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Case Report

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Kidney allograft failure due to acute phosphate nephropathy associated with severe secondary hyperparathyroidism

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Abstract
Intratubular calcification is a common finding in renal allografts. However, possible harmful effect of this calcification is not well recognized, and allograft failure purely due to this condition has not been reported. We report a kidney transplant recipient who suffered from severe secondary hyperparathyroidism and unexplained early allograft failure. A diagnosis of acute phosphate nephropathy was made subsequently based on serial allograft biopsy findings. This case calls for a high index of suspicion to look for this rare cause of allograft dysfunction among high-risk patients. It also highlights the importance of good calcium–phosphate control before renal transplantation.

Keywords: acute phosphate nephropathy; hyperparathyroidism; nephrocalcinosis; tubular injury

Background

Nephrocalcinosis with calcium–phosphate deposition has been observed in the renal allografts of patients with pre-transplant hyperphosphataemia with or without secondary hyperparathyroidism [1–3]. However, the harmful effect of this deposition on allograft outcome is not widely recognized, and allograft failure purely due to this condition has not been reported. We describe a patient with severe secondary hyperparathyroidism and grossly elevated serum calcium–phosphate product presenting with unexplained early allograft failure. Acute phosphate nephropathy was subsequently diagnosed based on serial allograft biopsy findings.

Case report

A 44-year-old lady suffered from end-stage renal failure secondary to IgA nephropathy and was started on continuous ambulatory peritoneal dialysis in January 2002. She developed an episode of peritonitis due to *Mycobacterium chelonei* in October 2007. It necessitated peritoneal catheter removal and switching to haemodialysis. Since the switch to chronic haemodialysis, she was noted to have worsening control of serum phosphate level and secondary hyperparathyroidism. Her intact parathyroid hormone level had progressively increased to 318 pmol/L in January 2010. The pre-dialysis phosphate and corrected serum calcium levels ranged from 3.1 to 3.9 mmol/L and 2.5 to 2.65 mmol/L, respectively. She received no calcium supplement. A total parathyroidectomy was originally planned in late February.

She received a cadaveric renal transplant in early February 2010. A session of haemodialysis was delivered immediately before the surgery. The pre-dialysis serum phosphate and corrected calcium were 3.4 and 2.6 mmol/L, respectively. The deceased donor was a 48-year-old lady who died from intracerebral haemorrhage and was on inotropic support before organ retrieval. Both the donor and the recipient were O positive in blood group with four human leukocyte antigen mismatches. The cold ischaemia time was 17 h. The immunosuppressive regimen consisted of prednisolone, mycophenolate sodium and cyclosporin.

The initial graft function was inadequate. An allograft renal biopsy was performed on Day 3 and it revealed Type IA acute T-cell-mediated rejection and acute tubular necrosis (ATN) (Figure 1). She was treated with 3 days of pulse intravenous methylprednisolone, and cyclosporin was switched to tacrolimus for maintenance immunosuppression. However, the response was suboptimal and she was restarted on regular haemodialysis on Day 7. The allograft did not function well throughout the first month post-transplantation, and she remained dialysis dependent during this period. Allograft biopsy on Day 16 and 27 both demonstrated no evidence of acute rejection but features of ATN persisted, albeit less severe as compared with the first biopsy. She finally became dialysis independent 2 months after transplantation, but the graft function remained unsatisfactory with her serum creatinine staying between 310 and 397 μmol/L. Serum samples of the recipient taken at Week 2 and 8 post-transplantation identified no donor-specific antibody. Subsequent biopsy on Day 58 and 106 also failed to reveal any evidence of rejection but persistent acute tubular injury with prominent regenerative changes.

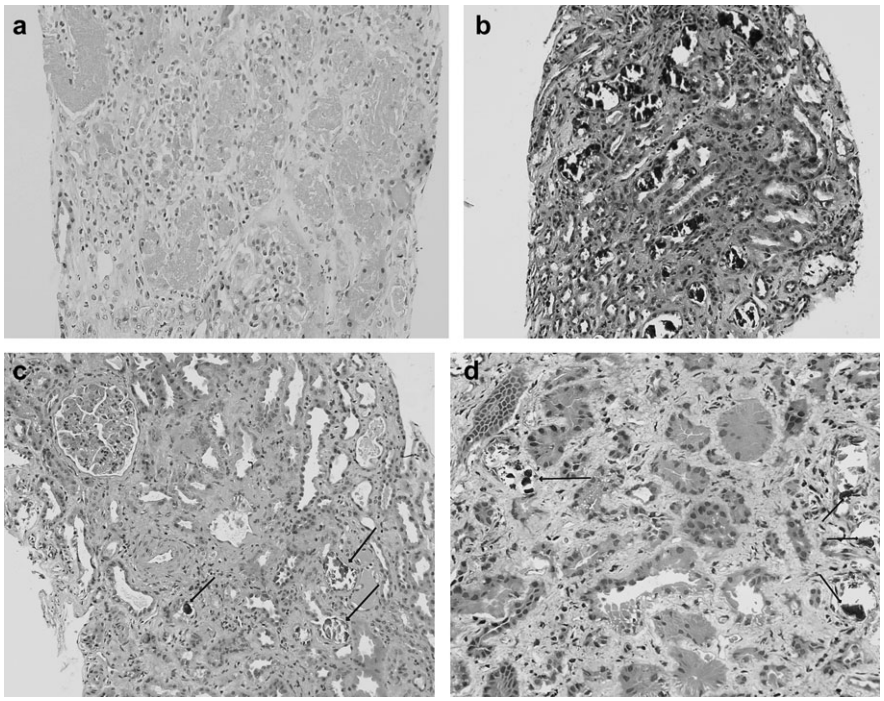

Fig. 1. Histopathological findings. (**a**) Biopsy on Day 3 demonstrating extensive necrosis of tubular epithelium with tubular lumens filled by eosinophilic debris. No significant intratubular calcifications are seen yet. Other changes of acute cellular rejection are present elsewhere. (Haematoxylin and eosin stain, ×100 magnification). (**b**) Second renal biopsy at post-operative Day 16 shows many intratubular calcifications (stained black). (Von Kossa stain counterstained with haematoxylin and eosin, ×100 magnification). (**c**) Biospy on Day 58 shows regenerative changes of the tubular epithelium, progressive interstitial fibrosis and tubular atrophy. Tubulointerstitial calcifications (marked with thin arrows) remain conspicuous. (Haematoxylin and eosin stain, ×200 magnification). (**d**) Biopsy at post-operative Day 106 shows marked interstitial fibrosis and tubular atrophy. Intratubular calcifications (marked with thin arrows) remain present. (Haematoxylin and eosin stain, ×200 magnification).

C4d and SV40 stainings had been negative throughout the five consecutive allograft biopsies, and no viral inclusion body had ever been detected in these specimens. However, there were intratubular calcification, which was consistent with calcium–phosphate crystal deposition and chronic changes, first evident in the second biopsy done on Day 16, which progressively increased in amount in the subsequent biopsies. The allograft biopsy on Day 58, indeed, displayed numerous intraluminal calcifications in the tubules with obstruction and distension of tubules. In the biopsy on Day 106, prominent intratubular calcifications persisted but, in addition, there were also moderate-to-severe tubular atrophy and interstitial fibrosis, while ATN became less conspicuous. The overall picture was compatible with nephrocalcinosis due to acute phosphate nephropathy resulting in chronic allograft damage. The trends of her serum calcium and phosphate levels after transplantation are shown in Figure 2.

At 5 months post-transplantation, the allograft function further deteriorated and the patient returned to regular haemodialysis.

Discussion

Nephrocalcinosis with intratubular calcification is commonly encountered in allograft kidney and could be identified in 6.1, 8.2 and 17.8% of specimens at 6 weeks, 3 months and 6 months post-transplatation, respectively, especially among patients with delayed graft function [4, 5]. Nevertheless, it is unclear whether this finding merely represents inadequate calcium–phosphate clearance in patients with impaired allograft function, a deleterious effect of the intratubular calcification on the allograft function, or both. At the same time, the relationship between allograft dysfunction and hyperparathyroidism and/or hyperphosphataemia remains controversial [6–8].

Until recently, Boom *et al.* [5] reported a positive association between elevated serum creatinine at 1 year and the presence of allograft calcification at 3 months post-transplantation. Nevertheless, given the many patients with significant secondary hyperparathyroidism undergoing cadaveric renal transplant, it is intriguing to note that adverse impact on the allograft function is not widely observed in daily clinical practice. Indeed, reports on this aspect are rather scarce.

Our case likely represents an extreme case, where the crystal load was extremely challenging and tubular cells were highly vulnerable. She had multiple risk factors for the development of intratubular calcification; these included severe secondary hyperparathyroidism, an extremely high serum calcium–phosphate product, and damaged allograft tubular epithelium related to prolonged cold ischaemic time and acute rejection. Recent studies indeed showed that tubular damage from whatever insults would readily predispose the allograft to the development of crystal retention, while the retained crystal could, in return, lead to further tubular damage by causing tubular obstruction, inducing production of inflammatory mediators and oxidative stress [9]. In normal situation, the kidney has a defence

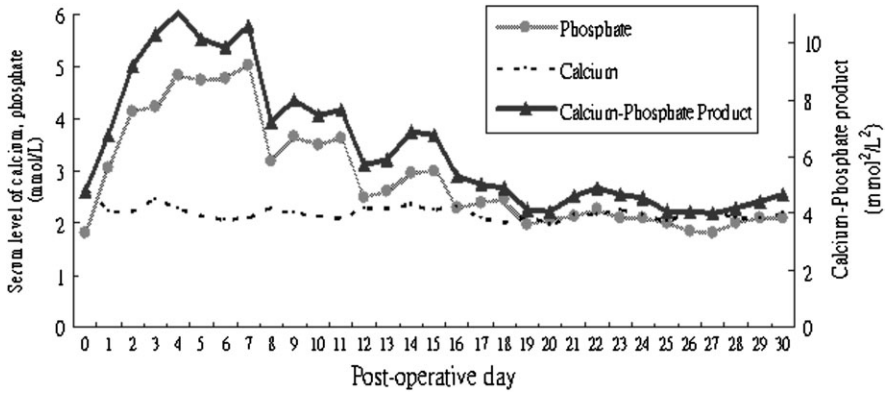

Fig. 2. Diagram showing the levels of serum phosphate, corrected calcium and calcium–phosphate product of the patient during the first month after renal transplantation.

mechanism against intratubular crystal persistence and spontaneous clearance of crystal could indeed occur in healthy kidneys [9]. Nevertheless, renal injury would occur if this clearance mechanism is compromised and/or when it is overwhelmed by a large crystal load. In a worst-case scenario, a vicious cycle could be triggered resulting in relentless renal damage like our case.

This report highlights the need and importance of good calcium–phosphate control before transplantation. Patients with severe hyperphosphataemia and secondary hyperparathyroidism should be optimized before renal transplantation. In addition, a high index of suspicion should be given for those patients with delayed allograft function to look for nephrocalcinosis-related renal damage, especially in the context of suboptimal serum calcium–phosphate control. Although there has not been any prospective study on the treatment strategy, some previous case reports seem to suggest some benefits with aggressive interventions such as intensive haemodialysis and urgent parathyroidectomy [2, 3, 10]. In any case, these treatments should be considered promptly once the diagnosis is made. By doing so, hopefully, it could minimize the crystal load and salvage the kidney from irreparable damage.

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Conflict of interest statement. None declared.

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