Hepatitis C Virus Infection and Membranoproliferative Glomerulonephritis in Japan


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ABSTRACT

The prevalence of hepatitis C virus (HCV) infection was determined in 146 adult patients with various types of glomerulonephritis and renal diseases monitored between 1990 and 1993. Serum HCV antibody (HCV Ab) was evaluated, and positive cases were tested for HCV RNA by polymerase chain reaction. HCV infection was present in 1 (1.7%) of 58 cases of immunoglobulin A nephropathy, 0 (0%) of 14 cases of lupus nephritis, 0 (0%) of 12 cases of minimal change nephrosis, and 0 (0%) of 28 cases of other renal diseases, which is similar to the 2% prevalence observed in healthy blood donors in Japan. In contrast, HCV Ab was observed in 2 (6.3%) of 24 cases of membranous nephropathy and 6 (60%) of 10 cases of membranoproliferative glomerulonephritis (MPGN) Type I. The prevalence of HCV infection in MPGN patients was significantly higher than the frequency of HCV infection observed in the other patients with renal diseases (P < 0.001). HCV RNA was present in all cases in which HCV Ab was present. The six patients with HCV-MPGN were similar to the four patients with idiopathic MPGN with respect to age, presence of nephrotic syndrome, and renal dysfunction, but had a higher incidence of liver dysfunction, cryoglobulinemia, rheumatoid factor, and hypocomplementemia (low C3). HCV infection is present in a large percentage of patients with MPGN in Japan and clinically may differ slightly from other cases of MPGN.

Key Words: Hepatitis C, membranoproliferative glomerulonephritis, cryoglobulin

Membranoproliferative glomerulonephritis (MPGN) was originally described by West et al. (1) and Gotoff et al. (2) and has been recognized as a histologically distinct type of glomerulonephritis that displays certain clinical and serologic characteristics. At present, two types of MPGN (Type I and Type II) are generally accepted on the basis of the ultrastructural morphology (3). MPGN Type I and MPGN Type II are two separate and probably unrelated diseases. MPGN Type II is extremely rare in Japan. The causes of MPGN Type I have not yet been defined. Patients with lupus nephritis (4), virus infection (5), bacterial endocarditis, and other infectious diseases sometimes show histologic changes like MPGN I, and it is likely that the pathogenesis of MPGN I involves immune complex deposition in glomeruli.

Hepatitis C virus (HCV), first identified in 1989, is a major cause of non-A, non-B hepatitis (6, 7). We have previously reported that some patients with both cryoglobulinemic and noncryoglobulinemic MPGN have active HCV infection (8). To further examine this observation, we determined the prevalence of HCV infection in our patients with primary glomerular diseases and attempted to identify distinguishing characteristics of HCV-infected patients with MPGN.

METHODS

The subjects were 146 adult patients who were all receiving renal biopsy between April 1990 and July 1993 in Hirosaki University Hospital. The patients included 58 cases of immunoglobulin (Ig)A nephropathy, 24 cases of membranous nephropathy, 14 cases of lupus nephritis, 12 cases of minimal change nephrosis, 10 cases of MPGN, and 26 cases of various renal diseases (10 of MPGN without IgA deposition, 3 of focal glomerular sclerosis, 2 of diabetic nephropathy, 2 of amyloidosis, 1 of Henoch-Schoenlein purpura nephritis, 1 of nephritis with MCTD, 1 of nephrosclerosis, 1 of acute tubular necrosis, 1 of interstitial nephritis, 1 of crescentic glomerulonephritis, 5 of normal glomeruli with urinary abnormalities). All cases of MPGN showed increased cellularity and capillary duplication in a lobular pattern. Serum HCV antibody (HCV Ab) was evaluated in all cases at the same time as the renal biopsy by the use of HCV EIA Abbott (Dinabot, Tokyo, Japan), which detects antibody to the antigen c100–3, until April 1992 and then by HCV PHA Dinabot (Dinabot) second-generation assay, which measures antibodies to the c100–3, pHCV34 (core), and pHCV31(NS 3 4) antigens. Patients with positive HCV Ab were further examined for the presence of HCV RNA in their serum and cryoprecipitates as previously described (8). HCV RNA was detected by use of the polymerase chain reaction with primers...
ers derived from the 5' -noncoding, highly conserved region of
the HCV genome (8). HCV genotyping was also performed by
polymerase chain reaction with primers specific for the HCV
core region (9) and was confirmed by sequence analysis of the
NS 5 region as reported by Simmonds et al. (10).

RESULTS
Prevalence of HCV Infection

The prevalence of HCV infection in various types of
glomerulonephritis is summarized in Table 1. HCV Ab
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TABLE 1. Prevalence of HCV Infection in various types of glomerulonephritis

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Patients</th>
<th>Sex</th>
<th>Mean Age (yr)</th>
<th>Age Range</th>
<th>No. of Patients Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
<td>Female</td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>IgA Nephropathy</td>
<td>58</td>
<td>31</td>
<td>27</td>
<td>32.4</td>
<td>15-72</td>
</tr>
<tr>
<td>Minimal Change Nephrosis</td>
<td>12</td>
<td>7</td>
<td>5</td>
<td>33.3</td>
<td>15-69</td>
</tr>
<tr>
<td>Lupus Nephritis</td>
<td>14</td>
<td>13</td>
<td>1</td>
<td>28.8</td>
<td>15-56</td>
</tr>
<tr>
<td>Membranous Nephropathy</td>
<td>24</td>
<td>15</td>
<td>9</td>
<td>56.4</td>
<td>21-75</td>
</tr>
<tr>
<td>MPGN</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>55.4</td>
<td>41-74</td>
</tr>
<tr>
<td>Others</td>
<td>28</td>
<td>14</td>
<td>14</td>
<td>42.2</td>
<td>16-71</td>
</tr>
</tbody>
</table>

Histologic Characteristics

Histologic data are summarized in Table 3. All 10
patients showed MPGN with increased cellularity in a
lobular pattern. Glomerular deposition of C3, IgM,
and IgG were dominant in all cases. Electron micros-
copy revealed subendothelial immune deposits in six
cases. There were no distinct differences in renal
histology between either group.

DISCUSSION

HCV is a major cause of both sporadic and transfu-
sion-associated non-A, non-B hepatits, and may
progress to chronic active hepatitis, cirrhosis, and
possibly, hepatocellular carcinoma (14–16). The ob-
ervation that most patients with HCV infection con-
tinue to have HCV RNA detectable in their serum
despite a strong humoral immune response (15) sug-
gests that these patients may be at risk for chronic
immune complex–associated diseases. This is sup-
ported by recent findings that HCV may be a major
cause of “essential mixed cryoglobulinemia” (EMC)
(17,18). The majority of patients with EMC have HCV
RNA and HCV Ab in their blood, and HCV RNA and
HCV Ab can also be shown to be concentrated in the
cryoglobulins (17).

We (8) and others (19–24) have recently observed
that chronic HCV infection may also be associated
with an acute glomerulonephritis that histologically
resembles MPGN I. These patients may or may not
have cryoglobulinemia, and even if present, they fre-
cently lack other symptoms of EMC such as purpura
or arthralgia (8). Many also have no physical signs of
liver disease, although they often have biochemical
evidence for mild liver dysfunction (8). However, liver
biopsy often reveals chronic active hepatitis or cirrho-
sis.

In this study, we determined the prevalence of HCV
infection in patients with various glomerular diseases
and in addition examined whether there were any
distinguishing characteristics that separated HCV-
infected from non-HCV-infected patients with MPGN.
TABLE 2. Clinical data of six MPGN patients with HCV infection compared with four MPGN patients without HCV infection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63</td>
<td>58</td>
<td>42</td>
<td>51</td>
<td>58</td>
<td>48</td>
<td>60</td>
<td>41</td>
<td>74</td>
<td>57</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Risk factors of HCV</td>
<td>Blood transfusion</td>
<td>Blood transfusion</td>
<td>Drug abuse</td>
<td>Not done</td>
<td>Not done</td>
<td>HCV transfusion transfusion</td>
<td>Urinary Protein (g/day)</td>
<td>0.5</td>
<td>5.0</td>
<td>12.0</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dL)</td>
<td>0.8</td>
<td>2.9</td>
<td>0.8</td>
<td>2.3</td>
<td>3.1</td>
<td>0.6</td>
<td>1.1</td>
<td>1.4</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>C3 (mg/dL)</td>
<td>42</td>
<td>27</td>
<td>49</td>
<td>89</td>
<td>58</td>
<td>43</td>
<td>84</td>
<td>62</td>
<td>80</td>
<td>18</td>
</tr>
<tr>
<td>C4 (mg/dL)</td>
<td>2.0</td>
<td>14</td>
<td>7.0</td>
<td>21</td>
<td>29</td>
<td>9.0</td>
<td>20</td>
<td>10</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Rheumatoid Factor</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
<td>(-)</td>
<td>(+)</td>
</tr>
<tr>
<td>Liver injury</td>
<td>Cirrhosis, cancer</td>
<td>Hepatitis</td>
<td>Hepatitis</td>
<td>Hepatitis</td>
<td>Hepatitis</td>
<td>Cirrhosis</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Anti-HCV HCV RNA</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
</tr>
<tr>
<td>Serum Cryoglobulins</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
</tr>
<tr>
<td>Genotype of HCV RNA</td>
<td>II</td>
<td>II</td>
<td>IV</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>II</td>
</tr>
</tbody>
</table>

The normal value is less than 1.2 mg/dL.

The normal value is more than 15 mg/dL.

Not done

The normal value is more than 60 mg/dL.

Anti-HCV of this patient was examined by first-generation assay. The patient died, and the possibility of HCV infection could not be ruled out. The liver injury in Patients 1, 2, 6, and 10 was defined by biopsy or autopsy, and in other patients, it was evaluated by the elevation of transaminase and ultrasonography.

TABLE 3. Histologic characteristics of six MPGN patients with HCV infection compared with four patients without HCV infection

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MPGN With HCV Infection</th>
<th>MPGN Without HCV Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPGN in Light Microscopy Immunofluorescence</td>
<td>6/6 (100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>IgG</td>
<td>5/6 (83%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>IgA</td>
<td>4/6 (67%)</td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>IgM</td>
<td>5/6 (83%)</td>
<td>3/4 (75%)</td>
</tr>
<tr>
<td>C3</td>
<td>6/6 (100%)</td>
<td>4/4 (100%)</td>
</tr>
<tr>
<td>Subendothelial Deposits in Electron Microscopy</td>
<td>4/4 (100%)</td>
<td>2/2 (100%)</td>
</tr>
</tbody>
</table>

The most impressive finding was that 60% of the MPGN patients had active HCV infection. Even when corrected for age, the prevalence of HCV infection in comparable healthy blood donors is only about 4% (11). This suggests that HCV infection may be a major cause of MPGN in Japan. A slightly higher prevalence was observed in membranous nephropathy, which is difficult to interpret given the small number of patients, but which is nevertheless interesting in light of recent reports (25,26) that HCV infection may be associated with this disease as well.

The analysis of HCV genotype in 80 patients with hepatitis C in Japan showed that the prevalence of Type II was 60%, Type III was 23%, Type IV was 10%, and Type I was 5% (9). This is very similar to the prevalence of HCV genotype in our patients with MPGN and suggests that HCV-MPGN is not associated with any specific genotype of HCV in Japan.

In conclusion, these studies provide evidence that HCV infection may be a major cause of MPGN I in Japan. Patients often present with proteinuria and renal dysfunction without clinical evidence of cryoglobulinemia or liver disease. However, many patients do have laboratory evidence of cryoglobulinemia, rheumatoid factors, and hypocomplementemia. Whereas most patients have evidence of mildly elevated liver function tests, liver biopsy usually reveals severe disease. Evidence of HCV infection should be sought in all patients presenting with MPGN.

REFERENCES


