Anti-HBs-Positive Liver Failure Due to Hepatitis B Virus Reactivation Induced by Rituximab

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Abstract

A 59-year-old man developed acute hepatitis with reactivated hepatitis B virus (HBV) following administration of rituximab (anti-CD20 monoclonal antibody). The patient was diagnosed with malignant lymphoma in 1998, and virus marker testing indicated HBV surface antigen (HBsAg)-negative and anti-HBs antibody (anti-HBs)-positive results when chemotherapy including rituximab was started. Levels of aminotransferases were elevated, and HBsAg results turned positive. Despite therapy for late-onset hepatic failure, the patient died. Rituximab appears likely to have induced HBV reactivation in this case. Anti-viral agents should be administered for both HBsAg-positive and anti-HBs-positive patients who are scheduled to receive rituximab.

Key words: hepatitis B virus, reactivation, rituximab

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Introduction

Hepatitis B virus (HBV) is one of the most prevalent viral causes of hepatitis. Approximately 350 million people worldwide are living with chronic HBV infection (1). The majority of these cases are associated with alanine aminotransferase (ALT) levels within normal ranges, anti-HBV envelope (HBe) antibody-positive status and low viral load (inactive HBV carrier or asymptomatic HBV carrier with anti-HBe-positive status). Reactivation of HBV in such HBV carriers is infrequent, but frequently occurs during immunosuppressive therapy. HBV reactivation occurs in 14% of HBV surface antigen (HBsAg)-negative patients and in 70% of HBsAg-positive patients (2).

Reactivation of HBV in anti-HBs antibody (anti-HBs)-positive patients is extremely rare and has been described in very few reports (3-6). Herein we report a case of HBV reactivation induced by chemotherapy including rituximab in a patient who had been anti-HBs-positive. Administration of anti-viral agents appears warranted in patients undergoing treatment with rituximab.

Case Report

A 59-year-old man was admitted to our hospital with icteric symptoms. Malignant lymphoma was diagnosed in 1998 and was treated using chemotherapy. After chemotherapy, lymph nodes were reduced in size and remission was considered to have been achieved. The patient was defined as HBsAg-negative, anti-HBs-positive (×16 passive hemagglutination method), with anti-HBc antibody (anti-HBc) 99.8% in undiluted serum (not examined in ×200 diluted serum) in April 2000. Malignant lymphoma recurred in 2001 and aminotransferase levels were normal during chemotherapy (cyclophosphamide 6300 mg, vincristine 8 mg and mitoxantrone hydrochloride 60 mg intravenously, prednisolone 300 mg orally). In 2003, chemotherapy (irinotecan 740 mg, dexamethasone sodium phosphate 140 mg and vincristine 8 mg intravenously) was administered with no reduction lymph node swelling. In January 2004, chemotherapy was re-administered (dexamethasone sodium phosphate 100 mg and vincristine 10 mg intravenously, prednisolone 20 mg/day orally), then in April 2004 the regimen was changed.
Figure 1. Clinical course and HBV markers. State was HBsAg-negative, anti-HBs-positive (×16 passive hemagglutination method), anti-HBc 99.8% in undiluted serum (not examined in ×200 diluted serum) in April 2000. The patient was HBsAg- and anti-HBs-positive with elevation of amino-transferases in September 2004. Hepatic encephalopathy appeared from November 26 and the patient died in January 2005 from liver failure.

Table 1. Laboratory Data on Admission (etoposide 2400 mg intravenously, prednisolone 10 mg/day orally). In July 2004, the patient was treated with chemotherapy including rituximab, to prevent recurrence of malignant lymphoma (rituximab 3600 mg, etoposid 1400 mg and dexamethasone sodium phosphate 70 mg intravenously, prednisolone 15 mg/day orally). As of 2 months later, in September 2004, the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated, and the patient was transferred to our hospital in November 2004 (Fig. 1). He was icteric on admission, and laboratory data revealed: HBsAg-positive; anti-HBs-negative; HBV-DNA, 6.9 log copies/ml; anti-HBe-negative; HBe antigen-negative; HBV genotype C; core promoter mutation-positive; precore mutation-positive; total bilirubin, 26.4 mg/dl; ALT, 359 IU/l; prothrombin time, 35.8%; antinuclear antibody (ANA)-negative; CD19 cell, 0%; and CD 20 cell, 0% (Table 1). Lamivudine (100 mg/day) was administered from October 8 and steroid pulse therapy (methylprednisolone 5250 mg over 10 days) was started after admission. Levels of AST, ALT and HBV-DNA improved during therapy, but prothrombin time and total bilirubin levels did not improve. Hepatic encephalopathy appeared from November 26, so late-onset hepatic failure (LOHF) caused by HBV reactivation was diagnosed. Plasma exchange therapy with fresh frozen plasma and continuous hemodiafiltration (CHDF) were initiated to improve encephalopathy, but the patient died in January 2005 from liver failure. HBV-DNA levels were high during therapy. Autopsy revealed atrophic changes in the liver, which weighed 909 g. Histological examination identified multilobular necrosis (Fig. 2).

Discussion

The present report describes a case of HBV reactivation after immunosuppressive treatment including rituximab. HBV causes persistent infection in the human body, so reactivation can occur under immunosuppressive conditions. However, patients infected with HBV and displaying anti-HBs-positivity have been considered to display few copies of HBV, and HBV rarely reactivates under such circum-
stances. Some reports have discussed reactivation of HBV despite the presence of anti-HBs after solid-organ transplantation, bone marrow transplantation or during the clinical course of AIDS (7-9). Anti-cancer drugs like cyclophosphamide, vincristine and prednisolone can reactivate HBV in patients with leukemia, even under HBsAg-negative status (10). In addition to such drugs, immunosuppressive drugs used for organ transplantation and HIV or other immunosuppressive viruses can also reactivate HBV proliferation. Rituximab induces suppression of B cells, and has thus been used to treat malignant B-cell lymphoma. The characteristics of rituximab suggest that this agent could readily induce reactivation of persistent viral infections. Acute hepatitis occurring in an anti-HBs-positive patient receiving rituximab treatment was first reported in 2001 (3). A case in which the use of fludarabine likely contributed to HBV reactivation has also been reported (11). However, whether rituximab alone or the combination of rituximab with other anti-cancer drugs like VP-16 induced reactivation in the present case is unclear. The possibility of sexual transmission could be excluded. B-lymphocytopenia by rituximab appears to inhibit the production of virus-specific antibody, facilitating HBV reactivation (5). In the present case, the population of CD20\(^+\) cells remained at 0%, and serum immunoglobulin levels were low during the stay in our hospital. Before admission to our hospital, IgG level was 1047 mg/dl in November 2001, 1068 mg/dl in July 2003, and 479 mg/dl in November 2004 (normal range: 870-1700 mg/dl). Zinc sulfate turbidity test (ZTT) yielded results of 8.2 U in August 1998, 5.4 U in September 2001, 4.6 U in July 2004, 5.1 U in September 2003 and 1.6 U in August 2004 (normal range: 4-10 U). These data indicate impairments in the number and function of B cells at the time of HBV reactivation. Clinical course indicated that aminotransferase levels became elevated after rituximab administration, but no other chemotherapies had previously induced adverse effects. These findings support the contention that HBV reactivation was caused by rituximab. The possibility that the patient was in a carrier state of mutant HBV in the S region (escape mutant) could not be excluded. Anti-HBs was positive in this case, meaning that the possibility of an escape mutant was quite low, since anti-HBs can neutralize HBsAg from the S region of escape mutant HBV.

HBV is widely believed to be completely cleared during acute viral hepatitis. However, HBV can persist for decades after recovery from acute viral hepatitis (12). Another report has mentioned that HBV exists in the liver of healthy HBCAb-positive, but HBsAg-negative, anti-HBs-negative individuals, and HBV can reactivate after liver transplantation by immunosuppressive treatment (13). The present case patient was anti-HBs-positive, yet HBV was reactivated. In this case, anti-HBs turned negative during therapy with rituximab, then HBV was reactivated. When immunosuppressive drugs like rituximab are used even for anti-HBs-positive patients, care should be taken regarding the possibility of HBV reactivation, and the levels of anti-HBs must be monitored during therapy (14).

Rituximab has recently been expected to prove useful not only in treating malignant lymphoma, but also in collagen diseases (15, 16). HBsAg-negative and anti-HBs-positive status is usually considered to indicate that the patient has been infected with HBV previously, but is not currently a carrier of HBV. In such cases, rituximab is readily used, and the number of therapies using rituximab appears likely to in-

Figure 2. Autopsy specimen. Atrophic changes are apparent in the liver (909 g). Histopathological staining of the liver shows massive necrosis.
crease in the future. Using HB immunoglobulin while monitoring anti-HBs titer should provide good treatment. However, HB immunoglobulin is expensive and not particularly easy to use. Novel anti-viral drugs such as lamivudine and adeefovir are now available for HBV treatment. In patients undergoing immunosuppressive therapy, use of these kinds of anti-viral drug should be considered before treatment (17). As indicated by the present case, care is required when dealing with patients with HBV, even if anti-HBs-positive status is identified. In Japan, around 20% of HBV patients display anti-HBs-positive results. As HBV is readily reacti-

References


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