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Rapidly growing cutaneous ulcers in the setting of calciphylaxis: A case report

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Abstract

Calciphylaxis is an uncommon but often fatal condition frequently associated with end-stage renal disease. Currently, the pathophysiology remains elusive and treatment options are scarce. We present the case of a 33-year-old woman with past medical history of end-stage renal disease on hemodialysis who presented with multiple painful ulcerations on all four of her extremities. Initial laboratory findings revealed a parathyroid hormone level of 858 pg/dL, a calcium level of 7.1 mg/dL, and a phosphate level of 5.2 mg/dL. While taking punch biopsies of the ulcerations, the tissues were noted to have chalky texture and further examination confirmed calciphylaxis. In patients with end stage renal disease presenting with rapidly growing, painful skin ulcerations, physicians should maintain a high index of suspicion for calciphylaxis and establish a multimodal treatment regimen combining medical (antibiotic treatment, sodium thiosulfate, calcitriol, electrolyte management, wound care) and surgical (parathyroidectomy, wound debridement) therapies.

Keywords

calciphylaxis; calcific uremic arteriolopathy; end-stage renal disease; sodium thiosulfate; parathyroidectomy; hungry bone syndrome

Abbreviations

CUA: Calcific uremic arteriolopathy; ESRD: End-stage renal disease; PTH: Parathyroid hormone; STS: Sodium thiosulfate; HD: Hemodialysis; HTN: Hypertension; EKG: electrocardiogram; MWF: Monday, Wednesday, Friday

Introduction

Calciphylaxis or calcific Uremic Arteriolopathy (CUA) is a rare (1-4% of the population with ESRD) but lethal disease that carries high morbidity and mortality [7]. Calciphylaxis is a poorly understood disorder with a pathogenesis yet to be elucidated. It is hypothesized that it is a continuum of systemic vascular and soft-tissue calcification commonly occurring in ESRD patients [4]. While many ESRD patients have vascular calcification, very few develop calciphylaxis, which suggests a contribution of other factors.

Clinical manifestations are the result of reductions in arteriolar blood flow, usually in dermic-hypodermic arterioles [7]. Reduced blood flow is caused by calcification, fibrosis, and thrombus. Medial vessel calcification occurs first, and the ongoing vascular endothelial injury causes arteriolar narrowing

and a hypercoagulable state that causes tissue infarction [7]. Calciphylaxis is characterized by areas of excruciatingly painful, necrotic skin lesions characterized by violaceous, plaque-like lesions that progress to eschars once vascular thrombus is advanced [4].

There are no specific laboratory values for calciphylaxis. Elevated parathyroid hormone (PTH), and abnormalities in calcium, phosphorus, and calcium x phosphorus product (Ca x P) may be observed, though these are not always present.

The optimal treatment is unknown, and there is currently no standardized treatment regimen. Recommended approaches to calciphylaxis are heterogeneous [2]. A multi-interventional strategy is likely to be more effective than a single therapy alone [4]. Treatment focuses are on wound and pain management, normalization of calcium and phosphate levels, reduction of elevated PTH levels, and administration of sodium thiosulfate (STS). STS is supposed to prevent and reduce critical calcium phosphate precipitation in small vessels, though the exact mechanism is still unknown [7].

Here we report a case of successful management of calciphylaxis in a patient with ESRD who was on heparin bridging to warfarin and present a possible model for an effective therapeutic approach.

Case Description

This case is of a 33-year-old female with ESRD on hemodialysis (HD) who presented with painful necrotic ulcerations in all four of her extremities. A month prior, her left fistula site had clotted and she was started on heparin bridging to warfarin at an outside hospital. While on heparin, before starting warfarin, the patient noted red “bruising” on her extremities with no evidence of trauma. Heparin was discontinued after a few days and warfarin was started. After discharge, the warfarin was continued for about seven days and discontinued by her primary care physician after her “levels were appropriate”. While on warfarin, the patient's lesions worsened over the next several weeks and she noticed that the lesions began to become black, exquisitely painful, and ulcerated. She also noted that they had rapidly enlarged and had encompassed all four of her extremities. The patient visited the emergency department multiple times and was given pain medication. Eventually the patient was admitted into the ICU due to these worsening skin ulcerations.

The patient has a history of hypertension (HTN) and ESRD on HD three days a week since she was twenty-two. The etiology of her renal failure was unknown (patient had refused renal biopsy). She did, however, have a strong family history of ESRD with her mother and four maternal aunts diagnosed with ESRD. She had a history of long-standing poorly controlled hyperparathyroidism. Of note, she had difficulty tolerating cinacalcet and had an extensive history of non-adherence. Her surgical history was unremarkable and her only known allergy was to ciprofloxacin.

Her physical examination revealed extensive 2-7cm circular skin ulcerations with black central necrotic tissue on her extremities (Figure 1, 2). Some of the older lesions had developed dry, black eschars with no open lesions. Dorsalis pedis and radial artery pulses were palpable and there were no signs or symptoms of peripheral artery disease. Radiography demonstrated diffuse vascular calcifications as well as areas of diffuse soft tissue, tendinous, and ligamentous calcifications and areas of bone resorption related to hyperparathyroidism. While taking a punch biopsy of the skin lesions, it was noted that the tissue had a “chalky like” texture on examination. Histopathologic examination of the biopsy showed epidermal

necrosis and basophilic degeneration of inflammatory cells within the papillary dermis. Several fibrin thrombi were also appreciated in superficial dermal vessels (Figure 3). Examination of the subcutaneous adipose revealed the diagnostic feature of calciphylaxis, finely stippled calcium deposits within the walls of small caliber vessels (Figure 4).Biochemical profile demonstrated severe hyperparathyroidism (Table 1), hyperphosphatemia (phosphate 5.2 mg/dL, reference range 3.0-4.5 mg/dL), and hypocalcemia (calcium 7.1 mg/dL, reference range 8.6-10.6 mg/dL).

We established a multimodal treatment regimen. Wounds were painted with betadine for bioburden control. Pain was controlled with morphine. For this patient, urgent/emergent parathyroidectomy was scheduled with the goal of cessation of calcium deposition and thus the ongoing ischemic lesions. We planned a three and one-half parathyroidectomy to normalize parathyroid function immediately. Total gland exploration with partial parathyroid replantation would result in a period of complete hypoparathyroidism and likely prolong hospitalization. Following the procedure, the patient was started on calcium gluconate, oral calcium, as well as calcitriol for hungry bone syndrome. Calcium levels, symptoms of hypocalcemia/hypercalcemia, and her EKG's were monitored closely. To dissolve tissue calcium deposition, the patient was started on sodium thiosulfate with HD on post-operative day four, dosed at 25g infusion during the last hour of dialysis for a duration of three weeks. Hemodialysis was scheduled MWF. Wound debridement was delayed until lesion demarcation ceased and no new lesions developed with the plan for surgical debridement after discharge or approximately two to three weeks after HD. After a length of stay of thirteen days, her lesions ceased to grow and no new lesions developed. The patient was deemed stable she was discharged to subacute rehab.

Conclusion

Here we describe the successful management of a case of calciphylaxis in a patient with ESRD on hemodialysis who developed signs and symptoms while on anticoagulation prior to starting warfarin. Details of the multimodal management above may possibly provide an outline for systematic treatment in the future. Although calciphylaxis is typically associated with ESRD, uncontrolled hyperparathyroidism, and long-standing warfarin use, this case describes a patient who developed signs and symptoms prior to and soon after initiation of warfarin therapy. This case demonstrates how early diagnosis of calciphylaxis and multimodal intervention, including wound care, antibiotics, parathyroidectomy, careful electrolyte balance, and sodium thiosulfate, can be associated with cessation and stability of the skin lesions.

Calciphylaxis is a complex, multifactorial disease in which the pathogenesis is unclear [3]. Risk factors include ESRD, coagulopathy, warfarin exposure, obesity, diabetes, and hyperparathyroidism. Hyperparathyroidism may be a major cause of this deadly condition, and severe hyperparathyroidism was a distinctive feature in this case. Additionally, this patient had a history of ESRD and warfarin exposure, although the exposure to warfarin appears to have followed the pathologic lesions.

In our patient with advanced, late-diagnosed calciphylaxis, a multimodal intervention including wound care, antibiotics, parathyroidectomy, sodium thiosulfate, and careful electrolyte balance was associated with cessation and stability of the skin lesions as well as the patient's symptoms.

Early diagnosis, assessment of risk factors, and treatment may, in theory, limit the aggressiveness of calciphylaxis. Unfortunately, the disease is often overlooked on the differential diagnosis, and it is only when the disease has progressed to the late, ulcerative stages that the diagnosis is made. Consequently, this is correlated with a poorer prognosis. In the case described here, the initial differential diagnoses were peripheral artery disease, warfarin skin necrosis, and malignancy. Biopsy material, whether punch or excisional, should include an adequate amount of subcutaneous tissue for microscopic examination. Superficial biopsies containing only dermis may result in the mis diagnosis of a thrombotic vasculopathy if only fibrin thrombi involving dermal vessels are identified.

Overall, the contribution of a single component in a multimodal therapy is difficult to discern, especially in a solitary case study as described here. However, our case does demonstrate the vital importance of early diagnosis and aggressive multimodal therapy. Although no literature currently exists documenting better outcomes and survival of this disease in the past decades, the current prevailing view is that treatment should focus on optimal wound care, adequate analgesia, antibiotic treatment, and normalization of parathyroid hormone levels (by medical or surgical intervention) and electrolyte levels (including calcium and phosphate).

Proper wound care is critical. When cutaneous manifestations develop, mortality increases by two-fold [9]. Additionally, adequate analgesia and antibiotic treatment are important for preventing complications such as sepsis. Opioid medications are favored over morphine as morphine can cause hypotension, thereby slowing flow to arterioles, and thus further increasing risk of thrombosis [8].

Hyperparathyroidism is held as a major causal factor in this deadly condition [5]. Severe hyperparathyroidism was a hallmark in our case. Therefore, it was imperative to treat the hyperparathyroidism with urgent parathyroidectomy.

STS is held as a major disease-modifying agent in calciphylaxis. The favorable action of STS is generally attributed to its calcium chelation and possible dissolution of calcium phosphate deposits and inhibition of vascular calcification in damaged blood vessels [4]. In this case, STS was given intravenously in the last hour of hemodialysis sessions to achieve high serum concentrations and possibly stop lesion growth. In the largest case series on calciphylaxis published thus far, the combination of STS and cinacalcet was associated with complete regression of the skin lesions in six of seven cases in a series of Canadian patients by *Baldwin et al (1).* In a case series of Australian patients, 52% had complete regression while 19% had partial regression of the same lesions while on STS and cinacalcet [6]. Our patient was not given cinacalcet due to her history of intolerance to this medication. Of note, in the Australian study, the death rate was as high as 52% in a 3 month follow up period while the death rate was 25% in an average follow-up of about twenty months in the Canadian study.

In our case, both calcitriol and calcium carbonate were chosen to counteract the hypocalcemia and hungry bone syndrome induced by the parathyroidectomy. Additionally, to monitor for any cardiac symptoms of hypocalcemia, daily EKG's were performed.

Overall, our observations are consistent with the hypothesis that a multimodal regimen, including STS to counteract the progressive vascular ischemia and surgery to treat the uncontrolled hyperparathyroidism, may be lifesaving in patients with calciphylaxis. This hypothesis is in line with recent pre-established multimodal approaches to the treatment of calciphylaxis. This case report in

particular adds to previous observations and contributes to the current understanding of this disease which will hopefully serve as a basis for future investigations of combined interventions in the treatment of calciphylaxis.

Figures

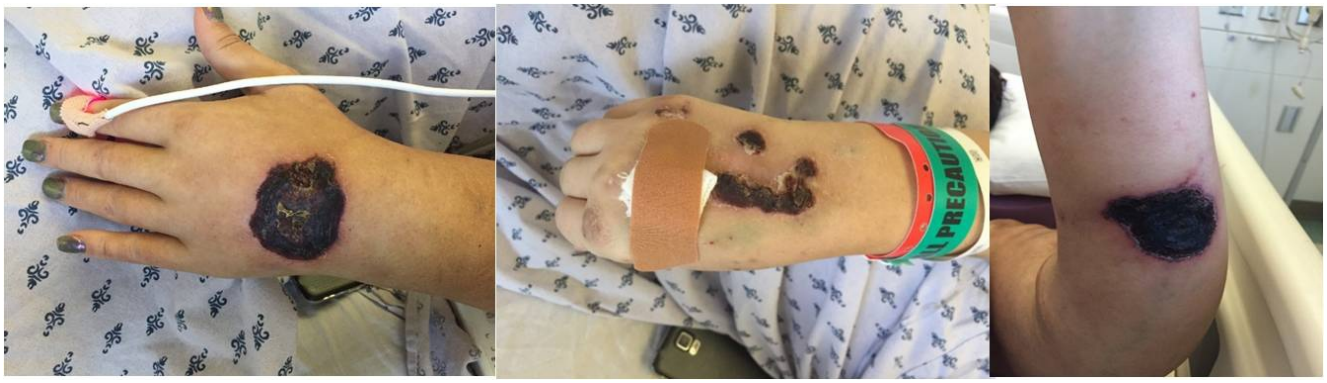

Figure 1: (A)-(C) Examination of her upper extremities show finely demarcated 2 to 7 cm circular skin ulcerations with central necrotic tissue that have developed eschars.

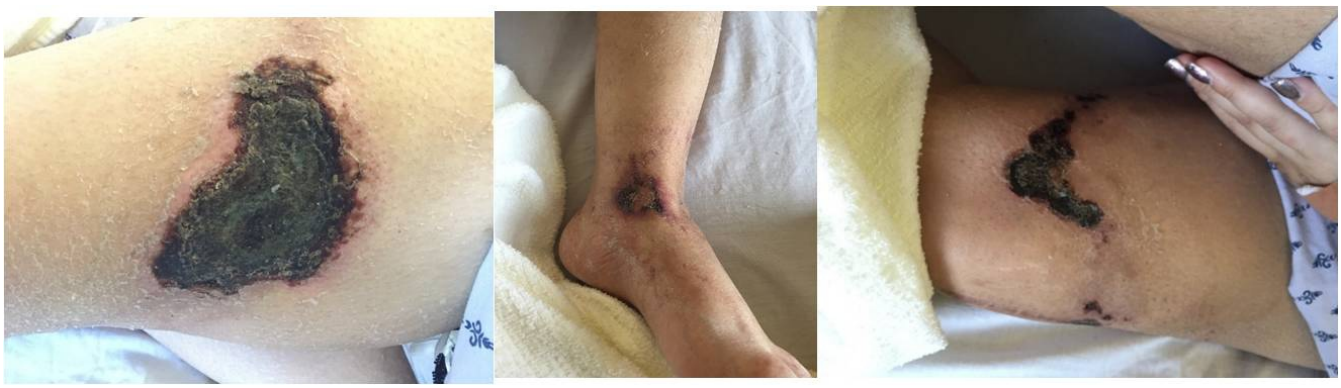

Figure 2: (A)-(C) Examination of her lower extremities show a similar pattern to her upper extremities with finely demarcated circular ulcerations with central necrotic tissue that have developed eschars.

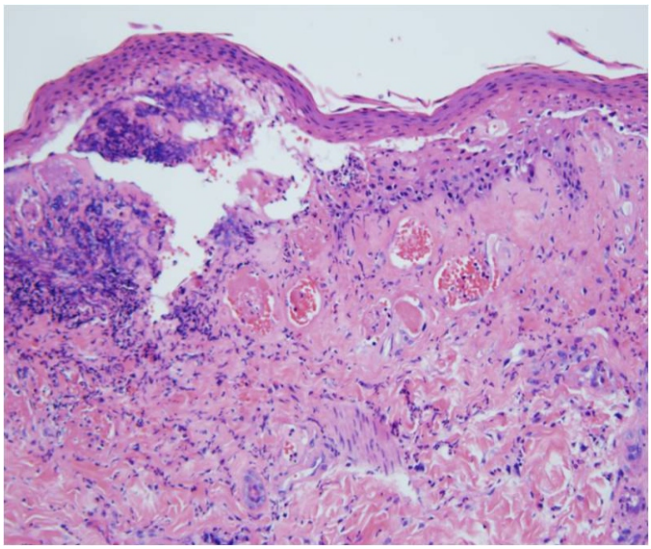

Figure 3: The punch biopsy shows epidermal necrosis and fibrin thrombi within vessels of the superficial dermis.

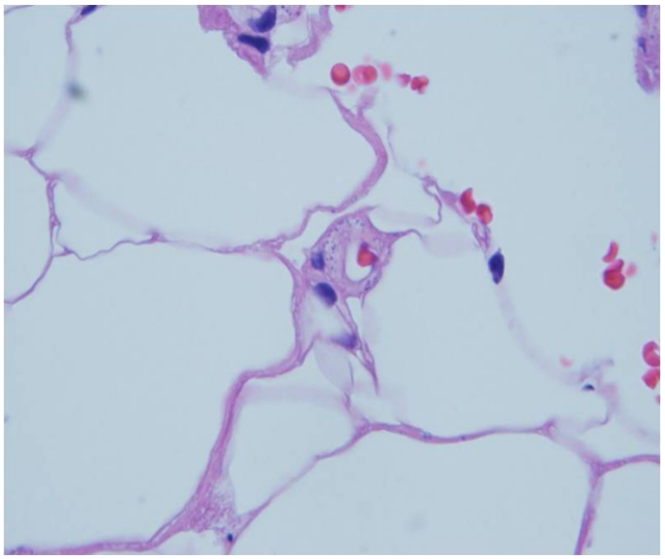

Figure 4: Close examination of the subcutaneous adipose reveals finely stippled basophilic calcium deposits present within the wall of a small vessel.

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