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ORIGINAL ARTICLE

Technical refinements of bile duct division in living donor liver surgery

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Abstract
Background/purpose In spite of the great risk involved, the donor bile duct division procedure has not been thoroughly addressed in the literature. The purpose of this study is to show the appropriate approach to bile duct division in living donor hepatectomy.
Methods Of 87 living donor liver surgeries, we performed bile duct division by marking the cutting point using a small vascular clip under ordinary cholangiography in the first 37 patients, while the current procedure was used in 50 patients by encircling the cutting point using a radiopaque marker filament under real-time C-arm cholangiography.
Results Regarding the procurement of the 51 right lobe grafts, the incidence of multiple bile ducts in the graft was significantly reduced by our novel procedure [20/28 (71%) vs. 7/23 (30%), $P < 0.01$, Fisher's test]. Overall, there were no biliary strictures after surgery in any of the donors, with a median follow-up period of 43 months (range 8–136).
Conclusions Our procedure of bile duct division in living liver donor surgery enabled us to avoid the biliary stricture while cutting the bile duct of the donor with great accuracy.

Keywords Liver transplantation · Living donor · Bile duct

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Introduction

Living donor liver transplantation (LDLT) has been established as an effective modality for the treatment of various end-stage liver diseases. However, compared to deceased donor liver transplantation, more technical and ethical dilemmas exist, primarily because it is difficult to strike a balance between donor safety and recipient benefit. Regarding biliary reconstruction in this context, the recipient requires a large, single bile duct orifice in order to reduce the risk of post-surgical biliary complications [1, 2]. Thus, while it is desirable to cut the bile duct as close as possible to the hepatic hilum during donor surgery, this leads to significant concerns about biliary stricture in the donor. Donor safety should be the top priority in LDLT, and therefore the bile duct must be cut with great caution and according to the most appropriate procedure. In spite of the great risk involved, the donor bile duct division procedure has not been thoroughly addressed in the literature. The aim of this study was therefore to describe our technical refinements to the procedure of bile duct division in living donor liver surgery.

Patients and methods

Patients

Eighty-seven living donor hepatectomies for primary liver transplantation were performed at our institution from August 1997 to April 2008. The living donors consisted of 44 males and 43 females with a median age of 39 (range 19–67). The following types of grafts were procured: 9 left lateral segments, 2 left lobes without the middle hepatic vein (MHV), 8 extended left lobes with the MHV, 12

extended left lobes with the caudate lobe, 51 right lobes without the MHV, and 5 right posterior segments. These cases were divided as follows into two groups according to the treatment period: group A (August 1997 to December 2004, $n = 37$) and group B (January 2005 to April 2008, $n = 50$) (Table 1). Preoperative evaluation of the biliary anatomy was performed by magnetic resonance cholangiopancreatography in both groups. In group A, we adapted a right lobe graft only for adult-to-adult LDLT, but thereafter we used various types of grafts (e.g., left liver grafts and right posterior segment grafts), primarily to enhance donor safety. Moreover, we altered the bile duct division procedure. Initially, we carried out ordinary cholangiography after the cholecystectomy via a catheter that had been placed at the cystic duct, and the bile duct was cut prior to parenchymal transection by marking the cutting point using a small vascular clip (Fig. 1). However, we frequently encountered patients with multiple bile ducts during right lobe graft procurement, such that we adapted the previous procedure to arrive at the current approach to bile duct division, as described below. This procedure was adapted in group B.

Surgical procedure of bile duct division

During hilar dissection, the gall bladder was dissected away from the liver, and the hepatic artery and portal branch were fully exposed and isolated from the hilar plate. Particular attention was paid to retaining the surrounding tissue of the hilar plate without exposing the bile duct; in order to avoid heat injury, electric cautery should not be used at this step. At the final step of the subsequent parenchymal transection, the hilar plate was fully exposed and encircled with a radiopaque marker filament obtained from surgical gauze (Fig. 2a). Real-time cholangiography using C-arm fluoroscopy was then performed via the catheter, which was placed in the cystic duct (Fig. 2b). To verify the optimal point for cutting the bile duct, the radiopaque filament was retracted (Fig. 2c), and the C-arm was rounded to adjust the apparatus to the accurate angle. After confirmation of the accurate cutting point, parenchymal transection was further advanced using a liver hanging-maneuver technique [3] with preservation of the hilar plate. We then interposed the surgery after completion of the liver parenchymal transection. When the surgeon for

Table 1 Characteristics of donor and recipient

	Group A ($n = 37$)	Group B ($n = 50$)	P value
Donor			
Age	39 (21–67)	37 (19–64)	NS
Gender	Male 16, female 21	Male 28, female 22	NS
Graft			
RL	28	23	NS
LL + CL	0	12	<0.01
LL	0	10	<0.01
LLS	9	0	<0.01
RPS	0	5	<0.01
Multiple ducts in RL graft	20/28 (71%)	7/23 (30%)	<0.01
Biliary stricture	0	0	NS
Recipient			
Age	41 (0–65)	57 (11–68)	NS
Gender	Male 20, female 13	Male 32, female 18	NS
Disease			
BA	8	1	<0.01
Viral cirrhosis	11	33	<0.01
With HCC	5	27	
W/o HCC	6	6	
FHF	7	2	<0.01
Others	11	13	NS
Biliary reconstruction			
HJ	13	7	<0.05
DD	24	43	
Biliary stricture	9	8	NS
Follow-up period	79 months (52–136)	24 months (8–48)	<0.01

Statistical analyses were performed with Fisher's test

RL right lobe, *LL* left lobe, *CL* caudate lobe, *LLS* left lateral segment, *RPS* right posterior segment, *BA* biliary atresia, *HCC* hepatocellular carcinoma, *FHF* fulminant hepatic failure, *HJ* hepaticojejunostomy, *DD* duct to duct

the recipient required the graft, the hilar plate, including the hepatic duct, was precisely divided with scissors, and the stump of the remnant bile duct was closed with continuous, 6-0 absorbable monofilament sutures (PDS II, Ethicon, Somerville, NJ). Cholangiography with C-arm fluoroscopy was then performed once again in order to check for biliary leakage and strictures in the remnant bile duct (Fig. 2d). The liver graft was then removed after the hepatic artery, portal vein, and hepatic vein were divided.

Biliary reconstruction in recipients

Biliary reconstruction in the recipients was performed by Roux-en-Y hepaticojejunostomy or duct-to-duct anastomosis, with or without biliary stenting, and with interrupted, 6-0 absorbable monofilament sutures (PDS II, Ethicon, Somerville, NJ) (Table 1). Duct-to-duct anastomosis was the first line, and hepaticojejunostomy was performed only in cases of biliary atresia and primary sclerosing cholangitis, and in cases in which the quality of the recipient bile duct was not good for various reasons, such as biliary ischemia. In case of multiple bile ducts in the graft, duct plasty was performed whenever possible [4], and duct-to-duct anastomosis was still the first line for biliary reconstruction. Concerning decreasing the incidence of biliary atresia, the incidence of hepaticojejunostomy was significantly lower in group B (Table 1).

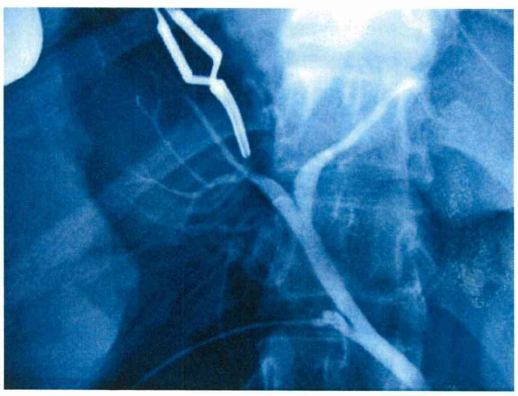

Fig. 1 Our original procedure for bile duct division. The bile duct is divided under ordinary cholangiography by placing a small vascular clip around the hepatic duct

Results

Incidence of multiple bile ducts in grafts

The characteristics of the biliary anatomy increase the probability of multiple bile ducts in right lobe grafts over that in left lobe grafts [5]. The incidence of multiple ducts in right lobe grafts was compared between groups. In the procurement of 51 right lobe grafts, the incidence of multiple bile ducts was significantly reduced by the current procedure [20/28 (71%) in group A vs. 7/23 (30%) in group B, $P < 0.01$, Fisher's test]. In these cases, anatomic variation was similar in both groups, i.e., according to the classification system of Varotti et al. [5] (Fig. 3): type 1 [right anterior and right posterior hepatic ducts (HD) join together to form the right HD: 19/28 (67.9%) in group A

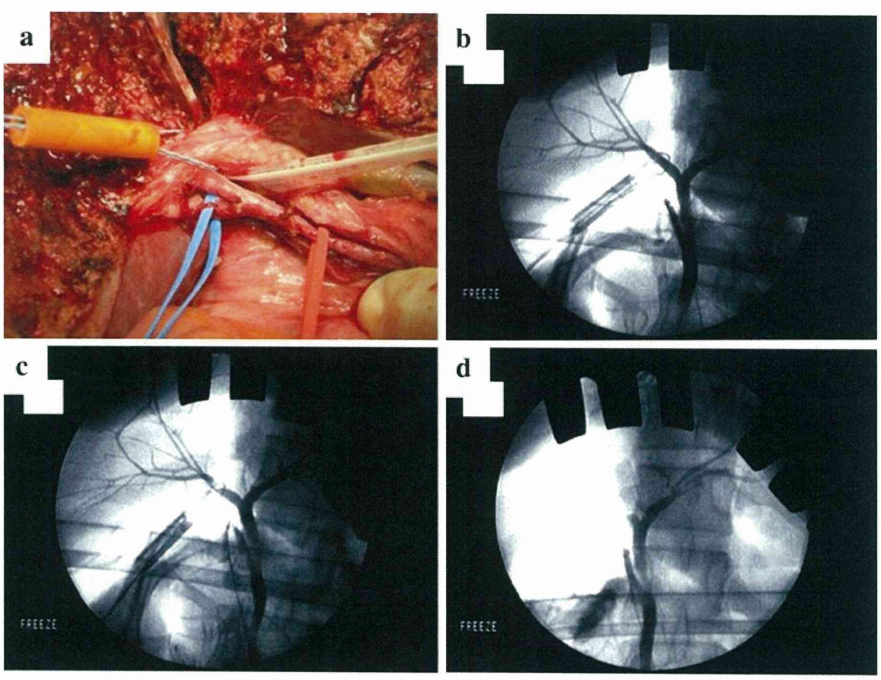

Fig. 2 Bile duct division in the procurement of a right lobe graft. The right hilar plate is encircled with a radiopaque marker filament, and sufficient surrounding tissue is preserved without exposure of the bile duct (**a**). C-arm cholangiography revealed that the radiopaque marker filament was placed at an adequate point at the right hepatic duct (**b**). The radiopaque marker filament was pulled in order to verify the cutting point (**c**). C-arm cholangiography after bile duct division revealed that the bile duct was cut at the optimal point, without inducing a stricture in the remnant left hepatic duct (**d**)

vs. 17/23 (73.9%) in group B]; type 2 [the right HD is absent and the right anterior HD and right posterior HD join directly to the confluence with the left HD to form the common HD: 2/28 (7.1%) in group A vs. 3/23 (13.0%) in group B]; type 3 [the right anterior HD or the right posterior HD open directly into the left HD: 6/28 (21.4%) in group A vs. 3/23 (13.0%) in group B]; type 4 [the right anterior HD or the right posterior HD open directly into the common HD: 1/28 (3.6%) in group A vs. 0/23 (0%) in group B)].

Bile duct division in complex cases

In cases involving multiple bile ducts in the graft, one hilar plate was encircled, including all of the hepatic ducts (Fig. 4). In these cases as well, the use of a radiopaque marker filament as the reference for the optimal cutting point was feasible and allowed preservation of the surrounding tissue. In cases involving a right posterior segment graft, it can generally be relatively difficult to determine the optimal cutting point, because the targeted point tends to be more distal and supports smaller bile duct(s); however, in all of our five donor cases involving this type of graft, we easily identified the optimal cutting point without any difficulty (Fig. 5). In some cases involving a complex variation in the bile duct branching pattern (i.e., right posterior hepatic duct independently branching from the left hepatic duct), we were able to avoid bile duct injury in the donor by clearly making the cutting point with pulling the radiopaque marker filament (Fig. 6).

Biliary complications in donors

A total of 16 complications (18.4%) were seen in the donors (6 bile leakages, 3 wound infections, 2 pleural effusions, 2 cases of gastric stasis, 1 portal vein thrombosis, 1 case of postoperative bleeding, and 1 paralytic ileus). All

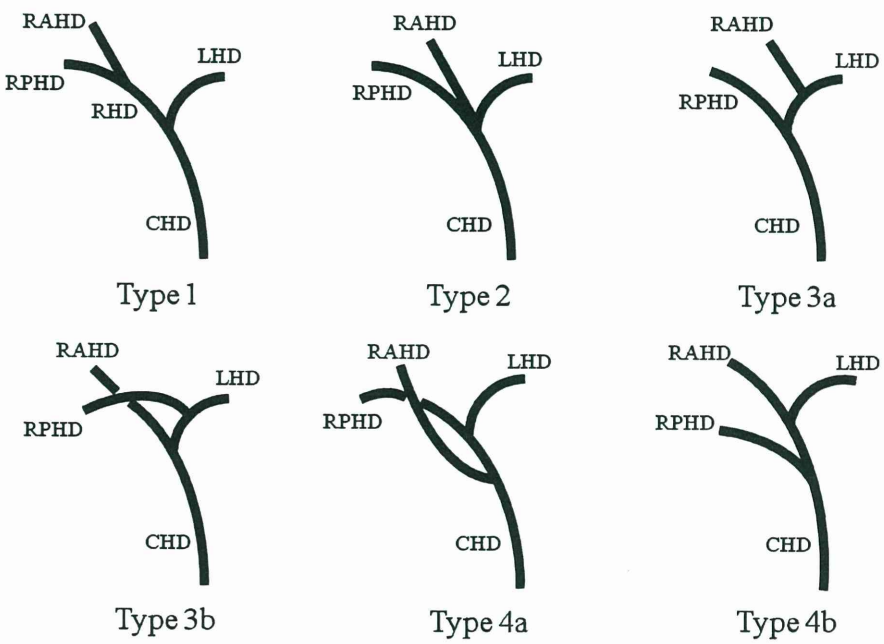

Fig. 3 Classification of the biliary tree anatomy by Varotti et al. [5]. *CHD* common hepatic duct, *LHD* left hepatic duct, *RAHD* right anterior hepatic duct, *RPHD* right posterior hepatic duct

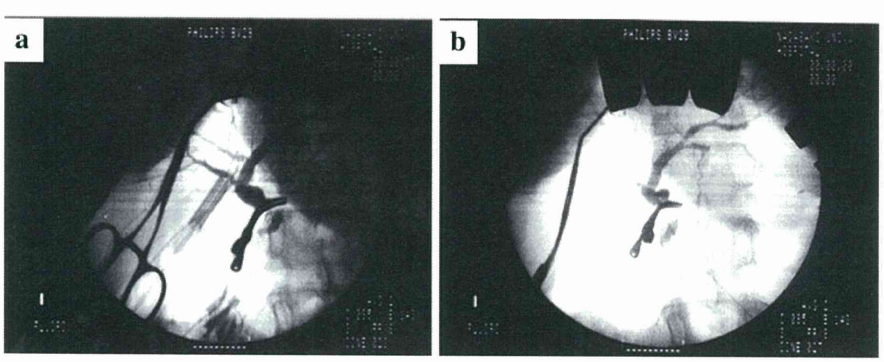

Fig. 4 Bile duct division in the procurement of a right-lobe graft with multiple ducts. The right hilar plate, including both the right anterior branch and the right posterior branch, is encircled by a radiopaque marker filament (**a**). There was no stricture in the remnant left hepatic duct after division (**b**)

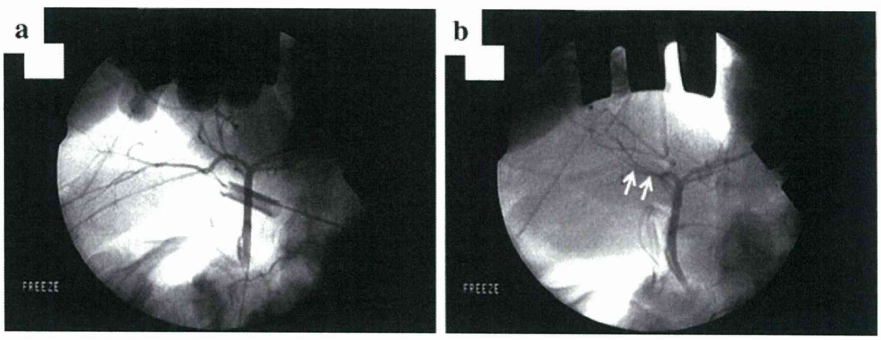

Fig. 5 Bile duct division in the procurement of a right posterior segment graft. A radiopaque marker filament was placed at an adequate point in the right posterior hepatic duct (**a**). After division of the right posterior hepatic duct, there was no stricture in the remnant right anterior hepatic duct (*arrows*, **b**)

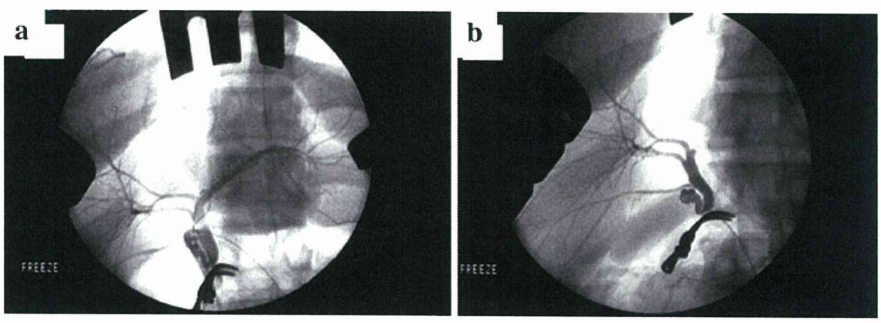

Fig. 6 Bile duct division in the procurement of a left lobe graft, in which the right anterior hepatic duct branched from the left hepatic duct (**a**). The bile duct was divided at an adequate point without subsequent stricture in the remnant right anterior hepatic duct (**b**)

bile leakage cases were treated by percutaneous drainage, and all spontaneously resolved without requiring surgical intervention. There was no significant difference in the incidence of bile leakage between the groups [4/37 (10.8%) in group A vs. 2/50 (4.0%) in group B]. No biliary strictures were observed in any of the donors in either of the groups. All donors are alive and currently doing well, carrying out normal daily activities after a median follow-up period of 43 months (range 8–136).

Biliary complications in recipients

The incidence of biliary stricture requiring endoscopic or surgical treatment of recipients was compared between adult cases in both groups (>18 years). It would not be appropriate to formally compare the incidence of biliary complications in recipients according to the groups as defined here, because the follow-up period for group B was significantly shorter than that for group A. However, it should be noted that the incidence of biliary stricture was non-significantly lower in group B than group A [i.e., 9/37 (24.3%) in group A vs. 8/50 (16.0%) in group B].

Discussion

Biliary stricture is one of the most significant complications in liver transplant recipients. The etiology of this complication is multifactorial, and especially in LDLT, the presence of tiny, multiple ducts can contribute to a higher incidence of biliary stricture than that encountered in deceased donor liver transplantation. Although the relationship between the presence of multiple ducts and the incidence/severity of biliary complication remains controversial [6, 7], several studies have indicated that the presence of multiple bile ducts in a graft is a risk factor for biliary complication [1, 2]. Additionally, biliary ischemia is an important, well-documented factor that affects biliary stricture [8, 9]. Considering these factors, surgical innovations are required not only in recipient surgeries, but also in donor surgeries. In order to maintain the blood supply, it is desirable to harvest a large bile duct orifice in the graft, together with a sufficient amount of surrounding tissue. However, there are still several technical and ethical dilemmas associated with this procedure. In particular, in order to obtain a graft containing a single large orifice, it is necessary to cut the bile duct as close as possible to the hepatic hilum, which can lead to biliary stricture in the residual bile duct of the donor. Additionally, in the attempt to cut the bile duct at a precise point, it becomes necessary to expose the bile duct by also dissecting back the surrounding tissue, which can lead to biliary ischemia. The technical innovations described in this study yielded a resolution to these problems. By encircling the hilar plate using a radiopaque marker filament, the cutting point was easily identified, and the surrounding tissue of the hilar plate could be maintained. Under real-time C-arm cholangiography while pulling the filament, the cutting point

was clearly visualized in a three-dimensional image. This procedure using a radiopaque marker filament and C-arm cholangiography was originally introduced by Chen in Taiwan [10]. We then modified the procedure by pulling the filament in order to render the cutting point more clear, as described above. Initially, we adopted this approach for the procurement of right lobe grafts because of the high incidence of multiple bile ducts encountered in these grafts [11]. After the adoption of this novel technique, the incidence of encountering multiple ducts in grafts was significantly reduced without increasing the rate of biliary stricture in donors. Biliary stricture is one of the most significant complications in living donors. According to a survey conducted by the Japanese Liver Transplantation Society, 11% of 1852 donors had biliary leaks and strictures, the majority of which occurred after right lobe hepatectomy; a total of 10 donors underwent surgical revision for biliary complications [12]. To date, we have not observed any biliary complications requiring surgical treatment among our donors. Six cases (7.7%) exhibited minor bile leakage, which in each case was successfully treated by percutaneous drainage alone, i.e., no subsequent biliary strictures developed in any of these donors. With the increasing rate of adult LDLT, several types of graft have been introduced (e.g., left lobe with or without the caudate lobe, right posterior segment graft). In all cases presented here, our novel approach was found to be very effective at enhancing the accuracy of setting the cut point for resection of the bile duct.

One disadvantage of this technique could be possible bile duct injury during encirclement of the hilar plate. Thus, very careful attention should be taken at this step to notice any resistance and thus to avoid forced penetration of the Kelly clamp into the fibrous tissue. Furthermore, it remains important to obtain clear preoperative visualization of the biliary anatomy, thereby to avoid missing any significantly aberrant branching pattern around the hilum. Here, we used magnetic resonance cholangiopancreatography for the preoperative evaluation of the biliary anatomy, and no significant bile duct injuries occurred. In general, the key point of the present procedure is that the hilar plate (i.e., not the bile duct) should be fully exposed before it is marked with the radiopaque marker filament. Thus, the hilar anatomy should be clearly visualized, including assessment of the relationship between the hepatic artery, the portal vein, and the hilar plate. As long as the tissue of hilar plate is preserved, no significant biliary ischemia is likely to occur. Once the encirclement of the hilar plate was completed, this procedure was found to be useful even in cases involving complex bile duct branching patterns. Intraoperative cholangiography just prior to the encirclement of the hilar plate may be helpful in yielding the most secure bile duct division possible.

Whereas donor safety should be the top priority in LDLT, the recipient's outcome is almost equally important in terms of rewarding the donor for his or her devotion to the patient. Our current procedure contributed to a reduction in the incidence of biliary stricture in recipients as well. Randomized and controlled studies would be ideal, but until we have access to such studies, we believe that harvesting a single orifice with sufficient surrounding tissue of bile ducts is a feasible means of performing the most straightforward surgery possible, and this novel approach is expected to contribute to successful outcomes. Moreover, simple anastomosis using a single orifice might facilitate the treatment of any remaining cases involving biliary stricture.

In conclusion, the present procedure of dividing the bile duct during living-donor liver surgery using a radiopaque marker filament and C-arm cholangiography is feasible for avoiding biliary stricture in the donor while maintaining graft quality with sufficient surrounding tissue and reducing the chance of encountering multiple bile duct orifices.

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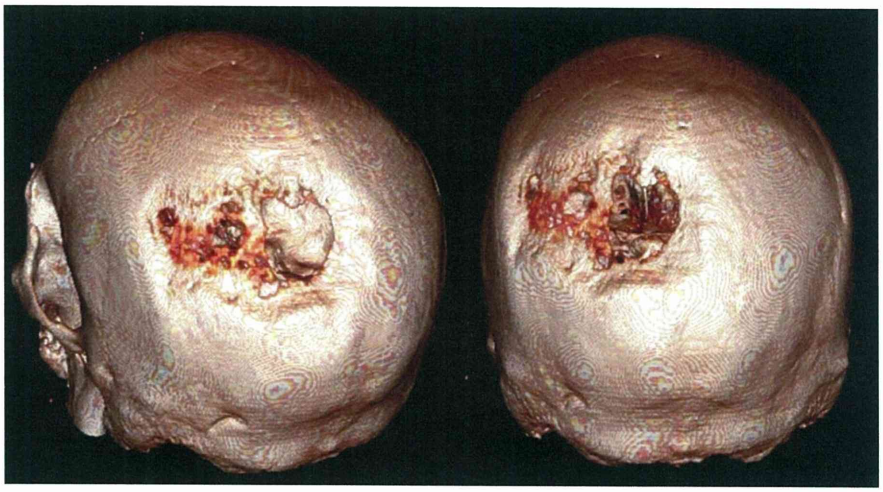

Fig. 1. Posterolateral (left) and posterior (right) view of unilateral Catlin mark.

Dear Editor,

Colonic explosion by electronic cautery during living donor liver transplantation

Colonic gas explosion by electric cautery is rare, but severe complication both in general surgery and endoscopic intervention.

Three factors are prerequisite to trigger an explosion of digestive gases: the presence of combustible gases (hydrogen, methane), combustive gas (oxygen) and an initiating heat source (endoscopic or surgical electrocautery).[1] Since Limbling and Tuffert reported the first case of explosion in 1944,[2] several cases have been reported.[3,4] Here, we report a case of colonic gas explosion during a living donor liver transplantation with intraoperative video.

A 65-year-old female underwent living donor liver transplantation for hepatitis B virus cirrhosis, using left liver graft that was donated from her 55-year-old younger sister. Transplant surgery was uneventfully completed, and at the final step, we found that transverse colon was so expanded with gas, that we could not close the abdomen. After the unsuccessful colonoscopy, we finally decided to deflate the colon by making a small hole by electric cautery. At the moment that we made a hole by electric cautery in the transverse colon, it went up in an explosion, and the whole colonic serosa was torn longitudinally along the taenia. After the colon gas was suctioned, the splitted taenia was sutured, and the stoma was created at the end of the ileum. Fortunately, post-transplant course was uneventful, and the patient is currently doing well with normal liver function and ordinary oral intake 19 months after surgery. The stoma was closed with bowel anastomosis 6 months after the liver transplantation. Although it did not lead to life-threatening condition in this case, the surgeons should recognize this serious complication.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video Clip S1 Transverse colon was so expanded with gas that we deflated the colon by making a small hole by electric cautery. At the moment, it went up in an explosion.

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JOURNAL OF MEDICAL CASE REPORTS

CASE REPORT Open Access

Living donor liver transplantation from a donor previously treated with interferon for hepatitis C virus: a case report

Masaaki Hidaka[1], Mitsuhisa Takatsuki[1], Akihiko Soyama[1], Hisamitsu Miyaaki[2], Tatsuki Ichikawa[2], Kazuhiko Nakao[2], Takashi Kanematsu[1] and Susumu Eguchi[1*]

Abstract

Introduction: Selecting a marginal donor in liver transplantation (LT) remains controversial but is necessary because of the small number of available donors.

Case presentation: A 46-year-old Japanese woman was a candidate to donate her liver to her brother, who had decompensated liver cirrhosis of unknown origin. Eight years before the donation, she had a mild liver dysfunction that was diagnosed as a hepatitis C virus (HCV) infection (serotype 2). She had received anti-viral therapy with interferon α-2b three times weekly for 24 weeks and had a sustained viral response (SVR). A biopsy of her liver before the donation showed normal findings without any active hepatitis, and her serum was negative for HCV-RNA. Only 67 patients have undergone LT from a cadaveric donor in Japan. The family in this case decided to have living donor LT. A careful selection for the liver graft donation was made; however, since she was the only candidate, we approved her as a living donor. She was discharged nine days after the liver donation. Her liver function recovered immediately. A computed tomography scan showed sufficient liver regeneration one year later. Her brother also had good liver function after LT and had no HCV infection 48 months after surgery and no *de novo* malignancy. Neither of the siblings has developed an HCV infection.

Conclusions: A patient with SVR status after interferon therapy might be considered a candidate for living donor LT but only if there are no other possibilities of LT for the recipient. A careful follow-up of the donor after donation is needed. The recipient also must have a very close follow-up because it is difficult to predict what might happen to the graft with post-transplant immunosuppression.

Introduction

The number of deceased donor liver transplantations (DDLTs) in Japan is extremely small. There were 67 cases between February 1999 and January 2010, according to the Japan Organ Transplant Network [1]. Therefore, living donor liver transplantation (LDLT) is the most frequent treatment option for patients with end-stage liver disease in Japan. The main advantage of LDLT over DDLT is that the donor can be completely evaluated, before the operation, to exclude many medical problems. However, the indications for a living donor should be strict and the risk to the donor must be avoided with the greatest care. Donors with possibly morbid liver conditions, including fatty infiltration or a history of viral hepatitis, and older donors offer "marginal grafts", which should be used only after very careful evaluation. A hepatitis B virus (HBV) core antibody seropositive donor can be accepted as long as HBV surface antigen is seronegative and anti-viral treatment is administered to the recipient after transplantation [2,3]. In this way, donor safety also is established, according to several reports of this type of case [4-6]. Some investigators reported that the patients obtained a sustained viral response (SVR) after interferon therapy showed that there was no tendency to develop fibrotic liver in the future [7,8]. HCV-RNA was not detected in 88% of the serum and liver biopsies of patients with an SVR [9]. The infection rate of the recipient from an HCV-

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positive graft should be low after LT. The rate of carcinogenesis has increased at an annual rate of 0.11% after an SVR was maintained with anti-viral therapy [10]. Using a graft with a positive hepatitis C virus (HCV) antibody although HCV-RNA was not detected in the blood remains controversial in Western countries [11-13]. To the best of our knowledge, there is no actual data that shows the outcome of liver transplantation with a graft from patients who acquire an SVR after successful anti-viral therapy. Here, we report the case of a living donor who had an SVR before LDLT. The case is described and discussed in detail.

Case presentation

A 46-year-old Japanese woman donated the right lobe of her liver to her 36-year-old brother, who had decompensated cirrhosis of unknown origin. She experienced mild liver dysfunction (117IU/L in alanine aminotransferase, normal range of 5 to 30IU/L) eight years before the donation. Her condition was diagnosed as chronic active HCV infection (serotype 2) on the basis of a liver biopsy and viral study that showed that her level of HCV-RNA was 13 kcopy/mL by real-time polymerase chain reaction analysis. The histological diagnosis showed chronic hepatitis A1/F1 (Figure 1). She received anti-viral therapy with intra-muscular interferon α-2b three times weekly for 24 weeks. Her serum HCV assay results were negative after two weeks of effective anti-viral therapy.

She was doing well and no HCV-RNA had been detected. She maintained an SVR without any complications until she was evaluated as a living donor. The donor evaluation revealed anti-HCV antibody, but her liver function test results were normal and HCV-RNA was negative by polymerase chain reaction analysis. She underwent an ultrasound-guided needle biopsy of her liver, and the pathological findings were normal and there were no findings of active hepatitis (Figure 2). She was approved as a living donor after a thorough evaluation by the ethics committee of the Nagasaki University Graduate School of Biomedical Sciences. She was discharged nine days after the liver donation. Her liver function recovered immediately. A computed tomography scan one year later showed that she had sufficient liver regeneration. Her brother was also doing well after the LT and had no HCV infection 40 months after surgery and no *de novo* malignancy.

Discussion

Selecting a living donor in this case might be controversial, although a marginal donor can also sometimes be a candidate. The risks in this case included HCV transmission to the recipient, HCV reactivation in the recipient after LDLT, and donor risk during surgery. A number of studies have reported that the results with recipients of an HCV-infected graft were comparable to those of recipients of an HCV-negative graft [11-13]. The Scientific Registry of the United Network for Organ

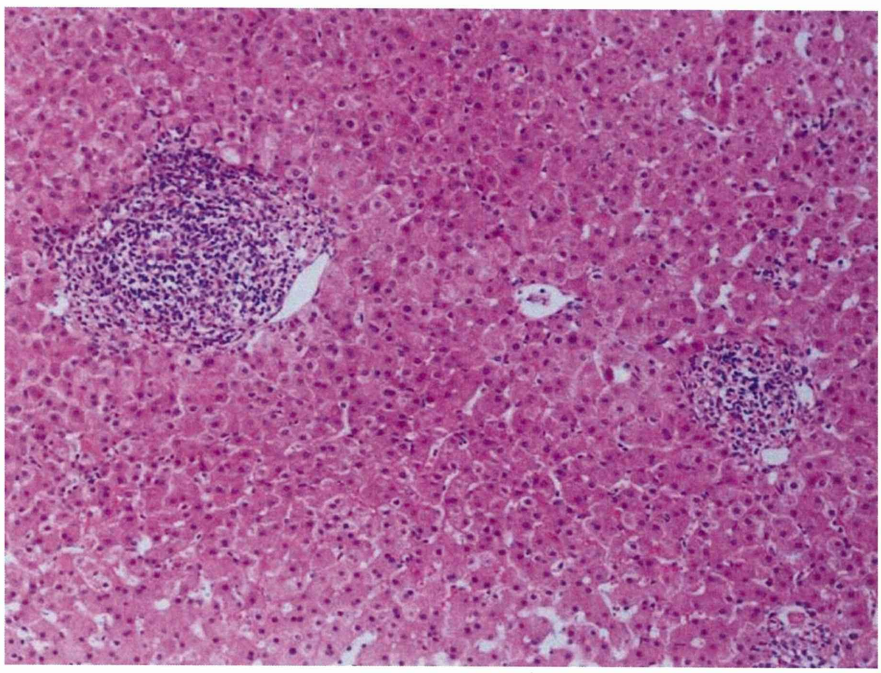

Figure 1 A liver biopsy showed chronic active hepatitis A1/F1 before interferon therapy.

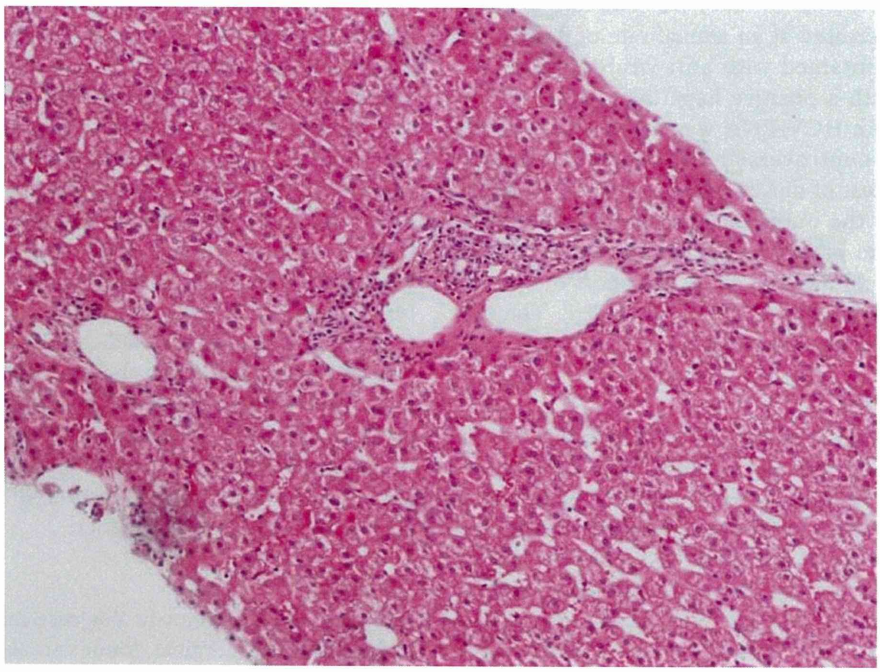

Figure 2 A liver biopsy shows normal liver tissue without hepatitis before the liver donation.

Sharing reported that the survival rate of 96 patients was significantly higher in the recipients of HCV-positive grafts than in recipients of HCV-negative grafts [13]. These results demonstrated that the use of an HCV-positive graft may also be acceptable in cadaveric LT. In contrast, an HCV-infected graft was not acceptable in LDLT. Patients who have HCV and who acquire an SVR after interferon therapy can be considered living donor candidates.

In this case, it was difficult to determine the indications for the donor selection before transplantation. Patients with serotype 2 HCV are more likely to achieve an SVR after interferon therapy than those with serotype 1. Our donor achieved an SVR of HCV. She and her brother were fully informed of the risk of peri-operative complications and the possibility that he would receive an HCV infection from the graft although she had obtained an SVR after anti-viral therapy. In theory, it is unlikely that a recipient would develop a viral infection from a graft that achieved an SVR.

Conclusions

We report a case of LDLT from a donor previously treated with interferon for HCV. A patient with SVR status after interferon therapy might be considered a candidate for LDLT only if there are no other possibilities of LT for the recipient. A careful follow-up of the donor after donation is needed. The recipient also must have a very close follow-up because it is difficult to predict what might happen to the graft with post-transplant immunosuppression.

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations

DDLT: deceased donor liver transplantation; HBV: hepatitis B virus; HCV: hepatitis C virus; LDLT: living donor liver transplantation; LT: liver transplantation; SVR: sustained viral response.

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Authors' contributions

MH and SE shared responsibility for the management of this patient and were involved in drafting the manuscript or revising it critically for important intellectual content. MT shared responsibility for the management of this patient. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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SURGERY TODAY

Case Report

Hemophagocytic Syndrome After Liver Transplantation: Report of Two Cases

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Abstract
We report two cases of hemophagocytic syndrome (HPS), a rare but fatal complication after living-donor liver transplantation (LDLT). Despite their recovery from pancytopenia following treatment with steroid pulse therapy, granulocyte stimulating factor, and intravenous γ-globulin, both patients died. The outcomes reported in cases published in English are devastating, with only 4 survivors among the total 14 patients including ours. Pancytopenia is frequently recognized postoperatively in liver transplant recipients, although its cause is difficult to establish. When pancytopenia accompanying persistent high fever is recognized in LDLT recipients, HPS should be suspected and bone marrow aspiration performed as promptly as possible because of the poor prognosis of this syndrome. There is still no optimal treatment for HPS after liver transplantation.

Key words Granulocyte-colony stimulating factor · Hemophagocytic syndrome · Hepatocellular carcinoma · Intravenous globulin · Liver transplantation · Pancytopenia

Introduction

Hemophagocytic syndrome (HPS) is hypercytokinemia caused by activated T lymphocytes and macrophages, and characterized by a high fever, pancytopenia, and systemic proliferation of histiocytes showing hemophagocytosis in the bone marrow and spleen.[1] This syndrome is life-threatening and the associated prognosis is poor.[2] Although immunocompromised patients are more prone to the development of this syndrome, HPS in liver transplant (LT) recipients has been reported only sporadically. We report two cases of HPS developing after living-donor liver transplantation (LDLT).

Reprint requests to: S. Eguchi
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Case Reports

Case 1

A 57-year-old man with decompensated liver cirrhosis secondary to hepatitis C virus (HCV) infection, who had multiple bilobular hepatocellular carcinoma (HCC) beyond Milan criteria, was referred as a candidate for LDLT. Although the HCC was more advanced than the Milan criteria, because the patient and his family insisted we performed LDLT with informed consent after extensive discussion within the multidisciplinary commission in our institute. The laboratory findings before LDLT were: serum total bilirubin 22.9 mg/dl, serum direct bilirubin 15.2 mg/dl, serum albumin 3.7 g/dl, prothrombin time (PT) 55%, platelet count 91000/μl, HCV-RNA <5 kIU/ml, α-fetoprotein (AFP) 23710 ng/ml, and protein induced by vitamin K absence or antagonists-II (PIVKA-II) 46403 mAU/ml. The Model for End-stage Liver Disease (MELD) score was 22. The preoperative viral status was as follows: cytomegalovirus (CMV) IgG-positive, Epstein–Barr (EB) viral capsid antigen IgG antibodies <1:10, and anti-EB nuclear antigen IgG antibodies 0.8.

Since there was no preoperative evidence of extrahepatic metastases or vascular invasion, the patient received a right lobe graft, without the middle hepatic vein. The donor was his wife, whose blood type AB was identical. The weight of the graft was 520 g, which was equivalent to 41.2% of the recipient's standard liver volume. The pathological diagnosis was poorly differentiated HCC with invasion of the portal vein and intrahepatic bile duct. According to the Japanese Tumor-Node-Metastasis (TNM) staging system for

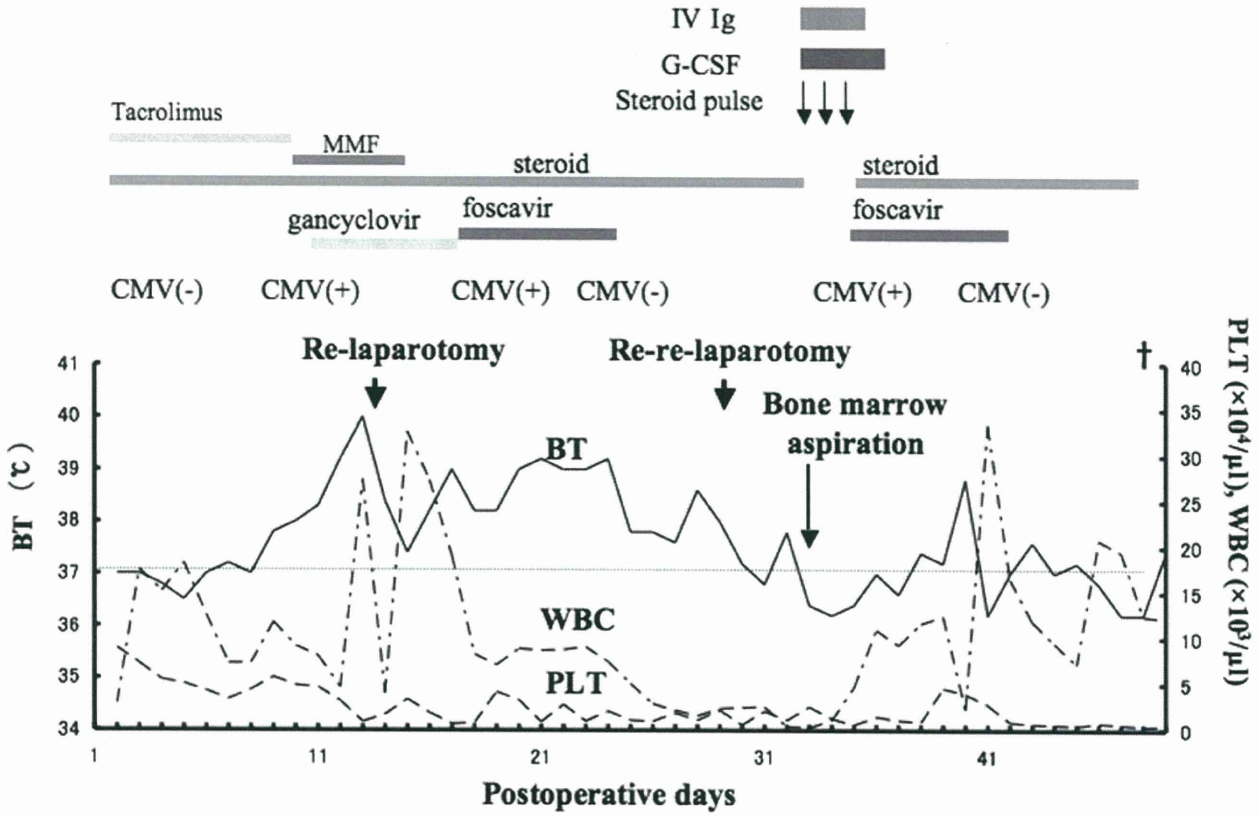

Fig. 1. Clinical course of Case 1 after liver transplantation. *WBC*, white blood cell count; *PLT*, platelet count; *BT*, body temperature; *IV Ig*, intravenous immunoglobulin; *G-CSF*, granulocyte-colony stimulating factor; *MMF*, mycophenolate mofetil; *CMV*, cytomegalovirus

primary liver cancer,[3] the tumor stage was IVa (T4N0M0).

The post-transplant course is shown in Fig. 1. The patient received post-transplant immunosuppression with tacrolimus and steroid taper, and a fever above 39°C developed on postoperative day (POD) 13. An intra-abdominal infection was suspected, but a laparotomy revealed no apparent lesion. The high fever persisted even after the laparotomy, and on POD 17 the platelet count had decreased to 7000/μl. These findings were attributed to disseminated intravascular coagulation (DIC) accompanying sepsis or a side effect of ganciclovir at the dosage of 500 mg twice a day, which had been administered for CMV antigenemia on POD 11. The CMV antigenemia assay had shown eight CMV pp65-positive cells per 2×10^5 leukocytes. Therefore, treatment for DIC and sepsis was initiated and the antiviral agent was changed from ganciclovir to foscavir. The patient's platelet count was persistently less than 10000/μl despite all these treatments.

On POD 29, Gram-negative rods were detected in the ascites fluid. A second explorative laparotomy was performed with intra-abdominal lavage. Since the laboratory findings showed bicytopenia, with a white blood cell count of 400/μl and a platelet count of 11000/μl, 3 days after the laparotomy a bone marrow aspiration was obtained for diagnosis. The bone marrow aspirate revealed activated macrophages showing phagocytosis of hematopoietic cells (Fig. 2), strongly suggestive of HPS. Hemophagocytic syndrome was differentiated from anticonvulsant hypersensitivity syndrome, because the patient had no history of anticonvulsant use. The diagnosis of HPS was established based on the results of the bone marrow aspiration, the persistently high fever (>38.5°C), and pancytopenia, and a high ferritin level of 1557 ng/ml. The serum lactate dehydrogenase (LDH) level did not increase significantly, maintaining a level of 400 IU/l.

Treatment was initiated with steroid pulse therapy, given as methylprednisolone 1 g/day for 3 days. The leukocytopenia was treated with the continuous administration of granulocyte-colony stimulating factor (G-CSF; 250 μg/day) for 4 days until the leukocytopenia improved, followed by intravenous immunoglobulin (IVIg) 5 g/day

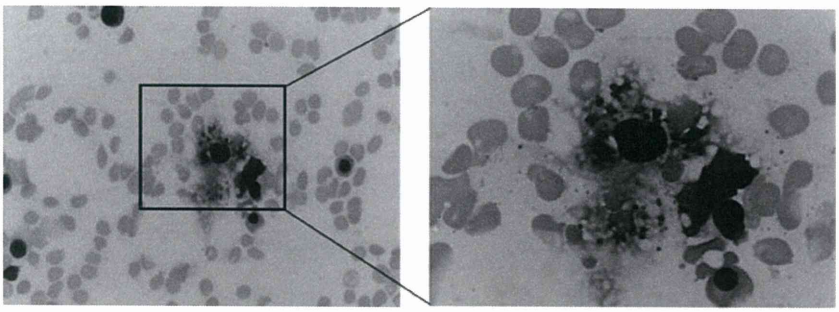

Fig. 2. Bone marrow biopsy specimen from Case 1 showed hemophagocytosis (×200)

for 3 days. During this period the patient's serum bilirubin levels were persistently high and the PT was persistently prolonged. Persistent ascites production was also recognized.

Despite the improvement in the pancytopenia in response to the combination therapy with G-CSF, the patient died on POD 49, of multiple organ failure resulting from generalized sepsis caused by methicillin-resistant *Staphylococcus aureus*. There was no familial history of hematological disease. Throughout the postoperative course, his HCV status did not show signs of recurrence. An autopsy showed hemophagocytosis in the bone marrow.

Case 2

A 63-year-old man with HCC with a cirrhotic liver as a result of chronic hepatitis B was referred as a candidate for LDLT, with his son as a donor candidate. The laboratory findings just before LDLT were as follows: serum total bilirubin 1.1 mg/dl, serum albumin 3.7 g/dl, PT 72%, PT-International normalized ratio 1.19, platelet count 70000/μl, serum creatinine 0.9 mg/dl, AFP 2.7 ng/ml, and PIVKA-II 109 mAU/ml. The hepatitis B virus (HBV)-DNA was decreased to 2.9 LC/ml with entecavir preoperatively. The MELD score was 9, the CMV IgG was positive, and EB viral serological status showed a pattern of past infection (EB viral capsid antigen IgG antibodies 1:20, anti-EB nuclear antigen IgG antibodies 1:10). Preoperative imaging examinations showed a solitary tumor lesion in segment 4, 4.5 cm in size, which was within the Milan criteria.

The donor blood type was A, which was incompatible with the recipient blood type O. The patient had been prepared before the transplantation according to our protocol, based on previous reports.[4] For HBV management, we administered hepatitis B immune globulin (HBIG) during the operation and on POD 1. The pathological diagnosis of the tumor was well-differentiated HCC. According to the Japanese TNM staging system for primary liver cancer,[3] the tumor stage was II (T2N0M0). The post-transplant course is shown in Fig. 3. The patient was given tacrolimus and steroid taper for immunosuppression. As an anti-HBV treatment, the patient received entecavir throughout the postoperative course. Furthermore, HBIG was administered only when the anti-HBs antibody titer dropped below 200 IU/l. On POD 10, the patient underwent relaparotomy for hepatic arterial thrombosis and reanastomosis was performed using the recipient's right gastroepiploic artery. On POD 17 thrombocytopenia was recognized, but a bone marrow aspiration showed no evidence of hemophagocytosis. The patient did not have a familial history of hematological disease or a history of anticonvulsant use. Sepsis developed on POD 21, and the patient was transferred to the intensive care unit. On POD 35, he passed a tarry stool and endoscopy showed oozing from gastric mucosa. G-CSF was administered for the persistent pancytopenia. Despite this, additional transfusions of five units of fresh frozen plasma and ten units of platelets per day were necessary until POD 60. During this period, the anti-A antibody did not increase.

Because of the persistent thrombocytopenia, bone marrow was aspirated again on POD 81. The aspirate revealed activated macrophages showing phagocytosis of hematopoietic cells, strongly suggestive of HPS. A high ferritin level of 1060 ng/ml was also suggestive of HPS, although the serum LDH level was 236 IU/l. For the suspected HPS, the patient was commenced on methylprednisolone 500 mg/day, with tapering over 5 days, as well as IVIg 5 g/day for 3 days. The leukocytopenia was treated with G-CSF for 6 days. Although the pancytopenia improved, renal failure developed on POD 99. The serum LDH did not increase significantly (404 IU/l). Despite a temporary improvement in renal function achieved by hemodialysis, it deteriorated again with progressing hemodynamic instability. The patient died on POD 132. Throughout the postoperative course, the HBV status had not shown any signs of active hepatitis. The patient's serum bilirubin levels were continuously high, the PT was persistently prolonged, and there

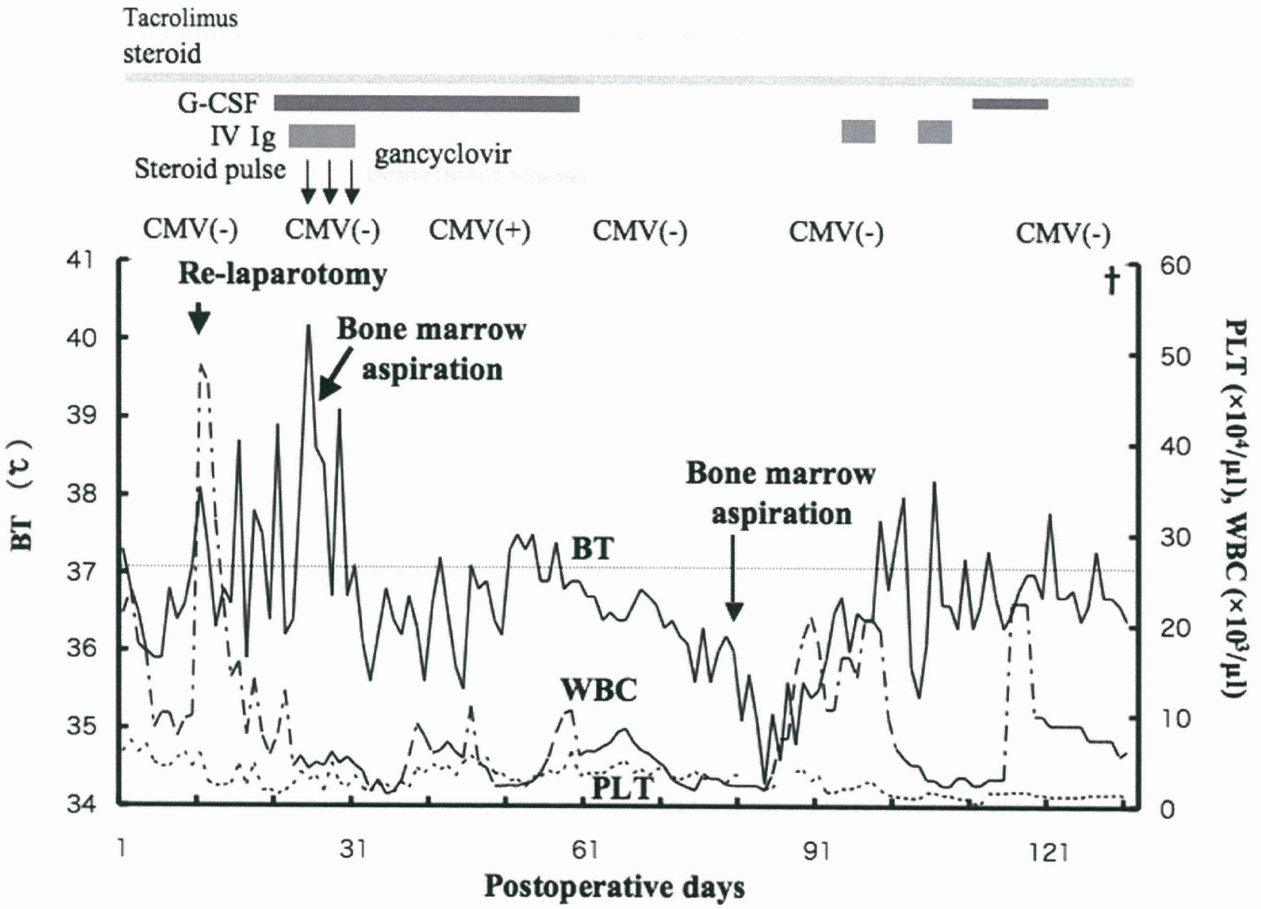

Fig. 3. Clinical course of Case 2 after liver transplantation. *WBC*, white blood cell count; *PLT*, platelet count; *BT*, body temperature; *IV Ig*, intravenous immunoglobulin; *G-CSF*, granulocyte-colony stimulating factor; *CMV*, cytomegalovirus

was continuous ascites production. Autopsy showed hemophagocytosis in the spleen and the bone marrow.

Discussion

Because of the scarcity of cadaveric liver grafts, LDLT has emerged as a popular alternative to deceased-donor liver transplantation (DDLT), especially in Asia. In fact, the outcomes of LDLT in Japan are comparable with those of DDLT in Western countries, despite its relatively short history of performing LT.[5] However, occasional rare complications have been described among the large number of LDLT experiences in Japan. The first report of HPS in LT recipients described its development in two babies after LDLT for biliary atresia.[6] To our knowledge, only 14 cases including the present cases have been reported in English.[6–14] Risdall et al. described the case of a patient with an active viral infection, whose bone marrow showed histiocytic hyperplasia with prominent hemophagocytosis. They proposed that this condition is "virus-associated hemophagocytic syndrome," and theirs was the first report of reactive or secondary HPS.[15] Reactive HPS is associated not only with a virus, but also with various types of disseminated infections caused by bacteria, tuberculosis, fungi, and parasites. Hemophagocytic syndrome associated with an underlying infection is called infection-associated HPS (IAHS). The causative organisms in the reported cases of HPS following LT were Epstein–Barr virus, cytomegalovirus, hepatitis C virus, and *Aspergillus*, respectively (Table 1). Hemophagocytic syndrome related to a solid tumor has rarely been described, but a case of HPS related to an undifferentiated HCC was reported.[16] Therefore, it might be necessary to consider HCC itself as a cause of HPS following liver transplantation for HCC, especially in patients with advanced or poorly differentiated HCC. Since the most frequent cause of HPS is a virus,