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【 CASE REPORT 】

A Hepatitis B Virus Reactivation Case Potentially Triggered by the Onset of Diffuse Large B Cell Lymphoma

Kentaro Sato[1], Hidemichi Imamura[2], Yu Watahiki[2], Hiromasa Hazama[2], Takeaki Hashimoto[2], Shinji Mukae[2] and Hiromasa Ohhira[3]

Abstract:
An 81-year-old man underwent rituximab-containing chemotherapy for chronic lymphocytic leukemia (CLL). Thirteen years after his last chemotherapy, he was diagnosed with hepatitis B virus (HBV) reactivation. He was then treated with entecavir, and improvement was seen in his liver injury. He developed diffuse large B cell lymphoma (DLBCL) after improvement in his hepatitis. Despite chemotherapy, he contracted the coronavirus disease 2019 (COVID-19) and died of COVID-19. We suspect that HBV reactivation was triggered by DLBCL. When HBV reactivation occurs a long time after chemotherapy has concluded, the onset of DLBCL should be considered.

Key words: hepatitis B virus reactivation, diffuse large B cell lymphoma

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Introduction

The World Health Organization estimated that there are 296 million chronic hepatitis B virus (HBV) carriers in the world in 2019. Furthermore, 1.5 million people are newly infected each year. HBV is major health problem worldwide.

Chemotherapy or immunosuppressive therapy in current or previously infected persons with HBV causes HBV reactivation. Patients receiving rituximab-containing chemotherapy are at a particularly high risk of HBV reactivation (1, 2). Generally, HBV reactivation occurs within one year after chemotherapy or immunosuppressive therapy (3). The Japan Society of Hepatology guidelines therefore recommend that monthly HBV-DNA monitoring be performed during chemotherapy and for at least 12 months after its completion to prevent HBV reactivation in patients receiving chemotherapy. There have been no reports of HBV reactivation occurring more than 10 years after chemotherapy has concluded.

We encountered a patient who experienced HBV reactivation 13 years after rituximab-containing chemotherapy treatment had concluded. The patient developed diffuse large B cell lymphoma (DLBCL) after the hepatitis B improved. The HBV reactivation in this case may have been triggered by DLBCL.

Case Report

An 81-year-old man with chronic lymphocytic leukemia (CLL) received cyclophosphamide (CPA), doxorubicin (DXR), vincristine (VCR), and prednisolone (PSL) (CHOP) therapy with rituximab and fludarabine in 2007. After chemotherapy, he was followed up in the Department of Hematology in our hospital without further treatment. Before chemotherapy, hepatitis B core antibody (HBc-Ab) and hepatitis B surface antigen (HBs-Ag) had been negative. Hepatitis B surface antibody (HBs-Ab) was not inspected. HBV follow-up was not conducted after chemotherapy.

The patient was referred to our department because of liver enzyme abnormalities in July 2020. Because he was positive for HBs-Ag, had elevated hepatitis B virus DNA (HBV-DNA), and was negative for IgM-HBc-Ab, we diagnosed him with HBV reactivation, and he was hospitalized. He had no history of blood transfusion and was sexually in-

[1]Department of Gastroenterology, Aizu medical center, Japan, [2]Department of Gastroenterology, Ohta Nishinouchi Hospital, Japan and [3]Department of Gastroenterology, Fukushima Medical University School of Medicine, Japan
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Correspondence to Kentaro Sato, s-ken@fmu.ac.jp

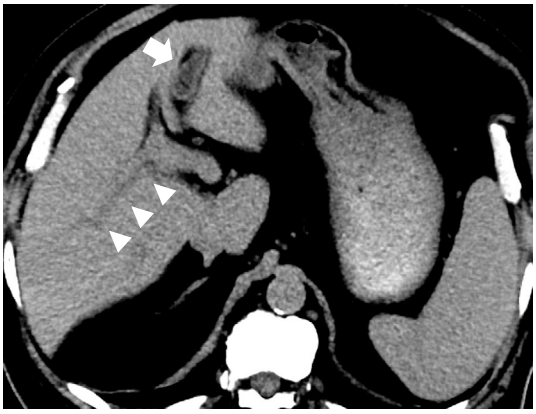
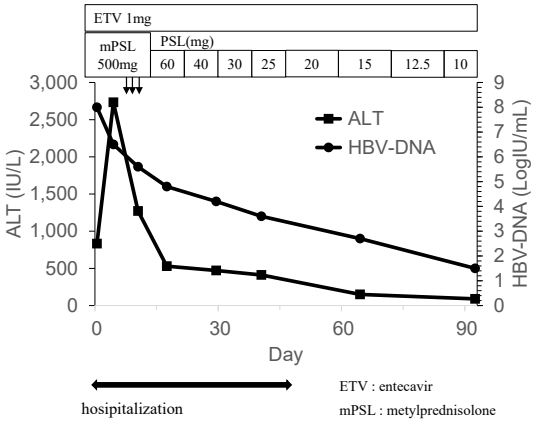


Figure 1. CT imaging at the time of admission in July 2020 revealed gallbladder wall thickening (white arrow), periportal collar sign (white arrowhead), and splenomegaly.



Progress chart after hospitalization in July 2020. Administration of entecavir was started on the day of admission and steroids was started at day8. After administration, liver damage improved and HBV-DNA decreased.

Figure 2. Progress chart after hospitalization in July 2020. Administration of entecavir was started on the day of admission and steroids was started at day8. After administration, liver damage improved and HBV-DNA decreased.

active.

His body temperature was 36.7 °C, and there was no abdominal tenderness. His laboratory data were as follows: white blood cell count (WBC), 5,100/μL; hemoglobin (Hb), 15.0 g/dL; platelet count (Plt), 14.2×10^4/μL; prothrombin time (PT), 69.5%; albumin (Alb), 3.8 g/dL; total bilirubin (T-Bil), 0.9 mg/dL; aspartate aminotransferase (AST), 696 U/L; alanine aminotransferase (ALT), 833 U/L; alkaline phosphatase (ALP), 75 U/L; γ-glutamyl transpeptidase (γ-GTP), 80 U/L; soluble interleukin-2 receptor (sIL-2R), 1,400 U/mL; HBs-Ag, 32,366 IU/mL; HBs-Ab, unmeasurable; hepatitis B e antigen (HBe-Ag), 1,470 S/CO; hepatitis B e antibody (HBe-Ab), 0.0 S/CO; HBc-Ab, unmeasurable; IgM-HBc-Ab, 0.86 S/CO; HBV-DNA, 8.0 LogIU/mL; IgM-hepatitis A antibody (HA-Ab), 0.13 S-CO; IgG, 873 mg/dL; IgA, 116 mg/dL; IgM, 177 mg/dL; IgG-cytomegalovirus antibody (CMV-Ab), >250 AU/mL; IgM-CMV-Ab, 2.21 AU/mL; Epstein-Barr virus viral capsid antigen (VCA)-IgG, 640; VCA-IgM, <10; Epstein-Barr virus nuclear antigen Ab, 40; anti-mitochondrial M2 Ab, 2.1 U/mL; antinuclear Ab (ANA), <80. Computed tomography (CT) imaging revealed gallbladder wall thickening, periportal collar sign, and splenomegaly (Fig. 1). The findings of acute hepatitis were thickening of the gallbladder wall and a periportal collar sign. Common bile duct dilation and stones was not detected.

On the same day of the hospitalization, he was started on entecavir 1 mg/day. However, his transaminase levels worsened (AST 1,882 U/L, ALT 2,771 U/L on day 8), so intravenous methylprednisolone therapy (500 mg/day) was administered for 3 days, followed by oral prednisolone (PSL) therapy (Fig. 2). We started oral PSL at 60 mg/day and gradually decreased the dose. After initiating treatment, the transaminase levels decreased. When the PSL dose was 20 mg/day, he was discharged from the hospital. We tapered the PSL therapy without any transaminase elevation.

The patient presented to our hospital with anorexia and a difficulty moving in December 2020. A laboratory analysis revealed an elevated inflammatory response, progression of anemia, thrombocytopenia, and decreased renal function (WBC 1.56×10^4/μL, Hb 10.6 g/dL, Plt 8.2×10^4/μL, and Cre 1.73 mg/dL). The HBs-Ag was negative, and the HBV-DNA was not elevated compared to the pre-hospital examination, although the transaminase level was elevated (HBV-DNA 1.7 LogIU/mL, AST 133 U/L, ALT 52 U/L). CT revealed that splenomegaly had worsened compared with 2020 July (Fig. 3A). In addition, the sIL-2R level had also worsened (sIL-2R 25,599 U/mL). We considered the possible onset of a blood disease, so a bone marrow biopsy was performed. B-cell malignant lymphoma was suspected based on a bone marrow aspiration fluid microscopic examination (Fig. 3B), so oral PSL therapy of 60 mg/day was started. Later, we diagnosed him with DLBCL, based on the flow cytometry results.

The patient then underwent three courses of pirarubicin (THP), cyclophosphamide (CPA), vincristine (VCR), and PSL (THP-COP) therapy, resulting in a decrease in the sIL-2R level (Fig. 4). At the same time, COVID-19 nosocomial infection appeared, and he became infected with the disease. We therefore suspended chemotherapy. Although antiviral drugs and steroids were started, his respiratory state worsened, and the sIL-2R level was elevated. He ultimately died of COVID-19 infection on day 104.

Discussion

We can take away two points from the present case. First, the HBV reactivation can happen more than 10 years after chemotherapy is concluded. Second, DLBCL can trigger the HBV reactivation.

Generally, HBV reactivation occurs within one year after chemotherapy or immunosuppressive therapy is completed. However, Seto et al. reported cases of HBV reactivation in HBs-Ag-negative and HBc-Ab-positive patients with lymphoma receiving rituximab-containing chemotherapy at a

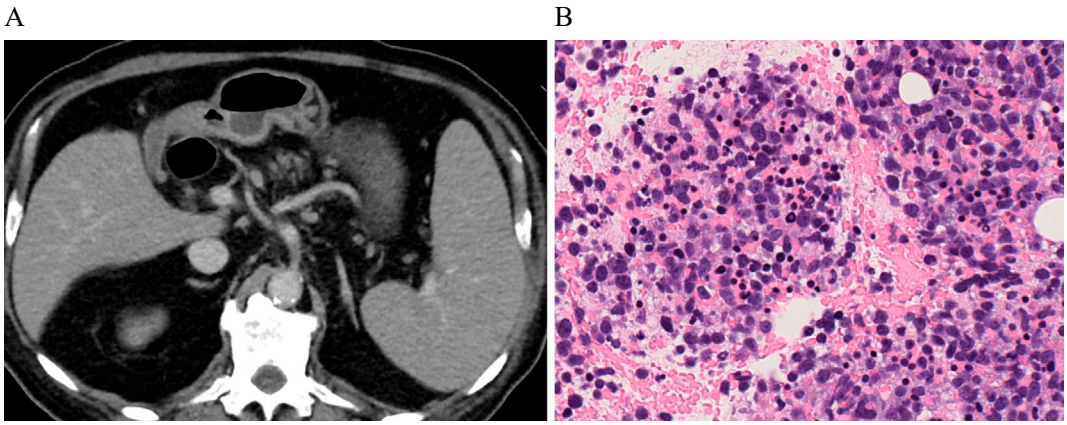
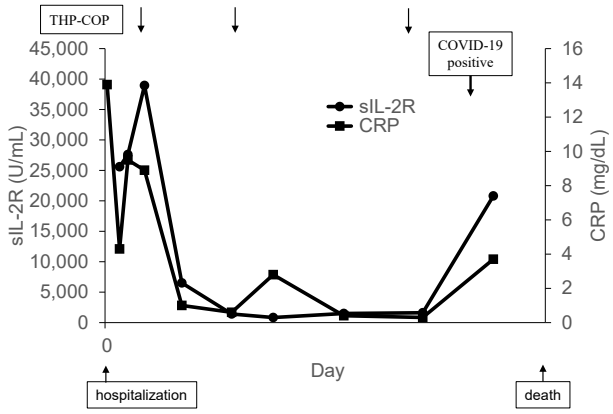


Figure 3. **A: CT imaging at the time of admission in December 2020 revealed that splenomegaly got worse than the imaging in July 2020. B: The bone marrow aspiration fluid microscopic examination revealed lymphocytes with swollen nuclei.**



Progress chart after hospitalization in December 2020. Chemotherapy for DLBCL reduced sIL-2R, but chemotherapy was discontinued due to COVID-19 infection. After that, he died on day104 due to the worsening of COVID-19.

Figure 4. **Progress chart after hospitalization in December 2020. Chemotherapy for DLBCL reduced sIL-2R, but chemotherapy was discontinued due to COVID-19 infection. After that, he died on day104 due to the worsening of COVID-19.**

median of 23 weeks, with a range of up to 100 weeks (4). Furthermore, there has been a case report of HBV reactivation occurring 55 months after rituximab-containing chemotherapy and autologous peripheral blood stem cell transplantation were completed (5). In addition, a case of HBV reactivation was reported 57 months after rituximab-containing and fludarabine-containing chemotherapy were completed (6). Why HBV reactivation occurred up to almost five years after chemotherapy had been completed was not mentioned in these reports. In our case, when HBV reactivation occurred in July 2020, the HBV-DNA was high (8.0 Log IU/mL), and IgM-HBc-Ab was negative (0.86 S/CO). The IgM-HBc-Ab levels of patients with acute infection have been shown to be significantly higher than those of patients with acute-on-chronic infection (7). For this reason, HBV reactivation was considered the most likely entity. Because the genotype of HBV was not measured, we cannot rule out the possibility of HBV of genotype A infection between chemotherapy in 2007 and the onset of hepatitis.

We considered the possibility that the immune function decreased due to the occurrence of DLBCL and HBV replication. After that, the immune function was rebuilt and caused HBV reactivation. Lymphoma cell growth that developed in a malignant neoplasm is highly dependent upon the ability to escape natural host defenses (8). IL-10 and TGF-β, which have potent immunosuppressive properties, are recruited to the lymphoma microenvironment. As an IL-10 functions, regulatory T cells (Tregs) are mobilized around a lymphoma (9). [This sentence means as follows. IL-10 is one of cytokines. Regulatory T cells migrate to around lymphoma cells guided by IL-10.] In addition, Ranjan et al. reported that Tregs were increased in the peripheral blood in patients with malignant lymphoma (7). Although Tregs serve to limit autoimmune responses, they are often hijacked by tumors to promote tolerance. The quantitative and functional imbalance of Tregs is related to persistent HBV infection and hepatitis development (10, 11). Elpek K.G et al. generated a lymphoma mouse model with depleted Tregs, and the mouse tumor-free survival was significantly prolonged compared with control mouse (12). Interestingly, this effect was not seen in depletion studies following the palpable tumor establishment, suggesting an integral role in early lymphoma development. Given these findings, fluctuation of the Treg function may exist in the tumor progression process. We believe that this fluctuation may be related to the host immune function, with HBV reactivation occurring as a result.

According to the acute and late onset liver failure case survey in Japan, there was a previously HBs-Ag-negative infected case that developed HBV reactivation without stimulants, such as chemotherapy or immunosuppressive therapy (13). In addition, Kamitsukasa et al. reported that HBV reactivation occurred in two elderly patients despite the absence of immunosuppressive therapy (14). Those authors mentioned that aging and surgical stress as well as disease complication associated with compromised immunity, such as cancer and arteriosclerosis, may trigger spontaneous HBV

reactivation. HBV reactivation may develop without obvious stimulation. These previously reported cases may have involved an unexplained HBV reactivation mechanism.

One reason why HBV reactivation occurs a long time after chemotherapy has been completed is reported the administration of statins and nonalcoholic steatohepatitis (NASH). Morii et al. reported a case of *de novo* hepatitis B associated with statin administered 64 months after allogenic hematopoietic stem cells transplantation (15). In addition to lowering cholesterol levels, statins exert pleiotropic effects, such as antioxidant effects, which improves the vascular endothelial cell function, anti-inflammatory effects, and immunosuppressive effects (16). As an immunosuppressive mechanisms, statins induced Treg differentiation (17, 18). This immunosuppressive effect may be related to HBV reactivation. In the present case, the patient had been taking statins for seven years before the HBV reactivation occurred. However, the relationship between statins and HBV reactivation may be weak. Hayashi et al. reported that HBV reactivation developed following statin administration to NASH patients at 44 months after rituximab-containing chemotherapy for DLBCL (19). Moderate or severe steatosis is associated with a high HBs -Ag seroclearance rate.[Because this article is a continuation of Hayashi et al.'s report, I would like to include it in the same paragraph.] Hepatocytes apoptosis might increase the viral clearance in patients with NAFLD. Statin administration decreased hepatocytes apoptosis in mice with NASH and improved the liver injury in patients with NASH (20, 21). Hayashi et al. suggested that the alleviation of hepatocytes apoptosis by statin administration might influence HBV reactivation via the viral clearance reduction induced by NASH. However, there were no findings of fatty liver on CT imaging at HBV reactivation in our case. In addition, whether or not there were histological NASH findings was unclear, as we did not perform a liver biopsy.

Although there was no evidence of DLBCL when the HBV reactivation occurred in the present case, early-onset malignant lymphoma may be asymptomatic. CT performed when HBV reactivation occurred in July 2020 revealed mild splenomegaly, and the laboratory data showed an elevated sIL-2R level (sIL-2R 1,400 U/mL). Tsujioka et al. reported that the median sIL-2R level in patients with B cell lymphoma was 1,220 U/mL (22). Based on this, DLBCL may have already developed when HBV reactivation occurred. In addition, DLBCL may be suppressed by PSL administration for HBV reactivation. We suspect that DLBCL worsened with gradual PSL reduction.

A history of CLL may affect DLBCL through a phenomenon known as the Richter's syndrome. Conversion to DLBCL in patients with CLL occurs at a rate of 0.5%-1.0% per year and 5%-16% in a patient's lifetime (23). Chemotherapy treatment for Richter's syndrome often does not work, and the median survival with chemotherapy is less than 10 months (24). Richter's syndrome was considered negative in this case because the chemotherapy response was relatively good.

In conclusion, the HBV reactivation can happen more than 10 years after chemotherapy has concluded, and DLBCL can trigger the HBV reactivation. Longer HBV follow-up may be needed after chemotherapy. When HBV reactivation occurs a long time after chemotherapy, we need consider the possibility of DLBCL onset.

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

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