Case Report
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Hepatitis B Virus Reactivation Under Treatment with Ibrutinib, A Known and Still Dangerous Entity: A Clinical Case Description

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ABSTRACT

During therapies for hematologic malignancies, hepatitis B virus (HBV) reactivation is a frequently reported event. Ibrutinib is a drug prescribed, since a few years, for the treatment of hematologic disease, which inhibit Bruton tyrosin kinase and is metabolized in the liver. Contrary to others molecules, there are no guidelines concerning antiviral systematic prophylaxis against HBV reactivation. Here, we describe a lethal case of hepatitis B reactivation in a patient under Ibrutinib treatment. The purpose of this case report is to emphasize the importance of strict monitoring of serological and molecular markers of hepatitis B in patients treated by Ibrutinib and to draw attention to the delicate interpretation of virological results with the risk of false negative HBsAg detection in the context of a high and brutal increase of the virus replication by hook-effect.

Keywords: *Hepatitis B Virus (HBV), Reactivation, Ibrutinib, Immunosuppressed Patient*

Introduction

During therapies for hematologic malignancies, such as Rituximab, hepatitis B virus (HBV) reactivation is a frequently reported event (Herishanu *et al*., 2017; Hammond *et al*., 2018; de Jésus Ngoma *et al*., 2015; Tsuruya *et al*., 2021; İskender and Ertek, 2020). Ibrutinib is a drug prescribed since a few years, for treatment of mantle cell lymphoma, chronic lymphocytic leukemia and Waldenstrom macroglobulinemia. This molecule inhibits Bruton tyrosine kinase, leading to interruption of B-cell receptor signal transduction. Ibrutinib is metabolized in the liver and cases of acute liver failure have been reported with this molecule (Kleijwegt *et al*., 2019). Risk of hepatitis B virus reactivation with Ibrutinib is also described in summary of product characteristics ("Imbruvica | European Medicines Agency," n.d.) among precautions for use, but only a few cases are reported on literature. It is recommended to determine Hepatitis B status before treatment initiation and patients with positive

serology, but HBsAg-negative, should be monitored by HBsAg and/or HBV DNA every 1-3 months during and after treatment to survey Hepatitis B reactivation. However, contrary to Rituximab (EASL, 2017), there are no guidelines concerning antiviral systematic prophylaxis against HBV reactivation for patients treated by Ibrutinib (Tedeschi *et al*., 2017; Pattullo, 2016). In this article, we describe a lethal case of hepatitis B reactivation in a patient under Ibrutinib treatment and highlight the dramatic risk of fulminant forms of this entity. Also, close monitoring of serological and molecular markers of hepatitis B are crucial to survey hepatitis B reactivation.

Case Report

The patient is a 71 years-old man, diagnosed with stage III lymphocytic lymphoma with clonal chronic lymphocytic leukemia in January 2019. Hepatitis B serology in March 2019 was compatible with past infection. It showed positive HBcAb and HBsAb (841 IU/L) and negative HBsAg (CMIA – Abbott/Architect). He was treated in first line with Bendamustine/Rituximab for 6 cycles from April to September 2019. In October 2020, Ibrutinib was started for lymphocytic lymphoma progression. Prior to Ibrutinib introduction, HBV DNA was controlled negative. Hepatic function was monitored monthly, but not HBV DNA nor HBV serology. On 23rd February 2021, transaminases levels (Alanine aminotransferase (ALAT) and Aspartate aminotransferase (ASAT)) suddenly increased to 20x normal and 18x normal respectively. On 1st March, a control showed hepatic failure with massive cytolysis. Transaminases were at very high levels (ALAT: 48x normal and ASAT: 61x normal), mixed icterus with total bilirubin at 142 μmol/L (normal: 5,0 – 21,0) and increased Prothrombine Time. Serologies were negatives for HCV, HIV, HEV IgM and HBV (HBsAg, HBsAb and HBcAb negative) (EIA – Beckman Access/DXI) and Epstein Barr Virus (EBV) serology showed past infection. Patient was admitted on 2nd March in intensive care. Clinical exam showed mucocutaneous jaundice without skin rash, patient reported dark-colored urine and no stools for one week. Biological check-up at patient admission showed aggravation of hepatic failure, with ALAT ad ASAT respectively at 58x normal and 100x normal, total bilirubin at 223 μmol/L (normal: 1 – 17). Serologies were negative for HAV, HCV, HIV, HEV, HTLV, CMV. Serologies showed past infections for VZV and HSV. Serology for HBV was discordant with the previous serology because it showed HBsAg positive, confirmed by seroneutralization, HBsAb and HBcAb IgG-IgM negative, HBeAg positive and HBeAb negative (CMIA – Abbott/Architect). Firstly, seroneutralization was not conclusive, serum needed to be diluted according to Abbott's recommendations. Levels of HBsAg were extremely high, quantification was not possible despite of dilution (HBsAg > 124925 UI/mL). HBV DNA in plasma was also very high, > 1, 000 000 000 UI/mL (TMA – Hologic/Panther). On 4th March, treatment with Entecavir was introduced. On 8th March, HBV was also detected on liver biopsy. Hepatic function deteriorated in a few days, leading to hepatic encephalopathy, multiple organ failure and death on 10th March. The

diagnosis timeline and virological markers detection are presented in the Fig. 1.

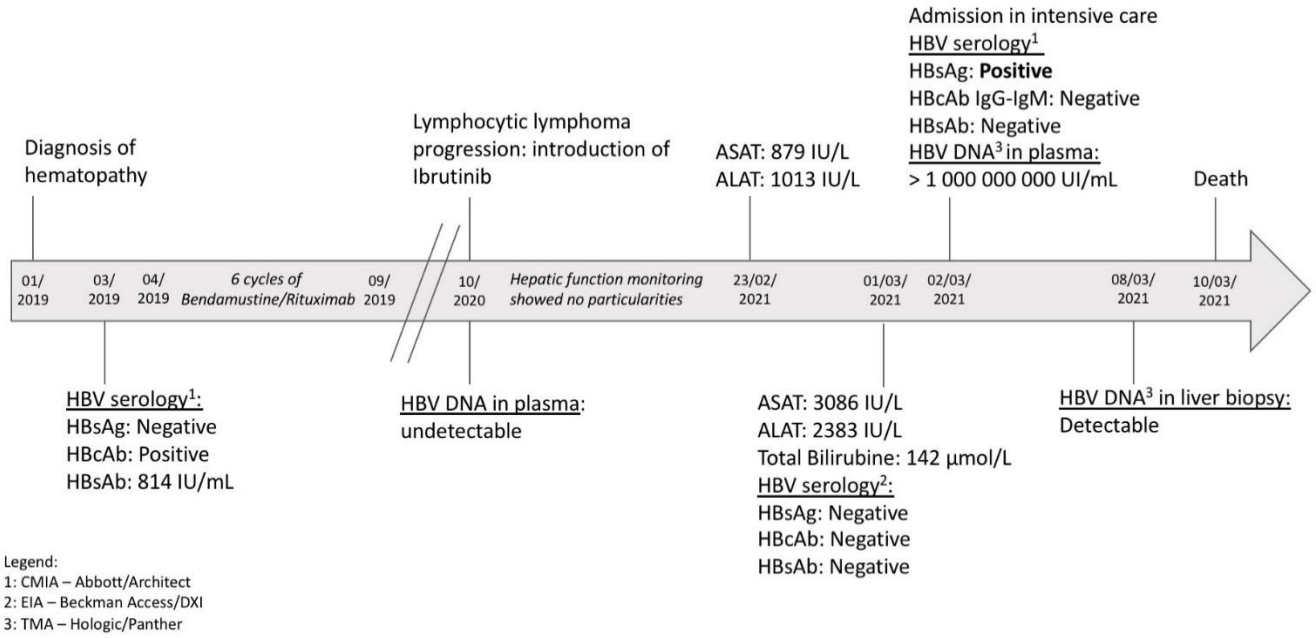

Figure 1: Diagnosis Timeline and Virological Markers Detection

Discussion

This case is the first description of fulminant hepatitis leading to death in patient with past hepatitis B infection, treated with Ibrutinib. Hepatic failure occurred only 4 months after Ibrutinib introduction. Several cases of hepatitis B virus reactivation are described in literature, delays varied from 5 to 42 months after starting treatment with ibrutinib (Herishanu *et al*., 2017; Hammond *et al*., 2018; Ngoma *et al*., 2015; Tsuruya *et al*., 2021; skender and Ertek, 2020). All patients recovered, most of them received antiviral treatment, with Entecavir or Tenofovir. Reactivation of hepatitis B is likely due to the profound inhibition of B cell activity as occurs with Rituximab (Smalls *et al*., 2019) which appears to lead to increased viral replication due to immune suppression, followed by immune recovery and acute liver injury. Some of reported cases described occult Hepatitis B reactivation with negative HBsAg (Innocenti *et al*., 2019; de Jésus Ngoma *et al*., 2015; Hammond *et al*., 2018). In our case, HBsAg was falsely negative, due to hook effect, which delayed appropriate care and hospitalization of the patient (Yang *et al*., 2020). Hook effect is the consequence of a saturated assay signal, due to very high concentration of HBsAg, leading to a false negative result. Serum dilution is the solution to eliminate hook effect. HBsAb and HBcAb were not detected, probably because there were no free Ab circulating due to high levels of Ag. The assay does not detect complexed forms (Ab-Ac).

Conclusions

This case highlights the dramatic risk of fulminant forms of Hepatitis B reactivation with Ibrutinib. There is a need to study the risk and the mechanism of theses reactivations and to define guidelines about patients monitoring. Clinical practice guidelines defined by European Association for the Study of the Liver (EASL) in 2017 recommends pre-emptive therapy for HBsAg-negative and HBcAb-positive patients in situations with moderate (<10%) or low (<1%) risk of HBV reactivation (EASL, 2017). This pre-emptive therapy consists in HBsAg and/or HBV DNA monitoring, every 1-3 months during and after immunosuppression, and starting antiviral treatment in case of reactivation. We conclude that these EASL guidelines should be considered during Ibrutinib treatment in patients with Hepatitis B prior history.

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