Hypogammaglobulinemia, a new risk factor for hepatitis B virus reactivation : about two cases.

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Abstract

Reactivation of the hepatitis B virus (HBV) with immunosuppressive status has been well established, mainly due to medications such as immunosuppressive therapy like cytotoxic chemotherapy, rituximab and biologic therapy, immunosuppression after solid and bone-marrow transplantation or long-term corticosteroids therapy. We report here two cases of HBV reactivation due to global hypogammaglobulinemia. Regular HBV serologic screening and PCR for HBV-DNA should be applied for each patient with primary immunosuppressive status and history of chronic HBV infection. The necessity of a preemptive treatment remains debated. (Acta gastroenterol. belg., **2023,** 86, **493-494**).

Keywords: Hepatitis B reactivation, immunosuppression, hypogammaglobulinemia, common variable immunodeficiency.

Introduction

Reactivation of the hepatitis B (HBV) virus with immunosuppressive status has been well established. This is mainly due to immunosuppressive therapy like cytotoxic chemotherapy, rituximab and biologic therapy, long-term corticosteroids therapy and due to immunosuppression after solid and bone-marrow transplantation (1,2). We report here two cases of HBV reactivation in the context of hypogammaglobulinemia.

Case reports

Case n°1:

In September 2015, a 78-year-old woman was admitted to our hepatology ward for asthenia, abdominal pain and jaundice. She was known for an unclear history of hepatitis B in 1958. In 2009, she was diagnosed with an autoimmune hemolytic anemia (AIHA) and a hypogammaglobulinemia. She was treated by glucocorticoids for three months. Splenectomy was performed in 2010 due to glucocorticoid-dependency. The pathological examination of the spleen did not show any hematological malignancy. In 2010, she was HBs antigen (HBsAg)-negative, anti-HBc- and anti-HBs- positive (73 UI/L), at that time her total IgG was 1,71 g/L (NV 7-16 g/L). Unfortunately, no HBV-DNA was performed at that time. On admission, her serology results showed a HBV reactivation: HBsAg positive, anti-HBc positive and anti-HBs negative. Physical examination revealed jaundice and pain in the right hypochondrium. She was treated by sotalol, furosemide, zolpidem, pantoprazole and aspirin. Laboratory tests showed : total bilirubin 28,4 mg/dL (23 x ULN); conjugated bilirubin 24,4 mg/dL (81 x ULN); aspartate aminotransferase 1256 U/L (34 x ULN); alanine aminotransferase 1428 U/L (40 x ULN); gamma glutamyl transpeptidase 120 U/L (3 x ULN); alkaline phosphatase 296 U/L (3 x ULN); LDH 657 U/L (2,5 x ULN); hemoglobin 9.9 g/dL (NV 12.2 – 15 g/dL); white blood cell count 10 670/µL (NV 4000 – 10 000/µL); platelet count 329 000/mm³ (NV 150 000 – 300 000/mm³); INR 1.40 (NV 0,8 – 1,2); renal function was normal. Immunoglobulins subclasses were as follows: IgA 0,27 g/L (NV 0,7 – 4 g/L), IgM < 0,2g/L (NV 0,4 – 2,3 g/L), IgG 1,2 g/L (NV 7 – 16 g/L). Abdominal ultrasound was normal. A transjugular liver biopsy with hepatic catheterism was performed and showed a porto-systemic gradient of 6 mmHg. Histology was compatible with a severe acute hepatitis of viral origin. The degree of fibrosis was low (Metavir F1). Immunolabelling was negative for HBs, but positive for HBc in a few hepatocytes. Serum PCR for HBV-DNA was highly positive (11620.52 x10³IU/mL).

All other causes of acute hepatitis were excluded. The patient denied any risk behavior for *de novo* HBV infection.

We concluded a diagnosis of severe acute hepatitis due to HBV reactivation in a context of hypogammaglobulinemia. We did not identify any other favoring factor (immunosuppressive medications, hematological malignancies, human immunodeficiency virus (HIV) co-infection and protein-losing enteropathies).

The patient was treated with tenofovir 245mg/day, with rapid clinical and biological improvement. In January 2018, she developed low grade lymphoma treated with rituximab. In March 2018, we observed loss of HBs Ag but no development of anti HBs antibodies and negative PCR for HBV-DNA. Tenofovir treatment was eventually stopped in October 2018. She currently remains negative for HBs Ag but retains a deep hypogammaglobulinemia.

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Case n°2:

In May 2022, a 74-year-old man followed in the hematology department for chronic lymphocytic leukemia (CLL), classified Binet A with associated hypogammaglobulinemia developed abnormal liver tests. He was known for a history of hepatitis B. In 2011, he was HBsAg negative and anti-HBc positive and IgG level was 5,71 g/L (NV 7-16 g/L). Immunoglobulin levels were normal in 2009.

His treatment consisted in tamsulosine and bilastine. During a routine blood test in May 2022, moderate hepatic cytolysis was detected for the first time: aspartate aminotransferase was 60 U/L (NV 19 – 48 U/L) and alanine aminotransferase was 88 U/L (NV 10 – 40 U/L). Total bilirubin, gamma glutamyl transpeptidase and alkaline phosphatase were normal. Immunoglobulins subclasses were as follows: IgA 0,34 g/L (NV 0,7 – 4 g/L), IgM 1,1 g/L (NV 0,4 – 2,3 g/L), IgG 4,9 g/L (NV 7 – 16 g/L). His serology results showed a HBV reactivation: HBsAg positive, anti-HBc positive and anti-HBs negative. Serum PCR for HBV-DNA was highly positive (226 902,508 x10³IU/mL). Unfortunately, no HBV-DNA was performed previously. All other causes of elevated liver function tests were excluded, and he denied any risk behavior for *de novo* HBV infection. Moreover, no other favoring factor of reactivation has been identified. A treatment with entecavir was then started.

Discussion

Although immunosuppressive therapies are the most important triggers in HBV reactivation, some medical conditions may also cause HBV reactivation. Cases of HBV reactivations after hepatitis C (HCV) eradication are increasingly reported in the new direct antiviral agents' era (3) , as well as cases of reactivations after local therapies of hepatocellular carcinoma including transarterial chemoembolization. HBV reactivation in HIV patients has also been described. In these cases, we observe a reverse seroconversion with loss of protective anti-HBs antibodies and HBs-Ag reappearance (4). Patients with a medical condition leading to an immunosuppressive status outside of immunosuppressive therapies should be given particular attention. In these patients, a screening of their HBV status should be carried out as well as a thorough investigation of their medical history.

In these two cases the loss of protective anti-HBs antibodies due to hypogammablobulinemia is probably the trigger of HBV recurrence. Interestingly, a case of HBV reactivation in a patient with hypogammaglobulinemia in the context of Good syndrome has recently been described and may support our hypothesis (5). In our first patient, hypogammaglobulinemia is chronic and affects all Ig subclasses. Common variable immunodeficiency (CVID) could be a diagnosis of exclusion in this patient. AIHA is one of the autoimmune disorders frequently associated with CVID. The patient developed an Epstein-Barr virus (EBV)-induced lymphoma three years later that was successfully treated with rituximab. Non-Hodgkin lymphomas occur at a markedly increased rate among patients with common variable immunodeficiency. Our second patient had a hypogammaglobulinemia associated with a chronic lymphocytic leukemia that was under surveillance. Both cases showed CD4 T-cells in the normal ranges and normal CD4/CD8 ratio compared to the previously published patient with Good syndrome.

The risk of HBV recurrence varies according to serological and virologic profiles, the underlying disease and the duration and type of immunosuppressive treatment or condition. The monitoring of HBV reactivation and the start of oral antiviral prophylaxis are decided according to the reactivation risk profile (6). Unfortunately, in our patients, we had no data on HBsAg evaluation by ultra-sensitive methods nor HBV-DNA evaluation prior to the diagnosis of reactivation.

In the light of these two clinical cases, a regular HBs-Ag screening and PCR for HBV-DNA should be applied for each patient with immunosuppressive condition and a history of chronic HBV infection. In the case of primary immunosuppression not linked to a drug, the necessity of a prophylactic treatment is still debated and should be discussed on a case-by-case basis.

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Authors contributions

Dr. Florence de Leuze and Prof. Geraldine Dahlqvist contributed equally to the writing of this paper. All the authors contributed to the diagnosis and the management of the patients. All authors approved the final draft.

Disclosure of interest

The authors declare that they have no competing interest.

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