A Fatal Case of Non-Uremic Calciphylaxis: A Case Report and Literature Review

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Conflict of interest: None declared

Patient: Female, 61
Final Diagnosis: Non-uremic calciphylaxis
Symptoms: Pain • skin ulcers
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Rare disease
Background: Calciphylaxis is a rare cutaneous disease, also known as calcific uremic arteriolopathy, that occurs most frequently in patients with advanced chronic kidney disease and on long-term hemodialysis.

Case Report: We describe the case of a 61-year-old female patient with worsening chronic kidney disease not on dialysis therapy, who presented with severe progressive calciphylaxis on both lower limbs.

Conclusions: Calcific uremic arteriolopathy is a rare fatal condition that requires prompt diagnosis and treatment. It is classically described in patients with end-stage kidney disease on long-term renal replacement therapy but can present in patients with an earlier stage of kidney disease. Non-uremic calciphylaxis should be suspected in patients with earlier stages of kidney disease, especially in those with other concurrent risk factors or co-morbid conditions, to avoid the high risk of morbidity and mortality associated with such cases.

MeSH Keywords: Calciphylaxis • Renal Insufficiency, Chronic • Vascular Calcification

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Background

Calciphylaxis is a rare cutaneous disease, also known as calcific uremic arteriolopathy (CUA), that occurs most frequently in patients with advanced chronic kidney disease and on long-term hemodialysis [1]. It is a rare condition, described in 1% to 4% of patients on dialysis, mainly in those with a history of diabetes mellitus (DM), liver disease, and calcium-phosphate product level of more than 70 mg/dL² [2].

The term “calciphylaxis” was first used by Hans Selye in 1961; he performed laboratory experiments to induce diffuse subcutaneous soft tissue calcification in rats by using different preparations such as parathyroid extracts and vitamin D as sensitizing agents in addition to trauma as a challenging factor [3].

We describe a case of a 61-year-old female patient with chronic kidney disease who was not on hemodialysis and with no evidence of uremia, who presented with severe progressive calciphylaxis on proximal lower limbs bilaterally.

Case Report

The patient had a past medical history of chronic kidney disease (CKD) in the setting of poorly controlled hypertension with multiple emergency room and outpatient office visits secondary to hypertensive urgency. She also had diabetes mellitus (DM) type II that was poorly controlled, with average glycohemoglobin values of 9–18, due to medications non-compliance. Her medical record revealed well-controlled DM for the last year prior to admission after she was started on insulin therapy provided by her caregiver, with hemoglobin A1c readings of 6.5–7.0. Her past medical history was also significant for congestive heart failure with preserved ejection fraction (HFrEF), severe obesity (BMI of 56), and obstructive sleep apnea (OSA).

Review of her medical records revealed CKD that was stage II at 2 years prior to her current presentation, which progressed to stage III several months prior to admission, with intermittently elevated alkaline phosphatase levels (80–400 s).

The patient presented with progressive leg pain that was associated with painful skin ulcers on both thighs. Symptoms started several weeks prior to the emergency room visit, with no reported fever, chills, trauma, claudication, bleeding, purulent discharge, or history of previous similar lesions. Physical exam revealed an obese woman with peripheral edema and unstageable painful necrotic skin ulcers 4×7 cm in diameter on the medial side of proximal lower limbs bilaterally, with black eschar and surrounding erythema (Figures 1, 2).

Laboratory investigations were consistent with acute kidney injury and worsening kidney function compared to her baseline (blood urea nitrogen of 44 and serum creatinine of 2.2) (Figure 3). Complete blood count was significant for a hemoglobin level of 7.4 due to anemia of chronic disease with no evidence of leukocytosis or band cells. Platelet count was 250 with a normal international normalized ratio (INR) of 1.1. Chemistry report was remarkable for normal anion gap metabolic acidosis, in addition to normal parathyroid hormone and
Calciphylaxis was suspected based on clinical and radiological data in the form of diffuse calcification of arterial blood vessels of the lower extremities (Figure 4). Skin biopsy and histological evaluation revealed non-specific inflammation and necrosis with calcification involving small arteries and surrounding fibroadipose tissue, but no findings suggestive of vasculitis. Ultrasound and MRI were performed and revealed no signs of infection, fasciitis, osteomyelitis, or abscess.

Skin lesions were managed with daily wound care in the form of regular dressing and topical therapy with methylene blue and antibiotics. The vascular surgery team recommended continuing daily wound care with no invasive surgical interventions. The case was discussed with the nephrology team, who started the patient on systemic sodium thiosulfate therapy of 12.5 mg twice a day for a total duration of 4 weeks. The patient’s condition continued to worsen without improvement of her kidney function (eGFR of 18–25) or skin lesions. The nephrologist recommended a trial of dialysis but the patient refused this option. The patient subsequently developed a wound infection complicated by clinical sepsis. Vancomycin and piperacillin/tazobactam were started empirically and wound debridement was performed by the surgical team. Blood cultures remained negative and her condition deteriorated with the development of toxic encephalopathy due to worsening kidney function in the setting of systemic infection.

Goals of care and prognosis were discussed with the family, who continued to decline dialysis therapy and elected to proceed with palliative and comfort measures with no further invasive surgical or medical interventions. Prabhakar et al. described a similar case of non-uremic calciphylaxis in a patient with recent liver transplant, who was successfully treated with sodium thiosulfate and hyperbaric oxygen therapy [4].

Discussion

Calcific uremic arteriolopathy (CUA) is a form of calciphylaxis that is more common in patients with end-stage renal disease requiring long-term renal replacement therapy in the form of either peritoneal dialysis or hemodialysis [5,6]. Other risk factors include female sex, obesity, white ethnicity, DM, liver disease, high alkaline phosphate, warfarin therapy, and elevated calcium and phosphate levels [5,7–10]. Calcific uremic arteriolopathy is associated with high morbidity and mortality, especially in a patient with ulcerated lesions and multiple co-morbidities, with a reported 1-year mortality of 30–80% [11].

Calciphylaxis can occur in patients with chronic kidney disease who are not on renal replacement therapy and is termed non-uremic calciphylaxis (NUC). Nigwekar et al. conducted a systematic review on 36 cases of NUC and described risk factors seen in those patients. NUC seems to be related to hyperparathyroidism, underlying malignancies, alcoholic liver disease, and connective tissue disorders. Mortality due to NUC was found to be 52%, with sepsis as the leading cause of death [12].

The pathogenesis is not well understood, but is thought to be due to vascular calcification leading to soft tissue necrosis that is usually described in patients with end-stage kidney disease on dialysis [5]. Clinical manifestations in CUA are mainly due to diminished arteriolar supply caused by calcification and fibrosis. Various theories to explain calciphylaxis have been suggested and usually involve an elevated calcium-phosphate product, but the pathophysiology remains unclear [13]. One theory focuses on excess levels of parathyroid hormone and vitamin D as described in animal studies [14]. Another theory describes deficiency of vascular calcification inhibitors such as Fetuin-A, a glycoprotein that helps clear excess calcium-phosphate product [15].

Skin lesions are typically described as livedo reticularis-like plaques that progress to painful necrotic ulcers, which are more prone to infections due to poor healing secondary to diminished vascular supply. Common areas affected are the lower limbs and skin regions with dense adipose tissue [16].

Diagnosis requires a high degree of suspicion based on clinical features and can be supported by imaging studies. Skin biopsy remains the criterion standard method to provide a definitive diagnosis. Histologic findings on biopsy include intravascular calcification and intimal hyperplasia with inflammatory changes and tissue necrosis [17].

Figure 4. Calcification of the anterior (orange arrow) and posterior (red arrow) tibial arteries.
Treatment should utilize a multi-disciplinary approach. Management is mainly directed toward local wound care and prevention of local and systemic infection, in addition to optimizing medical therapy for associated co-morbid conditions [18]. Local wound care remains the mainstay of treatment and involves frequent wound dressing, while surgical interventions remain controversial [19,20].

Sodium thiosulfate has been shown to be an effective treatment option that can be administered as a local or systemic therapy to promote wound healing [21–23]. Local administration is in the form of intra-lesion injections as described by Strazzula et al. [24]. Hyperbaric oxygen therapy can also be used as an alternative form of treatment, with favorable results reported in prior studies [25,26]. Surgical and chemical wound debridement should be considered on a case-by-case basis, and systemic antibiotic therapy should be administered for ulcers complicated by infections or sepsis [27].

Conclusions

Calciphylaxis remains a rare fatal condition that can present in patients with or without end-stage renal disease, regardless of presence of uremia. Early identification of such patients is important to allow prompt treatment to avoid the high morbidity and mortality associated with calciphylaxis.

Conflicts of interest.

None.

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