

# Reactivation of Hepatitis B Virus without Core Antibody

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**We present the case of a male patient not vaccinated against hepatitis B virus (HBV) and with reactivity to a surface antibody who, after immunosuppression for a multiple myeloma, had HBV reactivation. Pharmacological HBV suppression was tried, but viremia could not be suppressed. Production-detection core mutations or immunity issues can explain this clinical phenomenon.**

## CASE REPORT

A 57-year-old Caucasian man presented to our viral hepatitis outpatient clinic due to a positive PCR result for hepatitis B virus (HBV).

There was no relevant history, except alcohol and tobacco abuse. He was not vaccinated against HBV. In March 2006, he began to experience very severe low back pain, and a lumbar column plasmacytoma was diagnosed. Before starting chemotherapy, his blood analyses showed that he was serologically nonreactive for human immunodeficiency virus type 1 (HIV-1) and HIV-2 (Prism HIV Ag/Ab Combo; Abbott) and hepatitis C virus (HCV) (Prism HCV; Abbott). The HBV markers were nonreactive for surface antigen (HBsAg) and core antibody (HBcAb) (0.6 signal-to-cutoff ratio [S/CO]; laboratory cutoff, 0.9 S/CO) and reactive for surface antibody (HBsAb; 28.5 IU/liter), using chemiluminescent methods (Prism HBsAg and Prism HBcore, Abbott; Architect Anti-HBs, Abbott). He was treated for the plasmacytoma with thalidomide at 200 mg plus dexamethasone at 40 mg (6 months) and local radiotherapy (10 sessions; total radiation dose, 30 Gy). Despite the treatment, his plasmacytoma progressed and multiple myeloma IgG/lambda was detected in 2007. The Durie-Salmon stage was IIIA. In 2007, he had peripheral blood progenitor cells collected and a tandem autologous hematopoietic stem cell 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 a 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 at 50 mg daily. He was well until December 2010, when he complained about pain in the left side of his pelvis. The computed tomography scan showed a large lytic lesion in the body of the left iliac bone. He was treated with bortezomib at 1 mg and dexamethasone at 40 mg (4 treatment cycles) and local radiotherapy (12 sessions; total radiation, 3Gy). An autologous hematopoietic stem cell transplant was tried, but the mobilization was not effective. After that treatment, he was again on maintenance treatment with thalidomide at 50 mg daily. At the beginning of 2013, an increase in the monoclonal peak was documented and he was started again on bortezomib at 1 mg and dexamethasone at 40 mg (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 nonreactive.

The HBV analysis showed the following data: HBsAg, reactive; HBcAb, nonreactive; HBsAb, negative (0.64 IU/liter); PCR HBV, 40,258,300 IU/liter (7.60 log) (Cobas Ampliprep/Cobas TaqMan HBV test, version 2.0; Roche); e antigen (HBeAg), reactive; e antibody (HBeAb), nonreactive (Architect HBeAg and Anti-HBe; Abbott). The HBV genome sequencing (HBV Sequencing; Abbott) result showed HBV genotype A and the following substitutions: N122H, M129L, T150IT, W153Q, V163I, I253V, H271N, and V278I (reverse transcriptase [RT] domain); P142PS, G145R, S207N, and I213T (SHB protein); 142S and 145R (escape). The HBV resistance predicted by geno2pheno showed susceptibility to all drugs available in the test. There was no hepatic cytolysis or sign 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 hepatitis B (March 2013), the patient received only 11 platelet concentrate transfusions. He did not receive any other blood or blood product.

Suppression of the HBV was needed to perform the hematopoietic stem cell transplant. We immediately began administration of entecavir (Baraclude; Bristol-Myers Squibb) at 0.5 mg once daily. After 1 month of therapy, there was a 2 log decrease in the viral load (189,051 IU/liter) (5.27 log). Three months after therapy initiation, the load decreased another 2 log (1,471 IU/liter) (3.16 log). However, as HBV suppression had not been reached, the entecavir dose was increased to 1 mg. In the next 4 months, there was no additional decrease in the HBV load. Therefore, we added tenofovir disoproxil fumarate (TDF) (Viread; Gilead) (245 mg) to the 1-mg entecavir dose. At the time that we combined the two drugs, the multiple myeloma started to progress and he began to have thoracic and low back pain, nausea, and malaise. His TDF treatment was stopped due to the difficulty of distinguishing ad-

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verse tenofovir 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 a protective titer (the presence only of HBsAb). However, in certain patients after several years of contact with the virus and cure of the infection, the HBcAb titer decreases and cannot be detected. Because of the multiple myeloma, treatment with immunosuppressors was started. Unfortunately, as he did not have detectable HBcAb and he showed reactivity only for HBsAb, antiviral treatment was not started. Actually, even in patients with HBcAb and HBsAb positivity, antivirals such as lamivudine and treatment with entecavir or TDF should be started before the beginning of immunosuppression to prevent the reactivation of HBV (which is stored in the liver as covalently closed circular DNA [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 reemerged, and he had a “flare” of his hepatitis B.

We believe that the probability of hepatitis B virus transmission by a transfusion is null or very low. The residual infectious risk represented by 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 platelet concentrates: none has been involved in a look-back process, none has converted to hepatitis B, and none is involved in a case of hepatitis B seroconversion for 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 the therapy is for a limited period. We

started the therapy with entecavir at 0.5 mg (the recognized dose when there are no resistance mutations). However, virus suppression was not possible, even with increased doses.

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

The hepatitis B 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 from some commercial assays, evasion of anti-HBV immunoglobulin therapy, and avoidance of vaccine-induced immunity (3). This patient could have had 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) and response immunity problems of the patient (4). Although we did not perform a sequence analysis of the core region, the immunosuppression of this patient can explain the lack of antibodies to core, surface, and e antigens.

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