

Case Report

Two cases of atopic cough successfully treated by oral cleansing with amphotericin B: Relationship with Basidiomycetes detected from pharyngeal swab

Haruhiko Ogawa,¹ Masaki Fujimura² and Yohei Tofuku¹

¹The Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital and ²Pulmonary Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

ABSTRACT

We report herein two cases of atopic cough in which Basidiomycetes was detected from pharyngeal swabs and in which gargling with amphotericin B was efficacious. One case is a 38-year-old woman and the other is a 54-year-old woman. Both patients visited Ishikawa-ken Saiseikai Kanazawa Hospital for the diagnosis and treatment of isolated severe non-productive cough. They did not have bronchial hyperresponsiveness to methacholine or heightened bronchomotor tone. Bronchodilator therapy was not effective for their coughing. Basidiomycetes was isolated from pharyngeal swabs in both cases. Oral cleansing with amphotericin B at 300 mg/day for approximately 2 weeks was effective in treating the severe coughs. This is the first report concerning the effectiveness of oral cleansing with amphotericin B for atopic cough, in which Basidiomycetes was detected from pharyngeal swabs.

Key words: amphotericin B (oral cleansing), antifungal drug, atopic cough, Basidiomycetes, pharyngeal swab.

INTRODUCTION

Cough is a common presenting symptom in general practice and in the chest clinic. Patients presenting

with isolated chronic non-productive cough resistant to antibiotics and the usual antitussive agents are frequently referred to our clinic for diagnosis and treatment. Gastroesophageal reflux-associated cough, post-nasal drip-induced cough, angiotensin-converting enzyme inhibitor-induced cough and cough variant asthma are known as causes of non-productive cough.¹ In addition, we have proposed a bronchodilator-resistant non-productive cough associated with global atopic constitution (abbreviated as atopic cough; AC) as another cause of non-productive cough since 1992.^{2–6} The discovery of causative antigens is recommended through environmental surveys and fungal culture of sputum and pharyngeal swabs, especially when usual treatment fails to improve the symptoms. We have reported atopic cough patients caused by a hypersensitivity to *Trichosporon asahii*,⁷ *Pichia guilliermondii*,⁸ *Streptomyces albus*⁹ and Basidiomycetes, which has been corrected from *Humicola fuscoatra* by Centraalbureau voor Schimmelcultures (CBS).¹⁰

We have proposed that low-dose antifungal drugs (itraconazole) would be an additional strategy in treating severe atopic cough in which an allergic reaction to fungal antigens is thought to be an etiology of eosinophilic airway disorder.⁸ We now report herein two cases of atopic cough in which Basidiomycetes was detected from pharyngeal swabs and successfully treated with oral cleansing with amphotericin B.

CASE REPORTS

Case 1

A 38-year-old woman visited our hospital on 5 November 2002 because of non-productive cough with ticklish

Correspondence: Dr Haruhiko Ogawa, The Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, Ni-13-6 Akatsuchi-machi, Kanazawa-city, Ishikawa 920-0353, Japan. Email: saiseikh@po3.nsknet.or.jp

Received 9 December 2003. Accepted for publication 20 January 2004.

throat discomfort for 11 weeks. She was a housekeeper and lived in a 15-year-old wooden house. She was a non-smoker.

Physical examination revealed the following: her temperature was 36.2°C. The conjunctivae were not anemic or icteric. Cardiac examination was entirely within normal limits. Auscultation of the lungs revealed no adventitious breath sounds. There was no lymphadenopathy. The patient's white blood cell count was 7400 / μ L with a differential of 75.0% segmented neutrophils, 17.8% lymphocytes, 5.7% monocytes and 1.3% eosinophils. C-Reactive protein was 0.0 mg/dL and the total serum IgE level was 131 U/mL. Specific IgE antibody was negative against *house-dust 6*, *Dermatophagoides*, *Candida*, *Alternaria*, *Penicillium* and *Aspergillus*. The following laboratory findings were normal or negative: urinalysis, stools for ova and parasites, serum electrolytes, total protein and albumin, and bacterial, mycobacterial and fungal cultures of sputum. Basidiomycetes was cultured from a pharyngeal swab. The chest radiograph showed normal findings. The immediate skin test for Basidiomycetes was 10 \times 8/14 \times 14.

According to the standards of the American Thoracic Society,¹¹ a pulmonary function test using a Collins DS system (Collins GS/Plus System; Braintree, MA, USA) revealed forced vital capacity (FVC) 3.21 L (104.9% of predicted value), forced expiratory volume in 1 s (FEV₁) 2.77 L (89.6% of predicted value) and an FEV₁/FVC ratio of 86.3%. To assess bronchial reversibility, spirometry was performed before and after 30 min inhalation of 300 μ g salbutamol sulfate. The bronchodilator therapy did not significantly increase FEV₁ (from 2.78 to 2.82 L), indicating that that patient's bronchomotor tone was not increased.

Bronchial responsiveness to methacholine was measured according to the method of Cockcroft *et al.*¹² The provocative concentration of methacholine required to cause a 20% fall from baseline FEV₁ (PC₂₀) was 20 mg/mL. The capsaicin cough threshold, measured by our previously reported method,^{13,14} was 0.98 μ mol/L. This suggested cough reflex hypersensitivity. Bronchodilator therapy, inhaled salbutamol sulfate 200 μ g on demand, was entirely ineffective for this patient's daily coughing.

These findings suggested that the diagnosis for this case would be AC.²⁻⁶ She was treated with both the histamine H₁ receptor antagonist cetirizine hydrochloride (10 mg/day) and beclomethasone dipropionate inhalation (BDP; 400 μ g/day) for approximately 10 days, but her coughing was not sufficiently relieved on this treatment.

Basidiomycetes was isolated from a pharyngeal swab sample from the patient cultured in sterile Petri dishes containing Sabouraud's agar medium supplemented with antibiotics. For the preparation of an antigenic solution, Basidiomycetes was cultured on a medium (1% peptone, 2% glucose) with 0.5% yeast extract for 20 days and dried by acetone. The skin test to the fungal antigen (polysaccharide) was performed by intradermal injection of 0.02 mL of the solution (1 mg protein/mL). The immediate-type skin reaction was positive for Basidiomycetes.

Based on these results, the patient was administered oral cleansing with amphotericin B at 300 mg/day. Her symptoms subsided within 2 weeks and her capsaicin cough threshold increased from 0.98 to 3.92 μ mol/L. Fungal culture of a pharyngeal swab obtained after oral cleansing with amphotericin B did not yield any fungus.

Case 2

A 54-year-old woman visited our hospital on 9 September 2002 because of non-productive cough with ticklish throat discomfort for 20 months. Physical examination revealed the following: temperature 36.8°C and blood pressure 118/76 mmHg. The conjunctivae were not anemic or icteric. Cardiac examination was entirely within normal limits. Auscultation of the lungs revealed no rales.

The white blood cell count was 5700 / μ L, with a differential of 60.0% segmented neutrophils, 29.6% lymphocytes, 8.5% monocytes and 1.5% eosinophils. C-Reactive protein was 0.0 mg/dL and the total serum IgE level was 72 U/mL. Specific IgE antibody titers were negative against *house-dust 6* and *Dermatophagoides pteronyssinus*.

A pulmonary function test revealed FVC 3.53 L (138.4% of predicted value), FEV₁ 2.94 L (137.4% of predicted value) and an FEV₁/FVC ratio of 83.3%. Inhalation of 300 μ g salbutamol sulfate did not significantly increase FEV₁ (from 2.94 to 3.01 L). The methacholine PC₂₀ was 20 mg/mL. The capsaicin cough threshold was 1.95 μ mol/L. This suggested cough reflex hypersensitivity. Bronchodilator therapy (oral clenbuterol at 40 μ g/day and inhaled salbutamol sulfate at 200 μ g on demand) was entirely ineffective for this patient's daily coughing.

Although these findings suggested that this case would be diagnosed as AC, treatment with cetirizine hydrochloride (10 mg/day) or fluticasone propionate inhalation (FP; 400 μ g/day) failed to relieve coughing.

Basidiomycetes was isolated from a pharyngeal swab culture. Based on these results, the patient was treated with oral cleansing with fungizone syrup (300 mg/day). Her symptoms subsided within 2 weeks and her capsaicin cough threshold increased from 0.98 to 31.4 $\mu\text{mol/L}$. Fungal culture of a pharyngeal swab obtained from the patient after oral cleansing with amphotericin B did not yield any fungus.

DISCUSSION

We have described two patients who presented with isolated chronic bronchodilator resistant non-productive cough with an atopic constitution, eosinophilic tracheo-bronchitis and airway cough receptor hypersensitivity without bronchial hyperresponsiveness, which we have termed 'atopic cough'.²⁻⁶ Cough variant asthma¹⁵ (in which the cough responds to bronchodilators) is recognized as a precursor of typical asthma, but atopic cough is not.⁴ Because atopic cough differs from cough variant asthma with regard to both outcome and pathophysiological features, we strongly recommend that AC should be recognized as a new clinical entity presenting with isolated chronic non-productive cough.³

Based on our series of clinical studies on chronic cough, the clinical features of AC are considered as follows.

1. Chronic bronchodilator-resistant non-productive cough with 'tickle' in the throat lasting for more than 8 weeks.
2. The absence of wheezing, dyspnea, hemoptysis or pleurisy and no adventitious lung sounds on examination.
3. The presence of one or more of the following global atopic findings: past history and/or complication of allergic diseases, except for bronchial asthma, family history of allergic diseases, peripheral blood eosinophilia, elevated total IgE level in serum, positive specific IgE antibody to common aeroallergens and positive allergen skin test.
4. The existence of eosinophils in hypertonic saline-induced sputum and/or submucosa of biopsied trachea and/or bronchi.
5. Normal FEV₁, FVC and FEV₁/FVC ratio.
6. No bronchial reversibility defined as a less than 5% increase in FEV₁ after inhalation of 300 mg salbutamol following 250 mg aminophylline injection.
7. Bronchial responsiveness within normal limits.
8. Increased airway cough reflex sensitivity.
9. Complete relief of the cough on treatment with histamine H₁ receptor antagonists and/or corticosteroid therapy.

The discovery of causative antigens is important not only in allergic eosinophilic pneumonia and allergic bronchopulmonary fungal disease,^{16,17} but also in severe AC in which the histamine H₁ receptor antagonists and/or corticosteroid therapy are insufficient for the treatment of coughing.

We have reported patients with severe AC caused by a hypersensitivity to *T. asahii*,⁷ *P. guilliermondii*,⁸ *S. albus*⁹ and Basidiomycetes.¹⁰

We previously reported the first case of non-asthmatic sputum eosinophilia caused by allergic reaction to Basidiomycetes antigen.¹⁰ In that case, the increase of eosinophils in the patient's induced sputum was closely related to the appearance of Basidiomycetes in his house, as determined through a repeated environmental survey.

According to our experience of a case of AC caused by *P. guilliermondii*⁸ in which an antifungal drug (itraconazole, 150 mg/day for 2 weeks) was effective for the treatment of severe cough, we have also reported another two cases of AC caused by Basidiomycetes antigen successfully treated with a low dose of antifungal drugs (itraconazole, 150 mg/day for 2 weeks).

Gregory and Hirst reported a possible role for Basidiospores as air-borne allergens in 1952.¹⁸ The Basidiomycetes class, the most advanced of all fungi, has between 20 000 and 25 000 species and has been shown that members of this class are present in high atmospheric concentrations in certain geographic areas.^{19,20} In addition, it has been reported that between 42 and 68% of atopic asthmatics have demonstrated positive type I wheal-and-flare skin reactivity to Basidiomycetes metabolic and somatic antigens.²¹ Basidiomycetes is important as an environmental fungus. We have reported a case of cough variant asthma successfully treated with antifungal therapy and the cleansing of the filter of the car air-conditioner.²²

Our speculation concerning the results in the present report is that Basidiomycetes colonizing on the pharyngeal mucosa would act as an exacerbating antigen of AC and the low dose of itraconazole could remove the fungus from the pharynx, resulting in the successful outcome. If this idea is correct, even oral cleansing with antifungal drugs that are well-known to be effective in the treatment of oral candidiasis²³ and gastroesophageal candidiasis²⁴ may remove the fungus.

The recommended dosage for oral cleansing with amphotericin B is 1 mL (100 mg) four times daily. The suspension should be administered between meals to permit prolonged contact with the oral lesions and be

dropped directly on the tongue with the calibrated dropper. Patients should be directed to swish the medication in the mouth for as long as reasonably possible before swallowing.

In conclusion we have reported two cases of atopic cough in which Basidiomycetes was detected from pharyngeal swab and treatment with oral cleansing with amphotericin B successfully relieved the patients' coughing. This is the first report concerning the efficacy of oral cleansing with amphotericin B for AC caused by an allergic reaction to Basidiomycetes antigen. We propose that low-dose antifungal drugs would be an additional strategy in treating AC in which an allergic reaction to antigens from fungi colonizing in the airway is thought to be an exacerbating antigen of eosinophilic airway disorder.²⁵

ACKNOWLEDGMENTS

The authors thank Centraalbureau voor Schimmelcultures (CBS, Utrecht, The Netherlands) and Dr Masakatsu Seo (Seo Laboratory, Ashikaga, Japan) for identification of the fungus species.

REFERENCES

- 1 Irwin RS, French CT, Smyrniotis NA, Curley FJ. Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. *Arch. Intern. Med.* 1997; **157**: 1981–7.
- 2 Fujimura M, Sakamoto S, Matsuda T. Bronchodilator-resistant cough in atopic patients: bronchial reversibility and hyperresponsiveness. *Int. Med.* 1992; **31**: 447–52.
- 3 Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin. Exp. Allergy* 2000; **30**: 41–7.
- 4 Fujimura M, Ogawa H, Nishizawa Y, Nishizawa K. Comparison of atopic cough with cough variant asthma: Is atopic cough a precursor of asthma? *Thorax* 2003; **58**: 14–18.
- 5 Shirai T, Suzuki K, Inui N, Suda T, Chida K, Nakamura H. Th1/Th2 profile in peripheral blood in atopic cough and atopic asthma. *Clin. Exp. Allergy* 2003; **33**: 84–9.
- 6 Fujimura M, Nishizawa Y, Nishitsuji M, Abo M, Kita T, Nomura S. Longitudinal decline in pulmonary function in atopic cough and cough variant asthma. *Clin. Exp. Allergy* 2003; **33**: 588–94.
- 7 Ogawa H, Fujimura M, Amaike S et al. Seasonal chronic cough with sputum eosinophilia caused by *Trichosporon cutaneum* (*Trichosporon asahii*). *Int. Arch. Allergy Immunol.* 1998; **116**: 162–5.
- 8 Ogawa H, Fujimura M, Matsumoto Y, Matsuda T. A case of atopic cough caused by *Pichia guilliermondii* successfully treated with anti-fungal therapy. *J. Jpn. Respir. Soc.* 1999; **37**: 209–13 (in Japanese).
- 9 Ogawa H, Fujimura M, Myou S, Kitagawa M, Matsuda T. Eosinophilic tracheobronchitis with cough hypersensitivity caused by *Streptomyces albus* antigen. *Allergol. Int.* 2000; **49**: 83–7.
- 10 Ogawa H, Fujimura M, Tofuku Y. Isolated chronic cough with sputum eosinophilia caused by *Humicola fuscoatra* antigen: The importance of environmental survey for fungus as an etiologic agent. *J. Asthma* 2002; **39**: 331–6.
- 11 American Thoracic Society. Standardization of spirometry: 1987 update. *Am. Rev. Respir. Dis.* 1987; **136**: 1285–98.
- 12 Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin. Allergy* 1977; **7**: 503–13.
- 13 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.
- 14 Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Cough receptor sensitivity and bronchial responsiveness in normal and asthmatic subjects. *Eur. Respir. J.* 1992; **52**: 291–5.
- 15 Corrao WM, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N. Engl. J. Med.* 1979; **300**: 633–7.
- 16 Ogawa H, Fujimura M, Amaike S, Matsumoto Y, Kitagawa M, Matsuda T. Eosinophilic pneumonia caused by *Alternaria alternata*. *Allergy* 1997; **52**: 1005–8.
- 17 Ogawa H, Fujimura M, Tofuku Y. Allergic bronchopulmonary fungal disease caused by *Saccharomyces cerevisiae*. *J. Asthma* 2004; **41**: 223–8.
- 18 Gregory. PH, Hirst. JM. Possible role of Basidiospores as air-borne allergens. *Nature* 1952; **70**: 414.
- 19 Gregory. PH, Hirst. JM. The summer airspora at Rothamsted in 1952. *J. Gen. Microbiol.* 1957; **17**: 135–52.
- 20 Hyde. HA, Adams. KF. Airborne allergens at Cardiff 1942–59. *Acta. Allergol.* 1960; **15**: 159.
- 21 Lopez M, Salvaggio JE, Butcher BT. Allergenicity and immunogenicity of Basidiomycetes. *J. Allergy Clin. Immunol.* 1976; **57**: 480–8.
- 22 Ogawa H, Fujimura M. A case of cough variant asthma successfully treated with anti-fungal therapy and the cleansing the filter of car-airconditioner. *Allerugi no Rinsyo* 2003; **23**: 57–60 (in Japanese).
- 23 Kutscher AH, Zegarelli EV. Amphotericin B in the treatment of oral monilial infections. *Oral Surg. Oral Med. O* 1964; **17**: 31–5.
- 24 Kods BE, Wickremesinghe PC. *Candida* esophagitis: A prospective study of 27 cases. *Gastroenterology* 1976; **71**: 715–19.
- 25 Brightling CE, Ward R, Goh KL, Wardlaw AJ, Pavord ID. Eosinophilic bronchitis is an important cause of cough. *Am. J. Respir. Crit. Care Med.* 1999; **160**: 406–10.