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FEATURES OF ALLERGIC RHINOSINUSITIS WITH SENSITIZATION TO FUNGAL ALLERGENS

Resume. *The prevalence of allergic pathology of the upper respiratory tract reaches 25–40%, with a tendency to constant growth. Recently, cases of fungal sinusitis have become more frequent, the diagnosis of which is often established late, already after antibacterial therapy or surgical treatment. Propolis demonstrated fungicidal activity against fungi *Candida famata*, *C. glabrata*, *C. kefyr*, *C. pelliculosa*, *C. parapsilosis* and *Pichia ohmeri*, where the fungicidal effect was associated with the presence of flavonoids.*

We analyzed the results of treatment of 35 patients who were on outpatient treatment in polyclinic and pulmonology-allergology departments of the regional hospital in Chernivtsi.

The effectiveness of the therapy was evaluated in terms of objective (levels of general and specific IgE, results of cultures of smears on the flora, acute-phase indicators of peripheral blood, dynamics of objective signs of damage to the mucous membrane of the nasal cavity) and subjective signs.

According to the scoring scale, after using the proposed treatment regimen, a significantly better effect was observed compared to other treatment regimens for allergic fungal rhinosinusitis. In a comparative study of traditional and additional proposed measures for the treatment of allergic fungal rhinosinusitis, it was established that infusions of a hypertonic solution in combination with a 10% oral alcohol solution of propolis (at least a month), which are used in addition to traditional treatment, have greater effectiveness, which is recommended to be taken into account in clinical practice.

Key words: *allergy, fungal rhinosinusitis, propolis.*

The prevalence of allergic pathology of the upper respiratory tract reaches 25–40%, with a tendency to constant growth. Rhinosinusitis is a serious problem of modern medicine, because it reduces the quality of life of patients due to deterioration or complete blockage of nasal breathing, impaired sense of smell, headache and chronic hypoxia. According to many epidemiological studies, the incidence of rhinosinusitis has increased several times over the past decades, and the specific weight of hospitalized patients increases annually by several percent on average [3]. Recently, cases of fungal sinusitis have become more frequent, the diagnosis of which is often established late, already after antibacterial therapy or surgical treatment [1]. The term "allergic fungal rhinosinusitis" (AFRS) explains in more detail the pathogenesis of one of the most severe forms of polypous sinusitis, the fungal etiology of which is verified according to the data of an untimely allergological examination. AFRS was first described as a separate clinical form in 1976,

combined with the clinical form of fungal mycetoma as a form of non-invasive fungal disease of the sinuses, separate from invasive fungal pathology of the sinuses and not related to it. The disease is a unique pathology that is largely determined by the presence allergic fungal mucin, which is a thick, viscous, eosinophilic secretion with characteristic histological features. This mucin is largely and microscopically similar to that found in the lungs of patients with allergic bronchopulmonary aspergillosis. Since its initial characterization in the 1970s, AFRS has been the subject of much debate and controversy regarding its pathogenesis, diagnosis, classification, and optimal treatment [9]. According to the literature [2], this form of the disease is not rare, it is often interpreted as an ordinary polyposis sinusitis combined with bronchial asthma (BA). The reason for insufficient diagnosis is the untimeliness of laboratory confirmation of fungal allergy, and the lack of knowledge of specialists in the field of fungal allergology.

Polyp tissue is infiltrated mainly by eosinophils, lymphocytes, plasmocides, and mast cells. Activated eosinophils infiltrating polyp tissue produce a large number of toxic proteins. In addition to these mediators, eosinophils are also able to produce many cytokines and other mediators that contribute to the increase of tissue infiltration [2, 3, 10].

In patients with nasal polyposis who do not suffer from allergies, BA and are tolerant to aspirin, an increase in the level of IL-4,5-producing cells is not detected. A more aggressive inflammatory response is noted in people who have large polyps that are prone to multiple relapses after surgical treatment. Correlation between the severity of eosinophilia and the severity of the disease is also characteristic of BA [3, 11, 13]. The disease is associated with BA in 65% [12]. Given the fact that the formation of polyps is limited to a certain area of the mucous membrane, it is important to note that in the nasal cavity, the number of eosinophils in the middle turbinate exceeds that in the lower turbinate [2, 5]. Approximately 40% of patients may have each of the following signs: expansion of the affected sinus, remodeling and thinning of bony sinus walls, sinus wall erosion [12].

Allergic fungal sinusitis is most often caused by fungi of the genus *Aspergillus*, as well as *Fusarium*, *Curvularia*, etc. Diagnostic criteria for this type of sinusitis include a computed tomography (CT) or MRI scan, dark green or black thick sinus discharge (peanut butter type), so-called "allergic mucin". During a specific allergological examination, hypersensitivity of the immediate type to various fungal allergens is more often detected (70%-75%), although other types of reactions are also observed, in particular hypersensitivity of the delayed type. With fungal variants of rhinosinusitis, phenomena of endogenous intoxication and immunological imbalance develop, which cannot be sufficiently corrected by traditional means of therapy. In addition, some drugs, affecting one pathogenetic link of the disease, do not take into account the state of other functional systems and create an additional antigenic load on the patient's body. The possibility of using allergen-specific immunotherapy for the treatment of AFRS is controversial and not routine [1].

Natural biologically active substances do not have an immediate effect on the main links of the pathological process. However, they affect the root causes of diseases, not just symptoms. Beekeeping products are, rightly recognized, a group of the most powerful natural biologically

active substances [4]. There are many indications for the use of propolis in the treatment of various diseases: gastrointestinal, dental, otorhinolaryngological, respiratory system. One of the few contraindications to the use of propolis is individual hypersensitivity. The probability of an allergic reaction to propolis is about 0.3%. Among beekeepers, this percentage is equal to 0.05%. Due to the presence of resins, aromatic substances, flavone derivatives, benzoic acid, propolis is active against more than 100 types of bacteria, fungi and viruses (among them the causative agents of pneumonia, tuberculosis, syphilis, diphtheria, influenza, salmonellosis, typhus, etc.) [7, 8]. Propolis demonstrated fungicidal activity against fungi *Candida famata*, *C. glabrata*, *C. kefyr*, *C. pelliculosa*, *C. parapsilosis* and *Pichia ohmeri*, where the fungicidal effect was associated with the presence of flavonoids. Propolis is the bee product with the highest antifungal activity, as tested on 40 yeast strains *C. albicans*, *C. glabrata*, *C. krusei* and *Trichosporon* spp. [7, 15]. A hypertonic solution of propolis based on sterile seawater improves the function of the ciliated epithelium, which increases the resistance of the mucous membrane of the nose and paranasal sinuses to the penetration of any pathogenic factors, promotes thinning of mucus, and has a local anti-inflammatory effect [7, 8].

The current research aimed to study the effectiveness of the local effect of hypertonic solution and 10% alcohol solution of propolis for oral administration, in patients with AFRS against the background of protocol treatment.

Methods. The criteria for selecting patients was the presence of clinical and laboratory signs of AFRS with confirmed sensitization to fungal allergens (specific immunoglobulins). The criterion for exclusion from the study is hypersensitivity reactions to any beekeeping products in the patient's history.

The results of treatment of 35 patients who were on outpatient treatment in polyclinic and pulmonology-allergology departments of the regional hospital in Chernivtsi were analyzed. The age of the patients ranged from 22 to 69 years (average age 42.4 ± 4.3 years), there were 15 women and 20 men. All patients underwent a general clinical examination and counseling by related specialists. A special ENT examination included: anterior and posterior rhinoscopy, cytological examination of secretions from the nasal passages, culture of secretions for microflora, inspection X-ray of the paranasal sinuses, endoscopy of the nasal cavity, research of respiratory function, computer tomography of

the paranasal sinuses was performed in some patients. Determination of total and specific IgE was also carried out. All patients had clinical signs of infectious syndrome of immunopathology. The history ranged from 2 to 12 years, against the background of concomitant pathology of the bronchopulmonary system (in 48.0%, $\phi \geq 2.7$, $p < 0.05$), curvature of the nasal membrane (in 47.3% of patients, $\phi \geq 2, 6$, $p < 0.05$). After the course of treatment, objective (including with the participation of an otorhinolaryngologist) and subjective data (4 weeks after the initial examination and 6 months) were analyzed.

The control group consisted of 12 patients with AFRS who used conventional treatment. The effectiveness of the therapy was evaluated in terms of objective (levels of general and specific IgE, results of cultures of smears on the flora, acute-phase indicators of peripheral blood, dynamics of objective signs of damage to the mucous membrane of the nasal cavity) and subjective signs: duration, severity, frequency of acute respiratory viral infections episodes during the year; the state of nasal breathing, the nature of secretions from the nasal cavity. A survey of patients was conducted regarding the results of treatment using a questionnaire, where the maximum manifestations of symptoms, as a whole, were counted by patients as 12 points.

Inclusion of patients in the study was carried out subject to their informed consent.

Earlier, we detected changes in general immunity in patients with allergic rhinitis with sensitization to fungal allergens:

- decrease in the functional activity of T-lymphocytes by 1.5-fold, $p < 0.05$;
- increase in the specific gravity of B-lymphocytes by 2.7-fold, $p < 0.05$; IgM by 2.3-fold, $p < 0.05$; IgG by 1.5-fold, $p < 0.05$; reduction of IgA by 3.2-fold ($p < 0.01$);
- increase of circulating immune complexes by 1.8-fold ($p < 0.05$);
- an increase in the concentration of interleukin-1 β by 1.9-fold ($p < 0.05$);
- a 2-fold decrease in the level of interferon- γ ($p < 0.01$) relative to reference values.

Results. Positive changes in the microbial landscape of patients were accompanied by signs of activation of protective factors of general immunity:

- ✓ restoration of the functional activity of T-lymphocytes by 1.4-fold, $p < 0.05$;
- ✓ increase in the level of interferon- γ by 1.6-fold, $p < 0.05$;
- ✓ concentration of interleukin-1 β by 1.4-fold, $p < 0.05$;

- ✓ population of B-lymphocytes by 0.9-fold, $p < 0.05$;

- ✓ tendencies towards the normalization of the immunoregulatory index.

According to the scoring scale, after using the proposed treatment regimen, a significantly better effect was observed compared to other treatment regimens for AFRS.

After 6 months, a significant reduction in symptoms (from 8 to 2 points) in newly diagnosed patients was determined in 5 patients, from 10 to 4 points in the main group in 12 patients, from 12 to 5 points in 11 patients, which is 20% better than after topical corticosteroid and standard therapy ($p < 0.05$). Improvement of nasal breathing, improvement of sense of smell, discharge of mucus from the nose were evaluated among the subjective criteria. After 6 months, the absence of relapses was noted by 30% more compared to standard therapy ($p < 0.01$). Symptoms of AFRS at the level of 6 points are 25% less compared to standard therapy ($p < 0.05$). Thus, it became clear that the patients who received the proposed remedy in addition to the traditional therapy had an objective recovery of nasal breathing, a significant improvement of the sense of smell than the patients of the control group. Also, 22 patients (75.9%) noted a decrease in the number of acute respiratory viral infections episodes within 6 months.

Discussion. Propolis not only suppresses the development of pathogens, but also demonstrates a powerful immunotropic effect. In recent years, in vitro and in vivo assays have provided new insights into its mechanisms of action, involving the innate and adaptive immune responses. In vitro and in vivo studies demonstrated the modulating effect of propolis on murine peritoneal macrophages, increasing their microbicidal activity. Its stimulating effect on the lytic activity of natural killer cells against tumor cells, as well as on the production of antibodies, was demonstrated. The inhibitory effect of propolis on lymphoproliferation is associated with its anti-inflammatory properties. In immunological tests, the best results were observed with short-term administration of propolis to animals. Antitumor properties of propolis, its anticarcinogenic and antimutagenic potential are discussed [14].

It is noted that long-term use of antibiotics, especially repeated courses, is accompanied by the formation of resistance to them by pathogenic microorganisms. The uniqueness of the antibacterial properties of propolis is that it does not develop resistance and does not cause

dysbacteriosis. The experiment proved that propolis enhances the action of streptomycin and tetracycline up to 10 times, although it does not affect the activity of penicillin and chloramphenicol. Propolis increases the secretion of the gallbladder, reduces the number of stomach ulcers, reduces the level of total cholesterol and triglycerides, has hepatoprotective properties, stimulates the hematopoietic process, promotes the removal of cholesterol and triglycerides from the body, reduces blood coagulation and prevents the formation of blood clots, relieves vascular spasm, stimulates the glands of internal secretion [7].

Conclusions.

1. The development of allergic fungal rhinosinusitis occurs against the background of immunopathological processes. Insufficiency of suppressor cells is accompanied by an increase in the pool of helpers and, accordingly, immunoregulatory index, which increases the risk of developing autoimmune processes. Dysimmunoglobulinemia and an increase in the level of circulating immune complexes against the background of immunoregulation indicates hyperactivation of the humoral immune response, the formation of an autoimmune component against the background of an infectious syndrome. Therefore, it is advisable to include specific immunological studies, which should preferably be evaluated dynamically, in the program of examination of patients with allergic fungal rhinosinusitis.

2. In a comparative study of traditional and additional proposed measures for the treatment of allergic fungal rhinosinusitis, it was established that infusions of a hypertonic solution in combination with a 10% oral alcohol solution of propolis (at least a month), which are used in addition to traditional treatment, have greater effectiveness, which is recommended to be taken into account in clinical practice.

In the future, it is planned to study the long-term results of the proposed comprehensive treatment and the optimal number of courses during the year.

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