Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3028-19
Intern Med 58: 2963-2968, 2019
http://internmed.jp

【 CASE REPORT 】

Acute Liver Failure Caused by the Transmission of Hepatitis B Virus from the Spouse after 38 Years of Marriage

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Abstract:
A 65-year-old man presented with acute liver failure and grade IV coma caused by hepatitis B virus (HBV) infection in 2017. The patient died on day 12 from the disease onset. The HBV isolated from the patient was genotype/subgenotype B/B1 and had multiple genomic mutations. The patient's wife was hepatitis B surface antigen (HBsAg)-positive when she delivered her first daughter in 1979. The HBV isolates of the patient and the wife shared 100% similarity over the entire genome. Because the patient's HBsAg value had been negative one year earlier, we considered the source of HBV transmission to be his wife.

Key words: hepatitis B virus, acute liver failure, mutation, interspousal transmission

(Intern Med 58: 2963-2968, 2019)
(DOI: 10.2169/internalmedicine.3028-19)

Introduction

Hepatitis B virus (HBV) can cause acute hepatitis in an adult individual who does not possess anti-hepatitis B surface (HBs) antibody. In most cases, acute hepatitis B is self-limited with a time course of several weeks. However, in approximately 1% of cases, acute hepatitis B progresses to acute liver failure with coma, also referred to as fulminant hepatitis. Once fulminant hepatitis develops, 50-60% of patients die (1, 2). Thus, the appropriate management of patients with HBV infection and the education of high-risk groups are important in order to prevent further HBV transmission.

At present, sexual contact is the leading cause of HBV infection in Japan (3). Individuals without anti-HBs antibody have a high risk of contracting HBV infection if their partner is an HBV carrier. Indeed, among couples where one spouse is HBs antigen (HBsAg)-positive, the partner is frequently found to be an HBV carrier (4). It is estimated that HBV transmission occurs within 2 years of marriage in 86.7% of such couples (5). When these patients contract HBV infection, most present with a mild clinical course, with only 10.9% showing acute hepatitis (5). In contrast, although HBV transmission after 10 years of marriage is rare, fulminant hepatitis has been reported in the spouse (6).

Seroconversion from hepatitis B e antigen (HBeAg) to the corresponding antibody (anti-HBe) is believed to be an indicator of a favorable clinical course, as this seroconversion can lead to a reduction in the levels of HBV DNA and serum transaminases (7). At that time, the viral genome of HBV develops mutations under sustained immunological pressure from the host (8). Among mutations, G1896A is well known to inhibit the production of HBeAg. In contrast, multiple mutations can alter the biological features of HBV. For instance, G1896A coupled with G1889A mutations in the precore region has been reported to increase HBV replication (9). In addition, these mutations are observed in patients with fulminant hepatitis (6).

We herein report a case of acute liver failure caused by

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Received: March 14, 2019; Accepted: April 16, 2019; Advance Publication by J-STAGE: June 27, 2019
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Table 1. Laboratory Data on Admission.

Peripheral blood		Biochemical		Viral markers	
WBC	13,500 /μL	TP	5.6 g/dL	HBsAg	24.11 IU/mL, (+)
RBC	3.95×10^6 /μL	Albumin	3.3 g/dL	Anti-HBs	0.36 mIU/mL, (-)
Hemoglobin	12.3 g/dL	T-Bil	4.5 mg/dL	HBeAg	1.95 S/CO, (+)
Hematocrit	38.8 %	AST	8,598 U/L	Anti-HBe	30.4 INH%, (-)
Platelet	5.0×10^4 /μL	ALT	8,589 U/L	Anti-HBc	6.49 S/CO, (+)
Coagulation		LDH	9,004 U/L	IgM anti-HBc	21.6 S/CO, (+)
PT	102.1 sec	ALP	655 U/L	HBV DNA	4 LogIU/mL
PT%	3.1 %	γ-GTP	124 U/L	HBV genotype	B
PT-INR	9	BUN	36 mg/dL	IgM anti-HAV	–
Serology		CRE	6.09 mg/dL	Anti-HCV	–
ANA	±	Na	141 mmol/L	HIVAg/Anti-HIV	–/–
AMA	–	K	6.5 mmol/L	IgM/IgG anti-HSV	–/+
		Cl	94 mmol/L	IgM/IgG anti-CMV	–/+
		NH_3	691 μmol/L		

HBV markers were examined in Jichi Medical University Hospital on Day 5. Other data were obtained in a local hospital on Day 4 after the onset.

WBC: white blood cells, RBC: red blood cells, PT;prothrombin time, INR: international normalized ratio, ANA ;antinuclear antibody,AMA: anti-mitochondria antibody, TP: total protein, T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP;alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, BUN: blood urea nitrogen, CRE: creatinine, Ag: antigen, HAV: hepatitis A virus, HCV: hepatitis C virus, HIV: human immunodeficiency virus, HSV: herpes simplex virus, CMV: cytomegalovirus. S/CO: signal/cut-off

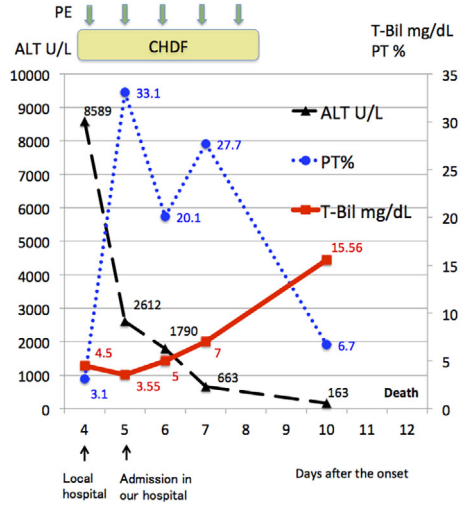

Figure 1. The clinical course of the present case. PE: plasma exchange therapy, CHDF: continuous hemodiafiltration. The day indicates the date from the onset of hepatitis.

HBV. Although the patient's wife had been diagnosed with HBV infection at the time of her first delivery, HBV transmission was avoided until 38 years after marriage. We therefore analyzed the HBV genomes and discussed the cause of this case of HBV transmission after a long-lasting marriage.

Case Report

A 65-year-old Japanese man first noticed a fever and then presented with bleeding in the oral cavity on day 4 from the onset of hepatitis. He was admitted to a local hospital on the same day and transferred to our hospital on day 5 due to severe hepatic injury (Table 1) and grade IV hepatic coma (as proposed by the Inuyama Symposium) (10).

The laboratory data and level of consciousness met the criteria for acute liver failure with coma, also referred to as fulminant hepatitis. A serum analysis showed a high titer of IgM class antibody against HBV core (IgM anti-HBc) and excluded other causes of hepatic injury, including hepatitis A, hepatitis C, autoimmune hepatitis, and cytomegalovirus and herpes simplex virus infections. Although we continued to provide intensive care, including plasma exchange therapy, entecavir (0.5 mg every 48 hours), and continuous hemodiafiltration (CHDF), the clinical status did not improve (Fig. 1). CT scans showed the progress of liver atrophy and ascites (Fig. 2a and b). On day 7, he was withdrawn from the liver transplantation program because of irreversible central nervous system damage, which included brain edema (Fig. 2c and d) and a loss of the brain-stem reflex and light reflex. He ultimately died on day 12 after the onset of hepatitis.

Because the patient had been HBsAg-negative at a health checkup one year earlier, we conducted a careful interview to determine the potential route of transmission. He had no history of blood transfusion or acupuncture therapy. He had no risk factors for HBV infection with the exception of his wife, who had a chronic HBV infection; however, the couple had had no sexual contact for several years. Table 2 showed the HBV status of the patient's family. They had been married in 1978, and the HBV infection of the wife was first detected in 1979 when she delivered her first daughter. In 2004, she was diagnosed as an inactive HBV carrier by her private doctor because her serum alanine aminotransferase (ALT) levels remained normal between

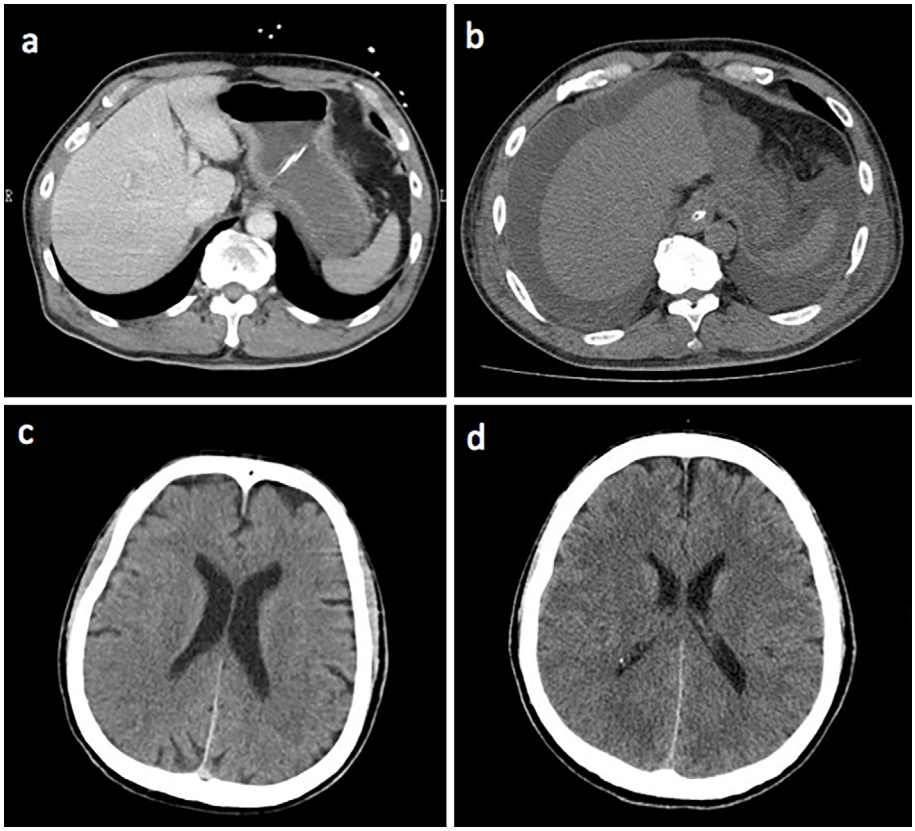

Figure 2. **CT scans for the abdomen (a, b) and the brain (c, d) obtained on Day 4 and Day 7 from the onset, respectively. Liver atrophy with ascites was observed during the course. Brain edema was noted on Day 7.**

Table 2. **HBV Status in Family Examined in 2017.**

Family	Age/ Gender	ALT (U/L)	HBsAg/Anti-HBs	Anti-HBc	HBeAg/Anti-HBe	HBV DNA	Outcome
spouse	63/F	61	+/-	8.04 S/CO	-/+	5.4 logIU/mL	Tx
daugter	38/F	14	-/-	-	-/-	N.D	Vaccinated
daugter	36/F	17	-/+	7.63 S/CO	-/+	N.D	Followed

N.D: not detected, Tx: Treated with a nucleotide analog

2002 and 2004 (the status of HBV-associated markers was unknown, with the exception of HBsAg positivity). The wife did not seek further medical attention even after her serum ALT values were found to be elevated (53 U/L) at a health checkup in 2007. The index patient and his wife had no risk factors for HBV reactivation, including the use of immunosuppressive agents and/or anti-cancer drugs.

The wife started treatment with tenofovir, a nucleotide analog, two months after the death of her husband. The first daughter underwent HBV vaccination because all HBV-related markers were negative. The second daughter, born in 1981, did not receive any additional treatments because her HBs antibody titer was 183.1 mIU/mL. However, the cause of the elevated anti-HBs and anti-HBc antibodies in the second daughter was unknown.

The analysis of the HBV genome

After obtaining informed consent, we determined the full genomic sequence of the HBV isolates recovered from the patient and his wife, as previously reported (11), and deposited the sequences in the DDBJ/EMBL/GenBank databases [the patient (LC461174); the wife (LC461175)]. A phylogenetic analysis confirmed that HB17-0186 (patient) and HB 17-0824 (wife) were classifiable into genotype B and further into subgenotype B1 (Fig. 3). The HBV genome isolated from the patient was 3,215 nucleotides in length. Multiple mutations associated with fulminant hepatitis B (8) were observed: T1754G in the basic core promoter region; G1896A and G1899A in the precore region; and T1961C and C1962A in the core region. No nucleotide insertions or deletions were observed. The HBV genome isolated from the wife was a quasispecies with 22 mixed nucleotides (7 A/G, 6 T/C, 3 A/C, 3 A/T, 2 G/T and 1 G/C) over the entire genome. The HBV nucleotide identity between the patient and the wife was 99.6%, and we estimated that it would show 100% similarity if the mixed nucleotides and either of

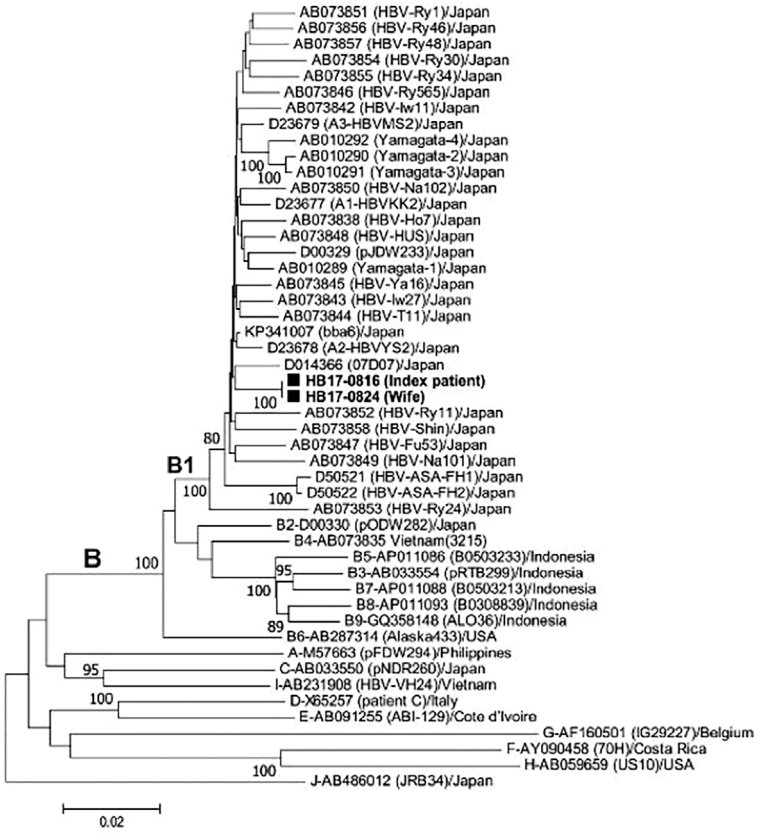

Figure 3. **The phylogenetic tree constructed by the neighbor-joining method based on the entire nucleotide sequences of HBV isolated from the patient (HB-17-0816) and his wife (HB-17-0824) as well as representative HBV strains of genotypes A-J. Both HBV genomes were classifiable into genotype B and further into subgenotype B1.**

them at an equivalent nucleotide position were regarded as the same. Based on a medical interview and the analysis of viral genomes, we considered that HBV had been transmitted from the patient's wife after 38 years of marriage.

Discussion

We reported a case of acute liver failure with coma caused by HBV that was transmitted to the patient from his wife after 38 years of marriage. In Japan, genotype B HBV infection is the third- and second-most common cause of acute and chronic hepatitis B, respectively (3). In general, the clinical course of genotype B shows early HBsAg clearance in acute hepatitis and HBeAg seroconversion in chronic hepatitis (3, 12, 13). However, the frequency of acute liver failure is higher in genotype B than in other genotypes (14). Ozasa et al. reported that subgenotype B1 is a risk factor for fulminant hepatitis B (15). In addition, age >34 years old, HBeAg-negativity, total bilirubin >10 mg/dL, and precore mutation G1896A have been reported as independent risk factors for fulminant hepatitis (15). Of note, the present case possessed four of these risk factors.

Multiple mutations in HBV genome have been reported in fulminant hepatitis B (6, 8). In the present case, mutations that are associated with fulminant hepatitis were observed within the core promoter, precore, and core gene regions, including T1754G, G1896A, G1899A, T1961C, and C1962A. The frequency of T1754G, G1896A, and G1899A in fulminant hepatitis is reported to be 33%, 67%, and 25%, respectively (9). Although the biological significance of T1754G is unknown, G1896A coupled with G1899A was reported to increase the HBV DNA level (9). Host factors are also important for the development of fulminant hepatitis. Because it is hypothesized that mutations in the core region modify the HBV epitope, which is recognized by T cells (8), T1961C and C1962A may alter the host immune response of the patient. Thus, these mutations might have contributed to the increased multiplication of HBV in the wife as well as the heightened immune response in the index patient.

Because the cause of HBV transmission after a long-lasting marriage was not fully investigated, we considered the potential mechanism. We speculated that the HBV DNA load of the wife had been low at the time of marriage but increased after 2007, based on the following facts: 1) HBV had not been transmitted early in the marriage; 2) their first daughter was negative for any HBV-associated markers; 3) the private doctor diagnosed the wife as an inactive HBV carrier in 2004 (although detailed data of HBV markers were not available); and 4) the wife's serum ALT levels increased after 2007. Thus, further mutations, which were associated with the increase in the HBV DNA level, might have emerged around 2007. Indeed, the HBV DNA level of

Table 3. Characteritics of Patients who Contracted HBV Infection from the Spouse and Developed Fulminant Hepatitis B after over 10 Years of Marriage.

Case	Ref	Age/ Gender	Years of marriage	Patient	Spouse	Mutations in precore/CP	HBV genotype	Outcome	Coma	Days*
				HBeAg/anti-HBe	HBeAg/anti-HBe					
1	16)	51/F	>20 years	–/+	–/+	+/+	B	Survived	G2	3
2	17)	54/M	20 years	–/+	–/+	+/–	C	Survived	G2	5
4	18)	46/F	20 years	–/+	–/+	+/–	B	Survived	G2	9
3	6)	69/F	49 years	–/+	–/+	+/–	C	Survived	G2	13
5	19)	48/F	25 years	–/+	ND	+/+	ND	Survived	G4	6
6	18)	59/F	30 years	+/–	–/+	+/–	B	Died	G3	22
7	18)	44/M	13 years	–/+	–/+	+/+	C	Died	G3	5
8	6)	71/F	50 years	–/+	–/+	+/+	B	Died	G3	2
9	17)	34/F	10 years	–/+	–/+	+/ND	C	Died	G3	5
10	20)	58/F	30 years	–/+	–/+	+/+	B	Died	G4	4
11		65/M	38 years	+/–	–/+	+/+	B	Died	G4	4

Coma leves were determined according to the criteria proposed by Inuyama Symposium. *Days mean the date presented hepatic coma from the onset.
CP: core promoter, ND: not determined, G: grade

the wife was 5.4 logIU/mL in 2017. The route of HBV transmission is another issue of interest in the present case. The couple's two children were both negative for HBsAg, so transmission from their children was denied. Sexual and blood-borne transmissions were also denied based on a medical interview. Although the couple saw the same dentist, they visited the dental clinic separately. In addition, they did not share commodities, including toothbrushes, towels, and sharps. We were therefore unable to determine the transmission route in the present case.

To date, 11 Japanese patients, including the present case, have been reported to show acute liver failure with coma as a result of interspousal HBV transmission after more than 10 years of marriage (Table 3) (6, 16-20). The timing of the onset of acute liver failure after marriage varied in these cases. In all case, the spouse was HBeAg-negative with mutations in the precore regions. Genotype B and acute liver failure were predominant among these cases. Among the 11 patients, 6 (54.5%) died; most of the patients presented with grade III to IV coma. The patients who died tended to have mutations in the core promoter region in addition to the G 1896A precore mutation. The present case had grade IV coma and mutations in the precore and core promoter regions, which were also observed in most of the previous patients who died.

The present case alerted us to the difficulties of managing HBeAg-negative HBV carriers. If the HBV-related markers of the wife had been monitored after 2004, the risk of transmission might have been reduced by conducting appropriate management of HBV. Although HBeAg seroconversion has been believed to be an indicator of "inactive HBV carrier", it still has the potential to reactivate with age (7). To prevent HBV transmission, including horizontal transmission, the Japanese government decided to start conducting universal HBV vaccination for newborns in October 2016. This will supplement selective HBV vaccination that was started in 1986 to prevent vertical transmission in Japan. Because universal and selective HBV vaccinations have been shown to reduce the HBV carrier rates in many foreign countries (21) and Japan (22), interspousal HBV transmission may also decline in the future. However, individuals who fail to participate in such vaccination programs have the potential to contract HBV infection. Thus, HBV vaccination is highly recommended for at-risk individuals without anti-HBs antibody, even among couples in which one partner is an HBeAg-negative HBV carrier.

In conclusion, HBV transmission can occur in couples even after a long-lasting marriage. We should not stop monitoring the viral load in HBeAg-negative HBV carriers in order to be sure of the disease status as well as to prevent HBV transmission to individuals who have no immunity against HBV.

The authors state that they have no Conflict of Interest (COI).

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