Calciophylaxis in a 33-year-old man with end-stage renal disease

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Calciophylaxis is an uncommon and poorly understood cutaneous phenomenon associated with chronic renal failure (CRF). The cardinal features are cutaneous purpura and necrosis as well as histopathologic findings of calcifications of cutaneous vessel walls. There is significant morbidity from this disease, which is mainly caused by overwhelming sepsis.¹

Case Report

A 33-year-old man known to have end-stage renal disease (ESRD) of unknown cause who had kidney transplantation twice was referred to the dermatology clinic in November 2002 with a one-week history of rash over both thighs associated with a severe burning sensation.

The patient was diagnosed with ESRD requiring haemodialysis in 1988. He underwent a first renal transplantation (living, unrelated) in India in 1991 and had a rejection after 3 years, which required a return to haemodialysis. Four months prior to presentation he had a second renal transplantation in Iran (living, unrelated), which also rejected after 6 weeks. As a consequence he was put on hemodialysis again. This patient had severe hyperparathyroidism as well. Current medications were oral prednisolone 17.5 mg once daily, oral tacrolimus 2 mg twice daily, oral ferrous sulphate 325 mg thrice daily, gancyclovir 500 mg orally thrice weekly, amlodipine 5 mg orally once daily, omeprazole 20 mg orally once daily, prazosin hydrochloride 2 g orally thrice daily and aluminum hydroxide 2 tablets thrice daily.

Physical examination revealed multiple purpuric macules and papules over the medial aspect of both upper thighs down to the knees. The legs and buttocks were not involved. Systemic examination was unremarkable. Blood work showed a low haemoglobin and haematocrit (Table 1). Mean corpuscular volume, mean corpuscular haemoglobin, white blood cell count, platelets count, bilirubin level, prothrombin time, and partial thromboplastin time were normal. Parathyroid hormone was very high. Serum urea and serum creatinine were elevated. Serum sodium, chloride, protein C, protein S and fasting glucose were within normal limits. Total calcium was normal, but due to low albumin, the corrected calcium was high. Serum phosphate was elevated, and accordingly, the calcium phosphorus product was high. Urinalysis is shown in Table 1. HIV serology was negative. X-ray of lower limbs showed a significant calcification of blood vessels.

Initial skin histopathological examination showed intradermal hemorrhage but no evidence of vasculitis. Two weeks later, the patient showed up in clinic with more progressive lesions, which were very painful. There were multiple large subcutaneous indurated plaques covered with multiple small hemorrhagic vesicles and black eschar over both thighs (Figure 1). A second skin biopsy revealed that the epidermis, dermis and subcutaneous tissue were necrotic and there was a

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Table 1. Laboratory parameters.

Parameter	Value (normal range)
Hematology	
Haemoglobin (g/L)	78 (132-172)
Haematocrit (%)	0.248 (0.38-0.52)
Parathyroid hormone (ng/L)	1423 (16- 65)
Serum urea (mmol/L)	19 (4.2-7.2)
Serum creatinine (μmol/L)	500 (65-129)
Total serum calcium (mmol/L)	2.45 (2.1-2.55)
Serum albumin (g/L)	24 (32-48)
Corrected serum calcium (mmol/L)	2.85
Serum phosphate (mmol/L)	2.05 (0.7-1.45)
Calcium phosphorus product	5.84 (≤4.4)
Urinalysis	
pH	Normal
Blood	3+
Bilirubin and ketone	Negative
Leukocytes	2+
White blood cells (/hpf)	>50
Red blood cells (/hpf)	>50
Epithelial cells (/hpf)	>50
Glucose	1+

significant amount of microthrombi. Several subcutaneous vessels contained calcium deposits in their walls (Figure 2). This picture is consistent with calciphylaxis. Bacterial, fungal and mycobacterial cultures were all negative.

The patient was admitted to hospital and had a parathyroidectomy. Histopathological examination revealed hyperplasia of all parathyroid glands. Despite parathyroidectomy, the patient showed progressive skin necrosis and blistering over thighs, legs, feet, abdomen, buttocks and distal fingers (Figure 3). Wound dressing was carried out daily, without significant improvement.

Discussion

Calciphylaxis occurs mostly in patients with chronic renal failure and recent renal transplantation, although patients with normal renal function have been reported.² Pre-dialysis patients and those undergoing both haemodialysis and peritoneal dialysis have presented with calciphylaxis.³ Kidney transplant recipients account for 32% to 38% of calciphylaxis cases, including patients with normally functioning grafts.^{4,5} Our patient had ESRD and was on haemodialysis after rejection of two kidney transplants.

He received glucocorticoids and immunosuppressive medications, mycophenolate mofetil, tacrolimus, and ferrous sulphate. All are known precipitating factors for calciphylaxis.^{6,7}

Because of lowered vitamin D in ESRD patients (the active metabolite of vitamin D is transformed in the kidney), there is decreased calcium absorption from the intestine. Low serum vitamin D, low serum calcium, and high serum phosphate lead to secondary hyperparathyroidism. Most patients with calciphylaxis have abnormalities of calcium-phosphate homeostasis with elevated levels of parathyroid hormone, but these changes as well as an elevation of the calcium-phosphorus product are not always present in this disease.⁵ This suggests that other important elements must contribute to calciphylaxis. Skin biopsy of the lesions showed numerous organized thrombi, which means a coagulation defect might be the missing link.⁸ Our patient had severe hyperparathyroidism.

A pre-existing hypercoagulable status has also been hypothesized to predispose affected patients to calciphylaxis.^{8,9} In support of this mechanism, functional abnormalities in either protein C or protein S have been reported in several patients with calciphylaxis. However, these proteins have also been normal in other patients, including our case.^{4,5,10}

Early lesions of calciphylaxis manifest either as non-specific violaceous mottling, livedo reticularis, purpuric patches and plaques or as erythematous papules, plaques or nodules. More developed lesions have a stellate purpuric configuration with central cutaneous necrosis. Later lesions are exquisitely tender, extremely firm to touch, evolving into irregular ulcers covered by thick dark eschars. Lesions can be distributed proximally (on the thighs, buttocks and abdomen) or distally (below the knee). Our patient had proximal lesions initially, which later extended distally. Ninety percent of lesions are found on the lower extremities.^{1,11,12} Necrosis of the penis secondary to calciphylaxis has also been described.^{7,13}

Despite the dramatic cutaneous necrosis, no internal organ failure is reported in patients with calciphylaxis. Our patient's cutaneous manifestations started as a very mild purpura over the thighs, which did not suggest calciphylaxis. Two weeks later they progressed to full-blown typical calciphylaxis lesions with bullae (which is a rare manifestation). Typical histologic findings are calcification within the media of small and medium-sized arterioles with extensive intimal hyperplasia and fibrosis. Subcutaneous calcium deposits with panniculitis and fat necrosis may

sometimes be found. Frequently, vascular microthrombi are seen. Necrosis of overlying epidermis, and often surrounding dermis and subcutis is frequently seen.^{1,14} In our patient, typical histological findings were obvious.

Treatment of calciphylaxis is largely supportive. Aggravating conditions should be addressed and trigger factors eliminated. Normalization of abnormal calcium and phosphorus levels by diet, phosphate binding agents, low-calcium hemodialysis and parathyroidectomy might help.^{1,15} Aggressive wound care and careful debridement of necrotic tissue are necessary to avoid wound infection and sepsis. Treatment of infections with appropriate antibiotics can be helpful.⁹ Treatment with hyperbaric oxygen¹⁶ and prednisone¹⁷ have been anecdotally reported.

Patients with hypercoagulability may benefit from judicious anticoagulation. However, the role of anticoagulation in other cases of calciphylaxis is controversial. Prophylactic use of warfarin or heparin is probably not indicated since precipitation of calciphylaxis has occurred with indiscriminate use. In addition, most patients with ESRD have a prolonged bleeding time due to the uremic condition so anticoagulation may be contraindicated.^{8,18}

Total or subtotal parathyroidectomy with autotransplantation is of therapeutic benefit to many but not all patients.^{1,19} Only few studies have been able to demonstrate a decrease in mortality rate in those patients who underwent parathyroidectomy.^{20,21} Normalization of calcium and phosphorus, continuous wound dressing, and total parathyroidectomy did not help our patient. Because of a normal coagulation profile and protein C and S levels, he was not a candidate for anticoagulation.

The prognosis in patients with calciphylaxis is poor and the mortality rate is as high as 80%.⁴ In a review of 104 cases, Hotner et al found that 75% of patient with distal localization of lesions survived compared to 25% with proximal lesions.²² Unfortunately, most patients with calciphylaxis die of overwhelming infection and sepsis resulting from a compromised skin barrier in an immunosuppressed patient with chronic renal failure or after kidney transplantation.¹⁴ No data exist regarding long-term survival, if one survives an episode of calciphylaxis.

Two important and unique points about our case are the initial presentation with trivial purpuric lesions and the appearance of blisters, which is a rare manifestation of calciphylaxis. Fortunately, calciphylaxis is a rare disease. Its prevalence has not been established in our area, but is probably lower than

Figure 1. Bilateral well-defined black necrotic eschar over the medial aspect of both lower limbs (top); Close-up view showing the black necrotic eschar with two small tense vesicles (bottom).

Figure 2. Intravascular calcium deposition with microthrombi in adjacent smaller blood vessels (hematoxylin and eosin stain x 40).

estimations in other reports. Because of its generally aggressive behavior, and lack of effective treatment in most cases, early recognition of this disease is crucial. Our poor knowledge of the exact pathophysiology is still the limiting factor for intervention.

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Figure 3. Dark brown-to-black necrotic plaques on the palmar aspect of the distal fingers.

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