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ORIGINAL ARTICLE

Maternal grafts protect daughter recipients from acute cellular rejection after pediatric living donor liver transplantation for biliary atresia

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Keywords
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Summary

Some studies have found that gender mismatch between donors and recipients are related to poor graft prognosis after liver transplantation. However, few studies have investigated the impact of gender mismatch on acute cellular rejection (ACR) in pediatric living donor liver transplantation (LDLT). This retrospective study investigated the clinical significance of these factors in ACR after pediatric LDLT. Between November 2001 and February 2012, 114 LDLTs were performed for recipients with biliary atresia (BA) using parental grafts. We performed univariate and multivariate analyses to identify the factors associated with ACR. The donor–recipient classifications included mother donor to daughter recipient (MD; $n = 43$), mother to son ($n = 18$), father to daughter (FD; $n = 33$), and father to son (n = 20) groups. The overall incidence rate of ACR in the recipients was 36.8%. Multivariate analysis showed that gender mismatch alone was an independent risk factor for ACR ($P = 0.012$). The FD group had a higher incidence of ACR than the MD group ($P = 0.002$). In LDLT, paternal grafts with gender mismatch were associated with a higher increased incidence of ACR than maternal grafts with gender match. Our findings support the possibility that maternal antigens may have an important clinical impact on graft tolerance in LDLT for patients with BA.

Introduction

The impact of gender mismatch between donors and recipients on the outcome of liver transplantation (LT) appears to be controversial. Although some reports have indicated that gender mismatch has an impact on graft failure, specifically in male recipients receiving grafts from female donors in deceased donor LT [1–4], Lehner *et al.* [5] have reported that gender mismatch does not play a role in the outcome of LT. Recently, Yoshizumi *et al.* [6] reported that a male recipient receiving a graft from a female donor was an independent risk factor for recipient mortality in adult living donor liver transplantation (LDLT). In contrast, in pediatric LDLT, Nijagal *et al.* [7] reported that recipients of maternal grafts had lower rates of graft failure and refractory rejection than recipients of paternal grafts. Thus, the impact of gender mismatch between donors and recipients on graft prognosis may differ among deceased donor LT, adult LDLT, and pediatric LDLT.

Biliary atresia (BA) is a severe cholestatic disease of unknown etiology in neonates. If untreated, it progresses

to cirrhosis, end-stage liver disease, and death by 2 years of age [8]. Although the initial surgical treatment for BA is an early Kasai portoenterostomy to establish bile flow to the gastrointestinal tract [9,10], LT is indicated in cases where Kasai portoenterostomy fails or is not feasible. Recently, maternal chimerism has been demonstrated in the liver of patients with BA, suggesting a possible role of maternal cells in disease pathogenesis [11–15]. Induction of tolerance by microchimerism in the field of organ transplantation was first proposed by Startzl *et al.* [16]. Although microchimerism may cause tolerance resulting in acceptance of an allograft bearing antigens shared by the microchimeric cells, a functional linkage between microchimerism and tolerance has been difficult to establish [17,18]. Maternal microchimerism in blood and various organs has been found to be directly correlated with non-inherited maternal antigens [19,20], and exposure to maternal antigens can have tolerogenic effects on offspring, resulting in acceptance or rejection of allografts expressing the maternal antigens [21]. Therefore, LDLT for pediatric patients using parental grafts and for patients with BA who may have increased levels of maternal chimerism may be used to examine the role of maternal microchimerism in graft tolerance or the effect of a maternal graft on graft outcome after LT.

Few studies have investigated the role of gender matching and the use of parental donors in acute cellular rejection (ACR) in the field of pediatric LDLT for patients with BA [7]. This retrospective study investigated the impact of these factors on ACR after pediatric LDLT and the impact on graft tolerance in maternal LDLT for patients with BA.

Patients and methods

Patients

Between November 2001 and February 2012, 114 ABO-identical and ABO-compatible LDLTs were performed in pediatric BA recipients using parental liver grafts at the Department of Transplant Surgery, Jichi Medical University, Japan. The baseline demographic data pertaining to the recipients, donors, and grafts are presented in Table 1. In comparison, 39 ABO-identical and ABO-compatible LDLTs were performed for other original diseases using parental liver grafts in the same period. The original diseases were ornithine transcarbamylase deficiency in 11, Alagille syndrome in 9, fulminant hepatic failure in 3, congenital extrahepatic portosystemic shunt in 3, Wilson disease in 2, primary sclerosing cholangitis in 2, neonatal hemochromatosis in 2, liver cirrhosis in 2, Byler disease in 1, cystic fibrosis in 1, carbamoyl phosphate synthetase 1 deficiency in 1, hepatoblastoma in 1, and citrullinemia in 1 patient. The ABO blood types were identical in 29 patients and compatible in 10.

Table 1. Demographic data for recipients and donors and grafts.

Recipient characteristics	
Gender	Male: 38; Female: 76
Age (months)	14 (5–234)
Body weight (kg)	9.5 (5.8–59)
PELD or MELD	9.9 (−14.3–37.3)
Operation time	15 h 07 min (7 h 02 min–37 h 10 min)
Cold ischemic time	2 h 06 min (25 min–16 h 19 min)
Warm ischemic time	1 h 00 min (30 min–4 h 27 min)
Blood loss volume (ml/kg)	81.1 (1.6–760.1)
Transfusion volume (ml/kg)	91.6 (0–471.2)
Donor and graft characteristics	
Gender	Father: 53; Mother: 61
Age (years)	34 (23–54)
ABO compatibility	Identical: 91; compatible: 23
GV/SLV (%)	74.0 (33.0–130.0)

PELD, pediatric end-stage liver disease; MELD, model for end-stage liver disease; GV/SLV, ratio of graft volume to standard liver volume.

Immunosuppressive therapy

Tacrolimus (Tac) and methylprednisolone (MP) were used as the standard postoperative immunosuppressive therapy for ABO-identical or ABO-compatible LDLT. The target trough level of Tac was 15–20 ng/ml during the first week, 8–12 ng/ml during the first month, 5–8 ng/ml during the first six months, 3–5 ng/ml during the first year, and 2–4 ng/ml thereafter. Recipients with encephalopathy or nephropathy associated with Tac were converted to cyclosporine A (CsA). MP was administered at an initial dose of 20 mg/kg intravenously on the morning of the operation and before graft reperfusion. The MP dose was thereafter decreased gradually to 3 mg/kg/d on postoperative day (POD) 1, 0.5 mg/kg/d on POD 7, and 0.25 mg/kg/d at one month post-LDLT, and MP was discontinued within one year, except in patients for whom immunosuppression could not be maintained at the lower dose. Mycophenolate mofetil (MMF) was used when more potent immunosuppression was required, for example, in recipients with steroid-resistant ACR episodes and recipients with liver dysfunction following the cessation of MP therapy.

Diagnosis of ACR

All episodes of ACR were diagnosed on the basis of pathological examinations of liver biopsy samples. In all specimens, the diagnosis of ACR was evaluated by highly experienced pathologists according to the Banff scheme [22]. The degree of portal infiltration by lymphocytes, bile duct inflammation or damage, and venous endothelial inflammation as stipulated in the Banff scheme was evaluated using the rejection activity index (RAI). Liver biopsy was indicated when any liver function parameter (viz.,

aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, and total bilirubin levels) showed an abnormal value suggesting ACR. There were no protocol liver biopsies.

Donor and recipient gender combinations

The BA recipients were classified into four groups according to the donor and recipient gender combinations as follows: mother donor to daughter recipient (MD; $n = 43$), mother to son (MS; $n = 18$), father to daughter (FD; $n = 33$), and father to son (FS; $n = 20$). We compared these four groups for the incidence of ACR. In comparison, the other original diseases had the following frequencies of communications: MD for 8, MS for 11, FD for 8, and FS for 12.

Analysis of ACR episodes

We retrospectively performed univariate and multivariate analyses of recipient, donor, and graft values to identify the factors associated with ACR.

Statistical analysis

The significance of differences among the four groups was determined using Fisher's exact test, and the significance of differences between pairs of groups was evaluated using the chi-squared test. Associations between recipient, donor, or graft variables, and ACR were evaluated using univariate and backward selection multivariate Cox regression methods. Graft survival was calculated using the Kaplan–Meier product-limited method, and differences in survival between two groups or among all four groups were then compared using the log-rank test. All statistical analyses were performed using the StatView software package (SAS Institute, Cary, NC, USA), and differences where $P < 0.050$ were considered to be significant.

Results

The overall incidence rate of ACR in the recipients with BA was 36.8% (42/114). The baseline demographic data pertaining to the recipients associated with ACR are presented in Table 2. The median number of ACR in each recipient was 1 (range: 1–9 times), and the mean period between the first ACR and LDLT was 98 ± 313 days (5–1701 days). The immunosuppressive therapies used to treat ACRs were Tac+MP for 39 patients, Tac+MMF for 2, Tac for 1, and CsA+MP for 1. The mean degree of ACR was 4.4 ± 1.4 according to the RAI, and the ratio of steroid-resistant to total ACRs was 19.0% (8/42). The recent immunosuppressive therapies for recipients with ACR were Tac+MP+MMF for 14, Tac for 14, Tac+MMF for 11, Tac+MP for 1, CsA+MMF for 1, and death occurred in 1 patient. The recent immunosuppressive therapies for recipients without ACR were Tac for 43, Tac+MMF for 17, Tac+MP+MMF for 6, Tac+MP for 2, CsA for 1, and none for 1; death occurred in 2 patients. There were no significant differences in graft survival rate between recipients with ACR and without ACR, but there were significant differences in the rate of recent use

Table 2. Demographic data for recipients associated with acute cellular rejection.

	Recipient with ACR (42 cases)	Recipient without ACR (72 cases)	*P*-value
Characteristics of recipient with ACR			
Number of ACR (times)	Median 1 (1–9)	–	–
Period between ACR and LDLT (days)	98 ± 313 (5–1701)	–	–
Immunosuppressive therapy at ACR	Tac+MP: 39; Tac+MMF: 2; Tac: 1; CsA+MP: 1	–	–
Degree of ACR (RAI)	4.4 ± 1.4	–	–
Ratio of steroid-resistant ACR	19.0%	–	–
Overall 1-year graft survival	100%	95.8%	0.180
Overall 5-year graft survival	97.6%	95.8%	0.617
Recent immunosuppressive therapy			
Type of immunosuppressive therapy	Tac+MP+MMF: 14; Tac: 14; Tac+MMF: 11; Tac+MP: 1; CsA+MMF: 1; death: 1	Tac: 43; Tac+MMF: 17; Tac+MP+MMF: 6; Tac+MP: 2; death: 2; CsA: 1; none: 1	–
Use of three immunosuppressive agents	33.3%	8.3%	<0.001
Tac trough level (ng/ml)	4.1 ± 2.5 (1.2–16.1)	3.3 ± 1.3 (0.1–11.2)	0.048

ACR, acute cellular rejection; LDLT, living donor liver transplantation; RAI, rejection activity index; Tac, tacrolimus; MP, methylprednisolone; MMF, mycophenolate mofetil; CsA, cyclosporine A.

Table 3. Risk factors for acute cellular rejection after living donor liver transplantation: univariate analysis.

Recipient variables	Incidence of ACR (%)	*P*-value
Gender		
Male (n = 38) vs. female (n = 76)	39.5 vs. 35.5	0.680
Age		
<1 year (n = 47) vs. ≥1 year (n = 67)	36.2 vs. 37.3	0.899
Body weight		
<10 kg (n = 51) vs. ≥10 kg (n = 63)	33.3 vs. 38.1	0.637
PELD or MELD		
≥20 (n = 30) vs. <20 (n = 84)	39.2 vs. 34.9	0.643
Operation time		
≥15 h (n = 59) vs. <15 h (n = 55)	37.3 vs. 36.4	0.920
Cold ischemic time		
≥2 h (n = 59) vs. <2 h (n = 55)	39.0 vs. 34.5	0.623
Warm ischemic time		
≥1 h (n = 60) vs. <1 h (n = 54)	36.7 vs. 37.0	0.964
Blood loss volume		
≥80 ml/kg (n = 59) vs. <80 ml/kg (n = 55)	35.6 vs. 38.2	0.775
Transfusion volume		
≥100 ml/kg (n = 51) vs. <100 ml/kg (n = 63)	33.3 vs. 39.7	0.485
Donor and graft variables		
Gender		
Father (n = 53) vs. mother (n = 61)	47.2 vs. 27.9	0.033
Age		
≥35 years (n = 53) vs. <35 years (n = 61)	45.2 vs. 29.5	0.082
Donor-recipient gender		
Mismatch (n = 51) vs. match (n = 63)	51.0 vs. 25.4	0.005
ABO compatibility		
Compatible (n = 23) vs. identical (n = 91)	43.5 vs. 35.2	0.460
HLA-A compatibility		
Mismatch (n = 83) vs. match (n = 31)	25.8 vs. 41.0	0.136
HLA-B compatibility		
Mismatch (n = 107) vs. match (n = 7)	36.4 vs. 42.9	0.733
HLA-DRB1 compatibility		
Mismatch (n = 99) vs. match (n = 15)	39.4 vs. 20.0	0.147
Lymphocyte cross-matching		
≥2 × (n = 51) vs. negative (n = 63)	39.2 vs. 31.7	0.210
GV/SLV		
<60% (n = 34) vs. ≥60% (n = 80)	38.2 vs. 36.3	0.841
Graft		
Left lateral segment (n = 85) vs. others (n = 29)	37.6 vs. 34.5	0.760

ACR, acute cellular rejection; PELD, pediatric end-stage liver disease; MELD, model for end-stage liver disease; GV/SLV, ratio of graft volume to standard liver volume.

of the three immunosuppressive agents and recent Tac trough level ($P < 0.001$ and $P = 0.048$, respectively). There were no recipients in whom ACR was associated with adherence to medications.

The impact of various recipient, donor, and graft variables on ACR was assessed, and the results are summarized in Table 3. Univariate analysis revealed the following risk factors for ACR after LDLT: use of a paternal donor and donor–recipient gender mismatch ($P = 0.033$ and $P = 0.005$, respectively). The only variable between $P < 0.050$ and $P < 0.100$ was donor age (≥35 years, $P = 0.082$). Multivariate analysis including these variables revealed that gender mismatch was an independent risk factor for ACR after LDLT ($P = 0.012$) (Table 4).

Table 4. Risk factors for acute cellular rejection after living donor liver transplantation: multivariate analysis.

Variables	Odds ratio	95% CI	*P*-value
Donor gender			
Father vs. mother	1.65	0.752–3.935	0.199
Donor age			
≥35 years vs. <35 years	0.02	0.471–2.359	0.898
Donor–recipient gender			
Mismatch vs. match	6.38	1.271–6.693	0.016

CI, confidence interval.

Figure 1 shows the overall graft survival between paternal and maternal LDLT across the 4 groups. The 1- and 5-year graft survival rates for paternal LDLT were 98.1% and 96.2%, respectively, and those for maternal LDLT were 96.7% and 96.7%, respectively. The 1- and 5-year graft survival rates in the MD group were 97.7% and 97.7%, respectively, and those in the MS group were 94.4% and 94.4%, respectively. The corresponding rates in the FD group were 97.0% and 97.0%, respectively, and those in the FS group were 100.0% and 95.0%, respectively. There were no significant differences in graft survival rate between paternal and maternal LDLT or among the 4 groups ($P = 0.908$ and $P = 0.953$, respectively).

Fisher's exact test revealed significant differences among the 4 groups classified according to gender combination on acute rejection ($P = 0.022$). The FD group had a higher rate of ACR than the MD group ($P = 0.002$; Table 5).

The demographic data pertaining to recipients with elder siblings are presented in Fig. 2. In the MS group ($n = 18$), there were 4 recipients who had an elder brother, and their occurrence of ACR was 50.0%. There were no significant differences in the incidence rate of ACR between recipients with elder brothers and sisters in the MS group ($P = 0.386$). In this study, there were 17 pubertal recipients, and their occurrence of ACR was 41.2% (7/17). There were no significant differences in the incidence rate of ACR between pubertal and nonpubertal recipients ($P = 0.688$).

In contrast, the overall incidence rate of ACR in recipients with other original diseases was 33.3% (13/39). The 1- and 5-year graft survival rates for paternal LDLT were 100% and 100%, respectively, and those for maternal LDLT were 95.0% and 90.0%, respectively. There were no signifi-

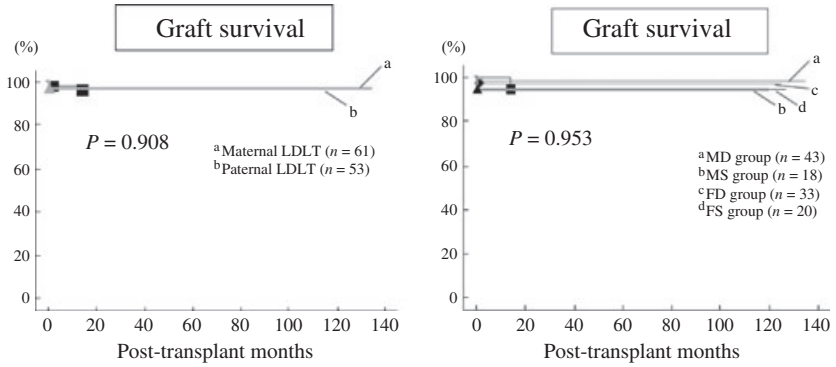

Figure 1 Graft survival after LDLT for paternal and maternal LDLT and among 4 groups classified on the basis of gender combinations. There were no significant differences in graft survival between paternal and maternal LDLT or among the 4 groups ($P = 0.908$ and $P = 0.953$, respectively). LDLT, living donor liver transplantation; MD, mother donor to daughter recipient; MS, mother donor to son recipient; FD, father donor to daughter recipient; FS, father donor to son recipient.

Table 5. Impact of gender combinations on acute cellular rejection for patients with BA.

Gender combinations	No ACR	ACR	Rate of ACR (%)	*P*-value
MD group ($n = 43$)	34	9	20.9	$P = 0.002$
MS group ($n = 18$)	10	8	44.4	
FD group ($n = 33$)	15	18	54.5	
FS group ($n = 20$)	13	7	35.0	

MD, mother donor to daughter recipient; MS, mother donor to son recipient; FD, father donor to daughter recipient; FS, father donor to son recipient; ACR, acute cellular rejection. $P = 0.022$ (Fisher's exact test).

Table 6. Impact of gender combinations on acute cellular rejection for patients with the other original diseases.

Gender combinations	No ACR	ACR	Rate of ACR (%)	*P*-value
MD group ($n = 8$)	7	1	12.5	$P = 0.106$
MS group ($n = 11$)	8	3	27.3	
FD group ($n = 8$)	4	4	50.0	
FS group ($n = 12$)	7	5	41.7	

MD, mother donor to daughter recipient; MS, mother donor to son recipient; FD, father donor to daughter recipient; FS, father donor to son recipient; ACR, acute cellular rejection. $P = 0.374$ (Fisher's exact test).

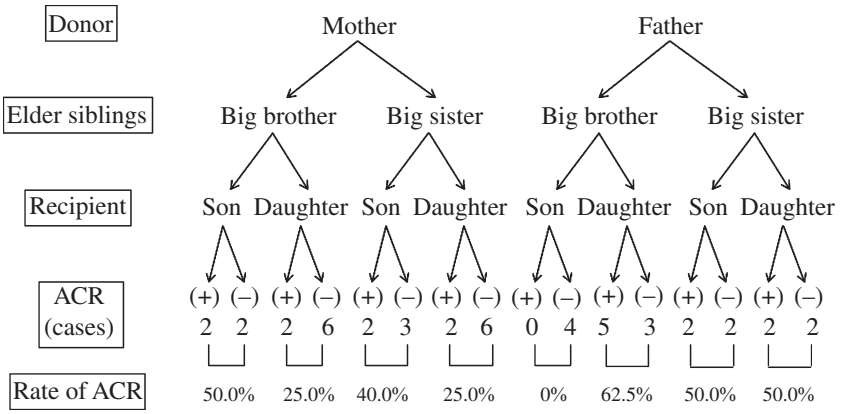

Figure 2 Demographic data pertaining to the recipients with elder siblings. In the mother donor to son recipient (MS) group ($n = 18$), 4 recipients had an elder brother, and their occurrence of ACR was 50.0%. There were no significant differences in the incidence rate of ACR between recipients with elder brothers and those with elder sisters in the MS group ($P = 0.386$).

cant differences in graft survival rate between paternal and maternal LDLT. Fisher's exact test revealed no significant differences among the 4 groups classified according to gender combination on acute rejection ($P = 0.374$). The FD group tended to have a higher rate of ACR than the MD group ($P = 0.106$; Table 6).

Discussion

The impact of gender mismatch between donors and recipients on the outcome of LT appears to be controversial. Some reports have indicated that gender mismatch has an impact on graft failure, specifically in male recipients receiving grafts from female donors in adult deceased donor LT and adult LDLT [1–4,6]. Although the poor graft prognosis was thought to result from reduced serum estrogen levels in male recipients and a lower number of estrogen receptors in male recipients of grafts from female donors [3,6,23–25], further long-term study is warranted to clarify how hormonal factors affect the outcome of LT. In contrast, Nijagal *et al.* [7] found that, in pediatric LDLT, recipients receiving maternal grafts had lower rates of graft failure and refractory rejection than those receiving paternal grafts, and our results support their findings. The impact of gender mismatch on graft prognosis and rejection may differ between adult LDLT and pediatric LDLT using parental grafts. In general, for pediatric LDLT using parental grafts, the long-term outcome for patients with BA who do not suffer relapse is reportedly better than that for adult LDLT [26–29]. In addition, it was recently reported that a high proportion of pediatric recipients of parental LDLT underwent withdrawal of immunosuppression without experiencing rejection [30]. Therefore, the good long-term survival of BA recipients after pediatric LDLT may be associated with tolerance resulting from the use of parental grafts. In our study, although the multivariate analysis showed that only gender mismatch was an independent risk factor for ACR ($P = 0.012$), a significance difference in ACR with regard to gender mismatch was detected only between the FD and the MD groups. It appears that maternal grafts and gender matching are related to graft tolerance in LDLT.

Maternal–fetal cellular trafficking during pregnancy results in bidirectional microchimerism with potential long-term consequences for the mother and her fetus [19,31]. It has been reported that the presence of maternal cells in the fetus (maternal microchimerism) promotes the formation of regulatory T cells that suppress the fetal immune response to noninherited maternal antigens and is therefore an important component of maternal–fetal tolerance [32]. It is possible that this tolerance may be long-lived and have an impact on the success of organ transplantation when the mother serves as a donor. A beneficial effect of noninherited maternal antigens exposure has been reported in bone marrow transplantation [33,34], but results in the context of kidney transplantation have been mixed [35–37]. In LT, Nijagal *et al.* found that in pediatric LDLT for BA, recipients receiving maternal grafts had lower rates of graft failure and refractory rejection than those receiving paternal grafts, and maternal microchimerism may have been responsible for the observed tolerance [7,38]. In our present study, a multivariate analysis showed that only gender mismatch was independently correlated with ACR ($P = 0.016$). In addition, the FD group had a higher rate of ACR than the MD group ($P = 0.002$). Therefore, our findings support the results of Nijagal *et al.* and suggest that noninherited maternal antigens may have an important impact on graft tolerance in pediatric LDLT for patients with BA. We performed the same study in other original diseases. Thirty-nine ABO-identical and ABO-compatible LDLTs were performed for other original diseases using parental liver grafts during the same period. There were no significant differences in graft survival rate between paternal and maternal LDLT. The FD group tended to have a higher rate of ACR than the MD group ($P = 0.106$; Table 6). Nearly the same result as for the patients with BA was obtained, and the difference was not significant. Maternal microchimerism in BA may be associated with these results.

In contrast, with regard to the reason for the association of paternal grafts with worse outcomes, presence of the H-Y antigen or a specific rejection of paternal antigens in the grafts can be considered [39]. Furthermore, major histocompatibility antigens, such as HLA and ABO, were not associated with independent risk factors for ACR in our study, and there were no significant differences in graft survival among the various combinations of parental and gender matches in LDLT. In the MS group ($n = 18$), 4 recipients had elder brothers and their occurrence of ACR was 50.0%. There were no significant differences in ACR rate between recipients with elder brothers and those with elder sisters in the MS group ($P = 0.386$). Therefore, our findings suggest that minor histocompatibility antigens originating from the father and mother may have an important impact on the incidence of ACR. In light of the good long-term results we obtained in our series, the ACR associated with these histocompatibility factors may be treatable simply by adjusting the immunosuppressant regimen.

One limitation of the present study was that we did not directly measure maternal microchimerism and cannot therefore conclude that that factor contributes to tolerance. We are currently planning a retrospective analysis of maternal chimerism to clarify the association between maternal antigens and ACR.

In conclusion, paternal grafts with gender mismatch are associated with a higher incidence of ACR than maternal grafts with gender match in LDLT. Our findings support the possibility that maternal antigens may have an important clinical impact on graft tolerance in LDLT for patients with BA.

Authorship

YS: study design, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. YK, AM, JA, K-iN, NS, NI, and TA: study design and interpretation of data. YH, NY, NO, TW, YI, and TU: acquisition of data. YY, KT, and KM: critical revision of the manuscript for important intellectual content.

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