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CLINICAL CASE REPORT

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Left Lateral Sectionectomy of the Native Liver and Combined Living-Related Liver–Kidney Transplantation for Primary Hyperoxaluria Type 1

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Abstract: Primary hyperoxaluria type I (PH1), the most severe form of primary hyperoxalurias, is a liver disease of the metabolic defect in glyoxylate detoxification that can be corrected by liver transplantation. A 21-year-old man presented to our center after 4 months of regular hemodialysis for kidney failure caused by nephrolithiasis. A diagnosis of PH1 was confirmed by mutations of the *AGXT* gene. Left lateral sectionectomy of the native liver was performed; and auxiliary partial orthotopic liver transplantation (APOLT) and kidney transplantation were carried out synchronously using a living donor. After transplantation, the patient's plasma oxalate and creatinine levels substantially decreased and the patient recovered well with good dual grafts function. APOLT and kidney transplantation can compensate the liver deficient in liver enzyme production and aid the renal elimination of oxalate, thus serving as an effective treatment option for patients with PH1. In conclusion, left lateral sectionectomy of the native liver and combined living-related liver–kidney transplantation can be a surgical option for PH1.

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Abbreviations: AGT = alanine glyoxylate aminotransferase, APOLT = auxiliary partial orthotopic liver transplantation, PH1 = primary hyperoxaluria type 1.

INTRODUCTION

Primary hyperoxaluria type I (PH1) is an autosomal recessive genetic disorder of primary hyperoxalurias that occurs when a deficiency of alanine glyoxylate aminotransferase (AGT) leads to the endogenous overproduction of oxalate. Oxalate is the least soluble of all calcium salts; therefore, if present in excess, oxalates may solidify and cause end-stage renal disease that requires organ replacement therapy. Simultaneous or sequential liver–kidney transplantation have been performed in patients with PH1 using organs from deceased and living donors[1,2]; more recently, combined partial liver and renal replacement has been undertaken to correct the enzymatic deficit associated with PH1. To the best of our knowledge, 3 case reports have described simultaneous auxiliary partial orthotopic liver transplantation (APOLT) and kidney transplantation for PH1.[3–5] This is the first report of adult-to-adult APOLT and kidney transplantation performed using double grafts from a living donor.

CASE PRESENTATION

A 21-year-old man was referred to our center following 4 months of hemodialysis due to kidney failure. He had previously been diagnosed with PH1 at another hospital, where he had undergone molecular genetic testing that confirmed the mutations of the *AGXT* gene at the following sites: *c.346G>A(p.Gly116Arg)*, *c.823_824dupAC(p.Ser275ArgfsX38)*.[6] His plasma oxalate level was 24 μmol/L, and the results of imaging tests showed calculi in both the kidneys. His older brother had died years earlier because of kidney failure, the suspected cause of which was PH1. The patient's oxalate level reduction was partially responsive to pyridoxine therapy. Oxalosis was not detected outside 2 kidneys, defined less severe despite high plasma oxalate level. His liver function was unremarkable and liver anatomy was normal.

Based on the higher risk associated with whole liver replacement and the potential for a novel therapeutic breakthrough, we decided to perform APOLT rather than whole liver replacement. In China, not all people opt for organ donation after cardiac or brain death and live donation holds an advantage over deceased donation in terms of graft quality. The patient weighed 65 kg, which was similar to his mother's weight of 63 kg. The patient provided written, informed consent, and the operation was approved by the hospital's organ transplantation ethics committee. On confirmation of ABO compatibility, the patient's mother donated her left liver and right kidney. We used an in situ splitting technique to harvest the left liver (weight 450 g) without the middle hepatic vein and to harvest the right kidney. The donor's operation was uneventful, total blood loss was about 300 mL, and the course of her recovery was excellent.

The recipient underwent left lateral sectionectomy of his native liver, followed by implantation of the donor's graft. The donor's left hepatic vein was anastomosed with the recipient's inferior vena cava; the recipient's left portal vein and left hepatic artery were connected to the donor's corresponding sites, hepaticohepaticostomy with a T tube was conducted for biliary reconstruction. The weight of the excised left lateral section was 430 g. When implantation of the liver graft was completed, the diseased right kidney was removed and the donor kidney was orthotopically transplanted; the ureteroureterostomy was performed and a double-J stent was placed in the

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TABLE 1. Postoperative Values of Oxalate and Creatinine

Postoperative Time	31 d	55 d	6 mo	12 mo	18 mo	26 mo
Plasma oxalate, μmol/L	4.4	4.1	2.7	1.9	1.2	1.2
Plasma creatinine, mg/dL	1.1	1.2	1.1	1.0	1.3	1.2
Urinary oxalate, μmol/h	13.7	12.8	12.2	10.9	10.6	10.8

Reference range. Plasma oxalate: 0.4–3 μmol/L; Plasma creatinine: 0.7–1.3 mg/dL; Urinary oxalate: <20 μmol/h.

ureter where it remained for 2 months. Total blood loss from the procedure was estimated to be about 400 mL.

The patient's immunosuppressive regimen included an induction dose of basiliximab and maintenance therapy consisting of the following: prednisone (1 mg/kg, tapered by 10 mg each week down to 10 mg and discontinued after 3 months); mycophenolate mofetil (1 g orally twice a day, discontinued after 6 months); and tacrolimus (0.025 mg/kg, started on day 4 posttransplantation, and maintained at a trough level of 8–12 ng/mL for 3 months followed by a trough level of 5–7 ng/mL). Hyperhydration, pyridoxine, magnesium, and potassium citrate were also administered.

The partial liver and renal grafts functioned well following transplantation (Table 1). Volumetric analysis of the graft was performed by computerized tomography at 3 time points: 1 week before transplantation; 55 days and 15 months after transplant. The graft to whole liver volume ratios were 18.1%, 16.9%, and 17.9%, respectively, and the graft was small relative to the entire liver (Figure 1A and B).

DISCUSSION

PH1 is a monogenic metabolic disorder of the liver that can be, in theory, cured when a liver transplantation reestablishes the normal production of AGT. Whole or partial liver replacements have been reported as treatments for PH1. Whole liver transplantation has been proven to correct the enzyme deficiency[7,8]; however, the procedure has several disadvantages. For example, use of a whole liver allograft carries substantial risk of graft loss due to immunological or nonimmunological insults. Moreover, removal of a patient's whole liver poses a significant physiopsychological burden, which may be unnecessary when the structure and functions of the native liver are completely normal except for an enzyme deficit. Additionally, patients tend to be very young, often below the age of 30; the 5-year survival rate is about 62% for combined whole liver and kidney transplantations.[9–11] In the event of graft failure, retransplantation is the only choice. Finally, there is a large gap between the finite donor supply of whole livers and growing recipient demand. Therefore, APOLT may be preferable to whole liver transplantation while preserving most native liver mass and reducing the risk of future liver failure[3,12] (Table 2).

The exact amount of graft volume needed for supporting metabolic needs has not been established; however, approximately 20% to 30% of the whole liver (Sg2, 3) was transplanted according to the previous reports, and this was sufficient to support enzyme production in cases of metabolic disease.[3] In our case, the graft to whole liver ratio was <20%. Oxalate levels decreased due to added liver tissue, pyridoxine response, renal graft excretion, and the fluid environment (pH 6.2–6.8) from potassium citrate.

APOLT is a controversial treatment option for PH1. Trotter and Milliner[13] assumed that APOLT is ineffective and a risky procedure. In their understanding of PH1, the genetically altered liver produces abnormal amounts of oxalate that is excreted by the kidneys as the only route of elimination of oxalate. The excessive amount of oxalate overwhelms renal excretion leading to stone formation and kidney failure. Based on this understanding, the addition of extrahepatic tissue through auxiliary transplant would have no real biological effect on PH1 because the genetically abnormal native liver will continue to produce excess oxalate. This contention merits further research. Trotter and Milliner[13] do not account for the fact that APOLT and kidney transplantation have resulted in improved hyperoxaluria in PH1 patients.[3,4] We theorize that the added partial liver tissues delicately regulate the excess

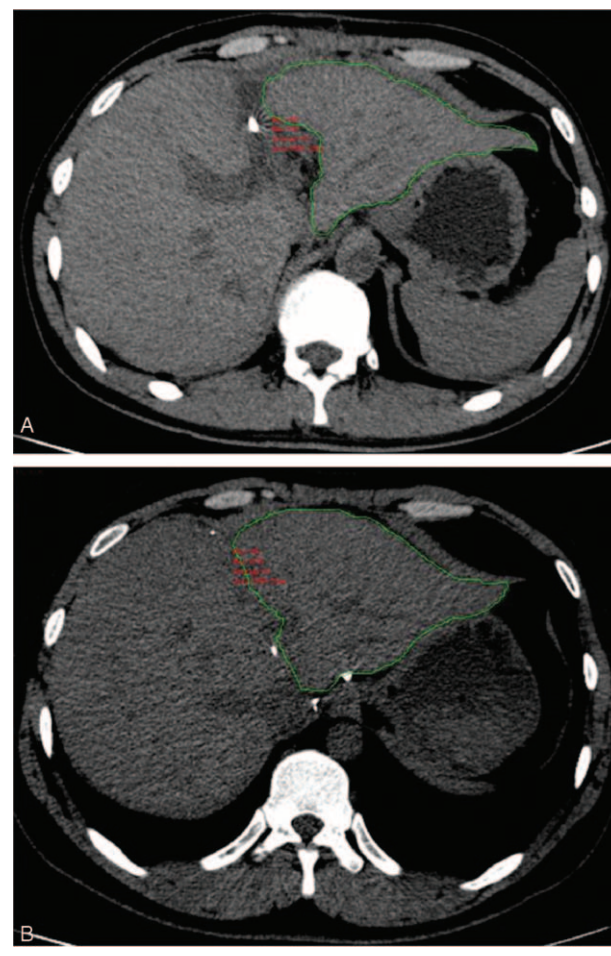

FIGURE 1. Enhanced computed tomography scan of native liver and graft. (A) Two months after the transplant. (B) Fifteen months after the transplant, no difference in the graft size is noted.

TABLE 2. Advantage and Disadvantage of Full and Partial Liver Replacement for PH1

	Full Graft	Partial Graft
Oxalate producing	No	Yes
Ethic issue	Great	Small
Donor pool	Shrink	No effect
Complemented therapy	No need	Need
Alternatives (on graft loss)		
Retransplantation	Only	Many
Cell transplantation	No	Yes
Hemodialysis	No	Yes
Others	No	Yes*

PH1 = primary hyperoxaluria type I. Complemented therapy: pyridoxine, hyperhydration, and magnesium and potassium citrate.
* Gene therapy, *Oxalobacter formigenes*, etc.

glyoxylate that is converted to glycolysis or the tricarboxylic acid cycle via pyruvate, so there is less conversion to toxic oxalate; this is desirable as it occurs in line with energy needs and body function, and as a result, production of oxalate decreases.[14] It should be noted that AGT activity testing was not available due to invasive sample acquisition.

It has also been reported that APOLT may cause the native liver remnant to compete with the graft for sufficient blood supply, leading potentially to atrophy. Research conducted at Kyoto University suggested that this phenomenon was frequently encountered, and thus transection of portal flow to the native liver was performed preemptively.[15] Conversely, a survey of APOLT practices in several European centers found that this phenomenon was not observed in many patients, and portal diversion was never used.[16] In our case, we maintained the portal blood flow to the native liver, and there was no evidence of problems with the portal flow steal phenomenon. A careful review of the cases in Kyoto revealed frequent immune rejection events, and durable rejection will damage the liver sinusoids. As resistance to portal flow increases, blood flow to the graft decreases, so hepatofugal flow is the result of durable immunologic insults. Portal flow diversions may, we think, have worked as a salvage option when grafts started to lose function and atrophy.[4] In our case, partial liver graft volume was stable after 28 months.

Standard renal transplantation is performed in the iliac fossa to monitor the renal graft, and binephrectomy is performed primarily or in 2-stage fashion for PH1 to prevent pain, potential infection, and de novo carcinoma of the native kidneys and ureters. For our case, the right kidney was excised out and the renal graft was orthotopically transplanted due to fewer traumas, whereas the left native kidney was kept intact for future nephrectomy (although the patient declined due to no discomfort). We propose that optimal immunosuppressive therapy or the protective effect of the simultaneous liver graft on the kidney will greatly decrease immunological rejection episodes. Concurrently, biopsy is easily guided and performed with ultrasound. After close follow-up of the patient for 28 months, no episodes of renal graft rejection occurred. In conclusion, combined APOLT and kidney transplantation can be an effective alternative treatment for PH1, especially for younger patients.

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