CASE REPORT

Hepatitis C virus-related glomerulonephritis with acute kidney injury requiring hemodialysis that improved with virus removal and eradication using double-filtration plasmapheresis without interferon

Akiko Morisue · Kosuke Fukuoka ·
Ruiko Goto · Kosuke Ota · Haruhiro Yamashita ·
Yoko Shinno · Ichiro Yamadori

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Abstract A 66-year-old, hepatitis C virus (HCV)-positive woman was admitted to our hospital with oliguria, systemic edema, and rapid deterioration of renal function. Laboratory examination showed increased serum creatinine and decreased serum albumin levels, complement activity, and cryoglobulin positivity. The HCV RNA genotype was found to be 1b, and the viral load was high. Kidney biopsy examination showed type I membranoproliferative glomerulonephritis with capillary deposition of IgM and C3, indicating HCV-related glomerulonephritis. After hospitalization, hemodialysis was immediately required because of uremia and oliguria. Her renal function did not improve despite corticosteroid therapy. To treat the increasing HCV load, virus removal and eradication by double-filtration plasmapheresis therapy without interferon was performed, since the patient was allergic to interferon therapy. This treatment improved renal function and allowed the withdrawal from hemodialysis. This report presents a case of successful VRAD without interferon therapy in a patient with HCV-related glomerulonephritis and acute kidney injury that required hemodialysis.

Keywords HCV genotype 1b · Membranoproliferative glomerulonephritis · Virus removal and eradication by double-filtration plasmapheresis

Introduction

The most common hepatitis C virus (HCV)-related nephropathy is membranoproliferative glomerulonephritis (MPGN), usually in the context of cryoglobulinemia. Most cryoglobulinemic HCV-infected patients have no symptoms or nonspecific clinical manifestations. Renal involvement is reported in one-third of cryoglobulinemic patients [1], but the reasons for renal disease development in a selective group of patients remain unknown. Renal signs of cryoglobulinemia include proteinuria and microscopic hematuria with mild to moderate renal insufficiency [2]. Glomerular disease may manifest acutely as oliguric acute renal failure in 5 % of cases [1].

Treatment with pegylated interferon (peg-IFN) and ribavirin or monotherapy with peg-IFN or standard interferon (IFN) has been reported to be beneficial to HCV-related glomerulonephritis [1]. However, published case reports and uncontrolled studies have only included a small number of patients, and the results have been controversial [3]. In a recent Japanese study [4], double-filtration plasmapheresis (DFPP) was used as antiviral treatment with IFN and ribavirin for chronic hepatitis C patients, and significantly higher reductions in viral load and better sustained virological response (SVR) rates were achieved compared with a non-DFPP group. Moreover, in a case of HCV-related glomerulonephritis, this combination therapy reduced viral load and thereby induced clinical remission of MPGN [5]. Given these favorable results, we performed virus removal and eradication by DFPP (VRAD, the

A. Morisue · K. Fukuoka (✉) · R. Goto · K. Ota
Department of Nephrology, National Hospital Organization
Okayama Medical Center, 1711-1 Tamasu, Okayama 701-1192,
Japan
e-mail: fukuokakousuke@gmail.com

H. Yamashita
Department of Gastroenterology, National Hospital Organization
Okayama Medical Center, Okayama, Japan

Y. Shinno · I. Yamadori
Department of Pathology, National Hospital Organization
Okayama Medical Center, Okayama, Japan

trademark of Asahi Kasei Medical, Tokyo, Japan) therapy without IFN, which improved renal function in a patient with HCV-related glomerulonephritis accompanied by acute kidney injury (AKI) requiring hemodialysis.

Case report

A 66-year-old woman consulted a hospital in March 2012 because of reduced urine output, weight gain, and systemic edema. She had been diagnosed with chronic hepatitis C at the age of 40 years. In August 2011, she had been treated with peg-IFN and ribavirin combination therapy, but only five rounds of this therapy could be completed, because she developed adverse reactions, namely, fever, systemic rash, and increased blood pressure. In January 2012, standard IFN monotherapy was administered, but the patient again discontinued treatment because of the same adverse reactions. Three months later, she was admitted to our hospital for treatment of rapid deteriorating renal function.

She was 160 cm tall, weighed 77.5 kg (10 kg more than usual), and her blood pressure was 157/83 mmHg. Her conjunctiva was anemic but not icteric. Normal vesicular breath sounds were heard over the lungs, and no cardiac murmur was audible. Her abdomen was soft and distended because of ascites, but she had no hepatosplenomegaly. Systemic edema was noted, particularly in both legs. Neurological examination showed normal cranial nerve function and normal limb strength. Laboratory findings on admission were as follows: white blood cell count, 6000/ μL ; red blood cell count, $2.75 \times 10^6/\mu\text{L}$; hemoglobin level, 8.3 g/dL; serum total protein level, 4.9 g/dL; serum albumin level, 2.5 g/dL (M component, 7.2 %); blood urea nitrogen level, 64 mg/dL; serum creatinine level, 4.39 mg/dL; serum aspartate aminotransferase, 62 IU/L; serum alanine aminotransferase, 24 IU/L; IgG, 672 mg/dL; IgM, 427 mg/dL; IgA, 170 mg/dL. Cryoglobulin was positive and immunoglobulin (Ig) M (kappa) was identified in immunofixation. The level of the third complement component (C3) was 45 mg/dL (normal 50–130 mg/dL), and that of the fourth component (C4) was 1 mg/dL (normal 10–50 mg/dL); hemolytic complement activity via the classical pathway (CH50) was <12 U/mL (normal 25.0–48.0 U/mL). The level of rheumatoid factor was 12 IU/mL; anti-nuclear antibody was negative, and myeloperoxidase (MPO) and proteinase 3 (PR3) anti-neutrophil cytoplasmic antibody (ANCA) were not detected. Urinalysis yielded the following results: urinary protein level, 1.12 g/g creatinine; red blood cell count, 30–49/HPF (and showing deformation). Red blood cell, hyaline, granular, and waxy casts were detected in urinary sediment. Virological studies showed that hepatitis B surface antigen was negative, but anti-HCV antibody was positive. Genotype

characterization showed HCV type 1b with a high viral load (6.2 logIU/mL). Abdominal computed tomography (CT) showed significant ascites and slight splenomegaly, and the form and size of the kidneys were normal.

At the time of hospitalization, percutaneous kidney biopsy examination was not performed because of the large amount of ascites. However, HCV-related cryoglobulinemic glomerulonephritis was suggested by the findings of persistent hypocomplementemia, cryoglobulinemia, M proteinemia, and high HCV load. IFN therapy to reduce the HCV load was not an option because the patient had developed adverse reactions in the past. Hemodialysis was started three times a week for her uremia and oliguria, and corticosteroid monotherapy was started to treat the cryoglobulinemia. From hospitalization day 5, 250 mg/day of methylprednisolone pulse therapy was administered for 3 days, followed by oral prednisolone (PSL) at 20 mg/day (Fig. 1). On the 10th day, her urinary volume increased to 1 L/day, and hemodialysis was discontinued from the 12th day. However, her urinary volume then decreased to 200–300 mL/day, and 2nd and 3rd times methylprednisolone pulses were performed for 3 days from the 17th day and the 23rd day, respectively. However, her urine volume did not increase, and hemodialysis was resumed at three times a week. A dose of up to 40 mg/day of PSL was administered, but hemodialysis had to be continued. Moreover, the viral load increased to 7.0 logIU/mL. Therefore, VRAD therapy without IFN was administered in addition to the standard treatments.

VRAD therapy was administered as described previously [4–6]. A PlasmfloTM OP-08W (Asahi Kasei Medical) and an EvafloTM 5A20 (Asahi Kasei Medical) were used as the plasma separator (first filter) and plasma fractionator (second filter), respectively. To avoid bleeding complications, the fibrinogen level (>100 mg/dL) and

Fig. 1 Changes in daily urinary excretion, creatinine, and body weight during hospitalization

platelet count ($>50000/\mu\text{L}$) were checked before each session. The 15 cm triple-lumen GentleCathTM vascular access catheter (COVIDIEN JAPAN, Tokyo, Japan) that had been inserted for hemodialysis and was indwelling in the right cervical vein was used for vascular access. During each session, 3500 mL of plasma was processed for 2.5 h at a flow rate of 24 mL/min. Nafamostat mesilate was used as an anticoagulant, since heparin was considered to affect reverse-transcription polymerase chain reaction, which was used for HCV RNA measurement. VRAD therapy was performed five times from hospitalization day 44 within 2 weeks. No major adverse events were observed; although the platelet count and fibrinogen levels reduced temporarily during VRAD therapy, they recovered to the initial levels within 2 weeks, and there were no bleeding events.

After the fifth session of VRAD therapy, her urine volume increased significantly, because of which hemodialysis could be stopped on the 62nd day (Fig. 1). Proteinuria had become undetectable on the 49th day. Further, the HCV load had decreased to 5.2 logIU/mL, and the M component was 1.2 %. Moreover, the reduction in ascites made renal biopsy examination possible.

A percutaneous renal biopsy specimen containing 12 glomeruli revealed MPGN pattern, characterized by lobularity of the glomeruli with diffuse mesangial proliferation and consistent thickening of the capillary walls caused by the double contours of the basement membrane (Fig. 2). Immunofluorescence revealed granular staining of IgM, C3, and fibrinogen within the mesangium. On the basis of laboratory data, pathological findings, and clinical course, the patient was diagnosed with HCV-related glomerulonephritis.

A sufficient quantity of urine output induced weight loss from 80 kg (maximum) to 63 kg. Systemic edema and ascites also improved. Serum creatinine level decreased to around 1.3 mg/dL without dialysis. The dose of oral PSL was gradually decreased from 40 mg/day for 4 weeks to 30 mg/day for 3 weeks and then 25 mg/day for 1 week. On hospitalization day 103, after 3 weeks of PSL at 20 mg/day, the patient was discharged from the hospital.

Discussion

There is increasing evidence of the association between HCV infection and glomerular disease. Type I MPGN associated with type II cryoglobulinemia is known to frequently manifest as renal disease [7]. Antiviral treatment has been used in HCV-related glomerulonephritis to eradicate HCV from the serum and to improve renal disease [8, 9]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [10] suggested that for HCV-related glomerulonephritis, particularly MPGN, antiviral treatment adjusted for the estimated glomerular filtration rate should

Fig. 2 Renal biopsy findings. **a** Periodic acid-Schiff (PAS) stain showing lobularity of glomeruli with diffuse mesangial proliferation. **b** Periodic acid silver-methenamine (PAM) stain showing thickening of capillary walls caused by double contours of basement membranes

be considered; this includes peg-IFN and ribavirin combination therapy, peg-IFN monotherapy, and standard interferon therapy. Further, in patients with nephrotic-range proteinuria and/or rapidly progressive loss of kidney function and an acute flare of cryoglobulinemia, one of the following therapies might be considered: plasma exchange, rituximab, and cyclophosphamide plus methylprednisolone pulses.

The therapeutic response to antiviral treatment is affected by HCV genotype as well as the HCV RNA load. In a previous study, a SVR was achieved in only 30–50 % of patients with genotype 1 receiving IFN α and ribavirin, but in 65–90 % of those with genotype 2 or 3 [3]. Unfortunately, our patient was infected with viral genotype 1 and had a high viral load, both of which are associated with resistance to IFN therapy [11]. Moreover, she had had two

severe adverse reactions to IFN therapy in the past. Because we considered that the adverse effects of IFN might overwhelm its efficacy, we did not administer IFN therapy to this patient.

The direct-acting antiviral drugs telaprevir and boceprevir targeted against HCV are two new potent protease inhibitors that have been recently licensed by the United States Food and Drug Administration (FDA). Recent guidelines now recommend the use of these drugs in combination with peg-IFN and triple antiviral therapy in treatment-naïve and treatment-experienced patients with genotype 1 chronic HCV infection. Telaprevir and boceprevir apparently do not require dose adjustments depending on renal function, but evidence regarding the safety of the abovementioned triple therapy in chronic kidney disease patients is currently unavailable; therefore, safety issues need to be carefully addressed [12].

Corticosteroid therapy for HCV-related glomerulonephritis was recommended together with IFN therapy in the KDIGO guidelines [10], and there are several reports of corticosteroid therapy for HCV-related glomerulonephritis [13, 14]. In a randomized controlled study, Dammacco et al. [15] reported the use of corticosteroid therapy for type II mixed cryoglobulinemia. Komatsuda et al. [16] reported that 5 of 11 patients treated with steroids showed improvement in renal impairment. In the present case, despite concerns about increased viral reproduction and risk of infection, corticosteroid therapy was administered for HCV-related glomerulonephritis to decrease cryoglobulinemia. As a result, the effect of the therapy was temporary, and it was difficult to discontinue hemodialysis because of the high viral load.

Several studies have reported the use of DFPP for HCV treatment [4–6]. Fujiwara et al. [4] demonstrated that DFPP plus IFN combination therapy produced a considerable reduction in the viral load during the early stage of treatment and yielded a high SVR rate. Subsequently, Namba et al. [5] also reported the use of DFPP plus IFN combination therapy to reduce HCV RNA blood levels in the early stage of IFN therapy. Our case is the first successful report of VRAD therapy without IFN for HCV-related glomerulonephritis. VRAD therapy is considered to be the more possible treatment as not only an alternative method if antiviral therapy (such as IFN and ribavirin) can not be used, but also supportive therapy with antiviral therapy to achieve SVR.

It is noteworthy that the VRAD therapy without IFN in our case adequately improved diuresis to allow the withdrawal from hemodialysis that had been continuously administered for 2 months. Not just the viral load but also the M protein level and IgM level decreased after VRAD therapy. From these results, we may speculate that reduced production of unusual immunoglobulins by HCV-infected

B cells contributed to the decrease in immune complex deposition in the mesangial area.

A previous mathematical study showed that HCV has a serum half-life of 3 h and a viral production rate of 1.0×10^{12} virions/day [17]. Because it is predicted that the viral load increases for several hours immediately after VRAD therapy is stopped, continuous VRAD therapy is necessary to maintain a low viral load. Thus, in the present case, VRAD therapy should be scheduled regularly and HCV eradication should be continued to prevent the relapse of nephritis. However, thus far, there is no firm evidence regarding the amount of plasma processing required and the duration, times, or intervals. Physicians must consider the most appropriate way to improve the effect of therapy on an individual basis.

In conclusion, HCV-related glomerulonephritis with AKI requiring hemodialysis improved with VRAD therapy without IFN in a patient allergic to IFN. This treatment improved the patient's renal function and led to the withdrawal from hemodialysis. VRAD therapy without IFN may be proposed as an effective treatment for HCV-related glomerulonephritis in cases where IFN use is not suitable.

Conflict of interest The authors have no conflict of interest to declare.

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