

Analysis of the results of the study on the determination of cytokines in patients with chronic hepatitis c depending on the presence of crioglobulinemia

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Abstract. 40 patients with CHC with extrahepatic manifestations were involved in the conducted studies to determine the cytokines IL-10 and IL-18 in patients with CHC, depending on the presence of cryoglobulinemia. The results of the study showed that in patients with chronic hepatitis C with extrahepatic manifestations, the anti-inflammatory cytokine IL-10 was reduced by 2.37 times in patients, and there was a significant increase in the content of pro-inflammatory cytokine IL-18 in the blood serum by 2.71 times in relation to normal values.

1 Introduction

Among chronic liver diseases, viral hepatitis is in the first place, accounting for 40-60% of the total number of patients with chronic hepatitis. Currently, there are more than 175 million people infected with the hepatitis C virus in the world. The significance of this pathology is due to a high incidence rate, an increase in the number of virus carriers, a change in the age structure of infected people with a predominance of young people, and an increase in the percentage of extrahepatic manifestations [1].

It was found that the pathogenesis of extrahepatic manifestations in chronic hepatitis C (CHC) is based on various mechanisms: the possibility of hepatitis C virus replication in the extrahepatic region, the manifestation of immunocompetent cells - the connection of HCV infection with B-lymphocyte occurs using CD81; heterogeneity of genotypes and frequent mutations of the virus genome due to prolonged presence of the virus in the body; induction of a cascade of immunopathological reactions that lead to the induction of lipid peroxidation processes in the hepatic parenchyma [2,15].

However, chronic HCV infection is known to cause a number of systemic disorders, and these disorders are called extrahepatic manifestations of HCV and cover a wide range of conditions, from clinically insignificant presence of various autoantibodies to vasculitis, skin diseases, kidney damage, lymphoproliferative disorders, diabetes, neurological and neuropsychiatric changes, and other diseases. In 74% of patients with HCV infection, extrahepatic manifestations may occur, which may appear long before the manifestation of liver disease [4, 5, 6].

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Prolonged stimulation of B-lymphocytes with viral antigens is the cause of mixed cryoglobulinemia [7]. According to detectability data, cryoglobulinemia is observed in 42-96% of patients. [8, 9].

The main mediators of the inflammatory process are-cytokines, which are responsible for the formation of specific immunity and provide information about the natural elimination of the hepatitis C virus [10, 11, 14]. Manifestations of polymorphic cytokine genes, as well as their promoters, can lead to changes in the level of expression of the genes of inflammatory mediators themselves, to modification of the final product, and thereby affect the immune response [12]. The chronic process of infectious genesis develops with the production of polymorphic cytokine genes, long-term persistence of the virus, and resistance to antiviral therapy observed in chronic hepatitis C [13, 14].

Thus, questions concerning the role of the immune system in the progression of pathology, the development of extrahepatic manifestations, as well as questions regarding the effect of cryoglobulinemia on cytokine status remain open.

2 Purpose of the study

It consists of determining and evaluating the immunological parameters of patients with chronic hepatitis C with extrahepatic manifestations, depending on the presence of cryoglobulinemia.

3 Materials and methods

120 patients with chronic viral hepatitis were examined, including 52 patients with extrahepatic manifestations (the main group) and 68 patients with chronic viral hepatitis C without extrahepatic manifestations (the comparison group) under the age of 70 years, in addition, 25 healthy individuals were studied (the control group).

The diagnosis of CHC in patients was established on the basis of epidemiological history, clinical data, and laboratory and instrumental diagnostics.

Hematological parameters were studied using an automatic hematology analyzer BC-20S Mindray (China). Biochemical parameters of the blood test: total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, glucose (GLU), urea, creatinine were determined using an automatic biochemical analyzer MINDRAY VS-30 (China).

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For our scientific work, qualitative, quantitative analysis for hepatitis C virus (virus RNA) and genotyping of the virus by PCR diagnostics was determined using DTlite 4 (RF).

The concentration of pro-inflammatory IL-18 and anti-inflammatory IL-10 in blood serum was determined by solid-phase ELISA using test systems of JSC Vector-Best (Novosibirsk, Russia), in accordance with the manufacturer's recommendations.

4 Results and discussions

40 patients with CHC with extrahepatic manifestations were involved in the conducted studies to determine the cytokines IL-10 and IL-18 in patients with CHC, depending on the presence of cryoglobulinemia, who were divided into three groups representative by gender and age: (Fig. 1).

Group 1-examined adult patients with CHC with extrahepatic manifestations without cryoglobulinemia (n=20).

Group 2-examined adult patients with CHC with extrahepatic manifestations with cryoglobulinemia (n=20).

The control group consisted of practically healthy individuals with a history of unverified HCV (n=25).

The results obtained for determining the quantitative content of IL-10 showed that this cytokine in normal healthy individuals was 18.61 ± 1.02 pg / ml, which is 2.37 times statistically significantly more than in the examined patients - 7.86 ± 0.92 pg / ml ($P < 0.001$). A decrease in the concentration of this anti-inflammatory cytokine in the blood serum indicates a decrease in anti-infective (antiviral) protection in the examined patients.

Further studies were conducted on the effect of cryoglobulinemia on the detection of IL-10 in blood serum in adult patients with chronic hepatitis C with extrahepatic manifestations.

The results of studies show that in this category of patients with cryoglobulinemia, the concentration of IL-10 increases (up to 9.42 ± 0.99 pg / ml), compared to patients without cryoglobulinemia by 1.50 times (6.29 ± 0.84 pg / ml, $P < 0.05$) - Fig.1.

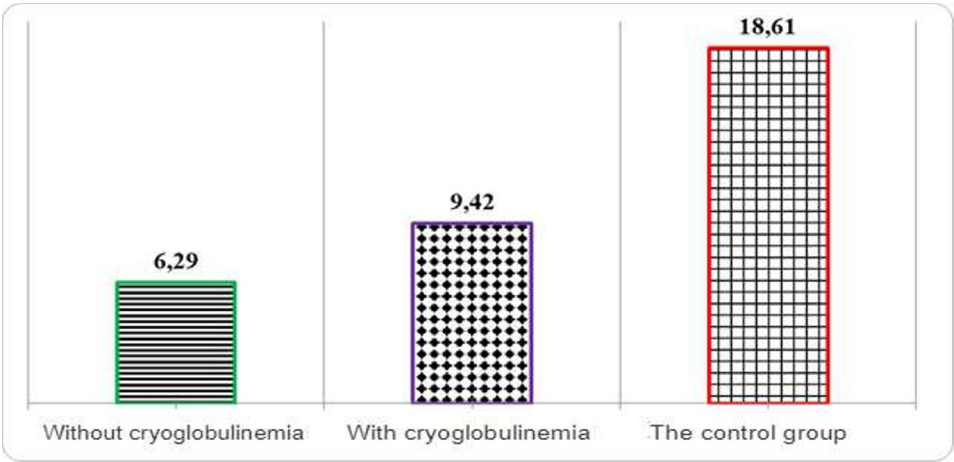


Fig. 1. Parameters of IL-10 detectability in serum in patients with CHC with extrahepatic manifestations in patients with and without cryoglobulinemia, pg/ml.

Both parameters obtained were 1.98 and 2.96 times lower ($P < 0.001$), respectively, than the level of this cytokine in the blood serum of healthy individuals (18.61 ± 1.02 pg / ml). The established fact indicates that the presence of cryoglobulinemia has a certain effect on the quantitative content of IL-10 in the blood serum of the examined patients, expressed in the form of a decrease in the increase in the content of this cytokine.

At the next stage of research, the proinflammatory cytokine IL-18 was determined in the same category of patients, depending on the presence of cryoglobulinemia in the body.

Studies have established that in healthy individuals (control group) IL-18 was 68.02 ± 2.30 pg / ml, and in patients with chronic hepatitis C with extrahepatic manifestations, the quantitative content of this cytokine in the blood serum was 184.57 ± 14.42 pg / ml, which is 2.71 times higher than the control values ($P < 0.001$). As can be seen, the decrease in IL-10 and increase in IL-18 in relation to the data of the control group in patients with chronic hepatitis C with extrahepatic manifestations are inversely proportional to each other, which indicates their functions in the body of the studied patients.

In addition, the content of IL-18 in the blood serum of patients with CHC with extrahepatic manifestations was studied depending on the presence of cryoglobulinemia, the results of which are shown in Figure 2.

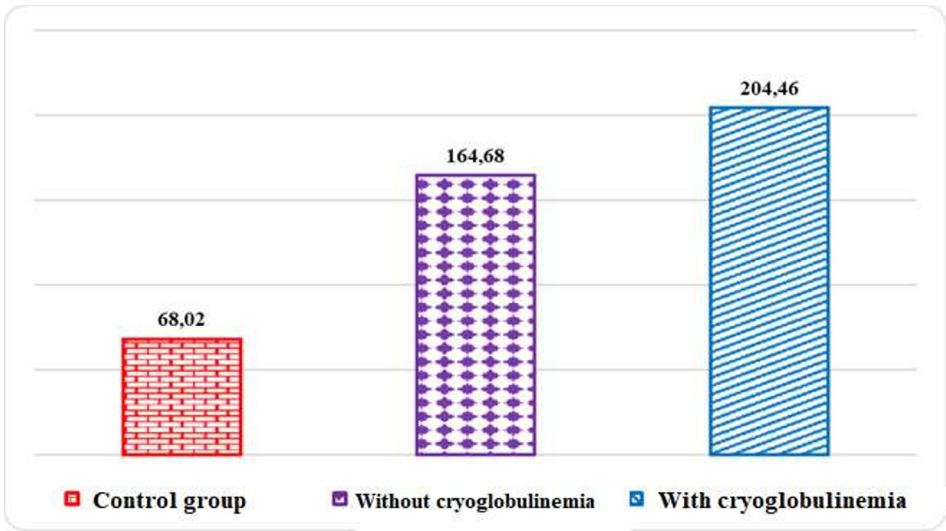


Fig. 2. Parameters of IL-18 detectability in the blood serum of patients with CHC with extrahepatic manifestations with and without cryoglobulinemia, pg/ml.

It was found that the presence of cryoglobulinemia is accompanied by an increased content of this cytokine compared to the results of patients without cryoglobulinemia. This is proved by the fact that cryoglobulinemia supports the inflammatory process in the body of patients with CHC with extrahepatic manifestations.

Comparative parameters of cytokine content in blood serum in patients with CHC with extrahepatic manifestations with and without cryoglobulinemia are shown in Table 1.

Table 1. Comparative indicators of cytokine status in patients with CHC with extrahepatic manifestations with and without cryoglobulinemia.

Cytokines	Control group	of CHC with extrahepatic manifestations	
		without cryoglobulinemia	with cryoglobulinemia
IL-10, pg/ml	18,61±1,02	6,29±0,84*	9,42±0,99* ^ ↑
IL-18, pg/ml	68,02±2,36	164,68±12,20*	204,46±16,64* ^ ↑

Note: * - reliability in relation to the control; ^ - reliability in relation to parameters without cryoglobulinemia; ↑ - direction of changes.

The results obtained show that the proinflammatory cytokine IL-18 tended to increase significantly in the blood serum relative to the control ($P<0.001$). In patients without cryoglobulinemia, the content of IL-18 was 164.68 ± 12.20 pg/ml, which is 2.42 times higher compared to the control ($P<0.001$), and in patients with cryoglobulinemia, the content of this cytokine increased even more, amounting to 204.46 ± 16.64 pg / ml, which is 3.01 times higher compared to normal value ($P<0.001$). It is interesting to note that the content of IL-18 in the blood serum of CHC patients with extrahepatic manifestations with cryoglobulinemia was significantly increased in relation to patients without cryoglobulinemia by 1.24 times ($P<0.05$).

5 Conclusions

Thus, in patients with chronic hepatitis C with extrahepatic manifestations, there is a significant increase in the content of pro-inflammatory cytokine IL-18 by 2.71 times in relation to normal values, in addition, the effect of cryoglobulinemia on the content of IL-18

in the blood serum of this category of patients is noted, the difference between the groups was 1.24 times in favor of patients with the presence of the phenomenon. The effect of cryoglobulinemia on the content of proinflammatory cytokine IL-18 in the blood serum of the examined patients was proved. In the presence of cryoglobulinemia, both interleukins-IL-18 and IL-10-were elevated relative to the data of patients without cryoglobulinemia.

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