Acute renal failure secondary to oxalosis in a recipient of a simultaneous kidney–pancreas transplant: was mycophenolate the cause?

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Mycophenolate mofetil (MMF) is now the preferred antimitabolite for post-transplant immunosuppression [1]. Although leucopenia and diarrhoea are the main side effects, there are case reports of a malabsorption syndrome caused by MMF [2].

Oxalosis, either primary or secondary, is a well-recognised cause for renal failure. Secondary hyperoxaluria is caused by increased intestinal oxalate absorption and can be aggravated by excessive dietary oxalate intake. Particular gastro-intestinal disorders such as short bowel syndrome, chronic inflammatory bowel disease and fat malabsorption syndromes, e.g. chronic pancreatitis, are known to increase the risk of secondary hyperoxaluria [3]. Oxalosis causing renal allograft failure has also been reported [4,5].

To our knowledge, MMF has not previously been implicated in the development of secondary hyperoxaluria and acute renal failure in kidney or kidney–pancreas transplant patients.

We report a patient with prolonged MMF-associated diarrhoea who presented with acute renal failure caused by oxalosis.

Case history

A 51-year-old man with type 1 diabetes mellitus and chronic renal failure underwent simultaneous pancreas and kidney transplants. The pancreas was enteric drained. He received two 30 mg doses of Alemtuzumab (Mab-Campath, Schering Health Care Ltd, UK) as induction immunosuppression and was then maintained on Tacrolimus (Prograf, Astellas Pharma Ltd, UK) (trough levels 8–12 ng/mL) and 500 mg of MMF (CellCept, Roche Registration Ltd, UK) twice daily. There were no postoperative complications. He was discharged home on the 12th postoperative day with stable blood glucoeses and a plasma creatinine of 164 µmol/L (eGFR = 41 mL/min).

Six months after transplantation, he developed persistent diarrhoea and lost 10 kg of weight over 3 months. He described his stool as pale and greasy with 3–6 episodes of bowel movements a day, but a quantitative stool fat test was not formally done. Stool culture, Clostridium difficile toxin were both negative as was cytomegalovirus (CMV) PCR and urine cytology for BK virus. No change was made to his medication.

He underwent two upper gastro-intestinal endoscopies and duodenal biopsies, both revealing subtotal villous atrophy with no increase in intra-epithelial lymphocytes. His biopsies were negative for parasites including Giardia lamblia. No antibodies to tissue anti-glutaminase and glutamic acid decarboxylase (GAD) were detected. Faecal elastase was slightly reduced at 147 µg/g stool (normal range 200–500 µg/g stool).

He had a 2-week trial of gluten-free diet but there was no improvement in the diarrhoea. He underwent colonoscopy with biopsies that showed no evidence of colitis. An abdominal transit study excluded overflow diarrhoea.

The transplant kidney function deteriorated. The serum creatinine increased from a baseline of 190 µmol/L to 340 µmol/L. He underwent a transplant kidney biopsy, which showed oxalate nephropathy with no evidence of rejection (Figure 1a). Urine and serum oxalate levels were both elevated. His serum oxalate level was 40 µmol/L (reference lab range <10 µmol/L). His urine oxalate excretion was 839 µmol/24 h (reference lab range 100–460 µmol/24 h). His urine oxalate/creatinine ratio was also elevated at 118 µmol/mmol creatinine (reference lab range 1–38 µmol/mmol). Urine cytology at the time of biopsy demonstrated numerous oxalate crystals (Figure 1b) but no evidence of BK nephropathy. He was dialysed three times but this did not reduce the plasma
oxalate concentration. MMF was considered a possible cause for his malabsorption syndrome and diarrhoea, and was therefore replaced with azathioprine (IVAX Pharmaceuticals Ltd, UK) 50 mg/day. Following this change, his symptoms improved and his diarrhoea stopped. The urine oxalate excretion decreased in 5 days to 477 µmol/24 h and his urine oxalate/creatinine ratio was 89 µmol/mmol creatinine.

Two months after the change in his medication the urine oxalate excretion had fallen to a normal level of 80 µmol/24 h. He no longer had diarrhoea but the plasma creatinine was still raised at 411 µmol/L (eGFR = 14 mL/min). A repeat biopsy was not performed.

Discussion

The introduction of mycophenolate has improved transplant outcomes [6]. Leucopenia and diarrhoea are the most frequently experienced side effects. Although very common, the mechanism of diarrhoea is unknown [2]. In the case reports of MMF-associated malabsorption syndrome, villous atrophy has been proposed as a possible mechanism for diarrhoea. Clearly, this has to be differentiated from coeliac disease. In our patient, the normal number of intraepithelial lymphocytes and the absence of marker antibodies argue against a diagnosis of coeliac disease. In patients with post-transplantation diarrhoea, a systematic search for unusual sources of infection is mandatory [7]. These were excluded in our patient. Persistent diarrhoea without fever in renal transplant recipients in the absence of infection may be due to mycophenolic acid metabolites, and in such cases, reduction or cessation of MMF can be the only effective course of action [8].

Secondary hyperoxaluria may be a consequence of increased intestinal oxalate absorption associated with a variety of gastro-intestinal conditions [3], but hyperoxaluria and oxalate nephropathy in association with MMF-induced diarrhoea has not been previously reported. Hyperoxaluria secondary to malabsorption is a result of the unabsorbed fat binding intra-luminal calcium, which would normally bind to and precipitate the oxalate. Free oxalate is then available for absorption [9]. Although the urinary oxalate excretion is usually lower than in primary hyperoxaluria, it may be sufficient to cause oxalate stones and oxalate deposition in the kidney itself [3].

Hyperoxaluria, either primary or secondary, is well documented as a cause for renal failure and renal allograft failure [4,5]. The renal failure is usually permanent, even when the cause for the hyperoxaluria is reversed. In patients with hyperoxaluria attempts are made to decrease oxalate absorption by reducing the dietary intake, administering oral calcium supplements to bind and precipitate oxalate. Because plasma oxalate increases as GFR falls patients must be kept well hydrated. If renal function is very reduced attempts should be made to reduce the plasma concentration by haemodialysis. This is usually too late.

The irreversibility of oxalate nephropathy and its acute onset are such that early recognition is essential to prevent its progression. We suggest that mycophenolate should be added to the list of causes of this problem.

Conflict of interest statement. None declared.

References


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