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Case Report

Recurrent Hepatitis B Following Recurrence of Hepatocellular Carcinoma after Living Donor Liver Transplantation

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Abstract

Hepatitis B virus (HBV) recurrence after liver transplantation for HBV-associated liver diseases results in decreased patient and graft survival. Herein we have reported two cases of HBV recurrence following relapse of hepatocellular carcinoma (HCC) after living donor liver transplantation (LDLT). Both cases had LDLT for end-stage liver disease secondary to HBV infection with nodules of HCC exceeding the Milan criteria. HBV prophylaxis using hepatitis B immunoglobulin with nucleos (t) ide analogues were given and HBV DNA levels were consistently undetectable after LDLT. HCC recurred at 5 months and 13 months posttransplant respectively, and chemotherapy and radiation therapy were performed. HBV recurrence occurred during the treatment of HCC. HBV DNA levels increased despite the treatment with anti-HBV agents after HBV recurrence. In hepatitis B surface antigen positive recipients, HBV prophylaxis should be intensified during the treatment of recurrent HCC.

Key words : Recurrence・Hepatitis B・Hepatocellular carcinoma・Living donor liver transplantation

Introduction

End-stage liver disease secondary to hepatitis B virus (HBV) is one of the major indications for liver transplantation (LT)[1)~3)]. Before the use of appropriate prophylactic treatment, posttransplant HBV recurrence was a main problem with a cumulative HBV recurrence rate of about 80%[1)]. Prophylactic use of hepatitis B immunoglobulin (HBIG) in combination with nucleoside analogue lamivudine (LAM) has markedly decreased the risk of posttransplant HBV recurrence rate, however, approximately 10% of transplanted patients develop recurrent HBV infection[4)~6)].

Chronic HBV infection remains the major cause of hepatocellular carcinoma (HCC) in the world[7)]. Although LT is an effective treatment for HCC that provides excellent oncological results as well as a cure for cirrhosis, risk estimation of posttransplant HCC recurrence is an essential

Abbreviations
HBV ; hepatitis B virus, HCC ; hepatocellular carcinoma, LDLT ; living donor liver transplantation, LT ; liver transplantation, HBIG ; hepatitis B immunoglobulin, LAM ; lamivudine, ADV ; adefovir dipivoxil, anti-HBs ; antibody to hepatitis B surface antigen, HBsAg ; hepatitis B surface antigen, PCR ; polymerase chain reaction, HBeAg ; hepatitis B e antigen, CT ; computed tomography, AFP ; alpha-fetoprotein, HBcAb ; hepatitis B core antibody, 5-FU ; 5-fluorouracil, Gy ; gray, ETV ; entecavir, DCP ; des-gamma-carboxy prothrombin, lipiodol ; iodized oil, ALT ; alanine aminotransferase

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element in selecting patients. The size of the tumor, the number of tumors, and the presence of major vessel invasion have been incorporated into the Milan criteria, which predicts a good prognosis for transplant patients with HCC[8].

Previous studies have shown that pretransplant HBV viral load and HBIG monoprophylaxis might be significant predictors of posttransplant HBV recurrence[9][10]. Recent data suggests that posttransplant HCC recurrence is also associated with HBV recurrence[11]. Herein, we report on two patients who presented with HBV recurrence following relapse of HCC after living donor liver transplantation (LDLT).

Case reports

Both patients had LDLT for end-stage liver disease secondary to HBV infection with multiple HCCs exceeding the Milan criteria. LAM and adefovir dipivoxil (ADV) were administered preoperatively and HBIG was added to them for HBV prophylaxis after the LDLT. The patients received HBIG, with an initial dose of 10,000 U during the anhepatic phase during the LDLT, followed by 5,000 U/day for 1 week after the LDLT. Thereafter, 5,000 U/day of HBIG was administered every 1 to 3 months and the antibody to hepatitis B surface antigen (anti-HBs) titers had been kept consistently above 200 IU/L.

Case 1

The patient was a 46-year-old man. Before LDLT, he had positive serum hepatitis B surface antigen (HBsAg), HBV DNA (measured by amplification using polymerase chain reaction (PCR)) (lower level of detection 2.6 log copy/mL) and hepatitis B e antigen (HBeAg). His HBV DNA titer was 3.9 log copy/mL. Abdominal computed tomography (CT) revealed nodules in segment II, V and VIII suspicious for HCC, with the maximal diameter of the tumors being 6.0 cm in segment V. At that time, his serum alpha-fetoprotein (AFP) level was 88.9 ng/mL (normal level < 6.2 ng/mL). LDLT was performed using the right lobe graft donated by his wife with positive hepatitis B core antibody (HBcAb). His immunosuppression consisted of tacrolimus, mycophenolate mofetil and corticosteroids. The posttransplant course was uneventful. The histology of the explanted liver showed a nodule of combined HCC and cholangiocellular carcinoma (6.6 x 4.3 cm) in the segment V with portal venous invasion with the presence of multiple nodules of HCC. His HBV DNA level became undetectable immediately after the LDLT, and AFP level decreased to 7.4 ng/mL 2 months after the LDLT. Thereafter, HBsAg and HBV DNA had been consistently negative, however, AFP level increased gradually. At 5 months posttransplant, abdominal CT revealed multiple metastatic lymph nodes around the aorta, and therefore, chemotherapy consisted of intravenous cisplatin, 5-fluorouracil (5-FU) and gemcitabine was introduced. A repeat abdominal CT was performed at 7 months posttransplant and the lymph nodes had grown. Therefore, chemoradiotherapy with oral S-1 (80 mg given daily, for 28 days) was initiated. Radiation therapy was administered once daily, five fractions a week at 2 gray (Gy) per fraction, with a total of 46 Gy administered over 5 weeks. At 8 months posttransplant, he demonstrated positive HBsAg during the chemoradiotherapy despite continuous HBV prophylaxis with HBIG, LAM and ADV. Immediately before HBV recurrence his anti-HBs titer was 509 IU/L and both HBsAg and HBV DNA were negative. Although combination therapy with entecavir (ETV) and ADV was started, his HBV DNA level increased thereafter. After the chemoradiotherapy, a CT scan showed the presence of multiple nodules throughout the whole liver graft and bone metastases. Finally, he died of recurrent HCC at 12 months posttransplant. The postoperative course of this patient is summarized in Figure 1A.

Case 2

The patient was a 58-year old woman. Before LDLT, she had positive HBsAg and negative HBV

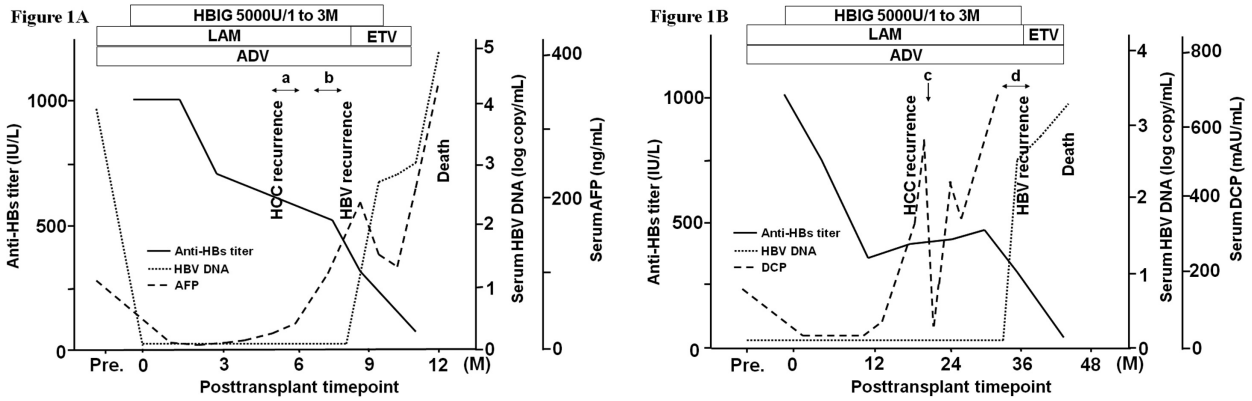

Fig. 1 Changes in serum anti-HBs titer, HBV DNA, AFP and DCP levels after LDLT. HBV recurred after relapse of HCC. (A). Case 1. a : intravenous chemotherapy. b : chemoradiotherapy with oral S-1. (B). Case 2. c : resection of lung metastasis. d : transarterial chemo-lipiodolization and radiation therapy.

DNA and HBeAg. Abdominal CT revealed multiple nodules of HCC throughout the whole liver. At that time, her serum AFP level was 2.4 ng/mL and des-gamma-carboxy prothrombin (DCP) level was 194 mAU/mL (normal level < 40 mAU/mL). LDLT was performed using the extended left lobe plus caudate lobe graft donated by her daughter with positive HBcAb. Her immunosuppression consisted of cyclosporine, mycophenolate mofetil and corticosteroids. The posttransplant course was uneventful. Her HBV DNA had been consistently negative by PCR, and DCP level decreased to 14 mAU/mL 2 months after the LDLT. At 13 months posttransplant, DCP level increased to 70 mAU/mL, and chest CT revealed a small (10 mm) nodule in the right lower lobe suspicious for metastatic disease. At 18 months posttransplant, thoracic surgery performed a video assisted thorascopic wedge resection of the metastasis in the right lung. At 30 months posttransplant, abdominal CT revealed two nodules in the liver graft invading to the inferior vena cava. Therefore, transarterial chemo-lipiodolization using a mixture of epirubicin and iodized oil (lipiodol) and radiation therapy were performed. Radiation therapy was administered once daily, five fractions a week at 2 Gy per fraction, with a total of 50 Gy administered over 5 weeks. After the therapy, she demonstrated positive HBsAg and HBV DNA at 36 months posttransplant despite continuous HBV prophylaxis with HBIG, LAM and ADV. Immediately before HBV recurrence her anti-HBs titer was 223 IU/L and both HBsAg and HBV DNA were negative. Combination therapy with ETV and ADV was started, however, her HBV DNA level increased thereafter. Although repeat CT scans showed regression of the tumors in the liver graft, multiple lung metastases were identified. She was subsequently started on sorafenib but it was ineffective. Finally, she died of recurrent HCC at 43 months posttransplant. The postoperative course of this patient is summarized in Figure 1B.

Discussion

In this report, we have shown two cases of recurrent HBV following recurrence of HCC after LDLT. Our patients received continuous HBV prophylaxis with HBIG, LAM and ADV, and their HBsAg and HBV DNA were consistently negative before HCC recurrence. Both had multiple HCCs exceeding the Milan criteria at the time of LDLT. Case 1 with a high serum AFP concentration had a large tumor with the presence of histological portal vein invasion, and Case 2 with a high serum DCP had multiple tumors throughout the whole liver. Chemotherapy and radiation therapy were performed for the treatment of HCC recurrence without any adjuvant chemotherapy after the LDLT. In our cases, HBV DNA levels increased despite combination antiviral treatment with ETV and ADV after HBV

recurrence.

HBV recurrence after LT for HBV-associated liver diseases results in decreased patient and graft survival[3]. Although combined prophylaxis with HBIG and LAM has dramatically produced excellent results, about 10% of HBsAg-positive recipients experience recurrent HBV infection[4)~6)]. Several studies have shown that high HBV viral loads at the time of transplantation are strongly associated with posttransplant HBV recurrence[9)12)]. Marzano et al suggested that serum HBV DNA titers should be below 100,000 copies/mL in order to reduce the risk of HBV recurrence[9]. In our cases, we presume that their low HBV viral loads at the LDLT did not affect the HBV recurrence.

Several mechanisms may contribute to recurrent HBV following recurrence of HCC. Antitumor chemotherapy may be important risk factor for HBV recurrence. Both immunosuppression due to chemotherapy and immunosuppressive therapy after LDLT can facilitate the replication of HBV. In previous reports, several risk factors have been proposed for reactivation of HBV during or after chemotherapy[13]. Although elevated pre-chemotherapy serum alanine aminotransferase (ALT) and HBV DNA load have been reported to be associated with developing reactivation[14], our patients had normal ALT and undetectable HBV DNA levels. Case 1 presented with recurrent HBV infection after the chemoradiotherapy with oral S-1 following chemotherapy consisted of intravenous cisplatin, 5-FU and gemcitabine. In Case 2, HBV recurrence occurred after the transarterial chemo-lipiodolization using a mixture of epirubicin and lipiodol and radiation therapy. Yeo et al have reported systemic chemotherapy for HCC has been associated with HBV reactivation in HBs-Ag positive patients[15]. Jang JW et al have shown that transarterial chemo-lipiodolization was also a risk for HBV reactivation[16]. Moreover, in a recent study, radiation therapy has been demonstrated to induce HBV reactivation caused by the release of IL-6[17].

Recently, we reported 3 recurrent HBV patients after LDLT for liver cirrhosis due to HBV, and one of the patients had HCC at the time of LDLT without HCC recurrence after the LDLT[18]. All the patients were treated with LAM and ADV, and their HBV DNA were consistently negative after HBV recurrence. On the other hand, in this report, both HBV DNA levels increased after HBV recurrence despite the continuous treatment with ETV and ADV. Faria et al have shown that HCC recurrence itself is associated with HBV recurrence, because HBV replication in HCC cells may act as a viral source[11]. Therefore, we presume that rapid HCC progression had effect on the increasing HBV DNA levels in our patients after HBV recurrence. In addition, their anti-HBs titers gradually decreased despite the intravenous HBIG administration, possibly because viral production in the recurrent HCC might increase HBIG consumption. In some situations, prevention of HCC recurrence may help reduce the risk of HBV recurrence after LT. Pretransplant transarterial embolization and reduced immunosuppression after LT have recently been shown to decrease the risk of HCC recurrence[19)20)]. However, further studies are needed to develop effective strategies to prevent posttransplant HCC recurrence.

In this report, our patients developed recurrent HBV after relapse of HCC, and their HBV DNA levels increased despite the treatment with anti-HBV agents. In HBsAg-positive recipients, it is possible that severe and progressive recurrent HBV may occur following HCC recurrence, and therefore, HBV prophylaxis should be intensified during the treatment of recurrent HCC.

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（和文抄録）

生体肝移植後肝細胞癌再発後の慢性 B 型肝炎の再発

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肝移植後の B 型肝炎の再発は移植成績を低下させる．生体肝移植後に肝細胞癌再発を認め，その後 B 型肝炎の再発を認めた 2 例を経験したので報告する．いずれもミラノ基準を超えた肝細胞癌と B 型肝炎による非代償性肝硬変に対する生体肝移植後であった．B 型肝炎に対する免疫グロブリンと核酸アナログが投与され，B 型肝炎の再発予防が行われ，いずれも血中の B 型肝炎は検出できないレベルでコントロールされていた．肝細胞癌はそれぞれ移植後 5ヶ月，13ヶ月後に再発し，放射線療法と化学療法が施行された．抗ウイルス療法にもかかわらず，再発肝細胞癌に対する治療中に B 型肝炎の DNA レベルは上昇した．HBs 抗原陽性のレシピエントにおいては再発肝細胞癌の治療の間，B 型肝炎再発予防を十分注意しながら行う必要がある．