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

Naoto Sato, Shunji Watanabe, Kouichi Miura, Rie Goka, Naoki Morimoto, Yoshinari Takaoka, Hiroaki Nomoto, Mamiko Tsukui, Norio Isoda, Shigeo Nagashima, Masaharu Takahashi, Hiroaki Okamoto and Hironori Yamamoto

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

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...
Table 1. Laboratory Data on Admission.

| Peripheral blood | Biochemical | Viral markers |
|------------------|-------------|---------------|
| WBC 13500 / μ L  | TP 5.6 g/dL  | HBsAg 24.11 IU/mL, (+) |
| RBC 3.95 x 10¹² / μ L | 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 8598 U/L | Anti-HBe 30.4 INH%, (-) |
| Platelet 5.0 x 10¹¹ / μ L | ALT 8589 U/L | Anti-HBc 5.49 S/CO, (+) |
| Coagulation LDH 9004 U/L | IgM anti-HBc 2.16 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 —/+ |
| NH₃ 691 μ mol/L |

WBC: white blood cells, RBC: red blood cells, PT: prothrombin time, INR: international normalized ratio, ANA: antinuclear antibody, AMA: anti-mitochondrial 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. 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.

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
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-HBe | 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.E: not examined, ND: not detected, Tx: Treated with a nucleotide analog.

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 ALT levels remained normal between 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 HB17-0824 (wife) were classifiable into genotype B and further into subgenotype B1 (Fig. 3). The HBV genome isolated from the patient was 3215 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 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 (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

**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.
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 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). 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 G1896A 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 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).

References

1. Takikawa Y, Suzuki K. Clinical epidemiology of fulminant hepatitis B in Japan. Hepatol Res 38 (SUPPL. 1): 14-18, 2008.
2. Oketani M, Ido A, Nakayama N, Takikawa Y, Naiki T, Yamagishi Y, et al. Etiology and prognosis of fulminant hepatitis and late-onset hepatic failure in Japan: Summary of the annual nationwide survey between 2004 and 2009. Hepatol Res 43: 97-105, 2013.
3. Ito K, Yotsuyanagi H, Sugiyama M, Yatsushiri H, Kario Y, Takikawa Y, et al. Geographic distribution and characteristics of genotype A hepatitis B virus infection in acute and chronic hepatitis B patients in Japan. J Gastroenterol Hepatol 31: 180-189, 2016.
4. Liu J, Zhang S, Wang Q, Shen H, Zhang M, Zhang Y, et al. Prevalence of HBsAg/HBeAg amongst 1 936 801 couples prepar-
ing for pregnancy in rural China: An observational study. J Viral Hepat 24: 679-686, 2017.
5. Okushin H, Yamada G, Manabe K, Kinoyama S, Kunitomi T, Eguchi K, Nagashima H. Transmission of hepatitis B virus (HBV) from HBsAg-positive females with positive e antigen to their husbands. Kanzo 27: 160-164, 1986. in Japanese.
6. Okamoto D, Nakayama H, Ikeda T, Ikeya S, Nagashima S, Takahashi M, Sugai Y, Okamoto H. Molecular analysis of the interspousal transmission of hepatitis B virus in two Japanese patients who acquired fulminant hepatitis B after 50 and 49 years of marriage. J Med Virol 86: 1851-1860, 2014.
7. Alexopoulou L, Karayiannis P. HBeAg negative variants and their role in the natural history of chronic hepatitis B virus infection. World J Gastroenterol 20: 7644-7652, 2014.
8. Mina T, Amini Bavil, Olyaee S, Tacke F, Maes P, Van Ranst M, Pourkarim MR. Genomic Diversity of Hepatitis B Virus Infection Associated With Fulminant Hepatitis B Development. Hepat Mon 15: e29477, 2015.
9. Inoue J, Ueno Y, Wakui Y, Fukushima K, Kondo Y, Kakazu E, et al. Enhanced replication of hepatitis B virus with frameshift in the precore region found in fulminant hepatitis patients. J Infect Dis 204: 1017-1025, 2011.
10. In: Hepatitis type A and fulminant hepatitis. The proceedings of the 12th Inuyama Symposium. Chugai Igaku-sha, Tokyo, 1982. in Japanese.
11. Mulyanto, Pancawardani P, Depamede SN, Wahyono A, Jirintai S, Nagashima S, et al. Identification of four novel subgenotypes (C13-C16) and two inter-genotypic recombinants (C12/G and C13/B) of hepatitis B virus in Papua Province, Indonesia. Virus Res 163: 129-140, 2012.
12. Orito E, Mizokami M, Sakugawa H, Michitaka K, Ishikawa K, Ichida T, et al. A case-control study for clinical and molecular biological differences between hepatitis B viruses of genotypes B and C. Hepatology 33: 218-223, 2001.
13. Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: Recent advances. J Gastroenterol Hepatol 26 (SUPPL. 1): 123-130, 2011.
14. Imamura T, Yokosuka O, Kurihara T, Kanda T, Fukai K, Imazeki F, et al. Distribution of hepatitis B viral genotypes and mutations in the core promoter and precore regions in acute forms of liver disease in patients from Chiba, Japan. Gut 52: 1630-1637, 2003.
15. Ozasa A, Tanaka Y, Ono E, Sugiyama M, Kang JH, Higa S, et al. Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. Hepatology 44: 326-334, 2006.
16. Kou K, Horikawa H, Ebinuma H, Ojiro K, Hirata K, Chu PS, et al. A case of fulminant hepatitis B via interspousal transmission after delivering of four children who had been married for years to her HBV-carrier spouse. Nihon Shokakibyo Gakkai Zasshi 107: A 367, 2010. in Japanese.
17. Tanaka M, Fujiyama H, Nagahama H, Sasaki Y. Intra-familial transmission of hepatitis B virus: between husband and wife. Nippon Rinsho 62: 195-198, 2004. in Japanese.
18. Yotsumoto S, Kojima M, Shoji I, Yamamoto K, Okamoto H, Mishiro S. Fulminant hepatitis related to transmission of hepatitis B variants with precore mutations between spouses. Hepatology 16: 31-35, 1992.
19. Takeda S, Takasu M, Okuno H, Miyazaki H, Kadota Y, Fukushima S, et al. A case of fulminant hepatitis B transmitted from the spouse 25 years after the marriage. Kanzo 37: 159, 1996. in Japanese.
20. Izumi Y, Hiramatsu N, Itose I, Inoue S, Egawa S, Nishida T, et al. A case of acute fulminant hepatitis B who showed deep coma 15 hours after onset and died. Kanaz 45: 109-115, 2004. in Japanese.
21. Lok AS. Hepatitis B: 50 years after the discovery of Australia antigen. J Viral Hepat 23: 5-14, 2016.
22. Noto H, Terao T, Ryou S, et al. Combined passive and active immunoprophylaxis for preventing perinatal transmission of the hepatitis B virus carrier state in Shizuoka, Japan during 1980-1994. J Gastroenterol Hepatol 18: 943-949, 2003.