Prolonged Hepatitis after Acute Infection with Genotype H Hepatitis B Virus


Abstract

We present a case report of a Japanese patient who showed prolonged infection after acute hepatitis B with genotype H. The patient was a 60-year-old man who underwent an annual health care check every year for several years and was never pointed out to have any liver damage, and markers for hepatitis B and C were negative. He was found to be positive for hepatitis B surface antigen (HBsAg) at his health care check in December 2005. After one month, he had an elevated aminotransferase level with hepatitis B e antigen and a high level of serum HBV DNA. He was diagnosed as having acute hepatitis B. On HBV genotype, he had genotype H by the direct sequence method, and he was given a 100 mg of lamivudine daily. However, his acute hepatitis tended to go toward prolonged infection. After two months, he was treated with interferon daily for 28 days. He had negative HBsAg in August 2006. Genotype H, the newest type of hepatitis B, could be the type which shows a poor response to lamivudine. The present paper is the first report, describing the clinical course of acute hepatitis B with genotype H from onset to remission.

Key words: acute hepatitis B, HBV genotype H, prolonged infection

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Introduction

Hepatitis B virus (HBV) infection is related to many liver diseases, acute or fulminant hepatitis, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. It is estimated that approximately 350 million are chronically infected. Annual mortality rate is 500 000-700 000 (1, 2). Many of the adult patients with acute hepatitis B are cured through the natural course (2). However, there are some individuals who are continuously with HBV and developed to cirrhosis or hepatocellular carcinoma.

Phylogenetic analysis has classified HBV into eight genotypes, designated A to H. The genotypes have different biological properties; these differences affect the clinical outcome and response to antiviral therapy (3). Genotype H has been newly found in Nicaragua and in the U.S.; it seems to be distributed in Central America (4). The prolonged prognosis and response to antiviral therapy in acute hepatitis B patients with genotype H is still obscure. We present here a patient who was suffered from acute hepatitis B with genotype H and had a prolonged clinical course after receiving intensive treatment for hepatitis B. This is the first report to describe the whole clinical course, including the period before onset, of a patient with acute hepatitis B due to HBV genotype H.

Case Report

The patient was a 60-year-old man. He underwent an annual health exam for several years. He had never been pointed out to have any liver damage, and he was negative for markers of hepatitis B or C. At the annual health care check in December 2005, he was found to be positive for serum hepatitis B surface antigen (HBsAg), along with aspartate aminotransferase (AST) 31 IU/l, alanine aminotransferase (ALT) 39 IU/l and was referred to the Toranomon Hospital. He did not have any complaints at that time. One
month later, he just complained of slight fatigue and showed elevated AST and ALT.

He was admitted to our hospital for suspected acute hepatitis B in January, 2006. On admission he showed no jaundiced and was relatively healthy. He was positive for hepatitis B e antigen (HBeAg) and 8.2 LGE/ml of serum HBV-DNA as measured by transcription-mediated amplification and hybridization protect assay [Chugai Daiagnostics Science Co., Tokyo, Japan (5)]. Serum levels of AST and ALT were relatively low. Serological markers for HBsAg, HBeAg were strongly positive and serum level of HBV-DNA was high. IgM antibody to hepatitis B core antigen was high (21.9 S/CO) by the CLIA method (Abbott Japan Co., Ltd., Tokyo, Japan) as shown in Table 1. Therefore, he was diagnosed as having acute hepatitis B. No personal or family history of liver disease was recorded. Serological markers for antibodies to hepatitis C virus and antibodies to HIV type 1 and 2 were negative. However, he was a homosexual habit and went to a ‘meeting’ two to three times each month near his residence. In the meeting he had sexual contacts with unknown persons.

Lamivudine (LMV), a nucleoside analogue, was prescribed for him to reduce activity in the liver and HBV-DNA serum levels. He was given 100 mg of LMV daily. One month later from the initiation of lamivudine, his transaminase level began to increase, and natural interferon (IFN) beta (Toray Industiries, Inc., Tokyo, Japan) was started by intravenous injection from one more week later. Interferon was started at 6 MU daily. But neutropenia was seen in one week. The dose was then decreased to 3 MU. Unfortunately, three more weeks later, he had complained of depression which was suspected to be an interferon related side effect and IFN therapy was discontinued within one month. Over that time, HBV-DNA had gradually decreased (Fig. 1). Mu-
Figure 2. Phylogram generated by neighbor-joining analysis of genetic distance in the full-length sequence of HBV. Thirty strains (without TT0601; indicated by underline) were retrieved from the GenBank/EMBL/DDBJ database.

The full genome sequence analysis by PCR direct sequencing technique before treatment revealed that the patient was infected with genotype H virus (Fig. 2). The sequence was named HBV-TT0601. When compared with previously reported HBV isolates with full genome sequences, ST0404 showed high overall identity (99.2%) with a prototype of the Los Angeles strain (AY090460) and 97.5% identity with a Nicaragua strain (AY090457) of the genotype H group at the nucleotide level. Moreover, ST0404 showed higher overall identity (99.8%, 99.4% and 98.8%) with Japanese strains (AB179747, AB205010 and AP007261 respectively) (7-9).

Five months after the onset, needle liver biopsy under laparoscopy was performed. Portal Tracts had edematous enlargement with lymphocytic infiltration and increased collagen fiber. Moreover, the lobular area showed necroinflammatory activity. Inflammatory changes remained within the liver five months after the onset of acute hepatitis B (Fig. 3). With the continuous treatment by LMV, eight months after onset from acute hepatitis, serum HBsAg converted to negative.

Discussion

Here, we report a 60-year-old man infected with genotype H HBV, who had a prolonged clinical course after onset of acute hepatitis B. The present case was suspected for infection from homosexual contact. The genotype H of this patient was reported three times in Japan previously (7-9).

This patient had several features. First, he showed a low level of serum aminotransferase and total bilirubin in spite of a high titer of serum HBV DNA level. In our previous report, we described that patients with a low serum level of aminotransferase and total bilirubin in acute hepatitis B have a high possibility of persistence (10). Low maximum ALT levels (<500 IU/l) and high baseline HBV-DNA levels (>8.7 LGE/ml) were going to persistent in patients with genotype A. Thus, we selected the intensive care for the present case of acute hepatitis B in order to prevent disease progression from acute to the chronic phase.

Second, acute hepatitis B with genotype H has the possibility of being prolonged or persistent in spite of intensive treatment. Generally, acute hepatitis B with HBV genotype A tends to be persistent (11). On the other hand, most patients with acute hepatitis B due to genotype B and C are...
usually cured without antiviral drugs. The present patient showed a prolonged course after the onset of acute hepatitis by histological examination. HBV replicates by reverse transcription of an RNA intermediate, pregenomic RNA (pgRNA). For pgRNA to be encapsulated, its 5’ end is folded into a stem-loop structure, known as the encapsidation signal. PgRNA is transcribed from the distal Precore region and proximal C gene and consists of 60 nucleosides (positions 1847-1906, numbering from the EcoR1 site) (12-14). In general, the patients with HBV genotype A show adenosine at position 1858 in sequence. On the other hand, the patients with HBV genotype B or C show uracil at position 1858 in sequence. The present patient with genotype H had adenosine at position 1858 in sequence. We suggest that stability of pgRNA in HBV genotype A and H is associated with the clinical course after the onset of acute hepatitis B.

Thirdly, the present patient did not show a good response after lamivudine therapy. In most cases, acute hepatitis is cured with rest and observe. Therefore, antiviral treatment is rarely used for such cases. When antiviral drugs, such as lamivudine, are given the patients with acute hepatitis B in one or two months after onset, most patients show a decrease in the serum levels of ALT and HBV DNA level decrease (9). However, the present patient responded poorly to LMV treatment and had prolonged hepatitis. The serum level of ALT decreases slowly after the initiation of IFN therapy. IFN therapy may aid in decreasing aminotransferase.

Eight genotypes (A-H) of HBV have now been described. In brief, genotypes B and C are prevalent in Asia and the Far East, while genotype A is prevalent in northwestern Europe, North America and Africa. Genotype D is predominant in the Mediterranean area and India (15), while genotype E circulates in sub-Saharan Africa (16). Genotype F is found in Central and South America (17). Genotype G has been reported from France and North America (18). Genotype H has been described only recently, and the first report was from Central America (4). The strain in the present case showed high homology with those reported in Japan (7-9) and Los Angeles (4). However in the future, acute hepatitis B due to genotype H could be spread. Moreover, based on the difference of HBV-genotype, persistence rate is different (2, 10). Limitation of this case was other immuno-suppressive factors. The patient was a homosexual. Homosexual men can be associated with poor responsibility for treatment of hepatitis (19).

In conclusion, the acute hepatitis B patients in Japan have shown various genotypes recently. We encountered a rare case of acute hepatitis B with genotype H which led to a prolonged state of acute hepatitis. LMV and IFN were effective for changing HBsAg to negative.

References