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Case Report
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HBV Reactivation in a Non-Hodgkin Lymphoma Patient with Resolved HBV Receiving Rituximab Maintenance Therapy

*Chen YT[1], Chang CH[2], Yeh HZ[2,3], Chang CS[2,4] and Yang SS[2,3]**

[1]Division of Gastroenterology & Hepatology, Feng Yuan Hospital of the Ministry of Health & Welfare, Taichung, Taiwan

[2]Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan

[3]Faculty of Medicine, National Yang-Ming University, Taipei, Taiwan

[4]Department of Medicine, Chung-Shan Medical University, Taichung, Taiwan

Abstract

Introduction: Rituximab induced hepatitis B virus (HBV) reactivation in both HBsAg-positive and HBsAg-negative chronic hepatitis B patients had been reported. Among these studies, most rituximab therapy was concomitant with chemotherapy including steroid. Whether rituximab maintenance monotherapy could induce HBV reactivation and resulting in serious complications is unknown.

Case Presentation and Conclusion: We report one patient who has negative hepatitis B surface antigen (HBsAg-negative) and positive antibodies to hepatitis B surface antigen (anti-HBs-positive) prior to rituximab-containing chemotherapies develops HBV reactivation followed by fulminant hepatic failure when he was undergoing rituximab maintenance therapy. Patients with resolved HBV, rituximab-based regimen induces reactivation of hepatitis B more frequent than other chemotherapy regimens, and those patients have a higher rate of mortality compared to HBsAg-positive cohorts in the mean while. Monitoring serum ALT level monthly with HBV serology check-up mainly HBsAg (and/or serum HBV DNA) every 3 months in those patients undergoing rituximab-based chemotherapy are highly recommended.

Keywords: Hbv Reactivation; Resolved Hbv; Rituximab; Lymphoma

Introduction

The chimeric monoclonal anti-CD20 antibody rituximab has been used to treat non-Hodgkin lymphoma (NHL) [1]. Recently, rituximab induced hepatitis B virus (HBV) reactivation in both HBsAg-positive and HBsAg-negative patients were reported [2]. Among these studies, most rituximab therapy was concomitant with chemotherapy including steroid. Whether rituximab maintenance monotherapy could induce HBV reactivation and resulting in serious complications is unknown. Here we report one patient who has negative hepatitis B surface antigen (HBsAg-negative) and positive antibodies to hepatitis B surface antigen (anti-HBs-positive) prior to rituximab-containing chemotherapies develops HBV reactivation followed by fulminant hepatic failure when he was undergoing rituximab maintenance therapy.

Case Presentation

This 57-year-old man presented with progressive enlargement of bilateral neck lymph nodes and B-cell chronic lymphocytic leukemia with small lymphocytic lymphoma was diagnosed by right neck lymph node biopsy. He received monthly R-CVP (rituximab, cyclophosphamide, vincristine, and prednisolone) for three courses followed by five courses monthly R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) treatment between September 2009 and February 2010. Serum HBsAg was negative and anti-HBs antibody was positive throughout this period.

Rituximab monotherapy was administered every twelve weeks as maintenance therapy from May 2010, and he developed acute jaundice (serum total bilirubin level = 8.1 mg/dL, normal upper

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Correspondence:
Yang SS, Division of Gastroenterology & Hepatology, Department of Internal Medicine, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sec. 4, Taichung, Taiwan, Fax: +886 4 23741331;
E-mail: yansh@vghtc.gov.tw

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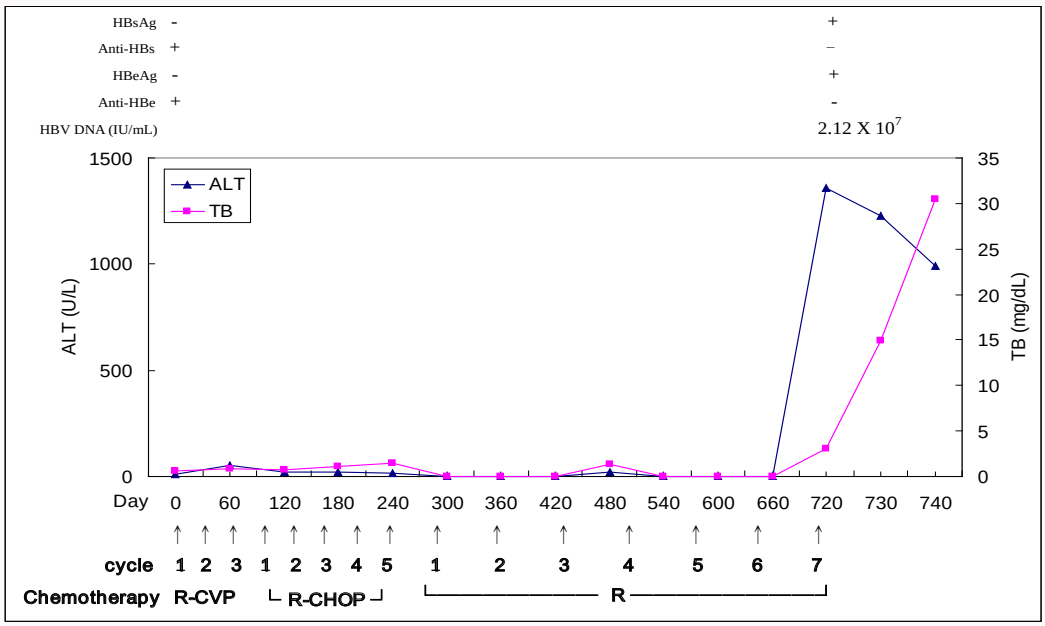

Figure 1: Serum alanine aminotransferase (ALT) and total bilirubin (TB) levels during and after rituximab-based chemotherapy. R-CVP = rituximab, cyclophosphamide, vincristine, and prednisolone; R-CHOP = rituximab, cyclophosphamide, doxorubicine, vincristine, and prednisolone; R= rituximab.

limit 1.2 mg/dL) and elevated aminotransferase levels (AST/ALT = 1330/1590 U/L, normal upper limit < 38/50 U/L) seventeen months later. HBsAg & HBeAg became positive and serum HBV DNA was greater than 2.12 X 10^7 IU/mL (above detection upper limit, real-time PCR, Taqman method, Roche Amplicor, US) in the meantime (Figure 1). Anti-HBV agents with entecavir 0.5 mg/day plus telbivudine 600 mg/day were administered immediately upon HBsAg positivity reporting; however, the liver enzymes increased gradually as well as jaundice and coagulopathy in the follow-up studies and he died of fulminant hepatic failure 20 days after commencing anti-HBV therapy.

Discussion

High prevalence of HBV reactivation and mortality rate of rituximab-based chemotherapy had been reported [3], including patients with positive hepatitis B surface antigen (HBsAg) and positive antibodies to hepatitis B surface antigen (anti-HBs). Rituximab-based chemotherapy (R-CVP and R-CHOP) had been reported to increase the rate of HBV reactivation in Non-Hodgkin lymphoma patients with prior resolved HBV status (HBsAg negative and antibody to hepatitis B core antigen [anti-HBc] positive ± antibody to hepatitis B surface antigen [anti-HBs] positive) [4].

The rate of HBV reactivation in resolved HBV patients would increase when anti-HBs titre < 100 IU/mL or two lines of chemotherapies were administered [5,6]. Mutation in pre-core/basal core promoter and genotype non-A (especially genotype B, C, D) had been reported to be associated with HBV reactivation [7,8], and rituximab plus steroid-containing regimen prone to induce more reactivation of HBV than other chemotherapy regimens [9].

Current HBV treatment guidelines recommend routine HBV serology test for high risk of HBV infection patients before the initiation of chemotherapy, and prophylactic anti-HBV agent should be administered to HBV carriers prior to starting chemotherapy and maintained for at least 3-6 months after cessation of chemotherapy [10].

HBsAg-negative patients (including occult and resolved HBV carriers) were relatively low risk for HBV reactivation when receiving conventional chemotherapy. Lok et al. [10] reported that HBV reactivation developed in only 2.7% (2 out of 72) of HBsAg-negative patients [11]. But Pei et al. [2] demonstrated a 22.1% (15 out of 95) HBV reactivation in HBsAg-negative patients who undergoing rituximab-based therapies.

The clinical course and prognosis of HBV reactivation were worse than those of acute hepatitis; 27% HBV reactivation group developed fulminant hepatitis, compared with 7% in the acute hepatitis B group [12] and in patients with fulminant hepatitis, the HBV reactivation group had a higher rate of mortality than the acute hepatitis B group (100% vs. 44%) [12].

According to recent AASLD practice guidelines, HBsAg and [IgG] anti-HBc test should be performed in patients who have high risk of HBV infection. Prophylactic antiviral therapy should be administered to hepatitis B carriers (regardless of baseline serum HBV DNA level) at the onset of cancer chemotherapy or a finite course of immunosuppressive therapy, and maintained for 6 months after cessation of chemo- or immunosuppressive therapies [10]. But there is no enough information regarding routine prophylaxis for patients who are HBsAg-negative but anti-HBc or anti-HBs-positive and in those with isolated anti-HBc-positive.

For HBsAg-negative patients, HBV reactivation happened not only in Non-Hodgkin lymphoma treatment but also in other cancers and autoimmune disease treatments. Mastsumoto et al. [13] reported that reactivation of HBV in patients with resolved HBV after receiving adalimumab treatment for rheumatoid arthritis.

No standard management to prevent HBV reactivation has been established for HBsAg-negative patients seropositive for anti-HBc and/or anti-HBs. According to Japanese guidelines, it is recommended that serum HBV DNA should be monitored monthly in anti-HBc or anti-HBs positive patients during and after chemotherapy for at least

1 year [14]. Because virus replication occurs one to two months before elevation of serum transaminases, prompt antiviral therapy without delay is suggested once HBV-DNA becomes detectable during follow up period.

In summary, patients with resolved HBV, rituximab plus steroid-containing regimen induces reactivation of hepatitis B more frequent than other chemotherapy regimens, and those patients have a higher rate of mortality compared to other cohorts in the meanwhile. Monitoring serum ALT level monthly with HBV serology check-up mainly HBsAg (and/or serum HBV DNA) every 3 months in resolved HBV patients undergoing rituximab-based chemotherapy are highly recommended.

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