Membranoproliferative Glomerulonephritis and Leukocytoclastic Vasculitis without Cryoglobulin in Chronic Hepatitis C Virus Infection

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Abstract

The etiopathogenesis of extrahepatic manifestations including vasculitis in the context of HCV infection is still unknown. We report a case with lethal extrahepatic manifestations due to chronic hepatitis C virus (HCV) infection. The patient presented leukocytoclastic vasculitis, sensorimotor neuropathy and membranoproliferative glomerulonephritis with positive rheumatoid factor but lacked cryoglobulin. Hypocomplementaemia and deposition of IgM and C3 in the vascular lesion and glomeruli suggested that immune complex disease played a role in the pathogenesis of extrahepatic manifestations independent of cryoglobulin. Although HCV was successfully eliminated by treatment with interferon α, she died of cryptococcal infection.

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Key words: cryptococcus, immune complex disease, extrahepatic manifestations, interferon α, opportunistic infection

Introduction

Various clinical and biological extrahepatic manifestations are reported in 38 to 74% of patients with chronic hepatitis C virus (HCV) infection. Among them, cryoglobulin is a crucial biological manifestation which is present in 47–56% of HCV-positive patients (1–3). Not all cryoglobulin-positive patients are symptomatic but cryoglobulin-positive patients tend to have severe immunological abnormalities (3). Recently, different types of vasculitis, i.e. small vessel vasculitis (such as cryoglobulinemia) and larger vessel disease [such as polyarteritis nodosa (PN)] are thought to be associated with HCV, and cryoglobulin is often found in most of the patients with these severe types of vasculitis (4–7). Therefore the presence of cryoglobulin can be one of the important indicators of severe extrahepatic manifestations including some type of vasculitis that sometimes determine the prognosis of patients (4, 7).

Here, we report a patient with chronic HCV infection, who had sensorimotor neuropathy, leukocytoclastic vasculitis, and membranoproliferative glomerulonephritis. As the prevalence of extrahepatic manifestations is lower in Japan than in other Western countries (8) and she was constantly negative for cryoglobulin, it was difficult to diagnose that her extrahepatic manifestations were ascribed to HCV. Interferon α successfully eliminated HCV in this patient but she died of cryptococcal infection. We discuss the renal involvement and vasculitis independent of cryoglobulin and opportunistic infection in the context of HCV.

Case Report

A 64-year-old woman developed low-grade fever, weakness, purpura and livedo reticularis, in addition to dysesthesia of her lower extremities in December 1995. Her past history included blood transfusion at surgery for gastric ulcer when she was 33. She had no history of excess alcohol consumption or intravenous drug abuse. She had erythema nodosum on her legs intermittently for 8 years.

Liver dysfunction, positive rheumatoid factor, hypergammaglobulinemia, and HCV-antibody (HCV-Ab) positivity were detected in May 1996. The serotype of HCV was group II. Cryoglobulin was negative. The ultrasonographic findings for the liver were consistent with chronic hepatitis. A skin biopsy performed in October 1996 from the purpuric lesion revealed prominent inflammation around the capillar-
ies of the dermis, indicating leukocytoclastic vasculitis (Fig. 1). She had no fever, photosensitivity, symptoms of sicca, Raynaud's phenomenon, nephritis, or ischemic abdominal pain. HCV mRNA level was under 0.50 MEQ/ml as measured by the branched HCV DNA (bDNA) probe method [<0.50 MEQ/ml] and 34.0 Kcopy/ml as measured by the reverse transcription-polymerase chain reaction (RT-PCR) method [<1.0 Kcopy/ml]. The patient refused treatment with interferon α. Administration of 20 mg per day of prednisolone and concomitant glycyrrhizin normalized amino-transferase levels and improved her purpura and dysesthesia to some extent. Prednisolone was tapered to 15 mg per day and was continued at that dose (Fig. 2).

The palpable purpura and livedo reticularis increased in severity and spread to her upper arms, bilateral thighs, and abdomen, and she was admitted to our hospital on April 28, 1997. Physical examination revealed a temperature of 37.6 °C and a blood pressure of 190/110 mmHg. She was anemic and anicteric. Her liver was enlarged but there was no ascites or splenomegaly. Pitting edema was detected on her lower extremities. She had herpes zoster eruptions on her right back and chest at the 6th thoracic vertebra level. Skin ulcers were present on the lateral sides of both ankles. Dysesthesia,
hypesthesia, tendon hyporeflexia, and muscle weakness were detected in both the upper and lower distal extremities.

Laboratory data on admission are summarized in Table 1. On urinalysis, 1.2 g/day of proteinuria and microhematuria were detected with hyaline casts and epithelial casts. She had hypoalbuminemia with hypergammaglobulinemia and mild liver dysfunction (aspartate aminotransferase (AST): 59 IU/l, alanine aminotransferase (ALT): 49 IU/l). Tests for hepatitis B virus antigen and antibody were negative, and anti-nuclear antibody, antineutrophil cytoplasmic myeloperoxidase antibody (MPO-ANCA), and other antibodies associated with liver or collagen diseases were negative (Table 1). Cryoglobulin was negative. C3, C4, and CH50 were all reduced, to 30 mg/dl, 1 mg/dl, and 13 U/ml, respectively, and immune complexes (anti-C3d antibody method) were elevated to 16.4 µg/ml [≤9.2 µg/ml]. Electromyography revealed reduction of both sensory and motor neuron conduction velocities in the distal extremities, supporting the presence of sensorimotor neuritis. Other serious systemic conditions such as infectious diseases, collagen diseases including systemic lupus erythematosus, Henoch-Schönlein purpura, and malignancies including lymphoproliferative disorders were excluded.

Administration of aciclovir ameliorated her herpes zoster eruption and fever. CRP subsequently became negative. Amlodipine besilate was commenced for her hypertension. A liver biopsy specimen obtained on May 27 showed chronic active hepatitis with prominent ballooning of hepatocytes and scattered free acidophilic bodies. The level of HCV mRNA increased to over 40 MEQ/ml as determined by bDNA probe method and 730 Kcopy/ml as determined by the HCV RNA RT-PCR method. Aggravation of renal function was also detected (Fig. 2), but no other causes of renal injury such as infection, malignancies, or other collagen diseases were detected. Interferon α was administered and ameliorated her purpura, liver dysfunction, and proteinuria. Serum creatinine decreased from 1.4 mg/dl to 0.7 mg/dl. The level of HCV decreased to below the limit of detection. However, she developed fever and several widespread regions of subcutaneous induration with tenderness on her right thigh. Yellowish pus was aspirated on July 22 and Cryptococcus Neoformans was determined by PAS and Grocott stain. Fluconazole and antibiotics were administered followed by extensive debridement. Massive pleural effusion and cavity formation emerged with scattered nodular lesions in her right middle lung. Sensorimotor neuropathy persisted and renal dysfunction was aggravated. She died of cryptococcal infection on August 18, 1997.

Postmortem examination of the kidneys revealed double contour of the thickened loop, proliferation of mesangial and mesangial cells (Fig. 3). Deposition of C3 and IgM was detected in most of the glomeruli exhibiting lobular accentuation with granular peripheral capillaries and mesangial deposits supporting the presence of membranoproliferative glomerulonephritis (MPGN). Vasculitis with fibrinoid formation was detected in the small vessels in both lower extremities and in the retroperitoneum. Deposition of IgM was detected in the vessel walls in the dermis. Cryptococcus was also detected in kidneys, thyroid, and lymph nodes with granuloma formation.

**Discussion**

In this article we describe a patient with various extrahepatic manifestations in chronic HCV infection. She presented purpura and livedo reticularis due to leukocytoclastic vasculitis, sensorimotor neuropathy, and MPGN accompanied by the presence of immune complexes and hypocomplementemia but lacked cryoglobulin. She had no
Extrahepatic Manifestations of HCV Infection

The HCV virus can be found in cutaneous vasculitic lesions in patients with MPGN associated with HCV infection, and no pathological difference is suggested irrespective of cryoglobulin (13–15). Therefore, it is probable that immune complex disease plays a role in the pathogenesis of vasculitis independent of cryoglobulin in HCV infection. Based on these supposed pathomechanisms and the pathological autopsy findings, we inferred that various extrahepatic manifestations were introduced in the context of HCV infection irrespective of cryoglobulin in the present case.

The reason for the occurrence of opportunistic infection in this patient is not yet elucidated. Opportunistic infections are rarely reported in patients with primary chronic HCV infection (16) without organ transplantation or human immune deficiency virus (HIV) infection. Moreover, opportunistic infection is not usually induced by treatment with interferon α for HCV infection (17–19). We attempted to determine why our patient was susceptible to opportunistic infection. She was not very old (67 years old) and did not consume alcohol. She had no malignancy or other collagen diseases. She had been treated with up to 20 mg per day of prednisolone for about 6 months, but this amount of prednisolone does not usually cause opportunistic infection. We did not examine for HIV infection, but she did not have drug addiction or extramarital sex. Her white blood cell count and CD4+ lymphocyte count and serum level of immunoglobulin were all normal. But her complement levels were consistently extremely low at least during these two years. Moreover some unpleasing and undetectable modification might have affected her immune system for more than 10 years while she had erythema nodosum attributable to HCV, since HCV is both hepatotropic and lymphotrophic.

HCV was successfully eliminated and renal function was once improved by interferon α but concurrent intractable infection probably caused multiple organ failure including renal impairment. The possibility that interferon α precipitated other autoimmune diseases and exacerbated renal impairment may be excluded in this patient (20, 21), because overall serious side effects of interferon α were few and her clinical course was not so severe and the autopsy findings did not present severe angiitis.

For future benefit, the notion that several extrahepatic manifestations can occur in HCV infection irrespective of cryoglobulin should be noted. Earlier introduction of interferon α and subsequent intensive immunosuppressive therapies including high-dose glucocorticoid, plasmapheresis, or immunosuppressive agents will likely achieve a better prognosis (4, 7, 10, 20).

References


