CASE REPORT

Idiopathic Calciphylaxis with Cutaneous Necrosis: A Case Report

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ABSTRACT

Calciphylaxis is a rare medical condition that is characterized by calcification, microthrombosis, and fibrointimal hyperplasia within cutaneous arteries. This condition is associated with high morbidity and mortality. However, there are limited management guidelines available. We present a patient case of a woman with a prior prolonged hospital stay who presented with chronic wounds secondary to idiopathic, non-uremic calciphylaxis. She required multidisciplinary inpatient care and was subsequently discharged to a long-term care facility for chronic wound care and antibiotics. We also review relevant literature on treatment strategies, including antibiotics, wound debridement, and hyperbaric oxygen therapy.

BACKGROUND

Calciphylaxis is a rare medical condition that is characterized by calcification, microthrombosis, and fibrointimal hyperplasia in cutaneous arteries leading to ischemia and septal panniculitis. This condition predominantly affects patients with end-stage renal disease receiving dialysis but can also occur in patients without kidney failure.[1] For example, the current annual incidence of uremic calciphylaxis is approximately 35 per 10,000 patients.[2] In the German Calciphylaxis Registry, 10% of calciphylaxis patients had either normal kidney function or chronic kidney disease not requiring dialysis.[3] Additionally, a recent study from Mayo Clinic showed that nearly 20% of all calciphylaxis patients had a glomerular filtration rate greater than 60 mL/min.[4] Calciphylaxis is associated with high morbidity due to severe pain, non-healing wounds, recurrent hospitalization, superimposed infections, and sepsis. The exact pathophysiology, diagnosis, and management of calciphylaxis remain unclear. As such, a multidisciplinary approach from nephrology, dermatology, pain management, nutrition, and wound care is strongly recommended.

CASE PRESENTATION

A 47-year-old woman with a history of deep vein thrombosis (DVT), pulmonary embolism (PE)—now on apixaban for anticoagulation—opioid abuse, and morbid obesity presented as a transfer from an outside hospital (OSH) for worsening pain and non-healing, bilateral, lower extremity (BLE) ulcers due to calciphylaxis. Her initial, indurated, subcutaneous lesions quickly ulcerated and necrosed within a span of 1 month. The patient was previously admitted to the OSH for non-healing leg wounds as well as nausea and vomiting which she stated was related to pain. The appearance of her wounds raised concern for calciphylaxis.

Her labs were significant for hyperphosphatemia, elevated creatinine of 4.22 mg/dL, and elevated parathyroid hormone (PTH; Table 1).

TABLE 1: Renal function, calcium, phosphorus, and parathyroid hormone levels over the course of the patient's previous outside hospital admission

Labs at Outside Hospital	Day 1	At Discharge
Creatinine	4.22 mg/dL	0.75 mg/dL
Blood Urea Nitrogen (BUN)	152 mg /dL	8 mg/dL
Calcium	7.2 mg/dL	7.9 mg/dL
Phosphorus	9.2 mg/dL	4.1 mg/dL
PTH	93 pg/mL	

The patient's alkaline phosphatase was also noted to be mildly elevated at 181. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were within normal limits. The patient's initial acute kidney injury (AKI) was likely secondary to prerenal azotemia, as creatinine trended down during hospitalization and corrected with intravenous (IV) fluids, decreasing to 0.75. This value was approximately the patient's baseline from labs checked a year prior to this admission.

Along with these persistent wounds, a three-phase bone scan demonstrated significant radiotracer uptake in the BLE. The patient underwent surgical debridement several times and began aggressive local wound care and 25g of intravenous sodium thiosulfate every 48 hours. The remainder of her lab tests normalized over the course of her admission. After discharge, she missed infusion appointments due to weather conditions and significant pain. As a result, she was admitted again and transferred to our hospital for worsening ulcerations, pain, and superimposed bacterial infection. A complete blood count (CBC) did not show significant leukocytosis with a white blood cell (WBC) count of 7.4. Moreover, a comprehensive metabolic panel (CMP) revealed no electrolyte derangements with a normal calcium level of 9.1 and normal renal function with a creatinine of 0.64 (Table 2).

TABLE 2: Renal function, calcium, phosphorus, and parathyroid hormone levels over the course of the patient's current medical admission

Labs During Current Admission	Day 1	At Discharge
Creatinine	0.64 mg/dL	0.60 mg/dL
BUN	10 mg/dL	8 mg/dL
Calcium	9.1 mg/dL	9.4 mg/dL
Phosphorus	4.2 mg/dL	4.5 mg/dL
PTH	37 pg/mL	

On admission, she started a 7-day course of intravenous vancomycin and oral metronidazole. The patient was also started on 25g of intravenous sodium thiosulfate every 48 hours, as well as zinc sulfate and pentoxifylline. The largest lesion on the medial left thigh measured 24x20x2cm with 80% eschar and 20% slough with multiple necrosed wounds throughout her BLE (Figure 1 and Figure 2). Punch biopsies and tissue cultures performed by dermatology demonstrated small subcutaneous vessels with calcifications consistent with calciphylaxis, as well as infection with methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus dysgalactiae*.

Initial differential diagnoses included vasculitic, embolic, and infectious etiologies. Vascular surgery determined that her condition was not due to vascular abnormalities, and general surgery subsequently recommended aggressive local wound care. Endocrinology, nephrology, and rheumatology determined that her condition was not related to endocrine, nephrological, or rheumatologic etiologies due to a lack of endocrine or renal disease and a nonspecific positive lupus anticoagulant panel. Protein electrophoresis, cryoglobulin, and cryofibrinogen were also negative. Due to concern for underlying neoplastic or paraneoplastic processes, a whole-body positron emission tomography and computed tomography (PET CT) scan, carcinoembryonic antigen (CEA), and cancer antigen (CA) 19-9 were obtained, all of which returned without concern for malignancy.

FIGURE 1: Left thigh necrotic wound on admission

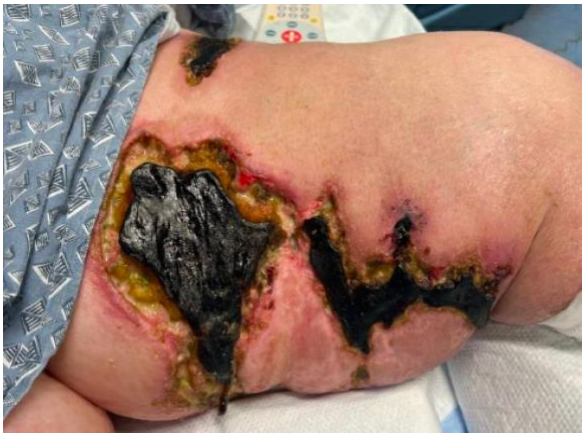
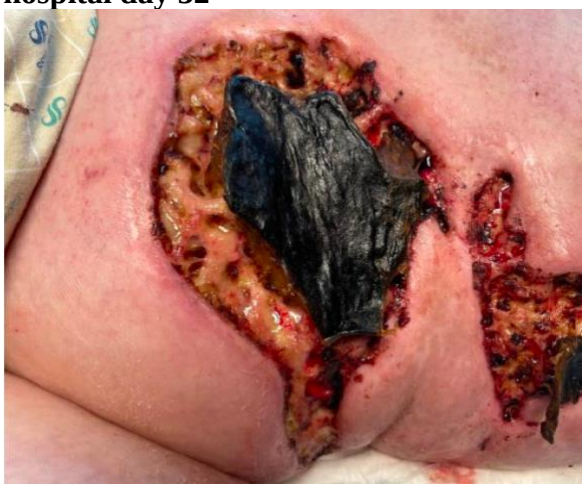


FIGURE 2: Left thigh necrotic wound, hospital day 32



An intralesional sodium thiosulfate injection (250 mg/mL) was administered on the third day. Dermatology continued daily wound care and intralesional sodium thiosulfate injections until discharge. Antibiotics were administered to target culture-identified organisms with recommendations from the infectious disease team. Calcium, vitamin D, warfarin, corticosteroids, and iron therapy were avoided for potential exacerbation of calciphylaxis. Palliative care and anesthesia were consulted for goals of care and pain management. The patient remained afebrile with stable vital signs, white count, creatinine, and pain. She was eventually discharged to a long-term care facility for the remainder of her care. She missed the outpatient follow-up visit.

DISCUSSION

The patient's diagnosis is idiopathic non-uremic calciphylaxis, a diagnosis of exclusion established due to her lack of renal, vascular, endocrine, rheumatologic, and neoplastic or paraneoplastic disease.

Calciphylaxis is a rare condition that predominantly affects patients with chronic kidney failure on dialysis.[5] However, it has also been associated with several medications. Some of these directly modulate calcium levels, such as calcium-based phosphate binders, active vitamin D, and corticosteroids. Another commonly used medication associated with calciphylaxis is warfarin. It is thought that some endogenous inhibitors of vascular calcification, such as the matrix Gla protein, require vitamin K for activation.[6] Regardless of the cause, this condition has high morbidity due to severe pain, non-healing wounds, recurrent hospitalizations, and superimposed infections. Calciphylaxis with ulcerated lesions has a reported 1-year mortality rate of 45-80%, with sepsis as the leading cause of death.[6] The lesions can present as livedo reticularis, reticulate purpura, violaceous plaques, or indurated nodules. The ulcerated lesions often exhibit black eschar, as with our patient. Histologically, calciphylaxis is characterized by calcification, microthrombosis, and fibrointimal hyperplasia in cutaneous arteries, leading to ischemia and septal panniculitis.[7] It is hypothesized that vascular calcification leads to endothelial dysfunction and injury. However, the exact pathophysiology, diagnosis, and management of this devastating condition remain unclear.[8]

Calciphylaxis is linked to a wide range of underlying disorders and conditions. Frequently associated factors include chronic renal failure, hypercalcemia, hyperphosphatemia, elevated calcium-phosphate product, hyperparathyroidism, and vascular calcification. Noteworthy associations also involve aluminum toxicity, coagulation abnormalities, and the use of iron dextran. Clinical observations have suggested potential connections to renal transplantation, the use of immunosuppressive agents, corticosteroid administration, and obesity as possible contributors to the development of calciphylaxis.[9] For our patient, the risk factors were female sex and morbid obesity.

Despite the lack of standardized management, Nigwekar et al. recommend a multidisciplinary approach including input from nephrology, dermatology, pain management, nutrition, and wound care.[6] Etiologies including vascular disease, cholesterol emboli, autoimmune disease, hyperparathyroidism, vasculitis, and paraneoplastic syndrome must be ruled out before idiopathic calciphylaxis can be diagnosed. Intravenous or intralesional sodium thiosulfate and hyperbaric oxygen therapy may be used for treatment.[6,9] The optimal dosage of intralesional sodium thiosulfate for the treatment of calciphylaxis has yet to be firmly established. Surgical debridement may be considered on a case-by-case basis, as one retrospective study revealed a significant increase in 1-year survival

(61.6% vs. 27.4%).[10] Additional debridement was not pursued in this case due to recurrence. Additionally, pain management, nutrition, and palliative care should be consulted to elucidate the goals of care and optimize patient comfort.

Notes

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REFERENCES

1. Brandenburg VM, Kramann R, Specht P, Ketteler M. Calciphylaxis in CKD and beyond. Nephrol Dial Transplant. 2012 Apr;27(4):1314-8. [PMID: 22344774] doi: 10.1093/ndt/gfs015
2. Altman K, Shinohara M. Demographics, Comorbid Conditions, and Outcomes of Patients With Nonuremic Calciphylaxis. JAMA Dermatol. 2019 Feb 1;155(2):251-252. [PMID: 30601879] doi: 10.1001/jamadermatol.2018.4937
3. Brandenburg VM, Kramann R, Rothe H, Kaesler N, Korbiel J, Specht P, Schmitz S, Krüger T, Floege J, Ketteler M. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. Nephrol Dial Transplant. 2017 Jan 1;32(1):126-132. [PMID: 26908770] doi: 10.1093/ndt/gfv438
4. McCarthy JT, El-Azhary RA, Patzelt MT, Weaver AL, Albright RC, Bridges AD, Claus PL, Davis MD, Dillon JJ, El-Zoghby ZM, Hickson LJ, Kumar R, McBane RD, McCarthy-Fruin KA, McEvoy MT, Pittelkow MR, Wetter DA, Williams AW. Survival, Risk Factors, and Effect of Treatment in 101 Patients With Calciphylaxis. Mayo Clin Proc. 2016 Oct;91(10):1384-1394. [PMID: 27712637] doi: 10.1016/j.mayocp.2016.06.025
5. Budisavljevic MN, Cheek D, Ploth DW. Calciphylaxis in chronic renal failure. J Am Soc Nephrol. 1996 Jul;7(7):978-82. doi: 10.1681/ASN.V77978. PMID: 8829111.
6. Nigwekar, S., Kroshinsky, D., Nazarian, R., Goverman, J., Malhotra, R., Jackson, V., Kamdar, M., Steele, D. and Thadhani, R., 2015. Calciphylaxis: Risk Factors, Diagnosis, and Treatment. *American Journal of Kidney Diseases*, 66(1), pp.133-146. [PMID: 25960299] doi: 10.1053/j.ajkd.2015.01.034.
7. Mochel, M., Arakaki, R., Wang, G., Kroshinsky, D. and Hoang, M., 2013. Cutaneous Calciphylaxis. *The American Journal of Dermatopathology*, 35(5), pp.582-586. [PMID: 23328789] doi: 10.1097/DAD.0b013e31827c7f5d
8. Au, S. and Crawford, R., 2002. Three-dimensional analysis of a calciphylaxis plaque: Clues to pathogenesis. *Journal of the American Academy of Dermatology*, 47(1), pp.53-57. [PMID: 12077581] doi: 10.1067/mjd.2002.120927.
9. Lal G, Nowell AG, Liao J, Sugg SL, Weigel RJ, Howe JR. Determinants of survival in patients with calciphylaxis: a multivariate analysis. Surgery. 2009 Dec. 146(6):1028-34.
10. Vedvyas, C., Winterfield, L. and Vleugels, R., 2012. Calciphylaxis: A systematic review of existing and emerging therapies. *Journal of the American Academy of Dermatology*, 67(6), pp.e253-e260. [PMID: 21821309] doi: 10.1016/j.jaad.2011.06.009.
11. Weenig, R., Sewell, L., Davis, M., McCarthy, J. and Pittelkow, M., 2007. Calciphylaxis: Natural history, risk factor analysis, and outcome. *Journal of the American Academy of Dermatology*, 56(4), pp.569-579. [PMID: 17141359] doi: 10.1016/j.jaad.2006.08.065.