Pediatric Surgery International (2019) 35:765–771
https://doi.org/10.1007/s00383-019-04487-0

ORIGINAL ARTICLE

The effect of maternal grafts in early acute cellular rejection after pediatric living-donor liver transplantation

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Accepted: 10 May 2019 / Published online: 20 May 2019

Abstract

Purpose Living-donor liver transplantations (LDLTs) with maternal grafts can be more successful than those with paternal grafts because of their tolerance to non-inherited maternal antigens. We reviewed LDLT patients to investigate the relationship between acute rejection and donor sex.

Methods LDLT patients between January 2010 and November 2015 were enrolled. ACR was defined by a rejection activity index of >3.

Results Forty-six patients (22 males and 24 females), of whom 28 had biliary atresia, were enrolled. The median age of the patients was 2.8 years and the donor types were maternal ($n=25$) and paternal ($n=21$). Acute cellular rejection (ACR) was observed in 22 patients. Twelve (48%) of the 25 patients in the maternal group had at least one episode of rejection compared with 10 (48%) of the 21 in the paternal group. Among the patients with ACR, the first rejection in the maternal group occurred significantly earlier than that in the paternal group ($p<0.01$). In the multivariable analysis, the only variable significantly related to the first rejection day after LDLT was donor sex (male) ($p<0.005$).

Conclusion Our results showed that maternal grafts had an effect on causing earlier ACR in LDLT.

Keywords Living-donor liver transplantation · Maternal microchimerism · Acute cellular rejection · Antibody-mediated rejection · Pediatric · Biliary atresia

Introduction

Liver transplantation is a critical treatment for patients with liver failure. Despite remarkable advances in immunosuppressive therapy, rejection remains the leading cause of graft failure. Among liver transplantations, living-donor liver transplantation (LDLT) is still almost the only way to save the lives of children with end-stage liver disease in areas such as Japan, where organs from deceased donors are scarce [1]. In LDLT, organs are usually donated from the mothers or fathers of the patients.

Biliary atresia (BA) is the most common neonatal cholestatic disorder, characterized by complete fibrotic obliteration of the lumen of all or part of the biliary tree within 3 months of birth. Although the first treatment of BA is portoenterostomy, approximately 70–80% of children with BA will eventually require liver transplantation after the procedure, and BA alone accounts for almost 50% of all liver transplants performed in children [2]. One of the hypothetical causes of the illness has been thought to be an immune-mediated process triggered by a stimulus that is yet to be determined [3].

Maternal–fetal cellular trafficking (MFCT) is the bidirectional passage of cells between a mother and her fetus, resulting in long-lived maternal cells in the fetus [4]. The presence of maternal cells in the fetus, which is referred to as maternal microchimerism, has been demonstrated in approximately one in ten infants and such infants have ~0.07% maternal lymphocytes at the time of birth [5]. Maternal microchimerism may play a role in the etiopathogenesis of

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BA by causing an alloimmune reaction. Several reports have demonstrated higher numbers of maternal cells in the livers of patients with BA [6–10]. They proposed that bile duct epithelial cells may function as antigen-presenting cells in these patients because human leukocyte antigens (HLAs), especially HLA-DR (MHC class II molecules), which is not normally expressed in the bile duct epithelium, were reported to be aberrantly expressed in liver specimens from these patients [11–13]. These findings suggested that maternal cells acquiring tolerance to the fetal immune system may contribute to disease pathogenesis by initiating a graft-versus-host reaction in the liver. BA and graft-versus-host disease (GVHD) have been reported to share some similarities, such as injury of the bile duct epithelium and infiltration of immunologically active and proliferating lymphocytes [14, 15].

The high occurrence of maternal microchimerism in healthy individuals, however, has suggested that maternal cells can acquire tolerance to the infant immune system, where the presence of these maternal cells can promote the formation of fetal regulatory T cells that suppress the immune response to non-inherited maternal antigens (NIMAs), and reside quietly in the fetus [16]. Although maternal microchimerism probably has a pathogenic impact in the development of BA as it does in GVHD, tolerance to maternal cells, or NIMAs, in the fetus can play beneficial tolerogenic effects in the context of transplantation. The MFCT phenomenon and subsequent maternal microchimerism can be seen not only in patients with BA, but also in those with other liver diseases and even in normal individuals as mentioned above [6]. However, the beneficial effect of maternal liver transplantation has been reported in only restricted cases, wherein the underlying disease was BA [17]. Therefore, the question of whether maternal microchimerism has beneficial effects on patients receiving grafts from their mothers during transplantation remains controversial. In this study, we reviewed cases of patients who had undergone LDLT in our institute to investigate the relationship between acute cellular rejection (ACR) and maternal grafting.

Patients and methods

Patient inclusion criteria and data collection

Patients who had LDLT between January 2010 and November 2015 at our institute were included in this study. Written informed consent was obtained from each patient and their parents, to whom the details of the necessity of routine liver biopsies after LDLT were explained. Recipient and donor age at LDLT, sex, primary disease of the recipient, standard liver volume (SLV) of the recipient, graft volume (GV), GV/SLV, number of donor HLA mismatches against recipient HLA, graft type, and first rejection day after LDLT were gathered from the patients' charts.

As a long-term evaluation of liver function, we collected some blood tests, such as total bilirubin (T-bil) (mg/dL), Albumin (Alb) (g/dL), Prothrombin time (PT) (%), aspartate amino-transferase (AST) (U/L) and alanine amino-transferase (ALT) (U/L), at 1 year after LDLT. Patients who died within 1 year after LDLT were excluded for the evaluation.

For analysis, we divided the patients into two groups: patients with BA and patients with other liver diseases. Patients with BA were further divided into two groups: with and without ACR. We investigated HLAs including HLA-A, HLA-B, and HLA-DR. Patients were considered to have HLA mismatch if at least one different allele of each donor was observed.

Protocol of immunosuppression

Post-operative immunosuppressive drugs including steroids and tacrolimus were administered. Steroids at 20 mg/kg were injected intravenously during and immediately after LDLT, and thereafter the dose was gradually decreased. At 7 days after LDLT and thereafter, steroids were administered orally, and the dose gradually decreased as much as possible if patients showed no evidence of ACR. In the case of patients without any ACR after LDLT, steroids were administered on alternate days for 1 month from 13 weeks after LDLT onward and stopped thereafter. Tacrolimus at 0.10 mg/kg/day was prescribed after LDLT and the dose was finely adjusted on the basis of drug monitoring.

In ACR conditions, the dose of steroids was increased or pulse treatment (20 mg/kg) was performed. If patients experienced severe ACR that did not improve with such treatments, thymoglobulin at 1.5 mg/kg/day was added for 7–14 days.

Liver biopsy and pathological evaluation of ACR

Liver function tests, including biopsy, of the patients enrolled in this study were performed routinely at 1, 2, 3, and 5 years after LDLT, and thereafter every 5 years even if the patients showed no ACR. Additional tests, including a liver biopsy, Epstein–Bar virus (EBV) and cytomegalovirus (CMV) serology, were performed when ACR was suspected in patients with fever, fatigue, jaundice, elevation of transaminases, and deteriorating accumulation of ascites. We further investigated C4d staining in the biopsy sample and donor specific antibody (DSA) when antibody-mediated rejection (AMR) was suspected.

The biopsied specimens were stained with hematoxylin–eosin or by histochemical or immunohistochemical methods as required. ACR in the stained biopsies was

defined as greater than 3 points in the Banff Rejection Activity Index (RAI). The RAI is a criterion that can be used to score liver allograft biopsies with acute rejection and comprises three components scored from 0 to 3 as defined by the World Gastroenterology Consensus Document: venous endothelial inflammation (E), bile duct damage (B), and portal inflammation (P) [18].

Statistical analysis

All patients or patients with BA were divided into maternal and paternal graft groups and analyzed. The variables described above were compared between these two groups with Mann–Whitney's *U* test for continuous values and Fisher's test for categorical values. Kaplan–Meier curves between the two groups, in which the first day on which rejection occurred after LDLT was defined as the event, were analyzed with the log rank test. The threshold for significance was $P < 0.05$. Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient demographics

Forty-six patients (22 males and 24 females) were enrolled as shown in Table 1. The median age of these patients was 2.8 years (ranging from 0.61 to 20.7 years) and the proportion of patients with BA was approximately 60%. The median age of the donors was 39.5 years (ranging from 21 to 52 years) and the donor types were maternal ($n = 25$) and paternal ($n = 21$). The median SLV and GV/SLV were 437 mL (ranging from 279 mL to 853 mL) and 66.6% (ranging from 44.0 to 84.6%), respectively. The most adopted type of transplanted graft was the lateral graft (~ 50%) and the second most adopted was the left-lobe graft (~ 35%). All patients except for four had at least one HLA mismatch. ACR was observed in 22 patients (~ 50%), among which only one patient needed to be treated with thymoglobulin because of severe rejection. In this study, only two cases needed cadaveric liver retransplantation [2/46 (4.35%)]. Four patients had died within 1 year after LDLT, two of whom were the cases with the cadaveric liver retransplantation. The causes of death of these patients were recurrence of the original disease ($n = 2$; Hepatoblastoma and fulminant hepatitis of unknown origin) and ACR ($n = 2$).

When AMR was suspected in a case, we further performed C4d-staining on the liver biopsy ($n = 6$). As a result, we found three C4d-positive cases among those cases [3/6 (50%)]. We also checked DSA in 11 cases with suspicion of AMR and found that the total number of cases with positive DSA was three (27.3%).

Comparisons between maternal and paternal grafts

In all patients

Twelve (48%) of the 25 patients in the maternal group and 10 (48%) of the 21 patients in the paternal group had at least one episode of rejection after transplantation. This result demonstrates that there was no significant difference in the proportion of rejection between maternal and paternal grafts. There were also no significant differences in any liver function tests at 1 year after LDLT as a long-term evaluation between the two groups. Furthermore, when we suspected involvement with an acute rejection in a case, we also checked viral markers, especially EBV and CMV. However, there were no significant differences in these viral infection statuses between the two groups. On the other hand, LDLTs were performed with maternal graft in all C4d-positive cases and all DSA-positive cases (Table 1).

In patients with BA

There were no significant differences in all variables, including the proportion of rejection, between patients with BA and those with other liver diseases (not shown). In patients with BA, there was also no significant difference in the proportion of rejection between patients receiving grafts from their mothers and from their fathers. In addition, there were no significant differences in any liver function tests at 1 year after LDLT as a long-term evaluation and in viral infection statuses between maternal and paternal groups as well (Table 2).

In patients with ACR

After confirming that there were no significant differences in characteristics, except for the number of HLA mismatch, between patients with and without ACR (Table 3), we divided patients with ACR into maternal and paternal groups and analyzed them with the Kaplan–Meyer method. We found that the first rejection day in the maternal group occurred significantly earlier than that in the paternal group ($p = 0.0079$), with a median post-operative day of first rejection of 15 in patients with maternal grafts [95% confidence interval (CI) = 7–29] and 191 in patients with paternal grafts (95% CI = 7–359) (Fig. 1).

Table 1 Patient characteristics and the differences in each value between the maternal and paternal groups

	All	Maternal	Paternal	*P*
N	46	25	21	
Sex (male)	22 (47.8)	12 (48.0)	10 (47.6)	N.S.
Recipient age (year)	2.8 (0.60–21)	5.6 (1.1–11)	2.7 (1.1–7.2)	N.S.
Primary disease				
Biliary atresia	28 (60.9)	13 (52.0)	15 (71.4)	N.S.
Non-BA	18 (39.1)	12 (48.0)	6 (28.6)	
Donor age (year)	39 (32–43)	34 (32–40)	42 (39–45)	0.003[c]
GV/SLV (%)[a]	66.6 (44.0–84.6)	61.2 (43.0–83.4)	68.5 (45.7–88.5)	N.S.
The number of recipient ⇒ donor mismatch[a]				
0	4	1	3	N.S.
1	5	4	1	
2	18	10	8	
3	17	9	8	
Graft type				
Lateral	22 (47.8)	15 (60.0)	7 (33.3)	N.S.
Reduced lateral	5 (10.9)	2 (8.0)	3 (14.3)	
Left	16 (34.8)	7 (28.0)	9 (42.9)	
Left + S1	2 (4.3)	1 (4.0)	1 (4.8)	
Reduced S3	1 (2.2)	0 (0.0)	1 (4.8)	
Liver function test at 1 year after LDLT[b]				
T-bil (mg/dL)	0.50 (0.40–0.80)	0.50 (0.40–0.80)	0.50 (0.40–0.75)	N.S.
Alb (g/dL)	4.0 (3.8–4.3)	3.9 (3.7–4.3)	4.0 (3.8–4.3)	N.S.
PT (%)	74.5 (65.3–83.8)	75.0 (62.5–82.0)	74.0 (68.5–85.0)	N.S.
AST (U/L)	40.0 (30.3–49.5)	39.0 (31.5–47.0)	42.0 (27.5–53.5)	N.S.
ALT (U/L)	26.0 (22.0–48.8)	26.0 (21.5–48.5)	26.0 (22.5–46.5)	N.S.
Rejection	22 (47.8)	12 (48.0)	10 (47.6)	N.S.
Viral infection status at LDLT				
EBV	10/22 (63.6)	6/12 (50.0)	4/10 (40.0)	N.S.
CMV	14/22 (63.6)	7/12 (58.3)	7/10 (70.0)	N.S.
Lymphocyte crossmatch at LDLT[a]				
Positive	4/17 (23.5)	3/9 (33.3)	1/8 (12.5)	N.S.
$C4d^{+a}$	3/6 (50.0)	3/4 (75.0)	0/2 (0.0)	N.S.
DSA^{+a}	3/11 (27.3)	3/6 (50.0)	0/5 (0.0)	N.S.

Age and GV/SLV, as continuous values, show median (range), whereas sex, primary disease, graft type, and the number of mismatches, as categorical values, show the total number (proportion). N.S. indicates not significant

[a]These variables had some missing values

[b]Patients who died within 1 year after LDLT ($n = 4$) were excluded

[c]These values were significant

Multivariable analysis for possible factors related to the first rejection day

Finally, we conducted multivariable analysis with Cox proportional hazard regression to assess the effect of donor sex on the first rejection day, in which donor age and primary disease (BA or non-BA) were taken into consideration as confounding factors. The only variable significantly related to the first rejection day after LDLT was donor sex (male) ($p = 0.00372$; hazard ratio = 0.147, 95% CI = 0.0404–0.537).

Discussion

This study investigated the impact of maternal grafts on ACR in patients undergoing LDLT and showed that there were no significant differences in the proportion of patients with rejection and in liver function tests at 1 year after LDLT as a long-term evaluation of the graft between the maternal and paternal groups in all patients and in patients with BA. However, the first instance of ACR

Table 2 The differences in each value between the maternal and paternal groups in BA recipients

	BA		*P*
	Maternal	Paternal	
N	13	15	
Sex (male)	4 (30.8)	8 (53.3)	N.S.
Recipient age (year)	1.6 (1.0–5.5)	2.3 (0.9–9.8)	N.S.
Donor age (year)	34 (30–40)	40 (37–43)	N.S.
GV/SLV (%)[a]	71.1 (54.3–86.1)	74.9 (45.0–98.9)	N.S.
The number of recipient ⇒ donor mismatch[a]			
0	0	0	N.S.
1	2	1	
2	8	8	
3	3	6	
Graft type			
Lateral	7 (46.7)	5 (33.3)	N.S.
Reduced lateral	2 (15.4)	3 (20.0)	
Left	3 (23.1)	6 (40.0)	
Left + S1	1 (7.7)	0 (0.0)	
Reduced S3	0 (0.0)	1 (6.7)	
Maternal	–	–	–
Liver function test at 1 year after LDLT[b]			
T-bil (mg/dL)	0.50 (0.48–0.80)	0.50 (0.40–0.68)	N.S.
Alb (g/dL)	3.9 (3.9–4.0)	4.0 (3.9–4.1)	N.S.
PT (%)	64.0 (58.3–74.8)	73.5 (66.3–78.0)	N.S.
AST (U/L)	40.0 (32.5–43.5)	41.5 (30.8–45.3)	N.S.
ALT (U/L)	24.0 (20.5–34.5)	27.0 (22.3–40.5)	N.S.
Rejection	6 (46.2)	8 (53.3)	N.S.
Viral infection status at LDLT			
EBV	1/6 (16.7)	3/8 (37.5)	N.S.
CMV	3/6 (50.0)	6/8 (75.0)	N.S.
Lymphocyte crossmatch at LDLT[a]			
Positive	1/6 (16.7)	1/6 (16.7)	N.S.
$C4d^{+a}$	1/1 (100)	0/1 (0.0)	N.S.
DSA^{+a}	1/3 (33.3)	0/4 (0.0)	N.S.

Age and GV/SLV, as continuous values, show median (range), whereas sex, primary disease, graft type, and the number of mismatches, as categorical values, show the total number (proportion). N.S. indicates not significant

[a]These variables had some missing values

[b]Patients who died within 1 year after LDLT ($n = 4$) were excluded

occurred earlier in patients receiving maternal grafts than in those receiving paternal grafts.

The first result is not consistent with those in some previous reports that demonstrated that pediatric patients with BA receiving liver grafts from their mothers had better outcomes than those receiving paternal grafts. BA patients receiving maternal grafts had lower rates of graft failure compared to those receiving paternal grafts (3.7% vs. 10.5%) and, consequently, required fewer episodes of

Table 3 The differences in each value between patients with and without ACR

	Rejection	No-rejection	*P*
N	22	24	
Sex (male)	10 (45.5)	12 (50.0)	N.S.
Recipient age (year)	2.5 (0.93–7.9)	5.2 (1.6–10.2)	N.S.
Original disease			
Biliary atresia	14 (63.6)	14 (58.3)	N.S.
Donor age (year)	40 (32–43)	38 (33–43)	N.S.
SLV (ml)[a]	381 (240–747)	522 (323–958)	N.S.
GV/SLV (%)[a]	75.9 (54.3–86.1)	61.2 (42.8–80.4)	N.S.
The number of recipient ⇒ donor mismatch[a]			
0	0	1	N.S.
1	2	1	
2	6	14	
3	13	7	
Transplanted graft			
Lateral	10 (45.5)	12 (50.0)	N.S.
Reduced lateral	5 (22.7)	0 (0.0)	
Left	6 (27.3)	10 (41.7)	
Left + S1	1 (4.5)	1 (4.2)	
Reduced S3	0 (0.0)	1 (4.2)	
Maternal	12 (54.5)	13 (54.2)	N.S.

Age and GV/SLV, as continuous values, show median (range), whereas sex, primary disease, graft type, and the number of mismatches, as categorical values, show the total number (proportion). N.S. indicates not significant

[a]These variables had a few missing values

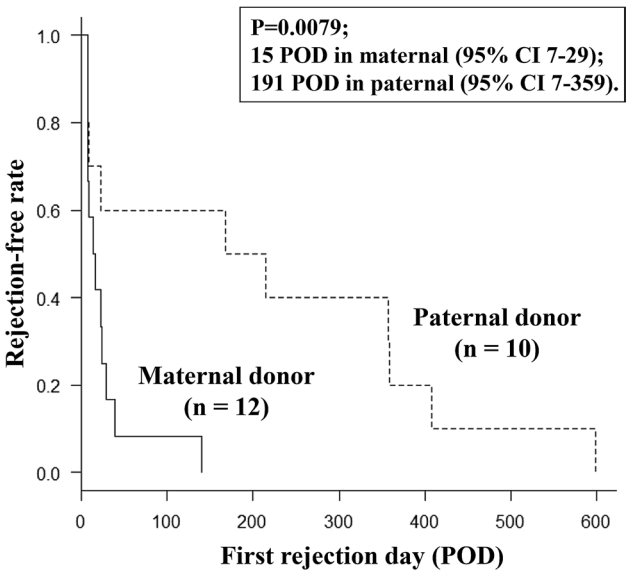

Fig. 1 The difference in rejection-free survival between the maternal and paternal groups in patients with ACR. POD: post-operative day

re-transplantation (2.7% vs. 7.5%). These differences were not observed among non-BA patients or BA patients who received grafts from deceased female donors [17]. However, the result in our study indicates that maternal grafts could have a greater negative effect than paternal grafts on early ACR in patients, regardless of their primary disease.

It has been reported since the 1950s that in utero exposure to maternal antigens results in the acceptance of transplanted organs expressing them [19], but some previous studies have shown complicated results on the impact of maternal grafts on the outcome of LDLT, especially between patients with BA and those with other liver diseases as mentioned above [16]. In addition, in other cases, such as renal transplantation, there was no advantage to maternal grafts [20, 21] and even higher rates of ACR have been identified [22]. In the latter report, graft survival in recipients of kidneys from siblings expressing maternal HLAs not inherited by the recipient was higher at 5 years and 10 years after transplantation than that in recipients of kidneys from siblings expressing paternal HLAs not inherited by the recipient (86% vs. 67% at 5 years and 77% vs. 49% at 10 years). Paradoxically, there was a higher incidence of early rejection in the maternal HLA group [22], which is consistent with our results. Accordingly, there is a possibility that exposure to NIMAs in utero can result in a priming rather than a tolerogenic impact, especially in the early phase after LDLT. A study involving animal experiments reported that neonates developed cytotoxic responses and memory allospecific Th1/Th2 responses, thus strengthening the hypothesis. The result suggested that early exposure to NIMAs may lead to an immunologic priming effect on T-cell adaptive immunity rather than tolerance [23]. Our results showed that there were no significant differences in the proportion of patients with rejection and in liver function tests at 1 year after LDLT between the maternal and paternal graft groups, which indicates that NIMAs may have few immunological effects on LDLT in the long run. However, results showing that patients receiving grafts from their mothers had earlier first rejection than those receiving grafts from their fathers suggest that the exposure of NIMAs can work as primers even in patients with BA in the short run. Furthermore, we investigated C4d-staining on biopsy specimens when AMR was suspected. Indeed, we did not check the staining in all the cases, but among the cases with C4d staining done, we found three C4d-positive cases [3/6 (50%)]. Interestingly, the donated organ was from their mother in all these C4d-positive cases. In addition, we also checked DSA in some cases with suspicion of AMR and found that the total number of cases with positive DSA was 3 of 11 cases with DSA checked. Impressively, in all the cases with positive DSA, LDLTs were also performed with maternal graft. These results may indicate the possible priming effects of NIMAs. However, we were not able to prove it with statistically significance because of the small number of cases in this study.

All the results in this study are the first to refer to the possible priming effects of NIMAs in the earlier phase after LDLT, regardless of the underlying disease. The reason that there was no significant difference in the proportion of patients with rejection in the long run may be that the presence of allogeneic cells could gradually induce de novo recipient regulatory T cells or other suppressor cells to their microenvironment. In patients with BA, it has been reported that the number of regulatory T cells in hepatic hilar lymph nodes was higher than that in patients without BA. However, a few regulatory T cells still existed in the lymph nodes in patients without BA, probably as a result of the response to maternal microchimerism [24]. Therefore, it is reasonable to presume that such cells can increase in number after LDLT as a result of the response to allogenic cells in the transplanted organ. These cells can suppress the reaction of recipient lymphocytes against donor cells and create a new favorable milieu for the transplanted organ with the help of immunosuppressive agents. In the microenvironment of the early phase after LDLT, however, such immunosuppressive factors may not be induced sufficiently and the priming effect of maternal microchimerism may have a greater impact on the recipient immune system and cause earlier ACR.

The management plan we can recommend on the basis of the results of this study is that we should offer a close monitoring program for the recipients of maternal graft. Furthermore, given the fact that grafts in all cases with positive C4d and DSA were from their mother, it may be better to choose even different immunosuppressive regimen for these recipients, for example, with higher trough levels than recipients with paternal graft at least for short period of time immediately after transplantation.

In summary, we investigated whether maternal grafts could have positive effects on ACR in patients undergoing LDLT and found that maternal grafts had negative, not positive, effects on early ACR, regardless of the primary disease of the patients. Because our results did not demonstrate the existence of maternal cells or antigens in situ in our patients, it is still uncertain whether NIMAs worked as antigenic effectors against the fetal immune system. Therefore, further clinical investigations should be conducted in the future, especially in LDLT conditions, and basic research should be performed to reveal the direct effects of NIMAs in the immune system.

Acknowledgements We would like to thank Editage (www.editage.jp) for English language editing.

References

1. Sugawara Y, Makuuchi M, Takayama T et al (2001) Small-for-size grafts in living-related liver transplantation. J Am Coll Surg 192:510–513
2. Balistreri WF, Grand R, Hoofnagle JH et al (1996) Biliary atresia: current concepts and research directions. Summary of a Symposium. Hepatology 23:1682–1692
3. Desmet VJ (1998) Ludwig symposium on biliary disorders—part I. Pathogenesis of ductal plate abnormalities. Mayo Clin Proc 73:80–89
4. Maloney S, Smith A, Furst DE et al (1999) Microchimerism of maternal origin persists into adult life. J Clin Invest 104:41–47
5. Schröder J, Tiilikainen A, De la Chapelle A (1974) Fetal leukocytes in the maternal circulation after delivery. I. Cytological aspects. Transplantation 17:346–354
6. Hayashida M, Nishimoto Y, Matsuura T et al (2007) The evidence of maternal microchimerism in biliary atresia using fluorescent in situ hybridization. J Pediatr Surg 42:2097–2101
7. Kobayashi H, Tamatani T, Tamura T et al (2007) Maternal microchimerism in biliary atresia. J Pediatr Surg 42:987–991
8. Muraji T, Hosaka N, Irie N et al (2008) Maternal microchimerism in underlying pathogenesis of biliary atresia: quantification and phenotypes of maternal cells in the liver. Pediatrics 121:517–521
9. Suskind DL, Rosenthal P, Heyman MB et al (2004) Maternal microchimerism in the livers of patients with biliary atresia. BMC Gastroenterol 4:14
10. Muraji T (2014) Maternal microchimerism in biliary atresia. Chimerism 5:1–5
11. Kobayashi H, Puri P, O'Briain DS, Surana R, Miyano T (1997) Hepatic overexpression of MHC class II antigens and macrophage-associated antigens (CD68) in patients with biliary atresia of poor prognosis. J Pediatr Surg 32:590–593
12. Jurado A, Jara P, Camarena C, Hierro L, Lahoz C, Palomino P (1997) Is extrahepatic biliary atresia an HLA-associated disease? J Pediatr Gastroenterol Nutr 25:557–558
13. Nakada M, Nakada K, Kawaguchi F et al (1997) Immunologic reaction and genetic factors in biliary atresia. Tohoku J Exp Med 181:41–47
14. Davenport M, Gonde C, Redkar R et al (2001) Immunohistochemistry of the liver and biliary tree in extrahepatic biliary atresia. J Pediatr Surg 36:1071–1075
15. Strasser S, Shulman H, Flowers M et al (2000) Chronic graft-versus-host disease of the liver: presentation as an acute hepatitis. Hepatology 32:1265–1271
16. Mold JE, Michaëlsson J, Burt TD et al (2008) Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science 322:1562–1565
17. Nijagal A, Fleck S, Hills NK et al (2012) Decreased risk of graft failure with maternal liver transplantation in patients with biliary atresia. Am J Transplant 12:409–419
18. Demetris AJ, Batts KP, Dhillon AP, Ferrell L, Fung J, Geller SA, Hart J, Hayry P, Hofmann WJ, Hubscher S, Kemnitz J (1997) Banff schema for grading liver allograft rejection: an international consensus document. Hepatology 25:658–663
19. Billingham RE, Brent L, Medawar PB (1953) 'Actively acquired tolerance' of foreign cells. Nature 172:603–606
20. Opelz G (1990) Analysis of the "NIMA effect" in renal transplantation. Collaborative transplant study. Clin Transpl 63:63–67
21. Panajotopoulos N, Ianhez LE, Neumann J et al (1990) Immunological tolerance in human transplantation. The possible existence of a maternal effect. Transplantation 50:443–445
22. Burlingham WJ, Grailer AP, Heisey DM et al (1998) The effect of tolerance to noninherited maternal HLA antigens on the survival of renal transplants from sibling donors. N Engl J Med 339:1657–1664
23. Opiela SJ, Levy RB, Adkins B (2008) Murine neonates develop vigorous in vivo cytotoxic and Th1/Th2 responses upon exposure to low doses of NIMA-like alloantigens. Blood 112:1530–1538
24. Sakamoto N, Muraji T, Ohtani H et al (2017) The accumulation of regulatory T cells in the hepatic hilar lymph nodes in biliary atresia. Surg Today 47:1282–1286