CYTOKINE PROFILE IN PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS (WEGENER'S)

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Abstract. *According to the 2012 Chapel Hill nomenclature, granulomatosis with polyangiitis (Wegener's) (GPA) is a necrotizing granulomatous inflammation, usually involving the upper and lower respiratory tract, and a necrotizing vasculitis involving small and medium-sized vessels.*

Keywords: *neutrophil chemotaxis, bronchoalveolar lavage.*

Antineutrophil cytoplasmic antibodies (ANCA) are detected in the blood serum of patients, reacting with several lysosomal enzymes of neutrophils and leukocytes (especially proteinase 3 - c-ANCA). This disease is also characterized by the presence of granulomatous and non-granulomatous inflammation outside the vessel wall [1]. GPA remains one of the most severe and prognostically unfavorable systemic vasculitis [2]. When analyzing the course of the disease, local (with damage to the upper respiratory tract, organs of vision and hearing) and generalized (with damage to the upper respiratory tract, organs of vision and hearing in combination with damage to the lungs and/or kidneys, as well as the gastrointestinal tract, nervous system) are distinguished , skin) GPA options. Generalized GPA includes early systemic, generalized and severe variants of the disease, which are distinguished in accordance with the classification of the European Vasculitis Society (EUVAS) [3]. The disease is most often diagnosed in people aged 64–75 years [4]. The incidence of GPA is 2–12 cases per 1 million population per year, the prevalence is 23–160 cases per 1 million population [5]. To assess disease activity, the BVAS (Birmingham Vasculitis Activity Index) scale is used. Organ damage is assessed using the VDI (Vasculitis damage index). GPA is based on various disorders of cellular and humoral immunity. Cytokines that regulate all aspects of immunological reactivity are important for the development of autoimmune processes. Cytokines are a special class of endogenous polypeptide mediators of intercellular interaction that regulate a number of physiological functions and the maintenance of disturbed homeostasis [6]. They affect the functional activity of cells participating in the reactions of innate and acquired immunity. By influencing T- and B-lymphocytes, cytokines are able to stimulate antigen-induced processes in the immune system [7]. The study of the role of cytokines in the development of the immunopathological process in patients with GPA is of particular interest in connection with the possibility of using biological drugs in this group of patients [11]. The study of cytokines in patients with GPA allows us to get closer to understanding the mechanisms of development of the immunoinflammatory process, as well as the influence of cytokines on the formation of organ lesions in GPA [12]. Study of cytokines in various forms of hpa and damage to various organs and tissues. Cytokines in local and generalized GPA. Previous studies have indicated that patients with localized and generalized GPA have differences in gene

expression and cytokine production. In 2001, Reinhold-Keller et al. suggested that the administration of interferon (INF) α could probably provoke the development of a generalized form of GPA in patients with an initially local form [13]. At the same time, Muller et al. conducted a study of the expression and production of Th1 and Th2 cytokines in tissues (biopsy material) and in peripheral mononuclear cells in patients with local and generalized forms of GPA. Higher production of IFN-γ was found in nasal biopsies, as well as in peripheral mononuclear cells of patients with a local form of GPA, compared with patients with a generalized form of GPA. The level of interleukin (IL)-10 messenger RNA in activated peripheral mononuclear cells in patients with the local form of GPA was higher compared to that in the generalized form or in healthy volunteers. The authors concluded that in the nasal tissue, due to the predominance of IFN-γ positive cells, the Th1 type of immune response predominates. In addition, the development of a local immune response was accompanied by an increase in the level of IFN-γ and IL-10 in peripheral mononuclear cells [14]. Study of cytokines responsible for the development of types 1 and 2 of the immune response in patients with GPA. In 1999, 2 studies were performed to assess the predominance of one or another type of immune response in patients with GPA. Csernok et al. determined the content of INF-γ and IL-4 in patients with GPA in the nasal mucosa, bronchoalveolar lavage and peripheral blood using polymerase chain reaction and enzyme-linked immunosorbent assay (ELISA) methods. T cells isolated from an area of granulomatous inflammation of the nasal mucosa produced only IFN-γ, while T cell lines isolated from bronchoalveolar lavage expressed both IFN-γ and IL-4, with a predominance of IFN-γ . A study of IFN-γ production by peripheral mononuclear cells did not show statistically significant differences compared to healthy volunteers. However, in patients with GPA, a significant increase in the production of IFN-γ by T cells was noted compared to healthy volunteers. The level of IL-4 production in patients with GPA did not change statistically significantly compared to healthy volunteers. The authors concluded that the type 1 immune response predominates in the area of granulomatous inflammation in patients with GPA [15]. In order to study the pathogenetic role of cytokines in the development of autoimmune vasculitis, Tomer et al. In the experiment, mice were immunized with human immunoglobulin G (IgG) - ANCA, obtained from patients with GPA. After immunization, the lungs and kidneys of mice were examined to detect vasculitis. After 2 weeks after immunization, the levels of IL-1β, IL-2, IL-4, IL-6, IFN-γ and tumor necrosis factor α (TNF-α) were studied by ELISA. It was noted that immunized mice developed perivascular mononuclear cell infiltration in the lungs, regarded as vasculitis. Levels of IL-4, IL-6, and TNF-α, but not IL-1β, IL-2, or IFN-γ, were significantly increased at 2 weeks. after immunization. The authors suggested the pathogenetic role of IL-4, IL-6 and TNF-α in the initial phase of autoimmune vasculitis and the development of type 2 immune response during the initiation of experimental pulmonary vasculitis, similar to that in GPA [16]. In 2009, in the work of S.V. Dolgikh presented the results of a study of cytokines in patients with ANCA-associated vasculitis. These patients showed: a significant increase in IL-1β content compared to patients with periarteritis nodosa; the content of TNF-α is the same in patients with periarteritis nodosa and healthy volunteers; significant increase in IL-10 compared to healthy volunteers. In addition, in patients with ANCA vasculitis, compared with healthy volunteers, the levels of IL-2, IFN-γ, IL-4 and IL-5 significantly increased. The author comes to the conclusion that in patients with ANCA-associated vasculitis there is an increase in the levels of Th1 and Th2 cytokines [17]. Study of cytokines in patients with exacerbation and remission of GPA. Balding et al. studied the content of cytokines in biopsies of

the nose and kidneys of patients with GPA. Previous studies of T cells in peripheral blood have demonstrated an increase in IFN-γ and the development of a type 1 immune response. In this study, the content of cytokines in the nasal mucosa was examined using immunohistochemistry in 10 patients with an active form of GPA. An increase in the expression of IL-4, a suppression of the expression of IL-2, and a lack of expression of IFN-γ were noted. The authors concluded that during exacerbation of the disease, cytokines responsible for the development of type 2 immune response occur locally in the nasal mucosa. In addition, increased expression of IL-2 and IL-4 was noted in kidney biopsies from patients with active GPA [18]. In the work of Lúdvíksson et al. It was noted that in patients with an active form of GPA, ELISA revealed changes in the content of cytokines in the peripheral blood, in contrast to healthy volunteers. There was a significant increase in the level of INF-γ, responsible for the development of the Th1 type of immune response, and unchanged production of IL-4 and IL-5, involved in the development of the Th2 type of immune response [19].

In 2011, Tomasson et al. studied the content of platelet activation markers and inflammatory markers during exacerbation of GPA. The ELISA method was used to determine the levels of C-reactive protein, IL-6, IL-8 and ANCA to proteinase-3 in patients with exacerbation of the disease. According to the results of the examination, it was revealed that all indicators, except for the level of IL-6, change with exacerbation of the disease [20]. In the work of Abdulahad et al. The results of a study of the levels of IL-17, IL-4 and IFN-γ in patients with remission of GPA are presented. The content of cytokines in peripheral blood cells was studied using flow flowmetry. An increased content of Th17 cells (IL-17) and Th2 cells (IL-4) was noted in patients with remission of GPA, in contrast to healthy volunteers. When comparing the blood of patients with GPA in remission and healthy patients, no significant difference in the content of Th1 cells (INF-γ) was detected [21].

Perkins et al. We studied the level of IL-8 in patients with exacerbation and remission of GPA using ELISA. It was noted that the level of IL-8 significantly correlates with disease activity [22]. Using flow flowmetry, Rani et al. found that in patients with an active form of GPA, compared with patients in the remission phase, there is a decrease in the expression of IL-10, which indicates a decrease in the function of T-regulatory cells in the active phase of the disease [23]. In 2009, Novick et al. studied the level of the pro-inflammatory cytokine IL-18 and its inhibitor, IL-18-binding protein in the serum of patients with GPA at different stages of the disease. It was revealed that the levels of IL-18, IL-18-binding protein and free IL-18 in patients with an active form of the disease were almost 2 times higher than the protein levels in patients with remission. During the period of remission, the levels of these markers were comparable to those in the blood of healthy volunteers. Increased levels of IL-18 and IL-18-binding protein in patients with exacerbation of GPA suggests that these markers play a role in the pathogenesis and course of GPA. The authors note that despite the increase in IL-18-binding protein during exacerbation of GPA, free IL-18 remains elevated during exacerbation, suggesting it as a potential target for therapeutic intervention through the addition of exogenous IL-18-binding protein [24]. Since T cells occupy a significant portion of the granuloma in GPA, Lúdvíksson et al. We studied the cytokine profile of T cells in patients with GPA using ELISA. It was found that the level of IL-12 was increased both in the phase of exacerbation of GPA and in the remission phase. In addition, it was noted that in vitro IFN-γ production decreases depending on the amount of IL-10 added. The authors suggest that increased production of IFN-γ and TNF-α in patients with GPA is caused by

impaired secretion of IL-12 and that IL-10 may thus be a target for therapeutic intervention [19]. The influence of cytokines on lymphocytes, monocytes, neutrophils. Cytokines have pleiotropic biological effects. The same cytokine can act on many types of cells, causing different effects [7]. In this regard, the influence of cytokines was studied not only on the development of exacerbation of the disease in general, but also on individual cells: lymphocytes, monocytes, neutrophils. IL-2 is a marker of lymphocyte activation in patients with systemic diseases. The level of soluble IL-2 receptor has been studied repeatedly. It has been noted that the level of plasma soluble IL-2 receptor increases in patients with active GPA [25].

Neutrophil-induced lung injury in patients with GPA was studied by Hattar et al. It has been shown that when isolated human polymorphonuclear leukocytes are exposed to TNF-α, there is an induction of surface expression of proteinase-3. Coperfusion of TNF-α, stimulated neutrophils, and monoclonal antibodies to proteinase-3 induces an increase in isolated lung weight in rats. According to the authors, c-ANCA-induced edema developed against the background of an increase in capillary filtration coefficient, a marker of increased permeability of the pulmonary vascular endothelium [26]. Hattar et al. also studied the effects of antibodies to antiproteinase-3 on the production of cytokines by monocytes. The authors found that proteinase-3 is expressed on the surface of isolated monocytes. Stimulation with antibodies to proteinase-3 resulted in a significant release of cytokines, primarily TNF-α and IL-1β. A decrease in the production of IL-6, IL-8 and thromboxane A2 by monocytes was noted. The authors conclude that antibodies to proteinase-3 are potential inducers of cytokine production by monocytes. And TNF-α, IL-1β and thromboxane A2 function as mediators in the formation of the secretory response [27]. In 2009, Uehara et al. published the results of their studies examining the effect of ANCA to proteinase-3 on the activation of mononuclear cells in patients with GPA. Flow cytometry demonstrated that stimulation of mononuclear cells with antibodies to proteinase-3 increases the expression of Toll-like receptors and NOD1 and NOD2 receptors, while the level of IL-8 in plasma increases. The same stimulating effect was noted regarding the production of IL-6 and TNF-α [28]. In 2014, Park et al. found that in patients with GPA, alternative activation of monocytes occurs. A study of the level of TNF-α 4 and 24 hours after stimulation of monocytes with high concentrations of lipopolysaccharides showed that stimulated monocytes in patients with GPA produce significantly less TNF-α compared to monocytes of healthy volunteers. The authors concluded that monocytes/macrophages in patients with GPA are activated via an alternative pathway [29]. Considering that neutrophils play a leading role in the pathogenesis of the disease, ELISA was used to study cell cultures in patients with GPA and healthy volunteers for the presence of chemokines that could activate or recruit neutrophils. It was revealed that endothelial cells of patients with GPA expressed high levels of neutrophil-activating chemokines, in particular IL-8 [30]. In 2011, Richter et al. conducted a study of neutrophil chemotaxis in patients with GPA. The authors argue that due to the presence of ANCA in these patients, neutrophils play a key role in the pathogenesis of the disease. In the bronchoalveolar lavage of patients with GPA, the amount of IL-8 and IL-1β was determined by ELISA [31]. An increased content of neutrophils in the bronchoalveolar lavage fluid of patients with exacerbation of GPA has previously been described [32]. Cytokines play an important regulatory role in the migration of neutrophils to sites of inflammation [33]. Increased cytokine concentrations resulted in neutrophilia, which is associated with acute lung injury and pulmonary fibrosis caused by increased chemotaxis in the alveolar region [34, 35]. Previous studies have found increased levels of neutrophilia-inducing chemokines

[36, 37] in the serum of patients with GPA and increased CXC chemokine ligand (CXCL8) in the glomeruli of patients with exacerbation of GPA. When studying the content of cytokines in the bronchoalveolar lavage of patients with GPA, a significant increase in the content of IL-8 was found both during exacerbation and remission of the disease. There was no significant difference in the content of IL-1β in the bronchoalveolar lavage of patients with GPA. The entry of neutrophils into tissue is a multistep process that is coordinated in part by cytokines. The number of neutrophils in the bronchoalveolar lavage of patients with GPA correlates with IL-8 and IL-1β, so it can be assumed that these cytokines influence the entry of neutrophils into tissues. While the role of IL-8 as a neutrophil chemoattractant has been well studied, the role of IL-1β remains controversial, although it is known that IL-1β can cause neutrophil aggregation and induces the production of neutrophil chemoattractants, including IL-8. IL-8 and other cytokines, including TNF-α, also stimulate the translocation of proteinase-3 to the cell surface, thereby increasing the likelihood of binding to ANCA. Experimental results from Richter et al. suggest an important role in the development of neutrophil chemotaxis in bronchoalveolar lavage for IL-8 and the CXCR2 receptor [31].

Treatment of GPA and changes in cytokine levels.

The currently accepted standards for the treatment of GPA indicate that the tactics of therapy are largely determined by the severity of the disease [38]. In severe (generalized) forms of the disease, early treatment with an aggressive regimen including cyclophosphamide and glucocorticosteroids is necessary. Patients with localized GPA, on the contrary, respond well to a less aggressive treatment regimen using methotrexate and glucocorticosteroids [39]. Several uncontrolled studies—Stone et al., Bartolucci et al., Lamprecht et al., Booth et al. It has been reported that the use of TNF-α inhibitors significantly reduces the exacerbation of GPA [40–43]. But a subsequent double-blind, placebo-controlled study using etanercept (a competitive inhibitor of TNF-α binding) found different data. The etanercept study involved 180 patients with GPA who were divided into two groups: a group receiving etanercept and a group receiving placebo in addition to standard therapy [44]. Standard therapy included prednisolone and cyclophosphamide (for severe forms of the disease) and methotrexate (for local GPA). Etanercept was administered subcutaneously at a dose of 25 mg twice a week. or placebo. The dose of glucocorticosteroids was gradually reduced over 6 months. This study demonstrated that the use of etanercept did not affect the rate of long-term remission in patients with GPA [45]. The effect of GPA therapy was determined by Lamprecht et al. The levels of IL-12, TNF-α and IL-8 were studied using flow flowmetry. It was found that intercytoplasmic expression of IL-12 and TNF-α was significantly increased in patients with exacerbation of GPA compared with healthy volunteers. IL-8 levels were not increased in vitro. After prescribing a standard dose of cyclophosphamide and glucocorticosteroids after 2 and 12 weeks. Accordingly, the onset of remission was noted. According to the examination, a decrease in the expression of IL-12 and TNF-α was found until their levels normalized. The authors conclude that the active metabolite of cyclophosphamide reduces the amount of IL-12 messenger RNA in vitro. Monocyte cytokines, especially IL-12, may play an important role in the formation of an early immunoregulatory response in favor of Th1. It can be seen that cyclophosphamide in combination with glucocorticosteroids exerts its effects by normalizing the Th1-type cytokine response, and cyclophosphamide can support this model of cytokine response development [46]. Currently, to induce remission in patients with newly diagnosed GPA with severe organ damage or a life-threatening course, it is recommended to use

combination therapy with glucocorticosteroids and rituximab. Rituximab is a genetically engineered biological drug, a mouse/human chimeric monoclonal antibody. It specifically binds to the CD20 transmembrane antigen on B cells and initiates immunological responses that mediate B cell lysis. In terms of effectiveness, rituximab is not inferior to cyclophosphamide, and in the RAVE study it even showed an advantage over the latter in patients with relapse of ANCA-associated vasculitis. Rituximab can be used to preserve reproductive function in younger patients. There are no cases of infertility during treatment with rituximab, while cyclophosphamide can cause infertility in both women and men [47].

Conclusion.

The pathogenetic role of cytokines in the development of GPA has been studied for a long time. The development of a local immune response in GPA is accompanied by an increase in the level of IFN-γ (type 1 immune response), however, with exacerbation of the disease, the expression of cytokines responsible for the development of type 2 immune response increases. Several studies have noted that the level of IL-8 significantly correlates with GPA activity. And the increase in the level of IL-18 and IL-18-binding protein in patients with exacerbation of GPA suggests that these markers play a certain role in the pathogenesis and course of the disease. Standard treatment regimens exert their effects by normalizing the cytokine response in patients with GPA. Currently, further study of the cytokine profile in patients with GPA is an urgent task in connection with the possibility of using biological drugs.

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