

Case Report

Delayed spontaneous resolution of nephrotic syndrome in a patient with hepatitis C virus-associated membranoproliferative glomerulonephritis

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Abstract

Treatment with antiviral and/or immunosuppressive therapy is considered the standard care in patients with hepatitis C virus (HCV)-associated membranoproliferative glomerulonephritis (MPGN). However, even with an adequate therapy, a favourable response is not always guaranteed. In patients with HCV-associated MPGN, a delayed spontaneous remission of nephrotic syndrome is rare. We present here one such case. Our patient refused antiviral (and immunosuppressive) therapy throughout the course of his illness and was thus managed symptomatically. More than 8 months after presentation, an unexpected gradual resolution of his nephrotic syndrome was noted. The urine protein/creatinine ratio decreased from ~16 000 mg/g of creatinine on presentation to 500 mg/g of creatinine in the 12th month. This was however not accompanied by resolution of HCV or cryoglobulinaemic activity. Our case demonstrates the possibility of a delayed spontaneous remission occurring in this disease. This must be considered when weighing treatment options in such patients.

Keywords: hepatitis C virus; membranoproliferative glomerulonephritis; nephrotic syndrome; spontaneous delayed resolution

Introduction

Type I membranoproliferative glomerulonephritis (MPGN), with or without features of cryoglobulinaemia, has been associated with chronic hepatitis C virus (HCV) infection. We report here an unusual case of delayed spontaneous remission of nephrotic syndrome in a patient with hepatitis C virus-associated MPGN.

Case report

Our patient was a 56-year-old white male, who was referred to the Nephrology Clinic for a 1-week history of

worsening dyspnoea on exertion, hypertension, pedal oedema and a recent increase in his serum creatinine level. Six months prior to presentation, he was diagnosed with coronary artery disease (CAD) for which he required coronary artery stent placement. His home medications included aspirin, clopidogrel, hydrochlorothiazide, atorvastatin, enalapril and metoprolol.

On examination, the patient was obese and had bilateral pitting oedema up to the knees. His blood pressure was 196/100 mmHg (baseline was 130/86 mmHg), and pulse 66 beats/min. He had no rash, purpura or leg ulcers. Laboratory analysis revealed worsening of the serum creatinine level to 1.9 mg/dL (167.96 µmol/L; laboratory range: 0.7–1.4 mg/dL) from a baseline of 1.3 mg/dL (114.92 µmol/L). He had an associated nephrotic range proteinuria (urine protein/creatinine ratio 11 918 mg/g creatinine), microscopic haematuria, and markedly elevated rheumatoid factor of 123 IU/mL (123 IU/mL; laboratory range: <20 IU/mL). In addition, there was a decreased level of complement C4 7 mg/dL (0.07 g/L; laboratory range: 16–47 mg/dL) with a normal level of complement C3 98 mg/dL (0.98 g/L; laboratory range: 90–180 mg/dL). Serologic analysis revealed a negative anti-nuclear antibody (ANA), anti-glomerular basement membrane antibody, anti-neutrophilic cytoplasmic antibody and hepatitis B surface antigen (HBsAg). The levels of immunoglobulin G (IgG), immunoglobulin A (IgA) and immunoglobulin M (IgM) were normal. The hepatitis C RNA was 58 100 IU/mL (58 100 IU/mL; laboratory range <5 IU/mL). In view of acute renal failure in the presence of markedly elevated RF, nephrotic syndrome and active HCV serology, a presumptive diagnosis of cryoglobulinaemic glomerulonephritis was made.

The patient refused antiviral therapy. He was thus treated symptomatically. An angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB) were added to achieve blood pressure control. In addition, he continued to receive aspirin (325 mg) and clopidogrel (75 mg) as part of the management for his CAD. Even though

Table 1. Summary of the pertinent laboratory values over a 12-month period (starting from 0 as baseline)

	0	1	3	4	5	6	7	8	9	10	11	12	13
Urea nitrogen, serum (mg/dL)	46	44	64	59	58	56	52	58	54	62	65	60	55
Creatinine (mg/dL)	1.6	1.9	2.0	2.3	2.4	2.4	2.5	2.8	2.8	2.3	2.2	2.2	1.9
Rheumatoid Factor (IU/mL)		123			220				266			224	264
C3 complement (mg/mL)		98			114				114	101		102	106
C4 complement (mg/mL)		7			6				12	11		18	18
HCV RNA	5100				4732								44524
Urine protein/creatinine		11918		14162	15865		15529		10753	2871	1066	1039	471

Conversion factors for SI units (wherever applicable) and laboratory range: serum creatinine (in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; laboratory range 0.7–1.4 mg/dL), serum urea nitrogen (in mg/dL to mmol/L, $\times 0.357$; laboratory range 7–18 mg/dL), rheumatoid factor [in International units (IU)/mL, laboratory range <20 IU/mL], C3 complement (in mg/dL to g/L, $\times 0.01$; laboratory range 90–180 mg/dL), C4 complement (in mg/dL to g/L, $\times 0.01$; laboratory range 16–47 mg/dL), Urine protein to creatinine ratio in milligram per gram of creatinine. The HCV RNA was 58 100 IU/mL (laboratory range ≤ 5 IU/mL) in the first month and 44 524 IU/mL in the 12th month. The patient never received anti-viral therapy.

the blood pressure improved to 130/86 mmHg after the addition of ARB and CCB, his nephrotic syndrome and renal failure worsened over the next 5 months (Table 1). The patient ultimately agreed to a renal biopsy 6 months after the initial presentation. This showed features of MPGN type 1, but with no overt evidence of intracapillary globular accumulations of eosinophilic material ('protein thrombi') and no ultrastructural features of cryoglobulin (Figure 1).

The patient continued to refuse anti-HCV therapy, and his creatinine increased to 2.8 mg/dL (247.52 $\mu\text{mol/L}$; laboratory range: 0.7–1.4 mg/dL) in the eighth month after presentation. Subsequently, and without any change in his therapy or medication regimen, an unexpected gradual partial resolution of his nephrotic syndrome was seen, which was also associated with an improvement of his serum creatinine and a normalization of his C4 level. There was no decrease in the viral load or the level of rheumatoid factor. The HCV RNA was 58 100 IU/mL (58 100 IU/mL) on presentation and 44 524 IU/mL (44 524 IU/mL) in the 12th month. The pertinent laboratory values over the 12-month period are summarized in Table 1.

Discussion

Type 1 MPGN is a well-documented extra hepatic manifestation of chronic HCV infection [1]. Type 2 mixed cryoglobulins are often present. These constitute of a monoclonal component (usually of IgM kappa) with rheumatoid factor

(RF) activity against polyclonal IgG [1]. In our patient, the presence of type 1 MPGN, reduced levels of C4 (and essentially normal C3 levels) and markedly elevated RF with an associated active HCV serology all pointed towards cryo-MPGN as the underlying cause of the patient's renal failure. A delayed spontaneous remission of nephrotic syndrome is extremely rare in such patients [2]. Even in those treated with antiviral and/or immunosuppressive therapy, favourable response is not always guaranteed.

In our patient, the exact mechanism of his renal improvement is unclear. Adequate blood pressure control with an ARB, ACE and CCB was not associated with a decrease in the level of proteinuria for almost 5 months. It is therefore unlikely to be an explanation for the delayed partial resolution of his nephrotic syndrome and improvement of his renal function. To date, the patient has no improvement in the HCV or cryoglobulinaemic activity, as evident from the HCV viral load and markedly elevated level of rheumatoid factor. Anti-platelet agents have been reported to cause amelioration of nephrotic syndrome, but their exact role in the treatment of MPGN is debated [3]. The dose of aspirin recommended in MPGN is 975 mg, much less than what our patient was on. Though he was also taking another anti-platelet agent, clopidogrel, the above are unlikely to have been the cause of remission since the patient was on the same anti-platelet agents at presentation.

A case of delayed complete resolution of renal failure in a patient with cryo-MPGN (after 6 months of haemodialysis) has been described by Bertrand *et al.* [2]. The reported

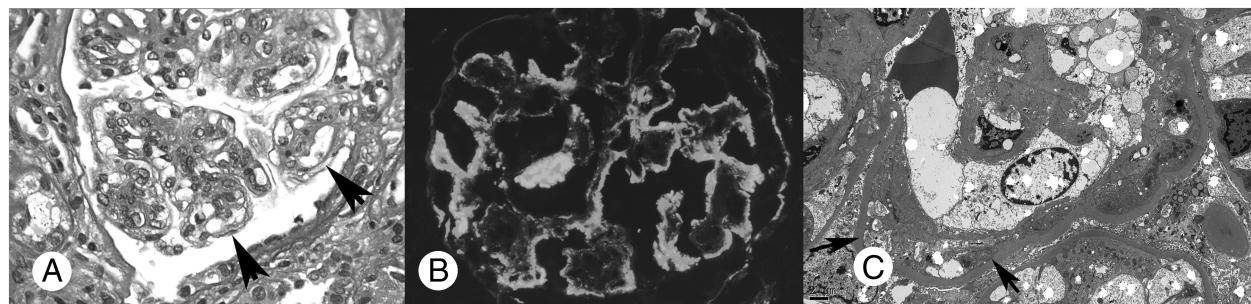


Fig. 1. Light microscopy showed diffuse endocapillary proliferative glomerulonephritis with membranoproliferative features (arrows, A). Also noted were moderate acute tubular injury, interstitial fibrosis and arteriosclerosis. On immunofluorescence (B), glomerular capillary walls stained for IgM and C3, consistent with immune complex-mediated glomerulonephritis due to HCV infection. On electron microscopy, mild diffuse thickening of the glomerular basement membrane (GBM) was associated with characteristic segmental duplication due to the cellular interposition. Granular electron-dense deposits were present within the mesangium and subendothelium (arrows, C).

patient received cyclophosphamide with steroids on presentation and required 6 months of haemodialysis before an unexpected complete resolution of his renal failure. Furthermore, as was seen in our case, the improvement in renal function was not accompanied by resolution of HCV infection or activity of cryoglobulinaemia.

In conclusion, a delayed spontaneous partial or complete remission can occur in patients with HCV-associated type 1 MPGN. This must be considered when weighing treatment options in such patients.

Conflict of interest statement. None declared.

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Received for publication: 12.2.10; Accepted in revised form: 12.4.10