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Case Report

Living Donor Liver Transplantation to a Survivor of Liver Resection for Hepatocellular Carcinoma with Major Portal Vein Invasion

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We present a case of living donor liver transplantation to a 3-year disease-free survivor of liver resection for hepatocellular carcinoma (HCC) with major portal vein invasion. A 48-year-old man had HCC in the right lobe with a portal venous tumor thrombus extending into the left portal vein. An extended right lobectomy with thrombectomy was performed to remove the thrombus. Three years after liver resection, the patient experienced liver failure, with massive ascites and jaundice due to the formation of a thrombus in the main and left portal veins. During the 3 years after liver resection, no metastasis or recurrence of HCC had been detected, and tumor markers had been within normal ranges. The portal venous thrombus did not show any arterial enhancement under contrast-enhanced computed tomography, suggesting that the co-existence of any HCC component in the portal venous thrombus may have been negative. Based on these findings, living donor liver transplantation was performed using a right lobe graft from the patient's son. The patient is alive at 87 months after the transplantation, with no evidence of HCC recurrence.

Key words: living donor liver transplantation, hepatocellular carcinoma, portal vein invasion, liver resection

The outcome of liver transplantation for patients having previously undergone liver resection for hepatocellular carcinoma (HCC) has been investigated [1–3]. In many of those patients, the HCC was reported to be within the Milan criteria (a solitary liver nodule not exceeding 5 cm in maximum diameter, or 2 or 3 tumors not exceeding 3 cm in diameter) both at the time of liver resection and at the time of liver transplantation. Patients who have HCC with macroscopic vascular invasion are contraindicated for liver transplantation because the rate of HCC recurrence after liver transplantation in such cases is extremely high [4–8].

Portal venous tumor thrombus (PVTT) is one of the most ominous prognostic factors in patients with HCC [9–14]. Even when curative liver resection with thrombectomy for PVTT can be carried out, long-term patient survival after such liver resections has still been poor. However, 10% to 20% of patients who received liver resection for HCC with PVTT have shown long-term survival with no tumor recurrence [11–14].

We report a case of living donor liver transplantation (LDLT) to a 3-year disease-free survivor of liver

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resection for HCC with PVTT extending into the contralateral portal vein. At 87 months after LDLT, this patient is currently alive and well, with no evidence of HCC recurrence.

Case Report

A 48-year-old man was diagnosed with hepatitis B virus infection. In January 2002, computed tomography (CT) scans revealed HCC with a diameter of 7.0 cm located in the anterior and medial segments, whereupon the HCC was treated with transarterial chemoembolization using lipiodol and epirubicin (Fig. 1A). Additionally, the PVTT derived from the main HCC filled the right portal vein and extended into the left portal vein (Fig. 1B). No intra-hepatic metastasis of HCC was detected. The serology of the hepatitis B virus (HBV) was as follows: hepatitis B surface antigen (+), hepatitis B surface antibody (−), hepatitis Be antigen (−), hepatitis Be antibody (+), and hepatitis B core antibody (+). The level of HBV DNA in the blood was less than 3.7 LGE/mL as measured by the transcription-mediated amplification method. The serum level of alpha-fetoprotein (AFP) was elevated at 853 ng/mL. The serum level of protein induced by vitamin K absence or antagonist (PIVKA-II) was 54 mAU/mL (normal laboratory range is <28 mAU/mL). In March 2002, because the liver function of this patient was well preserved and the remnant liver volume was sufficient, an extended right lobectomy with thrombectomy for PVTT was performed. Macroscopic and histological examinations of the resected specimen showed a moderately differentiated HCC with PVTT extending into the left portal vein (Fig. 1C). The postoperative clinical course was uneventful, and postoperative checkups including ultrasonography and/or CT scans were performed every 3 months after discharge.

In November 2004, the level of HBV DNA was elevated to 2.9 log copy/mL as measured by the polymerase chain reaction method, and the serum total bilirubin level increased to around 3.0 mg/dL. Antiviral treatment with lamivudine (100 mg daily) was commenced. In February 2005, the patient developed massive ascites, and the serum total bilirubin level increased to 5.7 mg/dL. CT scans showed a mural thrombus, occupying one-fourth of the main portal vein and extending to the left portal vein (Fig. 2A). Also, a localized thrombus was detected in the umbilical portion of the portal vein, occluding most of the lumen (Fig. 2B). The portal venous thrombus did not show any arterial enhancement on contrast-enhanced CT scans. Additionally, the serum AFP and PIVKA-II concentrations were within the normal ranges. These findings suggested that the co-existence of an HCC component in the portal venous thrombus may have been negative. Anti-coagulation therapy with warfarin was commenced for the portal venous thrombus.

Although the thrombus was reduced by about half at 1 month after the initiation of anti-coagulation therapy, the massive ascites did not diminish and the serum total bilirubin level increased to 6.0 mg/dL. In April 2005, the patient's model for end-stage liver disease score was 18 and his Child-Pugh score was 11. No metastasis or recurrence of HCC in the remnant liver or to other organs was detected through magnetic resonance imaging, CT scans, bone scintigraphy, and positron emission tomography CT. Because liver failure had developed in spite of medical treatment and there had been no evidence of HCC recurrence during the 3 years after liver resection, the decision was made to perform LDLT.

In May 2005, LDLT was performed using a right lobe graft from the patient's son. The graft weighed 690 g, and the graft weight/recipient weight ratio was 1.1%. There were severe adhesions around the remnant liver and the hepatoduodenal ligament. In addition, the wall of the main portal vein was extremely thin and fragile due to the previous liver resection. Therefore, the recipient's main portal vein was removed and portal venous reconstruction was performed by interposing the left internal jugular vein graft (Fig. 3). The operative time was 645 min, and the intraoperative blood loss was 3,800 mL. Histological examination of the removed specimen showed liver cirrhosis. There was no evidence of HCC recurrence in the removed liver or in the thrombus of the main and left portal veins. Although acute cellular rejection requiring steroid pulse therapy developed on postoperative day 9, the patient was discharged on postoperative day 21. He is currently alive and well with no evidence of HCC recurrence at 87 months after LDLT.

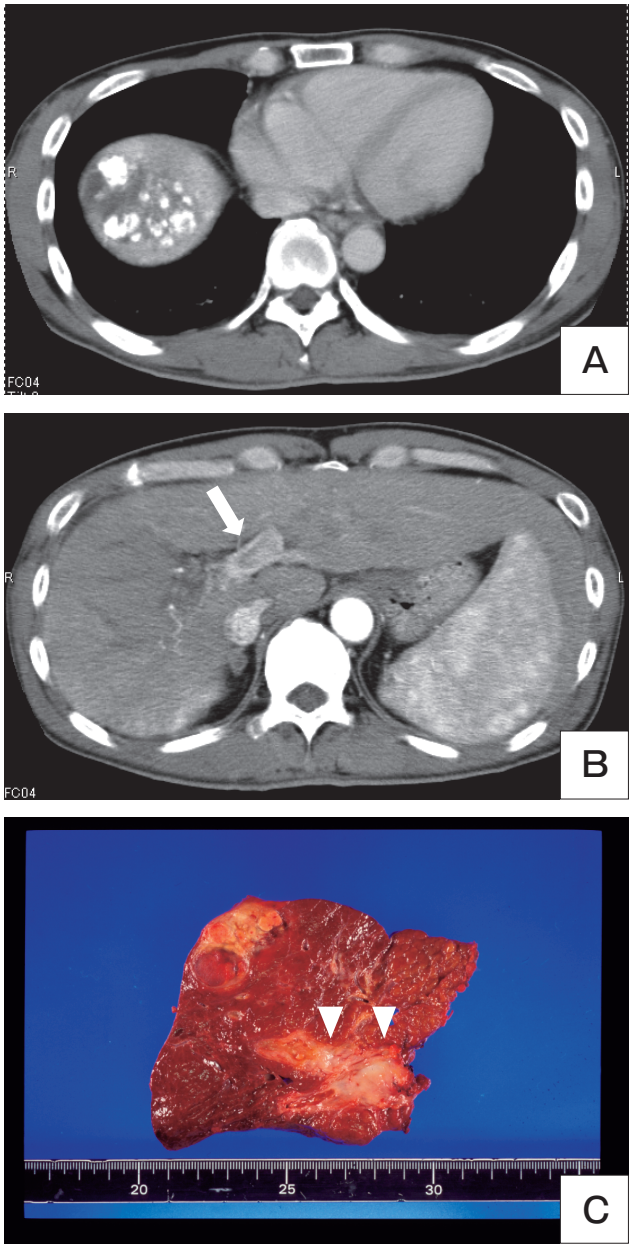

Fig. 1 Computed tomography (CT) images before liver resection, and macroscopic examination of the resected specimen. **A**, Dynamic CT scan showed hepatocellular carcinoma (HCC) with a diameter of 7.0 cm located in the anterior and medial segments; the HCC was then treated with transarterial chemoembolization using lipiodol and epirubicin; **B**, Portal venous tumor thrombus (arrow) derived from the main HCC extended into the left portal vein; **C**, Macroscopic examination of the resected liver specimen revealed portal venous tumor thrombus (arrowhead) filling the right portal vein.

Discussion

Liver transplantation has been performed for patients who had previously undergone liver resection for HCC. In many of those patients, the HCC was within the Milan criteria both at the time of liver resection and at the time of liver transplantation because of the low rates of tumor recurrence after liver transplantation [1–3]. On the other hand, liver transplantation is contraindicated in patients having HCC with major vascular invasion because of the high rates of tumor recurrence and the associated poor long-term survival [4–8]. Therefore, for those patients, liver resection remains the only therapeutic option that may offer a chance for disease-free survival. In this study, we report a case of LDLT to a 3-year disease-free survivor of liver resection for HCC with PVTT extending into the contralateral portal vein. At 87 months after LDLT, this patient is currently alive, with no evidence of HCC recur-

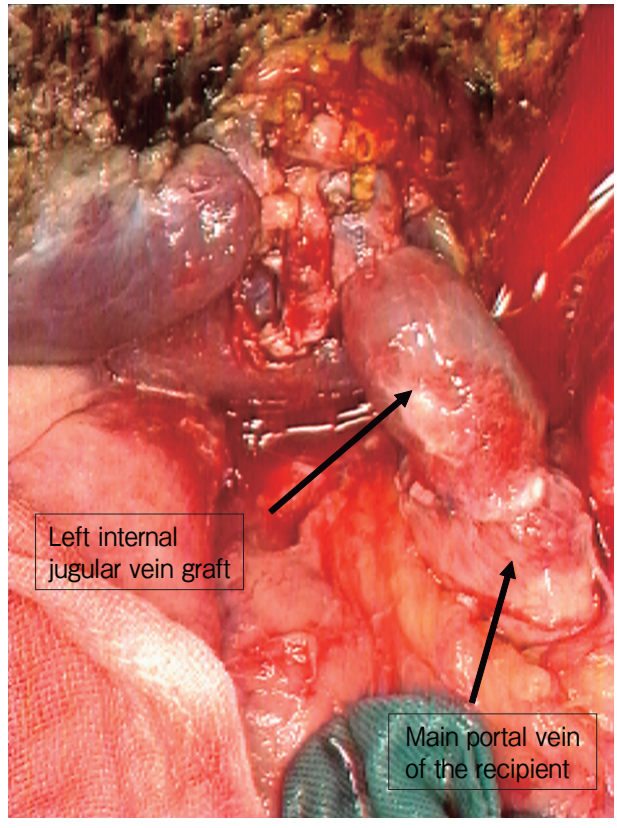

Fig. 3 Interposition using the left internal jugular vein graft was performed for portal venous reconstruction of the liver graft.

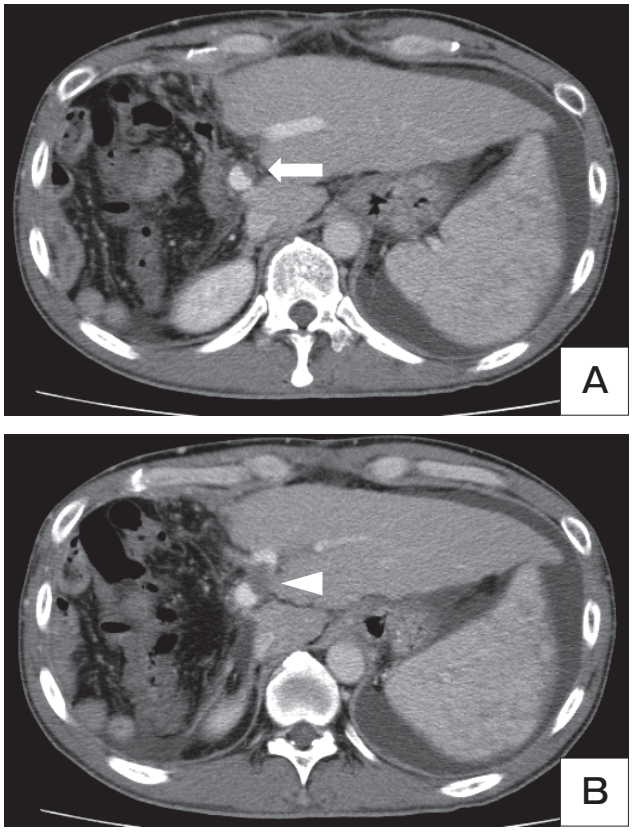

Fig. 2 Computed tomography (CT) images before living donor liver transplantation. **A**, The thrombus was found on the left wall of the main and left portal veins (arrow), with massive ascites and severe splenomegaly; **B**, The localized thrombus (arrowhead) was detected in the umbilical portion of the portal vein, occluding most of the lumen.

rence. Thus it is a rare case of long-term disease-free survival through liver resection and LDLT.

The indication for liver transplantation in patients who have disease-free survival after liver resection for HCC with major vascular invasion is controversial and difficult. This is because the rate of HCC recurrence after liver transplantation cannot be estimated in those patients. Although the prognosis after liver resection for HCC with major vascular invasion remains poor, some patients (10%–20%) are reported to have long-term survival without tumor recurrence [11–14]. According to these studies, in most cases, tumor recurrence develops within 2 years of liver resection, and the disease-free survival rate tends to be unchanged 3 years and onwards following liver resection. In the present case, as a result of systemic imaging, there was no evidence of HCC recurrence during the 3 years after liver resection for HCC with PVTT. Additionally, the findings of contrast-enhanced CT scans, which showed no arterial enhancement in the portal venous thrombus, suggested that the co-existence of any HCC component in the portal venous thrombus may have been negative. Although the effect of immunosuppression on tumor recurrence after liver transplantation could not be estimated in the present case, we believe that the risk of HCC recurrence after LDLT was low.

Previous studies have reported that, in most cases, liver transplantation is performed as a rescue therapy for intra-hepatic recurrences after liver resection for HCC [1, 15, 16]. On the other hand, in the present case LDLT was performed for chronic liver failure without HCC recurrence, resulting in a relatively rare indication for liver transplantation after liver resection for HCC. Mergental *et al.* [15] suggested that macrovascular invasion, lymph node involvement, and time interval between liver resection and transplantation <12 months were independently associated with poor overall and tumor-free survival rates after liver transplantation. Those authors suggested that the presence of any of these 2 risk factors should be considered a contraindication for liver transplantation after liver resection for advanced HCC [15]. Although the present case had HCC with macrovascular invasion at liver resection, LDLT was performed for chronic liver failure because there had been no evidence of HCC recurrence during the 3 years after liver resection.

Belghiti *et al.* [1] analyzed the influence of previous liver resection for HCC on the outcome of liver transplantation. They reported that liver transplantation following major liver resection appeared to be more difficult, resulting in longer operating time, increased blood transfusion rate, and longer hospital stay. In the present case, interposition using the internal jugular vein graft was necessary for portal venous reconstruction because the wall of the main portal vein became fragile due to the previous liver resection.

In this patient, the combination of liver resection and LDLT were effective for obtaining disease-free long-term survival. Further investigations, including molecular and genomic analyses, will be necessary to refine the indication for liver transplantation in disease-free survivors of liver resection for advanced

HCC with major vascular invasion.

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