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CASE REPORT

Surviving calciphylaxis

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Abstract Calciphylaxis is a rare disorder with high mortality, which commonly occurs, but not limited to, patients with end-stage renal disease. We present a successful case in which a patient survived this serious disorder of vasculopathy, highlighting the physical and emotional morbidities associated with this condition and alerting physicians of the key elements in its management. Further understanding of calciphylaxis may advance our knowledge in endotheliopathy and vascular ossification.

Keywords Calciphylaxis · Hyperparathyroidism · Ulcer · Renal failure · Diabetes

Introduction

Calciphylaxis is an uncommon but serious disorder with a prevalence of 4% in patients receiving haemodialysis [1], and a mortality rate exceeding 80% [2], especially when it involves proximal extremities, which are associated with the worst prognosis. Our case illustrates the physical and emotional morbidities associated with this condition and highlights prevention as the key to the management of calciphylaxis.

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Case report

A 58-year-old woman presented to the emergency department with a 2-week history of generalised abdominal pain, nausea and vomiting. Her past history included hypertension, dyslipidaemia, atrial fibrillation and type II diabetes diagnosed seven years prior. Glycaemic control was suboptimal with HbA1c varying between 8% and 9%, and she had multiple complications, including peripheral neuropathy, proliferative retinopathy and peritoneal dialysis-dependent nephropathy. Continuous cycling peritoneal dialysis with a low calcium dialysate (calcium = 1.25 mmol/L) had been the renal replacement therapy for the previous 5 years with satisfactory control of calcium and phosphate balance (calcium–phosphate product < 4 $mmol^2/L^2$, until 6 months prior to her admission, when it increased to 4.5 $mmol^2/L^2$). Calcium-based phosphate binder was substituted with aluminium hydroxide, with dose titration to 2,400 mg before meals. Other medications included gliclazide (sustained release) 90 mg daily, neutral insulin 30%, isophane insulin 70% (® Mixtard 30/70) 30 units mane, metoprolol 25 mg twice daily, ramipril 10 mg daily, aluminium hydroxide 2,400 mg before meals, digoxin 62.5 mcg daily, warfarin 2 mg daily, and atorvastatin 40 mg daily.

Physical examination revealed generalised abdominal tenderness without signs of acute peritonitis. She was afebrile and haemodynamically stable. A 5-cm painful superficial ulcer was evident over the left trochanter with no surrounding cellulitus or palpable crepitus. Peripheral pulses were present with no signs of embolic or vasculitic skin

lesions. Normal microscopy and negative culture of peritoneal fluid excluded bacterial peritonitis. Abdominal plain radiography, ultra-sonography and CT scanning revealed constipation with no evidence of visceral inflammation, perforation or abscess formation. Bone scintigraphy showed no evidence of osteomyelitis. Serum biochemistry demonstrated chronic renal impairment and hypercalcaemia with tertiary hyperparathyroidism (Table 1).

A provisional diagnosis of decubitus trochanteric ulcer was made. Conservative management with regular dressings and narcotic analgesia did not improve the clinical situation. The ulcer progressively expanded with secondary infection by methicillin-resistant *Staphylococcus aureus* requiring therapy with vancomycin. The ulcer failed to heal despite antibiotic treatment and surgical debridement. Multiple new ulcers appeared over the right hip and anterior abdominal wall. A diagnosis of skin ulcers secondary to calciphylaxis was confirmed on skin biopsy, which demonstrated arterial occlusion and calcification with chronic calcifying septal panniculitis.

Total parathyroidectomy was performed with histology consistent with severe parathyroid nodular hyperplasia. Despite normalisation of calcium biochemistry (Table 1), wound healing remained poor despite antibiotic treatment, surgical debridement, and careful wound care. Her mental state deteriorated with development of depression, leading to poor appetite and sleep, further worsening of her nutritional status. At one stage, she refused treatment resulting in barriers to best medical care. Glycaemic control became a major challenge in the setting of sepsis, uraemia and erratic eating habits. We identified at that stage severe protein malnutrition as the major contributor to her clinical deterioration. A multi-disciplinary approach involving nutritional supplements, psychiatric support, further active surgical debridement and careful wound care eventuated in gradual healing of multiple ulcers. The patient was discharged following a 4-month hospital stay, with full healing of all ulcers, and regained full independence and returned to her pre-morbid state of health.

Discussion

Although calciphylaxis is commonly associated with hyperparathyroidism in patients with end-stage renal failure with abnormal vitamin D metabolism, it has been reported in patients with breast carcinoma, hepatic cirrhosis, and vasculitic disorders in the absence of chronic renal failure, and most patients with hyperparathyroidism do not develop calciphylaxis. Serum calcitriol and calcium levels do not show direct correlation with the risk of developing calciphylaxis. In summary, none of the classic "risk factors" entirely explains the occurrence of calciphylaxis.

The presence of abnormal calcium, vitamin D and parathyroid hormone metabolism in uraemic patients creates a metabolic microenvironment predisposing them to the development of calciphylaxis when impacted by additional factors, which increase the vulnerability of skin vessels to ischaemic damages. These include, but are not limited to, an altered coagulation system either from warfarin therapy or intrinsic protein C or protein S deficiencies [3], obesity resulting in excess stress on dermal vessels, local skin trauma, and hypoalbuminaemia.

Hyperglycaemia in our patient introduces an added dimension to the toxic microenvironment. Diabetes is associated with a high incidence of lower extremity ulceration, secondary to vascular insufficiency, peripheral neuropathy, and increased vulnerability to bacterial infection due to immune dysfunction [4]. Although the location was atypical of arterial and venous ulcers, vascular studies should be considered in diabetic patients who presented with ulcerations, and other diagnoses, including vasculitis, paraneoplastic phenomenon, necrobiosis lipoidica diabeticorum or nephrogenic fibrosing dermopathy in those with previous gadolinium exposure [5], should be considered. Whether local trauma from subcutaneous insulin injections contributed to calciphylaxis in our patient was uncertain. It should be balanced against glycaemic optimization to minimize microvascular complications, which can also increase the risk of ulceration.

Table 1 Serum biochemistry before and after parathyroidectomy

	Pre-parathyroidectomy	Post-parathyroidectomy	Reference
Sodium	135 mmol/L	142 mmol/L	135–145
Potassium	4.5 mmol/L	4.1 mmol/L	3.5–4.5
Creatinine	780 μmol/L	693 μmol/L	40–90
Corrected calcium	2.6 mmol/L	2.15 mmol/L	2.1–2.6
Phosphate	3.5 mmol/L	0.96 mmol/L	0.7–1.4
Albumin	28 mmol/L	25 mmol/L	35–40
Parathyroid hormone	55.7 pmol/L	<0.1 pmol/L	1–7
25-hydroxy vitamin D	26 mmol/L	–	60–150
1,25-hydroxy vitamin D	<10 pmol/L	–	36–120
HbA1c	8.7%	–	

We hereby present a case of triumph in which our patient survived proximal calciphylaxis. While neither her presentation nor the treatments she received were novel, our case report aims to highlight the clinical approach to this difficult and rare problem in practice to maximize survival.

The primary aim of the management of calciphylaxis focuses on prevention. It necessitates a multi-disciplinary approach. While the traditional emphasis of minimising the calcium–phosphate product is essential, its monitoring could easily be overlooked in the complex medical management of patients with end-stage renal failure. Although the formula advocated by Levin [6] incorporating serum calcium, phosphate, parathyroid hormone and alkaline phosphate is complicated and not universal in predicting the risk of calciphylaxis, its calculation could be incorporated as a standard measure along with weight and other laboratory parameters in nephrology out-patient clinics, as part of at-risk patient monitoring. Non-calcium based phosphate binders should be encouraged as should follow-up with dieticians to minimise protein malnutrition or obesity.

No single therapeutic intervention has been proved to cure calciphylaxis. It is associated with significant morbidity and mortality once ulceration develops. The management of established calciphylaxis focuses on the prevention of secondary infection. Active surgical debridement with early use of antibiotics and careful wound care are the cornerstones in minimising mortality. Hyperbaric oxygen can be considered in patients whose ulcer oxygen content is high [7]. As our case demonstrates, the psychological morbidity is substantial and frequently overlooked in such patients, and may further worsen malnutrition in depressed patients with anorexia. Malnutrition has been shown to be independently associated with chronic renal failure [8], and hypoalbuminaemia is associated with increased mortality [9]. Adequate analgesia and intensive nutritional support with psychological counselling are paramount in the enhancement of mental well-being and recovery.

Although various "definitive" treatments have been advocated in the management of calciphylaxis, none has been proven to be universally effective. Parathyroidectomy reverses abnormal calcium–phosphate balance, as illustrated in our case, but has not been shown to consistently prolong survival [10, 11]. Cinacalcet, a parathyroid gland calcimimetic, is effective in suppressing hyperparathyroidism and can lead to complete healing of skin necrosis [12]. Medical therapy with cinacalcet can be considered as an alternative to parathyroidectomy. Sodium thiosulphate has been used in the effective treatment of necrotic ulcers by promoting the formation of the more soluble calcium thiosulphate salt with ensuing neutralisation of oxidative species [13]. Bisphosphonate on the other hand achieves the same result by inhibiting bone resorption [14], thereby preventing the release of inflammatory mediators and further vascular calcification.

Despite our poor understanding of the pathogenesis, and the limited options of treatment available, calciphylaxis is a unique model to advance our understanding of endotheliopathy. The endothelium serves as a first line barrier to reactive oxidative species. In vitro and in vivo studies demonstrate the transformation of multi-potential pericytes and vascular smooth muscle cells into osteoblast-like cells [15], leading to vascular calcification. The relationship between vasculopathy and abnormal calcium balance is intriguing, and calciphylaxis is an illustration of the potential link between the two conditions. Recent studies demonstrated increased bone turnover and hyperparathyroidism as independent predictors of cardiovascular mortality [16], which is congruent to the complex pathophysiology behind calciphylaxis.

In conclusion, calciphylaxis is a rare but serious disorder. Management should focus on early prevention by minimizing calcium–phosphate product and the maintenance of optimal nutritional status, with consideration of specific therapy in selected patients based on individual biochemical profile and clinical presentation. While the pathophysiology of the condition remains poorly understood, it is a unique model which may help to advance our understanding of premature vasculopathy.

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