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Membranoproliferative Glomerulonephritis Associated with HCV Infection in Native Kidneys and Renal Allograft

Hepatitis C viral infection occurs relatively low in Korea compared to hepatitis B. However, it progresses into chronic hepatitis and cirrhosis more frequently than HBV. It may be associated with cryoglobulinemia and glomerulonephritis, both in native and transplanted kidneys. We report three cases of membranoproliferative glomerulonephritis type I in anti-HCV positive, but cryoglobulin-negative patients, presenting massive proteinuria, two in native kidneys and one in an allograft. HCV-RNA was positive in sera of two patients. Two were cirrhotic and ALT was mildly elevated in two. In addition to the characteristic membranoproliferative feature, two native kidneys overlapped with features of diabetic nephropathy. Immunofluorescence demonstrated mainly IgM and C3 deposits along the peripheral capillary walls. Subendothelial electron dense deposits were present in the glomeruli of all three cases with subepithelial and intramembranous deposits in two. HCV-RNA was associated not only with a greater amount of immune deposits but also with subepithelial and intramembranous deposits, indicating the role of active infection.

Key Words: *Hepatitis C-like virus; Glomerulonephritis, membranoproliferative*

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INTRODUCTION

Glomerulonephritis can develop in association with hepatitis C infection, mostly of the membranoproliferative (1-7) or rarely membranous types (8-11). The pathogenic role of the virus in the development of glomerulonephritis remains uncertain. Some argue that cryoglobulinemia, especially of type II, is responsible for glomerulonephritis, based on the frequent association and morphological similarities between them (12-18). However, some cases of noncryoglobulinemic glomerulonephritis have been reported (19), implicating the crucial role of HCV in the mediation of glomerular injury. Recently Cosio et al. (20) reported a large group of HCV-infected patients and speculated that the virus mediates injury either directly or via indirect inflammatory and immunologic stimulation. They suggested that HCV was responsible for not only immune complex deposition, but also endothelial injury and subendothelial widening similar to transplant glomerulopathy. We experienced 3 cases of glomerulonephritis with membranoproliferative features, both in native as well as graft kidneys of anti-HCV positive, cryoglobulin-negative patients. All had immune complex deposition in the glomeruli which tended to be massive in the presence of HCV-RNA in the serum. We reviewed the clinical history of these cases and discuss the role of HCV in glomerulonephritis.

CASE HISTORY

Case 1

A 61-year-old chronic alcoholic male was admitted because of abdominal distension for 2 months. He had suffered from diabetes mellitus for 20 years without retinopathy and from liver cirrhosis for about 8 months. He had suffered from renal problems the previous year. He was mildly icteric. The abdomen was distended with a fluid wave sign and shifting dullness. Pitting edema was present on both lower extremities. Blood pressure was 110/70 mmHg, pulse rate 70/min, and body temperature 36.1℃. On admission, hemoglobin was 9.8 g/dL, hematocrit 30%, white blood cells 5,260/mm^3 and platelet 173,000/mm^3. Sodium was 135 mM/L, potassium 5.4 mM/L, chloride 109 mM/L and CO_2 content 18 mM/L. Blood urea nitrogen was 25 mg/dL, creatinine 1.4 mg/dL, total protein 4.7 g/dL, albumin 1.9 g/dL,

cholesterol 154 mg/dL, urate 4.7 mg/dL, AST 7 IU/L, and ALT 28 IU/L. Serologic markers for B and C hepatitis were as follows: HBs Ag(−), anti-HBs Ab(−), anti-HBc Ab(+) and anti-HCV Ab(+). HCV-RNA detected by RT-PCR was negative. Urinalysis revealed proteinuria of more than 300 mg/dL, and 3+ blood with 15-20 red blood cells/HPF under microscopy. Alpha fetoprotein was less than 2 IU/mL. Antinuclear antibody (ANA), anti-DNA Ab, cryoglobulin were negative. CRP was 0.47 mg/dL, ASO titer 199 IU/mL, rheumatoid factor 21 IU/mL, and ESR 42 mm/hr. IgG was 1,530 mg/dL, IgA 547 mg/dL, and IgM 89 mg/dL. C3 was 62 mg/dL and C4 23 mg/dL. Glycated hemoglobin was 7.1%. Twenty-four-hour urine protein was 20.4 g and creatinine clearance was 37 mL/min/1.73 mm^2. Renal biopsy was performed on the 8th hospital day.

Case 2

A 44-year-old female was admitted because of abdominal distension for 1 month. She had suffered from diabetes mellitus for 10 years, and was being treated with insulin. Diabetic retinopathy and hypertension had been diagnosed the previous year. She had a past history of left adrenalectomy 20 years ago and ectopic pregnancy 13 years ago. HCV hepatitis with liver cirrhosis was diagnosed 3 years ago. There was no history of habitual alcohol intake or smoking. She complained of generalized malaise, headache, nausea, vomiting, anorexia and edema of the lower extremities. She was mildly icteric. The abdomen was distended with a fluid wave sign. The liver was palpable at one finger breadth below the costal margin. Pitting edema was present on both lower extremities. Blood pressure was 160/90 mmHg, pulse rate 68/min, respiratory rate 20/min and body temperature 36.2 ℃. On admission, hemoglobin was 10.1 g/dL, white blood cells 4,700/mm^3 and platelet 131,000/mm^3. Sodium was 135 mM/L, potassium 4.5 mM/L, chloride 102 mM/L and CO_2 content 24 mM/L. Blood urea nitrogen was 23 mg/dL, creatinine 1.1 mg/dL, calcium 8 mg/dL, phosphorus 4 mg/dL, total protein 5.5 g/dL, albumin 2.6 g/dL, cholesterol 183 mg/dL, urate 5.9 mg/dL, AST 12 IU/L, ALT 39 IU/L, gamma glutamyl transferase 13 IU/L. Serologic markers for B and C hepatitis were as follows: HBs Ag(−), anti-HBs Ab(−), antiHBc Ab(+) and anti-HCV Ab(+). HCV-RNA detected by RT-PCR was positive. Urinalysis revealed proteinuria of more than 300 mg/dL, glucose of more than 1 g/dL, and 3+ blood with many red blood cells/HPF under microscopy. ANA, anti-DNA Ab and cryoglobulin were negative. CRP was 0.38 mg/dL, ASO titer 51.8 IU/mL, rheumatoid factor 39.2 IU/mL. IgG was 1,560 mg/dL, IgA 333 mg/dL, and IgM 155 mg/dL. C3 was 52 mg/dL and C4 41 mg/dL. Twenty-four-hour urine protein was 4.2 g and creatinine clearance was 69.8 mL/min/1.73 mm^2.

Case 3

A 42 year-old male received a renal allograft from a living unrelated donor in October 1991. He had chronic glomerulonephritis of undetermined type. He had started chronic ambulatory peritoneal dialysis (CAPD) in 1985. In 1986, he suffered from hepatitis and at that time HBs Ag was negative. Peritoneoscopic liver biopsy disclosed acute viral hepatitis of the NANB type. Anti-HCV Ab was positive before transplantation. His posttransplant course was uneventful with no episodes of acute rejection for 1.5 years, when hypoalbuminemia and proteinuria developed. Urinalysis showed proteinuria of 300 mg/dL, blood 3+ with red blood cells of 10-30/HPF and some coarsely granular casts. Twenty-four-hour urine protein excretion was 4.7 g. Hemoglobin was 14.1 g/dL. Blood urea nitrogen was 65.4 mg/dL, creatinine 1.9 mg/dL, total protein 5.1 g/dL, albumin 3.0 g/dL, AST 30 IU/L, ALT 48 IU/L. HBs Ag and anti-HBs Ab were negative, but anti-HBc Ab was positive. IgG anti-HCV Ab was positive, but IgM anti-HCV Ab was negative. HCV-RNA was detected by polymerase chain reaction. ANA, anti-mitochondrial antibody and antineutrophil cytoplasmic autoantibody, rheumatoid factor and cryoglobulin were negative. Circulating immune complex level was 39 μg/mL (control 25 μg/mL) (Table 1).

Table 1. Summary of clinical and laboratory data

Parameter	Case 1	Case 2	Case 3
Age (yrs)/sex	61/M	44/F	42/M
Associated disease	DM	DM	
Serology			
BUN/S. creatinine (mg/dL)	25/1.4	23/1.1	65.4/1.9
T. Protein/Albumin (g/dL)	4.7/1.9	5.5/2.6	5.1/3.0
AST (mg/dL)	7	12	30
ALT (mg/dL)	28	39	48
CIC* (μg/mL)(control<25)	ND	ND	39
C3 (mg/dL)	62	52	ND
C4 (mg/dL)	23	41	ND
cryoglobulin	−	−	−
rheumatoid factor (IU/mL)	21	39.2	−
ANA/antiDNA Ab	−/−	−/−	−/−
antineutrophil autoantibody	ND	ND	−
Creatinine clearance (mL/min/1.73 mm^2)	37	69.8	90.6
24 hour urine protein (g/d)	20.4	4.2	4.7
microhematuria	3+	3+	3+
Viral marker			
HBs Ag/antiHBs Ab/antiHBc Ab	−/−/+	−/−/+	−/−/+
antiHCV Ab/HCV-RNA	+/−	+/+	+/+

*CIC: circulating immune complex

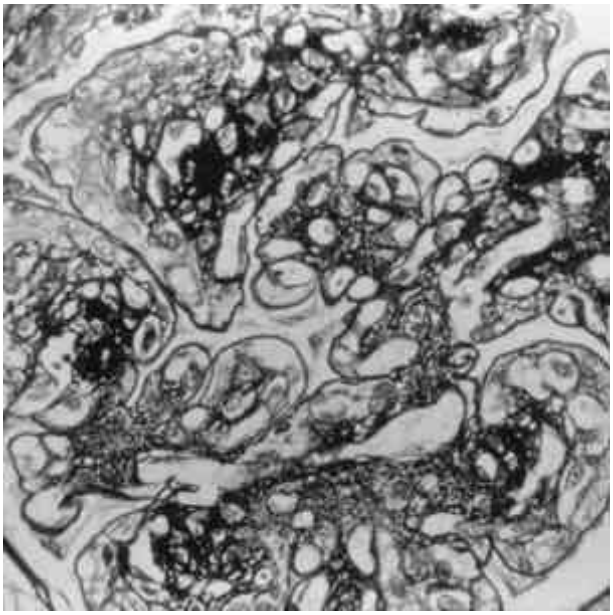

Fig. 1. This photomicrograph depicts an enlarged glomerulus with mesangial proliferation and thickening of peripheral basement membranes (methenamine silver-periodic acid, ×400).

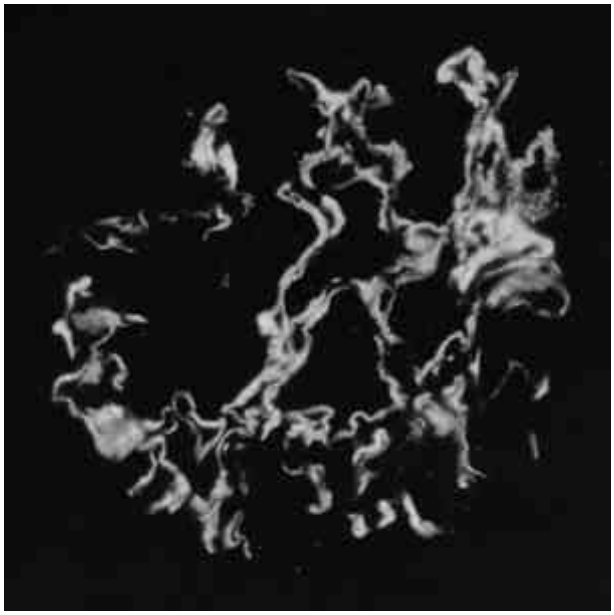

Fig. 2. Immunofluorescence microscopy shows pseudolinear and granular staining of IgG mainly along the peripheral capillary walls (IgG, ×200).

Renal biopsy findings

Case 1

The biopsy core revealed two glomeruli, one with global sclerosis and the other with an increased mesangial matrix and thickened basement membranes (Fig. 1). Interstitium was moderately fibrotic with minimal mononuclear cell infiltration. Tubules were focally atrophied and contained casts. Arterioles were thickened by subendothelial hyalin. Immunofluorescence revealed five glomeruli with minimal IgM, IgA and C3 deposition. Electron microscopy revealed thickened lamina densa with subendothelial and mesangial electron dense deposits. Epithelial foot processes were diffusely effaced.

Case 2

The biopsy revealed 12 glomeruli with irregular thickening of the glomerular basement membrane and mesangial widening. Tubules were irregularly dilated by casts. Both afferent and efferent arterioles showed hyalinized thickening. Immunofluorescence examination revealed 24 glomeruli with granular IgM(++), IgA(+), C3(++), C1q (++) and fibrinogen deposits along the capillary walls, and minimal IgA, IgM, C3 and fibrinogen deposits in the mesangium. Electron microscopy showed marked thickening of the glomerular basement membranes by homogenous thickening of lamina densa, complicated by electron dense deposits and interposition of cells at the periphery. Electron dense deposits were present in subendothelial, intramembranous and subepithelial areas and minimally in the mesangium. Epithelial foot processes were effaced focally. Some glomerular capillary lumen was nearly obliterated by swollen endothelial cells.

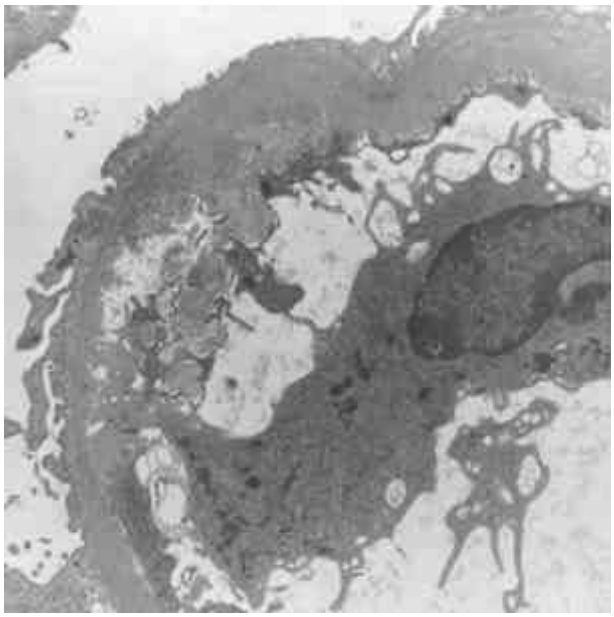

Fig. 3. Glomerular basement membrane is markedly thickened with subepithelial and subendothelial electron dense deposits. The area of resolution was done by a monocyte. Epithelial foot processes are diffusely effaced (uranyl acetate and lead citrate, ×5,200).

Case 3

Biopsy cores contained 14 glomeruli with glomerular enlargement and lobular accentuation. The mesangium was widened by increased matrix and mesangial cells. Segmental sclerosis was present in four glomeruli. Cellular crescent was seen in four glomeruli. Glomerular basement membranes were thickened and showed double-contour feature. Interstitium was focally infiltrated by inflammatory cells. Signs of acute or chronic rejection was not seen. Sections of immunofluorescence enclosed 13 glomeruli with deposition of IgG(++), IgM(+), C3(++) and fibrinogen(+) along the capillary loops in granular and pseudolinear patterns (Fig. 2). Glomerular basement membranes were thickened, which contained electron dense deposits in the subendothelial as well as subepithelial areas. Widening of subendothelial area by electron lucent granular material was found in a few loops. Mesangium was expanded by an increase of fibrillar matrix with minimal electron dense deposits. Epithelial foot processes were diffusely effaced and showed microvillous transformation (Fig. 3).

DISCUSSION

In contrast to hepatitis B infection which is endemic in Korea, hepatitis C infection is relatively low in the general population. The prevalence of antibodies to HCV in the general population is 1.35% (21), which is similar to that of the United States (22) and Europe (23). But the rate increases 3.3-10.3% in peritoneal dialysis and hemodialysis patients (24). In addition to hepatitis, including cirrhosis and even transformation to hepatocellular carcinoma, the hepatitis C virus can present extrahepatic manifestations, among which are essential mixed cryoglobulinemia and glomerulonephritis. Glomerular diseases can develop both in native kidneys and renal allografts in patients with chronic HCV infection. Several reports have supported the relationship between membranoproliferative glomerulonephritis and HCV, both in native kidneys and allografts (1-7). In addition, occasional reports of membranous nephropathy (8-11), acute proliferative and exudative glomerulonephritis (25), focal glomerulosclerosis (20, 26) and even rapidly progressive glomerulonephritis (27) have been reported. However, Garcia-Valdecasas et al. (23) reported that the prevalence of HCV positivity was not statistically different between patients with primary and secondary chronic glomerulonephritis. Cosio et al. (20) argued that the increased prevalence of HCV positivity in focal glomerulosclerosis could be attributed instead to other risk factors such as intravenous drug abuse.

Membranoproliferative glomerulonephritis developing in HCV-infected patients is frequently associated with cryoglobulinemia type II or rarely type III, but not type I (16-18). A close relationship between HCV infection and cryoglobulinemia has been supported by several reports (12-14). Cryoglobulinemia was discovered in 36% to 59% of patients with HCV infection (25). Therefore, in many cases of membranoproliferative glomerulonephritis, histologic changes were expected as the result of associated cryoglobulinemia. However, our three cases had neither detectable cryoglobulins nor symptoms related to cryoglobulinemia. Organoid deposits were not present in the glomeruli. Therefore, it is reasonable to assume that immune deposits were the result of an immune reaction to HCV. However, the possibility is still present that cryoglobulin can be found during the later course of the disease.

Membranoproliferative glomerulonephritis in association with HCV infection is no different from idiopathic membranoproliferative glomerulonephritis by renal histology. They both have peripheral capillary deposits of IgM, IgG, and C3, with IgM deposits being the most prominent in HCV positive cases (6, 9). Rare peripheral C4, C1q and minimal mesangial deposits can also be seen. Although subendothelial deposits are noted in all cases, subepithelial and intramembranous deposits may be present. In our cases, two had subepithelial and intramembranous deposits, both being serologically positive for HCV-RNA. HCV-RNA in the patient's serum is almost always present in cases where HCV antibody is present. Viral RNA as demonstrated by RT-PCR indicates active viral replication and potential infectivity. Interferon therapy has been reported to decrease deposition of immune complexes and help negative conversion of HCV-RNA (28, 29). Our results support the idea because HCV-RNA positive cases not only had a greater amount of immune deposits, but also subepithelial and intramembranous deposits. Because HCV is lymphotropic, it could be present in the liver and peripheral blood mononuclear cells, but not in the serum (30).

Patients with HCV-associated glomerulonephritis presented proteinuria, and were nephrotic in 71% (25). In our two cases, they had liver cirrhosis with ascites and were complicated by diabetes mellitus, which contrasts with Johnson et al. (25) that signs of clinical liver disease were infrequent. Liver enzymes are not appropriate markers for liver dysfunction, since only 31% (31)-to-33% (32) of HCV-infected patients had abnormal levels of liver enzymes. Because diabetes mellitus and liver cirrhosis can be overlapped by other primary or secondary glomerulonephritis, we examined the possibility by histologic examination. Arteriolar hyalin was prominent in one of two cases. Thickening of lamina densa, characteristic of diabetic nephropathy, was present in the non-

sclerotic glomeruli of the two native kidneys. Glomerular capillary IgA deposit frequently accompanying cirrhotic glomerulosclerosis was minimal. Although we do not know what kind of influence diabetes mellitus has in our two cases, immunosuppressive status in general may predispose immune complex deposition. Furthermore, impaired clearance of immune complexes by the liver may contribute to the immune complex deposition (25).

The role of HCV in glomerular injury remains unknown. The direct role of HCV in causing glomerulonephritis was supported by Yamabe et al. (6) and Sansonno et al. (33), who demonstrated the presence of c22 antigen of HCV in the glomerular lesion and HCV-like particles in the mesangium. Conversion of HCV-RNA and a decrease of proteinruia with alpha interferon treatment may support its role (34). Cosio et al. (20) showed a strong association between HCV and transplant glomerulopathy without immune complex deposition. They speculated that the virus may mediate injury by causing endothelial injury by elaborating cytokines, and inflammatory and immunologic stimulation. In case 2, endothelial swelling was present, which might support the role of HCV in nonimmunologic endothelial injury.

Tissue-specific autoantibodies such as antithyroid microsomal, antithyroglobulin and anti-LKM1 autoantibodies (35) can be associated with HCV infection, but not antinuclear or antineutrophil cytoplasmic antibodies. Rheumatoid factor has been reported to be positive in two-thirds. Complement hemolytic activity (CH50) and C3 levels have been reported to be significantly lower (28), with an elevated or normal range of circulating immune complexes (35). However, our cases had none of the factors mentioned above, and an increased level of circulating immune complex in one case. Complement levels were all in the normal range. We are not certain whether autoantibodies were associated with cryoglobulinemia rather than HCV itself. In the presence of autoantibodies, immune complex deposition in the glomeruli may be facilitated.

REFERENCES

1. Johnson RJ, Gretch DR, Yamabe H, Hart J, Bacchi CE, Hartwell P, Couser WG, Corey L, Wener MH, Alpers CE, Willson R. *Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. N Engl J Med 1993; 328: 465-70.*
2. Bursten DM, Rodby RA. *Membranoproliferative glomerulonephritis associated with hepatitis C virus infection. J Am Soc Nephrol 1993; 4: 1288-93.*
3. Harle JR, Disdier P, Dussol B, Bolla G, Casanova P, Weiller PJ. *Membranoproliferative glomerulonephritis and hepatitis C infection. Lancet 1993; 341: 904.*
4. Gonzalo A, Barcena R, Mampaso F, Zea A, Ortuno J. *Membranoproliferative glomerulonephritis and hepatitis C virus infection. Nephron 1993; 63: 475-6.*
5. Doutrelepont J-M, Adler M, Willems M, Durez P, Yap S-H. *Hepatitis C infection and membranoproliferative glomerulonephritis. Lancet 1993; 341: 317.*
6. Yamabe H, Johnson RJ, Gretch DR, Fukushi K, Osawa H, Miyata M, Inuma H, Sasaki T, Kaizuka M, Tamura N, Tsunoda S, Fujita Y, Onodera K. *Hepatitis C virus infection and membranoproliferative glomerulonephritis in Japan. J Am Soc Nephrol 1995; 6: 220-3.*
7. Rostoker G, Pawlotsky JM, Bastie A, Weil B, Dhumeaux D. *Type I membranoproliferative glomerulonephritis and HCV infection. Nephrol Dial Transplant 1996; 11(Suppl 4): 22-4.*
8. Rollino C, Roccatello D, Giachino O, Basolo B, Piccoli G. *Hepatitis C virus infection and membranous glomerulonephritis. Nephron 1991; 59: 319-20.*
9. Cruzado JM, Gil-Vernet S, Ercilla G, Seron D, Carrera M, Bas J, Torras J, Alsina J, Grinyo JM. *Hepatitis C virus-associated membranoproliferative glomerulonephritis in renal allografts. J Am Soc Nephrol 1996; 7: 2469-75.*
10. Hammoud H, Haem J, Laurent B, Alamartine E, Diab N, Defilippis JP, Berthoux P, Berthoux F. *Glomerular disease during HCV infection in renal transplantation. Nephrol Dial Transplant 1996; 11(Suppl 4): 54-5.*
11. Morales JM, Campistol JM, Andres A, Rodicio JL. *Glomerular diseases in patients with hepatitis C virus infection after renal transplantation. Curr Opin Nephrol Hypertens 1997; 6: 511-5.*
12. Ferri C, Marzo E, Longombardo G, Lombardini F, La Civita L, Vanacore R, Liberati AM, Gerli R, Greco F, Moretti A, Monti M, Gentilini P, Bombardieri S, Zignego AL. *Interferon-alpha in mixed cryoglobulinemia patients: a randomized, crossover-controlled trial. Blood 1993; 81: 1132-6.*
13. Agnello V, Chung RT, Kaplan LM. *A role of hepatitis C infection in type II cryoglobulinemia. N Engl J Med 1992; 327: 1490-5.*
14. Misiani R, Bellavita P, Fenilli D, Borelli G, Marchesi D, Massazza M, Vendramin G, Comotti B, Tanzi E, Scudeller G, Zanetti A. *Hepatitis C virus infection in patients with essential mixed cryoglobulinemia. Ann Intern Med 1992; 117: 573-7.*
15. Lunel F, Musset L, Cacoub P, Frangeul L, Cresta P, Perrin M, Grippon P, Hoang C, Vall D, Piette JC, Huraux J-M, Opolon P. *Cryoglobulinemia in chronic liver disease: role of hepatitis C virus and liver damage. Gastroenterology 1994; 106: 1291-300.*
16. Cacoub P, Fabiani FL, Perrin M, Franguel L, Leger JM, Huraux J-M, Piette J-C, Godeau P. *Mixed cryoglobulinemia and hepatitis C virus. Am J Med 1994; 96: 124-32.*
17. Pasquareillo A, Ferri C, Miroconi L, LaCivita L, Longonbardo G, Greco F, Zignego AL. *Cryoglobulinemic membranoproliferative glomerulonephritis associated with hepatitis C virus. Am J Nephrol 1993; 13: 300-4.*

18. D'Amico G, Fornasieri A. *Cryoglobulinemic glomerulonephritis: a membranoproliferative glomerulonephritis induced by hepatitis C virus. Am J Kidney Dis 1995; 25: 361-9.*
19. Roth D, Cirocco R, Zucker K, Ruiz P, Viciana A, Burke G, Carreno M, Esquenazi V, Miller J. *De novo membranoproliferative glomerulonephritis in hepatitis C virus-infected renal allograft recipients. Transplantation 1995; 59: 1676-82.*
20. Cosio FG, Roche Z, Agarwal A, Falkenhain ME, Sedmak DD, Ferguson RM. *Prevalence of hepatitis C in patients with idiopathic glomerulopathies in native and transplant kidneys. Am J Kidney Dis 1996; 28: 752-8.*
21. Kim YS, Pai CH, Chi HS, Kim DW, Min YI, Ahn YO. *Prevalence of hepatitis C virus antibody among Korean adults. J Korean Med Sci 1992; 7: 333-6.*
22. Gumber SC, Chopra S. *Hepatitis C a multifaceted disease. Ann Intern Med 1995; 123: 615-20.*
23. Garcia-Valdecasas J, Bernal C, Garcia F, Cerezo S, Umana WO, von Albertini B, Kimmel PL. *Epidemiology of hepatitis C virus infection in patients with renal disease. J Am Soc Nephrol 1994; 5: 186-92.*
24. Korean Society of Nephrology, Registry Committee. *Renal replacement therapy in Korea - Insan memorial registry 1996. Korean J Nephrol 1997; 16(Suppl 2): S1-26.*
25. Johnson RJ, Gretch DR, Couser WG, Alpers CE, Wilson J, Chung M, Hart J, Willson R. *Hepatitis C virus-associated glomerulonephritis. Effect of alpha-interferon therapy. Kidney Int 1994; 46: 1700-4.*
26. 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.*
27. Usalan C, Erdem Y, Altun B, Nar A, Yasavul U, Turgan C, Caglar S. *Rapidly progressive glomerulonephritis associated with hepatitis C viral infection. Clin Nephrol 1998; 49: 129-31.*
28. Johnson RJ, Willson R, Yamabe H, Couser W, Alpers CE, Wener MH, Davis C, Gretch DR. *Renal manifestations of hepatitis C virus infection. Kidney Int 1994; 46: 1255-63.*
29. Yamabe H, Johnson RJ, Gretch DR, Osawa H, Inuma H, Sasaki T, Kaizuka M, Tamura N, Tsunoda S, Fujita Y, Sato A, Onodera K. *Membranoproliferative glomerulonephritis associated with hepatitis C virus infection responsive to interferon-alpha. Am J Kidney Dis 1995; 25: 67-9.*
30. Navas S, Bosch O, Castillo I, Marriott E, Carreno V. *Porphyria cutanea tarda and hepatitis C and B viruses infection: a retrospective study. Hepatology 1995; 21: 279-84.*
31. Pol S, Romco R, Zins B, Driss F, Lebkiri B, Carnot F, Berthelot P, Brichot C. *Hepatitis C virus RNA in anti-HCV positive hemodialysis patients: significance and therapeutic implications. Kidney Int 1993; 44: 1097-100.*
32. Chan TM, Lok ASF, Cheng IKP, Chan RT. *Prevalence of hepatitis C virus infection in hemodialysis patients: a longitudinal study comparing the results of RNA and antibody assays. Hepatology 1993; 17: 5-8.*
33. Sansonno D, Gesualodo L, Manno C, Shena FP, Danmacco F. *Hepatitis C virus-related proteins in kidney tissue from hepatitis C virus-infected patients with cryoglobulinemic membranoproliferative glomerulonephritis. Hepatology 1997; 25: 1237-44.*
34. Sarac E, Bastacky S, Johnson JP. *Response to high-dose interferon-alpha after failure of standard therapy in MPGN associated with hepatitis C virus infection. Am J Kidney Dis 1997; 30: 113-5.*
35. Rostaing L, Modesto A, Cisterne JM, Izopet J, Oksman F, Duffaut M, Abbal M, Durand D. *Serological markers of autoimmunity in renal transplant patients with chronic hepatitis C. Am J Nephrol 1998; 18: 50-6.*