16 Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL and Makuuchi M: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg *250*: 187-196, 2009.

17 Takenaka K, Kawahara N, Yamamoto K, Kajiyama K, Maeda T, Itasaka H, Shirabe K, Nishizaki T, Yanaga K and Sugimachi K: Results of 280 liver resections for hepatocellular carcinoma. Arch Surg *131*: 71-76, 1996.

18 Kanematsu T, Furuta T, Takenaka K, Matsumata T, Yoshida Y, Nishizaki T, Hasuo K and Sugimachi K: A 5-year experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. Hepatology *10*: 98-102, 1989.

19 Shirabe K, Kanematsu T, Matsumata T, Adachi E, Akazawa K and Sugimachi K: Factors linked to early recurrence of small hepatocellular carcinoma after hepatectomy: univariate and multivariate analyses. Hepatology *14*: 802-805, 1991.

20 Fan ST, Ng IO, Poon RT, Lo CM, Liu CL and Wong J: Hepatectomy for hepatocellular carcinoma: the surgeon's role in long-term survival. Arch Surg *134*: 1124-1130, 1999.

21 Fuster J, García-Valdecasas JC, Grande L, Tabet J, Bruix J, Anglada T, Taurá P, Lacy AM, González X, Vilana R, Bru C, Solé M and Visa J: Hepatocellular carcinoma and cirrhosis. Results of surgical treatment in a European series. Ann Surg *223*: 297-302, 1996.

22 Yamanaka N, Okamoto E, Toyosaka A, Mitunobu M, Fujihara S, Kato T, Fujimoto J, Oriyama T, Furukawa K and Kawamura E: Prognostic factors after hepatectomy for hepatocellular carcinomas. A univariate and multivariate analysis. Cancer *65*: 1104-1110, 1990.

23 Taketomi A, Kitagawa D, Itoh S, Harimoto N, Yamashita Y, Gion T, Shirabe K, Shimada M and Maehara Y: Trends in morbidity and mortality after hepatic resection for hepatocellular carcinoma: an institute's experience with 625 patients. J Am Coll Surg *204*: 580-587, 2007.

24 Matsumata T, Ikeda Y, Hayashi H, Kamakura T, Taketomi A, Sugimachi K: The association between transfusion and cancer-free survival after curative resection for hepatocellular carcinoma. Cancer *72*: 1866-1871, 1993.

25 Yamashiki N, Yoshida H, Tateishi R, Shiina S, Teratani T, Yoshida H, Kondo Y, Oki T, Kawabe T and Omata M: Recurrent hepatocellular carcinoma has an increased risk of subsequent recurrence after curative treatment. J Gastroenterol Hepatol *22*: 2155-2160, 2007.

26 Shirabe K, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S and Maehara Y: The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma-with special reference to the serum levels of des-gamma-carboxy prothrombin. J Surg Oncol *95*: 235-240, 2007.

27 Taketomi A, Sanefuji K, Soejima Y, Yoshizumi T, Uchiyama H, Ikegami T, Harada N, Yamashita Y, Sugimachi K, Kayashima H, Iguchi T and Maehara Y: Impact of des-gamma-carboxy prothrombin and tumor size on the recurrence of hepatocellular carcinoma after living donor liver transplantation. Transplantation *87*: 531-537, 2009.

28. Yamashita Y, Tsuijita E, Takeishi K, Fujiwara M, Kira S, Mori M, Aishima S, Taketomi A, Shirabe K, Ishida T and Maehara Y: Predictors for microinvasion of small hepatocellular carcinoma ≤2 cm. Ann Surg Oncol *19*: 2027-2034, 2012.

29 Koike Y, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yoshida H, Shiina S and Omata M: Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. Cancer *91*: 561-569, 2001.

Received May 9, 2014
Revised June 16, 2014
Accepted June 17, 2014

Living Donor Liver Transplantation Followed by Total Gastrectomy – A Two-stage Planed Operative Strategy for Early Gastric Cancer Concomitant with Decompensated Liver Cirrhosis

SHO NISHIMURA, HIROSHI SAEKI, TORU IKEGAMI, KOJI ANDO, YO-ICHI YAMASHITA, EIJI OKI, TOMOHARU YOSHIZUMI, MASARU MORITA, KEN SHIRABE and YOSHIHIKO MAEHARA

Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Higashi-ku, Fukuoka, Japan

Abstract. *Aim: With the recent popularization of living donor liver transplantation (LDLT), providing treatment for comorbidities in LDLT recipients has become important. We report the first case of a patient who was successfully treated with LDLT followed by total gastrectomy for early gastric cancer concomitant with decompensated liver cirrhosis. Case Report: A 64-year-old female was admitted for the treatment of severe liver cirrhosis. The patient's preoperative liver function was evaluated as Child-Pugh classification grade C. Upper gastrointestinal endoscopy revealed early gastric cancer. We first performed LDLT to improve her liver function and coagulopathy. Nineteen days after the LDLT, we performed total gastrectomy. Results: The patient's postoperative course was uneventful and she left our hospital on the 18th day after gastrectomy. The final pathological diagnosis of gastric cancer was Stage IA. Conclusion: Aggressive and adequate surgical strategy including LDLT is effective as curative treatment in patients with controllable malignancy concomitant with severe liver dysfunction.*

Surgical treatment for malignancy after liver transplantation is an important topic as an increase in the incidence of cancer in immunocompromised patients has been suggested (1). Concerning gastric cancer after liver transplantation, some case reports have demonstrated the successful use of gastrectomy to treat newly-developed gastric cancer after liver transplantation (2-4).

Correspondence to: Yoshihiko Maehara, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel: +81 926425466, Fax: +81 926425482, e-mail: maehara@surg2.med.kyushu-u.ac.jp

Key Words: Early gastric cancer, primary biliary cirrhosis, liver transplantation, gastrectomy, coagulopathy.

On the other hand, the indications for living donor liver transplantation (LDLT) in patients carrying synchronous malignant disease have not been definitively documented. However, it is considered that conducting a strict preoperative evaluation and appropriately selecting patients and treatment strategies can make it possible to provide safe and curative treatment for such patients.

We herein report the case of a patient who was successfully treated with LDLT followed by total gastrectomy for early gastric cancer concomitant with decompensated liver cirrhosis. This is the first case report to show a successfully staged operative strategy including LDLT for decompensated liver cirrhosis with curative surgery for synchronous malignancy.

Case Report

A 64-year-old Japanese female was admitted to the Kyushu University Hospital for the purpose of LDLT to treat decompensated cirrhosis due to primary biliary cirrhosis. Hepatic encephalopathy was developing in her. The patient's hematological laboratory data on admission after medical treatment were as follows: white blood cell count, 2,240/μl (normal range: 3,500-9,000); hemoglobin, 10.9 g/dl (normal range: 12.0-16.0); platelet count, 5.4×10^4/μl (normal range: 14.0-44.0); total bilirubin, 2.6 mg/dl (normal range: 0.3-1.2); albumin, 3.2 g/dl (normal range: 4.0-5.0); prothrombin time (%), 56% (normal range: 70-130); carcinoembryonic antigen (CEA), 1.8 ng/ml (normal range: 0-5.0); carbohydrate antigen(CA)19-9, 46.7 U/ml (normal range: 0-37). Computed tomography (CT) showed marked liver cirrhosis, splenomegaly and a splenorenal shunt (Figure 1). The preoperative liver function was evaluated as Child-Pugh classification grade C, with a Child-Pugh score of 10 points and an MELD(Model for End Stage Liver Disease) score of 14 points.

0250-7005/2014 $2.00+.40

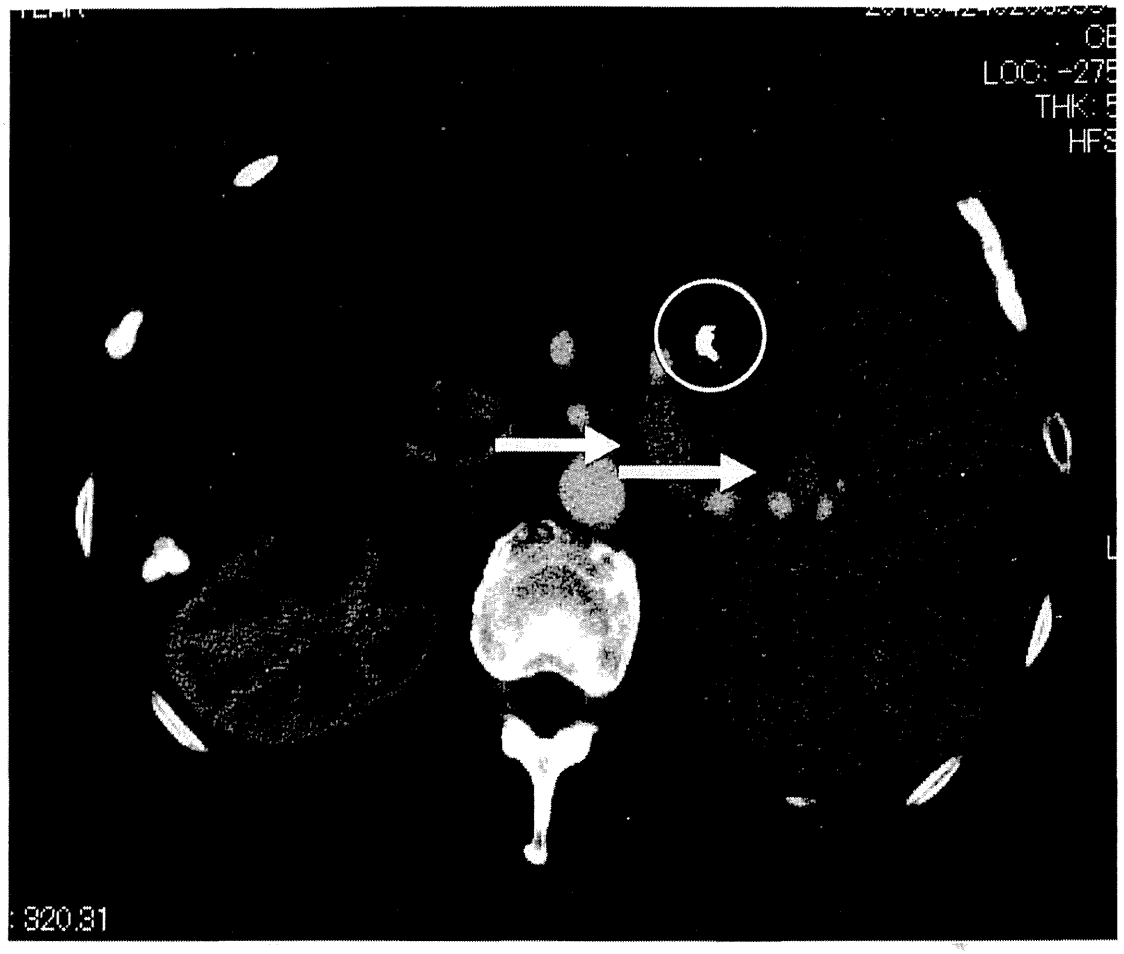

Figure 1. *Preoperative abdominal CT. Findings of severe liver cirrhosis, splenomegaly, a splenorenal shunt (white arrows) and intragastric clips (encircled).*

Upper gastrointestinal endoscopy for preoperative inspection revealed 0-IIc type (5) early gastric cancer in the lower gastric corpus (Figure 2a). Histopathology demonstrated signet ring cell carcinoma with poorly-differentiated carcinoma. During a biopsy, bleeding from the gastric lesion due to a bleeding tendency and portal hypertension was noted and it was necessary to attach clips in order to achieve complete hemostasis (Figure 2b). CT revealed no lymph node or distant metastasis. The preoperative diagnosis was gastric cancer: Clinical T1b N0 M0 Stage IA.

We decided to first perform LDLT, splenectomy and splenorenal shunt ligation in order to improve the patient's liver function and coagulopathy. For the second operation, we planned to perform total gastrectomy because de-vascularization of short gastric vessels accompanied by splenectomy was required in the first operation.

During the first operation, we performed LDLT using a right lobe graft obtained from the patient's daughter, splenectomy and splenorenal shunt ligation. The amount of bleeding was 3,924 g and the length of operation was 17 h and 46 min. The patient's postoperative course was uneventful and her capacity for blood coagulation subsequently returned to normal levels. After the LDLT procedure, immunosuppression with steroids, tacrolimus and mycophenolate mofetil was administered. The hematological laboratory data 18 days post LDLT were as follows: white blood cell count, 7,840/μl; hemoglobin, 10.5 g/dl; platelet count, 33.1×10^4/μl; total bilirubin,1.6 mg/dl; PT(%), 96%.

Total gastrectomy was performed 19 days after LDLT. Since there was adhesion, especially between the liver graft and lesser curvature side of the stomach, we dissected the lesser omentum along the lesser curvature so as not to damage the reconstructed vessels. Reconstruction was performed according to the antecolic Roux-en-Y (6). The amount of bleeding was 286 g and the length of operation was 3 h and 38 min. No blood transfusions were performed. Treatment with tacrolimus was restarted on the first postoperative day through a nasal feeding tube for perioperative immunosuppression.

There were no postoperative complications after total gastrectomy. The patient resumed oral intake on the seventh postoperative day and was discharged from the hospital on the 18th day after total gastrectomy (the 32nd day post

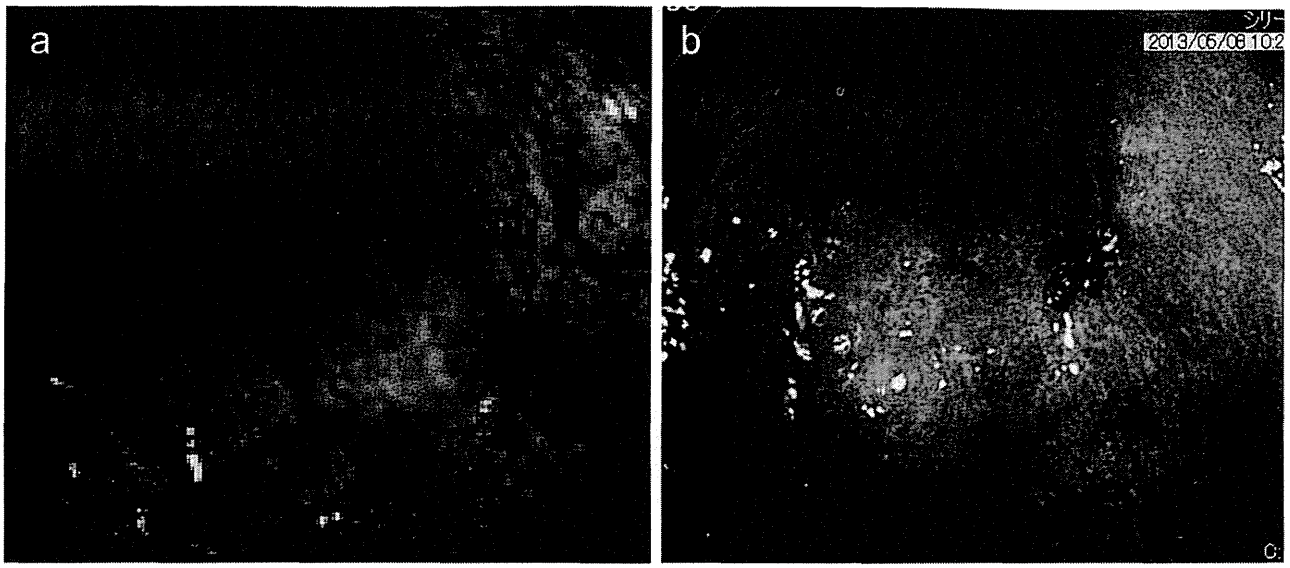

Figure 2. *Preoperative gastroscopy. (a): 0-IIc type early gastric cancer in the lower gastric corpus, (b): Clips attached for hemostasis after the biopsy examination.*

LDLT). The final pathological diagnosis of gastric cancer was poorly-differentiated adenocarcinoma with signet ring cell and pT1b (SM1) N0 M0 Stage IA. To date, we are continuing follow-up her in the outpatient department without recurrence for one year after the operation.

Discussion

Since the surgical results of LDLT have improved, the number of long-term survivors after LDLT has increased (7). Accompanying this background, the development of malignancy after LDLT has become a serious problem. The overall incidence of malignancy in transplant recipients has been estimated to be as high as 20% in the 10-year period after transplantation (8).

Synchronous malignancy is also a disputable point in patients indicated for liver transplantation. Liver transplantation is generally a contraindication in recipients with uncontrollable extrahepatic malignancy (9). However, liver transplantation should be carefully considered in cases involving controllable malignancy, such as early gastric cancer. To the best of our knowledge, this is the first report to demonstrate the use of LDLT followed by total gastrectomy as a two-stage operative strategy for early gastric cancer concomitant with decompensated liver cirrhosis.

In the current case, the patient had a potentially resectable early gastric cancer and a favorable long-term outcome was thus expected for curative surgery. On the other hand, the liver damage was too severe to be controlled with conservative therapy alone. LDLT was thought to be the only treatment capable of managing the patient's liver dysfunction. One-staged LDLT with total gastrectomy was considered as a possible treatment. However, this strategy appeared to be more risky with respect to development of intraoperative and postoperative complications, such as severe bleeding due to coagulopathy and delays in wound healing. Additionally, the patient's liver dysfunction, not early gastric cancer, was life-threatening at the time of her initial presentation. Therefore, we planned to first perform LDLT in order to improve her liver function and coagulopathy, followed by total gastrectomy as the second-stage operation. Total gastrectomy was required in this case because simultaneous splenectomy was performed as a formulaic procedure in LDLT in order to decrease the portal vein pressure and improve the patient's pancytopenia (10). The appropriate interval between LDLT and total gastrectomy in this two-staged operation is debatable. We thought that the second operation should be performed as soon as the patient's liver function recovered and before severe fibrous adhesion occurred. The second operation was performed 19 days after the LDLT and, as a result, the two-staged operation was safely and successfully completed.

The indications for LDLT in patients with malignancy should be carefully determined because healthy donors must undergo surgery. At this time, there are no guidelines clearly describing the indications for LDLT in this patient population. We consider that it is reasonable to perform LDLT and surgery for malignancy when the long-term results of surgical treatment for concomitant malignancy are estimated to be better than those of LDLT. The 1-, 5- and 10-year patient survival rates of LDLT in our institute are 85.6%, 77.9% and 69.5%, respectively (7). These survival

rates constitute now our standard for determining the indication for surgery. However, this issue should be carefully investigated by accumulating large numbers of cases, as the results of surgery for malignancy among patients in an immunosuppressive state are debatable.

In conclusion, we herein reported the case of a patient who received LDLT followed by total gastrectomy for early gastric cancer concomitant with decompensated liver cirrhosis. Conducting careful preoperative screening for sub-clinical malignancy is important among candidates for LDLT. Furthermore, aggressive and adequate surgical treatment including LDLT is a feasible curative strategy in patients with controllable malignancy concomitant with severe liver damage.

Conflicts of Interest

Sho Nishimura and the other co-authors have no conflict of interest.

Acknowledgements

We thank Brian Quinn for assisting with the preparation of the manuscript.

References

1 Vallejo GH, Romero CJ and de Vicente JC: Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol *56*: 87-99, 2005.

2 Nagata Y, Eguchi S, Takatsuki M, Enjoji A, Ichikawa T, Hayashi T and Kanematsu T: Experience of gastric cancer in a patient who had received a living-donor liver toransplantation. Gastric Cancer *10*: 187-190, 2007.

3 Shimizu T, Hayashi M, Inoue Y, Komeda K, Asakuma M, Hirokawa F, Miyamoto Y, Tanigawa N and Uchiyama K: A case of gastric cancer after living donor liver transplantation. Ann Transplant *17(2)*: 122-126, 2012.

4 Lee MS, Kim EY, Lee JH, Jee YS, Park do J, Kim HH and Kim SY: Laparoscopy-assisted distal gastrectomy for gastric cancer after liver transplantation. J Korean Surg Soc *80*: S1-5, 2011.

5 Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon. Gastointest Endosc *58*: S3-43, 2003.

6 A, Devaud N, Perez G, Crovari F, Boza C, ViViavi P, Ibanez L and Guzman S: Antecolic versus retrocolic alimentary limb in laparoscopic Roux-en-Y gastric bypass:a comparative study. Surg Obes Relat Dis *3*: 423-427, 2007

7 SoejimaY, Shirabe K, Taketomi A, Yoshizumi T, Uchiyama H, Ikegami T, Ninomiya M, Harada N, Ijichi H and Maehara Y: Left lobe living donor liver transplantation in adults. Am J Transplant *12*: 1877-1885,2012.

8 Buell JF, Gross TG and Woodle ES: Malignancy after transplantation. Transplantation *80*: S254-264, 2005.

9 Murray KF and Carithers RL Jr.: AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation. Hepatology *41(6)*: 1-26, 2005.

10 Yoshizumi T, Ikegami T, Bekki Y, Ninomiya M, Uchiyama H, Iguchi T, Yamashita Y, Kawanaka H, Shirabe K and Maehara Y: Re-evaluation of predictive score for 6-month graft survival in living donor liver transplantation in modern era. Liver Transpl *20(3)*: 323-332, 2014.

Received May 27, 2014
Revised June 13, 2014
Accepted June 16, 2014

Case Reports in Gastroenterology

Case Rep Gastroenterol 2014;8:148–155

DOI: 10.1159/000362440
Published online: April 24, 2014

1662–0631/14/0081–0148$39.50/0
www.karger.com/crg

Karger Open access

Spontaneous Massive Necrosis of Hepatocellular Carcinoma with Narrowing and Occlusion of the Arteries and Portal Veins

Takahiro Tomino[a] Yo-ichi Yamashita[a] Tomohiro Iguchi[a] Shinji Itoh[a] Mizuki Ninomiya[a] Toru Ikegami[a] Tomoharu Yoshizumi[a] Yuji Soejima[a] Hirofumi Kawanaka[a] Tetsuo Ikeda[a] Shinichi Aishima[b] Ken Shirabe[a] Yoshihiko Maehara[a]

[a]Department of Surgery and Science and [b]Department of Anatomic Pathology, Pathological Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

Key Words
Spontaneous necrosis · Hepatocellular carcinoma · Alcoholic liver disease · Hepatectomy

Abstract
We herein present the case of a 77-year-old man who had fever and right hypochondriac pain. He visited his doctor and underwent contrast computed tomography (CT), and he was suspected to have a liver abscess. He received an antibiotic treatment and his symptoms soon disappeared, but the tumor did not get smaller and its density on contrast CT image got stronger. He underwent biopsy and moderately differentiated hepatocellular carcinoma (HCC) was found. Extended left hepatic and caudate lobectomy was performed. Histological examination showed moderately differentiated HCC with narrowing and occlusion both in the arteries and portal veins associated with mild chronic inflammation. The mechanisms of spontaneous regression of HCC, such as immunological reactions and tumor hypoxia, have been proposed. In our case, histological examination showed the same findings. However, the mechanism is complex, and therefore further investigations are essential to elucidate it.

Takahiro Tomino, MD
Department of Surgery and Science
Graduate School of Medical Sciences, Kyushu University
Fukuoka 812-8582 (Japan)
E-Mail takahiro.tomino0320@gmail.com

KARGER

Introduction

Spontaneous necrosis or regression of malignant tumors has been reported mainly in neuroblastoma, renal cell carcinoma, malignant melanoma, malignant lymphoma and leukemia [1]. It is a rare event occurring with a rate of 1 in 60,000–100,000 tumors [2] and has also been reported in hepatocellular carcinoma (HCC). In 1972, spontaneous regression of HCC was first described in a 3-year-old girl who had developed biopsy-proven HCC while on chronic androgen-anabolic steroid treatment for aplastic anemia [3]. Since this initial report, several mechanisms have been suggested to explain the etiology of spontaneous regression of HCC, including the administration of herbal remedies [4, 5] or the withdrawal of a possible causative agent such as alcohol [6], tobacco [5] or exogenous androgens [3, 7]. In spite of various opinions, its mechanism is unclear and there have been few reports with evidence based on a scientific basis, such as radiological findings and histological examinations.

Here we report a case of spontaneous massive necrosis of HCC with various histological examinations of narrowing and occlusion in the arteries and portal veins, and review the literature with special reference to its pathological findings.

Case Report

A 77-year-old man, who had alcoholic liver damage, had a fever and right hypochondriac pain. He underwent ultrasonography and contrast computed tomography (CT). Ultrasonography showed a heterogeneous liver mass in the caudate lobe of the liver with a diameter of approximately 3 cm that had a hyper- and a hypoechoic area. Contrast CT showed the tumor to have a ring enhancement area and a high- to low-density round area (fig. 1a–c). These imaging studies indicated a liver abscess, and the patient received an antibiotic treatment, whereupon his symptoms soon improved. One month later, he underwent contrast CT again; the tumor had not shrunk, and moreover its density had become stronger. Therefore, he was suspected to have a liver tumor such as metastatic liver tumor. His gastrointestinal tract was checked by esophagogastroduodenoscopy and colonoscopy, but his doctor could not reveal the primary site. Moreover, his doctor performed positron emission tomography-CT (PET-CT) and magnetic resonance imaging (MRI). PET-CT showed no increased fluorodeoxyglucose uptake. The T1-weighted image showed a high-intensity round area in a low-intensity area, the T2-weighted image showed a high-intensity round area in a low-intensity area, and gadoxetic acid-enhanced MRI showed a slightly contrasted low-intensity area in the same segment (fig. 1d–f). Finally, his doctor performed a biopsy of the tumor. Cellular and structural atypia, enlarged hyperchromatic nuclei and two or three layers of trabecular pattern, which indicated moderately differentiated HCC, were found in the specimen (fig. 2).

Consequently, the patient was sent to us for surgical treatment. His blood test data before surgical treatment were as follows: white blood cell count 3,470/μl (normal 3,500–9,000/μl), red blood cell count 380 × 10^4/μl (normal 450–550 × 10^4/μl), serum hemoglobin concentration 13.1 g/dl (normal 14–18 g/dl), serum platelet count 15 × 10^4/μl (normal 14–44 × 10^4/μl), serum aspartate aminotransferase 39 IU/l (normal 13–33 IU/l), serum alanine aminotransferase 24 IU/l (normal 6–30 IU/l), serum alkaline phosphatase 199 IU/l (normal 115–359 IU/l), serum gamma glutamic transpeptidase 304 IU/l (normal 10–47 IU/l), total serum bilirubin 0.9 mg/dl (normal 0.3–1.2 mg/dl), serum albumin 3.7 g/dl (normal 4.0–5.0 g/dl), and serum C-reactive protein 0.03 mg/dl (normal <0.1 mg/dl). The serum concentration of proteins induced by vitamin K antagonism or absence (PIVKA-II) was

19 mAU/ml (normal <40 mAU/ml), and that of alpha-fetoprotein was 5.6 ng/ml (normal <6.2 ng/ml), carcinoembryonic antigen was 8.6 ng/ml (normal <3.2 ng/ml), and carbohydrate antigen 19-9 was 27.5 U/ml (normal <37.0 U/ml). The indocyanine green clearance rate at 15 min was 9.5% (normal <10%). Hepatis B surface antigen and hepatitis C virus antibody were negative. The Child-Pugh classification of his liver belonged to category A.

Extended left hepatic and caudate lobectomy was performed 18 days after the biopsy. The tumor consisted of viable and necrosis areas with well-demarcated nodular lesions in the caudate lobe (S1). The viable tumor size was 11 mm in diameter (fig. 3a). Histological examination showed a trabecular and pseudo-glandular structure with enlarged nuclei and hyperchromatins, which indicated moderately differentiated HCC in the viable area (fig. 3b). The necrosis area consisted of sclerotic fibrous stroma and liquefaction, and hyalinized degeneration with hemosiderin-laden macrophages, plasmacytes and fibroblasts was found (fig. 3c, d). Vessel occlusion with organization (fig. 3e), stenotic arteries with wall thickness (fig. 3f) and mild chronic inflammation in fibrously enlarged portal areas were found in the necrotic area. The non-cancerous area of his liver showed mild chronic inflammatory infiltrate in the bridging fibrosis. Mallory-Denk bodies and ballooning were seen in the non-cancerous area.

The patient's postoperative course was uneventful. He is presently doing well and has no sign of any recurrent tumor 7 months after the operation.

Discussion

Spontaneous regression among patients with HCC was reported to happen in 0.4% [8]. Up to date, many spontaneous regressions of HCC have been described and various mechanisms have been proposed.

First, it has been proposed that immunological reactions may bring about the tumor regression [9]. For example, biopsy [9] and fever [10] might trigger immunological reactions and bring about tumor regression. Several reports documented the presence of elevated cytokine levels, suggesting a systemic inflammatory response. Abiru et al. [11] noted elevated IL-18 in three patients with regression of HCC. IL-18 has been shown to induce interferon gamma production by T cells and natural killer cells, thus potentially producing enhanced cytotoxic activity targeted at cancer cells. Jozuka et al. [12] proposed a similar mechanism after detecting elevated levels of natural killer cell activity, IL-2, IL-6, IL-12 and interferon gamma throughout the course of the patient's spontaneous regression.

Second, the current analysis revealed multiple patients in whom regression appeared to be associated with tumor hypoxia [9]. Several occurrences were related to occlusion of either the hepatic artery or the portal vein, which probably led to a direct ischemic insult. Other patients experienced profound systemic hypoperfusion, such as sustained hypotension associated with a massive variceal bleed. Tumor hypoxia as a mechanism is intuitively appealing in that it mirrors established treatment modalities for HCC. For example, both hepatic artery embolization and the agent sorafenib can be considered to rely upon the induction of tumor hypoxia for their effect [13].

Most cases of spontaneous regression of HCC were diagnosed by radiological findings. On the other hand, histological examination was performed only in 24 cases (summarized in table 1). Almost all reports only mentioned the tissue type of HCC, and few reports mentioned detailed histological examination. For example, 11 reports showed the findings of inflammatory cell infiltration, 3 reports arterial thrombosis, 2 reports portal vein thrombosis and 1 report hepatic venous thrombosis.

In our case, the patient had a fever and biopsy. Histological examination showed various findings of inflammatory cell infiltration in the specimen, narrowing and occlusion in the arteries and portal veins, and liquefaction and hyalinized degeneration of the tumor. This seems to be the first report of spontaneous necrosis of HCC having all of these various histological findings together. It was suggested that fever and biopsy were the triggers of the necrosis, and these suspected triggers would bring about the narrowing and occlusion in the arteries and portal veins. Inflammatory cell infiltration was also found, but it was not so dominant. Therefore, we suspected that inflammatory cell infiltration was not the cause, but the result of the degeneration of this case.

On the other hand, it is possible to think that the fever and right hypochondriac pain were not the cause, but the result of the spontaneous necrosis of HCC. Thickening of the vessel wall intima caused tumor hypoxia, which in turn caused the degeneration of HCC, and the patient felt a fever and right hypochondriac pain at that moment. Considering that thickening of the vessel wall intima and portal vein thrombosis were confined to the tumor area, cytokines produced in the tumor cells may relate to thickening of the vessel wall intima and thrombus formation. For example, tumor growth factor beta accelerates thickening of the vessel wall intima [14] and promotes production of plasminogen activator inhibitor-1, which leads to thrombus formation [15, 16].

According to previous reports, including ours, it is sure that the mechanism of the spontaneous regression of HCC, just as that of other tumor regression, is complex. Therefore further findings, particularly concerning the progress of the immunological status during tumor regression and detailed histological examinations, will be essential to elucidate the mechanism of spontaneous regression of HCC.

Disclosure Statement

The authors have no conflict of interest.

References

1 Papac RJ: Spontaneous regression of cancer. Cancer Treat Rev 1996;22:395–423.
2 Cole WH: Efforts to explain spontaneous regression of cancer. J Surg Oncol 1981;17:201–209.
3 Johnson FL, Lerner KG, Siegel M, Feagler JR, Majerus PW, Hartmann JR, Thomas ED: Association of androgenic-anabolic steroid therapy with development of hepatocellular carcinoma. Lancet 1972;2:1273–1276.
4 Chien RN, Chen TJ, Liaw YF: Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1992;87:903–905.
5 Kato H, Nakamura M, Muramatsu M, Orito E, Ueda R, Mizokami M: Spontaneous regression of hepatocellular carcinoma: two case reports and a literature review. Hepatol Res 2004;29:180–190.
6 Gottfried EB, Steller R, Paronetto F, Lieber CS: Spontaneous regression of hepatocellular carcinoma. Gastroenterology 1982;82:770–774.
7 McCaughan GW, Bilous MJ, Gallagher ND: Long-term survival with tumor regression in androgen-induced liver tumors. Cancer 1985;56:2622–2626.
8 Oquiñena S, Guillen-Grima F, Iñarrairaegui M, Zozaya JM, Sangro B: Spontaneous regression of hepatocellular carcinoma: a systematic review. Eur J Gastroenterol Hepatol 2009;21:254–257.
9 Huz JI, Melis M, Sarpel U: Spontaneous regression of HCC is most often associated with tumor hypoxia or systemic inflammatory response. HPB (Oxford) 2012;14:500–505.
10 Stoelben E, Koch M, Hanke S, Lossnitzer A, Gaertner HJ, Schentke KU, Bunk A, Saeger HD: Spontaneous regression of hepatocellular carcinoma confirmed by surgical specimen: report of two cases and review of the literature. Langenbecks Arch Surg 1998;383:447–452.
11 Abiru S, Kato Y, Hamasaki K, Nakao K, Nakata K, Eguchi K: Spontaneous regression of hepatocellular carcinoma associated with elevated levels of interleukin 18. Am J Gastroenterol 2002;97:774–775.

12 Jozuka H, Jozuka E, Suzuki M, Takeuchi S, Takatsu Y: Psycho-neuro-immunological treatment of hepatocellular carcinoma with major depression – a single case report. Curr Med Res Opin 2003;19:59–63.
13 Xie B, Wang DH, Spechler SJ: Sorafenib for treatment of hepatocellular carcinoma: a systematic review. Dig Dis Sci 2012;57:1122–1129.
14 Kanzaki T, Shiina R, Saito Y, Oohashi H, Morisaki N: Role of latent TGF-beta 1 binding protein in vascular remodeling. Biochem Biophys Res Commun 1998;246:26–30.
15 Pedroja BS, Kang LE, Imas AO, Carmeliet P, Bernstein AM: Plasminogen activator inhibitor-1 regulates integrin alphavbeta3 expression and autocrine transforming growth factor beta signaling. J Biol Chem 2009;284:20708–20717.
16 Christ G, Hufnagl P, Kaun C, Mundigler G, Laufer G, Huber K, Wojta J, Binder BR: Antifibrinolytic properties of the vascular wall. Dependence on the history of smooth muscle cell doublings in vitro and in vivo. Arterioscler Thromb Vasc Biol 1997;17:723–730.
17 Andreola S, Audisio RA, Mazzaferro V, Doci R, Milella M: Spontaneous massive necrosis of a hepatocellular carcinoma. Tumori 1987;73:203–207.
18 Mochizuki T, Takehara Y, Nishimura T, Takahashi M, Kaneko M: Regression of hepatocellular carcinoma. AJR Am J Roentgenol 1991;156:868–869.
19 Imaoka S, Sasaki Y, Masutani S, Ishikawa O, Furukawa H, Kabuto T, Kameyama M, Ishiguro S, Hasegawa Y, Koyama H, et al: Necrosis of hepatocellular carcinoma caused by spontaneously arising arterial thrombus. Hepatogastroenterology 1994;41:359–362.
20 Ozeki Y, Matsubara N, Tateyama K, Kokubo M, Shimoji H, Katayama M: Spontaneous complete necrosis of hepatocellular carcinoma. Am J Gastroenterol 1996;91:391–392.
21 Markovic S, Ferlan-Marolt V, Hlebanja Z: Spontaneous regression of hepatocellular carcinoma. Am J Gastroenterol 1996;91:392–393.
22 Izuishi K, Ryu M, Hasebe T, Kinoshita T, Konishi M, Inoue K: Spontaneous total necrosis of hepatocellular carcinoma: report of a case. Hepatogastroenterology 2000;47:1122–1124.
23 Uenishi T, Hirohashi K, Tanaka H, Ikebe T, Kinoshita H: Spontaneous regression of a large hepatocellular carcinoma with portal vein tumor thrombi: report of a case. Surg Today 2000;30:82–85.
24 Matsuo R, Ogata H, Tsuji H, Kitazono T, Shimada M, Taguchi K, Fujishima M: Spontaneous regression of hepatocellular carcinoma – a case report. Hepatogastroenterology 2001;48:1740–1742.
25 Morimoto Y, Tanaka Y, Itoh T, Yamamoto S, Mizuno H, Fushimi H: Spontaneous necrosis of hepatocellular carcinoma: a case report. Dig Surg 2002;19:413–418.
26 Iiai T, Sato Y, Nabatame N, Yamamoto S, Makino S, Hatakeyama K: Spontaneous complete regression of hepatocellular carcinoma with portal vein tumor thrombus. Hepatogastroenterology 2003;50:1628–1630.
27 Li AJ, Wu MC, Cong WM, Shen F, Yi B: Spontaneous complete necrosis of hepatocellular carcinoma: a case report. Hepatobiliary Pancreat Dis Int 2003;2:152–154.
28 Blondon H, Fritsch L, Cherqui D: Two cases of spontaneous regression of multicentric hepatocellular carcinoma after intraperitoneal rupture: possible role of immune mechanisms. Eur J Gastroenterol Hepatol 2004;16:1355–1359.
29 Ohta H, Sakamoto Y, Ojima H, Yamada Y, Hibi T, Takahashi Y, Sano T, Shimada K, Kosuge T: Spontaneous regression of hepatocellular carcinoma with complete necrosis: case report. Abdom Imaging 2005;30:734–737.
30 Ohtani H, Yamazaki O, Matsuyama M, Horii K, Shimizu S, Oka H, Nebiki H, Kioka K, Kurai O, Kawasaki Y, Manabe T, Murata K, Matsuo R, Inoue T: Spontaneous regression of hepatocellular carcinoma: report of a case. Surg Today 2005;35:1081–1086.
31 Yano Y, Yamashita F, Kuwaki K, Fukumori K, Kato O, Kiyomatsu K, Sakai T, Yamamoto H, Yamasaki F, Ando E, Sata M: Partial spontaneous regression of hepatocellular carcinoma: a case with high concentrations of serum lens culinaris agglutinin-reactive alpha fetoprotein. Kurume Med J 2005;52:97–103.
32 Meza-Junco J, Montaño-Loza AJ, Martinez-Benítez B, Cabrera-Aleksandrova T: Spontaneous partial regression of hepatocellular carcinoma in a cirrhotic patient. Ann Hepatol 2007;6:66–69.
33 Arakawa Y, Mori H, Ikegami T, Hanaoka J, Kanamoto M, Kanemura H, Morine Y, Imura S, Shimada M: Hepatocellular carcinoma with spontaneous regression: report of the rare case. Hepatogastroenterology 2008;55:1770–1772.
34 Park HS, Jang KY, Kim YK, Cho BH, Moon WS: Hepatocellular carcinoma with massive lymphoid infiltration: a regressing phenomenon? Pathol Res Pract 2009;205:648–652.
35 Hsu CY, Sun PL, Chang HC, Perng DS, Chen YS: Spontaneous regression of advanced hepatocellular carcinoma: a case report. Cases Journal 2009;2:6251.
36 Storey RE, Huerta AL, Khan A, Laber DA: Spontaneous complete regression of hepatocellular carcinoma. Med Oncol 2011;28:948–950.
37 Sasaki T, Fukumori D, Yamamoto K, Yamamoto F, Igimi H, Yamashita Y: Management considerations for purported spontaneous regression of hepatocellular carcinoma: a case report. Case Rep Gastroenterol 2013;7:147–152.

Table 1. Previous reports of spontaneous regression of HCC with histological examination

First author	Year	Age	Sex	Staining method	Histological finding	Proposed mechanism
Andreola [17]	1987	75	M	HE, PAS, Masson's trichrome, Weigert, immunostaining	complete necrosis, venous thrombosis	venous thrombosis
Mochizuki [18]	1991	61	M	unknown	partial necrosis	radiation for another cancer
Imaoka [19]	1994	65	M	HE	partial necrosis, arterial thrombosis	arterial thrombosis
Ozeki [20]	1996	69	F	unknown	complete necrosis	herbal medicine
Markovic [21]	1996	62	M	unknown	complete necrosis	biological effects by cytokines
Stoelben [10]	1998	56	M	HE	partial necrosis	biological effects triggered by infection
Stoelben [10]	1998	74	M	HE	partial necrosis	biological effects triggered by infection
Izuishi [22]	2000	50	M	HE, reticulin silver	complete necrosis	ischemia or immune response
Uenishi [23]	2000	65	M	HE	partial coagulative necrosis surrounded by inflammatory cells, portal vein thrombosis	portal vein thrombosis
Matsuo [24]	2001	72	M	HE, reticulin silver	complete necrosis, severe inflammatory cell infiltration	tumor hypoxia or immune response
Morimoto [25]	2002	73	M	unknown	complete necrosis, arterial thrombosis	arterial thrombosis
Iiai [26]	2003	69	M	HE	complete necrosis	portal vein tumor thrombosis, discontinuation of smoking
Li [27]	2003	53	M	unknown	complete necrosis, growth of the connective tissue with lymphocyte	biological effects by cytokines
Blondon [28]	2004	64	M	unknown	partial necrosis	immune response, intraperitoneal spread of tumor
Blondon [28]	2004	70	F	unknown	partial necrosis	immune response, intraperitoneal spread of tumor, tamoxifen
Ohta [29]	2005	74	M	HE, reticulin silver	complete coagulative necrosis, inflammatory cell infiltration, arterial thickening and thrombosis	immune response, tumor hypoxia (arterial sclerosis)
Ohtani [30]	2005	69	M	HE	complete necrosis, inflammatory cell infiltration	tumor hypoxia (a thick capsule)
Yano [31]	2005	71	F	HE, Weigert	partial coagulative necrosis, inflammatory cell infiltration	tumor hypoxia
Meza-Junco [32]	2007	56	F	HE	complete necrosis	tumor hypoxia (a thick capsule)
Arakawa [33]	2008	78	F	HE	complete necrosis, inflammatory cell infiltration	portal vein tumor thrombosis, immune response
Park [34]	2009	57	M	HE, streptavidin-biotin complex	partial necrosis, severe inflammatory cell infiltration	infiltrating lymphocyte
Hsu [35]	2009	66	M	HE	partial coagulative necrosis, tumor thrombosis of the right posterior branch of the portal vein	tumor hypoxia, immune response, silymarin
Storey [36]	2011	52	M	HE	complete necrosis, inflammatory cell infiltration	abstinence from alcohol
Sasaki [37]	2013	79	M	HE, immunological staining using a monoclonal antibody against CD68	partial necrosis	unclear
This report	2014	77	M	HE	partial necrosis, inflammatory cell infiltration, narrowing and occlusion in the arteries and portal veins	tumor hypoxia, fever, biopsy

HE = Hematoxylin and eosin staining; PAS = periodic acid-Schiff stain.

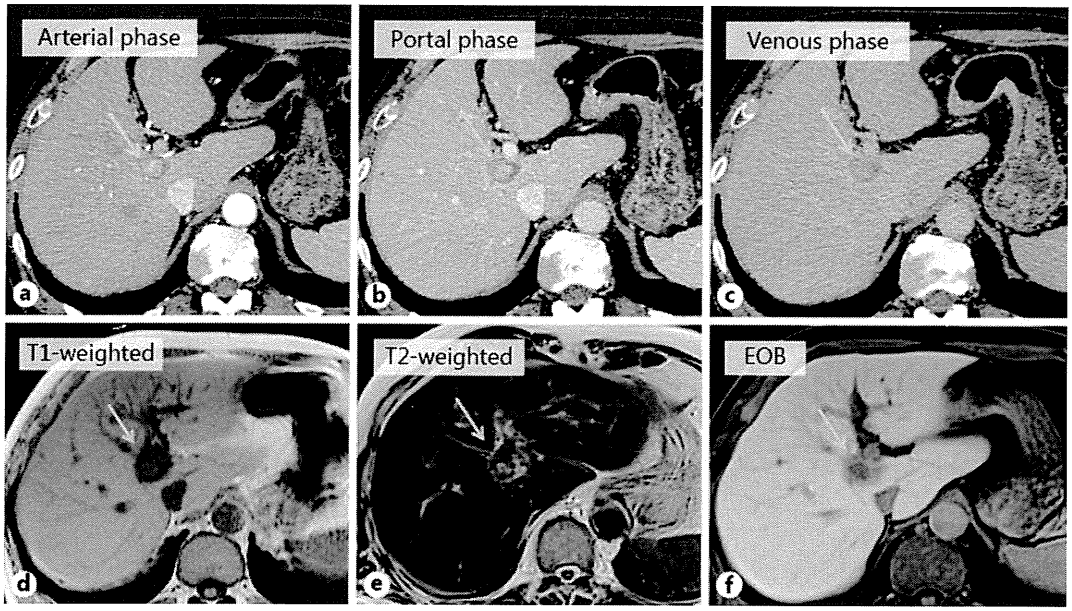

Fig. 1. **a–c** CT findings. Contrast CT showed the tumor to have a ring enhancement area in the caudate lobe of the liver and a high- to low-density round area was shown in the internal part of the tumor. Arrows indicate the tumor. **d–f** MRI findings. The T1-weighted image showed a high-intensity round area in a low-intensity round area, the T2-weighted image showed a high-intensity round area in a low-intensity round area, and gadoxetic acid-enhanced MRI (EOB) showed a slightly contrasted low-intensity area in the caudate lobe of the liver. Arrows indicate the tumor.

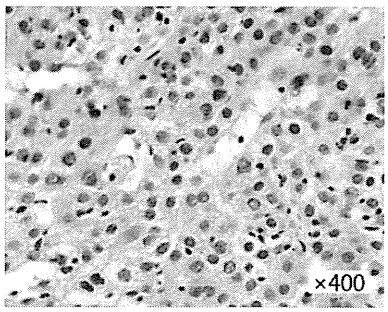

Fig. 2. Biopsy finding. Cellular and structural atypia, enlarged hyperchromatic nuclei and two or three layers of trabecular pattern, which indicated moderately differentiated HCC, were found in the specimen.

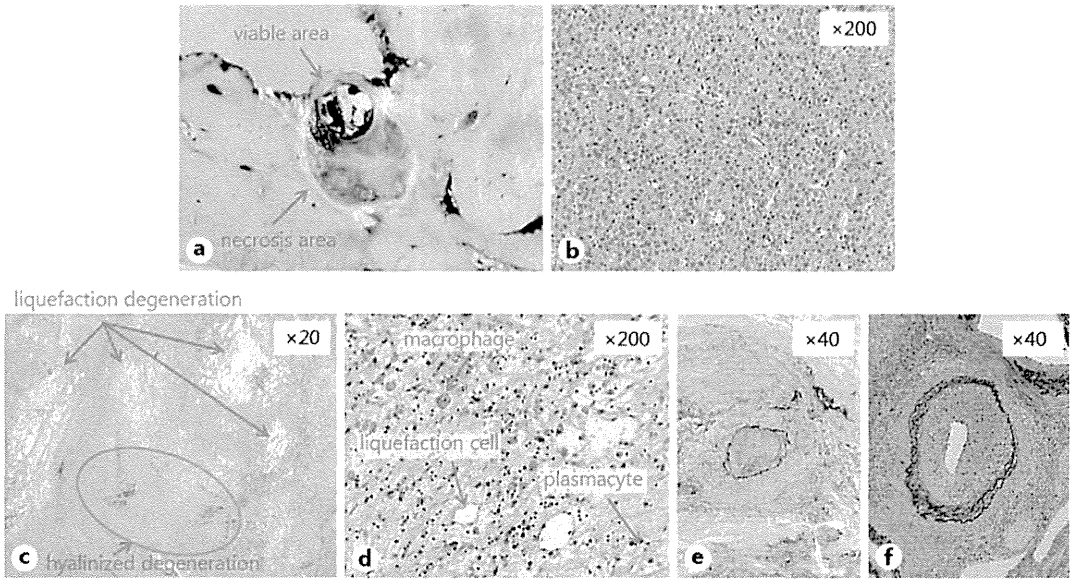

Fig. 3. Macroscopic and pathological finding of the resected specimen. **a** The tumor consisted of viable and necrosis areas with well-demarcated nodular lesions at the caudate lobe (S1). The viable tumor size was 11 mm in diameter. **b** Histological examination showed a trabecular and pseudo-glandular structure with enlarged nuclei and hyperchromatins, which indicated moderately differentiated HCC in the viable area. **c**, **d** The necrosis area consisted of sclerotic fibrous stroma and liquefaction (arrows), and hyalinized degeneration (arrow) with hemosiderin-laden macrophages, plasmacytes and fibroblasts was found. **e**, **f** Vessel occlusion with organization (**e**), stenotic arteries with wall thickness (**f**) and mild chronic inflammation in fibrously enlarged portal areas were found in the necrotic area.

ELSEVIER CrossMark

rs8099917 and Viral Genotyping as Indications for Living Donor Liver Transplantation for Hepatitis C: A Case Report

Y. Yoshida, T. Ikegami*, T. Yoshizumi, T. Toshima, Y.-I. Yamashita, S. Yoshiya, K. Shirabe, and Y. Maehara

Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan

ABSTRACT

Introduction. Appropriate antiviral treatment is essential for living donor liver transplantation (LDLT) to be effective for treating hepatitis C. However, it has never been reported that pre-LDLT genetic analyses of both host and virus, with prediction of the outcome of post-LDLT antiviral treatment, indicated LDLT for a borderline case.

Case Report. We have reported the case of a 68-year-old woman with liver cirrhosis caused by genotype 1b hepatitis C, a history of ruptured esophageal varices, and adequately controlled minor ascites. Her liver function was classified as Child–Pugh grade B. The donor was a 42-year-old woman with an estimated left lobe graft volume (GV) of 33.8% based on the standard liver volume of the recipient. Molecular analyses used to confirm the indication of LDLT for this combination revealed the following: The rs8099917 genotype was T/T in the donor and recipient, the HCV core protein was double wild type, there were no mutations in the interferon sensitivity-determining region, and 8 mutations were found in the interferon/ribavirin resistance-determining region. LDLT was performed because very high sensitivity to interferon treatment was predicted.

Discussion. Six months after LDLT and uneventful post-LDLT courses, pegylated interferon-α2a and ribavirin were administered under immunosuppression with cyclosporine and mycophenolate mofetil. This regimen was continued for 48 weeks, resulting in a viral response at 10 weeks and a sustained viral response, as predicted.

Conclusions. We have reported the usefulness of molecular analyses of host and viral factors for indicating LDLT to treat hepatitis C in a borderline case.

ALTHOUGH HEPATITIS C VIRUS (HCV) is a major indication for liver transplantation (OLT), HCV reinfection in a newly transplanted graft is a widespread, unaddressed, and serious event [1]. Interferon (IFN) treatment, including pegylated IFN (Peg-IFN) and ribavirin (RBV), is the only treatment option for recurrent HCV after OLT [2]. However, it was reported that the rates of viral response and sustained viral response (SVR) after such treatments are as low as 50%–60% and 30%–40%, respectively, after OLT, and these treatments are associated with a variety of adverse events [1–5]. Serious disease progression with advanced graft fibrosis may also occur within a few years in patients with no viral response [1–5].

It was recently demonstrated that interleukin-28B genotypes, including rs8099917, are significantly associated with IFN sensitivity in treating hepatitis C [6]. We previously reported that the rs8099917 genotype T/T in donors and recipients is the most significant determinant of SVR after Peg-IFN and RBV treatment for recurrent HCV after living donor OLT (LDLT) [7]. Therefore, the rs8099917 genotype in the host and recipient could serve as an indication for LDLT in borderline patients.

In this report, we have described an elderly patient with nearly decompensated cirrhosis caused by genotype 1b

Supported by a Grant-in-Aid for Scientific Research from the Ministry of Health, Labour and Welfare of Japan.

*Address correspondence to Toru Ikegami, MD, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. E-mail: tikesurg@surg2.med.kyushu-u.ac.jp

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2013.09.059

HCV with preserved performance status. After assessing rs8099917 genotype and HCV mutation status, we performed LDLT followed by Peg-IFN and RBV treatment, which achieved SVR, as predicted.

CASE REPORT

A 68-year-old woman with a history of liver cirrhosis caused by HCV was referred to our hospital for possible LDLT. At 67 years old, she experienced ruptured esophageal varices treated by endoscopic varices ligation. She had a history of minor ascites that was well-controlled with once-daily oral furosemide (20 mg). She had experienced several episodes of hepatic encephalopathy that were controlled by oral laxatives. Laboratory data included: White blood cell count, 2090/μL; hemoglobin, 9.1 g/dL; platelet count, 6.9 × 104/μL; total bilirubin, 1.1 mg/dL; total protein, 7.9 mg/dL; albumin, 3.3 g/dL; creatinine, 0.52 mg/dL; sodium, 140 mEq/L; ammonia, 49 μg/dL; and percent prothrombin time, 68%. The patient was classified as Child–Pugh grade B with 9 points, and her Model for End-stage Liver Disease score was 10. She was negative for hepatitis B surface antibody but was positive for HCV antibody. Her HCV-RNA titer was 6.1 log10 IU/mL and her HCV genotype was 1b. Tumor markers included: α-Fetoprotein, 34.3 ng/mL: and des-γ-carboxyprothrombin, 21 mAU/mL. The serum HCV-RNA titer was determined by a real-time HCV assay (AccuGene HCV; Abbott Molecular Inc., Des Plaines, IL).

Although abdominal plain computed tomography (CT) revealed several small high-intensity nodules in segment VIII of the cirrhotic liver (Fig 1A), contrast enhancement showed no definite hepatocellular carcinomas. CT also revealed splenomegaly, dilated cardioesophageal varices, and small ascites in the pelvis (Fig 1B). Upper endoscopy showed some high-risk esophageal varices.

The donor was a healthy 42-year-old woman who was a daughter of the patient. CT volumetry showed that the predicted graft volume (GV) of her left lobe was 353 mL, corresponding with 33.8% of the standard liver volume (SLV) of the recipient. Her left lobe had 2 hepatic arteries and no anatomic abnormalities were found.

Based on the characteristics of the host and donor, the risk of LDLT in this combination seemed to be low, except that the likelihood of post-LDLT recurrent HCV was unknown. Therefore, we determined the rs8099917 genotype in the donor and recipient, and mutations in HCV core proteins. The molecular methods used to determine the rs8099917 genotype and 70/91 mutations in the HCV core protein, including the IFN sensitivity-determining region and the IFN-RBV resistance-determining region, are described elsewhere [7]. Molecular analyses showed that the rs8099917 genotype was T/T in the host and recipient (Fig 2A, B), the HCV core protein was wild type for 70R (Fig 2C) and 91L (Fig 2D), and there were no mutations in the IFN sensitivity-determining region (Fig 2E); however, there were 8 mutations were found in the IFN/RBV resistance-determining region (Fig 2F). These findings suggested that Peg-IFN and RBV treatment would be successful for recurrent HCV after LDLT, and we decided to perform LDLT.

The donor and the recipient operative procedures are described in more detail elsewhere [8,9]. Laparotomy revealed a cirrhotic liver, an enlarged spleen, and minor ascites (Fig 1C). The recipient's liver was removed and the donated left lobe graft was implanted (Fig 1D). The actual GV was 307 g, corresponding with 29.4% of the recipient's SLV. Splenectomy was also performed to enable IFN therapy after LDLT [10]. The total operating time was 626 minutes and total blood loss, including ascites, was 3000 mL. Immunosuppression consisted of cyclosporine with mycophenolate mofetil and steroids, as previously described [4]. The post-LDLT course was uneventful and she was discharged from hospital 14 days after surgery.

Peg-IFN with RBV treatment was started, as planned, 6 months after LDLT. At that time, her aspartate aminotransferase and alanine aminotransferase activities were 158 and 113 IU/L, respectively, and her HCV-RNA titer was 6.1 log10 IU/mL. Liver biopsy showed recurrent chronic hepatitis C, which required Peg-IFN and RBV. Peg-IFN-α2a (180 μg; Pegasys; Chugai Pharmaceutical Co., Ltd., Chuo-ku, Tokyo, Japan) was administered weekly

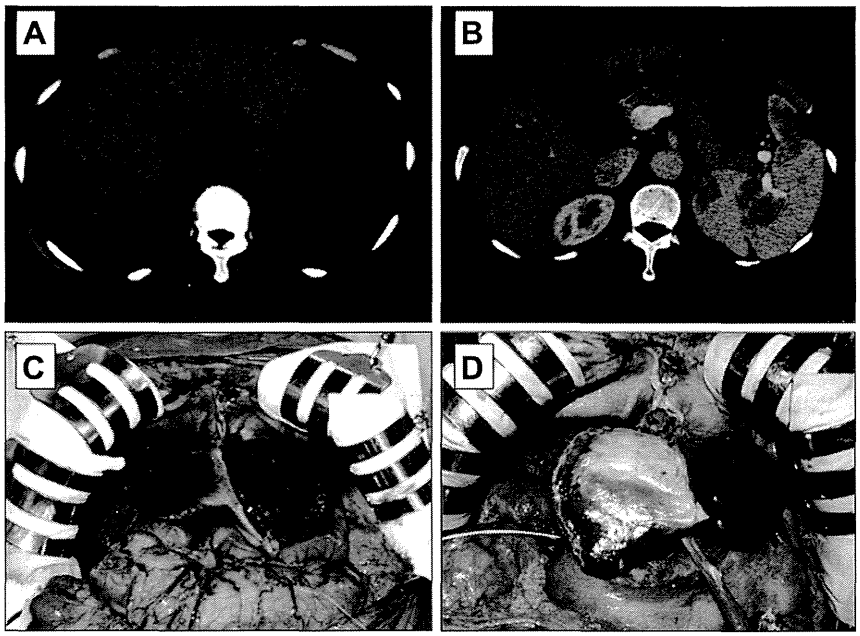

Fig 1. **(A)** Plain computed tomography (CT) revealed several small, high-intensity nodules in Segment 8 of the cirrhotic liver. **(B)** Contrast-enhanced CT revealed splenomegaly but no definitive hepatocellular carcinomas. Native **(C)** and transplanted **(D)** liver.

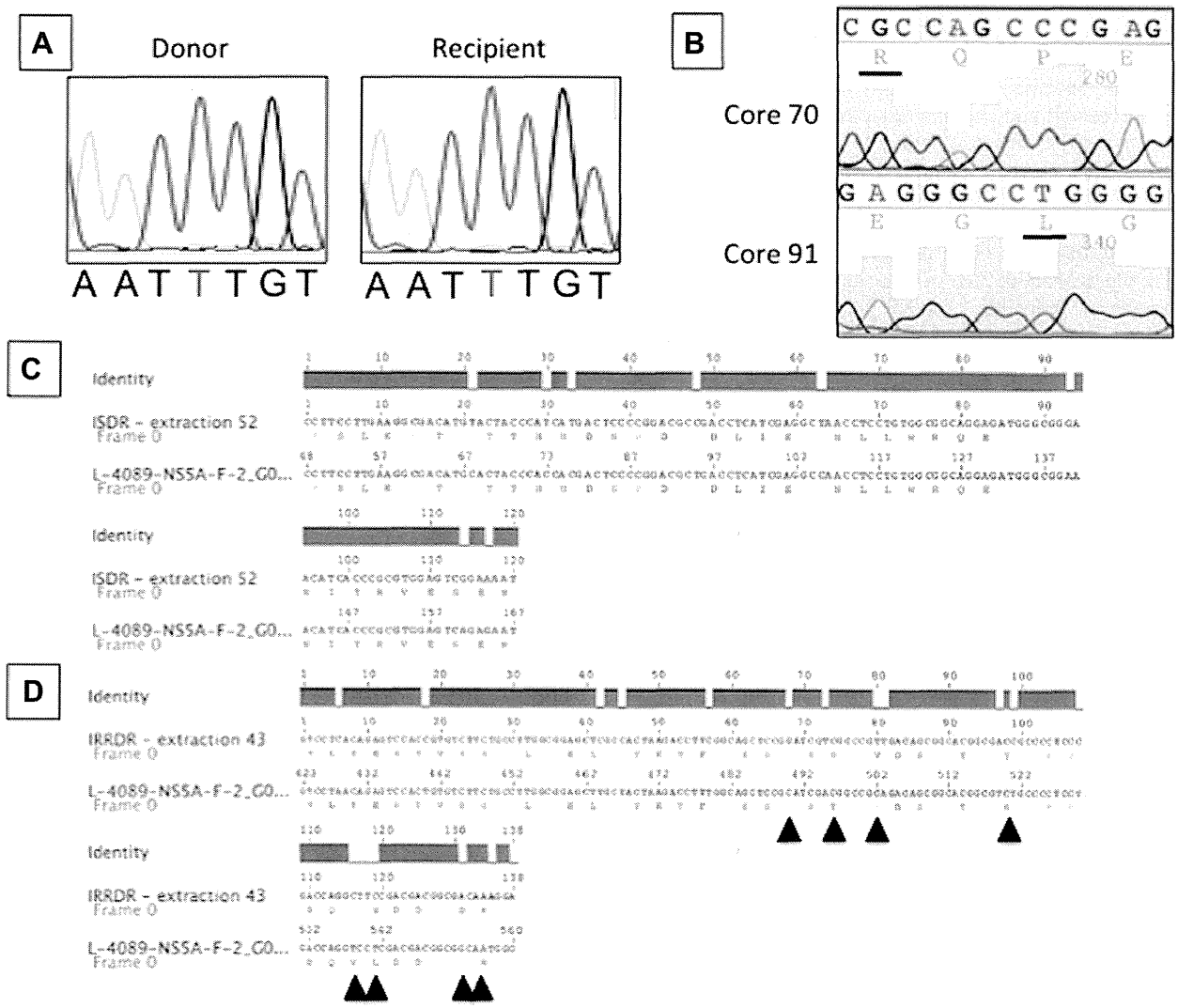

Fig 2. **(A)** Genotyping studies showed that the rs8099917 genotype was T/T in the donor and recipient. **(B)** Molecular analyses showed that the recipient had wild-type hepatitis C core proteins, including 70R and 91L, had no mutations in the interferon sensitivity-determining region **(C)**, and had 8 mutations in the interferon/ribavirin resistance-determining region **(D)**. The sites of mutations are indicated by black arrows.

and RBV (400 and 200 mg on alternate days; Copegus; Chugai Pharmaceutical Co., Ltd.) was administered daily for 48 weeks. During antiviral treatment, immunosuppression consisted of 50 mg cyclosporine daily with a trough level of 70–100 ng/mL, and 1 g mycophenolate mofetil daily. Her HCV-RNA titer was undetectable at 10 weeks, corresponding with early viral response, and remained negative at 6 months after completing treatment. Therefore, she achieved SVR as planned.

DISCUSSION

The overall success of LDLT is dependent on 2 factors, namely perioperative short-term survival, and long-term quality and survival after LDLT. To achieve short-term graft and patient survival after LDLT, important factors include an attenuated deterioration in the recipient's condition, good performance status, and low MELD score, together with good liver graft quality and an appropriate GV [11,12]. Although end-stage liver disease precipitates LDLT, advanced liver disease with a poor general condition could contraindicate LDLT considering the risk of poor outcomes [11,12]. Therefore, appropriate timing is valuable for a reasonable indication of LDLT. The present case had a history of varices rupture, ascites, and hepatic encephalopathy together with active chronic hepatitis C, although her Child–Pugh grade was B with 9 points. These factors may predict good short-term graft survival after LDLT [11,12]. The donor was 42 years old. The GV/SLV of the left lobe graft was 33.8% in the recipient. We previously

reported that our reference index of GV/SLV for good recipient outcomes was 35% [8]. Therefore, this graft could not be used in a recipient with a deteriorated clinical status. However, because the current recipient's general health was well-preserved and she had less-advanced liver disease, we considered that this graft could be safely used.

Another important factor in this case was inevitable HCV reinfection after LDLT. Control of HCV recurrence determines long-term graft quality and survival. As previously reported, recurrent HCV reinfection after OLT progresses to cirrhosis in about 25% of patients within 5–10 years in the absence of effective antiviral treatment [5]. Moreover, cholestatic-type recurrent HCV might cause graft loss within a few months [3]. However, about 30%–40% of recipient treated with Peg-IFN and RBV after LDLT achieve SVR and are permanently free from HCV [1–5]. Therefore, IFN sensitivity is a significant determinant of the long-term outcomes of grafts in HCV-infected patients, and predicting IFN sensitivity before LDLT could determine the indication for LDLT in borderline patients, as in the current case.

We previously reported that the combination of rs8099917 genotypes in the donor and recipient is a significant determinant of the outcomes of Peg-IFN and RBV treatment for recurrent HCV after LDLT; the SVR rate was 56% if the genotype was T/T in both the donor and recipient, but decreased to 10% if either the donor or recipient had the T/G or G/G genotypes [7]. In that study, we also found that HCV factors, including double wild-type 70/91 core protein, $\geq$2 mutations in the IFN sensitivity-determining region, and $\geq$6 mutations in the IFN/RBV resistance-determining region were favorable factors in recipients with the T/T genotype who received T/T liver grafts. Because this patient had double wild-type core protein and 8 mutations in the IFN/RBV resistance-determining region without mutations in the IFN sensitivity-determining region, the predicted SVR rate after Peg-IFN and RBV was 86%, which we considered was fairly acceptable for this patient.

In conclusion, we have described an elderly patient with a borderline indication for LDLT with a smaller graft. We evaluated the indication for LDLT after checking the rs8099917 genotype in the donor and recipient, as well as HCV mutations in the recipient. Using these findings, we predicted that the patient would show very high IFN sensitivity and achieve SVR. Based on our experience of this case, we propose that molecular analyses of host and viral factors are useful for indicating LDLT to treat HCV, especially in borderline cases.

REFERENCES

[1] Brown RS. Hepatitis C and liver transplantation. Nature 2005;436:973–8.

[2] Berenguer M. Natural history of recurrent hepatitis C. Liver Transpl 2002;8:S14–8.

[3] Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. Liver Transpl 2010;16:1228–35.

[4] Ikegami T, Taketomi A, Soejima Y, Yoshizumi T, Fukuhara T, Kotoh K, et al. The benefits of interferon treatment in patients without sustained viral response after living donor liver transplantation for hepatitis C. Transplant Proc 2009;41:4246–52.

[5] Wiesner RH, Sorrell M, Villamil F. International Liver Transplantation Society Expert Panel. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. Liver Transpl 2003;9:S1–9.

[6] Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet 2009;41:1105–9.

[7] Fukuhara T, Taketomi A, Motomura T, Okano S, Ninomiya A, Abe T, et al. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. Gastroenterology 2010;139:1577–85.

[8] Taketomi A, Morita K, Toshima T, Takeishi K, Kayashima H, Ninomiya M, et al. Living donor hepatectomies with procedures to prevent biliary complications. J Am Coll Surg 2010;211:456–64.

[9] Ikegami T, Soejima Y, Taketomi A, Yoshizumi T, Harada N, Uchiyama H, et al. Explanted portal vein grafts for middle hepatic vein tributaries in living-donor liver transplantation. Transplantation 2007;84:836–41.

[10] Ikegami T, Toshima T, Takeishi K, Soejima Y, Kawanaka H, Yoshizumi T, Taketomi A, Maehara Y. Bloodless splenectomy during liver transplantation for terminal liver diseases with portal hypertension. J Am Coll Surg 2009;208:e1–4.

[11] Ikegami T, Shirabe K, Yoshizumi T, Aishima S, Taketomi YA, Soejima Y, et al. Primary graft dysfunction after living donor liver transplantation is characterized by delayed functional hyperbilirubinemia. Am J Transplant 2012;12:1886–97.

[12] Ikegami T, Shirabe K, Soejima Y, Yoshizumi T, Uchiyama H, et al. Strategies for successful left-lobe living donor liver transplantation in 250 consecutive adult cases in a single center. J Am Coll Surg 2013;216:353–62.

Surg Today (2014) 44:2077–2085
DOI 10.1007/s00595-014-0836-1

ORIGINAL ARTICLE

Three-dimensional computed tomography analysis of variations in the middle hepatic vein tributaries: proposed new classification

Hiroto Kayashima · Ken Shirabe · Rumi Matono · Shohei Yoshiya · Kazutoyo Morita · Kenji Umeda · Toru Ikegami · Tomoharu Yoshizumi · Yuji Soejima · Yoshihiko Maehara

Received: 18 February 2013 / Accepted: 5 November 2013 / Published online: 29 January 2014

Abstract
Purpose To evaluate the anatomical variations in the middle hepatic vein tributaries (V5/V8) for determining the reconstruction strategy in right lobe living donor liver transplantation (LDLT).
Methods The V5/V8 variations were examined in 268 patients and were classified into three and two types, respectively. The reconstruction rate (RR), patency rate (PR) and clinical outcomes were retrospectively evaluated in 46 right lobe LDLT cases.
Results In terms of V5 variations, the RR and PR were significantly higher for type 2 than type 3 (82.6 vs. 44.4 % and 73.7 vs. 25.0 %, respectively). The alanine aminotransferase level on postoperative day (POD) 5 in the V5 patent group was significantly lower than in the occluded group (123 vs. 191 IU/dL). Regarding V8 variations, the RR and PR were significantly higher for type 1 than type 2 (44.4 vs. 17.6 % and 75.0 vs. 33.3 %, respectively). The aspartate aminotransferase level on POD 3 was significantly lower in the V8 patent group than in the occluded group (50 vs. 121 IU/dL).
Conclusion For right lobe grafts with single large V5 (type 2) or V8 (type 1) variations, reconstruction is necessary. Our new classification of the MHV tributaries is useful for determining the reconstruction strategy to use in right lobe LDLT.

H. Kayashima (✉) · K. Shirabe · R. Matono · S. Yoshiya · K. Morita · K. Umeda · T. Ikegami · T. Yoshizumi · Y. Soejima · Y. Maehara
Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan
e-mail: hkaya@surg2.med.kyushu-u.ac.jp

Keywords Congestion · Drainage vein · Living donor liver transplantation · Reconstruction · Right lobe graft

Introduction

Since the first report in 1989, living donor liver transplantation (LDLT) has become widely accepted worldwide as a treatment of choice for end-stage liver failure [1]. However, in right lobe LDLT, the presence of hepatic venous congestion (HVC) in the right anterior sector, caused by deprivation of drainage from the middle hepatic vein (MHV) tributaries, remains one of the most serious complications [2]. Lee et al. reported two cases of severe HVC in a graft without reconstruction of the MHV tributaries, in which one graft resulted in sepsis due to congestive infarction and the other caused the development of prolonged massive jaundice [3]. Recent reports have demonstrated that the reconstruction of the MHV tributaries improved the outcomes of right lobe LDLT [4, 5], and that preoperative estimation of the graft volume (GV) and venous congestion rate (VCR) caused by occlusion of the MHV tributaries was of great importance [6, 7]. In other words, the evaluation of anatomical variations in the MHV tributaries draining segment V (V5) and VIII (V8) plays an essential role in determining the appropriate reconstruction strategy in right lobe LDLT.

Recently, preoperative liver volumetry based on three-dimensional computed tomography (3D-CT) has resulted in significantly improved outcomes in comparison with the use of two-dimensional computed tomography [6–8]. In addition, 3D-CT visualization is very useful in the preoperative evaluation of the VCR and variations in the MHV tributaries.

The purpose of the present study was to analyze the anatomical variations in V5 and V8 using 3D-CT.

We retrospectively examined 268 patients, 116 of whom were donors and 152 of whom were donor candidates, and evaluated the correlation between the type of V5 and V8 and the clinical outcomes following the reconstruction in 46 cases of right lobe LDLT.

Methods

Patients

From August 2003 to March 2008, 3D-CT was applied for 268 patients at Kyushu University Hospital. These patients included 116 donors and 152 donor candidates. In all patients, the liver volumes were measured, and the anatomical variations in the portal and hepatic veins were examined, including the MHV tributaries. The patients included 155 males and 113 females. Their median age was 35 years (range 19–64), and their median body mass index was 22.1 kg/cm^2 (range 15.4–36.7). The median values of the 3D-CT estimated total liver volume, extended left and caudate lobe volume and right lobe volume were 1118 cm^3 (range 606–1931), 417 cm^3 (range 195–712) and 693 cm^3 (range 326–1332), respectively. In the 116 donors, the grafts included 65 left lobe grafts, 46 right lobe grafts, two extended right lobe grafts, two extended left lateral segment grafts and one posterior segment graft.

3D-CT evaluation of the anatomical variations in hepatic veins

Preoperative multidetector helical CT (MDCT) images were made using 2-mm-thick slices represented on CT machines. Enhancement was achieved using an intravenous bolus injection of nonionic contrast medium (Iopamion^{TM}, Schering, Erlangen, Germany) at a speed of 5 mL/s. The 3D reconstructions of the liver, portal and hepatic venous branches were obtained from the MDCT data using the 3D-CT software program, ZIO M900 (Zio Software Inc.,

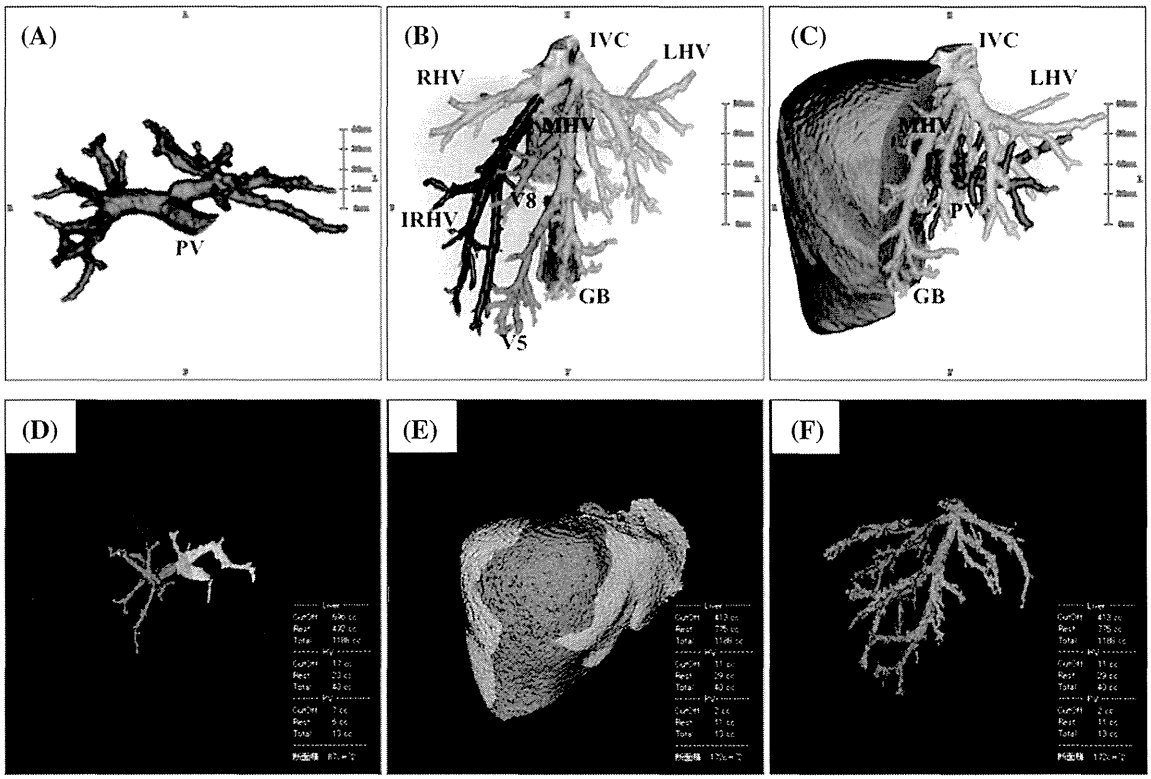

Fig. 1 3D-CT images of a liver. **a–c** The preoperative 3D reconstruction of the liver, portal and hepatic venous branches visualized using a Zio M900. **a** A 3D image of the PV. **b** A 3D image of the hepatic vein. **c** A 3D image of the right graft. The LHV, RHV and IVC are colored aqua. The PV, MHV and IRHV are colored *dark blue*, *yellow* and *red*, respectively. The V5 and V8 are colored *purple*. **d–f** The preoperative 3D reconstruction of the liver and the HVC volume of the MHV tributaries visualized using liver segmentation software. **d** A 3D image of the right graft. **e**, **f** A 3D image showing the HVC volume (*orange color*) of the MHV tributaries in total (*pink color*). *3D-CT* three-dimensional computed tomography, *GB* gallbladder, *HVC* hepatic venous congestion, *IRHV* inferior right hepatic vein, *IVC* inferior vena cava, *LHV* left hepatic vein, *MHV* middle hepatic vein, *PV* portal vein, *RHV* right hepatic vein, *V5* the MHV tributaries draining segment V, *V8* the MHV tributaries draining segment VIII

Tokyo, Japan). These findings made it possible to freely fix cut-off lines (Fig. 1a–c).

3D-CT evaluation of the liver volume and the VCR

The 3D reconstruction of the liver and the HVC volumes of the V5 and V8 was obtained from the MDCT data using another 3D-CT software program (Liver Segmentation Software; Hitachi Medico, Tokyo, Japan), which was used to calculate the liver volume and the volume of each vessels' (both portal and hepatic venous branches) territories from their diameter and length. The 3D images reconstructed using this software program reflected the actual congestion volume. The right lobe volume was calculated from the right portal vein (PV) territory, and the HVC volume of each hepatic venous branch was calculated automatically (Fig. 1d–f). The VCR of each hepatic venous branch was calculated as follows: HVC volume of each hepatic venous branch/right lobe volume (%).

Classification of V5 variations

The variations in V5 were classified into the following three types: type 1 anatomy, in which the MHV extends straight from the peripheral gallbladder bed to the inferior vena cava (IVC) along the Cantlie line, and several small V5s enter the MHV (Fig. 2a). Except for cases with type 1 anatomy, the MHV does not run to the distal side, and the V5 enters the MHV on the more proximal side. In type 2 cases, a single large V5 enters the MHV (Fig. 2b). In type 3 cases, the superior vein draining the segment V (V5sup) and the inferior vein draining the segment V (V5inf) enter the MHV separately (Fig. 2c).

Classification of V8 variations

The variations in V8 were classified into the following two types. In type 1, a single large V8 enters the root of the MHV (Fig. 3a). In type 2, the superior vein draining the segment VIII (V8sup) and the inferior vein draining the segment VIII (V8inf) enter the MHV separately (Fig. 3b). The distinction between V8inf and V5sup was made rigorously according to the variations in the PV branches that were visualized using 3D-CT. In some cases, the V8 entered the IVC directly, and these cases were defined as an unclassified type.

Graft selection

The criteria used for graft selection have been described elsewhere [9, 10]. In brief, a left lobe graft is initially considered as a graft with respect to donor safety. A right lobe graft is selected when a left lobe graft is insufficient for the recipient and the remnant liver volume of the donor is >35 %.

Criteria for reconstruction of the MHV tributaries

Our criteria for reconstruction of the MHV tributaries were that the estimated VCR in the MHV tributaries was >25 %, or the deducted HCV from the graft volume was <40 % [7].

Surgical procedures

The surgical procedures for donors and recipients have been described elsewhere [10–12]. In brief, donor

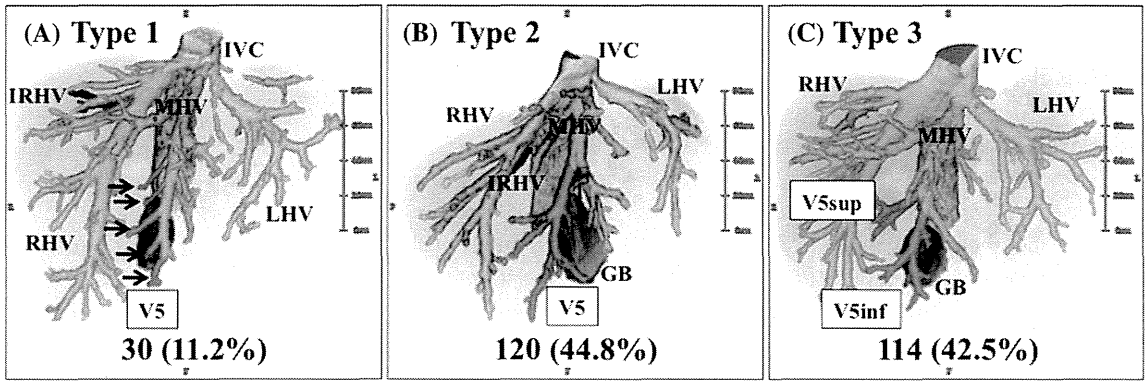

Fig. 2 3D-CT images of V5 variations. **a** Type 1 anatomy. The MHV extends straight from the peripheral GB bed to the IVC along the Cantlie line, and several small V5s (*arrows*) enter the MHV. With the exception of type 1, the MHV does not run to the distal side, and V5s enter the MHV on the more proximal side. **b** In type 2, a single large V5 enters the MHV. **c** In type 3, the V5sup/V5inf enters the MHV separately. The LHV, RHV and IVC are colored aqua. The MHV and IRHV are colored *yellow* and *red*, respectively. The V5, including V5sup/V5inf, is colored *purple*. *3D-CT* three-dimensional computed tomography, *IRHV* inferior right hepatic vein, *IVC* inferior vena cava, *GB* gallbladder, *LHV* left hepatic vein, *MHV* middle hepatic vein, *RHV* right hepatic vein, *V5* the MHV tributaries draining segment V, *V5sup/V5inf* the superior/inferior veins draining segment V