□ CASE REPORT □

Progressive Renal Failure and Blindness Due to Retinal Hemorrhage after Interferon Therapy for Hepatitis C Virus-associated Membranoproliferative Glomerulonephritis

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Abstract

We treated a 67-year-old Japanese woman with membranoproliferative glomerulonephritis (MPGN) and chronic active hepatitis associated with hepatitis C virus (HCV) infection. Treatment commenced with a daily dose of 6 MU IFN α-2b for 2 weeks, which was changed to three times weekly thereafter. After 2 weeks, HCV RNA in the serum was undetectable and there was a concomitant reduction in proteinuria. Treatment with IFN α-2b was discontinued because of severe headache and fever. Five weeks after the discontinuation of IFN α-2b, the patient experienced the sudden onset of visual loss due to retinal hemorrhage. Subsequently, proteinuria and renal function progressively deteriorated though HCV RNA was undetectable. This case exemplifies the need for careful monitoring of renal function and retinal lesions not only in patients receiving IFN but also in those following the discontinuation of IFN treatment.
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Key words: cryoglobulinemia, nephrotic syndrome

Introduction

A variety of extrahepatic immunologically mediated manifestations are associated with hepatitis C virus (HCV) infection, including membranoproliferative glomerulonephritis (MPGN), essential mixed cryoglobulinemia, Sjögren's syndrome, porphyria cutanea tarda, and thyroiditis (1–3). In some cases of HCV-associated MPGN, treatment with interferon (IFN) was recently reported to result in the disappearance of HCV from the serum and in a concomitant improvement in proteinuria (4, 5). IFN has multiple biologic functions, acting on numerous cells and organs, and its adverse effects are observable systemically in numerous organ systems, including the kidney, lung, retina, endocrine system, and central nervous system. However, this secondary damage is usually reversible following the discontinuation of IFN treatment (6, 7). Among these symptoms, retinopathy consisting of retinal hemorrhage or cotton-wool spots is manifest in more than 50% of patients receiving IFN (7). Retinopathy caused by IFN is usually mild and seldom induces visual abnormalities; the visual abnormalities are improved during IFN treatment.

We report herein a female patient diagnosed with MPGN and chronic active hepatitis associated with HCV infection, in whom IFN treatment induced progressive renal failure and blindness caused by retinal hemorrhage.

Case Report

A 67-year-old Japanese woman was admitted on November 2, 1998 to Hamamatsu University School of Medicine because of proteinuria, hematuria and edema. She had a history of blood transfusion in 1965, but was otherwise in good health until 1994, when she was discovered to have proteinuria. Nephrotic-range proteinuria and ankle edema were noted in 1998.

Upon admission, blood pressure was 132/111 mmHg and pulse rate was regular at 76 beats/minute. Physical examinations were unremarkable except for ankle edema. No purpura in the lower extremities was noted. Optical fundoscopic findings showed no hypertensive or hemorrhagic changes.

Urine tests showed 3(+) for protein and the urinary sediment contained 100 red blood cells per high-power field. Massive proteinuria of 4.0 g/24 hours was detected. Laboratory examination showed the following values: 20.3 mg/dl blood urea nitrogen; 0.88 mg/dl serum creatinine; 6.2 mg/dl total protein; 3.2 mg/dl albumin; 43 IU/*l* aspartate aminotransferase (AST); 27 IU/*l* alanine aminotransferase (ALT); 42.4% hematocrit; 7,800/μl white blood cell count with normal differential; and 96,000/μl platelet count. Complements and coagulation tests were normal. Cryoglobulin was weakly positive in

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the serum. The serum was positive for HCV antibody on the third-generation test and HCV RNA by reverse transcription-polymerase chain reaction with genotype 2a. The amount of HCV RNA in the serum was found to be below 0.5 mEq/ml by the DNA probe method. Anti-nuclear antibody was negative. All markers of antigen and antibody for hepatitis B virus were negative in the serum.

Needle biopsies of the kidney and liver were performed. In the renal biopsy specimen, 7 of 24 glomeruli obtained showed global sclerosis. A fibrocellular crescent was observed in one glomerulus. In the remaining glomeruli, lobular formation, double contour, and endocapillary proliferation were found. Atherosclerosis of the renal arterioles was not prominent. Immunofluorescent staining for IgG and C3 was positive in the glomerular capillaries with the fringe pattern. These pathological findings are consistent with MPGN. The liver biopsy specimen revealed chronic active hepatitis (F1/A1) by the New Inuyama Classification (8).

The patient's clinical course during hospitalization is shown in Fig. 1. On December 10, 1998, IFN α-2b treatment commenced with a daily dose of 6 MU for 2 weeks, which was changed to three times weekly thereafter. After 2 weeks, HCV RNA disappeared from the serum and there was a concomitant reduction in proteinuria to approximately 1 g/24 hours. Cryoglobulin in the serum became negative following IFN α-2b therapy. On January 8, 1999, following the disappearance of HCV RNA from the serum and the reduction in proteinuria, the patient was discharged. Upon discharge, her condition was unremarkable except for headache and fever. Serum creatinine and urinary protein excretion were 0.78 mg/dl and 1.1 g/24 hours, respectively. The liver function tests were normal during the clinical course.

The patient's clinical course following discharge is shown in Fig. 2. On January 28, 1999, treatment with IFN α-2b was discontinued (total dose of 234 MU) because of a persistent severe headache and sustained fever. Five weeks after the discontinuation of IFN α-2b treatment, the patient experienced sudden onset of blindness caused by retinal hemorrhage, when HCV RNA was negative. Upon follow-up one year after the discontinuation of IFN therapy, fundoscopic findings showed no retinal hemorrhage, but visual activity was only slightly improved. In late April 2000, massive proteinuria (9.2 g/24 hours urinary protein excretion) and a progressive decline in renal function (4.47 mg/dl serum creatinine) were detected,

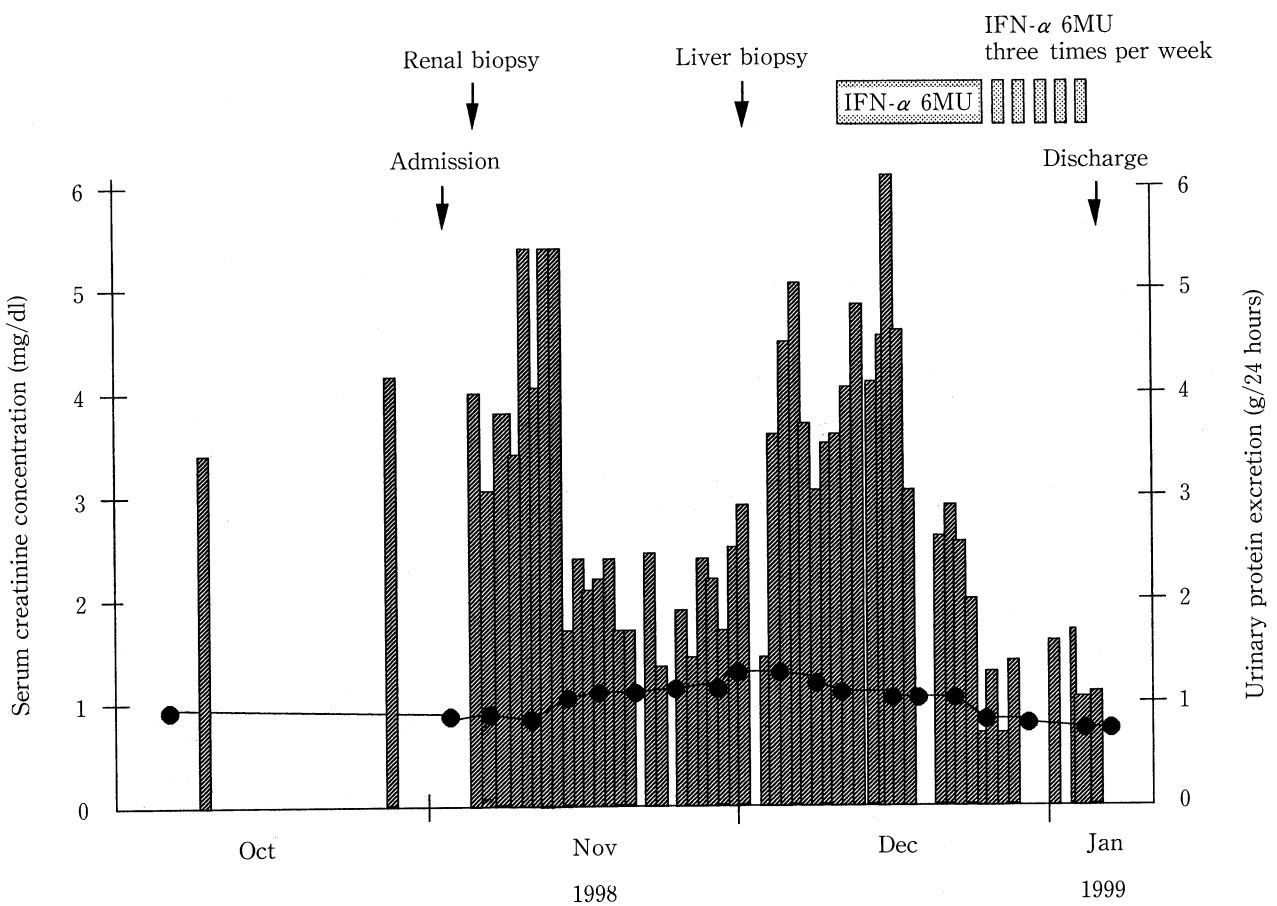

Figure 1. Clinical course during hospitalization. Closed circles and shaded bars represent serum creatinine and urinary protein excretion, respectively.

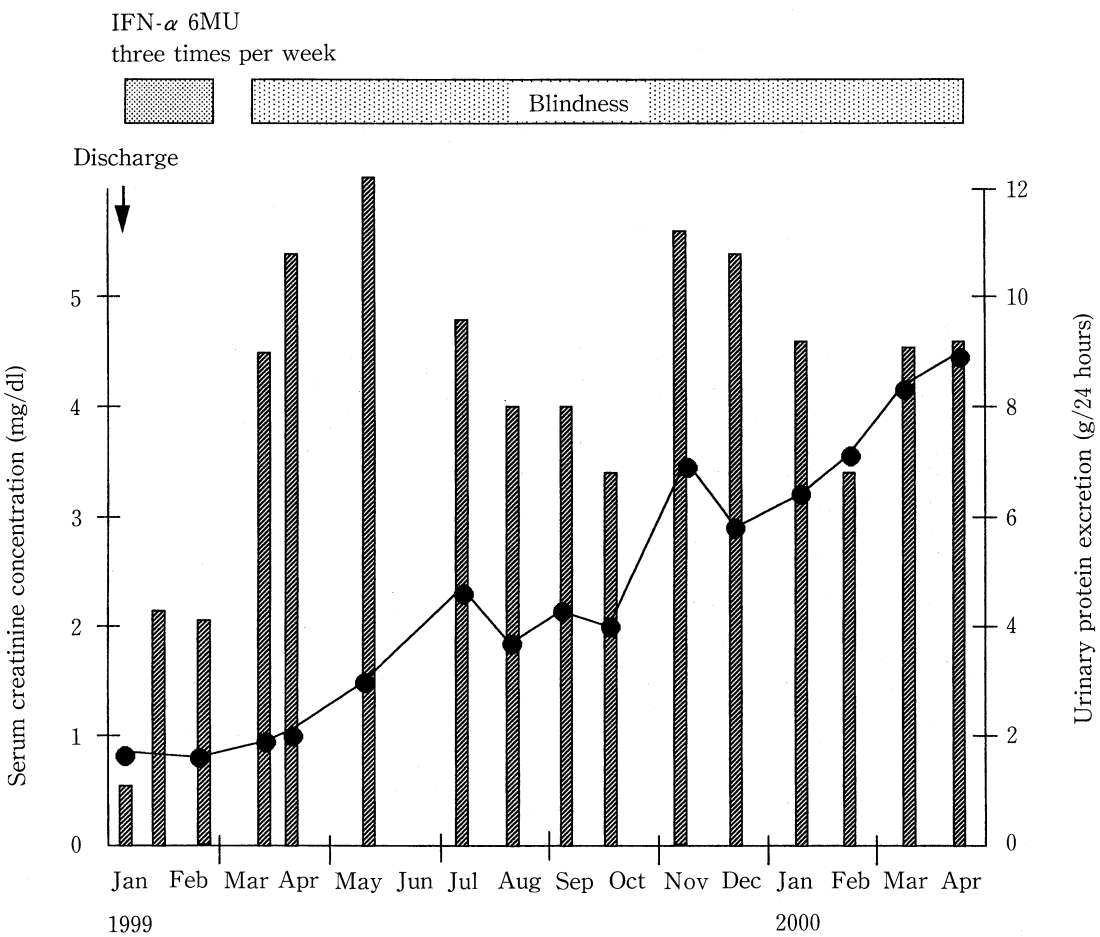

Figure 2. Clinical course following discharge. Closed circles and shaded bars represent serum creatinine and urinary protein excretion, respectively.

where the liver function tests remained normal.

Discussion

Treatment with IFN for HCV infection in the present case resulted in the disappearance of HCV from the serum and in a concomitant reduction in proteinuria. However, although IFN therapy had been discontinued, the patient experienced the serious complication of sudden onset blindness caused by retinal hemorrhage.

Renal involvement associated with HCV, including MPGN, membranous nephropathy, mesangial proliferative glomerulonephritis, and cryoglobulinemic glomerulonephritis have been recently reported (9–11). In the present case, cryoglobulin in the serum which was weakly positive upon admission became negative following IFN α-2b therapy, indicating that the contribution of cryoglobulinemia to the progression of renal disease seems extremely unlikely.

Treatment with IFN for patients with HCV-associated MPGN has recently been reported to result in the disappearance of HCV from the serum and in the concomitant reduction in proteinuria (4, 5). Johnson et al demonstrated that a significant reduction in proteinuria without improvement in renal function was found in 14 of 19 patients who underwent a 6–12 month course of IFN-α therapy (5).

As the number of patients undergoing treatment with IFN has increased, so has the recognition of the systemic adverse effects caused by IFN. These secondary disorders include glomerulonephritis, acute interstitial nephritis, retinopathy, diabetes mellitus, interstitial pneumonitis, thyroiditis, and depression, but these are usually reversible following discontinuation of IFN treatment (6, 7). Mild and reversible retinopathy, manifesting as retinal hemorrhage or cotton-wool spots in more than 50% of patients receiving IFN (7), is usually noted within 8 weeks of the commencement of IFN treatment. Blindness, as observed in the present case, is rarely seen (12). Furthermore, the majority of retinal lesions heal spontaneously in the face of continued IFN treatment (7). The present case of severe retinopathy following the discontinuation of IFN therapy is thus of great clinical interest. Clinicians should carefully monitor for the development of retinal lesions in patients receiving IFN.

In the case of renal complication arising during IFN treat-

ment, Ohta et al demonstrated that treatment with IFN for HCV infection may exacerbate the underlying glomerulopathies through direct or indirect effects on glomerular endothelial and epithelial cells (13). Few case reports have been published describing IFN-induced nephrotic syndrome, interstitial nephritis, or thrombotic microangiopathy in patients without underlying renal diseases (14–23).

Although the mechanisms for the adverse effects of IFN remain to be clarified, IFN can alter the balance of Th1 and Th2. IFN-α promotes the differentiation of allergen-specific T cells into Th1, instead of Th2 (24–26). The Th1-dominant response reportedly induces severe crescentic glomerulonephritis (27). In addition, the immune complex composed of anti-IFN-α IgG antibody and IFN-α is involved in the development of IFN-induced MPGN (20). Since we were unable to perform a second renal biopsy in the present case, the renal pathological findings contributing to massive proteinuria and progressive renal failure remained unknown. Relapse of viremia and renal disease is common after stopping IFN therapy (5). However, since HCV RNA was undetectable in the serum following the discontinuation of IFN therapy, it seems unlikely that the progressive renal failure and concomitant massive proteinuria observed in the present case was due to the discontinuation of this therapy. In terms of the massive proteinuria, progressive renal deterioration, undetectable HCV RNA and cryoglobulinemia noted following IFN therapy, the progressive renal failure in this patient was not due to the minimal change disease, interstitial nephritis, hemolytic uremic syndrome, as a side effect of IFN, and HCV associated glomerulonephritis. When we consider the clinical course and laboratory findings in the present case, we speculate that these changes might have been mediated by the immune complex formation, although we were unable to confirm the presence of the anti-IFN-α IgG antibody.

The pathogenesis of interferon-associated retinopathy is unclear. Isaka et al (28) reported that thrombocytopenia may be involved in the pathogenesis of interferon-associated retinopathy. But in the present case, thrombocytopenia was not observed. And it is unlikly that blood pressure and the red blood cell counts were related to the development of retinopathy. Guyer et al (29) suggested that IFN might cause deposition of immune complexes in the retinal vasculature. And such deposition has been suggested as a possible mechanism for interferon-associated retinopathy. Both retinal hemorrhage and massive proteinuria appeared simultaneously, suggesting that the pathogenesis of glomerulopathy and retinopathy in this case may be the same. Thus, we speculate that the IFN-induced massive proteinuria and retinopathy observed in this case may be caused by immune complex formation. As with IFN-induced nephropathy (20), the occlusion caused by the deposition of the immune complex, composed of anti-IFN-α IgG antibody, and IFN-α into capillaries may be involved in the development of retinopathy caused by IFN (29).

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