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## CHRONIC HEPATITIS C WITH CRYOGLOBULINEMIA: FEATURES AND MANIFESTATIONS

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### ABSTRACT

Demographic, clinical, laboratory, epidemiological aspects of cryoglobulinemia in chronic HCV infection in patients of the Crimean population remain insufficiently studied.

To study the incidence of cryoglobulinemia in chronic HCV infection and analyze the features of chronic HCV infection with the presence of cryoglobulinemia in the study population of patients.

**Materials and methods.** A study was conducted on 65 patients with chronic HCV infection (with chronic hepatitis C and liver cirrhosis). All patients underwent blood testing for the presence of cryoglobulins. Standard diagnostic tests included a biochemical blood test with determination of the levels of total bilirubin, ALT, AST, alkaline phosphatase, rheumatoid factor. The stage of liver fibrosis was determined using ultrasound elastography. The diagnosis of liver cirrhosis was established based on the results of a comprehensive clinical, laboratory and instrumental study; scores were calculated on the Model for End-stage Liver Disease scale and the Child-Pugh scale.

**Results and its discussion.** Among 65 patients with chronic HCV infection, 37 % ( $n = 24$ ) had a positive test for the presence of cryoglobulins in the blood. Groups with and without cryoglobulins were comparable in gender ( $p > 0.05$ ), BMI ( $p > 0.05$ ) and duration of infection ( $p > 0.05$ ). In the group with cryoglobulinemia, patients with the syndromes of hepatomegaly ( $p < 0.001$ ), splenomegaly ( $p < 0.05$ ), ascites ( $p < 0.05$ ), and there were also lower platelet counts ( $p < 0.001$ ) and higher rates of AST ( $p < 0.01$ ),  $\gamma$ -glutamyl transpeptidase ( $p < 0.01$ ), bilirubin ( $p < 0.05$ ), ESR ( $p < 0.01$ ) and rheumatoid factor ( $p < 0.001$ ), which indicates the severity of the disease. A higher incidence of patients with already developed cirrhosis was found in the group of HCV infection with the presence of cryoglobulinemia ( $p < 0.001$ ).

**Conclusions.** The study revealed a high incidence of cryoglobulinemia (37 %) in the study population of patients and showed that chronic HCV infection with the presence of cryoglobulinemia is characterized by polymorphism and severity of clinical manifestations.

**KEYWORDS:** chronic hepatitis C, cryoglobulinemia, extrahepatic diseases

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## INTRODUCTION

Chronic infection caused by the hepatitis C virus (HCV infection) is widespread in the world, which, along with the progressive course of the disease and the variety of immune reactions, including mixed cryoglobulinemia, makes it one of the most important not only in hepatology, but also in internal medicine in general [Asrani SK et al., 2018; Roubertou Y., 2022; Rajendran N, 2023].

Historically HCV infection accounted for the majority of mixed cryoglobulinemia [Miaillhes P., 2018; Boleto G, 2020].

It has been established that HCV can exhibit hepatotropic and lymphotropic properties with the predominant involvement of B-lymphocytes [Kopp-Sarda M et al., 2020]. The resulting effect of the interaction of virus antigens with specific receptors on the surface of B-lymphocytes is poly-, oligo- or monoclonal proliferation of B-lymphocytes with the formation of immune complexes, including mixed cryoglobulins [Codes-Méndez H., 2024, Vermeersch P, 2008], which creates a substrate for immunopathological reactions [Ignatova T et al., 2017]. In some (8–10 %) patients, a prolonged period of B-lymphocyte activation with the accumulation of genetic mutations leads to the transformation of B-lymphocytic proliferation into malignant B-cell lymphoma [Zhu X. et al., 2019].

There is evidence of numerous extrahepatic manifestations and syndromes that are associated with HCV and cryoglobulinemia and involve one or more organs and systems [Aydeniz A. et al., 2010; Karadag O, 2021; Kondili LA., 2022].

It should be noted that despite the great interest in the problem of cryoglobulinemia in chronic HCV infection, some of its aspects, including demographic, clinical, laboratory, epidemiological, in patients of the Crimean population remain insufficiently studied. Thus, the frequency of occurrence of CHE in chronic HCV infection and the spectrum of extrahepatic diseases (EHDs) and syndromes are unclear.

Objective: to study the incidence of cryoglobulinemia in chronic HCV infection and analyze the features of chronic HCV infection with the presence of cryoglobulinemia in the study population of patients.

## MATERIALS AND METHODS.

A study was conducted in a sample of 65 patients with chronic HCV infection.

The study included individuals who sought medical help of both sexes, aged 20 to 80 years, with chronic hepatitis C and liver cirrhosis, and whose blood contained antibodies to HCV (anti-HCV) and HCV RNA. All patients underwent blood testing for the presence of cryoglobulins.

Criteria for non-inclusion in the study:

- viral hepatitis B
- autoimmune hepatitis
- concomitant HIV infection
- history of liver and kidney transplantation
- receiving antiviral treatment
- refusal to test for the presence of cryoglobulins.

All patients included in the study completed the full range of planned procedures. Demographic and epidemiological data were collected, including information on age, gender, estimated duration of the infectious process (more than 20 years or less than 20 years), and methods of infection. The duration of HCV infection was assessed only in individuals with an established epidemiological history, calculated from the date of blood transfusion or from the date of initial exposure to other potential parenteral sources.

Standard diagnostics tests included a biochemical blood test with determination of the levels of total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, rheumatoid factor, as well as a general blood and urine test. All patients underwent blood tests for cryoglobulins, chest radiography and ultrasound of the abdominal organs and kidneys.

The stage of liver fibrosis was determined using ultrasound elastography. The diagnosis of liver cirrhosis was established based on the results of a comprehensive clinical, laboratory and instrumental study, scores were calculated on the Model for End-stage Liver Disease scale and the Child-Pugh scale.

The presence of pathologies classified in the literature as extrahepatic [Milovanova S. et al., 2014] was determined by analysis of outpatient records. When extrahepatic manifestations were initially detected in patients, consultations and additional examinations were carried out with specialists in order to establish a final clinical diagnosis. These extrahepatic mani-

festations were classified according to ICD-10 and were subsequently referred to as extrahepatic diseases [Adinolfi LE.,2003].

Descriptive statistics in the study population for quantitative variables were presented by median (Me), for qualitative variables – frequency and percentage. Group comparisons on quantitative variables were performed using the Mann-Whitney test. The results of the analysis were considered statistically significant at  $p < 0.05$ . Calculations were carried out in the statistical package R (version 3.6).

### RESULTS AND ITS DISCUSSION.

Among 65 patients with chronic HCV infection, 37 % ( $n = 24$ ) had a positive test for the presence of cryoglobulins in the blood, 63 % ( $n = 41$ ) had a negative test.

Groups with and without cryoglobulins were comparable in gender ( $p > 0.05$ ), BMI ( $p > 0.05$ ) and duration of infection ( $p > 0.05$ ). In the group with cryoglobulinemia, patients over 60 years of age were more common. The data is presented in Table 1.

The risk factors for infection presented in Table 2 showed that in the group with the presence of cryoglobulinemia, patients with a history of previous surgical interventions were identified statistically significantly more often ( $p < 0.001$ ).

When systematizing clinical data in the group of HCV infection with the presence of cryoglobulinemia in comparison with the group without cryoglobulinemia, a higher incidence of patients with already developed cirrhosis was found ( $p < 0.001$ ). This relationship may indirectly indicate an existing relationship between the presence of cryoglobulins in a pa-

TABLE 1

Demographic data and duration of infection of patients with chronic HCV infection ( $n = 65$ )

Indicators	Cryoglobulin detected		P
	No ( $n = 41$ )	Yes ( $n = 24$ )	
Age, years	55	58	0.021
Gender, n (%):			
women	24 (58.5 %)	13 (54 %)	0.105
men	17 (41.5 %)	11 (46 %)	
BMI, ( $kg/m^2$ )	27.7	27.9	0.913
Disease duration $\geq 20$ years*, n (%)	18/26 (69 %)	13/18 (72 %)	0.479

NOTES: \* - in patients with established epidemiological history

TABLE 2

Possible risk factors for infection of patients with HCV infection according to the survey ( $n = 65$ )

Risk factors for infection	Cryoglobulin detected				P
	No (n = 41)		Yes (n = 24)		
	n	%	n	%	
Parenteral administration of psychotropic substances	1	2.4	1	4.1	0.556
Surgical interventions	22	53.6	15	62.5	<0.001
Blood transfusions	8	19.5	4	16.6	0.361
Dialysis	1	2.4	0	0	
Tattoos, piercings	4	9.7	0	0	
Visiting the dentist	3	7.3	2	8.3	0.981
Medical activities associated with the risk of occupational infection	3	7.3	1	4.1	0.977

TABLE 3

Clinical and laboratory data of patients with chronic HCV infection ( $N = 65$ )

Clinical and laboratory data	Cryoglobulin detected		P
	No ( $n = 41$ )	Yes ( $n = 24$ )	
Clinical diagnosis, n (%):			
- chronic hepatitis C	31 (74.6)	13 (54.2)	<0.001
- liver cirrhosis	10 (24.4)	11 (45.8)	
Hepatomegaly, n (%)	8 (19.5)	12 (50)	<0.001
Splenomegaly, n (%)	15 (36.6)	11 (45.8)	<0.05
Ascites, n (%)	7 (16.7)	5 (23.8)	<0.05
Platelets, ( $\times 10^9/l$ ),	160	132	<0.001
Leukocytes, ( $\times 10^9/l$ )	5.3	5.4	<0.05
ESR, (mm/h), Me	11	13	<0.01
Bilirubin, ( $\mu mol/l$ ),	15.5	19.6	<0.05
Alanine aminotransferase, (U/l)	63.1	74.8	<0.05
Aspartate aminotransferase, (U/l)	55.6	78.0	<0.001
Alkaline phosphatase, (U/l)	99	109	<0.05
Gamma-glutamyl transferase, (U/l)	44	56.3	<0.01
Rheumatoid factor, (IU/ml)	31.3	68.2	<0.001



tient and liver cirrhosis.

In addition, in the group with cholinesterase, patients with the syndromes of hepatomegaly ( $p < 0.001$ ), splenomegaly ( $<0.05$ ), ascites ( $p < 0.05$ ), and there were also lower platelet counts ( $p < 0.001$ ) and higher rates of AST ( $p < 0.01$ ), GGTP ( $p < 0.01$ ), bilirubin ( $p < 0.05$ ), ESR ( $<0.01$ ) and rheumatoid factor ( $p < 0.001$ ), which indicates the severity of the disease. The data is presented in Table 3.

An analysis of patient complaints upon admission to hospital or during outpatient consultations made it possible to combine them into three main syndromes (Table 4). More than 50 % of patients had complaints that were characteristic of asthenovegetative and dyspeptic syndromes, less than 50 % had manifestations characteristic of arthralgic syndrome. When studying the frequency of occurrence of syndromes in the study groups, it was found that in chronic HCV infection with the presence of cryoglobulinemia, each of them occurred statistically significantly more often ( $p < 0.001$ ).

Along with the detected changes in clinical and laboratory parameters that characterize the involvement of the liver in the pathological process, in patients with HCV infection, attention is drawn to the presence of various immunopathological diseases, classified in the literature as extrahepatic manifestations of viral hepatitis C [Milovanova S.Yu., et al., 2014; Bonacci M., 2017]. An overview of the data is presented in Table 5.

Analysis of extrahepatic diseases showed that during HCV infection, diseases of the following groups were identified with varying frequencies: 1) diseases of the musculoskeletal system and connective

TABLE 4

Frequency of occurrence of the main clinical syndromes in patients with HCV infection (n = 65)

Clinical syndromes	Cryoglobulin detected				P
	No		Yes		
	(n = 41)		(n = 24)		
	n	%	n	%	
Asthenovegetative syndrome	30	73.2	19	79.2	<0.001
Arthralgic syndrome	11	26.8	10	41.7	<0.001
Dyspeptic syndrome	23	56.1	17	70.8	<0.001

TABLE 5

Incidence of extrahepatic diseases in patients with chronic HCV infection (n = 65)

Extrahepatic diseases and syndromes	Frequency of occurrence	
	n	%
Diseases of the musculoskeletal system and connective tissue, as well as certain disorders involving the immune mechanism		
Cryoglobulinemic vasculitis (D89.1)	13	20.0
Rheumatoid arthritis (M05, M06)	6	9.2
Ankylosing spondylitis (M45)	3	4.6
Systemic lupus erythematosus (M32)	1	1.5
Antiphospholipid syndrome (D68.6)	3	4.6
Dermatomyositis (M33.1)	1	1.5
Endocrine system diseases:autoimmune thyroiditis (E06.3)	11	16.9
Diseases of the skin and subcutaneous tissue, cutaneous sarcoidosis		
Psoriasis (L40)	6	9.2
Vitiligo (L80)	2	3.1
Vasculitis (L95)	4	6.1
Scleroderma (L94)	1	1.5
Erythema nodosum (L52)	2	3.1
Livedo mesh (L95)	3	4.6
Purple (D 69)	3	4.6
Lichen planus (L43)	2	3.1

TABLE 6

Frequency and the incidence of extrahepatic diseases in chronic HCV infection (n = 65)

Clinical syndromes	Cryoglobulin detected				P
	No		Yes		
	(n = 41)		(n = 24)		
	n	%	n	%	
No extrahepatic diseases	34	82.9	2	8.3	<0.001
Diseases of the musculoskeletal system and connective tissue, as well as certain disorders involving the immune mechanism	5	12.2	21	87.5	<0.001
Endocrine system diseases: autoimmune thyroiditis	3	7.3	8	33.3	<0.001
Diseases of the skin and subcutaneous tissue, cutaneous sarcoidosis	3	7.3	20	83.3	<0.001

tissue, as well as certain disorders involving the immune mechanism; 2) diseases of the endocrine system (autoimmune thyroiditis); 3) diseases of the skin and subcutaneous tissue and cutaneous sarcoidosis. This aspect characterized the systematic manifestation of the disease.

In the course of the comparative analysis presented in Table 6, it was revealed that in case of HCV infection with the presence of cryoglobulinemia, the proportion of patients with extrahepatic diseases of the first, second and third groups was statistically significantly higher than in the absence of cryoglobulinemia ( $p < 0.05$ ).

In development extrahepatic diseases in case of HCV infection, immune reactions that occur in response to virus replication in the liver and in tissues of lymphoid and non-lymphoid origin are of primary importance [Rose K, 2024]. Along with immune disorders, the presence of a direct cytopathic effect of HCV is important for the occurrence of systemic damage; in this case, EDs often serve as the only manifestation of the infectious process and can determine the prognosis and treatment tactics [Baykova T. et al., 2013].

The pathogenesis of chronic HCV infection is characterized by the development of extrahepatic manifestations of predominantly immunocomplex origin, including disruption of the intestinal microbiota, as described in hepatic steatosis [Maksimova E.V., et al., 2022], often caused by the formation of CHE. The frequency of detection of CH in individuals with chronic viral hepatitis C in different populations varies from 19 % to 66 % [Baykova T. et al., 2013; Galossi A. et al., 2007]. The incidence

of extrahepatic diseases in mixed cryoglobulinemia ranges from 40 % to 74 % [Ignatova T.M., et al., 2017]. Differences in methodological features of studies and geographical differences in samples are discussed as the main reasons for this heterogeneity. Regarding the first factor, since the methods for detecting cryoglobulinemia are the same in almost all studies, it seems unlikely that methodological features could significantly affect the results obtained by the authors. Geographical differences are important and require additional targeted study in each specific country. Taking this fact into account, we carried out a statistical analysis of the incidence of cryoglobulinemia and extrahepatic diseases in chronic HCV infection in the Republic of Crimea.

One clinical study found that the main variables associated with the presence of extrahepatic diseases or cholinesterase in patients with HCV infection were female sex, older age, and advanced fibrosis [Galossi A. et al., 2007]. Studies by other authors have identified an association between CHE and female gender, low viral load and low platelet levels, duration of HCV infection, higher stage of fibrosis and liver cirrhosis [Batsaikhan B. et al., 2018].

## CONCLUSIONS

The study revealed a high incidence of cryoglobulinemia (37 %) in the study population of patients and showed that chronic HCV infection with the presence of cryoglobulinemia is characterized by polymorphism and severity of clinical manifestations. The results obtained are consistent with the literature data.

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