

## Original Article

# Bronchial biopsy and sequential bronchoalveolar lavage in atopic cough: In view of the effect of histamine H<sub>1</sub>-receptor antagonists

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### ABSTRACT

We have shown that some patients presenting with chronic bronchodilator-resistant non-productive cough have global atopic tendency, airway cough hypersensitivity without non-specific bronchial hyperresponsiveness and eosinophilic inflammation of the trachea and bronchi, abbreviated as atopic cough (AC). Histamine H<sub>1</sub> receptor antagonists are effective in relieving the cough in some patients with AC but not in others in whom corticosteroids are needed to improve the cough. The aim of the present study was to compare the intensity of eosinophil infiltration in biopsied bronchial submucosa and sequential bronchoalveolar lavage (SBAL) fluids between two subgroups of patients with AC: (i) group A, successfully treated with histamine H<sub>1</sub> receptor antagonists; and (ii) group B, requiring corticosteroids. Sequential BAL was performed using three 50 mL aliquots of physiologic saline solution and then bronchoscopic bronchial biopsy was performed in group A ( $n = 9$ ) and B ( $n = 9$ ) patients. Sequential BAL was also performed in normal controls (NC;  $n = 13$ ). The first SBAL fraction was analyzed as bronchial lavage fluid (BLF) and the mixed fluid of the second and third SBAL fractions as bronchoalveolar lavage fluid (BALF). The number of eosinophils in the bronchial subepithelium was significantly ( $P = 0.0134$ ) greater in group B patients

(median 8.3 cells/mm<sup>2</sup>; range 3.6–21.9 cells/mm<sup>2</sup>) compared with group A (median 3.6 cells/mm<sup>2</sup>; range 0–10.0 cells/mm<sup>2</sup>). However, there were no significant differences in the number or percentage of eosinophils in BLF or BALF between group A, group B and NC subjects. These findings confirm that eosinophils do not infiltrate the peripheral airways of AC and suggest that corticosteroids are required to relieve the cough in more severe illness of AC, in which submucosal eosinophilic inflammation of the central bronchi is more intensive compared with the milder illness successfully treated with histamine H<sub>1</sub> receptor antagonists.

**Key words:** atopic cough, atopy, bronchial biopsy, bronchial lavage, bronchoalveolar lavage, chronic non-productive cough, eosinophils, sequential bronchoalveolar lavage.

### INTRODUCTION

Cough is a common presenting symptom in both general practice and in the chest clinic. Patients presenting with chronic non-productive cough resistant to antibiotics and the usual antitussive agents are frequently referred to our clinic for diagnosis and treatment. Post-nasal drip-induced cough, gastroesophageal reflux (GER)-associated cough and cough variant asthma (CVA) are well-known causes of non-productive cough.<sup>1</sup> Cough variant asthma is characterized by mild bronchial hyperresponsiveness and a good response to bronchodilators, such as  $\beta_2$ -adrenoceptor agonists and theophylline.<sup>2,3</sup> Sensitivity of the cough response to inhaled capsaicin is not heightened in either CVA<sup>4,5</sup> or classical asthma.<sup>6</sup>

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We have proposed a bronchodilator-resistant non-productive cough associated with global atopic basis (abbreviated as atopic cough; AC) as a new clinical entity,<sup>7</sup> which is successfully treated with selective histamine H<sub>1</sub> receptor antagonists and/or glucocorticosteroids.<sup>4,5,7,8</sup> In such patients, non-specific bronchial responsiveness is within normal limits<sup>4,5,7,8</sup> and airway cough sensitivity to inhaled capsaicin is heightened.<sup>4,5,7</sup> Eosinophils are frequently detected in hypertonic saline-induced sputum<sup>5</sup> and biopsied submucosa of the trachea and bronchi, but not in bronchoalveolar lavage fluid (BALF).<sup>7</sup> Thus, eosinophilic tracheobronchitis with airway cough hypersensitivity is the fundamental feature of AC.<sup>7</sup>

Histamine H<sub>1</sub> receptor antagonists are effective in nearly 60% of patients with AC, and oral (prednisolone 20 mg/day for 14 days or less) and/or inhaled corticosteroids (beclomethasone dipropionate, 400–800 µg/day) successfully improve the cough that is resistant to histamine H<sub>1</sub> receptor antagonists within 14 days in the majority of patients.<sup>4,5,7,8</sup> The present prospective study was conducted to elucidate whether the intensity of bronchial eosinophilic inflammation contributes to the requirement of corticosteroids and to ensure no BAL eosinophilia in AC that we previously reported,<sup>7</sup> using the sequential bronchoalveolar lavage (SBAL) technique.

## METHODS

### Patients

The present study was approved by the local ethics committee of Ishikawa Prefectural Central Hospital. Of 86 consequent patients who were referred to our pulmonary subspecialty clinic for further examination of their chronic non-productive cough between April 1991 and March 1992, 18 immunocompetent patients participated in the study and underwent bronchoscopic examinations including bronchial biopsy and SBAL. All patients gave their informed consent after the purpose of the study had been explained. Each patient met the following diagnostic criteria of AC: (i) chronic non-productive cough with a 'tickle' in the throat lasting for more than 8 weeks that was resistant to bronchodilator therapy (oral clenbuterol, 40 µg/day, and inhaled procaterol on demand for at least 1 week); (ii) the absence of wheeze, dyspnea, hemoptysis or pleurisy and no adventitious lung sounds on examination; (iii) non-specific bronchial responsiveness to methacholine within normal limits; (iv) the presence of one or more of the following atopic findings as a global feature:

a past history and/or complications of allergic diseases except for bronchial asthma, a family history of allergic diseases, peripheral blood eosinophilia, elevated total IgE levels in serum, positive specific IgE antibody to common aeroallergens and positive allergen skin test; (v) normal forced expiratory volume in 1 s (FEV<sub>1</sub>), forced vital capacity (FVC) and FEV<sub>1</sub>/FVC ratio; (vi) no bronchial reversibility defined as a less than 10% increase in FEV<sub>1</sub> after inhalation of 300 µg salbutamol; (vii) complete relief of cough following treatment with histamine H<sub>1</sub> receptor antagonists (terfenadine, ketotifen and/or azelastine) and/or glucocorticoid therapy (inhaled beclomethasone dipropionate and/or short-term oral prednisolone); and (viii) the absence of well-known causes of cough such as GER, post-nasal drip and chronic bronchitis.

Bronchial responsiveness was measured using methacholine according to the method described by Takishima *et al.*<sup>9</sup> (Astograph TCK-6000 CV; Chest Co. Ltd, Nagoya, Japan). Results are expressed as the provocative concentration of methacholine required to cause a 35% decrease from the baseline respiratory conductance (PC<sub>35</sub>-Grs, mg/mL).

Peripheral blood eosinophils were counted using a Microx Cell Analyzer HEG-120 (Omron, Kyoto, Japan) on the day before bronchoscopy. Total serum IgE levels were determined using the Phadebas paper radioimmunosorbent test (Pharmacia Diagnostics, Uppsala, Sweden). Serum-specific IgE antibodies were also measured by the Phadebas radioallergosorbent test (Pharmacia Diagnostics). All patients had normal sinus and chest radiographs.

Thirteen normal non-smokers without respiratory symptoms (seven men and six women; median age 58 years; range 17–70 years) underwent SBAL as a control group.

### Sequential bronchoalveolar lavage and bronchial biopsy

Before treatment, flexible fiberoptic bronchoscopy (Olympus BF 1T-20; Olympus, Tokyo, Japan) was performed under local anesthesia with lidocaine following premedication with atropine sulfate and hydroxyzine. Sequential BAL was performed in the right middle lobe using three 50 mL aliquots of physiologic saline solution. The first lavaged fraction and the mixed fluid of the second and the third lavaged fractions were separately analyzed as bronchial lavage fluid (BLF) and BALF, respectively. A part of the recovered BALF was used for bacteriological and cytological examinations. After parts

of the BLF and the BALF were diluted with an equal volume of Türk solution, cells were counted in a Bürker chamber (Nichirim Co. Ltd, Tokyo, Japan). After the remaining BLF and BALF were passed through a double layer of Dacron net, cells were pelleted at 300 g for 10 min and resuspended in 10 mL RPMI-1640 (Grand Island Biological Co., Grand Island, NY, USA). The fluids were resuspended to a concentration of  $2 \times 10^5$  cells/mL. Smears for differential counts were prepared by cytocentrifugation (Cytopin 2; Shadon Southern Instruments, Sewickley, USA) at 70 g for 10 min. After staining with May-Grünwald-Giemsa, a differential cell count was done in 300 cells.

Histologic examination was performed with special emphasis on eosinophils. Airway mucosa specimens were obtained by bronchoscopic forceps biopsy at a bifurcation of the right upper lobe bronchus and truncus intermedicus and/or at the opening of the right middle lobe as bronchial mucosa (total of two or three specimens). Biopsied specimens were fixed in formalin solution, embedded in paraffin and cut through its entire thickness at 4  $\mu$ m, all sections being mounted and stained with hematoxylin and eosin. Light microscopic examination was performed independently by two pathologists, who were not aware of the clinical findings, in order to identify the number of eosinophils. Numbers of eosinophils in subepithelium were counted using an eyepiece graticule and the counted eosinophil numbers of two or three specimens were then averaged. Results are expressed as the average of the eosinophil numbers counted by the two pathologists (cells per 1 mm<sup>2</sup> area of subepithelium).

### Treatment protocol

After bronchoscopic examinations, each patient was given a 7 day oral course of histamine H<sub>1</sub> receptor antagonists (ketotifen 2 mg/day, azelastine 4 mg/day or terfenadine 120 mg/day). If the cough did not fully resolve on treatment, glucocorticoid therapy (prednisolone 0.5 mg/kg/day for 7–14 days) was added.

### Statistical analysis

Data are shown as the median (range). Statistical differences were determined by Mann-Whitney *U*-test between any pairs of groups. Spearman's regression analysis was used in assessing correlations between the degree of eosinophil infiltration in biopsied bronchi and eosinophil counts in BLF, BALF and peripheral blood. Significance was based on a 95% confidence level ( $P < 0.05$ ).

## RESULTS

The cough was completely relieved by oral histamine H<sub>1</sub> receptor antagonists in nine of 18 patients (patients 1–9; group A). In the remaining nine patients (patients 10–18; group B) the cough was not fully relieved following histamine H<sub>1</sub> receptor antagonist treatment but was completely resolved following oral glucocorticoid therapy within 7–14 days (Table 1).

Intraepithelial eosinophil infiltration was not investigated in any patient. Eosinophils were detected in the subepithelial lamina propria in seven patients in group A and nine patients in group B (Fig. 1). The degree of eosinophil infiltration observed in the biopsied bronchi was significantly ( $P = 0.0134$ ) stronger in patients in group B (median 8.3 cells/mm<sup>2</sup>, range 3.6–21.9 cells/mm<sup>2</sup>) than group A (median 3.6 cells/mm<sup>2</sup>, range 0–10.0 cells/mm<sup>2</sup>).

Bronchial lavage fluid was successfully recovered from nine and seven patients in groups A and B, respectively. Total cell counts in BLF were 0.6 (0.3–3.5), 1.1 (0.2–2.8) and 0.6 (0.04–3.4)  $\times 10^5$  cells/mL in group A, group B and the control group, respectively, and there were no significant differences between any pairs of the groups. Although an increase of percentage eosinophils in BLF (5% or more) was investigated in one patient each of group A and group B (Fig. 2), the percentage of eosinophils in BLF was not significantly different among group A, group B and the control group. The absolute number of eosinophils in BLF was 0.0 (0.0–0.36), 0.01 (0.0–2.38) and 0.0 (0.0–0.34)  $\times 10^4$  cells/mL in group A, group B and the control group, respectively, and the values were not significantly different.

Bronchoalveolar lavage fluid was obtained from all patients. The total cell count was 1.2 (0.8–3.1), 1.8 (1.0–4.4) and 1.5 (0.3–3.8)  $\times 10^5$  cells/mL in group A, group B and the control group, respectively, and these values were not significantly different. There was no increase of eosinophils in BALF, whereas lymphocytes were increased to 20% or more in two and three patients of groups A and B, respectively (Fig. 3). The number of eosinophils or lymphocytes was not significantly different among group A, group B and the control group.

Two patients (patients 1 and 14) had an increase in total cells and neutrophils in BLF and further examination revealed that they were complicated with very mild sino-bronchial syndrome. When the biopsy, BLF and BALF data were re-analyzed excluding the two patients, the significant difference between group A and group B was observed only in bronchial submucosal eosinophils.

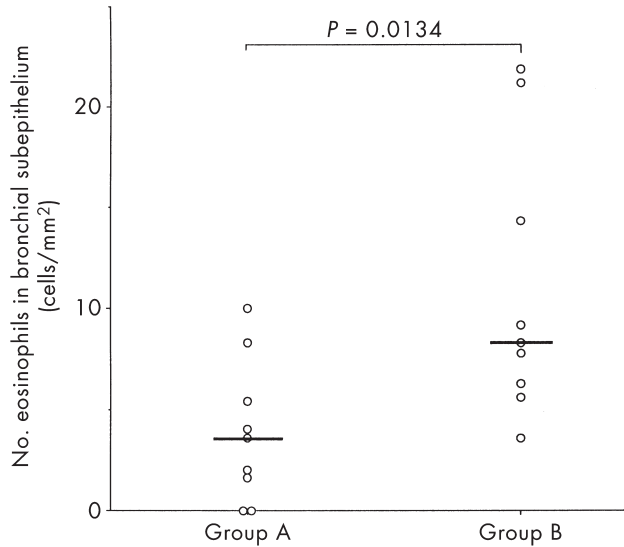
**Table 1** Clinical characteristics of patients with chronic bronchodilator-resistant non-productive cough associated with an atopic basis

Patient no.	Age (years)	Sex	Duration (months)	History of allergic disease	Eosinophil in PB( $\mu$ L)	IgE(R1ST) (U/mL)	IgE (RAST)	FVC (% pred.)	FEV <sub>1</sub> (% pred.)	FEV <sub>1</sub> /FVC (%)	PC <sub>35</sub> -Grs (mg/mL)	Successful treatment
<b>Group A</b>												
1	37	F	6	AC	504	240	-	120	85	72	>20.0	Ketotifen
2	58	M	2	-	344	810	-	92	81	85	>20.0	Terfenadine
3	17	F	6	AR	186	150	-	100	84	85	18	Azelastine
4	39	M	12	AR and AC	360	27	-	118	119	88	>20.0	Terfenadine
5	50	F	3	-	46	360	Mite	106	106	84	>20.0	Terfenadine
6	48	M	36	-	183	23	JC	113	108	84	20	Ketotifen
7	43	F	4	AR	164	15	-	97	86	82	19	Ketotifen
8	33	M	2	AR	470	900	HD, mite	137	122	89	9.3	Ketotifen
9	42	F	3	-	840	15	-	103	96	86	>20.0	Terfenadine
Median	42	M:4, F:5	4	-	344	150	-	106	96	85	>20	
Range	17-58		2-36		46-840	15-900		92-137	81-122	72-89	9.3->20	
<b>Group B</b>												
10	53	M	3	AR and urticaria	147	68	-	117	115	84	>20.0	PSL
11	42	M	9	-	340	34	JC	97	76	79	4.3	PSL
12	48	F	2	AR	936	22	-	94	80	85	10	PSL
13	48	M	3	AR	270	3600	Mite	97	87	75	>20.0	PSL
14	71	M	2	-	68	37	JC	92	72	79	>20	PSL
15	52	M	5	-	1020	52	-	87	77	88	10	PSL
16	66	M	6	AR	544	14	-	105	82	78	>20.0	PSL
17	58	M	2	Urticaria	120	280	-	91	71	79	10	PSL
18	32	M	60	-	0	19	Mite	94	94	94	>20.0	PSL
Median	52	M:8, F:1	3	-	270	37	-	94	80	79	>20	
Range	32-71		2-60		0-1020	24-3600		87-117	71-115	75-94	4.3->20	

Group A patients (no. 1-9) had chronic bronchodilator-resistant non-productive cough that was relieved by histamine H<sub>1</sub> receptor antagonists. Group B patients (no. 10-18) had chronic bronchodilator-resistant non-productive cough that was fully improved by glucocorticoid therapy but not sufficiently improved by histamine H<sub>1</sub> receptor antagonists.

M, male; F, female; AR, allergic rhinitis; AC, allergic conjunctivitis; PB, peripheral blood; HD, house dust; JC, Japanese cedar; PSL, prednisolone; FVC, forced vital capacity; FEV<sub>1</sub>, forced expiratory volume in 1 s; PC<sub>35</sub>-Grs, provocative concentration of methacholine causing a 35% fall in respiratory conductance; R1ST, radioimmunosorbent test; RAST, radioallergosorbent test; % pred., % of predicted value.

Peripheral blood eosinophil counts, serum IgE level, pulmonary function, or PC<sub>35</sub>-Grs were not significantly different between group A and group B (Table 1).



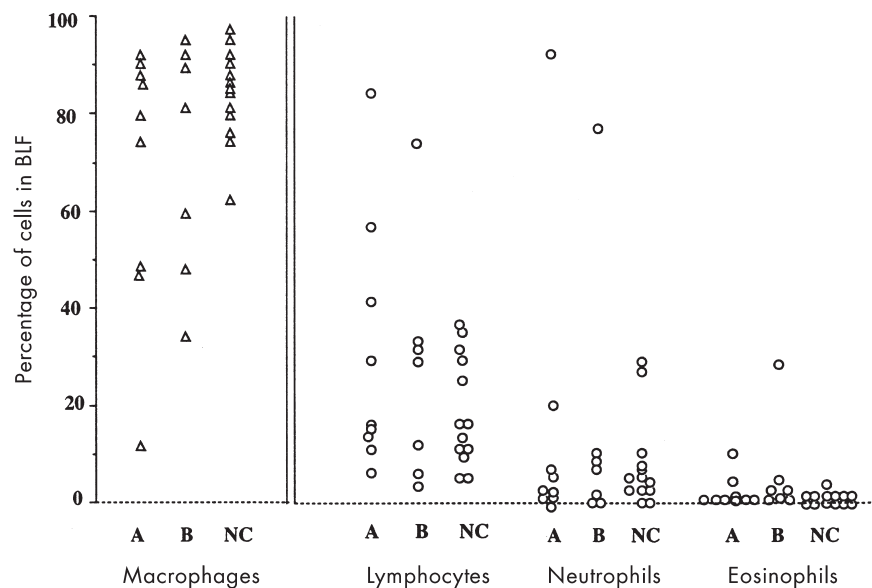
**Fig. 1** Number of eosinophils in bronchial submucosa was determined from transbronchoscopic biopsies from patients with chronic bronchodilator-resistant non-productive cough associated with an atopic basis (atopic cough). Group A, patients whose cough was relieved by histamine H<sub>1</sub>-antagonists ( $n = 9$ ); group B, patients whose cough was relieved by glucocorticoids, but not by histamine H<sub>1</sub>-antagonists ( $n = 9$ ). Each horizontal bar represents the median. Difference was determined by Mann–Whitney  $U$ -test.

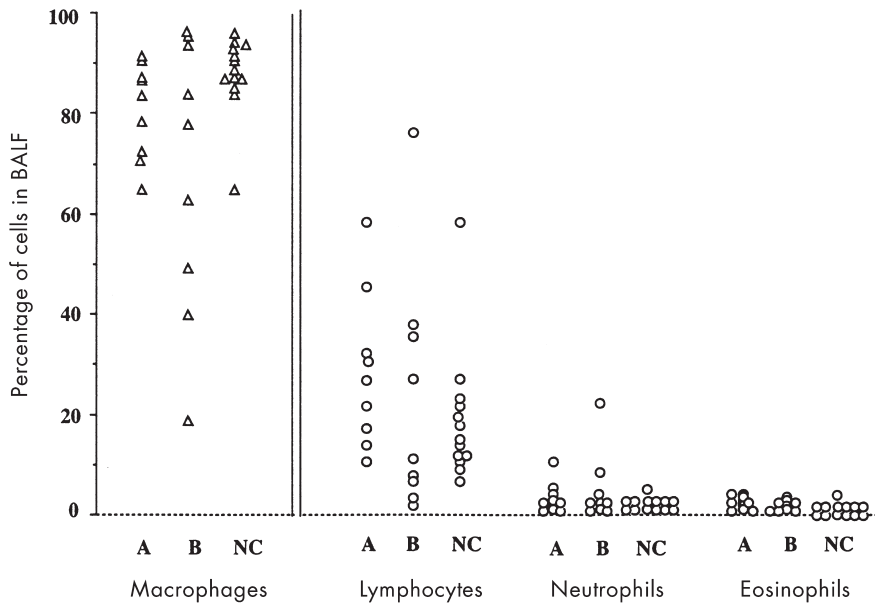
The degree of eosinophil infiltration in the subepithelium was not significantly correlated with the percentage or the number of eosinophils in BLF or BALF, the number of peripheral blood eosinophils, serum IgE levels or PC<sub>35</sub>-Grs in patients with chronic cough (group A plus group B; Table 2).

## DISCUSSION

Chronic persistent non-productive cough is pathologic to be troublesome itself, whereas productive cough is physiologic to expectorate abnormal secretions and foreign bodies from the lower respiratory tract. Our working hypothesis is that the pathologic cough occurs because of at least the following two mechanisms: (i) bronchoconstriction based on mild bronchial hyperresponsiveness in CVA;<sup>2,3</sup> and (ii) cough receptor hypersensitivity in AC,<sup>4,5</sup> cough induced by angiotensin-converting enzyme inhibitors,<sup>10</sup> GER-associated cough<sup>11</sup> and idiopathic dry, unproductive cough.<sup>10</sup> Hyperstimulation has been postulated as another mechanism of coughing in post-nasal drip-induced cough.<sup>12</sup> Sensitivity of the cough reflex is independent of bronchial responsiveness<sup>6</sup> and bronchomotor tone.<sup>13</sup> Recently, AC has been recognized as a new clinical entity presenting with chronic non-productive cough resistant to bronchodilator therapy.<sup>7</sup> Eosinophilic tracheobronchitis and airway cough hypersensitivity are histologic and pathophysiologic features of AC, respectively.<sup>7</sup> We have experienced more patients whose illness

**Fig. 2** Individual data on cell differentials in bronchial lavage fluid (BLF) recovered from patients with chronic bronchodilator-resistant non-productive cough associated with an atopic basis (atopic cough). The BLF refers to the first fraction of sequential bronchoalveolar lavage. A, patients whose cough was relieved by histamine H<sub>1</sub>-antagonists ( $n = 9$ ); B, patients whose cough was relieved by glucocorticoids, but not by histamine H<sub>1</sub>-antagonists ( $n = 7$ ); NC, normal controls.





**Fig. 3** Individual data on cell differentials in bronchoalveolar lavage fluid (BALF) recovered from patients with chronic bronchodilator-resistant non-productive cough associated with an atopic basis (atopic cough). The BALF refers to mixed fluid of the second and third fractions of sequential bronchoalveolar lavage. A, patients whose cough was relieved by histamine H<sub>1</sub>-antagonists ( $n = 9$ ); B, patients whose cough was relieved by glucocorticoids, but not by histamine H<sub>1</sub>-antagonists ( $n = 9$ ); NC, normal controls.

**Table 2** Correlation of degree of eosinophil infiltration in bronchial subepithelium to eosinophil counts in bronchial lavage fluid, bronchoalveolar lavage fluid and peripheral blood and serum total IgE levels in patients with chronic bronchodilator-resistant non-productive cough with an atopic basis

	<i>P</i>	<i>P</i>
Bronchial lavage fluid		
%	0.389	0.1324
10 <sup>5</sup> cells/mL	0.421	0.1033
Bronchoalveolar lavage fluid		
%	0.090	0.7116
10 <sup>5</sup> cells/mL	0.014	0.9548
Peripheral blood (%)	0.041	0.8644
Total IgE (IU/mL)	0.191	0.4305

was diagnosed as AC in comparison with those with CVA. Previous data<sup>14</sup> have shown that AC, CVA and others were, respectively, diagnosed in 34 (56.6%), 24 (40.0%) and two (3.4%) of 60 consequent patients presenting with chronic non-productive cough only who were referred to our chest and allergic clinic between 1 June 1990 and 31 January 1992.

The present study, with special emphasis on eosinophils, showed that eosinophils infiltrated in the subepithelium, but not the epithelium, of biopsied bronchi, while eosinophils in BLF or BALF were not increased in patients with AC. In addition, the intensity of eosinophil infiltration in the bronchial submucosa was not correlated with the absolute number or percentage of eosinophils in

BLF or BALF. Eosinophils in BLF were increased above 5% or more in only two of 16 patients in whom BLF was successfully recovered. The two patients seem to be consistent with eosinophilic bronchitis without asthma (EB), as described later. When the patients were excluded for data analysis, the results regarding bronchial submucosal, BLF and BALF eosinophils remained unchanged. These findings confirm our previous results that eosinophils are detected in subepithelium of trachea and/or bronchi, but not in BALF, from patients with AC.<sup>7</sup> It is well known that eosinophilic inflammation is present throughout large bronchi to peripheral airways in CVA,<sup>15</sup> as well as in classical asthma.<sup>16</sup> Thus, the pathological feature of AC is different to those of CVA and asthma.

We assigned studied patients with AC to one of two subgroups based on the successful treatment: (i) histamine H<sub>1</sub> receptor antagonists were sufficiently effective in group A ( $n = 9$ , 50%); and (ii) oral glucocorticoid therapy was required to relieve the cough in group B ( $n = 9$ , 50%). Namely, patients in group B are thought to have a more severe illness. This result is in agreement with that of previous reports<sup>4,5,8</sup> that the cough is successfully treated with histamine H<sub>1</sub> receptor antagonists in nearly 60% of patients and oral and/or inhaled glucocorticoids successfully improve cough that is not fully relieved by histamine H<sub>1</sub> receptor antagonists. The present study showed that bronchial eosinophilic inflammation was more severe in patients in group B rather than in group A, suggesting that histamine H<sub>1</sub> receptor antagonists are sufficiently effective for the milder illness and

that glucocorticoid therapy is necessary for the more severe cases.

Boulet *et al.*<sup>17</sup> have shown that BALF contains an increased number of inflammatory cells and bronchial biopsy presents an increased epithelial desquamation and inflammatory cells, particularly mononuclear cells, in 19 patients with chronic cough for which post-nasal drip and GER were the etiology. In those patients, no increase in eosinophils was found in BALF or biopsied bronchi. We did not perform bronchial biopsy in normal subjects and did not make a quantitative analysis on mucosal lymphocyte infiltration in the present study. Although the presence of lymphocyte infiltration in biopsied bronchi was qualitatively observed in most patients with AC, there was no significant increase in lymphocytes in BALF, while 20% or more lymphocytes were seen in BLF or BALF in six of 18 patients. These findings suggest that the histologic feature of AC is different from that of post-nasal drip-induced cough and GER-associated cough with regard to airway eosinophil infiltration.

Recently, Gibson *et al.*<sup>18</sup> showed that eosinophils and gene expression of interleukin (IL)-5 and granulocyte-macrophage colony stimulating factor were increased in BALF from patients with EB and these findings did not differ from those of asthmatic patients. Moreover, the cough is productive in EB<sup>18,19</sup> and non-productive in AC. Accordingly, AC is thought to be different from EB in the view of character of cough and BALF eosinophilia: non-productive cough compared with productive cough and absence compared with presence of BALF eosinophilia. Recently, however, it has been reported that EB is diagnosed in 10–15% of patients with isolated chronic cough referred to a respiratory specialist<sup>20,21</sup> and that non-productive cough is a sole manifestation in a part of patients with EB<sup>20</sup> (P Gibson, pers. comm., 1999). Furthermore, a case of EB developing irreversible airflow obstruction was reported.<sup>22</sup> Effects of histamine H<sub>1</sub> receptor antagonists in EB or long-term prognosis of AC or EB are unclear. Further studies are needed to clarify whether AC and eosinophilic bronchitis without asthma are different or not.

Two patients included in the present study had an increase in neutrophils in BLF. Further examination after complete relief of their non-productive cough revealed that they were complicated with very mild sinobronchial syndrome.<sup>23</sup> Sinobronchial syndrome is a very common chronic upper and lower respiratory tract inflammatory disorder presenting with chronic expectoration in Japan.<sup>24</sup> After their severe non-productive cough had

completely resolved following treatment with ketotifen or glucocorticoids, we found that they had a small amount of sputum expectoration and throat clearing. As these symptoms were not troublesome, they required no additional treatment.

The prevalence of allergen-specific IgE was low in comparison with the high prevalence of eosinophils in bronchial submucosa in the present study. In our experience, house dust mite or Japanese cedar antigen are unlikely causative agents for AC because the onset of coughing does not coincide with the season. Recently, we have experienced patients with AC in whom uncommon environmental fungal antigens are causative based on an environmental survey and antigen challenging.<sup>25–27</sup> Thus, routine work-up for specific IgE may be merely useful for the evaluation of global atopic tendency, but not causative antigens, in seeing patients with AC.

Although AC is the most common cause of chronic non-productive cough in our district, as mentioned above, and has been recognized in other regions of Japan, it is unknown whether this clinical entity is relevant in other countries. It has been reported that GER is a common cause of chronic cough in Caucasians (5–20% of chronic cough),<sup>1,28</sup> but it is very rare in Japan (less than 1%),<sup>29</sup> suggesting the possibility of racial or regional differences in the causes of pathologic cough. Further studies are required to establish AC in Japan in comparison with EB and to elucidate the possibility of differences in causative disorders presenting with chronic cough between countries.

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