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Case Report

Spontaneous Seroconversion of Hepatitis B Surface Antigen in a Young Woman with Chronic Carrier

Katsuhisa OMAGARI,[1] Jun-ichi MASUDA,[1,2] Hideki KINOSHITA,[2] Shiho AKAZAWA,[1] Yoshiko KADOKAWA,[1] Hiroaki HAZAMA,[1] Kazuo OHBA,[1] Ken OHNITA,[1] Kenji HAYASHIDA,[1] Yohei MIZUTA,[1] Shigeru KOHNO[1]

[1] Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan

[2] Department of Internal Medicine, Goto Chuo Hospital, Goto, Nagasaki, Japan

The incidence of spontaneous seroconversion of hepatitis B surface antigen (HBsAg) in the natural history of patients with chronic hepatitis B virus (HBV) infection is considered to be low in patients aged under 40 years. The clinical course and outcome of chronic HBV infection are complex and heterogeneous, and may be influenced by many factors such as HBV genotype, viral mutations, gender, age, host immune status, other viral co-infections, and alcohol consumption. We encountered a Japanese woman in whom HBsAg seroconversion had occurred when she was 32 years old, 3 years after she had given birth without any anti-viral therapy. In this case, alcohol intake, pregnancy and delivery may have affected the host-virus interaction.

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Introduction

Hepatitis B virus (HBV) is one of the most common infectious agents in the world. It has been estimated that 350 million people worldwide are chronic HBV carriers, although the prevalence shows striking geographic and ethnic variations from high (>8%) to low (<2%).[1] There are four stages of chronic HBV infection based on viral-host interaction. The first stage is characterized by immune tolerance, with the presence of hepatitis B e antigen (HBeAg) and large quantities of HBV-deoxyribonucleic acid (DNA) in the serum. The second stage is the period of symptomatic hepatitis. By the third stage, most of the virus-infected cells have been cleared, mediated by the host immune response. Replication ceases, and HBeAg disappears despite the presence of circulating hepatitis B surface antigen (HBsAg). In the fourth stage, HBsAg has been cleared and the presence of antibody to HBsAg (anti-HBs) signals the development of full immunity to the virus.[2-5] Liver cirrhosis and hepatocellular carcinoma are two major long-term complications of chronic HBV infection that significantly increase morbidity and mortality.

The natural course of persistent HBV infection is not fully understood, but the spontaneous clearance of HBsAg in a chronic carrier is considered to be an unusual event[4-6] especially in the patient's first, second or third decade of life. We report herein a case of chronic carrier in whom the spontaneous HBsAg seroconversion occurred when she was 32 years old.

Case report

A 26-year-old Japanese woman visited Nagasaki University Hospital in February 2000 with the 11-year history as an HBeAg-positive asymptomatic carrier. There was no family history of liver diseases including HBV-related liver diseases, and she had never received a blood transfusion. Alcohol intake included 3 liters of beer per day for 6 years. Physical examination disclosed no abnormalities. Laboratory data at the time of this examination are shown in Table 1. The HBV genotype determined by restriction fragment length polymorphism (RFLP)[7] (SRL Inc., Tokyo, Japan) was genotype C. This patient was determined to be a chronic HBV carrier with the disease in the first stage, characterized by immune tolerance with the pres-

Address correspondence: Katsuhisa Omagari, M.D., Second Department of Internal Medicine, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501 JAPAN

TEL: +81-(0)95-849-7281, FAX: +81-(0)95-849-7285, E-mail: omagari@net.nagasaki-u.ac.jp

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Table 1. Laboratory data on February 23, 2000

Test	Results	Normal range
Peripheral blood		
White blood cells (/μL)	7,300	3,500-9,000
Red blood cells ($\times10^4$/μL)	474	380-480
Hemoglobin (g/dL)	12.9	11.5-14.5
Platelets ($\times10^4$/μL)	23.9	14-33
Prothrombin time (%)	98	82-127
Blood chemistry		
Total bilirubin (mg/dL)	0.8	0.3-1.5
Total protein (g/dL)	6.8	6.7-8.3
Albumin (g/dL)	4.7	4-5
Aspartate aminotransferase (IU/L)	18	13-33
Alanine aminotransferase (IU/L)	16	8-42
Lactate dehydrogenase (IU/L)	117	119-229
Alkaline phosphatase (IU/L)	154	115-359
Leucine aminopeptidase (IU/L)	50	30-70
Gamma-glutamyl transpeptidase (IU/L)	15	10-47
Cholinesterase (IU/L)	92	107-233
Thymol turbidity test (U)	7.8	0-4
Zinc turbidity test (U)	7.9	4-12
Total cholesterol (mg/dL)	160	128-220
Triglyceride (mg/dL)	52	38-207
Amylase (IU/L)	69	40-130
Blood urea nitrogen (mg/dL)	15	8-22
Creatinine (mg/dL)	0.6	0.4-1.1
Virus markers		
Hepatitis B surface antigen (HBsAg) (index)	48.9	<2.0
Antibody to HBsAg (anti-HBs) (index)	0.7	<2.0
Hepatitis B e antigen (HBeAg) (index)	130.6	<2.0
Antibody to HBeAg (anti-HBe)	0	<30
Antibody to hepatitis B core antigen (anti-HBc) (%)	100.2	<30
Anti-HBc (×200) (%)	61.1	<30
HBV-DNA genotype[a]	C	
Antibody to hepatitis C virus (anti-HCV) (COI[b])	0.3	<1.0
Immunology and tumor marker		
Anti-nuclear antibody	×20 (speckled)	
Alpha-fetoprotein (ng/mL)	0.5	<10

[a]The HBV-DNA genotypes were determined by restriction fragment length polymorphism (RFLP) (SRL Inc., Tokyo, Japan) using stocked serum.
[b]COI=Cut-off index (third-generation enzyme-linked immunosorbent assay).

ence of HBeAg.[2,3,5] The patient was subsequently examined at our outpatient clinic every 2 months but not treated with anti-viral drugs. Her serum levels of total bilirubin, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) had been within normal limits until March 2002. In June 2002, she was in the 9th week of pregnancy and her serum AST and ALT levels began to increase. By November 2002, her serum total bilirubin level had increased to 5.9 mg/dL, serum AST level was 828 IU/L, and ALT level was 608 IU/L. By the beginning of December 2002, her serum total bilirubin, AST and ALT levels had returned to within normal limits without medication, and she gave birth to her first son through a normal delivery near the end of December 2002. Subsequently, her HBeAg status turned negative and antibody to HBeAg (anti-HBe) appeared in January 2004 (HBeAg seroconversion); HBsAg clearance occurred in March 2005, followed by the appearance of anti-HBe in October 2005 (HBsAg seroconversion) without elevation of serum AST and ALT levels (Figure 1).

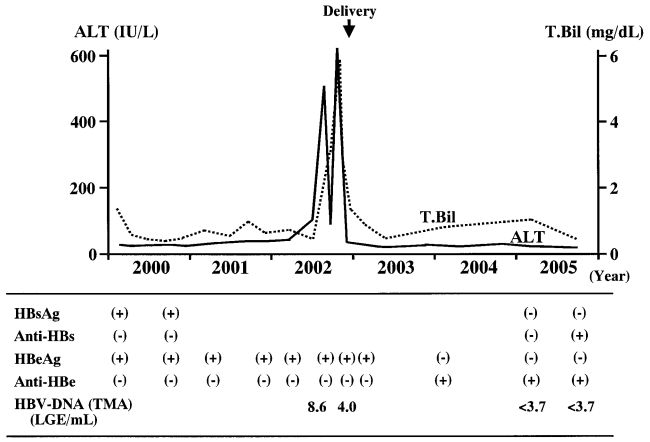

Figure 1. Clinical course. ALT: alanine aminotransferase; T.Bil: total bilirubin; HBsAg: hepatitis B surface antigen; Anti-HBs: antibody to HBsAg; HBeAg: hepatitis B e antigen; Anti-HBe: antibody to HBeAg; HBV-DNA: hepatitis B virus-deoxyribonucleic acid; TMA: transcription mediated amplification method.

Discussion

Perinatal transmission of HBV, particularly mother-to-child transmission (i.e., vertical infection), is the most common mode of infection, especially in East Asia, and frequently leads to a chronic carrier state (the first stage).[8] In Japan, most patients who are chronic carriers develop liver disorders during adolescence (the second stage) and exhibit HBeAg seroconversion (from HBeAg to anti-HBe) (the third stage), resulting in "transient hepatitis". However, chronic hepatitis develops in approximately 10% of these patients and liver cirrhosis eventually develops in 10-20% of the patients with chronic hepatitis, ultimately leading to hepatocellular carcinoma.[9] The annual HBeAg seroconversion rate is reported to be around 10% (2.7-21.1%), but the incidence of delayed HBsAg clearance in the natural history of patients with chronic HBV infection is considered to be low.[4,6,8,10-14] However, some carriers eventually become HBsAg-negative and develop anti-HBs. It is reported that the incidence of delayed HBsAg clearance is 1-2% per year in Western countries, but only 0.05-0.8% per year in endemic areas where HBV infection was often acquired perinatally or during early childhood.[3,6,10] Of these latter cases, women and older carriers have higher clearances of HBsAg.[3] Kato et al.[8] reported, on the basis of a long-term follow-up study in Goto Islands of Nagasaki, Japan, that spontaneous loss of HBsAg occurred in 38 (29%) of 131 HBsAg carriers, independent of gender or the results of liver function tests, during the follow-up of 12.2 years on average; the mean annual incidence was about 2.5%. They further reported that this loss was seen more frequently in carriers aged 40 years or more, and concluded that the spontaneous loss of HBsAg, largely attributable to the clearance of viremia, occurs age-dependently in chronic carriers.[8] The subsequent development of anti-HBs, which is thought to imply a good prognosis,[15] may be necessary to confirm the termination of HBV infection.[6] However, Huo et al.[14] reported that hepatitis B viremia might persist in some HBsAg-clearance patients irrespective of the status of serum anti-HBs, and that adverse complications including liver cirrhosis, hepatocellular carcinoma, and fulminant hepatic failure were not rare in such patients.

The patient in the present report was a heavy drinker and had HBV genotype C; HBsAg seroconversion occurred when the patient was 32 years old, 3 years after giving birth. As described above, the clinical course and outcome of HBV infection are complex and heterogeneous, and may be influenced by many factors such as HBV genotype, viral mutations, gender, age, host immune status, other viral coinfections, and alcohol consumption.[8] Hepatitis B virus is classified into eight genotypes (A-H) based on the intergroup divergence of 8% or more in the complete nucleotide sequence of viral genomes,[16] and in Japan, HBV genotype C is the most prevalent genotype (approximately 80%) among patients with type B chronic liver diseases.[17] It has been reported that spontaneous HBeAg seroconversion occurred one decade later in genotype C patients compared with genotype B patients.[18] The genotype distribution of HBV may also account for differences in annual HBsAg clearance rates. However, since this patient had HBV genotype C, genotype does not seem to account for early HBsAg seroconversion.

Pregnancy and delivery may also affect immune response. During pregnancy, there is increased production of certain hormones including adrenal corticosteroids, estrogen, and progesterone, which have immunosuppressive properties. After delivery, these hormones decrease rapidly and the immunosuppression state is then removed.[19] Pregnancy also causes a shift from T helper 1 (Th1) response to T helper 2 (Th2) response.[20] Therefore, these complicated immune responses could alter the host-virus interaction. Indeed, Lin et al.[19] reported that subsidence of HBV replication was precipitated by delivery in one-third of HBeAg-positive carrier mothers, and this occurred most frequently 1-2 months postpartum. However, our patient had overt hepatitis during pregnancy that subsided before delivery. One possible explanation for this clinical course is that the patient stopped drinking during pregnancy and the subsequent lactation period. Because heavy alcohol intake may alter immune regulation leading to immunodeficiency or autoimmunity,[21] it would be conceivable that physiologic rebound of the waning immunosuppressive state occurred after alcohol intake ceased in the present case. The HBV-DNA concentration decreased during delivery, and subsequently HBeAg and HBsAg seroconversions occurred after delivery.

In conclusion, heavy alcohol intake, pregnancy and delivery may have affected the early HBsAg seroconversion in the present case. A more accurate understanding of the complicated host-virus interaction is needed.

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