Prevalence and Clinical Relevance of Allergic Rhinitis in Patients with Classic Asthma and Cough Variant Asthma

Tomoko Tajiri\textsuperscript{a} Akio Niimi\textsuperscript{a, b} Hisako Matsumoto\textsuperscript{a} Isao Ito\textsuperscript{a}
Tsuyoshi Oguma\textsuperscript{a} Kojiro Otsuka\textsuperscript{a, c} Tomoshi Takeda\textsuperscript{a, d} Hitoshi Nakaji\textsuperscript{a, e}
Hideki Inoue\textsuperscript{a} Toshiyuki Iwata\textsuperscript{a} Tadao Nagasaki\textsuperscript{a} Michiaki Mishima\textsuperscript{a}

\textsuperscript{a}Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, \textsuperscript{b}Division of Respiratory Medicine, Department of Medical Oncology and Immunology, Nagoya City University School of Medical Sciences, Aichi, \textsuperscript{c}Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Hyogo, \textsuperscript{d}Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, and \textsuperscript{e}Department of Respiratory Medicine, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

Key Words
Allergic rhinitis · Classic asthma · Cough variant asthma · Eosinophilic airway inflammation

Abstract
Background: A clinically relevant relationship between classic asthma and allergic rhinitis has been reported. However, the possible link between cough variant asthma (CVA) and allergic rhinitis remains unknown. Objectives: To clarify the prevalence and clinical relevance of perennial allergic rhinitis or seasonal allergic rhinitis in CVA patients compared to classic asthma patients. Methods: We retrospectively studied adult patients with classic asthma (n = 190) and those with CVA (n = 83). The prevalence of perennial allergic rhinitis or seasonal allergic rhinitis and associations of concomitant perennial or seasonal allergic rhinitis with asthma severity, forced expiratory volume in 1 s (% predicted), fractional exhaled nitric oxide (FeNO) levels, and eosinophil proportions in sputum and blood were analyzed in the two groups. Results: The prevalence of perennial allergic rhinitis and/or seasonal allergic rhinitis was significantly higher in classic asthma patients than in CVA patients (all p < 0.05). Concomitant perennial allergic rhinitis was associated with higher FeNO levels and eosinophil proportions in sputum and blood in classic asthma patients (p = 0.035, p = 0.036, and p = 0.008, respectively) and with higher asthma severity, FeNO levels, and sputum eosinophil proportions in CVA patients (p = 0.031, p = 0.007, and p = 0.010, respectively). Concomitant seasonal allergic rhinitis was only associated with higher sputum eosinophil proportions in CVA patients with active rhinitis symptoms during the sensitized pollen season (p = 0.025). Conclusions: Perennial allergic rhinitis may be relevant for CVA patients as well as classic asthma patients by consistently augmenting eosinophilic lower airway inflammation.

Introduction
Asthma and allergic rhinitis often coexist. Allergic rhinitis and its impact on asthma guidelines suggest that rhinitis occurs in over 75% of patients with allergic asthma.
and in over 80% of patients with nonallergic asthma [1]. In a review examining 12 published studies from 1983 to 2004, Gaugris et al. [2] reported that the point prevalence of allergic rhinitis ranged from 24 to 94%, and the lifetime prevalence ranges from 50 to 100% among adult asthmatic patients in the USA and Europe. In Japan, allergic rhinitis is present in 67.3% of asthmatic patients [3].

A strong link between asthma and allergic rhinitis has been reported in epidemiological and clinical studies. Allergic rhinitis often precedes the development of asthma [4–7], suggesting that it may be a risk factor for asthma. The presence of concomitant allergic rhinitis in asthmatics results in more frequent asthma attacks, emergency room visits [8], and asthma-related hospitalizations [9], as well as higher asthma-related medication costs [9, 10]. Nonasthmatics with allergic rhinitis have elevated numbers of eosinophils in the bronchial mucosa [11–13]. In asthmatics with allergic rhinitis, nasal provocation with specific allergens increases eosinophils in the bronchial mucosa [14] and bronchial responsiveness to methacholine [15]. Conversely, eosinophil infiltration is present in the nasal mucosa of asthmatics without allergic rhinitis [16]. Thus, asthma and allergic rhinitis share a similar inflammatory process, which leads to the concept of ‘one airway, one disease’ [1].

Cough variant asthma (CVA) is one of the most common causes of chronic cough [17]. This variant form of asthma presents solely with cough and is associated with airway hyperresponsiveness and responsiveness to bronchodilators [18] and other antiasthma treatments [19]. Although a relationship between classic asthma and allergic rhinitis has been reported, a possible relationship between CVA and allergic rhinitis is unknown.

In this study, we analyzed the prevalence and clinical relevance of allergic rhinitis in CVA patients compared to classic asthma patients with wheezing.

**Materials and Methods**

**Patients**

This was a retrospective study involving consecutive adult patients with classic asthma (n = 190) and CVA (n = 83) who were newly referred to the asthma clinic of Kyoto University Hospital between September 1, 2007, and August 31, 2009. Patients who had smoked for >5 pack-years or who had smoked within the previous 6 months were excluded. Patients with classic asthma were diagnosed according to American Thoracic Society criteria [20]. The diagnosis of CVA was based on an isolated cough without dyspnea or wheezing, airway hyperresponsiveness to methacholine, and symptomatic improvement of the cough with β2-agonists [18]. When patients presented normo-sensitive results to inhaled methacholine, but responded to bronchodilator therapy, they were diagnosed with CVA. After the minimum medication required to achieve control was determined, the disease severity of classic asthma and CVA was classified according to the Japanese guidelines for asthma [21] as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent). We used this system because no validated severity scores for CVA have been reported, except in our previous report [22]. Patients with allergic rhinitis were diagnosed by otolaryngologists or pulmonologists according to nasal symptoms, questionnaires regarding rhinitis symptoms, a nasal physical examination, and serum-specific IgE antibody results. This study was approved by the Ethics Committee of Kyoto University, and written informed consent was obtained from all participants.

**Measurements**

Fractional exhaled nitric oxide (FeNO) measurements, spirometry, methacholine challenge, sputum induction, blood tests, and questionnaires were performed during each patient’s first visit, as described below.

**FeNO Levels**

FeNO levels were measured with a chemiluminescence analyzer (NOA 280; Sievers, Boulder, Colo., USA) according to the current guidelines [23]. We measured FeNO levels at an expiratory flow rate of 50 ml/s during a single unobstructed expiration [24].

**Pulmonary Function Test**

After FeNO measurements, patients underwent spirometry using a Chestac-65V spirometer (ChestTM, Tokyo, Japan) according to the guidelines [25]. Prebronchodilator values of forced expiratory volume in 1 s [FEV1 (% predicted)] were examined.

**Methacholine Challenge**

We determined the airway responsiveness by measuring the respiratory resistance (cm H2O/l/s) (Astograph; Chest) under continuous methacholine inhalation as previously described [26]. The index of airway sensitivity was Dmin, i.e., the cumulative dose of inhaled methacholine at the inflection point where respiratory resistance began to continuously increase. Based on the results of our previous study [22], positivity for airway hyperresponsiveness was defined as a Dmin <12.5 units.

**Sputum Induction and Processing**

Sputum was induced and processed as described [27, 28]. Briefly, after premedication with salbutamol, participants inhaled a hypertonic (3%) saline solution for 15 min from an ultrasonic nebulizer. Adequate plugs of sputum were treated with 0.1% dithiothreitol (Sputasol; Oxoid Ltd., Hampshire, UK) followed by Dulbecco’s phosphate-buffered saline. After centrifugation, cell differentials were determined by counting at least 400 nonsquamous cells stained with the May-Grünewald-Giemsa method. Correlations between sputum eosinophil proportions and FeNO levels were analyzed.

**Blood Tests**

Eosinophil proportions and serum IgE levels were determined in blood samples. The serum levels of total and specific IgE antibodies against common aeroallergens [house dust, Dermatopha-
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Respiration 2014;87:211–218
DOI: 10.1159/000355706

Results

Characteristics of the Patients

The patient characteristics are shown in table 1. The disease duration was longer and the FEV1 was lower in classic asthma patients than in CVA patients. Disease severity, total serum IgE levels, FeNO levels, and eosinophil proportions in sputum and blood were higher in classic asthma patients than in CVA patients.

Prevalence of Allergic Rhinitis

A total of 104 classic asthma patients and 32 CVA patients answered that they had rhinitis symptoms during the pollen season, and 96 classic asthma patients and 23 CVA patients answered that they had rhinitis symptoms throughout the year.

The prevalence of perennial allergic rhinitis and/or seasonal allergic rhinitis was significantly higher in classic asthma patients than in CVA patients (fig. 1).

Specific IgE Antibody

Sensitization to house dust, D. pteronyssinus, cat dander, and dog dander was significantly higher in classic asthma patients than in CVA patients. Sensitization to pollens did not differ between the two groups. The mean

goides pteronyssinus, Japanese cedar pollen, mixed gramineae pollen (orchard grass, sweet vernal grass, Bermuda grass, timothy, and reeds), mixed weed pollen (ragweed, mugwort, goldenrod, dandelion, and oxeye daisy), mixed mold (Candida, Alternaria, Penicillium, Aspergillus, Helminthosporium, and Cladosporium), Trichophyton rubrum, cat dander, and dog dander] were measured with radioimmunosorbent tests and the CAP method (Pharmacia Diagnostics, Uppsala, Sweden) [29]. Specific IgE antibody results were considered positive if the response levels exceeded 0.35 IU/ml [30].

Questionnaires

The participants answered questionnaires with the following questions: ‘Do you start to sneeze, get a runny nose, or get a stuffy nose during the pollen season?’ and ‘Do you have nasal allergies such as sneezing, a runny nose, and a stuffy nose throughout the year?’ The sensitized pollen seasons were defined as February to April for Japanese cedar pollen, April to June and August to October for mixed gramineae pollens, and September to October for mixed weed pollens, according to the Japanese guidelines for allergic rhinitis [31].

Statistical Analysis

JMP system version 6 (SAS Institute Japan, Tokyo, Japan) was used for statistical analysis. Data are expressed as means ± SD or medians (range). To compare two groups, a χ2 test or the Wilcoxon rank-sum test was used as appropriate. Spearman’s correlation coefficients were used to analyze the relationships among the data. p < 0.05 was considered statistically significant.

Table 1. Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Classic asthma</th>
<th>CVA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>190</td>
<td>83</td>
<td>0.86</td>
</tr>
<tr>
<td>Age, years</td>
<td>49±19</td>
<td>48±18</td>
<td>0.90</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>54/136</td>
<td>23/60</td>
<td>0.007</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>7±12</td>
<td>2±6</td>
<td></td>
</tr>
<tr>
<td>Use of inhaled corticosteroids at the first visit (yes/no)</td>
<td>43/147</td>
<td>13/70</td>
<td>0.18</td>
</tr>
<tr>
<td>Dose of inhaled corticosteroidsa, μg/day</td>
<td>451±229</td>
<td>442±240</td>
<td>0.6</td>
</tr>
<tr>
<td>Use of antihistamines (yes/no)</td>
<td>15/175</td>
<td>12/71</td>
<td>0.09</td>
</tr>
<tr>
<td>Use of leukotriene receptor antagonists (yes/no)</td>
<td>20/170</td>
<td>7/76</td>
<td>0.59</td>
</tr>
<tr>
<td>Never smoker/ex-smoker</td>
<td>164/26</td>
<td>70/13</td>
<td>0.66</td>
</tr>
<tr>
<td>FEV1 (n = 271), % predicted</td>
<td>91±23</td>
<td>103±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Disease severityb</td>
<td>2.8±0.1</td>
<td>2.5±0.1</td>
<td>0.0006</td>
</tr>
<tr>
<td>Total serum IgE (n = 273), IU/ml</td>
<td>130 (5–2,916)</td>
<td>54 (5–2,600)</td>
<td>0.0001</td>
</tr>
<tr>
<td>FeNO level (n = 265), ppb</td>
<td>60±78</td>
<td>32±27</td>
<td>0.001</td>
</tr>
<tr>
<td>Sputum eosinophil proportion (n = 140), %</td>
<td>11±21 (n = 95)</td>
<td>3±7 (n = 45)</td>
<td>0.003</td>
</tr>
<tr>
<td>Blood eosinophil proportion (n = 273), %</td>
<td>5±5 (n = 190)</td>
<td>3±3 (n = 83)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dmin (n = 174), units</td>
<td>1.819 (0.011–48.898)</td>
<td>2.77 (0.044–27.705)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Values are given as means ± SD or medians (range) unless otherwise stated. a Equivalent to fluticasone propionate. b Defined as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent) after the minimum medication required to achieve control had been determined in accordance with the Japanese guidelines for adult asthma [21].
number of positive allergens per patient was significantly higher in classic asthma patients than in CVA patients (table 2).

**Clinical Relevance of Allergic Rhinitis in Patients with Classic Asthma and CVA**

Classic asthma patients with perennial allergic rhinitis had significantly higher FeNO levels and higher eosinophilic proportions in sputum and blood than those without (table 3a). CVA patients with perennial allergic rhinitis had significantly higher asthma severity, FeNO levels, and sputum eosinophil proportions than those without (table 3b).

Meanwhile, the presence of seasonal allergic rhinitis was not associated with the clinical index in patients with classic asthma (table 3a) and CVA (table 3b). Even when patients with active rhinitis symptoms who were examined during the sensitized pollen season were selected, the presence of seasonal allergic rhinitis was only associated with higher sputum eosinophil proportions in CVA patients than in those without (8 ± 10% and 3 ± 8%; p = 0.025).

We also reanalyzed the data for a subset of steroid-naive patients with classic asthma (n = 147) and CVA (n = 70) and observed similar results (data not shown).

**Correlations between FeNO Levels and Sputum Eosinophil Proportions**

Regardless of the presence of perennial allergic rhinitis (fig. 2a, b) or seasonal allergic rhinitis (fig. 2c, d), FeNO levels were positively and significantly correlated with sputum eosinophil proportions in the combination of patients with classic asthma and those with CVA who had succeeded in sputum induction (n = 140).

**Discussion**

This study showed that: (1) the prevalence of allergic rhinitis in classic asthma patients was higher than that in CVA patients and (2) concomitant perennial allergic rhinitis was clinically relevant for CVA patients as well as classic asthma patients by augmenting eosinophilic lower airway inflammation. To our knowledge, this is the first study to investigate a possible link between CVA and allergic rhinitis.

In Japan, rhinitis is present in 67.3% of asthmatic patients [3]. Our data for classic asthma patients are consistent with this report. The prevalence of allergic rhinitis in CVA patients was lower than that in classic asthma patients. CVA is a phenotype of asthma that presents solely with coughing [18] and shares several pathophysiological features with classic asthma. Compared to classic asthma, CVA shows similar levels of eosinophilic airway inflammation [22, 32] and a milder degree of airway remodeling [32] and airway hyperresponsiveness [33]. The reason for the difference in prevalence of allergic rhinitis between the two groups remains unclear. Asthma and allergic rhinitis share common risk factors for their onset, including atopic status. In this study as well as in our previous study [30], the degree of atopic status that was assessed with to-

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**Table 2. Specific IgE antibodies against common allergens**

<table>
<thead>
<tr>
<th>Allergen</th>
<th>Classic asthma (n = 190)</th>
<th>CVA (n = 83)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>House dust</td>
<td>98 (51.5)</td>
<td>28 (33.7)</td>
<td>0.007</td>
</tr>
<tr>
<td><em>D. pteronyssinus</em></td>
<td>98 (51.5)</td>
<td>27 (32.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Japanese cedar pollen</td>
<td>115 (60.5)</td>
<td>42 (50.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mixed gramineae pollen&lt;sup&gt;a&lt;/sup&gt;</td>
<td>57 (30)</td>
<td>19 (22.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>Mixed weed pollen&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25 (13.1)</td>
<td>8 (9.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mixed mold&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27 (14.2)</td>
<td>6 (7.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Cat dander</td>
<td>40 (21.0)</td>
<td>5 (6.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Dog dander</td>
<td>45 (23.6)</td>
<td>4 (4.8)</td>
<td>0.0002</td>
</tr>
<tr>
<td><em>T. rubrum</em></td>
<td>23 (12.1)</td>
<td>8 (9.6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Sensitization to any allergen</td>
<td>138 (72.6)</td>
<td>51 (61.4)</td>
<td>0.065</td>
</tr>
<tr>
<td>Sensitized allergens, n</td>
<td>2 (0−9)</td>
<td>1 (0−7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Values are given as numbers (%) or medians (range). <sup>a</sup> Orchard grass, vernal grass, Bermuda grass, and timothy grass. <sup>b</sup> Ragweed, mugwort, oxeye daisy, dandelion, and goldenrod. <sup>c</sup> *Penicillium, Cladosporium, Aspergillus, Candida*, and *Alternaria*. 

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**Fig. 1.** Prevalence of allergic rhinitis in patients with classic asthma (white bars) or CVA (black bars).
Table 3. Clinical relevance of allergic rhinitis

<table>
<thead>
<tr>
<th></th>
<th>Perennial allergic rhinitis</th>
<th>Seasonal allergic rhinitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+ (n = 96)</td>
<td>− (n = 94)</td>
</tr>
<tr>
<td><strong>FEV</strong>₁, % predicted</td>
<td>90±20</td>
<td>93±25</td>
</tr>
<tr>
<td>Disease severity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.9±0.9</td>
<td>2.8±0.9</td>
</tr>
<tr>
<td>FeNO level, ppb</td>
<td>69±74</td>
<td>52±83</td>
</tr>
<tr>
<td>Sputum Eos proportion, %</td>
<td>16±24</td>
<td>7±15</td>
</tr>
<tr>
<td>Blood Eos proportion, %</td>
<td>6±5</td>
<td>4±4</td>
</tr>
</tbody>
</table>

Values are given as means ± SD. Eos = Eosinophils. <sup>a</sup> Defined as 1 (mild intermittent), 2 (mild persistent), 3 (moderate persistent), 4 (severe persistent), or 5 (most severe persistent) in accordance with the Japanese guidelines for adult asthma [21].

Fig. 2. Relationship between FeNO levels and sputum eosinophil proportions in classic asthma patients (open circles) and CVA patients (closed circles) with (a) or without (b) perennial allergic rhinitis and with (c) or without (d) seasonal allergic rhinitis. Eos = Eosinophils.
Allergic rhinitis and observed no difference in eosinophil counts between asthmatics with and without perennial allergic rhinitis was also not associated with FEV$_1$ (% predicted) in asthmatics. One study showed that concomitant allergic rhinitis was associated with disease severity in CVA patients. Although an increasing number of studies have shown that perennial allergic rhinitis affects the disease state in classic asthma patients, no study has examined the effects in CVA patients. First, regarding asthma severity, self-reported concomitant allergic rhinitis results in more frequent emergency room visits and asthma attacks in patients with chronic asthma [8]. Another retrospective study showed that asthmatics with concomitant allergic rhinitis visited general practitioners more frequently, had more asthma-related hospitalizations, and had higher asthma-related medication costs than those without [9]. In the present study, concomitant perennial allergic rhinitis was associated with disease severity in CVA patients.

Second, two studies have examined the effects of concomitant allergic rhinitis on pulmonary function in asthmatics. One study showed that concomitant allergic rhinitis was not associated with impaired lung function including FEV$_1$ (% predicted) in asthmatics [34]. Another study observed no difference in FEV$_1$ (% predicted) between asthmatics with and without allergic rhinitis [35]. In the present study, concomitant perennial allergic rhinitis was also not associated with FEV$_1$ (% predicted) in patients with classic asthma and CVA.

Third, several studies have examined lower airway inflammation in patients with nonasthmatic rhinitis, but few have shown the additional effects of allergic rhinitis in asthmatics. Based on examination of cross-sectional data, patients with nonasthmatic rhinitis have significantly higher FeNO levels [36–38], sputum eosinophil counts [39], and eosinophil cationic protein levels [37] than healthy controls. One study compared FeNO levels between asthmatics with and without perennial allergic rhinitis and observed no difference [36]. In the present study, we first showed that FeNO levels and eosinophil proportions in sputum and/or blood were significantly higher in classic asthma patients and CVA patients with perennial allergic rhinitis than in those without. Nasal NO contamination was unlikely because significant correlations were observed between FeNO levels and sputum eosinophil proportions regardless of the presence of allergic rhinitis. These results suggest a link between upper and lower airway inflammation, which may be induced by inflammatory mediators from the initial site of inflammation moving into the systemic circulation [40].

In contrast to perennial allergic rhinitis, the clinical effects of seasonal allergic rhinitis in asthmatics have been reported to vary between during and outside the pollen season. The effects in CVA patients remain unknown. First, the effects of seasonal allergic rhinitis on asthma severity have been inconsistently reported. In a retrospective study, although asthmatics with seasonal allergic rhinitis had significantly higher total asthma symptom scores than those without, the need for a β$_2$-agonist as a rescue medication was similar between the two groups [41]. In this study, pollen species and levels were not taken into consideration. In large epidemiological studies that considered pollen species and levels, Tobias et al. [42] and Erbas et al. [43] showed effects of ambient pollen on asthma-related hospital admissions, but Anderson et al. [44] and Rossi et al. [45] did not. These inconsistencies among studies may have resulted from differences in pollen species, levels, and sensitization. In the present study, concomitant seasonal allergic rhinitis was not associated with disease severity in patients with classic asthma and CVA. The most common allergen for seasonal allergic rhinitis in Japan is Japanese cedar pollen [31]. In contrast to grass or birch pollen, the effects of Japanese cedar pollen on asthma severity remain unclear. Further prospective studies on Japanese cedar pollen are needed.

Second, one study has examined the effects of concomitant seasonal allergic rhinitis on pulmonary function in asthmatics. Patients with asthma alone showed lower FEV$_1$ (% predicted) than those with asthma and seasonal allergic rhinitis [41]. In the present study, concomitant seasonal allergic rhinitis was not associated with the FEV$_1$ (% predicted) in patients with classic asthma and CVA.

Third, several studies have reported the effects of seasonal allergic rhinitis on lower airway inflammation in patients with nonasthmatic rhinitis. However, none has examined the additional effects of seasonal allergic rhinitis in asthmatics. In previous studies, natural pollen exposure during the pollen season caused a significant elevation of FeNO levels in patients with seasonal allergic rhinitis alone [48–50]. In those with rhinitis, sputum eosinophil counts were also elevated compared to those of healthy controls during the pollen season [51]. No significant difference in sputum eosinophil counts was observed between the two groups outside the pollen season [52]. Collectively, the effects of seasonal allergic rhinitis may depend on whether they are assessed during or outside the pollen season. In the present study, we observed only slight effects of concomitant seasonal allergic rhinitis...
tis on the sputum eosinophil proportion in CVA patients with active rhinitis symptoms during the sensitized pollen season.

Our study has several limitations. First, the study was retrospective, and we cannot draw definite conclusions regarding the effects of allergic rhinitis on classic asthma and CVA. Additional prospective studies are required. Second, the pollen species, levels, and sensitization were not considered. Instead, we reanalyzed the data for the subset of patients with active rhinitis symptoms during the sensitized pollen season. Third, we included some patients who used inhaled corticosteroids. We therefore reanalyzed the data for the subset of steroid-naïve patients only and confirmed a similar clinical impact of perennial allergic rhinitis or seasonal allergic rhinitis on these patients. Fourth, some patients failed at sputum induction. We did not observe any differences in age, sex, disease duration, use of inhaled corticosteroids, FEV1, asthma severity, or FeNO levels between patients who failed sputum induction and those who succeeded (all p > 0.10; data not shown).

Conclusions

We found consistent associations of concomitant perennial allergic rhinitis with airway inflammation indices, such as sputum and blood eosinophils and FeNO levels, in CVA patients as well as in classic asthma patients. For CVA patients, perennial allergic rhinitis may also be implicated in disease severity. Perennial allergic rhinitis may be involved via augmentation of eosinophilic lower airway inflammation. The clinical relevance of concomitant seasonal allergic rhinitis in airway inflammation was only slight for CVA patients with active rhinitis symptoms during the sensitized pollen season. Further prospective studies are needed to clarify the clinical impact of seasonal allergic rhinitis, and in particular rhinitis induced by Japanese cedar pollen.

Acknowledgements

The authors are grateful to Ms. Aya Inazumi for her help with sputum processing.
20 Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma – this official statement of the American Thoracic Society: Bronch was adopted by the ATS board of directors, November 1986. Am Rev Respir Dis 1987; 136:225–244.


