Domestic Infection of Hepatitis E in Japan

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Abstract

In most cases of hepatitis E in Japan, patients acquire the viral infection abroad in countries where hepatitis E is endemic. However, in Nagano Prefecture, Japan, we encountered a patient with hepatitis E who had never been abroad. The diagnosis was made on finding hepatitis E viral RNA and antibodies against the virus in the serum. Prompt normalization of liver function test occurred without medication. The nucleotide sequence of the virus isolated from this patient was closely related to the sequence of previously isolated viruses of genotype III. The source of infection could not be identified. (Internal Medicine 43: 807–810, 2004)

Key words: domestic infection of hepatitis E, genotype III, swine

Introduction

Hepatitis E virus (HEV) infection, which is frequently endemic or epidemic in developing countries, has been generally regarded as an imported infection in Japan. Recently, however, it has been suggested that HEV strains indigenous to Japan also exist (1–8). Here, we report the case of a 55-year-old Japanese man with acute hepatitis due to HEV of genotype III. He had no history of overseas travel.

Case Report

The patient was a 55-year-old Japanese businessman. He lived in Japan, and had never been abroad. He consumed a small amount of alcohol occasionally. He did not have a history of blood transfusions or tattoos, and there was no family history of liver disease. The patient became conscious of general fatigue, anorexia, nausea, and headache on July 10, 2002. Five days later, he visited a family doctor who found liver dysfunction, and he was admitted to Shinonoi General

Hospital the next day under a diagnosis of acute hepatitis. Prior to this event, he had not ingested any medicine or “health food”, nor had he eaten any raw meat.

On admission, he was afebrile and there was no lymphadenopathy. He was slightly icteric, and the liver was palpable 2 cm below the costal margin with moderate tenderness. Biliary enzymes and serum aminotransferases were markedly elevated on admission (Table 1). However, all of these values normalized and the symptoms subsided without medication within 2 weeks (Fig. 1A). Examination of the liver with ultrasonography revealed no abnormality, thus excluding the possibility of cholestatic jaundice. The patient was discharged on the 19th hospital day.

Antibodies for hepatitis B virus, hepatitis C virus, hepatitis A virus of IgM class, cytomegalovirus, and Epstein-Barr virus were negative on admission. Accordingly, we considered the possibility of acute hepatitis E, and tested for the presence of serum anti-HEV antibodies and HEV RNA. The antibodies were positive (Fig. 1B) and HEV RNA, HE-JA23, was detected in the sera obtained on the second hospital day. HE-JA23 belongs to genotype III, the same genotype as the

Table 1. Laboratory Data on Admission

Total protein	7.5 g/dl
Albumin	4.6 g/dl
Aspartate aminotransferase	3,058 IU/l
Alanine aminotransferase	3,234 IU/l
Alkaline phosphatase	606 IU/l
Lactate dehydrogenase	2,236 IU/l
γ -glutamyl transpeptidase	347 IU/l
Total bilirubin	4.1 mg/dl
Total cholesterol	181 mg/dl
WBC	4,700/mm ³
RBC	458×10 ⁴ /mm ³
Platelet	12.4×10 ⁴ /mm ³
Prothrombin time	100%
Activated partial thromboplastin time	33.1 sec
Fibrinogen	327 mg/dl

WBC: white blood cell, RBC: red blood cell.

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Figure 1. Changes in the liver function test values (Fig. 1A), titer of antibodies against hepatitis E virus, and the presence or absence of viral RNA in the sera (Fig. 1B). ALT: alanine aminotransferase, T.Bil: total bilirubin, HEV: hepatitis E virus, IgM: immunoglobulin M, IgG: immunoglobulin G, HEVRNA: hepatitis E virus RNA. The values for ALT are shown on a log scale.

HEV previously reported as being indigenous to Japan (1–3, 5) (Fig. 2). The data was compatible with the fact that HEV infection of the patient was domestic.

Temporal profiles of titers of antibodies and HEV RNA are illustrated in Fig. 1B. HEV RNA was detectable in the sera until the 9th hospital day, even though a clear-cut improvement of liver function was seen by then. Anti-HEV IgM titer was high within the first 16 days and intermediate thereafter, and its positivity lasted for 3 months at a lower level. In contrast, anti-HEV IgG titer was lowest on admission, increased rapidly thereafter, and remained high throughout the remainder of the 3-month observation period.

Discussion

Hepatitis due to HEV infection is generally more severe than that caused by hepatitis A virus infection. The case-fatality rate for hepatitis A ranges from 0.1% to 2.7%, whereas pregnant women with hepatitis E exhibit a case-fatality rate averaging 20% (9). The incidence of fulminant hepatic failure due to HEV infection among pregnant women has been reported to be as high as 32% (9).

Hepatitis E has mainly been reported in tropical and subtropical countries, and therefore HEV infection in non-tropical, industrialized countries was considered to be a disease acquired abroad. However, sporadic cases were recently reported in areas where HEV infection is not endemic. In addition, the genotype of HEV isolated from the patients

Figure 2. Phylogenetic tree of hepatitis E virus (HEV). Genotype of HEV recovered from the sera of the present case, which belongs to genotype III, is shown in the rectangle: a classification proposed by Schlauder and Mushahwar (14) with modification.

in these areas was closely related to that isolated from swine, rats, wild boars and deer (1–8, 10–13). Therefore, it has been suggested that there may be a possibility of cross-species infection of HEV between humans and animals. HEV may already have started spreading in these areas.

In Japan, sporadic cases of hepatitis E in patients who had never been abroad have recently been documented (1–8). In addition, three strains of swine HEV (swJ570, swJ681 and swJ791) belonging to genotype III and one strain of deer HEV (JDEER-Hyo03) belonging to type III, were documented in farm pigs (12) and deer (7) respectively, in Japan. These strains share certain features. All together, it is highly likely that HEV began spreading in Japan among pigs and deer. The HEV in the current case belongs to genotype III

(HE-JA23 accession no. AB115544), and it is phylogenetically close to swine HEV (swJ570) (Fig. 2) (3). Accordingly, we explored the possibility of HEV infection from animals, especially pigs. The only connection discovered involved pork: the patient had a preference for pork at a yaki-niku restaurant (an establishment serving roast meats). But we were unable to prove that this was the route of infection.

In conclusion, we confirmed a new case of domestic HEV infection in Japan, which caused a self-limited form of acute hepatitis.

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