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Case Report

Enteric Hyperoxaluria from Mycophenolate Mofetil in a Patient with Simultaneous Pancreas Kidney Transplant

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Abstract:

Mycophenolate mofetil (MMF) is well known to cause gastrointestinal adverse effects. However, enteric hyperoxaluria due to malabsorption caused by mycophenolate mofetil is infrequently reported in the literature. We present the case of a 60-year-old man on mycophenolate mofetil following a simultaneous pancreas-kidney (SPK) transplant, who presented with diarrhoea and weight loss seven years post-transplant. A transplant renal biopsy was performed for deteriorating renal function which showed tubular injury and oxalate crystals. His symptoms resolved and 24-hour urinary oxalate excretion level returned to normal when mycophenolate mofetil was replaced with azathioprine. His secondary hyperoxaluria is attributed to increased oxalate availability in the colon due to decreased calcium availability from fat malabsorption caused by MMF. Although symptoms resolved and urinary oxalate levels returned to normal, his renal function did not return to baseline. This case report highlights the fact that enteric hyperoxaluria induced by MMF does not always manifest early on. Transplant nephrologists and renal pathologists must exercise a high index of suspicion and meticulous clinicopathologic correlation. Early detection and intervention may improve outcomes by lowering the absorption of oxalate, the formation of calcium oxalate crystals in the kidneys, and irreversible damage.

Key words: hyperoxaluria; mycophenolate mofetil; transplant

Introduction

Mycophenolic acid (MPA), a reversible inhibitor of inosine 5"-monophosphate dehydrogenase (IMPDH), selectively inhibits T- and B-cell proliferation. MPA is the preferred antimetabolite for post-transplant immunosuppressants [1]. MMF, an immediate-release formulation of MPA is absorbed in the stomach and small intestine. Gastrointestinal toxicity is the most common dose-limiting side effect of this medication [2].

Hyperoxaluria, either primary or secondary, is a well-recognized cause of kidney stones and renal failure. Primary hyperoxaluria is a hereditary condition with at least three different genetic enzymatic defects whereas secondary hyperoxaluria can be idiopathic or arise due to intestinal hyperabsorption of oxalate or extreme dietary oxalate intake.

Colonic involvement from mycophenolate mofetil is commonly reported in the literature; however, there is limited data on MMF causing transient enteric hyperoxaluria and crystal nephropathy.

Case Report

A 60-year-old man with end-stage renal disease (ESRD) secondary to diabetic nephropathy with a past medical condition of type 1 diabetes mellitus complicated by retinopathy, neuropathy, gastropathy, and nephropathy underwent a simultaneous pancreas-kidney (SPK) transplant in 2009. Neither the donor nor recipient has a history of kidney stones or hypercalcemia. The patient did not have any previous bariatric surgery. There was no family history of kidney stones.

The patient was on tacrolimus and mycophenolate mofetil without steroids for maintenance immunosuppression. Other medications include aspirin, atorvastatin, nifedipine, omeprazole, bisoprolol, and cholecalciferol. His renal function was stable after the transplant. Creatinine was around 180µmol/L with eGFR around 35ml/min/1.73m^2. The patient was insulin independent with normal glycaemic control and an HbA1c of 34.4 mmol/mol.

Over a two-year period beginning in 2016, the patient experienced severe weight loss of 12kg along with chronic and profuse diarrhoea. In view of

the symptoms, he underwent extensive investigations by the gastroenterologist. Gastroscopy and colonoscopy with biopsies were performed with no significant abnormalities detected. Cytomegalovirus was not detected. Campylobacter-like organism (CLO) test was negative. Faecal elastase test was more than 500µg/g indicating that the pancreas was functioning as it should. Coeliac serology was negative. Positron emission tomography and computerized tomography scans performed were negative for cancer. His breath test for bacteria overgrowth was positive and he was given a short course of rifaximin. When his symptoms were still persistent, he was given a trial of cholestyramine and creon which improved his symptoms slightly.

His creatinine was noted to have risen sharply to 390µmol/L during his renal follow-up in February 2021. An urgent allograft ultrasound (US) and renal transplant biopsy were performed for the rapidly deteriorating renal function. The allograft US showed no urinary obstruction, normal resistive indices, and perfusion. The renal transplant biopsy was significant for scarring associated with calcium oxalate crystal (CaOx) deposition and acute tubular injury but no evidence of rejection **(Figure 1a, 1b, 1c, 1d).**

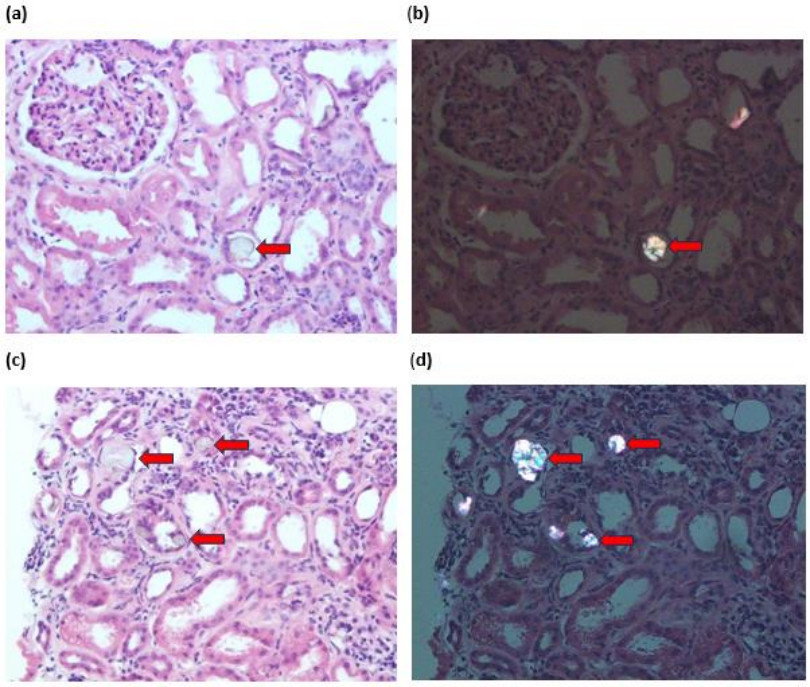

Figure 1 (a) and (b): Renal transplant biopsy showing acute tubular injury and intratubular oxalate crystals (arrows) with limited intertubular inflammation. Note the normal glomerulus. (hematoxylin and eosin (H&E) stain, x200; H&E stain under polarized light, x200 respectively). **(c) and (d)** Another area of the renal transplant biopsy showing more frequent refractile multi-coloured oxalate crystals (arrows) (hematoxylin and eosin (H & E) stain, x200; H & E stain under polarized light, x200 respectively).

In view of CaOx deposition, clinical evaluation was performed for hyperoxaluria. He had a 24-hour urine oxalate of 1055µmol (normal range 100 - 460µmol) on 18 March 2021. He was investigated for causes of secondary hyperoxaluria but, excessive oral intake of oxalate-containing foods (including vitamin C), ethylene glycol intoxication, or use of methoxyflurane was not found. The clinical impression was enteric hyperoxaluria secondary to MMF toxicity. MMF was replaced with azathioprine and a repeated 24-hour urine oxalate on 28 October 2021 improved to 297µmol (normal range 100 - 460µmol). His diarrhoea completely resolved after MMF was stopped and his appetite and weight improved. Before the symptoms appeared, his weight was 81 kg, but at his lowest, it was just 69 kg. When MMF was changed to azathioprine, his weight increased to 79 kg over the following year. However, his acute kidney injury did not resolve and creatinine remained elevated at around 350µmol/L and eGFR between 17-20ml/min/1.73m^2.

Discussion

Oxalate nephropathy is a known cause of acute and chronic renal failure. Our patient presented with renal allograft oxalate nephropathy more than 10 years post-renal transplant. The temporal sequence rules out primary hyperoxaluria. Moreover, pretransplant imaging of the native kidneys did not reveal any kidney stones.

In our patient who had a SPK transplant, his pancreas was functioning well, and unlikely the cause of his symptoms or hyperoxaluria.

Jahromi et al, in 2008 reported a similar case of acute renal failure secondary to oxalate nephropathy in a recipient of a simultaneous kidney-pancreas transplant [3]. His patient also had prolonged MMF-associated diarrhoea and presented with acute renal failure. Renal allograft biopsy confirmed oxalate nephropathy. Despite switching MMF with azathioprine, his gastrointestinal problems resolved, and his 24-hour urine oxalate levels improved, his plasma creatinine level remained elevated two months after switching immunosuppressants.

In recent years, there has been a growing recognition of the role that secondary hyperoxaluria plays in allograft dysfunction. In the intestine, dietary calcium normally binds to oxalate and is eliminated as CaOx in the stool. Enteric hyperoxaluria, the most prevalent cause of secondary hyperoxaluria, is caused by fat malabsorption, which reduces the availability of intestinal calcium and increases oxalate absorption.

Enterocytes are susceptible to the antimetabolic effects of MMF since they rely 50% on the de novo pathway of purine synthesis. This process inhibits the proliferation and reproduction of small intestinal epithelial cells, which disrupts fluid absorption and results in diarrhoea [4]. The colon is susceptible to the harmful effects of MMF, which include mucosal alterations such as oedema, erythema, erosions, and ulcerations. Apoptosis of crypt cells and architectural distortion are two histopathologic indications of MMF injury [4]. The typical latency period

between the start of MMF exposure and the onset of enterocolitis is around three years. This ranges from six months to fifteen years [5].

There are currently no guidelines available to help clinicians treat enterocolitis caused by MMF. After stopping MMF, several case studies reported that diarrhoea becomes better in three to five days [6, 7]. One systemic review revealed that in 98% of the cases, diarrhoea resolves within 20 days upon discontinuation of the MMF [5]. In our patient, his symptoms improved within days after his MMF was substituted with azathioprine.

Urinary oxalate levels in individuals with renal failure can be misleadingly high or low, making screening and clinical surveillance for hyperoxaluria difficult [8]. In the context of chronic renal failure, oxalate builds up in serum and tissue and has an inverse relationship with glomerular filtration rate [9]. Pretransplant screening is therefore not feasible. Apart from cases of chronic renal (allograft) failure, oxalate crystals in allograft biopsies are rather prevalent in the first posttransplant period but remarkably uncommon after that [10, 11]. The finding of oxalate on biopsy three or more months post-transplantation should prompt clinicopathologic investigation.

Patients with biopsy-proven oxalate nephropathy have a somewhat guarded clinical outcome. Damage to the kidney transplant in our patient as well as the case reported by Jahromi et al due to oxalate nephropathy were irreversible. In a systemic review by Lumlertgul et al in 2018, only 42% of the patients had partial recovery with 58% of the patients progressing to end-stage renal failure [12]. Kidney failure was observed to be associated with greater creatinine levels upon presentation, as well as a higher tubular atrophy and interstitial fibrosis score. According to a study by Buysschaert et al., individuals with oxalate nephropathy who did not have renal failure soon after diagnosis were able to retain independent kidney function for almost 30 months, indicating a benefit from treatment [13].

Conclusion

Our case report illustrates the importance of considering enteric hyperoxaluria causing oxalate nephropathy as a consequence of gastrointestinal side effects of MMF. To identify and treat allograft oxalate nephropathy, transplant nephrologists, and renal pathologists must exercise a high index of suspicion and meticulous clinicopathologic correlation as enteric hyperoxaluria induced by MMF does not always manifest early on. In transplant patients who develop secondary oxalosis because of MMF, treatment options include increasing fluid intake, dietary restrictions, calcium supplements taken with meals, lowering MMF dosage, or substituting MMF with another immunosuppressant. Prompt diagnosis and treatment may help to reduce oxalate absorption and deposition of calcium oxalate crystals in the kidney and irreversible damage therefore affording a better outcome. Allograft oxalate nephropathy is expected to be a growing cause of allograft dysfunction in the transplant population as obesity and malabsorptive pretransplant bariatric surgery become more common.

Disclosures

Author contributions: All authors contributed to the literature search and approved the final version of the manuscript. W. Yeon wrote the initial manuscript and is the article's guarantor. S. Moochhala and G. Jones revised the manuscript. M. Sheaff provided the pathology slides, labeled the captions, and reviewed the manuscript.

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Informed consent was obtained for this case report.

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