Title: Reactivation of a Hepatitis B without core antibody: a case report.

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Abstract

We present the case of a male patient not vaccinated to HBV and with reactivity to surface antibody that after immunosuppression for a multiple myeloma, had HBV reactivation. Pharmacological HBV suppression was tried but viraemia could not be supressed. Production/detection core mutations or immunity issues can explain this clinical phenomenon.

Keywords: hepatitis B virus, occult hepatitis B infection, multiple myeloma.
Case Report

A 57 years old Caucasian man presented to our viral hepatitis outpatient clinic due to a positive polymerase chain reaction (PCR) for hepatitis B virus (HBV).

There was no relevant previous history, except alcohol and tobacco abuse. He was not vaccinated for HBV. In March 2006 he began very severe low back pain and a lumbar column plasmacytoma was diagnosed. Before starting chemotherapy, his blood analyses showed that he was serologically non-reactive for HIV-1/2 (Prism HIV Ag/Ab Combo®, Abbott) and HCV (Prism HCV®, Abbott). The HBV markers showed non-reactive for HBsAg and HbcAb (0.6 S/CO; laboratory cut-off 0.9 S/CO) and reactive for surface antibody (HBsAb; 28.5 UI/L), using chemiluminescent methods (Prism HBsAg® and Prism HBcore®, Abbott; Architect Anti-HBs®, Abbott). For the plasmacytoma he was treated with thalidomide 200mg plus dexamethasone 40mg (6 months) and local radiotherapy (10 sessions, total radiation dose 30 Gy). Despite the treatment, his plasmacytoma progressed and in 2007 a multiple myeloma IgG/lambda was diagnosed. The Durie Salmon staging was IIIA. In 2007 he had a collection of peripheral blood progenitor cells and a tandem autologous hematopoietic stem cells transplant.

Before the transplantation, according to the Portuguese law, nucleic acid tests were performed. We simultaneously screened for HBV DNA, HCV RNA and HIV-1/2 RNA, in minipool (multiplex nucleic acid test, COBAS® TaqScreen MPX Test, version 2.0, Roche) and the result was negative. After the transplant, he was on maintenance treatment with thalidomide 50 mg daily. He was well until December 2010 when he complained about pain in the left pelvis. The computerized tomography scan showed a large lytic lesion in the body of the left iliac bone. He was treated with bortezomib 1mg and dexamethasone 40mg (4 treatment cycles) and local radiotherapy (12 sessions, total...
radiation 3Gy). An autologous hematopoietic stem cells transplant was tried, but the mobilization was not effective. After that treatment, he was again on maintenance treatment with thalidomide 50mg daily. At the beginning of 2013, an increasing in the monoclonal peak was documented and he started again bortezomib 1mg and dexamethasone 40mg (5 treatment cycles). On March 2013, peripheral blood was collected to perform a second autologous transplant. However, the multiplex nucleic acid test was positive. The HIV and HCV serological tests remained non-reactive. The HBV analysis showed: HBsAg reactive, HBcAb non-reactive, HBsAb negative (0.64 IU/L), PCR HBV 40258300 IU/L, 7.60 log (COBAS® Ampliprep/COBAS TaqMan HBV Test, version 2.0, Roche), e antigen (HBeAg) reactive and e antibody (HBeAb) non-reactive (Architect HBeAg and Anti-HBe®, Abbott). The HBV genome sequencing (HBV Sequencing®, Abbott), showed a HBV genotype A and the following substitutions: N122H, M129L, T150I, W153Q, V163I, I253V, H271N, V278I (RT domain); P142LS, G145R, S207N, I213T (SHB protein); 142S, 145R (escape). The HBV resistance predicted by geno2pheno® showed susceptibility to all drugs available in the test. There was no hepatic cytolysis or signs of hepatic insufficiency. The autologous transplant was cancelled and he was referred to our viral hepatitis consultation. Between the diagnosis of the plasmacytoma (March 2006) and the diagnosis of the hepatitis B (March 2013), the patient received only eleven platelet concentrates transfusions. He didn’t receive any other blood or blood product. Suppression of the HBV was needed to perform the hematopoietic stem cells transplant. We immediately began entecavir 0.5mg (Baraclude®, Bristol-Myers Squibb) once daily. After one month of therapy, there was a 2 log decrease in viral load (189051 IU/L, 5.27 log). Three months after therapy initiation, two more log decreased
(1471 IU/L, 3.16 log). However, as HBV suppression has not been reached, the entecavir dose was increased to 1mg. In the next four months, there was no additional decrease in the HBV viral load. Therefore, we added tenofovir disoproxil fumarate (TDF) 245 mg (Viread ®, Gilead) to the entecavir 1mg. At the time we associated the two drugs, the multiple myeloma started to progress and he began to have thoracic and low back pain, nausea and malaise. He stopped TDF due to the difficulty of distinguishing tenofovir adverse effects from multiple myeloma progression. He was maintained on entecavir. During the treatment, there was no HBe or HBs seroconversion. The patient died due to progression of the multiple myeloma.

The serologic markers of this patient revealed a possible prior vaccination with protective titer (only presence of HBsAb). However, in certain patients after several years of contact with the virus and cure of the infection, the HBCaAb titre decreases and cannot be detected. Because of the multiple myeloma, immunosuppressors were started. Unfortunately, as we did not have detectable HBCaAb and he only showed reactivity for HBsAb, antiviral treatment was not started. Actually, even in patients with HBCaAb and HBsAb positivity, antivirals like lamivudine, entecavir or TDF should be started before the beginning of immunosuppression to prevent the reactivation of HBV (that is stored in the liver as cccDNA) (1). This patient was immunosuppressed with multiple drugs: thalidomide, dexamethasone and bortezomib. As a consequence of this severe immunosuppression, there was a loss of protective immunity, the HBV re-emerged and he had a “flare” of his hepatitis B.
We believe that the probability of a hepatitis B transmission by a transfusion is null or very low. The residual infectious risk of our blood bank is very low: 1.9 per million donations for hepatitis B (2). In addition to this, we retrospectively reviewed all the donors of these platelets concentrates: none is involved in a look-back process, none has converted to hepatitis B and none is involved in a case of hepatitis B seroconversion on the receptors of the donations.

When we evaluated the patient for the first time, the patient was in the “immune tolerant” phase - HBeAg positivity, high levels of serum HBV DNA and normal levels of aminotransferases (1). Some authors recommend lamivudine in cases of immunosuppression therapy when therapy is for a limited period. We started the therapy with entecavir 0.5mg (the preconized dose when there are no resistance mutations). However, the virus suppression was not possible, even with increased doses.

The analysis of the genome substitutions by geno2pheno® did not show any drug resistance.

The HBV virus is the most variable virus among the DNA viruses. However, mutations that are clinically relevant arise slowly. Some of these mutations, especially those affecting the antigenicity of HBsAg, could be responsible for false-negative results by some commercial assays, evasion of anti-HBV immunoglobulin therapy and avoidance of vaccine induced immunity (3). This patient could have an escape mutant virus, which is consistent with a reduction of the protective immunity driving selection of vaccine escape virus.

We do not have a clear explanation for our case. There are two possible explanations: mutations in regions that could affect the production and/or the detection by
commercial assays of HBcAb (3) or response immunity problems of the patient (4).

Although we didn’t perform a sequence of the core region, the immunosuppression of this patient can explain the lack of antibodies to core, surface and e antigens.
References


