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LIVER TRANSPLANTATION 20:391-393, 2014

LETTER FROM THE FRONTLINE

Hepatocyte Transplantation Using a Living Donor Reduced Graft in a Baby With Ornithine Transcarbamylase Deficiency: A Novel Source of Hepatocytes

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TO THE EDITORS:

We performed hepatocyte transplantation (HT) in an 11-day-old infant with ornithine transcarbamylase deficiency (OTCD). We used cryopreserved hepatocytes prepared from remnant liver tissue, a byproduct of a hyper-reduced left lateral segment from living donor liver transplantation (LDLT). The patient exhibited hypothermia, drowsiness, and apnea at 3 days of age; these symptoms were accompanied by hyperammonemia (1940 μg/dL at maximum), although there were no abnormalities at birth or an obvious family history (Fig. 1). Further examinations confirmed that the hyperammonemia was the result of OTCD. Multimodal treatments, including alimentotherapy, medications, and continuous hemodiafiltration (CHDF), did not improve the patient's clinical state, and severe hyperammonemia attacks recurred. Because of the patient's small body size (2550 g) and the lack of an available liver donor, HT was indicated. Hepatocytes of the same blood type were chosen from an institutional repository of cryopreserved hepatocytes prepared from the remnant tissue of segment III from unrelated living donors. Thawed hepatocytes were transplanted twice at 11 and 14 days of age with a double-lumen catheter inserted into the left portal vein via the umbilical vein (Fig. 2). The amounts of transplanted hepatocytes were 7.4×10^7 and 6.6×10^7 cells/body, and the viability rates were 89.1% and 82.6%, respectively. The portal flow was kept stable at greater than 10 mL/kg/minute, and the pressure was maintained at less than 20 mm Hg during and after HT. The immunosuppressive treatment followed the same protocol used for LDLT with tacrolimus and low-dose steroids.[1] The patient was weaned from CHDF and the ventilator at 26 and 30 days of age, respectively, with a stable serum ammonia level of 40 μg/dL. The patient was ultimately discharged 56 days after HT. During the 3 months of follow-up, the baby did well with protein restriction (2 g/kg/day), medication for OTCD, and immunosuppression. No neurological sequelae related to hyperammonemia have been observed so far (Fig. 1).

DISCUSSION

For children with metabolic liver disease, HT is indicated as an alternative or bridge to liver transplantation.[2] HT is less invasive than liver transplantation and can be performed repeatedly. Limitations to the widespread application of HT include the poor availability of hepatocytes. Therefore, it is important to find new sources of high-quality hepatocytes. We previously prepared a repository of hepatocytes obtained from remnant liver tissue, a byproduct of hyper-reduced left lateral segmentectomy in LDLT.[1]

The cell donor was an unrelated volunteer with the same blood type who had previously undergone hyper-reduced left lateral segmentectomy. The main unit of segment II was used as a monosegmental liver graft for the primary recipient with end-stage liver disease, and the remnant was used to isolate hepatocytes with fully informed consent. The hepatocytes were isolated according to the collagenase perfusion method, as described elsewhere,[3] with Liberase MTF C/T GMP grade (Roche). All procedures were performed at our cell processing center according to a strictly controlled protocol based on good manufacturing practices. The total number of transplanted live hepatocytes was 1.4×10^8 cells/body; the ammonia removal rate was more than 200 fmol/cell/hour (203.4 and 265.4 fmol/cell/hour with the first and second injections, respectively). The dose was judged to be sufficiently high to obtain therapeutic effectiveness according to our theoretical background.[4]

This work was supported by a grant-in-aid from the National Center for Child Health and Development and the Highway Program for the Realization of Regenerative Medicine (Japanese Science and Technology Agency). This study protocol was approved by institutional review board in National Center for Child Health and Development (reference number 433).

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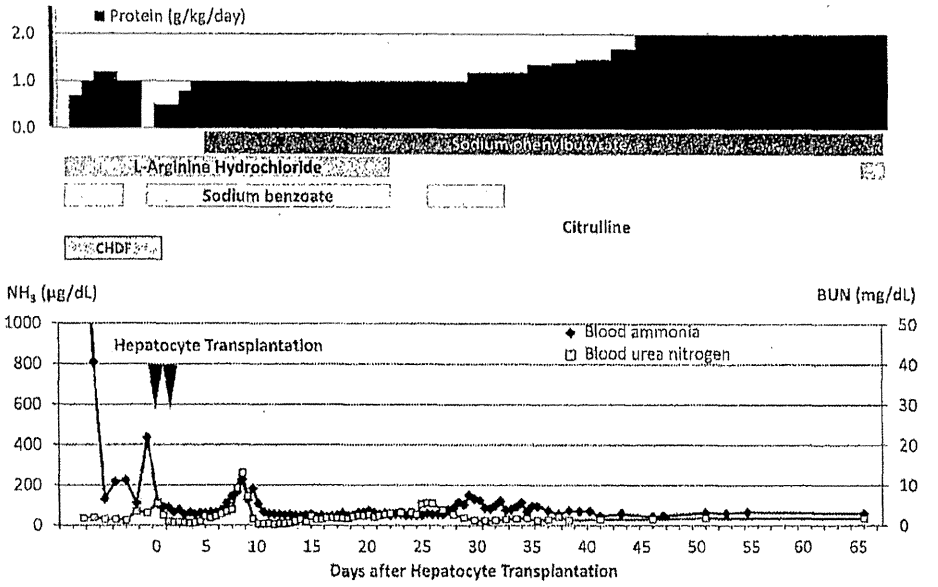

Figure. 1. Treatment schedule (top) and patient condition (bottom). The changes with time for blood ammonia and blood urea nitrogen are shown. The baby was delivered vaginally as a first child. At 3 days of age, hypothermia, low oxygen saturation, and, finally, respiratory arrest occurred. The patient was incubated and given artificial respiration. Concurrently, hyperammonemia (1940 μg/dL) was found, and continuous hemodiafiltration (CHDF) was started in addition to alimentotherapy (protein withdrawal) and medications. Whenever the administration of essential amino acids was restarted, the blood ammonia level became elevated, and at 9 days of age, despite the suspension of essential amino acid administration, the level increased up to 434 μg/dL. At 11 days of age, HT was performed for the first time, and it was performed for the second time at 14 days of age. After HT, amino acid intake was restarted along with the continuation of multimodal treatments, and blood ammonia was controlled well except for episodic increases. The patient was weaned from CHDF and the ventilator at 26 and 30 days of age, respectively, and the patient was ultimately discharged 56 days after HT.

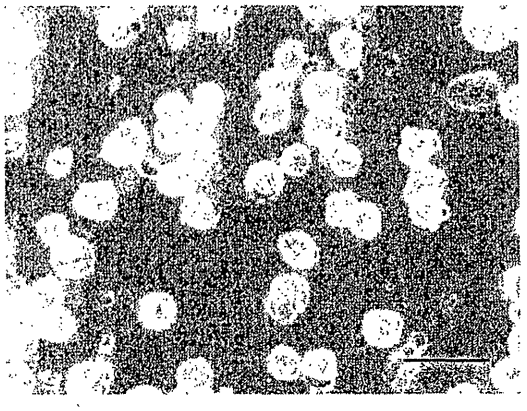

Figure. 2. Hepatocytes transplanted during the first injection. The cells showed a glazed and firm surface. The bar indicates 50 μm.

Because liver transplantation is approved as a treatment for end-stage hepatic failure, donor livers are preferentially allocated for organ transplantation and not for hepatocyte isolation. On rare occasions, the lack of appropriate donor-recipient matching (eg, infant donor livers) provides good-quality hepatocytes.[2] Fetal livers are also considered to be an alternative cell source, although ethical issues remain to be resolved. At present, we have little choice but to use marginal donor tissues, such as livers obtained from donors after cardiac death and organs with steatosis, fibrosis, or a long ischemia time. However, there are unfavorable issues related to the use of marginal donors, including low viability and vulnerability to cryopreservation. In this respect, the remnant liver tissue of hyper-reduction procedures used in LDLT has the same quality as that of left lateral segment grafts. As for availability, there are 5 cases of hyper-reduction per year at our institution on average.[5] The use of remnant liver tissues obtained from hyper-reduced LDLT procedures will, therefore, help to address the shortage of hepatocyte donors.

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ANNALS OF TRANSPLANTATION

CASE REPORT

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Urgent living donor liver transplantation for biliary atresia complicated by a strangulated internal hernia at Roux-en Y limb: A case report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: When BA patients with end-stage liver dysfunction have bowel obstruction, especially strangulated internal hernia, selecting optimal surgical therapeutic options is crucial.

Case Report: An 11-month-old female with end-stage biliary atresia (BA) was admitted for a strangulated internal hernia at the Roux-en Y limb and frequent episodes of gastrointestinal bleeding requiring blood transfusion. She was scheduled within a month to receive a portion of the liver from her blood-type identical mother. Despite intensive care, her clinical condition obviously needed a prompt surgical intervention. The operative findings at laparotomy revealed exudative moderate ascites and a dilated and ischemic afferent loop that was strangulated by a band extending from the mesentery to the transverse mesocolon. The attachment of the band was released, and gangrenous changes were recognized in the incarcerated bowel, although there were no obvious findings of intestinal perforation. After the gangrenous afferent loop was resected, the remnant afferent loop was too short to anastomose again. Following these procedures, as the patient's vital signs remained stable, we decided to simultaneously perform living donor liver transplantation (LDLT). She successfully underwent LDLT and her post-transplant course was uneventful.

Conclusions: When faced with candidates for LT as an urgent life-saving surgery, determining whether LDLT should be performed simultaneously during perioperative management is necessary to save the life of the patient.

Keywords: Liver Transplantation • Biliary Atresia • Living Donor Liver Transplantation • Strangulated Hernia

Full-text PDF: http://www.annalsoftransplantation.com/download/index/idArt/890213

1263 — 2 12

Background

Postoperative bowel obstruction continues to be the most common complication after laparotomy [1]. Strangulated internal hernia is a lethal condition that can lead to gangrene of the small bowel, with septic shock if not appropriately treated in time [2]. Biliary atresia (BA) is a leading indication for pediatric liver transplantation (LT), and patients with BA who undergo portoenterostomy after birth have a risk of bowel obstruction [3]. The need for relaparotomy for bowel obstruction is reported in approximately 10% of patients who undergo portoenterostomy [4]. When BA patients with end-stage liver dysfunction have bowel obstruction, especially strangulated internal hernia, selecting optimal surgical therapeutic options is crucial.

We herein present the case of a patient with BA complicated by a strangulated internal hernia at the Roux-en Y limb who successfully underwent LDLT.

Case Report

An 11-month-old female weighing 6.7 kg was transferred to our institute with disordered consciousness requiring intubation due to gastrointestinal bleeding. At 5 months of age, the patient was diagnosed with BA and portoenterostomy was performed at a local hospital. However, her clinical condition had not improved, and she exhibited growth failure (weight z-score: −2.1) and frequent episodes of gastrointestinal bleeding requiring blood transfusions, with a pediatric end-stage liver disease score of 17 [5]. The patient was referred to our institute with an indication for LT, which was scheduled within a month by receiving a portion of the liver from her blood-type identical mother.

The patient was admitted to the emergency room due to abdominal distension. Enhanced computed tomography (CT) demonstrated dilated loops of intestine with wall thickening suspicious of bowel obstruction at the Roux-en Y limb. CT also revealed narrowing of the portal venous trunk with developed collateral vessels (Figure 1). Abdominal Doppler ultrasound revealed a decreased portal venous flow and an accelerated hepatic arterial flow in the hilum of the liver. Over the course of the next 6 hours, despite the administration of gastrointestinal decompression using a nasogastric tube, the patient's abdominal distension worsened, with ascites formation and further progression of dilated intestines. Therefore, the patient's clinical condition required prompt surgical intervention. A pre-operatively laboratory evaluation showed total serum bilirubin 7.25 mg/dl, aspirate aminotransferase 95 IU/l, alanine aminotransferase 51 IU/l, albumin 3.0 g/dl, and international normalized ratio of prothrombin time 1.24. Because the patient's mother had been assessed to become a living donor without any medical problems, LDLT was considered as a surgical option.

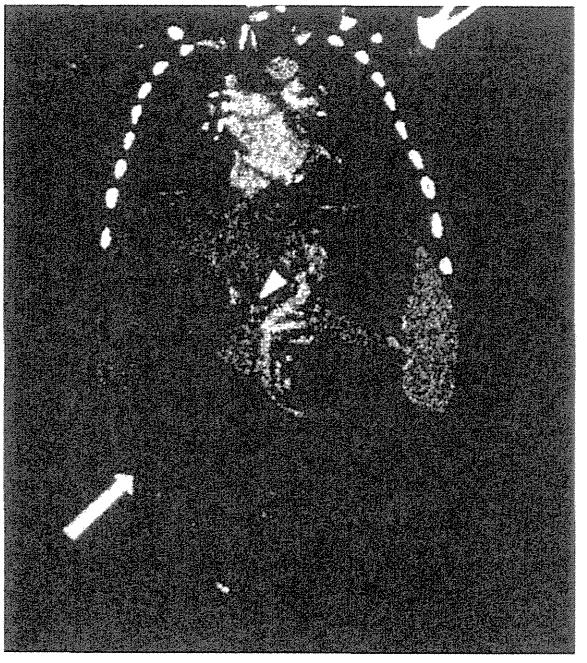

Figure 1. Enhanced abdominal computed tomography demonstrated dilated loops of intestine with wall thickening at the Roux-Limb (white arrow) and narrowing of the portal venous trunk (white arrowhead).

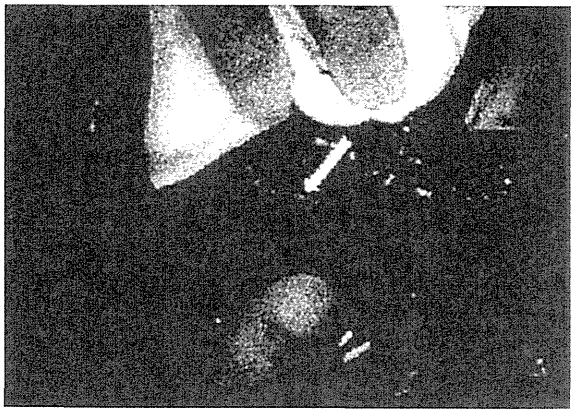

Figure 2. The operative findings at laparotomy revealed a dilated and ischemic afferent loop that was strangulated by a band (white arrow) extending from the mesentery to the transverse mesocolon.

The operative findings at laparotomy revealed exudative moderate ascites and a dilated and ischemic afferent loop that was strangulated by a band extending from the mesentery to the transverse mesocolon (Figure 2). The attachment of the band was released, and gangrenous changes were recognized in

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the incarcerated bowel, although there were no obvious findings of intestinal perforation. After the gangrenous afferent loop was resected, the remnant afferent loop was too short to anastomose again. Following these procedures, because the patient's vital signs remained stable, we decided to simultaneously perform LDLT. A liver graft left sector weighing 256 g, representing 3.82% of the graft-to-recipient weight ratio, was procured. The operation employed a standard LDLT technique, and portal vein anastomosis was performed with the branch patch technique, because a sufficient hepatopetal flow was obtained following devascularization of the collateral vessels. The operation lasted 8 hours and 25 minutes, with a blood loss of 73.5 ml/kg. The explanted liver showed marked cholestasis with intrahepatic bile duct proliferation, fibrosis, and cirrhosis, which were consistent with extrahepatic biliary atresia. Immunosuppressive treatment was initiated with tacrolimus and low-dose steroids. As the presence of *Streptococcus oralis* in a blood culture collected at the time of admission was confirmed on postoperative day 2, antimicrobial therapy with vancomycin and piperacillin-tazobactam was therefore cautiously continued for 10 days after LDLT. The patient's postoperative course was uneventful, except for an episode of a graft rejection, and she was discharged on postoperative day 42 without any surgical complications. She was found to be doing well 1 year after the LDLT.

Discussion

The present patient developed several medical problems before undergoing LDLT, which complicated our decision-making regarding the optimal surgical therapeutic options; specifically, whether LDLT should be performed simultaneously. The patient's primary medical problem was deterioration in the liver function, which resulted in poor portal flow, gastrointestinal bleeding, and malnutrition. Long-term fasting for LDLT because of gastrointestinal bleeding is too invasive for unstable patients and can result in a high mortality rate [6]. Post-transplant immunosuppression, as well as preoperative malnutrition, can increase the risk of bacterial infection following LDLT [7]. On the other hand, in the operative findings at laparotomy, the entire afferent loop had become gangrenous. In this situation, external biliary drainage through the previous Roux-en Y limb with or without resection of the gangrenous intestines and redo hepatic portoenterostomy were considered as the other therapeutic option. However, the possibility of bacterial translocation from the gangrenous intestines was high enough to trigger sepsis and there is a high complication rate after redo hepatic portoenterostomy under such severe end-stage liver disease (ESLD). Moreover, among patients with a strangulating obstruction, intestinal perforation can occur more readily and severely in those with ESLD [8]. In the present case, the patient's vital signs were stable during surgery, and there were no findings of intestinal perforation; therefore, LDLT was performed simultaneously rather than at a second surgery, with careful consideration of the patient's chances for survival between these 2 therapeutic surgeries. Because the patient's mother had been assessed to become a living donor without any medical problems, LDLT was considered to achieve timely surgical intervention in this case; nevertheless, other types of surgical intervention should have been considered. Regarding infection control after LDLT, unfortunately, our patient had a positive blood culture collected before LDLT. However, the patient did not have any infectious complications after the procedure due to the administration of appropriate antibiotic therapy proposed by infectious disease specialists. For such unstable patients with immunosuppression, daily consultations with infectious disease specialists are crucial. Moreover, bacterial cultures should be performed promptly when any suspicious signs of infectious disease are detected, at which time appropriate antibiotic therapy must be initiated.

Previous studies have suggested that a decreased portal venous flow is often observed in patients affected by BA before LT, which is indicative of a poor prognosis [9]. Patients with BA often exhibit a sclerotic portal venous trunk due to inflammation of the hepatoduodenal ligament and recurrent cholangitis, as previously reported in approximately 80% of patients with BA who undergo portoenterostomy at the time of LDLT [10]. Technical difficulties in performing portal venous reconstruction at the time of LT may lead to serious morbidity and mortality [11]. Moreover, the use of LT in children younger than 1 year of age is associated with an especially high risk of morbidity and mortality due to the need for difficult technical approaches [12]. In the present case, although the preoperative radiological findings revealed narrowing of the portal venous trunk with a decreased blood flow, the portal venous trunk macroscopically appeared to be patent without sclerotic changes. Portal vein reconstruction was performed using the branch patch technique with a sufficient hepatopetal flow.

Conclusions

The patient presented herein was able to survive because a hepatic graft from a living donor was quickly obtained. When faced with candidates for LT as an urgent life-saving surgery, determining whether LDLT should be performed simultaneously during perioperative management is necessary to save the life of the patient. Selecting optimal surgical therapeutic options is crucial in patients with strangulated bowel obstruction at the Roux-en Y limb with end-stage BA.

Conflicts of interest

There are no conflicts of interest from any of the authors.

Indexed in: [Science Citation Index Expanded] Index Medicus/MEDLINE] [Chemical Abstracts] [Scopus]

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Abstract

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Technical considerations of living donor hepatectomy of segment 2 grafts for infants.

Sakamoto S[1], Kanazawa H[2], Shigeta T[2], Uchida H[2], Sasaki K[2], Hamano I[2], Fukuda A[2], Nosaka S[3], Egawa H[4], Kasahara M[2].

Author information

Abstract

BACKGROUND: The selection of an adequate graft to mitigate the problems associated with a large-for-size graft is essential to ensure the success of liver **transplantation** for smaller children. Reduced left lateral **segment** (LLS) **grafts** have been introduced to overcome this issue.

METHODS: Five **infants** underwent **living donor** liver **transplantation** (LDLT) with **segment 2 grafts**. In the preoperative assessment, the graft-to-recipient weight ratio (GRWR) and the ratio of the thickness of the **donor** LLS were used as a reference index for graft size matching, and a 3-dimensional (3D) computer-generated model of the **donor** liver was used for the analysis of the intrahepatic vasculature. During the **donor** operation, the relevant portal vein branches feeding to the reduced part of **segment** 3 were first exposed and divided, and then the parenchymal transection was performed.

RESULTS: Segment 2 grafts were selected in 3 cases and reduced **segment 2 grafts** were selected in the other **2** cases. The graft reduction was achieved with 46.6 ± 8.**2**% of the actual LLS, and thus the GRWR was reduced from 5.33 ± **2**.09% to **2**.70 ± 0.82%. The actual graft thickness was reduced by approximately half after the graft reduction. Primary abdominal closure was performed in all of the recipients. No **surgical** complications occurred in any of the **donors** or recipients.

CONCLUSION: A **segment 2** graft could be a valuable option for graft type selection in LDLT for smaller children. Precise planning using a 3D computer-generated model of the **donor** liver and meticulous **operative procedures** are necessary to obtain a viable graft.

PMID: 24909347 [PubMed - in process]

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Abstract

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Transplant Proc. 2014 Jun;46(5):1371-6. doi: 10.1016/j.transproceed.2013.12.054. Epub 2014 May 15.

Clinical outcomes and evaluation of the quality of life of living donors for pediatric liver transplantation: a single-center analysis of 100 donors.

Fukuda A[1], Sakamoto S[2], Shigeta T[2], Uchida H[2], Hamano I[2], Sasaki K[2], Kanazawa H[2], Loh DL[2], Kakee N[3], Nakazawa A[2], Kasahara M[2].

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Abstract

There are few reports about the **quality** of **life** (QOL) and morbidities of **pediatric living** donor **liver transplantation** (LDLT) **donors**. We evaluated the potential morbidities and identified the predictive factors regarding the QOL of **living donors** after **pediatric** LDLT. This cross-sectional study was a single-center analysis of 100 **donors** for **pediatric** LDLT. The severity of morbidities was assessed with the Clavien classification, the QOL was investigated with the short form-36 (SF-36), and the decision-making process regarding donation was analyzed with questionnaires. The median follow-up period was 3.8 years (range, 2.2-6.0 years). A total of 13% of the **donors** developed postoperative complications of Clavien grades I (7%), II (3%), and IIIA (3%). There was no grade IV morbidity or mortality. Eighty-one **donors** responded to the questionnaire and SF-36. The analysis of the questionnaires revealed that the **donors** had difficulty in the decision-making process, and suggested that it may be necessary to administer multistep informed consent. We identified unique predictive risk factors for lower SF-36 scores in the **donors**, which were the time to donation (more than 4 weeks) and the predonation self-oriented perception. The **donors** who have risk factors require enhanced pre- and post-donation psychological care.

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Pediatr Transplantation 2014: 18: E120–E123

Pediatric Transplantation
DOI: 10.1111/petr.12255

Central pontine myelinolysis following pediatric living donor liver transplantation: A case report and review of literature

Uchida H, Sakamoto S, Sasaki K, Hamano I, Shigeta T, Kanazawa H, Fukuda A, Nosaka S, Kubota M, Kasahara M. Central pontine myelinolysis following pediatric living donor liver transplantation: A case report and review of literature.

Abstract: CPM is one of the most serious neurological complications that can occur after OLT and is characterized by symmetrical demyelinization in the basis pontis. The etiology of CPM remains unclear, although the rapid correction of the serum sodium and CNI concentrations may be associated with the development of CPM. With recent advances in MRI technology, early diagnosis of CPM has become possible. Here, we present the case of a five-yr-old female who developed CNI-associated CPM after undergoing LDLT. A decreased level of consciousness and dysphasia was noted one wk after LDLT, and MRI revealed findings compatible with a diagnosis of CPM. The patient fully recovered from the neurological deficits related to CPM following the switch from the CNI to sirolimus. We propose MRI to be promptly considered for patients with abnormal neurological findings, together with the substitution of CNI with an mTOR inhibitor as a management regimen for CNI-related CPM.

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Key words: sirolimus – neurological complications – pediatric liver transplantation – living donor liver transplantation – calcineurin inhibitors

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The development of CPM following OLT was first reported by Starzl et al. (1). CPM is considered to be the most serious neurological complication of OLT, with a risk of early mortality (2). Although most previously reported cases of CPM were diagnosed at autopsy, recent advances in MRI technology now allow for the early diagnosis of CPM (3, 4). It has been reported that electrolyte imbalances, the rapid correction of the serum sodium concentration and the administration of immunosuppressive agents are associated with the development of CPM following organ transplantation (5, 6). Previous reports have focused on adult liver transplant patients with CPM, and there are few case reports of pediatric CPM patients. We herein present the case of pediatric patient who developed CNI-associated CPM after LDLT, whose neurological symptoms exhibited a complete reversal following a switch from the CNI to an mTOR inhibitor.

Abbreviations: ADC, apparent diffusion coefficient; CNI, calcineurin inhibitor; CPM, central pontine myelinolysis; CT, computed tomography; DWI, diffusion-weighted image; FLAIR, fluid-attenuated inversion recovery; LDLT, living donor liver transplantation; LT, liver transplantation; MRI, magnetic resonance imaging; mTOR, mammalian target of rapamycin; OLT, orthotopic liver transplantation; POD, post-operative day; PRES, posterior reversible encephalopathy syndrome.

Case report

A five-yr-old female was transferred to our institution due to fulminant hepatic failure of unknown etiology. On admission, she presented with jaundice, coagulopathy and hepatic encephalopathy. Brain CT did not show any cerebral edema. Despite the administration of intensive medical treatment, the liver atrophy rapidly progressed with sustained liver dysfunction. Consequently, the patient underwent LDLT with a partial liver from her ABO blood type compatible father. Standard LDLT technique was employed for the operation.

The post-operative immunosuppressive regimen consisted of tacrolimus and low-dose steroids. The patient was fully alert and underwent extubation on POD 7. However, her level of consciousness gradually worsened and she developed swallowing dysfunction. Laboratory parameters, including the serum level of sodium (135–144 mEq/L) and the trough level of tacrolimus (6.4–12.2 ng/mL), were maintained within acceptable ranges. Brain MRI images obtained on POD 13 revealed an increased signal on DWIs and a decreased signal on ADC images in the pons (Fig. 1). These observations were compatible with the findings of CPM. Neurological symptoms, including dysphagia, a weak cough and increased patellar tendon reflexes, were identified. Despite the replacement of tacrolimus by cyclosporine (due to the possibility of tacrolimus-induced encephalopathy), the patient's neurological symptoms did not dramatically improve. Brain MRI performed on POD 23 revealed progressed neuroradiological findings, including new abnormal T2 hyperintensity in the middle cerebellar peduncle to the pons (Fig. 2). Following the introduction of sirolimus and the complete cessation of the CNI, the patient's neurological symptoms disappeared. She was discharged three and a half months after LDLT. Follow-up brain MRI did not show any abnormal findings (Fig. 3). Throughout the one-yr follow-up, her liver function tests remained excellent on sirolimus monotherapy.

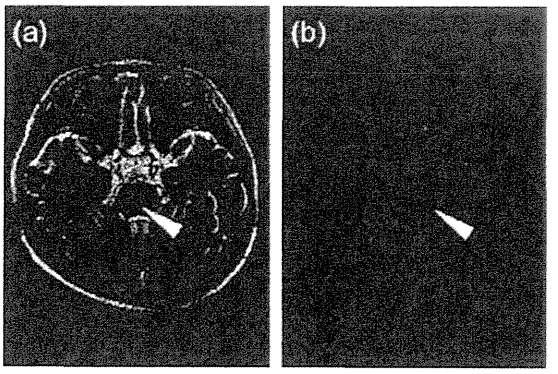

Fig. 2. (a) T2-weighted images showing hyperintensity in the middle cerebellar peduncle to the pons (arrowhead). (b) DWI sequence clearly showing an increased signal in the pons (arrowhead).

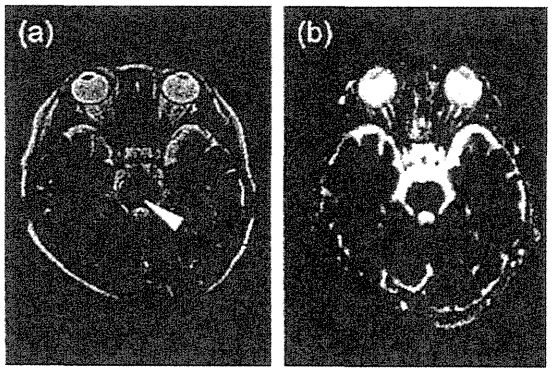

Fig. 3. (a) Improved findings in the pons on T2-weighted images, as evidenced by the slightly hyperintense area (arrowhead). (b) ADC map showing almost normal findings.

Discussion

CPM is a neurological disorder characterized by symmetrical demyelinization and severe damage of the myelin sheath of nerve cells in the basis pontis (2). A late diagnosis of CPM often results in a high mortality rate owing to the development of irreversible brain damage (7). Recently, however, CPM can be detected much earlier by paying particular attention to the rapid changes in electrolytes, together with the timely MRI (4, 8–10).

To the best of our knowledge, 10 cases of CPM after pediatric LT were reported worldwide between 1989 and 2012 (Table 1) (3, 8–12). Five patients died, and they were only diagnosed with

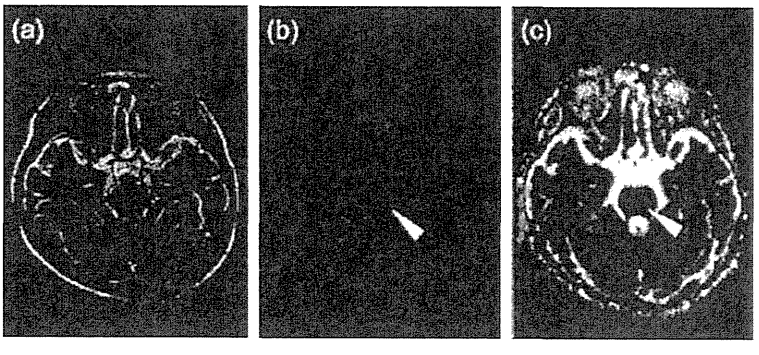

Fig. 1. (a) T2-weighted images showing normal findings in the pons. (b) DWI showing an increased signal in the pons due to restricted water diffusion (arrowhead). (c) ADC map showing a decreased signal in the pons (arrowhead).

Table 1. Patients with CPM following pediatric LT

Reference (issue year)	Age (yr), sex	Indication for LT	Onset (day)	HE	Neurological manifestation	Risk factor(s)	Diagnostic approach	Treatment	Outcome	Neurological impairment
3 (1989)	4, F	BA	NA	NA	Seizure	CNI (CsA)	Autopsy	NA	Died	NA
	8, F	FHF	NA	NA	NA	CNI (CsA)	Autopsy	NA	Died	NA
	18, M	CAH	NA	NA	NA	Hyponatremia	Autopsy	NA	Died	NA
8, 9 (1991)	8, F	FHF	1	Yes	Decreased LOC	NA	Autopsy	NA	Died	NA
	16, F	CAH	38	No	Seizure	NA	Autopsy	NA	Died	NA
10 (2000)	17, F	WD	NA	No	None	CNI (CsA)	MRI	None	Alive	No
11 (2002)	0.8, M	BA	NA	Yes	None	CNI (Tac)	MRI	None	Alive	No
	15, F	BA	NA	Yes	None	CNI (Tac)	MRI	None	Alive	No
12 (2012)	11, M	PSC	9	Yes	Decreased LOC	Hyponatremia, CNI (Tac)	MRI	Conversion from Tac to SRL	Alive	Yes
The presented case	5, F	FHF	8	Yes	Decreased LOC	CNI (Tac, CsA)	MRI	Conversion from CNI to SRL	Alive	No

BA, biliary atresia; CAH, chronic active hepatitis; CsA, cyclosporine; F, female; FHF, fulminant hepatic failure; HE, hepatic encephalopathy; LOC, level of consciousness; M, male; NA, not available; Tac, tacrolimus; PSC, primary sclerosing cholangitis; SRL, sirolimus; WD, Wilson's disease.

CPM at autopsy. On the other hand, five patients survived, providing an overall survival rate similar to that of adult patients (6). Among the five survivors, three patients without any neurological symptoms were incidentally found with CPM on the imaging follow-up of LT. The other two survivors, including the present case, revealed neurological symptoms at onset, and then, they were diagnosed with CPM. The present case was the only patient to have exhibited a complete neurological recovery. To the contrary, the other patient, who displayed hyponatremia and cerebral edema before LT, suffered from neurological sequelae (10). The pre-existing condition might have caused neurological sequelae (5, 6).

Although there are several initial symptoms of CPM, including stupor, dementia, dysarthria and dysphagia, none of these is specifically associated with pontine lesions (8, 9). Diagnosing CPM based on clinical manifestations can be difficult, as the signs and symptoms of CPM are often absent or masked by other neurological abnormalities unrelated to the pontine lesions (13). In our case, the occurrence of hepatic encephalopathy before LT due to fulminant hepatic failure complicated the diagnosis process, although Erol et al. reported that the presence of encephalopathy before LT is not a risk factor for neurological complications in pediatric patients (14).

The underlying mechanisms of the development of CPM remain largely unknown. However, some cases of CNI-related CPM have been reported (2, 5, 10). The occurrence of CNI-related neurotoxicity after LT, including CPM and PRES, is observed in 1–10% of patients (10, 14). Recently, CNI-related neurotoxic side effects have been reported to be relatively common in pediatric recipients (14). In pediatric patients, PRES is a rare neurological complication that can occur after LT in association with the administration of CNIs, such as tacrolimus and cyclosporine; however, this condition should be distinguished from CPM. Brain MRI demonstrates characteristic PRES findings that can be used to differentiate between CPM and PRES. ADC mapping of PRES patients shows increased diffusion in areas that exhibit high signal intensity on FLAIR images, whereas ADC mapping of CPM patients demonstrates decreased diffusion, as observed in this case.

Sirolimus, an inhibitor of mTOR, is known to be an effective immunosuppressant for the prevention of acute rejection in renal transplant recipients (15). In spite of that, there is a lack of reports on the use of mTOR inhibitors as the primary immunosuppressants in LT patients (16, 17). Currently, mTOR inhibitors are mainly used to treat steroid-resistant rejection in children who underwent LT (18). Sirolimus does not usually cause neurotoxicity in LT recipients, which may be attributed to the different mechanism of action of mTOR inhibitors compared with that of CNIs. CNIs bind to immunophilin, forming a ternary complex with calcineurin, which constitutes more than 1% of the total protein in the central nervous system (CNS), while mTOR inhibitors bind the same immunophilin as tacrolimus. However, mTOR inhibitors act downstream by blocking the activation of a cell cycle kinase, mTOR, which has a negligible impact on the CNS (15, 19). To date, there are several reports that suggest a switch from CNI to an mTOR inhibitor may improve the neurological prognosis of LT patients with CNI-related neurotoxicity (10, 20). Despite the withdrawal of the CNI at an early

phase after LT, our patient achieved the desired outcome through sirolimus monotherapy without any complications such as acute rejection, drug-related effects or neurological sequelae.

In summary, making an early diagnosis is crucial in patients with neurological manifestations after LT. The importance of using promptly to facilitate the early diagnosis of CPM cannot be overstated. We also suggest the switching from CNI to an mTOR inhibitor as a potentially feasible approach to treating CNI-related CPM.

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Authors' contributions

H.U.: study design, writing of the paper; S.S. and M.K.: study design and critical revision of the article for clinical content; K.S., I.H., H.K., A.F. and T.S.: collection of the data; S.N.: critical revision of the article for radiological content; and M.K.: critical revision of the article for neurological content.

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Hepatic artery reconstruction preserving the pancreaticoduodenal arcade in pediatric liver transplantation with celiac axis compression syndrome: Report of a case

Uchida H, Sakamoto S, Matsunami M, Sasaki K, Shigeta T, Kanazawa H, Fukuda A, Nakazawa A, Miyazaki O, Nosaka S, Kasahara M. (2014) Hepatic artery reconstruction preserving the pancreaticoduodenal arcade in pediatric liver transplantation with celiac axis compression syndrome: Report of a case. *Pediatr Transplant*, 18: E232–E235. DOI: 10.1111/petr.12329.

Abstract: CACS is rare, although it has been reported to be a potential risk factor for hepatic artery thrombosis following LT. We herein present the case of a 14-yr-old male with stenosis of the origin of the celiac trunk. Preoperative CT and color ultrasonography showed narrowing of the proximal celiac artery. The patient underwent DDLT with standard arterial reconstruction without dividing the gastroduodenal artery. His postoperative course was uneventful, with an excellent hepatic artery flow on Doppler ultrasonography. Applying a meticulous preoperative evaluation and the appropriate surgical technique is crucial in patients with CACS.

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Key words: celiac artery compression syndrome – hepatic artery thrombosis – median arcuate ligament – pediatric liver transplantation

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CACS has been reported to be a potential risk factor for hepatic artery thrombosis after LT (1), with an incidence of 24% among the general population (2). This paper describes the management of hepatic artery reconstruction in a patient with CACS in which the pancreaticoduodenal artery arcade was preserved.

Case report

The patient was a 14-yr-old male with type II citrullinemia. The diagnosis of type II citrullinemia was suspected at five days of age due to persistent hyperbilirubinemia, hyperammonemia, increased plasma citrulline/arginine levels, and a specific mutation with a relevant family history of an affected sister. Treatment with protein restriction and medication with sodium benzoate, phenyl acetate, and arginine were subsequently administered as the initial therapy. Despite the administration of medical treatment, several episodes of fulminant hyperammonemia and hepatic dysfunction followed at eight yr of age, requiring repeat hospitalization. The patient had been on the waiting list for DDLT beginning when he was 14 yr of age. Preoperative CT and color ultrasonography revealed stenosis of the origin of the celiac trunk (Fig. 1a,b). A diagnosis of CACS was suspected, given that the hepatic arterial blood supply ran primarily through the pancreaticoduodenal artery arcade via the superior mesenteric artery (Fig. 1c). The patient received a piggyback DDLT with a whole liver graft. Due to the sufficient front flow of the proper hepatic artery in the recipient, standard

Abbreviations: CACS, celiac axis compression syndrome; CT, computed tomography; DDLT, deceased donor liver transplantation; LT, liver transplantation; MAL, median arcuate ligament.

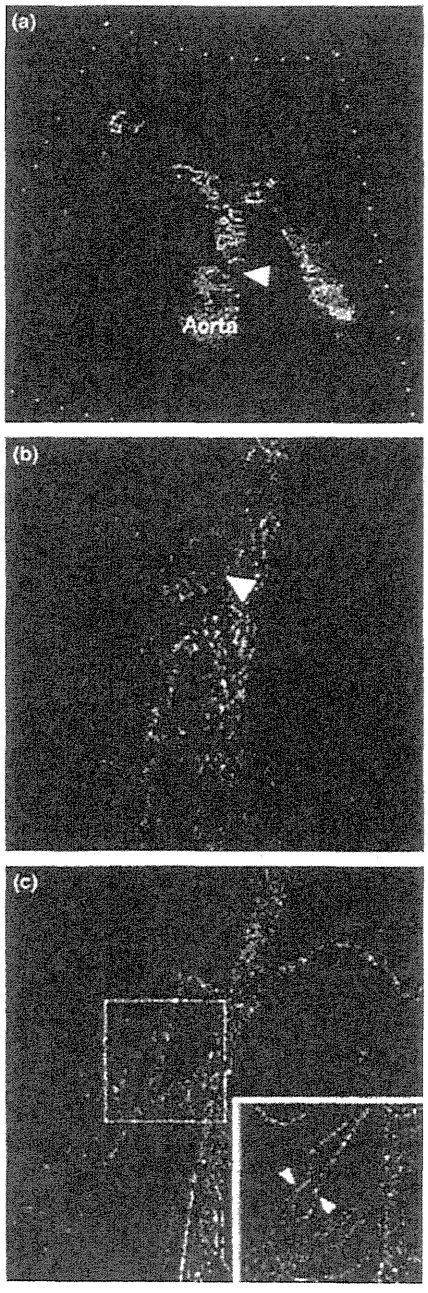

Fig. 1. (a) Color ultrasonography showing focal residual stenosis at the proximal celiac artery (arrowhead). (b) CT angiography showing the characteristic hooked narrowing of the proximal celiac artery on a 3D reconstruction image (arrowhead). (c) CT angiography showing the mesenteric hepatic collateral via the pancreaticoduodenal arcade (square box). A partial enlarged view of the lower right shows the collaterals (arrowhead).

reconstruction between the proper hepatic artery without diversion of the gastroduodenal artery and a common hepatic artery graft was accomplished using the microvascular technique (3). The vessel anastomosis was performed in an end-to-end fashion using interrupted sutures with 9-0 nylon. The intrahepatic arterial blood flow was 788 mL/min, with a resistance index of 0.56. The patient was discharged 17 days after DDLT. His postoperative course was uneventful, with an excellent hepatic artery flow on Doppler ultrasonography. Furthermore, he has been doing well without either protein restriction or any additional medication for the original liver disease.

Discussion

CACS is a well-described anatomical entity caused by compression of the celiac axis by the MAL that was first described by Harijola in 1963 (4). Affected patients usually exhibit various clinical manifestations, including postprandial abdominal epigastric pain, nausea, occasional diarrhea, and weight loss (5); however, the present patient was asymptomatic. The incidence of CACS among transplant recipients has been reported to be 3.7–10.0% (1, 6, 7). The presence of CACS may predispose the patient to hepatic artery thrombosis, as it decreases common hepatic artery blood flow by more than 50% (1).

Recently, it has become possible to diagnose celiac axis compression with three-dimensional (3D) CT angiography and/or Doppler ultrasonography, especially in children (8). It has been documented that during expiration in the presence of celiac artery compression, the blood flow falls from optimal values of 400 mL/min to values <200 mL/min (1, 9). We do not measure the flow volume of the celiac artery routinely; however, we did note that there was a significant celiac arterial flow reduction from 35.7 to 16.6 cm/s in maximum velocity during expiration in the present case. We also did not perform any direct measurement of the pressure in the hepatic artery prior to/during the LT. However, such measurement would help to provide a definite diagnosis of the presence of CACS. Furthermore, aneurysms of the pancreaticoduodenal artery are occasionally found in the patient with CACS, and a proper diagnosis could facilitate the treatment for such a patient (10). Therefore, careful planning and follow-up are crucial in patients with CACS before LT, with strict assessment of the radiological findings.

Three types of hepatic artery reconstruction have been described in LT for CACS: release of the MAL, aortohepatic graft interposition, and standard reconstruction with preservation of the native gastroduodenal artery (7). Release of the MAL has been reported as the initial treatment in pediatric patients treated without LT, with a

reported successful rate of 67% (5). This unsatisfactory result may be explained by the relevant presence of atheromatic plaque in association with MAL, resulting in restenosis of the celiac artery (7). Moreover, the condition induced celiac trunk injury in 11.7% of LT cases (1). Meanwhile, Lindner et al. stated that the release of the compressing cuirass of the celiac plexus could be needed, in addition to the resection of MAL (11).

Hepatic artery reconstruction with aortohepatic graft interposition is performed with an iliac artery or prosthetic graft and the graft is implanted on the infrarenal aorta. However, aortohepatic graft reconstruction is associated with a relatively high incidence of thrombosis, with an incidence of 5.3–21.8% (12, 13). Normally, hepatic artery reconstruction is accomplished with 9-0 nylon interrupted sutures with a surgical microscope. The gastroduodenal artery of the recipient is ligated to the retrograde dissection of the hepatic axis down to the aorta until an adequate lumen of the gastro-hepatic artery and a normal arterial pressure are obtained. However, in the present case, we could obtain sufficient front flow of the proper hepatic artery without ligation of the gastroduodenal artery. Preserving the gastroduodenal arterial flow might be key for successful hepatic artery reconstruction in CACS cases. Tying the splenic artery to increase the hepatic arterial flow is not always performed, because it can reduce the portal venous flow/pressure and cause portal venous complications, especially in the pediatric patients with biliary atresia (14).

Percutaneous angioplasty with stenting has recently been reported as an alternative option for the treatment of MAL (15). Although it is a minimally invasive intervention, its long-term patency is not fully documented, especially in pediatric liver transplanted patients with immunosuppression. The efficiency and efficacy of the stenting in pediatric recipients should be discussed on case-by-case basis.

Between November 2005 and December 2013, 260 children underwent LT (including 11 cases of DDLT) at the National Center for Child Health and Development, Tokyo, Japan. Microvascular surgery for hepatic artery reconstruction has been employed since the beginning of the program, and no cases of hepatic artery thrombosis have been observed in our series. In addition to postoperative ultrasonography, intra-operative Doppler ultrasonography has been routinely used to evaluate the vascular patency at our center to make an early diagnosis of vascular and biliary complications. If the hepatic arterial flow is not sufficient with a low pulsatility index, we consider further dissection of the hepatic axis down to the aorta or splenic artery ligation, if the portal venous flow is sufficient. There have been some reports that the intra-operative assessment of the hepatic artery is important to reduce vascular complications (16, 17). Intra-operative Doppler ultrasonography might also prevent early hepatic artery complications (18).

In the present case, standard arterial reconstruction without division of the gastroduodenal artery was accomplished with the microsurgical technique. Lubrano et al. mentioned according to standard arterial reconstruction technique for patient with CACS and stated that the preserving gastroduodenal flow is feasible for LT cases performed in adults (7). The present case demonstrates that preserving the pancreaticoduodenal artery arcade may be appropriate for children, if the native proper hepatic arterial flow is sufficient, in the setting of hepatic artery reconstruction among CACS patients evaluated with a meticulous preoperative assessment and treated with the proper surgical technique.

Authors' contributions

H.U.: Study design, writing of the paper; S.S.: Study design, critical revision of the article for clinical content; M.M., K.S., H.K., A.F., T.S.: Collection of the data; A.N.: Critical revision of the article for physiological content; O.M., S.N.: Critical revision of the article for radiological content; M.K.: Study design, critical revision of the article for clinical content.

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Technical refinement in living-donor liver transplantation for hepatoblastoma with main portal vein tumor thrombosis – a pullout technique

Kanazawa H, Sakamoto S, Matsunami M, Sasaki K, Uchida H, Shigeta T, Fukuda A, Matsumoto K, Nakazawa A, Tanaka R, Kasahara M. (2014) Technical refinement in living-donor liver transplantation for hepatoblastoma with main portal vein tumor thrombosis – a pullout technique. *Pediatr Transplant*, 18: E266–E269. DOI: 10.1111/petr.12357.

Abstract: We present a case of a two-yr-old boy diagnosed with HBT with complete main PVTT. HBT was located in the bilateral lobe with PVTT involving the confluence of the SMV and the SpV. Cisplatin-based neoadjuvant chemotherapy was delivered; main tumor shrank and AFP levels decreased to below one hundredth. However, PVTT remained in the bilateral portal branches to the main trunk of PV. We describe the technical details of the portal venous tumor thrombectomy that was succeeded by a LDLT. The patient remained healthy 2.5 yr after LDLT, showing good patency of the PV with no evidence of recurrence of tumor.

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Key words: hepatoblastoma – liver transplantation – portal vein tumor thrombosis

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HBL is the most common malignant liver tumor in early childhood, accounting for 60–85% of all pediatric hepatic tumors (1). As it is a surgical tumor, the main form of treatment is surgical resection. Advances in imaging technology, systemic cisplatin-based neoadjuvant chemotherapy, and surgical resection have improved survival rates (2). Patients with HBL with resectable tumors have a disease-free survival rate of 80–90% (3). While more than 60% of lesions that appeared unresectable at initial imaging shrank with chemotherapy and eventually became resectable (2), some cases of HBL remained unresectable despite chemotherapy to control extrahepatic lesion. In such cases, whole liver resection is necessary, with liver transplantation being recognized as a valid therapeutic option to accomplish complete resection (4). HBL that invades the bilateral portal branches or the main portal trunk with tumor thrombosis is one of the most unresectable forms of tumor. Although macrovascular invasion posed as a

Abbreviations: FDG, F^{18}-fluoro-2-deoxy-D-glucose; HBL, hepatoblastoma; LDLT, living-donor liver transplantation; PET, positron emission tomography; POST-TEXT, post-treatment extent of disease; PRETEXT, pretreatment extent of disease; PV, portal vein.; PVTT, portal vein tumor thrombosis; SMV, superior mesenteric vein; SpV, splenic vein.

poor prognostic factor, the main aim is still to achieve complete resection for chemosensitive HBL through surgery (5).

Here, we report a pediatric patient with PVTT that remained in the SMV and the splenic venous junction (SMV-SpV junction) despite neoadjuvant chemotherapy. The patient eventually underwent complete surgical resection with PV thrombectomy and LDLT. We describe the details of the surgery of the PV thrombectomy that employed the use of a "pullout technique."

Case

The patient was a 2.5-yr-old boy 12 kg in weight. The chief complaint was abdominal distension. A computed tomography (CT) showed multifocal liver tumors occupying the whole liver with a PVTT that extended to the SMV-SpV junction (Fig. 1a). PET with FDG study showed that huge liver tumor, PVTT, and the segment 6 of the right lung were positive. At the time, serum AFP level was markedly elevated at 580 000 ng/mL (normal range: <10 ng/mL). The case was assessed using the PRETEXT grouping system for HBL, as PRETEXT IV, C1, E0a, F1, H0, M1p, P2a, and V1 (6). Needle biopsy findings showed fetal and embryonic mixed-type HBL. Neoadjuvant chemotherapy by cisplatin–pirarubicin (tetrahydropyranyl–adriamycin) (CITA) was introduced in accordance with the protocol of the Japanese Study Group for Pediatric Liver Tumor protocol-2 (7). At the end of the third cycle of CITA, AFP levels decreased to 2373 ng/mL and the size of the tumor size was reduced. While a lung metastasis was no longer present after the fourth cycle of chemotherapy by ifosfamide, carboplatin, tetrahydropyranyl–doxorubicin, and etoposide (ITEC), AFP levels rose again to 6450 ng/mL. It was determined at that stage that the primary liver tumors could not be sufficiently controlled, prompting the need for transarterial chemoembolization. In addition, a systemic chemotherapy comprising cisplatin, vincristine, and fluorouracil (C5V) was delivered due to the suspicion that the patient might have impaired response to the previous rounds of chemotherapy (8). Subsequently, AFP level decreased to 2532 ng/mL. However, the PVTT, which assumed an atrophic shape and was negative in FDG–PET study, remained in the SMV-SpV junction. CT showed enlarged and tortuous collateral vessels had developed along the common bile duct in the hepatoduodenal ligament (Fig. 1b). The case was assessed again using POST-TEXT grouping system for HBL, as POST-TEXT III, C0, E0, F1, H0, M0, P2a, and V0. We scheduled an LDLT for total resection of HBL and removal of PVTT by either thrombectomy or total resection (including PV). The patient's 40-yr-old mother volunteered to have her left lateral segment, weighing 242 g, donated as a graft. The graft-to-recipient body weight ratio was 1.95%.

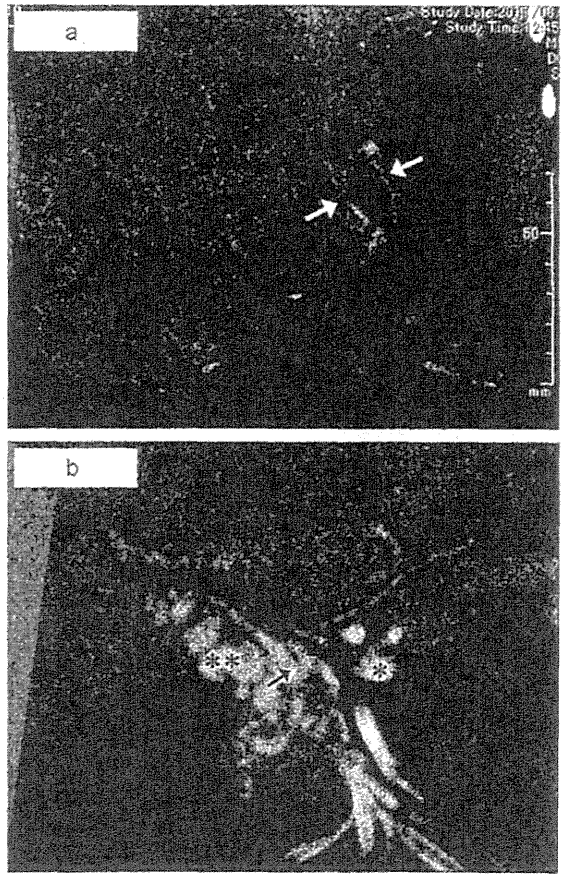

Fig. 1. (a) Large PV thrombosis (white arrow) in coronary view revealed by computed tomography. (b) Thin and long PV thrombosis (black arrow) from the bilateral portal branch to the confluence of the SMV and the SpV (asterisk). A collateral vein was present in the hepatoduodenal ligament (double asterisk).

Surgical procedures

Both collateral vessels and the PV were isolated and taped with vessel loops, and preserved until total hepatectomy. Intra-operative ultrasonography provided definitive imaging of the location of the PVTT which extended into the SMV-SpV junction; however, it was atrophic and appeared "floating." The SMV-SpV junction was exposed with meticulous dissection of the tributaries into the portal venous system. The SMV and the SpV were isolated and clamped at a distal site of the