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Successful Treatment of Primary Hyperoxaluria Type 2 with a Combined Liver and Kidney Transplant

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Received 20 December 2022; revised 3 March 2023; accepted 20 March 2023; published online 23 March 2023

Kidney Int Rep (2023) **8,** 1469–1472; https://doi.org/10.1016/j.ekir.2023.03.013
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INTRODUCTION

Primary hyperoxaluria type 2 (PH2) is a rare autosomal recessive disorder of endogenous oxalate overproduction caused by variants of the *GRHPR* gene. Deficiency of GRHPR enzyme activity leads to the accumulation of glyoxylate and hydroxypyruvate upstream of the deficient enzyme, resulting in hyperoxaluria. PH2 is characterized by recurrent nephrolithiasis, nephrocalcinosis, and chronic kidney disease. Progression to kidney failure has been reported in in up to 25% to 35% of patients in several large cohorts.[1,2] Liver and kidney transplantation has been widely employed in primary hyperoxaluria type 1 patients that develop kidney failure because the causative gene *AGXT* appears to be primarily expressed in the liver. However, because lower levels of GRHPR activity have been detected in extrahepatic tissues, liver and kidney transplantation has not traditionally been performed for PH2 patients with kidney failure, unlike for primary hyperoxaluria type 1.

CASE PRESENTATION

A 30-year-old African American man presented at our center for evaluation of chronic kidney disease stage 4 secondary to PH2. He had recurrent episodes of urinary stones after age 18 years requiring 4 lithotripsy procedures, but a diagnosis of PH2 was not made until genetic testing at age 28 years identified 2 pathogenic variants in *GRHPR* (c.103delG [p.Asp35Thrfs*11]; c.781_782delinsTAC [p.Gly261Tyrfs*2]). His initial serum creatinine (SCr) at our center was 4.71 mg/dl (estimated glomerular filtration rate 18 ml/min per 1.73 m^2) with a plasma oxalate (Pox) of 21.9 μmol/l (normal <2) and urinary oxalate (Uox) of 228 mg/24h (normal <41). Urinary L-glycerate-to-creatinine ratio was markedly elevated at 197 mg/g (normal <25), consistent with PH2. Abdominal imaging revealed an atrophic left kidney with several small stones on the right. Medications included potassium citrate, magnesium oxide and chlorthalidone. His kidney function progressively declined over the next 5 months at which time SCr was 8.79 mg/dl (estimated glomerular filtration rate 8 ml/min per 1.73 m^2) and Pox 28.8 μmol/l. There was no evidence of systemic oxalosis on electrocardiogram, echocardiogram, bone films, bone density, physical examination, or symptom review. Given the marked degree of hyperoxaluria and potential for recurrent oxalate nephropathy, the patient was evaluated for combined liver-kidney transplant (CLKT), which he subsequently received 6 weeks after activation on the waiting list, never requiring renal replacement therapy.

Immunosuppression consisted of antithymocyte globulin induction, and low-dose steroids, mycophenolate, and tacrolimus for maintenance. Both deceased donor allografts had good initial function and the patient did not require postsurgical hemodialysis. Pox progressively fell from 39.6 μmol/l (preoperatively) to 9.1 μmol/l (12 hours postop) and 6.8 μmol/l (36 hours postsurgery), then remained <3 μmol/l through the next 6 weeks. Correspondingly, Uox decreased to 21 mg/24h by 5 weeks after transplant (Figure 1) and urinary L-glycerate normalized to 3 mg/g Cr. SCr ranged between 1.86 and 2.01 mg/dl (estimated glomerular filtration rate 48−55 ml/min per 1.73 m^2) once stabilized after discharge (Table 1). His postoperative course was complicated by recurrent ascites,

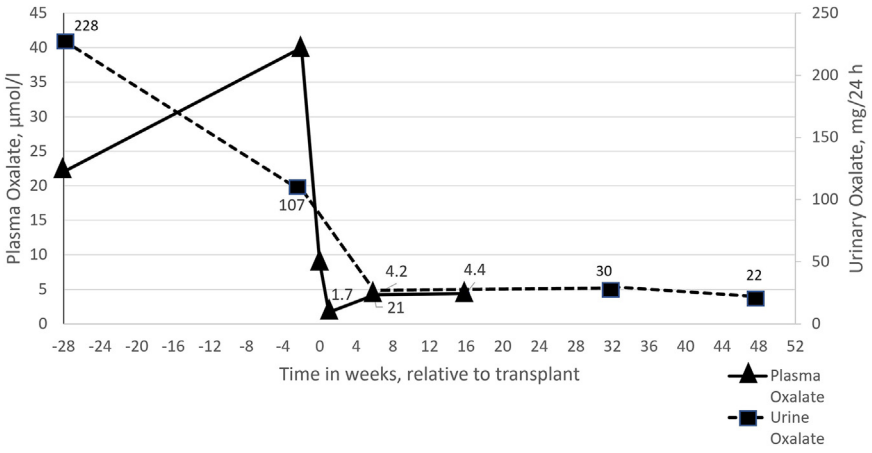

Figure 1. Changes in plasma oxalate and urinary oxalate excretion over time. Baseline UOx was 228 mg/24h, whereas POx had increased to 40 µmol/l. Both had dramatically decreased by 1 week post CLKT and remained low thereafter.

and a transjugular hepatic venogram revealed mild narrowing of the intrahepatic inferior vena cava which was managed conservatively.

At 4 months post-transplant, SCr was 4 mg/dl and Pox 4 µmol/l. Protocol renal biopsy showed mild acute tubular injury without evidence of acute cellular or antibody-mediated rejection; 2 intratubular calcium oxalate crystals were identified. Protocol liver biopsy revealed features of venous outflow impairment with centrilobular hepatocyte atrophic congestion, red cell extravasation, and patchy perisinusoidal fibrosis. The interlobular bile ducts, portal vein branches, and hepatic arterioles were intact. Because of recurrent large volume ascites accumulation, the patient underwent stenting of his inferior vena cava and hepatic vein at the time of the transjugular hepatic biopsy, with drop in the transinferior vena cava gradient from 5 to 0 mm Hg, and from 10 to 1 mm Hg across the hepatic vein. The procedure was complicated by postprocedure thrombosis of the hepatic vein stent which was successfully treated with balloon angioplasty. This was further complicated by periprocedural hemodynamic instability and oliguric acute kidney injury that required 6 days of continuous renal replacement therapy. Thereafter, kidney and liver function improved, and no further dialysis was necessary. Over the next month after discharge, the patient continued to require intermittent large volume paracentesis at a gradually decreasing frequency, at which time they were no longer required.

At the last follow-up 12 months after transplant, the patient was doing well without recurrent ascites and with increasing exercise tolerance. SCr was 1.54 mg/dl (estimated glomerular filtration rate 61 ml/min per 1.73 m^2), 24h urine oxalate excretion 22 mg, and urine L-glycerate-to-creatinine ratio was normal at <1 mg/g.

DISCUSSION

Two clinically relevant questions when it comes to liver transplantation for PH2 patients who develop chronic kidney disease are as follows: (i) Does liver transplantation correct the metabolic abnormality (does it work)? (ii) Does the benefit outweigh the risk (is it worth it)? This case, together with 2 others in the literature[3,4] informs the first question and provides additional evidence that liver transplantation provides clinically significant correction of the metabolic abnormality for this patient group, that is, significantly reduces total body oxalate generation and hence Pox and Uox. Specifically, in our patient, Pox and Uox, and therefore presumably hepatic oxalate production,

Table 1. Laboratory values before and after liver and kidney transplantation

Time in wks, relative to transplant	Plasma oxalate (normal <2 µmol/l)	Urinary oxalate (normal <41 mg/24h)	Urinary L-glycerate (normal <25 mg/g Cr)	Serum creatinine (mg/dl)
−28 (initial evaluation)	22	228	197	4.71
−2	40	107	71	10.12
0 (12 h after transplant)	9	-	-	6.72
1	1.7	-	-	1.93
6	1.5	21	4	2.16
16	4.4	-	2	4.07
32	-	29.9	-	1.42
48	-	22.0	<1	1.62

Table 2. Teaching points

Pre-kidney transplant evaluation of chronic kidney disease patients with a history of nephrolithiasis should include PH screening.
Recurrent oxalate nephropathy can result in rapid allograft failure in PH2 patients after isolated kidney transplantation.
Limited evidence now suggests that liver transplantation provides clinically significant correction of the metabolic abnormality in PH2, but it comes with significant risk of hepatobiliary complications that are associated with this procedure, as our case demonstrates.
If isolated kidney transplantation is contemplated for a PH2 patient, a regimen for treatment of the persistent hyperoxaluria and the risk for recurrent stones and oxalate nephropathy in the perioperative period and beyond is essential.

PH2, Primary hyperoxaluria type 2.

normalized rapidly after liver transplantation, and Uox and L-glycerate remained normal at 12 months posttransplant.

It should be noted that hemodialysis was needed in the 2 other reported cases of liver and kidney transplantation for PH2 because of delayed graft function, making it difficult to interpret Pox in the early postoperative period. However, no dialysis was required for our current patient in the immediate postoperative period, likely because of the prompt transplantation after onset of kidney failure that minimized the opportunity for tissue oxalate accumulation. Although PH2 patients can do well following kidney alone transplantation,[5] kidney allograft failure because of recurrent oxalate nephropathy has been reported in a significant number of cases,[3,6–8] and marked Uox excretion as in this case has been identified as a risk for kidney failure in PH patients.[9] Kidney failure can progress to graft failure in less than a year. Therefore, isolated kidney transplant might not be optimal for all PH2 patients.

This case is, to the best of our knowledge, the third report of a CLKT for PH2, and the first primary CLKT for that indication. The prior 2 CLKTs were performed after failure of an isolated kidney transplant. Uox remained normal at last follow-up in the cases reported by Dhondup *et al*. (6 years unpublished data),[3] Del Bello[4] (8 months), and this case 12 months after CLKT. All 3 cases experienced significant hepatobiliary complications, highlighting the potential risks to recipients of liver transplantation. Therefore, weighing the risks and benefits in a given patient remains important, because the question about whether CLKT is preferred to isolated kidney transplant remains an individualized one. If systemic oxalosis has developed by the time of transplantation, recurrent oxalosis in the renal allograft remains a concern with either transplant strategy; and aggressive dialysis preoperatively and postoperatively to keep Pox under the supersaturation threshold will likely be required. It is possible that small interfering ribonucleic acid (siRNA) therapies or other strategies that reduce hepatic oxalate generation in PH2 patients will negate the need for liver transplantation in this patient group in the future. This strategy can currently be considered for PH1 patients because lumasiran, a siRNA against glycolate oxidase, can effectively reduce oxalate generation in PH1 (and not PH2).[S1] Early data regarding effectiveness of siRNA agents against lactate dehydrogenase-A (LDHA) in PH2 animal models and in PH2 patients have been equivocal.[S2–S4] The current and previous case reports suggest that a strategy that effectively reduces hepatic oxalate generation in PH2 patients should be effective, and that the limited effect size of siRNA agents directed against LDHA seen in animal models and human PH2 patients to date is not because of extrahepatic oxalate generation. However, it remains possible that the pathways to oxalate generation in PH2 are incompletely understood, and that even very effective blockade of LDHA might not be sufficient to normalize oxalate generation.

CONCLUSION

The normalization of urine oxalate excretion in our patient supports the hypothesis that liver is the primary source of oxalate in PH2 and that restoration of normal hepatic GRHPR though liver transplantation can be beneficial in patients with this disease. The important teaching points of this case are summarized in Table 2.

DISCLOSURE

DSM has received consulting fees from OxThera, Dicerna, Allena, Alnylam, and Synlogic; and grant support from the NIDDK, OxThera, Dicerna, and Alnylam. JCL receives consulting fees from the American Board of Internal Medicine, Alnylam, Federation Bio, OxThera, Precision Biosciences, Cantero/Bridgebio, Dicerna, Synlogic, Orfan, Intellia, Mirium, Biomarin, and Novobiome; and grant support from Alnylam, Allena, Retrophin, Synlogic, Novobiome, OxThera, NIDDK, and Dicerna. DJS has received grant funding from Alnylam and Dicerna, as well as consulting fees from Advicenne. KMG declared no conflict of interest.

PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

ACKNOWLEDGMENTS

We thank the Rare Kidney Stone Consortium study coordinators for all their hard work on behalf of our patients.

Funding

This work is partly supported by a grant from the National Institute of Diabetes and Digestive and Kidney Diseases

(DK133171). In addition, this work was also funded by the Rare Kidney Stone Consortium (U54DK83908), which is part of Rare Diseases Clinical Research Network, an initiative of the Office of Rare Diseases Research, National Center for Advancing Translational Sciences. This consortium is funded through collaboration between National Center for Advancing Translational Sciences, and the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported by funds from the Oxalosis and Hyperoxaluria Foundation, and Mayo Foundation. Those funding the study had no role in study design, analysis, reporting, or decision to submit the manuscript for publication.

Data Availability

The data that support this study are available from the corresponding authors on reasonable request.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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