Two Cases of Porphyria Cutanea Tarda Associated with Chronic Hepatitis Positive for the Antibody against Hepatitis C Virus

ATSUSHI KANNO, HITOSHI AMAKASU, WAKIO TORINUKI*, TAKESHI YAMAMOTO †, MOTOYASU ISHII †, NOBORU NUMATA‡ and HITOSHI OHORI‡

Department of Internal Medicine, *Department of Dermatology, Tohoku Koseinenkin Hospital, Sendai 983, †The Third Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980, and ‡Department of Microbiology, Sendai Municipal Institute of Public Health, Sendai 983

KANNO, A., AMAKASU, H., TORINUKI, W., YAMAMOTO, T., ISHII, M., NUMATA, N. and OHORI, H. Two Cases of Porphyria Cutanea Tarda Associated with Chronic Hepatitis Positive for an Antibody against Hepatitis C Virus. Tohoku J. Exp. Med., 1994, 172 (1), 83-90 — We report two cases of porphyria cutanea tarda (PCT) positive for the antibody against hepatitis C virus (anti-HCV). The serological and histological examinations revealed that they were persistently infected with HCV and were suffering from liver disease compatible with chronic viral hepatitis. It is suggested that one of the factors which contribute to liver damage of patients with PCT may be HCV infection. It now may be advisable to examine anti-HCV in PCT patients with liver disease.

Porphyria cutanea tarda (PCT) is a disorder with an abnormality in the biosynthesis of heme. It is characterized by photosensitive skin lesions and urinary excretion of excessive amounts of uroporphyrin (Elder 1977). PCT generally appears in two forms. One is the sporadic form. It usually requires environmental factors for the clinical expression of PCT (Elder 1990) such as alcohol, iron overload, estrogen and hexachlorobenzene. The other is the familial form which is inherited as an autosomal dominant. Patients with PCT frequently associate liver diseases with miscellaneous hepatic changes including steatosis, hemosiderosis, focal lobular necrosis, portal inflammation or fibrosis (Cortés et al. 1980; Lefkowitch and Grossman 1983). Hepatocellular carcinoma (HCC) sometimes develops (Salata et al. 1985). Many PCT patients have an underlying cause...
A. Kanno et al.

for the hepatic injury, e.g., an alcohol abuse. However, there exist patients having no apparent cause for the liver disease. Recently, a specific complementary DNA clone for non-A, non-B (NANB) hepatitis was isolated (Choo et al. 1989), and the NANB hepatitis virus positive for this clone was termed hepatitis C virus (HCV). A specific assay to detect an antibody against HCV (anti-HCV) has been developed (Kuo et al. 1989), and it has been demonstrated that most of posttransfused NANB hepatitis are caused by HCV. However, anti-HCV has been found in some liver diseases other than NANB hepatitis, such as autoimmune hepatitis (Esteban et al. 1989) or alcoholic liver disease (Parés et al. 1990). With regard to the prevalence of anti-HCV in PCT with liver disease, 4 reports were recently made from Europe (Fargion et al. 1992; Siersema et al. 1992; DeCastro et al. 1993; Herrero et al. 1993). According to these studies, anti-HCV was frequently detected in PCT, and it was speculated that HCV was one of the important pathogenic factors of the liver disease in PCT. This promoted us to examine anti-HCV in PCT patients in our hospital. We report here two cases of PCT with liver disease positive for anti-HCV, and discuss the relationship between the liver disease and the HCV infection.

**Case Reports**

*Case 1*

A 51-year-old Japanese man visited Tohoku University Hospital in October 1984, with a 6-month history of vesicles and pigmentationations on the face. His illness was diagnosed as PCT by the characteristic skin lesions and excessive urinary excretion of uroporphyrin. Simultaneously, an abnormality of biochemical liver function tests was pointed out and the histological diagnosis of the liver was chronic active hepatitis (CAH). He was a heterosexual and had no history of drinking and of intravenous drug abuse. He had a history of receiving a blood transfusion at the operation for appendicitis in 1967.

Since May 1989, he has been a patient of Tohoku Koseinenkin Hospital. At his first visit he had hypertrichosis, hyperpigmentation and sclerodermatous changes on the face and dorsal hands. The urinary excretion of uroporphyrin was still excessive (Table 1). Urinary porphobilinogen (PBG) and delta-aminolebulinic acid (δ-ALA) levels were within normal range. Alanine aminotransferase (ALT) levels fluctuated within 100 IU/liter during the observation period. The test for anti-HCV in serum was positive by the first generation enzyme-linked immunosorbent assay (EIA) detecting an antibody against c100–3 recombinant protein derived from a nonstructural region of HCV-RNA (Ortho Diagnostic Systems, Raritan, NJ, USA). Furthermore, the positive result was confirmed by the first generation recombinant immunoblot assay (RIBA) detecting antibodies against HCV-coded nonstructural antigens c100–3 and 5–1–1, and an antibody against superoxide dismutase was negative (Chiron, Emeryville, CA, USA, and Ortho Diagnostic Systems). It was also positive for anti-HCV by the second generation EIA detecting antibodies against both a core antigen c22–3 and nonstructural antigens c33c, c100–3 and c200 (Ortho Diagnostic Systems). HCV-RNA was demonstrated by polymerase chain reaction (PCR) method using 5’non-coding region primers of HCV genome (Numata et al. 1993). Both hepatitis B surface antigen (HBsAg) and antibody against HBsAg (anti-HBs) were negative. Anti-nuclear antibody (ANA) was positive.

Percutaneous liver biopsy was performed in July 1991. The histological findings showed mononuclear lymphocyte infiltrations and fibrosis in portal areas, and focal necrosis,
Porphyria Cutanea Tarda Positive for Anti-HCV

85

Table 1. Laboratory findings of 2 PCT patients at first visiting

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum: AST&lt;sup&gt;b&lt;/sup&gt; (&lt;35 IU/liter)</td>
<td>58</td>
<td>88</td>
</tr>
<tr>
<td>ALT&lt;sup&gt;c&lt;/sup&gt; (&lt;34 IU/liter)</td>
<td>71</td>
<td>112</td>
</tr>
<tr>
<td>ANA&lt;sup&gt;d&lt;/sup&gt; (&lt;1: 40)</td>
<td>1: 80</td>
<td>&lt;1: 40</td>
</tr>
<tr>
<td>HBSAg/Anti-HBs</td>
<td>/-</td>
<td>/-</td>
</tr>
<tr>
<td>Anti-HCV 1st EIA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2nd EIA</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>1st RIBA&lt;sup&gt;f&lt;/sup&gt; c100-3</td>
<td>+</td>
<td>±</td>
</tr>
<tr>
<td>5-1-1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SOD&lt;sup&gt;g&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HCV-RNA&lt;sup&gt;h&lt;/sup&gt;</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Urine: Uroporphyrin (&lt;30 μg/day)</td>
<td>563</td>
<td>298</td>
</tr>
<tr>
<td>δ-ALA&lt;sup&gt;i&lt;/sup&gt; (&lt;5 mg/liter)</td>
<td>4.3</td>
<td>2.5</td>
</tr>
<tr>
<td>PBG&lt;sup&gt;j&lt;/sup&gt; (&lt;2 mg/100 ml)</td>
<td>0.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>PCT, porphyria cutanea tarda; <sup>b</sup>AST, aspartate aminotransferase; <sup>c</sup>ALT, alanine aminotransferase; <sup>d</sup>ANA, anti-nuclear antibody; <sup>e</sup>EIA, enzyme-linked immunosorbent assay; <sup>f</sup>RIBA, recombinant immunoblot assay; <sup>g</sup>SOD, superoxide dismutase; <sup>h</sup>HCV-RNA, hepatitis C virus-ribonucleic acid; <sup>i</sup>δ-ALA, delta-aminolevulinic acid; <sup>j</sup>PBG, porphobilinogen; +, positive; -, negative; ±, intermediate. Number in parentheses indicates the normal range of value.

acidophilic bodies, fatty depositions and hepatocyte ballooning in parenchyma (Fig. 1a). Piecemeal necrosis was not found. These findings were compatible with chronic persistent hepatitis (CPH). A moderate degree of hemosiderosis was also found. A high degree of red fluorescence was elicited in several areas of the liver specimen under the ultraviolet (UV) light (Fig. 1b).

Case 2

A 55-year-old Japanese man visited Tohoku University Hospital in December 1985, with a 4-month history of vesicles on the dorsal hands. PCT was diagnosed by excessive excretion of uroporphyrin. Simultaneously, liver dysfunction was pointed out. The histological diagnosis was CPH. He had a history of receiving blood transfusions when he was suffered from cerebromeningitis in 1950 and at the surgical operation for spondylosis in 1959. After the last blood transfusion he contracted icteric hepatitis. He was a heterosexual and no history of drug abuse. He had a history of drinking, approximately 30 g of ethanol every day, for 30 years.

Since January 1991, he has been a patient in our hospital. At his first visiting our hospital, he had hypertrichosis, hyperpigmentation and sclerodermatous changes on the face and the dorsal hands. A moderate elevation of ALT levels was found (Table 1). The test for anti-HCV in serum was positive by both the first and the second generation EIA. Although it was an intermediate result by the first RIBA, HCV-RNA was positive. Both HBsAg and anti-HBs were negative. ANA was negative. Percutaneous liver biopsy was performed in July 1991. The histological findings showed mononuclear lymphocyte infiltrations and fibrosis in portal areas, and focal necrosis, acidophilic bodies, fatty depositions and ballooning of the hepatocyte in parenchyma (Fig. 2a). Piecemeal necrosis was found. These findings were compatible with CAH. A slight degree of hemosiderosis was
A moderate degree of red fluorescence was also observed in the liver specimen under the UV light (Fig. 2b).

**DISCUSSION**

In PCT, a coexisting liver disease is often found. The severity of the liver disease varies from minimal hepatic changes to chronic hepatitis and cirrhosis. The histological findings are not specific, but hemosiderosis is the most frequent feature of PCT (Cortés et al. 1980; Lefkowitch and Grossman 1983) as shown in our cases. Recently, it was found that HLA-linked hemochromatosis alleles were
Porphyria Cutanea Tarda Positive for Anti-HCV

common in patients with sporadic PCT and might account for their hepatic hemosiderosis (Edward et al. 1989). Unfortunately, we have no available data on HLA in our cases. Although iron in the liver is thought to be important in the pathogenesis of PCT, the mechanism by which iron exerts its effect is not ascertained. It is hypothesized that iron ions inhibit uroporphyrinogen decarboxylase activity in the liver (Mukerji et al. 1984). However, another study showed that iron ions had no effect on inhibition of the enzyme activity (Sassa et al. 1983). It is unknown whether the accumulation of uroporphyrin in the liver causes hepatic damage. In fact, the fluorescent area of the liver elicited by UV light did not
quite correspond to the area with necrosis or inflammation in our cases. It is well known that PCT patients often have the history of excessive intake of alcohol (Grossman et al. 1979). Our patients had no or a minimal intake of alcohol. Furthermore, histological findings suggestive of alcoholic liver disease such as pericellular fibrosis, hyaline central sclerosis and Mallory bodies were not found. On the other hand, the mononuclear lymphocyte infiltrations in portal areas and the focal necrosis in parenchyma, which are compatible with chronic viral hepatitis (Lefkowitch and Apfelbaum 1989), were observed. PCT is sometimes caused by ingestion of estrogen (Grossman et al. 1979) or hexachlorobenzene (Cripps et al. 1984). In our two patients, however, these risk factors were not identified. ANA was positive in Case 1. It is well known that autoantibodies including ANA are frequently detected in patients with autoimmune hepatitis. In this case, however, the histological changes suggestive of autoimmune hepatitis such as prominent plasma cell infiltrations in the portal area were not found. On the other hand, it was recently reported that ANA was frequently detected in chronic type C hepatitis patients and that the mean titer of the antibody is low (Abauf et al. 1993) like our patient. Both patients were positive for anti-HCV and HCV-RNA, and the same positive results were also obtained in Case 1 in 1985 and in Case 2 in 1986, respectively (data not shown). This indicates that these two patients had been persistently infected with HCV for at least several years. Taking these histological and serological findings into consideration, it can be said that HCV contributed largely to the damage on the liver of our PCT patients. We have only two patients with PCT during these several years in our hospital. Interestingly, they are all positive for anti-HCV. This is compatible with the high prevalence of anti-HCV in PCT reported from Europe (Fargion et al. 1992; Siersema et al. 1992; DeCastro et al. 1993; Herrero et al. 1993). Several cases in which PCT had developed after acute viral hepatitis were reported (Burnett et al. 1977; Coburn et al. 1985). Although the basis for the association between PCT and HCV is not known, it is speculated that type C hepatitis induced the clinical manifestation of PCT in our patients who might possess an underlying impairment of porphyrin metabolism. In order to verify the hypothesis, the urinary uroporphyrin level needs to be measured in their relatives. It may be advisable to examine anti-HCV in PCT patients with liver disease. When patients with PCT are positive for anti-HCV, they must be followed in consideration of development of the liver disease to chronic hepatitis, cirrhosis or HCC (Farinati et al. 1992).

References

2) Burnett, J.W., Lamon, J.M. & Levin, J. (1977) Haemophilia, hepatitis and porphyr-
Porphyria Cutanea Tarda Positive for Anti-HCV


