CASE REPORT

A Case of Calciphylaxis

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Abstract

Introduction: Calciphylaxis (calcific uremic arteriolopathy), is a condition primarily observed in patients with end-stage renal disease (ESRD).

Aim: To increase clinical awareness of calciphylaxis and to consider it a differential diagnosis in the presence of atypical skin nodules or ulcers occurring in patients with chronic kidney disease (CKD), especially in patients on hemodialysis and non-hemodialysis patients with the background of diabetes mellitus and secondary hyperparathyroidism.

Case Report: We present the case of a 77-year-old woman with CKD and diabetes mellitus as well as severely painful, firm, indurated plaques on the lower extremities. The plaques progressed to involve larger areas with associated local ulceration and necrosis. Laboratory testing revealed hyperparathyroidism and incisional skin biopsy confirmed calciphylaxis.

Conclusion: Each single CKD patient with diabetes mellitus and signs of secondary hyperparathyroidism with extremely painful ischemic cutaneous lesions or painful subcutaneous nodules without skin changes, although at times, pain may precede the development of the lesions, is a candidate for skin biopsy. Calciphylaxis is a rare but serious kidney complication.

Keywords: calciphylaxis, chronic kidney disease, prognosis, treatment.

Learning Objectives

- Identify the risk factors for calciphylaxis.
- Describe the pathophysiology of calciphylaxis.
- Present treatment and management options available for calciphylaxis.
- Explain the importance of a multidisciplinary team approach for the effective treatment of calciphylaxis.

INTRODUCTION

Calciphylaxis, also known as calcific uremic arteriolopathy, is a condition primarily observed in patients with end-stage renal disease (ESRD), though it can occasionally occur in those without ESRD (non-uremic calciphylaxis) (1). This condition is marked by the calcification of the medial layer of arterioles in the dermis and subcutaneous fat, leading to endothelial damage and microthrombi formation (1,2). These changes result in painful skin lesions, tissue ischemia, necrosis, and ulceration. Calciphylaxis has a high morbidity and mortality rate, with an estimated six-month survival rate of around 50% (2-4). A deficiency in vascular calcification inhibitors, such as fetuin-A and matrix Gla protein, may contribute to its development (5). It is more prevalent in females and is mainly linked to kidney disease, hyperparathyroidism, and diabetes mellitus, as well as conditions like obesity, liver disease, hypoalbuminemia, malignancies, and autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis) (2-5). Certain medications, including warfarin, corticosteroids, calcium-based phosphate binders, activated vitamin D, and iron therapy, are associated with calciphylaxis; for instance, warfarin reduces the vitamin K-dependent activation of matrix Gla protein (5). The aim of article is to enhance clinical awareness of calciphylaxis and consider it as a differential diagnosis when atypical skin nodules or ulcers appear in patients with kidney disease, particularly those undergoing hemodialysis and with diabetes and secondary hyperparathyroidism.

CASE PRESENTATION

A 77-year-old female patient was assessed in the outpatient nephrology clinic. She reported severe leg pain that had been ongoing for several months. During the physical examination, local erythema and necrotic ulcerations of the skin were noted (Figure 1).

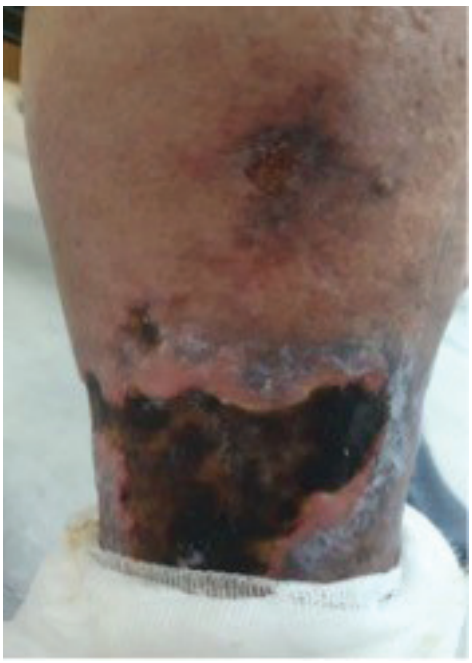

Figure 1. Necrotic ulcerations

The skin changes were initially described as diabetic ulcerations. The lesions began as red, itchy areas, but over time, necrosis and inflammation of the surrounding tissue developed, accompanied by intense pain.

Patient's medical history included hypertension, diabetes mellitus, hyperlipidemia and chronic kidney disease (CKD). In our case, laboratory investigations were consistent with chronic kidney injury as late complication of diabetic nephropathy. Within chronic kidney disease stage IV/V (eGFR13.3 mL/min/1.73m^2), electrolyte imbalance with signs of secondary hyperparathyroidism is also observed ((Ca 2.56 mmol/L - reference range 2.10-2.55 mmol/L) and PO4 1.63 mmol/L - reference range 0.81-1.59 mmol/L), PTH 50.1 pmol/L (reference range 1.6-6.9 pmol/L).

Based on the typical clinical grounds, and history of CKD with secondary hyperparathyroidism and diabetes, we suspected calciphylaxis and requested a skin lesion biopsy. Pathophysiological findings included extravascular and intravascular calcinosis of small and medium-sized blood vessels, and the appearance of erosions on the surface of the skin, which could fit into the clinical diagnosis of calciphylaxis (Figure 2).

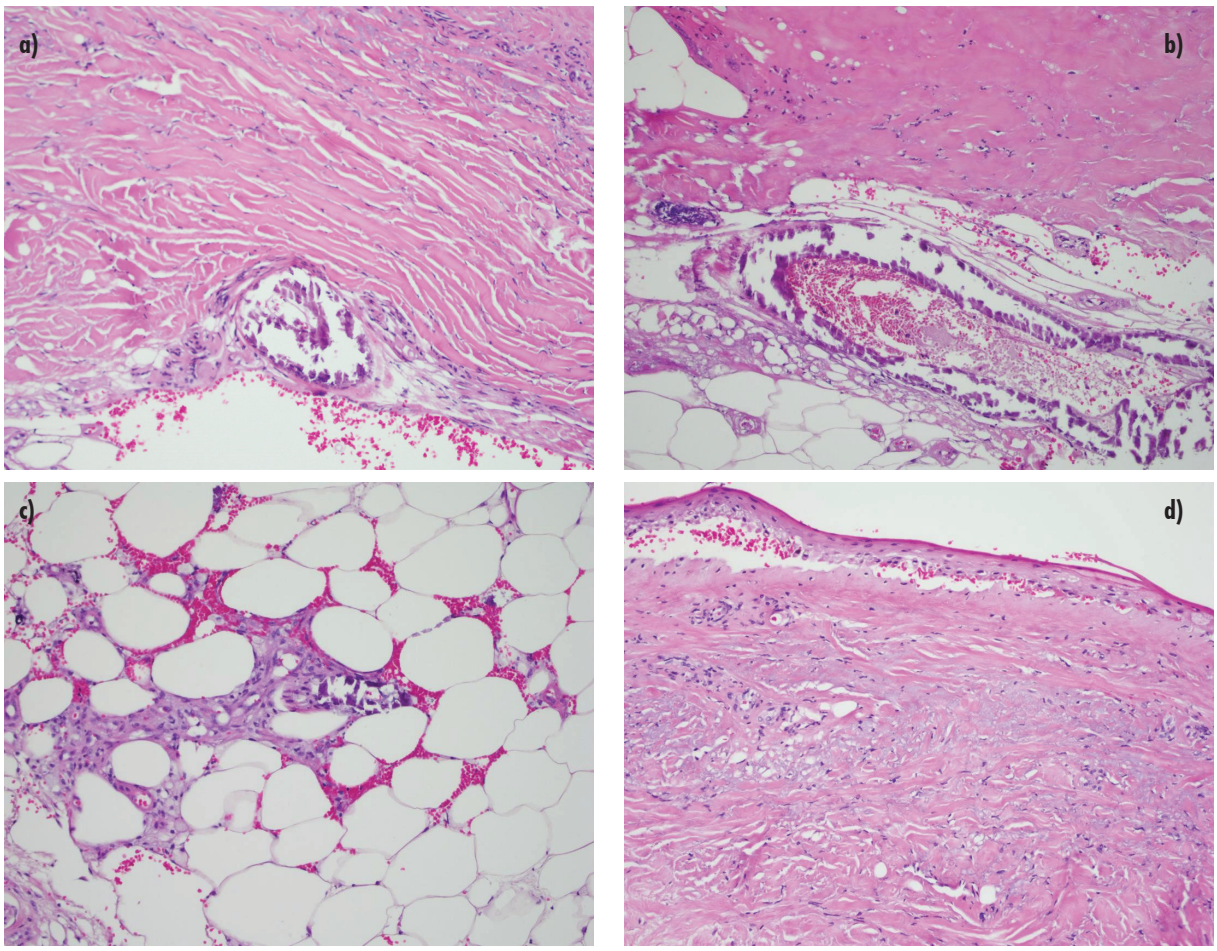

Figure 2. a) Intramural intravascular calcium deposit in the reticular layer of dermis (HE, 200 x); b) Calcium deposit in the vein wall in the subcutaneous fat tissue (HE, 400 x); c) Calcium deposit in the capillary wall in subcutaneous fat tissue (HE, 400 x); d) Skin appendages reduction and mucin deposits in superficial dermis (HE, 200x); d) Skin appendages reduction and mucin deposits in superficial dermis (HE, 200x)

DISCUSSION

In our case, laboratory investigations indicated chronic kidney injury as a late complication of diabetic nephropathy. Calciphylaxis was suspected based on clinical findings. A skin biopsy and histological evaluation showed specific inflammation and necrosis with calcification affecting small arteries and surrounding fibroadipose tissue. The laboratory workup should encompass all potential implications of CKD, with particular focus on calcium and phosphate levels, as well as any evidence of skin or systemic infection.

Treatment should prioritize local wound care and metabolic control, specifically by managing hypercalcemia, hyperphosphatemia, and hyperparathyroidism (5-9). Suggested therapies include oral anticoagulants, sevelamer carbonate, calcitriol, vitamin K, and ongoing management for diabetes mellitus and hypertension. Debridement may be necessary, although surgical debridement is controversial due to the heightened risk of sepsis and increased pain. Pain management is also critical, along with efforts to prevent both local and systemic infection (7-9).

In patients with advanced CKD, diagnosis primarily relies on physical examination, where painful, ulcerated lesions covered by black eschar are observed. The definitive diagnosis is confirmed through a biopsy of the affected skin, which is recommended if there is uncertainty. Differential diagnoses include warfarin-associated skin necrosis, antiphospholipid syndrome, cholesterol embolization, vasculitis, and cellulitis (8).

There is currently no approved treatment for calciphylaxis (5-9). A multidisciplinary approach is necessary, focusing on wound care and pain management, as well as

addressing infected wounds through surgical debridement and antimicrobial therapy to prevent sepsis, the leading cause of death in these patients. Hyperbaric oxygen therapy may also aid in wound healing for some individuals. Hyperphosphatemia and hypercalcemia should be managed, with non-calcium-containing phosphate binders recommended. Secondary hyperparathyroidism should be treated with cinacalcet. Additionally, optimizing dialysis and medication regimens is essential. For specific treatment of calciphylaxis, intravenous sodium thiosulfate (STS) may be considered.

Given that calciphylaxis is an extremely painful and debilitating condition, nutritional and psychological support, along with specialized pain management, are crucial. In our case, care goals and prognosis were discussed with the family, who chose to pursue palliative and comfort measures without further invasive surgical or medical interventions.

Early signs of calciphylaxis are extreme pain, before there are any visible signs of calciphylaxis (purple or red skin markings, sores that do not heal) with background of chronic kidney disease and diabetic nephropathy and hyperparathyroidism secondary.

In our case, at the beginning, there was extreme pain but no skin lesions. For the second control examination, the patient came with eschar, a wound covered with thick, dry, black necrotic tissue. We have missed the first skin lesion signs due to the patient's failure to come to an examination. The described lesions were the reason for our working diagnosis of calciphylaxis and the indication for skin biopsy.

CONCLUSIONS

Every CKD patient with diabetes mellitus and signs of secondary hyperparathyroidism, who presents with extremely painful ischemic skin lesions or painful subcutaneous nodules, sometimes with pain preceding the appearance of the lesions, is a candidate for a skin biopsy. Calciphylaxis is a rare but serious complication associated with CKD.

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Consent: The authors have obtained written consent from the patient to submit and publish this case report, including images and accompanying text, in accordance with COPE guidelines.

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