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INTEGRAL EVALUATION OF THE CYTOKINE SYSTEM IN VIRAL MYOCARDITIS

Peremot S. D., Volyansky A. Y., Smelyanskaya M. V., Kashpur N. V., Yudin I.P., Klysa T.L.

Mechnikov Institute of Microbiology and Immunology

Diagnosis of viral myocarditis, which is based on a convincing evidence base, remains one of the key problems of modern medicine [2]. Moreover, the symptomatology of myocarditis often appears in the period of convalescence of an acute viral infection, or is accompanied by a low-symptom course of myocarditis. Unfortunately, the timely diagnosis of erased, subclinical and chronic forms of the course of viral myocarditis in the clinic is virtually impossible, because the use of "routine" methods of examining patients in this case does not solve the problem, and the use of endomyocardial biopsy without a pronounced clinical manifestation seems unfounded [3,4].

In recent years, special attention has been paid to clarifying the etiology of myocarditis, since the success of the patient's treatment depends on this. Well studied myocarditis in bacterial infections, such as typhoid fever, diphtheria, streptococcal sepsis, streptococcal infection, tuberculosis, syphilis, leptospirosis, typhus, recurrent typhoid, systemic tick-borne borreliosis. For a long time, the main role in the development of non-rheumatic myocarditis was assigned to bacterial infections, which is partly due to the inadequate use of virological studies in the diagnosis of respiratory, intestinal and other infections [2].

However, at the present stage the situation has changed and bacterial pathogens are inferior to viral ones. It is the virus, according to numerous studies, cause the development of myocarditis and, as a consequence, lead to the development of myocardial dysfunction. Until recently the most cardiotropic were the Coxsackie viruses of group A, B [5]. However, in recent years, the role of enteroviruses has been revised in favor of representatives of persistent viruses, especially the Herpesviridae family [15].

It should be recognized that the diagnostic procedure of the controlled multi-zone endomyocardial biopsy, which is actively used in the developed countries of the world, along with certain advantages, has a number of significant disadvantages, like high cost, low accessibility for wide practical use (in Ukraine it can only be performed in a cardiosurgical hospital). In addition, the Dallas diagnostic criteria, which guide the verification of the diagnosis of myocarditis, are limited to the morphological changes in cardiomyocytes and do not take into account the etiologic factor, indicate the defeat of the heart muscle with moderate and severe myocarditis, and not the activity of the inflammatory process [6]. The greatest difficulties in diagnosing arise with persistent herpesviral infections, the course of which remains without attention of clinicians, but residual myocardial changes in them are often fatal, which is explained by the long period of inflammation in cardiomyocytes and its chronicity, which is caused by the persistence of viruses in the myocardium [7]. Insufficiency of the immune response, in turn, can also lead to a prolonged persistence of the virus in the body, but excessive or distorted one – to the development of autoimmune myocarditis [2,8].

Ubiquitarity and pantropism Herpesviridae determines their direct participation in etiopathogenesis, clinical manifestations, recurrence and consequences of herpesviral pathology of the cardiovascular system [9]. The unique biological properties of all herpesviruses is their ability to escape from immune defense factors by synthesizing proteins that block HLA receptors, thus causing a violation of signaling to proliferation and differentiation throughout the immune system response [10]. Thus, the transformation of acute herpesvirus infection into a chronic process occurs with the so-called "forced consent" of the immune system and usually without vivid clinical manifestations at the onset of the disease [11].

However, it should be noted that a significant number of aspects of herpesvirus infection remain insufficiently studied and that is why there is a need to develop clear and unified diagnostic criteria for this polynosological problem. [12,13]. That is why the problem of determining the features of the reorganization of the immune system and, in particular, the mechanisms of this restructuring in conditions of viral persistence, as well as the features of the functioning of the immune system in herpesviral myocarditis, require a detailed study [14,15].

Timely determination of the degree of immunological imbalance in a complex of diagnostic tests will help improve the diagnosis of subacute and chronic forms of myocarditis and thereby prevent the development of dilated heart cavities and reduce myocardial contractility that lead to severe forms of heart failure. It is the development and introduction into medical practice of new informative methods for diagnosis of myocarditis with the definition of etiological factors that will reveal the true scales of viral myocarditis in the structure of cardiovascular diseases and mortality in Ukraine [16].

The aim of the study was to determine changes in the inflammatory mediator system in patients with subacute and chronic herpesviral infectious myocarditis on the basis of an integral assessment of the levels of opposing groups of cytokines.

Materials & methods. To achieve this goal, we conducted a determination and analysis of changes in the cytokine profile in 87 patients with subacute (from 2 to 6 months) and chronic (more than 6 months) myocarditis due to an integral assessment of the mediator levels of inflammation of opposing groups in patients with herpesviral myocarditis on treatment in medical institutions of the Kharkov city. The diagnosis was established in accordance with the recommendations of the Association of Cardiologists of Ukraine and experts of the European Society of Cardiology, according to the formation of definitions of diseases in the International Classification of Diseases (ICD-10) of the tenth revision. The etiological role of representatives of the family Hepresviridae (*HSV1, 2, VZV, EBV, CMV, HHV6*) was confirmed on the basis of previously conducted molecular biological and serological studies. The main group of subjects was divided into two subgroups. The first was 44 patients with subacute flow (the duration of the disease is from 2 to 6 months), the second - 43 patients with chronic infectious myocarditis (more than 6 months), including those with chronic recurrent or primarily chronic myocarditis. The average age of patients from the main group was ($27 \pm 7, 4$) years. Criteria for exclusion from the group were: a diagnosis of myocarditis of bacterial etiology,

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acute infectious myocarditis (disease duration < 2 months), acute coronary syndrome or myocardial infarction less than 6 months old, congenital and acquired heart defects, infective endocarditis less than 6 months old, hypertrophic cardiomyopathy, myocardial hypertrophy (dimensions of the left ventricle > 14 mm), systemic vasculitis and systemic connective tissue diseases, sarcoidosis, amyloidosis and lymphoproliferative diseases, as well as patient's refusal to participate in the research.

The control group was attracted to 40 people without clinical manifestations of cardiovascular diseases and in the anamnesis of which there were no data on the transferred inflammatory diseases of the myocardium. The groups studied were completely comparable.

The removal of material from patients was carried out according to the rules for the collection of infectious material. The concentration of cytokines: IL-2, IL-4, IL-6, IL-10, INF-γ, TNF-α in serum was measured by solid-phase linked immunosorbent assay using commercial enzyme immunoassay kits for Thermo Scientific ™ (IL-2R IL-4, IL-6, IL-10, TNF alpha, IFN gamma ELISA Kit, Human, USA) and Stat Fax 303 Plus spectrophotometer.

Statistical processing of all received data was carried out on a personal computer using the program Statistica, version 6.1 (StatSoft Inc., USA) [1].

Results & discussion. Viral myocarditis is a heterogeneous group of diseases not only due to etiological factors that belong to different families of the Vira kingdom, but also are characterized by a unique mechanism of the inflammatory process and cytokine levels for each of them. Unfortunately, in the available literature, we did not find an analysis of the data of a complex cardio-immunological study that would take into account the features of the course of herpesviral myocarditis.

According to the results of preliminary studies, markers of herpesviruses were found in biological material of 100% of patients. Moreover, a significant (75%) specific weight of a combination of different herpesviruses in patients with infectious myocarditis has been established. Mostly it is *HHV6* with *HHV5, HHV1, 2, HHV4* and *HHV3*.

It is a complex algorithm for parasitizing these pathogens, which allows the formation of latent, persistent or reactivated forms of infection, and which is the cause of diagnostic errors in practice. We carried out a determination of the features of the state of the immune system with a complex analysis of cytokine profile data, immune and interferon status in subacute and chronic forms of herpesviral myocarditis.

It should be noted that herpesvirus persistence has a determining effect on the course of the myocardial inflammatory process. It causes disease progression due to the formation of an inadequate immune response, which makes it impossible to eliminate the virus from cardiomyocytes as occurs in myocarditis caused by representatives of other families of viruses [18, 19].

The course of the inflammatory process with the provision of intercellular interaction of activated immunocytes is regulated by a complex system of so-called cytokines, mediators of inflammation of protein nature. It is known that the nature of the immune response in myocarditis is determined by the balance of T-helper types 1 and 2 (Th1, Th2). Th1 producers include IL-2, IL-6, TNF-α, INF [20]. These cytokines activate macrophages, NK cells, maturation of cytotoxic T-lymphocyte-killers, providing predominantly development of the cellular immune response, including intracellular infection, and herpesviral infection. However, IL-4 and IL-10, which are responsible for the development of the cellular immune response, including production of IgE, are produced by Th2. In addition, IL-10 is an inhibitor of Th1. Therefore, it is reasonable to evaluate the functional activity of Th1 in the production of the most significant regulatory pro-inflammatory cytokines: TNF-α, INF and IL-2, IL-6, and Th2 by production of IL-10 or IL-4.

We have analyzed the level of pro- and anti-inflammatory cytokines in patients with myocarditis (Table 1). The data obtained indicate an imbalance in their system, which is characterized primarily by a significant increase in the level of proinflammatory IL-6 to (134.09 ± 22.72) pg / ml (control level 11.83 ± 1.64 pg / ml) and relatively a moderate increase in the levels of IL-2 and TNF-α in subacute myocarditis. Such an increase in the level of IL-6, in our opinion, is due to the dualism of the action of this interleukin, the proinflammatory nature of its action at the final stage of inflammation changes to anti-inflammatory. As a consequence, in combination with IL-10, it limits the secretion of TNF-α. That is why its level remains high and with chronic herpesviral myocarditis and exceeds the level of the control group more than 8 times. In addition, in the chronic form of the course of herpesviral myocarditis, an increase in the levels of anti-inflammatory IL4 and IL-10 cytokines is observed in 2.9 and 3.1 times, respectively. And the level of IL-10 increased not only in comparison with the level of the control group, but also exceeded by 1.5 times the corresponding index for subacute myocarditis.

Table 1 – Characterization of the cytokine status of patients with subacute and chronic infectious myocarditis.

Indicator, pg / ml	Patients with herpesviral infectious myocarditis		Control group (n=40)
	subacute (n=44)	chronic (n=43)	
TNF-α	78,46 ± 8,21*, **	68,14 ± 6,81*	40,62 ± 6,23
INF-γ	48,20 ± 3,75*, **	57,14 ± 4,37	59,22 ± 9,46
IL-2	72,33±6,81*, **	51,68±9,54*	30,02 ± 0,84

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IL-4	51,86 ± 9,22*	91,76 ± 12,75*, **	31,46 ± 2,52
IL-6	134,09 ± 22.72*, **	98,21 ± 27,64*	11,83 ± 1,64
IL-10	7,26 ± 1,02*	10,94 ± 0,23*, **	3,58 ± 0,11

*Notes: * - the reliability of the differences between the indicators in the subgroups of patients and the control group, ** - the reliability of the differences between the indicators of patients with different forms of the course of herpesvirus myocarditis.*

A number of researchers believe that an elevated level of TNF-α plays an important role in the progression of myocarditis due to cytopathic effects on cardiomyocytes, especially in combination with interferon [21]. It is known that INF-γ limits the spread of the virus to undamaged cardiomyocytes by blocking their ribosomal synthesis. However, among the patients examined with a progressive course of herpesviral myocarditis, the dynamics of changes in the level of interferon had certain peculiarities. INF-γ is a pro-inflammatory interleukin, and therefore, its level was expected to be higher in subacute myocarditis compared to chronic. Instead, we received a reduction, and it was in the patients with subacute flow that the value of the indicator was the lowest.

In our opinion, this phenomenon can be associated with the severity of the course of the disease. All patients examined by us had different degrees of heart failure. In severe forms of flow, with the formation of heart failure, there is an increase in predominantly TNF-α levels and to a lesser extent INF-γ, which may be a result of the activity of mast cells and in turn affect the synthesis of collagen and myocardial remodeling processes.

Based on the results of our studies of the study groups, the level of this cytokine is highest in the group of patients with chronic myocarditis. This is consistent with the published data, which indicate the accumulation of interferon in inflammatory foci in acute myocarditis, followed by release into the bloodstream when inflammation changes to cardiosclerosis in the course of progression and chronic infection of myocarditis.

The data of the literature testify that in the acute stage of viral myocarditis, the reactions of the cellular immunity, accompanied by the production of pro-inflammatory cytokines, are activated in the first place [13]. In the case of infectious herpesviral myocarditis, rapid elimination of the virus does not occur. This is due to the lymphotropism of this family of viruses and the development in this connection of the virus-induced immunosuppressive state, the result of which is a longer residence time of the virus particles both in the blood and directly in the cardiomyocytes. In turn, this feature is a prerequisite for the formation of chronic infectious myocarditis with classical clinical and morphological components of inflammation in the myocardium and the formation of secondary postinfection immunodeficiency.

In order to optimize the analysis of the cytokine imbalance, and also taking into account the synergism and pleiotropicity of cytokines in the responses of the immune response, in our opinion, it is justified to conduct an integral evaluation of inflammatory mediators' levels from opposing subgroups. The need for such a comprehensive assessment of the balance of cytokines makes it possible to more fully characterize the changes in immunological homeostasis in conditions of virus-induced chronic inflammation, dictates the validity of calculating the integral index of cytokine imbalance in the patient groups under examination (Table 2). Calculation of the integral indicator (II) was carried out by determining the values of cytokine indices as the ratio of the levels of proinflammatory and anti-inflammatory in the blood serum of the examined patients to the reference values of the control group and the calculation of the arithmetic mean for each opposing group of cytokines expressed in conventional units. The optimal balance of cytokines corresponded to the level of II ≤ 1 c.u. and testified to the absence of inflammation, but the activity of the inflammatory process was characterized by its excess more than 1 c.u.

This approach to the analysis of mediator levels allows us to determine not only the activity of the cytokine link in the inflammatory process and objectively assess the extent of deviations within the cytokine cascade, and, equally important, to track the dynamics of these changes in order to determine the tactics of immunocorrecting therapy and the prognosis of the course of the disease. Thus, it becomes possible to identify not only generalized features of the formation of the immune response of the study groups of patients with different forms of the course of infectious myocarditis, but also to assess the individual features of the immunological imbalance for the purpose of diagnosing the phase of the inflammatory process of a particular patient. This is very relevant in clinical practice. This provides a personalized approach to both the choice of tactics and immunorehabilitation tools, and the evaluation of the prognosis of herpesviral myocarditis in each specific case.

According to our data, in the group of patients with subacute flow, the imbalance in the levels of the opposing groups of cytokines was the most pronounced, and the integral cytokine balance in this group of patients was 6.27 c.u., exceeding the corresponding calculated indicator of a group of patients with chronic course in more than 1.6 times (3.82 c.u.). So, the higher the II deviation from 1 c.u. is, the deeper the violations of immunological homeostasis.

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Table 2 – The levels of integrated indicators in patients of the studied clinical groups.

Course of the myocarditis	Cytokine Indices (c.u.)						Integral indicator (c.u.)
	TNF-α	INF-γ	IL-2	IL-4	IL-6	IL-10	II
Subacute (n=44)	1,93±0,03	0,81±0,03	2,4±0,03	1,65±0,03	11,33±0,03	2,03±0,03	6,27±0,03
Chronic (n=43)	1,68±0,03	0,96±0,03	1,72±0,03	2,92±0,03	8,3±0,03	3,05±0,03	3,82±0,03

Moreover, it is likely that the longer such an imbalance in favor of prolonged cytopathic effect on cardiomyocytes, the deeper the structural changes in the architecture of the myocardium and the more likely the development of heart failure, as a result of such a prolonged inflammatory process. In favor of this assumption is the fact that in all patients with chronic herpesvirus myocarditis with II more than 4.0 c.u. there were signs of cardiac insufficiency of II - III class. But in patients with subacute flow with the same level of II, signs of heart failure were in 35 %, and mostly I-II class according to the classification of NYHA.

On the positive side, in this case, there is also the possibility of an individual evaluation of immunological disorders pathogenetically related to the inflammatory process in order to determine the prognosis of the course of the disease for a particular patient and the selection of preventive measures to prevent possible complications. In the clinic, such a calculated indicator will be diagnostic and prognostic in assessing the dysfunction of the immunological status and can be used even at preclinical stages of pathology development.

Conclusion. It was found that imbalance in the cytokine system in subacute and chronic herpesviral myocarditis is a universal immune system response, which is characterized by an increase in the levels of proinflammatory cytokines against a background of moderate growth of anti-inflammatory ones. The level of the integral cytokine indicator is more than 1 c.u. indicates the dysfunction of the immunological status of the patients being examined and can be used as an additional diagnostic criterion for the unfavorable course of the disease with a propensity to progress, and more than 4 c.u. in patients with chronic course of herpesvirus myocarditis characterizes the prerequisites for the formation of heart failure. Calculation of II defines a personalized diagnosis of cytokine imbalance with the ability to determine on its basis therapeutic approaches and the choice of immunorehabilitation tools, and also allows evaluating the effectiveness of selected anti-inflammatory agents for treatment of infectious herpesvirus myocarditis.

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INTEGRAL EVALUATION OF THE CYTOKINE SYSTEM IN VIRAL MYOCARDITIS

Peremot S. D., Volyansky A. Y., Smelyanskaya M. V., Kashpur N. V., Yudin I.P., Klysa T.L.

The need for an individual approach in the choice of means for the prevention of complications in inflammatory processes in cardiomyocytes, the course of which unfolds against a persistent viral infection, dictates the need to determine the general mechanisms for maintaining and progressing of the pathological process and an objective evaluation of immunological changes. **The aim of the study** was to determine changes in the system of inflammatory mediators in patients with subacute and chronic herpesviral infectious myocarditis on the basis of an integral assessment of the levels of opposing groups of cytokines. **Materials & methods.** To achieve this goal, we conducted a determination and analysis of changes in the cytokine profile in 87 patients with subacute (from 2 to 6 months) and chronic (more than 6 months) myocarditis due to an integral assessment of the mediator levels of inflammation of opposing groups in patients with herpesviral myocarditis on treatment in medical institutions of the Kharkov city. The average age of the patients was (27 ± 7.4) years. The control group was attracted to 40 people without clinical manifestations of cardiovascular diseases and in whose anamnesis there were no data on the transferred inflammatory diseases of the myocardium. Both groups of subjects were comparable in age and gender. The main group of subjects was divided into two subgroups. The first was 44 patients with subacute flow, the second - 43 patients with chronic infectious myocarditis. The diagnosis was established in accordance with the recommendations of the Association of Cardiologists of Ukraine and experts of the European Society of Cardiology, according to the formation of definitions of diseases in the International Classification of Diseases (ICD-10) of the tenth revision. The removal of material from patients was carried out according to the rules for the collection of infectious material. The concentration of cytokines: IL-2, IL-4, IL-6, IL-10, INF-γ, TNF-α in serum was measured by enzyme-linked immunosorbent assay using commercial enzyme immunoassay kits for Thermo Scientific ™ (IL-2R IL-4, IL-6, IL-10, TNF alpha, IFN gamma ELISA Kit, Human, USA) and Stat Fax 303 Plus spectrophotometer. Statistical processing of all received data was carried out on a personal computer using the program Statistica, version 6.1 (StatSoft Inc., USA) [1]. **Results & discussion.** Analysis of levels of pro- and anti-inflammatory cytokines in patients indicates an imbalance in their system, which is characterized primarily by a significant increase in the level of IL-6 prophylaxis to (134.09 ± 22.72) pg / ml (control level 11.83 ± 1, 64 pg / ml) and a relatively moderate increase in IL-2 and TNF-α levels in subacute myocarditis. Such an increase in the level of IL-6, in our opinion, is due to the dualism of the action of this interleukin, the proinflammatory nature of its action at the final stage of inflammation changes to anti-inflammatory. As a consequence, in combination with IL-10, it limits the secretion of TNF-α. That is why its level remains high and with chronic herpesviral myocarditis and exceeds the level of the control group more than 8 times. In addition, in the chronic form of the course of herpesviral myocarditis, an increase in the levels of anti-inflammatory IL4 and IL-10 cytokines is observed in 2.9 and 3.1 times, respectively. And the level of IL-10 increased not only in comparison with the level of the control group, but also exceeded by 1.5 times the corresponding index for subacute myocarditis. In order to optimize the analysis of cytokine imbalance, an integral assessment of the levels of inflammatory mediators from opposing groups was carried out. Calculation of the integral indicator (II) of the cytokine balance was performed by determining the values of cytokine indices as the ratios of the levels of proinflammatory and anti-inflammatory sera in the examined patients to the reference values of the control group and the arithmetic mean for each opposing group of cytokines expressed in conventional units (c.u.). The optimal balance of cytokines corresponded to the level of II ≤ 1 c.u. and indicated the absence of inflammation, but the activity of the inflammatory process was characterized by exceeding the level of more than 1 condition. In the group of patients with subacute myocarditis, II was 6,27 c.u., exceeding the corresponding calculated indicator of a group of patients with chronic course in more than 1.6 times (3,82 c.u.). Therefore, the higher the deviation of the II from 1 cu is, the deeper the violation of immunological homeostasis. **Conclusion.** It was found that

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imbalance in the cytokine system in subacute and chronic herpesviral myocarditis is a universal immune system response, which is characterized by an increase in the levels of proinflammatory cytokines against a background of moderate growth of anti-inflammatory ones. The level of the integral cytokine index is more than 1 cu indicates the dysfunction of the immunological status of the patients being examined and can be used as an additional diagnostic criterion for the unfavorable course of the disease with a propensity to progress. Calculation of II defines a personalized diagnosis of cytokine imbalance with the ability to determine on its basis therapeutic approaches and the choice of immunorehabilitation tools, and also allows evaluating the effectiveness of selected anti-inflammatory agents for treatment of infectious herpesvirus myocarditis. **Keywords**. Cytokine, viral myocarditis, herpesviruses.

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