

Renal Involvement in Patients With Hepatitis C Virus Infection

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Introduction. Hepatitis C virus (HCV) infection is a hepatotropic virus causing a variety of extrahepatic immunological manifestations and is a risk factor of a variety of extrahepatic diseases, such as mixed cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN), which is the most common glomerulonephritis. The aim of this study was to evaluate renal involvement in HCV-infected patients.

Materials and Methods. A total of 300 randomly-selected HCV antibody-positive outpatients at the HCV clinic of Shariati hospital were enrolled. Serum creatinine was measured and glomerular filtration rate was estimated accordingly. Urine proteinuria was measured in 24-hour urine samples.

Results. The patients were 249 men (83.2%) and 51 women (16.8%) with a mean age of 37.8 ± 11.7 years (range, 18 to 70 years). Proteinuria was found in 12 HCV antibody-positive adults (4%), 1 of whom underwent biopsy. He was a 55-year-old man with a 4-month history of facial and lower extremities edema and 3-g proteinuria with a normal kidney function (glomerular filtration rate, 85 mL/min) and normocomplementemia. Kidney biopsy specimens showed MPGN. The frequency of low glomerular filtration rate was 0.7% (2 patients) in the HCV antibody-positive adults. There was no significant relationship between HCV seropositivity and low glomerular filtration rate.

Conclusions. Our observations showed renal involvement in HCV antibody-positive patients. Among immune complex glomerular kidney diseases, MPGN without cryoglobulins is thought to be the most common in these patients.

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INTRODUCTION

Hepatitis C virus (HCV) is a hepatotropic virus and a common cause of chronic hepatitis. It can cause a variety of extrahepatic immunological manifestations, as well.¹ Chronic HCV infection and cirrhosis are risk factors of a variety of extrahepatic diseases such as mixed cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN).² Among these, glomerulonephritis, arthritis, dermal vasculitis, and sialadenitis are

thought to develop as a result of the deposition of immune complexes. Membranoproliferative glomerulonephritis is thought to be the most common extrahepatic HCV infection, either cryoglobulinemic or noncryoglobulinemic.^{3,4} An association between HCV infection and focal segmental glomerulosclerosis (FSGS) and membranous nephropathy has also been reported.^{5,6} Other forms of kidney disease have been previously linked to chronic HCV infection, including acute

exudative and proliferative glomerulonephritis and immunoglobulin M nephropathy.⁷

The seroprevalence of HCV is thought to be greater in individuals with chronic glomerulopathy compared with those suffering from other kidney diseases.⁸ It has also been noted that exacerbations of autoimmune diseases has been occurring during interferon therapy. Antiviral therapy is effective in the treatment of some of the extrahepatic disorders associated with HCV.⁹ The appropriate response to antiviral therapies in HCV-associated kidney disease encourage physicians to detect the disease and treat it. The aim of this cross-sectional study was to evaluate renal involvement in HCV-infected patients.

MATERIALS AND METHODS

Patients

From January 2007 to March 2009, a total of 300 HCV antibody-positive adults who were visited at the outpatient HCV clinic of Shariati University Hospital were enrolled in this study. These patients were selected randomly during the study period. All 300 patients provided written informed consent and met the following inclusion criteria: age older than 18 years, positive results for HCV antibody on second-generation enzyme-linked immunosorbent assay, and presence of circulating HCV RNA (polymerase chain reaction assay). Patients were excluded if they had risk factors such as diabetes mellitus, collagen vascular disease, kidney calculus, chronic pyelonephritis, and reflux nephropathy; any confounding factor for proteinuria (such as fever, exercise, and dehydration); a positive test for hepatitis B virus or human immunodeficiency virus; current interferon or ribavirin therapy protocol.

Methods

Blood samples were collected after an overnight fast. Serum creatinine was measured by means of the modified kinetic rate Jaffe method. The Cockcroft-Gault method was used to estimate creatinine clearance.¹⁰ Patients with increased serum creatinine were double-checked. A low estimated glomerular filtration rate (GFR) was defined as a GFR level lower than 60 mL/min.¹¹ A random spot urine sample was obtained from each participant using a clean-catch technique and sterile containers, and the sample was analyzed on frozen nonhematuric specimens. Urine protein was

measured in a 24-hour urine sample, and proteinuria was defined as a urine protein level higher than 500 mg (Dipstick, Biosystem, Germany). Direct immunofluorescence studies were used to measure polyclonal antibodies for complement (C) 3, C4, and C1q components. A kidney biopsy specimen was obtained with a disposable biopsy instrument (TSK, Human Meditec, Japan). Cryoglobulinemia was measured in patients with proteinuria.

RESULTS

A total of 300 HCV antibody-positive patients (249 men and 51 women) with a mean age of 37.8 ± 11.7 years (range, 18 to 70 years) were included in this study. Proteinuria was detected in 12 patients (4%), in whom cryoglobulinemia was negative except for 1 patient. All of the patients with proteinuria were men. The mean GFR was 114.1 ± 31.6 mL/min (range, 47.6 min/mL to 228.08 min/mL). The frequency of low GFR in the patients was 0.6% (2 patients).

Kidney biopsy was not performed in 6 patients because of ongoing coagulopathy, and pathologic examination of the kidney specimen was not possible because of inadequate tissue in 4 patients. Among the 4 patients with inadequate tissue, the 24-hour urine protein level was between 500 mg and 1000 mg, and they were all symptom free.

Among the patients with coagulopathy, there was a 47-year-old man who was suffering from cirrhotic disease; there were dysmorphic erythrocytes and microalbuminuria in the morning spot urine sample. In this patient, serum creatinine level and GFR level were 1.4 mg/dL and 74.03 mL/min, respectively. This patient was not eligible for kidney biopsy also due to thrombocytopenia. The 2nd patient was a 30-year-old man with a single kidney who was suffering from acute tubular necrosis following ribavirin and interferon therapy. Furthermore, he was a known case of mild chronic kidney disease with a GFR level of 50.87 mL/min. He also had microalbuminuria. The 3rd patient was a 57-year-old man with a 4-month history of HCV infection who was also suffering from cirrhotic disease. The patient also had palpable purpura in the upper and lower extremities and the abdomen (Figure). Laboratory findings revealed dysmorphic erythrocytes in the morning spot urine sample, serum creatinine and GFR levels of 3.1 mg/dL and 47.6 mL/min, respectively,



Palpable purpura on the abdomen, lower extremities, and upper extremities.

a decrease in C3 level, and subnephrotic-range proteinuria (1400 mg/24 h urine). The patient was antibody-positive for cryoglobulin. However, he refused to undertake kidney biopsy and was lost to follow-up due to the emergence of severe acute respiratory syndrome. The tentative diagnosis was HCV-related cryoglobulinemia.

The only patient with pathology examination results was a 55-year-old man with a 4-month history of facial and lower extremities edema, 3-g proteinuria with a normal kidney function (GFR, 85 mL/min), and normal complement levels. This patient was antibody-negative for cryoglobulin. Kidney biopsy specimens showed mesangial proliferation by light microscopy with immunofluorescence staining for immunoglobulins, complements, or both. The subepithelial glomerular lesions revealed massive virus-like particles within unusual multilayers of electron-dense deposits, suggesting the existence of HCV in the glomeruli.

DISCUSSION

Hepatitis C virus infection is a global health problem affecting a significant portion of the world's population. In addition to liver disease, HCV infection has been associated with a wide variety of extrahepatic manifestations including mixed cryoglobulinemia and renal involvement.¹ The recent observation that HCV infects peripheral blood mononuclear cells, such

as CD8+ T lymphocytes, CD19+ B lymphocytes, and monocytes/microphages, has given an insight into the possible mechanisms of HCV-associated autoimmunity.⁹ The most common form of kidney disease is cryoglobulinemic MPGN (MPGN type 1).¹² This finding is consistent with a report that postulated HCV was a significant cause of MPGN, especially in countries where HCV was highly prevalent.¹³ Another study also confirmed this observation, in which MPGN was present in 39% of HCV-infected patients.¹⁴ It is important to note that the prevalence of HCV antibodies among patients with glomerulopathy was higher than that among healthy blood donors, which could be attributed to the association of HCV with kidney disease.¹⁴ This finding is compatible with a study in which MPGN type 1 was very common in patients with end-stage cirrhosis due to chronic HCV infection.¹⁵ In another study, it was shown that MPGN associated with type II cryoglobulinemia was the predominant type of HCV-related glomerulonephritis.¹⁶

Results of our study also confirmed previous reports indicating high prevalence of MPGN with and without cryoglobulins in HCV-infected patients. Our study showed that the prevalence of proteinuria in HCV antibody-positive adults was 4% (12 patients). In only 1 patient, renal histological evaluation was done by light microscopy, which showed changes in favor of MPGN and evidence of immune complex deposits in the glomeruli.

Therefore, this data validate the results of previous studies. This patient was also serologically negative for cryoglobulinemia. This finding confirms a report from one study that indicated symptomatic cryoglobulinemia occurs in 1% or less of the patients,¹⁷ and reports of similar cases in the literature showed the normocomplementemia and negative or slightly positive cryoglobulins, as well as seropositivity for circulating immune complexes containing HCV RNA.¹⁸

Our data also supported the association between HCV infection and cryoglobulinemia; 1 cirrhotic patient had palpable purpura and hypocomplementemia. The association of HCV infection with mixed cryoglobulinemia has been previously reported. However, its pathogenesis is not completely understood, nor does formal treatment guidelines exist.¹⁹ This finding, together with a study in which HCV-associated cryoglobulinemia was in conjunction with hypocomplementemia and palpable purpura, led us to conclude that MPGN should be the target lesion.²⁰

Our results also showed an association between chronic HCV infection and cirrhosis regarding 2 cirrhotic patients who were suffering from kidney disease. This finding is compatible with a study in which one-third of chronically infected patients presented moderate to severe hepatitis within 20 years of infection.²¹ Inflammation and hepatic cell necrosis may lead to bridging fibrosis, and cirrhosis appears in 15% to 20% of patients with chronic infection.²¹

CONCLUSIONS

In summary, our observations showed that chronic HCV infection and cirrhosis are risk factors of a variety of extrahepatic immunological manifestations, such as glomerular kidney diseases. Among glomerulopathies, MPGN with and without cryoglobulins are thought to be the most common in these patients. Therefore the results of this study are important because of existence of proteinuria in HCV-infected patients that supports the hypothesis of the benefits of screening all patients with HCV infection for kidney involvement.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wilson RA. Extrahepatic manifestations of chronic viral hepatitis. *Am J Gastroenterol.* 1997;92:4-15.
2. Ali A, Zein NN. Hepatitis C infection: a systemic disease with extrahepatic manifestations. *Cleve Clin J Med.* 2005;72:1005-8, 10-4, 16 passim.
3. Johnson RJ, Gretch DR, Couser WG, et al. Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. *Kidney Int.* 1994;46:1700-4.
4. Ohsawa I, Ohi H, Endo M, Fujita T, Seki M, Watanabe S. High prevalence of hepatitis C virus antibodies in older patients with membranoproliferative glomerulonephritis. *Nephron.* 1999;82:366-7.
5. Altraif IH, Abdulla AS, al Sebayel MI, Said RA, al Suhaibani MO, Jones AA. Hepatitis C associated glomerulonephritis. *Am J Nephrol.* 1995;15:407-10.
6. Stehman-Breen C, Alpers CE, Couser WG, Willson R, Johnson RJ. Hepatitis C virus associated membranous glomerulonephritis. *Clin Nephrol.* 1995;44:141-7.
7. Kamatsoda A, Imai H, Wahui H, et al. Clinicopathological analysis and therapy in HCV associated nephropathy. *Intern Med.* 1996;35:529-33.
8. Daghestani L, Pomeroy C. Renal manifestations of hepatitis C infection. *Am J Med.* 1999;106:347-54.
9. Durazzo M, Mariani GM, Sacchi C, Biava MA. [HCV and extrahepatic diseases]. *Minerva Gastroenterol Dietol.* 1998;44:91-104.
10. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31-41.
11. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med.* 2003;139:137-47.
12. D'Amico G, Colasanti G, Ferrario F, Sinico RA. Renal involvement in essential mixed cryoglobulinemia. *Kidney Int.* 1989;35:1004-14.
13. Bandi L. Renal manifestations of hepatitis C virus infection. Extrahepatic complications often are silent—and thus overlooked. *Postgrad Med.* 2003;113:73-6, 86.
14. Sabry A, A EA, Sheashaa H, et al. HCV associated glomerulopathy in Egyptian patients: clinicopathological analysis. *Virology.* 2005;334:10-6.
15. McGuire BM, Julian BA, Bynon JS, Jr., et al. Brief communication: Glomerulonephritis in patients with hepatitis C cirrhosis undergoing liver transplantation. *Ann Intern Med.* 2006;144:735-41.
16. Kamar N, Rostaing L, Alric L. Treatment of hepatitis

- C-virus-related glomerulonephritis. *Kidney Int.* 2006;69:436-9.
17. Meyers CM, Seeff LB, Stehman-Breen CO, Hoofnagle JH. Hepatitis C and renal disease: an update. *Am J Kidney Dis.* 2003;42:631-57.
18. Uchiyama-Tanaka Y, Mori Y, Kishimoto N, et al. Membranous glomerulonephritis associated with hepatitis C virus infection: case report and literature review. *Clin Nephrol.* 2004;61:144-50.
19. Zaltron S, Puoti M, Liberini P, et al. High prevalence of peripheral neuropathy in hepatitis C virus infected patients with symptomatic and asymptomatic cryoglobulinaemia. *Ital J Gastroenterol Hepatol.* 1998;30:391-5.
20. Chen YC, Kuo MC, Chen HC, Lai YH, Hwang SJ. HCV infection complicated with nephrotic syndrome, immune complex crescentic glomerulonephritis and acute renal failure: a case report. *Kaohsiung J Med Sci.* 2005;21:470-4.
21. Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med.* 2001;345:41-52.

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