Primary Hyperoxaluria: Simultaneous Combined Liver and Kidney Transplantation from a Living Related Donor

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Primary hyperoxaluria type 1 (PH1) is a rare inherited metabolic disorder in which deficiency of the liver enzyme AGT leads to renal failure and systemic oxalosis. Timely, combined cadaveric liver-kidney transplantation (LKT) is recommended for end-stage renal failure (ESRF) caused by PH1; however, the shortage of cadaveric organs has generated enthusiasm for living-related transplantation in years. Recently, successful sequential LKT from the same living donor has been reported in a child with PH1. We present a sister-to-brother simultaneous LKT in a pediatric patient who suffered from PH1 with ESRF. Twelve months after transplantation, his daily urine oxalate excretion was decreased from 160 mg to 19.5 mg with normal liver and renal allograft functions. In addition to the well-known advantages of living organ transplantation, simultaneous LKT may facilitate early postoperative hemodynamic stability and may induce immunotolerance and allow for low-dose immunosuppression. (*Liver Transpl 2003;9:433-436.*)

Primary hyperoxaluria type 1 (PH1) is a rare, inherited metabolic disorder caused by a deficiency of the liver-specific peroxisomal alanine-glyoxylate aminotransferase (AGT). It is characterized by increased synthesis and urinary excretion of oxalate that leads to renal failure attributable to urolithiasis, nephrocalcinosis, and, subsequently, to oxalate accumulation in various extra-renal tissues such as the skeleton and the cardiovascular system. Because the liver is the site of the metabolic defect, isolated kidney transplantation (KT) is not a reasonable therapeutic alternative because of a rapid diffuse oxalate deposition in the allograft.[1] Preemptive liver transplantation (LT) has been successfully performed in some children before serious renal damage occurred.[2] If end-stage renal failure (ESRF) has been reached, early simultaneous or sequential liver-KT (LKT) may avoid the deleterious consequences of systemic oxalosis.[3]

Shortage of donor organs remains the critical factor limiting the use of organ transplantation. This shortage has generated enthusiasm for living-related transplantation, offering hope not only for children but also for adolescents and even adults. Partial LT alone or sequential LKT from living donors have been successfully performed for PH1.[4,5] To date, there have been no reports describing combined simultaneous LKT from the same living donor in the treatment of PH1 complicated with ESRF.

Case

A 9-year-old boy (32 kg) with hyperoxaluria, nephrocalcinosis, and urinary tract infection progressed to ESRF, with a glomerular filtration rate (GFR) of 18 mL/min/1.73 m^2 despite maximal medical management; he commenced dialysis in September, 2001. His older brother (20 years old) had died of severe systemic oxalosis and uremia waiting for a suitable combined cadaveric donor. His sister (19 years old, 65 kg) decided to share a part of her liver and right kidney with her younger brother. Her evaluation revealed no physical or psychologic contraindication for surgery. They were both haplotype-identical siblings. In the recipient, pretransplant assessment of cardiac function revealed no significant abnormalities, and no major site of oxalate accumulation was determined.

In November, 2001, after 3 consecutive days of hemodiafiltration, sister-to-brother, combined, right-kidney and left-liver (segments 2-3-4) transplantation was performed. Simultaneously with the hepatectomy

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in the donor, vena cava sparing hepatectomy and binephrectomy was performed in the recipient. The left-liver allograft (420 g) was transplanted orthotopically with 95 minutes of cold ischemia (graft weight/body weight ratio: 1.3%). The arterial anastomosis was performed with 9/0-suture material and a surgical microscope. Biliary reconstruction was established by Roux-en-Y bilio-enteric anastomosis. After implantation of the left liver graft and assuring optimal hemodynamic and biochemical stability of the recipient, the right kidney of the donor, which was already dissected but left in situ, was procured and transplanted in the left iliac fossa of the recipient. Both allografts started to function immediately after reperfusion. Two units of autologous packed red blood cells were transfused during the donor operation. The early postoperative period for the donor and the recipient was uneventful.

Immunosuppression was consisted of cyclosporine A (induction with 2 mg/kg/d intravenously, then maintenance dose of 5 mg/kg/d PO-Neoral; Novartis Pharma AG, Basel, Switzerland), prednisolone (starting with 1 mg/kg/d and tapering to 10 mg/d), and mycophenolate mofetil (500 mg twice per day). The average whole-blood trough levels of cyclosporine (mean ± SD) were 211 ± 58 ng/mL, 216 ± 41 ng/mL, and 188 ± 54 ng/mL during the first month, first 6 months, and last 6 months, respectively. No episode of acute rejection was encountered. The donor was discharged home without any complication by the end of the first postoperative week and she had an uneventful follow-up thereafter. The recipient received hyperhydration (urine output, 2,800 ± 350 cc/d) and suppression treatment for oxalate precipitation (thiazide, pyridoxine, and magnesium) starting immediately after LKT. The urine oxalate excretion was decreased gradually from 5 mg/kg to 0.67 mg/kg/24 hours during the 12 months after transplantation (Table 1). Renal ultrasound revealed no sign of oxalate accumulation, and the recent resistive index in parenchyma was measured as 0.58.

Discussion

In the treatment of PH1, long-term graft survival cannot be achieved after KT. Because of ongoing enzyme defect and oxalate accumulation, approximately 50% to 80% of kidney grafts fail within 3 years after transplantation.[1,3] On the other hand, isolated orthotopic LT may be considered to establish AGT activity in patients with residual renal function.[2] However, in this situation, the timing of LT is not clear. Tissue oxalate accumulation has shown to accelerate when GFR is less than 40 mL/min/1.73 m^2,[7] but the course of renal disease is hard to predict in PH1. Thus, LT is recommended when the GFR is between 40 to 60 mL/min/1.73 m^2 and the disease is following an aggressive course.[2] However, even when oxalate production is normalized after liver transplant, it might be difficult to achieve a negative oxalate balance because of marginal renal function.

If ESRF has occurred, combined LKT was recommended with 5-year patient and graft survival rates of 72% and 62%, respectively.[3] This may correct the enzyme defect and enables optimal oxalate excretion by a functioning kidney allograft. However, in patients with severe systemic oxalosis, the amount of mobilized oxalate after surgery is large and can oversaturate the urine and threaten the transplanted renal graft. Thus, some authors have suggested performing the LT first, followed by the KT after a period of intense hemodialysis to reduce tissue stores of calcium oxalate.[6] In contrast, others have advocated early combined LKT, even before the onset of frank renal failure, to minimize the amount of tissue oxalate that needs to be mobilized after transplantation.[8,9] In addition, being the most effective route for oxalate removal, a functioning renal graft greatly simplifies the postoperative management in a LKT recipient in terms of maintenance of body fluid balance and hemodynamic stability. In contrast to sequentially performed LKT, simultaneous procedure also avoids the need of long-term hemodialysis and the

Table 1. Postoperative Liver and Kidney Graft Function

Postoperative days	1	3	7	15	30	60	120	240	300
AST (U/L)	102	45	34	27	24	22	24	23	21
Bilirubin (mg/dL)	0.99	0.93	0.93	0.87	0.8	0.76	0.82	0.56	0.62
PT (sec)	38	18.2	20.6	17.4	14.6	12.5	12.3	12.1	12.8
BUN (mg/dL)	24.5	8	21	16.7	18.7	16.5	14.2	11.4	12.4
Creatinine (mg/dL)	2	0.6	0.5	0.8	1.2	1	0.9	0.8	0.8
Oxalate (mg/24 h urine)	160	133	147	58	51	48	44	27	21

associated risk of septic complications. Furthermore, there is an immunologic advantage because the liver graft evidently has the potential to protect a simultaneously transplanted kidney from rejection.[10,11]

In the present case, the donor and the recipient are both haplotype-identical siblings. However, unlike in KT, the effect of human leukocyte antigen (HLA) compatibility on LT outcome is controversial.[12-15] Because the data are obtained from cadaveric, mostly unrelated donor LTs, the introduction of living-related liver transplantation (LRLT) provides an opportunity to study the results of better matched transplants. The higher success rate in children with related-donor LT compared with unrelated or cadaveric liver transplants suggested an important role of histocompatibility in LT.[16] Recently, prospective analysis of the recipients transplanted with grafts from one or both haplotype-identical parents has shown better graft survival and the possibility to withdraw immunosuppression in the 0-mismatch group.[17] On the other side, some authors emphasized the potential risk of fatal graft-versus-host disease in transplantation from a homozygous donor.[17-19] Thus, the use of pretransplant tissue typing in LRLT was recommended to detect and avoid transplant from a homozygous donor with a complete one-way donor-to-recipient HLA match.

In the embarrassing environment of organ shortage, living-related organ transplantation has emerged as a reasonable therapeutic alternative. Therefore, in addition to cadaveric LT, we have started to perform LRLT. As we reported in previously, LRLT has proven to be a safe procedure for the donor and beneficial for the recipient.[20] This patient with PH1 and ESRF is the first case reported in whom simultaneous combined LKT was performed from the same living donor. Recently, sequential LKT from same living donor was reported in three children with chronic liver disease and renal failure.[5] The authors have advocated postponing KT until the clinical condition and liver function have become stabile. Finally, a simultaneous combined LKT from a same living donor for a patient with rapidly deteriorating hepatitis B virus cirrhosis and ESRF has been reported.[21] Although the recipient has died of postoperative complications, the authors have found that the use of organs from living donors acceptable for patients who otherwise would die because of the shortage of cadaver organs.

To date, early combined LKT is the optimal treatment in PH1 complicated with ESRF. It avoids the adverse effects of a prolonged period of dialysis with systemic deposition of oxalate. In midst of cadaveric organ shortage, simultaneous combined LKT from a living-related donor may be a reasonable therapeutic alternative in patients with PH1. We believe that, in this particular case, logistic and immunologic advantages of timely performed simultaneous combined LKT from a living related HLA-identical donor may provide optimum chance for long-term recipient and graft survival. In addition, with a regimen of low-dose cyclosporine and rigorous hydration, the simultaneously transplanted renal allograft could excrete oxalate maximally and achieve a negative oxalate balance.

References

1. Scheinman JI, Alexander M, Campbell ED, Chan JC, Latta K, Cochat P. Transplantation for primary hyperoxaluria in the USA. Nephrol Dial Transplant 1995;10(Suppl 8):42-46.
2. Cochat P, Scharer K. Should liver transplantation be performed before advanced renal insufficiency in primary hyperoxaluria type 1? Pediatr Nephrol 1993;7:212-218.
3. Jamieson NV. The results of combined liver/kidney transplantation for primary hyperoxaluria (PH1) 1984-1997. The European PH1 transplant registry report. European PH1 Transplantation Study Group. J Nephrol 1998;11(Suppl 1):36-41.
4. Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben-Ari Z, Bar-Nathan N, et al. Primary hyperoxaluria type 1: Improved outcome with timely liver transplantation: A single-center report of 36 children. Transplantation 2001;72:428-432.
5. Nakamura M, Fuchinoue S, Nakajima I, Kitajima K, Tojimbara T, Takasaki K, et al. Three cases of sequential liver-kidney transplantation from living-related donors. Nephrol Dial Transplant 2001;16:166-168.
6. Yamauchi T, Quillard M, Takahashi S, Man NK. Oxalate removal by daily dialysis in a patient with primary hyperoxaluria type 1. Nephrol Dial Transplant 2001;16:2407-2411.
7. Barratt TM, van't Hoff WG. Are there guidelines for a strategy according to glomerular filtration rate, plasma oxalate determination and the risk of oxalate accumulation? Nephrol Dial Transplant 1995;10(Suppl 8):22-23.
8. Watts RWE, Danpure CJ, De Pauw L, Toussaint C. European Study Group on Transplantation in Hyperoxaluria Type 1. Combined liver-kidney and isolated liver transplantation for primary hyperoxaluria type 1: The European experience. Nephrol Dial Transplant 1991;6:502-511.
9. Ellis SR, Hulton SA, McKiernan PJ, Goyet JV, and Kelly DA. Combined liver-kidney transplantation for primary hyperoxaluria type 1 in young children. Nephrol Dial Transplant 2000; 16:348-354.
10. Rasmussen A, Davies HF, Jamieson NV, Evans DB, Calne RY. Combined transplantation of liver and kidney from the same donor protects the kidney from rejection and improves kidney allograft survival. Transplantation 1995;59:919-921.
11. Jeyarajah DR, McBride M, Klintmalm GB, Gonwa TA. Combined liver-kidney transplantation: What are the indications? Transplantation 1997;64:1091-1096.
12. Thorogood J, van Houwelingen JC, van Rood JJ, Zantvoort FA, Schreuder GM, Persijn GG, et al. Factors contributing to long

term kidney transplant in Eurotransplant. Transplantation 1992;54:152-158.
13. Donaldson PT, Alexander GJ, O'Grady J, Neuberger J, Portmann B, Thick M, et al. Evidence for an immune response to HLA class I antigens in the vanishing-bile duct syndrome after liver transplantation. Lancet 1987;1:945-948.
14. O'Grady JG, Alexander GJ, Sutherland S, Donaldson PT, Harvey F, Portmann B, et al. Cytomegalovirus infection and donor/recipient HLA antigens: Interdependent co-factors in pathogenesis of vanishing bile duct syndrome after liver transplantation. Lancet 1988;2:302-305.
15. Nikaein A, Backman L, Jennings L, Levy MF, Goldstein R, Gonwa T, et al. HLA compatibility and liver transplant outcome. Transplantation 1994;58:786-792.
16. Emond JC, Heffron TG, Kortz EO, Gonzales-Vallina R, Contis JC, Black DD, et al. Improved results of living related liver transplantation with routine application in a pediatric program. Transplantation 1993;55:835-840.
17. Kasahara M, Kiuchi T, Uryuhara K, Uemoto S, Fujimoto Y, Ogura Y, et al. Role of HLA compatibility in pediatric living-related liver transplantation. Transplantation 2002;74:1175-1180.
18. Martin PJ, Petersdorf EW, Anasetti C, Hansen JA. HLA homozygosity and the risk of graft-versus-host disease. Tissue Antigens 1997;50:119-123.
19. Whitington PF, Rubin CM, Alonso EM, McKeithan TW, Anastasi J, Hart J, et al. Complete lymphoid chimerism and chronic graft-versus-host disease in an infant recipient of a hepatic allograft from an HLA-homozygous parental living donor. Transplantation 1996;62:1516-1519.
20. Astarcıoglu I, Karademir S, Coker A, Astarcıoglu H. Transplantation of the right liver lobe from a living donor to an adult recipient. J Clin Exper Surg 1999;7:153-158.
21. Haberal M, Abbasoglu O, Buyukpamukcu N, Bilgin N, Telatar H, Simsek H, et al. Combined liver-kidney transplantation from a living-related donor.Transplant Proc 1993;25:2211-2213.