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Fatal Masquerade: A Case of Calciphylaxis Concealed as Cellulitis

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Abstract

Skin inflammation that progresses to circulatory shock is most often attributed to infection as the first hypothesis. Fluids, antimicrobial drugs, and surgical debridement are sometimes necessary. However, non-infectious causes should be considered in a patient undergoing dialysis. Differentiating between cellulitis and calciphylaxis or calcific uremic arteriolopathy (CUA) is challenging; however, the mortality rate associated with CUA is generally high. We report the case of a woman with end-stage chronic kidney disease undergoing dialysis, who complained of lower abdominal pain. The patient presented with subcutaneous infiltration and painful erythematous skin lesions in the hypogastric region. Initially, erysipelas was suspected, and antibiotic treatment was initiated. Extensive surgical debridement of the necrotic tissue was urgently performed. Histopathological examination revealed calcifications in the wall of small vessels. The patient's condition worsened within 24 h to refractory shock, ultimately leading to death from circulatory shock.

Keywords

Calciphylaxis, Chronic Kidney Disease, Thiosulfate, Warfarin

1. Introduction

In skin inflammation rapidly progressing to circulatory shock, the first hypothesis is to most often attribute it to infections. The immediate administration of antimicrobials and intravenous fluid resuscitation within the first hour is the golden rule. Surgical management is often necessary when necrotizing soft tissue infection occurs in patients with very advanced diseases. However, non-infectious causes should be considered in the absence of a response. Delayed recognition of

calciphylaxis or calcific uremic arteriolopathy (CUA) leads to long-term morbidities and a high mortality rate exceeding 50% [1]. CUA is a rare but potentially fatal condition characterized by calcification of subcutaneous arteries, thrombosis, and tissue ischemia. Differentiating between cellulitis and CUA is challenging. CUA is mostly observed in patients with advanced chronic kidney disease (CKD), generally affecting the lower extremities. The diversity of clinical presentation contributes to delays in diagnosis, with skin biopsy currently considered the gold standard for confirming the diagnosis. The aim of reporting this case is to show that the most important factor in CUA is early recognition to improve the prognosis of patients.

2. Case Description

A 73-year-old woman presented with lower abdominal pain ongoing for 2 weeks before hospital admission. Upon physical examination, subcutaneous infiltration with painful erythematous skin lesions limited to the hypogastric region was observed. Abdominal computed tomography (CT) revealed edematous infiltration of subcutaneous fat and hepatic steatosis/cirrhosis. Laboratory investigations are shown in Table 1. She had a history of renal cell carcinoma with pulmonary and bone metastases, treated by nephrectomy 6 years previously and immunotherapy. The patient was in complete remission. Moreover, she was obese, had diabetes, and had been undergoing dialysis for chronic renal failure for 5 years. She also had severe secondary hyperparathyroidism and was treated with etelcalcetide. Furthermore, she was on an anticoagulant (fenprocoumon), which was initiated 2 months before admission, due to refractory dysfunction of the hemodialysis catheter and paroxysmal atrial fibrillation. The diagnosis of erysipelas was initially suspected, and she was treated as an outpatient with oral amoxicillin-clavulanate. Five days later, vancomycin was added (administered during dialysis) because there was no improvement, and the frequency of dialysis was increased. Subsequently, she experienced increased abdominal pain and presented to the emergency department with hypotension, rapid atrial fibrillation, and lactic acidosis. Upon physical examination, a painful erythematous subcutaneous infiltration with extensive purpuric lesions was observed in the hypogastric region (Figure 1).

Table 1. Laboratory values.

Parameters	10 days before admission	Normal values	Emergency room
Hemoglobin	10.3	[12.0 - 16.0] g/dL	8.0
Total leucocyte count	8800	[3.5 - 10.0] $10^3/mm^3$	18.8
C-reactive protein	290	[<5] mg/dL	130.3
Blood urea	54	[15 - 45] mg/dL	63
Serum creatinine	3.37	[0.5 - 0.9] mg/dL	4.6
Serum sodium	138	[135 - 145] mmol/L	149
Serum potassium	4.0	[3.5 - 5] mmol/L	5.3

Continued

Serum alkaline phosphatase	146 U/L	[35 - 104] U/L	85
Serum phosphorus	1.0	[0.81 - 1.45] mmol/L	2.89
Serum calcium	2.82	[2.15 - 2.55] mmol/L	2.23
Serum PTH	2048.9	[18.5 - 88.0] ng/L	
Serum albumin	29.1	[35 - 51] g/dL	28

PTH, parathyroid hormone.

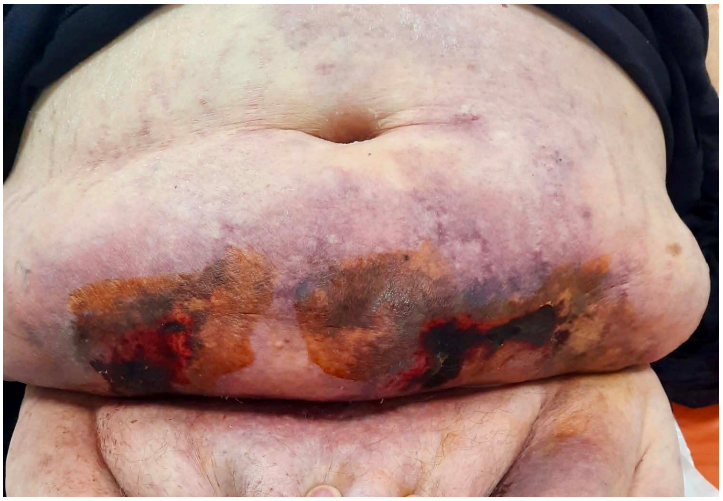

Figure 1. Ulcer with black eschar, irregular violaceous boundaries, surrounding erythema, and retiform purpura.

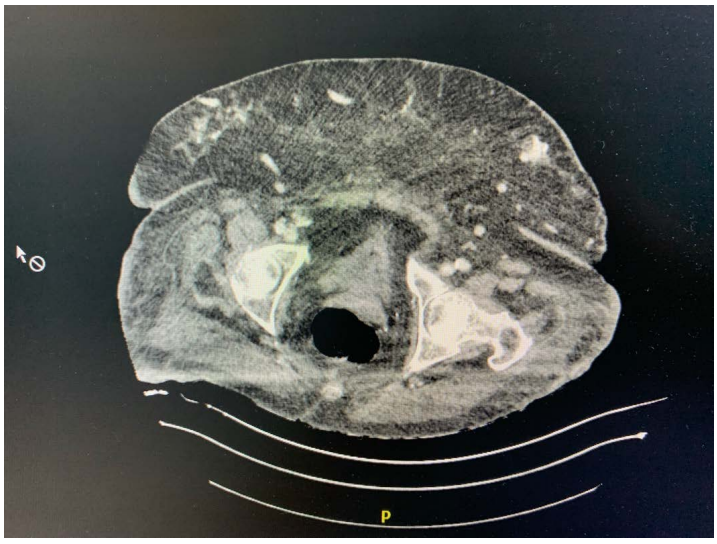

Figure 2. Abdominal computed tomography: deep collection in subcutaneous fat corresponding to the area of necrosis.

The patient's medications included simvastatin, levothyroxine, pantoprazole, etelcalcetide, calcitriol, and enoxaparin. A subsequent abdominal CT revealed a deep collection within the subcutaneous fat in contact with the muscular wall with

high density, corresponding to an area of necrosis (Figure 2). Laboratory tests conducted at the emergency unit showed elevated inflammatory markers (Table 1). Extensive surgical debridement of the necrotic tissue was urgently performed, and the antibiotic regimen was modified to piperacillin-tazobactam, clindamycin, and vancomycin. However, the patient's condition worsened within 24 h to refractory circulatory shock and multiorgan failure.

After a discussion with the family regarding the goals of management and prognosis, they opted for palliative care and comfort measures without further medical treatment. Sodium thiosulfate was not prescribed.

Histopathological examination revealed calcification within subcutaneous adipose tissue and necrosis (Figure 3), circumferential calcification with adjacent fibrin thrombus (Figure 4), vascular ectasia in the middle dermis, and calcifications in the walls of small vessels (Figure 5), without evidence of gangrenous pyoderma. Von Kossa staining provided further evidence in favor of CUA.

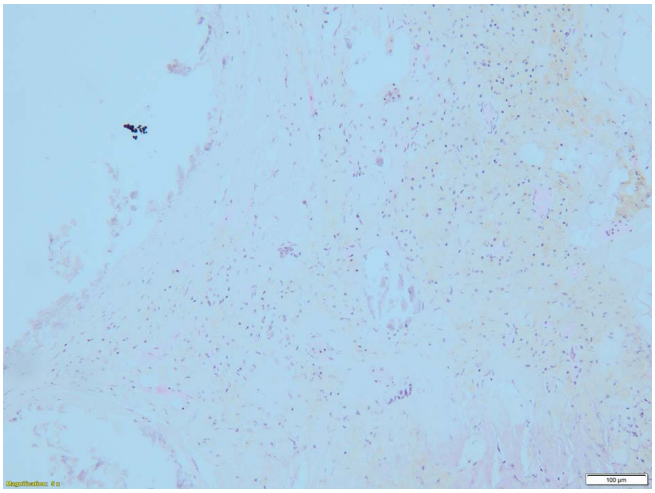

Figure 3. Histological features: calcification within subcutaneous adipose tissue and necrosis.

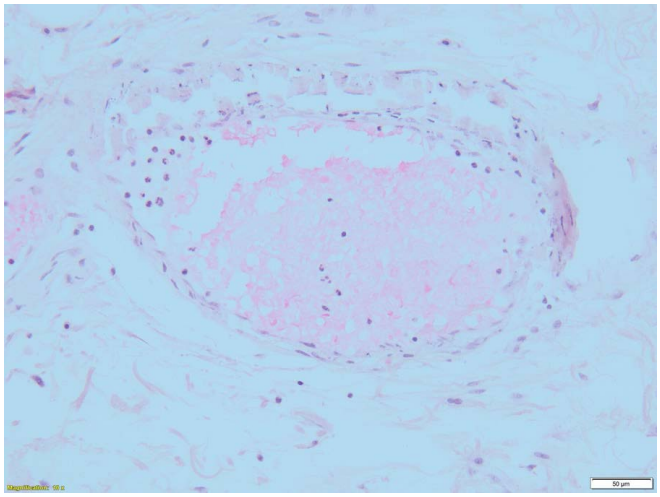

Figure 4. Circumferential calcification with adjacent fibrin thrombus.

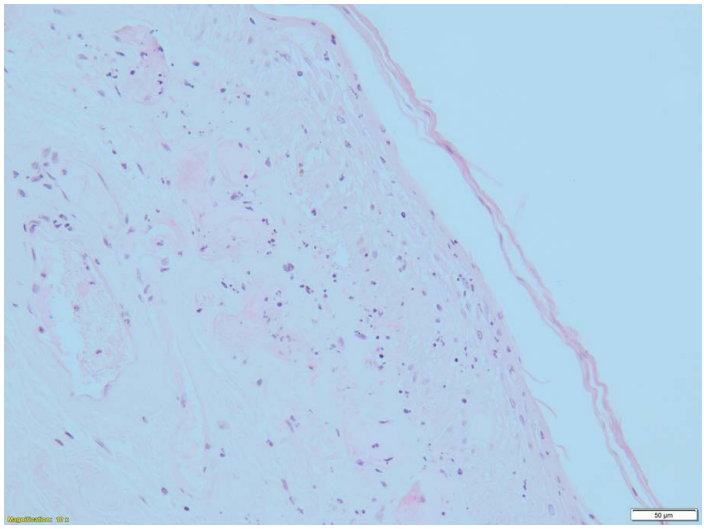

Figure 5. Necrosis of the epidermis and microcalcification.

3. Discussion

Calciphylaxis or CUA is a rare and aggressive vascular occlusive disease. Calcification within small caliber vessels leads to progressive narrowing of their lumens and subsequent tissue ischemia due to thrombosis. Seyle [2] first described CUA in rodents by inducing subcutaneous calcification through "sensitization" with parathyroid extracts, hypervitaminosis, and high phosphorus diet followed by the application of a "challenging" agent such as local trauma, egg albumin, or metallic salts. Moe et al. demonstrated that in response to hyperphosphatemia, hypercalcemia, and hyperglycemia, vascular smooth muscle cells transform into osteoblast-like cells able to produce and deposit hydroxyapatite crystals [3]. However, calciphylaxis has been described with normal or minimally elevated calcium and phosphate levels. Other factors contributing to the development of CUA include deficiencies in vascular calcification inhibitors such as fetuin-A, osteoprotegerin, and matrix G1a protein (MGP) [4]. Fetuin-A is a glycoprotein that binds calcium and phosphorus, potentially preventing the calcification of vessels and soft tissues. MGP inhibits calcification but requires vitamin K activity [5]. In addition, aberrant adipocytes, proinflammatory cytokines, and recurrent vascular endothelial injury may also play a role [6]. Physical trauma may lead to endothelial damage and subsequent activation of the coagulation cascade resulting in thrombosis, a phenomenon known as the Koebner phenomenon. The largest study from Fresenius Medical Care North America reported that the incidence rate of CUA was 3.4/1000 patients among those undergoing maintenance hemodialysis [7]. The incidence of CUA is lower in patients with normal renal function, known as non-uremic or non-nephrogenic CUA [8]. Additional risk factors for CUA include diabetes, obesity, female sex, protein C or S deficiency, iron infusions, corticosteroid use, immunosuppressive drugs, and warfarin use, as well as hypoalbuminemia and autoimmune processes.

Typically, lesions associated with CUA are extremely painful, and livedo

reticularis may also develop due to ischemia. The lesions subsequently progress to ulceration with the development of necrosis and eschar. CUA ulcerations can be mistaken for pyoderma gangrenosum or warfarin and heparin-induced necrosis, antiphospholipid syndrome, or infected diabetic ulcers [4]. Moreover, plaques may be mistaken for cellulitis, as patients with both conditions present with redness, warmth, and tenderness. The rapid progression to ulcers with black eschar is the hallmark of CUA presentation.

Patients mostly present with lesions on the lower extremities, whereas upper extremity involvement is less common. Distal lesions generally have a better prognosis compared to proximal lesions, which may occur on the thighs, buttocks, and abdomen [1]. CUA is a clinical diagnosis, but a definitive diagnosis relies on biopsy findings. However, the association between the Koebner phenomenon and calciphylaxis has led to debate regarding the hazards of biopsy, including the potential risk of new ulceration, bleeding, and infection. Biopsy can demonstrate medial calcification and intimal proliferation of small arteries, leading to ischemic epidermal necrosis [9]. Sensitivity is improved using special stains such as von Kossa or Alizarin red, for the detection of microcalcification. In the differential diagnosis, warfarin-induced skin necrosis is particularly important and typically responds to warfarin withdrawal. However, surgical debridement may be necessary in some cases. Patients should discontinue all medications that possibly contribute to CUA, including warfarin, iron, calcium, and vitamin D supplements. The treatment of hypercalcemia and hyperphosphatemia can be achieved with an intensified dialysis regimen and low-calcium dialysate. Severe hyperparathyroidism should be treated with calcimimetics. Sodium thiosulfate, known for its vasodilatory and antioxidant properties, increases calcium solubility to form a dialyzable salt and reduces intravascular and extravascular calcifications. Intravenous administration of sodium thiosulfate at a dose of 25 g, administered during each hemodialysis, has demonstrated good efficacy [10]. Regarding patients weighing less than 60 kg, reducing the doses helps to prevent adverse events such as vomiting, metabolic acidosis, hypotension, and volume overload. Wound management plays a pivotal role in the treatment of calciphylaxis. Therefore, multidisciplinary collaboration between dermatologists, surgeons, and burn centers is important to optimize wound care and determine the need for surgical debridement.

In our patient, calciphylaxis was considered as a potential diagnosis due to predisposing factors. Metabolic control with intensified dialysis was performed without improvement of the patient's clinical condition. A skin biopsy was not considered by the dermatologist at the beginning. Antibiotics and surgical debridement do not stop the progression of fulgurant illness. The administration of thiosulfate or hyperbaric oxygen therapy was rejected by the family because of poor prognosis.

4. Conclusion

Calciphylaxis or CUA is a rare and potentially lethal disease, mainly affecting

patients with end-stage renal disease. Diverse clinical presentations often result in delayed diagnosis. Skin biopsy remains the gold standard for diagnosis and typically reveals calcium deposits within the vessels of the dermis and subcutaneous fat, as well as thrombi and ischemic necrosis. A multidisciplinary approach is essential to assess the need for surgical debridement and optimize wound care. Treatment focuses on improving metabolic control, discontinuing causative medications, and wound care. Additionally, sodium thiosulfate may provide benefits; however, further research is necessary to determine how to optimize care for this devastating disease.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

CUA: calcific uremic arteriolopathy

CKD: chronic kidney disease