原著：

Association with Cryoglobulinemia and Renal Disorder in Patients with Hepatitis C Virus Infection

— Their Relationships to the Presence of Hepatic Disorder —

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It is considered that hepatitis C virus (HCV) infection may be a pathogenic factor in cryoglobulinemia and glomerulonephritis. The purpose of this study was to determine whether there is any relation between the presence of hepatic disorder due to HCV infection and the association with cryoglobulinemia and urinary abnormalities, i. e. proteinuria and/or hematuria, in HCV-infected patients. Cryoglobulinemia was found in 11.4% of our HCV patients. However, seropositivity of cryoglobulin detected in all the patients was low. The prevalence of the association with cryoglobulinemia in patients with hepatic disorder was significantly higher than that in patients without hepatic disorder. Urinary abnormalities were found in 10.0% of the HCV patients. No significant difference was observed in the prevalence of urinary abnormalities between patients with and without hepatic disorder. In addition, there was no significant difference in the prevalence of urinary abnormalities between the association with and without cryoglobulinemia. These results suggest the close relation between the presence of hepatic disorder due to HCV infection and the association with cryoglobulinemia. However, renal involvement may have no relation with the presence of hepatic disorder and cryoglobulinemia.

①hepatitis C virus ②cryoglobulinemia ③hepatic disorder ④renal disorder

Introduction

Hepatitis C virus (HCV) infection is characterized by persistent, prolonged viremia. Resolution of viremia is uncommon, but patients may present few or no clinical symptoms. However, HCV is a major cause of both short-term and long-term hepatic damage and also has been associated with cryoglobulinemia and glomerulonephritis¹⁾. Cryoglobulinemia is a sys-

temic immunological disorder characterized by purpura, arthralgias, weakness and by organ involvement such as glomerulonephritis²⁾. Many investigators have demonstrated a very high rate of positivity of cryoprecipitable HCV RNA and/or antibodies in the serum and the renal deposits of patients with cryoglobulinemia^{1,3~12)}. In a study assessing the prevalence of exposure to HCV infection in patients with chronic renal disease, 7.9% of patients were infected with HCV, compared with a significantly lower prevalence in the normal population (1.03% in blood donors, 0.98% in pregnant women)¹³⁾. Furthermore, a higher prevalence of

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HCV seropositivity was observed in patients with glomerulonephritis than in patients with other renal disease¹³. The high prevalence of HCV seropositivity in patients with glomerulonephritis suggests that HCV infection may be a causal factor in the pathogenesis of nephropathy.

In the present study, to determine whether the presence of hepatic disorder due to HCV infection affects the association with cryoglobulinemia and renal disorder, we divided patients with HCV infection into two groups, i. e. patients with and without hepatic disorder, and examined the relation between the presence of hepatic disorder (particularly, the elevation of serum alanine aminotransferase (ALT) level) and the association with cryoglobulinemia and urinary abnormalities, i. e. proteinuria and/or hematuria.

Subjects and Methods

This study was carried out in 140 male patients with HCV infection. The patients were divided into two groups – patients without hepatic disorder (76 men, normal hepatic function group) and those with hepatic disorder (64 men, hepatic disorder group) in which serum transaminase, particularly ALT, level was elevated. We used ALT level as the marker of the presence of hepatic disorder due to HCV infection, because abnormal ALT level is considered to be the surrogate marker for viral hepatic disorder including the necrosis of hepatic cells^{14–16}. The age range of subjects in the normal hepatic function group was 26–60 years with a mean of 43 years. The average level of ALT was 25 IU/l with a range of 6–35 IU/l

(normal range: 0–35 IU/l). For the hepatic disorder group, the age range was from 27 to 64 years with a mean of 39 years. The average ALT level was 66 IU/l with a range of 36–216 IU/l. We further performed the urinary examination in all the patients and checked proteinuria and/or hematuria as the marker of renal disorder. The measurements of ALT level and the presence of serum cryoglobulin were performed using the automatic analyzer (type 7250, Hitachi Co., Tokyo) and serum reaction to circulating cryoglobulin by the cold precipitation method, respectively. Antibody to HCV was measured by second-generation enzyme immunoassay using Immucheck F-HCV C50 Ab[®] (Kokusai-Shiyaku Co, Kobe). Furthermore, the rheumatoid factor was measured in patients with cryoglobulinemia by means of nephelometry (Nephelometer II, Behring Co., Germany). Patients with hepatic disorder due to hepatitis B virus, diabetes mellitus, and hypertension were excluded from this study.

Statistical analysis

Chi-square analysis was conducted to assess the differences in prevalence between the two groups. P value less than 0.05 was considered significant. Data are expressed as mean + / – SEM.

Results

As shown in Table 1, serum cryoglobulin was detected in 16 out of the 140 patients with HCV infection (11.4%) — 4 out of the 76 patients in the normal hepatic function group (5.3%) and 12 out of the 64 patients in the hepatic disorder group (18.8%). The prevalence of

Table 1 Prevalence of the association with cryoglobulinemia in HCV patients with and without hepatic disorder

with hepatic disorder	without hepatic disorder	p
12/64 (18.8%)	4/76 (5.3%)	<0.05

Table 2 a Prevalence of the association with urinary abnormalities in HCV patients with and without hepatic disorder

with hepatic disorder	without hepatic disorder	p
3/64 (4.7%)	11/76 (14.5%)	ns.

Table 2 b Prevalence of the association with urinary abnormalities in HCV patients with and without cryoglobulinemia

with cryoglobulinemia	without cryoglobulinemia	p
1/16 (6.3%)	13/124 (10.5%)	ns.

the association with cryoglobulinemia in the hepatic disorder group was significantly higher than that in the normal hepatic function group. Seropositivity of cryoglobulin detected in all the 16 patients was low. Purpura, arthralgias, weakness, peripheral neuropathy, and skin ulcers were not observed in all the 16 patients.

Table 2a shows the prevalence of the association with urinary abnormalities in the normal hepatic function and hepatic disorder groups. Urinary abnormalities were found in 10.0% of the 140 patients with HCV-infection. The prevalence of the association with urinary abnormalities in the normal hepatic function group (14.5%) was higher than that in the hepatic disorder group (4.7%). However, the difference in the prevalence was not significant. Furthermore, the serum level of ALT did not correlate to the degree of proteinuria and/or hematuria. As Table 2b shows, the prevalences of the association with urinary abnormalities in HCV patients with and without cryoglobulinemia were 6.3% (1/16 patients) and 10.5% (13/124 patients), respectively. There was no significant difference in the prevalence of the association with urinary abnormalities between patients with and without cryoglobulinemia. Furthermore, the serum level of the rheumatoid factor in the patients with cryoglobulinemia was 81 ± 6 IU/ml (range, 25 to 107 IU/ml).

Discussion

It is known that the majority of patients with cryoglobulinemia have antibody to HCV detected and that the relation between HCV infection and cryoglobulinemia is especially strong^{1,3-11}. HCV infection is considered to be a pathogenic factor in cryoglobulinemia. In the present study serum cryoglobulin was detected in 16 out of 140 patients with HCV infection (11.4%). Previously, Levey et al. reported that the prevalence of the association with cryoglobulinemia in HCV-infected patients is 13%¹⁰, which is approximate to our finding. Furthermore, our results demonstrated the significantly higher prevalence of the association with cryoglobulinemia in patients with hepatic disorder compared with that in patients without hepatic disorder. This result suggests that the presence of hepatic disorder due to HCV infection is closely related with the production of serum cryoglobulin.

It is also known that HCV infection and cryoglobulinemia may cause glomerular disorder^{1,2}. According to Johnson et al.¹², all their eight HCV patients, in whom renal biopsy showed membranoproliferative glomerulonephritis, had hypoalbuminemia, abnormally elevated serum aminotransferase (serum ALT level was 110 ± 27 IU/l), and diminished total hemolytic complement levels (8 IU/ml) and rheumatoid factor activity (8 IU/ml). All the patients

had proteinuria; the majority had more than 3.5 g/day. Urinalysis revealed red blood cell casts in 37.5% of patients. And approximately two-thirds of patients had cryoglobulinemia and circulating immune complexes. Our study showed no significant difference in the prevalence of the association with urinary abnormalities between patients with and without hepatic disorder. A possible reason may be that the degree of the elevation of serum ALT (the degree of hepatic disorder) observed in our patients is mild compared with that in the patients of Johnson et al.¹²⁾. The development of glomerulonephritis is also considered to be dependent on serum cryoglobulin activity. Renal disease is especially common if the concentration of circulating cryoglobulin exceeds 1 g/dl¹⁷⁾. Serum cryoglobulin is considered to act in the glomerulus as trapped immune complexes which bind complements¹⁸⁾, and which are composed of immunoglobulins with rheumatoid factor activity^{19, 20)}. Furthermore, the report by Johnson et al.¹²⁾, suggests a potential role of IgM as a rheumatoid factor in the formation of complex capable of damaging the glomerulus. Also, a possible increase in protein concentration leading to an increase in viscosity of glomerular capillaries may be a factor that enhances their vulnerability in renal disorders. In our study the prevalence rates of the association with urinary abnormalities in HCV-infected patients with and without cryoglobulinemia were 6.3% and 10.5%, respectively. The present study failed to show the significant relation between urinary abnormalities and cryoglobulinemia in patients with HCV infection. A possible reason may be a low concentration of serum cryoglobulin in all patients, in whom it was detected. Also, a higher level of rheumatoid factor (81 + / - 6 IU/ml) in the HCV-infected patients with cryoglobulinemia in the present study suggests that the trapped immune complexes,

which are composed of immunoglobulins with rheumatoid factor activity, in the glomerulus are less than those found by Johnson et al.¹²⁾, suspecting that the damage of the glomerulus is mild.

In conclusion, a higher prevalence of the association with cryoglobulinemia in HCV patients with hepatic disorder compared with those without hepatic disorder suggests a close relation between the presence of hepatic disorder due to HCV infection and the production of serum cryoglobulin. However, renal involvement may have no relation with the presence of hepatic disorder and cryoglobulinemia.

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C型肝炎ウイルス感染者における クリオグロブリン血症および腎障害の合併 —— 肝障害の有無との関係 ——

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C型肝炎ウイルス（HCV）感染は、短期的および長期的に肝障害の誘因となるほか、クリオグロブリン血症や糸球体腎炎を併発することが知られている。今回、HCV感染による肝障害の存在が、クリオグロブリン血症および尿異常（蛋白尿、血尿）の合併に影響を及ぼすか否かをHCV感染者（男性140人）において検討した。クリオグロブリン血症は、HCV感染者の11.4%に認められた。しかし、全ての保持者のクリオグロブリンに対する血清反応は弱陽性であった。肝障害を持つ患者のクリオグロブリン血症合併率は、肝障害を持たない患者より有意に高かった。また、尿異常はHCV感染者の10.0%に認められた。肝障害の有無による尿異常合併率には有意差は認められなかった。さらに、クリオグロブリン血症の合併の有無による尿異常合併率にも有意差は認められなかった。これらの所見は、HCV感染による肝障害とクリオグロブリン血症の合併には関係があることを示唆している。しかし、腎障害の合併は肝障害、クリオグロブリン血症の有無には関係はないと考えられた。

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