Kidney Pathology and HCV

Vazquez Martul, Eduardo
Complejo Hospitalario Universitario A Coruña (CHUAC)

Introduction

Hepatitis C virus (HCV) infection are a common and potentially serious health problem throughout the world with different variations depending the geographic area, between an 0’5% to 2’8%, in Europe and Western countries, 2’8% in USA or Canada, or more of the 20% of the population in Egypt or Romania. In addition the patients with chronic renal disease increase the prevalence because their frequent exposure to blood from transfusion, to HCV contaminated medical equipment exposure or immunodepressed status in transplanted kidney population.

The major complication of acute HCV infection is chronic hepatitis in up to 70% of cases. Chronic HCV infection has been associated with extrahepatic manifestations. The most of these extrahepatic manifestations with kidney repercussion is the mixed essential cryoglobulinemia. Typical renal manifestation of cryoglobulinemia includes proteinuria, hematuria, renal insufficiency with renal glomerular affectation.

HCV-related glomerular disease

HCV is probably a principal cause of idiopathic membranoproliferative glomerulonefritis (MPGN). This type of renal disease typically occurs in adults after a HCV liver affectation but the HCV also are related with different types of glomerular disease such as IgA nephropathy, membranous glomerulonefritis (MG), focal sclerosis, fibrillary or immunotactoid glomerulopathy, TMA and vasculitis.

The associations between MPGN and Essential Mixed Cryoglobulinemia (EMC) rise up 90% of the cases. Otherwise there is a wide variations related the frequency of this association. In our experience the 37% of MPGN there was an associations, but only in 1’7% of MG and 1’8 of IgA was possible to demonstrate a relationship between HCV and glomerular disease.

The pathogenesis of the glomerular injury in HCV infection is not known. The injury may be is the result from deposition of circulating immune deposits with participation of HCV, anti-HCV and Rheumatoid factor (RF) at the site of injury. The HCV envelop protein E2, able to bind CD81 molecule expressed on B-lymphocites, might be involved in the first steps of HCV-driven autoimmune phenomena. The interaction between HCV-E2 and CD81 may the frequency of VDJ rearrangement in antigen B-cell. The B-cell is responsible for autoantibody and immune-complex production, including mixed cryoglobulobling and vasculitis.

HCV, Cryoglobulinemia and Membranoproliferative glomerulonephritys (MPGN).

Histology characteristic.

The MPGN is the glomerular form more frequently associated to Essential mixed cryoglobulinemia (EMC) up 80% the cases. The typical clinic characteristic consists in:
hypocomplementemia, wild/moderate kidney insufficiency, proteinuria, microhematuria, and high blood pressure.

HCV RNA positivity was demonstrated in PMGN associated Cryoglobulinemias as so as in the cryoprecipitates.

The MPGN associated HCV usually is the type I, indistinguish of the other MPGN no related with the virus, but some differences were related: presence of hyaline thrombi in capillary loops with less endocapillary proliferation, massive leucocyte/monocyte infiltration, small and medium vessels with fibrinoid necrosis. At the ultrastructural level, the presence of tubular deposits and/or dense round deposits in the mesangium or in subendothelial position has been described.

A lobular patter was another light microscopy feature described in 20% of the cases. In our experience after to review a total of 32 MPGN in the 37’5% there were an association in the 37’5%, only we have seen hyaline thrombi in 2 cases.

The immune fluorescent observation, deposition of C3, IgM, IgG are usually finding but not invariably shown in mesangial and capillary wall.

In summary, HCV associated GN cryoglobulinemia glomerulonephrytis has similar histologic characteristic that non cryoglobulinemic MPGN in the most of the cases, but the presence of large deposits filling the capillary lumen, fibrillary or cristaloid structures by electron microscopy and the massive infiltration of monocytes are findings suggestive of the cryoglonulnephritina glomerulonephrytis.

Other forms of glomerulonefritis associated with HCV

An association with HCV infection and other glomerulonephritis has been described. Membranous glomerulonephritys (MGN) has been documented in several series with a variation between 1’75%, in autopsy cases, to 8’3% in renal biopsies series. In our experience the MGN HCV association is the 1’7%.

Up to 80% HCV RNA positivity has been described in MGN associated HCV.

The IgAGN is other HCV associated glomerulonephritis. There is a classical relation between chronic hepatic disease and IgA glomerular deposits. It is possible the glomerular IgA deposits related with chronic hepatitis C has a different pathogenetics mechanism respect to cirrhosis HCV non related.

Postinfections glomerulonephritis, focal and segmental glomerulonephritis, fibrillary/immunotactoid glomerulopathy and TMA, are differents forms, also associated to HCV infection.

HCV in Kidney Transplanted Patients

There is not uniform data respect to HCV infection and its adverse relation with the follow up in kidney transplanted patients. Also there is significant rates variations. In USA series the variations range between 6% to 46%. In our transplanted kidney populations the 8’5% are HCV positive.

After a comparative study between HCV positive and HCV negative patients with allograft biopsies the differences with p significances were chronic allograft dysfunction, and chronic rejection. In 2.000 transplanted patients, non estadistic (p<0’1) differences we found related with other parameters as: clinical features, delayed graft function, acute cellular rejection or “de novo” or recurrent glomerular disease.
The recipients of HCV positive donors have a mortality independent risk as so as the presence of cirrhosis before transplantation.

Conclusions

- HCV infections with a variable incidence depending of geographic areas.
- Direct relation between HCV infection, essential mixt cryoglobulinemia and special form of MPGN.
- Less frequent association with other glomerulonephritis: IgA, Focal sclerosis, infectious glomerulonephritis, fibrillary/immunotactoid glomerulopathy and TMA.
- Non significant impact of HCV after transplantation except in long-term survival (10 to 20 years).
- More Incidence of chronic rejection related with HCV in our experience.

Tables

MPGN type I

Table 1. Histological findings (cryoglobulinemic vs non-cryoglobulinemic MPGN)

<table>
<thead>
<tr>
<th></th>
<th>Cryoglobulinemic (4/12)</th>
<th>Non-cryoglobulinemic (8/12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n%</td>
<td>n%</td>
</tr>
<tr>
<td>Lobular pattern</td>
<td>1 25</td>
<td>3 37.5</td>
</tr>
<tr>
<td>Celular crescents</td>
<td>0 0</td>
<td>5 62.5</td>
</tr>
<tr>
<td>Hyaline thrombi</td>
<td>2 50</td>
<td>3 37.5</td>
</tr>
<tr>
<td>Fibrinoid necrosis</td>
<td>0 0</td>
<td>0 0</td>
</tr>
<tr>
<td>Exocitosis/leucocytes</td>
<td>2 50</td>
<td>2 25</td>
</tr>
<tr>
<td>Arteriolar hyalinosis</td>
<td>1 25</td>
<td>1 12.5</td>
</tr>
</tbody>
</table>

*p* values indicate statistical significance.
MPGN type I

Table 2. Demographics, clinical and laboratorial features

<table>
<thead>
<tr>
<th></th>
<th>HCV positive (n=169)</th>
<th>HCV negative (n=169)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Causes of patient’s death</td>
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<tr>
<td>CVD</td>
<td>11</td>
<td>23.9</td>
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<tr>
<td>Neoplastic</td>
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<tr>
<td>Infectious</td>
<td>15</td>
<td>32.6</td>
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<tr>
<td>Others</td>
<td>8</td>
<td>17.4</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>13.0</td>
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<tr>
<td>Graft outcome</td>
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<tr>
<td>Functioning graft</td>
<td>86</td>
<td>39.1</td>
<td>76</td>
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<td>Lost graft</td>
<td>57</td>
<td>33.7</td>
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<tr>
<td>Death of the recipient with functioning graft</td>
<td>46</td>
<td>27.2</td>
<td>28</td>
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<tr>
<td>Acute rejection</td>
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<td>Yes</td>
<td>45</td>
<td>26.9</td>
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<tr>
<td>No</td>
<td>122</td>
<td>73.1</td>
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<td>Diabetes before KT</td>
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<td>NODAT</td>
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<tr>
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<td>143</td>
<td>85.6</td>
<td>147</td>
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### Table 4  Graft survival: comparative study between HCV+ and HCV -

<table>
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<th>years</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>
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<th>10</th>
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<tbody>
<tr>
<td>HCV +</td>
<td>88.7%</td>
<td>85.1%</td>
<td>80.5%</td>
<td>78.1%</td>
<td>75.1%</td>
<td>75.1%</td>
<td>72.9%</td>
<td>66.0%</td>
<td>61.9%</td>
<td>60.3%</td>
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<tr>
<td>HCV -</td>
<td>79.9%</td>
<td>77.8%</td>
<td>77.0%</td>
<td>74.7%</td>
<td>73.8%</td>
<td>71.8%</td>
<td>70.8%</td>
<td>68.6%</td>
<td>65.2%</td>
<td>60.1%</td>
</tr>
</tbody>
</table>

#### Patient survival

Log rank: 4.754 ; $p=0.029$

**Bibliografia**


Fabrizio F., Colucci P., Ponticelli C., and Locatelli F.


MGCGn+ hyalin thromby + exocitosis + monocytes vasculitis