Hyperoxaluria and Rapid Development of Renal Failure Following a Combined Liver and Kidney Transplantation: Emphasis on Sequential Transplantation

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Abstract Primary hyperoxaluria type I (PH I) is a rare genetic disorder that leads to end stage renal disease (ESRD) at an early age due to excessive deposition of calcium oxalate in the kidney. Combined liver-kidney transplantation (LKTx) has been advocated as the treatment of choice for patients with PH I who have progressive renal disease. With combined LKTx the risk of early renal failure secondary to oxalate deposition is anticipated. Here we report a patient with PH I who developed ESRD and underwent a combined LKTx. He lost the kidney graft secondary to early recurrence of oxalosis. Repeat kidney transplantation 13 months after the initial procedure was successful. Elevated plasma oxalate levels persisted for a long time following LKTx and lead to further deposition of oxalate in the second kidney graft. Combined LKTx for patients with PH I requires meticulous preparation and very careful post operative management. Sequential liver transplantation followed by kidney transplantation is to be considered for PH I patients who have ESRD and very high oxalate load.

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Introduction

Primary hyperoxaluria (PH) is a rare autosomal recessive disorder caused by distinct enzyme deficiencies that lead to an accumulation of the poorly soluble oxalate in various tissues, especially the kidney. PH I which is more common and more severe than type II is caused by deficiency of the hepatic enzyme alanine: glyoxalate aminotransferase (AGT), which is encoded by the AGXT gene. This deficiency will result in failure to transaminate glyoxylate, which will accumulate as glyoxylate and in turn will be oxidized to oxalate. A third type of PH has been recently identified (Belostotsky et al. 2010). Excessive deposition of oxalate in the kidney will lead to the formation of oxalate stones and severe interstitial nephritis. Unlike PH II and III, patients with PH I have a high risk of developing end stage renal disease (ESRD) at an early age or during early adulthood. Since the enzyme exists within the hepatic peroxisomes, liver transplantation is hoped to provide the cure by replacing the missing enzyme and correcting the underlying biochemical defect. A combined liver and kidney transplantation has been advocated in many centers as the main approach to patients with PH I who have ESRD. The outcome of this procedure has been variable. Here we report on a patient with PH I complicated by ESRD. He underwent a combined LKTx, which resulted in an early loss of the kidney graft due to excessive deposition of oxalate. The subsequent kidney transplantation was successful.

Case Report

A 20-year-old male was born to a healthy first cousin Saudi couple. His first presentation was at the age of 18 years

with symptoms of renal colics and he was found to have a serum creatinine (Cr) of 765 $\mu\text{mol/L}$ (reference range 62–105) corresponding to an estimated glomerular filtration rate (eGFR) of 8.5 ml/min. Kidney ultrasound confirmed the presence of multiple and bilateral kidney stones. He underwent several urological procedures, including nephrostomies and lithotripsy, with little effect. Stone analysis showed 100% calcium oxalate (CaOx) monohydrate crystals. His kidney biopsy revealed severe CaOx crystal deposition in the proximal and distal tubules (Fig. 1). Chemical analysis of the urine showed the following: glycolate 54 $\mu\text{g}/\text{mg}$ Cr (reference range <9), glycerate 0 $\mu\text{g}/\text{mg}$ Cr (reference range <9), oxalate 169 $\mu\text{g}/\text{mg}$ Cr (reference range <57), and glyoxylate 3.7 $\mu\text{g}/\text{mg}$ Cr (reference range <3.0). The plasma oxalate level was 87 $\mu\text{mol/L}$ (reference range <1.8). The activity of the enzyme AGT in the hepatocytes was 1.9 $\mu\text{mol}/\text{h}/\text{mg}$ proteins (reference range 19.1–47.9). Genetic study showed a homozygous c.473C>T (p.Ser158Leu) missense mutation at the AGXT gene. Both parents were confirmed to be heterozygous for the same mutation. The patient progressed to ESRD and was started on hemodialysis (HD) in September 2007. He received conventional, 4 h, thrice weekly HD aiming at a KT/V of 1.3 in addition to pyridoxine and multivitamin supplements. In December 2008, 15 months after initiation of dialysis, he underwent a combined liver and kidney transplantation from a deceased donor. The immunosuppression protocol included steroids, mycophenolate mofetil, and tacrolimus. Although the patient had an immediate kidney allograft function, his urine output dropped on the third post operative day despite hydration and he had to go back on HD. He received daily dialysis for 2 months with the hope of restoring the kidney graft function. A kidney allograft biopsy on the 47th day post transplantation showed heavy deposition of CaOx with no evidence of rejection. The liver allograft function remained very good. The patient was maintained on HD three times per week aiming at a KT/V of 1.3. Thirteen months after the initial liver and kidney transplantation, the

Fig. 1 Light microscopy of the native kidney showing extensive oxalate deposition with advanced interstitial fibrosis

patient underwent a second kidney transplantation, which was successful. The immunosuppression protocol included steroids, mycophenolate mofetil, and tacrolimus. The patient was placed on a regimen of high fluid intake, magnesium, and citrate replacement. Four months later, his creatinine started to increase and a kidney biopsy showed scattered deposition of oxalate with no evidence of rejection. The plasma oxalate levels after the liver transplantation decreased, but remained above the normal values as shown in Fig. 2. Urinary oxalate values at different time points are listed in Table 1. At 1 year following the second kidney transplantation serum creatinine was 175 $\mu\text{mol/L}$ corresponding to eGFR of 45 ml/min.

Discussion

PH I is a rare autosomal recessive disorder. It is characterized by deficiency of the hepatic peroxisomal enzyme alanine: glyoxylate aminotransferase (Hepatic AGT) that leads to overproduction and accumulation of CaOx in different tissues (Danpure 2005; Jamieson 2009). The most important affected organ is the kidney, where patients may develop nephrolithiasis, renal dysfunction, and possibly ESRD. The onset of ESRD in PH I patients varies from infancy to adolescence and possibly adulthood (Bobrowski and Langman 2008). Some patients are diagnosed late with advanced renal failure. Others may present with bilateral nephrolithiasis and get subjected to various and futile urological procedures such as lithotripsy and nephrosotomy tube insertions. Supportive therapies to prevent renal failure using pyridoxine supplementation, urinary crystallization inhibitors, and hydration have been used with variable success (Bobrowski and Langman 2008). Oxalate-degrading bacteria (probiotics) have also been tried to prevent oxalate absorption in the gut (Hoppe et al. 2005). Novel approaches using hepatocyte cell transplantation, or enzyme replacement by recombinant gene therapy may emerge in the future as the treatment of choice (Bobrowski and Langman 2006). Until now, organ transplantation of the kidney alone, LK transplantation either combined or sequential or a preemptive liver transplantation, have offered the only potential for cure (Jamieson 2009; Bobrowski and Langman 2008; Kemper 2005; Brinkert et al. 2009; Millan et al. 2003; Gagnadoux et al. 2001; Cochat et al. 2006; Jamieson and European PHI Transplantation Study Group 2005; Saborio and Scheinman 1999). The experience with organ transplantation in PH I has been variable. Recurrence of oxalosis following kidney transplantation alone is anticipated since the underlying biochemical defect is not corrected (Broyer et al. 1990). Combined LK transplantation has been advocated for patients with PH I by the European transplant registry

Fig. 2 Plasma oxalate levels at different time points in relation to liver/kidney transplantation (LK Tx)

Table 1 Hyperoxaluria urine panel before, and after the transplant procedures

	Pre-transplant (S. Cr 765)	10 months post-LK transplantation (S. Cr 722)	2 weeks post second K transplantation (S. Cr 97)
Glycolate (ref value<79)	54	9	53
Glycerate (ref value<9)	0	6	1
Oxalate (ref value<57)	169	61	342
Glyoxylate (ref value<3.0)	3.7	3.9	1.2

Values are expressed in μgm/mg creatinine

S. Cr serum creatinine expressed in μmol/L, L liver, K kidney

(Jamieson and European PHI Transplantation Study Group 2005; Broyer et al. 1990). However, a report analyzing data from the United States Renal Data System has recommended that kidney transplantation alone could be a first option for patients with PH I (Saborio and Scheinman 1999). Patients with PH I especially those of pediatric age group have significant morbidity and mortality post organ transplantation and need very careful and expertise post operative care. These patients may have a large load of oxalate that not only affects the kidneys but also other organs such as the cardiovascular system leading to significant morbidity and mortality (Mookadam et al. 2010). The large oxalate load may exert its effect on the newly transplanted kidney even in the setting of a combined LK transplantation subjecting the patients to considerable morbidity and mortality. In one report, two out of six patients with PH I who underwent organ transplantation died (Ellis et al. 2001). Recent reports have shown more favorable results for combined LKTx. For example, Millan et al. from Stanford University have reported 100% patients and organ survival among six patients with infantile PH I who received simultaneous LKTx

(Millan et al. 2003). More recently, Brinkert et al. have reported on their experience on 13 patients with PH I at the University of Hamburg, Germany (Brinkert et al. 2009). In this study, two patients who were planned for sequential transplantation died after liver surgery and prior to receiving a kidney transplant. However, those who underwent pre-emptive liver transplantation (four patients) or received combined LKTx (seven patients) had an excellent long term outcome with 100% patient survival at a median follow-up of 11.6 and 3.3 years, respectively. The organ survival was 86% and 100% for the kidney and liver grafts, respectively.

Combined LK transplantation has some advantages including subjecting patients to one rather than two surgical procedures and limiting the risk of anesthesia and post operative complications. In addition there may be some immunological advantages by transplanting both organs from the same donor. However, rapid recurrence of oxalosis in the transplanted kidney in addition to high postoperative morbidity is of a big concern. In a recent study, Harps et al. have reported that patients with PH I had a more prolonged stay in the intensive care unit following combined LKTx compared with those who had polycystic disease

(Harps et al. 2011). Patients with PH I require careful pre- and postoperative management including intense preoperative dialysis, postoperative hydration, urine alkalization, vitamin supplementation, and forced diuresis. Continuous veno-venous hemofiltration may be utilized to decrease the oxalate load and was performed routinely by the Hamburg team for the first postoperative days (Harps et al. 2011).

It is, however, important to mention that both hemo- and peritoneal dialysis do not clear oxalic acid efficiently, and secondary oxalosis is not an uncommon finding in patients undergoing dialysis (Hoppe et al. 1996; Ogawa et al. 2004; Alkhunaizi and Chan 1996).

Sequential liver followed by kidney transplantation should theoretically provide better protection of the kidney allograft. Similarly, preemptive liver transplantation has been shown recently to be effective in arresting the long-term deterioration of renal function in patients with PH I (Perera et al. 2011). The best time to do the kidney transplantation is, however, not known since the total body load of oxalate is difficult to quantify. A strategy of daily dialysis for several months using high flux membranes to reduce the oxalate load while enzyme replacement is offered by the liver graft should in theory reduce further oxalate formation and deposition. Serial measurements of plasma oxalate should aid in determining the best time of the procedure. Urinary oxalate excretion on the other hand depends on the GFR and urinary volume and may not provide a clear picture of the status of oxalate load. Due to the rarity of PH I, organ transplantation should ideally take place in a center where there is established expertise in dealing with the disease and where monitoring of both plasma and urinary oxalate levels is available.

Our patient is an example of the detrimental role of the body's oxalate load on the newly transplanted kidney despite having a simultaneous LK transplantation. Although plasma oxalate levels decreased after the initial transplantation, they were still elevated above the normal values at 17 and 21 months later. This has led to further deposition of CaOx in the second kidney graft. In addition, lack of prior experience with this disease may have contributed to the early loss of the first kidney graft.

Our patient was found to be homozygous for c.473C > T (p.Ser158Leu) missense mutation at the AGXT gene. Both of his parents were confirmed to be heterozygous for the same mutation. This mutation is known to be associated with severe enzyme deficiency. Identifying the disease-causing mutation for this family will provide a good tool to screen the remaining asymptomatic family members. Early diagnosis has the advantage of an early medical intervention and brings hope of improving the clinical outcome for those unfortunate individuals.

In conclusion, simultaneous liver and kidney transplantation carries the risk of early renal failure due to extensive oxalate deposition and requires careful pre- and postoperative management. A sequential liver followed by kidney transplantation should be considered for patients with PH I and ESRD who have a very high oxalate load.

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