

Case Report

Hepatitis B Virus Reactivation in a Case With Non Hodgkin Lymphoma Treated by Rituximab Containing Regimen: Treatment With Dual Anti-Viral Combination

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Abstract

Rituximab is a chimeric monoclonal antibody targeting CD20 expressed on pre-B and mature B lymphocytes. This antibody has been used for a more than 20 years in cases with B cell non-Hodgkin lymphomas (B-NHL). The use of rituximab has some complications and one of the most important complications is Hepatitis B reactivation (HBV-R). HBV-R can lead to severe complications like hepatitis reactivation and death. Here we present a case with B-NHL developing HBV reactivation and successful treatment with combined anti-viral treatment.

Keywords: Hbv reactivation, rituximab, non-Hodgkin lymphoma

Cite This Article: Soysal RS, Paydas S. Hepatitis B Virus Reactivation in a Case With Non Hodgkin Lymphoma Treated by Rituximab Containing Regimen: Treatment With Dual Anti-Viral Combination. EJMA 2022;2(3):142–145.

Rituximab is a chimeric monoclonal antibody targeting CD20 expressed on pre-B and mature B lymphocytes. This antibody has been used for a more than 20 years in cases with B cell non-Hodgkin lymphomas (B-NHL) and also in cases with autoimmune disorders. Due to the widespread use of rituximab, extensive research has been done on its complications and one of the most important complications is Hepatitis B reactivation (HBV-R).^[1,2] HBV reactivation may occur in patients with chronic HBV infection (HBsAg-positive patients) and in patients with occult HBV infection (HBsAg-negative/anti-HBcpositive patients).^[3] HBV-R can lead to severe complications like hepatitis reactivation and death up to 7.9% and 1.7% of these patients, respectively.^[4] Here we reported a case with B-NHL developing HBV reactivation and successful treatment with combined anti-viral treatment.

Case Report

A 31 year old male patient applied to the general surgery department of our hospital with pain and palpable mass in the epigastric region in February 2019. Patient was diagnosed as NHL -Follicular lymphoma (FL), Stage IIIB disease. He had the history of HBV positivity since 2011 and has been followed up without treatment. Pre-treatment laboratory results: AST/ALT:43/61 U/L (normal upper limit < 41/40 U/L), INR:1,04, HbSAg: 6634 COI, Anti-HbS:2 U/L, HbEAg: 0,088 OCI (Negative), Anti HbC: 0,006 COI (Positive), Anti-HCV:0,041 COI (negative), Anti-Delta: negative, HBV-DNA:1300 IU/ml. R-CHOP chemotherapy regimen was planned. Tenofovir disoproxil fumarate (tenofovir DF) prophylaxis was started due to risk of HBV-R. He received 6 cycles of R-CHOP chemotherapy. The PET/CT showed complete remission on June 11, 2019. However, 10 days after

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Submitted Date: August 15, 2022 **Accepted Date:** August 15, 2022 **Available Online Date:** October 10, 2022

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the last chemotherapy, the patient admitted with widespread body pain, weakness, sore throat and jaundice. Laboratory tests; AST/ALT: 635/724 U/L, total bilirubin: 3,76 mg/DL (limit 1,2 mg/dl), PT/INR;20/1,73. HbsAg level was 4170 COI, HbEag was again negative. HBV DNA level increased to 170.000.000 IU/ml. Patient was questioned about the anti-viral prophylaxis, he mentioned irregular use of his antiviral prophylaxis. HBV-R was thought. His clinical condition was good, there was minimal hepatosplenomegaly. Hepatosteatosis was detected at abdominal ultrasonography. Liver enzyme levels increased in follow-up (AST/ALT:1003/1441 U/L). Entecavir was added to his anti-viral treatment. After entecavir treatment was initiated, the patient's HBV DNA and liver enzyme levels began to decrease (AST/ALT: 529/771 U/L) (Figs. 1, 2) and he was discharged and proposed frequent follow-up visits. Lastly he admitted to oncology outpatient clinic and his laboratory tests were within normal limits.

Discussion

The R-CHOP chemotherapy regimen is the gold standard for lymphoma treatment and HBV-R is important in cases with HbsAg positive and occult HBV infection. HBV screening is recommended for all patients before initiating treatment with chemotherapy especially rituximab.^[5] HbsAg-positive patients are considered to be at very high risk for HBV reactivation and, in the rituximab era, 59%– 80%

of these patients develop HBV reactivation after R-CHOP or rituximab containing regimens.^[6] Three mechanisms have been speculated to explain the etiology of the higher risk of HBV-R in patients with lymphoma than other solid tumors.^[7] First: lymphoma is a malignancy that originates from immune cells and lymphoma patients may have an intrinsic immune defect.^[8] Second: the treatment regimen for lymphoma contains steroids that can suppress T cell function and even directly stimulate HBV replication. Third: a higher rate of HbsAg positivity has been reported in lymphoma patients than in other cancer patients and HBV is speculated to be involved in B-cell lymphomagenesis.^[7,9]

Several anti-viral drugs are used to prevent HBV-R. Lamivudine (LMV) is first-generation nucleoside analog that can suppress HBV-R and improve hepatitis. However, there is a high incidence of acquired viral resistance to lamivudine, resulting in breakthrough hepatitis, especially in patients receiving long-term anti-viral prophylaxis with this drug. Lamivudine resistance was reported as 24% at 1 year and 50% at 5 years in patients with chronic HBV infection.^[10] Entecavir and tenofovir are new-generation nucleoside analogs that have greater potential to suppress HBV replication and there is a lower incidence of viral resistance mutation. The rate of antiviral resistance in previously untreated patients has been reported for entecavir in 1.2% of patients in 5 years.^[11] Reports of TDF resistance are difficult to find because TD resistance is rare.^[12] Although the current evidence regarding prevention of HBV reactivation is insufficient for a definitive recommendation, it would seem that entecavir or tenofovir is better option as a first-line anti-viral drug in view of the higher efficacy and less potential for resistance. LMV is considered in countries with limited resource.^[13] Two published cases of LMV-resistant strains in severe acute hepatitis B by a German group in 2008, reported primary LMV resistance and were salvaged successfully by switching to entecavir or to 'add-on' adefovir respectively.^[14] Reported in another case, a treatment-naive adult non-HIV patient with severe acute hepatitis B (AHB), who responded successfully to tenofovir following clinical failure to LMV monotherapy, suggesting LMV resistance. The importance of identifying the viral genotype and its resistance pattern at baseline prior to commencing treatment in order to guide the appropriate choice of antiviral should be emphasized.^[15] Combination therapies can be used in patients with poor response to treatment or refractory to treatment.^[16] Combination therapy reported successful treatment of HBV-R using combination therapy with entecavir plus tenofovir in an HSCT recipient.^[17] In another study of patients infected with HBV strains resistant to multiple antiviral drugs, regardless of their genotypic resistance profile, the combination of ETV/TD was shown to be an effec-

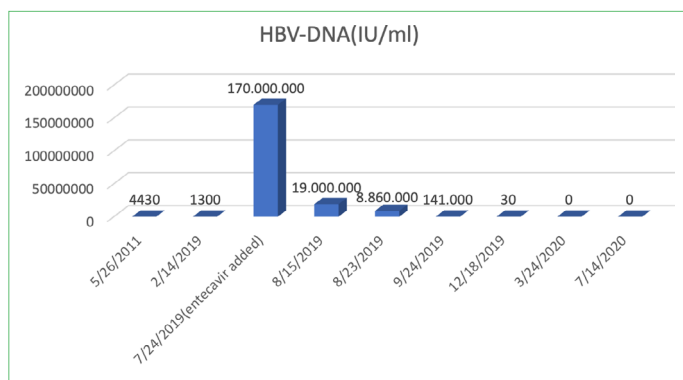


Figure 1. HBV DNA levels.

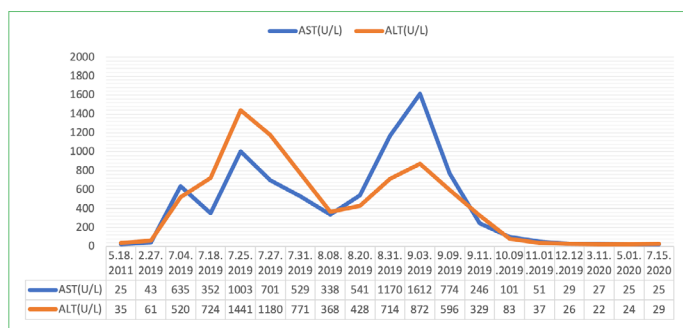


Figure 2. Liver enzyme levels.

tive and safe rescue therapy for chronic hepatitis B.^[18]

There is no clear consensus for the optimum treatment duration for antiviral prophylaxis. Anti-viral prophylaxis is to be stopped safely for HBsAg-positive patients according to the following criteria: 1-completion of planned immunosuppressive therapy, 2-undetectable HBV DNA levels by real-time PCR assay and 3-both conditions in 1 and 2 maintained at least for 1 year. More importantly, regular monitoring of HBV DNA until at least 6 months after cessation of anti-viral prophylaxis is desirable because HBV-R was observed within 6 months after cessation of anti-viral therapy. Anti-viral prophylaxis must be used before one week of chemotherapy until 12 months after discontinuation in HBsAg-positive patients and 18 months in cases treated with rituximab containing regimens. This may be applied to other drugs affecting B cell functions but the data is insufficient.^[6]

In conclusion, Hepatitis B surface antigen was positive in our patient before the treatment and TD was started prophylactically. However, the patient did not use his drug regularly and HBV-R developed. Entecavir was added to the patient's treatment and was treated with dual anti-virals. Liver function tests were within normal limits and HBV DNA was negative after five months of anti-viral therapy. There is no clear data in cases developing HBV-R in cases used anti-HBV prophylaxis and also stopping treatment while they are using prophylactic anti-viral treatment. We could not determine the viral genotype and resistance pattern in this case but used combination was found to be effective. Dual antiviral treatment in cases detected HBV-R in cases treated by rituximab.

Disclosures

Informed Consent: Written informed consent was obtained from the patients' family for the publication of the case report and the accompanying images.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.P.; Design – R.S.S., S.P.; Supervision – R.S.S., S.P.; Materials – R.S.S., S.P.; Data collection and/or processing – R.S.S., S.P.; Analysis and/or interpretation – R.S.S.; Literature search – R.S.S.; Writing – R.S.S., S.P.; Critical review – R.S.S., S.P.

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