Hepatitis B Virus Reactivation 55 Months Following Chemotherapy Including Rituximab and Autologous Peripheral Blood Stem Cell Transplantation for Malignant Lymphoma

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Abstract:
A 54-year-old woman underwent chemotherapy including rituximab and autologous peripheral blood stem cell transplantation (auto-PBSCT) for diffuse large B-cell lymphoma. Before the treatment, she exhibited a resolved hepatitis B virus (HBV) infection. She was diagnosed with HBV reactivation based on positive serum HBV-DNA test results, 55 months after her last treatment. Subsequently, she was treated with tenofovir alafenamide fumarate (TAF) therapy and her liver function improved. Patients undergoing chemotherapy including rituximab and auto-PBSCT are at a high risk of HBV reactivation. In such cases, careful and long-term observations may be required to detect HBV reactivation.

Key words: hepatitis B virus reactivation, de novo hepatitis, rituximab, peripheral blood stem cell transplantation

Introduction
Hepatitis B virus (HBV) reactivation has emerged as a major complication induced by long-term chemotherapy or immunosuppressive therapy (1). De novo hepatitis B, a form of HBV reactivation, can occur as a result of the reactivation of latent HBV infection in subjects who are negative for hepatitis B surface antigen (HBs-Ag), but positive for anti-hepatitis B core antibody (HBc-Ab), anti-HBs antibody (HBs-Ab) or both (2, 3). It is well known that patients receiving chemotherapy, including rituximab and hematopoietic stem cell transplantation (HSCT), are at high risk of HBV reactivation (4-6). Among HSCT recipients with resolved HBV, the risk of HBV reactivation is higher with allogeneic HSCT (allo-HSCT) than with autologous HSCT (auto-HSCT) (7). HBV reactivation usually develops a few months after chemotherapy or immunosuppressive therapy. Long-term HBV-DNA monitoring after transplantation is recommended (4), because the time interval between HSCT and HBsAg-positive conversion can be long. However, currently, there is no definitive indication for how long the viral load should be monitored in such cases. We herein present the case of a patient who experienced HBV reactivation 55 months after chemotherapy including rituximab and autologous peripheral blood stem cell transplantation (auto-PBSCT), and de novo hepatitis B improved with tenofovir alafenamide fumarate (TAF) therapy.

Case Report
A 54-year-old woman presented to our hospital with a continuous low-grade fever. Her workup revealed stage IVB diffuse large B-cell lymphoma (DLBCL). Her laboratory findings were negative for HBs-Ag and HBV-DNA, but was positive for HBs-Ab and HBc-Ab. She had no family history of HBV infection. She underwent 4 courses of rituximab, cyclophosphamide (CPM), doxorubicin, vincristine (VCR),

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HBs-Ag were no longer detectable, while the HBs-Ab gradually decreased. After five months, HBV-DNA, and therapy, the patient’s transaminase and HBV-DNA levels degree of inflammation (Fig. 2). During the course of TAF lymphocyte infiltrate in the portal vein area, with a moderate revealed slight cross-linked fibrosis between portal veins and a

Two months later, the patient developed hepatitis due to HBV reactivation 55 months after the end of chemotherapy. In this case, the patient developed hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT. HBV reactivation is a common and potentially fatal complication in patients with past HBV infection undergoing immunosuppressive therapy (1-3). Patients receiving chemotherapy, including rituximab and auto-PBSCT, are at a high risk of HBV reactivation (4-6). To prevent HBV reactivation in patients receiving HSCT, the Japan Society of Hepatology (JSH) guidelines recommend that monthly HBV-DNA monitoring be performed during treatment and for at least 12 months after its completion. It also recommends long-term HBV-DNA monitoring after HSCT. HBV reactivation is not uncommon in HSCT recipients. In particular, patients undergoing allo-HSCT are at a very high risk of HBV reactivation, and the time interval between transplantation and HBs-Ag conversion can be long (8, 9). The risk of HBV reactivation is lower with auto-HSCT than with allo-HSCT (7); however, the rate of reactivation is still 5.4-16.7% in patients with resolved HBV infection (7, 10, 11). Rare cases have been reported where HBV reactivation occurred more than 1 year after auto-HSCT (12, 13) (Table 2). Auto-HSCT is accepted as a comparatively effective treatment for blood diseases, and the current protocol for patients receiving auto-HSCT therapy is to source stem cells from peripheral blood (14). Our patient developed de novo hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT.

In this case, the patient developed hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT. HBV reactivation is a common and potentially fatal complication in patients with past HBV infection undergoing immunosuppressive therapy (1-3). Patients receiving chemotherapy, including rituximab and auto-PBSCT, are at a high risk of HBV reactivation (4-6). To prevent HBV reactivation in patients receiving HSCT, the Japan Society of Hepatology (JSH) guidelines recommend that monthly HBV-DNA monitoring be performed during treatment and for at least 12 months after its completion. It also recommends long-term HBV-DNA monitoring after HSCT. HBV reactivation is not uncommon in HSCT recipients. In particular, patients undergoing allo-HSCT are at a very high risk of HBV reactivation, and the time interval between transplantation and HBs-Ag conversion can be long (8, 9). The risk of HBV reactivation is lower with auto-HSCT than with allo-HSCT (7); however, the rate of reactivation is still 5.4-16.7% in patients with resolved HBV infection (7, 10, 11). Rare cases have been reported where HBV reactivation occurred more than 1 year after auto-HSCT (12, 13) (Table 2). Auto-HSCT is accepted as a comparatively effective treatment for blood diseases, and the current protocol for patients receiving auto-HSCT therapy is to source stem cells from peripheral blood (14). Our patient developed de novo hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT. This prompts us to question the current recommended timeframe of viral load monitoring in HSCT recipient. The prophylactic use of NA in HBs-Ag

Discussion

In this case, the patient developed hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT. HBV reactivation is a common and potentially fatal complication in patients with past HBV infection undergoing immunosuppressive therapy (1-3). Patients receiving chemotherapy, including rituximab and auto-PBSCT, are at a high risk of HBV reactivation (4-6). To prevent HBV reactivation in patients receiving HSCT, the Japan Society of Hepatology (JSH) guidelines recommend that monthly HBV-DNA monitoring be performed during treatment and for at least 12 months after its completion. It also recommends long-term HBV-DNA monitoring after HSCT. HBV reactivation is not uncommon in HSCT recipients. In particular, patients undergoing allo-HSCT are at a very high risk of HBV reactivation, and the time interval between transplantation and HBs-Ag conversion can be long (8, 9). The risk of HBV reactivation is lower with auto-HSCT than with allo-HSCT (7); however, the rate of reactivation is still 5.4-16.7% in patients with resolved HBV infection (7, 10, 11). Rare cases have been reported where HBV reactivation occurred more than 1 year after auto-HSCT (12, 13) (Table 2). Auto-HSCT is accepted as a comparatively effective treatment for blood diseases, and the current protocol for patients receiving auto-HSCT therapy is to source stem cells from peripheral blood (14). Our patient developed de novo hepatitis due to HBV reactivation 55 months after the end of chemotherapy and auto-PBSCT. This prompts us to question the current recommended timeframe of viral load monitoring in HSCT recipient. The prophylactic use of NA in HBs-Ag
Figure 1. Clinical course of the patient’s condition. Solid thick black arrow indicates the time of liver biopsy. Solid think black arrow indicates the time of chemotherapy including rituximab and auto-PBSCT. auto-PBSCT: autologous peripheral blood stem cell transplantation

![Graph showing ALT and HBV-DNA levels over time](image)

**Table 2.** Presenting Clinical Features of 3 Cases of HBV Reactivation in Resolved HBV Patients after Auto-HSCT and Our Patient.

| No | Disease | Sex | Age | Anti-HBs | Period to reactivation | Peak HBV DNA (log IU/mL) | Peak ALT (IU/L) | Treatment of reactivation | Evolution | Reference |
|----|---------|-----|-----|----------|------------------------|--------------------------|----------------|--------------------------|-----------|-----------|
| 1  | HL      | M   | 68  | Positive | 18 months              | >8.2                     | ×2UNL          | TDF                      | Resolved  | [12]      |
| 2  | MM      | F   | 72  | Negative | 12 months              | 7.2                      | 21             | LMV                      | Resolved  | [13]      |
| 3  | MM      | M   | 60  | Positive | 20 months              | 6.7                      | 261            | No treatment            | Resolved  | [13]      |
| 4  | DLBCL   | F   | 54  | Positive | 55 months              | 8.0                      | 640            | TAF                      | Resolved  | Our case  |

auto-HSCT: autologous hematopoietic stem cell transplantation, anti HBs: anti-hepatitis B surface, HL: hodgkin’s lymphoma, MM: multiple myeloma, DLBCL: diffuse large B-cell lymphoma, ULN: upper limited normal, TDF: tenofovir disoproxil fumarate, LMV: lamivudine, TAF: tenofovir alafenamide fumarate, HBV: hepatitis B virus
negative, HBc-Ab positive HSCT recipients is recommended by the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD) guidelines (5, 6), although the optimal duration of prophylaxis is not known. The incidence of HBV reactivation after HSCT in patients with resolved HBV infection is about 40% (9), suggesting that more than half of HSCT patients do not require NA prophylactic administration. Thus, NA prophylaxis for all patients with past HBV infection are monitored for HBV markers carefully or receive anti-HBV prophylaxis. By adopting this strategy, there have been few reports of pathological HBV reactivation with severe acute fatal hepatitis (16-18). Although the timing of liver biopsy from the onset of de novo hepatitis is almost unchanged, fibrosis was more advanced than that observed in previous cases receiving immunosuppressive therapy for preventing graft-versus-host disease (17, 18). The patient in this study did not require receive immunosuppressive therapy, reported to improve clinicopathologic findings for severe hepatitis (19), following the treatment. It has been reported that hepatic fibrosis does not progress after HBsAg seroclearance (20, 21), and that fibrosis or chronic changes may sometimes occur before HBV seroclearance. Further study is needed regarding the histopathology, including the progression of liver fibrosis, in patients with HBV reactivation to address these issues.

Certain virologic features have been linked to HBV reactivation. For instance, mutations in the core promoter region (A1762T and G1764A) and in the precore region (G1896A) are reported to be associated with HBV reactivation (22, 23). Additionally, a recent study used next-generation sequencing and showed that mutation in the precore region (G1899A) are also associated with HBV reactivation (24). Further studies are required to elucidate the mechanisms that contribute to such virologic features in HBV reactivation.

In the latest JSH, EASL, and AASLD guidelines, entecavir (ETV), tenofovir disoproxil fumarate (TDF), and TAF are recommended as first line anti-HBV treatments for prophylaxis against HBV reactivation (4-6). TAF has demonstrated safety and efficacy in achieving viral suppression in patients with chronic hepatitis B (25-27). In our patient, TAF was used effectively and safely against de novo hepatitis B.

Tamori et al. (28) suggested that NA therapy can be discontinued in patients with HBV reactivation after the HBs-Ab test shows consistent positive results. In our patient, the HBs-Ab test was positive, but HBCr-Ag remained detectable. HBCr-Ag is considered a marker of intrahepatic HBV [covalently closed circular DNA (cccDNA)], and serum HBCr-Ag positivity is a risk factor for HBV reactivation in patients undergoing immunosuppressive therapy (29). As such, our findings suggest that TAF therapy should be continued until serum HBCr-Ag becomes undetectable.

In conclusion, we herein described a case of HBV reactivation 55 months after chemotherapy including rituximab and auto-PBSCT. In such high-risk cases, the recommended guidelines should be followed, and careful long-term follow-ups, including the possibility of lifelong observation, are warranted.

The authors state that they have no Conflict of Interest (COI).

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