Hepatitis B Virus Reactivation in a Surface Antigen-negative and Antibody-positive Patient after Rituximab Plus CHOP Chemotherapy

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Rituximab is a monoclonal antibody that targets B-lymphocytes, and it is widely used to treat non-Hodgkin's lymphoma. However, its use has been implicated in HBV reactivation that's related with the immunosuppressive effects of rituximab. Although the majority of reactivations occur in hepatitis B carriers, a few cases of reactivation have been reported in HBsAg negative patients. However, reactivation in an HBsAg negative/ HBsAb positive patient after rituximab treatment has never been reported in Korea. We present here an HBsAg-negative/HBsAb-positive 66-year-old female who displayed reactivation following rituximab plus CHOP chemotherapy for diffuse large B-cell lymphoma. While she was negative for HBsAg at diagnosis, her viral status was changed at the time of relapse as follows: HBsAg positive, HBsAb negative, HBeAg positive, HBeAb negative and an HBV DNA level of 1165 pg/ml. Our observation suggests that we should monitor for HBV reactivation during rituximab treatment when prior HBV infection or occult infection is suspected, and even in the HBsAg negative/HBsAb positive cases.

Key Words: Rituximab, Hepatitis B virus, Lymphoma

INTRODUCTION

It is well known that hepatitis B virus (HBV) reactivation can occur during chemotherapy or immunosuppressive therapy. Reactivation usually occurs in hepatitis B carriers who are positive for surface antigen (HBsAg), and this leads to variable manifestations from sub-clinical serum aminotransferase elevation to fatal fulminant hepatitis (1). Therefore, the current recommendations include lamivudine prophylaxis for HBsAg positive patients prior to chemotherapy (2). Since the introduction of rituximab, which is an anti-CD20 monoclonal antibody that targets the B-cells in non-Hodgkin’s lymphoma, it has been suggested that rituximab treatment might augment the risk of HBV reactivation compared to chemotherapy alone (3). Although the majority of reactivations associated with rituximab have been reported in hepatitis B carriers who are positive for HBsAg, a few cases have been reported in HBsAg negative, anti-hepatitis B surface antibody (HBsAb) positive patients (4-7).

Reactivations in HBsAg negative subjects might be associated with a minute presence of HBV DNA in the blood or liver in the absence of detectable serum HBsAg; this is designated as an occult infection (8). Because the prevalence of occult HBV infection is likely related to the incidence of HBV (9), the prevalence of occult infection in Korean people without HBsAg and normal serum ALT levels has been calculated to be as high as 16% (10). However, reactivation has never been reported in an HBsAg negative/HBsAb positive patient during rituximab treatment in Korea. We report here on a case of reactivation after rituximab plus CHOP chemotherapy in an HBsAg negative/HBsAb positive patient with diffuse large B-cell lymphoma.

CASE REPORT

A 66-year-old female who was diagnosed in July 2004 with diffuse large B-cell lymphoma, stage IIb (both tonsils were involved with bilateral cervical neck node enlargement) presented for treatment. She did not have any prior history of diseases such as diabetes, infection, hepatitis etc. The laboratory values on admission, including the complete blood cell counts and the renal function and liver function tests, were within the normal ranges. The results of the liver function tests and the tests for viral markers were as follows: aspartate aminotransferase (AST): 23 IU/L, alanine aminotransferase (ALT): 22 IU/L, total bilirubin: 0.8 mg/dl, HBsAg negative, HBsAb positive, HBeAg negative, HBeAb positive and anti-HCV negative. She was treated with combination chemotherapy of rituximab plus CHOP (rituximab 375 mg/m² IV on day 1, cyclophosphamide 750 mg/m² IV on day 1, adriamycin 50 mg/m² IV on day 1, vincristine 1.4 mg/m² IV on day 1 and...
Chemotherapy-related HBV reactivation is a serious problem for patients with malignant lymphoma as it may cause life-threatening complications such as fulminant hepatic failure. Therefore, prophylactic lamivudine administration has been strongly recommended for hepatitis B carriers who are positive for HBsAg. This anti-viral prophylaxis reduces the incidence of HBV reactivation and morbidity for patients receiving chemotherapy (11). However, there are no clear guidelines for patients with negative HBsAg, even though several cases of fulminant hepatic failure have been reported in HBsAg negative patients (5,6).

Since the first reported case of HBV reactivation in an HBsAg negative patient who was receiving rituximab [4], there have been several cases of reactivation observed in HBsAg negative, HBsAb positive patients (Table 1). All the cases were regarded as reactivation during or after rituximab-containing chemotherapy because of the evidence for prior HBV infection, such as HBeAb or anti-HBc IgG antibody. All these cases progressed to fulminant hepatic failure that led to death. It has been shown that HBV replication may persist after resolution of acute hepatitis B. Thus, PCR can detect HBV DNA in the blood or liver of patients with a resolved chronic HBV infection and sustained clearance of HBsAg from their serum.

### DISCUSSION

Chemotherapy-related HBV reactivation is a serious problem for patients with malignant lymphoma as it may cause life-threatening complications such as fulminant hepatic failure. Therefore, prophylactic lamivudine administration has been strongly recommended for hepatitis B carriers who are positive for HBsAg. This anti-viral prophylaxis reduces the incidence of HBV reactivation and morbidity for patients receiving chemotherapy (11). However, there are no clear guidelines for patients with negative HBsAg, even though several cases of fulminant hepatic failure have been reported in HBsAg negative patients (5,6).

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Table 1. Summary of the reported cases of HBV reactivation associated with the use of rituximab in surface antigen-negative patients

<table>
<thead>
<tr>
<th>Age/ gender</th>
<th>Primary disorder</th>
<th>HBV status prior to treatment</th>
<th>Treatment regimen</th>
<th>Onset of HBV reactivation</th>
<th>HBV reactivation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>53/male B-chronic lymphocytic leukemia</td>
<td>HBs Ag (−), Anti-HBs (+), Anti-HBe (+)</td>
<td>Rituximab 300 mg monthly</td>
<td>3 months later from the start of rituximab</td>
<td>HBs Ag (−), Anti-HBs (+), Anti-HBe (+) HBV DNA &gt; 200,000 copies/ml</td>
<td>Sarrecchia C, et al. 2005</td>
<td></td>
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<tr>
<td>59/male B-cell lymphoma</td>
<td>HBs Ag (−), Anti-HBs (+), Anti-HBe (+), HBe Ag (−), HBe Ab (−), HBV DNA: not done</td>
<td>Rituximab, etoposide, dexamethasone</td>
<td>2 months later from the start of treatment</td>
<td>HBs Ag (+), Anti-HBs (−), HBe Ag (−), HBe Ab (−), HBV DNA: 6.9 log copies/ml</td>
<td>Sera T, et al, 2006</td>
<td></td>
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<tr>
<td>54/male B-cell lymphoma</td>
<td>HBs Ag (−), Anti-HBe: not done, HBV DNA: not done</td>
<td>Rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone</td>
<td>7 months later from the start of treatment</td>
<td>HBs Ag (+), Anti-HBe Ab: low HBV DNA &gt; 7.7 log copies/ml</td>
<td>Yamagata M, et al. 2007</td>
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In this case, the positive anti-HBe findings could suggest a past exposure to HBV. Therefore, in endemic countries, anti-HBe may be more useful in HBsAg negative, HBsAb positive patients to evaluate for a history of immunization or past infection. This could help exclude the presence of occult infection and prevent reactivation during chemotherapy. If the HBcAb is positive, then testing for HBV DNA should be considered. The anti-HBs titer was relatively low (20 mUI/ml) in our case. This could suggest that the protective power of anti-HBs might have been weaker at the time of diagnosis in patients who are receiving chemotherapy.

In this case, we used rituximab plus CHOP, which is now the standard therapy for B-cell lymphoma. This regimen included rituximab and prednisone, and both increase the risk of HBV reactivation. Rituximab induces B cell suppression, leading to impairment of B-cell immunity. Therefore, rituximab may affect HBV immunity and result in viral replication. However, it is still controversial whether rituximab increases HBV replication via a specific glucocorticoid-response element in the HBV genome (15). Thus, when considering the adverse effects of rituximab plus CHOP and the high probability of long-term survival for patients with malignant lymphoma, adequately monitoring the status of HBV reactivation should be done not only for HBV carriers, but also for those patients who are HBsAg negative.

In conclusion, we report here on a case of reactivation after administering rituximab plus CHOP for treating diffuse large B-cell lymphoma in an HBsAg negative, HBsAb positive patient. We suggest that the status of HBV infection should be monitored during and after rituximab treatment, and especially when evidence of prior or occult infection is present, even though the patient shows to be negative for HBsAg and positive for HBsAb. Furthermore, immediate anti-viral treatment should be considered for patients with evidence of HBV reactivation.

REFERENCES