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Investigation into withdrawal of entecavir after 20 months in an HBsAb-positive patient who received HBsAg allogeneic stem cell transplantation

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ABSTRACT. Hepatitis B virus (HBV) infection of donors and recipients is not an absolute contraindication for allogeneic stem cell transplantation (allo-HSCT). We studied a patient who received allo-HSCT from an HBsAg-positive donor. The patient was administered long-term immunosuppressive therapy and treated with the oral anti-viral medication, entecavir (ETV). During this treatment, there was no hepatitis B activity, which suggested that the treatment could effectively prevent the incidence of activated hepatitis. HBsAb was detected prior to stopping treatment with ETV, and hepatitis B activity occurred after stopping ETV. This suggested that the recipient was HBsAb-positive before transplantation, with the use of strong immunosuppressive agents, it is possible that HBV infection could occur after stopping ETV treatment because of reactivation of a latent HBV infection or receiving an allo-HSCT from HBsAg-positive donors. The recipient of an allo-HSCT from an HBsAg-positive donor

should be given preventive anti-HBV medication when they receive long-term immunosuppressive therapy.

Key words: HBsAb-positive; Allogeneic stem cell transplantation; Entecavir; Drug withdrawal

INTRODUCTION

Currently, hepatitis B virus (HBV) infection of donors and recipients is not a contraindication for allogeneic stem cell transplantation (allo-HSCT). Possible complications that may arise after transplantation include infection with HBV or reactivation of a latent HBV infection (turn positive for HBsAg). Many studies have investigated the impact of infection and reactivated infection of HBV after transplantation and have proved the importance of relevant measures including monitoring for infection of HBV after transplantation and enhancing preventive treatments for HBV. Now, we would like report the clinical treatment process for one case that was complicated by hepatitis B after drug withdrawal of entecavir (ETV) for 20 months in our hospital. The patient had acute lymphoblastic leukemia and was HBsAb-positive before transplantation. She then received the allo-HSCT from an HBsAg-positive donor.

MATERIAL AND METHODS

Sample

A 34-year-old, female patient (ID number: ZA2778608, hospital admission number: 514152) was diagnosed with acute lymphoblastic leukemia (ALL-L2) in our hospital in March 2010. From March 2010 to May 2010, she received chemotherapy in our hospital. The HBV serum markers showed that HBsAb was positive while HBsAg, HBeAb, and HBcAb were negative before chemotherapy. During chemotherapy, HBV serum markers for HBsAb, HBeAb, and HBcAb were positive. On April 24, 2011, the titer of HBsAb was 971.7 IU/mL as detected by chemiluminescence (Abbott Laboratories, Abbott Park, IL, USA), no HBV DNA was detected by real-time PCR (Daan, Shenzhen, China), and the marrow was in complete remission upon reexamination (ALL-CR). The patient received peripheral blood stem cell reinfusion from her sister on May 10, 2011. Because of the HBsAg-positive status of the donor, the patient was administered 0.5 mg ETV once a night and 50 mg cyclosporine A daily to prevent rejection. Subsequently, reexamination every 3 months indicated HBsAb-positive and HBV DNA-negative status and a normal liver zymogram. The next reexamination result showed HBsAb was positive at a titer of 14.1 IU/mL and HBV DNA was negative on January 10, 2013, so ETV treatment was stopped while treatment with cyclosporine A to prevent rejection was continued.

Reexamination on October 8, 2013 in our hospital revealed the following results: HBsAg-positive, HBcAb-positive, HBeAb-positive, normal liver zymogram, and 3.85×10^5 copies/mL of HBV DNA. In light of these results, the patient was treated with ETV again. On December 27, 2013, the reexamination of blood biochemistry showed that alanine aminotransferase (ALT) was 191.6 U/L, aspartate aminotransferase (AST) was 133.9 U/L, and HBV DNA was 2.03×10^3 copies/mL, so she was hospitalized for treatment in our department.

The patient denied having other sexual partners and the use of injections. She had no history of transfusion, trauma, operations, or drinking. Her husband was HBsAb-positive and HBV DNA-negative.

After hospitalization, the hepatitis B virus serum markers results were as follows: HBsAg was positive at 4499.4 IU/ml as detected by chemiluminescence (Abbott Laboratories, Abbott Park, IL), HBeAb and HBcAb were positive, HBsAb and HBeAg were negative, and alpha-fetoprotein (AFP) was negative. Blood biochemistry results were ALT 98.9 U/L, AST 61.8 U/L, and ceruloplasmin (CER) 0.24 g/L. Routine examination of the patient's blood was normal. A test of coagulation function resulted in a prothrombin test time of 11.6 s. Antibodies related to autoimmune liver disease were negative, and antibodies to cytomegalovirus IgM and to EB virus were negative. Thyroid function was normal. The abdominal ultrasound revealed a light spot in the liver, homogeneous echo distribution, and a normal spleen. Reexamination of blood biochemistry on January 10, 2014 showed liver enzymes results of ALT 71.0 U/L and AST 52.0 U/L; thus, the patient was treated with ETV after discharge.

RESULTS

Reexamination of biochemistry on March 30, 2014 showed results of ALT 48.1 U/L, AST 45.8 U/L, and HBV DNA negative by real-time PCR (Daan, Shenzhen). The graph depicting the development of disease is shown in Figure 1.

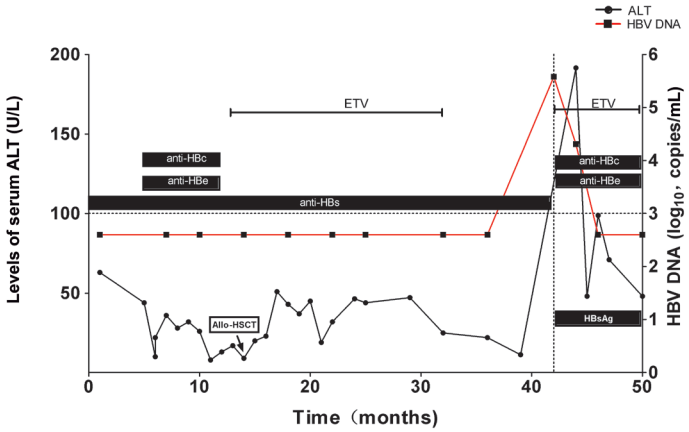

Figure 1. Alanine aminotransferase (ALT) levels, viral markers, and HBV DNA loads after chemotherapy and allo-hematopoietic stem cell transplantation. ETV = entecavir.

DISCUSSION

In this study, we reported that an HBsAb-positive patient presented with hepatitis B after stopping ETV treatment after 20 months of following allogeneic stem cell transplantation from an HBsAg-positive donor.

We wanted to determine the source of the HBV infection. One possibility was that a latent HBV infection had been reactivated. The patient had no hepatitis B vaccination history before the incident. HBsAb was positive before chemotherapy, while HBsAb, HBeAb, and HBcAb were all positive after chemotherapy, which suggested that the patient was infected with HBV. HBsAg may not have been detected because some factors may have inhibited the expression and secretion of HBsAg, resulting in low HBsAg levels. HBcAb was positive in the patient's serum revealing that there might be a small amount of HBV cccDNA in her liver (Werle-Lapostolle et al., 2004; Yuen et al.,

2008). Since the patient had received high dose chemotherapy and long-term immunosuppressive agents, her immune function had not recovered post-transplantation and was lacking in self-secreted IgG. This may have caused the reactivation of HBV and reactivity to hepatitis B. The detection of HBV cccDNA is the gold standard to determine whether the reactivity was due to HBV. However, the patient did not opt for a liver biopsy, and therefore, we could not assess HBV cccDNA levels. To date, we have not been able to confirm whether reactivation of latent HBV induced the hepatitis B infection. Another possibility was an external infection of HBV. The patient's husband was HBsAb-positive and HBV DNA-negative. Throughout treatment, the patient denied having other sexual partners or use of injections. Additionally, she had no history of transfusion aside from her sister, no trauma, operations, or alcohol consumption, which could exclude the source of the HBV infection as being from her husband and other non-blood relations. We theorized that she was infected with HBV from her sister, so we analyzed the HBV sequence from both the patient and her sister. The analysis showed that the amplification of the small S region belonged to the B2 subtype; the sequence was similar but not identical. The heterogeneity of the S region sequence was about 0.4%, which indicates it is possible that the HBV is from the same source (Figure 2 and Figure 3). If the HBV had been from her parents, the heterogeneity of the sisters' S region would be much higher (Dumpis et al., 2001; Pourkarima et al., 2009). Therefore, the sequence alignment supported our theory that the source of the virus was the patient's sister.

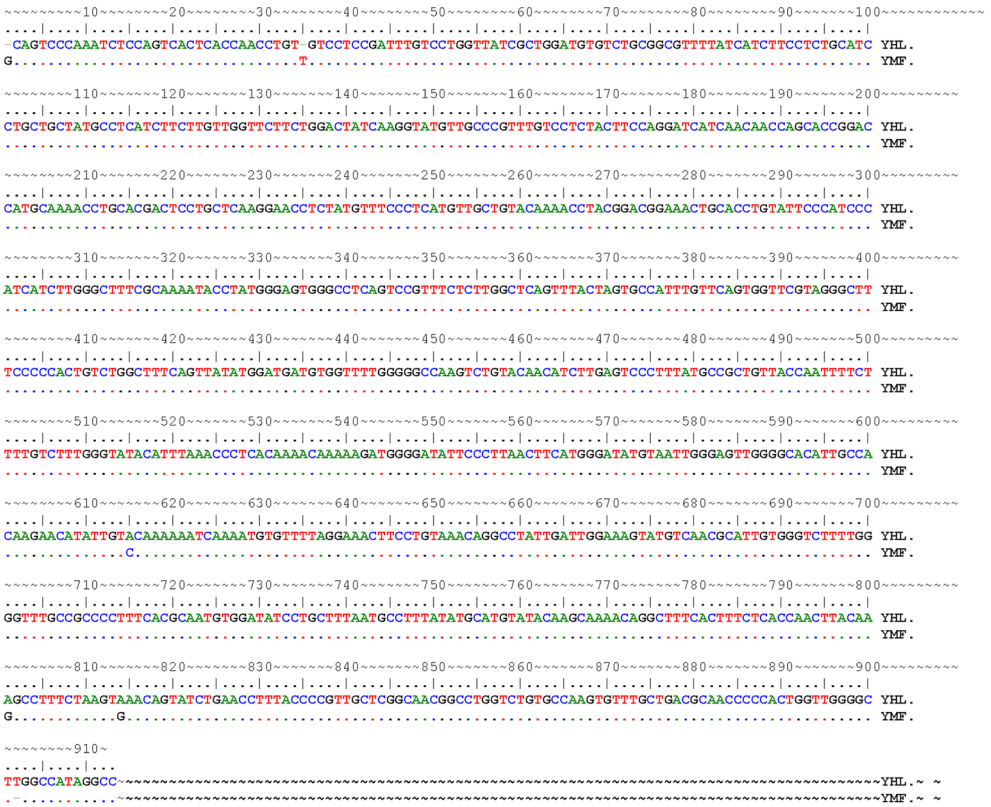

Figure 2. Sequence alignment of the HBV S region between the patient and her sister.

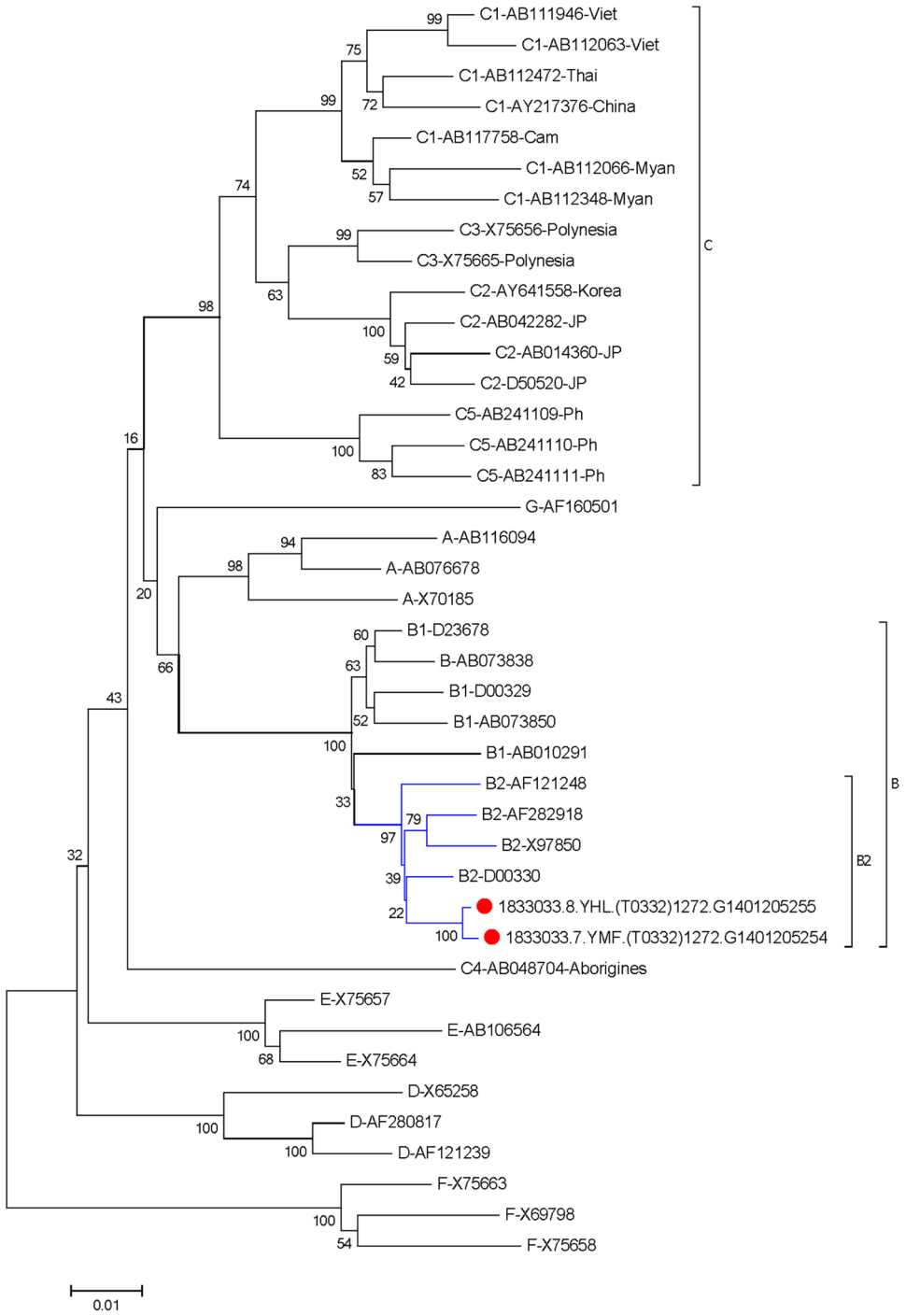

Figure 3. Phylogenetic analysis of plasma HBV S region from the patient and her sister.

The recipient of allo-HSCT HBsAg should be given preventive anti-hepatitis B medication when they receive long-term treatment with immunosuppressants (European Association for the Study of the Liver, 2012). The patient in this report was HBsAb-positive prior to transplantation and her titer was high. We gave her preventive treatment with ETV because she was reinfused with blood from her HBsAg positive sister and treated with cyclosporine A to prevent rejection.

Throughout her treatment, numerous examinations revealed HBsAb positivity and HBV DNA below the level of detection. After treatment with ETV for 20 months, the titer of HBsAb was 14.1 IU/mL, which was lower than before, but HBsAb was still positive, so we decided to discontinue the ETV treatment. The patient turned HBsAg-positive nine months after stopping ETV treatment and HBV DNA level was 3.85×10^5 copies/ml, so she was further treated with oral ETV. Over the next two months, the level of HBV DNA decreased to 2.03×10^3 copies/mL, but hepatitis B infection was still active. Increasing levels of ALT and AST might contribute to hepatitis activity lagging than the suppression of virus replication . Upon continuous treatment with ETV, HBV DNA level decreased and ALT and AST levels returned to normal. The patient has remained stable thus far.

The patient received allo-HSCT from an HBsAg-positive donor along with long-term immunosuppressive therapy and treatment with the oral anti-viral medication, ETV. Throughout the duration of ETV treatment, there was no hepatitis B activity, which suggested that the treatment could effectively prevent the incidence of activated hepatitis (Giaccone et al., 2010). HBsAb remained positive prior to stopping ETV treatment, but hepatitis B activity occurred after stopping ETV. This suggested that the recipient was HBsAb-positive before transplantation, with the use of strong immunosuppressive agents, it is possible that HBV infection could occur after stopping ETV treatment because of reactivation of a latent HBV infection or receiving an allo-HSCT from HBsAb-positive donors.

Conflicts of interest

The authors declare no conflict of interest.

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