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Case Report

Hepatitis B Reverse Seroconversion and Transmission in a Hemodialysis Center: A Public Health Investigation and Case Report

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In March 2013, public health authorities were notified of a new hepatitis B virus (HBV) infection in a patient receiving hemodialysis. We investigated to identify the source and prevent additional infections. We reviewed medical records, interviewed the index patient regarding hepatitis B risk factors, performed HBV molecular analysis, and observed infection control practices at the outpatient hemodialysis facility where she received care. The index patient's only identified hepatitis B risk factor was hemodialysis treatment. The facility had no other patients with known active HBV infection. One patient had evidence of a resolved HBV infection. Investigation of this individual, who was identified as the source patient, indicated that HBV reverse seroconversion and reactivation had occurred in the setting of HIV (human immunodeficiency virus) infection and a failed kidney transplant. HBV whole genome sequences analysis from the index and source patients indicated 99.9% genetic homology. Facility observations revealed multiple infection control breaches. Inadequate dilution of the source patient's sample during HBV testing might have led to a false-negative result, delaying initiation of hemodialysis in isolation. In conclusion, HBV transmission occurred after an HIV-positive hemodialysis patient with transplant-related immunosuppression experienced HBV reverse seroconversion and reactivation. Providers should be aware of this possibility, especially among severely immunosuppressed patients, and maintain stringent infection control.

INDEX WORDS: Hepatitis B virus (HBV); reverse seroconversion; reactivation; hemodialysis; immunosuppression; HIV infection; infection control; blood contamination; environmental transmission; false-negative; viral testing; viral surveillance; case report.

Primary hepatitis B virus (HBV) infection can be acute and self-limiting or progress to chronic infection.[1] Residual HBV DNA can remain integrated in host hepatocytes despite serologic evidence of inactive chronic infection or previously resolved (ie, cleared) infection. Moderate immunosuppression can promote renewed HBV replication, or reactivation, among persons with inactive chronic infection (Box 1). Rarely, severe immunosuppression can promote reverse seroconversion (reappearance of hepatitis B surface antigen [HBsAg] and circulating HBV DNA) and reactivation among persons with previously resolved infection.[2-5]

HBV can contaminate and persist in an infectious state on environmental surfaces. Medical procedures with a high potential for environmental blood contamination (eg, hemodialysis) provide opportunities for HBV exposure, particularly when infection control recommendations are not followed.[6] Previous transmission events have led to hemodialysis-specific HBV control recommendations, including routine screening to identify infected patients and hemodialysis of HBsAg-positive patients in isolation with dedicated staff and equipment.[1,6] Recommendations do not include routine screening to detect HBV reverse seroconversion and reactivation among severely immunocompromised patients with resolved infection.[6]

In March 2013, public health authorities were notified of a new HBV infection in a hemodialysis patient (index patient) with no other identified risk factors. Although hemodialysis-related transmission was suspected, no patients with acute or chronic HBV infection had been identified at the hemodialysis facility.

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The index patient, a woman in her 80s, had negative test results for total antibody to hepatitis B core antigen (anti-HBc) when outpatient hemodialysis therapy was initiated in 2011 and had no detectable antibody to HBsAg (anti-HBs) response upon completion of 2 HBV vaccination series in April 2012[6] (Fig 1). She was consistently HBsAg negative by monthly testing during July 2011 to February 2013 until her first HBsAg-positive result in March 2013, after which she began dialyzing in isolation at the facility. Though the index patient did not develop jaundice, her infection met the acute hepatitis B surveillance case definition, with exposure likely during September 2012 to February 2013.[7] Her only identified hepatitis B risk factor was long-term hemodialysis therapy. The facility had no other patients with known acute or chronic HBV infection. However, 1 patient (source patient) had serologic results consistent with resolved infection (ie, anti-HBc positive, HBsAg negative, and anti-HBs positive).

We observed infection control practices during a facility site visit. We reviewed HBV serologic results of all facility patients (N = 112) and the HBsAg testing procedures at a commercial laboratory (designated Laboratory A herein). To assess HBV relatedness among HBsAg-positive patients, we determined HBV genotypes using the InnoLIPA HBV assay (Fujirebio Europe) and performed whole viral genome sequencing.[8] For HBsAg-positive patients, we compared viral sequences and performed phylogenetic analysis using MEGA5 (Biodesign Institute); HBV viral load was measured as part of clinical care and repeated at the Centers for Disease Control and Prevention (CDC) using Roche COBAS Ampliprep and COBAS Taqman HBV test v2.0 (Roche Diagnostics Corp).

The source patient, a man in his 40s, had received a diagnosis of acute HBV infection in 1989 and HIV (human immunodeficiency virus) infection with secondary end-stage renal disease in 1997. Subsequently, long-term hemodialysis therapy was initiated in 1997. The source patient had received antiretroviral therapy for HIV infection, including HBV-suppressive tenofovir, which had been discontinued during preparation for kidney transplantation in November 2011 (Fig 1). During early 2012, he experienced acute transplant rejection and received antithymocyte globulin. After transplant failure in May 2012, the source patient returned to outpatient hemodialysis therapy and was documented as HBsAg negative. In October 2012, acute transplant rejection was again diagnosed and prednisone was prescribed. The source patient was reported to be anti-HBs negative in January 2013 by routine testing initiated though standing orders at the facility. This result, interpreted as possible waning immunity, prompted HBsAg testing in February 2013 at Laboratory A, the laboratory used by the facility for urgent testing. His first HBsAg test result in February 2013 was initially reported as positive. However, after a confirmatory neutralization step, the presence of HBsAg was not confirmed and the final result was reported as HBsAg negative. After a subsequent negative HBsAg test result at Laboratory A in February 2013 with a different source patient sample, he received a single dose of HBV vaccination.

In April 2013, the source patient was reported to be HBsAg positive at Laboratory B, the laboratory used by the facility for routine testing, and began dialyzing in isolation. Due to the HBsAg-positive result, additional HBV serologic tests were conducted at Laboratory A and were available in early May 2013; HBsAg was not detected, despite a positive test result for hepatitis B e antigen (HBeAg) and high viral titer, a discrepancy not identified by facility staff despite their practice of reviewing all laboratory results upon receipt and again at weekly rounds (Fig 1). In late May 2013, he was reported to be HBsAg positive at Laboratory A and resumed hemodialysis therapy in isolation. The source patient died in December 2013; HBV infection was not listed as a contributing cause.

Box 1. HBV Serologies and Related Terminology

HBsAg: hepatitis B surface antigen
anti-HBs: antibody to hepatitis B surface antigen
anti-HBc: total antibody to hepatitis B core antigen
IgM anti-HBc: IgM antibody to hepatitis B core antigen
HBeAg: hepatitis B e antigen
anti-HBe: antibody to hepatitis B e antigen
HBV reverse seroconversion: reappearance of HBsAg and circulating HBV DNA in a person with previously resolved HBV infection
HBV reactivation: renewed HBV replication in a person with inactive chronic HBV infection

Note: HBV DNA determined using a quantitative nucleic acid assay.

Abbreviations: HBV, hepatitis B virus; IgM, immunoglobulin M.

Samples obtained during July 2013 from the index and source patients revealed HBV viral loads $> 1.1 \times 10^8$ IU/mL. Both patients' HBV genotypes were A; HBV whole genome sequences analysis indicated 99.9% genetic homology. The index patient developed chronic HBV infection and remained HIV negative.

Observations at the facility, an outpatient clinic with 31 treatment stations, revealed multiple infection control breaches. Though an appropriate disinfectant (1:100 dilution of sodium hypochlorite) was used, stations were not consistently and thoroughly disinfected.[9] Patient care materials were carried between stations. Certain injectable medications were prepared on a mobile cart located near stations.

The index and source patients shared the same station 3 times weekly during May 2012 to March 2013, with the index patient dialyzing immediately after the source patient. All 112 facility patients treated during May 2012 to May 2013 were screened for HBsAg and anti-HBs; those without protective anti-HBs titers were rescreened 6 or more months after their last possible exposure to the source patient. No new HBV infections were identified.

Laboratory A failed to strictly adhere to the HBsAg test manufacturer's guidelines for adequate dilution of patient serum samples during the confirmatory neutralization step.[10] Samples with a non-neutralized result of ≥0.80 signal/cutoff and percent neutralization < 50% were not adequately diluted and retested.[10] Therefore, the source patient's sample might not have been adequately diluted in February and May 2013, resulting in potentially false-negative HBsAg results.

DISCUSSION

HBV transmission occurred after an HIV-positive hemodialysis patient with transplant-related immunosuppression experienced reverse seroconversion and reactivation. To our knowledge, this is the first reported hemodialysis-related HBV transmission from a patient with reverse seroconversion and reactivation and the first published hemodialysis-related HBV transmission reported in the United States since 1999.[11]

Our investigation supports hemodialysis-related HBV transmission from the source patient to the index patient. These patients used the same hemodialysis station for 10 months. Observations revealed infection control breaches with potential for HBV environmental contamination, facilitating transmission.[6] HIV, which