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Invited review article

Association and management of eosinophilic inflammation in upper and lower airways

Mitsuhiro Okano [a, *], Shin Kariya [a], Nobuo Ohta [b], Yoshimasa Imoto [c], Shigeharu Fujieda [c], Kazunori Nishizaki [a]

[a] Department of Otolaryngology – Head & Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan
[b] Department of Otolaryngology, Yamagata University School of Medicine, Yamagata, Japan
[c] Department of Otorhinolaryngology – Head & Neck Surgery, Faculty of Medical Sciences, University of Fukui, Fukui, Japan

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Abbreviations:
AERD, Aspirin-exacerbated respiratory disease; AR, Allergic rhinitis; BHR, Bronchial hyperresponsiveness; CRS, Chronic rhinosinusitis; ECRS, Eosinophilic chronic rhinosinusitis; INS, Intranasal corticosteroids; JCCP, Japanese cedar/cypress pollinosis; LT, Leukotriene; NP, Nasal polyps; PBMCs, Peripheral blood mononuclear cells; PEF, Peak expiratory flow; QOL, Quality of life; SCUADs, Severe chronic upper airway diseases; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy

ABSTRACT

This review discussed the contribution of eosinophilic upper airway inflammation includes allergic rhinitis (AR) and chronic rhinosinusitis (CRS) to the pathophysiology and course of asthma, the representative counterpart in the lower airway. The presence of concomitant AR can affect the severity of asthma in patients who have both diseases; however, it is still debatable whether the presence of asthma affects the severity of AR. Hypersensitivity, obstruction and/or inflammation in the lower airway can be detected in patients with AR without awareness or diagnosis of asthma, and AR is known as a risk factor for the new onset of wheeze and asthma both in children and adults. Allergen immunotherapy, pharmacotherapy and surgery for AR can contribute to asthma control; however, a clear preventive effect on the new onset of asthma has been demonstrated only for immunotherapy. Pathological similarities such as epithelial shedding are also seen between asthma and CRS, especially eosinophilic CRS. Abnormal sinus findings on computed tomography are seen in the majority of asthmatic patients, and asthmatic patients with CRS show a significant impairment in Quality of Life (QOL) and pulmonary function as compared to those without CRS. Conversely, lower airway inflammation and dysfunction are seen in non-asthmatic patients with CRS. Treatments for CRS that include pharmacotherapy such as anti-leukotrienes, surgery, and aspirin desensitization show a beneficial effect on concomitant asthma. Acting as a gatekeeper of the united airways, the control of inflammation in the nose is crucial for improvement of the QOL of patients with co-existing AR/CRS and asthma.

Introduction

Upper airway inflammation includes otitis media, rhinitis, rhinosinusitis, tonsillitis, and pharyngo-laryngitis. Due to the spread of guidelines and the development of new treatments, most of these diseases can be controlled by medical interventions including patient education, pharmacotherapy, immunotherapy and surgery. On the other hand, some of these diseases are refractory to treatments and lead to a long-lasting impairment of the quality of life (QOL), the so called “severe chronic upper airway diseases” (SCUADs).[1] SCUADs include uncontrolled allergic rhinitis, eosinophilic rhinosinusitis, aspirin exacerbated respiratory disease, ciliary dyskinesia and cystic fibrosis. Comorbid lower airway inflammation such as bronchitis and asthma is often seen in SCUADs. In this review, we focus on two major eosinophilic inflammatory diseases in the upper airway, allergic rhinitis (AR) and chronic rhinosinusitis (CRS), and discuss their contribution to the pathophysiology of asthma, the representative counterpart in the lower airway.

* Corresponding author. Department of Otolaryngology – Head & Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, 2-5-1 Shikatacho, Okayama 700-8558, Japan.
E-mail address: mokano@cc.okayama-u.ac.jp (M. Okano).
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Allergic rhinitis and asthma

Pathological similarities and differences between AR and asthma

Upper and lower airways share common structures including ciliary epithelium, basement membrane, lamina propria, glands and goblet cells, the so called "United airways".[2] Thus AR and asthma share pathological characteristics including the involvement of Th2-type cytokines such as IL-5, IL-13 and IL-31, eosinophilia-associated chemokines such as eotaxins, and cystenyl leukotrienes, which lead to pathological changes such as thickness of the basement membrane and goblet cell hyperplasia[3–6] (Fig. 1). For example, we have shown that peripheral blood mononuclear cells (PBMCs) of two thirds of the patients with Japanese cedar/cypress pollinosis (JCCP) produced a substantial amount of IL-31 in response to pollen allergens, which was associated with the severity of the disease (Fig. 2).[3] In addition, we also found that IL-31 induces MUC5AC gene expression in human airway epithelial cells.[4] Furthermore, IL-31 was reported as a potential indicator in patients with allergic asthma; for example, IL-31 significantly induced vascular epithelial growth factor in human bronchial epithelial cells.[5]

On the other hand, differences between the upper and lower airways do exist. Thus, nasal mucosa attaches to bone whereas bronchial mucosa attaches to cartilage. Nasal mucosa is enriched with vessels whereas bronchial mucosa is enriched with smooth muscle cells. Thus the major cause of airway obstruction, especially in the early phase of the allergic response, is different; upper airway obstruction is caused by vascular dilation whereas lower airway obstruction arises from smooth muscle constriction (Fig. 2). In terms of remodeling, epithelial shedding is frequently seen in asthmatic bronchi but not in the nose of patients with AR.

Presence and characterization of comorbidity of allergic rhinitis and asthma

It is well-known that AR and asthma co-exist. In general, asthma occurs in 10–40% of patients with AR whereas AR occurs in 20–80% of patients with asthma.[7–13] Variation in the percentage with comorbidity may arise from differences in diagnostic criteria (e.g. questionnaire differences) and/or subjects sampled (e.g. age and time differences). For example, a recent cross-sectional nationwide survey in Japan called the SACRA study indicated that AR was present in 68.5% of asthmatic patients who used the self-administered questionnaire and in 66.2% of those who received the physician-administered questionnaire.[13] Among patients with AR, those with poly-sensitization to inhaled allergens showed a tendency to have concomitant asthma as compared to mono-sensitized patients, and furthermore, sensitization to mites or cats induced comorbidity of asthma in mono-sensitized patients with AR.[7,9]

The presence of concomitant AR can affect the severity of asthma in patients who have both diseases. Nasal condition is closely associated with the severity of the self-assessed asthma condition and with poor asthma control both in adults and children.[14,15] A birth cohort study in the United Kingdom demonstrated that asthmatic children with AR were 2.89 fold more likely to experience frequent attacks of wheezing, 3.44 fold more likely to experience severe attacks of wheezing limiting speech, 10.14 fold more likely to have to frequently visit their doctor because of asthma, and 9 fold more likely to miss school as compared to those without AR.[16] In addition, concomitant AR leads to a delay in the recovery of pulmonary function tests after asthma exacerbation in children.[17] On the other hand, it is still debatable whether the presence of asthma affects the severity of AR according to the ARIA (allergic rhinitis and its impact on asthma) guidelines.[8,9]

Effect of allergic rhinitis on lower airway inflammation and function

In the past, a "seesaw" phenomenon was proposed in which nasal symptoms were alleviated when asthma was exacerbated and vice versa in patients with coexisting rhinitis and asthma. However, it is currently suggested that the severity of AR and asthma is synchronized in general, and that the onset and/or exacerbation of AR leads to refractory asthma.[18,19] For example, 35.1% of asthmatic patients suffering from JCCP showed an

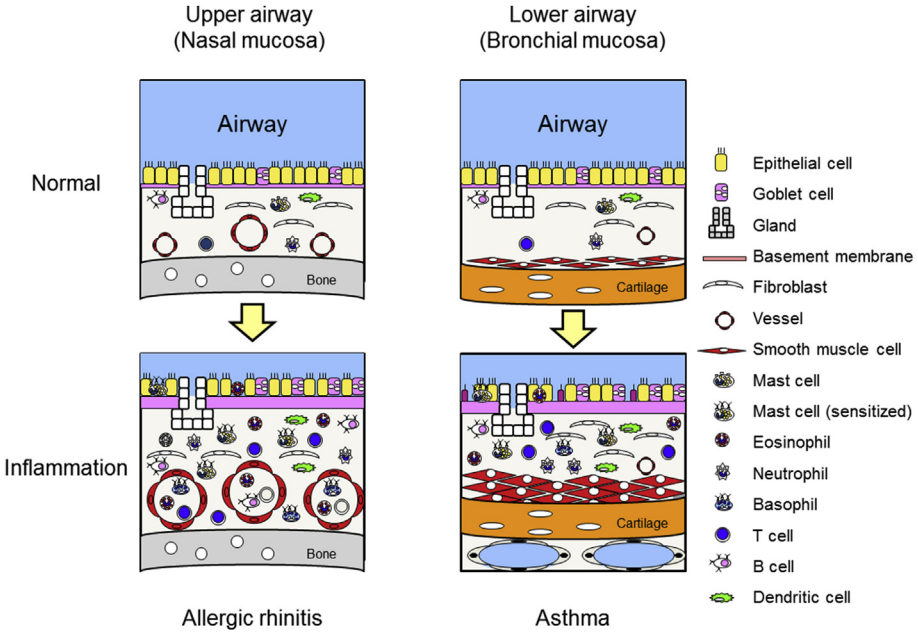

Fig. 1. Pathological similarities and differences between allergic upper and lower airway inflammation.