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【 CASE REPORT 】

# Hepatitis B Virus Reactivation after Receiving Cancer Chemotherapy under Administration of Leuprorelin Acetate

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**Abstract:**
An 88-year-old man was admitted for elevated liver enzyme levels. Nine years earlier, the patient had been diagnosed with diffuse large B-cell lymphoma (DLBCL) and undergone rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, prednisone (R-CHOP) therapy. This patient previously had had a hepatitis B virus (HBV) infection before chemotherapy. After the chemotherapy, he was administered an luteinizing hormone-releasing hormone (LHRH) agonist for prostate cancer. We diagnosed him with HBV reactivation because of positive serum HBV-DNA. HBV reactivation can occur a long time after chemotherapy, particularly if another treatment with immunity-altering drugs is added. In such cases, additional surveillance may be required to detect HBV reactivation.

**Key words:** hepatitis B virus reactivation, R-CHOP, LH-RH agonist

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## Introduction

Hepatitis B virus reactivation (HBVr) is a serious complication, similar to hepatitis, and liver failure and even death can occur in patients undergoing immunosuppressive therapy and cytotoxic chemotherapy (1). HBV carriers (HBs-Ag-positive patients) are at a higher risk of reactivation during and after these treatments (1, 2) than resolved HBV patients (HBs-Ag negative, HBc-Ab positive and/or HBs-Ab positive), although the latter still need to be monitored carefully (3).

The rate of HBVr in resolved HBV patients has been reported to be 16.9%, and the seroreversion rate is 20-40%. HBVr can occur up to 12 months after the cessation of B-cell-depleting drugs (delayed beyond 12 months in a small number of cases), indicating the potency of the immunosuppressive effect of this drug class and the prolonged immune reconstitution phase (4). Performing HBV screening tests before chemotherapy is therefore important. However, there is no evidence that pre-emptive therapy helps HBV patients to avoid developing HBVr.

The details regarding how best to monitor and treat patients with resolved HBV are not unified and differ among the guidelines of the American Association for Study of Liver Diseases (AASLD), European Association for the Study of Liver (EASL), Asian Pacific Association for the Study of the Liver (APASL), and Japan Society of Hepatology (JSH) (5-9). However, every guideline recommends following and monitoring patients with resolved HBV who are receiving immunosuppressive therapy or chemotherapy, and the average monitoring period after such therapy is 1-2 years. Nevertheless, cases of HBVr beyond this monitoring period are sometimes encountered.

We herein report a case of HBVr in a patient with resolved HBV after receiving cancer chemotherapy under

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**Table 1. Laboratory Data on the Admission.**

| Variable | | Variable | |
|---|---|---|---|
| **White blood cells (/μL)** | 3,600 | **Total bilirubin (mg/dL)** | 1.8 |
| **Red blood cells ($10^4$/μL)** | 302 | **Direct bilirubin (mg/dL)** | 1.0 |
| **Hemoglobin (g/dL)** | 10.8 | **AST (U/L)** | 811 |
| **Hematocrit (%)** | 33.4 | **ALT (U/L)** | 493 |
| **Platelets ($10^4$/μL)** | 12.8 | **LDH (U/L)** | 819 |
| **Prothrombin time (%)** | 86 | **ALP (U/L)** | 550 |
| **PT-INR** | 1.07 | **GGT (U/L)** | 471 |
| **PT (%)** | 72 | **ChE (U/L)** | 117 |
| | | **IgG (mg/dL)** | 1,322 |
| **TP (g/dL)** | 6.8 | **ANA (FANA) (dil)** | <40 |
| **Albumin (g/dL)** | 3.6 | **HBsAg (IU/mL)** | 995.79 |
| **C-reactive protein (mg/dL)** | 0.2 | **HBscAb (COI)** | 0.01 |
| **BUN (mg/dL)** | 18 | **IgM-HBc (S/CO)** | 0.16 |
| **Creatinine (mg/dL)** | 1.0 | **HBV-DNA (log copies/mL) (log IU/mL)** | 6.2 (5.4) |
| **NH3 (μg/dL)** | <20 | **HBV genotype** | C |

PT: prothrombin time, BUN: blood urea nitrogen, AST: aspartate aminotransaminase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, GGT: gamma glutamyltranspeptidase, ChE: cholinesterase, ANA (FANA): anti-nuclear antibody (fluorescent ANA)

long-term administration of an luteinizing hormone-releasing hormone (LHRH) agonist.

## Case Report

An 88-year-old man was diagnosed with diffuse large B-cell lymphoma (DLBCL) stage IA according to the international prognostic index in September of Year X. His laboratory findings before chemotherapy showed negative results for HBs-Ag and HBV-DNA (<2.1 log copies/mL, not detected) and positive results for HBc-Ab, showing that this patient previously had had an HBV infection. Therefore, we started periodical monitoring of HBV DNA based on the management scheme in Japan. Eight courses of R-CHOP therapy were administered from November of Year X to March of Year X+1, and complete remission was induced until Year X+8.

After chemotherapy was completed, the serum prostate-specific antigen (PSA) level increased. He was diagnosed with prostate cancer in June of Year X+1; therefore, we started the ongoing administration of leuprorelin acetate (LHRH agonist). From the start of chemotherapy to February of Year X+3, his serum levels of HBV-DNA were measured periodically and found to be negative. In addition, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured continuously by the family doctor from X+3 years until X+8 years.

Seven years after the chemotherapy had been administered, this patient presented with increased levels of liver enzymes (AST, 811 IU/L, ALT, 493 IU/L). A further examination showed positive findings for HBs-Ag (995.79 IU/mL) and HBc-Ab (0.01 COI), HBV-DNA (6.2 log copies/mL; 5.4 log IU/mL) (Table 1). HBc-Ab was analyzed by an electrochemiluminescence immunoassay (ECLIA) and found to be positive (Cut off Index: COI≤1). He had no history of blood transfusions and was sexually inactive. We diagnosed him with HBVr.

Subsequently, treatment with entecavir 0.5 mg/day was started under hospitalization. After administration of entecavir for 1 month, the HBV-DNA decreased to 2.7 log IU/mL, and the values of other liver enzymes, prothrombin time (PT), and total bile improved (AST, 48 IU/L; ALT, 68 IU/L; T.Bil, 1.4 mg/dL; PT, 74.4%) (Figure). Therefore, he started outpatient visits after leaving the hospital. After 5 months of medication, he was in a good condition, with normal blood tests (AST, 17 IU/L; ALT, 9 IU/L; T.Bil, 0.7 mg/dL; PT, 85.9%) and negative HBV-DNA (HBV-DNA<2.1 log IU/mL). At present, he is continuing to take entecavir while leuprorelin acetate has been discontinued.

## Discussion

We identified important clinical issues from this case which suggested that “late” HBVr can occur in the patients with resolved HBV as well as in hematological patients. In the present case, we screened for and managed chronic HBV infection during and after 2 years of chemotherapy (R-CHOP), and HBVr occurred 7 years (84 months) after the completion of chemotherapy. We discontinued HBV-DNA monitoring 12 months after chemotherapy, which complied with the Japanese Society of Hypertension (JSH) guidelines.

There have only been eight cases (including the present case) of HBVr occurring after more than one year in a patient with resolved HBV and no prophylactic administration (10-14) (Table 2). As shown in Table 2, seven of eight late HBVr patients were treated with rituximab. According to the JSH, HBVr is classified into two types: 1) reactivation from the carrier state and 2) reactivation in a patient with resolved HBV infection (HBs-Ag negative, and anti-HBc antibody or anti-HBs antibody positive). In the second

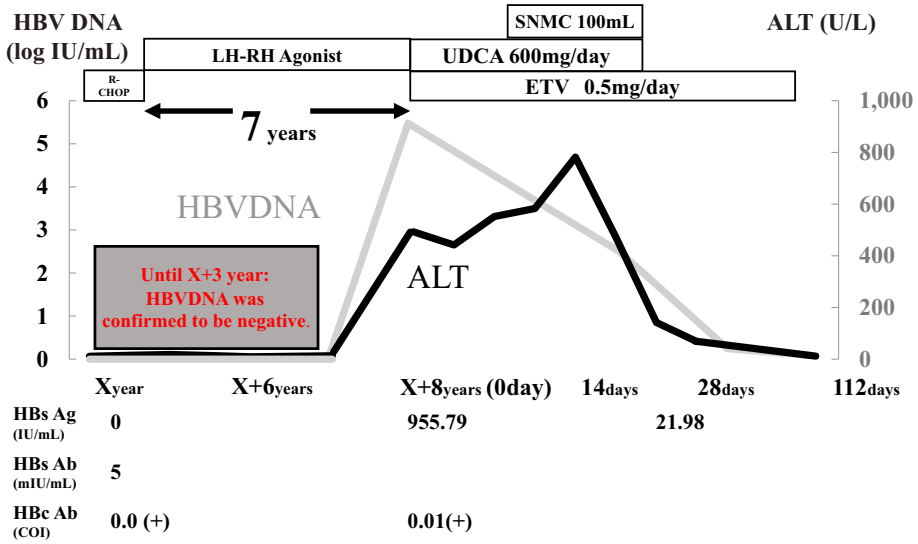


**Figure.** **The patient's clinical progress. Serum HBs-Ag and HBV-DNA were negative before chemotherapy. After chemotherapy, he started taking leuprorelin acetate (LHRH agonist) for prostate cancer. For two years after the start of chemotherapy, HBV-DNA remained undetected. However, seven years after the end of chemotherapy (R-CHOP), serum HBs-Ag and HBV-DNA became positive. After 112 days, the laboratory data improved, and HBV-DNA became negative.**

**Table 2.** **Presenting Clinical Features of 7 Cases of HBVr in Resolved HBV Patients and Our Patients.**

| No | Gender | Age | Disease | Treatment | Period to reactivation | Treatment of reactivation | Reference |
|---|---|---|---|---|---|---|---|
| 1 | ND | Elderly | DLBCL | R-CVP | 1 year | LAM | [10] |
| 2 | F | 68 | DLBCL | R-CVP | 72 weeks (1.4y) | ETV | [11] |
| 3 | F | 87 | MM | MP | 533 days (1.5y) | ETV | [12] |
| 4 | F | 84 | LPL | Rituximab | 80 weeks (1.5y) | ETV | [11] |
| 5 | F | 53 | DLBCL | R-CEOP | 100 weeks (1.9y) | ETV | [11] |
| 6 | M | 77 | DLBCL | R-CHOP | 33 months (2.8y) | ETV | [13] |
| 7 | M | 82 | DLBCL | R-CHOP | 41 months (3.4y) | ETV | [14] |
| **8** | **M** | **88** | **DLBCL** | **R-CHOP** | **2,555 days (7y)** | **ETV** | **Our Case** |

DLBCL: diffuse large B-cell lymphoma, LPL: lymphoplasmacytic lymphoma, MM: multiple myeloma, R-CVP: rituximab, cyclophosphamide, vincristine sulfate, prednisone, R-CEOP: rituximab, cyclophosphamide, vincristine, etoposide, prednisone, R-CHOP: rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, prednisone, ETV: entecavir

group, preventing hepatitis is extremely important (5). The JSH recommends that when immunosuppressive therapy or chemotherapy including powerful agents, such as rituximab (± corticosteroid) or corticosteroids, or immunosuppressant agents or molecular-targeted therapy with immunosuppressant or immunomodulator activity is administered, the HBV-DNA levels should be monitored monthly during treatment and for at least 12 months afterward. The HBV-DNA levels should be measured every one to three months, with the interval and duration tailored to the individual therapy regimen (5). A previous study reported that 12 months (4-20 weeks) had lapsed from the end of chemotherapy until the HBV-DNA elevation, and subsequently, hepatitis developed after 18.5 months (12-28 weeks) (15). Our patient developed hepatitis 84 weeks after chemotherapy was completed, which was longer than previously reported cases. This prompts the question of precisely how long and in whom should we continue measuring the viral load over the generally recommended duration.

Further information, such as the incidence and clinical characteristics of late HBVr, is lacking. According to a previous report, HBVr can occur in ≥20% of HBs-Ag-positive patients undergoing cytotoxic chemotherapy (16). In addition, late HBVr with rituximab-containing chemotherapy has been reported up to 170 days after the last dose of chemotherapy in up to 13% of cases (17). While this ratio is relatively low, we should not disregard late HBVr, as the risk of associated death is very high. AST/ALT should be monitored once every 1-3 months for ≥24 months after chemotherapy, and when the serum levels of AST/ALT seem to be elevated, we should also check for HBV-DNA as it can prevent severe hepatitis. In addition, the hormonal agent (LHRH agonist) may have been involved in HBVr in the present case. However, the details of the relationship be-

tween LHRH agonist and HBVr are unclear.

Previous reports have indicated that the lengthy administration of an LHRH agonist can lead to testosterone supression, the enhancement of immune cell expression in the thymus, and the promotion of cytokine production. (18-20), although this has only been reported in *in vitro* studies. The effect of LHRH agonist on cytokines, immune cell expression and testosterone might increase viral replication and viral protein expression on the surface of infected hepatocytes. The lengthy administration of LHRH agonist might increase viral replication and viral protein expression on the surface of infected hepatocytes, we believe that LHRH agonist may be involved in HBVr and hepatitis. The findings in our case might be associated with the treatment of an LHRH agonist. However, we did not perform any *in vitro* studies, because this is just a case report. The longterm administration of LHRH agonist might therefore trigger HBV reactivation, but this is just an assumption that we considered based on the findings of past studies. In this regard, we propose that physicians should take care when administering immunomodulators.

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

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