Spontaneous resolution of de novo hepatitis B after living donor liver transplantation with hepatitis B core antibody positive graft: a case report

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Abstract

Background: Hepatitis B core antibody (HBcAb)-positive graft is reported to cause de novo hepatitis B after liver transplantation with a probability of 38–100 % without prophylaxis. Hepatitis B surface antigen loss is reported to be achieved with a probability of only 3–8 % in the patients treated by antiviral agents. We present an extremely rare case of spontaneous resolution of de novo hepatitis B after living donor liver transplantation (LDLT) with HBcAb-positive graft.

Case presentation: An 8-year-old female patient underwent LDLT for end-stage biliary atresia using an HBcAb-positive left lobe graft. After transplantation, she did not receive any prophylactic agents for hepatitis B. Two years after LDLT, she was diagnosed with chronic hepatitis B. Six years after LDLT, liver fibrosis and hepatitis activity were advanced and lamivudine was started. Two years after lamivudine administration, emergence of a lamivudine-resistant YMDD mutant was detected and adefovir dipivoxil was combined with lamivudine. Hepatitis B virus deoxyribonucleic acid (HBV-DNA) became undetectable soon after the addition of adefovir dipivoxil. Twelve years after transplantation, acute rejection occurred and steroid pulse therapy was performed, but hepatitis B did not become severe and HBV-DNA continued to be undetectable. Fifteen years after LDLT, she voluntarily discontinued medication of all drugs, including immunosuppressive agents and antiviral drugs for 1 year because of mental instability. After an interval of 1 year, liver function was normal and her serological HBV status was as follows: HBsAg(−), HBsAb(+), HBeAb(−), HBeAb(+), HBcAb(+) and HBV-DNA(−). From these results, we diagnosed her condition as spontaneous clearance of de novo hepatitis B. The patient is free of antiviral therapies and continues to take a low dose of immunosuppressive drugs and is leading a normal life.

Conclusions: In this case, HBsAg loss is finally achieved but we need to follow carefully for HBV reactivation with the fibrosis of the graft in mind.

Keywords: De novo hepatitis B, Hepatitis B core antibody positive graft, Living donor liver transplantation, Spontaneous resolution
Background
Liver transplantation is the standard treatment for various end-stage liver diseases and acute liver failure. To resolve the organ shortage, hepatitis B core antibody (HBcAb)-positive graft is used in Japan. The HBcAb-positive graft is reported to cause de novo hepatitis B after liver transplantation with a probability of 38–100 % without prophylaxis [1, 2]. The combination of hepatitis B immunoglobulin (HBIG) and nucleoside analogue, such as lamivudine and entecavir, markedly prevents the onset of de novo hepatitis B after liver transplantation using HBcAb-positive grafts [3, 4].

Serum hepatitis B virus deoxyribonucleic acid (HBV-DNA) level is well correlated with the incidence of hepatocellular carcinoma (HCC) [5, 6]. Antiviral therapies, including nucleoside analogue, lead to sustained viral suppression, which leads to the prevention of cirrhosis and HCC [7–9]. Serologic resolution of HBV infection is ideally defined as the loss of hepatitis B surface antigen (HBsAg), seroconversion to hepatitis B surface antibody (HBsAb), and undetectable serum HBV-DNA [10], but HBsAg loss is reported to be achieved with a probability of only 3–8 % in the patients treated by antiviral agents [11, 12]. Current antiviral therapies aim for long-term virological control, and serologic resolution of HBV is rarely achieved.

We report an extremely rare case of spontaneous resolution of de novo HBV after living donor liver transplantation using an HBcAb-positive graft.

Case presentation
A 91-day-old female patient had undergone Kasai’s operation for biliary atresia (BA). After the operation, liver failure gradually advanced and she was diagnosed with liver cirrhosis at 8 years old. All hepatitis B serological markers before transplantation, including HBV-DNA, HBsAg and HBsAb, were negative (Table 1). The donor was her mother and the donor’s pre-transplant HBV status was as follows: HBsAg(−), HBsAb(+), hepatitis B envelope antigen (HBeAg(−)), hepatitis B envelope antibody (HBeAb(+)) and HBcAb(+).

She underwent living donor liver transplantation (LDLT) for end-stage BA using an HBcAb-positive left lobe graft and began an immunosuppression regimen of cyclosporine A (CsA) and steroid. After transplantation, she did not receive HBIG prophylaxis because it was not well known that the HBcAb-positive graft was a risk factor for hepatitis B at that time.

Two years after LDLT, the hepatitis B markers were changed as follows: HBsAg(+), HBeAg(+), HBeAb(−) and HBV-DNA(+), and she was diagnosed with chronic hepatitis B (Fig. 1). Other liver functions were normal, and she was followed closely without antiviral treatment.

Six years after LDLT, the level of transaminases increased and liver biopsy was performed. From the results of the pathological findings, liver fibrosis and hepatitis activity were advanced (Fig. 2a, b) and lamivudine was started. HBV-DNA became undetectable soon after the start of the antiviral treatment, and the liver function continued to be at a normal level for several years. Two years after lamivudine administration, the serum HBV-DNA level became detectable again and emergence of a lamivudine-resistant YMDD mutant (YIDD) was detected. Adefovir dipivoxil was combined with lamivudine. HBV-DNA became undetectable soon after the addition of adefovir dipivoxil. Liver biopsies, which were performed during the period, showed improvement of the liver fibrosis and hepatitis activity (Fig. 2c, d).

Twelve years after transplantation, acute rejection occurred and steroid pulse therapy (250 mg/day, 3 days) was performed. Hepatitis B did not become severe, and HBV-DNA continued to be undetectable during and after the treatment for acute rejection.

Fifteen years after LDLT, she had obsessive thoughts and suddenly stopped a routine visit and voluntarily discontinued medication of all drugs, including immunosuppressive agents and antiviral drugs for 1 year. During the period, there were no episodes of severe hepatitis and rejection.

She visited our hospital after an interval of 1 year. Mental status was relatively stable and liver function was normal, and her serological HBV status was as follows.

Table 1 Change of hepatitis B serological markers in the clinical course

| Viral marker | Recipient | Before LDLT | After LDLT | After antiviral therapy | Before anti-rejection therapy | After anti-rejection therapy | Before 1-year cessation | After 1-year cessation | Donor Before donation |
|--------------|-----------|-------------|------------|-------------------------|------------------------------|----------------------------|------------------------|------------------------|---------------------|
| HBsAg (IU/ml) | 0.29      | 99.9        | >2000.0    | >2000.0                 | 146.9                       | 177.6                     | 0.01                   | 0.25                   |                     |
| HBsAb (mIU/ml) | 0.26     | 0.0         | 0.3        | 0.1                     | 5.0                         | 5.0                       | 19.2                   | 35.46                  |                     |
| HBeAg         | −         | +           | +          | −                       | −                           | +                         | −                      | −                      | −                   |
| HBeAb         | −         | −           | −          | −                       | −                           | −                         | −                      | −                      | −                   |
| HBcAb         | −         | +           | +          | +                       | +                           | +                         | +                      | +                      | +                   |
| HBV-DNA (log copies/ml) | <2.6 | >7.6 | <2.6 | <2.6 | <2.6 | <2.6 | <2.6 | <2.6 | <2.6 |
Table 1: HBsAg(−), HBsAb(+), HBeAb(−), HBeAb(−), HBcAb(+) and HBV-DNA(−). From these results, we diagnosed her condition as a spontaneous clearance of de novo hepatitis B. The patient is free of antiviral therapies and continues to take a low dose of immunosuppressive drugs (CsA and steroid) and is leading a normal life.

Discussion

The HBcAb-positive graft is reported to cause de novo hepatitis B after liver transplantation with a probability of 38–100 % [1, 2]. This case received no prophylaxis after transplantation, because it was not well known at the time of liver transplantation that the HBcAb-positive

Fig. 1 Major events and treatments in the clinical course. The panel shows a timeline of the clinical course after liver transplantation. The periods of antiviral agents and immunosuppressive drugs are shown by the grey bars. LAM lamivudine, ADV adefovir dipivoxil

Fig. 2 Pathological findings of liver biopsy specimens. a, b Liver tissue before the treatment of de novo hepatitis B (a HE stain ×100, b HE stain ×400). Lymphocytic invasion to Glisson’s capsule and piecemeal necrosis were shown. c, d Liver tissue after lamivudine and adefovir dipivoxil therapy (c HE stain ×100, d HE stain ×400). Mild invasion of lymphocyte was shown, and liver fibrosis and the activity of hepatitis B were significantly improved
HBV status: HBsAg(−), the serological resolution of de novo hepatitis B is the serological resolution, HBV cccDNA remains in hepatocytes and circulating peripheral mononuclear cells [18, 19]. The necessary conditions of the cessation of antiviral therapy were reported [20, 21], and we think that the cessation of antiviral therapy could be performed safely if the serological HBV status is HBV-DNA(−), HBeAg(−) and/or HBsAg(−). This case fulfilled the necessary conditions and stopped antiviral therapy, but a low dose of immunosuppressive drugs was administered in order to prevent rejection and the fibrosis of the graft.

**Conclusions**

We present an extremely rare case of the spontaneous resolution of de novo hepatitis B after LDLT with an HBcAb-positive graft. HBsAg loss is finally achieved, but we need to follow the patient carefully for HBV reactivation with the fibrosis of the graft in mind.

**Abbreviations**

HBcAb: Hepatitis B core antibody; HBeAg/Ab: Hepatitis B envelope antigen/antibody; HBsAg/Ab: Hepatitis B surface antigen/antibody; HBV-DNA: Hepatitis B virus deoxyribonucleic acid; LDLT: Living donor liver transplantation

**Authors’ contributions**

All authors conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

**Competing interests**

The authors declare that they have no competing interests.

**Consent for publication**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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