

# *De novo* hepatitis B surface antigen (HBsAg)-positive, core antibody (anti-HBc)-negative, hepatitis B virus infection post-liver transplant from an anti-HBc, HBsAg-negative donor

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## Abstract

Liver transplant donors and recipients are routinely screened for hepatitis B virus (HBV) infection by measuring the levels of hepatitis B surface antigen (HBsAg) and hepatitis B core (anti-HBc) antibodies. Organs are accepted from donors who are HB-negative, and increased monitoring is required for organs from donors considered at increased risk. Transplant recipients are vaccinated if there is no sign of previous infection or immunity and monitored for reactivation in case of previous HBV infection. In cases where both the donor and the recipient are HBV-negative, no antiviral prophylaxis is used post transplant. This report describes a case of an HBV-immunized, anti-HBc-negative patient who underwent an orthotopic liver transplant from an anti-HBc-negative donor. The patient did not receive post-transplant antiviral prophylaxis due to mutual anti-HBc-seronegative status. However, the recipient developed HBV infection with isolated HBsAg and persistently negative anti-HBc. Mutations in the core/pre-core regions of the HBV gene were not implicated for unique serology in this case. Immunosuppression post liver transplant is the likely etiology for isolated HBsAg seroconversion despite significantly elevated HBV DNA. Our experience suggests that HBV DNA screening of liver transplant donors and recipients, in addition to HBV DNA monitoring of recipients, may reduce the risk of transplant-associated HBV.

**Keywords:** Hepatitis; hepatitis B; Hepatitis B surface antigen reactivity; liver transplant; seroconversion.

## Introduction

Hepatitis B virus (HBV) infection is one of the most common infections in the world, with an estimated 257 million carriers worldwide.<sup>[1]</sup> HBV is a notifiable disease in Canada, requiring public health authority notification to a provincial and territorial surveillance program. Chronic hepatitis B (CHB) infection in Canada is mostly attributed to migration from an endemic country or susceptible, unvaccinated adults with exposure risk factors. For those born in Canada, risk factors for HBV infection include having family members who are chronic HBV carriers, injection drug use, high-risk sexual activity, body piercing and tattoos, and a history of blood transfusions, particularly before 1971–72, when routine blood donor HBsAg screening was implemented in Canada.<sup>[2,3]</sup> In addition, patients who are immunocompromised, due to causes such as HIV infection, chemotherapy, immunosuppressive post-transplant medications, or those with genetic abnormalities, such as common variable immunodeficiency, remain at higher risk of HBV reactivation.<sup>[4]</sup>

Hepatitis B surface antigen (HBsAg) testing is one of the most important laboratory screening measures for HBV infection. It is one of the first markers of an acute infection. However, HBsAg can also seroconvert following HBV vaccination. For example, Ly et al.<sup>[5]</sup> and Rysgaard et al.<sup>[6]</sup> demonstrated transient HBsAg seroconversion in 9 dialysis patients after HBV immunization. Vaccine-related HBsAg seroconversion typically reverts within a few weeks, without other seromarkers associated with acute HBV infection, such as hepatitis B core antibody (anti-HBc), and specifically immunoglobulin M (IgM) antibodies. A quantifiable HBV DNA level is mandatory to guide treatment, and may indicate the phase of HBV infection based on other serological markers.<sup>[1,7]</sup>

The above serological profile is typically present in acute HBV infection. The present case describes the occurrence of HBV infection with positive HBsAg and detectable HBV DNA findings, but persistently negative anti-HBc results in a previously HBsAg- and anti-HBc-negative, HBV-immunized, liver transplant patient whose source liver was from a HBsAg- and anti-HBc-negative donor.

## Case Report

A 27-year-old female had previously undergone a liver transplant for end-stage liver disease secondary to Wilson's disease. She suffered from graft loss due to ischemic cholangiopathy and underwent a second orthotopic liver transplant 6 years later. She was immunized

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against HBV 2 years after her original transplant (twice) and then a year later, with persistently negative HBsAg and anti-HBc antibody test results. The hepatitis B surface antibody (HBsAb) measurement after the third vaccine was 46 [IU]/mL (Cobas e 602; Roche Diagnostics, Basel, Switzerland). After the second liver transplant, the patient was discharged with the standard early immunosuppressive regimen of tacrolimus, mycophenolate mofetil, and tapered prednisone. Post liver transplant, she continued to remain well with negative serology results for HBV infection, including negative HBsAg, negative anti-HBc IgM and IgG antibodies, and HBsAb levels >10 [IU]/mL. However, a routine screening in May 2020 revealed a reactive HBsAg result with negative anti-HBc. Repeat testing was confirmatory, including consistent serology results using a different analyzer (Architect; Abbott Laboratories, Lake Bluff, IL, USA), and an HBV DNA level of 11,600 [IU]/mL (Cobas HBV; Roche Diagnostics, Basel, Switzerland) with negative anti-HBc results. There was no elevation of liver enzymes, including alanine aminotransferase (ALT), and she remained asymptomatic post transplant. Nucleoside antiviral treatment with entecavir was initiated, and follow-up testing demonstrated persistently negative anti-HBc results.

As the liver donor and recipient were both HBsAg- and anti-HBc negative prior to transplantation, antiviral prophylaxis was not administered immediately post transplant. In addition, the donor had been immunized prior to transplant. In terms of risk factors for HBV infection, the patient had not had any invasive dental procedures or blood transfusions since re-transplantation, and did not engage in any high-risk activities. Contact tracing of family members and partner demonstrated non-reactive HBsAg and anti-HBc results.

Amplicon-based next-generation sequencing targeting the core/pre-core region (nucleotides 1672 – 1946; coreF:TAAGAGGACTCTTGAC; coreR:AAGAAGTCAGAAGGCAA) was performed using a MiSeq Reagent Kit v2 Nano (Illumina Inc., San Diego, CA, USA) to investigate the potential of a mutation in the pre-core/core region; however, no mutation was identified.

## Discussion

Acute HBV infection usually presents with positive HBsAg and positive anti-HBc IgM antibodies.<sup>[7]</sup> As HBV infection resolves, HBsAg becomes undetectable, but anti-HBc IgG persists. However, if HBsAg persists for longer than 6 months, spontaneous clearance is less likely. Chronic HBV infection is characterized by a persistence of HBsAg and anti-HBc IgG antibodies.<sup>[7]</sup> Our patient was an interesting case of HBV infection 10 months after liver transplantation with unusual serology results of a positive HBsAg finding but persistently negative anti-HBc IgM and IgG antibody results. Although isolated HBsAg positivity can be found in the initial incubation period after infection, to the best of our knowledge, this is the first reported presentation of persistently isolated HBsAg-positivity despite a significantly detectable HBV viral level of over 11,000 [IU]/mL in an immunized patient who received a liver transplant from an anti-HBc negative patient. This could be due to agent or host factors, including infection with an HBV mutant, immune tolerance, or a lack of response by the host immune system.

The HBV C-gene (C-ORF) has 2 main regions: the core region (183 amino acids), which encodes the viral nucleocapsid, and the pre-core gene (29 amino acids), which encodes the HBe-antigen in combination with the core gene.<sup>[8]</sup> Fiordalisi et al.<sup>[9]</sup> sequenced the HBV pre-C/C regions and found familial heterogeneity in the samples, with single base

deletions causing generation of stop codons, thereby leading to synthesis of truncated proteins.<sup>[9]</sup> These truncated proteins are not recognized by the immune system; and therefore, there is a lack of antibody formation. Kreutz et al.<sup>[10]</sup> found that core-deletion mutants were often observed in those with chronic HBV infection (related to low level of viremia). Another related mutation is in the X-ORF (X-region) of HBx (protein X), which is known to transactivate transcriptional regulatory elements, which include enhancer and core protein elements.<sup>[11]</sup> Patients with an X-ORF mutation may suppress the replication and expression of HBV DNA, leading to suppression of anti-HBc synthesis.<sup>[11]</sup> They may also demonstrate low or negative HBsAg, and negative anti-HBc, despite low HBV DNA replication. Despite this established phenomenon, sequencing of our patient's samples did not reveal a mutation in the core or pre-core region of the HBV genome.

Immune tolerance is another mechanism attributed to a lack of anti-HBc production. There are several proposed mechanisms by which the host immune response fails to respond to acute HBV infection with HBe antibodies. One proposed mechanism is that of T-cell anergy. T cell anergy refers to a development of immune system tolerance after an initial exposure to the antigen. After the initial exposure, T cells are functionally inactive, but remain alive in a hypoactive state.<sup>[12]</sup> T-cell anergy is essential to the development of self-tolerance and regulation of the cellular immune response. The role of T-cell anergy has been implicated in the lack of anti-HBc development in infants born to HBsAg-carrier mothers.<sup>[13]</sup> Ni et al.<sup>[13]</sup> studied 10 children with persistently seropositive HBsAg, HBe-antigen, and HBV DNA. The subjects were exposed to HBV perinatally, and developed immune tolerance to the HBe antigen in early infancy and maintained isolated HBsAg seroconversion. As the immune tolerance waned, the children developed anti-HBc antibodies between the age of 2 and 8 years. Laperche et al.<sup>[14]</sup> postulated a similar reasoning for the lack of HBe antibodies in 2 blood donors who had positive HBsAg findings, but lacked anti-HBc and had a normal ALT level.<sup>[14]</sup> Both donors were immunocompetent and did not demonstrate any mutations in their HBV core or pre-core genes, but were thought to have developed immune tolerance due to HBV exposure in utero.

In addition to T-cell anergy, a lack of anti-HBc response has also been attributed to immunosuppression. Melegari et al.<sup>[15]</sup> studied 12 children undergoing chemotherapy, most of whom had hematological malignancies. All of the patients were thought to have acquired nosocomial HBV infection from undetected infective blood, characterized by positive HBsAg, HBeAg, and HBV DNA, but negative anti-HBc IgM and IgG status throughout chemotherapy. Avettand-Fenoel et al.<sup>[16]</sup> studied 39 patients with HBV infection, characterized by isolated HBsAg positivity and negative anti-HBc. The patients were primarily immunosuppressed due to HIV infection or a solid organ transplant (kidney, heart, or bone marrow), and 1 patient had HCV co-infection. More recently, Brousseau et al.<sup>[17]</sup> reported a case of acute HBV infection in a patient receiving rituximab for low-grade non-Hodgkin lymphoma with isolated HBsAg positivity. The patient developed anti-HBc 6 months after the first positive HBsAg result, and the delay was attributed to immunosuppression due to rituximab use. Both Avettand-Fenoel et al.<sup>[16]</sup> and Brousseau et al.<sup>[17]</sup> demonstrated that patients developed HBe antibodies once immunosuppression was less pronounced or after completion of chemotherapy, further establishing the role of immune suppression in the lack of anti-HBc response in acute HBV infection.

Our patient was immunosuppressed due to tacrolimus, mycophenolate mofetil, and prednisone use post liver transplant. The profound immunosuppression is the likely reason for the lack of seroconversion of an-

ti-HBc despite a significant HBV DNA viral load and isolated HBsAg presentation. At the time of writing, she remains on entecavir antiviral treatment and 10 months after the initial HBsAg seroconversion, test results continued to indicate that she is anti-HBc negative.

Our patient likely acquired her HBV infection via the donor source liver, as she did not have any known risk factors for acute HBV infection, and the results of testing of all of her familial and social contacts were negative for HBV, HBsAg, and anti-HBc, which are used for screening donors and recipients prior to liver transplantation to identify HBV infection status and determine the role of antiviral prophylaxis after transplantation. Both the donor and the recipient in our case had negative HBsAg and anti-HBc serology results, and the donor had been immunized for HBV prior to transplant with detectable HBsAb >10 [IU]/mL; therefore, no antiviral prophylaxis was initiated.

HBV DNA detection is the most accurate tool available for detection of HBV infection. It is usually obtained using quantitative molecular assays, which can be limited due to resource constrictions, such as cost or availability. Our case illustrates the concern that screening using HBsAg and anti-HBc alone may not be sufficient to rule out donor-liver HBV infection. Additionally, it highlights the need to consider post-transplant antiviral prophylaxis against HBV to prevent potential post-transplant viremia and/or consider post-transplant monitoring with nucleic acid amplification testing.

**Informed Consent:** Written informed consent was obtained from the patient for the publication of the case report.

**Peer-review:** Externally peer-reviewed.

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