Type I membranoproliferative glomerulonephritis and HCV infection

G. Rostoker, J. M. Pawlotsky, A. Bastie, B. Weil and D. Dhumeaux

Departments of Nephrology, Bacteriology-Virology and Hepatology, Hôpital Henri Mondor, 51 avenue du Maréchal de Lattre de Tassigny, 94010 Créteil, France

Abstract. Type I membrano-proliferative glomerulonephritis (MPGN) is secondary to chronic bacterial, parasitic, viral (HB) infections, to autoimmune disorders or primary or malignant haemopathies. MPGN are thought to be linked to the deposition of immune complexes preformed in the circulation or formed in situ in the glomeruli. A link between HCV and type I MPGN was reported for the first time in 1993. In some patients, the renal clinical pattern is the most obvious (nephrotic syndrome) whereas in others liver disease or cryoglobulinaemia prevail. A risk factor of HCV infection exists in 80% of cases. Renal biopsy and scanning electron microscopy usually substantiate cryoglobulinaemia. Circulating cryoglobulins are most often detected, usually of type II. CH50 is decreased in 90% of patients and rheumatoid factors have been found in two-thirds of patients. The cryoprecipitate contains viral RNA and anti-HCV antibodies. The viral RNA is nearly always found in the cryoprecipitate. Analysing the viral genotype does not elicit predominance of any particular type. Viral genome detection in renal biopsy specimens appears to be technically difficult. Type I MPGN secondary to HCV infection appear to be improved by interferon-α therapy but treatment suspension is immediately followed by the recurrence of viraemia and nephrotic syndrome. That glomerulopathy would be the human equivalent of the experimentally induced chronic serum nephropathy.

The link between the hepatitis C virus and type I MPGN

The hepatitis C virus (HCV), cloned in 1989 from the plasma of a chimpanzee that had been inoculated with factor VIII containing hepatitis non-A, non-B virus belongs to the Flaviridae family. HCV was promptly associated to viral non-A, non-B liver diseases parenterally transmitted, which include chronic hepatitis, cirrhosis and some cases of hepatocarcinoma occurring on top of cirrhosis. A link was quickly suspected, then confirmed, between HCV and the so-called essential mixed cryoglobulinaemias, type II in particular [1]. HCV is now known to be the main agent responsible for these affections.

Richard Johnson in 1993 reported eight cases of HCV-infected patients referred to nephrology for assessment of abundant proteinuria associated in most cases with renal function impairment; extrarenal signs were not constant [2]. Renal biopsy elicited type I...
Type I MPGN and HCV infection

MPGN with a cryoglobulinaemic kidney image under the electronic microscope. Circulating cryoglobulin was detected in five patients. The cryoprecipitate contained viral RNA and anti-HCV antibodies [2]. The same year, Gonzalo reported a case of type I MPGN without extrarenal signs in a 28-year-old woman with cryoglobulinaemia and HCV infection [3]. Several publications later reported the existence of type I MPGN in patients with HCV infection and systemic manifestations linked to cryoglobulinaemia [4–6].

Recently, Johnson has published the characteristics of 34 patients with HCV infection detected by ELISA, who were referred to the Washington University department of nephrology for renal assessment [7]. The mean age of patients was 46 years; there were 60% men and a risk factor for HCV infection was found in 80% of patients (drug abusers = 56%; previous blood transfusion = 18%; sexual contamination by HCV + partner(s) = 6%). Fifteen patients exhibited systemic signs upfront, evocative of mixed cryoglobulinaemia; cryoglobulinaemia was found in 11 of them. In 19 patients, beside the presence of anti-HCV antibodies, which motivated the investigation, the clinical pattern appeared to be essentially renal although cryoglobulinaemia was evidenced in nine of these patients. In the course of later follow-up, one circulating cryoglobulin was detected in nine of the 14 initially negative patients. Seventy-one per cent (71%) of the patients in that series were nephrotic. Type I MPGN was noted in 28 patients and type III in three cases. The other three patients had endocapillary proliferative glomerulopathy. Clear signs of hepatic disease were scarce (18% of patients) but elevated liver enzymes were noted in two-thirds of the patients.

Cryoglobulin typing could only be performed in seven cases and always revealed mixed type II. CH50 was reduced in 90% of patients and rheumatoid factors were detected in two-thirds of patients. Detection of HCV circulating RNA was always positive. Viral RNA was almost always found in the cryoprecipitate. Viral genotype analysis did not reveal any predominance of a particular type [7].

Type I MPGN biopsies are usually negative for viral genome but the technique is apparently quite difficult to use and very few monoclonal antibodies are currently available, that have high affinity and sufficient specificity for immuno-histochemical studies [1–7].

From the pathophysiological standpoint, three theories have been proposed to account for MPGN:

- Nephropathy linked to the deposits of excessive antibody titre immune complexes composed of the genome and/or viral proteins, specific antibodies but also IgM with both rheumatoid and idiotypic activities [2,7].
- Conversely, Agnello believes that the HCV, also lymphotropic, would induce clonal or oligoclonal B escape with the formation of cold-precipitating IgM–IgG complexes that would induce glomerulopathy; this in fact would merely be a particular form of cryoglobulinaemic nephropathy [1].
- To D’Amico et al., the HCV would infect the B cells which trigger the synthesis of monoclonal IgMx included in the composition of type II cryoglobulins, with an antibody activity against glomerular constituents, especially fibronectin of the mesangial matrix. D’Amico’s team have just reproduced the affection by parenteral administration of purified monoclonal IgMx in mice [8].

Type I MPGN (mainly) secondary to HCV infection appear to be improved by administration of interferon α (7). Johnson et al. so treated 19 HCV+ patients with Intron-A® at the dose of 3 million units thrice a week for 6–12 months. They noted a significant decrease in proteinuria in nearly all patients, and improved renal function in 11 of them. Viraemia became negative in a number of patients; thus subgroup of patients appeared to better respond to therapy than those who remained viraemic. Stopping interferon treatment is usually followed by recurrence of viraemia and nephrotic syndrome [7].

One case of lasting remission with improved histology following interferon α treatment has been reported by Yamabe [9].

Sero-epidemiological data on the prevalence of HVC infection in ‘seemingly’ primary type I MPGN

The existence of HCV infections that do not exhibit purely nephrological patterns has led some authors to suggest that a non-negligible—or even important—proportion of ‘seemingly’ primary type I MPGN would in fact be secondary to that viral infection [2–7]. Few serologic screenings for anti-HCV antibodies in that group of patients were performed and have produced conflicting results: in Japan, Yamabe in 1993 noted the presence of anti-HCV antibodies in six out of 10 MPGN [10]. In the USA, Johnson observed two cases of HCV infection out of the 10 primary type I MPGN studied [7].

In contrast, Pasquarello in Italy found no case with any relation to HCV in 23 idiopathic type I MPGN, whereas all 26 cryoglobulinaemic MPGN had anti-HCV antibodies [6]. In Henri Mondor hospital, we studied the sera of 35 adult patients with primary type I MPGN; none had detectable cryoglobulins. Anti-HCV antibodies were detected by two different, second-generation ELISA tests and 20 of these patients were re-tested after at least 6 months by third-generation ELISA [11]. We did not detect any HCV seropositive cases. More recently, circulating viral RNA was investigated in these patients: it always turned out negative. Three recent studies, one in Spain [12], one multicentre study in Italy [8], and the third in St-Etienne, (France) [13] have reached identical conclusions. Table 1 summarizes the bulk of literature data.
Table 1. Sero-epidemiological studies of HCV infection during seemingly idiopathic type I MPGN

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Patients (I)</th>
<th>HCV Ab+</th>
<th>PCR +</th>
<th>Tested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamabe [10]</td>
<td>1993</td>
<td>Japan</td>
<td>0</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pasquariello [6]</td>
<td>1993</td>
<td>Italy</td>
<td>23</td>
<td>0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Gonzalo [12]</td>
<td>1995</td>
<td>Spain</td>
<td>5</td>
<td>0</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>D’Amico [8]</td>
<td>1995</td>
<td>Italy</td>
<td>128</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

There is a documented link between cryoglobulinaemic MPGN and chronic HCV infection. For the seemingly primary type I MPGN without cryoglobulinaemia (as verified by repeated testing) this link does not seem to exist in Europe. Sero-epidemiological studies involving larger populations of patients with primary type I MPGN in various regions of the world are therefore necessary to specify the relationships between HCV infection and that form of glomerulopathy.

**References**