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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.

Ключові слова: змішана кріоглобулінемія, хронічний гепатит С.

Запорізький медичний журнал. – 2018. – Т. 20, № 2(107). – С. 188–192

Клініко-патогенетичне значення імунних порушень у маніфестації змішаної кріоглобулінемії у хворих на хронічний гепатит С

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Мета роботи – з'ясувати роль імунних порушень у розвитку клінічних проявів змішаної кріоглобулінемії у хворих на хронічний гепатит С.

Матеріали та методи. У дослідження залучили 214 хворих на хронічний гепатит С. Проаналізували частоту виявлення та кількісний вміст органонеспецифічних автоантитіл і циркулюючих імунних комплексів у взаємозв'язку з наявністю та ступенем виразності змішаної кріоглобулінемії.

Результати. Виявили розширення спектра автоантитіл, збільшення їхнього кількісного вмісту та вмісту циркулюючих імунних комплексів у хворих на хронічний гепатит С при появі та прогресуванні ознак змішаної кріоглобулінемії. За наявності клінічних проявів геморагічного кріоглобулінемічного васкуліту з формуванням тріади Мельтцера частота виявлення кардіоліпіну IgG становила 82,1 % , а RF-IgM – 100 % і перевищувала цей показник у пацієнтів інших груп ($p < 0,01$). Кількісний вміст RF-IgM і RF-IgG у сироватці крові був найвищим ($p < 0,01$) у хворих на хронічний гепатит С із наявністю клінічних проявів змішаної кріоглобулінемії порівняно з пацієнтами, які не мають клініко-біохімічних проявів або мають тільки біохімічні ознаки змішаної кріоглобулінемії. Рівень кардіоліпіну IgM й IgG був найвищим за умов появи геморагічного кріоглобулінемічного васкуліту ($p < 0,01$). Прогресування ознак змішаної кріоглобулінемії поєднувалось із наростанням ($p < 0,01$) вмісту циркулюючих імунних комплексів, що корелювало з RF-IgM ($r = +0,36$, $p < 0,05$), кардіоліпіном IgM ($r = +0,38$, $p < 0,05$) й кардіоліпіном IgG ($r = +0,45$, $p < 0,05$).

Висновки. У хворих на хронічний гепатит С частота виявлення RF-IgM і RF-IgG, кардіоліпіну IgM й IgG та їхній кількісний вміст збільшується за умов появи та прогресування клінічних ознак змішаної кріоглобулінемії. Збільшення частоти виявлення органонеспецифічних автоантитіл і підвищення їхнього кількісного вмісту у хворих на хронічний гепатит С при появі та прогресуванні клініко-біохімічних ознак змішаної кріоглобулінемії поєднується з наростанням вмісту ЦІК у сироватці крові, що корелює з RF-IgM та RF-IgG, кардіоліпіном IgM й IgG.

Ключевые слова: смешанная криоглобулинемия, хронический гепатит С.

Клинико-патогенетическое значение иммунных нарушений в манифестации смешанной криоглобулинемии у пациентов с хроническим гепатитом С

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Цель работы – выяснить роль иммунных нарушений в развитии клинических проявлений смешанной криоглобулинемии у больных хроническим гепатитом С.

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Материалы и методы. В исследование включено 214 больных хроническим гепатитом С. Проведен анализ частоты выявления и количественного содержания органонеспецифичных аутоантител и циркулирующих иммунных комплексов во взаимосвязи с наличием и степенью выраженности смешанной криоглобулинемии.

Результаты. Отмечено расширение спектра аутоантител, увеличение их количественного содержания и содержания циркулирующих иммунных комплексов у больных хроническим гепатитом С при появлении и прогрессировании признаков смешанной криоглобулинемии. При наличии клинических проявлений геморрагического криоглобулинемического васкулита с формированием триады Мельтцера частота выявления кардиолипина IgG составляла 82,1 %, а RF-IgM – 100 % и превышала этот показатель у пациентов других групп ($p < 0,01$). Количественное содержание RF-IgM и RF-IgG в сыворотке крови было высоким ($p < 0,01$) у больных хроническим гепатитом С с наличием клинических проявлений смешанной криоглобулинемии по сравнению с пациентами, которые не имеют клинико-биохимических проявлений или имеют лишь биохимические признаки смешанной криоглобулинемии . Уровень кардиолипина IgM и IgG был самым высоким в условиях появления геморрагического криоглобулинемического васкулита ($p < 0,01$). Прогрессирование признаков смешанной криоглобулинемии сочеталось с нарастанием ($p < 0,01$) содержания циркулирующих иммунных комплексов, коррелировало с RF-IgM ($r = +0,36$, $p < 0,05$), кардиолипином IgM ($r = +0,38$, $p < 0,05$) и кардиолипиновыми IgG ($r = +0,45$, $p < 0,05$).

Выводы. У больных хроническим гепатитом С частота выявления RF-IgM и RF-IgG, кардиолипина IgM и IgG и их количественное содержание увеличивается в условиях появления и прогрессирования клинических признаков смешанной криоглобулинемии. Увеличение частоты выявления органонеспецифичных аутоантител и повышение их количественного содержания у больных хроническим гепатитом С при появлении и прогрессировании клинико-биохимических признаков смешанной криоглобулинемии сочетается с нарастанием содержания ЦИК в сыворотке крови, что коррелирует с RF-IgM и RF-IgG, кардиолипиновыми IgM и IgG.

Especial part in the development of extrahepatic disease manifestations, that increase mortality risks, is assigned to chronic hepatitis C (CHC) [1–3]. The main extrahepatic manifestation is mixed cryoglobulinemia (MC) that can be the first clinical onset of the disease or can progress several years after the pathogen is detected [3,4].

Immune responses play the leading role in the development of extrahepatic manifestations. Such reflects emerge in response to HCV replication not only in a liver but also beyond. The lymphotropicity of this mainly B-cell virus makes conditions for development of extrahepatic manifestations of CHC [5,6]. Interaction of HCV surface antigens with the CD81 specific receptors on the B-cell membrane leads to reduce in their activation threshold and suppression of apoptosis. B-cells proliferation is accompanied by the increased production of autoantibodies, the formation of circulating immune complexes (CIC) and mixed cryoglobulins. This creates the substrate of pathological immune responses that are a ground for extrahepatic manifestations. According to the contemporary resources there is no organ or a system that can not be involved to the pathological process in case of HCV-associated mixed cryoglobulinemia [7,8]. Despite significant amount of researches that are related to the CHC issues the role of autoimmune disorders in extrahepatic manifestations formation have not been yet fully investigated.

Objective

Discover the role of immune disorders in clinical manifestations formation of mixed cryoglobulinemia in patients with CHC.

Material and research methods

214 patients with CHC of the hepatological centre of Zaporizhzhia Region Infectious Clinical Hospital were recruited into the study. Age of the patients was from 18 to 60 (Me 38(Q_{31}–Q_{51}) years. There were 122 male and 92 female among them. All patients were involved to the research randomly and by their informed consent.

Special investigation methods included determining of blood serum composition: mixed cryoglobulins through a spectrophotometric method; antinuclear antibodies (ANA) (MICROWELL ELISA, USA); rheumatoid factor (RF) IgM and IgG (ORGENTEC, Germany); cardiolipin IgM and IgG (MICROWELL ELISA, USA); CIC (Hycult biotech, USA); immunoferment method. 30 healthy people composed a control group. All special analysis were conducted in Educational medical and laboratory centre of ZSMU (Head of the department – Professor A. V. Abramov).

According to the presence and manifestation degree of mixed cryoglobulinemia in patients with CHC the patients were divided into the following groups: I group – 51 patients that had no clinical and biological marks of mixed cryoglobulinemia; II group – 67 patients who had only biochemical marks of mixed cryoglobulinemia without any clinical manifestations; III group – 68 patients with the biochemical marks of cryoglobulinemia and several manifestations of cryoglobulinemic syndrome (evident general weakness, arthralgia); IV group – 28 patients with biochemical marks of mixed cryoglobulinemia and manifestations of hemorrhagic cryoglobulinemia vasculitis.

Statistical data processing of the achieved results was performed with the help of the formed database of the examined patients and healthy people in the program «STATISTICA® for Windows 6.0» (StatSoft Inc., № AXXR712D833214FAN5). All special research results were presented as Me (Q_{25}–Q_{75}), where Me is median, Q_{25} – lower quartile, Q_{75} – upper quartile. Mann–Whitney's criterion was used to assess the validity of the difference in quantitative characteristics between two independent samples. The Chi-square method (χ^2) was used to assess the reliability of the difference between qualitative characteristics between two non-dependent samples. To assess the relationship between the features, the Spirman rank correlation method was used to calculate the correlation coefficient (r).

Research results and discussion

According to the comparison results of frequency of positive RF manifestation in blood serum composition in patients

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 (%)

Factor	Patients with CHC (n = 214)			
	I group (n = 51)	II group (n = 67)	III group (n = 68)	IV group (n = 28)
RF-IgM	36 (70.6)	56 (83.6)	66 (97.1) * **	28 (100.0) * **
RF-IgG	39 (76.5)	63 (94.0) *	68 (100.0) * **	28 (100.0) *
Cardiolipin IgM	19 (37.3)	32 (47.8)	37 (54.4)	21 (75.0) * **
Cardiolipin IgG	23 (44.1)	36 (53.7)	41 (60.3)	23 (82.1) * ** ***
ANA	5 (9.8)	8 (11.9)	15 (22.1)	8 (28.6)

*: 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 manifistations of mixed cryoglobulinemia, Me (Q_{25}–Q_{75})

Data, units	Patients with CHC (n = 214)				
	Healthy people (n = 30)	I group (n = 51)	II group (n = 67)	III group (n = 68)	IV group (n = 28)
RF-IgM, IU/ml	<20	121.7 (18.1–167.9)	134.8 (69.8–175.2)	180.8 (131.1–229.7) * **	263.1 (216.6–285.1) * ** ***
RF-IgG, IU/ml	<20	127.5 (50.0–168.0)	132.7 (76.9–187.3)	199.9 (142.8–242.1) * **	247.6 (187.9–305.3) * ** ***
Cardiolipin IgM, MPL	<15	12.8 (7.4–17.1)	15.7 (11.6–22.4) *	18.4 (11.3–32.3) *	22.7 (16.3–29.5) * **
Cardiolipin IgG, MPL	<10	9.1 (7.2–18.9)	17.4 (7.8–27.4) *	18.4 (8.2–36.4) *	24.6 (12.8–29.5) * **
CIC, mAU/ml	184.8 (156.8–197.3)	218.6 (184.1–281.5) #	349.2 (258.3– 85.6) # *	592.1 (426.9–691.4)	637.9 (579.6–829.1) # * **

*: 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 (χ^2 = 7.62, P = 0.005), the III group (χ^2 = 17.80, P = 0.00001), and patients with clinical signs of hemorrhagic cryoglobulinemia vasculitis (χ^2 = 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 cardiolipnin 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 (χ^2 = 10.20, P = 0.0014), the II group (χ^2 = 6.77, P = 0.009) and the III group (χ^2 = 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 (χ^2 = 10.30, P = 0.0013), and the II group as well (χ^2 = 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 the IV groups was higher in comparison with patients of the I andII 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-IgGin 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 cariolipin 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

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 of 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 cryoglobulines (40–74 %), RF (45–98 %), hypocomplementemia (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 autiantibodies, 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.

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