

Persistence of Hepatitis B Core IgM Antibody in HIV-positive Chronic Hemodialysis Patient

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Abstract

Health care-associated infections (HAIs) are a leading cause of morbidity and mortality in the hemodialysis population. Despite the encouraging trend in the steady decline in the incidence of hepatitis B (HBV) transmission in hemodialysis since the 1980s, prevention of hepatitis B infection at dialysis facilities continues to be, and should remain an important goal, as outbreaks occur from time to time. There is an increased chance of transmission and an increased morbidity once infection is acquired in this vulnerable population. Routine serologic testing, vaccination and infection control strategies are important to prevent newly acquired infections. However, the interpretation of serologic tests in hepatitis B may be challenging in certain clinical scenarios as well as assay itself. Here we report a human immunodeficiency virus (HIV)-infected patient with positive IgM hepatitis B core antibody (anti-HBc), which prompted us to investigate infectivity of this patient. We report on the pitfalls of a positive result.

Keywords: Health-care associated infection (HAI); Hepatitis B virus (HBV); End-stage renal disease (ESRD); Hemodialysis (HD); Human immunodeficiency virus (HIV)

Background

Healthcare-associated infections (HAI) are a major burden in end-stage renal disease (ESRD), and are a leading cause of morbidity, hospitalization and mortality. Viral hepatitis, like other HAIs, can also occur due to errors during the delivery of health care. Despite overall lowering of HBV prevalence due to improved infection control procedures and vaccination, health care associated hepatitis infections continue to occur sporadically and in outbreaks [1]. A prospective cross-sectional study, DOPPS (Dialysis Outcomes and Practice Patterns Study), shows that prevalence rates of chronic HBV infection in hemodialysis is between 0% and 7%, with majority of units having hepatitis B surface antigen seroconversion rate of 0 per 100 patient-years [2,3]. However, seroconversions can occur if the stringent criteria for infection prevention of HBV are not followed. Serologic surveillance of patients for antibody titers and vaccination of susceptible patients against HBV are crucial components in preventing spread of HBV infection during hemodialysis. However interpretation of the hepatitis B serology results can be challenging and may lead to inadvertent wrong decisions regarding patient isolation during treatment. Here we report an ESRD patient with chronic HIV infection, who tested positive for anti-HBc antibody in routine pre-dialysis screening. We would like to illustrate how to handle this scenario and what further tests were ordered to determine accurately the infectivity of the patient to aid appropriate isolation during the dialysis.

Case Presentation

A 67-year-old man, with history of HIV/AIDS on anti-retroviral treatment and ESRD on regular hemodialysis (HD), presented with shortness of breath. Initial lab data showed hyperkalemia (8.2 mEq/dl), metabolic acidosis (serum bicarbonate 15.1 mEq/dl), and azotemia (blood urea nitrogen of 124 mg/dl and serum creatinine of 17.0 mg/dl). Chest X-ray showed pulmonary vascular congestion and small bilateral pleural effusions, suggestive of fluid overload. Routine hepatitis serology panel

check before initiation of HD showed: negative hepatitis C Ab, reactive hepatitis B surface Ab (HBsAb), and negative hepatitis B surface Ag (HBsAg). Hepatitis B core total Ab and IgM reported the following day were reactive. The question that arose was, what isolation precautions if any to implement during hemodialysis. Positivity of IgM anti-HBc indicates acute infection of hepatitis B, and requires prompt isolation during hemodialysis to prevent spread of hepatitis B. However, further testing was done to determine the infectivity of this patient, including hepatitis B viral DNA, hepatitis B e antigen (HBeAg) and Hepatitis B e antibody (HBeAb), which came back as negative.

Discussion

Hepatitis B Virus is a 42-nm DNA virus belonging to the *Hepadnaviridae* family. HBV is transmitted by percutaneous and mucosal exposure to infectious blood or body fluid such as semen and saliva. After exposure to a susceptible host, HBV is transported to the liver by the bloodstream, where it replicates. Symptoms typically begin 2-3 months after HBV exposure (range: 6 weeks-6 months), though infection can be asymptomatic and this is why viral hepatitis infection remains a silent epidemic. Four phases of HBV infection are recognized, including immune tolerance, immune clearance, inactive carrier state, and reactivation [4]. Primary HBV infection can be self-limited, with elimination of virus from blood and gaining immunity against reinfection. Resolved infection is not a risk factor for subsequent chronic liver disease or hepatocellular carcinoma (HCC). The risk for progression to chronic infection is related to the immune status, gender, infection route and genotype, and inversely to age at the time of infection. Immunosuppression (e.g., hemodialysis patients and persons with HIV infection) increases the risk for chronic infection. When patients with resolved infection become immunosuppressed (e.g., from chemotherapy), reactivation of hepatitis B is known to occur with symptoms of acute illness [3,5-8], or it can progress to chronic infection with continuing viral replication. Prophylactic antiviral therapy can prevent reactivation and possible fulminant hepatitis in these HBsAg

positive patients [5,9,10]. Though blood has the highest concentrations of the virus, HBV remains viable and infectious in the environment for at least 7 days and can be present in high concentrations on inanimate objects, even in the absence of visible blood [10,11], making it a public health concern in dialysis facilities. To prevent HBV transmission, previous guidelines have recommended routine HBsAg testing for all hemodialysis patients. Other strategies for preventing spread are listed in the table 1.

Interpretation of serologic markers in Hepatitis B

The serologic patterns of chronic HBV infection are varied and can be complex. Routine serological studies to determine status of hepatitis B infection include HBsAg, anti-HBs, and anti-HBc antibody [12]. Serum HBsAg is the first detectable viral marker in acute HBV infection. Other serum markers of infection appear as patients develop symptoms, such as antibody (anti-HBc) to the hepatitis B core antigen (HBcAg), present exclusively in nuclei of infected hepatocytes. Immunoglobulin IgM anti-HBc seen in the acute phase of infection declines over 6 months, while IgG appears and persists for life. With successful resolution of infection, protective antibody against HBsAg (anti-HBs) appears and signifies immunity. The presence of total core IgG distinguishes prior infection from immunity due to vaccination and may be the sole marker of prior infection in some patients [3].

Infectivity can be further assessed by the presence of hepatitis B e Antigen (HBeAg) and circulating Hepatitis B viral DNA (HBV DNA). However, in ESRD patients, the viral load tends to be low, with the frequency of HBsAg seropositivity without detectable serum HBV DNA reported to be between 14% and 58%. Moutinho et al. [13] report high HBV DNA levels (>100,000 copies / ml) in only 6% of their population [14] with significantly higher levels in HBsAg+/ HBeAg+ compared to HBsAg+/HBeAg- patients. HBeAg in serum was seen only in 15-30% in HBsAg positive HD patients. This makes the interpretation of serological results even more challenging in ESRD patients.

Some individuals that test negative for both HBsAg and anti-HBs may be positive for IgG anti-HBc. This finding, known as “isolated anti-HBc”, is common, and may be seen in more than three-fourths of patients who are co infected with HIV-1 or hepatitis C virus (HCV) [15,16]. Despite its frequent occurrence, the implication of this finding is not certain. Isolated anti-HBc may represent either (1) resolved HBV infection with loss of anti-HBs, (2) occult chronic HBV infection with undetectable HBsAg, or (3) a false-positive test result [17]. The downside with a positive result for anti-HBc being interpreted as evidence of resolved HBV infection is that patients who test positive for isolated anti-HBc will not be offered hepatitis B vaccination [18].

False-positivity in IgM anti-HBc

In acute phase of hepatitis B infection, IgM anti-HBc may be the only positive serologic marker in the absence of anti-HBs, so-called “window period” [19]. This test captures IgM in serum when incubated with HBcAg and labeled anti-HBc binding to HBcAg [20]. Due to the non-specificity of IgM capture in this assay, the presence of any IgM cross-reactive to core antigen might be recognized as a positive result [21,22].

Serologic surveillance of patients for antibody titers
Monthly testing for Hepatitis B s Ag in susceptible patients
Use of isolation rooms
Restricted staff assignment
Dedicated use of the HD machine for HBsAg positive patients
Dedicated use equipment and supplies for HBsAg positive patients
Routine cleaning of machines and all surfaces with approved disinfectant

Table 1: Recommendations for control of HBV infection

For example, false positive result of IgM assays in both Epstein-Barr Virus (EBV) and cytomegalovirus (CMV) infection have been described in primary HIV infection [23]. False-positive antibodies are thought to be from strong immune response to the infecting agent and the subsequent polyclonal B-cell activation as the host attempts to clear it. It is therefore not unexpected that we should find higher values of IgM in those with HIV. IgM cross-reactivity was discussed extensively in various other infections [24]. IgM anti-HBc has also been reported to be persistently detectable after acute infection, making it difficult to distinguish between acute infections from acute exacerbation of chronic infection, using the presence of IgM anti-HBc. Researchers have described different cut-off values, in order to improve the diagnostic accuracy [20,25] and overcome the limitations of IgM anti-HBc in clinical scenarios.

In our patient, the initial positivity of IgM anti-HBc warranted us to investigate the infection status to determine the need of isolation during hemodialysis. As discussed above, the presence of IgM anti-HBc could be acute infection, acute exacerbation of chronic infection or a false positive result. According to the result of positive anti-HBs and negative HBsAg, it is conceivable that the patient has had prior remotely resolved infection without chronicity. Mutated protein or low levels of HBsAg can both make HBsAg undetectable by most diagnostic methods [21]; therefore, DNA of hepatitis B would be a helpful alternative, which was negative in our patient as were HBeAg and HBeAb. Although false-positivity of anti-HBc caused by primary HIV infection is described in the literature, the positivity of anti-HBc IgM in our patient was likely secondary to polyclonal antibodies produced by HIV infection instead of true acute infection of hepatitis B as borne out by a negative HBeAg/Ab test and undetectable HBV DNA. As a result our patient ended up receiving regular hemodialysis without further isolation.

This case essentially urges nephrologists to use caution in interpreting the serologic results of hepatitis B virus. Proper interpretation is essential to prevent HAI hepatitis infections, which is one of the priority areas of the federal national action plan for addressing viral hepatitis (VHAP) [26].

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None

Conflict of Interest

The authors declare no conflict of interest

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