**Case Report**

**A dramatic case of calciphylaxis 20 years after kidney transplantation**

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**Introduction**

Calciphylaxis, necrotizing livedo reticularis or calcific uraemic arteriolopathy (CUA) is an almost always fatal disease characterized by painful skin lesions localized on the lower extremities. This complication is typically observed in patients with end-stage renal disease on dialysis or after recent kidney transplantation [1,2]. Key histopathological features include calcification of the media of small and medium-sized vessels evolving to skin necrosis with secondary gangrene, sepsis and eventually death in 60% of cases [3].

The specific etiopathogenetic mechanisms involved in CUA are still poorly understood. Although dysregulation of calcium-phosphorus metabolism and secondary hyperparathyroidism are often prominent findings, there are many reports in which these parameters are completely normal [1].

We present a unique case of a patient with a normal kidney transplant function who developed fatal calciphylaxis more than 20 years after transplantation.

**Case**

In July 1998, a 43-year-old Caucasian man was admitted to hospital with excruciating pain in both legs. His antecedents consisted of chronic kidney disease secondary to obstructive urethra valves requiring haemodialysis in May 1975. After a bilateral nephrectomy, he received a cadaveric kidney transplantation in March 1977. The transplantation was complicated by two early acute rejection episodes, successfully treated with corticosteroids and resulted in a satisfactory long-term graft function with a creatinine clearance of 60 ml/min. His immunosuppression consisted of steroids and azathioprine.

Three months after transplantation he developed hypercalcaemia secondary to hyperparathyroidism. A subtotal parathyroidectomy was performed and he remained disease free until March 1997, when he presented with a syncope without prodromi. An EEG showed epileptic waves; on CT scan calcifications of the falx cerebri and tentorium cerebelli were found. He was treated with carbamazepine; in this period he was on calcium carbonate 4 g daily and calcitriol 2 \( \mu \)g daily because of marked hypocalcaemia and hypophosphataemia. On physical examination a heart murmur was noted and an echocardiography showed a calcified stenotic aortic valve with a calculated gradient of 40 mmHg.

In February 1998, he complained of pain in both legs, especially localized at the knees. Three months later a purple-coloured macula developed on the right thigh, which was not painful and did not disappear by local pressure. Laboratory data showed normal serum creatinine of 0.79 mg/dl, calcium of 9 mg/dl and phosphorus of 2.5 mg/dl and a creatinine clearance of 51 ml/min. The last PTH was measured in 1995 with a serum level of 9.1 ng/ml. On admission he took only 0.5 \( \mu \)g calcitriol. CaCO₃ was already stopped.

A tentative diagnosis was made of an infected haematoma and broad-spectrum antibiotics were started. One month later, extremely painful bilateral extensive ulcers developed on the lower extremities. Local wound care was applied and intravenous antibiotics were administered. Eventually he developed a fulminant sepsis with multi-organ failure and died 3 weeks later. A skin biopsy showed extensive medial calcification and intimal hyperplasia of small arteries in the hypodermis obliterating the lumen. There was a fibrinoid necrosis and a dense cellular infiltrate.
Discussion

CUA classically starts with livedo reticularis; this is an extremely painful, purplish or violaceus mottled skin lesion that is plaque-like or nodular. These lesions often progress to extensive ulcers with eschar formation, wound infection and eventually gangrene [1]. Infected ulcers cause sepsis and death in 60% of patients.

Earlier patients presented with ulcerative lesions especially localized on the lower extremities. At present, lesions appear in 80% of cases as non-ulcerative subcutaneous indurated plaques [2].

At present, the incidence is estimated to be 1% per year in haemodialysis centres. There has been a rise in the incidence over the last 15–20 years due to the increasing use of calcium-containing phosphate binders and vitamin D preparations [2]. The widespread use of coumadin preparations could also contribute to this rise. CUA is usually diagnosed in patients on dialysis or shortly after transplantation [1]. However, more recent reports describe patients with only moderate renal disease [4]. Furthermore, CUA has been reported in patients with normal kidney function suffering from primary hyperparathyroidism [5], liver cirrhosis [4], metastatic bone disease and acute renal failure.

The risk is associated with the serum phosphate and levels of alkaline phosphatase. Obesity and Caucasian race constitute other important risk factors [6,7]. Serum PTH as a risk factor remains under discussion [1,3]. Frequently, the calcium-phosphate product is completely normal, as in our case [4,5]. Metastatic bone disease and acute renal failure.

There are reports showing a better prognosis after parathyroidectomy, suggesting a role for parathormone [3].

The importance of protein inhibitors like the serum protein a2-Heremans-Schmid glycoprotein (Ahsg) has been discussed. They inhibit ectopic calcification in Ahsg-deficient mice causing severe calcification of organs with nephrocalcinosis and calciphylaxis. In experiments with mice kidney function is normal until calcification starts. Ahsg acts as a negative acute-phase protein down regulated after infection or trauma. In a screening of dialysis patients Ahsg serum concentrations were significantly lower than in the normal population. A recent article also found low titres in patients with CUA [8].

Our patient took corticosteroids and a high dose of calcitriol known to act as a triggering factor [3,9]. He took CaCO3 for a long time period before the calciphylaxis. He did not receive coumadin or low molecular weight heparin, also known as triggering factors. One hypothesis is that patients exist who are genetically predisposed with low Ahsg and other inhibitor titres. This could explain why calciphylaxis occurred in our patient.

The radiological findings vary from a diffuse, fine reticular pattern to a very coarse reticulo-nodular appearance with prominent vessel calcification [1]. Bone scintigraphy is a highly sensitive diagnostic tool, demonstrating abnormal subcutaneous isotope uptake in 97% of the cases [2]. Sometimes uptake is seen in visceral organs like the lungs. In our case there were calcifications in the brain and on the heart valves 1 year before the calciphylaxis, suggesting an association.

We presume that the seizure was secondary to the lesions seen on CT scan.

A skin biopsy with haematoxylin and eosin staining can determine the final diagnosis showing calcification of the media and intimal hyperplasia in small and medium-sized venules and arterioles of the dermis and subcutaneous tissue. An inflammatory infiltrate with predominantly lymphocytes but also neutrophils is common. In some venules fibrin thrombi are detected leading to tissue ischaemia and infarction [3]. Calcification of extravascular soft tissues and viscera is frequently found as was the case in our patient. If necessary, immunohistochemistry with von Kossa staining shows the calcium deposits in the vessel walls. Sometimes lesions deteriorate after biopsy, making bone scintigraphy the first choice [2].

As the exact mechanism is still unknown, therapy should include a combination of different measures [10]. The first priority is to lower the calcium-phosphate product with dialysis and a low phosphate diet [1,7,10]. It is probably useful to switch to non-calcium containing phosphate binders like sevelamer [7,10]. New therapeutic modalities such as the calcimimetics will probably have an important role in the near future.

The therapeutic role of parathyroidectomy is still debated because of many conflicting data [2,3,6]. Most authors propose only surgery in patients with high parathyroid hormone levels [7,10].

Hyperbaric oxygen therapy can be used in presence of extensive lesions, sometimes with spectacular results [1,10].

The use of corticosteroids is controversial and has been reported to act as a triggering factor [7]. A recent study recommends prednisolone at a dose of 30–50 mg for 3–8 weeks in patients without ulcerations. In 80% of the patients there was a dramatic improvement [2].

Other therapies have been tried, but none of them are really evidence-based.

Conclusion

CUA is a disease entity that occurs more frequently than reported earlier.

The diagnosis should be considered whenever symmetric plaques or skin ulceration develop in renal patients even when they have a normal kidney function as in our case.

Our case was unique because of its presentation 20 years after transplantation with good graft function and a normal calcium-phosphate product. Cases like this show that the pathogenesis cannot be explained by the existence of high calcium-phosphate levels or high parathyroid hormone levels alone.
Further research is necessary to reveal the role of protein inhibitors like Ahsg and identify other possible mechanisms.

Conflict of interest statement. None declared.

References


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