Development of de novo hepatitis B in patient during follow-up of liver-graft-versus-host disease associated with allogeneic peripheral blood stem cell transplantation

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\textbf{ABSTRACT}

A 66-year-old female patient with acute myeloid leukemia underwent remission-induction therapy and allogeneic peripheral stem cell transplantation. The patient was found to have a resolved hepatitis B virus (HBV) infection, as shown by her positivity for the hepatitis B surface (HBs) antibody and hepatitis B core antibody and negativity for the HBs antigen and HBV-DNA. Administration of an immunosuppressant was started after transplantation for the prevention of graft-versus-host disease (GVHD), and hepatic impairment developed four months after transplantation. No changes were observed in serum HBV-related marker levels, and a liver biopsy revealed GVHD. The course of hepatic impairment was followed up with the diagnosis of liver GVHD, without determining the level of HBV-related markers. Hepatic impairment recurred 13 months after transplantation. Determination of the HBV-related markers showed that the patient was positive for the HBs antigen and HBV-DNA. The patient was diagnosed as having de novo hepatitis B, and the hepatitis improved after the start of anti-viral therapy. In administering immunosuppressive therapy and chemotherapy for patients with a resolved HBV infection, it is important to test for viral markers regularly by paying constant attention to the possible onset of de novo hepatitis B, despite the existing hepatic disease.

\textbf{Key Words:} Hepatitis B virus, de novo hepatitis B, Liver graft-versus-host disease, Allogeneic peripheral blood stem cell transplantation

\section{1. INTRODUCTION}

Chemotherapy including steroid therapy for the treatment of cancer in hepatitis B virus (HBV) carriers induces severe hepatitis owing to HBV reactivation.\textsuperscript{[1,2]} It is required that HBV reactivation should be prevented by administering a nucleoside analogue to HBV carriers receiving immunosuppressive chemotherapy.\textsuperscript{[3]} Patients negative for the hepatitis
B surface (HBs) antigen but positive for the HBs antibody or hepatitis B core (HBc) antibody have been considered to have a resolved HBV infection and are in the state of clinical cure. However, it has been reported that, even in this state, some patients develop fatal severe hepatitis owing to HBV reactivation following immunosuppressive therapy for the treatment of various diseases including cancer, autoimmune disease, and organ transplant and that this hepatitis has been referred to as de novo hepatitis B.\[^{4–6}\] Because the rates of fulminant hepatitis B and fatal hepatitis B are high among de novo hepatitis patients,\[^{71}\] a careful follow-up is also recommended for patients with a resolved HBV infection and who underwent immunosuppressive therapy.

In this paper, we report the development of de novo hepatitis B in a patient with acute myeloid leukemia during the follow-up of liver-graft-versus-host disease (GVHD) associated with allogeneic peripheral blood stem cell transplantation (allo-PBSCT).

2. CASE PRESENTATION

A 66-year-old Japanese female developed acute myeloid leukemia (AML) in June 2008. She received remission-induction therapy with idarubicin (IDA) and cytarabine (Ara-C), and consolidation therapy with Ara-C and mitoxantrone hydrochloride. The patient was tested for hepatitis virus markers before chemotherapy, and test results showed that the patient was negative for the hepatitis C virus (HCV) and the HBs antigen, positive for the HBs antibody and HBc antibody, and negative for HBV-DNA at < 2.1 log copy/ml; these findings indicate as a resolved HBV infection. The patient underwent allo-PBSCT for AML in November 2008. Concomitant administration of cyclosporine (CyA) at a dose of 250 mg/day and methotrexate (MTX) at a dose of 15 mg/day was started. The administration of MTX was completed for 3 days, whereas the administration of CyA was continued, although the dose was reduced. The patient developed hepatic impairment with a serum aspartate aminotransaminase (AST) level of 207 IU/L and serum alanine aminotransferase (ALT) level of 160 IU/L in February 2009, and she was referred to our department. Her past medical history included partial resection for lung cancer performed at the age of 65. No recurrence of lung cancer has been detected to date. As the cause of the hepatic impairment, de novo hepatitis was suspected, because her resolved HBV infection was already detected. However, no reactivation of HBV was observed, as shown by her negativity for the HBs antigen and HBV-DNA. Figure 1 shows an image of histopathological specimen obtained by liver needle biopsy for detailed examination. Bile duct damage in the portal area, as well as sinusoidal endothelial cell damage in the liver parenchyma, was observed. These findings were consistent with GVHD. Therefore, the cause of the hepatic impairment was determined to be liver GVHD. Continued administration of CyA at a dose of 25 mg/day led to spontaneous remission of the hepatic impairment. In August 2009, skin rash and anorexia occurred. Taking into consideration these adverse reactions to CyA, the dose of the drug was reduced to 12.5 mg/day and concomitant administration of prednisolone (PSL) at a dose of 20 mg/day was started. In December 2009, hepatic impairment recurred with an AST level of 261 IU/L and an ALT level of 596 IU/L, and the patient was admitted to the hospital for detailed examinations and treatment. A physical examination of the patient at the time of admission showed lucidity, and blood biochemical findings included a serum AST level of 261 IU/L, an ALT level of 596 IU/L, a γ GTP level of 645 IU/L, and a total bilirubin level of 1.3 mg/dl, which indicate hepatic impairment without jaundice. The hepatitis virus marker test showed the following results: negative for the IgM-hepatitis A (HA) antibody, negative for the HCV antibody, positive for the HBs antigen (54,155 IU/ml), positive for the HBe antigen, negative for the HBe antibody, and an HBV-DNA level of > 9.0 log copy/ml. The results of the detailed examination showed the conversion of the HBs antigen and a high HBV-DNA level, leading to a diagnosis of de novo hepatitis B due to HBV reactivation. When the patient was determined to be positive for the HBs antigen, we started the administration of entecavir at a dose of 0.5 mg/day. Serum liver enzyme levels on day 14 after the start of administration decreased as follows: AST level, 132 IU/L; ALT level, 250 IU/L; and HBV-DNA level, 6.9 log copy/ml. Transient exacerbation of hepatic impairment was observed with an AST level of 185 IU/L and an ALT level of 352 IU/L. Therefore, a percutaneous liver needle biopsy was performed 26 days after the start of entecavir administration due to confirming a viral hepatitis. There were no findings of bile duct damage or endothelial cell disorder for characteristic of active GVHD in the 2nd liver biopsy (see Figure 2). Taking into consideration the possibility of entecavir administration at a dose of 0.5 mg/day failing to have a sufficient antiviral effect because of the receiving immunosuppressive therapy, the dose of entecavir was increased to 1.0 mg/day. Because further decreases in the liver enzyme levels were observed 42 days after the start of entecavir administration (an AST level of 75 IU/L, an ALT level of 151 IU/L, and an HBV-DNA level of 5.3 log copy/ml), its dose was reduced to 0.5 mg/day, and the patient was discharged from the hospital. The patient continuously received outpatient treatment with entecavir at a dose of 0.5 mg/day and there was no recurrence of hepatic impairment (see Figure 3).
3. DISCUSSION

It has been demonstrated that HBV-DNA replication continues at a very low level in hepatic cells over a long period even in patients negative for the HBs antigen and positive for the HBs antibody or the HBe antibody and in those who have been considered to have a resolved HBV infection and to be in the state of clinical cure. HBV-specific cytotoxic T lymphocyte persists for a long period in such patients and HBV proliferation is considered to be controlled by host cellular immunity. Hence, HBV reactivation potentially occurs in patients with a resolved HBV infection, which is associated with the administration of an immunosuppressant after organ transplant or that of rituximab (an antibody against the B cell surface antigen CD20) for the treatment of malignant lymphoma. Such a condition due to HBV reactivation in the HBs antigen or HBV-DNA negative state is referred to as de novo hepatitis B. A study conducted in Japan has recently demonstrated the higher incidence of de novo hepatitis B becoming fulminant hepatitis than of the common acute hepatitis B with a higher mortality rate. And also, the guideline for the prevention and treatment of HBV reactivation during immunosuppressive drug therapy was developed by the Clinical Practice and Quality Measures Committee (currently the Clinical Practice Guideline Committee) and approved by the AGA Governing Board. We treated a patient with de novo hepatitis B after allo-PBSCT for AML. It was reported that two types of PBSCT, i.e., autologous PBSCT (auto-PBSCT) and allo-PBSCT, induce post-transplantation de novo hepatitis B. Because immunosuppressive therapy is performed over a long period to suppress chronic GVHD particularly after allo-PBSCT, the transplantation potentially induces de novo hepatitis B at a higher incidence than auto-PBSCT and even after a long post-transplantation period. Large-scale studies on de novo hepatitis B have been conducted recently and typical drugs that could induce HBV reactivation have been identified. In general, the immunosuppressants were categorized into low-, moderate-, or high-risk groups based on estimates of reactivation using available evidence. The high-risk group was defined by anticipated incidence of HBV reactivation in > 10% of cases, and the moderate- and the low-risk groups were defined by anticipated incidence of HBV reactivation of 1% to 10% and < 1% of cases. The AGA recommends antiviral prophylaxis for patients at high risk undergoing immunosuppressive drug therapy, and suggests antiviral prophylaxis for patients at moderate risk group. However, the AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for HBV reactivation. Although the guideline have not addressed the issue of HBV reacti-
vation in hematopoietic stem cell transplantation, previous data indicated that the relatively high incidence of HBV reactivation occurred after allo-PBSCT. Therefore, we should not only consider risky in HBV reactivation with a careful follow-up, but also monitor serum HBV-related marker levels, especially serum HBV-DNA level. Moreover, in our patient, three drugs potentially associated with HBV reactivation, i.e., MTX, a typical metabolic antagonist, CyA, a cyclic polypeptide antibiotic, and prednisolone, a corticosteroid, were used after allo-PBSCT.\(^{[20–22]}\) In particular, the involvements of CyA administered until the onset of \textit{de novo} hepatitis B after allo-PBSCT and prednisolone started after the reduced dose of CyA owing to adverse drug reactions and used continuously, are suspected. It was also reported that, because HBV has a glucocorticoid enhancement element that has the same nucleotide sequence as that of glucocorticoid receptors at the viral gene replication initiation site, HBV proliferation is directly promoted by glucocorticoid.\(^{[26]}\)

There are various causes of hepatic impairment after allo-PBSCT, including pretransplantation treatment, post-transplantation hepatic disorder caused by a drug such as an immunosuppressant, various types of infection, liver GVHD, thrombotic microangiopathy (TAM), and veno-occlusive disease (VOD) of the liver.\(^{[27–29]}\) In addition, the presence of \textit{de novo} hepatitis B should be taken into consideration in patients with a resolved HBV infection as in our present patient. Detailed examination of our patient was conducted also with an eye on \textit{de novo} hepatitis B at the initial onset of hepatic impairment. However, \textit{de novo} hepatitis B was not considered on the basis of the serum HBV-related marker levels, and the patient was diagnosed as having liver GVHD on the basis of the findings of a percutaneous needle biopsy of the liver. Later, the hepatic impairment improved with the continued administration of CyA. After being diagnosed as having liver GVHD, however, the patient was followed up without the periodic determination of HBV-related marker levels, although she continuously received immunosuppressive therapy. Consequently, HBV reactivation was detected after the occurrence of a marked hepatic impairment, leading to a diagnosis of \textit{de novo} hepatitis B. The prompt initiation of antiviral therapy saved the life of this patient; however, if HBV-related marker levels had been determined periodically during the follow-up period, the antiviral therapy would have been introduced before the onset of hepatic impairment, making it possible to prevent the onset of hepatitis. When different causes of hepatic impairment after allo-PBSCT are already identified, careful attention should be paid to the possible existence of hepatic lesions. On the other hand, monitoring of serum HBV-related marker levels for any development of \textit{de novo} hepatitis B that had been followed up carefully in the beginning tends to be insufficient. Caution should be exercised with an eye on the onset of \textit{de novo} hepatitis B under any circumstances. Hui \textit{et al.} reported that an increased HBV-DNA level precedes the onset of hepatitis after HBV reactivation by an average period of 18.5 weeks (range: 12 to 28 weeks).\(^{[30]}\) Hence, this indicates that HBV reactivation will become detectable before the onset of hepatitis by periodic monitoring of HBV-DNA level and that hepatitis development will become preventable by the early administration of an antiviral drug. In Japan, guidelines stipulate that HBV marker levels should be checked prior to the start of treatment in all patients who will undergo immunosuppressive therapy and that the HBV-DNA level be determined periodically if a patient is positive for the HBs antibody or HBC antibody despite being negative for the HBs antigen. In particular, patients who undergo PBSCT are at a high risk and the guidelines should be strictly observed considering such cases.\(^{[31]}\)

We experienced treating a patient who developed \textit{de novo} hepatitis B during the follow-up of liver GVHD associated with allo-PBSCT for AML. It is considered that there is a broad range of concomitant causes of hepatic impairment associated with allo-PBSCT. In such a case, careful attention is usually paid to an existing hepatic lesion, whereas attention to \textit{de novo} hepatitis B is likely neglected. In particular, patients after PBSCT require follow-up monitoring with careful attention to not only the existing hepatic disease but also HBV-related marker levels.

4. \textbf{CONCLUSION}

\begin{itemize}
  \item Patients negative for the HBs antigen but positive for the HBs antibody or HBC antibody have been considered to have a resolved HBV infection.
  \item However, it has been reported that, even in a resolved HBV infection, some patients develop fatal severe hepatitis, referred to as \textit{de novo} hepatitis B, owing to HBV reactivation following immunosuppressive therapy.
  \item In administering immunosuppressive therapy and chemotherapy for patients with a resolved HBV infection, it is important to test for viral markers regularly by paying constant attention to the possible onset of \textit{de novo} hepatitis B, despite the existing hepatic disease.
\end{itemize}
REFERENCES


