CASE REPORT

Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment

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Abstract

A 27-year-old Caucasian female with hepatitis C virus (HCV) infection treated with interferon (IFN) who developed severe autoimmune hepatitis (AIH) is described. The infecting viral strain was of genotype Ib and the pre-treatment HCV viral load was at a high level. The patient was treated with pegylated IFN-alpha 2b and ribavirin, and her HCV-RNA became negative at wk 12, but after that she developed fulminant hepatic failure. The patient recovered after steroid pulse therapy consisting of methylprednisolone 1000 mg/d for three days which was administered twice. A needle liver biopsy revealed the typical pathological findings of AIH.

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Key words: Autoimmune hepatitis; Interferon; Ribavirin; Hepatitis C virus; Anti-viral therapy; Acute liver failure

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INTRODUCTION

The most effective treatment for hepatitis C virus (HCV) infection is pegylated interferon (peg-IFN) in combination with ribavirin (RBV) [1]. This treatment exerts a variety of immuno-modulatory effects and may unmask the underlying autoimmune diseases such as autoimmune thyroiditis and rheumatoid arthritis [2,3]. In a similar fashion, interferon (IFN) was reported to induce or exacerbate autoimmune hepatitis (AIH) [4-7]. We describe a patient who developed fulminant hepatic failure with AIH during the treatment with peg-IFN and RBV. The patient had no prior history of autoimmune diseases and the severe hepatitis occurred after the HCV RNA level decreased to below the detection limit.

CASE REPORT

Patient

The patient was a 27-year-old Caucasian woman from South Caucasian Country. She had never consumed alcohol. She had not received blood transfusions or undergone surgery. Her sister and mother were receiving treatment for Basedow’s disease, but she had no manifestation of Basedow’s disease or other autoimmune diseases.

Present illness

She was found to be infected with hepatitis C virus during her pregnancy and was referred to our department in October 2005. She hoped to receive IFN therapy to reduce the risk of transmission to her second baby. The HCV genotype was Ib and the HCV RNA viral load was 4600 kIU/mL (high range) (Table 1). Alanine aminotransferase (ALT) was 47 IU/L (normal < 35 IU/L). The markers of hepatic functional reserve were within normal ranges and ultrasonography of the liver indicated no abnormal findings. After delivery, interferon therapy was commenced with peg-IFN-alpha 2b (Peg-Intron®, Schering-Plough Corp., NJ, USA) and RBV (Rebetol®, Schering-Plough) on January 30, 2006. The clinical course of this anti-viral therapy is illustrated in Figure 1. The initial doses consisted of 100 µg peg-IFN per week and 600 mg RBV per day. This therapy was well tolerated with minimal adverse effects and HCV RNA became negative at wk 12. Around the same time, a rise of transaminase was noted: ALT, 83 IU/L (normal < 35 IU/L); and asparate aminotransferase (AST), 56 IU/L (normal < 30 IU/L). The dosage of peg-
IFN was reduced to 80 µg at wk 17, and 60 µg at wk 18 because of the persistent increase of ALT, and finally, the treatment was discontinued at wk 19. Glycyr rhizinate (Stronger neo-minophagen C®, Minophagen Pharmaceutical Co., Ltd., Tokyo, Japan) was administrated intravenously, and ALT indicated a decreasing tendency (peak ALT was 815 IU/L). After that, she showed jaundice and a prolongation of the prothrombin time (PT) was noted. Her human leukocyte antigen (HLA)-DR serotypes were DR17 and DR13. She was admitted to our hospital on June 30, 2006.

Physical examination revealed: height 167 cm, weight 56 kg, blood pressure 118/64 mmHg, body temperature 37.3°C, and clear consciousness. The bulbar conjunctiva was slightly icteric. No peripheral edema, vascular spiders, and flapping tremor were observed.

Clinical course
On admission, elevations of transaminases (ALT 280 IU/L, AST 311 IU/L) (Table 2) and total bilirubin (5.5 mg/dL) were noted. The prothrombin time (PT) was prolonged to 101.8%. The laboratory findings before interferon treatment and at onset of acute liver failure are shown in Table 1 and Table 2, respectively. The clinical course is shown in Figure 1.

**Table 1** Laboratory findings before interferon treatment

| Parameter | Value          |
|-----------|----------------|
| WBC       | 5300 /µL       |
| Hb        | 11.0 g/dL      |
| Plt       | 452 × 10^5 /µL |
| PT        | 101.8%         |
| AST       | 39 IU/L        |
| ALT       | 47 IU/L        |
| LDH       | 176 IU/L       |
| ALP       | 278 IU/L       |
| γ-GTP     | 11 IU/L        |
| ChE       | 386 IU/L       |

| Parameter | Value          |
|-----------|----------------|
| BUN       | 5.0 mg/dL      |
| Creatinine| 0.7 mg/dL      |
| Na        | 138 mEq/L      |
| K         | 3.9 mEq/L      |
| Cl        | 105 mEq/L      |
| Total cholesterol | 133 mg/dL |
| Glucose   | 127 mg/dL      |

**Table 2** Laboratory findings at onset of acute liver failure

| Parameter | Value          |
|-----------|----------------|
| WBC       | 5800 /µL       |
| Hb        | 12.2 g/dL      |
| Plt       | 200 × 10^5 /µL |
| PT        | 41.4%          |
| APTT      | 44.4 sec       |
| AST       | 311 IU/L       |
| ALT       | 280 IU/L       |
| LDH       | 245 IU/L       |
| ALP       | 571 IU/L       |
| γ-GTP     | 108 IU/L       |
| ChE       | 124 IU/L       |

| Parameter | Value          |
|-----------|----------------|
| BUN       | 5.0 mg/dL      |
| Creatinine| 0.7 mg/dL      |
| CRP       | 0.2 mg/dL      |
| CRP       | 0.2 mg/dL      |
| Total bilirubin | 5.5 mg/dL |
| Direct bilirubin | 3.3 mg/dL |
| Total protein | 7.4 g/dL |
| Albumin   | 3.1 g/dL       |

**Figure 1** Clinical course of peg-interferon (peg-IFN) plus ribavirin therapy for hepatitis C virus infection. ALT: Alanine aminotransferase; AST: aspartate aminotransferase; T-Bil: total bilirubin.
mg/mL) and decrease of blood urea nitrogen (BUN), uric acid (UA), and PT were detected. Hepatitis A, hepatitis B, cytomegalovirus, herpes simplex, and Epstein-Barr virusesl were negative. Anti-nuclear antibody (ANA) was × 160 (normal < × 80) and immunoglobulin G (IgG) 2436 mg/mL (normal < 1695 mg/mL), which were × 80 and 1635 mg/mL before the IFN treatment. Antibody to liver/kidney microsomes type 1 (LKM-1) was positive. Steroid pulse therapy (methylprednisolone 1000 mg/d for three days) was performed (Figure 2). Nevertheless, hepatic encephalopathy appeared on July 3. Abdominal computed tomography indicated massive necrosis of hepatocytes (Figure 3). Brain magnetic resonance imaging showed no abnormal findings. The findings of her electric encephalogram were typical of metabolic encephalopathy. Total parenteral nutrition was started. The protein load was restricted and lactulose enemas were performed. After that, the hepatic encephalopathy improved gradually. The ALT level rose again on July 14, and steroid pulse therapy was administered again. The ALT showed a decreasing tendency again, after which she started oral intake. PT, BUN, and UA had improved gradually. She was discharged from our hospital on August 10.

A needle liver biopsy was performed on October 16 and it showed the typical pathological features of autoimmune hepatitis. Interface hepatitis with infiltration of inflammatory cells including plasma cells and rosette formation, were found but no biliary change was noted (Figure 4). The serum ALT levels were normalized over the following six months by 10 mg of prednisolone per day.

**DISCUSSION**

IFN therapy for patients with HCV infection has been reported to induce or exacerbate AIH[4-7]. In the present case, severe hepatitis occurred after HCV RNA had decreased to below the detection limit after treatment with peg-IFN with RBV for 12 wk. The patient presented the typical clinical features of serum aminotransferase elevation, positive ANA and LKM-1, and hypergammaglobulinemia, and responsiveness to glucocorticoid therapy. The pathological findings showed the typical features of AIH, which included interface hepatitis with infiltration of plasma cells, and rosette formation.

One of the explanations for the occurrence of autoimmunity in HCV patients is the loss of self-tolerance due to molecular mimicry between viral proteins and self-antigen[8]. HCV infection is known to be related to autoimmune disease, and chronic hepatitis C patients show autoantibodies such as ANA and LKM-1, and hypergammaglobulinemia, and responsiveness to glucocorticoid therapy. The pathological findings showed the typical features of AIH, which included interface hepatitis with infiltration of plasma cells, and rosette formation.
In the present case, AIH occurred during IFN therapy and the patient developed fulminant hepatic failure when HCV RNA had decreased to below the detection limit. To our knowledge, there is no report of an HCV patient who developed fulminant hepatic failure after peg-IFN with RBV therapy. Peg-IFN with RBV is an established therapy for chronic hepatitis C patients but AIH should be considered as a potential complication of therapy leading to severe hepatitis. Especially, longer treatment duration (48 wk) and prolonged elevation of serum IFN levels in the pegylated-IFN could contribute to the development of autoimmune phenomenon. Liver biopsy in the early phase of acute liver injury to determine whether immunosuppression therapy may be required for such patients. In Asians, the development of AIH during antiviral therapy is believed to be rare, although the potential risk should be taken into consideration if female young Caucasian case is treated like this report. However, the treatment of recurrence of HCV after cessation of antiviral therapy due to the emergence of autoimmune hepatitis like our case is a very difficult clinical decision to make. Probably, the interferon based antiviral therapy, the most standard antiviral agent, could remain as the mainstream regimen for next decade. The balance between antiviral effects and possible autoimmune phenomena could be key factors as described previously. Small molecules such as HCV protease inhibitor, either as monotherapy or combined with other small molecules, could be the first choice for the treatment of the current case in future.

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