

Hepatitis B surface antigen escape mutations: Indications for initiation of antiviral therapy revisited

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Abstract

Approximately 240 million people are chronically infected with hepatitis B. The implementation of rigorous vaccination programs has led to an overall decrease in the prevalence of this disease worldwide but this may also have led to emergence of viral mutations that can escape the protection of hepatitis B surface antibody. As this phenomenon is increasingly recognized, concern for transmission to vaccinated individuals has also been raised. Herein, we describe two cases where the suspected presence of a hepatitis B surface antigen escape mutation impacted the decision to initiate early antiviral therapy, as well as provide a brief review of these mutations. Our findings described here suggest that a lower threshold for initiating therapy in these individuals should be considered in order to reduce the risk of transmission, as vaccination does not provide protection.

Key words: Hepatitis B virus; Hepatitis B surface antigen; Escape mutant; Hepatitis B immunoglobulin; Vaccination

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Core tip: Hepatitis B surface antigen escape mutations are being increasingly recognized, along with concern for the risk of transmission to vaccinated individuals.

The management of these patients and the natural history of the disease remain controversial due to insufficient data. However, transmission of this mutated virus to vaccinated individuals has been reported in the literature. Herein, we discuss two different clinical scenarios that led to the initiation of early antiviral therapy in order to decrease the risk of transmission to others due to the suspected presence of this mutation.

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INTRODUCTION

The World Health Organization estimates that over 2 billion people worldwide have been infected with hepatitis B virus (HBV). Approximately 240 million are chronically infected and therefore are at risk for life-threatening complications as a consequence of this disease^[1]. The introduction of universal vaccination at birth, as well as other HBV immunization campaigns, has led to a significant reduction in the transmission of HBV in endemic countries^[2,3]. However, with the success of these immunization strategies, there have been increasing reports of mutant viruses that develop despite vaccination, leading to concern about the threat they may pose to the public. These mutant viruses have been found to occur as a result of selection pressure from vaccination, hepatitis B immunoglobulin (HBIG) and have even been reported to occur spontaneously^[4-6]. Despite increasing awareness of the emergence of hepatitis B surface antigen (HBsAg) escape mutant virus, there is no consensus on the treatment and management of individuals infected with these mutants. At present, there is also no easily available assay to diagnose these individuals when they are suspected of harboring HBsAg escape mutants. Here we highlight two clinical cases in which recognition of the presence of HBsAg escape mutations influenced the decision to initiate early antiviral therapy, as well as provide a brief review of HBsAg escape mutants.

CASE REPORT

Case 1

A 35-year-old G1P0 Korean woman presented at 13 wk gestation for evaluation of HBV discovered on routine prenatal screening. She was HBV treatment naïve and had never received a liver biopsy. She otherwise had no significant past medical or surgical history. She moved to the United States from South Korea at the age of 17. Her family history is significant for chronic HBV in both her mother and sister but no history of hepatocellular carcinoma (HCC). She reported a history of vaccination

for HBV as a child.

Screening for virologic markers was positive for HBsAg, hepatitis B surface antibody (anti-HBs), hepatitis B core IgG antibody (anti-HBc IgG) and hepatitis B e antigen (HBeAg). She had negative markers to hepatitis B core IgM antibody (anti-HBc IgM) and hepatitis B e antibody (anti-HBe). Serum HBV DNA was detected with a viral level of 1707 copies/mL, mildly elevated alanine aminotransferase (ALT) level of 31 U/L (normal < 19 U/mL for women)^[7] and aspartate aminotransferase (AST) level of 31 U/L. Her alpha-fetoprotein (AFP) level was mildly elevated at 29.7 ng/mL, but this was felt to be consistent with her pregnancy, as AFP is known to be produced by human fetus and an abdominal ultrasound was negative for any suspicious liver lesion.

Her HBV DNA and ALT levels were monitored closely during her pregnancy without any evidence of hepatitis flare. She was sexually active with her husband who had previously been vaccinated for HBV but had not developed anti-HBs.

The patient was counseled on standard prevention of perinatal transmission with active and passive immunization of the infant. However, due to the concerns of transmission with HBV escape mutant, despite maintaining a low viral load throughout her pregnancy, she was started on treatment with tenofovir 300 mg orally once a day at 32 wk gestation, as HBV vaccination and administration of HBIG would be ineffective against HBsAg escape mutant HBV. The infant received hepatitis B vaccination as well as HBIG at birth and follow-up so far has shown the child to free of HBV infection.

Case 2

A 49-year-old Laotian man with chronic hepatitis B was referred for evaluation of a liver lesion discovered on screening ultrasound. He had previously been diagnosed with HBV in 2008, had no prior anti-HBV therapy, no prior liver biopsy, nor jaundice or other signs of hepatic decompensation. His past medical history was significant for latent tuberculosis, not treated given concern for isoniazid hepatotoxicity, and chronic sinusitis. He was born in Laos to Chinese immigrant parents and moved to the United States at the age of 16. He is married to a registered nurse, and they have a 17-year-old son. His family history is significant for a sister with chronic HBV, his father with HCC, and his mother with gastric cancer.

Screening for virologic markers was positive for HBsAg, anti-HBs, anti-HBc IgG, and anti-HBe. He had negative markers to anti-HBc IgM and HBeAg. Serum HBV DNA was detected with a viral level of 6100 copies/mL and mildly elevated ALT of 52 U/L (normal < 30 U/L for men)^[7] and normal AST of 25 U/L. His AFP was normal at 2 ng/mL. Liver ultrasound showed a stable 9 mm × 10 mm × 8 mm lesion consistent with a hemangioma and a new 3 mm × 3 mm × 3 mm lesion in the right lobe of the liver. Follow-up magnetic resonance imaging did not demonstrate any evidence of HCC or cirrhosis. FIBROspect II analysis was consistent

with F0-F1 (no fibrosis-portal tract fibrosis).

His wife was previously vaccinated against HBV and had protective anti-HBs as part of her employment screening as a nurse but reported that three years ago she was prevented from donating blood due to positive HBsAg. Previously, she was a regular blood donor. Although the patient was asymptomatic with a low HBV DNA level, normal ALT, and a reassuring FIBROspect, given the possibility that he likely infected his previously vaccinated wife with HBV escape mutant, the decision was made to start him on antiviral therapy to prevent further transmission among household contacts such as his son.

DISCUSSION

HBV with coexisting HBsAg and anti-HBs have long been reported in up to 10%-25% of patients with chronic hepatitis B, but were initially felt to be variants of no clinical importance^[8]. However, several studies have since shown that the coexistence of HBsAg and anti-HBs is associated with mutations in the a determinant region of the HBsAg^[9-12]. The significance and impact of these mutations was first recognized in 1988 when Zanetti *et al.*^[13] reported infants born to HBsAg carrier mothers who developed breakthrough infections despite receiving HBIG and HBV vaccine at birth. A single point mutation was identified in the surface antigen region from guanosine to adenosine at nucleotide position 587, resulting in amino acid (aa) substitution from glycine to arginine at position 145 in the a determinant of the HBsAg. This *G145R* mutation alters the conformation of the a determinant so that the neutralizing antibodies induced by vaccination are no longer able to recognize the virus, thereby resulting in breakthrough infection^[13]. Since this discovery, other surface gene (S-gene) mutations with the same ability to evade immunization and infect vaccinated individuals have been reported, leading to increasing concern that these mutations may overcome the wild type and infect those who have been vaccinated. These mutations were also later recognized to occur after administration of HBIG in liver transplant recipients^[14]. In addition, S-gene mutations have also been found to occur spontaneously, hypothesized to be due to the pressure of the host immune system, although the mechanism by which this occurs remains unclear^[10,15].

At present, the clinical significance of HBsAg escape mutations remains controversial. A mathematical model proposed in 1998 by Wilson *et al.*^[16] predicted the disappearance of wild-type HBV in 200 years and the emergence of the *G125R* mutant as the common HBV in 60-100 years, based on the assumption that the current vaccination does not protect against this mutation. Several surveys in Taiwan have shown that the proportion of mutant viruses in HBV-infected children had increased significantly since the implementation of the universal vaccination program: 7.8% in 1984 just before the program implementation to 28.1% in 1994

and 23.1% in 1999^[3,17]. A more recent epidemiologic survey published by Hsu *et al.*^[18] on the other hand, showed that with the reduction in the total number of children infected with HBV as a result of universal vaccination program, the prevalence of HBV mutants has actually decreased over time. This was also followed by a study published by Lai *et al.*^[19] which confirmed the decreased prevalence of HBV mutants in Taiwan. By measuring HBsAg, anti-HBs and anti-HBc from various age groups in 2007, the authors found that the HBsAg carrier rate, anti-HBc seropositive rate and infection rate was significantly lower in those who were born after the initiation of the vaccination program in Taiwan as compared to those who were born before the program. However, when compared across age groups, there was a significant increase in the HBV DNA positive rate for those who were 18-21 years of up to 3% as compared to those of younger age. In addition, the prevalence of HBsAg mutants was 2.63% in those > 18 years of age, but only 0.10% in those younger than 18. Thus, the authors concluded that although the prevalence of HBV infection has decreased with universal vaccination, continued monitoring for the presence of HBV infection is important due to the risk of mutant strains developing, particularly as this population continues to age^[19].

As discussed above, the long-term impact that these HBsAg escape mutations may have on the natural history of chronic HBV remains unknown. On a public health level, some studies have suggested that these viruses lack stability and tend to result in lower levels of viremia, thus perhaps explaining why the viruses have not become as large of a threat to immunization programs as originally predicted^[20]. On an individual level, however, there has been data to suggest that these patients may be at increased risk for active chronic hepatitis with higher HBV DNA levels and more advanced fibrosis^[9]. There is also concern that the accumulation of mutations may lead to failure of recognition of HBsAg by currently available diagnostic assays, thereby leading to a missed diagnosis of chronic HBV infection^[21,22]. In addition, there is a real concern regarding the risk of transmission to others, as vaccination does not provide protection from these mutated viruses. The risk of horizontal transmission is not currently well defined, but there are prior case reports in the literature^[23,24]. One Taiwanese study identified that at least 26% of the HBV mutant-infected children who experienced immunization failure were born to non-carrier mothers, implying the possibility of horizontal infection or a spontaneous emergence of the mutant during the course of chronic infection^[18].

In summary, while the threat that HBsAg escape mutants poses to the world at this time does not seem to be on as large a scale as initially feared, its significance may be considerable on individual patient levels. The possibility of transmitting the virus to other household and sexual contacts is real and needs to be addressed. In situations where the risk of sexual, vertical, or horizontal transmission is present, patients and their

family members should be counseled carefully, and consideration should be given towards having a lower threshold to initiating potent antiviral therapy in these individuals to reduce the risk of transmission. Studies have clearly shown that the coexistence of HBsAg and anti-HBs is not as rare as once thought. Therefore, screening tests for HBV should routinely include HBsAg, anti-HBs and anti-HBc, especially in those who have close contact with individuals with chronic HBV infection.

COMMENTS

Case characteristics

Herein are two cases of individuals with chronic hepatitis B presenting with coexisting hepatitis B surface antigen (HBsAg) and anti-HBs without symptoms.

Clinical diagnosis

Case 1 is a 35-year-old pregnant, but otherwise asymptomatic woman presenting with newly diagnosed hepatitis B virus (HBV) infection and Case 2 is a 49-year-old man with chronic HBV infection who likely transmitted HBV to his wife despite immunity from prior vaccination.

Differential diagnosis

Due to the history of prior vaccination and the presence of concomitant HBsAg and anti-HBs, it was felt likely that both patients were infected with HBsAg escape mutants.

Laboratory diagnosis

Both patients had serologies positive for HBsAg, anti-HBs, slightly abnormal liver enzymes and quantifiable HBV DNA tests.

Treatment

Initiation of antiviral therapy with tenofovir in both cases.

Related reports

Reports of HBsAg mutant strains of HBV have been increasingly recognized with the introduction of universal vaccination. There have been published case reports of this mutation transmitted to others despite the presence of protective antibodies from prior HBV vaccination.

Term explanation

HBsAg escape mutants are due to mutations in the a determinant region of the HBsAg. These mutations allow the virus to escape neutralizing antibodies from the administration of hepatitis B immunoglobulin and HBV vaccine.

Experiences and lessons

Physicians should maintain a level of suspicion in patients with coexisting HBsAg and anti-HBs in the appropriate clinical situation, and should counsel their patients on the risks and benefits of early treatment.

Peer-review

A limitation of this paper is the inability to perform molecular confirmation of HBsAg escape mutations. However, this is not available in real-world clinical practice. This manuscript describes two interesting case studies that generate clinically relevant questions for an infrequent but important issue in the management of patients with HBV infection.

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