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Case report

Isolated Hepatitis B Surface Antigen Positivity Following Vaccination Against Coronavirus Disease A report of two cases

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Abstract

Coronavirus disease 2019 (COVID-19)—a respiratory illness caused by a recently identified, highly transmissible virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has had considerable global morbidity and mortality.1,2 As a result, a number of anti-SARS-CoV-2 vaccines have been developed with unprecedented speed. Hepatitis B surface antigen (HBsAg) is the most common marker of acute HBV infection and is detectable between 1–9 weeks of exposure to the virus, with decreasing HBsAg concentrations indicative of resolving viremia. Herein, we report two cases of isolated HBsAg positivity after COVID-19 vaccination in the absence of other HBV markers, symptoms, risk factors, or recent vaccination. The test turn to ne negative after period of time in both cases. Laboratory technicians and clinicians alike should be aware of the possibility of HBsAg false-positivity following anti-SARS-CoV-2 vaccination.

Introduction

Coronavirus disease 2019 (COVID-19)—a respiratory illness caused by a recently identified, highly transmissible virus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—has had considerable global morbidity and mortality.1,2 As a result, a number of anti-SARS-CoV-2 vaccines have been developed with unprecedented speed.3 While these vaccines have satisfactory efficacy and safety profiles, experience with their use is undeniably limited.4,5 Accordingly, additional knowledge of rare side-effects is important to inform future recommendations.

Hepatitis B is a highly contagious liver infection caused by the hepatitis B virus (HBV), a virus transmissible via contact with contaminated bodily fluids, including blood, saliva, semen, or vaginal secretions; in addition, it can also be transmitted to an infant during childbirth.6 Up to 30% of the global population is believed to have a current or previous HBV infection.7 Hepatitis B surface antigen (HBsAg) is the most common marker of acute HBV infection and is detectable between 1–9 weeks of exposure to the virus, with decreasing HBsAg concentrations indicative of resolving viremia.8 Individuals who have achieved immune control of HBV infection will typically show HBsAg negativity approximately 15 weeks after infection onset.8

In 1981, the first HBV vaccine was approved for human use.7 Transient antigenemia is known to occur for up to two weeks after HBV vaccination, thereby leading to a false-positive diagnosis of HBV infection.9,10 However, there are as yet no reports of hepatitis B antigenemia following SARS-CoV-2 vaccination. Herein, we report two cases of isolated HBsAg positivity after COVID-19 vaccination in the absence of other HBV markers, symptoms, risk factors, or recent vaccination.

Case 1

A 37-year-old woman with no significant medical history underwent

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hepatitis screening during a routine medical check-up. Laboratory testing indicated HBsAg positivity and hepatitis C antibody negativity. No evidence of liver disease was found during a physical examination. She had received two doses of the BNT162b2 COVID-19 vaccine (Pfizer/BioNTech), with the last dose received 4 months earlier. The patient was a health care worker; however, there were no recognized self-reported risk factors for viral hepatitis, including needle stick injury. Furthermore, she had been vaccinated against HBV many years beforehand, with good immunity response, and an HBsAg test conducted two years earlier had been negative.

An HBV profile performed after one week using the neutralization method showed negative HBsAg findings (0.4 IU/mL) [Figure 1], a protective titer of HBsAg antibodies (anti-HBs; >1,000 IU/mL), and negative findings for hepatitis B core antibody (anti-HBc), hepatitis B envelope antigen (HBeAg), and hepatitis B envelope antibody. No viral load was detected with regards to HBV DNA.

Case 2

A 14-year-old boy underwent hepatitis screening during a routine sports medical evaluation. He had received two doses of the BNT162b2 COVID-19 vaccine (Pfizer/BioNTech), with the last dose received a month beforehand. All routine laboratory findings were within normal limits, except for HBsAg positivity. No hepatitis indicators were found during a physical examination. An HBV profile performed one week later failed to detect HBsAg (0.17 IU/mL) [Figure 2]. The boy had been vaccinated against HBV at one year of age as part of a routine child immunization program.

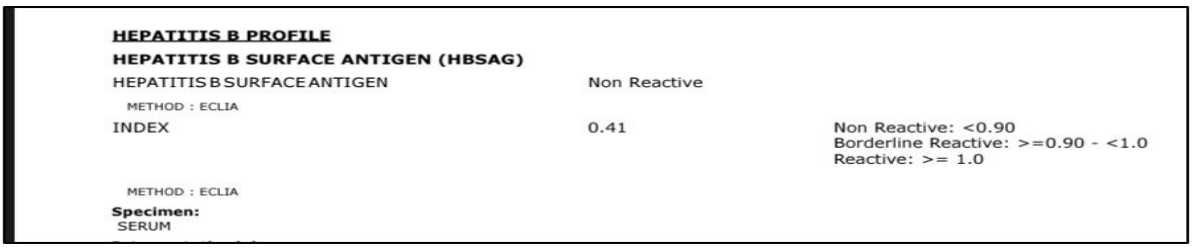
Discussion

Recommended testing to evaluate for HBV infection includes HBsAg, anti-HBs, and anti-HBc (immunoglobulin M [IgM] for acute in infection and IgG for past exposure).7,8 However, correct interpretation of the findings is paramount to avoid misdiagnosis and inappropriate management. Although transient antigenemia can persist for up to two weeks after HBV vaccination, neither of the patients described in this report had been vaccinated against HBV in the weeks prior to their presentation.9,10 In both cases, HBsAg positivity occurred in the absence of clinical indicators of an underlying HBV infection or HBV risk factors and positivity to other hepatitis B markers, highly suggestive of false positivity.

Different hepatitis B markers become detectable as the infection evolves and can therefore be used to differentiate between acute and chronic infections and susceptibility to future infection.11,12 In the early phase of acute infection, HBsAg is the first marker to develop, followed shortly by HBeAg approximately one week after HBsAg is detectable.12 In those who are symptomatic, there is a rapid rise and then a slow decrease in IgM anti-HBc. Finally, in the convalescence stage, anti-HBs positivity occurs at approximately 6 weeks to 6 months of exposure, once HBsAg has disappeared.11,12 Under normal circumstances, isolated HBsAg positivity therefore occurs only in the very early stages of acute HBV infection before the patient is symptomatic [Figure 3].

False-positive isolated HBsAg seropositivity has been described in other circumstances, including in the setting of malignancy.11,13 Costa et al. reported a 77-year-old female patient with a basal cell carcinoma who demonstrated persistent isolated HBsAg positivity, despite periodic testing over several months.11 Similarly, Tang et al. described a middle-aged female with primary hyperparathyroidism with repeated HBsAg positivity over a 5-week period prior to the surgical removal of a parathyroid adenoma.13 Other instances in which isolated HBsAg seropositivity may occur include mutated HBV variants and underlying immune conditions such as lupus.11,14

Both groups of researchers attributed the HBsAg positivity in their respective cases to heterophilic antibody



HEPATITIS B PROFILE

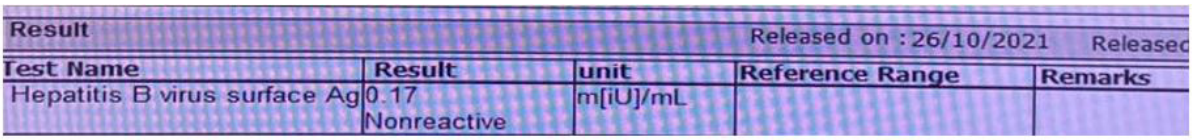
HEPATITIS B SURFACE ANTIGEN (HBSAG)

HEPATITIS B SURFACE ANTIGEN	Non Reactive	
METHOD : ECLIA		
INDEX	0.41	Non Reactive: <0.90 Borderline Reactive: >=0.90 - <1.0 Reactive: >= 1.0

METHOD : ECLIA

Specimen:
SERUM

Figure 1: *Final HBsAg results for Case 1.*



Result — Released on : 26/10/2021 — Released

Test Name	Result	unit	Reference Range	Remarks
Hepatitis B virus surface Ag	0.17 Nonreactive	m[iU]/mL		

Figure 2: *Final HBsAg results for Case 2.*

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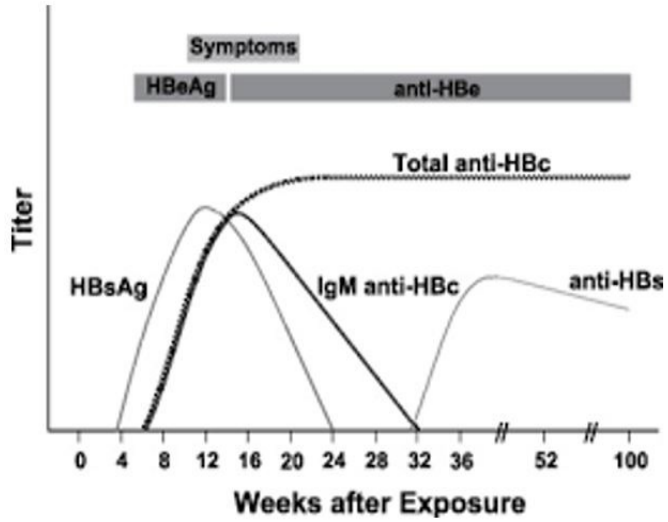

Figure 3: *Serological profile of an acute HBV infection.*

Reproduced from the Hepatitis B Foundation website.[8]

interference.11,13 Heterophilic antibodies are poorly defined, low-affinity immunoglobulins which can cross-react with a wide range of animal antigens. As such, the presence of heterophilic antibodies have been shown to affect findings from lateral-flow immunoassays by binding to the target antigen, thereby generating false-positive results.15 Consequently, Costa et al. recommended that initial positive HBsAg findings be confirmed using a neutralization technique in which anti-HBs is incubated with HBsAg to block the HBsAg signal.11

Other infections, such as Epstein-Barr virus, may also give rise to low levels of heterophilic antibodies that can persist for up to a year.11,16 Rheumatoid factor cross-reactivity has also been found to result in misleading immunoassay findings.11,17 The two cases of HBsAg positivity described in this report appeared to be isolated, with subsequent testing failing to show persistent antigenemia, lending support to the theory that the false positivity may have been due to an indigenous factor or an exogenous analytical or operational error.17 Appropriate blocking agents are therefore recommended in order to minimize the risk of false-positive reactions.17,18

Conclusion

To the best of the authors' knowledge, the two cases presented in this paper are the first reports of isolated HBsAg positivity following COVID-19 vaccination. Laboratory technicians and clinicians alike should be aware of the possibility of HBsAg false-positivity following anti-SARS-CoV-2 vaccination, although further research is needed to determine whether such findings are the result of the vaccination or due to other factors. Misdiagnosis of HBV can have potentially serious implications, including inappropriate management, unnecessary testing, surgical or treatment delays, adverse emotional consequences, and social stigma.

Declaration of Conflicting Interests

The authors declare no conflicts of interest.

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Patient Consent

No photographs or information which could be used to identify the individual patients described in this case report were included.

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