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Allergic rhinitis associated with nasal polyps and rhinosinusitis – histopathological and immunohistochemical study

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Abstract

Currently, allergic rhinitis (AR) is the most common allergic disease worldwide. AR is defined as immunoglobulin E (IgE)-mediated chronic inflammatory disease of the upper airways. It characterizes by symptoms like nasal obstruction, rhinorrhea, nasal itching, and sneezing. The immune system and genetic susceptibility in the interaction with the environment lead to the development of AR. Many cytokines, chemokines and cells maintain allergic inflammation. Studies show that 10% to 30% of the adult population are affected, and that prevalence rates are increasing world widely. AR, nasal polyps (NP), as well as chronic rhinosinusitis (CRS) are all associated with eosinophilic infiltration and large quantities of mast cells (MCs) within the mucosa. The diagnosis and management of chronic sinonasal diseases involves the analysis of eosinophilic infiltration, MCs, and their markers eosinophilic cationic protein (ECP) and tryptase. Regarding nasal cancer, nasal allergies were found to exhibit a dual function: immune surveillance may help in the defense against malignant cells, but an opposite effect is observed in tissues with chronic stimulation and inflammation. In the present paper, we studied a group of 70 patients diagnosed with AR and NP, rhinosinusitis or nasal cancer, admitted to the Ear, Nose & Throat (ENT) Clinic of the Emergency City Hospital, Timişoara, Romania, between January 2016 and December 2020, and we identified 37 (53%) patients diagnosed with AR and NP, 25 (36%) patients diagnosed with AR and rhinosinusitis, and eight (11%) patients diagnosed with AR and nasal cancer. The average age of the patients was 53 years old. Every patient included in the study was histopathologically and immunohistochemically diagnosed.

Keywords: allergic rhinitis and nasal polyps, rhinosinusitis, histopathology, immunohistochemistry.

Introduction

At present, the most common atopic disorder in the United States (US) is allergic rhinitis (AR). It occurs when the mucosa of nasal passages becomes inflamed; it is characterized by rhinorrhea, nasal congestion, postnasal drip, and itchiness of the nose [1, 2]. It affects 20–40 million people annually, which means up to 30% of adults and 40% of children [3]. In AR, the inflammatory cascade involves an immediate immunoglobulin E (IgE)-mediated mast cell (MC) response and a late-phase response of basophils, eosinophils, and T-cells driven by the interleukin (IL)-4 and IL-5 cytokines [2]. The most frequent risk factors for AR, in adults, include eczema and a family history of childhood atopy; risk factors for AR include cigarette smoking and higher blood IgE levels [4].

AR is considered a relatively benign disease in terms of the affiliated medical spectrum, but patients with AR can have an impaired quality of life (QoL). They can have difficulty in sleeping, day-time exhaustion, cognitive disturbances, and mood changes [4].

Chronic rhinosinusitis (CRS) is defined as a chronic inflammation of the nasal and paranasal sinus mucosa, characterized by persistent symptoms and typical features during nasal endoscopy and computed tomography (CT) scan [5]. Patients diagnosed with allergies are highly prone to develop sinusitis. Studies showed that the two conditions may coexist in 25% to 70% of patients, while another study found that 72 out of 121 patients with some chronic nasal symptoms and positive skin tests for allergies had positive sinus CT scans for sinusitis [4]. Berrettini *et al.* found a statistically significant increase of sinusitis highlighted by CT scans in patients with perennial AR compared with a control group, and Baroody *et al.*

determined that nasal allergen challenge induced eosinophilic inflammation in the maxillary sinus [6, 7].

CRS was typically divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP), based on the presence or not of polyps on endoscopic examination [5].

NP are typically bilateral inflammatory lesions, that project into the nasal airway. No specific genetic or environmental factors have been strongly linked to the development of this disorder to date, but males are more likely to be affected than females [8, 9].

NP are estimated to occur in 1% to 4% of the US general population [10–12].

NP can be observed in other clinical conditions, such as cystic fibrosis and malignancy, but they are most frequently associated with CRS, giving rise to the name of CRSwNP [8, 13–15].

Histologically, NP are not considered a precancerous condition, nor present an additional risk for the development of nasal cavity/paranasal sinus (NCPS) or nasopharyngeal cancers. The studies show that there is a possible connection between them. In the *Journal of Allergy and Clinical Immunology*, Kim *et al.* used and investigated a large database in Korea. This study suggests that there exists a significant increase in the prevalence of NCPS cancer or nasopharyngeal cancers [9].

Aim

This paper proposes the study the new biomarkers in AR associated with NP and rhinosinusitis, in a group of patients hospitalized within the Ear, Nose & Throat (ENT) Clinic of Timişoara, Romania, that can help us in the diagnosis and treatment of these diseases.

Patients, Materials and Methods

The study performed was a retrospective one, investigating patients admitted for various nasal diseases, between 2016 and 2020, in the ENT Clinic of the Emergency City Hospital, Timişoara, with the purpose of studying AR associated with NP and rhinosinusitis. The study was approved by the Ethics Committee of the Emergency City Hospital, Timişoara. The data referring to the patients' age, gender, social environment, clinical and biological aspects, and histopathological (HP) diagnoses were obtained from patient files and histopathology record.

For the selection of patients with rhinitis associated with NP and rhinosinusitis, there were included the diagnostic criteria for these diseases.

For AR, the selection criteria were patients who presented itchy nose and/or eyes, sneezing, watery rhinorrhea, and nasal congestion/obstruction, varying in duration and severity and positive Prick test.

For NP, patients were diagnosed based on the criteria of the *European Position Paper on Rhinosinusitis and Nasal Polyps* (EPOS) 2020, presenting two or more of the following symptoms: blockage/congestion, discharge, anterior/posterior drip, facial pain/pressure, reduction or loss of smell for at least three months, and endoscopic signs of NP [12,14].

The exclusion criteria for these patients were diseases such as cystic fibrosis, primary ciliary dyskinesia, and diseases with a severe impact on general immunity [14].

Another criterion of exclusion involved patients with histopathologically-confirmed nasosinusal, metastatic or recurrent tumors.

For rhinosinusitis, the inclusion criteria were in accordance with the *EPOS* 2020 Guidelines [14, 15], where CRS is defined as inflammation of the nose and paranasal sinuses characterized by the presence of two or more of the following symptoms for a duration of more than 12 weeks: nasal blockage/obstruction/congestion, nasal discharge, facial pain/pressure, and reduction or loss of smell.

All patients underwent CT scan to confirm the diagnosis.

All patients underwent endoscopic surgery under general anesthesia for the removal of polyps, tumors, or the sampling of the nasal or sinus mucosa for diagnostic purposes. The collected biological materials were fixed in 10% neutral buffered formalin solution and sent to the Laboratory of Pathology, Emergency City Hospital, Timişoara for HP study.

The tissue fragments were embedded in paraffin using the usual HP protocol. Then, they were sectioned with a microtome and stained with Hematoxylin–Eosin (HE) for the HP study.

For the immunohistochemistry (IHC) studies, the tissue sections were collected on special slides covered with poly-L-lysine to increase the adhesion between the section and the histological slide.

For the specific highlighting of inflammatory cells, the following antibodies were used: anti-cluster of differentiation (CD)3 (monoclonal mouse anti-human CD3, clone F7.2.38, Dako); anti-CD20 (monoclonal mouse anti-human CD20cy, clone L26, Dako); anti-CD79a (monoclonal mouse anti-human CD79a, clone JCB117, Dako); anti-CD68 (monoclonal anti-human CD68, clone KP1, Dako); anti-tryptase (monoclonal mouse anti-human MC tryptase, clone AA1, Dako).

Results

Of the total number of patients diagnosed with nasal pathology hospitalized within the ENT Clinic, Emergency City Hospital, Timişoara, between January 1, 2016 and December 31, 2020, we selected only 70 patients and we identified 41 (58.57%) patients with AR associated with NP, 29 (41.42%) patients with AR associated rhinosinusitis.

In the group of patients with AR and polyposis, there were 26 (63.41%) female and 15 (36.58%) male patients, 68% of these patients had disturbances of sleep.

In the group of patients with AR and sinusitis, there were 14 (48.27%) female and 15 (51.2%) male patients and 59% of these patients had sleep disorders.

Regarding the demographic data from the present study, there was no significant difference between the number of men and women with AR and NP.

It was observed that the patient distribution according to the area of origin is: 58% come from the urban area and 42% from the rural area, possibly due to the easier access to healthcare services.

The frequent allergies observed were pollens (like *Ambrosia artemisiifolia* in 75%), indoor allergens (50%), such as dust mites (55%), pets (43%), and some molds (49%).

Most patients with NP were middle-aged, around 45 years old. In the first group, the average age was 34 years old; in the second group, the average age was 39 years old.

In our study, there was found itchy nose and/or eyes in 85% of the patients, sneezing in 91%, watery rhinorrhea in 87%, and nasal congestion/obstruction in 95%.

The HP study showed major changes of the rhinosinusal mucosa in AR. The damage of the rhinosinusal mucosa was heterogeneous, because it varied from one patient to another and even from one area to another in the same patient. Most commonly, at the level of the covering epithelium, there was observed the reduction up to disappearance of the cilia in the pseudostratified epithelium, the enlargement of the intercellular spaces, the reduction of the caliciform cells with the tendency of squamous metaplasia, the thickening of the basal membrane and even necrosis and even epithelial erosion (Figures 1–3). In other areas of the rhinosinusal mucosa, especially in the glands, it was observed an increase in the number of caliciform cells (Figure 4). All these microscopic changes indicate the damage of the barrier function of the covering epithelium which, under these conditions, allows the penetration of pathogens and allergens into the depth of the rhinosinusal mucosa and the cause of a local inflammatory process in the *lamina propria*, responsible for the onset of clinical symptoms.

In the *lamina propria* of the rhinosinusal mucosa, a more or less intense chronic inflammatory process was identified, mainly formed of eosinophils, but also lymphocytes, plasma cells, MCs and macrophages (Figures 5 and 6). Also, the presence of a well-developed blood vascular network was observed, and, in some cases, the proliferation of local fibroblasts.

The use of IHC techniques allowed the selective identification of inflammatory cells in its own lamina. The use of the anti-CD20 antibody allowed the selective identification of B-lymphocytes. The density of B-lymphocytes was quite varied, being identified areas of rhinosinusal mucosa, more or less infiltrated with this type of cells. It was estimated that the infiltration of the rhinosinusal mucosa with B-lymphocytes was a reduced or moderate one (Figure 7). Instead, T-lymphocytes highlighted with the anti-CD3 antibody were much more identified in both the lamina and the cells of the surface epithelium (Figure 8). The use of anti-CD79a antibody allowed concomitant B-lymphocytes and plasma cells identification. Plasma cells are formed from local differentiation of B-lymphocytes. Together, they produce large amounts of antibodies that provide humoral immunity. As it can be seen on our images (Figure 9), in some areas the rhinosinusal mucosa may contain large amounts of B-lymphocytes and plasma cells, confirming the chronic onset of AR.

Similar to other inflammatory cells, macrophages were present in a larger or smaller number in their own lamina (Figures 10 and 11) by the amount of local antigens.

MCs have been identified in a large number in their own lamina, by using the anti-tryptase antibody. They presented an intense degranulation process all around (Figure 12), thus proving their involvement in the local inflammatory process.

Discussions

In the study conducted, no major difference was observed between the distribution of AR in males and females. Conducted studies reported that the incidence is different by gender during childhood, boys develop AR earlier than girls. They often show their first symptoms at puberty and after that. In the adult period, there were no differences observed [16].

Patients diagnosed with AR have a high predisposition for developing sinusitis. One study shows that both diseases (AR and sinusitis) exist in the same patient between 25–70% of the time [4, 14]. In our study, 36% of patients had AR and sinusitis at the same time. Another study found in a group that 72 of 121 (59.5%) patients with AR and positive skin tests for allergies had positive sinus CT scans for sinusitis [4].

In our study, only 36% of the patients with AR also presented rhinosinusitis. It was shown that, anatomically, patients with AR have some common symptoms like edematous nasal mucosa, damaged nasal cilia, and over-production of secretions, which could lead to a blockage of osteal drainage from the sinuses. This blockage favors the multiplication of bacteria and results in bacterial sinusitis [4, 15].

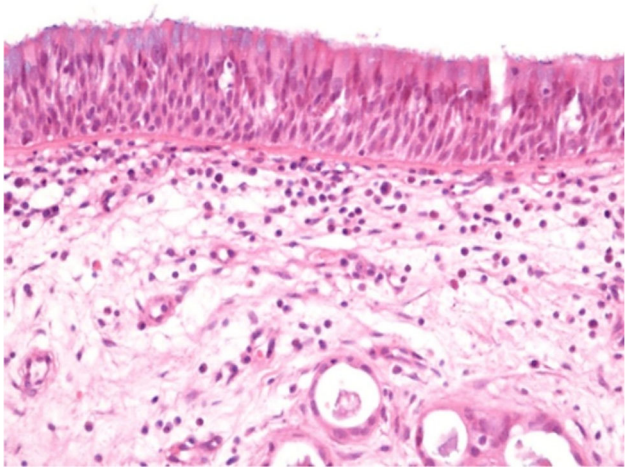

Figure 1 – ***Image of the rhinosinusal mucosa, where there is observed the reduction of cilia from the surface of the epithelium, the widening of the intercellular spaces, the thickening of the basal membrane and a moderate inflammatory infiltrate in the lamina propria. Hematoxylin–Eosin (HE) staining, ×200.***

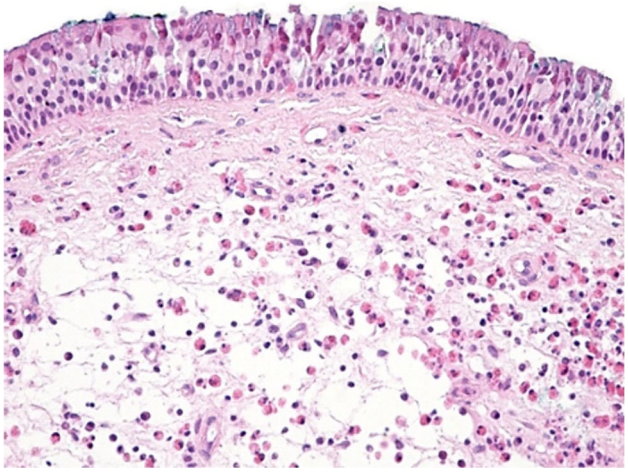

Figure 2 – ***Area of rhinosinusal mucosa with epithelium void of cilia, widening of the intercellular spaces, reduction in the number of caliciform cells and tendency to squamous metaplasia. The chorion is strongly infiltrated with inflammatory cells, mainly with eosinophils. HE staining, ×200.***

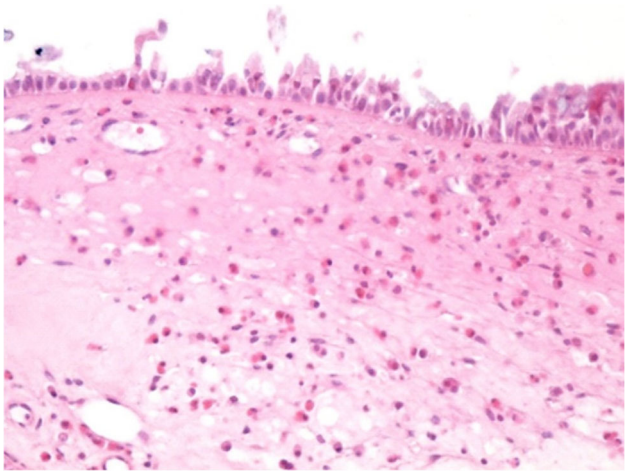

Figure 3 – ***Rhinosinusal mucosa area with partial necrosis of the surface epithelium; the chorion presents a diffuse inflammatory infiltrate formed most of the eosinophils. HE staining, ×200.***

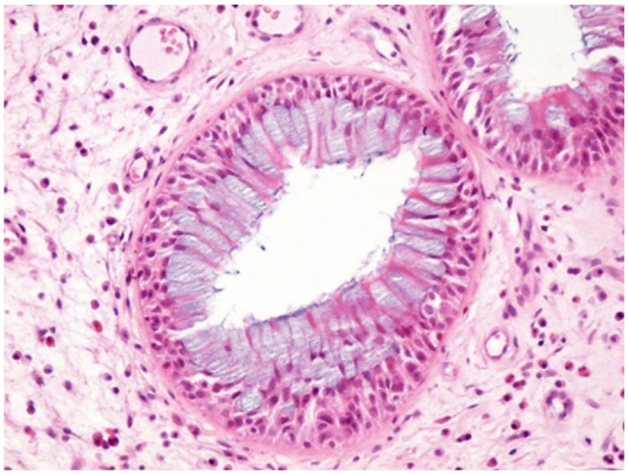

Figure 4 – ***The gland of the rhinosinus mucosa with hyperplasia and hypertrophy of the caliciform cells. HE staining, ×200.***

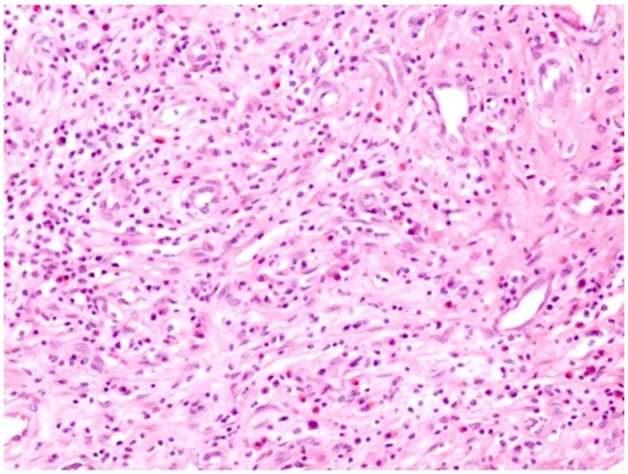

Figure 5 – ***Microscopic image of the lamina propria that is strongly infiltrated with round mononuclear lymphocytes, plasma cells and granulocytes. Of the granulocytes, the presence of an increased number of eosinophils is observed. HE staining, ×200.***

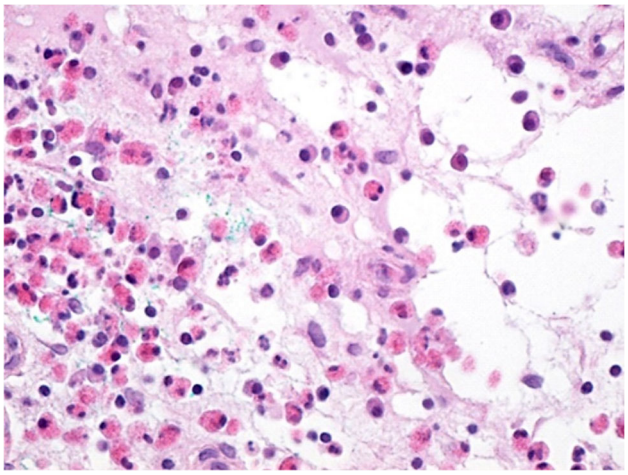

Figure 6 – ***Area of the lamina propria strongly infiltrated with eosinophils. HE staining, ×400.***

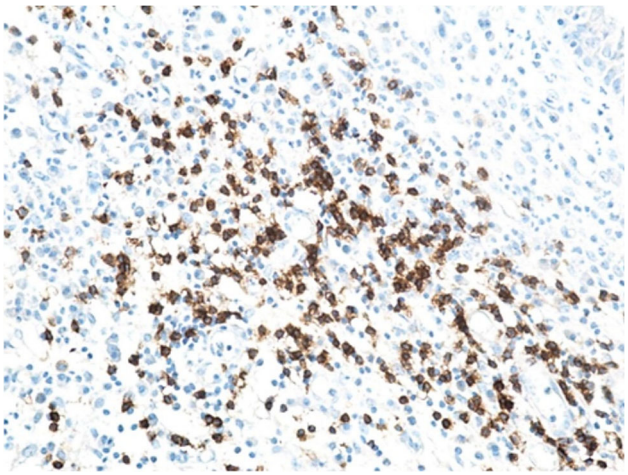

Figure 7 – ***Image of rhinosinusal mucosa with a moderate content of B-lymphocytes in the lamina propria. Immuno-marking with anti-CD3 antibody, ×200. CD3: Cluster of differentiation 3.***

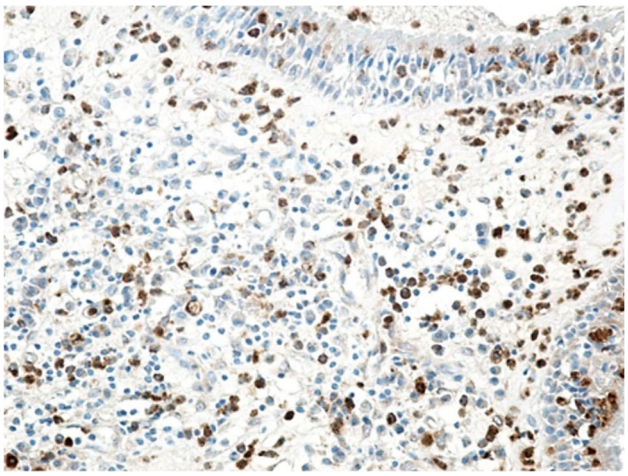

Figure 8 – ***CD3-positive T-lymphocytes present in a large number both in lamina propria and in the cover epithelium. Immunomarking with anti-CD3 antibody, ×200.***

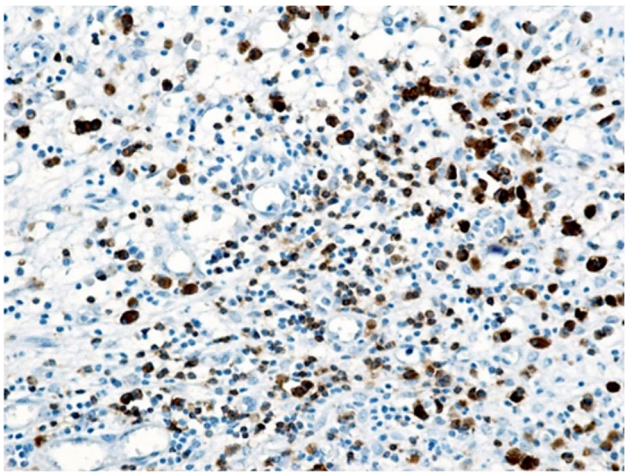

Figure 9 – ***CD79a-positive B-lymphocytes and plasma cells present in a very large number in lamina propria. Immunomarking with anti-CD79a antibody, ×200. CD79a: Cluster of differentiation 79a.***

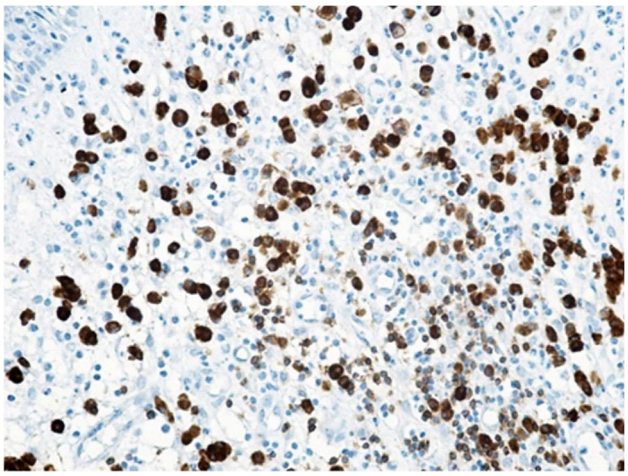

Figure 10 – ***Area of rhinosinusal mucosa with an abundant inflammatory infiltrate in lamina propria where macrophages are well represented. Immunomarking with anti-CD68 antibody, ×200. CD68: Cluster of differentiation 68.***

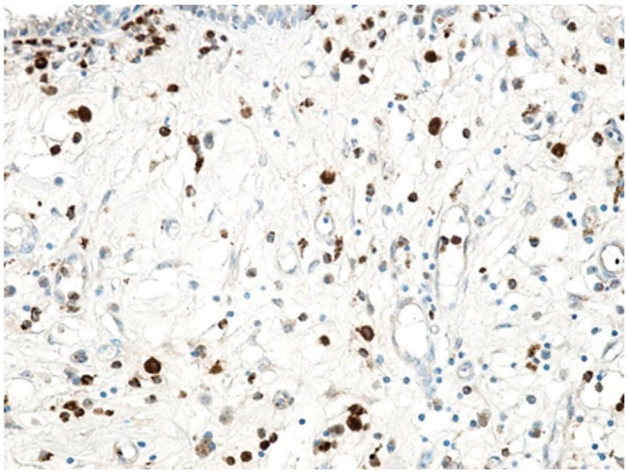

Figure 11 – ***Rhinosinusal mucosa area with a moderate inflammatory infiltrate and a small number of macrophages. Immunomarking with anti-CD68 antibody, ×200.***

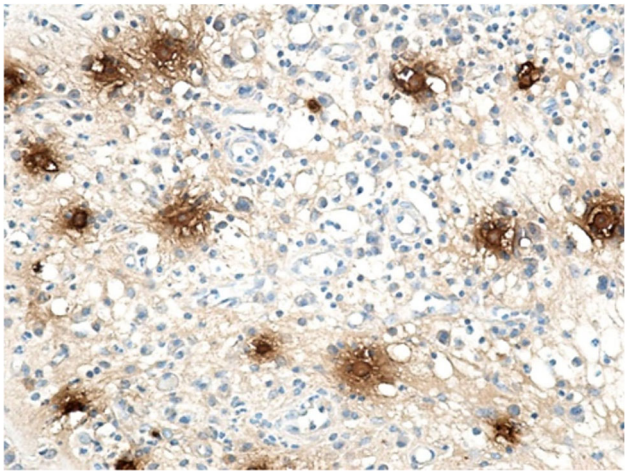

Figure 12 – ***Abundant inflammatory infiltrate with numerous mast cells in a full degranulation process. Immunomarking with the anti-tryptase antibody, ×200.***

The effects of AR have a significant impact on performance in daily activities, especially due to sleep. In the specialized literature, it is mentioned that approximately 61% of patients have disturbed sleep during the acute periods. In our study, the percentages were similar, namely 68%/ 59%/55% [17].

The cytokine profile is different in patients with allergies and sinusitis, when compared to patients with nonallergic sinusitis. NP readily display an increase in granulocyte macrophage colony-stimulating factor, IL-3, IL-4, and IL-5, along with an increased density of CD3- T-lymphocytes [4].

In the study by Hulse *et al.*, there was no significant difference between the median number of CD20+ cells in CRS tissues as compared with the control group [18, 19].

There are several studies in the medical literature describing the relationship between AR and cytokines. It is known that AR is a T-helper 2 (Th2)-dominant disease, as confirmed by multiple studies [1].

Studies show that reduced serum interferon-gamma (IFN-γ) levels were detected in AR patients, indicating the relationship of cytokines with AR to be similar to Th2-based IL-4 and IL-13 [1].

Like in the literature, we have observed that the average age of patients with NP is 50 years old [18, 20]. The type 2 inflammatory response defined by predominance of IL-4, IL-5, and IL-13, and a nasal infiltrate of eosinophils, MCs, and Th2-cells is found especially in patients with CRSwNP [10].

Eosinophilic/IL-5-enriched NP may be a strong predictor of severe NP disease marked by the need for repeated surgery within the patient's lifetime and is associated with severe asthma comorbidity [10].

It was observed that, in NP, the number of CD3+ cells, CD20+ cells, and plasma cells are significantly higher compared to those in other nasal diseases [18].

A key feature in understanding the risk for neoplasia is the nature of the underlying inflammatory pathology. One of the risk factors for malignant transformation is chronic

neutrophilic inflammation, along with viral infections [Epstein–Barr virus (EBV) and human papillomavirus (HPV)] and a genetic predisposition [9]. Squamous cell carcinomas of the sinonasal tract are the most common tumor type to arise in sinonasal cancer [20, 21]. As up to 30% of the population may suffer or may have suffered from AR, there are few studies that show a link between AR and cancer. A study conducted in Taiwan on 3191 patients with AR and cancer noted that the overall risk of developing cancer was 1.02% compared to another Swedish study that had a higher risk level of 1.36%. The highest risk of the development of cancer was for nasal cancer [3, 20].

Conclusions

There is no question that AR is a very common and often very burdensome disease, affecting the QoL in patients, especially daily activities. This leads to low productivity at work or at school, leading to absenteeism and then to economic losses. The main risk factor in this disease is chronic inflammation. The HP study revealed major changes in the rhinosinusal mucosa in patients with AR. At the level of the covering epithelium, the reduction to the disappearance of cilia from the pseudostratified epithelium, the widening of the intercellular spaces, the tendency to squamous metaplasia of the epithelium, the thickening of the basal membrane and even necrosis and epithelial erosions were noted. All these microscopic changes indicate an important alteration of the barrier function of the covering epithelium that allows pathogens and allergens to penetrate deep into the rhinosinusal mucosa and induce a local inflammatory process, responsible for the appearance of clinical symptoms. Sensitive and specific biomarkers are needed to identify for various CRS endotypes, to implement the work-up into clinical practice, and to select the patients who have the best chance of a positive therapeutic response to these innovative approaches.

Conflict of interests

The authors declare that they have no conflict of interests.

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