遺伝子型，ウイルス量，遺伝子変異が知られている．また，患者因子として肝線維化，男性，年齢などがある[11]．最新のリバビリンバビリンを併用した治療法では薬剤の組み合わせが協力になっていることからウイルス因子は効果予測に有用でなくなってきている．すなわち，HCV 1型で HCV RNA 量が多くても著効にいたる症例もあり，新たな視点からの検討が必要である．Bressler らは肥満が IFN 効果に悪影響を及ぼすとし，body mass index（BMI）が30kg/m²以上の患者では，それ以下の患者に比し20%の SVR であるとしている[12]．また，Romero-Gomez らによれば HCV 遺伝子型，線維化に加えてインスリン抵抗性が影響因子であると報告している．その根拠として HOMA-IR が著効例では1.55±1.01であるのに対して非著効例では2.21±1.47と有意に高く，かつ著効率は HOMA-IR が 2 以下で60.5%，2～4 では40%，4 以上では20%とインスリン抵抗性が増すに従い低下している[13]．治療薬剤が強力になるに従い治療効果を規定する要因として個体因子がより鮮明になるものと思われる．

現時点でのC型慢性肝炎の治療アルゴリズム

C型慢性肝炎に対する治療モダリティーは多岐にわたり，それとともに治療効果は上昇している．各々の治療法の適応と特性を理解したうえで患者一人一人に合った治療を行なうべきである．C型肝炎治療の基本的な考えとして，第1に HCV 感

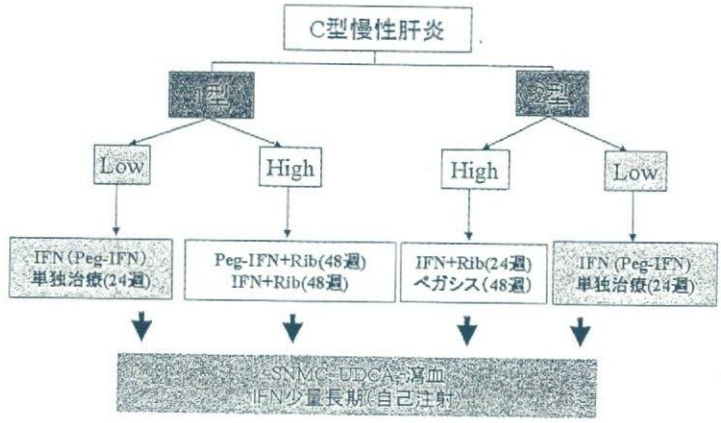

図2　初回治療例

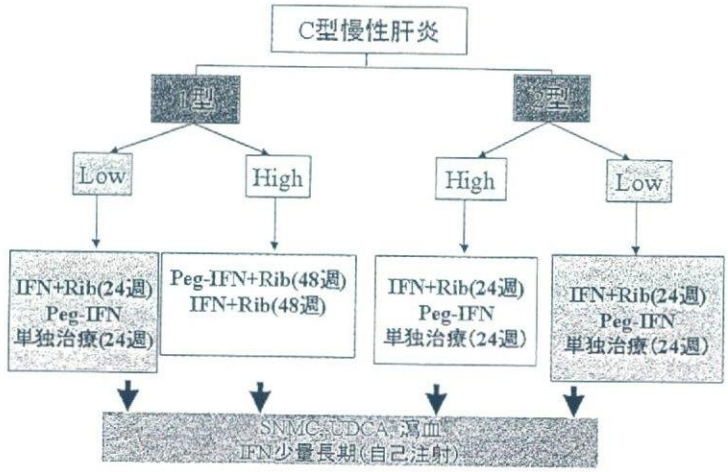

図3　再治療例

染を完全に根絶する（SVRを目指す），第2にそれが不可能な場合は肝癌発生を抑制するという視点からの治療を行なう．また初回治療であるか，再治療であるかにより治療法を考える必要がある．

初回治療例のアルゴリズムを図2に，再治療例のアルゴリズムを図3に示した．SVRを望めなくても肝発癌を抑制する観点から，少量のIFNα製剤を長期投与を行うことも可能となっている．

おわりに

C型慢性肝炎に対する抗ウイルス療法の進歩は著しい．どの患者ではどの治療法がよいかを見極め，患者に十分なインフォームド・コンセントを行なった上で行なうべきである．一方，副作用には十分注意して行なう必要がある．今回は抗ウイルス療法につき述べたが，無効例，非適応例には瀉血療法，UDCA療法，グリチルリチン注射療法など試みる価値がある．HCV感染に起因する肝発癌は着実に抑制されつつあるが，非著効者については今後の研究がさらに必要である．

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Case Report

Steroid-Resistant Late Acute Rejection after a Living Donor Liver Transplantation: Case Report and Review of the Literature

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Nakanishi, C., Kawagishi, N., Sekiguchi, S., Akamatsu, Y., Sato, K., Miyagi, S., Takeda, I., Hukushima, K., Aiso, T., Sato, A., Fujimori, K. and Satomi, S. *Steroid-Resistant Late Acute Rejection after a Living Donor Liver Transplantation: Case Report and Review of the Literature*. Tohoku J. Exp. Med., 2007, **211** (2), 195-200 —— The majority of acute cellular rejection occurs in the first few months after liver transplantation. It has been, however, reported that some recipients experience late acute rejection, which occurs more than 3 months after transplantation. We herein report a case of late acute rejection that occurred nearly 10 years after liver transplantation. The patient is a 27-year-old male who underwent a living donor liver transplantation when he was 17 years old. At 9 years 6 months after transplantation, the patient presented with the elevated serum levels of liver enzymes and total bilirubin. A liver biopsy showed acute cellular rejection. Steroid bolus therapy was not effective, but we successfully used deoxyspergualin as a rescue therapy. Late acute cellular rejection that occurs nearly 10 years after transplantation has so far been rarely reported. It is generally believed that late acute rejection may be more resistant to treatment and be associated with a higher rate of graft loss, as well being associated with the development of chronic ductopenic rejection. In this report, we have shown that deoxyspergualin is safe and effective for treatment of steroid-resistant late acute rejection, preventing from graft loss of chronic rejection. ———— liver transplantation; deoxyspergualin; late acute rejection; steroid-resistant

Acute cellular rejection usually occurs within 3 months after transplantation (Klintmalm et al. 1989). Late acute cellular rejection (LAR), which occurs more than 3 months after transplantation, affects 8-32% of pediatric liver transplant recipients (Sellers et al. 1997; D'Antiga et al. 2002) and 7-23% of adult recipients (Anand et al. 1995; Ramji et al. 2002). However, there have so far been very few reports on LAR that occurs nearly 10 years after transplantation.

The typical management of acute cellular rejection involves the optimization of the baseline immunosuppression such as tacrolimus and cyclosporine, and methylprednisolone boluses.

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However, it is generally believed that LAR may be more resistant to medical treatment and thus is associated with the development of chronic rejection and graft loss. LAR that is resistant to steroids is likely to progress to chronic rejection (Samuel et al. 1990).

Deoxyspergualin (DSG) was isolated from the *bacillus lacterosporus* found in Japanese fields, which inhibits not only the maturation of T lymphocytes but also the activation, differentiation and maturation of B lymphocytes (Fujii et al. 1990). It has been used as a rescue therapy in steroid-resistant acute cellular rejection in renal transplantation. In liver transplantation, Groth et al. (1990) reported the reversal of acute rejection with DSG in a patient in whom previous treatments with steroids and anti-CD3 murine monoclonal antibody (OKT-3) had failed. We used DSG, which showed a good efficacy and safety in patients with steroid-resistant rejection, after liver transplantation (Kawagishi et al. 2006).

We herein report a case of steroid-resistant LAR that occurred 9 years and 6 months after living donor liver transplantation, which we successfully treated with DSG.

Case Report

The patient, a 27-year-old male, who underwent Kasai's operation for biliary atresia on the 56th days after birth. Living donor liver transplantation (LDLT) was performed using a left liver graft from his father due to hepatic failure, when the patient was 17 years old. The patient underwent a choledochojejunostomy 3 times with the placement of as external biliary drainage tube, because of posttransplant biliary stenosis. Despite these efforts, he had to be admitted several times with recurrent bouts of cholangitis. The initial immunosuppression consisted of methylprednisolone and tacrolimus. Methylprednisolone was stopped at 1 year and 3 months posttransplant and the patient was then followed only with tacrolimus.

At 5 years after transplantation, the liver enzyme and total bilirubin levels were moderately elevated. Acute mild cellular rejection was diagnosed by a liver biopsy. A single course of methylprednisolone, 500 mg per day for 3 days, proved to be effective.

At 9 years 6 months after transplantation, he was admitted to our hospital presenting with the

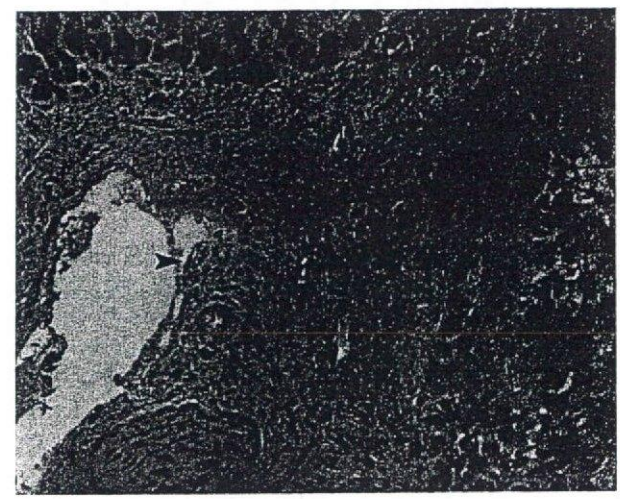

Fig. 1. A biopsy before methylprednisolone boluses therapy showed mild acute cellular rejection. The portal tract were expanded because of a predominantly lymphocytes infiltration (black arrow). Note also the subendothelial localization of lymphocytes in a small portal vein branch (black arrowhead). In this specimen, the bile duct was obscure. The rejection activity index (RAI) score was 4-5 (P2, B unknown, V1). Hematoxylin and eosin (× 200).

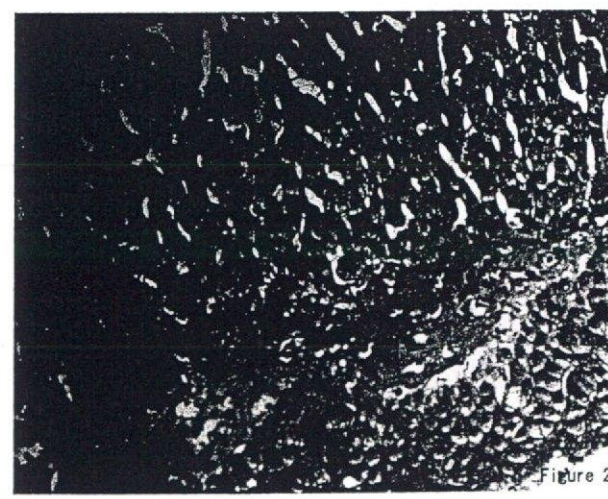

Fig. 2. Biopsy after deoxyspergualin therapy showed improvement of acute cellular rejection. Lymphocytes infiltrations in portal tracts improved (black arrow). The RAI score was 3 (P1, B1, V1). Hematoxylin and eosin (× 100).

elevated serum levels of the liver enzymes (AST 66 IU/l and ALT 90 IU/l) and total bilirubin (2.8 mg/dl). A liver biopsy showed acute mild cellular rejection (Fig. 1). His tacrolimus trough level on admission was 2.9 ng/ml, which he had kept the same level for many years. He received the bolus treatment with methylprednisolone, 500 mg per day for 3 days. The serum levels of the ALT and AST were increased to 319 IU/l and 127 IU/l, respectively. The tacrolimus trough level was 4.9 ng/ml after the bolus methylprednisolone therapy. Then a second liver biopsy was performed that showed no improvement. He was administered DSG (Spanidin®, Nippon Kayaku Co., Ltd., Tokyo) at a dose of 3 mg/kg/day for 8 days together with intravenous methylprednisolone over 5 days (it was started at a dose of 250 mg/day, then taped to 8 mg/day) and tacrolimus at a dose of 2 mg/day. The tacrolimus trough level increased to 5.7 ng/ml. The third liver biopsy, which was performed just after DSG therapy, showed improvement of the cellular rejection (Fig. 2). He was subsequently maintained on tacrolimus (3 mg/day), mycophenolate mofetil (MMF) (1,000 mg/day), and methylprednisolone (8 mg/day) as immunosuppressive agents. After these therapies, his liver function gradually improved and he was discharged at 53 days after DSG therapy (Fig. 3). The tacrolimus trough level was 6.9 ng/ml a week before discharge. There was no adverse effect associated with these therapies. The patient is currently in good condition without any signs of rejection at 10 months after discharge.

Discussion

The majority of acute cellular rejection occurs in the first few months after liver transplantation (Klintmalm et al. 1989), and most centers aim to taper off the steroids and minimize maintenance immunosuppression within the first year. On the other hand, LAR may occur under conditions of low immunosuppression. It is reported that LAR occurred in 7-23% of adult patients and in 8-32% of pediatric patients (Anand et al. 1995; Sellers et al. 1997; D'Antiga et al.

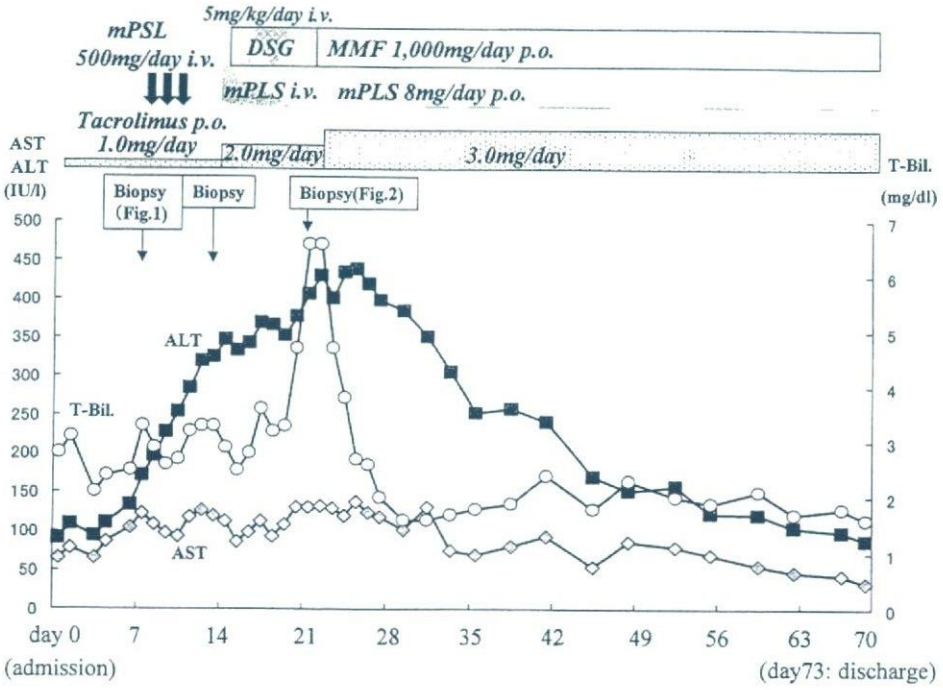

Fig. 3. Clinical course.
T-Bil, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; mPSL, methylprednisolone; DSG, deoxyspergualin; MMF, mycophenolate mofetil.

2002; Ramji et al. 2002). Florman et al. (2004) reported that forty-three (8.1%) recipients of 532 recipients with more than 1,000 days follow-up, who did not have hepatitis C, were identified, and had biopsy proven LAR at a mean of 1,545 ± 441 days post-transplant. In their report, 38 of the 43 (88.4%) patients with LAR had earlier episode of acute cellular rejection before 1,000 days post-transplant. In other word, only 5 (0.9%) of 532 recipients had initial episode of acute cellular rejection after 1,000 days. Furthermore, the initial episode of LAR occurred after more than 1,500 days in 21 (48.8%) of 43 patients and after more than 2,000 days in 6 (14%) of 43 patients (Florman et al. 2004).

Sundaram et al. (2006) reviewed 90 liver biopsies performed on pediatric patients at least 6 months posttransplant, and reported 15% of the biopsy specimens to have LAR. Furthermore, they suggested that centrilobular changes (inflammation, necrosis, or endothelialitis), when accompanied by elevated transaminase, should prompt consideration of LAR, even if they do not meet the classical criteria based upon characteristic portal tract features, such as portal tract lymphocytic infiltration or portal endothelialitis (Sundaram et al. 2006).

The factors predisposing patients to develop LAR include an underlying liver disease, a decreased immunosuppression, and poor compliance (Mor et al. 1992; Farges et al. 1996; Berlakovich et al. 1998; D'Antiga et al. 2002). The Canadian group reported that only patients undergoing transplantation with a pretransplantation diagnosis of viral liver disease were found to be less likely to develop an episode of LAR based on a multivariate analysis (Ramji et al. 2002). Florman et al. (2004) suggested that patients with primary sclerosing cholangitis (PSC) should cautiously be withdrawn from immunosuppression, because the patients with PSC had an unusually high incidence of LAR.

Moreover, a recent study showed that continuous treatment with MMF in conjunction with tacrolimus and steroids was associated with a decreased risk of LAR. Wiesner et al. (2006) studied adult primary liver transplant recipients with hepatitis C virus, hepatitis B virus or a non-viral primary cause of liver disease who were recorded as receiving continuous 3-(MMF + tacrolimus + steroids) vs 2-drug (tacrolimus + steroid) therapy for at least 6 months immediately posttransplant. In their study, multivariate regression confirmed 3- vs 2-drug therapy to be associated with a decreased risk of LAR.

In Japan, Akamatsu et al. (2006) reported 15 cases (7%) out of 204 adult living donor liver transplantation recipients to have experienced LAR, which occurred more than 6 months after the transplantation. They indicated that a cyclosporine-based immunosuppression regimen and lower recipient age were significant risk factors for LAR (Akamatsu et al. 2006).

The typical management of acute cellular rejection involves the optimization of baseline immunosuppression and methylprednisolone boluses. Approximately 90% of the patients with acute cellular rejection respond to high dose-steroid therapy. It is generally believed that LAR may be more resistant to medical treatment and it is also associated with a higher rate of graft loss, as well as the development of chronic ductopenic rejection. One study showed that as few as 51% of treated LAR patients completely respond to high-dose steroids, and that 27% of the patients developed chronic rejection and graft loss (Anand et al. 1995). On the other hand, the retrospective review of adult liver transplantation recipients in Western Canada showed that only 6% of LAR episodes were steroid-resistant and required OKT3 (anti-CD3 monoclonal antibody) (Ramji et al. 2002). However, there was a trend toward increased chronic rejection in patients who developed LAR (odd ratio, 2.58; $p = 0.04$) in this study.

Antithymocyte globulin or anti-CD3 monoclonal antibodies such as OKT3 have been used effective in many centers as first-line treatment for steroid-resistant rejection (SRR). These agents, however, have significant adverse effects, such as first-dose cytokine release syndrome that manifests such symptoms as fever, rigors, hypotension, and wheezing. OKT3 also causes immunosuppression, predisposing the patients to infection and lymphoproliferative disorders (Solomon

et al. 1993).

DSG is mainly used as a prophylactic and rescue therapy for acute rejection in kidney transplantation. The efficacy of DSG and that of OKT3 against SRR in renal transplantation have been reported to be comparable (Okubo et al. 1993). In addition, DSG causes less severe adverse effect than thymoglobulin and OKT3. The adverse effects observed in kidney transplant patients included numbness of the face, lips and limbs, gastrointestinal toxicity, bone marrow suppression and the occurrence of infection (Amemiya et al. 1990). Moreover, DSG has been found, in a rat model, to reverse acute liver graft rejection (Engemann et al. 1987). Groth et al. (1990) reported the reversal of liver graft rejection with DSG in a patient in whom previous treatment with steroids and OKT3 had failed. We previously reported that DSG was effective for SRR in 6 out of 8 living donor liver transplantation recipients without inducing any severe adverse effects (Kawagishi et al. 2006). This is our seventh patient, in whom DSG was effective for the treatment of SRR in liver transplantation. And in this case, DSG demonstrated a biopsy proven effect on SRR. In our experience, no significant adverse effects were observed in the liver transplantation recipients. Since DSG has the advantage of showing less severity regarding adverse effects over thymoglobulin and OKT3, DSG is a safe and effective alternative for the treatment of SRR in liver transplantation.

The precise mechanism of the immunological effect of DSG is not known, but DSG has been reported to inhibit the cell cycle at the G0/G1 phase (Nemoto et al. 1987). It also inhibited the maturation of T lymphocytes and the activation, differentiation and maturation of B cells (Fujii et al. 1990). It, furthermore, is believed to inhibit heat shock protein 70 (Nadler et al. 1992).

In summary, we experienced a patient who had LAR nearly 10 years after liver transplantation without either a decreased immunosuppression or poor compliance. In this patient, DSG was found to be a safe and effective treatment modality for steroid-resistant LAR, thereby preventing graft loss and chronic rejection.

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Journal of Gastroenterology

The model for end-stage liver disease score is useful for predicting economic outcomes in adult cases of living donor liver transplantation

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Background. The model for end-stage liver disease (MELD) is useful for assessing the recipients of liver transplants, namely, deceased-donor transplantation. The application of MELD for living donor liver transplantation (LDLT) is under investigation. Thus, the aim of this study was to analyze the impact of the MELD score in LDLT in Japan. ***Methods.*** Seventeen adult cases of LDLT during 2001 to 2005 were enrolled. Indications for LDLT were primary biliary cirrhosis, seven; liver cirrhosis, two; hepatocellular carcinoma (HCC), three; metabolic liver disease, one; primary sclerosing cholangitis, two; Caroli's disease, one; and biliary atresia, one. Total medical charges during the operative periods were retrospectively evaluated. The united network of organ sharing (UNOS) modified was obtained using preoperative clinical data. ***Results.*** The average medical expense of the 17 cases was approximately $97 901. The UNOS-modified MELD score was 22.1. A statistically significant positive correlation was found between the MELD score and medical expense (P = 0.0086, ρ = 0.657), and between the MELD score and the length of stay in the intensive care unit (ICU) (P = 0.0396, ρ = 0.515). The cause of the liver disease leading to transplantation was not related to MELD score, medical expense, or length of ICU stay. ***Conclusions.*** Although not originally designed for the application to LDLT, the MELD score is useful for predicting medical expenses in LDLT. Similar to those of deceased-donor liver transplantation, the disadvantage of high medical expenses associated with a high MELD score allow consideration of an earlier elective operation in suitable cases.

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Key words: MELD score, living donor liver transplantation, Milan criteria

Introduction

Various liver diseases are a leading cause of death worldwide. In Japan, more than 30 000 people die every year from liver-related causes, in particular, hepatocellular carcinoma (HCC). Moreover, the prevalence of HCC is expected to increase over the next 10 years in Japan, as well as in other countries such as the United States.[1,2] HCC usually develops after inflammatory hepatic disease, such as hepatitis B or hepatitis C. The prevalence of these viral induced liver diseases and of other intractable liver diseases such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) is also increasing. Thus, the need for liver transplantation is increasing globally. As a consequence, a shortage of donated organs has caused social problems worldwide, causing in turn the distribution of donated organs to become a critical issue. At the same time, indications for living donor liver transplantation (LDLT) are increasing owing to this organ shortage, and the economic impact is also becoming an important consideration for the distribution of social resources.

The model for end-stage liver disease (MELD) score has been used to evaluate the prognosis of patients with various liver diseases.[3–6] Although this model was originally developed to estimate the prognosis of patients with transjugular intrahepatic portosystemic shunts,[7] its prognostic application to acute liver failure and surgical operations for patients with cirrhosis has shown its potential utility.[8,9] In liver transplantation, the united network of organ sharing (UNOS) has used the MELD score for allocation of deceased-donor organs.[10] Also, in deceased-donor liver transplantation, the risks and costs are well related to the MELD score.[11–13] However,

in living donor liver transplantation, especially in adult cases, the usefulness of the MELD score has not been established. Moreover, the medical fees charged by public health care plans differ in each country. Thus, we evaluated the value of the MELD score in a single Japanese liver transplant center.

Methods

Patients

Between September 2001 and January 2005, 21 consecutive patients received adult living-donor liver transplants in Tohoku University Hospital. One patient with HCC who died during surgery was excluded. Three patients with acute liver failure, two with fulminant hepatitis B, and one with fulminant hepatic failure of unknown etiology were also excluded. The remaining 17 patients, who were followed up during at least 6 months of observation, were enrolled in this study. The etiology of liver disease was PBC, seven patients; chronic viral hepatitis, two; PSC, two; HCC, three; biliary atresia, one; adult onset type II citrullinemia, one; and Caroli's disease, one. These liver diseases were diagnosed on the basis of well-established diagnostic criteria using serological, biochemical, imaging, and, if possible, pathological modalities. Complete information on these patients is listed in Table 1. Of note, the Milan criteria for liver transplantation in HCC cases were met in one of the three patients, although the remaining two did not demonstrate extrahepatic metastasis or major vessel invasion. In all cases, the transplantations were permitted by the Tohoku University Liver Transplantation Indication Committee and Ethical Committee.

MELD score

The calculation of the MELD score (UNOS modified) was performed by using data from just before the plasma exchanges 3 to 4 days prior to liver transplantation. The calculation itself was performed by accessing the Mayo Clinic's Web site (http://www.mayoclinic.org/gi-rst/models.html).

Calculation of medical expenses

Total medical charges during the operative period (from 1 week before the operation until discharge) were calculated. Any expenses that were not considered to be for a standard therapeutic modality, such as plasma exchange for the prevention of hyperacute humoral rejection in ABO incompatible cases, were excluded from the calculation of the medical charges. Other expenses, such as anti-hepatitis B globulin, lamivudine, and interferons, were included. However, no patients were treated with interferon after the operation in the current study, nor did the patients with HCC receive antitumor chemotherapy. All expenses in the current study are expressed in US dollars, which were converted from Japanese yen at the rate of $1.00 = ¥110.0.

Table 1. Patients' profiles

No.	Age	Sex	Cause of liver disease	Hepatitis virus	Prognosis (months)
1	54	M	HCC	HCV	Alive, 44
2	47	F	PBC	None	Alive, 32
3	52	M	HCC	HBV	Alive, 30
4	60	F	PBC	None	Alive, 28
5	42	F	PBC	HBV	Alive, 27
6	55	F	PBC	None	Alive, 26
7	59	F	PBC	None	Alive, 25
8	31	M	CTLN2	None	Alive, 22
9	44	F	Caroli	None	Alive, 22
10	36	F	PSC	None	Alive, 21
11	50	M	CVH	HBV	Alive, 20
12	54	F	HCC	HBV	Alive, 17
13	55	F	PBC	None	Alive, 11
14	63	F	CVH	None	Alive, 10
15	28	M	PSC	None	Alive, 8
16	28	M	BA	None	Alive, 8
17	54	F	PBC	None	Alive, 6

M, male; F, female; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis, CTLN2, adult onset type II citrulinemia; Caroli, Caroli's disease; PSC, primary sclerosing cholangitis; CVH, chronic viral hepatitis; BA, biliary atresia; HCV, hepatitis C virus; HBV, hepatitis B virus

Other parameters

Besides medical expenses, other clinical information such as the cause of the liver disease and the sex and age of the patients was evaluated. Also, the length of stay in the intensive care unit (ICU) and the length of inpatient hospital stay of all recipients were evaluated.

Statistics

Spearman's rank correlation coefficient and the Kruskal-Wallis test were performed using StatView (version 5.1, Abacus Concepts, Berkeley, CA, USA), and differences were considered significant with $P < 0.05$.

Results

Overall patient medical expenses

The MELD (UNOS modification) score ranged from 8 to 39 (mean, 22.1; median, 22). Medical charges were from \$39664 to \$206391 (mean, \$97901; median, \$70573) (Table 2). The lengths of stay in the ICU ranged from 3 to 86 days (mean, 19 days; median, 16 days). Hospital stays were from 38 to 257 days long (mean, 109 days; median, 87 days).

The MELD score and medical expenses

There was a statistically significant correlation between the MELD (UNOS modification) score and medical expense [$P = 0.0086$, ρ (correlation coefficient) = 0.657] (Fig. 1A). Higher MELD scores were associated with a higher medical expense.

The MELD score and the length of stay in the ICU and length of hospital stay

There was a statistically significant correlation between the MELD score and the length of stay in the ICU ($P = 0.0396$; $\rho = 0.515$) (Fig. 1B). The higher MELD score related with a longer stay in the ICU. A weakly positive correlation was observed between the MELD score and overall length of hospital stay, but it was not statistically significant ($P = 0.3390$; $\rho = 0.245$).

The MELD score and cause of liver disease

The mean MELD scores analyzed in relation to the causes of liver disease are shown in Fig. 2A. The MELD score of adult onset type II citrullinemia was low. This disease is characterized by the accumulation of citrulline and hyperammonemia caused by a deficiency of arginosuccinate synthetase, the third enzyme of the urea cycle. Other functions of hepatocytes such as

Table 2. MELD score, medical expense, ICU stay, hospital stay, and complications

No.	MELD	Expense (US dollars)	ICU stay (days)	Hospital stay (days)	Complications
1	15	39664	12	149	Bile spillage, HCV re-infection
2	24	56682	16	52	Rejection, refractory ascites
3	19	66327	17	87	Bile spillage,[a] CMV infection
4	17	47191	8	54	
5	27	206391	24	126	Rejection, hypertension
6	21	93236	22	94	Intra-abdominal bleeding,[a] strangulation of intestine,[a] CMV infection
7	22	80600	16	58	Rejection
8	8	50527	25	38	Bile spillage, peritonitis[a]
9	22	178091	3	250	Rejection, diabetes mellitus
10	22	40600	8	41	
11	39	112645	13	82	Rejection, alive
12	22	66473	7	59	CMV infection
13	25	156955	23	88	Rejection, hypertension, convulsion
14	24	171255	86	257	Out-flow block,[a] pneumonia
15	26	166836	21	192	Intra-abdominal bleeding,[a] hepatic artery thrombosis,[a] cholangitis, liver abscess
16	23	60273	9	79	CMV infection, herpes zoster
17	19	70573	9	149	Drug-induced liver injury

MELD, model for end-stage liver disease (united network of organ sharing); ICU, intensive care unit; CMV, cytomegalovirus
[a] Surgical intervention needed

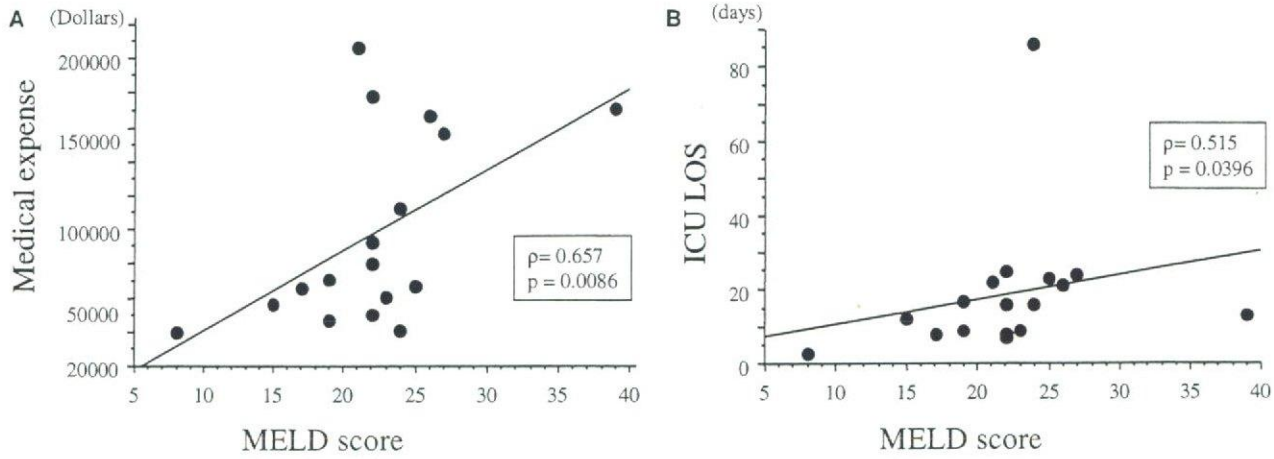

Fig. 1. **A** Relation between MELD score (UNOS) and medical expense. **B** Relation between MELD score (UNOS) and LOS in the ICU. *MELD*, model for end-stage liver disease; *UNOS*, united network of organ sharing; *LOS*, length of stay; *ICU*, intensive care unit

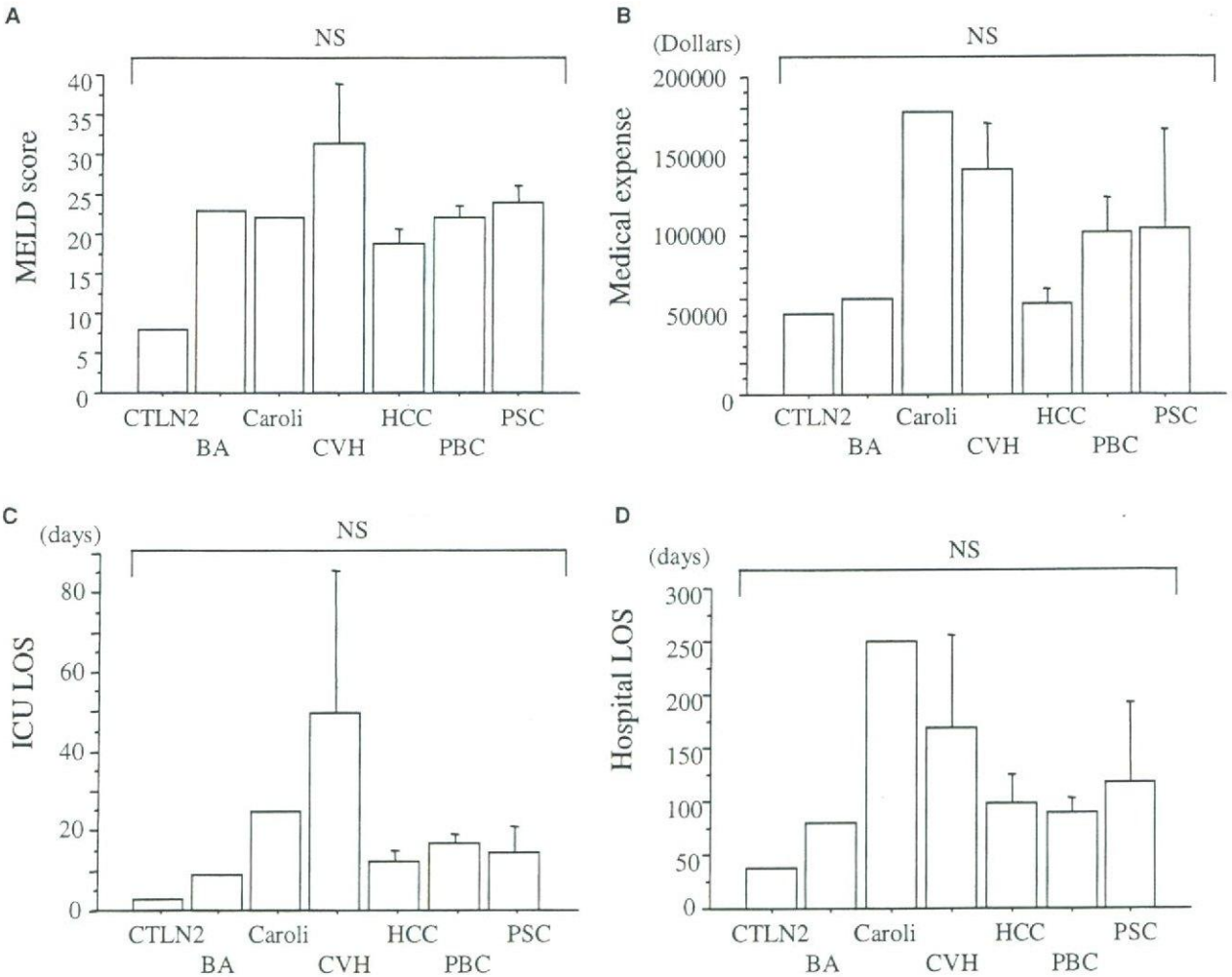

Fig. 2. **A** The MELD score (UNOS modification) and cause of liver diseases. **B** The medical expense and cause of liver diseases. **C** The ICU LOS and cause of liver diseases. **D** The hospital LOS and cause of liver diseases. *CTLN2*, adult onset type II citrullinemia; *BA*, biliary atresia; *Caroli*, Caroli's disease; *CVH*, chronic viral hepatitis; *HCC*, hepatocellular carcinoma; *PBC*, primary biliary cirrhosis; *PSC*, primary sclerosing cholangitis; *NS*, not significant

protein synthesis and bilirubin conjugation are preserved, thus yielding a low MELD score. The mean MELD scores of other diseases ranged from 18.7 to 31.5. There were no significant differences in MELD scores among the causes of liver disease.

Relation of cause of liver disease to medical expense, length of stay in the ICU, and length of hospital stay

The mean values for medical expense, length of stay in the ICU, and length of hospital stay in relation to the causes of liver disease are shown in Figs. 2B–D. There were no significant differences in medical expense, length of stay in the ICU, or length of hospital stay among causes of liver disease.

Complications

Complications during the hospital stay are listed in Table 2. Rejection was observed in six patients. The bile duct complications bile spillage and cholangitis were observed in four patients. Vascular complications such as out-flow block and hepatic artery thrombosis were also observed. Infectious episodes of pneumonia, cholangitis, liver abscess, peritonitis, cytomegalovirus, or herpes zoster were observed in six patients. Hepatitis C virus (HCV) reinfection was observed in one patient, although antiviral therapy with interferon was not administered owing to existing thrombocytopenia. Seven patients needed surgical intervention.

Discussion

Currently, living donor liver transplantation is practically the only available therapeutic options for patients with advanced liver disease in Japan, where the deceased donation rate has never exceeded 20 cases per year.[14] Thus, the number of LDLT cases is increasing every year.[14,15] In particular, HCC as an indication for LDLT is increasing dramatically.[15] The reasons for this trend include (1) the high prevalence of HCV infection in elderly Japanese; and (2) awareness of the limited efficacy of local ablation therapy for the treatment of HCC, especially for recurrences of HCC. In fact, we have reported that local therapy for HCC does not improve a patient's survival if the patient's background liver function meets Child-Pugh B or C.[16] Thus, the timing of liver transplantation is very important in HCC cases. Criteria for liver transplantation in HCC cases have been developed by several investigators.[17,18] Among them, the Milan criteria are most often used as the standard criteria for cadaveric liver transplantation.[17] In fact, several studies have shown that the Milan criteria are valuable in deceased-donor cases. Thus, they have also been applied as the inclusion criteria for LDLT by the public health insurance system of Japan since 2003. Moreover, the Milan criteria are useful for graft allocation in deceased-donor cases, justifying the allocation of donated social resources. In LDLT, graft allocation is not applicable, so the timing of liver transplantation is the more important issue. Recently, we reported that local therapy has a limited role in HCC; hence, it is more important to determine the appropriate timing of LDLT for HCC at an earlier stage.[16]

Besides tumor factors in HCC cases, the hepatic background conditions, such as in other end-stage liver diseases, are also important.[19,20] Although the MELD scoring system was originally developed to evaluate the prognosis of the patients with transjugular intrahepatic portosystemic shunts, a relationship between the MELD score and the prognosis of liver transplantation in deceased-donor cases has been documented.[21] Moreover, the score has been reported to correlate with medical expense and length of hospital stay.[11,13] However, the role of the MELD score in LDLT is not well established because (1) the history of LDLT is short compared with deceased-donor cases; (2) health care plans differ among countries; and (3) public sentiment regarding organ transplantation differs among countries. The policy for determining medical charges for LDLT is different among transplant facilities, because social medical coverage for LDLT is limited in Japan. Thus, a single-center study like the current study has an advantage over multicenter studies in that it avoids these policy biases. Also, public health insurance policy may be modified every year, making it practically impossible to conduct a longer-term study. Although this single-center study has a disadvantage of a small sample size, it demonstrated that a higher MELD score was related to higher economic expenses in a Japanese LDLT series. Moreover, the MELD score was related to a prolonged stay in the ICU. Thus, the MELD score can be useful for determining the optimum timing for liver transplantation, because a lower MELD score predicts a lower medical cost and possibly a shorter hospital day. Especially, in our study, no relationships were found between the causes of liver disease and medical expense.

Currently, the Japanese public health care program does not approve expenses for liver transplantation if the indication of HCC exceeds the Milan criteria.[15] In this case, not all medical expenses will be covered by social health care plans. In this regard, it is extremely important to obtain information by using the MELD score to predict the medical expense in adult cases of LDLT. Moreover, from the point of view of total medical expense, it is strongly recommended that liver transplantation be conducted before the total expenses increase significantly. The application of MELD to

adult cases will provide a certain rationale for determining the timing of LDLT.

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ELSEVIER

Continuous Low-Dose Human Atrial Natriuretic Peptide Promotes Diuresis in Oliguric Patients After Living Donor Liver Transplantation

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ABSTRACT

Human atrial natriuretic peptide (ANP) is beneficial for the prophylaxis of acute renal failure (ARF) after liver transplantation (OLT). We evaluated renal function in OLT patients with or without ARF, describing cases unresponsive to loop diuretics successfully treated with continuous low-dose ANP infusion without hemodialysis.

Twenty-seven consecutive adult-to-adult living donor liver transplantations (LDLTs) were performed in 26 patients. One case was excluded due to the need for continuous hemodialysis (HD) during the operation. Of the 26 cases, 6 (23%, group 2) developed ARF in the first 30 days after LDLT; the other 20 were ARF-free (group 1).

The median follow-up was 24 months. No patient required either continuous or intermittent HD. Only one patient died due to multiple liver abscesses. Mean preoperative serum creatinine (sCr) value and intraoperative blood loss in group 2 were significantly higher than those in group 1. Three cases in group 2 failed to improve on high-dose loop diuretics with low-dose dopamine, exhibiting fluid overload. The remaining three cases in group 2 responded to conventional diuretic treatments. Continuous low-dose ANP was started 2, 4, or 5 days after LDLT, and urine output significantly increased after ANP administration. The serum creatinine values were 1.1, 1.2, and 1.1 at 1 month and 1.0, 0.9, and 0.6 mg/dL at 6 months after LDLT. Massive blood loss during the operation caused ARF, but did not affect renal function after LDLT. Continuous low-dose ANP improved renal function and diuresis for oliguric ARF patients, preventing the need for HD or continuous venovenous hemodialysis.

POSTOPERATIVE acute renal failure (ARF) frequently occurs in patients undergoing liver transplantation (OLT).[1,2] Renal insufficiency has various causes, including preoperative intrinsic renal dysfunction, hepatorenal syndrome (HRS), renal ischemic injury during operation, and calcineurin-inhibitor-associated nephrotoxicity. It continues to be an important source of morbidity and mortality after OLT.[3,4]

Recently, cardiac natriuretic peptides have been used in clinical settings to treat congestive heart diseases.[5,6] These peptide hormones consist of three different prohormones; atrial natriuretic peptide (ANP, A-type natriuretic peptide), brain natriuretic peptide (BNP, B-type natriuretic peptide), and C-natriuretic peptide. However, the use of cardiac natriuretic peptides is controversial among cardiovascular physicians.[7] In OLT, some authors have investigated the use of cardiac natriuretic peptides, such as ANP and BNP, to enhance urinary output and improve renal function.[8–10]

In the present study, we have described cases unresponsive to loop diuretics successfully treated by continuous low-dose ANP infusion without continuous venovenous hemodialysis (CVVHD). We evaluated renal function in living donor liver transplant (LDLT) patients with or without ARF.

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PATIENTS AND METHODS

From March 2003 to December 2005, 27 consecutive adult-to-adult LDLTs were performed in 26 patients. Of these, one case was excluded because CVVHD was required during the operation due to severe hyperkalemia. Therefore, the present study included 26 LDLTs with one retransplantation.The patients included 11 men and 14 women. Mean follow-up was 34 months (range, 7–93 months). The 26 LDLTs were divided into two groups; those who developed ARF early in the postoperative period (group 2), and those who did not develop ARF (group 1). Acute renal failure was defined as a rise in the serum creatinine (sCr) level to more than 2.0 mg/dL.

Indications for LDLT were cholestatic disease (n = 11); viral hepatitis and cirrhosis with or without hepatocellular carcinoma (n = 5); primary biliary cirrhosis or primary sclerosing cholangitis with fulminant hepatic failure (n = 4); biliary atresia (n = 2); and others (n = 3). All but one patient underwent a right liver graft without the middle hepatic vein, as described previously.[11] Initial immunosuppression consisted of the use of tacrolimus (Tac) or cyclosporine (CsA) plus steroids with or without basiliximab. Tac was started within 24 hours after transplantation at an initial dose of 0.075 mg/kg/per day, given orally twice dailly. Target trough level of Tac was 12 to 16 ng/mL during the first month after transplantation and 8 to 12 ng/mL thereafter. CsA was administered intravenously over 4 hours at a dose of 3 mg/kg per day to maintain a trough level of 200 to 250 ng/mL during the first month and of 100 to 200 ng/mL thereafter, according to liver and renal functions.

All patients received dopamine (3–7 μg/kg per min) and prostaglandin E1 (10–20 ng/kg per min) during and after LDLT. If diuresis remained below 0.5 mL/kg per hour despite effective volume expansion, a high-dose of a loop diuretic (furosemide) was infused; the dose was adjusted according to a target urine output of 1.5 to 2.0 mL/kg per hour. When patients were unresponsive to treatment with high doses of furosemide, they received a continuous low-dose infusion of recombinant human ANP (HANP, Daiichi Asubio Pharmaceuticals, Tokyo, Japan) at an infusion rate of 0.015 μg/kg per min.

Results were expressed as mean values ± standard deviations (SD). Comparisons between groups were performed by the Mann-Whitney U test for nonparametric data. Statistical significance was designated as $P < .05$.

RESULTS

Of the 26 LDLTs, six (23%, group 2) developed ARF that was defined as a sCr level greater than 2.0 mg/dL in the first 30 days after LDLT; and 20 cases did not develop ARF (group 1). All but one patient survived the operation. The five patients (25%) in group 1 who developed severe hepatic encephalopathy were treated with CVVHD to maintain cerebral stability before LDLT. The clinical characteristics of the two groups are shown in Table 1. In the various preoperative factors, except renal function tests, there were significant differences only in the blood loss during the operation and the ratio of graft volume to standard liver volume between the two groups.

Table 1. Clinical Characteristics of 26 LDLT Patients

	Group 1 (n = 20)	Group 2 (n = 6)	P Value
Age (y)	45 ± 14	45 ± 13	NS
Male/female ratio	9/11	3/3	NS
MELD score	22.7 ± 8.5	24.2 ± 8.1	NS
GV/SLV (%)	53.6 ± 7.8	44.8 ± 5.1	.0126
Immunosuppression			
Tac/CsA	19/1	3/3	NS
BMX (yes/no)	15/5	4/2	NS
Blood loss (mL/kg)	147.5 ± 190.6	772.5 ± 598.2	.0008

Abbreviations: LDLT, living donor liver transplantation; MELD, models for end-stage liver diseases; GV/SLV, the ratio of the graft volume to standard liver volume; Tac, tacrolimus; CsA, cyclosporine A; BXM, basiliximab; NS, not significant.

Table 2. Changes in Renal Function Tests Between the 2 Groups

	Group 1 (n = 20)	Group 2 (n = 6)	P Value
Pre CCr (mL/min)	85.1 ± 31.5 (*1)	58.2 ± 9.9	.0365
sCr (mg/dL)			
Pre	0.57 ± 0.20 (*1)	1.30 ± 0.60	.0029
Peak	0.91 ± 0.36	2.75 ± 0.34	.0003
6mos	0.71 ± 0.28	1.08 ± 0.22	NS
1y	0.78 ± 0.38	1.27 ± 0.64	NS
Peak BUN (mg/dL)	35.3 ± 14.7	84.0 ± 26.5	.0007

Abbreviations: LDLT, living donor liver transplantation; (*1), 5 patients were excluded due to undergoing continuous hemodialysis before transplantation; sCr, serum creatinine value; Pre, pre-operation; Peak, peak values of serum creatinine within 1 month after liver transplantation; 6mos, 6 months after liver transplantation; 1y, 1 year after liver transplantation; CCr, creatinine clearance; BUN, blood urea nitrogen; NS, not significant.

The changes in renal function after LDLT are shown in Table 2. The mean values of preoperative sCr and creatinine clearance among group 2 patients were significantly higher than those among group 1. However, there was no significant difference between the two groups with regard to the values of mean sCr at 6 months and 1 year after LDLT.

Three patients in group 2 failed to respond to repeated high doses of furosemide plus low-dose dopamine in the first week after LDLT, exhibiting fluid overload. A continuous low-dose ANP regimen was subsequently initiated for these three patients for diuresis. Continuous low-dose ANP was started at 2, 4, or 5 days after LDLT; urine output significantly increased thereafter (Fig 1). All three patients showed restored renal function after continuous ANP therapy. However, in contrast to patients in group 1, sCr values in group 2 recovered with good renal function: 1.1, 1.2, and 1.1 at 1 month and 1.0, 0.9, and 0.6 mg/dL at 6 months after LDLT.

DISCUSSION

Despite significant advances in the management of ARF, cases requiring hemodialysis have been recognized to be at increased risk factor for early mortality after OLT.[3,4] Conservative treatments using diuretics such as furosemide and potassium canrenoate are frequently needed to achieve the desired urine output in the immediate to early postoperative periods following LDLT. However, intermittent administration of these conventional diuretics is sometimes unsuccessful, and CVVHD is required in some patients.[1–4]

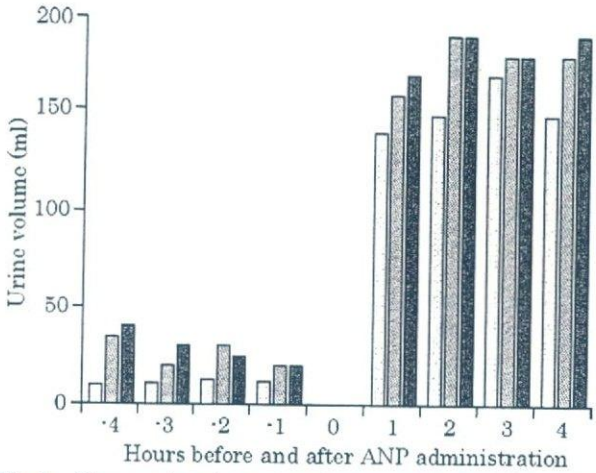

Fig 1. Changes in urine output before and after continuous low-dose ANP administration. (Abbreviations: ANP, atrial natriuretic peptide.)

Currently, in Japan, only ANP is clinically used, (HANP) and BNP is not commercially available. It remains controversial whether administration of ANP or BNP is effective to treat congestive heart failure with ARF.[5–7] In our series, the three patients (12%) who developed furosemide-resistant ARF, were successfully rescued by continuous low-dose ANP without CVVHD. The main factor affecting ARF in all patients with furosemide-resistant ARF was considered to be renal ischemic changes associated with massive blood loss during LDLT. Low-dose ANP was well tolerated in patients with such ARF due to massive blood loss, producing significantly enhanced urine output within the first hour immediately after infusion. In addition, low-dose ANP therapy showed no adverse effects such as hypotension or ventricular tachycardia.

HRS has been recognized to be reversible for the success of OLT, although its pathogenesis is complex. In our series, the number of patients with HRS was four in group 1 and three in group 2. Among them, all but one patient who developed chronic renal failure due to preexisting chronic glomerulonephritis showed a decreased sCr level compared to the normal range.

In conclusion, In this study, massive blood loss during the operation was an important risk factor for postoperative ARF but had no effect on renal function within 1 year after LDLT. Continuous low-dose ANP showed beneficial effects on renal function and on diuresis as a therapeutic agent for oliguric ARF patients, thereby preventing the requirement for HD or CVVHD. Further studies are needed to assess the effects of low-dose ANP therapy on diuresis in furosemide-resistant acute oliguric renal failure among a larger number of LDLT patients.

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Obstructive jaundice caused by biliary stone formation around the stent after liver transplantation

Kawagishi N, Matsuo C, Takeda I, Miyagi S, Satoh K, Akamatsu Y, Sekiguchi S, Fujimori K, Satomi S. Obstructive jaundice caused by a biliary stone formation around the stent after liver transplantation. Pediatr Transplantation 2006: 10: 835–837. © 2006 Blackwell Munksgaard

Abstract: We report an unusual case of obstructive jaundice caused by a biliary stone, which developed in the stump of a Roux-en-Y hepaticojejunostomy after undergoing LT. The patient was a 13-yr-old male. At 74 days after birth, a hepaticojejunostomy (Kasai's procedure) was performed for the treatment of biliary atresia. He underwent a reduced size deceased donor LT in the left subphrenic space twice at the age of one and three years in Australia. Eleven years after his second LT, he developed liver dysfunction and jaundice with a low grade fever. Computed tomography showed a marked jejunal loop enlargement by a rugby ball-shaped stone and the bile duct in the graft was thus dilated. A surgical exploration revealed the jejunal loop to be bent sharply while its stump side was dilated by stagnated bile including a biliary stone. The stone included a stent that had been previously used for the hepaticojejunostomy. This case suggests that a retained stent used for hepaticojejunostomy had thus caused biliary stone formation because of a combination of various conditions in the jejunal loop.

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Key words: biliary stone – obstructive jaundice – liver transplantation – situs inversus totalis – diagnosis – stent

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Biliary complications tend to be one of the difficult problems in LT. Among these complications, biliary stone formation is a well-recognized entity, resulting most frequently from bile stasis associated with the biliary strictures, either anastomotic or intrahepatic. However, biliary stone formation caused by a dislocated stent in the jejunal loop is very rare, and it is also not easy to predict. We herein report a very rare case of biliary stone formation caused by a dislocated stent in the jejunal loop. In addition, we discuss the findings of other similar reports including those describing recipients demonstrating situs inversus totalis.

Case report

A male infant had biliary atresia. Dextrocardia, abdominal situ inversus, and polysplenia were diagnosed in the neonatal period. At two months of age, he underwent a Kasai operation (porto-enterostomy) at our institution. However, he later needed a reduced-size deceased donor LT twice at the age of one and three years in Australia. He was in stable condition until the age of eight years, but he suffered from hepatic vein stenosis resulting in frequent interventional treatment. At the age of 12 years, he had metallic stent placed in the hepatic vein anastomosis and a good hepatic vein flow was obtained since that treatment. He was maintained on tacrolimus (1.4 mg/day) and prednisolone (3 mg/day) as immunosuppressive agents. At the age of 14 years, he suddenly developed jaundice with a deterioration of liver function tests and was therefore admitted to our hospital. He had mild fever with high levels of AST (158 IU/L), ALT (186 IU/L), T-Bil (3.9 mg/dL), and CRP of 1.80 mg/dL, with a white blood cell count of 2100/μL. The patient had no complaints except for mild fever. A physical examination showed a graft liver in the epigastric region with poor

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, biliary atresia; CRP, c-reactive protein; LT, liver transplantation; T-Bil, total bilirubin.

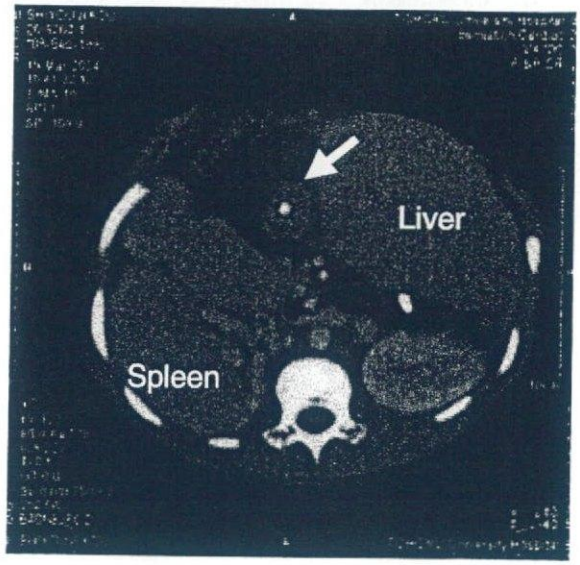

Fig. 1. Computed tomography of a dilated jejunal loop containing a biliary stone around stent tube (arrow head).

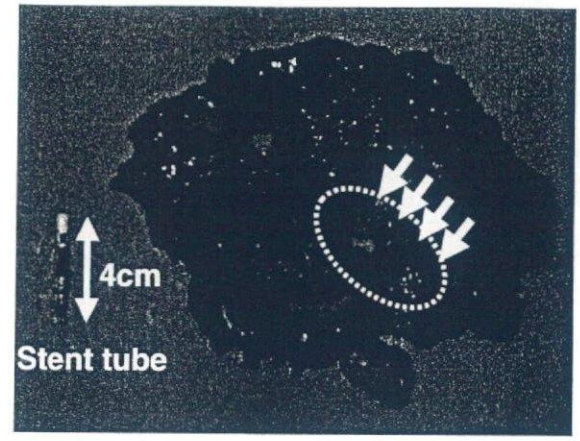

Fig. 2. Biliary stones and sludge with stent after removal. Arrow head shows the location of stent tube.

Table 1. Reported cases of jejunal loop obstruction by biliary stone after LT

Case	Age at Tx (yr)	Sex	Disease	Type of graft	Time to obstruction (yr)	Stent related stone	Reference
1	4	M	BA	Whole	18	No	(1)
2	3	F	BA	Whole	11	Yes	(2)
This case	1 and 3	M	BA	Reduced size	11	Yes	

BA, biliary atresia.

mobility and there was no abdominal tenderness. The superficial lymph nodes were not palpable. The palpebral conjunctivae were not pale and the bulbar conjunctivae were stained yellow. Computed tomography showed a marked jejunal loop enlargement by a rugby ball-shaped stone and the bile duct in the graft which was dilated (Fig. 1). The intra-graft blood flow including the hepatic vein, portal vein and hepatic artery was good based on the findings of Doppler ultrasonography, and no perfusion defects were observed in the graft by CT. An emergency operation was thus performed to correct the obstructive jaundice. A surgical exploration revealed the jejunal loop to be bent sharply and its stump side was dilated with stagnated bile including the presence of a biliary stone. The stone had formed around the stent which had been previously used for the hepaticojejunostomy and the diameter of the stone was about 4 cm (Fig. 2). An exploration of the inside revealed the jejunal loop to be filled with a brittle mass which mostly consisted of bile sludge. We therefore assumed that the bent jejunal loop had thus caused stagnation of the bile flow, and thereafter the dislocated stent had caused biliary stone formation: however, the stone had resulted in an obstruction of the hepaticojejunostomy. We removed the mass of bile sludge and clean out the lumen of the jejunal loop. And we inserted the drainage tube into the jejunal loop. After the operation the serum bilirubin temporarily increased, subsequently, it gradually decreased. On the 74th day, the patient was discharged without any symptoms and his liver function studies were within the normal range.

Discussion

We experienced the case of a boy with obstructive jaundice caused by a biliary stone, which developed in the stump of Roux-en-Y hepaticojejunostomy after LT. A dislocated stent used for hepaticojejunostomy causing biliary stone formation is, to our knowledge, one of the rarest causes thus far reported in the literature (1, 2) (Table 1). In addition, this case also had situs inversus totalis.

Biliary complications are considered the Achilles' heel of LT because of their frequency and their lethal potential on the eventual survival of both graft and recipient. The overall incidence of biliary complications after LT appears to be decreasing, from the 30% in the pioneering years to about 20% in the 1980s, and now to the current levels of 15%, except for an occasional series with a very low incidence (3). Some authors reported that the incidence of biliary complications was similar in reduced-size and full-size grafts (4). However, it is generally considered to be more difficult to reconstruct the biliary tract in

pediatric cases than in adult cases because of the small diameter of the biliary tract (5). The long-term outcome of such biliary complications has been discussed in the literatures (6, 7). In our case, the common bile duct was used for the anastomosis and the anastomotic site did not have a stricture, so that the use of an internal biliary catheter to stent the anastomosis became a late-onset life threatening complication. Previous studies have reported about stent-related morbidities and mortalities (8). However, from a historical point of view, the necessity of using stents for the biliary reconstruction has been reported from many institutions because of the high incidence of complications linked to these procedures. It was reported that some immunosuppressants had been associated with gallstone formation (9), but in this case it was not clear the relationships. This case had two biopsy proven rejections those were treated by pulse therapy and there were no infections like cholangitis before this operation.

In situs inversus totalis, the opposite orientation of the hilar vessels and biliary tract between the donor and recipient must be overcome in order to avoid distortion and kinking of the anastomosed vessels and intestine. This is a rare congenital condition which is estimated to affect one in 20 000 individuals and the cause is currently unknown although chromosomes involved in lateralization and polarity have been determined (10). In pediatric LT, in recipients with biliary atresia, there have been a few reports about situs inversus (11). Most were managed successfully with technical modifications and scrupulous attention in spite of the fact that the complex anomalies increased the technical difficulties of the operation. In our case, we could not identify the choledochojejunostomy because of severe adhesions, however, the biliary stone including the stent was extirpated completely. We therefore considered that the outcome in terms of the removal of the cause of biliary stenosis had thus been successfully completed and the anatomical difficulties associated with situs inversus were not affected by the operation.

In conclusion, a biliary stone developed around a dislocated stent, secondarily to a functional disorder of the efferent loop and in the absence of biliary or intestinal mechanical strictures, which caused obstructive jaundice. In recipients demonstrating situs inversus totalis, careful attention should be paid to avoid surgical failure because the anatomical orientation tends to be extremely complex.

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