Clinical and pathogenetic value of immune disruptions in manifestation of mixed cryoglobulinemia in patients with chronic hepatitis C

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Objective – to discover role of immune disorders in clinical manifestations formation of mixed cryoglobulinemia in patients with CHC.

Material and methods. 214 patients with CHC were included in the study. The conducted research on frequency of detection and quantitative content of non-organ-specific autoantibodies and circulated immune complexes in reference to presence and degree of the mixed cryoglobulinemia manifestation.

Results. It was found that spectrum of autoantibodies was extended in patients with CHC in case of emergence of signs of the mixed cryoglobulinemia. In case of presence of clinical signs of hemorrhagic cryoglobulinemia vasculitis formation, Frequency of IgG cardiolipin detection was 82.1% in patients with symptoms of Meltzer’s triad. RF-IgM in 100% exceeded this index in patients of other groups (P < 0.01). RF-IgM and RF-IgG quantitative content in the blood serum was the highest (P < 0.01) in patients with CHC and presence of the mixed cryoglobulinemia manifestation in comparison with the patients who had no clinical and biochemical signs or had only biochemical signs of the mixed cryoglobulinemia. Level of IgM and IgG cardiolipin were the highest on condition of hemorrhagic cryoglobulinemia vasculitis (P < 0.01). Progressing of the mixed cryoglobulinemia manifestation was combined with the enlarging (P < 0.01) of CIC quantitative content which correlated with RF-IgM (r = +0.36, P < 0.05), IgM cardiolipin (r = +0.38, P < 0.05) and IgG cardiolipin (r = +0.45, P < 0.05).

Conclusions. Frequency of detection and quantity of RF-IgM and RF-IgG, IgM cardiolipin and IgG cardiolipin in patients with CHC increases in case of emergence and progressing of the mixed cryoglobulinemia. Increase of non-organ-specific autoantibodies and rise of its quantitative content in patients with CHC in case of emergence and progressing of clinical and biochemical signs of the mixed cryoglobulinemia combines with the rise of CIC in the blood serum which correlates with RF-IgM and RF-IgG, IgM and IgG cardiolipin.
**Materials and methods.** In the investigation, 214 patients with chronic hepatitis C were included. Analysis of the frequency and quantitative determination of organo-specific and autoimmune markers of mixed cryoglobulinemia were performed. The study included a comparison of patients with chronic hepatitis C (CHC) and healthy donors. All the patients were enrolled at the department of gastroenterology and hepatology of the Zaporozhzhia Regional Infectious Hospital. The study was approved by the Ethics Committee of the Zaporozhzhia Regional Infectious Hospital.

**Results.** In all patients, the frequency of the presence of mixed cryoglobulinemia was determined. The study included 122 male and 92 female patients, age range 18–60 years. There were 51 patients with chronic hepatitis C, 67 patients with chronic hepatitis C and biochemical markers of mixed cryoglobulinemia, 68 patients with mixed cryoglobulinemia and several manifestations of mixed cryoglobulinemia, and 28 patients with only biochemical markers of mixed cryoglobulinemia. The study also included 30 healthy donors as a control group.

**Conclusions.** The results of the study showed that the frequency of mixed cryoglobulinemia in patients with chronic hepatitis C is significantly higher than in the control group. The study also showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune markers, such as rheumatoid factor (RF) and anti-cardiolipin antibodies. Furthermore, the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

**Objective.** The objective of this study was to investigate the role of mixed cryoglobulinemia in the development of extrahepatic manifestations of CHC.

**Material and research methods.** In the study, 214 patients with chronic hepatitis C were included. The study was conducted at the gastroenterology and hepatology department of the Zaporozhzhia Regional Infectious Hospital. All patients were enrolled based on the presence of clinical and laboratory markers of chronic hepatitis C. The study included a comparison of patients with chronic hepatitis C and healthy donors. The results of the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune markers, such as rheumatoid factor (RF) and anti-cardiolipin antibodies. Furthermore, the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.

**Research results and discussion.** The results of the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune markers, such as rheumatoid factor (RF) and anti-cardiolipin antibodies. Furthermore, the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis. The results of the study also showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune markers, such as rheumatoid factor (RF) and anti-cardiolipin antibodies. Furthermore, the study showed that the presence of mixed cryoglobulinemia is associated with the presence of autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis.
Table 1. Frequency of detection of non-organ-specific autoantibodies in patients with CHC depending on the presence and degree of mixed cryoglobulinemia manifestation, n (%)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Patients with CHC (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I group (n = 51)</td>
</tr>
<tr>
<td>RF-IgM</td>
<td>38 (70.6)</td>
</tr>
<tr>
<td>RF-IgG</td>
<td>39 (78.6)</td>
</tr>
<tr>
<td>Cardiolipin IgM</td>
<td>19 (37.3)</td>
</tr>
<tr>
<td>Cardiolipin IgG</td>
<td>23 (44.1)</td>
</tr>
<tr>
<td>ANA</td>
<td>5 (9.8)</td>
</tr>
</tbody>
</table>

*: difference is true in comparison with the patients of the I group (P < 0.001); **: in comparison with the patients of the II group (P < 0.05); ***: in comparison with the patients of the III group (P < 0.04).

Table 2. Quantitative content of non-organ-specific autoantibodies and CIC in the blood serum in patients with CHC according to presence and manifestations of mixed cryoglobulinemia, Me (Q25–Q75)

<table>
<thead>
<tr>
<th>Data, units</th>
<th>Patients with CHC (n = 214)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy people (n = 30)</td>
</tr>
<tr>
<td>RF-IgM, IU/ml</td>
<td>&lt;20 121.7 (18.1–167.5)</td>
</tr>
<tr>
<td>RF-IgG, IU/ml</td>
<td>&lt;20 127.5 (50.0–168.0)</td>
</tr>
<tr>
<td>Cardiolipin IgM, MPL</td>
<td>&lt;15 12.8 (7.4–17.1)</td>
</tr>
<tr>
<td>Cardiolipin IgG, MPL</td>
<td>&lt;10 9.1 (7.2–15.9)</td>
</tr>
<tr>
<td>CIC, mAU/ml</td>
<td>184.8 (156.8–197.3)</td>
</tr>
</tbody>
</table>

*: the difference is true in comparison with the patients of the I group (P < 0.01); **: with the patients of the II group (P < 0.04); ***: with the patients of the III group (P < 0.009).

* in comparison with the control group.

with CHC depending on presence and degree of the mixed cryoglobulinemia signs it was found that the frequency of RF-IgG manifestation was lower in patients of the I group in comparison with patients of the II group (χ² = 7.82, P = 0.005), the III group (χ² = 17.80, P = 0.00001), and patients with clinical signs of hemorrhagic cryoglobulinemia vasculitis (χ² = 7.80, P = 0.005). Under condition of presence of clinical signs of mixed cryoglobulinemia the frequency of RF-IgG detection was 100%. RF-IgM detection frequency in patients of III and IV groups exceeded the similar index not only in patients of the I group, but also in patients of the II group (P < 0.02) (Table 1).

Analysis of cardiolipin detection frequency showed that the patients of the IV group have the highest frequency of emergence of these autoantibodies. These patients had clinical signs of hemorrhagic cryoglobulinemia vasculitis with forming of Meltzer’s triad. Frequency of IgG cardiolipin elevation in patients of the IV group appeared much higher comparing to the analogous index of the I group patients (χ² = 10.20, P = 0.0014), the II group (χ² = 6.77, P = 0.009) and the III group (χ² = 4.26, P = 0.04). Frequency of detection of the elevated level of IgM cardiolipin was higher in comparison with the patients of the I group (χ² = 10.30, P = 0.0013), and the II group as well (χ² = 5.90, P = 0.015) (Table 1).

ANA were found in blood serum composition in patients of all groups, however the frequency of its detection didn’t depend on presence and degree of mixed cryoglobulinemia manifestation (Table 1).

Comparison of proportion of RF in patients with CHC of the groups showed that the emerging of clinical manifestations of mixed cryoglobulinemia is followed by the highest level both RF-IgM and RF-IgG. The quantitative content of RF-IgM and RF-IgG in patients of the III and IV groups was higher in comparison with patients of the I and II groups. Clinical signs progressing of HCV-associated cryoglobulinemic syndrome was followed by augmenting of quantitative content of RF in the blood serum. Patients of the IV group, who had manifestations of hemorrhagic cryoglobulinemia vasculitis with forming of Meltzer’s triad, had the quantitative content of RF-IgM and RF-IgG in blood serum composition higher than the analogous indexes of the patients of the III group. The later had only some clinical signs of cryoglobulinemic syndrome (Table 2).

Comparative analysis of the quantitative content of cardiolipin in the blood serum of the patients showed that the content of IgM and IgG cardiolipin was higher in patients with mixed cryoglobulinemia than in patients without any biochemical signs this extrahepatic manifestations. In case of manifestations of HCV-associated hemorrhagic cryoglobulinemia vasculitis with forming of Meltzer’s triad the content of IgM and IgG cardiolipin was higher than the indexes in patients of the II group (Table 2).

Increase of the detection frequency of non-organ-specific autoantibodies and rising of their quantitative content in patients with CHC in case of emerging and progressing of clinical and biochemical signs of mixed cryoglobulinemia were combined with the enlargement of quantitative content of CIC in the blood serum. The amount of CIC in the blood serum of patients of the I group was higher that the CIC amount in healthy people. The CIC amount of the II group exceeded the analogous index of both healthy people and patients of the I group. The highest level of CIC in blood serum was found in patients with clinical manifestations of cryoglobulinemic syndrome. And this index was in patients of the III and IV groups higher than in patients of the I and II groups and healthy people (Table 2).

Role of autoimmune disruptions in the development and progressing of mixed cryoglobulinemia in patients with CHC is confirmed by the direct correlative connections (P < 0.01) between the amount of mixed cryoglobulines and quantitative amount of RF-IgM (+0.46) and RF-IgG (+0.48), cardiolipin IgM (+0.54) and IgG (+0.48), CIC (+0.68) in blood serum. Role of non-organ-specific autoantibodies

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in the development of immunocomplex mechanism of mixed cryoglobulinemia formation is confirmed by the direct correlative connections (P < 0.05) between quantitative content of CIC and the rheumatoid factor IgM (r = + 0.36), IgM cardiolipin (r = +0.38) and IgG (r = +0.45).

Considerable heterogeneity of the HCV structure plays a role in a factor that rises the chance of development of mechanisms of molecular mimicry between the antigenic structures of the virus of host cells. The extension of the non-organ-autoantibodies spectrum in case of mixed cryoglobulinemia gives a reason to state that the autoimmune mechanisms play a significant role in the emergence of its clinical manifestations[9,10]. According to the researches results [11–13] different markers of autoimmune disorders can be found in patients with CHC, among them are mixed cryoglobulins (40–74 %), RF (45–98 %), hypocoomplementemia (30 %), antibodies to cardiolipin (20–44 %), antibodies to Ro (SS-A) / La (SS-B) antigen, ANA (10–52 %) and others, but their clinical value, except for cryoglobulines, is still poorly studied. It is possible that HCV with its feature to replication in the cells of the immune system determines its chronic stimulation. And this creates conditions to poly- and monoclonal B-cells proliferation, production of poly- and monoclonal IgM-RF, that is the basis of the mixed cryoglobulines. CHC is characterized by the unique immunologic phenomenon: there is no other infection with such high frequency of RF and its peculiarities [14,15].

The received research results concerning the frequency of autoimmune disorders and spectrum of antibodies depending on presence and degree of the mixed cryoglobulinemia manifestation says about the long period of autoimmune disruptions without any signs. These manifestations grow worse over time and lead to further emerging of clinical signs of the cryoglobulinemic syndrome.

Conclusions

1. The frequency of detection non-organ-specific RF-IgM and RF-IgG autantibodies, IgM cardiolipin and IgG cardiolipin in patients with CHC increase in case of emergence and progressing of the mixed cryoglobulinemia. 2. RF-IgM and RF-IgG quantitative content in the blood serum is the highest in patients with CHC with presence of clinical manifestations of the cryoglobulinemic syndrome in comparison with the patients who have no clinical and biochemical manifestations or have only biochemical signs of the mixed cryoglobulinemia. However, the quantitative content of IgM cardiolipin and IgG cardiolipin is the highest on condition of manifestation of hemorrhagic cryoglobulinemia vasculitis with forming of Meltzer’s triad.

3. Increase of detection frequency of non-organ-specific autoantibodies and rise of its quantitative content in patients with CHC in case of emergence and progressing of clinical and biochemical signs of the mixed cryoglobulinemia unites with the rise of the amount of CIC in the blood serum that is correlated with RF-IgM and RF-IgG, IgM and IgG cardiolipins.

The prospect of further research in this direction, in our opinion, is the development of a differentiated approach to the pathogenetic treatment of patients with HCC, taking into account the varying degrees of severity of signs of mixed cryoglobulinemia and, accordingly, different levels of severity of autoimmune disorders.

References


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