

Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough

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Summary

Background We have shown that some patients presenting with chronic bronchodilator-resistant non-productive cough have global atopic tendency and airway cough hypersensitivity without non-specific bronchial hyperresponsiveness, abbreviated as atopic cough. The cough is successfully treated with histamine H₁-antagonists and/or glucocorticoids.

Objective This prospective study was conducted to elucidate the histological feature of atopic cough.

Methods Tracheal and bronchial mucosa obtained by transbronchoscopic biopsy and bronchoalveolar lavage (BAL) cell component were studied with special emphasis on eosinophils in eight non-smokers diagnosed with atopic cough, all of whom had increased sensitivity of cough response to inhaled capsaicin, normal lung function and bronchial responsiveness to methacholine and normal chest roentgenogram. Their cough completely resolved on histamine H₁-antagonists and/or glucocorticoids. Transbronchoscopic tracheal and bronchial biopsy and BAL were also performed in healthy non-smokers as a control.

Results A small number of eosinophils was detected in subepithelium of trachea in six of seven patients and in subepithelium of bronchi in seven of eight cough patients. The numbers of eosinophils in subepithelium of trachea and bronchi were significantly increased in the patients compared with control subjects. There was no BAL eosinophilia in any patients.

Conclusion It is concluded that eosinophilic tracheobronchitis and cough hypersensitivity are pathological and physiological characteristics of atopic cough.

Keywords: airway cough sensitivity, atopic cough, bronchoalveolar lavage, chronic non-productive cough, eosinophilic tracheobronchitis

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Introduction

Cough is a common presenting symptom. There are so many patients with only chronic non-productive cough that the diagnosis and treatment is important for general practitioners as well as chest physicians and allergists. Although gastroesophageal reflux-associated cough, postnasal drip-induced cough, angiotensin-converting enzyme inhibitor-induced cough and cough variant asthma are known as causes of non-productive cough [1], we have proposed a bronchodilator-resistant non-productive cough associated

with atopic basis, referred to here as atopic cough, as another cause of non-productive cough since 1992 [2], in which non-specific bronchial responsiveness is within normal limits [2–4], airway cough sensitivity to inhaled capsaicin is heightened [3,4] and hypertonic saline-induced sputum contains eosinophils in most of the patients [4]. The cough is successfully treated with selective histamine H₁-antagonists and/or glucocorticosteroids [2–4]. Though induced sputum eosinophilia is common in cough variant asthma and atopic cough [4], these are different in view of the following: bronchial responsiveness is mildly heightened [5,6], sensitivity of cough response to inhaled capsaicin is within normal limits [3,4] as well as classical asthma [7], and bronchodilators such as β_2 -adrenoceptor

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agonists and theophylline effectively relieve the cough [5,6] in cough variant asthma.

As to association between airway eosinophilic inflammation and cough Niimi *et al.* [8] have reported that eosinophil numbers both in bronchoalveolar lavage (BAL) fluid and bronchial submucosa are not different between cough variant asthma and classical asthma. In addition, Gibson *et al.* [9,10] have shown that eosinophils in morning spontaneous sputum and BAL fluid are increased in patients with corticosteroid-responsive chronic cough productive of sputum which is resistant to bronchodilator therapy (eosinophilic bronchitis without asthma). Bronchial responsiveness has been shown to be within normal limits in the eosinophilic bronchitis without asthma [9,10].

The aim of this study was to directly assess the presence of eosinophils in tracheal and bronchial mucosa in atopic cough. We prospectively studied location and intensity of eosinophil infiltration in tracheal and bronchial biopsy specimens and BAL cell findings in patients with atopic cough and showed here that eosinophilic tracheobronchitis with airway cough hypersensitivity is a fundamental feature of atopic cough.

Subjects and methods

This study was approved by the local ethics committee. Eight non-smoking (six never-smoking and two ex-smoking) patients diagnosed atopic cough (Table 1) and eight healthy non-smoking (four never-smoking and four ex-smoking) subjects were enrolled as they gave informed consent for undergoing bronchoscopic examinations. Each patient met the following criteria of atopic cough (1) chronic non-productive cough with a 'tickle' in the throat lasting for more than 8 weeks which was resistant to bronchodilator therapy (oral clenbuterol 40 µg/day and inhaled procaterol on demand for at least 1 week), (2) absence of wheeze, dyspnea, haemoptysis, or pleurisy and no adventitious lung sounds on examination, (3) non-specific bronchial responsiveness to methacholine within normal limits, (4) increased sensitivity of cough response to inhaled capsaicin, (5) presence of one or more of the following findings indicative of atopy as a global feature: past history and/or complication of allergic diseases except for bronchial asthma, peripheral blood eosinophilia, elevated total immunoglobulin (Ig) E level in serum, positive specific IgE antibody to aeroallergens, and positive allergen skin test (Table 2), (6) normal FEV₁, FVC, and FEV₁/FVC ratio, (7) no bronchial reversibility defined as less than 10% increase in FEV₁ after inhalation of 300 µg salbutamol following aminophylline (250 mg) injection, (8) complete relief of the cough on treatment with histamine H₁-antagonists (terfenadine 60 mg twice daily or azelastine 2 mg twice daily) and/or corticosteroid therapy (oral prednisolone

20 mg once daily for 2 week or less and/or inhaled beclomethasone 400 µg twice daily) within 1 month, and (9) absence of well-known causes of cough such as gastroesophageal reflux, postnasal drip and chronic bronchitis. Gastroesophageal reflux-associated cough is very rare in Japan (less than 1% of chronic cough) [11] and each patient had never complained of heart burn or sour taste and his or her coughing was relieved completely with the therapy described above. None had postnasal drip-induced cough because throat clearing, postnasal drip, nasal obstruction, sneezing or watery rhinorrhea was not recognized and paranasal roentgenogram was normal. Chronic bronchitis was neglected as all patients were not current smokers.

Capsaicin cough threshold was measured as an index of airway cough sensitivity according to the method reported by us [12] at the first visit and after the cough completely resolved on the successful treatment (Table 1). The second capsaicin provocation was performed while the patients were free from treatment or on the treatment excluding oral corticosteroids (Table 1). The capsaicin cough threshold was defined as the lowest concentration of inhaled capsaicin eliciting five or more coughs. The bronchial reversibility was assessed at the first visit. The non-specific bronchial responsiveness to methacholine was assessed according to the method described by Cockcroft *et al.* [13] at the second visit. Results were expressed as the provocation concentration (mg/mL) required to cause a 20% fall from the baseline FEV₁ (PC₂₀).

Before the cough resolved on each successful treatment, flexible fibre optic bronchoscopy was performed under local anaesthesia with lidocaine following premedication with atropine sulphate and hydroxyzine. Bronchoalveolar lavage (BAL) was carried out in the right middle lobe using three 50 mL aliquots of physiological saline solution. After a part of the BAL fluid was diluted with an equal volume of Türk solution, cells were counted in a Bürker chamber. After the remaining BAL fluid was passed through a double layer of Dacron net, cells were pelleted at 300g for 10 min and resuspended in 10 mL of RPMI-1640 (Grand Island Biological Co., Grand Island, NY, USA). The fluid was resuspended to a concentration of 2×10^5 cells/mL. Smears for differential counts were prepared by cytocentrifugation (Cytopin 2, Shadon Southern Instruments, Sewickley, PA, USA) at 70g for 10 min. After staining with May-Grünwald-Giemsa, differential cell count was done in 300 cells. Airway mucosa specimens were taken with a cup of forceps at a bifurcation of the right upper lobe bronchus and truncus intermedius and/or at the opening of the right middle lobe as bronchial mucosa (total of two or three specimens), and at anterior wall of lower trachea 3 cm distant from the first carina as tracheal mucosa (two or three specimens). The biopsied specimens were fixed in formalin solution, embedded in paraffin, and cut through its

entire thickness at 4 μm , all sections being mounted and stained with haematoxylin and eosin. Light microscopic examination was performed independently by two pathologists, who were not aware of the clinical findings, in order to identify the location and number of eosinophils. Numbers of eosinophils in epithelium and subepithelium were counted at three different sites of each specimen using an eyepiece graticule, and then the counted eosinophil numbers of two or three specimens were averaged. The results were expressed as the average of the eosinophil numbers counted by the two pathologists (cells per 150 μm length of epithelium and cells per 1 mm^2 area of subepithelium).

Data were expressed as mean $\pm$ SD. Numbers of eosinophils in biopsied tracheal and bronchial mucosa were also shown as median and range. Statistical difference was determined by Mann–Whitney's *U*-test.

Results

Appropriate biopsy specimens were obtained from bronchi in eight patients and six control subjects, and from trachea in seven patients and six control subjects. The biopsy specimens revealed eosinophil infiltration in the subepithelium of bronchi in seven of the eight patients and of trachea in six of the seven patients as shown in Fig. 1. Subepithelial eosinophils were documented in trachea, bronchi or both in each patient. The numbers of eosinophils in the subepithelium of trachea (19.5 ± 19.4 cells/ mm^2 , median 15.7 and range 0–50 cells/ mm^2) and bronchi (16.6 ± 12.5 cells/ mm^2 , median 16.0 and range 0–43.3

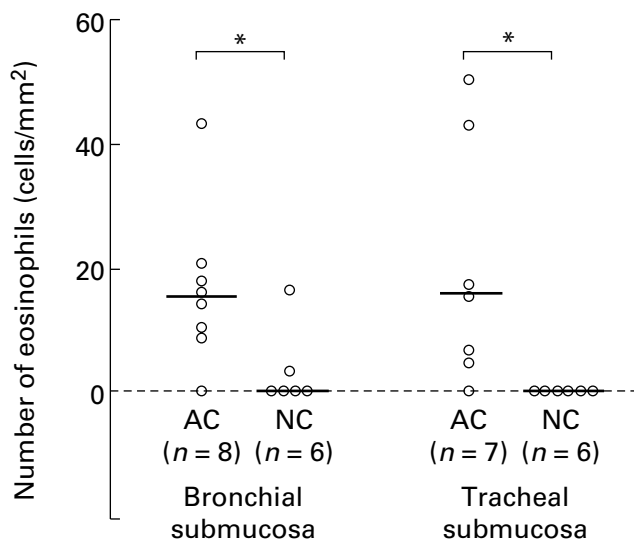


Fig. 1. Number of eosinophils in bronchial and tracheal submucosa obtained by transbronchoscopic biopsy from patients with chronic bronchodilator-resistant non-productive cough associated with atopic basis (AC) and control subjects (NC). Each horizontal bar represents median. * $P < 0.05$ by Mann–Whitney's *U*-test

cells/ mm^2) were significantly greater ($P < 0.05$ and $P < 0.05$, respectively) in the patients compared with the control subjects (0.0 ± 0.0 , median 0 and range 0–0 cells/ mm^2 and 3.4 ± 6.6 , median 0 and range 0–16.5 cells/ mm^2 , respectively). Eosinophils were detected in the epithelium of bronchi in two patients (patients 5 and 6) and in the epithelium of trachea in two patients (patients 4 and 6) but not in any of control subjects.

BAL was successfully performed in each patient and control subject. The BAL cell findings are shown in Table 3. Number of eosinophils in BAL fluid was not increased in any of the patients or control subjects and did not differ between the patients and the control subjects. Percentage lymphocytes and neutrophils in BAL fluid were significantly increased in the cough patients compared with normal subjects.

Discussion

The present study clearly showed that a small number of eosinophils infiltrated in the subepithelium of both trachea and bronchi while eosinophils in BAL fluid were not increased in patients with atopic cough. It is well known that eosinophilic inflammation is present throughout central to peripheral airways in both asthma and cough variant asthma because eosinophils are increased in both BAL fluid and biopsied bronchial mucosa in these airway disorders [5,14]. In addition the number of eosinophils in biopsied bronchial submucosa has been reported to be 30.4 and 50.1 cells/ mm^2 in classic asthma and cough variant asthma patients, respectively [8], which are greater than that in atopic cough patients shown in this study (16.6 cells/ mm^2). We also have shown that eosinophil number in hypertonic saline-induced sputum is greater in asthma and cough variant asthma than in atopic cough [4]. Although it is possible that BAL samples the airway lumen and lavaged eosinophils reflect intensity of mucosal eosinophil infiltrate, no increase in BAL eosinophils in atopic cough is considered to be meaningful. Thus, the pathological feature of atopic cough is thought to be different from those of asthma and cough variant asthma in the view of site and intensity of eosinophilic inflammation. Eosinophilic inflammation of trachea and central bronchi, but not peripheral airways, may be pathologically characteristic of atopic cough. To explore this concept further peripheral airway biopsy studies are needed.

Successful treatment reduces the increased cough sensitivity in atopic cough, but not in cough variant asthma in which cough sensitivity is within normal limits [3]. The reduction of cough hypersensitivity by the successful treatment in atopic cough is similar to angiotensin-converting enzyme inhibitor-induced cough in which the cyclooxygenase inhibitor sulindac relieves the cough and attenuates the cough hypersensitivity [15]. However, as the clinical

Table 1. Characteristics of patients with bronchodilator-resistant non-productive cough associated with atopy (atopic cough)

Patient	Age (years)	Sex	Smoking	Symptom duration (months)	FEV ₁ (% predicted)	FEV ₁ /FVC (%)	PC ₂₀ (mg/mL)	Bronchial reversibility (%)	Before treatment	After treatment	Treatment*	Interval† (days)	Successful treatment	Time‡ for relief of cough (day)
1	52	F	Never	24	95	82	>40	3.7	0.98	62.5	Terfenadine, BDP	91	Azelastine, PSL, BDP	14
2	68	F	Ex	2	103	83	>40	6.7	1.95	31.2	Terfenadine	60	Terfenadine, BDP	18
3	50	F	Never	3	81	81	10	6.2	0.49	3.9	BDP	107	Azelastine, BDP	9
4	70	F	Never	12	102	77	>40	0.7	0.98	3.9	Terfenadine	28	Terfenadine	12
5	50	F	Never	2	90	81	>40	1.4	0.98	7.8	Azelastine	139	Azelastine, BDP	18
6	61	F	Never	4	137	77	>40	3.8	1.95	31.2	None	85	Terfenadine, PSL, BDP	10
7	50	F	Ex	2	92	85	20	NT	0.49	3.9	Azelastine	49	Azelastine, BDP	13
8	59	M	Never	48	114	94	>40	3.2	1.95	7.8	None	28	Terfenadine	10
Mean	56.6			3.5§	102	83		3.7	1.07¶	11.6¶		73		13
sd	11.3			2–48	17	5		2.2	1.78	3.29		39		4

Cough threshold to inhaled capsaicin was significantly ($P < 0.02$) increased after treatment than before treatment by Wilcoxon signed rank test. *Treatment at the second capsaicin provocation; †interval between the first and the second capsaicin provocation; ‡time required to relieve cough on the successful treatment; §shown as median with range; ¶shown as geometric mean with geometric standard deviation of the mean. Never = never smoker, ex = ex-smoker, NT = not tested. BDP = beclomethasone dipropionate inhalation (200–400 µg twice daily), PSL = oral prednisolone (20 mg once daily) for less than 2 weeks.

Table 2. Findings indicative of atopy as a global feature

Patient	Total IgE (IU/mL)	Specific IgE	Allergen skin test for fungal allergen	eosinophils (%)	Complicated allergic disease
1	10	<u>Japanese cedar</u>	<i>Streptomyces albus</i>	3.6	<u>Allergic rhinitis</u>
2	4	–	Cladosporium	2.8	<u>Urticaria</u>
3	31	<u>House dust, mite</u>	Penicillium, Alternaria	0.8	<u>Urticaria</u>
4	<u>191</u>	–	Not done	3.7	–
5	<u>933</u>	<u>Aspergillus</u>	Not done	<u>6.1</u>	–
6	68	<u>Mite</u>	Not done	3.0	–
7	<u>200</u>	–	Alternaria, Aspergillus	1.1	–
8	114	<u>Alternaria, Aspergillus</u>	Alternaria, Aspergillus	<u>7.5</u>	–

Each patient had one or more positive findings indicative of atopy as a global feature. Positive results were indicated by underline.

entity of atopic cough has not yet been well established the present study was conducted to elucidate the clinical feature. It is likely that atopic cough is different from 'eosinophilic bronchitis without asthma' or 'corticosteroids-responsive chronic cough', in which cough is productive and eosinophils are increased in BAL fluid, described by Gibson and associates [9,10].

Our previous study [3] has clearly shown that the physiological feature of atopic cough is airway cough hypersensitivity without bronchial hyperresponsiveness, and the heightened cough sensitivity recovers to normal range after the cough completely relieves on the successful treatment. Although bronchial hyperresponsiveness is characteristic of asthma [16] and cough variant asthma [6],

Table 3. Cell differentials in broncho-alveolar lavage fluid in patients with bronchodilator-resistant non-productive cough (atopic cough) and control subjects

	Total cells ($\times 10^6/\text{mL}$)	Macrophages (%)	Eosinophils (%)	Neutrophils (%)	Lymphocytes (%)
<i>Patient</i>					
1	7.9	75.5	0	0	24.5
2	1.6	93.0	0	1.0	6.0
3	1.2	73.0	0	5.5	21.5
4	9.9	56.8	0	8.0	35.2
5	2.2	68.4	1.2	8.4	22.0
6	0.6	60.0	0	4.4	25.6
7	0.3	73.6	0.8	4.8	20.8
8	0.8	31.6	0.8	20.4	31.2
Mean	3.1	66.5	0.4	6.6	23.4
SD	3.7	17.9	0.5	6.3	8.6
<i>Control</i>					
1	3.1	90.3	1.0	2.3	6.3
2	0.8	91.3	0	0.3	8.3
3	1.3	87.0	0	0	13.0
4	3.8	95.7	0	0.3	4.0
5	1.5	83.7	0	0	16.3
6	0.3	85.0	0	1.0	14.0
7	3.1	94.0	0	0.5	5.5
8	1.4	86.7	0.3	1.0	12.0
Mean	1.9	89.2	0.2	0.7	9.9
SD	1.3	4.3	0.1	0.8	4.5
Difference	NS	$P < 0.01$	NS	$P < 0.02$	$P < 0.01$

Difference was analysed by Mann–Whitney *U*-test. NS = not significant.

sensitivity of cough reflex is within normal limits in these airway disorders [3,4,7]. These findings suggest that atopic cough, of which eosinophilic tracheobronchitis and cough hypersensitivity are pathologically and physiologically characteristic, may be a distinctive clinical entity. Recently, we experienced some patients with atopic cough in whom causative antigens such as *Trichosporon cutaneum* [17], *Pichia guilliermondii* [18], *Streptomyces albus* and *Humicola fuscoatra* (unpublished) were found by environmental survey and antigen challenging, but causative antigens are not discovered in most patients at present.

In the present study, lymphocytes and neutrophils in BAL fluid were increased in patients with atopic cough. We did not show the number of lymphocytes and neutrophils in the tracheal and bronchial mucosa because it was difficult to identify these cells in the specimens stained with haematoxylin and eosin using light microscopy. The increases in sub-mucosal lymphocytes and BAL neutrophils are non-specifically investigated in nonasthmatic chronic cough including postnasal drip-induced cough, gastro-esophageal reflux-associated cough and aetiology-unknown cough [19] as well as asthma [20]. BAL lymphocytes and neutrophils were slightly increased in atopic cough compared with control but the differences did not reach statistical significance in our another study (unpublished). Increase in BAL neutrophils was not remarkable in two ex-smoking patients (1.0% and 4.8%). The extreme BAL neutrophilia in patient 8 was thought to result from complicated sinobronchial syndrome [21], which was discovered by further study after improvement of the cough. When patient 8 was excluded, the BAL neutrophils were still increased ($4.6 \pm 1.2\%$). Thus, we do not know the meaning of the increased lymphocytes and neutrophils in the patients with atopic cough shown in this study.

We have experienced many patients with atopic cough, who are referred to our chest and allergic clinic because their cough is resistant to antibiotics, common antitussive drugs and bronchodilators. The cough is the most popular of chronic non-productive cough in our clinic: atopic cough 34 (56.6%); cough variant asthma 24 (40.0%); others two (3.4%) of 60 consequent patients presenting with only chronic non-productive cough who were introduced to our chest and allergy clinic between June 1, 1990, and January 31, 1992 [22]. Since we reported that the cough is successfully treated [2–4]; histamine H_1 -antagonists are effective in nearly 60% of patients and oral (prednisolone 20 mg/day for 14 days or less) and/or inhaled corticosteroids (beclomethasone dipropionate 400–800 $\mu\text{g/day}$) successfully improves cough resistance to histamine H_1 -antagonists within 14 days in a large part of patients as shown in Table 1. Not only chest physicians but also general practitioners can diagnose and successfully treat the cough of patients with atopic cough in Japan. Further clinical investigations are needed to evaluate

whether atopic cough presented in this study is available in other countries by means of studying whether it is included in a part of the idiopathic dry, unproductive cough described by McEwan *et al.* [15].

In summary, we conclude that increased airway cough sensitivity and eosinophilic tracheobronchitis are physiological and pathological features of bronchodilator-resistant non-productive cough associated with atopic basis. However, as the present study was cross-sectional, atopic control subjects were not studied and the effectiveness of bronchodilator therapy and successful treatment was judged by open label treatment, further studies are needed to assure the conclusion.

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