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Case Report .

Rituximab Therapy for Post-Liver Transplant Membranoprolifertive Glomerulonephritis Associated with Hepatitis C Viral Infection

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ABSTRACT

Post-transplant membranoprolifertive glomerulonephritis (MPGN), due to hepatitis C virus, is a serious immune complex disease with potential for both kidney and liver loss. Treatment with corticosteroids and immunosuppressive can activate viral infection and the use of interferon alpha can induce acute rejection of the transplanted liver. In this case report; a lady, with hepatitis C genotype 4, had developed severe nephrotic syndrome with progressive renal failure due to MBGN following liver transplant. Initially, she had received Harvoni (Ledipasvir/sofosbuvir) 90/400 mg daily for 12 weeks. Despite, clearance of hepatitis C viremia, she did not improve. Hence, Rituximab was started. Fortunately, her renal failure and nephrotic state improved without activation of hepatitis C infection or induction of rejection.

Key words: MPGN, Hepatitis C, Immune Complex Disease, Liver Transplant, Rituximab.

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INTRODUCTION

Hepatitis C virus (HCV) has been implicated in the pathogenesis of two renal diseases in native and transplanted kidneys[1] as well as liver transplantation.[2] Those diseases are membranoprolifertive glomerulonephritis (MPGN), with or without mixed cryoglobulinemia, and membranous glomerulopathy. There is a significant association between HCV infection and the occurrence of immune complex disease (ICD) manifesting as MPGN with progressive renal failure and anasarca.[3] The previous treatments of HCV viz. interferon alpha, Ribaverin and old protease inhibitors have limited role in such disease. Interferon alpha has been associated with acute rejection due to its immunostimulant effect[4] and data on the efficacy of Ribavirin are limited and treatment is not recommended for those with creatinine clearance below 50 ml/min.[5] Lastly, protease inhibitor such as Telprevir has been shown to significantly increase the concentration of both Cyclosporine and Tacrolimus.[6] Targeting HCV, with the most potent drugs i.e. Harvoni, was the first logical approach. Unfortunately, her MPGN persisted. Moreover, in her case, targeting ICD with Corticosteroids is contraindicated since they can activate HCV.[7] Based on its mechanism of action, Rituximab was used as the last resort and fortunately it was useful.

CASE REPORT

An orthotopic liver transplant was done, for a 54 year-old Kuwaiti woman with end-stage liver disease, due to HCV cirrhosis. Prior to transplant, her disease was complicated with hepatocellular carcinoma, refractory ascites with type 2 hepatorenal syndrome. Her past history was significant for type II diabetes mellitus, hypertension and HCV infection genotype 4 which was detected 4 years ago. Prior to her transplant her HCV PCR was 3^5 IU/ml and did not have hematuria or proteinuria. Review of her explants revealed a 3.7 cm tumor without angiolymphatic or vascular invasion. Post-transplant, she did well from the liver standpoint as manifested by normal liver enzymes, bilirubin, prothrombin time and ammonia level. Alpha feto protein dropped from 30 to normal. However, few weeks later, she developed progressive and severe lower limbs oedema, ascites associated with severe hypoalbuminemia and proteinuria. The condition was associated also with severe hypertension and progressive renal failure. Percutaneous kidney biopsy showed 10 glomeruli, 3 of which were sclerosed while one showed focal segmental sclerosis. The rest showed marked mesangial hypercellularity with focal lobular accentuation (Fig.1). Focal duplication of the glomerular capillary

loops was seen on silver and PAS stains. Trichrome stain showed mild to moderate interstitial fibrosis and tubular atrophy. Immunofluorescent stains showed granular glomerular basement membrane and mesangial deposits of IgG, IgM, IgA and properdin with arteriolar deposits of IgM and C3. Electron microscopy showed large electron-dense immune complex deposition in the glomerular basement membrane. These changes were consistent with HCV associated membroprolifertive glomerulonephritis, type I. Her HCV PCR was 10^6 IU/ml.

Initially, she was treated with a combination diuretics and an ACEI yet her ascites was refractory and needed large volume taps. Her medications were; Mycophenolate mofetil 500 mg X2, Tacrolimus 2 mg X2, Nifidipine XL 60 mg daily, Clonidine 0.2 mg X2, Lisinopril 40 mg daily, Lasix 80 mg and Metolazone 5 mg daily in addition to Lipitor 10 mg daily, and insulin (Lantos and Novorapid). On her initial physical examination, the patient was conscious and oriented X3. Her blood pressure was 120/80 mm Hg and temperature was normal. She was pale yet without jaundice or cyanosis. She had significant jugular venous distension, ascites as well as sacral and lower limbs oedema. Laboratory investigations showed progressive anemia and hypoalbuminemia as well as increase in serum urea, creatinine and protein output. Her peripheral leucocytic and platelets counts remained normal. Serum sugar, electrolytes, liver function tests, prothrombin time and ammonia level were normal. Tacrolimus levels were within normal limits. CMV and Polyoma virus were not detected by PCR testing. She was treated initially with Harvoni (Ledipasvir/ Sofosbuvir) 90/400 mg daily for 12 weeks and her HCV RNA was undetectable in her blood. However, her renal disease did not improve. As a last resort, she was treated with Rituximab. She received 1 g diluted infusions of rituximab in normal saline followed by 1 g 2 weeks later. The patient tolerated both infusions without allergic reactions. Two weeks later, her nephrotic state and renal failure started to improve and she was stable without further need for ascetic taps by 4 weeks (table.1). Unfortunately, 10 months later, she died of an acute coronary syndrome.

Table 1: Changes in serum creatinine, serum albumin, proteinuria and HCV RNA level post-transplantation and after Rituximab therapy

Parameters	Months post-transplant														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Serum creatinine (umol/L)	162	86	82	168	164	183	191	142	140	124	118	92	86	88	82
Serum albumin (g/L)	20	25	25	18	16	12	9	18	24	32	33	32	34	32	34
Proteinuria (g/day)	0.1	0.3	0.7	4	4.6	6	12	6	2	0.9	1.1	1.2	0.9	0.8	0.9
HCV RNA titer (IU/ml)	3^5				10^6		0							0	
Ascetic taps (per/month)	2	0	2	4	6	6	1	0	0	0	0	0	0	0	0
Treatment modality	← Conservative approach → Harvoni →						After Rituximab								

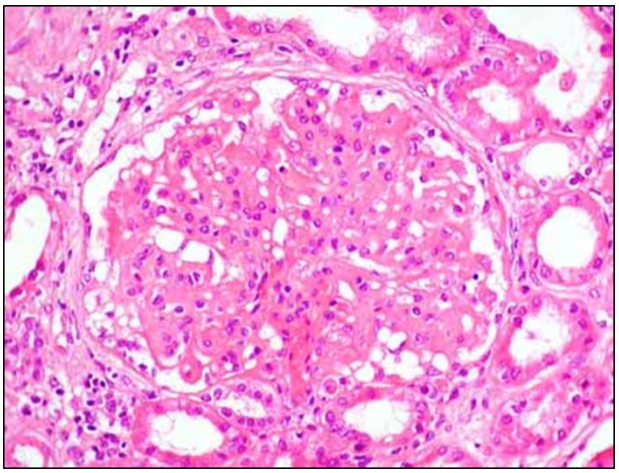

Figure 1: Photomicrograph of the kidney showing mesangial hypercellularity with focal lobular accentuation and duplication of the glomerular capillary loops (membranoprolifertive glomerulonephritis). (H&E X200)

DISCUSSION

The patient is a 54 year-old woman with HCV genotype 4 who developed end-stage liver disease due to cirrhosis and was treated with liver transplantation. Her post-operative course has been complicated by biopsy proven MBGN due to activation of HCV after transplant immunosuppression as evident by higher titers of HCV by PCR and the electron microscopy picture showing large electron-dense immune complex deposition in the glomerular basement membrane contrary to only subendothelial accumulation of electron lucent material in transplant glomerulopathy.[7] Ideally, HCV should be treated but her chances of achieving sustained virological response are limited since she has type 4, TC IL-28 genotype and significant renal insufficiency.[8] The previously available anti-viral drugs viz. interferon alpha, ribavirin and protease inhibitors have limited role in treatment of this patient. Treatment with interferon alpha is associated with acute rejection since it induces cytokine gene expression, increased cell-surface expression of HLA antigen and enhances the function of natural killer cells, cytotoxic cells and monocytes.[4] Ribavirin is not recommended for patients with creatinine clearance below 50 ml/min.[5] Finally, protease inhibitors such as Telprevir have been shown to significantly increase the concentration of both Cyclosporine and Tacrolimus.[6] Hence, she was treated with Harvoni for 12 weeks. Despite clearance of HCV; her MPGN persisted. Since, Corticosteroids can activate HCV; increment in her Prednisone 5 mg was not done.[7] Unfortunately, the conservative approach with antiproteinuric agents (ACEI/ARB) was clearly futile in controlling her rapidly fulminant renal disease and anasarca. In her case, Rituximab

was used since the mechanism of her MPGN is mediated by activation of HCV by post-transplant immunosuppression with subsequent increase of ICD leading to increase deposition of viral complexes in her glomeruli.[7] Rituximab is an anti-CD 20 chimeric monoclonal antibody that depletes B cells and decrease the production of immune complexes.[9] Successful treatment was reported in limited studies of cryoglobulinemic MPGN following renal transplantation.[10,11] It did not flare the HCV infection in 7 kidney transplant patients.[12] The present case provides treatment for non-cryoglobulinemic MPGN due to HCV post-liver liver transplantation.

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