CASE REPORT

Hepatitis B reactivation in a patient with rheumatoid arthritis with antibodies to hepatitis B surface antigen treated with rituximab.

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Abstract:
Hepatitis B virus (HBV) can still be found within the hepatocytes after its clearance and the control of viral replication depends on the immune response. However during immunosuppression, seroconversion of HBsAg has been described followed by disease reactivation. Hepatitis B virus reactivation represents an emerging cause of liver disease in patients undergoing treatment with biologic agents and in particular, by the use of rituximab (anti-CD20) and alemtuzumab (anti-CD52) that cause profound and long-lasting immunosuppression. We describe a case of a 64-year old female patient with rheumatoid arthritis and resolved HBV infection, who experienced a severe hepatitis B reactivation after the administration of rituximab.

Keywords: HBV reactivation, rituximab, rheumatoid arthritis, monoclonal antibodies

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Introduction

Approximately 2 billion people have been infected with hepatitis B virus (HBV) worldwide, with more than 350 million having chronic hepatitis B. Chronic HBV carriers have a 15-40% lifetime risk of developing serious complications of chronic liver disease[1,2]. The prevalence of chronic hepatitis B (CHB) among patients with rheumatic diseases is not greater than expected based on data from the general population in the same geographic area[3].

The HBV infection triggers a reaction of the immune system of the host, developing antibodies (anti-HBs) and clearing the virus from the hepatocytes. Thus persons who become HBsAg-negative usually develop antibodies and can be considered to have resolved hepatitis B. However, a small proportion of these persons, is found to have detectable HBVDNA in serum, although the levels are low and observed only intermittently. This state has been referred as occult or latent hepatitis B and in this respect the disease may be reactivated by severe immunosuppression[4,5].

HBV reactivation represents an important medical issue in HBV-infected patients treated with rituximab. Thus the identification of high-risk patients with active, inactive or occult HBV infection and the use of prophylactic antiviral treatment is crucial[6]. However, other reports showed that a low HBV (2%) reactivation was observed in patients with HBsAg/antiHBc positive and with B-cell lymphoma, receiving rituximab-based combination chemotherapy without concomitant antiviral prophylaxis[7].

The developing hepatitis due to reactivation in many cases is quite severe, with a morbidity ranging from 5% to 40%[8,9].

One of the most potent immunosuppressive drugs is rituximab, a chimeric antibody targeting the CD-20 receptor of the mature normal and abnormal B-lymphocytes resulting to their destruction. This agent is being used in non-Hodgkin lymphoma, in chronic lymphocytic leukaemia and, since 2006, in rheumatoid arthritis. References regarding reactivation of hepatitis B using rituximab in hematologic patients is abundant, whereas in rheumatoid arthritis the experience is rather limited. In this paper, we present a case of HBV reactivation, in a patient with rheumatoid arthritis treated with rituximab.

Case report

A 64-year-old female patient with rheumatoid arthritis was transferred to the Liver Unit from the Clinical Immunology Unit of the Internal Medicine Department in March 2011, due to elevated aminotransferases and the appearance of positive HBsAg, 2 years after the initiation of treatment with rituximab and methotrexate. She was diagnosed with rheumatoid arthritis since 2000 and from 2000 to 2008 she was treated with different agents i.e.

Table 1: Progression of patient's parameters by time.

	01/2009 (#)	11/2010	2/2011	3/2011	4/2011	5/2011	6/2011	7/2011	8/2011	9/2011	11/2011	12/2011
AST (U/ml)		32		246	249	501	52	26	19	16	18	22
ALT (U/ml)		39	70	605	423	565	71	17	14	19	15	13
γGT (U/ml)		25		154	323	346	127	72	47	39	29	36
HBVDNA(*)		-		$1,1x10^8$		$4,62x10^4$						
HBsAg	-	-	+	+			-	-		-	-	
anti-HBs (**)	+	+	76,53	102,89			+	>1000		658	292	
HBeAg		-	+	+			+	-		-	-	
anti-HBe		-	-	-			-	-		-	+	
anti-HBc	+	+	+	+			+	+		+	+	
anti-HBc IgM				-								
anti-HCV				-								

(*): IU/ml, (**): mIU/ml, (#): Administration of rituximab (1/2009).

azathioprine, salopyrine, cyclosporine and leflunomide. Since January 2009 and for two consecutive years, her treatment had been modified to methotrexate (5 mg every Saturday and Sunday) and rituximab (2 doses of 1000 mg with 15 days interval from dose to dose, per session - such sessions were repeated every 6 months).

The patient was known to have a resolved hepatitis B. During these years, she was regularly screened for aminotransferases and hepatitis serological markers since she was receiving immunosuppressive drugs (Table 1). In February of 2011, there was an increase in ALT and a seroconversion of HBsAg(-) to HBsAg (+). A few days later (March 2011), there was a further increase of aminotransferases levels (AST 246 U/ml, ALT 605 U/ml) and HBsAg, anti-HBs, HBeAg and anti-HBc were positive with negative anti-HBe and core IgM. At her admission to our Unit, the patient was asymptomatic, the liver and spleen were impalpable and there were no signs of decompensation. During her hospitalization, she underwent liver biopsy, all drugs were withdrawn and she underwent antiviral therapy with 1 mg entecavir.

The HBVDNA levels were very high (> $1,1*10^8$ IU/ml) whereas HBcAb-IgM were negative. The liver biopsy, performed in May 2011, showed severe impairment of the liver architecture due to chronic hepatitis, with moderate degree of fibrosis and extensive steatosis. According to the biopsy report, this image was consistent with reactivation of hepatitis B and extensive use of hepatotoxic drugs. Until May of 2011 there was a gradual increase of aminotransferases and γGT levels (maximum recorded values - AST 501, ALT 565, γGT 346), but the HBVDNA levels were decreased more than 4 $\log_{10}$ ($4,62x10^4$ IU/ml). At that time, the patient was discharged from the hospital.

From June 2011 and onwards a rapid decrease of the aminotransferases and γGT levels was observed. HBsAg became negative, with unchanged HBeAg (positive) and anti-HBe (negative). In July, the aminotransferase levels were normal with slightly increased γGT (72 U/ml). HBeAg became negative and anti-HBs reached levels of > 1000mIU/ml. In November of 2011, the anti-HBe became positive. At that time point we recommended the patient to continue the antiviral therapy with entecavir for one more year. The patient was symptom-free from her rheumatoid arthritis without any treatment.

Discussion

Rituximab is a chimeric monoclonal antibody which binds to the CD-20 receptors of B-lymphocytes. Rituximab leads to transient but almost complete depletion of B cells in the blood and only partial depletion in the bone marrow and synovial tissue. Since the B-cells secrete cytokines and antibodies and act as antigen presenting cells, their destruction disrupts both the innate and adaptive immune response.

The current licensed indication of rituximab is in patients with rheumatoid arthritis who qualify for treatment with biological agents. Patients with rheumatoid arthritis on rituximab should be prescreened for Hepatitis B and C. Patients with negative HBsAg but positive for anti-HBc are allowed rituximab therapy if negative for HBVDNA. While cases of HBV reactivation are widely described in the oncology literature, only one case report of HBV reactivation in a patient with rheumatoid arthritis treated with rituximab has been reported[10].

In the reported clinical case, the patient with resolved hepatitis, who was treated with rituximab, developed a reactivation of HBV infection, with seroconversion of HBsAg, anti-HBc and positive HbeAg, high aminotransferaces levels and high viral load. Interestingly, anti-HBs remained positive and increased at levels over 1000mIU/ml after 6 months. Another significant finding was the extended damage of the liver consistent to chronic hepatitis, severe degree of fibrosis and steatosis probably due to the use of hepatotoxic drugs i.e. methotrexate and rituximab. Intervention by antiviral treatment immediately after the diagnosis of HBV reactivation and stopping biologic treatment resulted in the control of HBV infection within a few months with gradual decline of aminotransferases

to normal levels, HBVDNA levels decline and seroconversion to HBsAg(-), HBeAg(-), anti-HBe(+).

Occult hepatitis B reactivation is an emerging concern in patients treated with monoclonal – antibody containing regimens and a serious cause of liver-related morbidity and mortality[11]. Recent studies suggest that antiviral prophylaxis should be provided to HBsAg-negative and anti-HBc+ and /or anti-HBs-positive patients undergoing immunosuppressive treatment, if they are anti-HBs negative and if close monitoring of HBVDNA is not guaranteed[12]. However EASL clinical practice guidelines recommend that these patients should be followed carefully by means of ALT and HBVDNA testing and treated with nuclesos(t)ides upon confirmation of HBV reactivation before ALT elevation[13].

As the host immune response plays a pivotal role in controlling HBV infection, suppression of immune responses would increase viral replication. It is now known that the liver damage due to HBV reactivation is a 2-stage process. Initially during intense cytotoxic or immunosuppressive therapy there is a marked enhanced viral replication as reflected by increase in serum levels of HBVDNA, HBeAg and HBVDNA polymerase, resulting in widespread infection of hepatocytes. On the subsequent restoration of immune function due to withdrawal of cytotoxic or immunosuppressive therapy, there is a rapid immune-mediated destruction of HBV-infected hepatocytes, which is manifested clinically as hepatitis, hepatic failure and even death. Thus, as hepatitis due to HBV reactivation is preceded by enhanced HBV viral replication, a high prechemotherapy viral load is the most important risk factor for postchemotherapy HBV reactivation. In HBsAg-negative patients suspected to have HBV reactivation testing for HBVDNA should be performed more closely and antiviral treatment promptly needs to be added.

Conflict of interest

Authors declare no conflict of interest.

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