Reactivation of Hepatitis B Virus: Inactive Carriers and Occult Infection

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Abstract

In recent years the group of inactive carriers and that of occult hepatitis B virus infection could become a main concern due to their epidemiological and clinical significance. At present, our top priority consists of identifying, prophylaxis and monitoring of these patients undergoing immunosuppressive treatment. This report describes hepatitis B virus reactivation in the two patients in different stages of chronic infection and discusses some of the crucial questions of this preventable complication.

INTRODUCTION

The natural course of chronic hepatitis B can be divided into several stages which can be interchangeable dependent on the immune control of viral replication, but the hallmark of the disease remains the fact that hepatitis B virus (HBV) cannot be eradicated completely from the organism [1]. Between these stages, the so-called "low replication or residual phases" of infection, inactive carrier state (ICs) and occult HBV infection (OBI) are associated with the possibility of disease reactivation in the setting of immunosuppression; this reactivation increases both morbidity and mortality in these patients [2-5].

Here we describe HBV reactivation in two patients treated with immunosuppressive therapy for different reasons in different phases of HBV infection.

CASES PRESENTATION

Case 1

A 59-year old Caucasian woman presented to our department in May 2015, with painless jaundice that had lasted for several days.

Her medical history revealed she had been diagnosed with non-Hodgkin follicular lymphoma in 2012 and treated with 8 cycles of immunochemotherapy by R-CHOP protocol (R-rituximab), C-cyclophosphamide, H-doxorubicin, O-vincristine, P-prednisolone) until August 2013, followed by maintenance therapy with rituximab, until December 2014. Prior to initiating chemotherapy our patient had been screened for hepatitis using enzyme-linked immunosorbent assay (ELISA), testing positive for HBsAg, anti-HBc and anti-HBe, and at that time HBV DNA was undetectable by polymerase chain reaction (PCR) using the Cobas AmpliPrep/Cobas TaqMan assay (Roche Diagnostics, Switzerland), which has a dynamic range of linear quantification of 20 to 1.7 x 10⁸ IU/ml (1 IU/ml is equivalent to 5.8 copies/ml HBV DNA). The patient has received a prophylactic treatment with lamivudin, that she stopped after 16 months, in December 2014 when chemotherapy was finished, without consulting her doctor. Since then she did not take any medication. During the chemotherapy no abnormalities in liver function tests were noticed.

At admittance the patient was icteric, in tremor with meteoristic abdomen. Initial ultrasonography of abdomen revealed liver with hyperchogenic structure and a significant quantity of ascites in abdominal cavity. Her clinical state deteriorated very fast with encephalopathy developing. Laboratory tests that have been done during hospitalisation yielded the following peak values: ALT peaked at 5980 U/L, AST peaked at 2915 U/L and bilirubin peaked at 405 mol/l. Prothrombin time was prolonged to 0.24 and INR was 2.48. Albumin level decreased to 30.9 g/L. The patient's control tests were positive for HBsAg and anti-HBe, HBV DNA was 4.59 x 10⁷ IU/ml using the same assay mentioned. The patient died on 4.5.2015.

Histology of liver tissue obtained at autopsies showed severe steatosis with complete necrosis of liver parenchyma and necrotizing hepatitis. Replication of HBV was abolished from the tissue. At May 2015 the patient presented with jaundice of unknown cause. The laboratory tests revealed that HBV DNA was undetectable, with ALT > 1000 U/L and AST > 3000 U/L. Within one month lamivudin treatment was reintroduced immediately after admittance. After one month of lamivudin, hepatic function dramatically improved: the ALT values dropped to 147 U/L, AST dropped to 182 U/L and bilirubin dropped to 104 umol/l; PV recovered to 0.67 and INR to 1.2; albumin level increased to 72 g/L. The patient was discharged in a favorable clinical condition and was recommenced to continue with lamivudin treatment. On subsequent follow-up, 5 months later, the patient was doing well; HBsAg, anti-HBe and anti-HBs were positive, while HBV DNA was undetectable (Figure 1).

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Case 2

A 56-year-old Caucasian man was asked to come to our department in November 2012, after his wife was hospitalized for acute hepatitis B. The patient’s medical history revealed that he had been diagnosed with osteomyelofibrosis in December 1995; he had had a transplant of allogenic bone marrow (BMT) from his brother (HBsAg and HBsAg negative) in June 1996 and was treated with immunosuppressive therapy (cyclosporine and methylprednisolone) during the next 5 months. The patient was tested for hepatitis markers twice before transplantation, the second time in December 1995; both times he was positive for anti-HBs and anti-HBc, and negative for HBsAg and HBeAg. HBV DNA was not done during this period. Two months after transplantation, in August 1996, a transitory elevation of transaminases was noticed, with ALT peaked 990 IU/L and AST 185 IU/L. Hepatitis markers were unchanged from those done before; HBV DNA was not tested again.

On subsequent regular follow-ups by hematologists, during the 18 years after the transplantation, hepatitis markers were not tested and the patient’s serum samples were not stored, so retrospective analysis was not possible; routine blood analyses have shown only a persistent profound thrombocytopenia and leucocytopenia.

When he came for check-up in November 2012, he had no symptoms, had a slightly elevated ALT level, was positive for HBsAg and HBeAg, negative for anti-HBs and anti-HBc, and had HBV DNA of $> 1.70 \times 10^8$ IU/ml. The treatment with tenofovir was started in February 2013. On his last follow-ups in October 2015 and March 2016 HBV DNA was $4.48 \times 10^3$ IU/mL and $4.74 \times 10^3$, respectively, transaminases were within the normal range (Figure 2).

DISCUSSION

In recent years — when the burden of acute hepatitis B is decreasing due to the vaccination programme worldwide and the burden of chronic hepatitis B is increasing [6] — the subgroups of inactive HBV carriers and occult HBV infection (OBI) could become a main concern.

Inactive carrier state is defined as HBeAg seroconversion and development of anti-HBe in patients with HBsAg, normal ALT, with HBV DNA serum level < 2000 IU/ml and minimal or absent histological changes of hepatitis [7]. It is estimated that inactive carriers are the largest subgroup of HBV carriers.

The natural history of inactive carrier state is basically benign, with a low risk of HBV reactivation. One study with a mean follow-up of 5.8 years showed reactivation of hepatitis B following HBeAg seroconversion in 3.3% patients per year [8]. The risk of developing cirrhosis, HCC or liver-related mortality is thought to be very low [9], although one long-term study, with a mean follow-up of 13.1 years, showed that inactive carriers have a substantial risk of HCC and liver-related deaths when compared with non infected controls, particularly in olders and those with alcohol abuse history [5]. However, immunosuppression puts these patients in a very high risk of HBV reactivation, particularly in those receiving chemotherapy for haematological malignancies and stem cell transplantation [4]. This reactivation may significantly influence the patient’s prognosis and survival. It was shown that without prophylaxis patients with non-Hodgkin receiving corticosteroids had a very high risk of HBV reactivation and a high death rate [10]. Besides, one meta-analysis showed a fivefold increase rate of HBV reactivation in patients receiving rituximab [11].

In our patient with the criteria of inactive HBV carrier

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**Figure 1** Virological and biochemical dynamics of reactivation in a patient with inactive carrier state.
state, HBV reactivation ensued 6 months after the lamivudin prophylaxis was stopped with a very severe clinical form of the disease. Lamivudin was introduced timely but was not prolonged for 12 months after the chemotherapy cessation according to the EASL recommendation [7]. This case showed that although it is generally accepted that inactive carriers confer a favourable long-term prognosis, the patients receiving chemotherapy should be treated with antivirals timely and completely to escape progressive liver disease. Also, the follow-up of these patients should be much closer and more frequent, at least every 3-4 months in the first year after the treatment protocol is finished. Today, although there is no consensus about the optimal oral prophylaxis of HBV reactivation, a recent meta-analysis showed that tenofovir and entecavir may be the drugs of choice [12].

OBI is defined as the persistence of HBV DNA (detectable in the liver, or at a low level or undetectable in blood) in HBsAg-negative patients. As a consequence of the host’s strong immune response the viral replication of covalently closed circular DNA in the nuclei of hepatocytes is suppressed and therefore the viral load could be undetectable [13]. The prevalence of OBI varies from 0 to >90%, mainly depending of the different endemicity of HBV infection [14].

OBI has clinical importance in different patient’s populations: in HBV chronic carriers, in HBV or HIV co-infected patients, in hepatocellular carcinoma (HCC), in liver-transplanted recipients, in hemodialysis patients; the possibility of HBV reactivation in OBI is of particular importance in immunocompromised patients and those receiving chemotherapy, with the highest risk in those with hematopoietic stem cell transplantation [15].

In our patient with the criteria of seropositive OBI, HBV reactivation or reverse seroconversion was noticed after very long time from the immunosuppressive therapy. Shortly, after the transplantation during the immunosuppressive treatment a transitory transaminitis developed, which was attributed to a minor graft-versus-host reaction; after that he was asymptomatic and transaminases were within normal limits for almost 20 years, chronic active hepatitis was discovered accidentally. Reverse seroconversion following BMT is a rare event and the mean time to HBsAg appearance in described cases was 23 months [16].

Our case points out the fact that while antiviral prophylaxis of HBV reactivation in HBsAg positive patients undergoing immunosuppressive treatment is well established and recommended [7], this is not the case with OBI patients. Also, there is no clear recommendation for a regular monitoring after the treatment is finished. Therefore, the most acceptable approach at present seems to be the antiviral prophylaxis at least for those OBI patients at the highest risk of HBV reactivation, i.e. with malignant diseases, particularly hematological and the associated immunosuppressive treatment [4]. Our case also points out the fact that OBI may be involved in the transmission of infection, which is of importance not only in the case of blood donation or organ transplantation but in sexual contact — the principal mode of HBV transmission — too. Besides, as showed in our patient, OBI may contribute to the development of very severe liver disease [17,18].

In conclusion, when taking into account the epidemiologic and clinical implications of inactive and OBI carriers, it is obvious that screening, identifying, treatment, prophylaxis and monitoring strategy for HBV infection need as soon as possible a consensus statement for all patients undergoing immunosuppressive therapy.
REFERENCES


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