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Case Report

Hepatitis C associated membranoproliferative glomerulonephritis treated with directly acting antivirals for hepatitis C

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ABSTRACT

Hepatitis C virus (HCV) infection affects kidneys with different histopathological patterns on kidney biopsy, which commonly include membranoproliferative glomerulonephritis (MPGN) pattern with mixed cryoglobulinemia (CG), thrombotic microangiopathy, membranous nephropathy and small to medium vessel vasculitis. Type 1 MPGN associated with type II mixed CG is the most common glomerulopathy associated with hepatitis C infection. Treatment of these glomerulopathies and cryoglobulinemic renal disease associated with HCV infection includes antiviral therapy for HCV, B-cell depletion therapy for prevention of immune complexes and cryoglobulins or nonspecific immunosuppressive therapy. We describe a patient who presented to us with HCV associated MPGN type 1 with cryogloblinemia and detectable HCV RNA, who recovered completely with directly acting antiviral agents (DAA) alone without immunosuppression.

Keywords: CG, Hepatitis C, MPGN, Directly acting antivirals

INTRODUCTION

Chronic HCV infection is associated with various extra hepatic syndromes such as mixed CG, polyarteritis nodosa and syndrome resembling Sjogren syndrome.[1,2] The association between HCV infection and CG is very strong with HCV antibodies present in 42 to 70 percent patients with HCV RNA in serum detected in 86% patients.[3-5] Several histopathological patterns on kidney biopsy have been reported in association with HCV infection which commonly include MPGN pattern with mixed CG, thrombotic microangiopathy, membranous nephropathy and small to medium vessel vasculitis.[6] At present, it is known that MPGN accompanied with CG is the most common form of HCV-related glomerulonephropathy, and it is often accompanied with hypocomplementemia, rheumatoid factor and CG.[7,8] The typical renal manifestations in HCV infection include hypertension, hematuria, proteinuria, nephritic or nephrotic syndrome. However, renal disease may be asymptomatic, so patients with HCV infection should be screened for proteinuria, hematuria and CG. Patients presenting with mild or moderate forms of HCV associated glomerular disease (stable renal function and/or non- nephrotic range proteinuria) should be treated with DAAs. Patients with HCV associated glomerular disease who are resistant or intolerant to DAA therapies should be treated with immunosuppressive agents.[9] All cases should be treated with antiproteinuric agents such as angiotensin-converting enzyme inhibitors and/or angiotensin-receptor blockers to achieve a maximal antiproteinuric response. Diuretics and other anti-hypertensive agents should be given wherever clinically indicated. Here we describe a patient with HCV associated MPGN with CG, who recovered completely with DAA without immunosuppression.

CASE REPORT

A 31-year-old male presented with complaints of pedal oedema associated with facial puffiness since last 2 months. On clinical examination he was hypertensive with blood pressure of 160/90 mmHg and had pallor, rest of the

physical examination was unremarkable. Investigations revealed Anemia with haemoglobin of 8.2 g/dl, serum creatinine of 2.2 mg/dl, creatinine clearance of (CrCl) 41ml/min/1.73 m^2, urine routine microscopy: 8-10 RBC/hpf, 4-5 WBC's/hpf, proteinuria 2+, 24 hour urinary protein 2.1 gm. Serology for HBV and HIV was negative while Anti HCV positive with viral load of 1400000 IU/ml. USG abdomen revealed bilateral normal sized kidneys with bilateral increased renal echogenicity with normal liver outline and echotexture, ANA was negative, rheumatoid factor was positive, complement levels reduced (C3 and C4 levels reduced). Kidney biopsy showed irregular glomerular basement membrane thickening, mesangial matrix expansion and mild to moderate endocapillary proliferation. Few hyaline thrombi seen within the lumen of capillary. Immunofluorescence showed granular reactivity on the glomerular basement membrane and mesangium with anti Ig G (2+), Ig M (2+), C3(1+), Kappa (2+), lambda (2+). IgA and C1q are negative, electron microscopy was not done. Kidney biopsy was suggestive of MPGN type 1. Patient was started on DAA (Sofosbuvir 400 mg with daclatasvir 60 mg once daily for 12 weeks) along with antihypertensive drugs-angiotensin receptor blockers (Telmisartan 40 mg once daily) and hematinics. Repeat investigations after 12 weeks showed clinical improvement with s. creatinine of 1.1 mg/dl improvement in urinary albumin and HCV RNA undetectable. Six months follow-up of patient had undetectable HCV RNA.

Table 1: Various clinical parameters of the patient at baseline and at 12 weeks.

Clinical parameters	Baseline	After 12 weeks
Hemoglobin (g/dl)	8.2	10.4
Serum creatinine (mg/dl)	2.2	1.1
Proteinuria	2+	Trace
HCV RNA (IU/ml)	1400000	Undetectable

DISCUSSION

Prevalence of hepatitis C infection is approximately 5.2% in certain geographic regions in India. HCV infection causes several distinct patterns of renal disease such as MPGN, essential mixed CG and membranous nephropathy. Its clinical manifestations may range from mild kidney disease to frank nephrotic syndrome to end stage renal disease (ESRD), may even present as rapidly progressive renal failure. The pathogenesis of HCV associated cryoglobulinemic glomerulonephritis (HCV cryo GN) includes HCV driven expansion of memory B cells clones which are responsible for the production of pathogenic monoclonal IgM with rheumatoid factor (RF) activity.[10] Patients who achieve sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy have reduced proportions of autoreactive memory B-cell clones. In some of the patients, HCV Cryo GN can persist despite achievement of Sustained virological response (SVR), likely because of residual RF producing B-cell clones. The presence of continued immunological activity, which is characterized by persistently elevated circulating cryoglobulins, RF seropositivity, and low C4, may help to stratify patients who are at a risk for persistent cryo-GN despite achieving SVR. B-cell depletion therapy with rituximab provides additional benefit in patients with HCV-cryo GN in whom antiviral therapies alone fail to induce clinical remission.[10] Our case emphasizes the efficacy of antiviral therapy alone for HCV-associated GN; mild kidney disease and the absence of aggressive involvement of other organs suggested an antiviral approach alone. Treatment of MPGN associated with HCV infection mainly involves treatment of HCV with newer DAA in clinically stable disease. The patients with active GN treated with DAA therapy experienced an improvement in renal functions and proteinuria.[11] Treatment with newer DAAs often results in remission of renal lesions and cryoglobulins in blood. In a case report by Nayak et al a patient with HCV associated MPGN without CG was successfully treated with DAA.[12] In addition to the treatment of HCV infection, these patients may also require the use of immunosuppression especially if they have a rapidly progressive renal failure, nephrotic range proteinuria or features of severe systemic vasculitis. Immunosuppressive agents such as rituximab with or without need for plasmapheresis and corticosteroids have been effective in such patients. The patient here improved rapidly with normalisation of renal functions, improvement in proteinuria and negative Hepatitis C viral load with DAA alone without need for any immunosuppressive therapy for MPGN. This is likely due to the higher efficacy of newer DAA's in eradicating the HCV and hence attenuating immune complex formation and further insult to the nephrons.

CONCLUSION

HCV infection can cause MPGN with or without detectable cryoglobulins. One should be aware that HCV-cryo-GN can occur in the absence of ongoing viral replication due to persistence of RF-producing memory B-cell clones. DAA therapy alone can induce complete recovery in stable MPGN with detectable cryoglobulins. However longer follow-up will help determine sustained immunological and clinical response rates in patients who receive DAA therapy alone, particularly those with renal involvement.

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