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Original Research Article

Navigating Calciphylaxis as a Complication in Chronic Kidney Disease

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Abstract: Calciphylaxis is a progressive, inflammatory disease characterized by the calcification of small and medium-sized arteries, leading to thrombotic ischemia. It is commonly associated with patients with chronic kidney disease; however, it can also manifest in patients without uremia. The incidence in patients undergoing dialysis can vary from 0.04% to 4%; it can affect multiple organs including the skin, brain, lungs, and muscle. Hyperphosphatemia, hypercalcemia, and hyperglycemia are common biochemical conditions in patients with this disease that induce the transformation of vascular smooth muscle cells into osteoblast-like cells, thus establishing the mechanism for vascular calcification through the formation of ectopic bone within the vessel wall. Additionally, there is a deficiency of calcification inhibitors in patients with chronic kidney disease. These factors promote the hardening and narrowing of affected arterioles, compromising their structural integrity and fostering an environment conducive to thrombosis. Cutaneous calciphylaxis can present as non-healing nodules, plaques, and ulcers. Currently, biopsy and histological analysis are the methods of choice for diagnosis. Treatment is multidisciplinary and includes early surgical debridement, symptom management, and modification of risk factors. We present the case of a female in her fifth decade of life with a history of chronic kidney disease who developed calciphylaxis with cutaneous manifestations requiring surgical treatment.

Keywords: Calciphylaxis, Chronic Kidney Disease, Vascular Calcification, Hyperparathyroidism.

INTRODUCTION

Calciphylaxis is a rare vascular condition but a potentially life-threatening etiology. It was first described in 1898 by Bryant and White and the term calciphylaxis was coined in 1962 by Hans Selye [1]. Also known as calcific uremic arteriolopathy, it is defined as a clinical syndrome characterized by necrotic skin ulceration due to calcification of the media and fibrosis of the intimal arterioles, followed by cutaneous ischemia due to thrombosis [2]. It is a progressive, inflammatory disease with a one-year mortality rate of up to 50%; it is commonly associated with end-stage chronic kidney disease. It is characterized by calcification of medium and small-caliber arterioles leading to thrombotic ischemia and various dermatological manifestations, ranging from small nodules and plaques to necrotic ulcers that can be located anywhere on the body [2, 3]. The disease is classically observed in patients with chronic kidney disease (CKD), where calcium and phosphate levels in the blood exceed their solubility limits and deposit in the arterial walls; however, this pathology can also be seen in non-uremic patients [4]. The incidence among patients undergoing dialysis treatment ranges from 0.4% to 4%, and this incidence has been increasing over the last decade [2, 4].

Calciphylaxis is a potentially fatal disease, with a reported mortality rate of 30% at 6 months and 50% at 12 months. In addition to the high mortality rate, there is a high morbidity, with patients experiencing recurrent hospitalizations, chronic pain, and non-healing lesions [5].

Currently, biopsy and histological analysis are the preferred methods for diagnosis. Treatment is multidisciplinary and includes early surgical debridement, wound care, antimicrobial therapy, pain management, and risk factor modification (optimization of renal function, bisphosphonates, systemic anticoagulation) [3, 6].

CASE PRESENTATION

A 46-year-old female with a hereditary history: of colon cancer. Surgical history: Tenckhoff catheter in 2021; medical history: type 2 diabetes diagnosed in 2016; systemic arterial hypertension; chronic kidney disease KDIGO G5D diagnosed in 2022 on renal replacement therapy (peritoneal dialysis); primary hyperthyroidism and secondary hyperparathyroidism.

Present illness began with burning, diffuse pain rated 8/10 (ENA) in the left hand, paresthesia, swelling, warmth, and redness in that area, progressively evolving; one week later, the coloration changed to a purplish tone in the distal phalanges of the fifth, fourth, and third fingers of the left hand. These lesions progressed to excavated eschar-type lesions in the mentioned phalanges, with progressive changes in coloration leading to distal necrosis, prompting a visit to the emergency department. Physical examination shows a dermatosis localized on both hands with dry necrosis of the distal portion of the left ring and little fingers and livedoid changes on both palms. A hand X-ray showed arterial calcification, laboratory tests reported hyperphosphatemia, elevated urea, and normocytic normochromic anemia grade III. Doppler ultrasound of the affected area revealed distal arterial insufficiency and atherosclerosis. Calciphylaxis secondary to CKD was diagnosed. Plastic surgery performed amputation and pathology examination showed calcification of vascular walls with a diagnostic conclusion of calciphylaxis.

Table 1: Laboratory Results

Serum electrolytes	**Results**	**Reference value**
Phosphorus	11.9 mg/dL	2.4-5.1 mg/dL
Calcium	7.5 mg/dL	8.3-10.6 mg/dL
Magnesium	2.3 mg/dL	1.3-2.7 mg/dL
Sodium	132.2 mmol/L	135-148 mmol/L
Potassium	5.3 mmol/L	2.5-5.3 mmol/L
Chlorine	94.5 mmol/L	98-109 mmol/L
Blood chemistry		
Urea	256 mg/dL	13-43 mg/dL
BUN	120 mg/dL	9-23 mg/dL
Creatinine	12.29 mg/dL	0.5-1.3 mg/dL
Hematologic biometry		
Leukocytes	11.26 (10x3/mL)	5-10 (10x3/mL)
Neutrophils	8.84 (10x3/mL)	41.4-73 (10x3/mL)
Hemoglobin	7.74 g/dL	12-16 g/dL
Hematocrit	22.15%	37-47%
MCV	85.9 pg	81-99 pg
MCHC	35 g/dL	32-36 g/dL
Platelets	321(10x3/mL)	150-400 (10x3/mL)

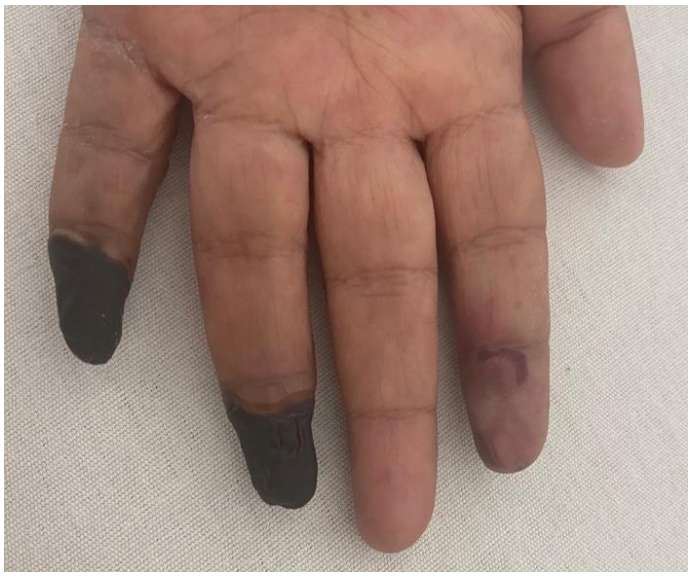

Figure 1: Necrotic lesions on the fourth and fifth distal phalanges, purplish coloration on the distal phalanx of the second finger

Figure 2: Purplish erythema with an incipient ulcer on the pulp of the distal phalanx of the second finger and necrosis of the distal phalanx of the fourth and fifth fingers

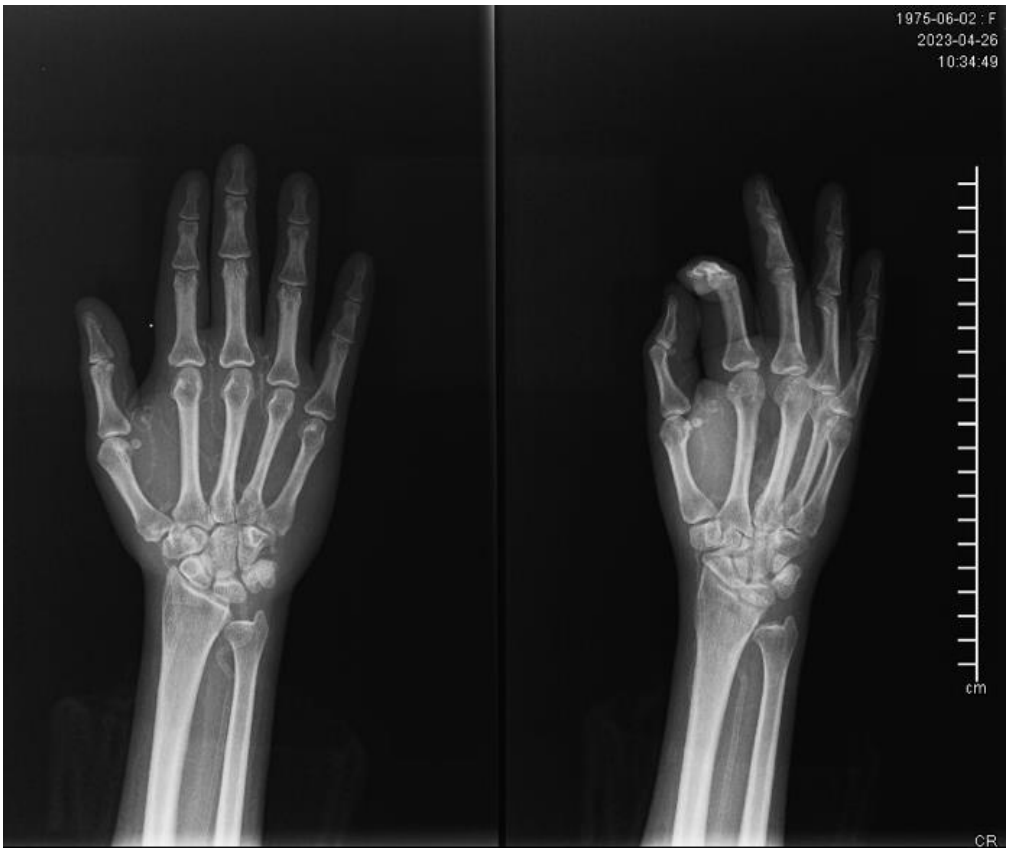

Figure 3: Anteroposterior X-ray of the left hand showing extensive arterial calcifications

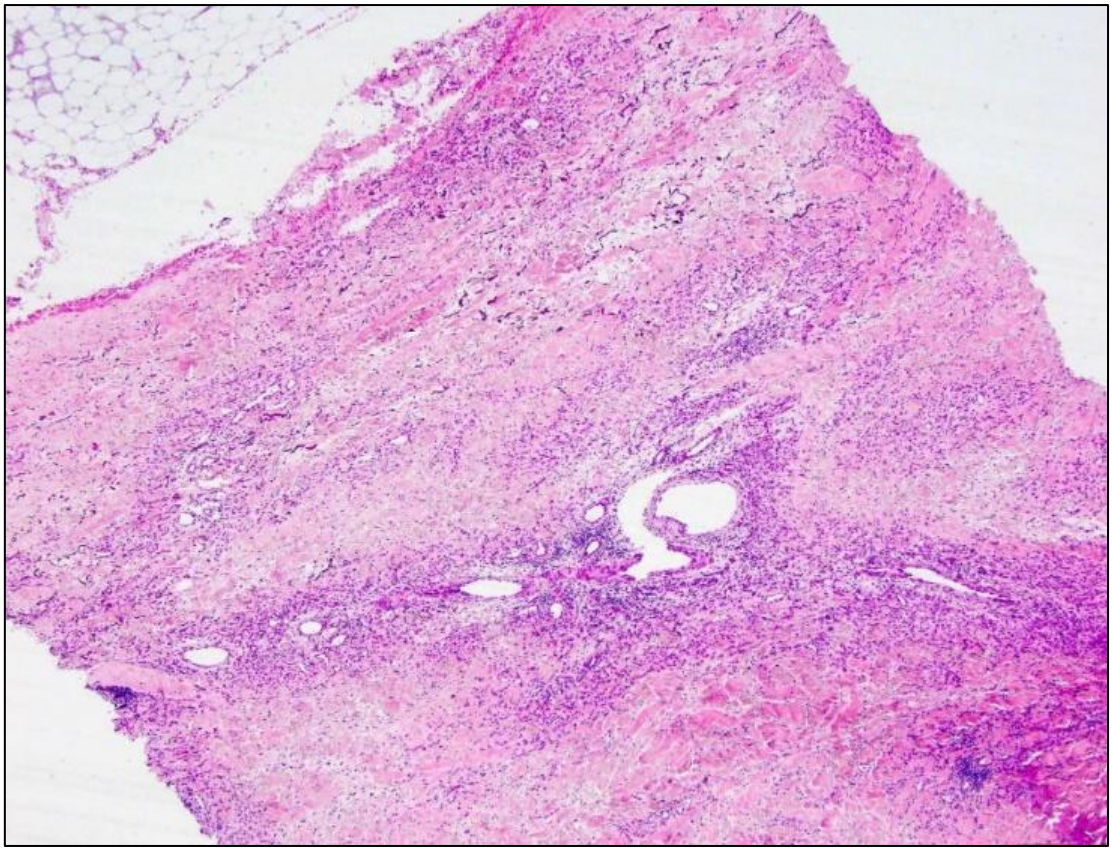

Figure 4: Skin biopsy: Hematoxylin-eosin staining (4x): Reticular dermis. Identification of calcification of vascular walls of the deep plexus with a diagnostic conclusion of calciphylaxis

DISCUSSION

Calciphylaxis is characterized by calcium deposition in blood vessels, skin, and other organs. It is a rare but devastating disease [6, 7]. Represents a complex condition with multiple etiological factors; although the exact pathogenesis of this entity has not been fully elucidated, it is known that abnormalities in calcium and phosphorus metabolism, inflammation, and a constant state of hypercoagulability are present in this pathology, which can result in vascular and extravascular calcification [8]. This calcification involves active cellular processes, not just passive mineralization, due to increased calcium-phosphate concentrations. Extensive medial vascular calcification is a finding in vasculopathy associated with chronic kidney disease and is associated with increased cardiovascular mortality. In vitro studies of human smooth muscle cells have shown increased expression of osteogenic markers that predispose patients to calcification when exposed to elevated phosphorus levels and other uremic toxins [8, 9].

Smooth muscle cells in calciphylaxis have increased expression of osteopontin, which is believed to promote arterial lumen occlusion. Additionally, bone morphogenetic protein (BMP-4), which participates in bone repair and development, is expressed and promotes calcification [10]. BMP-4 action depends on the production of reactive oxygen species (ROS) which can activate nuclear factor KAPPA B (NFκB). End-stage renal disease is a chronic inflammatory state associated with increased generation of NFκB and its receptor activator RANKL, suggesting the role of NFκB-osteoprotegerin/RANKL axis in bone tissue homeostasis and vascular calcification. Hemodialysis patients also have low levels of alpha2-Heremans-Schmid glycoprotein (AHSG, also known as fetuin-A) a circulating calcification inhibitor found in humans and animal models. AHSG production is also negatively regulated in inflammation [11, 12].

Risk factors include female gender, Caucasian ethnicity, warfarin treatment, diabetes, obesity, disturbances in calcium and phosphorus metabolism, hypoalbuminemia, prolonged dialysis status, protein C deficiency, and the use of phosphorus binders.

The calcification process requires two main factors:

1. Calcification of the media layer and fibrosis of the intima layer of arterioles.
2. Thrombotic occlusion resulting from progressive calcification and endothelial dysfunction; vascular calcification secondary to dysfunction of calcium, phosphorus, and parathyroid hormone regulatory Mechanisms [13].

Dermatological clinical presentation includes painful lesions characterized by nodules or plaques accompanied by livedo reticularis, evolving over days from superficial to deeper planes as ulcers forming a blackish eschar with centrifugal spread.

Two phases in the clinical presentation have been described: the first phase is insidious and usually asymptomatic, though it often involves itching and laminar erythema. The second phase, rapidly evolving, includes ischemic purpura, which is very painful, disproportionate to the skin lesion, and eventually progresses to ulceration and skin necrosis.

Both types of lesions can appear simultaneously; while the first type of lesion is associated with 30% mortality, the second type up to 80% mortality.

Regarding lesion distribution, two patterns can be distinguished:

1. Distal pattern: present in 90% of cases, lesions appear in the lower extremities (especially the ankle and calf) but can also appear on fingers, hands, and genitals. This pattern has the worst prognosis.
2. Proximal pattern: less common, affecting areas with more adipose tissue such as the trunk, inner thighs, buttocks, and breasts. Both patterns can be present in the same individual.

The approach should be multidisciplinary; the clinical examination of a patient with calciphylaxis involves two important goals: assessing the presence of any etiological factors and ruling out any potential disorders that might mimic physical examination findings.

If available, single-photon emission computed tomography (SPECT-CT) is recommended due to its 97% sensitivity and is useful for visualizing the extent of pathology and determining areas of microcalcifications [12, 14].

Laboratory tests including blood chemistry, serum calcium, alkaline phosphatase, phosphorus, liver function tests, and albumin; complete blood count to rule out infections; and screening for autoimmune diseases should be performed.

Skin biopsy is the ideal method for confirming Calciphylaxis; the main histological findings are calcification of the medial and internal laminae, hypertrophy, and local inflammation pattern resulting in vessel obstruction and skin necrosis. After diagnosis, appropriate and timely management plays a vital role in the patient's quality of life and avoidance of complications. The treatment should be multidisciplinary, involving nephrology, dermatology, wound care specialists, and nutrition. Pain management, wound care, adequate nutrition, and avoidance of predisposing and/or iatrogenic factors are essential. Management primarily focuses on local wound care and prevention of local and systemic infections, as well as optimizing the patient’s condition concerning associated comorbidities [15].

CONCLUSION

Calciphylaxis remains a rare condition but represents a significant cause of morbidity and mortality, particularly in patients with chronic kidney disease. Early detection is crucial; calciphylaxis should be promptly suspected in patients with CKD who develop ischemic and painful skin lesions.

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