CASE REPORT

Rare Occurrence of Type lll Membranoproliferative Glomerulonephritis in a patient with Hepatitis C in Sustained Virologic Response Phase

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ABSTRACT

Hepatitis C virus (HCV) infection is known to cause acute and chronic active hepatitis. In addition, HCV also has systemic disorder involvement that links to various extra-hepatic complications. We report a case of a patient which has been diagnosed to have Hepatitis C Genotype 3A who has been started on antiviral. He achieved end treatment response and sustained virologic response. During routine follow up, he experienced acute kidney injury. Renal biopsy showed type III membranoproliferative glomerulonephritis. His proteinuria improved greatly with the addition of angiotensin converting enzyme inhibitor. This case highlights the possibility of appearance of HCV related glomerulonephritis in patient who has sustained virological response.

Keywords: Hepatitis C, Virus, Membranoproliferative Glomerulonephritis, Sustained viral response

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INTRODUCTION

Hepatitis C virus (HCV) has been categorized as the only member of the genus hepacivirus. The association between HCV and kidney disease has been increasingly established. Patients with HCV related glomerulonephritis (GN) commonly present with asymptomatic proteinuria, microscopic hematuria and varying degrees of renal insufficiency. In almost all cases, the extra-hepatic manifestations are directly related to the presence of active HCV infection. We report here a case of unusual form of MPGN that occur after the HCV infection is in remission.

CASE REPORT

A forty-three-year old gentleman with a history of hypertension and dyslipidemia was diagnosed as having chronic HCV in 2010. His HCV was of genotype 3A with pre-treatment HCV RNA level of 324,000 IU/ML. He has completed 24-weeks pegylated interferon alfa-2a in October 2011. He achieved both end of treatment response (ETR) on 3rd of Nov 2011 and achieved sustained virologic response (SVR) on 29/5/2012. His HCV RNA level done yearly remains undetected.

His usual medications include tablet hydrochlorothiazide 25mg daily, tablet atenolol 25mg daily for his hypertension and tablet Simvastatin 40mg at night for his dyslipidemia. He was referred to the nephrology department in February 2017 when he was found that he found to have an elevated serum creatinine of 147 µmol/L (61 mL/min per 1.73 m2) during one of the regular medical check-ups. His baseline creatinine in 2012 was noted to be in normal range of 70-90 µmol/L. Systemic examinations were unremarkable and his blood pressure readings were within normal limit. His initial blood investigations in February 2017 are as follow: hemoglobin 13 g/dL, total white blood cell 13.4 x109/L, platelet 373 x109/L, urea 8 mmol/L, sodium 141 mmol/L, potassium 3.1 mmol/L, creatinine 217 µmol/L, serum albumin 25 g/L, corrected calcium 2.3 mmol/L and inorganic phosphate 1.29 mmol/L. His antinuclear antibody, complements level and thyroid function test were normal. Urine analysis shows albumin 4+ and his 24 hours urinary protein was 12 g.

The patient's ultrasound scan of the kidneys was normal in size and echogenicity with cortical thickness of 2.0 – 2.4cm. In view of his persistent significant proteinuria in nephrotic range, he was planned for renal biopsy. The renal histology showed rigid and thickened capillary walls (Fig 1). Subepithelial spikes and deposits are

diffusely seen with tram track duplication of basement membrane suggestive of subendothelial deposits (Fig 2). There is no HCV virus particle identified.

Immunohistochemical staining showed granular positivity along the basement membrane for Immunoglobulin (IG) M and C4d. IgG, IgA, C3 and C1q are negative. Morphological wise, the description fits for a Type III MPGN. He was started on perindopril 8mg and his renal function has been making gradual improvement with the latest serum creatinine of 154 µmol/L, albumin 39g/L and 2+ dipstick albuminuria in August 2018.

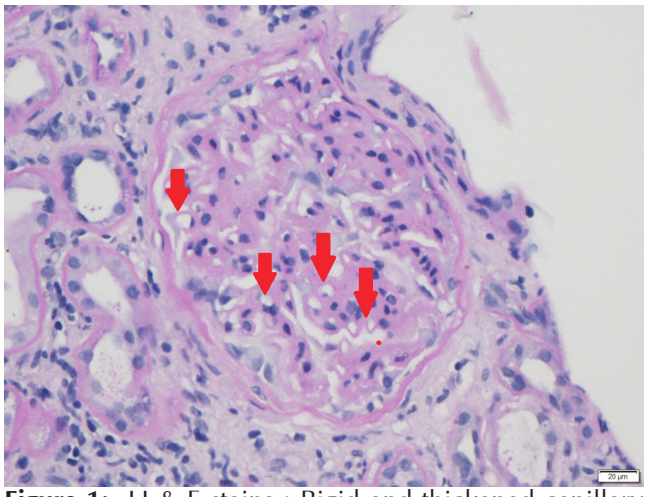

Figure 1: H & E stains : Rigid and thickened capillary walls

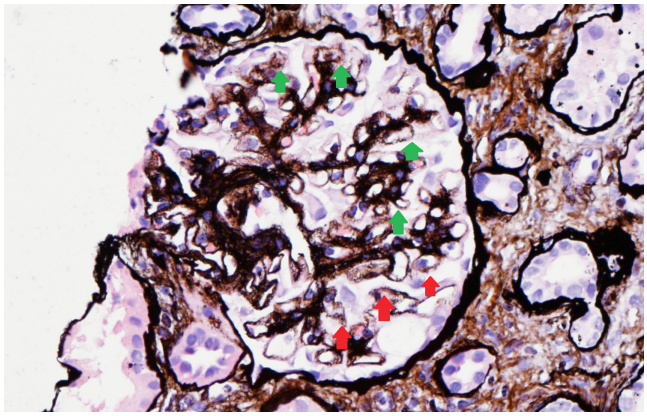

Figure 2: PAAG stains. Subepithelial spikes and deposits are diffusely seen with tram track duplication of basement membrane suggestive of subendothelial deposits

DISCUSSION

HCV-positive and chronic kidney disease (CKD) has always been known to be associated with each other. A meta-analysis shows patients with HCV-positive had a 23% greater risk of association with chronic kidney disease compared to uninfected individuals (1). A cohort study of a group of CKD patients also shows increase association between HCV infection in developing End Stage Renal Disease (ESRD) (2). Common renal manifestations in patients infected with HCV includes microscopic hematuria, proteinuria, acute nephritis and nephrotic syndrome. However most of the renal disease is asymptomatic as per our case. Apart from renal involvement, other established extra-hepatic manifestations include HCV-related autoimmune or lymphoproliferative disorders (benign mixed cryoglobulinemia to frank lymphomas), seronegative arthritis, cardiovascular disease, glucose metabolism disease and central nervous system disease. Our patient initial impaired renal function could be due to acute flare of MPGN.

Membranoproliferative glomerulonephritis (MPGN) is an extremely rare form of glomerulonephritis where it is characterized by the presence of matrix expansion, increased cellularity at the glomerular tufts with thickening of the capillary walls. The cause of MPGN may be idiopathic or secondary. Secondary causes are usually due to infection by viral, bacterial, and parasite. Traditionally, the classification of MPGN is dependent on the electron microscopic changes in the glomerular basement membrane (GBM). This can be type I (subendothelial deposits), type II (intramembraneous dense deposits) or type III (3). In type III MPGN, immune deposits are deposit in the subendothelial and mesangial regions. In addition, subepithelial deposition will occur. This classification can result in overlap between types I and III where both types it thought to be immune complex-mediated mediated.

MPGN arising from chronic antigenemia and/or circulating immune complexes can be seen in inflammatory conditions such as chronic infections, autoimmune diseases, and monoclonal gammopathies. MPGN resulting from HCV infection typically shows granular deposition of immunoglobulin M (IgM), C3, and both kappa and lambda light chains. Immunoglobulin G may or may not be present, and C1q is typically negative. This pattern may also be seen with MPGN induced by other viral infections (4). In MPGN, complement activation typically occurs and the C3 and C4 level is low. However, MPGN can have normal complement level as it can be caused by other postulated mechanism such as endothelial injury.

The pathogenesis of HCV related glomerulonephritis still remains unclear. Many consider that the deposition of immune complexes particles containing HCV in kidney disease is related to the on-going HCV infection. Ideally HCV antigens or HCV should be present in diseased glomeruli if HCV is the culprit causing the immune deposition. Yet, HCV antigens or RNA in the glomerular lesions has rarely been isolated or identified. This is similar to our case where the HCV particles are not identified in our renal biopsy. The possible reasons are masking of the antigen by various antibodies or the presence of small amount of HCV antigen or RNA which is below the detection limit (5).

Another interesting fact is that the appearance of MPGN in a HCV -affected patient that has been under SVR for more than 5 years. His complements level were also normal. This is to contrast with most of the confirmed cases of HCV related glomerulonephritis where there were clear evidence of active HCV Infections as demonstrated by the raised HCV RNA titires in the serum. He has no other known trigger for the appearance of MPGN.

There are 3 mainstay treatments that has been proposed to prevent the synthesis of immune-complexes and further damage of HCV on kidneys, namely HCV antiviral therapy, B-cell depletion therapy like rituximab and nonspecific immunosuppressive therapy like cyclophosphamide, mycophenolate mofetil and corticosteroids reducing inflammatory cells. In case in the presence of significant proteinuria and hypertension, renoprotection with antihypertensive and antiproteinuric agents such as renin-angiotensin system inhibitors and diuretics should be prescribed as needed. The efficacy of various forms of treatment for MPGN remains controversial; however, long-term steroid treatment seems to be effective only in children with nephrotic-range proteinuria.

This case has alerted us that despite Hepatitis C patient has sustained viral response, they should be continuously monitor for the appearance of extra-hepatic complications.

CONCLUSION

Our case highlights the need to have a high index of suspicion of HCV related glomerulonephritis in patient with HCV regardless whether they have achieved sustained virological response or not, especially those who had unexplained proteinuria, hematuria or derange renal function. Early recognition and high index of suspicion is needed so that renal biopsy and tailored treatment can be administered in a timely manner.

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