EDITORIAL

RHINOSINUSITIS AND ASTHMA: A VERY LONG ENGAGEMENT

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Upper and lower airways may be considered as a unique entity, interested by coexisting inflammatory processes that share common etiopathogenic mechanisms. Previous studies have strongly demonstrated a relationship between rhinosinusitis and asthma. This has led to the introduction of the concept of "united airways", which has also been included in the WHO document Allergic Rhinitis and its Impact on Asthma (ARIA); this concept has important consequences also on the treatment of these disorders. To better summarize the evident connection between upper and lower airway disease we decided to describe it as a multilayered construction, each level pointing out more deeply the relationship between these entities.

Upper and lower airways may be considered as a unique entity, interested by coexisting inflammatory processes that share common etiopathogenic mechanisms. Epidemiological, clinical and pathophysiological studies have strongly demonstrated a relationship between airway disorders, namely rhinosinusitis and asthma (1). This has led to the introduction of the concept of "united airways", also known as "one airway, one disease", which has also been included in the WHO document Allergic Rhinitis and its Impact on Asthma (ARIA) (2). According to this model, allergic rhinitis and asthma are one syndrome, expressed in two different parts of the respiratory tract; furthermore, allergic inflammation is associated with an increased likelihood of developing rhinosinusitis (3, 4).

This concept has important consequences on the treatment of these disorders (5, 6). Asthma must be treated considering its various triggers and possibly eliminating them. Consequently, after a diagnosis of asthma, a screening for upper airway diseases should be contemplated (5). Similarly, patients with rhinosinusitis should be evaluated for a possible concomitant asthma (6). To better summarize the evident connection between upper and lower airway disease we decided to describe it as a multilayered construction, each level pointing out more deeply the relationship between these entities.

EPIDEMIOLOGIC LEVEL

Epidemiology can highlight associations and cause-effect relationships between rhinosinusitis and asthma. Many studies have strongly shown the co-existence of rhinitis and asthma (1, 3, 7). Most patients with asthma also have rhinitis, whereas there is an increased risk of asthma in subjects with allergic rhinitis and to a lesser extent non-allergic rhinitis (4). In particular, epidemiological data suggest that up to 80% asthma patients also suffer from allergic rhinitis, and up to 40% of patients with rhinitis also have asthma (3). Allergic rhinitis often

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precedes the development of asthma in children, and this sequence is commonly called the atopic march. Large studies have found a link between the severity and/or control of both diseases in children and adults; in particular, poor asthma control is linked to moderate-severe rhinitis, which should be identified and treated (5). Numerous studies have also shown that treatment of AR will improve asthma outcome (1, 5). According to some studies (8), asthma is more common in patients with moderate-to-severe persistent rhinitis; according to others, there is no correlation between ARIA categories of rhinitis and prevalence of asthma (9). Rhinitis is a significant and independent risk factor for asthma onset, as it often precedes bronchial hyperreactivity (1). AR has also been linked to "small airway disease", defined as a reduction in forced expiratory flow (FEF) at 25%-75% of the pulmonary volume and a normal spirometry, which is suggested to be an early marker of bronchial involvement in patients with rhinitis who perceive only nasal symptoms (10).

On the contrary, the correlation between allergic rhinitis and the development of sinus pathology is not fully understood. Evidence is not enough to support the role of allergic rhinitis in the etiopathogenesis of chronic rhinosinusitis. A recent study (11) considered a cohort of 4,044 children with chronic rhinosinusitis and found a prevalence of allergic rhinitis of 27%, a value that falls within the range of prevalence of allergic rhinitis in the pediatric population, which has been estimated from 10 to 40% (12). Chronic rhinosinusitis encompasses a heterogeneous group of disorders that manifest themselves with chronic mucosal inflammation of nose and paranasal sinuses. Sinus inflammation has a multifactorial aetiology in which not only allergic inflammation, but also other factors are involved (4). IgE-mediated inflammation of nasal mucosa determines nasal congestion, leading to impaired drainage of mucus at the ostiomeatal complex (6). Stagnation of secretions, decreased ventilation, mucosal inflammation and decreased mucociliary transport all contribute to facilitate bacterial infection (6). Besides, recent works have shown that nasal challenge with allergen causes also secondary maxillary sinus inflammatory response in addition to nasal inflammatory changes (13). These findings might help explain the close relationship between allergic rhinitis and rhinosinusitis, two very common diseases that frequently coexist. There are not many studies on the comorbidity of asthma and chronic rhinosinusitis. While the epidemiological association between chronic rhinosinusitis and asthma has been clearly established, the exact pathophysiologic mechanism remains controversial (14). A recent Global Allergy and Asthma Network of Excellence (GA2LEN) survey (15) demonstrated a strong association of asthma with chronic rhinosinusitis. The relationship was greater in subjects with both chronic rhinosinusitis and allergic rhinitis, while chronic rhinosinusitis without nasal allergy was associated with late-onset asthma (15). It has been estimated that 20–33% of patients with chronic rhinosinusitis also have asthma, a prevalence nearly four times greater than that of the general population (15). On the other hand, 85% to 90% of patients with asthma have abnormal findings on CT scans of the sinuses (16). A recent Swedish survey showed that 63.9% of subjects with physician-diagnosed asthma had allergic rhinitis, 39.8% had chronic rhinitis and 8.4% had chronic rhinosinusitis (17). On the other hand, prevalence of physician-diagnosed asthma was 19.8% in allergic rhinitis, 16.5% in chronic rhinitis and 24.4% in chronic rhinosinusitis (17). Prevalence of asthma increased with the number of nasal conditions in the patient, including allergic rhinitis, nasal congestion and nose dripping; similarly, chronic rhinosinusitis was ten-fold more common in subjects with four symptoms of asthma than among subjects without asthmatic symptoms. These numbers are in agreement with the findings of a large European multicenter study (7), which demonstrated comorbid rhinitis in 50-77% of subjects with asthma and asthma in 8-23% of patients with rhinitis and with the results of a Belgian study (18), which found a prevalence of asthma of 24% of subjects with chronic rhinosinusitis. In the same Belgian study, 36% of patients with chronic rhinosinusitis had bronchial hyperreactivity (18). Other studies found even higher incidence of bronchial hyperresponsiveness after bronchial provocation test, up to 71% of subjects with chronic rhinosinusitis in the study of Okayama et al. (19). Several works have found a relationship between the severity of sinonasal pathology and that of asthma (1, 11, 20). A Dutch study including 89 patients with severe asthma demonstrated anomalies of CT

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scans in 84% of patients and extensive sinus disease in 24% of patients (21). Besides, there was a direct relationship between the extent of sinus disease, measured as thickness of sinonasal mucosa on CT scan and bronchial inflammation, reflected both by the presence of eosinophils in bronchi and blood and by the level of nitric oxide in exhaled air (21). Another study found that sinonasal pathology, as assessed by clinical symptoms and CT scan, was significantly worse in subjects with severe steroid-dependent asthma than in those with mild-to-moderate asthma, although global frequency of rhinosinusitis was similar in the two groups (16). Similarly, a more recent study showed that increasing severity of asthma was associated with greater radiological severity of chronic rhinosinusitis (evaluated on CT scan using Lund-Mackay score) and a higher prevalence of allergic sensitization and nasal polyposis (22). Interestingly, when the study population was stratified by the presence of polyps, there was no difference in radiological severity of chronic rhinosinusitis between asthmatic and non-asthmatic patients; this suggested that increasing radiological severity associated with worse asthma was attributable to the greater presence of nasal polyps (22). Furthermore, the study highlighted the potential role of allergic sensitization and nasal polyps as additional factors in disease pathogenesis (22). Asthma and chronic rhinosinusitis with nasal polyposis often co-exist, but their relationship is still unclear. A recent work demonstrated a high prevalence of asymptomatic lower airway dysfunction in subjects with chronic rhinosinusitis with nasal polyposis (23); alongside asthmatic individuals, in fact, many patients had a marked elevation of FeNO and/or asymptomatic bronchial hyperreactivity, an impairment of lower airways suggestive of an asthmatic phenotype without clinical asthma (23). The aforementioned Swedish survey found that asthma subjects with chronic rhinosinusitis more lower respiratory symptoms than those with allergic rhinitis as well as those without nasal comorbidities, suggesting that the degree of nasal pathology may be markers of different asthma phenotypes (17). Two clinical trials conducted by the American Lung Association-Asthma Clinical Research Centers (ALAACRC) enrolling asthmatic subjects showed that both allergic rhinitis and rhinosinusitis were associated with more severe asthmatic symptoms in patients with poorly controlled asthma at baseline (24); furthermore, rhinosinusitis (but not allergic rhinitis) was associated with more asthmatic exacerbations (24). In the same study, rhinosinusitis was also associated with worse asthma-related quality of life and more sleep disturbance (24). Globally, many recent works confirm the strong co-occurrence of chronic rhinosinusitis and asthma, suggesting a partially common etiopathogenesis.

ANATOMIC LEVEL

Upper and lower airways are linked both macroscopically and microscopically. The airways are a continuous pathway extending from nose and paranasal sinuses to pulmonary alveoli. The nose holds a pivotal position at the entry of the airways and contributes in protecting the following tract by humidifying, heating and filtering the inspired air. Nasal breathing provides a protective influence against the onset of exercise-induced asthma, whereas oral breathing is more likely to exacerbate symptoms (25). Mouth breathing allows inhaled gas to by-pass the conditioning processes of the nasal mucosa. As a result, increased concentrations of inhaled aeroallergens may reach the lower airways accompanied by increased drying and cooling of bronchial mucosal surfaces. Thus, inhaling cold, dry air at high ventilatory levels via the mouth, as occurs during exercise, can initiate a bronchoconstrictive response in some asthmatic subjects (25). Also nasal pathology leads to the interruption of nasal breathing and, consequently, of nasal shielding function, becoming a potential trigger for bronchial disorders (3). Besides, nasal sinuses become sources of inflammatory discharge, dripping in the lower airways. There are similarities between mucous membranes covering upper and lower airways. They are constantly exposed to the external environment, therefore they act as the first line of defense against microorganisms and atmospheric particulate matter. Both nose and bronchi are lined with a pseudostratified respiratory epithelium made up of columnar ciliated cells. The epithelium has an important barrier function and the loss of its integrity can cause major penetration of microorganisms and antigens, compromising the interaction between the

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host and environmental antigens and predisposing to inflammation (4). Dysfunctions of epithelial barrier can be due to both congenital and acquired factors. Multiple defects in the expression of different epithelially-derived genes could lead to defective barrier function in patients with chronic rhinosinusitis (26). The main constituents of the epithelial barrier are intercellular tight junctions, which have been demonstrated being altered in both asthma and chronic rhinosinusitis with nasal polyps (26, 27). A possible role of proinflammatory cytokines has been suggested by the observation of the disruption of epithelial integrity of the sinonasal mucosa by IFN-γ and IL-4 *in vitro* (26). There are also many environmental factors that can compromise epithelial barrier. For example, rhinovirus infection can disrupt airway epithelial barrier function, facilitating secondary bacterial infection and this effect is independent from proinflammatory cytokines (28). Besides, it was observed that synthetic double-stranded RNA (dsRNA), which reproduced viral dsRNA, could induce disruption of airway epithelial apical junctional complexes via a TLR-3 pathway (28). The greater penetration of inhaled allergens into the subepithelial space could explain the association between viral respiratory tract infections, airway inflammation and allergic sensitization. Similarly, it is known that the allergen Der p 1 of house dust mite Dermatophagoides pteronyssinus is a cysteine proteinase with proteolytic activity that can open epithelial tight junctions (29). Other substances, such as ozone, tobacco smoke, chlorination products and endotoxins are also able to break tight junctions and favor allergic sensitization (27). The airway submucosa is rich in vessels, mucous glands, connective tissue, immune system cells and nerves. Vascularization is richer in nasal mucosa, explaining the higher possible obstruction, while smooth muscle starts in the trachea and allows bronchial constriction (4). The nervous system plays a key role both in physiologic and in pathologic settings. The autonomic nervous system of airway submucosa includes adrenergic, cholinergic and non-adrenergic noncholinergic (NANC) nerves. Adrenergic control of nose and bronchi differs, since α-adrenergic agonists are nasal vasoconstrictors, while ß2-adrenergic agonists are bronchodilators; on the contrary, cholinergic nerves are bronchoconstrictors. Nose and bronchi seem to communicate through a neural reflex pathway. The nasobronchial reflex, first described in the late 1960s, consists of bronchoconstriction and increase in pulmonary resistance following exposure of the nose to cold air or irritants (27). Different studies show that allergen deposition in either nose or bronchi leads to inflammatory changes in a distant site of the airways (30). Consequently, nasal allergen provocation can cause bronchial hyperresponsiveness. The efferent pathway of nasobronchial reflex seems to be due to the activation of the NANC system. The NANC nerves are essentially sensory, but axon reflexes determined by antidromic stimulation of nerve fibers can lead to the release of inflammatory neuropeptides, and particularly substance P, by pulmonary nerves, a phenomenon called neurogenic inflammation (31).

IMMUNOLOGIC LEVEL

Evidence in recent literature demonstrates a systemic and not only anatomical connection between upper and lower airways (3). Inflammatory diseases of the upper airways, such as allergic rhinitis and chronic rhinosinusitis, determine a systemic immune response, with elevated levels of IL-5 in blood and increased bone marrow eosinopoiesis. Besides, nasal allergen provocation determines a raise in blood IL-5, bone marrow eosinopoiesis and blood eosinophilia (32). Inflammatory mediators are released from upper airways into the bloodstream; moreover, allergens are systemically absorbed through nasal mucosa and they could determine systemic activation of immune cells (32). Respiratory chronic inflammatory diseases, including asthma, allergic rhinitis and chronic rhinosinusitis, share several common features. Allergic inflammation is characterized by IgE-dependent mast cell activation and degranulation and by infiltration of eosinophils, determined by activated CD4+ Th_2 lymphocytes (33). The simple paradigm of non-overlapping stable Th_1 and Th_2 subsets of T-helper cells is now rapidly being replaced by that of a more complex spectrum of different Th cells that together drive or control different aspects of allergic inflammation and display more plasticity in their cytokine profiles. At present, these include Th_9, Th_{17}, Th_{22}, and Treg, in addition to Th_1 and Th_2 (33).

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The analysis of upper and lower airway biopsies of individuals suffering from both asthma and allergic rhinitis showed a parallel inflammatory response, with similar numbers of inflammatory cells and possible bidirectional extension of inflammation between the nose and bronchi (34). Hypothetically, different activation states of inflammatory cells could be responsible for the different clinical manifestations. Moreover, in non-asthmatic subjects with allergic rhinitis there is an inflammatory response in lower airways, which is intermediate between that observed in normal individuals and asthmatics and is characterized by the presence of submucosal eosinophils and mast cells (32). On the other hand, an eosinophil infiltration was demonstrated in the nasal mucosa of asthmatic individuals in the absence of allergic rhinitis (35). There is a remarkable overlap between histopathological characteristics of chronic rhinosinusitis and asthma, particularly eosinophilic inflammation and features of airway remodeling, such as shedding of the epithelium and basement membrane thickening (35). The fraction of exhaled nitric oxide (FeNO) has been widely used as a marker of airway inflammation in asthma in recent years. The measure of FeNO has also been used to show the presence of lower airway inflammation in rhinitic patients, with or without asthma (36). It has been demonstrated that forced expiratory flow between 25 and 75 percent of vital capacity (FEF_{25-75}) is strongly and inversely related with FeNO, and FEF_{25-75} may predict high FeNO levels in children with allergic rhinitis, asthma or both (36, 37). Furthermore, FeNO is also strongly related with the response to bronchodilation testing and could predict bronchial reversibility in children with allergic rhinitis or asthma (38).

Therefore, these airway inflammatory diseases might be different site-specific manifestations of the same disorder. Different classes of leukocytes are involved in the persistent inflammation of the nasal mucosa, including eosinophils, whose number is increased in biopsies of subjects with chronic rhinosinusitis, alongside the levels of GM-CSF, IL-3 and IL-5, in comparison to control tissue (33). Besides, a higher involvement of eosinophils has been demonstrated when chronic rhinosinusitis is associated with asthma (39). One study (39) analyzed the cytology of middle meatus lavage in patients with chronic rhinosinusitis, finding a relationship between the predominance of eosinophils in nasal secretions and asthma comorbidity. Therefore, there might exist an effect of upper airway eosinophils over the lower airways. The preponderance of activated eosinophils in an inflammatory infiltrate is associated with major basic protein (MBP) release, epithelial destruction and denudation of basement membrane. The propagation of eosinophil toxic inflammatory products, such as MBP, to the lower airways, both through the bronchi and through systemic circulation might aggravate inflammation of the lower airways (39). The levels of eosinophil products, like MBP, are raised both in asthma (33) and in chronic rhinosinusitis (39). In subjects without allergic diseases chronic rhinosinusitis is associated with non-allergic asthma, in which superantigens seem to play a major role (40). These are proteins derived from different sources, including bacteria, viruses and human hepatic tissue and they are able not only to induce polyclonal activation of T lymphocytes, but also to act broadly on the immune system, affecting B lymphocytes, mast cells, basophils, and chemokine production. Superantigens might also have a superallergen action, activating mast cells and basophils and determining a Th_2 pattern of inflammation, with class-switching of immunoglobulins to IgE (40). A broadly studied superantigen is *Staphylococcus aureus* enterotoxin B (SEB). It was demonstrated that airway mucosal application of SEB is capable of aggravating bronchial allergic inflammation, increasing bronchial eosinophilia, expression of IL-4, IL-5 and IFN-γ in bronchi and blood, bronchial expression of eotaxin-1 and TGF-b and polyclonal IgE levels (40). One study found that these polyclonal IgE antibodies, whose formation in nasal polyps is induced by *Staphylococcus aureus*, are functional and able to activate mast cells, contributing to chronic inflammation (40). Besides, IgE in nasal polyp tissue can be found independently of their presence in serum. In patients with chronic rhinosinusitis the rate of *Staphylococcus aureus* carriage observed at the middle meatus was approximately 35% (40). In subjects with nasal polyposis, on the other hand, specific IgE directed against *Staphylococcus aureus* enterotoxins could be found in nearly 50% of nasal polyp tissue samples (40). These samples were

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characterized by severe eosinophilic inflammation, demonstrated by the increase of IL-5, eotaxin, eosinophil-cationic protein (ECP) and cysteinyl-leukotriene synthesis. Furthermore, many of these individual had comorbid asthma and hypersensitivity to aspirin. A meta-analysis has shown that asthmatic patients were more likely than controls to have serum specific IgE to *Staphylococcus aureus* enterotoxins; on the other hand, the probability of a positive test for local or systemic exposure to *Staphylococcus aureus* and/or or its enterotoxins was higher in subjects with allergic rhinitis (40). Moreover, it was demonstrated that Staphylococcal enterotoxin IgE are risk factors for asthma severity (40). Consequently, *Staphylococcus aureus* superantigens may have a role in the onset and severity of allergic diseases, namely asthma and allergic rhinitis. Not only bacteria, but also fungi, especially Alternaria, may play a role in the generation of chronic rhinosinusitis (41). Cytokines produced by tissue-bound lymphocytes recruit eosinophils, which attack fungi, recognized as strangers by the immune system of patients with chronic rhinosinusitis. Hence, there might be a comorbid IgE-mediated hypersensitivity to molds, but eosinophilic inflammation seems to be driven by a non-IgE-mediated mechanism. Besides, Alternaria is able to induce eosinophil degranulation (41). Therefore, innate eosinophilic response to certain environmental fungi may be important in the onset of inflammatory airways diseases, such as asthma and chronic rhinosinusitis.

As mentioned before, the classic paradigm of Th_1/Th_2 cell-mediated immunity recently evolved to include a novel Th cell subset expressing IL-17, named as Th_{17} cell, which appears to be involved in a number of immune-mediated diseases, including asthma, and also allergic rhinitis and chronic rhinosinusitis (42). In particular, moderate and severe asthma phenotypes have been associated with increased neutrophils and increased Th_{17} cytokines, IL-17A, IL-17F, and IL-22, in the bronchoalveolar lavage fluid of patients (42). IL-17A has also been shown to be elevated in the sputum of patients with severe asthma and the levels correlated with neutrophil chemokines such as IL-8 as well as neutrophil numbers (42). In addition, Th_{17} cytokines also induce mucous cell metaplasia and have pleotropic effects on airway smooth muscle resulting in airway narrowing (42). Moreover, Th_{17} cells may promote both eosinophilic and neutrophilic inflammation in allergic rhinitis and chronic rhinosinusitis (43).

Despite these recent findings, further studies are needed to further define the role of Th_{17}-cytokines in regulating allergic airway inflammation.

GENETIC LEVEL

Allergic diseases, allergic rhinitis and asthma included, usually recur inside families, proving an underlying hereditary component. Nevertheless, the increase in the prevalence of these disorders has occurred in only a few decades, a time lapse too short for major changes in the genetic patrimony of the population. Therefore, environment and lifestyle modifications had an undeniable role in this epidemiological change. Several studies have led to the identification of genes possibly involved in development of IgE-mediated immune responses, sensitization to allergens or clinical manifestations of allergy (44). There are only a few genome-wide association studies concerning rhinitis, and they all seem to point to the importance of genes implicated in immunoregulation, Th_2 response and innate immunity. A recent genome-wide association meta-analysis identified only a few loci that associated with the risk of allergic rhinitis and grass pollen sensitization. The HLA variant rs7775228 was strongly associated with grass sensitization and weakly with allergic rhinitis; various loci in the HLA region have been implicated in candidate gene studies of asthma or allergic disorders (44). Polymorphism in the 11q13.5 locus was associated with both allergic rhinitis and IgE sensitization to grass; this locus is located near leucine-rich repeat containing 32 (LRRC32), a molecule which is critical for tethering TGF-beta to the cell surface on activated Tregs (45). The role of TGF-beta on Tregs appears to have dual functions, both Treg-mediated suppression and infectious tolerance mechanism. The third variant found was rs17513503, situated at 5q22. Furthermore, using a candidate gene approach the same study identified three genes of possible interest, thymic stromal lymphopoietin (TSLP), Toll-like receptor 6 (TLR6) and nucleotide-binding oligomerization domain containing 1 (NOD1/CARD4) (45). Concerning chronic rhinosinusitis, a hereditary basis has been

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suggested by the development of this condition in certain genetic disorders and by family and twin data. Despite that, genome-wide association studies are lacking at the moment and no single causative genes have been identified. Studies seem to implicate defects in innate immune response, including the TLR system, thus supporting the importance of environmental pathogens (e.g., bacteria) in the pathogenesis of the disease. To date, polymorphisms in more than 30 genes have been associated to chronic rhinosinusitis (46). The risk related to single nucleotide polymorphisms is modest, but taken as a group they can be important for the development of the disease. In conclusion, genetic determination of allergic disease is much more complicated than previously supposed, with distinct paths determining IgE production, sensitization, target organs and allergy. Besides, genetic variations are not enough to determine these disorders, but they can confer susceptibility for them. Therefore, gene-environment interactions are necessary in the development of allergic diseases.

THERAPEUTIC IMPLICATIONS

Given the strong comorbidity of airway inflammatory diseases, specifically allergic rhinitis, chronic rhinosinusitis and asthma and the trend to a synergic effect of these disorders, which tend to worsen one another, a global strategy of treatment is necessary to fully control their manifestations and consequences. The unified airway model, given the influences of pathological processes of upper airways on the lower airway, has led to therapies directed at both targets. The treatment of allergic rhinitis may provide a better control of comorbid asthma. Particularly, the use of nasal corticosteroids in subjects with allergic rhinitis has been demonstrated to reduce bronchial hyperresponsiveness, asthma-related symptoms and visits to emergency departments related to asthma (2, 5). Second- and third-generation antihistamines, besides being very effective in the treatment of allergic rhinitis, might have a role in treating mild-to-moderate asthma, at doses greater than those used for allergic rhinitis (2, 5). Leukotriene receptor antagonists, and specifically montelukast, are effective in the treatment of both allergic rhinitis and asthma, globally reducing airway and systemic inflammation (2, 5). Immunotherapy, besides reducing symptoms of allergic rhinitis, is effective in mild asthma and can even prevent the development of asthma and exacerbations and to improve quality of life in individuals with both asthma and persistent allergic rhinitis (2, 5). Recent reports have suggested a possible clinical use of omalizumab, a human anti-IgE monoclonal antibody, in allergic rhinitis and chronic rhinosinusitis with nasal polyps (47). In a recent randomized, double-blind, placebo-controlled trial, Gevaert et al. reported a significant reduction in total nasal endoscopic polyp scores with the use of omalizumab for the management of allergic and non-allergic patients with nasal polyps and asthma (47). Moreover, a recent meta-analysis of randomized clinical trials assessed the efficacy and safety of omalizumab in patients with poorly controlled AR (48).

However, both medical and surgical treatment of chronic rhinosinusitis were associated with improvements in asthma (49, 50). Endoscopic sinus surgery (ESS) for chronic rhinosinusitis in subjects with concomitant bronchial asthma reduces frequency of asthma attacks, number of hospitalizations and medication use and improves asthmatic symptoms, but apparently not lung function testing (49). One work demonstrated that the combination of ESS and medical postoperative therapy had a favorable long-term effect on asthma in patients with chronic rhinosinusitis. Asthma was better than it had been before the ESS for 90% of patients after a mean follow-up period of 6.5 years (49). In patients with nasal polyposis and comorbid asthma, a significant improvement in lung function and asthmatic symptoms and a reduction in the use of systemic corticosteroid were demonstrated after ESS, but not in subjects with aspirin-intolerant asthma (50).

CONCLUSIONS

Rhinosinusitis and asthma are two conditions frequently encountered, representing a range of overlapping diseases with a similar pathophysiological mechanism, where environmental stimuli, immunological predisposition, chronic airway mucosal inflammation and remodeling play a critical and integrating role in these diseases. Although

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further studies are certainly needed to clarify many aspects of this close relationship, in approaching an asthmatic patient, clinicians have to take into account the possible nasal involvement. In clinical practice, therefore, a rigorous treatment of comorbid factors of asthma, such as rhinosinusitis, could result in less asthma exacerbations, which will greatly improve the quality of life of difficult-to-control asthmatic patients.

In conclusion, treating asthma means also treating the nose, while treating patients with nasal symptoms has to be associated with a proper lung function evaluation, since the nose and the lungs should always be considered as a unique entity.

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