—Case Reports—

# A Case of Cryoglobulinemic Membranoproliferative Glomerulonephritis Induced by Hepatitis C Virus

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A 61-year-old man with bilateral purpura of the lower limbs and subsequent edema, was hospitalization after renal dysfunction developed. The presence of hepatitis C virus (HCV) RNA and cryoglobulin and the finding of membranoproliferative glomerulonephritis on renal biopsy led to a diagnosis of HCV-related glomerulonephritis due to cryoglobulinemia. Because of the pre-existence of nephrotic syndrome and the continuously increasing serum level of creatinine, treatment with cryofiltration, interferon, and steroids was started. After 5 cryofiltration sessions, the cryocrit level had decreased to 1% and the levels of serum creatinine and proteinuria had also decreased. However, 3 weeks after the start of treatment, nephrotic syndrome developed again and was accompanied by lower-extremity mononeuropathy and renal dysfunction. Thereafter, the patient showed disorientation, an affective disorder, and delirium, and his condition gradually deteriorated. Radiological examination of the head and examination of the cerebrospinal fluid showed no abnormalities. Despite the withdrawal of the interferon therapy and the reduction of the steroid dose, the patient's conditions remained unchanged, and the level of consciousness deteriorated. Although cryofiltration had beneficial effects and plasma exchange was continuously performed, the patient died on the 74th hospital day. Because of the significant changes due to ventilatory support and hemorrhage associated with disseminated intravascular coagulation, the autopsy findings did not allow us to definitively determine whether the symptoms had been caused by the HCV-related membranoproliferative glomerulonephritis or the interferon therapy or both. We have reported this case to provide insight into whether interferon therapy should be administered for HCV-related membranoproliferative glomerulonephritis with marked neurological symptoms due to cryoglobulinemia. (J Nippon Med Sch 2015; 82: 193–201)

**Key words:** membranoproliferative glomerulonephritis, cryoglobulinemia, hepatitis C virus, cryofiltration, hepatitis C virus-related glomerulonephritis

## Introduction

Hepatitis C virus (HCV) infection leads to chronic liver disease but also to extrahepatic manifestations, including kidney disease[1–3]. Membranoproliferative glomerulonephritis (MPGN) is the typical type of HCV-related glomerulonephritis[4–6]. Chronic infection with HCV can lead to the immune complex syndromes of cryoglobulinemia and membranoproliferative glomerulonephritis[7,8]. The pathogenetic mechanisms for these conditions remain unclear.

Treatment of HCV-related cryoglobulinemia and MPGN is difficult. Antiviral therapy is effective in clearing HCV infection in some patients, but these conditions can be severe and resistant to antiviral therapy[9,10]. Some reports have suggested that cryofiltration is effective[11–14].

Herein, we report a case of HCV-related membranoproliferative glomerulonephritis with marked neurological symptoms due to type II cryoglobulinemia.

## Case Report

A 61-year-old male agricultural laborer had chief complaints of purpura and edema. The patient's father had

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Table 1 Laboratory data on admission

| | | | |
|---|---|---|---|
| Peripheral blood | | Coagulation study | |
| WBC | 7,740 /μL | PT | 122 % |
| RBC | 2,240,000 /μL | APTT | 29 seconds |
| Hb | 6.8 g/dL | TT | 99.40 % |
| Ht | 21.20 % | HT | 101.10 % |
| Plt | 85,000 /μL | | |
| Ret | 3.00 % | Serological tests | |
| | | CRP | 0.5 mg/dL |
| Blood chemistry | | ESR | 116 mm/h |
| TP | 6.1 g/dL | HCV-Ab | (+) |
| Alb | 3.1 g/dL | HCV-RNA | 7.1 log IU/mL |
| ALP | 148 IU/L | HBsAg | (–) |
| AST | 27 IU/L | TPHA | (–) |
| ALT | 21 IU/L | RF | >1280 |
| LDH | | ANA | (–) |
| γGTP | 20 IU/L | MPO-ANCA | (–) |
| ChE | 151 IU/L | PR3-ANCA | (–) |
| CK | 109 IU/L | anti-GBM ab | (–) |
| AMY | 132 IU/L | CH50 | 25.9 U/L |
| BUN | 43.3 mg/dL | C3 | 51.3 mg/dL |
| Cr | 1.41 mg/dL | C4 | 16.5 mg/dL |
| UA | 10.7 mg/dL | C1q | <1.5 μg/mL |
| T-Bil | 0.46 mg/dL | C3d | 25 μg/mL |
| TC | 174 mg/dL | SMA | (–) |
| TG | 139 mg/dL | anti-LKM 1 | (–) |
| Na | 140 mEq/L | Cryoglobulin | (+) |
| K | 4.8 mEq/L | Cryocrit | 13 % |
| Cl | 110 mEq/L | | |
| Ca | 7.9 mg/dL | Urinalysis | |
| iP | 4.2 mg/dL | Protein | (3+), 4 g/Cr |
| Mg | 1.9 mg/dL | Sugar | (–) |
| FBS | 97 mg/dL | Occult | (3+) |
| BMG | 7.5 mg/L | Cast | (3+) |
| CEA | 3.9 ng/mL | | |
| AFP | <10 ng/mL | CCr | 35 mL/min/1.73 m$^2$ |
| CA19-9 | 12 U/mL | | |
| PIVKA-Ⅱ | <1 | | |

Underlined values are abnormal.

Abbreviations: WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; Ret, reticulocyte; TP, total protein; Alb, albumin; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; γGTP, γguanosine triphosphate; ChE, cholinesterase; CK, creatine kinase; AMY, amylase; BUN, blood urea nitrogen; Cr, creatinine; UA, uric acid; T-Bil, total bilirubin; TC, total cholesterol; TG, triglyceride; FBS, fasting blood sugar; BMG, β2-microglobulin; CEA, carcinoembryonic antigen; AFP, alpha fetoprotein; CA19-9, carbohydrate antigen 19-9; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time; HT, hepaplastin test; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; TPHA, Treponema pallidum hemagglutination assay; RF, rheumatoid factor; ANA, antinuclear antibody; MPO-ANCA, myeloperoxidase anti-neutrophil cytoplasmic antibody; PR3-ANCA, proteinase-3 anti-neutrophil cytoplasmic antibody; GBM, glomerular basement membrane; CH50, serum complement level; C3, complement factor 3; C4, complement factor 4; LKM 1, liver/kidney microsome type 1; CCr, Creatinine Clearance.

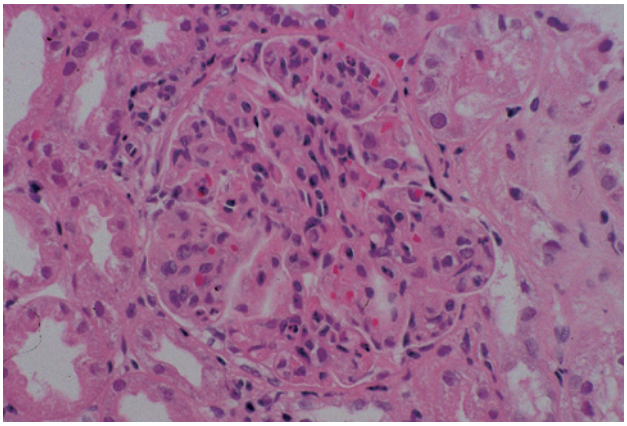

Fig. 1 Light microscopic findings of renal biopsy specimen (hematoxylin and eosin)
There is increased lobulation, hypercellularity in the mesangium, and thickening of the capillary wall (×400).

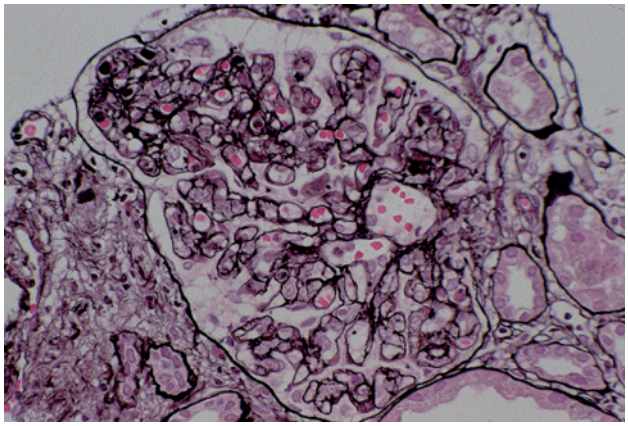

Fig. 2 Light microscopic findings of renal biopsy specimen (periodic acid-methenamine-silver stain)
Light microscopy shows hypercellular glomeruli with accentuated lobular architecture and double contouring of the basement membrane (×400).

died of carcinoma of the stomach, and his mother had died of carcinoma of the gallbladder. He had no significant medical history and had never received a blood transfusion. The patient had received a diagnosis of chronic HCV infection and had been treated at another hospital. Serum levels of aminotransferases were not elevated; therefore, the patient neither underwent hepatic biopsy nor received any interferon (IFN) treatment. He had noticed bilateral purpura of the lower extremities had not sought treatment. Because the purpura subsequently became darker and the area involved increased. And leg edema developed, the patient visited a nearby clinic. Urinalysis revealed protein and urinary casts, and the patient was referred to our department. Because our examinations revealed progressive kidney dysfunction, marked anemia, and thrombocytopenia, he was hospitalized.

The patient's consciousness was clear, and psychoneurological symptoms were absent. Physical examination of the chest and abdomen revealed no abnormalities. However, the lower extremities showed many purpura and moderate edema. Laboratory studies on admission showed renal dysfunction (creatinine, 1.41 mg/dL; blood urea nitrogen, 43.3 mg/dL), the presence of the HCV RNA (7.1 log IU/mL), and significantly elevated rheumatoid factor (>×1,280). The main laboratory findings are summarized in **Table 1**. Plain X-ray examination of the chest and abdomen revealed no abnormalities. No atrophy or enlargement of the kidneys was recognized. Results of endoscopic examination of the upper digestive tract and large intestine were within the normal range.

Percutaneous kidney biopsy was performed for histological diagnosis on hospital day 6. Observation with light microscopy revealed a total of 15 glomeruli, 3 of which were sclerotic. In all glomeruli, mesangial cells were swollen, and glomerular capillary walls were hypertrophic (**Fig. 1**). The glomerular capillary walls of some glomeruli were double (**Fig. 2**). Tubulointerstitial epithelial cells showed acid-fast changes. Immunofluorescence microscopic examination revealed diffuse staining for immunoglobulin (Ig) M (**Fig. 3**) but no significant staining for IgG, IgA, C3, or C4. On the basis of these histological findings, MPGN was diagnosed. Immunoelectrophoresis of cryoglobulins indicated a combination of polyclonal IgG and monoclonal IgMκ. We concluded that the MPGN was caused by type II mixed cryoglobulinemia due to HCV infection.

Cryofiltration was started on day 18, because the patient showed elevated serum creatinine levels and progressive kidney dysfunction. Also, treatment was also started with IFNα2-a (300 mU×3/week) and corticosteroids (prednisolone, 50 mg/day). The system circuit for cryoglobulin filtration was that for standard double-filtration plasmapheresis with an added thermoregulator. For plasma separation, a Plasmaflo OP-08W plasma separator (Asahi Kasei Medical Co., Ltd., Tokyo) was used. Then, the plasma was chilled to 4℃, and aggregated cryoglobulins were removed with a Cascadeflo EC50W plasma component separator (Asahi Kasei Medical) (**Fig. 4**). This procedure was performed a total of 5 times, and the cryocrit values decreased to as low as 1%, and the serum creatinine level decreased. However, the urinary protein level did not decrease significantly. The HCV RNA was not detected with the polymerase chain reac-

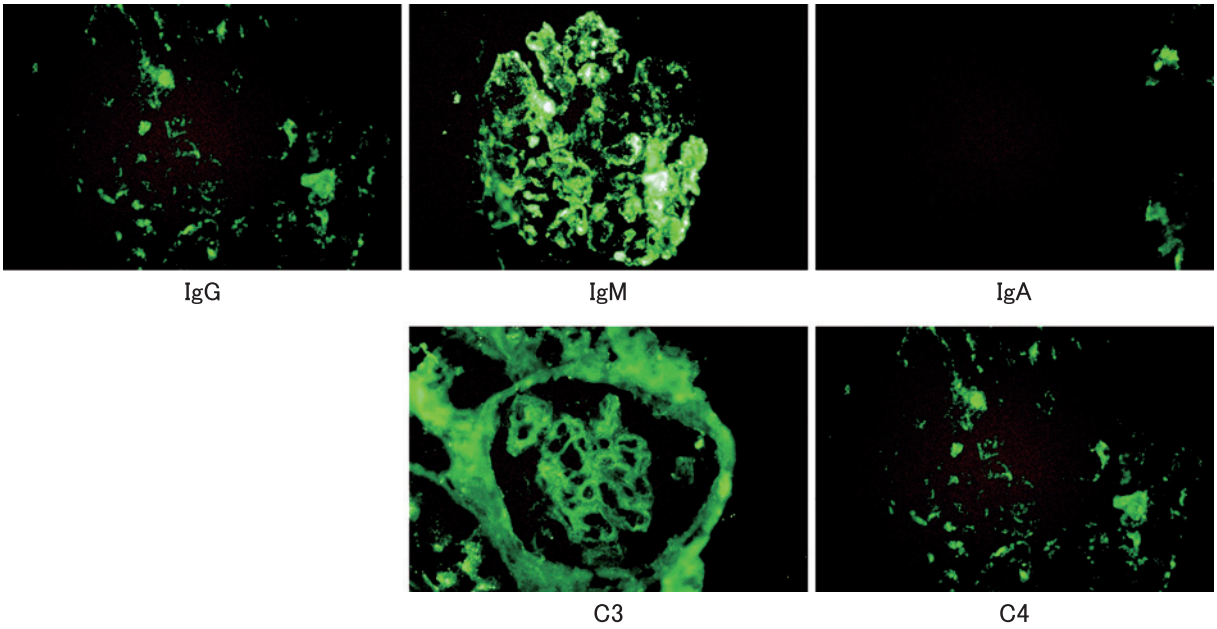


Fig. 3 Immunofluorescent staining of the glomerulus
Immunofluorescent study shows intense glomerular mesangial and capillary wall staining for IgM (×400).

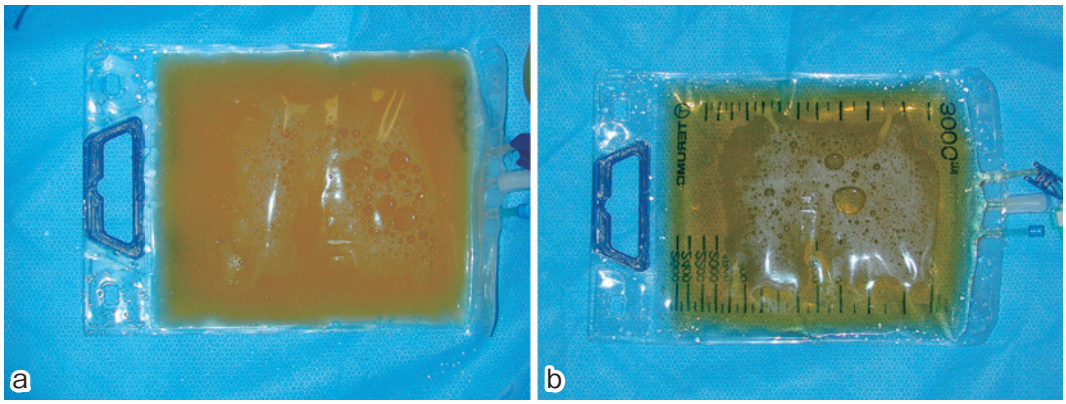


Fig. 4 Filtrate of cryoglobulinemic plasma
The left figure (a) shows the filtrate just after being obtained from the circuit. The right figure (b) shows the filtrate after being heated to 37°C.

tion. Liver function remained stable, and the level of HCV RNA did not increase.

However, 3 weeks after the start of treatment, kidney function deteriorated and nephrotic syndrome was worsened. Pleural and abdominal effusions developed; therefore, steroid-pulse therapy was performed for 3 days starting on day 26, and plasma exchange was performed 3 times a day starting on day 32. The serum creatinine levels were approximately 2 mg/dL and remained stable, but the urinary protein level increased to greater than 10 g/day. The patient had become significantly emaciated since the start of treatment and became aware of a tingling or pricking sensation on the left leg. The patellar reflex and the Achilles tendon reflex of the left leg became diminished, and position agnosia was recognized; therefore, mononeuropathy was suspected. A conduction velocity test of the peripheral nerves on day 19 elicited no evoked response of the sural nerve. The patient gradually became disoriented and showed an emotional incontinence and transient delirium. Adverse reactions to steroid treatment or, especially, IFN treatment rather than cryoglobulinemia were strongly suspected; therefore, IFN treatment was discontinued after 4 weeks. However, because the psychoneurological signs continued to worsen even after IFN was discontinued, cerebrospinal fluid examination was performed on day 43 and revealed only a slight elevation of the IgG level (6.0 mg/dL with a normal index of 0.7). Computed tomography and magnetic

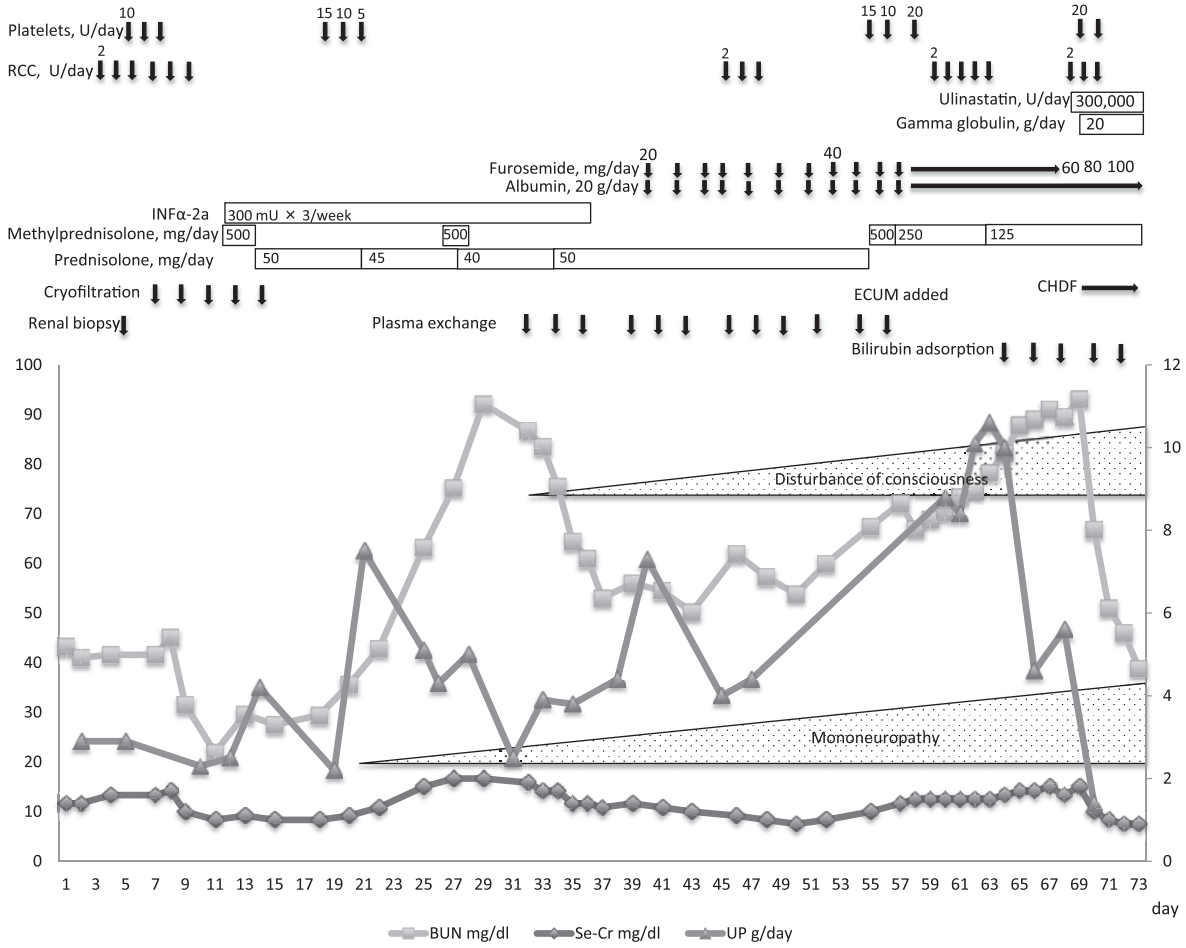


Fig. 5 Clinical course

Abbreviations: RCC, red cell concentrate; ECUM, extracorporeal ultrafiltration method; CHDF, continuous hemodiafiltration

resonance of the head, which were performed on days 43 and 48, respectively, revealed slight atrophy of the brain but no other abnormalities.

The patient's level of consciousness gradually decreased, and his general condition deteriorated. Nephrotic syndrome progressed, and the urine volume was decreased; however, the urinary protein level increased from 30 to 40 g/day. Generalized edema developed with pleural and abdominal effusions. Radiography of the chest revealed pneumonia, and after respiratory function worsened on day 57 the patient began to receive ventilatory support. Computed tomography of the brain indicated areas of decreased absorption in both cerebellar hemispheres; therefore, cerebellar infarction was suspected, despite the normal auditory brainstem response obtained on day 65. The general condition was unstable the serum bilirubin level increased, and acute pancreatitis developed; therefore, continuous hemodiafiltration was started on day 69. Bilirubin absorption therapy was performed in conjunction with the continuous hemodiafiltration; however, the patient died on day 74. The clinical course is summarized in **Figure 5**.

## Histological Findings

The systemic findings were acute renal failure due to HCV-related nephropathy in association with hemorrhagic diathesis. Neurological findings were: 1) respirator brain, with marked edema; 2) multiple fresh hemorrhages with septicemia, associated with disseminated intravascular coagulation and its sequelae; and 3) mild senile changes limited to the hippocampus through the entorhinal cortex, with senile plaques.

## Discussion

In the present case, the history of blood transfusion was not available, but the purpura, edema, and elevation of urinary protein during 8 years of HCV infection fulfill the criteria for HCV-induced glomerulonephritis. Furthermore, despite fluorescent HCV-core antibody techniques and enzyme immunoassay, we were not able to identify

HCV in the kidney tissues. However, the clinical course was consistent with previous reports that cryoglobulinemia is present in HCV-related glomerulonephritis.

The HCV is lymphotropic and hepatotropic virus that leads to various forms of immunological disease[3,7]. Recently chronic HCV infection is often complicated with MPGN; however, cryoglobulinemia and rheumatoid factors are also often present, and B cells infected with HCV are thought to monoclonally produce abnormal IgG, and the immunocomplexes can be expected to form against HCV[15,16]. The IgG may produce cryoglobulinemia. Cryoglobulins are thermolabile serum proteins that reversibly precipitate as a white substance or agarlike gel at temperatures of 0℃ to 4℃ and are dissolved upon rewarming at 37℃. They are classified into 3 groups: type I (monoclonal), type II (monoclonal mixed type), and type III (polyclonal mixed type)[17]. The cryoglobulinemia is classified as symptomatic (secondary) cryoglobulinemia, which is associated with various underlying diseases, or as essential cryoglobulinemia, in which no underlying diseases are identified. Essential cryoglobulinemia is rare, and the incidence is about 20% of the total cryoglobulinemia case[18]. The type of cryoglobulinemia associated with HCV infection is mostly type II, and the manifestation are thought to be produced as follows. Both abnormal immunoglobulins produced by HCV-infected B cells and immunocomplexes formed against HCV acquire antigenecity, and the Fc fragment of these antigen binds IgG with the Fab fragment of the antibodies; IgM[19]. The IgM antigens formed in these circumstances precipitate at low temperatures and are called cold agglutinins. The mixed-type cryoglobulins develop when these factors are present. In addition, IgM acts as a rheumatoid factor[20].

The manifestations of cryoglobulinemia include purpura, arthralgia, hepatopathy, renal failure, hypertension, lower extremity ulcers, and Raynaud's phenomenon. The most common complications are cutaneous lesions, present in 80% to 100% of cases, and are followed by kidney lesions, present in 20% to 60% of cases; however, cases with kidney lesions have an extremely poor prognosis[21]. The course of this present case showed rapidly progressive nephritic syndrome. Renal biopsy revealed MPGN, but crescents were not identified; however, crescentic glomerulonephritis often reflects a progression of MPGN[22]. Results of the postmortem examination also support the diagnosis of MPGN, and the findings were similar to those obtained before treatment. The minimal histological change, despite the rapid change in the clinical course, was an unexpected finding. The presence of renal lesions in cryoglobulinemia most often indicates MPGN, but membranous nephropathy and diffuse proliferative glomerulonephritis have also been reported[23]. The reason MPGN is seen in cryoglobulinemia is as follows. Type II cryoglobulins may have IgMκ as a rheumatoid factor, which has a strong affinity for cellular fibronectin. In mesangial cells, many cellular fibronectins are expressed; therefore, MPGN develops because cryoglobulins precipitate in the matrix[5]. Also, recent studies indicate that immunocomplexes form in situ and make the α-enolace in mesangial cells a target antigen[24].

Treatments for HCV-related glomerulonephritis include IFN, steroids, and cryofiltration, but there is no gold standard[25]. In the present case, IFN therapy was indicated by the serotype and the viral titer. Many reports support the efficacy of IFN therapy[15,26,27], which is widely accepted as a rationalized eradicative therapy for HCV-induced cryoglobulinemia[28]. Furthermore, IFN itself inhibits the increase in urinary protein and the growth of mesangial cells[29,30]. However, especially when splenoma is present, as in our case, treatment with IFN alone might not be able to inhibit memory B cells. The complete remission rate of chronic HCV infection with IFN therapy is about 30%[31]. New therapeutic agents, such as protease inhibitors and polymerase inhibitors, have recently been developed and are expected to have beneficial effects[32–34]. Because of renal dysfunction, ribavirin could not be used in the present case, and pegylated IFNα also could not be used at that time in our hospital.

The possibility has also been suggested that IFN aggravates primary glomerular diseases[31,35,36]. Previous reports indicate that in many cases of IFN-induced glomerulonephritis, remission was achieved by discontinuation of IFN therapy and appropriate treatment[35]. Also, HCV-related nephropathy can recur after IFN therapy. IFN has antiviral, antitumor, and immunomodulatory effects and can also induce autoantibodies and aggravate autoimmune diseases[28,37]. Therefore, IFN therapy should be chosen for HIV-related nephropathy on the basis of the type and titer of the virus and the predicted efficacy of therapy[30,38].

Like IFN therapy, steroid therapy is also controversial; however, to our knowledge, no cases of steroid therapy exacerbating cryoglobulinemia have been reported. In many case reports, steroids were the drugs of first choice[39]. Steroids have been expected, on a theoretical basis, to inhibit virus-induced autoimmunity; however, because of the possibility of viral replication due to steroid therapy, patients should be closely observed. Cryofiltra-

tion removes cryoglobulins from the serum to prevent their inducing nephritis or aggravating the disease, and good results have been reported in cases of rapidly progressive nephritic syndrome[14]. Another possible treatment for cryoglobulinemia is rituximab[40,41]. Also, rituximab has been reported to be effective against interstitial nephritis and vasculitis as well as glomerulonephritis[42].

In the present case, peripheral neurological and psychological symptoms manifested 3 weeks after treatment started; because a causal relationship with IFN was strongly suspected, IFN therapy was discontinued. However, because various neurological examinations revealed no evidence of cerebrovascular abnormalities or inflammatory conditions, such as cerebritis, we could not determine whether the symptoms were due to cryoglobulinemia or to IFN. Neurological symptoms due to cryoglobulinemia are usually peripheral neurological abnormalities; however, various CNS symptoms have occasionally been reported[17,43]. When CNS symptoms develop, plasma exchange therapy is reportedly effective. In the present case, steroid therapy and plasma exchange therapy were continued after IFN therapy was discontinued, and the cryocrit and HCV RNA did not increase to life-threatening levels. Therefore, we believe that IFN was unlikely to have exacerbated the cryoglobulinemia. Although IFN has neurological side effects, most are psychoneurological symptoms[44,45]. Also, in most cases, symptoms are alleviated or resolved after IFN therapy is discontinued, but such improvement did not occur in the present case. Cryoglobulinemia, HCV, and IFN can be considered possible causes of peripheral neurological symptoms in the present case, but because cryoglobulinemia had been diagnosed, is unlikely that HCV was exclusively attributed. Differentiating the other 2 causes, however, is difficult. As far as CNS symptoms are concerned, inflammatory conditions, such as angiopathy and cerebritis, were ruled out, and the symptoms were attributed to IFN therapy or cryoglobulinemia, although the mechanism remains unclear. However, in the present case, the cryoglobulinemia developed before hospitalization, and the cryoglobulinemia tended to worsen, and, the psychoneurological symptoms also developed after IFN therapy was started. Despite the discontinuation of IFN therapy and the continuing treatment for cryoglobulinemia, no improvement was seen; therefore, it was difficult to find out the etiology. A definitive cause could not be determined with autopsy because the patient had received ventilatory support, which affects the tissues, and bleeding was prominent because of disseminated intravascular coagulation at life-or-death crisis.

## Conclusion

We have reported a case of HCV-related nephropathy associated with marked psychoneurological symptoms. We could not definitively determine whether the symptoms were manifestations of the HCV-related nephropathy or side effects of IFN therapy or both. However, we believe this case report provides some insight into whether IFN therapy should be administered for HCV-related glomerulonephritis associated with cryoglobulinemia.

**Conflict of Interest:** The authors declare no conflict of interest.

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