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Case report

Late Hepatitis B reactivation after treatment with rituximab

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ABSTRACT

There is a large reservoir of individuals with past hepatitis B virus (HBV) infection that are in risk for HBV reactivation when immunosuppressed. On the setting of hematologic malignancy, the malignancy itself and currently used treatments, especially anti-CD20 agents, have risk of HBV reactivation. Antiviral prophylaxis is recommended by some international societies. We present a case of HBV reactivation more than 12 months after stopping rituximab containing treatment and 6 months of antiviral prophylaxis with entecavir, in a patient with HBV functional cure. The patient was restarted on antivirals and again obtain functional cure. The antiviral was stopped 1 year after seroconversion and the patient followed for another year without evidence of new reactivation. Most literature supports the use of antiviral prophylaxis in patients treated with rituximab. However, there are still conflicting indications and no consensus regarding the duration of prophylaxis. This clinical case and review of the literature supports a longer prophylaxis duration (more than 18 months after finishing rituximab treatments) instead of standard 12 months prophylaxis.

Introduction

There is a large reservoir of individuals with past HBV infection in whom hepatitis B surface antigen (HBsAg) clears from circulation [1]. In these individuals, although the virus is not active, complete sterilizing cure is not considered possible. That is due to the persistence of covalently closed circular DNA (cccDNA) in the nuclei of hepatocytes, which is a quite stable structurally and can persist in a latent state, serving as a reservoir for HBV reactivation [2–4]. Usually, in patients with past HBV infection (HBsAg-negative but hepatitis B core antibodies (anti-HBc) positive), reactivation consists of having detectable HBV DNA or reversion of HBsAg from negative to positive. When this happens, HBV becomes active again leading to adverse clinical consequences [3,5,6].

Active replication of the virus is controlled by both innate and adaptive immune responses, including HBV-specific T-cell responses and neutralizing antibodies produced by activated B cells. In the presence of immunosuppression, immune-mediated control of HBV replication is lost, and reactivation can occur [2,3]. On the setting of hematologic malignancy, the malignancy itself and the currently used treatments like chemotherapy and hematologic stem cell transplantation (HSCT), are associated with a risk of HBV reactivation [2,7–9]. Moreover, B-cell depleting biologics such as anti-CD20 agents are associated with even higher risk of HBV reactivation than more traditional cytotoxic chemotherapeutic agents. The role of rituximab in reactivation of both chronic and apparently resolved hepatitis B has been extensively documented, including some fatal cases. This risk is not always clearly quantifiable[8–11]. Testing for hepatitis B virus before chemotherapy and immunosuppressive treatments is a well-established practice and is recommended in current guidelines [4,5,10].

In patients considered at high risk for reactivation (more than 10% chance of HBV reactivation), both American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) recommend antiviral prophylaxis [3,4,6,10]. In selected patients, antiviral prophylaxis could be replaced by frequent (usually monthly) HBV-DNA monitoring and pre-emptive antiviral treatment in case of a positive result [6,8,10]. Due to their high efficacy and robust genetic barrier, the antiviral drugs recommended to HBV reactivation prophylaxis are entecavir, tenofovir diproxil fumarate and tenofovir alafenamide [2–4,6]. The optimal duration of prophylactic antiviral therapy and the monitoring strategy remains controversial [5,8].

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Case report

A 67 year-old male with chronic lymphocytic leukemia of B cells since 2009 and past HBV infection (HBsAg-negative, anti-HBc positive, anti-HBs and undetected HBV DNA) was diagnosed with Ritcher Syndrome in 2015 and proposed for chemotherapy with a rituximab containing protocol followed by hematopoietic progenitor cell autologous transplant. He was started on hepatitis B reactivation prophylaxis with entecavir in February 2016, before rituximab treatment. The last rituximab treatment was on May 11 2016, and the patient continued treatment with entecavir until November 2016, six months after finishing rituximab. However, due to misunderstanding of the recommendation to continue prophylaxis, he stopped treatment. No further immunosuppression therapy was prescribed.

On January 2017, 2 months after entecavir suspension, he maintained undetected HBV DNA and same HBV serology markers. Given that the prophylaxis had already been stopped, a preemptive strategy was assumed, and HBV DNA plus HBV serology markers were closely monitored. In September 2017, HBV reactivation was documented with HBsAg-negative but HBV DNA 1839 UI/mL. On the following month HBsAg was again detected on peripheral blood. No symptoms were associated with the HBV reactivation and no alteration on hepatic tests were detected on blood tests.

Antivirals were started again, first tenofovir, switched to entecavir after availability of resistance test. Undetected HBV DNA was again reached after 4 months of the new treatment. In October 2018, he presented again with loss of HBsAg and anti-HBs positive serology. Antiviral treatment was maintained until one year after new seroconversion. He was closely followed for one year after suspension of antivirals without new HBV reactivation.

Discussion

HBV reactivation in hematologic malignancy patients, especially in those who undergo rituximab containing treatments, is a well-recognized and preventable complication. Whether to use prophylaxis or preemptive therapy is still discussed and how long the prophylaxis when started is an ongoing debate for most immunosuppressing treatments [5]. However, current guidelines are in agreement on starting prophylaxis before rituximab containing regimens [4,6,10]. There is even some evidence that HBV screening and prophylaxis in these patients can be cost effective [7]. Based on this evidence and recommendations, our patient was started on entecavir.

The timing of HBV reactivation is highly variable and can occur at any time during or after immunosuppression, but the hepatitis and clinical manifestations related to reactivation typically occur after treatment has ended, when immune reconstitution takes place [2]. There has been reports of HBV reactivation from 2 weeks after starting rituximab treatment until more than one year after stopping it, including one recently publish case of a reactivation after 55 months of finishing rituximab treatment [5,12].

There is no consensus on current international guidelines regarding duration of antiviral prophylaxis. EASL guidelines recommends 18 months of antiviral prophylaxis after stopping Rituximab; European Society of Clinical Microbiology and Infectious Diseases Study Group for Infections in Compromised Hosts (ESGISH) consider 12–18 months of antiviral prophylaxis after stopping the drug; AASLD, American Gastroenterological Association (AGA) and American Society of Clinical Oncology (ASCO) maintain the antiviral prophylaxis for 6–12 months after finishing Rituximab [4,6,10,13,14]. Furthermore, lifelong prophylaxis has been proposed by some authors [5,8].

Although the patient failed to comply with the therapy and only kept the prophylaxis for 6 months after immunosuppressive treatment, reactivation occur more than 12 months after stopping rituximab. Even if complying with 12 months of treatment, the most common recommended duration on antiviral prophylaxis, the reactivation might occur. That lead the authors to ask if the recommendation of at least 18 months of antivirals after stopping treatment, is a safer approach to these patients.

Patients in high risk of HBV reactivation must be closely monitored, with frequent laboratory tests. The clinical manifestations of HBV reactivation vary from absence of symptoms to liver decompensation with symptomatic hepatitis, elevated aminotransferases, and liver failure with associated mortality [15]. Furthermore, even when lacking initial severity, hepatitis due to HBV reactivation may progress to chronic illness and associate with increased risk of late hepatic failure and hepatocellular cancer [1,2].

In the case reported, no symptoms were associated to the reactivation and no elevation of hepatic enzymes was detected so without a specific DNA HBV and HBV serology monitoring, the reactivation could be missed out.

Because of the unknown duration of risk, monitoring HBV reactivation should continue for another 6–12 months after the cessation of prophylactic antivirals. Serologic tests and HBV DNA should be tested every 3–6 months during prophylaxis and for at least 12 months after antivirals withdrawal as a large proportion of HBV reactivations develops after antiviral prophylaxis discontinuation [4,10,15]. That was also the strategy applied to the reported case. Another distinctive aspect of this case is that, even though the patient had HBV reactivation, after re-starting antiviral therapy he again regains control of the infection and seroconverted, obtaining a new functional cure.

Conclusion

Most literature supports the use of antiviral prophylaxis in patients treated with rituximab. However, there is still diverse indications regarding the duration of prophylaxis. This clinical case and review of the literature supports a longer prophylaxis duration (more than 18 months after finishing rituximab treatments) instead of standard 12 months prophylaxis. Further studies are needed to establish the optimal monitoring and prophylaxis in these patients.

CRediT authorship contribution statement

Sara Lacerda Pereira: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Raquel Duro**: Writing – review & editing. **António Sarmento**: Writing – review & editing, Supervision.

Consent for using clinical information

Written informed consent was obtained from the patient.

Authors contributions

Sara Lacerda Pereira conducted writing, research, and study revision. Raquel Duro was responsible for the conception of the paper and contributed to the writing and study revision. António Sarmento helped in revision and final approval of the draft manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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