Table 1 Characteristics of patients in tolerance cases and no tolerance cases

Tolerance cases									
Pediatric Case	Age at LDLT	Sex	Original disease	Duration of biopsy after cessation of IS	Fibrosis (F Stage)	Positive area of α-SMA (%)	Number of positive cells/5 fields α-SMA	CD68	CD79α
1	5 yr	M	BA	2 yr	0	2.10	377	395	19
(Period of IS: 5 yr 8 mo)				5 yr 4 mo	0	2.03	250	194	3
				6 yr 4 mo	0	2.26	147	422	3
				7 yr 4 mo	0	2.95	243	500	10
2	11 mo	F	BA	4 yr 9 mo	0	1.53	91	264	20
(Period of IS: 3 mo)				7 yr 9 mo	0	2.49	257	552	16
				8 yr 9 mo	1	2.69	398	490	27
				9 yr 9 mo	1	2.76	241	369	21
						2.3 ± 0.46	250.5 ± 102.8	398.2 ± 121.6	14.8 ± 8.7
No tolerance cases									
Pediatric Case	Age at LDLT	Sex	Original disease	Duration of biopsy after LDLT	Fibrosis (F Stage)	Positive area of α-SMA (%)	Number of positive cells/5 fields α-SMA	CD68	CD79α
3	11 yr	F	BA	1 yr	0	0.02	9	508	12
				2 yr	0	1.86	134	446	14
4	10 mo	M	BA	1 yr	0	0.47	1	332	8
				1 yr 6 mo	0	0.32	2	424	10
				2 yr	0	0.83	107	525	9
5	7 yr	M	BA	1 yr	0	1.08	178	537	0
				1 yr 6 mo	0	0.63	153	637	7
6	6 yr	F	BA	2 yr	0	0.38	15	92	12
				8 yr	0	0.70	37	202	16
				13 yr	0	1.26	60	432	15
						0.75 ± 0.53	69.6 ± 67.7	413.5 ± 164.2 (mean ± SD)	10.3 ± 4.6

LDLT: Living donor liver transplantation; IS: Immunosuppression; α-SMA: Alpha smooth muscle actin; BA: Biliary atresia; M: Male; F: Female.

CD68/CD79α-positive cells in the cases with and without tolerance were 398.2 ± 121.6/14.8 ± 8.7 and 413.5 ± 164.2/10.3 ± 4.6, respectively.

In addition, the number of α-SMA-positive cells was 227.5 ± 99.0 in the tolerant patients with F0 stage fibrosis, which was higher than that in the patients without tolerance. The α-SMA-positive area ratio was also calculated using the WinROOF software program. The α-SMA-positive area ratio in the patients without tolerance with any fibrotic stage was 2.3% ± 0.46%; it was 2.2% ± 0.47% in cases with fibrotic stage F0 and 0.75% ± 0.53% in the no-tolerance patients (all patients with fibrotic stage F0). Accordingly, even among patients with no findings of fibrosis, the α-SMA area ratio was higher in patients with tolerance than in those without tolerance.

Degree of α-SMA staining in LDLT cases with fibrosis

The α-SMA-positive area ratio was calculated for adult patients with fibrosis using the WinROOF software program. Liver specimens obtained from a total of 10 liver biopsies in fibrosis Cases 1 to 3 were subjected to the analysis (Figure 1). Figure 1A shows the timing of the biopsies, fibrosis grade, and α-SMA-positive area ratio. The α-SMA-positive area continued to increase over time in all patients, and the α-SMA-positive area also increased in all patients even when they were in the pre-fibrotic stage (arrowhead).

The α-SMA-positive area ratio in adult patients with fibrosis was also evaluated based on the fibrosis stage. The area ratio was 1.1% ± 0.5% in the F0-1 stage and 4.6% ± 1.2% in the F4 stage. The α-SMA area ratio was higher in the F0-1 stages than in the F4 stage (Figure 1B).

The α-SMA-positive area continued to increase over time in the pediatric patients with tolerance. Pediatric Case 1 showed F0 fibrosis in the liver at all time points, whereas pediatric Case 2 showed a slight progression of fibrosis (F1) eight years after the cessation of the immunosuppressant treatment (Figure 2). However, there were no significant increases in the α-SMA-positive area in the pediatric cases without tolerance (Figure 3).

DISCUSSION

Immune tolerance is the ultimate goal of transplantation, and many transplant patients have been reported to have ceased immunosuppressant medication for a long period while maintaining a favorable clinical course in clinical practice[6,7]. However, hepatic fibrosis has been reported to have developed in transplant patients who have ceased immunosuppressant medication[21], and there are some concerns over whether the cessation of immunosuppressive treatment leads to fibrosis. We performed a histological analysis in patients who had ceased immunosuppressant medication and examined the impact of the cessation on the liver graft.

As shown by the findings of this and previous studies[23], the expression of α-SMA increases with the progression of hepatic fibrosis because liver injury that is caused by hepatic viruses or medication allows T cells and Kupffer cells to release PDGF, IGF-I, TGF-β, activated

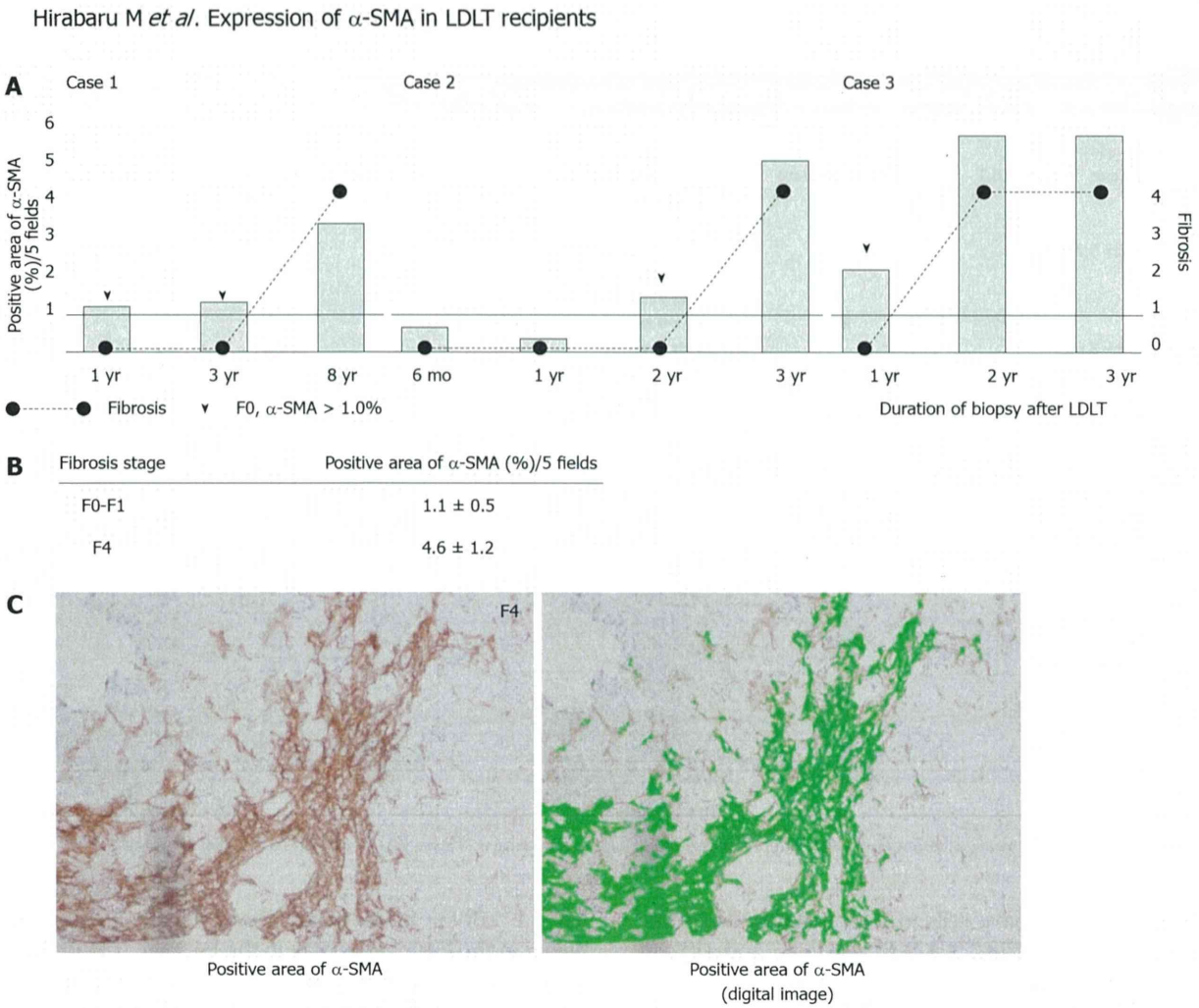

Figure 1 Changes in alpha smooth muscle actin expression in adult patients with fibrosis. A: The α-smooth muscle actin (SMA)-positive area continued to increase over time in all the patients, even when they were in the pre-fibrotic stage (arrow head); B: The α-SMA positive area ratio in the patients with fibrosis was calculated based on the fibrosis stage. The α-SMA area ratio was higher in the patients with F0-1 fibrosis than in those with F4 fibrosis; C: The photograph on the left shows the α-SMA staining in a representative case with F4 fibrosis. The photograph on the right shows a WinRoof digital image, with green corresponding to the area of α-SMA-positive staining. α-SMA: Alpha smooth muscle actin; LDLT: Living donor liver transplantation.

oxygen, lipid peroxide, and α-SMA into the cytoplasm of HSCs. Subsequently, type I collagen is produced and fibrosis develops[24]. Therefore, it is supposed that the α-SMA level is increase in the pre-fibrotic stage, although there have been no reports on the correlation between the α-SMA expression level and fibrotic changes.

Here, we investigated the association between α-SMA expression and the fibrotic stage in patients with hepatic fibrosis. An increase in α-SMA over time was observed in all patients with fibrosis, suggesting that there is a correlation between the progression of fibrosis and the increase in α-SMA. Furthermore, all patients with fibrosis had increased α-SMA expression at the pre-fibrotic stage. In the current study, in two cases of tolerance, the progression of fibrosis remained low, although the ratio of α-SMA-positive areas remained high in both cases. However, Yoshitomi *et al*[21] reported that liver fibrosis progression in tolerant patients was higher than that in non-tolerant patients. Therefore, we propose that α-SMA may be a potential marker of the progression of liver fibrosis. Thus, we should continue to follow these two cases carefully to ensure that the progression of fibrosis is not missed. Because this study was a retrospective analysis and the time of biopsy varied for the individual patients, periodic follow-up examination will be required to evaluate and support this hypothesis. These findings suggest that a routine protocol biopsy could be an important tool to understand the dynamic state of α-SMA in detail.

These assumptions suggest that the possibility of developing fibrosis is higher in tolerant patients than in patients who continue immunosuppression, because α-SMA expression was consistently high in the tolerant patients in this study. In addition, the expression of α-SMA gradually increased in the tolerant patients, indicating that care should be taken in future follow-ups for these patients to ensure that their liver function does not deteriorate.

The liver is known to be the organ most susceptible to immune tolerance compared with other organs, and phenomena in different animal species have been observed that demonstrate that the major histocompatibility complex was successfully engrafted without immunosuppressant medication after an allogeneic liver

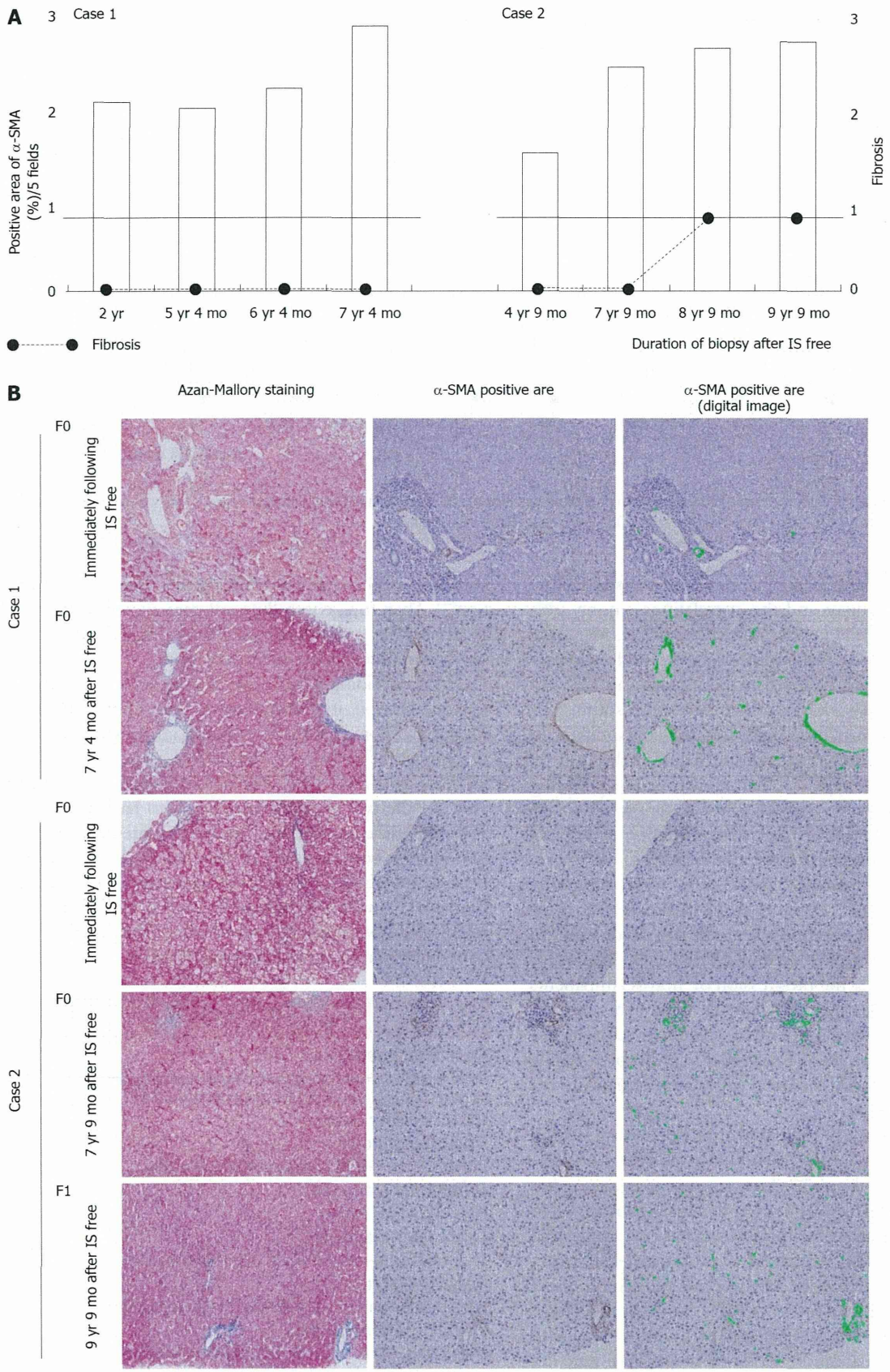

Figure 2 Change in alpha smooth muscle actin expression in the two pediatric cases with immune tolerance. A: The α-SMA-positive area continued to increase over time in both cases. Case 1 showed F0 fibrosis in the liver at all time points, whereas Case 2 showed a slight progression of fibrosis (F1) eight years after the cessation of immunosuppressive treatment; B: The findings of Azan-Mallory staining and the α-SMA-positive area determined by immunohistochemical analysis are shown. α-SMA: Alpha smooth muscle actin; IS: Immunosuppression.

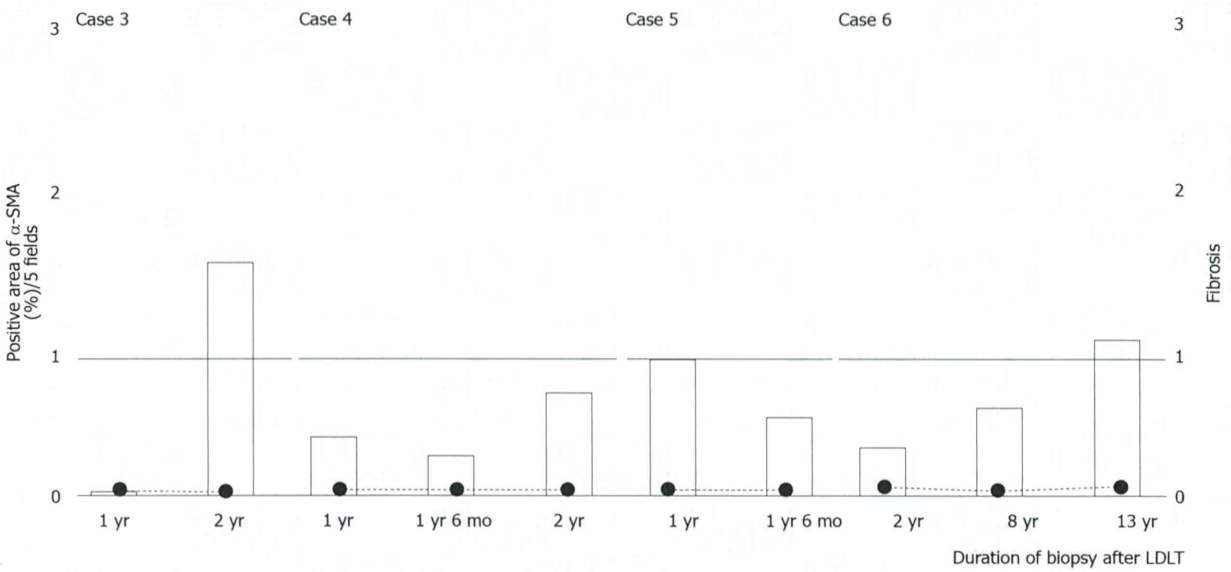

Figure 3 Changes in alpha smooth muscle actin expression in the four pediatric cases that continued immunosuppression. There was no clear increase in the α-SMA-positive area. α-SMA: Alpha smooth muscle actin; LDLT: Living donor liver transplantation.

transplant[27,28]. The effects of immunosuppressive factors produced in the liver and the correlations among antigen-presenting cells in the transplanted liver, including Kupffer cells, sinusoidal endothelial cells, and recipient-derived T cells, are believed to be involved in this immune tolerance. In addition, there have been some studies in mice showing that T cells became unresponsive to the antigen presented from sinusoidal endothelial cells of the specific donor type[29,30]. A treatment strategy leading to the acquisition of immune tolerance is considered to be important for human liver transplantation to prevent damage to hepatic sinusoidal endothelial cells.

CD68 (KCs) and CD79α (T cells) were immunostained to search for factors related to fibrosis in patients with and without immune tolerance, but there were no significant differences in either KCs or T cells. The major factor determining the progression of fibrosis in patients with immune tolerance still remains unknown, and predictors for the development of tolerance are also unknown. Therefore, we confirm that liver fibrosis staging assessed by biopsy is the main parameter influencing the treatment course.

A previous study indicated that calcineurin inhibitors (CNIs) may inhibit the activity of HSCs and the progression of fibrosis[21], but convincing evidence has not yet been provided. However, there is a good possibility that the cessation of immunosuppressant medication may cause a certain degree of rejection without abnormal hepatic function or histological rejection. There were also no differences in α-SMA expression between hepatitis C virus-infected patients with and without liver transplants[23]. In addition, CNIs administration may not always inhibit α-SMA expression if there is an infectious background. In addition, the infiltration of inflammatory cells stimulates the expression of pre-fibrotic growth factors[31], and inflammatory cells and activated HSCs are actually mixed in patients with chronic hepatic dysfunction[32]. Therefore, controlling inflammation is considered to inhibit the progression of fibrosis regardless of the use of immunosuppressant medication.

When deciding whether to resume immunosuppressant medication, it is important to determining whether the progression of fibrosis is due to an antigen response is important[33]. However, the factors associated with an increase in α-SMA were not determined in the present study in the two pediatric patients, who had most likely acquired immune tolerance. Immunosuppressant medication has not been resumed in these two pediatric patients because they have not shown clear abnormalities in liver function. However, we are performing a strict follow-up regime for both patients to determine whether they will continue to have a good long-term prognosis.

COMMENTS

Case characteristics

An 18-year-old male with a history of living donor liver transplantation (LDLT) for biliary atresia with no symptoms and an 11-year-old female with a history of LDLT for BA with no symptoms.

Clinical diagnosis

Immune tolerant state for a long period of time post-LDLT.

Differential diagnosis

Progression of liver fibrosis.

Laboratory diagnosis

The result of the liver function and all other tests were within normal limits.

Imaging diagnosis

In the imaging examinations, morbid findings were not detected.

Pathological diagnosis

In one patient, slight liver fibrosis was revealed by liver biopsy 9 years after the cessation of immunosuppressive therapy.

Experiences and lesson

This case report suggested that alpha smooth muscle actin may be a predictor of liver fibrosis; however, this assumption needs further validation from additional cases.

Peer review

This article provides possibility that the cessation of immunosuppressive therapy causes liver fibrosis.

REFERENCES

1 **Adam R**, McMaster P, O'Grady JG, Castaing D, Klempnauer JL, Jamieson N, Neuhaus P, Lerut J, Salizzoni M, Pollard S, Muhlbacher F, Rogiers X, Garcia Valdecasas JC, Berenguer J, Jaeck D, Moreno Gonzalez E. Evolution of liver transplantation in Europe: report of the European Liver Transplant Registry. *Liver Transpl* 2003; **9**: 1231-1243 [PMID: 14625822 DOI: 10.1016/j.lts.2003.09.018]

2 **Mells G**, Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. *Transplantation* 2007; **83**: 1141-1150 [PMID: 17496526 DOI: 10.1097/01.tp.0000262706.28513.6a]

3 **Ojo AO**, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, Arndorfer J, Christensen L, Merion RM. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003; **349**: 931-940 [PMID: 12954741 DOI: 10.1056/NEJMoa021744]

4 **Galve ML**, Cuervas-Mons V, Figueras J, Herrero I, Mata M, Clemente G, Prieto M, Margarit C, Bernardos A, Casafont F. Incidence and outcome of de novo malignancies after liver transplantation. *Transplant Proc* 1999; **31**: 1275-1277 [PMID: 10083569 DOI: 10.1016/S0041-1345(98)01994-0]

5 **Mells G**, Mann C, Hubscher S, Neuberger J. Late protocol liver biopsies in the liver allograft: a neglected investigation? *Liver Transpl* 2009; **15**: 931-938 [PMID: 19642126 DOI: 10.1002/lt.21781]

6 **Takatsuki M**, Uemoto S, Inomata Y, Egawa H, Kiuchi T, Fujita S, Hayashi M, Kanematsu T, Tanaka K. Weaning of immunosuppression in living donor liver transplant recipients. *Transplantation* 2001; **72**: 449-454 [PMID: 11502975 DOI: 10.1097/00007890-200108150-00016]

7 **Feng S**, Ekong UD, Lobritto SJ, Demetris AJ, Roberts JP, Rosenthal P, Alonso EM, Philogene MC, Ikle D, Poole KM, Bridges ND, Turka LA, Tchao NK. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. *JAMA* 2012; **307**: 283-293 [PMID: 22253395 DOI: 10.1001/jama.2011.2014]

8 **Jonas S**, Neuhaus R, Junge G, Klupp J, Theruvat T, Langrehr JM, Settmacher U, Neuhaus P. Primary immunosuppression with tacrolimus after liver transplantation: 12-years follow-up. *Int Immunopharmacol* 2005; **5**: 125-128 [PMID: 15589470 DOI: 10.1016/j.intimp.2004.09.014]

9 **Matthews JB**, Ramos E, Bluestone JA. Clinical trials of transplant tolerance: slow but steady progress. *Am J Transplant* 2003; **3**: 794-803 [PMID: 12814471 DOI: 10.1046/j.1600-6135.2003.0154.x]

10 **Tisone G**, Orlando G, Angelico M. Operational tolerance in clinical liver transplantation: emerging developments. *Transpl Immunol* 2007; **17**: 108-113 [PMID: 17306741 DOI: 10.1016/j.trim.2006.09.021]

11 **Assy N**, Adams PC, Myers P, Simon V, Minuk GY, Wall W, Ghent CN. Randomized controlled trial of total immunosuppression withdrawal in liver transplant recipients: role of ursodeoxycholic acid. *Transplantation* 2007; **83**: 1571-1576 [PMID: 17589339 DOI: 10.1097/01.tp.0000266678.32250.76]

12 **Eason JD**, Cohen AJ, Nair S, Alcantera T, Loss GE. Tolerance: is it worth the risk? *Transplantation* 2005; **79**: 1157-1159 [PMID: 15880061 DOI: 10.1097/01.TP.0000162084.46555.10]

13 **Mazariegos GV**, Reyes J, Marino IR, Demetris AJ, Flynn B, Irish W, McMichael J, Fung JJ, Starzl TE. Weaning of immunosuppression in liver transplant recipients. *Transplantation* 1997; **63**: 243-249 [PMID: 9020325 DOI: 10.1097/00007890-199701270-00012]

14 **Pons JA**, Yélamos J, Ramírez P, Oliver-Bonet M, Sánchez A, Rodríguez-Gago M, Navarro J, Bermejo J, Robles R, Parrilla P. Endothelial cell chimerism does not influence allograft tolerance in liver transplant patients after withdrawal of immunosuppression. *Transplantation* 2003; **75**: 1045-1047 [PMID: 12698096 DOI: 10.1097/01.TP.0000058472.71775.7D]

15 **Ramos HC**, Reyes J, Abu-Elmagd K, Zeevi A, Reinsmoen N, Tzakis A, Demetris AJ, Fung JJ, Flynn B, McMichael J. Weaning of immunosuppression in long-term liver transplant recipients. *Transplantation* 1995; **59**: 212-217 [PMID: 7839442]

16 **Sandborn WJ**, Hay JE, Porayko MK, Gores GJ, Steers JL, Krom RA, Wiesner RH. Cyclosporine withdrawal for nephrotoxicity in liver transplant recipients does not result in sustained improvement in kidney function and causes cellular and ductopenic rejection. *Hepatology* 1994; **19**: 925-932 [PMID: 8138267 DOI: 10.1002/hep.1840190419]

17 **Tisone G**, Orlando G, Cardillo A, Palmieri G, Manzia TM, Baiocchi L, Lionetti R, Anselmo A, Toti L, Angelico M. Complete weaning off immunosuppression in HCV liver transplant recipients is feasible and favourably impacts on the progression of disease recurrence. *J Hepatol* 2006; **44**: 702-709 [PMID: 16473433 DOI: 10.1016/j.jhep.2005.11.047]

18 **Tryphonopoulos P**, Tzakis AG, Weppler D, Garcia-Morales R, Kato T, Madariaga JR, Levi DM, Nishida S, Moon J, Selvaggi G, Regev A, Nery C, Bejarano P, Khaled A, Kleiner G, Esquenazi V, Miller J, Ruiz P, Ricordi C. The role of donor bone marrow infusions in withdrawal of immunosuppression in adult liver allotransplantation. *Am J Transplant* 2005; **5**: 608-613 [PMID: 15707417 DOI: 10.1111/j.1600-6143.2004.00743.x]

19 **Koshiba T**, Li Y, Takemura M, Wu Y, Sakaguchi S, Minato N, Wood KJ, Haga H, Ueda M, Uemoto S. Clinical, immunological, and pathological aspects of operational tolerance after pediatric living-donor liver transplantation. *Transpl Immunol* 2007; **17**: 94-97 [PMID: 17306739 DOI: 10.1016/j.trim.2006.10.004]

20 **Mazariegos GV**, Sindhi R, Thomson AW, Marcos A. Clinical tolerance following liver transplantation: long term results and future prospects. *Transpl Immunol* 2007; **17**: 114-119 [PMID: 17306742 DOI: 10.1016/j.trim.2006.09.033]

21 **Yoshitomi M**, Koshiba T, Haga H, Li Y, Zhao X, Cheng D, Miyagawa A, Sakashita H, Tsuruyama T, Ohe H, Ueda M, Okamoto S, Egawa H, Wood K, Sakaguchi S, Manabe T, Tanaka K, Uemoto S. Requirement of protocol biopsy before and after complete cessation of immunosuppression after liver transplantation. *Transplantation* 2009; **87**: 606-614 [PMID: 19307800 DOI: 10.1097/TP.0b013e318195a7cb]

22 **Wu TJ**, Wang YC, Wu TH, Lee CF, Chan KM, Lee WC. Inhibition of allogenic T-cell cytotoxicity by hepatic stellate cell via $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T cells in vitro. *Transplant Proc* 2012; **44**: 1055-1059 [PMID: 22564624 DOI: 10.1016/j.transproceed.2012.03.029]

23 **Cisneros L**, Londoño MC, Blasco C, Bataller R, Miquel R, Bruguera M, Ginès P, Rimola A. Hepatic stellate cell activation in liver transplant patients with hepatitis C recurrence and in non-transplanted patients with chronic hepatitis C. *Liver Transpl* 2007; **13**: 1017-1027 [PMID: 17600343 DOI: 10.1002/lt.21178]

24 **Wang J**, Leclercq I, Brymora JM, Xu N, Ramezani-Moghadam M, London RM, Brigstock D, George J. Kupffer cells mediate leptin-induced liver fibrosis. *Gastroenterology* 2009; **137**: 713-723 [PMID: 19375424 DOI: 10.1053/j.gastro.2009.04.011]

25 **Yu C**, Wang F, Jin C, Huang X, Miller DL, Basilico C, McKeehan WL. Role of fibroblast growth factor type 1 and 2 in carbon tetrachloride-induced hepatic injury and fibrogenesis. *Am J Pathol* 2003; **163**: 1653-1662 [PMID: 14507672 DOI: 10.1016/S0002-9440(10)63522-5]

26 **Ishak K**, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; **22**: 696-699 [PMID: 7560864 DOI: 10.1016/0168-8278(95)80226-6]

27 **Calne RY**, Sells RA, Pena JR, Davis DR, Millard PR, Herbertson BM, Binns RM, Davies DA. Induction of immunolog-

ical tolerance by porcine liver allografts. *Nature* 1969; **223**: 472-476 [PMID: 4894426 DOI: 10.1038/223472a0]

28 **Zimmermann FA**, Davies HS, Knoll PP, Gokel JM, Schmidt T. Orthotopic liver allografts in the rat. The influence of strain combination on the fate of the graft. *Transplantation* 1984; **37**: 406-410 [PMID: 6369673 DOI: 10.1097/00007890-198404000-00019]

29 **Crispe IN**, Dao T, Klugewitz K, Mehal WZ, Metz DP. The liver as a site of T-cell apoptosis: graveyard, or killing field? *Immunol Rev* 2000; **174**: 47-62 [PMID: 10807506 DOI: 10.1034/j.1600-0528.2002.017412.x]

30 **Khanna A**, Morelli AE, Zhong C, Takayama T, Lu L, Thomson AW. Effects of liver-derived dendritic cell progenitors on Th1- and Th2-like cytokine responses in vitro and in vivo. *J Immunol* 2000; **164**: 1346-1354 [PMID: 10640749]

31 **Bonacchi A**, Petrai I, Defranco RM, Lazzeri E, Annunziato F, Efsen E, Cosmi L, Romagnani P, Milani S, Failli P, Batignani G, Liotta F, Laffi G, Pinzani M, Gentilini P, Marra F. The chemokine CCL21 modulates lymphocyte recruitment and fibrosis in chronic hepatitis C. *Gastroenterology* 2003; **125**: 1060-1076 [PMID: 14517790 DOI: 10.1016/S0016-5085(03)01194-6]

32 **Marra F**. Chemokines in liver inflammation and fibrosis. *Front Biosci* 2002; **7**: d1899-d1914 [PMID: 12161342]

33 **Tullius SG**, Tilney NL. Both alloantigen-dependent and -independent factors influence chronic allograft rejection. *Transplantation* 1995; **59**: 313-318 [PMID: 7871557]

P- Reviewers: Boucek C, Pompili M **S- Editor**: Ma YJ
L- Editor: A **E- Editor**: Ma S

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327

J Hepatobiliary Pancreat Sci (2014) 21:E62–E64
DOI: 10.1002/jhbp.120

TECHNICAL VIEW

How to explant a diseased liver for living donor liver transplantation after previous gastrectomy with severe adhesion (with video)

Susumu Eguchi · Akihiko Soyama · Mitsuhisa Takatsuki · Masaaki Hidaka · Tomohiko Adachi · Amane Kitasato · Zhassulan Baimakhanov · Tamotsu Kuroki

Published online: 4 June 2014

Abstract We performed living donor liver transplantation (LDLT) in a patient who had undergone distal gastrectomy for gastric ulcer disease with Billroth I reconstruction 30 years before the LDLT. The adhesion was very severe between remnant stomach and hepatic hilum as well as left liver lobe with shortening of hepatoduodenal structures. After dissection of the infrahepatic inferior vena cava, the Spiegel lobe was identified from the dorsal side. The Spiegel lobe was then penetrated with a right angle dissector so that a plastic tape could be placed around the whole adhesion, including important structures in the hepatoduodenal ligament. Next, the right hepatic vein was transected with a vascular stapler using Pringle's maneuver using the plastic tape to fasten the entire adhesional structure. Subsequently, the trunk of the middle and left hepatic vein was transected after clamping. The remaining short hepatic veins in the left side were divided completely from the cranial to the caudal direction to dissect Spiegel's lobe. Finally, the hepatoduodenal ligament was identified from the attached remnant stomach and the duodenum and a vascular clamp was placed on the entire hepatoduaodenal ligament. Finally, the diseased liver was explanted for graft implantation. Thus, retrograde explantation of the liver was effective in decreasing the risk of damaging vital elements in the hepatoduodenal ligament, the remnant stomach, and the duodenum.

Keywords Adhesion · Explantation · Gastrectomy · Live donor · Liver transplantation · Retrograde

S. Eguchi (✉) · A. Soyama · M. Takatsuki · M. Hidaka · T. Adachi · A. Kitasato · Z. Baimakhanov · T. Kuroki
Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
e-mail: sueguchi@nagasaki-u.ac.jp

Introduction

A history of previous upper abdominal surgery, such as gastrectomy, sometimes precludes or makes it difficult to perform explantation of the diseased liver for subsequent liver transplantation. In particular, living donor liver transplantation (LDLT) requires a piggyback procedure due to the absence of inferior vena cava (IVC) in the graft liver [1]. However, no technical considerations for such cases have been published to date. Although LDLT donor hepatectomy in patients with a previous history of gastrectomy or gastrectomy for gastric cancer or morbid obesity after liver transplantation have been reported in detail [2–4], there have been few reports of liver transplantation after gastrectomy [5–7].

We recently performed LDLT in a patient who had previously undergone open distal gastrectomy with Billroth I reconstruction for gastric ulcer disease 30 years before the LDLT. We herein report our experience with retrograde explantation of the cirrhotic liver in this unique case with severe adhesion between remnant stomach and the diseased liver.

Technical view

The patient was a 63-year-old male who suffered from end-stage liver failure due to hepatitis C in May 2013. LDLT was indicated, and preoperative angiographic computed tomography suggested severe adhesion of the hepatoduodenal ligament to the diseased liver as well as collateral blood vessels around the esophagus and retroperitoneum. The adhesion would be very severe probably because of the previous use of silk ligature and von Pets stapling device at that time. He had an upper midline incision for previous distal gastrectomy for gastric ulcer disease done 30 years ago.

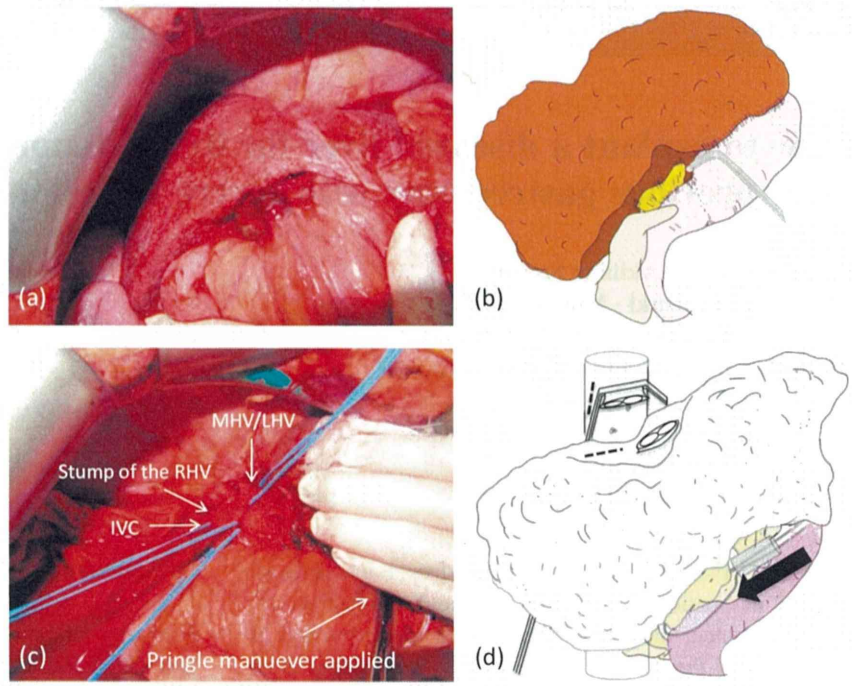

Fig. 1 (**a**) Severe adhesion between the remnant stomach and diseased liver with a shortened hepatoduodenal ligament. (**b**) Illustration of the procedure. The operators left fingers were used as a guide to penetrate the Spiegel lobe. (**c**) Under Pringle's maneuver, the right hepatic vein was transected using a vascular stapler, and the trunk of the middle and left hepatic veins was made ready for transection. (**d**) Illustration of the procedure. Arrows indicate the fastened plastic tape for Pringle's maneuver

A Mercedes-Benz incision was made. The adhesion between the anastomotic site in the stomach and the hepatic hilum, as well as the left liver lobe, was very severe (Fig. 1a, Video S1). In addition, a shortening of the hepatoduodenal structure was found.

Mobilization of the right lobe of the liver was started, and the short hepatic veins were separated from the right side as much as possible. Then, the adhesion between the infrahepatic IVC and the hepatoduodenal ligament was roughly dissected and the Spiegel lobe was identified from the dorsal side. Subsequently, after securing the infrahepatic IVC, the Spiegel lobe was penetrated with a right angle dissector using left index and middle fingers of the operator as a guide so that a plastic tape could be placed around the entire adhesion, including important structures in the hepatoduodenal ligaments, without injuring the remnant stomach (Video S2, Fig. 1c,d). However, transection of the whole hepatoduodenal ligament was still impossible because of the adhesion between remnant stomach and the left liver lobe, which created a shortening of the hepatoduodenal structure.

Therefore, we decided to proceed with retrograde explantation of the whole liver. The right hepatic vein was encircled with a vessel loop and transected with a vascular stapler (ECHELON FLEX ENDOPATH Staplers, Ethicon Endo-surgery; Johnson & Johnson, Cincinnati, OH, USA) under Pringle's maneuver, using the plastic tape to fasten the entire adhesional structure (Fig. 1b,c) [8]. Because of the sufficient collateral venous formation as seen in preoperative imaging, no severe intestinal edema was encountered. Subsequently, the trunk of the middle and left hepatic vein was transected after clamping for subsequent anastomosis. The remaining short hepatic veins were separated completely from the cranial to the caudal direction to dissect Spiegel's lobe. At this point, the adhesion between remnant stomach and left liver lobe was able to be dissected. Finally, all structures in the hepatoduodenal ligament were transected in a lump as close to the liver as possible after applying a vascular clamp (Video S3). The hepatic arteries and portal branches in addition to the hepatic ducts were then dissected, respectively. Vascular clamps on the portal vein and each hepatic artery were placed, and the patient was made ready for implantation of the graft liver under cross-clamping of the IVC. An extended left liver graft with middle hepatic vein from the patient's daughter was implanted in our regular fashion (graft weight 416 g) [8, 9]. Because enough length of the portal vein was dissected out, interpositional graft was not required.

No other significant events occurred throughout the LDLT procedure, with a total amount of blood loss of 16,000 g and a total operative time of 1,031 min including functional anhepatic time after Pringle's procedure until reperfusion of the graft of 231 min. The patient's postoperative course was rather uneventful, and he was discharged from our hospital on the 60th day after the LDLT. He was doing well 7 months after the LDLT at the time of writing.

Discussion

Performing LDLT in patients with a previous history of abdominal surgery is therapeutically challenging. In

particular, prior gastric surgery greatly precludes the ability to dissect the hepatoduodenal ligament and small omentum for LT. However, few previous reports on this topic have been published in the updated literature of the field of liver transplantation or hepatobiliary surgery. We herein presented a case of LDLT with retrograde explantation of the diseased liver for piggyback LDLT.

We performed retrograde explantation of the liver because it was impossible to mobilize the liver from the left side and dissect the hepatoduodenal ligament due to massive severe adhesion between the remnant stomach and the left liver lobe. After we recognized the situation on a preoperative 3D-reconstructed image, we presumed the possibility to perform retrograde explantation of the liver, achieving successful results. As one of the options to achieve safe and passable explantation of a diseased liver without damaging severely attaching neighboring organs, we believe that retrograde explantation could be considered for cirrhotic cases with sufficient collateral veins. Also in case of shortened hepatoduodenal ligament, this procedure could have a role. Recently, laparoscopic gastrectomy has become a routine procedure for treating early-stage gastric cancer, and the incidence of adhesion after gastrectomy should be less than that observed in open surgery [5]. In addition, the use of robotic gastrectomy was recently reported [4]. However, previous gastric surgery performed many years ago with silk threads, etc. sometimes presents a difficult situation at the risk of massive bleeding or damaging a remnant reconstructed stomach [10]. Also in our case, the shortening of the hepatoduodenal ligament due to massive adhesion precluded safe transection of hepatoduodenal ligament before transecting hepatic veins.

We believe that performing retrograde explantation of the liver can be one of the options for LDLT in such patients who had previously undergone open gastrectomy or other upper abdominal surgeries.

Conflict of interest None declared.

Author contributions Study design: SE, ZB. Acquisition of data: AS, MH. Analysis and interpretation: SE, MT. Manuscript drafted by: SE, MT. Critical revision: AS, MT.

References

1. Tzakis A, Todo S, Starzl TE. Orthotopic liver transplantation with preservation of the inferior vena cava. Ann Surg. 1989;210:649–52.
2. Uchiyama H, Shimada M, Imura S, Morine Y, Kanemura H, Arakawa Y, et al. Living donor liver transplantation using a left hepatic graft from a donor with a history of gastric cancer operation. Transpl Int. 2010;23:234–5.
3. Nagata Y, Eguchi S, Takatsuki M, Enjoji A, Ichikawa T, Hayashi T, et al. Experience of gastric cancer in a patient who had received a living-donor liver transplantation. Gastric Cancer. 2007;10:187–90.
4. Elli EF, Masrur MA, Giulianotti PC. Robotic sleeve gastrectomy after liver transplantation. Surg Obes Relat Dis. 2013;9:e20–2.
5. Lin MY, Tavakol MM, Sarin A, Amirkiai SM, Rogers SJ, Carter JT, et al. Laparoscopic sleeve gastrectomy is safe and efficacious for pretransplant candidates. Surg Obes Relat Dis. 2013;9:653–8.
6. Heimbach JK, Watt KD, Poterucha JJ, Ziller NF, Cecco SD, Charlton MR, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. Am J Transplant. 2013;13:363–8.
7. Taneja S, Gupta S, Wadhawan M, Goyal N. Single-lobe living donor liver transplant in a morbidly obese cirrhotic patient preceded by laparoscopic sleeve gastrectomy. Case Rep Transplant. 2013;2013:279651.
8. Soyama A, Takatsuki M, Adachi T, Kitasato A, Torashima Y, Natsuda K, et al. A hybrid method of laparoscopic-assisted open liver resection through a short upper midline laparotomy can be applied for all types of hepatectomies. Surg Endosc. 2014;28:203–11.
9. Eguchi S, Takatsuki M, Hidaka M, Tajima Y, Kanematsu T. Evolution of living donor liver transplantation over 10 years: experience of a single center. Surg Today. 2008;38:795–800.
10. Gemmell CG, Gorham SD, Monsour MJ, McMillan F, Scott R. The in-vitro assessment of a collagen/vicryl (polyglactin) composite film together with candidate suture materials for potential use in urinary tract surgery. III. Adherence of bacteria to the material surface. Urol Res. 1988;16:381–4.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Video S1 The adhesiolysis around the remnant stomach.
Video S2 Encircling the shortened hepatoduodenal ligaments through the Spiegel lobe.
Video S3 Retrograde hepatectomy with Pringle's maneuver and implantation of the graft liver.