



## Different outcomes of nosocomial infection with hepatitis C virus from the same origin

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### Abstract

The outcome of infection with hepatitis C virus (HCV) varies substantially from self-limiting infection to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma among the individuals. The mechanisms that determine the clearance or the persistence of HCV have not yet been clarified. Here, we experienced two cases of hospital-related infection with HCV from the same origin but with quite different outcomes. One case resolved after an episode of acute hepatitis, while the other case developed a chronic hepatitis although they were infected with HCV of the same origin. Although infected with the virus of the same origin, the clinical and virological courses were completely different. This suggests that host factors play a major role in conditioning the outcome of acute HCV infection.

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**Key words:** Nosocomial infection; Hepatitis C virus; HLA

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### INTRODUCTION

The outcome of infection with hepatitis C virus (HCV) varies from self-remission, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma<sup>[1-3]</sup>. About 20% of the people

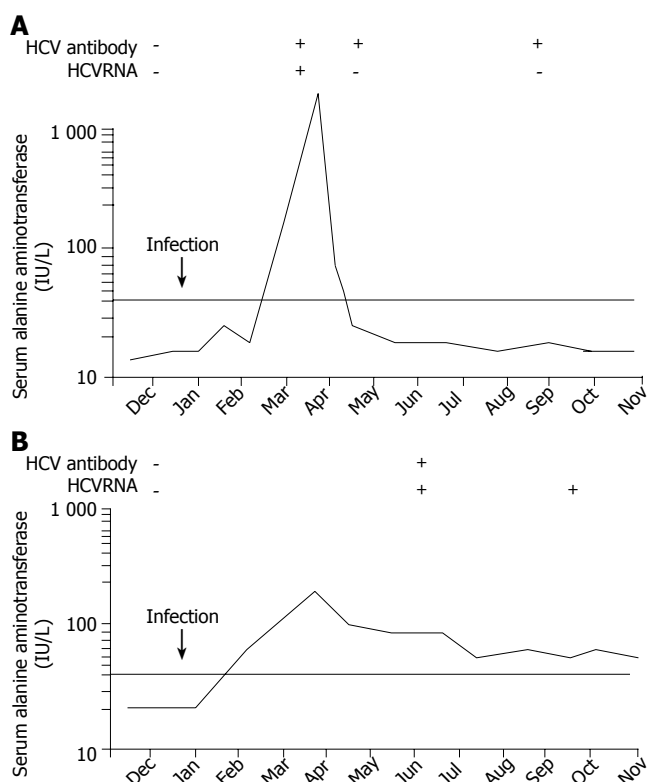
infected with HCV spontaneously clear the virus<sup>[4]</sup>. On the other hand, the rest of the patients cannot clear the virus and suffer from chronic infection<sup>[4]</sup>. The mechanisms that determine the clearance or the persistence of HCV have not yet been elucidated. Viral factors such as genotype could be involved in the outcome of the infection<sup>[5]</sup>. However, what determines the outcome of HCV infection is not totally clear. Here, we experienced two cases of hospital-related infection with HCV from the same origin but with two different outcomes. One case resolved subsequent to an acute hepatitis and the other case became a chronic hepatitis although they were infected with the same viral origin according to viral sequencing. This implies that host factors play a major role in conditioning the outcome of acute HCV infection.

### CASE REPORT

A 32-year-old woman (patient 1) and a 71-year-old man (patient 2) were admitted to the same floor of Gunma University Hospital on December 2001. Clinical, biochemical, and serologic profile of patients 1 and 2 are shown in Figure 1.

Patient 1 was diagnosed with idiopathic interstitial pneumonia on February 2001 and followed up as an out patient. She was complicated by a bacterial respiratory infection with dyspnea and she was readmitted on December 21. She showed normal aminotransferase level and was negative for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) on admission. The respiratory infection was treated with antibiotics and the patient gradually improved. Although there were no typical acute hepatitis-like symptoms except for appetite loss, the patient's serum aminotransferase level was elevated during a routine check-up on February 28, 2002. Anti-hepatitis A (HA) IgM antibody, HBsAg and hepatitis B core (HBc) IgM antibody were negative. However, HCVAb became positive at this time. HCV RNA was also positive (850 KIU/mL) and genotype was 1b. Peak level of aspartate aminotransferase (AST) was 1199 IU/L, alanine aminotransferase (ALT) was 1348 IU/L on March 25, respectively. Aminotransferase level became normal on April 15 and continued at a normal level. HCV RNA became negative on April 6 and continued to be negative. She was diagnosed with acute hepatitis C and finally recovered.

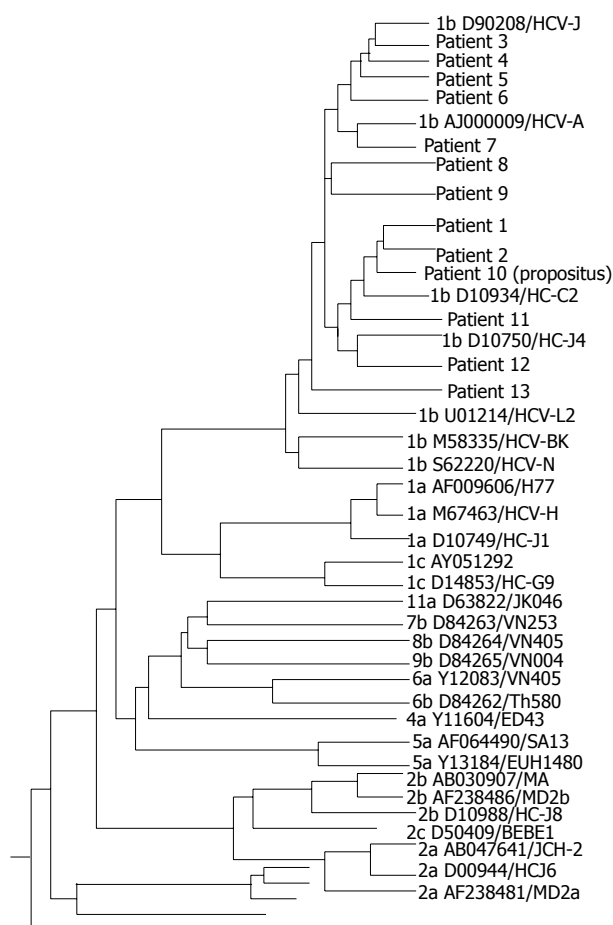
Patient 2 was first diagnosed with diabetes mellitus at the age of 44. He was treated with insulin and subsequently admitted for the control of blood sugar on December



**Figure 1** Clinical, biochemical, and serologic profile of patients. **A:** patient 1; **B:** patient 2. HCV antibodies were detected by third-generation tests and HCV RNA was detected in serum by reverse-transcription PCR. Alanine aminotransferase values are shown on a logarithmic scale, and the horizontal lines indicate the upper limit of the normal range.

18, 2001. At the age of 69, he was diagnosed with myelodysplastic syndrome. Upon admission aminotransferase levels were normal, and both HBsAg and HCVAb were negative. He was discharged on January 8, 2002 and followed up with his primary physician. He subsequently developed elevated aminotransferase levels and became positive for HCVAb in June 2002. There were no typical acute hepatitis-like symptoms during the follow-up period with his primary physician. Retrospectively, the aminotransferase level of the patient was elevated during a routine check-up in January 31, 2002. HCV RNA was also positive (250 KIU/mL) and genotype was 1b. Peak level of AST was 102 IU/L, ALT was 168 IU/L on March 28. Aminotransferase levels continued to be abnormal for 3 years after the onset. He was diagnosed with chronic hepatitis C.

We believe that HCV infection of both patients occurred during December 2001 to January 2002. There was no suspicious event in the history of the patient suggesting infection such as intravenous drug abuse, blood transfusion, tattoo nor transmission by sexual contact in both cases. Nosocomial infection was suspected and surveyed. HCV genotyping and the nucleotide sequence analysis of coding region for the envelope glycoprotein E1 were performed for the two patients. For the nucleotide sequence analysis, after reverse transcription, the first round of polymerase chain reaction used primers EF1 (sense: 5'-CGCCGACCTCATGGGGTA-3', nt 721 to 739) and ER1 (antisense: 5'-CGACCAGTTCATCATCATATCCCA-3', nt 1 289 to 1 313), and the second-round primers EF2 (sense: 5'



**Figure 2** Phylogenetic tree analysis comparing coding sequences in the HCV regions for the envelope glycoproteins E1. For phylogenetic tree analysis, 13 sequences obtained from the 13 patients involved in this study were compared with 33 sequences taken as unrelated controls (genotype and GenBank accession numbers are indicated).

-TTGCCCGGTTGCTCTTTTCTATC-3', nt 837 to 860) and ER2 (antisense: 5'-GCGGTGACCTGATACATGGC-3', nt 1 264 to 1 283). We performed direct-sequence analysis of nested polymerase chain reaction products of 447 bp (nt 837 to 1 283) encompassing the HCV envelope glycoprotein E1. The polymerase chain reaction products were gel purified and sequenced by automated sequencer. The HCV genotype of both patients was 1b. The sequences of HCV E1 region from both the patients were 99.7% in agreement. We considered that the origins of both infections were the same and these two hepatitis infections were hospital related. We checked up on all the patients who were admitted to the same floor from December 18, 2001 to January 8, 2002, the suspicious infection period in question. There were 16 patients positive for HCV antibody. These 16 patients were examined for the genotype of HCV and 11 of them were 1b. The nucleotide sequences of E1 region in these 11 patients (numbered patient 3-13) were compared by the same method. Phylogenetic tree analysis comparing coding sequences in the HCV E1 region are shown in Figure 2. For phylogenetic tree analysis, 13 sequences obtained from the 13 patients involved in this study were compared with 33 sequences taken as unrelated controls. One patient had close nucleotide sequenc-

ing with patients 1 and 2. A 70-year-old man (patient 10, named as *propositus*) with liver cirrhosis was considered as the *propositus* of this hospital-related infection of HCV. He was admitted for treatment of hepatic encephalopathy from December 26-29.

Thus, patient 1 had a complete resolution of acute hepatitis C, while patient 2 developed a chronic hepatitis C infection although both were infected by the same HCV strain (*propositus*, patient 10). Although it was not fully elucidated how the nosocomial infection occurred, intravenous catheter flushing with heparin retrieved from a multidose heparin solution in saline was thought to be one of the causes of the infection.

## DISCUSSION

Although the same HCV strain infected two patients, each patient showed a completely different outcome. One case was cured from acute hepatitis and the other case developed chronic hepatitis although they were infected with HCV of the same origin. Primary HCV infection is poorly characterized because most patients are asymptomatic and, therefore, it is rarely diagnosed<sup>[3,6,7]</sup>. Larghi *et al.*<sup>[8]</sup> reported the outcome of an outbreak of acute hepatitis C supposedly infected from a common source. Among the 14 patients followed up, 8 patients resolved spontaneously and 6 patients developed chronic infection<sup>[8]</sup>. The incubation period and the outcome of the acute phase of the disease were highly variable. The average incubation period was 10 wk, but the range was from 6 to 28 wk. In our case, the supposed incubation periods of patients 1 and 2 were 9 and 5 wk, respectively.

The clinical and virologic course also varied, both in patients in whom the infection resolved spontaneously and in those developing chronic infection<sup>[8]</sup>. This suggests that host factors play a major role in conditioning the outcome of acute HCV infection<sup>[9,10]</sup>. Thus, the host immune system is important for the clearance of virus. In view of the host factors, specific MHC class II alleles were reported to influence susceptibility or resistance to persistent HCV infection<sup>[10,11]</sup>. The associations of self-limiting HCV infection with HLA-DRB1\*1101 and HLA-DQB1\*0301 have been independently reported by some groups<sup>[10,11]</sup>. Persistent HCV infection was associated with HLA-DRB1\*0701, and HLA-DRB4\*0101. In our case, HLA was not fully evaluated in all the patients. However, *propositus* had DRB1\*0901, DRB1\*1502, DQB1\*0303, and DQB1\*0601. Patient 2 had DRB1\*0901, DRB1\*1403, DQB1\*0303, and DQB1\*0301. HLA-DQB1\*0301 was not a self-limiting factor in our case.

We were able to determine the *propositus* of the HCV infection; however, the route of infection was not fully understood. There was no procedure identified in these patients to directly cause the infection, such as endoscopy, surgery or hemodialysis. Finally, flushing of intravenous catheters with heparin retrieved from a

multidose heparin solution in saline was thought to have caused the infection. Since January 2002, our department has been using heparin solution packed for individual use for flushing of intravenous catheters. The period of this nosocomial infection was before the use of individual packed heparin solution was instituted. All had long-lasting intravenous catheters. Multidose vials used for flushing or treatment had probably been contaminated during periods of overlapping treatment. Contamination of multidosing vials was the most likely mode of HCV transmission<sup>[12]</sup>. Therefore, use of such vials should be avoided.

We experienced two cases of hospital-related infection of HCV from the same origin followed by different outcomes. One patient was cured of acute hepatitis and the other case developed chronic hepatitis although both were infected by the same *propositus*. Although they were infected by the same source, the clinical and virologic course was completely different. This suggests that the host factors play a major role in determining the outcome of acute HCV infection.

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