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LITERATURE REVIEW

Inflammatory cells characteristics in nasal polyposis and comorbidities

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ABSTRACT

Nasal polyposis is a common chronic inflammatory disease of the nasal mucosa characterized by the presence of edematous benign masses in the nasal and paranasal cavities, with a high prevalence, major impact on the quality of life of patients and potential association with asthma. All these led to an increasing interest in nasal polyposis pathophysiology as basis for better treatment modalities. The etiology of nasal polyposis is largely unknown, the common hypothesis suggesting chronic infections, inhalant or food allergies, T-cell disturbances, staphylococcal superantigens intervention, or aerodynamic factors. Chronic eosinophilic inflammation guided by T lymphocytes is the hallmark of nasal polyposis, similar to asthma and allergic rhinitis. An increased risk for allergic subjects to develop nasal polyps was not demonstrated, the association with atopy is controversial. The association of asthma and nasal polyposis is very frequent; in most of the cases, asthma is also associated with aspirin intolerance. Multiple chemical mediators and inflammatory cells have been identified in nasal polyps, but their significance has not been completely elucidated. Recent studies provide new information to allow a better understanding of the pathogenesis of nasal polyposis and possible identification of more efficient therapies.

KEYWORDS: nasal polyposis, inflammatory cells, asthma, allergic rhinitis

INTRODUCTION

Nasal polyposis (NP) is a common chronic inflammatory disease of the nasal mucosa, characterized by the presence of edematous benign masses in the nasal and paranasal cavities, originating from the ethmoidal cells and the middle meatus, and leading to nasal obstruction, secretion, loss of smell, headache, and reduced general well-being.

Treatment with corticosteroids alleviates symptoms, but often patients require recurrent surgical interventions and this, in combination with the symptoms, has a significant effect on the patients' quality of life[1].

The high prevalence of nasal polyposis, the major impact on the quality of life of patients and the potential association of this entity with asthma have led to an increasing interest in their pathophysiology as basis for better treatment modalities. Unfortunately, the etiology of NP is largely unknown. There are numerous hypotheses which include chronic infections (viruses, bacteria, fungi), inhalant or food allergies, T-cell disturbances, and aerodynamic factors. Nasal polyposis coexists in various proportions with allergic rhinitis and/or asthma. Data to support this correlation comes from epidemiological evidence and also from common inflammatory characteristics. Subpopulations of asthmatic patients with aspirin sensitivity or cystic fibrosis have a particular high incidence of nasal polyps. Interaction between the different immune cells that orchestrate the inflammatory process underlying the development of polyposis has been extensively studied. Chronic eosinophilic inflammation guided by T lymphocytes is the hallmark of nasal polyposis, similar to asthma and allergic rhinitis. The following material attempts to update the information about the involvement of inflammatory cells in nasal polyposis and their particularities in case of association of NP with asthma and/or allergic rhinitis.

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EPIDEMIOLOGICAL FEATURES IN NASAL POLYPOSIS

Recommended epidemiologic studies[2] are based on nasal endoscopy and/or specific questionnaires in order to identify the prevalence of nasal polyposis and its association with other comorbidities. According to data from literature, from 0.5 to 4.5% of subjects with allergic rhinitis have NP, similar with the normal population[2]. Some published data show a prevalence of allergy in patients with NP varying from 10%[3], to 54%[4] and 64%[5], but other studies failed to demonstrate that atopy is more prevalent in patients with NP[2]. Recently[6] was found an association between levels of total and specific immunoglobulin E and eosinophilic infiltration in NP. However, findings are unrelated with skin prick tests results[2]. There is also reported higher prevalence of food sensitivities revealed by questionnaires and intradermal tests for food allergens. Based on questionnaires, food allergy was found in 22[7] to 31%[8] of patients with NP, higher than in patients without NP, but the possible role of food allergy in initiation and persistence of NP remains to be investigated. In some studied groups, polyps were found in only 0.5% of 3000 consecutive atopic patients' examined[9]. An increased risk for allergic subjects to develop nasal polyps was not demonstrated. Seasonal allergen exposure in patients with nasal polyps also does not seem to enhance symptoms or markers of eosinophilic inflammation such as eosinophil percentage or eosinophil cationic protein concentration in nasal secretions. Although elevated total IgE was found in polyp fluid, there is no difference between polyps from allergic and non-allergic subjects. It was recently demonstrated that skin prick tests do not predict total IgE levels in polyp homogenates. In contrast, local high total IgE concentrations are most likely due to local production of *Staphylococcus aureus* enterotoxins, acting as superantigens and inducing polyclonal IgE formation[9].

Asthma-like symptoms are described in a subgroup of patients with NP[10], wheezing and respiratory discomfort being described in 31 to 42% of patients with NP, while diagnosed asthma was reported in 26% of patients[2], some studies reporting proportion of even 20–70%[11]. A long-term follow-up study confirmed that the incidence of subsequent clinically significant bronchial asthma was much higher than in the general population. Interestingly, it was reported that patients with nasal polyposis and asymptomatic bronchial hyperreactivity have an eosinophilic bronchial inflammation similar to that observed in asthmatic patients with nasal polyposis, whereas patients with nasal polyposis without bronchial hyperreactivity do not have eosinophilic lower airways inflammation[11].

Study of inverse correlation between asthma and polyposis showed the presence of NP in about 7% asthmatic patients with a higher prevalence in non-atopic asthma (13%) compared with atopic asthma (5%)[2]. Regarding the temporal relation between the development of asthma and polyposis, it has been shown that asthma develops first in approximately 69% of patients with asthma and NP, 10% develop NP and asthma simultaneously and the remainder develop NP first. The presence of NP is more important in patients with aspirin sensitivity (36-96%)[2], in the common clinical picture of aspirin intolerant asthma described as Widal triade. So, the prevalence of NP is increased in asthma, but this does not seem to be true also for patients with allergic rhinitis.

INFLAMMATORY CELLS IN NASAL POLYPOSIS

Usually, the histopathologic findings in polyp tissue are: epithelial damage, thickened basement membrane and edematous or fibrotic stromal tissue, with a reduced number of vessels and glands and no neural structure. The stroma of mature polyps is invaded by fibroblasts and inflammatory cells. The main inflammatory cells are represented by activated eosinophils, except for cystic fibrosis and chronic rhinosinusitis where the predominant cells are lymphocytes and neutrophils[2]. Nasal polyposis pathogenesis is not fully understood. It is possible that features of the NP are similar to those of comorbidities, but sometimes, characteristics of polyp tissue could be dictated by the type of associated disease. Similar typical findings can be found in microscopic examinations of nasal polyps, when compared with the bronchial mucosa of patients with asthma. In both tissues there is epithelial damage, goblet cell hyperplasia, thickening of the basement membrane, accumulation of extracellular matrix, fibrosis and eosinophil-dominated inflammation[12].

The link between asthma and NP is suggested also by the observation that the nasal polyp eosinophilic inflammation is significantly higher in NP patients with concomitant asthma, when compared with nonasthmatic NP patients[13-16].

On the other hand, it has been demonstrated that there are differences in eosinophil recruitment between allergic (IL-5) and nonallergic nasal polyps (granulocyte macrophage-colony stimulating factor (GM-CSF))[17]. These examples indicate the heterogeneity of

nasal polyposis and the difficulties in separating the factors important for the development of an underlying disease from the factors important for NP.

Eosinophils There is a declared similarity between NP and asthma: eosinophil-dominated inflammation[12]. The activated infiltrating eosinophils produce a large amount of toxic proteins, such as eosinophilic cationic protein (ECP) and major basic protein (MBP), cytokines, chemokines and growth factors (interleukin-5 (IL-5), GM-CSF, RANTES and GRO-a). All these molecules are important for perpetuating inflammation and prolong the life span of infiltrating eosinophils in an autocrine fashion. It is not well known what initiates the influx of activated eosinophils into nasal polyps. It is generally assumed that eosinophil infiltration is a hallmark of allergy. It was discovered that in patients with allergic rhinitis and NP the recruitment of eosinophil is dictated by the IL-5[17], different from non-allergic, nonasthmatic and aspirin-tolerant NP patients, where the eosinophil influx is determined by the GM-CSF. Finally, the eosinophil infiltration is similar in both atopic and nonatopic NP[18-21]. Instead, in asthmatic and aspirin-intolerant patients, polyp tissue contains high levels of eosinophils and total IgE[22] and there is a correlation between the extent of eosinophilia and disease severity[12]. Another study revealed that eosinophil infiltration and level of Alternaria-specific IgE in nasal tissue containing polyps is higher in polyp tissue than in non-polyp tissues, suggesting a possible role of Alternaria in eosinophil infiltration and nasal polyposis pathogenesis[23]. Nasal polyposis and rhinosinusitis in patients with aspirin sensitivity are characterized by highly intense tissue eosinophilia. Staphylococcus aureus-derived enterotoxins (SEs) are a group of molecules with superantigenic activity and potent stimulatory effect on T-cell, eosinophils, neutrophils and other inflammatory cells involved in asthmatic inflammation[24]. Presence of specific IgE to SEs has been originally associated with the development of eosinophilic inflammation in nasal polyps, but also with allergic rhinitis and atopic dermatitis[25]. Specific IgE antibodies to SEs may also be present in sera of apparently healthy subjects; however, both colonization rates and antibody titres are significantly increased in patients with chronic upper airway inflammatory diseases (rhinosinusitis, nasal polyposis and allergic rhinitis) and are related to other markers of eosinophilic inflammation (ECP, IL-5 and eotaxin)[26,27]. One study showed that patients with asthma have increased rate of sensitization to Staphylococcal enterotoxins when compared to healthy controls and found a weak association of the prevalence and concentration of anti-SEs IgE in serum of aspirin-sensitive asthmatics when compared to aspirin-tolerant patients, despite higher blood eosinophilia in the former group. This may suggest that increased immune response to SE antigens may represent a local mechanism related to aspirin-sensitive rhinosinusitis/polyposis[25]. In aspirin-intolerant subjects, adverse bronchial and nasal reactions to cyclooxygenase (COX) inhibitors are associated with over-production of cysteinyl-leukotrienes (cys-LTs) generated by the 5-lipoxygenase (5-LO) pathway. A high expression of LTC4 synthase in mucosal eosinophils is also present and is closely linked to aspirin intolerance in the nasal airway, as in the bronchial airways[28].

Lymphocytes Chronic rhinosinusitis with polyposis is characterized by biased Th2 inflammation, while chronic rhinosinusitis without nasal polyps by a Th1 immune response[29]. Published information about lymphocytes reveal an increased number of T-lymphocytes CD3+ and activated lymphocytes CD25 in NP patients compared to control group[2]. In non-allergic patients, polyp tissue tends to contain fewer CD4+ cells in the epithelium and more CD8+ cells in lamina propria[30].

Some researchers detected *Staphylococcus aureus* in the mucosa of NP and also intracellular in nasal polyp epithelial cells and demonstrated its capability to induce IL-6 synthesis, thus contributing to the TH-2 cytokine pattern in NP[31]. It seems that naïve B-lymphocytes (CD20) are not present in polyp tissue, although a significantly high number of plasma cells (CD138) is found in NP, associated with increased synthesis of IgA, IgE and IgG[2]. One recent study evaluated the regulatory T cells (T(reg)) in nasal mucosa of patients with allergic rhinitis (AR) and nasal polyposis[32] and the results showed that more forkhead box P3 (FoxP3)(+) cells were found in AR with polyps than in those with AR alone. Further studies revealed that these FoxP3(+) T cells from AR/NP group also expressed interleukin (IL)-17. In vitro studies showed that staphylococcal enterotoxin B (SEB) induced CD4(+) FoxP3(+) T cells to become FoxP3(+) IL-17(+) cells via facilitating the expression of IL-6, that in synergy with transforming growth factor-beta, induce the expression of IL-17 in FoxP3(+) cells. The mentioned studies conclusion was that the presence of IL-17(+) FoxP3(+) T cells may play a role in the remodeling of the nasal airways in certain people who develop polyps, irrespective of whether or not they are atopic. A small study of 32 NP patients and 32 controls[33] whose purpose was to determine CD4 and CD8 total lymphocyte count, showed that CD4/CD8 ratio was sig-

nificantly lower in the patients group, suggesting that a change in the amount of CD4 and CD8 lymphocytes and an increased level of local IgE contribute to nasal polyposis. A similar research[34] measured, using flow cytometry, the CD4+, CD8+, CD3+, CD19+, B7-H1+ and PD-1+ lymphocyte populations. Lymphocytes from nasal polyps had significantly fewer CD4+ but significantly more CD8+ T-cells compared with lymphocytes from the peripheral blood of patients and controls. The percentages of CD19+/B7-H1+ B-cells and of CD3+/PD-1+ T-cells were significantly higher in the nasal polyp samples than in those from peripheral blood of patients and controls. This study suggest that changes in the T-lymphocyte subpopulations and in the up-regulation of B7-H1 and PD-1 in lymphocytes infiltrating nasal polyps may be involved in the development of the chronic inflammation associated with nasal polyposis.

Another study characterized the varieties of T-cell infiltrates in tissue collected from patients with chronic rhinosinusitis with nasal polyps, analyzed the cytokine profiles of these infiltrating T cells, and determined whether infiltrating T lymphocytes are specific for superantigens[35]. The results revealed total numbers and proportions of CD3+, CD4+, and CD8+ T cells significantly higher in the mucosa and polyp tissue of patients with NP than in the control group. Furthermore, interferon-γ (IFN-γ) expression was significantly higher than interleukin (IL)-10 and IL-4 expression in infiltrating T cells isolated from both the mucosa and the polyp tissue. IFN-γ also showed significantly greater increases in expression compared to IL-4 and IL-10 when isolated T cells were stimulated with superantigens in vitro. Other findings related to NP and lymphocytes are that the migrating potential of Treg lymphocytes is decreased in patients with polyposis, and this may be one of the reasons why tissue number of Treg was lower as seen in the immunohistochemistry of nasal polyps from NP subjects[36].

In another study, examination of the infiltration of natural killer T (NKT) and type 1 helper T (Th1)/type 2 helper T (Th2) cells, and of the cytokine expression in the sinus mucosa showed that NKT cells are present in varying degrees in the sinus mucosa from asthmatic NP patients, but neither in the non-asthmatics nor in the nasal mucosa from the patients with allergic rhinitis. The Th2 cells and Th2 cytokines were expressed at significantly higher levels in the sinus mucosa from the chronic sinusitis patients with asthma in comparison to those without asthma[37]. B-cell responses may play a role in the pathogenesis of nasal polyposis via local IgA and IgE production and activation of eosinophils and mast cells. Levels of protein and mRNA for selected B-cell chemokines (B-cell attracting chemokine 1 (CXCL13/BCA-1/BLC)), thymus expressed chemokine (CCL25/TECK), mucosa-associated epithelial chemokine (CCL28/MEC), stromal cell-derived factor-1alpha (CXCL12/SDF-1alpha), and selected chemokine receptor genes (CXCR4, CXCR5, and CXCR7) were detected by ELISA and reverse-transcription polymerase chain reaction in polyp and inferior turbinate tissues. Higher levels of BCA-1 and SDF-1alpha protein in polyp tissue may account for an increased presence of B cells and their products, contributing to eosinophilic inflammation in patients with NP[38].

In a comparison of histopathological characteristics of polyps in asthmatic and nonasthmatic patients according to the following seven light microscopic findings: basement membrane thickness, goblet cell hyperplasia, subepithelial edema, submucous gland formation, eosinophilic infiltration, lymphocytic infiltration, and polymorphonuclear infiltration, the result was that basement membrane thickening, goblet cell hyperplasia, and eosinophilic and lymphocytic infiltration were more prominent in the asthmatic compared with the nonasthmatic group, whereas polymorphonuclear infiltration was more prominent in non-asthmatics. Asthmatic patients present histopathological characteristics of a marked chronic inflammatory reaction, which might explain the negative effect on chronic rhinosinusitis outcome and the severity of the disease in this group[39].

All the mentioned data contribute to a better understanding of cellular substrate of NP but also highlight the need for future studies.

MACROPHAGES AND DENDRITIC CELLS

According to published data[2], macrophage number is slightly increased in nasal polyps and the number of macrophage mannose receptors (MMR) and innate pattern recognizing receptors expressed by these cells is also increased[40]. Decreased phagocytosis of *Staphylococcus* aureus and a macrophage M2 (CD206(+) HLADR(+) CD14(+) CD11c(+) CD20(-)) activation phenotype in chronic rhinosinusitis with NP could potentially contribute to persistence of chronic inflammation because phagocytosis of *S.* aureus by human tissue derived macrophages is reduced in NP as compared to macrophages from the control inferior turbinates[41]. The expression of prolactine in nasal polyps was determined by immunohistochemical staining and the expression of macrophages (CD68) was investigated in a

group of NP patients, compared to group control. The results showed a stronger presence of prolactine with main cell source represented by macrophages, suggesting a role for prolactine derived from macrophages of nasal mucosa in the formation of nasal polyp through its local immune modulation[42]. Dendritic cell (DC) activation and antigen presentation to T cells are critical to innate and adaptive immunity and they have a very well defined role in allergy and asthma. The knowledge on dendritic cells in nasal polyposis is limited; they are present and express the high affinity IgE receptors[2]. Sinonasal biopsy specimens from patients with eosinophilic nonatopic nasal polyposis, allergic fungal sinusitis, and nondiseased patients were stained immunohistochemically for pattern recognition receptors (CD14, TLR2, and TLR4), mature DC marker (CD208), iDC marker (CD209), or isotype controls. The results indicate progressive DC activation and emigration of mature antigen-presenting cells from the epithelial surfaces of sinonasal mucosa[43].

Mast cells represent one of the most important cells in the development of sensitization and acute phase of allergic reactions. The number of mast cells is mentioned not to be different between controls and nasal polyps, but they are often IgE-positive, especially in asthma, independent of atopy[44]. Older studies mentioned a degranulation of mast cells lower in nasal polyposis than in allergic rhinitis or aspirin intolerance, suggesting that mast cell degranulation plays an important role in the formation of nasal polyps, but it may not only be an IgE-dependent mechanism[45]. However, the degranulation of mast cells is greater in polyp tissue compared to inferior turbinate[46]. In one study whose purpose was to detect cysteinyl leukotriene (Cys-LT) receptors in aspirin-sensitive nasal polyposis patients, and to compare them with nasal polyposis and chronic rhinosinusitis patients without aspirin sensitivity, the infiltration with mast cells and eosinophils of nasal polyps from aspirin-sensitive patients was higher, Cys-LT(1) receptor proportions in these inflammatory cells were found to be higher and Cys-LT(1) receptor immunoreactivity in eosinophils and mast cells was increased[47]. A recent study observed the pathologic characteristics, and investigated mast cell and its activation in chronic rhinosinusitis without nasal polyps and their relations with eosinophilic inflammation. More serious inflammation but no more mast cells compared with inferior turbinate were observed, and there were no correlations between mast cell and its activation with eosinophil count, which suggests that mast cell and eosinophilic inflammation mediated by it may not play an important role in the pathogenesis of chronic rhinosinusitis with nasal polyposis[48].

Neutrophils There is an increased number of neutrophils and also an increased amount of their contents in nasal polyps, but the neutrophils are much better represented in chronic rhinosinusitis without polyposis and even higher in NP from cystic fibrosis[2]. An analysis of the inflammatory patterns in chronic rhinosinusitis without nasal polyps and with nasal polyps revealed that nasal polyps do not represent one single entity; interleukin (IL)-5-positive nasal polyps can be differentiated from IL-5-negative forms by different inflammatory patterns, with predominance of eosinophils in the first form and a predominance of neutrophils in the second one[49].

EPITHELIAL CELLS AND ENDOTHELIAL CELLS

The epithelium is not just a physical barrier, but is also an active contributor to responses to allergens, pollutants, infectious agents and irritants. Epithelial damage has been implicated in the pathogenesis of polyps. The epithelial cells release various factors that play a role in the inflammatory response and subsequent repair. The epithelium of nasal polyps shows goblet cell hyperplasia and mucous hypersecretion that may play a role in nasal obstruction and rhinorrhea. It produces a wide range of mediators that can regulate inflammatory cell recruitment to the airways, has altered functions in asthma and epithelial cells, contribute to airway remodeling and also have an important role in immunoregulation in the airways[11].

Human nasal epithelial cells contain and secrete IL-8, GMCSF, eotaxin, eotaxin-2 and RANTES, and thus may provide enough growth factors to attract eosinophils[50, 51], with GMCSF being important for the survival of those cells[52].

Epithelial cells also release stem cell factor (SCF), a cytokine with chemotactic and survival activity for mast cells, with the expression of SCF mRNA correlating to SCF protein, and with the density of mast cells in epithelial and stromal layers of nasal polyps[2]. Nasal polyp epithelial cells also express increased amounts of LL-37, an antimicrobial peptide[53], but down-regulate the level of TLR9 expression[54], and are thus directly involved in innate immunity functions. An investigation of influence of epithelial cell secretions from both nasal polyps (NP) and normal nasal mucosa on in vitro eosinophil survival, eosinophil infiltration into the respiratory mucosa during allergic reaction and nasal

polyposis showed that these may be modulated at least in part by GM-CSF from epithelial cells; and, secondly, epithelial cells from NP might have a more potent effect on inducing eosinophil infiltration of the respiratory mucosa than epithelial cells from normal mucosa[55]. Recurrence of the nasal polyposis is prevalent and a severe problem and it seems that the proliferative activity in the surface epithelial cells of recurring nasal polyps is significantly higher than that in nonrecurring nasal polyps[56]. Staphylococcus aureus and intracellular residency of S. aureus in nasal polyp epithelial cells induce TH-2 cytokines response in vitro[57]. Leptin is a pleiotropic hormone that regulates food intake and metabolic and endocrine functions. Serum leptin levels have been reported to be increased in patients with allergic rhinitis and nasal polyposis. Leptin receptor expression was found stronger in the nasal polyps than in the normal nasal mucosa. In human nasal polyp epithelial cells, leptin increased the expression of major respiratory mucins (MUC5AC and MUC5B), in a dose- and time-dependent manner, at the gene and protein levels. The conclusion of the researchers is that the increased expression of leptin receptors in nasal polyps implies that leptin has a certain role in nasal polyposis. In addition, leptin appears to induce the expression of MUC5AC and MUC5B through leptin receptors in the human nasal polyp epithelial cells[58].

The nasal epithelium is the first barrier encountered by airborne allergens and is an active participant in airway inflammation. Fungi have been increasingly recognized as important pathogens in sinusitis and airway diseases. The stimulation with Alternaria and Aspergillus of nasal polyp epithelial cells obtained from patients was followed by an increased synthesis of Interleukin-8 (IL-8) and granulocyte macrophage colony-stimulating factor (GM-CSF by the epithelial cells. The results of this study showed that fungi interact with nasal epithelial cells and enhance the production of cytokines and TLR mRNA expression[59].

Endothelium maintains tissue homeostasis by stereotypical responses during coagulation, wound healing, inflammation, and immunity. Endothelial cells express adhesion molecules like VCAM-1, induced by IL-4 and IL13, which play an important role for the preferential recruitment of eosinophils and T lymphocytes[60]. Vascular permeability/vascular endothelial growth factor (VPF/VEGF) plays an important role in inducing angiogenesis and modulating capillary permeability. In fact, the expression of VPF/VEGF in specimens of nasal polyps was significantly stronger than in specimens of healthy nasal mucosa of controls[61]. Epithelium is a significant, but not the sole, source of VEGF in polyp tissue[62]. VEGF is a known potent endothelial cell mitogen and vascular permeability factor, an inducer of remodeling in asthma by enhancing helper T cell type 2–mediated antigen sensitization and inflammation in the lung and by increasing the number of activated DC2 dendritic cells. VEGF has been shown to be increased in asthmatic airways and correlates directly with disease activity and inversely with airway caliber and airway responsiveness. New data demonstrate that VEGF is a novel biomarker for chronic rhinosinusitis with hyperplastic sinonasal polyposis that functions in an autocrine feed-forward manner to promote nasal epithelial cell growth and to inhibit apoptosis[63]. The markedly increased expression in nasal polyps as opposed to healthy nasal mucosa suggests that VPF/VEGF may play a significant role in both the formation of nasal polyps and in the induction of heavy tissue oedema[64].

CONCLUSIONS

Nasal polyposis is a heterogeneous disease with immunological substrate and still debated pathogenesis. The etiology of nasal polyposis is largely unknown. The usual hypothesis suggests chronic infections, inhalant or food allergies, T-cell disturbances, staphylococcal superantigens intervention, or aerodynamic factors. Although the characteristic eosinophilic inflammation is a shared feature of asthma and allergic rhinitis, they are not necessarily similar diseases. The coexistence of asthma and nasal polyposis with or without aspirin intolerance is a frequent finding, with a higher incidence of nasal polyposis in asthma and aspirin intolerance.

An increased risk for allergic subjects to develop nasal polyps was not demonstrated, and the association with atopy is controversial. Multiple chemical mediators and inflammatory cells have been identified in nasal polyps, but their significance has not been completely elucidated. Recent studies provide new information to allow a better understanding of the pathogenesis of nasal polyposis, future studies are still needed for a more complete knowledge of the disease and possible identification of new therapeutic ways.

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