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A Rare Case of Calciphylaxis: A Case Report

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Established Facts

- Calciphylaxis is a rare and life-threatening condition characterized by calcification and occlusion of small blood vessels, leading to painful skin ulcers and tissue necrosis.
- It predominantly affects patients with end-stage renal disease on dialysis and those with secondary hyperparathyroidism.
- Risk factors include hypercalcemia, hyperphosphatemia, elevated calcium-phosphorus product, use of vitamin D analogs, and warfarin therapy.
- Diagnosis is clinical but may be supported by imaging studies or skin biopsy showing vascular calcification and tissue ischemia.
- Treatment typically involves optimizing calcium and phosphorus balance, sodium thiosulfate therapy, wound care, and pain management, with variable outcomes.

Novel Insights

- Highlighting the need for a multidisciplinary approach in the management of calciphylaxis, emphasizing the integration of nephrology, dermatology, surgery, and palliative care for improved patient outcomes.
- Underscoring the poor prognosis of calciphylaxis despite well-conducted treatment regimens, which warrants continued exploration of innovative therapies and approaches.
- Emphasizing the importance of thorough differential diagnosis to distinguish calciphylaxis from other causes of skin necrosis, as misdiagnosis can delay appropriate care.
- Recent studies and meta-analyses have raised questions about the efficacy of sodium thiosulfate in the treatment of calciphylaxis, suggesting that its role as a standard therapy may need to be reconsidered.
- Highlighting the potential of emerging therapeutic options, such as SNF472, which offers promise in the management of calciphylaxis through targeted mechanisms.
- Exploring the role of vitamin K as a novel therapeutic agent due to its inhibitory effects on vascular calcification, suggesting a possible avenue for improved outcomes in affected patients.

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Abstract
Introduction: Calciphylaxis is a rare and severe disorder characterized by obstructive small vessel disease in the subcutaneous adipose tissue and skin, leading to necrotic skin lesions. The condition poses a significant risk of mortality due to infectious and ischemic complications. ***Case Presentation:*** We present the case of a 60-year-old woman, with a history of renal lithiasis, hypertension, and end-stage renal disease on hemodialysis complicated by hyperparathyroidism and aortic valve replacement. She developed extensive necrotic lesions on both lower limbs and upper extremities, prompting a diagnosis of calciphylaxis. Radiographic and biopsy findings supported the diagnosis, revealing characteristic calcifications. Treatment involved antibiotics, oral thiosulfate, daily hemodialysis, hyperbaric oxygen therapy, and discontinuation of calcium and alfacalcidol, with alendronate initiation. Unfortunately, despite these interventions, the patient experienced a rapid clinical decline, developing septic shock necessitating bilateral leg amputations. Regrettably, she succumbed to the disease 10 days later. ***Conclusion:*** This case underscores the challenging prognosis of calciphylaxis and the need for effective therapeutic options, including surgical intervention and access to injectable thiosulfate.

Introduction

Calciphylaxis, or calcific uremic arteriolopathy, is a rare obstructive pathology affecting small vessels in fat and skin, leading to painful necrosis. Complications, including infection and ischemia, contribute to a nearly 50% mortality rate, particularly in fragile patients [1]. Commonly associated with chronic renal failure, its frequency varies from 0.5 to 4% depending on the study [2].

The term calciphylaxis was first used in 1961 by Hans Seyle, by analogy with the term anaphylaxis, to describe the calcification of cutaneous and subcutaneous tissues in rats, resembling a systemic hypersensitivity reaction. In humans, the diagnosis gained prominence with the observation of similar lesions in dialysis patients [1]. Anderson et al. [2], in 1968, associated calciphylaxis with autonomized secondary hyperparathyroidism and hypercalcemia.

The pathophysiology of calciphylaxis is multifactorial, involving more than just elevated calcium-phosphorus levels. Recent studies highlight the roles of arteriolar osteogenesis, BMP-2 (bone morphogenetic protein-2), and cellular transformation [3]. This pathology represents a real diagnostic and therapeutic challenge, given the multiplicity of differential diagnoses, the need for a skin biopsy which is not always possible, and the absence to date of an effective etiopathogenic treatment, the role of sodium thiosulfate remains controversial in this context.

Case Report

A 60-year-old female patient presented with a medical history of kidney lithiasis since 1982, hypertension since 1999 (currently untreated due to hypotension), and chronic end-stage renal failure secondary to vascular nephropathy, managed with hemodialysis since 2014. The condition was complicated by secondary hyperparathyroidism, for which she received calcium and alfacalcidol supplementation. In 2017, she underwent aortic valve replacement with a mechanical prosthesis and was initially prescribed Warfarin, later switched to rivaroxaban (5 mg/day) in 2018 following the development of calcified skin lesions on the right arm. She was admitted for evaluation of a rash affecting both lower limbs.

The disease course spanned 3 years, characterized by the progression of indurated plaques and necrotic spots on the right arm, resulting in limited joint mobility. Lesions subsequently developed on the left arm and both thighs. The current episode began 1 month ago with the appearance of bilateral retro-malleolar ulcerations, followed by an erythematous plaque with necrotic lesions extending to the mid-leg. The condition evolved in the context of apyrexia, anorexia, and no reported weight loss.

On clinical examination, the patient was obese, with a body mass index (BMI) of 35 kg/m^2 and a blood pressure of 100/60 mm Hg. Both legs displayed erythematous plaques with ulcerations, areas of necrosis, and phlyctenae. Indurated, non-inflammatory plaques with necrotic changes were also observed on the arms and thighs. Additionally, two fingers exhibited necrosis, and the patient showed signs of Raynaud's phenomenon. These clinical findings strongly supported a diagnosis of calciphylaxis (shown in Fig. 1).

Fig. 1. Skin lesions detected on clinical examination. (1) Ulcerations, (2) phlyctens, (3) skin induration, (4) necrosis.

The biological analysis revealed significant abnormalities. Parathyroid hormone (PTH) levels were elevated at 190 pg/mL (15–65 pg/mL), accompanied by hypercalcemia (Ca = 114 mg/L) and hyperphosphatemia (Phosphorus = 77 mg/L), resulting in a markedly elevated phospho-calcium product of 8,778 mg^2/L^2. Inflammatory markers were significantly elevated, with a C-reactive protein level of 232 mg/L, a white blood cell count of 13,200/mm^3, and procalcitonin levels of 15 ng/mL. The patient also exhibited normocytic normochromic anemia, with a hemoglobin level of 8.8 g/dL.

Blood tests further demonstrated elevated beta-2 microglobulin levels at 32 mg/L. Cryoglobulinemia was negative, but serum protein electrophoresis indicated a peak in beta-2 globulins, with no monoclonal peak detected by immunosubtraction. Coagulation parameters, including protein C (126%), protein S (90%), and antithrombin (94%), were within normal limits. However, homocysteine levels were elevated at 25.78 µmol/L. Immunological testing revealed elevated antinuclear antibodies at 320 IU/L in a speckled pattern, with negative results for anti-DNA, anticardiolipin, anti-Sm, anti-SSA, anti-SSB, anti-Scl-70, and anti-smooth muscle antibodies. Complement levels (C3 and C4) were normal. Radiological findings showed widespread vascular calcifications (medial calcinosis) involving all four limbs and the abdominal aorta, as well as mesh-like subcutaneous calcifications (shown in Fig. 2).

Skin biopsy findings were consistent with calciphylaxis, characterized by keratinocyte necrosis, chronic fibro-inflammatory remodeling, and calcium deposits within vessels. Van Kossa staining was not performed due to the unavailability of reagents (shown in Fig. 3). Swabbing of the skin lesions revealed a significant cellular reaction dominated by neutrophils. Culture results indicated the presence of *Pseudomonas* species and *Enterobacter cloacae*.

The patient received appropriate antibiotic therapy, daily local wound care, oral thiosulfate (due to the unavailability of injectable thiosulfate), daily hemodialysis with low-calcium dialysate (1.25 mmol/L), and daily hyperbaric oxygen therapy. Oral calcium and alfacalcidol were discontinued, a non-calcium-phosphorus binder (sevelamer) was introduced, and alendronate therapy was initiated. Pain management required morphine administration.

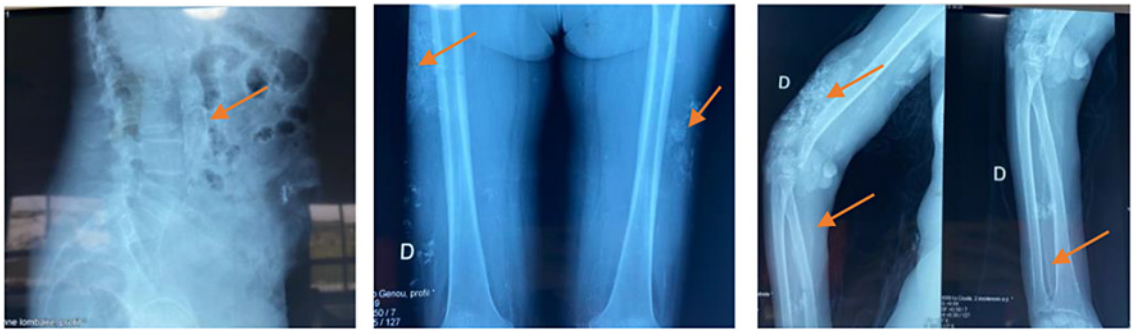

Fig. 2. Vascular and subcutaneous calcification.

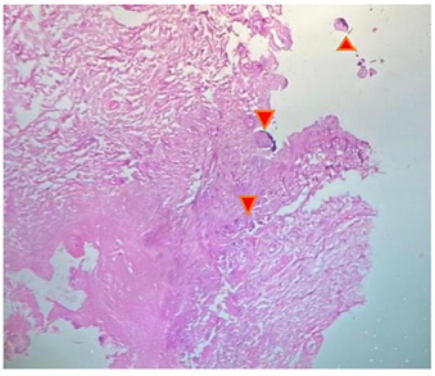

Fig. 3. Anatomopathological aspect of skin biopsy: skin tissue section showing large vessels within the dermis, with extensive calcifications (indicated by red arrows) (hematoxylin and eosin stain, magnification ×100).

The clinical course was complicated by the onset of septic shock, necessitating bilateral leg amputation. Despite these interventions, the patient's condition did not improve, and she succumbed to her illness within 10 days.

Discussion

Our patient presented with multiple risk factors predisposing her to calciphylaxis, including obesity, anticoagulant use (Warfarin), an elevated phospho-calcium product, female gender, and prolonged dialysis duration. This case underscores the challenges associated with managing calciphylaxis and highlights the necessity for a multidisciplinary approach to improve outcomes in such complex cases.

Calciphylaxis is a rare but devastating complication, affecting approximately 4% of dialysis patients [4]. The prognosis remains poor, with a reported 1-year mortality rate of up to 80%, primarily due to septic complications [5]. Despite this grim outlook, surgical debridement has shown promise, with a 1-year survival rate of 61.6% compared to only 27.4% in those who do not undergo intervention [5]. Distal forms of calciphylaxis, typically affecting the lower limbs, are associated with better prognoses [6]. However, our case diverged from this trend due to the patient's extensive and multifocal calcifications, compounded by her fragile health status, delayed diagnosis, and secondary infections of the lesions. Even with adherence to recommended treatments, her condition deteriorated, ultimately leading to her demise. This case underscores the complexity and challenges in managing calciphylaxis effectively.

Since 2004, intravenous sodium thiosulfate has been introduced as a systemic treatment option for calciphylaxis [7]. Its dual mechanism of chelating calcium salts and reducing oxygen-free radicals offers a theoretical benefit in mitigating both intravascular and extravascular calcifications [8]. Standard dosing typically involves a test dose of 12.5 g, followed by 25 g three times per week, although variations in dosage have been reported. Clinical studies have demonstrated promising results; for instance, in a study of 27 dialysis patients, 52% achieved complete remission and 19% partial remission [9]. Similarly, a study involving 53 hemodialysis patients treated with sodium thiosulfate showed complete resolution in 26% and significant improvement in 19% of cases [10]. However, recent meta-analyses have

raised questions regarding its efficacy. A pooled analysis of 12 studies involving 110 patients concluded that there was no significant difference in skin lesion improvement between patients receiving sodium thiosulfate and those in the comparator group (risk ratio, 1.23; 95% CI, 0.85–1.78). Furthermore, no notable difference was observed in mortality or overall survival. Interestingly, meta-regression analysis suggested that recent studies are less likely to show a positive association with sodium thiosulfate than earlier ones, highlighting potential biases in earlier publications (coefficient = −0.14; p = 0.008) [11]. Despite these findings, the efficacy of sodium thiosulfate remains an area requiring further investigation through well-conducted randomized clinical trials. Unfortunately, none of the three attempted trials have reported or published outcomes to date [12–14].

In addition to intravenous sodium thiosulfate, intralesional administration has been proposed as an alternative to reduce systemic side effects. Retrospective studies suggest no significant differences in survival outcomes between these two delivery methods, warranting further investigation [15].

Emerging therapeutic options, such as SNF472, offer potential advancements in the management of calciphylaxis. SNF472, a hexasodium salt of myo-inositol hexaphosphate, functions as a vascular calcification inhibitor and is currently being evaluated in phase 3 clinical trials [16]. Similarly, vitamin K has garnered interest as a therapeutic agent due to its role in inhibiting vascular calcification. Current clinical trials aim to explore its efficacy in calciphylaxis (ClinicalTrials.gov identifier: NCT02278692) [17].

Overall, the treatment of calciphylaxis remains non-standardized, with considerable variability and controversy surrounding therapeutic approaches. This rare but fatal condition necessitates a multidisciplinary management strategy, focusing on optimizing all modifiable risk factors. Such an approach is critical while awaiting the results of ongoing clinical trials and the development of standardized, effective treatment protocols.

Conclusion

Calciphylaxis represents a rare and severe complication necessitating prompt recognition through clinical manifestations, with biopsy serving as the gold standard diagnostic tool. Urgent therapeutic intervention mandates multidisciplinary deliberation.

The significance of this case lies in underscoring the importance of proactively managing mineral and bone complications in chronic dialysis patients (whether hemodialysis or peritoneal dialysis). Furthermore, it highlights the intricate diagnostic and management challenges associated with calciphylaxis – a rare yet formidable complication of chronic kidney disease.

It also raises concerns about the risk-benefit balance of administering antivitamin K therapy to patients with chronic renal failure. Additionally, it questions the role of screening for vascular and extravascular calcifications in this population, before patients progress to advanced stages of calciphylaxis, potentially complicated by superinfection. There is a growing interest in intervening with treatments known to effectively dissolve calcifications even before calciphylaxis develops (SNF472, Vitamin K, sodium thiosulfate?). Conducting randomized clinical trials appears necessary to advance management strategies.

Statement of Ethics

Ethical approval is not required for this study in accordance with national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Maria Lafrid and Dr. Narjiss Labioui: text redaction. Dr. Mohamed Hallak: bibliographic research. Prof. Abdelaali Bahadi, Prof. Driss El Kabbaj, and Prof. Yassir Zajjari: correction. Prof. Mohamed Allaoui: figure of anatomopathological aspect of skin biopsy.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participant but are available from the corresponding author M.L.

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