Allergology International (2000) **49**: 83–87

Case Report

Eosinophilic tracheobronchitis with cough hypersensitivity caused by *Streptomyces albus* antigen

Haruhiko Ogawa,[1,2] Masaki Fujimura,[2] Saori Myou,[2] Masanobu Kitagawa[3] and Tamotsu Matsuda[2]

[1]Division of Pulmonary Medicine, Toyama Red Cross Hospital, Toyama, [2]Third Department of Internal Medicine, Kanazawa University School of Medicine, Kanazawa and [3]First Department of Pathology, Toyama Medical and Pharmaceutical University School of Medicine, Toyama, Japan

Abstract

A 52-year-old woman is reported with atopic cough, in whom bronchoprovocation with *Streptomyces albus* antigen induced cough and bronchoscopic biopsy revealed eosinophilic tracheobronchitis. She was admitted for the diagnosis and treatment of severe non-productive cough. Although her induced sputum contained 8% eosinophils of nucleated cells and bronchoscopic biopsy specimens revealed eosinophil infiltration in both tracheal and bronchial wall, she did not have bronchial hyperresponsiveness to methacholine or heightened bronchomotor tone. Bronchodilator therapy was not effective for her coughing. Her symptoms worsened on returning home, suggesting the existence of some etiologic agents in her house. *Streptomyces albus* was isolated from her house. A high titer of anti-*S. albus* antibody was detected in her serum and the bronchoprovocation test with *S. albus* antigen was positive: development of coughing 15 min later and decrease in cough threshold to inhaled capsaicin 24 h later (3.9 μmol/L from 31.3 μmol/L prechallenge). This is the first report on eosinophilic tracheobronchitis with cough hypersensitivity caused by allergic reaction to *S. albus* antigen.

Correspondence: Haruhiko Ogawa MD, Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, Ni-13-6 Akatsuchi-machi, Kanazawa 920-0353, Japan.

Received 24 December 1998. Accepted for publication 2 September 1999.

Key words: atopic cough, capsaicin cough sensitivity, chronic cough, cough hypersensitivity, eosinophilic tracheobronchitis, *Streptomyces albus*.

Introduction

Cough is a common presenting symptom in general practice and in the chest clinic. Patients presenting with chronic non-productive cough resistant to antibiotics and the usual antitussive agents are frequently introduced to our clinic for diagnosis and treatment. It has been established that cough can be the sole manifestation of asthma, cough variant asthma,[1] with bronchial hyperresponsiveness, which is a fundamental feature of bronchial asthma. The cough is relieved on the bronchodilator therapy. However, some patients have a bronchodilator-resistant non-productive cough associated with global atopic tendency, in which the cough is diminished by selective histamine H_1-antagonists and/or glucocorticosteroids.[2–5] In such patients, non-specific bronchial responsiveness is within normal limits[2–4] and airway cough sensitivity to inhaled capsaicin is heightened.[3] Hypertonic saline-induced sputum contains eosinophils[4] and bronchoscopic biopsy shows eosinophil infiltration in bronchial tissue.[5] We have proposed that the chronic bronchodilator-resistant non-productive cough is associated with global atopic tendency and airway cough hypersensitivity without non-specific bronchial hyperresponsiveness, abbreviated as 'atopic cough', a clinical entity for the pathologic cough.

We report here the first case of atopic cough caused by allergic reaction to *S. albus* antigen, which was diagnosed by antigen inhalation challenge. In addition, we

have shown that a histologic feature of atopic cough is eosinophilic tracheobronchitis.

Clinical summary

A 52-year-old woman was admitted to our hospital on 9 September 1996, because of severe non-productive cough with ticklish throat and chest wall pain and urinary extravasation caused by the severe coughing for 2 months. Further questioning revealed that she had consulted a physician and had been diagnosed as having 'acute bronchitis' in summer 1995. She was an office worker and lived with her family in a 10-year-old wooden house. She had never smoked and did not drink any alcoholic beverages.

Physical examination revealed the following: temperature 36.5°C; blood pressure 140/88 mmHg; heart rate 66 beats/min. The conjunctivae were not anemic or icteric. Cardiac examination was entirely within normal limits. Auscultation of lungs revealed no rales. There was no lymphadenopathy. The abdomen was benign and without organomegaly. The extremities were intact for neurologic examination.

The white blood cell count was 5300 /μL with a differential of 64.9% segmented neutrophils, 24.9% lymphocytes, 7.0% monocytes and 3.0% eosinophils. The erythrocyte sedimentation rate was 12 mm/h. The C-reactive protein level was 0.11 mg/dL and the total IgE level was 1 U/mL. Specific IgE antibodies were negative for house dust 1, 2 and 6, *Dermatophagoides pteronyssinus* and *D. farinae*, Japanese cedar, ragweed, orchard grass, *Aspergillus* and *Candida* antigens. Arterial blood gas levels while breathing room air were PaO_2 83.9 mmHg, $PaCO_2$ 44.3 mmHg and pH 7.40. The following laboratory findings were normal or negative: urinalysis, stools for ova and parasites, serum electrolytes, total protein and albumin and mycobacterial and fungal cultures of sputum. Differential cell analysis of sputum induced by inhalation of hypertonic saline[4] revealed mild eosinophilia (8% of nucleated cells). The electrocardiogram showed normal sinus rhythm.

The chest radiograph and the chest computed tomographic (CT) scan on admission showed normal findings.

The pulmonary function test performed using a Collins DS system, according to the standards of the American Thoracic Society,[6] revealed forced vital capacity (FVC) 2.51 L (97.7% of predicted value), forced expiratory volume in 1 s (FEV_1) 2.02 L (91.4% of predicted value), FEV_1/FVC ratio 80.5%, total lung capacity (TLC) 3.84 L (96.5% of predicted value), respiratory volume (RV) 1.35 L (84.9% of predicted value), carbon monoxide diffusing capacity (DL_{CO}) 15.41 mL/min per mmHg (85.3% of predicted value) and DL_{CO}/alveolar ventilation (VA) ratio 4.97 mL/min per mmHg per L (101.4% of predicted value). To assess bronchial reversibility, spirometry was carried out before and 30 min after an inhalation of 300 μg salbutamol sulfate following an intravenous administration of 250 mg aminophylline. The bronchodilator therapy did not significantly increase FEV_1 (from 2.15 to 2.23 L) or FVC (from 2.57 to 2.53 L), indicating that the patient's bronchomotor tone was not increased. Bronchial responsiveness to methacholine was measured according to the method of Cockcroft *et al*.[7] The provocative concentration of methacholine required to cause a 20% fall from the baseline FEV_1 (PC20) was 20 mg/mL. Capsaicin cough threshold measured by our previously reported method[8,9] was 1.95 μmol/L, suggesting cough hypersensitivity.

Transbronchoscopic bronchial biopsy (TBBB) specimens obtained from a bifurcation of the right upper lobe bronchus and truncus intermedicus showed mild infiltration of eosinophils and lymphocytes in the edematous submucosal tissue (Fig. 1). Furthermore, we performed tracheal biopsy to examine whether eosinophilic inflammation

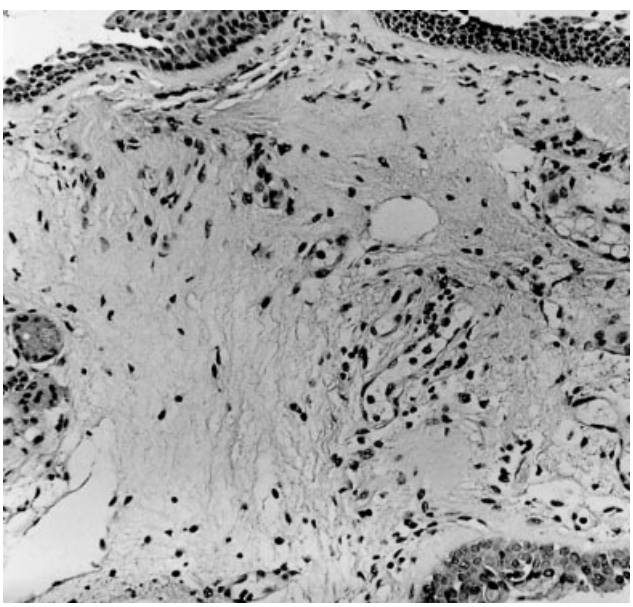

Fig. 1 Transbronchoscopic bronchial biopsy specimen showing mild eosinophil and lymphocyte infiltration in the edematous submucosal area. The biopsy specimen was obtained from a bifurcation of the right upper lobe bronchus and truncus intermedicus.

existed in her trachea. The successfully obtained tiny specimens demonstrated mild eosinophil infiltration in the submucosal area of the trachea (Fig. 2). Bronchoalveolar lavage fluid (BALF; total cells 7.9×10^{-6} cells/mL) recovered from the right S4 consisted of 75.5% macrophages, 0% eosinophils, 0% neutrophils and 24.5% lymphocytes.

These findings suggested that this case was bronchodilator-resistant cough associated with atopy (atopic cough).[2–5] Indeed, although bronchodilator therapy with procaterol aerosol (60 μg/day) failed to relieve her cough, a histamine H_1-antagonist, terfenadine (120 mg/day), and beclomethasone dipropionate (BDP) inhalation (600 μg/day) were effective.

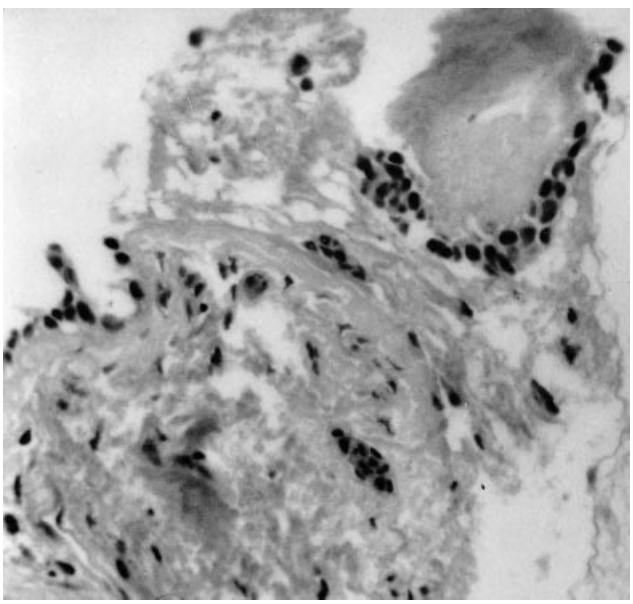

Fig. 2 Transbronchoscopic tracheal biopsy specimen showing mild eosinophil infiltration in the submucosal area.

Her coughing was worsened on returning home, suggesting existence of some etiologic agents. From the sterile Petri dishes containing Sabouraud's agar medium supplemented with antibiotics exposed for 10 min on the floor of every room in the patient's house with closed windows, *S. albus* and *Cladosporium sphaerospermum* were isolated in the living room.

For the preparation of antigenic solution, each fungus was cultured on the medium (1% peptone, 2% glucose) with 0.5% yeast extract for 20 days and dried by acetone. Skin tests of the fungal antigens (polysaccharide) were done by intradermal injection with 0.02 mL of the solutions (1 mg/mL). The immediate-type skin reactions were

Table 1 Allergologic findings

Test	*Streptomyces albus*	*Cladosporium sphaerospermum*
Skin test		
Immediate	0 × 0/5 × 3	0 × 0/5 × 3
6 h	0 × 0/8 × 4	0 × 0/11 × 9
24 h	0 × 0/13 × 13	0 × 0/0 × 0
48 h	0 × 0/0 × 0	0 × 0/0 × 0
Precipitating antibody	× 2	–

Skin test results are given in mm.

Table 2 Clinical and laboratory findings in the inhalation challenge test with *Streptomyces albus* and *Cladosporium sphaerospermum* antigens

	Pre	20 min	6 h	24 h
S. albus				
Cough	None	Mild	Mild	None
BT (°C)	36.7	36.9	36.7	36.9
CRP (mg/dL)	0.06			0.07
WBC (μL)	4300			4700
Eos. (%)	5.1			3.5
DL_{CO} (%)	85.3			88.9
Cough threshhold (μmol/L)	31.2			3.90
C. sphaerospermum				
Cough	None	None	None	None
BT (°C)	36.6	36.8	36.7	36.7
CRP (mg/dL)	0.1			0.12
WBC (μL)	5200			3900
Eos. (%)	3.2			4.3
DL_{CO} (%)	73.1			84.9
Cough threshhold (μmol/L)	62.5			125

BT, body temperature; CRP, C-reactive protein; WBC, white blood cells; Eos., eosinophils; DL_{CO}, carbon monoxide diffusing capacity.

negative and late-type skin reactions were weakly positive for both *S. albus* and *C. sphaerospernum* . The serum antifungus antibody titers referred to IgG based on the Ouchterlony method were × 2 for *S. albus* and negative for *C. sphaerospernum* (Table 1).

The bronchoprovocation test with *C. sphaerospernum* antigen (2 mL of culture-filtrate antigen (1 mg/mL)) performed under the informed consent was negative and that with *S. albus* was judged positive. Although none of the parameters examined for hypersensitivity pneumonitis changed, the patient developed cough attack with a significant increase in airway cough sensitivity, assessed by the capsaicin provocation cough test, during the next 24 h. The antigen-induced symptoms and signs had disappeared by 24 h after the challenge test (Table 2).

Based on these results, we advised the patient to cleanse the entire house, especially the living room contaminated with *S. albus*, and neither *S. albus* nor *C. sphaerospernum* were isolated in the room after cleaning.

Prednisolone (20 mg/day) was tapered to zero on 21st day, when her symptoms subsided.

Discussion

Although sputum eosinophilia is characteristic of bronchial asthma and eosinophilic pneumonia,[10] it is also seen in drug-induced eosinophilic bronchitis,[11] eosinophilic bronchitis without asthma described by Gibson *et al*.[12] and bronchodilator-resistant non-productive cough associated with atopy (atopic cough).[2–5]

In our case, absence of active pulmonary infiltrates on chest radiographic films and chest CT and normal diffusing capacity showed a lack of definite alveolitis, indicating that her sputum eosinophilia might have resulted from eosinophilic bronchitis but not from eosinophilic pneumonia. Although the patient's sputum contained 8% eosinophils, she did not have increased bronchial responsiveness to methacholine or heightened bronchomotor tone, the fundamental features of bronchial asthma. Furthermore, bronchodilator therapy was not effective for her coughing. We tried tracheal and bronchial biopsies in this case and successfully obtained specimens that revealed eosinophilic tracheobronchitis. These findings supported the diagnosis of eosinophilic tracheobronchitis with cough hypersensitivity without bronchoconstriction.

In the eosinophilic bronchitis without asthma described by Gibson and associates,[12,13] the cough is productive and eosinophils are increased in BALF. In contrast, the cough is non-productive and BALF eosinophilia is absent in atopic cough,[5] indicating that atopic cough is different from eosinophilic bronchitis without asthma. Thus, we have proposed atopic cough as a new clinical entity.[5] The term 'atopy' is generally recognized to be the hereditary productivity of IgE antibody and also means the factor that may develop atopic diseases in future from a global aspect. Based on our series of clinical studies on chronic cough, the clinical features of atopic cough are considered to be: (i) chronic non-productive cough with a 'tickle' in the throat lasting for more than 8 weeks; (ii) absence of wheeze, dyspnea, hemoptysis or pleurisy and no adventitious lung sounds on examination; (iii) presence of one or more of the global atopic findings: past history and/or complication of allergic disease (except for bronchial asthma), family history of allergic diseases, peripheral blood eosinophilia, elevated total IgE level in serum, positive specific IgE antibody to common inhalants or positive allergen skin test; (iv) existence of eosinophils in sputum, hypertonic saline-induced sputum and/or biopsied bronchial wall; (v) normal FEV_1, FVC, and FEV_1/FVC ratio; (vi) no bronchial reversibility defined as less than 5% increase in FEV_1 after inhalation of 300 μg salbutamol following aminophylline (250 mg) injection; (vii) no bronchial hyperresponsiveness; (viii) airway cough hypersensitivity; and (ix) complete relief from the cough on treatment with histamine H_1-antagonists and/or corticosteroid therapy. In addition, the tracheal biopsy findings seen in this case may add eosinophil infiltration in the trachea to this list.

The remarkable characteristic of our case was the recurrence of coughing after returning home,[14] suggesting the existence of some etiologic agents in the patient's house. Recently, because the acute form of eosinophilic pneumonia, suggesting a hypersensitivity reaction, had been described,[15,16] we conducted an environmental survey of her house.[17]

The conclusion that the eosinophilic tracheobronchitis with cough hypersensitivity in the present case was induced by *S. albus* antigen was based on the following evidence: (i) *S. albus* was isolated from the patient's house; (ii) anti-*S. albus* IgG antibody was detected in her serum; and (iii) a bronchoprovocation test with *S. albus* antigen, assessed by appearance of coughing and measuring of cough sensitivity to inhaled capsaicin, was positive.

Based on these findings, the patient was diagnosed with atopic cough caused by *S. albus* antigen and successfully treated by cessation of exposure to the antigen.

Although ubiquitous in soil, *Streptomyces* spp. are rarely associated with human diseases. In India, mycetomas of the lower extremities are known to occur[18] and hypersensitivity pneumonitis, caused by *S. albus*, has been reported by Steven *et al*.[19]

This is the first report of atopic cough caused by a hypersensitivity to *S. albus* antigen. The discovery of causative antigens is recommended through environmental survey and antigen bronchoprovocation in atopy-based chronic cough.

Acknowledgements

The authors wish to thank Dr Masakatsu Seo (Seo Laboratory, Ashikaga Tochigi, Japan) for his identification of fungus species.

References

1 Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N. Engl. J. Med.* 1979; **300**: 633–7.
2 Fujimura M, Sakamoto S, Matsuda T. Bronchodilator-resistive cough in atopic patients: Bronchial reversibility and hyperresponsiveness. *Intern. Med.* 1992; **31**: 447–52.
3 Fujimura M, Kamio Y, Hashimoto T, Matsuda T. Cough receptor sensitivity and bronchial responsiveness in patients with only chronic nonproductive cough: In view of effect of bronchodilator therapy. *J. Asthma* 1994; **31**: 463–72.
4 Fujimura M, Songur N, Kamio Y, Matsuda T. Detection of eosinophils in hypertonic saline-induced sputum in patients with chronic nonproductive cough. *J. Asthma* 1997; **34**: 119–26.
5 Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin. Exp. Allergy* 2000; in press.
6 American Thoracic Society. Standardization of spirometry – 1987 update. *Am. Rev. Respir. Dis.* 1987; **136**: 1285–98.
7 Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin. Allergy* 1977; **7**: 503–13.
8 Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Sex difference in the inhaled tartaric acid cough threshold in non-atopic healthy subjects. *Thorax* 1990; **45**: 633–4.
9 Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Cough receptor sensitivity and bronchial responsiveness in normal and asthmatic subjects. *Eur. Respir. J.* 1992; **5**: 291–5.
10 Liebow AA, Carrington CB. The eosinophilic pneumonias. *Medicine* 1969; **48**: 251–85.
11 Ogawa H, Fujimura M, Heki U, Kitagawa M, Matsuda T. Eosinophilic bronchitis presenting with only severe dry cough due to bucillamine. *Respir. Med.* 1995; **89**: 219–21.
12 Gibson PG, Dolovich J, Denburg J, Ramsdale EH, Hargreave EF. Chronic cough: Eosinophilic bronchitis without asthma. *Lancet* 1989; **i**: 1346–8.
13 Gibson PG, Zlatic K, Scott J, Sewell W, Woolley K, Saltos N. Chronic cough resembles asthma with IL-5 and granulocyte-macrophage colony-stimulating factor gene expression in bronchoalveolar cells. *J. Allergy Clin. Immunol.* 1998; **101**: 320–6.
14 Ogawa H, Fujimura M, Amaike S *et al*. Seasonal chronic cough with sputum eosinophilia caused by *Trichosporon cutaneum* (*Trichosporon asahii*). *Int. Arch. Allergy Appl. Immunol.* 1998; **116**: 162–5.
15 Allen JN, Pacht ER, Gadek JE, Davis WB. Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. *N. Engl. J. Med.* 1989; **321**: 569–74.
16 Ogawa H, Fujimura M, Matsuda T, Kumabashiri I, Kitagawa S. Transient wheeze: Eosinophilic bronchobronchiolitis in acute eosinophilic pneumonia. *Chest* 1993; **104**: 493–6.
17 Ogawa H, Fujimura M, Amaike S, Matsumoto Y, Kitagawa M, Matsuda T. Eosinophilic pneumonia caused by *Alternaria alternata*. *Allergy* 1997; **52**: 1005–8.
18 Taralakshmi VV, Pankajalakshimi VV, Kamalakannan R *et al*. Mycetomas caused by *Streptomyces pelletieri* in Madras. *Ind. Arch. Dermatol.* 1979; **114**: 204–6.
19 Steven LK, Jordan NF, Donald PS, Viswanath PK, Robert BF. *Streptomyces albus*: A new cause of hypersensitivity pneumonitis. *J. Allergy Clin. Immunol.* 1981; **68**: 295–9.