De Novo Superinfection of Hepatitis B Virus in an Anti-HBs Positive Patient with Recurrent Hepatitis C Following Liver Transplantation

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A 60-year-old woman with end stage liver cirrhosis caused by genotype 2 hepatitis C virus (HCV) infection received an orthotopic liver transplantation (OLT). The patient was negative for the hepatitis B surface antigen (HBsAg) and positive for the anti-hepatitis B surface antibody (anti-HBs) prior to and one and a half months following the OLT. Due to reactivation of hepatitis C, treatment with interferon-alpha and Ribavirin started two months following the OLT and resulted in a sustained virological response. We performed a liver biopsy because a biochemical response was not achieved. Surprisingly, liver pathology showed HBsAg-positive hepatocytes with a lobular hepatitis feature, which had been negative in the liver biopsy specimen obtained one and a half months post-OLT. High titers of both HBsAg and HBeAg were detected, while anti-HBs antibodies were not found. Tests for IgM anti-hepatitis B core antibody and anti-delta virus antibodies were negative. The serum HBV DNA titer was over 1×10⁷ copies/mL. A sequencing analysis showed no mutation in the “a” determinant region, but revealed a mixture of wild and mutant strains at overlapping regions of the S and P genes (S codon 213 (Leu/Ile); P codons 221 (Phe/Tyr) and 222 (Ala/Thr)). These findings suggest that de novo hepatitis B can develop in patients with HCV infection during the post-OLT period despite the presence of protective anti-HBs. (Gut Liver 2011;5:248-252)

Key Words: De novo hepatitis B virus infection; Occult hepatitis B virus infection; Post-orthotopic liver transplantation recurrent hepatitis C; Orthotopic liver transplantation

INTRODUCTION

Orthotopic liver transplantation (OLT) remains the only curative treatment for hepatitis C virus (HCV) induced end-stage liver cirrhosis (LC), although post-OLT recurrence of HCV infection is unavoidable in most of those patients. The recurrence of hepatitis C infection and concomitant disease in the liver graft may cause substantial morbidity after OLT; however, it is also possible that de novo infection of hepatitis B virus (HBV) from donor livers, which have had occult HBV infection, may play a role in post-OLT hepatitis.

It has previously been reported that the presence of anti-hepatitis B surface antibody (anti-HBs) before OLT effectively prevents de novo HBV infection from an anti-hepatitis B core antibody (anti-HBc) positive donor. However, another report has suggested that, despite the presence of a high titer of anti-HBs, de novo HBV infection from an anti-HBc positive donor could occur long after OLT, caused by a variant with an escape mutation in the “a” determinant region of the S gene.

Recently, we experienced a de novo infection by an HBV strain without a mutation in the “a” determinant in a case with a protective level of anti-HBs in the serum before and until one and half months after OLT; the infection occurred during the administration of interferon-alpha for the treatment of recurrent hepatitis C. There was a mixture of wild and mutant strains at overlapping regions of the S and P genes, resulting in changes in the respective frame, S codon 213 (Leu/Ile) vs. P codons 221 (Phe/Tyr) and 222 (Ala/Thr). Herein we describe the clinical course and virological data of the patient.
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CASE REPORT

A 60-year-old Korean woman underwent OLT for end-stage liver cirrhosis caused by chronic hepatitis C. Spontaneously acquired anti-HBs was detectable and at protective titer levels before and until one and half months after OLT. HCV RNA was not detected in serum 3 weeks post OLT. Liver biopsy was performed at one and half months after OLT because the patient’s serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) were elevated to 192/332 IU/L.

The first histopathologic finding did not show any evidence of acute rejection but was compatible with viral hepatitis (Fig. 1). HCV RNA became detectable in the serum at titers of 1.48×10^5 copies/mL (Roche Amplicor™; Roche Diagnostics, Branchburg, NJ, USA). The HCV genotype 2 (single) was identified using the restriction fragment mass polymorphism (RFMP) method. Its exact subtype, however, could not be determined because of sequence variation in the subtype-determinant region.

A combination treatment of interferon-alpha 2b (IntronA™; Schering-Plough Pharmaceuticals, Kenilworth, NJ, USA), 3 million units (MU) three times a week, and ribavirin, 600 mg per day, was started 2 months post-OLT. Soon after, however, ribavirin was withdrawn because the patient developed anemia. The time interval and dose of interferon-alpha were also adjusted to the patient’s degree of leukopenia, and the duration of administration was prolonged to one year.

In spite of suboptimal adherence to antiviral therapy, HCV RNA was again detected in the serum at one month post-treatment. Interferon-alpha injections continued for 4 months and were then stopped due to bile peritonitis, which developed 6 months post-OLT.

Though the serum aminotransferase level was normal during interferon treatment, HCV RNA was again detected in titers of 9.73×10^2 copies/mL, and the patient’s AST/ALT increased to around 80 IU/mL. Both virological and biochemical responses occurred 4 months after re-treatment and persisted for 3 months. While the virological response was sustained, the serum AST/ALT re-elevated to over 60 IU/mL 8 months after re-treatment.

A liver biopsy was again performed thirteen months after the first liver biopsy. The second set of histopathological findings revealed features of lobular hepatitis with confluent necrosis.