

EDITORIAL

Clinical and Experimental Allergy

Allergic Rhinitis and asthma: are they manifestations of one syndrome?

R. Pawankar

Department of Otolaryngology Nippon Medical School 1-1-5 Sendagi Bunkyo-Ku Tokyo 113-8603 Japan.

Introduction

Allergic rhinitis (AR) is the most common atopic disease worldwide and its increasing incidence to epidemic proportions is associated with a reduced quality of life of the patients, lower work productivity and school learning performance as well as increasing medical costs [1–5]. AR is an IgE-mediated inflammation of the nasal mucosa characterized by an inflammatory infiltrate made up of eosinophils, T cells, mast cells and basophils, which release several mediators, chemokines and cytokines (among these, histamine and cysteinyl-leukotrienes are the major vasoactive mediators), regulation of the local and systemic IgE synthesis, and communication with the immune system and the bone marrow [6]. Systemic circulation of inflammatory cells allows their infiltration into other tissues where chemoattractant and adhesion molecules already exist. Thus, besides local inflammation, AR also triggers a systemic inflammation, which can in turn augment inflammation in both the upper and lower airways. Consequently, AR is linked to other comorbid conditions: asthma, chronic hyper-plastic eosinophilic sinusitis, nasal polyposis and serous otitis media [7, 8].

Inflammation in allergic rhinitis

Upon allergen exposure, sensitized mast cells degranulate within minutes to release preformed and newly synthesized mediators that include histamine, proteases, cysteinyl leukotrienes (CysLTs), prostaglandins and cytokines [6, 9], some of which induce the characteristic early-phase symptoms of AR, while others orchestrate the late-phase response via the infiltration of inflammatory cells like eosinophils, basophils, and T cells into the nasal mucosa [6, 10, 11]. This infiltration of inflammatory cells can also be orchestrated by T-helper type 2 (Th2) cells within the local microenvironment. The subsequent release of addi-

tional mediators from these inflammatory cells, including histamine and CysLTs, sustains the inflammatory characteristic of the late-phase reaction [6]. In chronic on-going allergen inflammation, mast cells exhibit increased histamine releasability consequent to the enhanced FcεRI expression (increased numbers of IgE receptors) and surface-bound IgE, as well as enhancement of signal transduction pathways [10, 12, 13]. While these processes together induce the phenomenon of priming, mast cells in patients with AR also express increased levels of β1 integrins, and activation via the integrin receptors results in an enhanced release of inflammatory mediators even in the presence of lower amounts of allergen [14]. This process may in part contribute to the phenomenon of nasal hyper-responsiveness.

Systemic inflammation in allergic rhinitis

AR is not associated with just localized inflammation of the nasal mucosa but also has a systemic element to it. This may explain in a significant way the mechanisms underlying the rhinitis–asthma link. In individuals with seasonal allergic rhinitis (SAR) without co-existent asthma, nasal allergen provocation produced increased adhesion molecule expression, eosinophil infiltration in both the upper and lower airways, and increased bronchial hyper-reactivity [15, 16]. These results demonstrate that an allergic nasal reaction produces systemic inflammatory changes. In sensitized subjects, allergen exposure activates immune cells, including Th2 lymphocytes, dendritic cells, mononuclear cells, mast cells, and others, both within the nose and in nasal-associated lymphatic tissues. Some of these Th2 cells migrate to the bone marrow, where they stimulate the bone marrow to produce and recruit the inflammatory cells, including basophils, eosinophils and mast cell precursors, to the inflamed target tissues [17–19].

Link between allergic rhinitis and asthma

The increasing evidence on the links between AR and asthma comes from epidemiologic, immunologic, and

Correspondence:

Prof. Ruby Pawankar, E-mail: susan@nms.ac.jp

clinical studies [20]. Epidemiologically, up to 40% of patients with AR also have asthma, and up to 80% of patients with asthma experience nasal symptoms [21]. Furthermore, patients with AR are at three times the risk of developing asthma compared with those without AR and in children who develop rhinitis within the first year of life the chances of developing asthma are twofold greater as compared with those who develop rhinitis later in life [21, 22]. Therapeutic outcomes of treating AR in asthma have shown that AR treatment improves asthma symptoms and lowers overall costs and reduces hospitalizations [23], suggesting that upper airway disease is a risk factor for asthma [23, 24]. In a recent international survey on the impact of concomitant AR and asthma on patient health and quality of life, the presence of AR in children with asthma disrupted their lives by limiting their ability to get a good night's sleep (79% of adults and children), participate in leisure and sports (75% of adults and children), concentrate at work/school (69% of adults and 73% of children), or enjoy social activities (57% of adults

and 51% of children), and 79% reported that when AR symptoms flared up, asthma symptoms worsened [25].

Both AR and asthma are inflammatory diseases and their inflammatory mechanisms are similar in that they are characterized by an inflammatory infiltrate made up of eosinophils, T cells, and mast cells that release several mediators, chemokines and cytokines, local and systemic IgE synthesis, and a systemic link via the bone marrow. Typical early- and late-phase responses are also cardinal features common to both rhinitis and asthma. Studies have shown that patients with AR exhibit bronchial hyper-responsiveness (BHR) and increase in inflammatory cells, and that nasal allergen challenge further increases this hyper-reactivity. Eosinophils have been demonstrated in the nasal mucosa of patients with asthma, even in the absence of symptoms of rhinitis. In addition, patients with AR have increased number of inflammatory cells in their bronchial mucosa. This increase in bronchial inflammation in response to allergen-induced rhinitis might contribute to the exacerbations of asthma frequently seen in

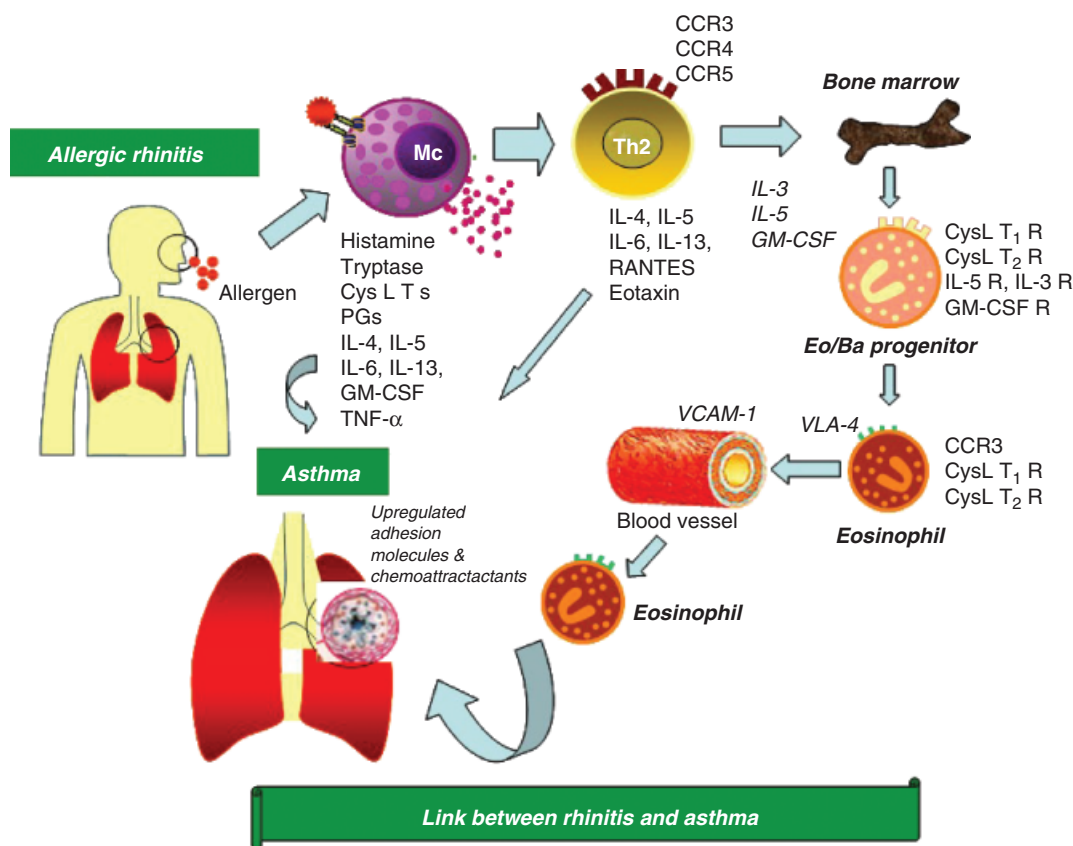


Fig. 1. Potential mechanisms linking allergic rhinitis (AR) and asthma. In patients with AR, activated mast cells, T-helper type 2 (Th2) cells and other immune cells release a variety of mediators, cytokines and chemokines. Postnasal drainage of these inflammatory mediators into lower airway, or absorption of mediators or chemotactic factors from the nose into the lower airway may in part serve as a potential mechanistic link. Moreover, a systemic link may exist that can contribute to this process. This comprises of Th2 cells that migrate from the nose to the bone marrow where the stimulate the bone marrow to produce progenitors of eosinophils, basophils and mast cells. These cells then enter the circulation and are selectively recruited to the nose but can also migrate to the lungs in the presence of up-regulated adhesion molecules like vacular cell adhesion molecule (VCAM)-1, and chemoattractants like eotaxin and RANTES in the lung.

individuals with underlying AR. Allergen challenge increased the bone marrow concentrations of both cytokines and progenitor cells both in animal models [26, 27] and in individuals with atopic asthma [28–30]. In addition, in atopic individuals who had late asthmatic responses and airway eosinophilia, allergen inhalation caused trafficking of T lymphocytes to the bone marrow, enhancing the ability of these lymphocytes to generate IL-5 [30]. Ultimately, these newly generated inflammatory cells enter the circulatory system, from where they are selectively recruited to the target organs (lungs and nose), exacerbating airway inflammation. In addition to stimulating inflammatory cell production, cytokines up-regulate the expression of adhesion molecules, further facilitating the recruitment of inflammatory cells into nasal and bronchial tissues [15]. This selective recruitment of inflammatory cells into the airways would occur only in individuals with pre-existing asthma in whom specific adhesion molecules, such as vascular cell adhesion molecule 1, and chemoattractants, such as eotaxin, already exist. Persons without asthma do not have these addressins in their airways and thus do not have the machinery in place to recruit inflammatory cells into their airways during exacerbations of rhinitis [31]. This parallel relationship is influenced by many interactions between the nose and the lower airways: some interactions stem from the fact that the nasal passages play a major homeostatic role by conditioning inhaled air, but perhaps even more important is the bidirectional interaction that results from the systemic inflammation that is produced after local allergic reactions [32] (Fig. 1).

Yet, the question remains as to why there are individuals who only manifest symptoms of rhinitis and not asthma. The hypothesis would be that those who have only rhinitis and no asthma may still be part of the continuum, but have a milder form of the disease. If so, not only are their lower airways less affected (no asthma), but their upper airways should be less severe as well. In this context, Corren and Gumarange [33] recently reported that nasal symptoms of subjects exposed to a 'cat room' were more severe if they had concomitant asthma than if they had rhinitis alone. In this issue of the journal, Stephens et al. [34] have tested this hypothesis by stimulating the nasal mucosa of patients with rhinitis and asthma as well as those with only rhinitis using a natural nasal stimulus: cold, dry air (CDA). Both on the basis of clinical symptoms as well as objective parameters by analysing the levels of histamine and lysozyme in nasal lavage fluids, these authors have demonstrated that patients with AR and asthma have stronger nasal responsiveness to CDA compared with patients with rhinitis alone.

Finally, from a socio-economic point of view, asthma and rhinitis are chronic conditions with a substantial economic impact on the patients and their families and

the health care systems [35]. This burden is composed of direct medical expenditures as well as indirect costs associated with loss of economic productivity. Persons with asthma or rhinitis must cope with both the immediate and long-term impact of a condition that often affects daily functioning. The world literature on the economic burden of asthma and rhinitis has only recently emerged, and to date has focused primarily on asthma. However, the few individual studies examining the economic impact of rhinitis also provide compelling evidence of its substantial impact, and patients who have both rhinitis and asthma have a higher economic burden than those who have either disease only.

Conclusion

The vast majority of patients with asthma have rhinitis, and rhinitis is a major independent risk factor for asthma in cross-sectional and longitudinal studies. The relationships between rhinitis and asthma can be viewed under the concept that the two conditions may be manifestations of one syndrome, the 'chronic allergic respiratory syndrome', occurring in two different parts of the respiratory tract. In a less-severe state of this syndrome, rhinitis may be the only manifestation, although pathologic abnormalities may exist in the lower airways. In the more severe state of the syndrome, rhinitis is usually more severe and clinical symptoms of asthma co-exist. Once manifested, the two conditions can manifest with equal severity and mutually augment inflammation and disease severity via the many bidirectional interactions between the nasal and the lower airways. Some interactions arise from the fact that the nasal passages play a major homeostatic role by conditioning inhaled air, but perhaps even more important is the bidirectional interaction that results from the systemic inflammation that is produced after local allergic reactions. Although there are cardinal structural differences between the nose and the lungs, these experimental and real-life observations on the link between rhinitis and asthma outweigh the differences and lend support to the concept that rhinitis and asthma may be considered as manifestations of one syndrome that has a wide spectrum of severity. Successful management of this chronic allergic respiratory syndrome requires an integrated view of the airways, understanding of their interactions, and an integrated approach of treatment also targeting systemic inflammation.

References

- 1 Strachan D, Sibbald B, Weiland S *et al.* Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). *Pediatr Allergy Immunol* 1997; 8:161–76.

- 2 Simons FE. Learning impairment and allergic rhinitis. *Allergy Asthma Proc* 1996; 17:185–9.
- 3 Cockburn IM, Bailit HL, Berndt ER, Finkelstein SN. Loss of work productivity due to illness and medical treatment. *J Occup Environ Med* 1999; 41:948–53.
- 4 Bousquet J, Bullinger M, Fayol C *et al.* Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 health status questionnaire. *J Allergy Clin Immunol* 1994; 94:182–8.
- 5 Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997; 99:22–7.
- 6 Naclerio RM. Allergic rhinitis. *N Engl J Med* 1991; 325:860–9.
- 7 Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (Suppl.):S147–334.
- 8 Young MC. Rhinitis, sinusitis, and polyposis. *Allergy Asthma Proc* 1998; 19:211–8.
- 9 Baroody FM, Ford S, Proud D, Kagey-Sobotka A, Lichtenstein L, Naclerio RM. Relationship between histamine and physiological changes during the early response to nasal antigen provocation. *J Appl Physiol* 1999; 86:659–68.
- 10 Pawankar R. Mast cells as orchestrators of the allergic reaction: the IgE-IgE receptor mast cell network. *Curr Opin Allergy Clin Immunol* 2001; 1:3–6.
- 11 Baraniuk JN. Pathogenesis of allergic rhinitis. *J Allergy Clin Immunol* 1997; 99:S763–72.
- 12 Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc epsilon1, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997; 1; 9:1492–9.
- 13 Smurthwaite L, Walker SN, Wilson DR *et al.* Persistent IgE synthesis in the nasal mucosa of hayfever patients. *Eur J Immunol* 2001; 31:3422–31.
- 14 Pawankar R, Yamagishi S, Takizawa R, Yagi T. Mast cell-IgE- and mast cell-structural cell interactions in allergic airway disease. *Curr Drug Targets Inflamm Allergy* 2003; 2:303–12.
- 15 Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol* 2001; 107:469–76.
- 16 Corren J, Adinoff AD, Irvin CG. Changes in bronchial responsiveness following nasal provocation with allergen. *J Allergy Clin Immunol* 1992; 89:611–8.
- 17 Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic aspects of allergic disease: bone marrow responses. *J Allergy Clin Immunol* 2000; 106 (Suppl.):S242–6.
- 18 Gaspar Elsas MI, Joseph D, Elsas PX, Vargaftig BB. Rapid increase in bone-marrow eosinophil production and responses to eosinopoietic interleukins triggered by intranasal allergen challenge. *Am J Respir Cell Mol Biol* 1997; 17:404–13.
- 19 Inman MD, Ellis R, Wattie J, Denburg JA, O'Byrne PM. Allergen-induced increase in airway responsiveness, airway eosinophilia, and bone-marrow eosinophil progenitors in mice. *Am J Respir Cell Mol Biol* 1999; 21:473–9.
- 20 Corren J. Allergic rhinitis and asthma: how important is the link? *J Allergy Clin Immunol* 1997; 99:S781–6.
- 21 Settiple RJ, Hagy GW, Settiple GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc* 1994; 15:21–5.
- 22 Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics* 1994; 94:895–901.
- 23 Crystal-Peters J, Neslusan C, Crown WH *et al.* Treating allergic rhinitis in patients with comorbid asthma: the risk of asthma-related hospitalizations and emergency department visits. *J Allergy Clin Immunol* 2002; 109:57–62.
- 24 National Institutes of Health. National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. Expert Panel report 2. NIH Publication no. 97-4051, 1997.
- 25 Pawankar R. Allergic rhinitis and asthma: the link, the new ARIA classification and global approaches to treatment. *Current Opinion in Allergy and Clinical Immunology* 2004; 4(1):1–4.
- 26 Saito H, Howie K, Wattie J *et al.* Allergen-induced murine upper airway inflammation: local and systemic changes in murine experimental allergic rhinitis. *Immunology* 2001; 104:226–34.
- 27 Wood LJ, Inman MD, Denburg JA, O'Byrne PM. Allergen challenge increases cell traffic between bone marrow and lung. *Am J Respir Cell Mol Biol* 1998; 18:759–67.
- 28 Sehmi R, Wood LJ, Watson R *et al.* Allergen-induced increases in IL-5 receptor α -subunit expression on bone marrow-derived CD34+ cells from asthmatic subjects. A novel marker of progenitor cell commitment towards eosinophilic differentiation. *J Clin Invest* 1997; 100:2466–75.
- 29 Wood LJ, Inman MD, Watson RM, Foley R, Denburg JA, O'Byrne PM. Changes in bone marrow inflammatory cell progenitors after inhaled allergen in asthmatic subjects. *Am J Respir Crit Care Med* 1998; 157:99–105.
- 30 Wood LJ, Sehmi R, Dorman S *et al.* Allergen-induced increases in bone marrow T lymphocytes and interleukin-5 expression in subjects with asthma. *Am J Respir Crit Care Med* 2002; 166:883–9.
- 31 Chakir J, Laviolette M, Turcotte H, Boutet M, Boulet LP. Cytokine expression in the lower airways of nonasthmatic subjects with allergic rhinitis: influence of natural allergen exposure. *J Allergy Clin Immunol* 2000; 106:904–10.
- 32 Togias A. Rhinitis and asthma: evidence for respiratory system integration. *Allergy Clin Immunol* 2003; 111:1171–83.
- 33 Corren J, Fish H, Gumarange J. Nasal response to natural cat allergen exposure is significantly greater in patients with rhinitis and asthma than in patients with rhinitis alone. *J Allergy Clin Immunol* 2005; 115:202–3.
- 34 Hanes LS, Issa E, Proud D, Togias A. Stronger nasal responsiveness to cold air in individuals with rhinitis and asthma, compared to rhinitis alone. *Clin Exp Allergy* 2006; 36:26–31.
- 35 Ray NF, Baraniuk JN, Thamer M *et al.* Direct expenditures for the treatment of allergic rhinoconjunctivitis in 1996, including the contributions of related airway illnesses. *J Allergy Clin Immunol* 1999; 103:401–7.