CASE REPORT

Persistence of hepatitis B surface antigen in blood in a chronic haemodialysis patient following vaccination booster

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SUMMARY

Patients receiving haemodialysis are at an increased risk of hepatitis B infection; regular screening for incident infection and vaccination of susceptible individuals is recommended. Haemodialysis patients often require repeated high-dose hepatitis B vaccination boosters because of impaired response. Since the hepatitis B surface antigen is used as an immunogenic agent for vaccination and as a marker of hepatitis B infection, it has occasionally been detected in the blood shortly after vaccine administration and can be mistaken for a new infection. These transient results, however, are unlikely to persist for longer than 14 days after vaccination. We report the case of a haemodialysis patient who tested weakly positive for hepatitis B surface antigen 52 days after a vaccine booster. This is the longest vaccine-induced antigenaemia described in the literature and indicates that vaccination can cause weakly positive hepatitis B surface antigen results for longer than previously reported.

BACKGROUND

Hepatitis B virus (HBV) is a highly infectious virus that can be transmitted through exposure to blood and other bodily fluids. HBV can survive for long periods on environmental surfaces and contact with small amount of infected blood can transmit the infection. Owing to the repeated exposure to bodily fluids during dialysis procedures, the increased likelihood to be hospitalised to undergo interventional procedures and to require blood product transfusions, patients receiving chronic haemodialysis (HD) are at an increased risk of HBV infection.¹ Furthermore, due to the uraemia-associated immune dysfunction, HD patients are also more likely to become chronic carriers once infected.² The key principles of HBV infection control in dialysis units include screening of all HD patients, segregation of those who are infectious and vaccination of susceptible individuals.³ The widespread implementation of these measures has led to a dramatic decline in the incidence of HBV infection in dialysis patients over the past decades; however, sporadic outbreaks continue to occur even in developed countries, due to breaches in infection control procedures and suboptimal immunisation of susceptible individuals.⁴

Hepatitis B surface antigen (HBsAg), a protein component of the viral envelope, is the serological hallmark of a current HBV infection and is the most commonly used marker to screen for the presence of HBV in the blood. All hepatitis B vaccines

currently available contain purified HBsAg. In responders, they induce production of antibodies (hepatitis B surface antibody, HbsAb) against the HBsAg that confer protection against acute HBV infection. A three-dose course of hepatitis B vaccine induces a response defined as a titre of HBsAb >10 IU/L in >90% of healthy individuals.⁵ Unfortunately, responsiveness rates are reduced in end-stage renal failure and HD patients, and even in responders HBsAb titres tend to decline more rapidly.⁶ For this reason, regular screening for hepatitis B serological markers for all patients and yearly double-dose vaccination boosters when HBsAb titres decline are often required.³

Since HBsAg is used as an immunogenic agent for vaccination and as a marker of HBV infection, recent vaccination may result in transiently detectable levels of HBsAg in blood. These false-positive results, however, usually do not persist beyond 14 days postvaccination, although few cases of more prolonged antigenaemia have been reported, the longest being 28 days in a HD patient.⁷

We report the case of a patient who tested weakly positive for HBsAg 52 days after administration of a double-dose vaccination booster for declining HBsAb titres. Owing to the long-time interval, the link between the vaccination booster and the HBsAg detection was not initially recognised and this led to the patient being dialysed in segregation until the results of the confirmatory investigations became available and the causative link with the booster was finally elucidated.

CASE PRESENTATION

As part of a routine three monthly screening for blood born viruses, a patient on regular HD tested weakly positive for HBsAg by chemiluminescent microparticle immunoassay. The HBsAg neutralisation assay was positive, ruling out a non-specific reactivity in the HBsAg screening assay. While awaiting the results of further investigations, the patient needed to receive dialysis in isolation as recommended for a patient with suspected hepatitis B infection. Other than the HD, no risk factors for hepatitis B acquisition were identified and no known breaches in the HD procedures had occurred in the preceding months. The patient did not present symptoms suggestive of an acute viral hepatitis, and alanine aminotransferase value was within the normal range. Looking back at previous serology results, 12 weeks prior to the positive HBsAg result the patient was HBsAg negative,

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hepatitis B core total antibody negative and had an HBsAb titre of 39 IU/L.

INVESTIGATIONS

On the following day the results of the confirmatory investigations on the same serum sample that tested weakly positive for HBsAg became available. No HBV DNA was detected (<10 IU/L), hepatitis B core IgM and total antibodies tested negative and HBsAb were detected at a titre of 303 IU/L.

OUTCOME AND FOLLOW-UP

Enquiring further about the vaccination history, it became clear that the patient received a double-dose (40 µg) booster of hepatitis B vaccine (HBVaxPro) 52 days prior to the weak HBsAg positivity. Retested after 4 days, at 56 days from booster administration, the HBsAg was negative. Three months later the patient died of an unrelated cause.

DISCUSSION

The presence of HBsAg in blood indicates current HBV infection and patients tested HBsAg positive are regarded as infectious. HBsAg is the earliest serological marker of an acute HBV infection and its persistence for longer than 6 months indicates a chronic HBV infection. HBsAg is usually detected by immunoassays that use HBsAb to capture antigen in the sample. As with all immunoassays, non-specific binding can produce false-positive results. Usually, a non-specific binding induces a weakly positive result but exceptions are not uncommon. The more specific neutralisation tests are commonly used to confirm HbsAg-positive results. In neutralisation tests, a reactive sample is incubated with reagent HBsAb and then run in parallel with an aliquot of sample that has not been treated with the reagent antibody. If truly present in the sample, HBsAg is neutralised by the antibody and a reduction of signal is seen when compared with the untreated aliquot of sample (positive neutralisation test). A positive neutralisation test result virtually rules out a non-specific HBsAg reactivity and is considered the definitive test result for HBsAg. Our patient's weak positivity in the HBsAg screening assay was confirmed by a positive neutralisation test, indicating the actual presence of HBsAg in the serum. This narrowed the spectrum of possibilities to endogenous production of HBsAg, as a result of a current hepatitis B infection, or exogenous inoculation of HBsAg, as a result of hepatitis B vaccination. The possibility of an acute hepatitis B seemed very unlikely because no breaches in the HD infection control procedures had occurred in the preceding months, nor other risk factors for hepatitis B infection could be identified, and because the patient did not present any clinical or biochemical sign of an acute viral hepatitis. Furthermore, the patient had been fully immunised for hepatitis B prior to starting HD and had responded to the vaccination course demonstrating an HBsAb titre >100 IU/L at the end of it, although the HBsAb titre had declined to 39 IU/L in the most recent sample. Nonetheless, cases of breakthrough hepatitis B infection in previously immunised patients have been reported, caused by HBV genotypes E and F towards which current vaccines do not confer full protection.^{8 9} The most likely explanation for the weakly positive HBsAg result in our patient seemed a recent vaccination; however, given the long interval between the vaccine booster administration and the HBsAg positivity the causative link was not initially recognised and the patient was dialysed in isolation for one session.

In the first years following the introduction of hepatitis B vaccination, it was thought that hepatitis B antigenaemia as a result

of immunisation did not occur; this assumption was based on Katkov's study that reported no positive HBsAg result 1 and 24 h after administration of the plasma-derived hepatitis B vaccine Heptavax-B.¹⁰ However, subsequent studies using the yeast-derived recombinant vaccine Engerix-B showed relatively high rates of HBsAg detection in the first few days following vaccination in infants as well as in adults.^{11 12} In adults, most of the cases are seen in HD patients; in a recent retrospective analysis of the vaccine-induced HBsAg weakly reactive tests observed in a tertiary care medical centre in a 17-month period, 10 of 11 cases occurred in HD patients.¹³ This could be due to the fact that HD patients are screened on a regular basis, are more likely to receive vaccine booster and are usually immunised with double dose (40 µg) of vaccine. It has also been hypothesised that the decreased ability to produce neutralising HBsAb following vaccination may result in a less-effective clearance of the inoculated HBsAg. Indeed, Santana Rodriguez *et al* reported a significant association between the presence of transient antigenaemia and the non-responder status in a group of HD patients. In their study, they also reported a rate of HBsAg positivity following vaccination of 31.5%, with no cases of antigenaemia persisting for longer than 11 days.¹⁴

As far as the duration of the antigenaemia is concerned, previous studies suggest that it is unlikely to persist for longer than 14 days.¹³ Nonetheless, a case of antigenaemia persisting for up to 28 days has been reported in a HD patient.⁷ The 52-day duration that we report is the longest that has been described so far. Notably, our patient was a vaccine responder and mounted a good response also to the last booster, as demonstrated by the increase in the HBsAb titre from 39 to 303 IU/L. Indeed, our patient had no defined immunodeficiency and the total lymphocyte count was within the normal range. Other factors, such as differences in body composition, tissue absorption, blood flow and density of antigen-presenting cells in the muscle, might have all contributed to the long antigenaemia described.

In conclusion, the case we report suggests that recent administration of hepatitis B vaccine, especially when given at a double dose, should be considered among the possible explanations for a newly detectable HBsAg for longer than previously thought.

Learning points

- ▶ Haemodialysis patients are at increased risk of hepatitis B infection and susceptible individuals should be regularly screened and vaccinated.
- ▶ Vaccination response is impaired in haemodialysis patients, and even responders require repeated boosters of high-dose vaccine due to rapid decline of hepatitis B surface antibody titres.
- ▶ Owing to hepatitis B surface antigen (HBsAg) being used as a marker of current hepatitis B virus infection and as the immunogenic agent in the vaccine, transiently detectable levels of HBsAg can occur following vaccination and can be mistaken for a new infection.
- ▶ Although vaccine-induced hepatitis B surface antigenaemia usually resolves within 2 weeks of vaccination, rarely it can persist for up to 7–8 weeks.

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