

Teaching Point
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Unexpected deterioration of graft function after combined kidney and pancreas transplantation

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Introduction

Kidney transplant recipients may develop chronic allograft failure due to immune and non-immune mechanisms, including chronic rejection, nephrotoxicity from calcineurin inhibitors, recurrent glomerular disease, BK viral infection and uncommon causes. We report two patients with chronic deterioration of graft function after combined kidney and pancreas allograft transplantation who presented with a rare, but not far-fetched cause of kidney failure.

Case 1

A 54-year-old Caucasian male with type 1 diabetes mellitus and diabetic nephropathy underwent combined cadaveric kidney and pancreas transplantation. Seven years after transplantation, he developed acute graft pancreatitis complicated by mesenteric ischaemia. His pancreas graft and the entire ileum were surgically resected. Subsequently, he developed chronic diarrhoea due to short bowel syndrome. Exocrine pancreatic insufficiency was treated with pancreatic enzyme supplements and cholestyramine, and he was subjected to a diet for short bowel syndrome containing low oxalate. Fourteen years after transplantation, a transplant biopsy was performed due to progressive graft failure. Graft ultrasound showed hyperechogenicity of the kidney cortex. The biopsy demonstrated focal interstitial fibrosis and tubular atrophy with interstitial lymphocytic infiltration. Numerous tubules and collecting ducts showed birefringent crystals, accompanied by partial rupture of the tubular basement membrane and foreign body giant cell reaction (Figure 1A and B). Graft oxalosis was diagnosed and confirmed by an elevated urinary oxalate excretion in the 24-h urine collection (0.97 mmol/24 h, normal value 0.1–0.5 mmol/24 h). The immunosuppressive therapy with tacrolimus and azathioprine was continued as previous. One year after biopsy and 15 years after transplantation, the patient developed end-stage graft failure and returned to haemodialysis.

Case 2

The second patient is a 52-year-old Caucasian female with diabetic nephropathy who received a simultaneous cadaveric kidney and pancreas transplant at the age of 42 years. Two years after transplantation, an ileus caused by a small bowel volvulus occurred followed by a hemicolectomy and resection of the entire small intestine. Consequently, she developed chronic diarrhoea due to short bowel syndrome. A specialized diet with additional cholestyramine and loperamide was initiated. Seven years after transplantation, a biopsy was performed demonstrating mesangial focal and segmental hypercellularity. In the interstitium, focal fibrosis and tubular atrophy was accompanied by plasma cell infiltration. In multiple tubules, intra-luminal birefringent crystals were present, which partly extended to the interstitium with formation of foreign body giant cells (Figure 1C and D). Urinary 24-h collection presented a daily oxalate excretion of 0.88 mmol/24 h. A low-oxalate diet adapted for short bowel syndrome was introduced, and the immunosuppressive therapy consisting of tacrolimus and azathioprine was continued unchanged. The latter was introduced 3 years before in exchange for mycophenolate mofetil to reduce gastrointestinal toxicity in context of chronic diarrhoea. Ten years after transplantation, and 3 years after diagnosis of oxalate nephropathy, her graft function is stable with an estimated glomerular filtration rate of 24 mL/min.

Discussion

Chronic allograft dysfunction is the major cause of progressive loss of kidney transplant function and consists of several different entities such as chronic antibody-mediated rejection, recurrent or *de novo* glomerular disease, use of calcineurin inhibitors and other causes. We were expecting a typical cause of graft failure such as chronic allograft nephropathy, however, we were surprised by some other interesting biopsy findings.

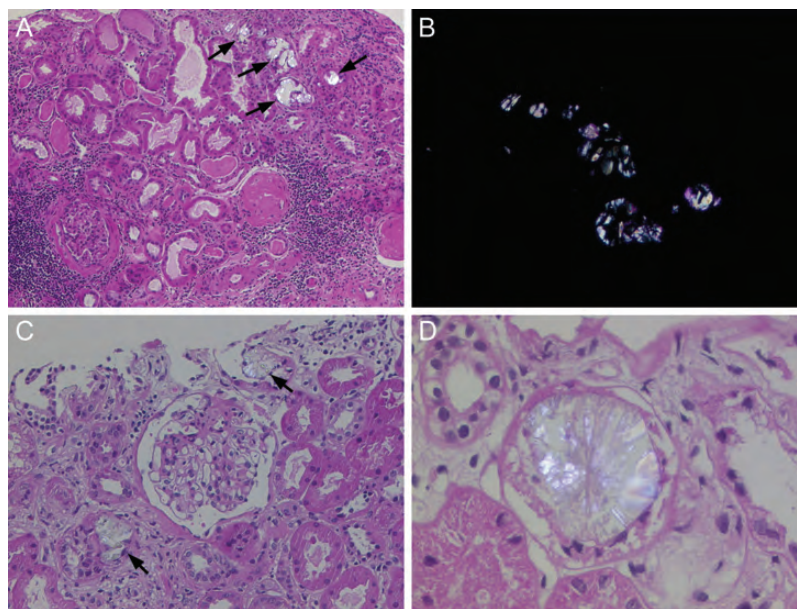


Fig. 1. (A) Kidney biopsy with focal tubulo-interstitial birefringent crystalloids (indicated by arrows), interstitial fibrosis, tubular atrophy and accompanying inflammation (HE stain, original magnification $\times 60$). (B) Birefringent oxalate crystals under polarized light (HE stain, original magnification $\times 100$). (C) Intra-tubular, birefringent oxalate crystals (indicated by arrows) (HE stain, original magnification $\times 125$). (D) Intra-tubular oxalate crystals (HE stain, original magnification $\times 320$).

Both of our patients' biopsies showed birefringent crystals, characteristic of calcium oxalate, deposited in tubules and in the interstitium which are specific histological findings in oxalate nephropathy [1]. Oxalate nephropathy is a major complication of hyperoxaluria. Hyperoxalurias are divided into primary and secondary types. Whereas primary hyperoxaluria (PH) is an inherited metabolic disorder, underlying causes of secondary hyperoxaluria are manifold. Secondary hyperoxaluria develops due to hyperoxalaemia, which may be the result of metabolic overproduction, gastrointestinal hyperabsorption or diminished renal excretion [2].

Oxalate is included in almost all food products. Dietary oxalate intake averages from 50 to 300 mg oxalate per day, of which 5–10% are absorbed in the intestine. The endogenously produced oxalate represents 50% of the daily oxalate load and originates partially from degradation of vitamin C in hepatocytes [3, 4]. The intake of high amounts of vitamin C causes increased oxalate excretion [5], leading to vitamin C-induced oxalate nephropathy in some cases [6].

Intestinal hyperabsorption of oxalate as a cause of secondary hyperoxaluria may develop in patients on a low-calcium or low-magnesium diet [3, 7] based on more free (luminal) oxalate, which allows for increased intestinal absorption. Another important cause of intestinal oxalate hyperabsorption is fat malabsorption resulting in increased levels of bile salts and free fatty acids, which interfere with luminal complexing of oxalate by binding to calcium and therefore providing more free oxalate in the gut lumen [8]. Further, *Oxalobacter formigenes*, a gram negative bacterium, has an influence on enteric oxalate absorption by degrading oxalate in the gut lumen and consequently reducing intestinal oxalate absorption [9]. In humans, the main mechanism of oxalate elimination is renal excretion by filtration and tubular secretion [2]. Under physiological conditions, intestinal oxalate clearance is low in humans; however, the adaptive increase

in advanced chronic kidney disease is not sufficient to prevent hyperoxalaemia [10]. Thus, a decrease in glomerular filtration rate (GFR) <30 – 40 mL/min leads to accumulation of oxalate due to insufficient clearance of the latter [10]. Both primary and secondary hyperoxalurias present elevated levels of oxalate in plasma, particularly when the GFR is declining. Deposits of calcium oxalate crystals are found in any tissue with the potential risk for organ dysfunction of the heart, bones, eyes, central nervous system and predominantly the kidney [11]. Kidney stones and intra-parenchymal deposits aggravate renal failure by tubular obstruction and parenchymal inflammation [2].

It has been suggested that oxalate nephropathy is the result of mechanical stress and/or toxic reaction. The crystals provoke tubulo-interstitial nephritis with consecutive interstitial and peri-glomerular fibrosis, tubular atrophy and infiltration of monocytes, lymphocytes and giant-cell formation [1, 8] as described in our cases.

In contrast to PH, where urinary oxalate levels typically exceed 1.0 mmol/24 h, amounts between 0.5 and 0.8 mmol/24 h have been reported in secondary hyperoxaluria [2]. In our cases, urinary oxalate excretion was elevated to values <1.0 mmol/24 h indicating secondary hyperoxaluria.

Recurrent calcium oxalate urolithiasis is the main clinical manifestation of hyperoxaluria. Interestingly, none of our patients developed kidney stones; however, ultrasound sonography in Case 1 revealed nephrocalcinosis with distinct hyperechogenicity of the kidney cortex. Accordingly, shrunken kidneys with granular surface and hyperechogenicity have been described in renal oxalosis [12].

Taken together, all our findings including histology, laboratory and clinical data confirmed the diagnosis of oxalate nephropathy in both patients with subsequent deterioration of graft function. The underlying common cause was enteric hyperoxaluria caused by short bowel syndrome.

Therapeutic options in secondary hyperoxaluria should primarily target the underlying cause. In addition, a general and effective treatment is high fluid intake to reduce the concentration and solubility of calcium and oxalate in urine [2]. Food containing high amounts of oxalate should be avoided [13]. Also, excessive substitution of vitamin C should be prevented. Notably, a sufficient amount of enteric calcium supplementation has an equal effect and may decrease the fraction of absorbed oxalate in urine by 35–50% [14].

In our patients, therapy was focused on dietary intervention with high intake of carbohydrates and adjusted mix of long and medium chain fatty acids. In addition, both patients were treated with cholestyramine, and loperamide. Patient 1 was also supplemented with pancreatic enzymes and sodium hydrogen carbonate while Patient 2 received high doses of oral calcium. The immunosuppressive regimen was continued in both patients because there was no evidence for a specific immunosuppressive therapy to be superior in the context of graft oxalosis.

To our knowledge there are no studies available if patients with short bowel syndrome after transplantation are on higher risk for oxalate nephropathy and subsequent graft failure. However, another case report [8] reported loss of two consecutive transplants due to undiscovered chronic pancreatitis in a patient with idiopathic renal dysplasia. Two additional cases have been published describing oxalate nephropathy in renal allografts, one based on exocrine pancreatic insufficiency [15] and one caused by mycophenolate mofetil-induced diarrhoea [16]. In our patients, graft function could be preserved by strict dietary intervention in one patient whereas the other patient developed end-stage graft failure and returned to haemodialysis.

In conclusion, underlying causes of chronic allograft failure in renal transplant patients are manifold. On suspicion of hidden causes such as enteric hyperoxaluria, early diagnosis including graft biopsy and appropriate prevention are potentially of prime importance because timely interventions may decelerate or even prevent progression of graft damage.

Teaching points

- (i) Underlying causes of chronic allograft failure in renal transplant patients are manifold.
- (ii) Secondary hyperoxaluria is insidious because of its slow progression and may be overseen, particularly in patients with other risks for chronic renal failure such as renal transplant patients.
- (iii) Early diagnosis including allograft biopsy is essential to initiate therapy and potentially prevent or delay graft loss.

- (iv) There is no evidence for a specific immunosuppressive therapy to be superior in graft oxalosis; however, replacement of mycophenolate mofetil by, e.g. azathioprine may decrease gastrointestinal toxicity.

Conflict of interest statement. None declared.

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