The Interesting Case

Calciphylaxis in two non-compliant patients with end-stage renal failure

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Case 1

A 46-year-old male with end-stage renal failure (ESRF) on the basis of long-standing poorly controlled hypertension was admitted with a 5-week history of progressive weakness and paraesthesia in both upper and lower limbs. He had been commenced on continuous ambulatory peritoneal dialysis (CAPD) 12 months prior to this admission. However he had been non-compliant with renal replacement therapy (including phosphate binders and antihypertensive agents) and frequently failed to attend outpatient review clinics. There was no other medical history.

On examination, he had signs of a severe proximal myopathy of the hip and shoulder girdles with an associated sensory peripheral neuropathy and a widespread violaceous rash over his abdomen and flanks (Figure 1). In addition there were signs of chronic uraemia and congestive cardiac failure.

His renal biochemistry revealed urea 48 mmol/l and creatinine 985 μmol/l. His serum calcium was 2.37 mmol/l and phosphate was 3.75 mmol/l. His intact parathyroid hormone level subsequently came back at greater than 2000 ng/l. His inflammatory markers were elevated with an ESR of 50 mm and a CRP of 74 mg/l. EMG studies were consistent with a severe myopathy with evidence of demyelination.

A clinical diagnosis of dermatomyositis was made and he was commenced on high dose methylprednisolone. A skin biopsy was obtained to confirm the diagnosis. Dialysis therapy was recommenced. There was no response to the steroid therapy and 4 days after his admission he had a cardiac arrest. Resuscitation was unsuccessful.

His post-mortem demonstrated metastatic calcification in all organs. This was also evident in the skin biopsy (Figure 2). He had mild triple vessel coronary artery disease, but extensive calcification of the smaller intramyocardial arteries and widespread cardiac interstitial fibrosis. There was atrophy of skeletal muscle due to denervation and metastatic calcification. There was no evidence of an inflammatory myopathy. Hypertensive nephropathy was confirmed as the aetiology of his renal failure.

Case 2

A 48-year-old male with a history of ischaemic heart disease, congestive heart failure and progressive renal failure was referred to the nephrology unit. He had a history of hypertension, and non-insulin-dependent diabetes but poorly controlled by diet and oral hypoglycaemic agents due to non-compliance. His plasma urea was 36 mmol/l and creatinine was 689 μmol/l, plus he had an elevated phosphate of 2.79 mmol/l. He was commenced on calcium carbonate and repeatedly advised to begin dialysis but he refused therapy.

His compliance remained poor and 3 months later was admitted to the intensive care unit with a profound metabolic encephalopathy, fluid overload and pericard-
Calciphylaxis is a rare and often fatal condition which results in progressive ischaemic necrosis secondary to widespread calcification of the medium and small vessels. The ischaemic necrosis may involve any organ but the skin and muscles are usually the most severely affected [1]. It is almost exclusively seen in ESRF patients. However, with the earlier diagnosis of renal failure and improved therapy, it has a low incidence. A high index of suspicion is necessary to make the diagnosis early, which is crucial in preventing progression and reducing morbidity [2,3]. It should be considered in all ESRF patients who present with a levido reticularis-type rash, painful skin nodules or plaques and in those with ulceration of the lower limbs or digital gangrene. A skin biopsy demonstrating widespread calcification and fibrinous thrombi plus the absence of inflammation confirms the diagnosis. It should also be considered in those individuals with
ESRF who present with a myopathy or evidence of infarction of the bowel, central nervous system or myocardium [4]. It may be frequently confused with a vasculitis, cryoglobulinaemia, panniculitis or atheromatous gangrene [4,5].

There may be an association with insulin-dependent diabetes mellitus and hypertension, both of which cause small and medium vessel pathology, which may exacerbate or accelerate calciphylaxis [2–4]. There is no evidence to suggest an underlying autoimmune mechanism, but it appears that other conditions are required for calciphylaxis to occur [2]. It is probable that in a predisposed individual there are triggers which may precipitate tissue calcification [6]. From animal studies and case reports, potential triggering factors may include corticosteroids, iron-containing compounds, topical egg albumin or yolk or even local trauma [1,3,4,7]. The relationship of these agents to the actual pathogenesis is unknown. The ischaemia that develops does not appear to be due to a mechanical obstruction (secondary to calcium deposition). Potential mechanisms include vasoconstriction related to elevated calcium or parathyroid hormone levels or thrombosis secondary to low levels of protein C which have been documented in patients with calciphylaxis [1,3–5].

The pathogenesis of calciphylaxis remains unknown. In almost all cases there is significant hyperphosphataemia in combination with long-standing poorly controlled renal failure and secondary hyperparathyroidism [1,3–5]. Secondary hyperparathyroidism may also contribute to the hyperphosphataemia by enhancing the release of calcium and phosphate from bone. The combination of hyperphosphataemia and low normal plasma calcium will result in an elevated calcium phosphate product and the tendency to metastatic calcification. There is considerable debate as to whether or not parathyroid hormone synthesis and secretion can be controlled at all by medical therapy once parathyroid hyperplasia has developed [8]. Quarles et al. [9], in a controlled study of pulse oral versus intravenous calcitriol for severe secondary hyperparathyroidism, demonstrated that hyperphosphataemia may cause non-responsive status of the parathyroid glands to the inhibitory actions of calcitriol on parathyroid hormone release. However, if there is good control of phosphate levels, then calcitriol may be effective in suppression of parathyroid hormone levels in severe secondary hyperparathyroidism [10,11].

Overall, the outlook for those who develop calciphylaxis remains poor. It is usually a fatal condition with the most common cause of death being sepsis secondary to wound infections. Prevention is by the early diagnosis of renal failure and the aggressive control of urea, phosphate and calcium with the suppression of secondary hyperparathyroidism using pulse calcitriol therapy [12]. Once calciphylaxis is established, the only way to influence progression is aggressive intervention with dialysis, exclusion of possible triggers, a low calcium and phosphate diet plus phosphate binders. Depending on the patient’s overall condition, early parathyroidectomy has been shown to reduce the calcium phosphate solubility product, by reducing the impact of the secondary hyperparathyroidism [8,11], and has been reported to reduce the pain level and improve wound healing [2–4]. Oral phosphate binders need to be continued following successful parathyroidectomy. Parathyroidectomy late in the disease has been shown to have unpredictable results but this may well be due to the severity of the calciphylaxis and the associated sepsis [2–4,13]. Aggressive dialysis, good wound care, early debridement or amputation and appropriate antibiotic therapy are the mainstays of conservative management for this condition.

References

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