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CASE REPORT

Effective balloon-occluded retrograde transvenous obliteration of the superior mesenteric vein–inferior vena cava shunt in a patient with hepatic encephalopathy after living donor liver transplantation

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Abstract Balloon-occluded retrograde transvenous obliteration (BRTO) has become a common and effective procedure for treating hepatic encephalopathy due to a portosystemic shunt related to cirrhosis of the liver. However, this method of treatment has rarely been reported in patients after liver transplantation. Here, we report the case of a 52-year-old patient who underwent living donor liver transplantation (LDLT) due to hepatitis C virus-infected hepatocellular carcinoma that was complicated with portal vein thrombosis and a large portosystemic shunt between the superior mesenteric vein (SMV) and inferior vena cava (IVC). The SMV–IVC shunt was not obliterated during LDLT because there was sufficient portal flow into the graft after reperfusion. However, the patient was postoperatively complicated with encephalopathy due to the portosystemic shunt. BRTO was performed and was demonstrated to have effectively managed the encephalopathy due to the SMV–IVC shunt, while preserving the hepatic function after LDLT.

Keywords BRTO · Living donor liver transplantation · Portosystemic shunt · Hepatic encephalopathy

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BRTO	Balloon-occluded retrograde transvenous obliteration
CECT	Contrast-enhanced computed tomography
IVC	Inferior vena cava
LDLT	Living donor liver transplantation
PV	Portal vein
SMV	Superior mesenteric vein
T.Bil	Total bilirubin

Introduction

Portal hypertension associated with the development of portal vein thrombosis often occurs in patients with cirrhosis of the liver. The subsequent formation of portosystemic shunts due to formed collateral vessels and hepatic encephalopathy as a consequence are also frequently observed [1]. These kinds of severe complications are generally resolved after liver transplantation without the need for occlusion of the prior portosystemic shunt [2]. However, persistent collateral vessels with a portosystemic shunt can remain, especially after living donor liver transplantation (LDLT), due to the smaller graft size, portal hyperperfusion and various other factors [3].

Here, we report the case of a patient who underwent effective balloon-occluded retrograde transvenous obliteration (BRTO) treatment for hepatic encephalopathy due to a persistent superior mesenteric vein (SMV)–inferior vena cava (IVC) shunt after LDLT.

Case report

A 52-year-old female patient underwent LDLT with splenectomy for hepatitis C virus-infected liver cirrhosis complicated with hepatocellular carcinoma. Before LDLT, contrast-enhanced computed tomography (CECT) revealed a thrombosis of the portal vein (PV) that was 4 cm in length starting 2 cm proximal from the superior mesenteric vein and splenic vein confluence as well as a direct SMV–IVC shunt with a diameter <1 cm (Fig. 1). A left lobe graft was transplanted from the patient's brother; the graft volume was 365 ml, corresponding to 34.6 % of the recipient's standard liver volume. On the first and second postoperative days, she underwent relaparotomy because of bleeding from the short gastric veins and inferior diaphragmatic veins, respectively, which improved after surgical treatment. On postoperative day 7, thrombosis in the PV was detected by CECT examination, and intravenous infusion of heparin (5,000 U/day) was started.

Two months after the transplant, the patient complained of drowsiness and confusion. The laboratory data showed slightly elevated levels of alanine aminotransferase (ALT; 56 U/l), aspartate aminotransferase (ALT; 57 U/l) and high levels of serum ammonia (185 μg/dl, normal range 0–70), alkaline phosphatase (821 IU/l) and total bilirubin (T.Bil; 12.8 mg/dl) which had been gradually decreasing after the LDLT (from 15.1 mg/dl). CECT revealed no evidence of increasing size of the collateral vein vessels or SMV–IVC shunt, and stable hepatic blood flow was confirmed by Doppler ultrasound examination. In addition, the previously detected PV thrombosis had disappeared. Cholangiography was performed and did not show biliary stenosis.

To treat the encephalopathy, an intravenous drip infusion of a branched-chain amino acid solution (Aminoleban®) at 500 ml/day and lactulose (30 ml/day) were started. During treatment, the ammonia level decreased to 92 μg/dl (T.Bil decreased to 4.7 mg/dl). After improvement and stabilization of the patient's general condition and laboratory data, she was discharged and transferred to a local hospital.

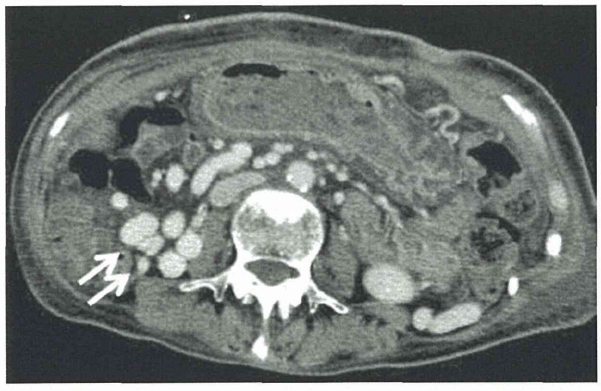

Fig. 1 Axial section of abdominal CECT showed collateral vessels with a direct SMV–IVC shunt (*white arrow*)

Four months later, i.e., 6 months after LDLT, the patient presented with a new episode of hepatic encephalopathy with mild confusion, and was readmitted to our department. CT scans revealed stenosis of the PV anastomosis, which was confirmed by angiography and successfully treated with stent placement and percutaneous transluminal angioplasty ballooning. Subsequently, the patient became asymptomatic and was discharged with recommended anticoagulation therapy. One year later, however, hepatic encephalopathy appeared again. The laboratory data showed an increased ammonia level (169 μg/dl) with normal liver and renal function tests (ALT 30 U/l, AST 35 U/l, T.Bil 0.8 mg/dl, prothrombin time 72 %, albumin 3.4 g/dl, platelets 22.9 × 10^4/μl and creatinine 0.48 mg/dl). CECT revealed satisfactory PV stent placement without stenosis. Furthermore, Doppler ultrasound examination showed sufficient hepatic blood flow. A biopsy showed mild hepatitis that was not considered severe enough to induce portal hypertension. Nevertheless, the encephalopathy was refractory to conservative pharmacotherapy, and the ammonia level continued to rise to 219 mg/dl. The hepatic encephalopathy was graded as Western Haven Criteria grade III. Ultimately, the previously detected SMV–IVC shunt (Fig. 2a, b) was deemed to be the main cause of hepatic encephalopathy, and BRTO was therefore indicated.

BRTO was performed according to the method reported by Kanagawa et al. [4]. In brief, a 6-Fr balloon catheter (Cobra type Selecon MP II, Terumo, Tokyo, Japan) was introduced into the SMV–IVC shunt via the right femoral vein. The SMV–IVC shunt was visualized after retrograde venography using Iopamiron 300 contrast medium (Schering, Osaka, Japan) under inflation of the balloon (Fig. 2c). Interlocking detachable coils were used to embolize the small outflow vessels. Initially, 10 % ethanolamine oleate solution was used as a sclerosing agent; however, the degree of blood flow stagnation was insufficient to use ethanolamine oleate. Therefore, the sclerosing agent was a mixture of *n*-butyl-2-cyanoacrylate and Lipiodol® (ratio 1:4) and a total volume of 4 ml was inserted through the 1.8-Fr microcatheter. After BRTO, control venography showed the disappearance of the portosystemic shunt with sufficient filling by the sclerosing agent (Fig. 2d). Afterwards, the whole catheter system was withdrawn. No complication occurred during the procedure. Subsequently, the patient's blood ammonia level decreased to within the normal range (51 μg/dl) with a normal liver function (ALT 50 U/l, AST 54 U/l, T.Bil 0.7 mg/dl, prothrombin time 60 %, albumin 3.6 g/dl, platelets 32.9 × 10^4/μl), and she has not experienced any

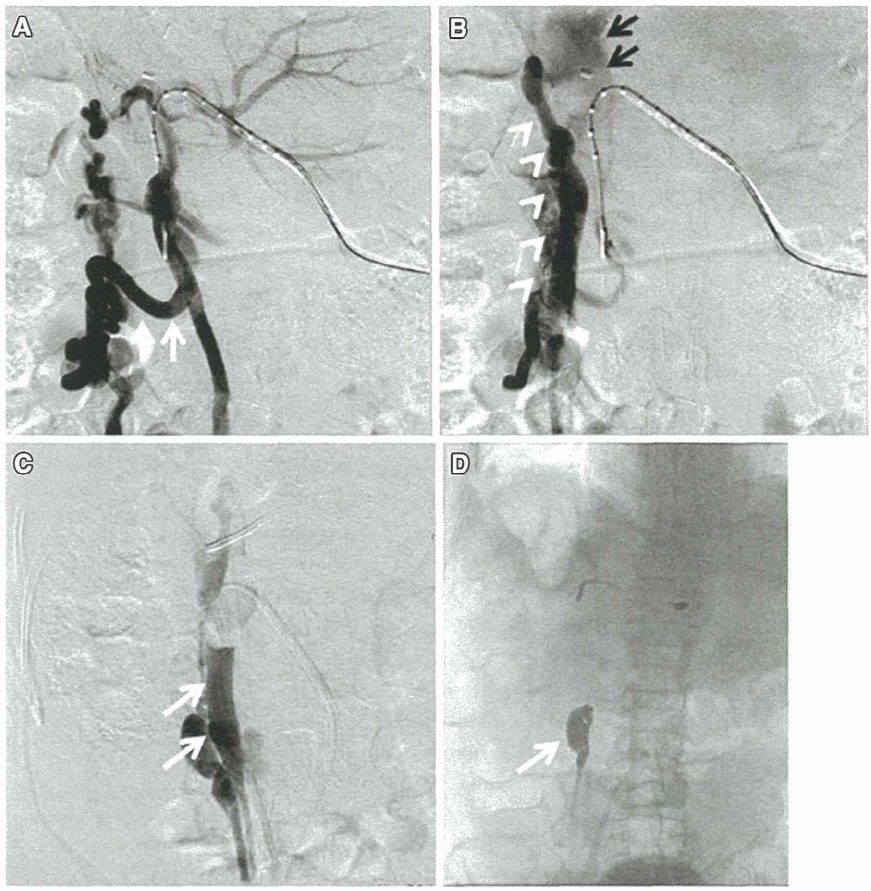

Fig. 2 **a** Portography showed collateral vessel from the SMV (*white arrows*) in the early phase. **b** The shunt (*white arrowheads*) was visualized directly going to the IVC (*black arrows*) in the late phase. **c** Retrograde venography before BRTO after inserting a 1.8 Fr microcatheter directly into the SMV–IVC shunt (*white arrows*). **d** The control view after BRTO showed that the shunt was sufficiently filled with sclerosing agent (*white arrow*)

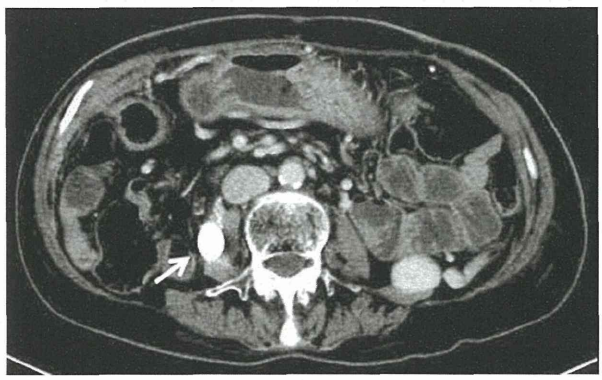

Fig. 3 Follow-up CT scan taken 9 months after BRTO showed the sclerosant (*white arrow*) with the complete disappearance of the SMV–IVC shunt

episodes of hepatic encephalopathy since then. Presently, 11 months after BRTO, the patient is well, and follow-up CT has shown no evidence of the portosystemic shunt (Fig. 3), with sufficient hepatic blood flow.

Discussion

It remains controversial as to whether a portosystemic shunt detected before liver transplantation should be occluded during liver transplantation. A portosystemic shunt could decrease the portal vein flow after liver transplantation, leading to the subsequent formation of portal vein thrombosis, graft atrophy and other serious consequences [5, 6]. On the other hand, the presence of a shunt can have a positive effect on liver perfusion in cases with relative portal hypertension in the early postoperative period, especially after LDLT [5, 7]. Moreover, even after shunt vessel ligation during LDLT, there is still a chance of recurrence after surgery and this procedure might be ineffective [8].

It should be noted that in our case, the portosystemic encephalopathy occurred 1 year after stent placement and percutaneous transluminal angioplasty ballooning for stenosis of the PV anastomosis. Even the stent placement without further recurrence of the PV stenosis and with sufficient hepatic blood flow did not prevent the occurrence of portosystemic encephalopathy due to the persistent portosystemic shunt.

Hepatic encephalopathy that occurs due to a portosystemic shunt after LDLT requires immediate and adequate treatment. Nevertheless, conservative therapeutic treatment for this complication is often applied, and may be ineffective, as in our case [9]. Therefore, BRTO has recently been reported to be a less invasive treatment method for portosystemic encephalopathy [6, 7, 9–12]. However, the effectiveness of BRTO treatment for portosystemic encephalopathy after LDLT has rarely been reported, and BRTO for an SMV–IVC shunt after liver transplantation has not been reported previously [13]. Yokoyama et al. [13] reported successful BRTO treatment for a patient with hyperammonemic encephalopathy, which occurred 10 years after LDLT; however, the patient did not have a cirrhotic liver and the cause of the portosystemic shunt was unknown. Therefore, this condition may occur at any time, despite the presence of a normal liver function without signs of portal hypertension, in patients with a persistent portosystemic shunt after LDLT.

The effectiveness of BRTO treatment for patients after LDLT with gastric varices and liver dysfunction, including hyperbilirubinemia and hyperammonemia, without hepatic encephalopathy caused by prolonged portosystemic shunts has also been reported [14]. BRTO seems to be an effective treatment, regardless of the interval between the development of symptoms due to the portosystemic shunt and LDLT.

In conclusion, the lower invasiveness and lack of impact on the transplanted graft function are the most important points of BRTO treatment for portosystemic encephalopathy after LDLT, especially for patients like the present case, with normal liver function and who have previously undergone several abdominal surgeries that have likely led to the formation of severe intra-abdominal adhesions. Moreover, the other advantages that we experienced were complete disappearance of the encephalopathy symptoms and rapid recovery after BRTO treatment. BRTO is therefore considered to be an effective management strategy for portosystemic encephalopathy that preserves the hepatic function after LDLT.

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Disclosures

Conflict of Interest: Zhassulan Baimakhanov, Akihiko Soyama, Mitsuhisa Takatsuki, Yusuke Inoue, Hajime Matsushima, Masaaki Hidaka, Amane Kitasato, Tomohiko Adachi, Tamotsu Kuroki, Ichiro Sakomoto and Susumu Eguchi declare that they have no conflict of intererst.

Humans/Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008(5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

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Clinical Transplantation

Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation

Takatsuki M, Soyama A, Muraoka I, Hara T, Kinoshita A, Yamaguchi I, Tanaka T, Kuroki T, Eguchi S. Post-operative complications requiring hospitalization more than one yr after living donor liver transplantation.

Abstract: Background/Purpose: The long-term outcomes after living donor liver transplantation (LDLT) have not been clearly established. This retrospective study assessed long-term outcomes after LDLT through reviewing complications requiring hospitalization more than one yr after engraftment.
Methods: Sixty-five LDLT recipients alive more than one yr post-transplantation were enrolled, 37 males and 28 females, with a median age at transplantation of 53 yr (range, 0–68 yr). We reviewed all post-operative complications requiring hospitalization more than one yr after LDLT.
Results: There were 61 post-operative complications requiring hospitalization in 43 of the 65 patients (66%), and the majority of these complications were transplantation related (59/61; 97%). Despite this, 43 (78%) of 55 surviving patients had normal liver function at their last follow-up, and 50 patients (91%) achieved normal activity (Karnofsky score 100%).
Conclusions: More than one-half of our LDLT recipients required hospitalization more than one yr post-LDLT to treat a complication. Most were able to maintain their quality of life and liver function with appropriate treatment.

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Key words: liver transplantation – living donor

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Living donor liver transplantation (LDLT) was developed as an alternative to deceased donor liver transplantation (DDLT), particularly in Eastern countries including Japan, where the number of DDLTs is fairly low and the short-term results of LDLT are comparable to those of DDLT. However, although several studies have examined long-term recipient LDLT technical complication and allograft original disease recurrence rates (1–4), long-term LDLT efficacy remains unclear. Complication severity determines the requirement for hospital treatment. Our study aim was to determine LDLT long-term patient outcomes through analyzing complications requiring in-hospital treatment more than one yr after LDLT.

Patients and methods

Patients

Ninety-three LDLTs were performed at Nagasaki University between August, 1997 and January, 2009. Of the 93 patients, 65 survived more than one yr after LDLT and were enrolled in this study, 37 males and 28 females, with a median age at transplantation of 53 yr (range, 5 months–68 yr). Seven (11%) of these cases were pediatric patients (less than 15 yr old). The original diagnoses were hepatitis C virus (HCV) cirrhosis - 21 patients (15 with hepatocellular carcinoma; HCC), hepatitis B virus (HBV) cirrhosis - 12 (10 with HCC), biliary atresia - 8, fulminant hepatic failure - 8, primary

biliary cirrhosis - 4, alcoholic cirrhosis - 3, and other diagnoses - 9 patients.

Perioperative management

The indication for transplantation in HCC cases was based on the Milan criteria. Splenectomy was performed in HCV cirrhosis recipients and pre-emptive HCV treatment with pegylated interferon and ribavirin was administered for several months post-transplantation. For HBV cirrhosis cases, lamivudine or entecavir was administered pre-transplantation and intravenous anti-HBV immunoglobulin was administered while the recipient was an-hepatic, and thereafter, with intermittent re-treatment to maintain HBV surface antibody levels post-transplantation. The target blood levels of antibody were; more than 200 IU/mL during the first month post-transplantation, 100–200 IU/mL for months one through 3 and 50–100 IU/mL thereafter.

Lamivudine or entecavir was continued post-LDLT. Base immunosuppression was with tacrolimus and steroids. Oral tacrolimus 0.05 mg/kg twice daily was begun on the first post-operative day. The target trough levels were: 10–15 ng/mL for the first month post-transplantation and less than 10 ng/mL, thereafter. Methylprednisolone was administered intravenously – 10 mg/kg for pediatric cases and 1 g for adult cases – during surgery, just after allograft reperfusion. Post-operative methylprednisolone tapering was from 0.5 mg/kg i.v. four times daily for the first three post-operative d to 0.5 mg/kg twice daily for the next three d to prednisolone 0.5 mg/kg once daily at day seven post-transplantation. Steroids were discontinued, after tapering, at six months if the liver function was stable. In selected cases, mycophenolate mofetil or azathioprine was added. Post-transplant antibiotic prophylaxis consisted of cefazolin and ampicillin, 1 g each, four times a day, for three d. When anti-cytomegalovirus immunoglobulin G was positive in the donor and negative in the recipient, prophylactic gancyclovir, 5 mg/kg/d twice daily for 14 d post-transplantation was administered. Trimethoprim-sulfamethoxazole 1 g daily was administered for three months post-transplantation for *Pneumocystis jirovecii* pneumonia prophylaxis.

Biliary reconstruction was through duct-to-duct anastomosis, when possible, except in patients with biliary atresia or primary sclerosing cholangitis. A chloride vinyl tube (2 mm diameter) biliary splint was placed at the anastomotic site to prevent stricture and this was externalized through the upper edge of the duodenum with a Witzel-type fistula. This tube was removed three to four months after the LDLT in a two-step protocol (5): the tube was withdrawn under X-ray control to the most peripheral part of the tract established by the Witzel's canalization. On the next day, after confirming the absence of bile leakage and peritonitis, the tube was completely removed.

Follow-up at the outpatient clinic

After discharge, patients were followed at an outpatient clinic every two wk to three months, the frequency being case determined. The patient's complete blood count, prothrombin time, serological studies, and standard liver function tests were checked routinely. Multi-detector computed tomography (MDCT) and/or a magnetic resonance imaging studies were performed routinely to determine liver regeneration, the blood vessel patency, and HCC recurrence every 6–12 months. Cytomegalovirus antigen and/or beta-D glucan levels were checked occasionally. HCV-RNA was checked monthly in HCV patients and HBV-DNA was checked in HBV cases.

When a study disclosed a significant abnormality, hospitalization was determined by the disease severity, the requirement for additional tests (e.g., liver biopsy) and the anticipated treatment. Usually, the decision to hospitalize was made by the attending physician at the outpatient clinic. When a patient developed liver failure, the indication for re-transplantation considered the patient's general condition including the existence of infections. The model for end-stage liver disease (MELD) score was considered, but not applied strictly.

Assessment of the daily activity

Karnofsky scoring was used to assess a patient's daily activity as follows:

1. 100% = normal, no complaints, no signs of disease
2. 90% = capable of normal activity, few symptoms or signs of disease
3. 80% = normal activity with some difficulty, some symptoms or signs
4. 70% = caring for self, not capable of normal activity or work
5. 60% = requiring some help, can take care of most personal requirements
6. 50% = requires help often, requires frequent medical care
7. 40% = disabled, requires special care and help
8. 30% = severely disabled, hospital admission indicated but no risk of death

9. 20% = very ill, urgently requiring admission, requires supportive measures or treatment
10. 10% = moribund, rapidly progressive fatal disease processes
11. 0% = death

This evaluation was done for each patient at the last follow-up by the same clinician (M.T.).

The incidence and types of complications, and their treatment and outcome, for all 65 patients were retrospectively reviewed.

Results

Complications more than one yr after LDLT

The overall one-, three-, and five-yr patient/graft survivals after LDLT were 90%/88%, 75%/74%, and 70%/69%. Sixty-one complications requiring hospitalization more than one yr after LDLT occurred in 43 patients (66%) with a median follow-up period of 42 months (range, 14–137 months). Most complications were related to transplantation (59/61; 97%). These complications were

1. Surgical complications in 18 patients (15 biliary strictures, two cases portal vein stenosis, one hepatic vein stenosis)
2. Complications of the original disease in 11 patients (with induction of HCV treatment in eight patients, untreated HCC recurrence in two, liver failure due to alcohol abuse in one)
3. Rejection in eight patients (acute cellular rejection in seven and chronic rejection in one)
4. Infectious complications in nine patients (enteritis in three patients, cellulitis in two, and one patient each with herpes zoster, spontaneous bacterial peritonitis, *Aspergillus* sinusitis, and human T lymphocyte virus-1 associated myelopathy [HAM]).
5. Other complications in 13 patients (de novo autoimmune hepatitis in four, non-B non-C hepatitis in one, surgery for cataracts possibly from steroid treatment in three, gastrointestinal bleeding due to portal hypertension in two, one renal failure possibly tacrolimus related, one pancreatitis, and one splenic artery embolization to increase the platelet count for anti-HCV interferon therapy)

Two complications unrelated to transplantation were iron deficiency anemia and gastric cancer. There were no complications from opportunistic infections or malignancy such as cytomegalovirus infection, Epstein–Barr virus infection or skin cancer.

During the study period, four patients underwent repeat LDLT, three of which were done within one yr after the primary LDLT. One patient underwent repeat LDLT 25 months after a primary LDLT for liver failure, due to a biliary stricture (described below).

Outcomes of treatment

Biliary stricture. Of the 15 episodes of biliary stricture, 14 were after duct-to-duct biliary reconstruction and the other was after hepaticojejunostomy. Eleven strictures were treated by endoscopic placement of a biliary stent and four by percutaneous transhepatic biliary drainage (PTBD). At their last follow-up, eight patients had normal liver function, two had slightly diminished liver function, and one patient developed liver failure, subsequently successfully undergoing repeat LDLT. Of the four remaining patients, three died from liver failure and two of these cases had associated biliary stricture. One patient died of HCV recurrence and another died of Langerhans histiocytosis (Table 1).

Vascular complications. Two cases of portal vein stenosis were successfully treated with balloon dilatation 38 and 16 months after LDLT. Each patient currently has reasonable portal flow and normal liver function. One patient with hepatic vein stenosis, which was treated with stent placement 14 months after LDLT, currently has good blood flow and normal liver function.

HCV recurrence. Eight of 21 patients (38%) undergoing LDLT for HCV cirrhosis required hospitalization more than one yr post-LDLT to treat HCV recurrence with interferon therapy. Most patients undergoing LDLT for HCV cirrhosis received interferon and ribavirin within one yr after LDLT as preemptive therapy and prior to the development of biopsy-proven hepatitis. Therefore, all treatments performed more than one yr post-LDLT involved re-induction with interferon and so the incidence of HCV clearance (HCV-RNA negative at the last follow-up) was significantly less than patients not requiring additional interferon therapy (1/12 vs. 7/9, $p < 0.05$ [Fisher's test]).

HCC recurrence. Two patients developed HCC recurrence and died 27 months and 40 months after LDLT, respectively. The former patient, a 62-yr-old male meeting the Milan criteria, developed pelvic dissemination of HCC, possibly related to a percutaneous ethanol injection prior to transplantation. During the preoperative surveillance there were no definitive extra-hepatic lesions so we

Table 1. Patients who died beyond one yr after LDLT

Case no.	Original diseases	Gender	Age at Tx	Graft	Blood type	Biliary stricture	Cause of death	Months after Tx
1	BA	F	1	LLS	Identical	(−)	GI bleeding	66
2	B-LC/HCC	M	56	RL	Identical	(+)	Liver failure	41
3	BA	F	1	LLS	Identical	(−)	GI bleeding	29
4	Alcoholic LC	M	47	RL	Identical	(−)	Liver failure (alcohol abuse)	46
5	FHF	F	0	LLS	Identical	(+)	Langerhans histiocytosis	35
6	C-LC	M	51	RL	Identical	(+)	Liver failure (HCV)	30
7	C-LC/HCC	F	54	ELL	Incompatible	(+)	Liver failure	23
8	C-LC/HCC	M	62	LL	Compatible	(−)	HCC recurrence	27
9	C-LC/HCC	M	50	RL	Identical	(−)	HCC recurrence	40
10	C-LC/HCC	M	67	RLS	Identical	(−)	Liver failure	18

BA, biliary atresia; B-LC, HBV cirrhosis; FHF, fulminant hepatic failure; C-LC, HCV cirrhosis; HCC, hepatocellular carcinoma; F, female; M, male; LLS, left lateral segment; RL, right lobe; ELL, extended left lobe; LL, left lobe; RLS, right lateral sector; GI, gastrointestinal.

performed LDLT; however, this man eventually died from HCC recurrence. The other patient, a 50-yr-old male with multiple HCCs beyond the Milan criteria, underwent an LDLT after informed consent. He died of multiple lung metastases after unsuccessful sorafenib treatment, without intrahepatic recurrence.

Rejection. Of the seven patients who developed acute cellular rejection, all recovered with increased immunosuppression that included steroid bolus therapy. Four are alive and well, two are alive with slightly abnormal liver function, and one pediatric patient died of Langerhans hystiocytosis 35 months after the LDLT. One patient developed chronic rejection and died of liver failure 23 months after the LDLT.

Infections. All but one mentioned infected patient recovered with appropriate treatment (i.e., conservative treatment for the enteritis cases, antibiotic therapy for cellulitis and spontaneous bacterial peritonitis, acyclovir for herpes zoster, and surgical resection for *Aspergillus* sinusitis). One patient who developed stable HAM experienced gradual progression of voiding problems and gait disturbance.

Mortality over one yr after LDLT. Ten patients died more one yr post-LDLT, at a median time post-LDLT of 35 months (range, 18–66 months) (Table 1). The causes of transplantation related death were: liver failure from biliary stricture in four patients, gastrointestinal bleeding in two, HCC recurrence in two, liver failure due to alcohol abuse in one, and chronic rejection in one. Both cases of gastrointestinal bleeding were pediatric. Each patient developed sudden massive bleeding due to portal vein obstruction. An attempted recanalization of the portal vein via a percutaneous transhepatic approach failed in one patient. We could not procure a second graft for LDLT, so only one patient underwent repeat LDLT for graft failure from biliary stricture.

Liver function at the last follow-up. Current liver function in our surviving patients has been maintained with median alanine aminotransferase and total bilirubin levels of 23 IU/L (range, 7–546) and 0.9 mg/dL (range, 0.3–8.6), respectively. Overall, a majority of patients (43/55, 78%) had normal alanine aminotransferase and total bilirubin levels.

Assessment of daily activity. Most patients surviving more than one yr post-LDLT have a normal daily Karnofsky activity score of 100% (50/55, 91%). The other five patients are experiencing slightly diminished activity (40–90%), from general fatigue related to liver dysfunction (three patients), chronic renal dysfunction and gait disturbance with HAM.

Discussion

We attempted to determine the long-term results of LDLT by analyzing the complications requiring hospitalization more than one yr post-LDLT. Most complications were transplantation related. Treatment of surgical complications and original disease recurrence were major reasons for hospitalization. Biliary stricture is well documented as one of the major surgical complications after LDLT (6, 7) and generally develops several months after surgery. Four of the 15 patients requiring treatment for biliary stricture died, while most of the surviving patients maintained good liver function. Timing of the treatment of biliary stricture is important so patients should be followed carefully in order to not miss an appropriate opportunity for re-transplantation. Other surgical complications included portal and hepatic vein stenosis,

each successfully treated with balloon dilatation or stent placement. Other studies have also reported promising results with this procedure (8, 9).

Hepatitis C virus and HCC disease recurrence were major causes of hospitalization. Our original strategy for HCV was to preemptively treat patients with interferon and ribavirin (10), consequently the majority of our HCV patients had already undergone therapy within one yr post-LDLT. As a result, patients requiring treatment more than one yr post-LDLT usually had refractory HCV recurrence and their HCV clearance was diminished. Other current studies have indicated that preemptive therapy may be associated with a lesser efficacy for controlling HCV recurrence (11), so the optimal strategy for preventing HCV recurrence is unresolved.

Hepatocellular carcinoma recurrence was a cause for hospitalization and death in two patients, one beyond the Milan criteria, the other within the Milan criteria but who had undergone a percutaneous ethanol injection pre-transplantation. Percutaneous therapy or biopsy may cause dissemination of HCC (12); even if patient imaging is within the Milan criteria, they should be carefully evaluated before LDLT, possibly including a laparoscopic assessment.

Late-onset infections were observed, despite most patients receiving reduced immunosuppression. Although infection is a major cause of early post-transplantation death, late-onset infections were simply controlled with appropriate treatment and the majority of patients survived. One patient with HAM experienced a gradual progression of urinary problems and gait disturbance.

Late-onset acute rejection was observed in seven patients and each recovered with reinforced immunosuppression. In liver transplantation, although weaning from immunosuppression is often possible (13, 14), late-onset rejection may lead to graft loss (15). Even well-functioning grafts years after transplantation should have immunosuppression levels checked to identify possible late-onset acute cellular rejection.

The main cause of death more than one yr post-LDLT was liver failure related to biliary stricture followed by gastrointestinal bleeding, in two pediatric cases. Both pediatric patients were doing well with acceptable liver function, but died from massive, sudden-onset, bleeding due to portal obstruction. Late-onset portal vein complications are a recognized possible cause of death in liver transplantation (16). Liver function is maintained, even when the portal flow is disturbed, so these patients should be followed closely with imaging and/or endoscopy. We annually endoscope both adult and pediatric cases, now, based on this experience.

The cause of death within the first yr after LDLT in this patient population was mostly infection-related multi-organ failure: no patients died of liver failure due to biliary stricture, HCV/HCC recurrence, or gastrointestinal bleeding (data not shown). So, these complications seem specific to long-term patients and care providers should be aware and on the lookout for these complications in the outpatient clinic. There is a limited number of DDLTs in Japan so re-transplantation is difficult and potential complications merit careful patient monitoring post-LDLT in outpatient clinics. Perhaps, LDLT patients should be treated with greater vigilance with hospitalization for even relatively minor complications, compared to DDLT patients.

Although many patients required hospitalization more than one yr post-LDLT, most were found to enjoy active daily lives with good graft function at their most recent follow-up. With careful follow-up and adequate treatment, long-term outcomes after LDLT can be expected to further improve. Because HCV cirrhosis is a major indication for liver transplantation in both living and deceased donor liver transplantation, more effective and safe treatment for HCV recurrence after transplantation is essential to improve this group's long-term outcome.

Conclusions

In conclusion, many of our patients required hospitalization more than one yr post-LDLT for the treatment of complications, but most of them were able to maintain their quality of life and liver function with appropriate treatment.

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