Cytokine Spectrum in Chronic Hepatitis C with an Autoimmune Component

The distinctive feature of HCV is its heterogeneity with development of the simultaneously existing and immunologically different antigen variants that possess significant potential for adaptation and abilities to avoid control of the immune system of the host organism, that probably leads to the highest level of chronization of the process in HCV infection. According to several authors the same features of pathogenesis of hepatitis C virus are basis for its autoimmune manifestations, but the role of this impairments in the development of the system disorders is not clear yet. 145 patients with blood serum anti HCV IgG positive test were examined. Comparative analysis of levels of regulatory cytokines (IL-10, IL-6, TNF-α) was conducted, depending on the activity of the process; the analysis showed chronic hepatitis C with an autoimmune component characterized by severe symptoms before immune inflammation together with decrease in activity of regulatory T cells. These features suggest a possible pathogenetic and clinical role of autoimmunity in viral lesions of the liver.

Keywords: Autoimmunity, cytokines, virus hepatitises

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Introduction

Infection caused by the hepatitis C virus (HCV) is an important health issue in many countries as well as in the Uzbekistan. There are already 500 mln. infected carriers detected in the world. Despite conducted epidemiological measures the incident of hepatitis C is growing (Bueverov, 1998; Loginov, Saregorodseva, Zotina et al., 2001). Especially, young people and adolescents are more susceptible to infection (Zalyalieva, Kurbanov, Yakubov et al., 2003; Loginov et al., 2001). The distinctive feature of HCV is its heterogeneity with development of the simultaneously existing and immunologically different antigen variants that posses significant potential for adaptation and abilities to avoid control of the immune system of the host organism, that probably leads to the highest level of chronization of the process in HCV infection (Semenenko, 2002). According to several authors the same features of pathogenesis of hepatitis C virus are basis for its autoimmune manifestations (Clifford, Donahue, Smith et al., 1995; Manns, 1997), but the role of this impairments in the development of the system disorders is not clear yet.

Despite significant increase in knowledge of etiology and immunopathogenesis of the chronic diseases of liver for the last decade, many questions related to mechanisms for the development and progression of the pathological process remain unclear. Until very recent mechanisms of the immune response were studied on some populations of cells of the immune system, in the same time deeper mechanisms as cytokine were not studied well. It is known that cytokines play an important role in the immune response, they take an active part in the developing of inflammatory process and destroying of liver, particularly in viral hepatitis B and C (Bueverov, 1998; Dyachenko and Dyachenko, 2003; Ketlinskiy, 1999; Mazur, Mazurek, Jurzak et al., 2001). There are contradictory data regarding role of the regulatory cytokines interleukin 10 (IL-10), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) in the course and outcome of hepatitis C and their connection with the development autoimmune disorders. In the same it is known that
regulatory cytokines (IL-10, IL-6, TNF-α) make significant contribution to the developing of chronic hepatitis C (Ivashkin and Bueverov 2001; Lukina, 1998; Mazur et al., 2001). Autoantibodies to denatured (single stranded) DNA (ssDNA) are not specific to certain diseases and are main parts of the majority nuclear antibodies (Suchkov, Naumova, Tretyak et al., 2002). Despite there might be given different explanation of the autoantibodies detection, there is no doubt, that they are markers of autoimmune process and have important diagnostic significance. Therefore, recently many researches are devoted to the study of occurrence of the different autoantibodies, including ssDNA in different diseases.

Materials and methods

Were examined 145 patients with blood serum anti HCV IgG positive test. At formation of clinical groups of patients with chronic hepatitis C following criteria of inclusion in research were considered:
1. clinical diagnosis authentically verified in the course of all-round medical examination;
2. presence laboratory confirmed (with methods IFA, PCR) virus hepatitises B and C;
3. age from 18 till 50 years;
4. the informed agreement of the patient on participation in the given research.

Criteria of an exception of research:
1. presence autoimmune diseases at the patient or its close relatives;
2. presence of virus mixt hepatitises;
3. presence of fibrous changes in a liver and a portal hypertensia at ultrasonic inspection;
4. presence of other virus disease (SGV, CMV, Epstein-Barr) in an active stage.

Duration of illness in examined patients was from 2 to 10 years. The diagnosis of the chronic hepatitis C was made based on the combination of collected clinical, epidemiological, laboratory and instrumental data according to the Regulatory Order of the Ministry of Health of Uzbekistan. Patients were divided into two groups according to the appearance of the autoantibodies to ssDNA (the first group with positive autoantibodies to ssDNA, the second group - negative). There were also 3 subgroups divided according to the activeness of the process, the evaluation of its included expression of cytolytic syndrome: the 1st subgroup with low activeness of process (ALT < N), 2nd subgroup with midlevel of activeness of the process (ALT:1N-2N), 3rd subgroup - with high level of activeness (ALT is higher 2N). Additionally, for confirmation of morphological lesions and chronic process the ultrasound of liver was conducted that revealed diffuse parenchyma changes and hepatosplenomegaly.

Levels of ssDNA, IL-10, IL-6, TNF-α in peripheral blood were detected by sandwich ELISA (solid-phase enzyme immunoassay (ElIA)) with using peroxidase as a indicator enzyme (reagents sets “Vector Best” Novosibirsk, the Russian Federation).

Results

The analysis of the collected data of the detected autoimmune disorders markers has shown: that in average 37.8% of the examined patients with chronic hepatitis C have autoantibodies to ssDNA, and it was detected in all subgroups regardless of the activity of the disease process. The lowest level was in the 1st subgroup, the highest in the 3rd.

IL-6 and TNF-α are primary anti inflammatory cytokines are extremely pleiotropic and activate tissues around them. They trigger wide range of biological activity by lymphoid and non lymphoid cells. It is detected that IL-6 and TNF-α induce before immune
response inflammation, regulate immune and acute phase response, inflammation, oncogenesis and hemogenesis. TNF-α also plays a role in the destroying of liver, exacerbate development of fibrosis and portal inflammation in hepatitis C patients. One of the major functions of IL-6 is to regulate the maturation process of the antibody producing cells from B cells, as well as a production of immunoglobulins. IL-6 participate in activation of T lymphocytes, induces synthesis of many acute phase proteins: fibrinogen, haptoglobin, C reactive protein.

Studying of the spontaneous production of IL-6 and TNF-α has shown significant difference between data of the both groups of patients with chronic hepatitis C and control group (p<0.05). All patients with chronic hepatitis C have higher levels of these cytokines in comparison with control group, but if in the group of patients without autoantibodies they have been higher in 1.57 for TNF-α and in 1.47 times for IL-6, in groups of patients with autoantibodies they were higher in 2.31 and in 2.18 times respectively (p<0.05).

Cytokine IL-10 that is produced by Th-2 cells, B-cells, monocytes, macrophages and mast cells is important in the pathogenesis of hepatic lesions. The main mechanisms of action of IL-10 are resolving, immunomodulatory, immunosuppressive. Moreover, IL-10 leads to transformation of B cells to plasma cells and stimulates the secretion of immunoglobulins. Additionally, the level of IL-10 is informative to assess the activity of regulatory T cells (Treg), which are major producers of the immunosuppressive cytokine IL-10 (Haitov, 2009).

Analysis of the collected data revealed that there is a tendency of the decrease of IL-10 in the chronic patients. It was shown, that patients with positive autoantibodies have levels of IL-10 suppressed by 3.2 fold (p<0.05) and patients without antibodies have levels of IL-10 were slightly below normal (p>0.05).

Conducted comparative analysis of levels of regulatory cytokines (IL-10, IL-6, TNF-α), depending on the activity of the process, had showed unidirectional changes, however, in the 3rd subgroup of patients identified changes were more pronounced.

**Conclusion**

As a result of researches it has been revealed, that at levels of inter-molecular regulations chronic hepatitis C with an autoimmune component characterized by sever symptoms before immune inflammation together with decrease in activity of regulatory T cells. These features correlate with the degree of activity of chronic HCV and suggest a possible pathogenetic and clinical role of autoimmunity in viral lesions of the liver.

Thus, testing of patients with a chronic virus hepatitis C on presence autoimmune infringements so revealing autoantibody in blood whey is the indication for the special approach to a choice of methods of their treatment is necessary.

**References**


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