Advantages of Immunohistochemical Assessment of Inflammation of the Nasal Cavity and Paranasal Sinuses in Allergic Rhinitis

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ABSTRACT

The use of the latest achievements of rhinosurgery allows you to influence only the final result of the pathological process, without affecting the cause and pathogenesis of polyposis, therefore, does not exclude the recurrence of the disease. Therefore, the problem of treating polypous rhinosinusitis should be considered primarily from a therapeutic, and not from a surgical standpoint. A detailed study of the etiopathogenesis of this disease, the creation of a base for the development of new highly effective and safe medications will allow for long-term remission, and possibly a complete cure. Despite numerous studies in this area, there is still no single view on the ethnology and pathogenesis of nasal polyposis. There are a large number of theories, but none of them explains all the causes and mechanisms of the development of this disease. The key role of cytokine-regulated eosinophil migration is generally recognized [Gevaert Ph., 2006]. The release of mediators such as histamine, tryptase, prostaglandin D2, leukotrienes (B4 and C4) and kinins is considered significant during the degranulation of mast cells of the submucosal layer of the nasal mucosa.

Keywords: Paranasal sinus, allergic rhinitis, morphology, assessment.

Rhinitis is a multidisciplinary problem, since it has a wide prevalence and various clinical and pathogenetic manifestations [2,3]. Every year more and more new cases are registered, and further growth of the disease is predicted. This pathology significantly reduces the quality of life, affects the ability to work in the socially active population. Quite often, a combination of various etiopathogenetic forms of rhinitis is detected. Often there is a combination of allergic rhinitis with bacterial rhinosinusitis. Clinical manifestations of combined pathology are more severe, the disease is characterized by a long course and unsuccessful pharmacotherapy. Effective allergen-specific immunotherapy in this category of patients is difficult. The greatest difficulty in matters of etiopathogenesis, differential diagnosis and therapy is AR, complicated by chronic upper respiratory tract infection, and in particular, chronic rhinosinusitis. According to the literature, the combination of AR with HRSBE occurs in 41% of cases [5, 6]. AR with HRSBE is characterized by chronic persistent inflammation of the nasal mucosa, while it is based on a combination of allergic and infectious components, which leads to a decrease in the protective function of the mucous membranes and a violation of local immunity [5]. One of the reasons for the aggravation of the course of the pathological process in AR with CRSBE is associated with the ability of antigens of microorganisms to exhibit the properties of superantigens and induce immune disorders [5, 6]. Many studies have been devoted to the study of the pathogenetic mechanisms of certain forms of rhinitis (allergic rhinitis or chronic rhinosinusitis). However,

many pathogenetic issues of the formation and progression of a chronic inflammatory process in the nasal mucosa with a combined form of the disease remain debatable and open. An important role in the pathogenesis of inflammation of the nasal mucosa in AR with CRSBE is played by the state of immune reactivity of the body. Of particular importance is the local immune response in the focus of inflammation. The mechanism of inflammation in the nasal mucosa in AR with CRSBE differs significantly from that in isolated AR and chronic bacterial rhinosinusitis, determining the features of the clinical course and response to therapy. Various mediators, cytokines and immunoglobulins are involved in the cascade of pathological immuno-inflammatory reaction. At the same time, the most informative value will be the change in these indicators in the focus of inflammation, namely nasal secretions. In this regard, it is of interest to study the cytokine profile of nasal secretions in patients with AR with CRSBE. According to modern concepts, cytokines are multifunctional mediators produced by immunocompetent cells in response to various stimuli, both of allergic and infectious origin. Cytokines have a wide range of biological activity and are involved in intercellular interactions, regulating the cascade immune-inflammatory response. The significant role of cytokines as mediators is to regulate the activity and duration of the immune response. In pathological conditions, they are responsible for the nature and intensity of the inflammatory process. A key cytokine in the development and maintenance of chronic allergic inflammation in the nasal mucosa is a mediator such as IL-4.

In the work of Kudaibergenov S.F. et al. in smears-prints from the nasal mucosa, a significant increase in the level of IL-4 was detected in patients with AR, while in infectious rhinitis, trace concentrations of this cytokine were observed both in serum and in nasal secretions. According to the authors, the increased level of IL-4 in nasal secretions from smears-prints from the nasal mucosa is a valuable diagnostic criterion and indicator of inflammation activity [14]. Foreign researchers have shown that stimulation of IL-4 B-cell supernatant in patients with upper respiratory tract allergopathology leads to suppression of IgA, IgG and IgM production and activation of IgE synthesis [48]. It is known that IL-4 promotes the remodeling of the nasal mucosa by stimulating the production of growth factor TGF-β, and also initiates the differentiation of lymphocytes by Th2-type and the expression of their cytokines [27, 32]. In the work of Bulkina O.Z. et al. it has been shown that in patients with AR complicated by foci of chronic infection of the oropharynx and nasopharynx, there is a violation of mucosal immunity, characterized by a significant increase in IL-4 and TGF-α and a decrease in the content of IFNy, sIgA in saliva in comparison with patients with AR without foci of chronic infection. According to the author, the revealed imbalance of the studied immune parameters is a negative prognostic marker indicating a violation of the regulatory function of cytokines, which contributes to the maintenance of the inflammatory process in AR in combination with chronic infection [5]. IL-10 is the most important anti–inflammatory cytokine, which mainly has anti-inflammatory and anti-cytokine effects. The main role of IL-10 is to suppress the cytokine cascade and thereby limit and stop the inflammatory process. IL-10 enhances the functional activity of B lymphocytes by activating Th2, and in combination with other cytokines, is able to induce Ig synthesis [12, 24]. TGF-β, being one of the main mediators of inflammation, exhibits three main types of biological activity: inhibits proliferation, has an immunosuppressive effect and enhances the formation of the intercellular matrix. TGF-β is secreted by various immunocompetent cells only when they are activated. TGF-β exists in the form of 3 isoforms, which are designated as TGF-β1, TGF-β2 and TGF-β3. TGF-β1 is characterized by pronounced expression and plays an important role in mucosal inflammation. TGF-β1 has important immunoregulatory properties, partly of an unfavorable nature: TGF-β1 inhibits the proliferation of B and T cells, differentiation and synthesis of antibodies, as well as maturation and activation of macrophages. In addition, it suppresses the activity of NK cells, and also blocks the synthesis of cytokines.

Determination of TGF-β1 in peripheral blood is recommended in the diagnosis of various diseases associated with chronic inflammatory process.

The purpose of the study. To experimentally study the morphological structure of the nasal mucosa and paranasal sinuses in acute sinusitis occurring against the background of allergic rhinitis.

Material and methods of research. Proceeding from the above, we experimentally studied the nature of the inflammatory process of the nasal mucosa and paranasal sinuses in acute sinusitis occurring against the background of allergic rhinitis on guinea pigs.

The result of the study. The content of total immunoglobulin E in the blood serum of patients did not significantly differ from the same indicator in healthy patients, which corresponds to the literature data [Bemstoin 1.M. 2005, Nikakhlagh S., 2009). Significant differences in its concentration were found only in patients with polypous rhinosinusitis and concomitant bronchial asthma, it was 381.8 IU/ml (median) compared with 122.8 IU/ma in patients without asthma ($p<0.05$). The content of total immunoglobulin E in patients with asthma also exceeded its level in the entire study group (173.1 IU/ml). This may be an indirect confirmation of the atopic nature of bronchial asthma in patients with polypous rhinosinusitis, while in the literature there is quite often evidence that PRS does not develop in atolic bronchial asthma.

As a result of a morphometric study, it was found that the optical density of nuclei in the shaped polypous tissue of patients with polypous rhinosinusitis significantly exceeded that of the control group (medials 0.7 and 0.5 nixels, respectively, $p=0.001$). The percentage of flat tissue edema in the preparations of polyps was also higher than in sections of healthy nasal mucosa (medians 70% and 49%, respectively, $p<0.05$). During the immunohistochemical study, it was revealed that the optical density of tryptase-antibody complexes in the field of vision in polypous patients with PRS was significantly higher than in healthy mucosal preparations (0.47±0.01 and 0.46±0.01 pixels, respectively, $p<0.05$).

This indicator reached the highest values in patients with intolerance to nonsteroidal anti-inflammatory drugs included in the aspirin triad (PRS, bronchial asthma, NSAID intolerance), and averaged 0.48 ± 0.08 pixels. The inverse dependence of this criterion on the duration of the disease is shown (Spearman coefficient 0.31, $p<0.05$). At the same time, the optical density of tryptase in polypose preparations positively correlated with blood eosinophilia (R, -0.46, $p<0.05$).

Significant positive correlations were revealed between the optical density of tryptase-antibody and immunoglobulin E-antibody complexes in sections of polypous tissue of patients with PRS, as well as between the number of these complexes in the field of view (Spearman correlation coefficients 0.43 and 0.46, respectively, $p<0.05$) (Table 1). In addition, the amount of immunoglobulin E in preparations of polyps it positively correlated with the concentration of immunoglobulin E in the blood serum of patients (R,-0.38, $p<0.05$).

The pathogenetic role of class E immunoglobulins in the development of polypous rhinosinusitis is currently not considered proven. Numerous studies show that there are no significant differences in their content in the serum of patients and healthy individuals (Bernstein J.M., 1999, Nikakhlagh S., 2009). In this regard, it is widely believed that the IdE-mediated mechanism of mast cell activation may not matter at all in the pathogenesis of nasal and paranasal sinus polyposis.

As a result of the immunohistochemical study of the tissues of the "ocular organ", namely the nasal mucosa and paranasal sinuses, it was found that the maximum amount of mast cell tryptase is found in nasal polyps at the initial stage of the disease during the aspirin trial. This correlated with an increased content of immunoglobulin E in the polypous tissue, which also reached maximum values with concomitant intolerance to NSAIDs, but was included in the result of steroid therapy. The positive interrelationships of these indicators

allow us to make a conclusion about the participation of nimunoglobulins in the activation of mast cells in polypous rhinosinusitis, including aspirin trila, When studying the indicators of antidotoxin immunity in patients with PRS, a statistically significant decrease in the average concentration of lipopolysaccharide-binding protein in blood serum was found compared to the control (12,2515,43 mi, respectively, 1-2,18, $p<0.05$).

Neither the level of LBP support nor, perhaps, to a certain extent have changed, contributing to the appearance of lipopolysaccharides of the macroorganism in polypositive rhinosinus. In fact, the inverse dependence of the concentration of the lipopolysaccharide binding protein on the duration of the disease was revealed in the group of patients with a disease duration of more than 5 years, the average level of 1.Blood pressure was lower than the same indicator in the group with a duration of PRS of less than 5 years ($p<0.05$) (Fig. 4

According to some data, in clinical practice, a high level of lipopolysaccharide-binding protein in blood serum can be viewed as a preview [Opal 8.M., 1999). In addition, our results do not contradict the literature data that corticosteroids intensify the synthesis of acute phase proteins against the background of infections, autoimmune, allergic oncological diseases (Pokrovsky V.N., 1999]. The literature also indicates that in some immunopathological disease, in particular in systemic lupus erythematosus, LBP is registered by an earlier and more sensitive criterion of acute gas response than, for example, the C-reactive protein Zubova T.N., 2006]. Taking into account such pronounced dynamics of the concentration of lipopolysaccharide-binding protein against the background of therapy, the effectiveness of which has been clinically confirmed, we consider it possible to propose the use of this indicator as a criterion for the effectiveness of the treatment of polypous rhinosinusitis, as well as for further correction of the dosages of the duration of therapy. The study of the concentration of antibodies to the endotoxin co-region did not reveal statistically significant differences in this indicator in the blood serum of patients with PRS in the control group. A negative relationship was found between the content of antibodies to the co-region of lipopolysaccharide in blood serum and the optical density of tryptase in the polypous tissue of patients (8.0,38, $p<0.05$). A tendency to increase their level after treatment was found, which can probably also be considered as a favorable prognostic sign, since the production of these antibodies belongs to the most important mechanisms of anti-endotoxin protection of the body [Barclay G. R. 2005,].

Conclusions. In the nasal mucosa with polypous rhinosinusitis, a high content of immunoglobulin E and the relationship of its level with the secretory activity of mast cells and with the concentration of immunoglobulin E in blood serum were revealed.

Antiendotoxin rhinosinusitis immunity in patients is characterized by a decrease in the polypose level of lipopolysaccharide-binding protein in blood serum, proportional to the duration of the disease.

Clinically effective drug therapy with the use of systemic and nasal glucocorticosteroids is accompanied by a 2-fold increase in the concentration of lipopolysaccharide-binding protein.

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