CASE REPORT

Successful treatment of calciphylaxis by a multidisciplinary approach

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SUMMARY

A 48-year-old woman performing peritoneal dialysis for end-stage renal disease presented with a painful leg ulcer. The investigation revealed an elevated parathyroid hormone level and the histological examination of the biopsy tissue from the ulcer revealed medial calcification of the arterioles, consistent with calciphylaxis. The patient developed additional ulcers in the lower limbs and treatment with antibiotics, cinacalcet, sevelamer, sodium thiosulfate, low calcium dialysate and hyperbaric oxygen therapy was instituted. The patient had a favourable outcome and after 9 months the ulcers had healed and the parathyroid hormone level reached the normal range. Calciphylaxis is a rare and life-threatening disorder associated with a mortality of 60–80%. Its pathogenesis is not fully understood hence there is no consensus in the treatment of this pathology.

BACKGROUND

Calciphylaxis is a rare and life-threatening disorder, estimated to occur in 1% of patients with end-stage renal disease each year, with a prevalence of 4.1–4.4% among haemodialysis patients in the Western world.^{1–4} The case reports published in literature suggest a female preponderance of approximately 3:1.¹

The failure to understand the pathogenesis of calciphylaxis results in treatment that is generally unsatisfactory and, because this is a rare disorder, it becomes difficult to perform controlled studies that could demonstrate the advantages of a particular therapeutic option.¹

Calciphylaxis carries an unfavourable prognosis, with a mortality rate of 60–80% in a short period of time after initial presentation.^{1 3 5}

This case report refers to a patient who presented with skin ulcers and was diagnosed with calciphylaxis. Despite the unfavourable prognosis associated with this disease, the patient was successfully treated by a multidisciplinary team.

CASE PRESENTATION

A 48-year-old woman, with a previous medical history of malignant hypertension and end-stage renal disease attributed to hypertensive nephroangiosclerosis, presented with a painful leg ulcer with 3 months of evolution. Peritoneal dialysis had been initiated 8 months before the presentation and the patient's long-term medication was nifedipine 30 mg twice a day. The physical examination was remarkable for an isolated 5×3 cm ulcer of the right leg (figure 1). This skin lesion presented irregular borders surrounded by violaceous skin,

but no necrosis was present. The patient's right pedal pulse was absent, but her ankle-brachial index corresponded to 1. The physical examination was otherwise unremarkable.

INVESTIGATIONS

Haematological and biochemistry investigations were normal apart from elevated urea (118 mg/dL, normal range 30–50 mg/dL) and creatinine (4.12 mg/dL, normal range 0.5–1.3 mg/dL), compatible with the patient's baseline renal failure.

Coagulation laboratory values were normal.

Ionogram, proteins, iron study and protein electrophoresis were all normal.

Total calcium was 10 mg/dL (normal range 8.5–10.1 mg/dL); inorganic phosphate 4 mg/dL (normal range 2.5–4.9 mg/dL) and magnesium 2.4 mg/dL (normal range 1.6–2.4 mg/dL).

Endocrine parameters were normal except for elevated parathyroid hormone (971.4 pg/mL, normal range: 14–72 pg/mL), as a consequence of secondary hyperparathyroidism.

Digital subtraction arteriography of the right lower limb identified occlusion of the anterior tibial artery at its medium portion, with no other changes.

Figure 1 Right leg skin ulcer at initial presentation.

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Figure 2 (A) Small subcutaneous artery with medial calcification and circumferential fibrosis. (B) Haemorrhage and necrosis of the surrounding lobular fat.

Microbiology of the ulcer tissue culture revealed methicillin-resistant *Staphylococcus aureus* sensitive to clarithromycin and linezolid.

Histological examination of the ulcer biopsy tissue revealed subcutaneous adipose tissue with fibrosis of the interlobular septa, containing arterioles with medial dystrophic calcification and intimal proliferation, consistent with calciphylaxis (figures 2A, B).

DIFFERENTIAL DIAGNOSIS

Atherosclerotic arterial disease of the lower limbs can cause ulcers resembling those seen in calciphylaxis. Since the patient presented with no palpable right pedal pulse and lower limbs arteriography revealed occlusion of the right anterior tibial artery, we were led to believe, before obtaining the histological examination of the ulcer biopsy tissue, that the ulcer had an atherosclerotic aetiology.^{1 3 5}

Some kinds of vasculitis, like systemic lupus erythematosus, antiphospholipid syndrome and cryoglobulinaemia, can resemble calciphylaxis.^{1 3 5}

TREATMENT

Since calciphylaxis is a rare disease with unfavourable outcomes and there is still no consensus in a standard treatment, this patient's therapeutic approach was evaluated and decided by a multidisciplinary team consisting of a nephrologist, endocrinologist, dermatologist and vascular surgeon.

Wound care and enzymatic debridement with hydrogel were applied. Surgical debridement was not performed due to the risk of infection and wound healing impairment.

Treatment with clarithromycin 500 mg/day for 2 weeks was started and then replaced with intravenous linezolid 600 mg twice a day for 2 weeks.

The patient started to perform intermittent haemodialysis with low calcium dialysate three times per week for a period of 4 h each shift.

Treatment with cinacalcet 60 mg/day, perfusion of sodium thiosulfate three times per week (concomitant with haemodialysis) and sevelamer 800 mg three times a day was instituted.

Treatment was initiated with alprostadil 0.02 mg twice a day for 3 weeks.

Hyperbaric oxygen therapy was instituted for a duration of 5 months, with a total of 54 sessions. Each session lasted for 90 min with 100% O₂ at 2.4 atm.

OUTCOME AND FOLLOW-UP

Before treatment was instituted, the ulcer showed progression with increasing size and the development of necrosis (figure 3). At the beginning of treatment, the patient developed additional

Figure 3 Evolution of right leg skin ulcer before treatment.

Figure 4 Skin ulcer in the medial face of the right leg.

necrotic ulcers of the ipsilateral and contralateral limbs (figures 4–6). During treatment, the ulcers began to reduce their dimensions and to present granulation tissue (figures 7 and 8) concomitantly with a progressive reduction in parathyroid hormone serum levels (from 971.4 to 454.8 pg/mL in 2 months). After 9 months of treatment, the parathyroid hormone serum level was almost normal (82.3 pg/mL) and all the lesions had healed (figure 9).

During follow-up, the patient remained free of recurrent skin lesions despite a raise in the parathyroid hormone level after cessation of treatment with cinacalcet (454 pg/mL).

DISCUSSION

Calciophylaxis can be defined as a chronic progressive syndrome of arteriolar calcification, which leads to ischaemia and necrotic ulceration.^{2–4} Although most calciophylaxis patients have abnormalities of the calcium–phosphate axis (hyperphosphataemia in 68%, hypercalcaemia in 20%) or elevated levels of parathyroid hormone (82% of patients), these abnormalities do not appear to be the primary causes of this disorder and the aetiology of calciophylaxis remains unclear.^{1–5} It has been hypothesised that hypercoagulable state caused by protein C deficiency could induce thrombosis in small vessels, resulting in skin ischaemia, necrosis and gangrene, but there are no sufficient data to correlate this disturbance with calciophylaxis.¹ Other metabolic disturbances that have been associated with calciophylaxis are hyperglycaemia, hypertension, hypercholesterolaemia, elevated serum calcium–phosphate product, parathormone (PTH) resistance and iatrogenic calcitriol excess.^{2–5} Risk factors associated to this disease include obesity, diabetes mellitus, inflammatory bowel disease, malignancy and cirrhosis.⁵

Despite the unknown aetiology of calciophylaxis, Kramann *et al*⁶ demonstrated an active, cell-mediated, bone morphogenic

Figure 5 Right foot ulcer.

Figure 6 Left leg skin ulcer.

protein 2 (BMP-2) driven osteogenic process, with extensive extracellular matrix remodelling in the subcutis of seven patients with calciophylaxis. In this cross-sectional study, they demonstrated an increased expression of BMP-2, Runx2 and sclerotin in all the seven calciophylaxis patients, when compared to controls. BMP-2 and Runx2 are responsible for increased expression of matrix proteins such as collagen and osteopontin, which promote osteogenesis. The authors concluded that this process of matrix remodelling and osteogenesis, although still unproven, could be responsible for the vascular calcification seen in calciophylaxis.⁶

Cutaneous calciophylaxis must be differentiated from systemic calciophylaxis, which is manifested by multiorgan calcification.^{1–3 7 8} In the former, clinical presentation usually starts with violaceous or livedo-like skin lesions that may become plaque-like or nodular. These lesions often progress to severe painful and non-healing ulcers, presenting with a bizarre shape, which may become haemorrhagic and evolve to dry necrosis.^{1–9} Bilateral lesions are frequently symmetric and involve medial areas of the extremities that come into contact, called kissing lesions.⁴ Potential complications from this process include gangrene and sepsis, which is associated with a mortality rate of 50–80%.^{1–5} Involvement of the lower extremities is almost universal (90% of cases), but the lesions can also appear in the trunk and the upper limbs (72% of cases). Proximal involvement of the extremities is seen in 68% of patients.¹

In the early stages of the disease, the lesions can resemble those seen in vasculitis, systemic lupus erythematosus, cryoglobulinaemia, scleroderma/CREST syndrome, antiphospholipid syndrome, protein C or S deficiencies, disseminated intravascular coagulation, atheroembolisation, cholesterol emboli or septic embolisation. The acral ulcerations and gangrene should also be

Figure 7 Evolution of the initial right leg ulcer 2 months after treatment.

distinguished from those related to atherosclerotic peripheral arterial disease (preserved peripheral pulses favour the diagnosis of calciphylaxis).^{1 3 5}

Figure 8 Evolution of the initial right leg ulcer 4 months after treatment.

Figure 9 Total healing of the lower limbs' trophic lesions after 9 months.

The time period for the onset of symptoms of calciphylaxis range from 1 month to 12 years after the onset of endstage renal disease (median 2 years).¹

A deep skin biopsy with subcutaneous adipose tissue is necessary to confirm the diagnosis. The most common histopathological finding is a septal calcifying panniculitis.^{2 3 9} Histological examination reveals intravascular calcium deposits, microvascular calcification and ischaemic epidermolysis. Small arterioles usually show calcification of the media and fibroblastic-intimal proliferation. Small veins tend to exhibit transmural involvement. This calcification leads to narrowing or occlusion of the small vessels lumen (in some cases the vessels may be occluded by microthrombi), which leads to adipose tissue and skin infarction and necrosis.^{1 2 5-10} In the process of calcifying arteriopathy, the smooth muscle cells of the vascular wall transdifferentiate into osteoid-like cells.^{2 3}

Small-vessel calcification is a common finding in patients with chronic renal failure; however, these lesions do not usually result in ischaemia and tissue injury. Therefore, it appears that a secondary insult is required for tissue infarction to arise. Some agents that have been reported as precipitants of calciphylaxis are low serum albumin, local trauma, intravenous iron dextran, corticosteroids, immunosuppressants, heparin and warfarin; but

direct causal evidence for these factors has not been established.^{1–3 5}

Partial or subtotal parathyroidectomy may be considered as a first-line treatment of extensive disease. However, no consensus exists in this matter because this procedure is not always successful and is associated with an increased mortality in dialysis patients in the first 6 months after surgery.^{1 5 11–13} The most recent articles have been showing the importance of cinacalcet as a first-line treatment for calciphylaxis. This agent directly decreases PTH concentration, through an increase in the sensitivity of the parathyroid cells calcium receptor, and is currently used in end-stage renal disease associated secondary hyperparathyroidism. The efficiency of this drug in the treatment of calciphylaxis has already been reported in some case reports.^{6 11–13} In these patients, the efficacy of action of cinacalcet appeared to match the results obtained with parathyroidectomy, as this agent is effective in normalising the levels of PTH, calcium, phosphate and calcium-phosphate product and leads to successful healing of skin ulcers.^{11–13} Intravenous sodium thiosulfate has also been administered in a few cases of calciphylaxis with good outcomes.^{5 7 14–16} Adjunctive measures include avoiding local injections to areas with significant adipose tissue, normalisation of the calcium-phosphate product through dietary changes, low calcium dialysate and non-calcium-containing phosphate binders.^{1 2 5 7} Antibiotics, wound care, surgical debridement and even amputation may be indicated, although the outcome related to debridement is poor because the underlying vasculopathy impedes wound healing.^{1 5 7}

Other therapies which have been reported to improve the outcome in some cases are hyperbaric oxygen therapy and bisphosphonates.^{2 5 8 13 17–20}

Calciphylaxis carries an unfavourable prognosis, with a mortality rate of 60–80% in a short period of time after initial presentation.^{1 3 5 8} Some authors believe that patients with distal location have a better outcome.^{1 10}

Learning points

- ▶ Calciphylaxis is a rare and life-threatening disorder associated with high mortality of 60–80%.
- ▶ Its pathogenesis is not fully understood and the therapeutic options are unsatisfactory.
- ▶ In a patient with end-stage renal disease and cutaneous necrosis, calciphylaxis should always be suspected.
- ▶ A multidisciplinary approach and treatment with cinacalcet, low calcium dialysate, sodium thiosulfate and hyperbaric oxygen therapy has shown good results in some cases.

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