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CASE REPORT

Late hepatitis B virus reactivation after lamivudine prophylaxis interruption in an anti-HBs-positive and anti-HBc-negative patient treated with rituximab-containing therapy

Laura Ceccarelli [a,*], Romina Salpini [b], Loredana Sarmati [a], Valentina Svicher [b], Ada Bertoli [b], Pasquale Sordillo [a], Alessandra Ricciardi [a], Carlo Federico Perno [b], Massimo Andreoni [a], Cesare Sarrecchia [a]

[a] *Infectious Disease Unit, Tor Vergata University Hospital, Rome, Italy*
[b] *Department of Experimental Medicine and Biochemical Sciences, Tor Vergata University, Rome, Italy*

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Summary We describe a case of an anti-HBs-positive patient who experienced hepatitis B reactivation 18 months after the discontinuation of rituximab and after 12 months of lamivudine prophylaxis. The patient carried a hepatitis B genotype D virus harbouring a single immune escape mutation, sT118K. No consensus guidelines regarding the optimal length of treatment or the best elective drug have been defined for antiviral prophylaxis for HBsAg-negative, anti-HBc- and/or anti-HBs-positive patients undergoing immunosuppressive treatment.

Screening based on HBV serological markers and HBV DNA testing is a critical issue to recognise hepatitis B reactivation as early as possible. Furthermore, it is of outstanding importance to identify alternative markers (e.g. cccDNA, HBV core related antigen, etc.), that could be predictive of HBV reactivation.

* Corresponding author. Infectious Disease Department, Tor Vergata University Hospital, Viale Oxford 81, 00133 Rome, Italy. Tel.: +39 0620902813; fax: +39 0620902811.
E-mail address: ceccadoc@yahoo.it (L. Ceccarelli).

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Background

Hepatitis B virus (HBV) persists in the liver even after successful immunological control of the infection indicated by HBsAg/anti-HBs seroconversion. This persistence is due to the ability of HBV to form covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes; this DNA form is the main template for the transcription of viral mRNAs. During immunosuppression, the presence of the cccDNA can cause the reactivation of HBV infection, defined by the reappearance of active necroinflammatory liver disease in inactive carriers or in patients with resolved hepatitis.[1]

Hepatitis B reactivation comprises two different stages: initially, the suppression of immune response determines the active replication of HBV with an increased serum level of HBV DNA. Subsequently, after the withdrawal of immunosuppression, the restoration of the immune system leads to a rapid destruction of infected hepatocytes. This process manifests clinically as hepatitis, liver failure or even death. The time interval between the peak of serum HBV DNA and the onset of clinical features of hepatitis B is variable, and the former could precede the latter even by 18 weeks.[2]

Hepatitis B reactivation is a widely recognised complication in HBsAg-positive patients undergoing immunosuppressive therapy. Less frequently, reactivation has been reported in HBsAg-negative patients, and this event is defined as reactivations of occult infection (OBI).[3,4]

There is strong recommendation to initiate prophylaxis with lamivudine in HBsAg-positive patients starting immunosuppressive therapy.[5]

Moreover, lamivudine prophylaxis is recommended for patients affected by haematological malignancies carrying at least one marker of past hepatitis B infection and are treated with immunosuppressive therapy or bone marrow transplantation.[6,7]

There is an increasing interest in the issue of hepatitis B reactivation in patients treated with monoclonal antibodies, such as anti-CD20, anti-CD52 and anti-TNF. Recent studies report the occurrence of reactivation 12—36 months after the last dose of these drugs has been administered. Rituximab treatment increases the risk of HBV reactivation, even in anti-S-positive patients.[8—10] Rituximab is a human-mouse chimeric monoclonal antibody that targets CD20 + B cells and has become essential for the treatment of B-cell non-Hodgkin lymphoma, alone or in combination with cytotoxic agents, such as fludarabine. Fludarabine has been reported to cause a specific depletion of STAT 1 protein which is essential for cell-mediated immunity and it is associated with prominent defects in the ability to control viral infections.[11]

We describe a case of an anti-HBs-positive patient who experienced hepatitis B reactivation 18 months after the discontinuation of rituximab and after 12 months of lamivudine prophylaxis.

Case report

We present the case of a 77-year old female who was admitted to Infectious Disease Clinic (Tor Vergata University-Hospital, Rome, Italy) with acute hepatitis syndrome in December 2010. Her past medical history was characterised by hypertension, ischaemic cardiomyopathy, scleroderma and psoriatic arthritis. In July 2007, she had a diagnosis of low-grade B-cell non-Hodgkin lymphoma and since July 2008, she has been treated with rituximab (375 mg/m^2) once weekly, for a total of 9 administrations. A pre-treatment virological screening showed that the patient was HBsAg-negative, anti-HBs-positive (21 mIU/ml) and anti-HBc-negative. The patient had not been vaccinated.

The qualitative PCR assay for HBV DNA performed in December 2008 was positive despite the presence of an adequate titre of anti-HBs antibodies (28 mIU/ml) (Table 1).

From January to June 2009, a second chemotherapy cycle with rituximab (375 mg/m^2) and fludarabine (20 mg/day) was administered. In January 2009, on the basis of HBV DNA positivity, lamivudine prophylaxis was started (100 mg/day) and continued for 12 months after the discontinuation of chemotherapy. At the beginning of June 2010, HBV DNA became negative, the anti-HBs titre increased up to 438 mIU/ml, and anti-core antibodies became, finally, positive, and thus lamivudine was stopped.

In August and in September 2010, two months after the discontinuation of prophylaxis, the serum HBV DNA levels were 94 IU/ml and 72 IU/ml, respectively. She was planned for a next visit in November, but she could be tested again only 1 month later when she was hospitalised.

In December 2010, the patient was admitted to the Infectious Disease Unit complaining of jaundice, tiredness, dark-coloured urine and pale stools. On admission, laboratory values of the liver function tests and the markers of viral hepatitis were as follows: aspartate aminotransferase (AST): 1998 IU/L, alanine aminotransferase (ALT): 2158 IU/L, total bilirubin: 7.16 mg/dl, direct bilirubin: 6.27 mg/dl, HBsAg-positive, anti-HBs negative, IgM and IgG anti-core positive, HBeAg positive, anti-HBe negative, anti-HDV and anti-HCV negative and past hepatitis A. The HBV DNA level was 230,000 IU/ml. The genotypic test documented subtype D and showed no reverse transcriptase (RT) mutations associated with drug resistance, confirming the full effectiveness of lamivudine. The genotypic analysis of the S region revealed the presence of a single mutation associated with immune escape, sT118K. A further genotype resistance test performed using a stored sample collected on August 2010, showed a superimposable genotypic profile in both RT and HBsAg, confirming the presence of sT118K.

Discussion

Occult hepatitis B reactivation is an emerging concern, especially in patients treated with monoclonal antibody-containing regimens. Recent studies suggest that antiviral prophylaxis should be provided to HBsAg-negative and anti-HBc- and/or anti-HBs-positive patients undergoing immunosuppressive treatment.[2,12]

It is currently recommended that lamivudine prophylaxis be initiated 2—3 weeks before starting the immunosuppressive therapy and be continued for at least 6—12 months after the end of the immunosuppressive therapy. To our knowledge, this case represents the most delayed HBV