoholic cirrhosis, prior history of continuous renal replacement therapy (CRRT), and other risk factors. We describe the patient's course and review relevant literature of this disease.

Case Report

A 42-year-old woman with steroid-induced type 2 diabetes mellitus, obesity, and recently diagnosed decompensated alcoholic cirrhosis presented to our hospital for higher level of care for wound management.

Approximately 2 months prior to presentation, the patient was admitted to an outside hospital where she received five days of continuous renal replacement therapy. A week later, the patient was started on prednisone 40mg daily. Approximately two weeks later, the first record of skin lesions was noted. The patient was transferred to a skilled nursing facility where she erroneously received double dose of her prescribed corticosteroids for a month. The patient's skin lesions continued to worsen, and she was brought to our hospital due to worsening wounds.

On admission to our hospital, the patient was tachycardic, but otherwise hemodynamically stable, though writhing in pain. She had large skin lesions with necrotic borders and granulated centers involving the medial and posterolateral aspects of her thighs, lower abdominal quadrants, and posterior calves bilaterally. Initial laboratory values included: white blood cell count of 25 x10E3/uL, INR of 16.5, sodium of 132 mmol/L, potassium of 4.1 mmol/L, bicarbonate of 21 mmol/L, blood urea nitrogen of 23 mg/dL, serum creatinine of 1.19, calcium of 9.8 mg/dL, phosphorus of 3.8 mg/dL. Alkaline phosphatase was 411 U/L and albumin was 2.2 g/dL. C-reactive protein and lactate were both elevated at 19.7 mg/dL and 23 mg/dL, respectively. CT of the abdomen and pelvis was unremarkable.

We were initially concerned for calciphylaxis with superimposed infection due to the history of liver disease, kidney injury, supra-therapeutic steroid use, steroid-induced type 2 diabetes mellitus, and leukocytosis. We also considered conditions such as systemic lupus erythematosus, vasculitis, and dermatomyositis.

During hospitalization we consulted nephrology, hepatology, dermatology, general surgery, rheumatology, palliative care, wound care, and nutrition. The patient was started on broad-spectrum empiric antibiotics, given opioids for pain management, and provided daily wound care. Additional labs and serologies included intact parathyroid hormone of 10 pg/mL, vitamin B12 of 1,499 pg/mL, 25-hydroxyvitamin D of 32 ng/mL, alpha-1-antitrypsin of 277 mg/dL, beta-2 glycoprotein IgA of 28, soluble interleukin-2 receptor of 2,265 U/mL, and negative anti-phospholipid antibodies. Bacterial and fungal blood cultures were normal and urine cultures were unremarkable. Skin punch biopsy revealed medium vessel calcification, fat necrosis with small vessel thrombi, and dystrophic calcification within adipose tissue. She was started on intravenous sodium thiosulfate three time weekly. However, she continued to decompensate developing worsening metabolic acidosis and hepatorenal syndrome. Goals of care discussion was held with family and the patient was placed on comfort care measures and died on day 13 of hospitalization.

Discussion

Calciphylaxis is a rare disease with an unclear epidemiology, which appears to be increasing.[1,2] Calciphylaxis most commonly occurs in females, with a female to male ratio of 2:1. It most often occurs in Caucasians in their 5th decade of life.[1] There are a number of risk factors associated with calciphylaxis. The strongest risk factor is renal failure with most cases occurring

in patients on dialysis or after renal transplantation. Abnormalities in calcium and phosphate metabolism, such as hyperphosphatemia, hypercalcemia, hyper-, and hypoparathyroidism, are also risk factors. Multiple conditions have been reported as risk factors for calciphylaxis. These include diabetes mellitus, obesity, autoimmune diseases, hypercoagulable conditions, and hepatitis. Medications including warfarin, calcium supplements, calcium-phosphate binders, active vitamin D, corticosteroids, iron, and trauma associated with subcutaneous heparin and insulin, are also reported to increase the risk of calciphylaxis.[1,3]

The pathogenesis of calciphylaxis is unclear, though it is thought to be due to a relative imbalance of pro-calcification versus anti-calcification mechanisms within the body.[3,4] One theory states that the pathogenesis of calciphylaxis is due to the differentiation of vascular smooth muscle cells into osteoblast-like phenotypes and chondrocytes that deposit hydroxyapatite crystals throughout the body in patients with hyperphosphatemia, hypercalcemia, and hyperglycemia. Additionally, when exposed to high levels of phosphorus, adipocytes have been shown to calcify and promote vascular smooth muscle cell calcification.[5] Another theory on the pathogenesis of calciphylaxis, reports vitamin K deficiency can lead to less activation of matrix gla protein – a protein that normally has an inhibitory effect on the calcification of tissue. [3] Furthermore, low levels of the inhibitors of calcification such as osteoprotegerin and fetuin-A and high levels of the promoters of calcification such as bone morphogenic protein-4 and osteopontin are thought to be involved in the pathogenesis.[4,6]

Patients with calciphylaxis can present with a variety of painful skin lesions including livedo reticularis, reticulate purpura, violaceous plaques, or indurated nodules. Blisters and ulcers, with or without black eschar, can also form, leading to superimposed infection.[1] It is important to have a high index of suspicion with calciphylaxis to allow for early recognition and initiation of treatment.[7] These lesions can present similarly to other conditions such as warfarin-induced necrosis, heparin-induced thrombocytopenia, atherosclerotic vascular disease, vasculitis, and nephrogenic systemic fibrosis.[1,3] Calciphylaxis can be diagnosed clinically, though, skin biopsy can confirm diagnosis.[7]

Management of calciphylaxis warrants a multidisciplinary approach that allows for patient-centered care. Wound care, including the removal of necrotic tissue, and adequate nutrition should be optimized to allow for wound healing.[3,7] Pain control may be difficult to obtain in these patients due to the intense pain of the lesions. Narcotics are often needed.[1] Surgery may be needed for debridement, as well as nephrology and palliative care.[7] Treatment of calciphylaxis is limited and continues to be studied. Sodium thiosulfate, an antioxidant that works to inhibit the calcification of adipocytes and prevent adipocytes from promoting vascular smooth muscle cell calcification, has been shown to be beneficial. It is well-tolerated, though adverse effects include metabolic acidosis, hypocalcemia, hypotension, and QT-prolongation. Additionally, vitamin K has also been used to prevent vessel calcification.[3,8]

Our patient had multiple risk factors that could have contributed to her development of calciphylaxis. The patient's calciphylaxis could have potentially been caused by her acute kidney injury requiring subsequent CRRT. Time from the initiation of dialysis to the onset of calciphylaxis can range from 30 to over 100 months,[8] however, cases report the occurrence of calciphylaxis following acute kidney injury.[9-13] This patient was also at risk for non-uremic calciphylxis due to liver disease and steroid use. Because of the exposure to multiple risks and the development of calciphylaxis occurring within close timing to each other, it is difficult to identify the major contributing factor for this patient.

Conclusion

We report calciphylaxis in a patient with multiple risk factors, both uremic and non-uremic. Calciphylaxis is a rare, severely painful disease with high mortality. High index of suspicion is needed to avoid delays in care, including identifying and potentially removing the risk factors and providing appropriate treatment. A multidisciplinary team approach is recommended to manage this complex disease. Current treatment is limited to sodium thiosulfate and vitamin K.

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