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Case Report

Acute post-transplant oxalate nephropathy: A case report and review of the literature

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Abstract

Calcium oxalate deposition in the kidney allograft remains an underappreciated cause of acute graft dysfunction. Diagnoses such as acute rejection, infection, hydronephrosis, and fluid collections are more immediately considered in the early post-transplant period. Risk factors include hyperoxaluria due to chronic fat malabsorption (post gastric bypass, inflammatory bowel disease), a diet rich in salt or animal protein, vitamin C ingestion, volume depletion, diabetes, and delayed graft function. We present the case of a patient who developed acute kidney injury secondary to oxalate nephropathy at 3 months post-transplant. Renal function improved with medical management, including volume repletion, calcium carbonate, and potassium citrate, without the need for hemodialysis. As more dialysis patients with morbid obesity requiring bariatric surgery, diabetes, and metabolic syndrome are being considered for renal transplantation, this entity merits more careful attention both prior to and after transplantation.

Introduction

Acute Kidney Injury (AKI) after kidney transplantation is a relatively frequent phenomenon. In a study by Nakamura et al., AKI (diagnosed using RIFLE criteria at least 3 months after a living donor kidney transplant) occurred in 20.4% of patients with 46 months of follow-up [1]. Causes can be divided into pre-renal (volume depletion, hypotension, Calcineurin Inhibitor (CNI) nephrotoxicity), renal (delayed graft function, rejection, disease recurrence, kidney transplant pyelonephritis, BK nephropathy, cytomegalovirus infection, thrombosis) and post-renal (hematoma, lymphocele, urine leak, ureteral stricture or stenosis, urinary retention due to Benign Prostatic Hyperplasia (BPH) or autonomic neuropathy, retained ureteral stents). The timing of injury often provides diagnostic clues with delayed graft function, hyperacute rejection, thrombosis, and surgical complications occurring earlier in the post-transplant period.

With the advent of highly sensitive screening technologies for anti-HLA Donor-Specific Antibodies (DSA), the implementation of kidney-paired exchange programs and the use of tacrolimus-based immunosuppression, alloimmune-mediated acute kidney injury has become less frequent in the early post-transplant period [2]. At the same time, among patients with diabetes as a cause of their ESRD who later developed allograft failure, a recent study showed that non-alloimmune causes were more common than alloimmune causes [3]. Therefore, non-alloimmune causes of post-transplant acute kidney injury remain underappreciated in contemporary kidney transplantation.

Case report

We present the case of a 60-year-old male with end-stage renal disease secondary to diabetic nephropathy, on hemodialysis since 2016, who underwent cadaveric kidney



transplantation on May 22, 2022. Past medical history was significant for morbid obesity, type 2 diabetes diagnosed in 1997, coronary artery disease, hypertension, hyperparathyroidism, BPH, and COVID-19 infection in January 2022. He underwent gastric banding in 2005 and a laparoscopic Roux-en-Y gastric bypass in March 2015 with 35 Kg weight loss. He subsequently underwent laparoscopic cholecystectomy in October 2015 for acute gangrenous cholecystitis. He also developed a 7 mm kidney stone at the left ureterovesical junction that was extracted in June 2020.

The deceased donor was a 63-year-old female with a known history of hypertension who died of a subarachnoid hemorrhage. There was no history of diabetes or tobacco use. Cold ischemic time was 14 hours and 44 minutes. The Kidney Donor Profile Index (KDPI) was 83%. Implant biopsy showed 20% glomerulosclerosis and 25% interstitial fibrosis and tubular atrophy (IFTA). The donor and recipient were both CMV IgG positive. There was no pretransplant DSA. There was 1 HLA mismatch at locus A, 2 at locus B and 2 at DR. Induction immunosuppression consisted of 2 doses of 25 mg basiliximab and pulse methylprednisolone. Maintenance immunosuppression consisted of advagraf, apo-myfortic, and prednisone.

Post-operative complications included 8 days of delayed graft function, pulmonary edema, and a type 2 NSTEMI treated medically. In early July, the patient developed significant left upper extremity edema and was diagnosed with extensive upper extremity deep vein thrombosis requiring 3 months of anticoagulation. The left jugular, brachio-cephalic, innominate, superior vena cava, and azygous veins were all involved.

Creatinine was 179 $\mu\text{mol/L}$ at discharge on June 10, 2022. Nadir creatinine was between 95–115 $\mu\text{mol/L}$.

On August 15, 2022 (almost 3 months post-transplant), the serum creatinine (measured on routine bloodwork) was 319

$\mu\text{mol/L}$ (Tables 1,2). The spot urine protein-creatinine ratio was 0.052 g/mmol. Urine culture was negative. Three weeks prior to admission lasix 20 mg twice daily was started for persistent left forearm edema. Ultrasound performed on August 1, 2022, showed mild-moderate hydronephrosis of the kidney allograft. Nonetheless, the JJ stent was removed on August 2, 2022. A follow-up ultrasound on August 4, 2022 showed persistent hydronephrosis. However, caliceal dilatation decreased from 21 mm prior to stent removal to 15 mm.

The patient was admitted to the hospital on August 16, 2022, for further investigation of his acute kidney injury. Lasix was stopped. Anticoagulation was switched to low molecular weight heparin. A Doppler ultrasound performed on admission showed a slight progression of hydronephrosis. Caliceal dilatation had increased to 19 mm. A MAG-3 renal scan performed with Lasix on August 17, 2022, showed a suboptimal, delayed response to Lasix suggestive of an obstructive etiology. Concomitant Acute Tubular Necrosis (ATN), however, could also not be completely excluded due to cortical retention of the radiotracer. Due to the severity of his AKI coupled with the results of imaging, a percutaneous nephrostomy tube was inserted on August 18, 2022. However, renal function did not improve (creatinine at 318 $\mu\text{mol/L}$ on August 18 and 338 $\mu\text{mol/L}$ on August 25). As a result, one gram total of pulse IV solumedrol was started on August 19, 2022, and administered over 4 days. A renal transplant biopsy was performed on August 23, 2022. DSA was negative. Donor-derived cell-free DNA was not performed. Screening for JC and BK viremia were negative. The percutaneous nephrostomy tube was removed on August 25, 2022.

Biopsy material was evaluated by direct immunofluorescence and light microscopy. Direct immunofluorescence was negative for IgG, IgA, IgM, C3, C1q, Kappa, Lambda, and C4d in peri-tubular capillaries. Light microscopy showed numerous intratubular crystals. These crystals were fan-shaped and clear on routine hematoxylin and eosin-stained slides (Figure 1). They were birefringent under polarized light. Epithelial

Table 1: Laboratory data at various times post-transplant. Time points include the date of admission for acute kidney injury, at 15 weeks and at 15 months post-discharge.

Blood chemistry	June 10, 2022 (discharge)	July 8, 2022	August 15, 2022 (admission)	September 1, 2022 (discharge)	December 19, 2022	November 27, 2023
Creatinine $\mu\text{mol/L}$ (ref 53-112)	179	95	319	235	135	129
Blood urea nitrogen mmol/L (ref: 3.3-8.8)	18.5	5.7	22.9	14.6	11.5	11.2
Bicarbonate mmol/L (ref: 23-34)	24	21	20	22	25	21
PTH pmol/L (ref: 1.4-6.8)				37.7	17.9	14.4
Calcium mmol/L (ref: 2.2-2.58)	2.18	2.25	2.24	2.23	2.22	2.17
Phosphorus mmol/L (ref: 0.72-1.44)	1.47	1.13	1.79	1.17	0.93	0.98
Plasma oxalate $\mu\text{mol/L}$ (ref: <1.8)			17.1			

Table 2: 24-hour urine studies during admission and at 15 weeks post-discharge.

Urine chemistry	August 30, 2022	December 12, 2022
24 hour-protein	0.72 g/day	0.53 g/day
24 hour-calcium (ref: 2.5 - 7.5 mmol/day)	0.8 mmol/day	0.9 mmol/day
24 hour-oxalate (ref: 0.08 - 0.49 mmol/day)	0.49 mmol/day	0.37 mmol/day
24 hour-citrate (ref: >150 mg/day if over 20 years of age + 7.11 mg/day/year over 20 years of age)	<20 mg/day	<20 mg/day

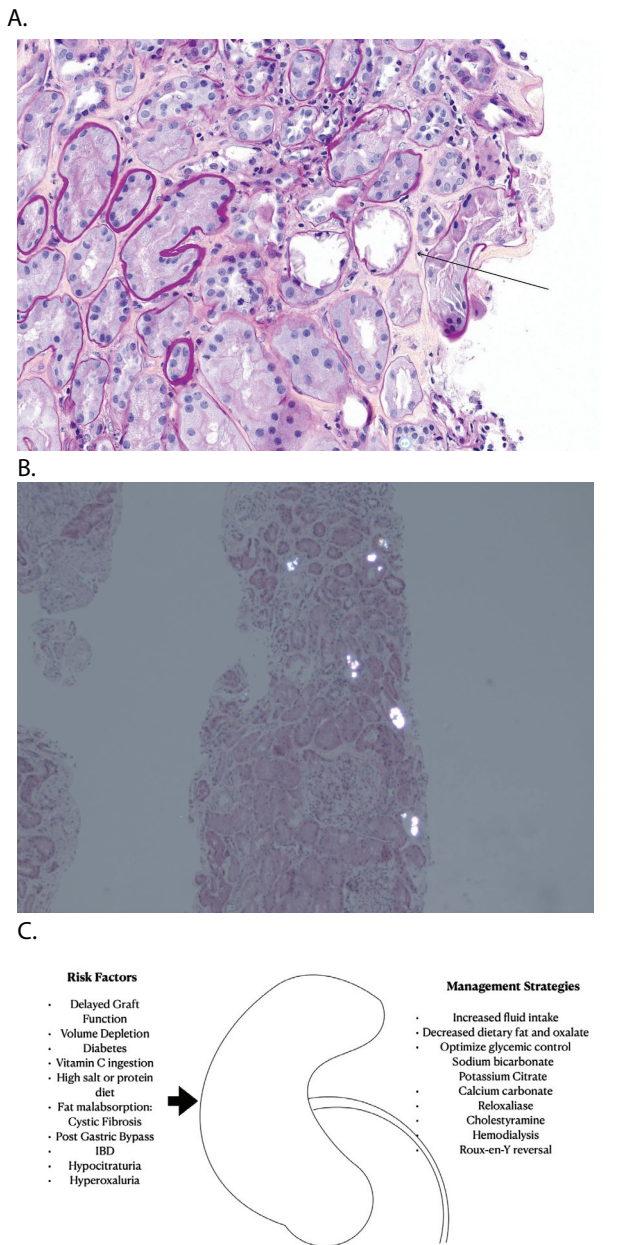


Figure 1: A. Kidney Transplant biopsy hematoxylin and eosin staining shows deposition of clear fan-shaped crystals (see arrow). B. Bright multicolored birefringence of calcium oxalate crystals under polarized light. C. A summary of risk factors and potential management strategies post-transplant. Data for use of rifaximin (a recombinant oxalate decarboxylase enzyme) and cholestyramine are limited. IBD: Inflammatory Bowel Disease.

simplification and mild interstitial inflammation were noted surrounding the crystals but there was no evidence of acute rejection. Chronic changes to the vessels and interstitium were similar to what had been described on the pre-implantation biopsy. These findings were consistent with oxalosis, which was the only explanation on this biopsy for the decreased renal function.

The patient was discharged on September 1, 2022. A diet low in oxalate-rich foods and hydration were advised. Calcium carbonate was increased to 1 gram tid with meals. Prescriptions were also provided for sodium bicarbonate (500 mg PO tid)

and potassium citrate (12.5 meq bid). Creatinine at discharge had improved to 235 $\mu\text{mol/L}$. Creatinine was 135 $\mu\text{mol/L}$ over 3 months post-discharge and 129 $\mu\text{mol/L}$ over 1-year post-discharge.

Discussion

About one-third of US adults are obese ($\text{BMI} > 30 \text{ kg/m}^2$) and obesity is an independent risk factor for CKD [4]. Approximately, 24% - 33% of all kidney diseases can be directly or indirectly attributed to obesity. Bariatric surgery is very effective in achieving sustained weight loss and improving metabolic parameters such as diabetes and hypertension. Within the CKD population, observational studies have shown that bariatric surgery is associated with a lower risk of developing stage 4 CKD or ESRD and a lower risk for eGFR decline of $> 30\%$. Furthermore, a lower risk of death and increased rate of kidney transplantation was noted among those with ESRD who underwent bariatric surgery.

Enteric hyperoxaluria develops in up to two-thirds of patients in the first year following Roux-en-Y gastric bypass [5]. Normally, orally ingested oxalate and calcium form complexes in the colon and are excreted in the feces. However, Roux-en-Y gastric bypass leads to a reduction in small bowel surface area and a concomitant increase in fatty acids in the colon. Because fatty acids preferentially bind calcium, more free, soluble oxalate is available for colonic absorption. High levels of serum oxalate can lead to hyperoxaluria, interstitial nephritis, and tubular injury and can clinically present as nephrolithiasis, acute kidney injury, oxalate nephropathy, and ESRD.

Although not the focus of this report, primary hyperoxalurias (types 1-3) are caused by mutations in genes involved in the metabolism of glyoxylate and they can have similar clinical manifestations. In the past, isolated kidney transplantation in these patients has been challenging despite the use of preventative measures such as hydration, pyridoxine, and hydrochlorothiazide [6]. Interestingly, a novel therapy against primary hyperoxaluria type 1, lumasiran, an RNA-interfering agent targeting glyoxylate oxidase, has been used to enable kidney transplantation under conditions that minimize the risk of recurrent oxalosis [7,8].

In this case, it remains unknown whether the patient was hyperoxaluric prior to kidney transplantation. The need to start renal replacement therapy shortly after his gastric bypass and his history of nephrolithiasis once on hemodialysis suggests that enteric hyperoxaluria may have contributed to ESRD progression and dialysis dependence.

Although pre-transplant dialysis, delayed graft function and a decline in renal function are known risk factors for calcium oxalate deposition post-transplant [9], kidney function, in this case, had normalised prior to the development of AKI. This suggests that factors other than DGF contributed. Diuretic-induced volume depletion, hyperglycemia, and excessive salt or animal protein intake can augment the risk of acute kidney injury secondary to oxalate deposition. Hypocitraturia is an



additional risk factor for oxalate nephropathy (citrate is an inhibitor of calcium oxalate crystallization) and was identified in more than half of patients after Roux-en-Y gastric bypass compared to BMI-matched controls [10]. In this case, both mild metabolic acidosis and citrate malabsorption may have caused lower urinary excretion of citrate. Hypocalciuria is also frequently detected following Roux-en-Y gastric bypass and plays a protective role against calcium oxalate crystallization by overriding the effects of hyperoxaluria and hypocitraturia [11]. Impaired intestinal calcium absorption is likely driving the process.

Medical management of acute oxalate nephropathy consists of increasing fluid intake, decreasing dietary oxalate and fat consumption, oral potassium citrate to correct metabolic acidosis and hypocitraturia, and oral calcium carbonate to bind oxalate in the intestinal lumen [12]. Other therapies are under investigation (Figure 1). Additional management strategies in severe cases include hemodialysis as well as a recent report describing the reversal of the Roux-en-Y bypass [13]. Four weeks after reversal, serum oxalate was reduced, hemodialysis was discontinued, renal function stabilised and a 3-month biopsy showed decreased intratubular oxalate crystal deposition.

If hyperoxaluria is diagnosed pre-transplant, oxalate levels can be reduced through intensive hemodialysis, dietary counselling, and calcium-based phosphate binders prior to renal transplantation. Furthermore, oxalate levels can be measured in the serum and urine post-transplant. However, causes of end-stage renal disease, as in this case, are often nebulous, and hyperoxaluria might only be diagnosed in the post-transplant period.

Conclusion

In today's era of kidney transplantation, wherein over 90% of patients are on tacrolimus and mycophenolate mofetil-based therapy, rejection has become a less common cause of acute kidney injury during the first year post-transplant. Instead, with a shift towards transplanting increasing numbers of patients with co-morbidities such as morbid obesity requiring bariatric surgery and diabetes, hyperoxaluria and acute oxalate nephropathy are diagnoses that need to be more carefully considered in post-transplant acute kidney injury, especially when surgical and infectious complications have been quickly ruled out.

Take home message: Acute oxalate nephropathy needs to be considered as a cause of acute kidney injury in any renal transplant recipient with a history of bariatric surgery.

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