REVIEW ARTICLE

EFFECT OF INFLAMMATORY FACTORS IN THE PATHOGENESIS OF CHRONIC RHINOSINUSITIS

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Abstract: Both immune mechanisms, involved in inflammatory processes induced by viral and bacterial pathogens or allergy-inducing agents, and non-immune mechanisms play a direct role in the pathogenesis of chronic rhinosinusitis (CRS).

Contrary to popular belief, bacterial infection plays a much smaller role. As a rule, this is a secondary process – following the development of inflammatory processes in the mucosa of the paranasal sinuses, its defense mechanisms are disrupted, which promotes the development of infection. Bacterial infection of the paranasal sinuses is associated with the formation of a biofilm responsible for the persistence of rhinosinusitis, or bacterial endotoxins acting as superantigens cause the persistence of the inflammatory process.

The main role in the inflammatory process is played by $CD4^+$ and $CD8^+$ T lymphocytes, as the centers regulating cytotoxic and humoral immune responses. They act in various ways, mainly cytotoxic, and as such can interact with virtually all nucleated host cells showing expression of antigens of endogenous origin and through cytokines, mainly pro-inflammatory cytokines, and they increase migration of inflammatory cells into the mucosa of the nasal cavity and paranasal sinuses. The paper discusses in detail the interaction of immunocompetent cells and their impact on chronic inflammatory processes in the mucosa of paranasal sinuses.

Atopy is another factor contributing to the CRS, increasing the action of pro-inflammatory cytokines and promoting processes that lead to obstruction of the ostiomeatal complex.

The complexity of the clinical picture of the CRS in relation to ongoing research on pathogenesis indicates that it is still not possible to strictly define the phenotypes of the disease.

Keywords: chronic rhinosinusitis, pathogenesis, $CD4^+$ T lymphocytes, $CD8^+$ T lymphocyte, cytokines, biofilm, atopy

INTRODUCTION

The nasal cavity and paranasal sinuses are an area of constant contact with the external environment and are subject to a number of infectious agents and a variety of protein structures. In its development, the human body has developed physical and immunological defense mechanisms to maintain the integrity of the respiratory system. These include the airway epithelium, mucociliary transport, as well as cellular and humoral immune mechanisms. If the defense mechanisms are broken, a germ enters the body and the inflammatory process develops. The resulting rhinosinusitis may disappear quickly and completely, or it may progress to a chronic inflammatory process [16].

CLASSIFICATION OF CHRONIC RHUNOSINUSITIS

According to current classifications, chronic rhinosinusitis (CRS) is a common clinical picture of a heterogeneous group of diseases with complex pathogenesis. In addition, the clinical picture of chronic rhinosinusitis consists of symptoms from other organs caused by various factors. Rhinosinusitis significantly affects the quality of life of patients. The rich symptomatology of the disease negatively affects their daily functioning [9,36].

The authors of the latest EPOS 2020 proposed another change in the division of the chronic rhinosinusitis. Currently, we divide chronic inflammation into primary CRS and secondary CRS. In addition, depending on the anatomical extent of the inflammatory lesions, into a localized or generalized form [16].

RISK FACTORS FOR CHRONIC SINUSINITIS

CRS is the subject of ongoing research and clinical observations to gain more knowledge on the pathogenesis of the disease. At least several hypotheses have been formulated in recent years that point to possible etiopathogenetic factors, including: conditioning by fungal infection, bacterial biofilm formation, the presence of a superantigen, the influence of eicosanoids, the importance of the microbiome and the immune barrier [28,49].

At the core of the consideration of the phenotypes of the CRS are the anatomical and functional conditions of the upper respiratory tract, i.e., the ostiomeatal complex, which are *de facto* responsible for shaping the clinical picture of the disease.

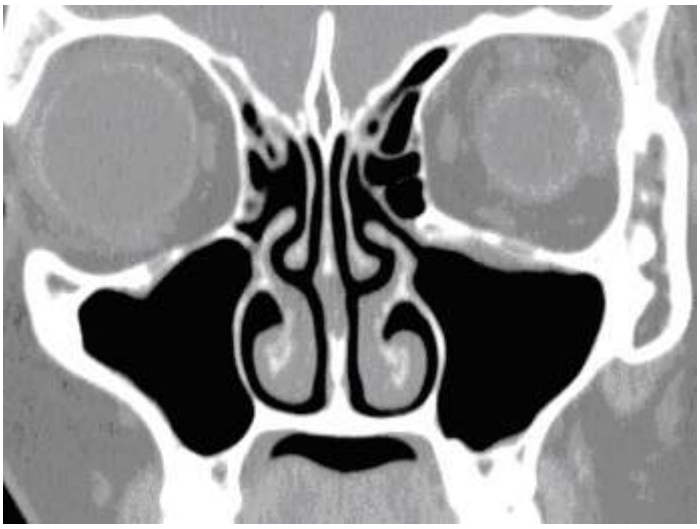

Fig. 1. Distribution of tympanograms of the right ear in group I in subsequent examinations.

The ostiomeatal complex (Fig. 1) is a functional structure in the anterior ethmoidal complex, which is the final common drainage and ventilation pathway of the frontal sinus, maxillary sinus and anterior ethmoidal cells. This space, which is limited medially by the middle nasal concha, laterally by the orbital plate, and on the top and in the back by the basal lamina of the middle nasal concha, includes: the middle nasal meatus, the ethmoidal infundibulum, the frontal recess, and the orifice of the maxillary sinus and anterior ethmoidal cells. The mucus drainage pathway from the aforementioned paranasal sinuses passes through here. For this reason, the region of the ostiomeatal complex is responsible for proper drainage and ventilation of the paranasal sinuses. Any disruption of mucociliary transport in this region can lead to the development of inflammatory changes in the maxillary sinuses, frontal sinuses and anterior ethmoidal cells [27,46].

The primary role in the defense mechanism of the paranasal sinuses is played by the mucociliary apparatus [47]. A properly functioning mucociliary transport mechanism allows the nasal and paranasal sinus mucosa to be constantly covered with a fresh, moist layer of mucus that renews itself every quarter of an hour. Ciliary cells and mucus play a primary role in mucociliary transport. The mucus transport is carried out toward the head, toward the nasal part of the throat. The movement of secretions in the paranasal sinuses toward natural outlets follows well-defined pathways [12,22].

Determination of the CRS by fungal infection formed the basis of the first hypothesis of pathogenesis, which was formulated by researchers at the Mayo Clinic in the US. This is because they detected the presence of airborne fungal elements in the patients' nasal and sinus structures. It was later shown in *in vitro* studies that *Altenaria* antigens can induce peripheral mononuclear hyperreactivity and enhance eosinophil migration and degranulation [8,13,23,37,48].

It is now accepted that the presence of fungi and their colonization may play an important role in modifying the clinical picture of the disease. This is because they contain proteolytic enzymes that can induce the release of inflammatory cytokines and a response involving Th2 lymphocytes. They may be responsible for the formation of a distinct phenotype of the CRS [35,39].

Another of the factors mentioned is bacterial biofilm. Bacterial biofilm formation is associated with the presence of bacterial infection, which is found in the nasal cavity and paranasal sinuses in 42-75% of those undergoing surgical treatment [11,18,42]. Colonization by microorganisms is possible due to their adhesive properties, and the structure of the resulting biofilm is stabilized by EPS (*extracellular polymeric substances*), forming the so-called glycocalyx. The mature form of the biofilm is surrounded by a thick layer of glycocalyx, to which minerals, organic compounds and cells of other microorganisms are adsorbed. The EPS includes polysaccharides, the largest fraction, as well as some proteins, nucleic acids, surfactants, lipids and water [18,25,36].

Biofilm formation is a multi-step process. A bacterial biofilm is a three-dimensional structure made up of microcolonies and glycocalyx. Microcolonies are separated by a network of open tubules, through which nutrients are transported and metabolic products removed. It is estimated that bacteria make up only 15% of the biofilm. Despite this structure, bacteria living inside the biofilm are exposed to oxygen limitation and therefore their metabolism changes – the activity of anaerobic metabolic pathways (desulfurification, denitrfication and fermentation) is increased, and the synthesis of certain enzymes (e.g. proteases, phospholipase C) and toxins is inhibited [10,18].

The adaptation of bacteria living in the biofilm to survive in harsh conditions also forces phenotypic changes, and there may be induction of point mutations of genes whose expression products increase the level of resistance of individual cells in the biofilm. Within the biofilm, horizontal gene transfer occurs. Plasmid transmission is one of the important mechanisms for the spread of resistance to drugs, disinfectants or other chemical agents. Horizontal gene exchange increases microorganisms' chances of survival.

According to the literature, bacterial biofilm is present in 70-75% of patients with the CRS. Gender, classification, duration of the disease, as well as the use of intranasal steroids and antibiotics were found to have no significant effect on its presence in the sinuses, subject to a chronic inflammatory process. Studies of patients undergoing functional endoscopic sinus surgery confirm the recurrence of biofilm, as it was found to be present again after surgical treatment in up to more than 70% of patients [15,17,21,42,44,51].

BACTERIOLOGY IN CHRONIC RHINOSINUSINITIS

Sinus infections occur in 80% of cases directly through the mucous membrane of the nasal cavity, and less frequently through the bloodstream or dental route. Rhinoviruses, coronaviruses, influenza viruses and parainfluenza viruses cause most colds, which are followed by a complication of acute rhinosinusitis in 10-15% of cases. Bacteria are present in 60% of cases of acute rhinosinusitis (ARS). The most common bacterial pathogens isolated from the material collected from sinuses are: *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. Rarer pathogens are anaerobic bacteria and *Staphylococcus aureus*.

Based on the literature, the primary pathogens of the CRS in adults are *Streptococcus pneumoniae* (20-40%), *Haemophilus influenze* (30-40%) and *Moraxella catarrhalis* (30-40%). Others also include S*taphylococcus aureus*. In the *Doyle et al.* study, Staphylococcus aureus accounted for 32% of paranasal sinus infections, while in the *Tan et al*. this percentage exceeded 56% of the patient group studied. The number of strains cultured usually depends on the size of the patient group studied. It is increasingly believed that staphylococcus aureus colonization occurs with increased frequency in patients with chronic rhinosinusitis with polyps, but not in patients without nasal polyps. The literature reports 21 classical pathogens and 61 non-classical pathogens in chronic rhinosinusitis. In some cases, rhinosinusitis is referred to as idiopathic [20,24,36,42,50].

Several mechanisms of bacterial action in this disease are assumed: it may be secondary to an existing inflammatory process. The presence of bacteria is the cause of the development of inflammation, bacterial biofilm is responsible for the persistence of rhinosinusitis or bacterial endotoxins acting as superantigens cause the persistence of the inflammatory process.

The demonstration that the presence of a superantigen produced by staphylococci enhances the local eosinophilic response was the basis for another hypothesis for the pathogenesis of the CRS [3].

Superantigens are proteins with high molecular weight and produced by various microorganisms (bacteria, fungi and viruses). Unlike classical antigens, superantigens bind directly to the major histocompatibility complex MHC class II outside the antigen binding site, which positively promotes the stimulation of large numbers of T lymphocytes. They stimulate several clones of lymphocytes, specifically recognizing the antigen, comparable to classical antigens, but all lymphocytes, having a given type of Vb chain, belonging to different clones, regardless of the specificity of the TCR. Thus, superantigens cause activation and polyclonal proliferation of CD4+ and CD8+ lymphocytes in the tissue and peripheral blood, in the case of certain superantigens this refers to up to 5–30% of all lymphocytes. The number of stimulated lymphocytes is thus 10-100 times greater than in the case of a reaction with a classical antigen [4,40].

The detection of immunoglobulin E directed against *Staphylococcus aureus* enterotoxins A and B *(Staphylococcus aureus SEA and SEB*) in nasal polyp homogenate confirmed for the first time that superantigens may play a role in the pathogenesis of nasal polyps and eosinophilic inflammation of the nasal cavity and paranasal sinuses. Tissue eosinophilia appears to be of primary importance in the development of the CRS, where its severity shows a positive correlation with the severity of the clinical course of the disease and the development of polyps when the level of eosinophils is high. Secreting a variety of inflammatory mediators, eosinophils, neutrophils, lymphocytes, macrophages and mast cells also affect the progression of changes observed in the inflammatory process [26].

Currently, it is accepted that staphylococcal superantigens can modify the clinical picture and course of the disease, promote the development of polyps, but it is difficult to consider them as an etiologic factor of the CRS [1,2,26,52].

ALLERGY AND CHRONIC RHINOSINUSINITIS

A broader look at allergic mechanisms points to the possible role of allergic mechanisms in shaping the clinical picture of the disease. It is known that allergic rhinitis can cause and can aggravate the course of sinusitis. Swelling of the nasal mucosa, regardless of the cause, impedes ventilation and drainage of the paranasal sinuses, which, of course, definitely increases the risk of their inflammation. Therefore, the thesis that atopy predisposes

to inflammation of the nasal mucosa of paranasal sinuses seems an obvious assumption. Abnormalities in the ostiomeatal complex contribute to sinus disease, and allergic rhinitis, characterized by mucosal swelling, can lead to reduced sinus ventilation and mucus retention, creating favorable conditions for the development of infection. Epidemiological data indicate that such a link is probable. In addition, evidence of common pathophysiological mechanisms links these diseases. Although a causal relationship has not been definitively clarified, there is a growing number of research supporting the credibility of reports that atopy is co-responsible in the development of the CRS [19,27].

Bousquet et al. [7], *Hellings et al.* [19], *Lin et al*. [32] report that 40% of patients with the CRS are also found to have allergic rhinitis. The association of the two diseases in many other studies ranged from 25% to 70%, depending on the criteria used and the study method. In recent years, a number of studies have attempted to prove that allergic mechanisms play an important role in the development of the CRS in patients suffering from an allergy – these mechanisms activate locally in the paranasal sinus mucosa. In their study, *Shaw et al*. [38] obtained a significant increase in mast cells in the sinus mucosa in patients suffering from CRS with polyps, regardless of the coexistence of atopy [6,7,19,33,34,38,41].

The effect of eicosanoid *(eicosanoid hypothesis*) on the occurrence of the CRS has been addressed in terms of aspirin intolerance and nasal polyp formation. The abnormal pathway of eicosanoid metabolism revealed in this process, along with increased production of pro-inflammatory leukotrienes and decreased synthesis of anti-inflammatory prostaglandins, indicated their role in shaping the pathology in the course of the disease [47]. Leukotrienes, which play a key role in allergic rhinitis, have been found to be present in chronic sinusitis, especially if there is an increased count of eosinophils. *Tan et al.* [43] in their study evaluated the prevalence of positive skin tests in patients with the CRS. They obtained results that differed significantly from other epidemiological studies. Positive results of the test were obtained for 82% of patients with chronic rhinosinusitis, most of which involved allergy to dust mites and ragweed pollen. In contrast, *Leo et al*. [30] found that the prevalence of allergy to airborne allergens in children with CRS was comparable to the general population of children in Italian society, and recommended not including routine allergy testing in the diagnosis of CRS. *Lill et al*. [31] did not confirm the high correlation of food allergy and CRS with nasal polyps. In their study, they found that 14% of patients with CRS were diagnosed with cow's milk allergy and 15% of patients were diagnosed with dust and cereal pollen allergy [30,31,41,43].

An interesting study was conducted by *Liu* [33], evaluating a possible link between the CRS resulting from food allergy and strong immunomodulation of Staphylococcal enterotoxin B from Staphylococcus aureus. The presence of enterotoxin B increases the dominant role of the Th2 lymphocyte, while at the same time causing an increased response of the sinus mucosa in the coexistence of food allergy. Serum levels of lymphocytes and a range of interleukins (IL-4; IL-13; IFN-γ) were assessed and nasal lavage fluid culture test was performed. The results of *in vitro* studies also showed a role for enterotoxin B in the increased response of Th2 lymphocytes to food allergens, compared to a group of patients with CRS but without food allergy [33,34].

CRS is characterized by changes in the mucous membrane of the sinuses. These include goblet cell hyperplasia, limited subepithelial edema, cellular infiltration and foci of fibrosis [16,51].

DISCUSSION

In the course of the CRS, there is an increase in the number of inflammatory cells such as mast cells, lymphocytes, macrophages, dendritic cells, eosinophils, basophils and neutrophils infiltrating the mucosa. In allergic CRS, increased IL-4 synthesis, increased transformation into Th2 lymphocytes, and increased IL-13 levels are observed in the mucosa after exposure to the allergen. The consequence of this process is an increased release of humoral pro-inflammatory factors, such as cytokines and growth factors [45,46].

The importance of the microbiome *(microbiome hypothesis*) in the pathogenesis of the CRS has been suggested based on the observation that externally induced changes in the gastrointestinal microbiome, leading to the development of secondary intestinal flora, can affect chronic inflammation. The microorganisms that make up the microbiome have the ability to produce antibacterial proteins and lipids that enable them to maintain homeostasis by depressing pathogen growth. This phenomenon is interpreted as a restoration of the microbiome via probiotics or inoculation of “healthy” bacteria that will help to cure the inflammation [5,14,29,46-48,51].

So far, studies and clinical observations have only pointed out the possibility that changes in the microbiome may be involved in the course of chronic inflammatory diseases, but so far there is no convincing evidence of a role in the pathogenesis of the CRS.

The importance of the immune barrier *(immune barrier hypothesis*) in chronic inflammation has long been known. Disruption of the physical barrier associated with the

anatomy of the nasal cavity and paranasal sinuses, as well as damage to the natural immune response, can lead to the development of the lesions seen in the CRS [12].

On the basis of currently available research results, it can be concluded that immune mechanisms, especially the disruption of the natural response, significantly affect the course of chronic inflammation, but they cannot be singled out as the sole factor responsible for causing the CS [23].

CONCLUSIONS

In conclusion, the complexity of the clinical picture of the chronic rhinosinusitis in relation to ongoing research on pathogenesis indicates that it is still not possible to strictly define the phenotypes of the disease. The involvement of immune mechanisms in the observed inflammatory process, regardless of the etiological factor, is undeniable. On the other hand, the influence of environmental factors can shape the clinical picture of the disease.

AUTHORS' DECLARATION

Study Design: Andrzej Wojdas. **Data Collection:** Andrzej Wojdas. **Manuscript Preparation:** Andrzej Wojdas. The Author declares that there is no conflict of interest.

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