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Acute glomerulonephritis in an HCV positive patient

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CLINICAL PRESENTATION

A 30-year-old male, married and father of 3 children, presented to the outpatient department (OPD) of our hospital with a 2-month history of facial and bipedal oedema along with history of hypertension. He gave 1-week history of decreased appetite and nausea and decreased urine output. He was smoker and alcoholic and belonged to low socioeconomic class. He was hepatitis C virus (HCV) positive, which was detected 8 years back, during blood donation screening, but was never treated, as he was asymptomatic. No past history of joint pains, rashes, or haematuria was elicited. No past history of surgical operation was available.

On examination, the patient was conscious and well oriented in time and space. He weighed 92 kg. Pedal oedema was 2+ and pitting type. Anaemia was negative. Jugular venous pressure (JVP) was not raised. His temperature was 98^{0} F, respiratory rate, 15/min, pulse, 110/min, and blood pressure, 170/110 mmHg.

The chest was clear in the upper and mid zones, while lower zones revealed basal crepitations on auscultation. The rest of the systematic examination, including abdominal, cardiovascular and central nervous system was unremarkable.

He was administered amlodopine, 10 mg BD, atenotol, 100 mg BD, hydralazine, 50 mg BD and injection lasix, 80 mg, intravenously (I/V) BD to control the high blood pressure and produce diuresis.

The laboratory investigations on the day of admission revealed blood urea, 109 mg/ dl; serum creatinine, 4.29 mg/ dl; serum albumin, 1.8 g/dl; random blood sugar, 92 mg/ dl; and serum calcium, 8.2 mg /dl. Urine dipstick examination revealed albumen, 4+; blood, 3+; and red blood cells (RBCs), numerous. The spot urine protein/creatinine ratio was 1.0. Liver function test (LFT) studies showed serum glutamic oxaloacetic transaminase (SGOT), 40 IU/L; serum glutamic-pyruvic transaminase (SGPT), 35 IU/L; and *gamma-glutamyl transferase (*GGT), 25 IU/L.

Ultrasound of the whole abdomen showed right kidney of 13.0 cm and left, 13.1 cm in size. Liver was normal in outline and echotexture. No free fluid was detected. No evidence of chronic liver disease (CLD) was found. Electrocardiogram (ECG) was normal; no left ventricular hypertrophy was seen. Echocardiogram showed normal left ventricular size and function, normal valves and no pericardial effusion. Ejection fraction was 72%. Upper gastrointestinal endoscopy was done, which was negative for oesophageal varices.

Meanwhile, his anti-hepatitis C virus (HCV) serology was reported positive. Also detected was HCV RNA. The HCV genotyping revealed 3a genotype. Serology showed low C3 (0.48) and C4 (0.16). Immunoglobulins were normal: IgG, 6 g/l, IgM, 9.99 g/l, and IgA, 0.71 g/l. Antinuclear antibody (ANA) and anti-dsDNA were negative. Both antineutrophil cytoplasmic antibodies (ANCAs) were also negative.

Antistreptolysin O titre (ASOT) was 143 units. Rheumatoid factor (RA) was very high at presentation (3380 U/ml); later, during the course of treatment, it decreased to 908 IU/ml.

His serum creatinine continued to rise. The values, after one week of admission, revealed blood urea 157 mg/dl and serum creatinine 6.67 mg/dl.

After optimization of the oedema and hypertension, a renal biopsy was done. The biopsy findings are discussed in the histological findings section below.

Serum cryoglobulins were also ordered ant turned out to be positive at 30%. The typing of the cryoglobulins revealed that both the immunoglobulins were of polyclonal nature (type III). The HCV RNA was not done in the cryoprecipitate sample. The serum creatinine still continued to rise to 8.01 mg/dl and haemodialysis was started.

Following the renal biopsy report, the pati ent was given injection methylprednisolone, 1g, I/V once daily for 3 days, then switched to oral prednisolone, 0.5 mg/kg daily. He was also given injection cyclophosphamide, 750 mg, I/V, along with injection interferon alpha 2a, 3 million units, thrice weekly. Plasmapharesis was also started four days later. Ten cycles were done. After the 5th session of plasmapharesis, the serum creatinine started to decrease. One week later, serum creatinine became 2.54 mg/dl. Repeat cryoglobulins at this time showed a declining trend and were 6.3%.

The patient was discharged after 10 sessions of plasmapharesis were completed. The discharge serum creatinine was 2.4 mg/dl. He was prescribed the following treatment: oral prednisolone, 0.5 mg/kg and injection interferon 3 million units thrice weekly. One month later, his serum creatinine was 1.7 mg/dl.

HISTOLOGICAL FINDINGS

Four small cores of renal biopsy were received consisting of both cortex and medulla. Up to 16 glomeruli were included. Of these, two were globally sclerosed and the rest showed diffuse mesangial proliferation of moderate to severe degree with extensive interpositioning into the peripheral capillary walls (Figs. 1, 2, and 3). Many glomeruli showed prominent hyaline thrombi in capillary lumena and wireloop thickening of the peripheral capillary walls (Figs. 3 and 4). In addition, four glomeruli showed cellular crescent formation (Figs. 5 and 6). No vasculopathy was seen. Mild to moderate patchy tubular atrophy was seen associated with interstitial inflammation and fibrosis (Figs. 1 and 2). Moderate acute tubular injury was also seen.

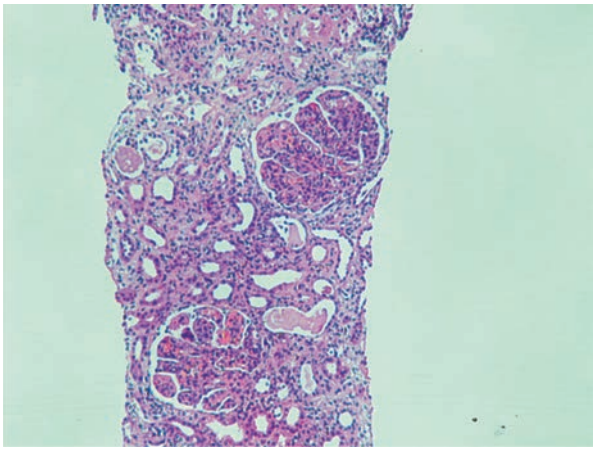

Figure 1

Haematoxylin and Eosin, (×100).

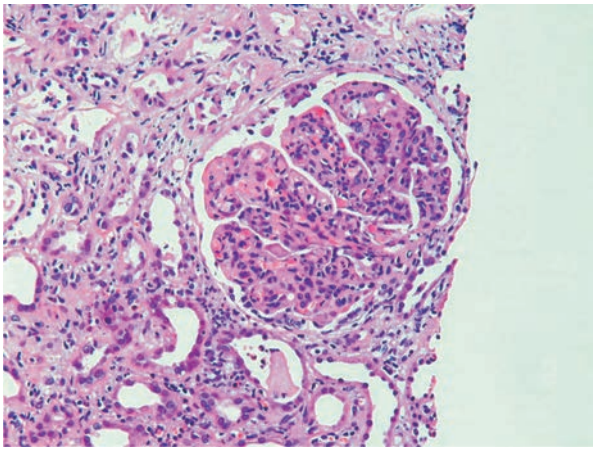

Figure 2

Haematoxylin and Eosin, (×200).

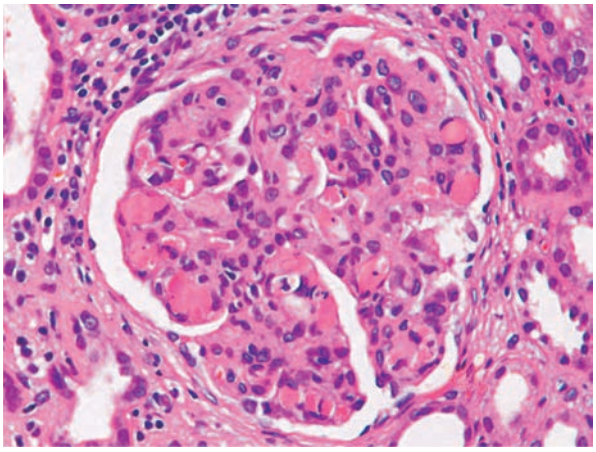

Figure 3
Haematoxylin and Eosin, (×400).

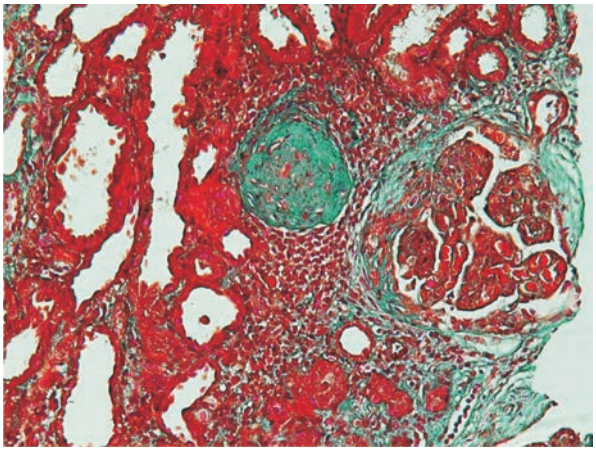

Figure 4
Masson's trichrome, (×200).

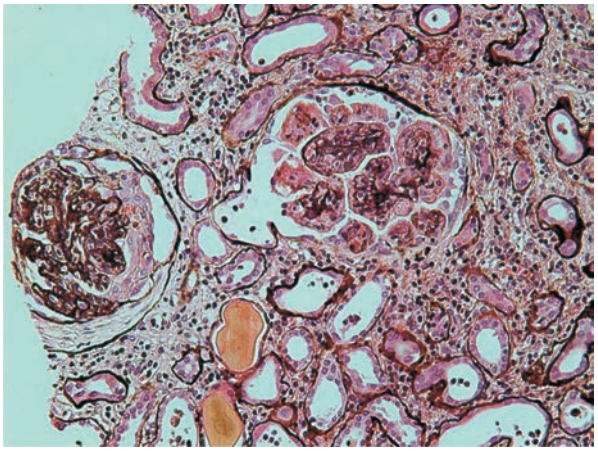

Figure 5
Silver methanamine, (×200).

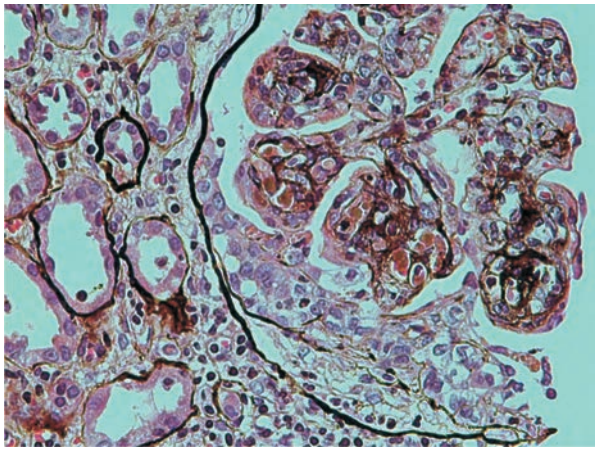

Figure 6
Silver methanamine, (×400).

Immunoflourescence (IF) showed diffuse mesangial and membranous positivity of IgG and IgM, while the remaining renal panel (IgA, C3 and C1q) was negative.

FINAL DIAGNOSIS

Membranoproliferative glomerulonephritis, type 1 due to cryglobulinemic glomerulonephritis, most probably related to HCV infection.

DISCUSSION

Hepatitis C virus infection primarily causes chronic active hepatitis, cirrhosis and liver failure; however, it can also involve a wide range of extra-hepatic tissues and organs in the body[1,2]. It is associated with a wide spectrum of histopathological lesions in both the native and transplanted kidneys, and is increasingly being implicated as a trigger of B cell lymphoproliferative disorders, including mixed cryoglobulinaemia (MC). Mixed cryoglobulins (MCs) are

immune complexes of mono- or polyclonal IgM that share rheumatoid factor (RF) activity and bind to polyclonal IgG; they are categorised as type II if the IgM RF is monoclonal, and type III if it is polyclonal[1-3].

The most frequent HCV-associated kidney disease is type I MPGN, usually in the context of type II MC. Besides MPGN, other types of glomerular lesions have been associated with HCV infection, which include IgA nephropathy, thrombotic microangiopathies, membranous nephropathy, post-infectious glomerulonephritis, focal and segmental glomerulosclerosis, and fibrillary or immunotactoid glomerulopathy[3,4].

The pathogenesis of HCV-related cryoglobulinaemic MPGN is unknown, but the glomerular damage in HCV-related cryoglobulinaemia may be due to the *in situ* or in-circulation binding of HCV antigens, polyclonal anti-HCV IgGs and non-specific IgGs to the IgM RF of MCs, with subsequent complement activation and cytokine production. The demonstration of HCV antigens or RNA in renal tissue have frequently produced conflicting results, possibly because of low tissue HCV proteins levels, the poor affinity of monoclonal antisera, or antigen masking by circulating antibodies[4].

Clinically, cryoglobulinaemic MPGN may range from isolated proteinuria to overt nephritic or nephrotic syndrome, with variable progression to chronic renal insufficiency.

TREATMENT AND EVOLUTION

The management of HCV-related cryoglobulinaemic glomerulonephritis is difficult and challenging[1-4]. Various approaches have been used for the treatment of HCV-related glomerulonephritis, including immunosuppressive therapy (corticosteroids and cytotoxic agents), plasma exchange and antiviral agents. Data on the antiviral treatment of HCV-associated glomerulonephritis are not abundant but encouraging results have been reported[4]. Distinct approaches should be employed for the treatment of HCV--associated cryoglobulinaemic glomerulonephritis according to the level of proteinuria and renal failure. Immunosuppressive therapy is particularly indicated for cryoglobulinaemic kidney disease. More recently evidence has been accumulated on rituximab therapy for HCV-related cryoglobulinaemic glomerulonephritis, but there is still controversy on several aspects of its use[4]. We used all the three modalities (immunosuppressive therapy, antiviral therapy, and plasmapharesis) and succeeded in salvaging the kidney function.

The prognosis of HCV-related glomerulopathies is highly variable. Although end-stage renal failure requiring dialysis is rare (about 10% of cases), patients with cryoglobulinaemic glomerulonephritis usually have a poor prognosis because of the unusually high incidence of infections and cardiovascular disease[4].

Conflict of interest statement: None declared.

References

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