

This article was downloaded by: [Uppsala University Library]

On: 3 March 2009

Access details: Access Details: [subscription number 786945401]

Publisher Informa Healthcare

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Asthma

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597262>

Eosinophilic Pneumonia Caused by *Aspergillus niger*: Is Oral Cleansing with Amphotericin B Efficacious in Preventing Relapse of Allergic Pneumonitis?

Haruhiko Ogawa ^a; Masaki Fujimura ^b; Yohei Tofuku ^a; Masanobu Kitagawa ^c

^a Division of Internal Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, Kanazawa, Japan ^b Respiratory Medicine, Cellular Transplantation Biology, Kanazawa Graduate University School of Medicine, Kanazawa, Japan ^c Pathology Laboratory, Hokuriku Central Hospital, Oyabe, Japan

Online Publication Date: 01 February 2009

To cite this Article Ogawa, Haruhiko, Fujimura, Masaki, Tofuku, Yohei and Kitagawa, Masanobu(2009)'Eosinophilic Pneumonia Caused by *Aspergillus niger*: Is Oral Cleansing with Amphotericin B Efficacious in Preventing Relapse of Allergic Pneumonitis?', *Journal of Asthma*, 46:1, 95 — 98

To link to this Article: DOI: 10.1080/02770900802127030

URL: <http://dx.doi.org/10.1080/02770900802127030>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

CASE REPORT

Eosinophilic Pneumonia Caused by *Aspergillus niger*: Is Oral Cleansing with Amphotericin B Efficacious in Preventing Relapse of Allergic Pneumonitis ?

HARUHIKO OGAWA, M.D.,^{1,*} MASAKI FUJIMURA, M.D.,² YOHEI TOFUKU, M.D.,¹ AND MASANOBU KITAGAWA, M.D.³

¹Division of Internal Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, Kanazawa, Japan

²Respiratory Medicine, Cellular Transplantation Biology, Kanazawa Graduate University School of Medicine, Kanazawa, Japan

³Pathology Laboratory, Hokuriku Central Hospital, Oyabe, Japan

Eosinophilic pneumonia was confirmed by bronchoalveolar lavage fluid examination and transbronchial lung biopsy. *Aspergillus niger* was cultured from the patient's pharyngeal swab and bronchoalveolar lavage fluid. Inhalation bronchoprovocation test with *A. niger* antigen was positive. Although the patient's condition improved promptly with 10 mg/day prednisolone administration, dry cough recurred approximately 2 months after completion of this therapy. Severe coughing disappeared on oral cleansing with 300 mg/day amphotericin B, and he recovered completely on 100 mg/day amphotericin B administration. Oral cleansing with amphotericin B may be efficacious in preventing relapses of eosinophilic pneumonia caused by allergic reaction to fungal antigen.

Keywords *Aspergillus niger*, eosinophilic pneumonia, environmental survey, bronchoprovocation test, amphotericin B (oral cleansing).

INTRODUCTION

A number of fungal species may cause respiratory disorders including allergic bronchopulmonary aspergillosis (ABPA) (1), bronchial asthma (2), eosinophilic pneumonia (3, 4), eosinophilic bronchitis (5, 6), atopic cough (7–11), and allergic bronchopulmonary mycosis (ABPM) (12–14). We had previously reported the importance of repeated sputum cultures and environmental surveys (8–11) for investigating the etiologic agent in allergic pulmonary diseases. Although it has been reported that *Aspergillus niger* (*A. niger*) antigen is one of the aeroantigens causing hypersensitivity pneumonitis (15), chronic necrotizing pulmonary aspergillosis (16, 17, and ABPA (18), there have been no reports that this antigen causes eosinophilic pneumonia. We report a case of eosinophilic pneumonia caused by *A. niger*. The recrudescence of severe dry cough, a subclinical manifestation of this allergic pneumonitis, disappeared by oral cleansing with amphotericin B.

CASE REPORT

On May 14, 2004, a 53-year-old man was admitted to our hospital because of dry cough, chest discomfort, and focal patchy shadow of pulmonary infiltrates. Further questioning revealed that the patient had been healthy without any history of atopic diseases until the onset of the present illness. He worked for an ironworks company and lived with his family in an apartment building. He had no history of smoking.

Physical examination revealed the following: body temperature 36.3°C; blood pressure 100/60 mmHg; and heart rate 72 beats/min. The conjunctivae were neither anemic nor icteric. Cardiac examination was entirely within normal limits. Auscultation of the lungs revealed late inspiratory fine crackles on the right lung field without wheezes or rhonchi.

Laboratory studies revealed that the white blood cell count (WBC) was 9400/ μ L and the differential count was as follows: 53.7% segmented neutrophils, 25.8% lymphocytes, 9.2% monocytes, and 11.0% eosinophils. The hemoglobin level was 13.7 g/dL with a hematocrit value of 43.1%. The erythrocyte sedimentation rate was 6 mm/h. The C-reactive protein (CRP) was 0.1 mg/dL and the IgE level was 36.5 U/mL. Specific IgE antibodies did not react against house-dust 6, *Dermatophagoides*, *Candida*, *Alternaria*, *Penicillium*, or *Aspergillus*. The following laboratory findings were either normal or negative: urinalysis, stool analysis for ova and parasites, serum electrolytes, total protein, albumin, and bacterial and mycobacterial cultures of sputum. Chest radiographs taken on admission (Figure 1), showed consolidation in the right lung field. Chest computed tomography (CT) scan taken on admission (Figure 2) showed a patchy shadow in the periphery of the right S.⁴

Pulmonary function test using the Collins DS system, which was performed according to the standards of the American Thoracic Society (19), revealed forced vital capacity (FVC) of 3.36 l (95.2% of the predicted value), forced expiratory volume in 1 s (FEV₁) of 2.82 l (99.6% of the predicted value), and FEV₁/FVC ratio of 83.9%. Differential cell analysis of the bronchoalveolar lavage fluid (BALF) revealed 22% alveolar macrophages, 22% lymphocytes, 1% neutrophils, 55% eosinophils, and an increased absolute total cell count of 16.810⁶ cells/mL. Histological examination of transbronchial lung biopsy (TBLB) specimens obtained from

*Corresponding author: Haruhiko Ogawa, M.D., Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital, Ni-13-6 Akatsuchimachi, Kanazawa 920-0353, Japan; E-mail: saiseikh@po3.nsknet.or.jp



FIGURE 1.—Chest radiographs on admission showing consolidation in the right lung field.

the right S⁴ a (Figure 3) showed mild eosinophil and lymphocyte infiltration into the parenchyma and airspace without extensive exudates or intraluminal organization.

Since *A. niger* was isolated from the patient's pharyngeal swab and his BALF, it was suspected that eosinophilic pneumonia in this case might have been caused by the *A. niger* antigen.

For preparation of fungal antigenic solutions, the fungus was cultured on a medium containing 1% peptone, 2% glucose, and 0.5% yeast extract for 20 days and dried using

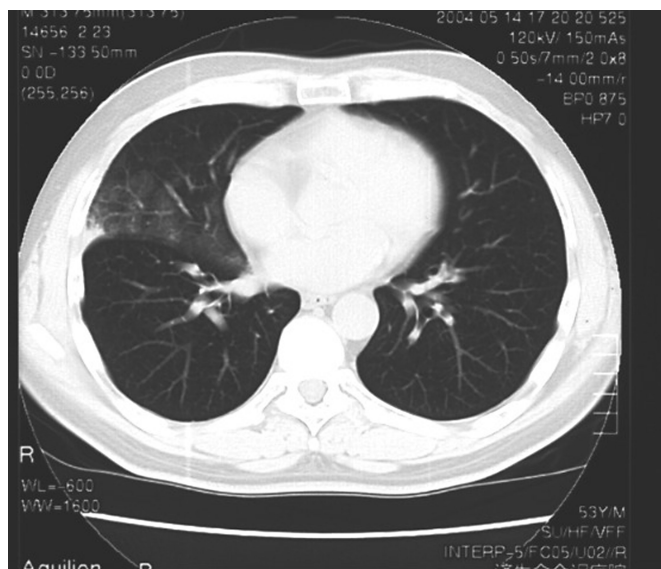


FIGURE 2.—Chest CT scan on admission showing a cylindrical shadow surrounded by small granular shadows in the right S⁴.

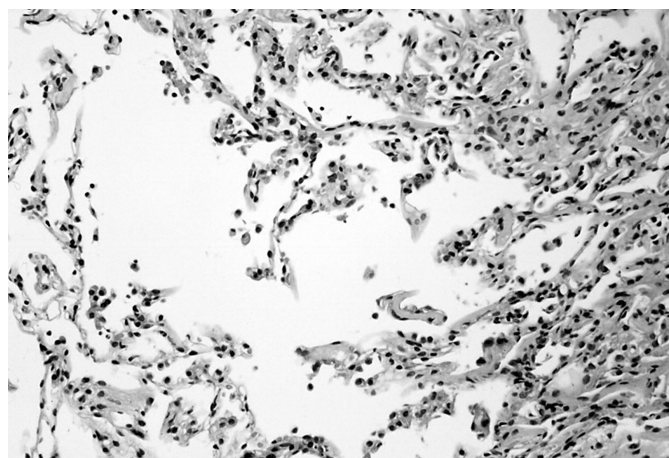


FIGURE 3.—Transbronchial lung biopsy (TBLB) from the bifurcation of the right B⁶ and the right lower bronchus showing mild eosinophil infiltration in addition to round cell infiltration in the alveolar walls (H.E. stain $\times 50$).

acetone. Skin tests with the fungal antigens were performed by intradermally injecting 0.02 mL of the antigen solution (1 mg/mL). The immediate (15 minutes) and delayed (48 hours) skin reactions were positive for *A. niger* (7 mm $\times$ 7 mm/35 mm $\times$ 35 mm and 6 mm $\times$ 6 mm/34 mm $\times$ 34 mm, respectively) but were negative for *Alternaria alternata* (*A. alternata*) as a control. The serum antifungus antibody titers were negative for 18 common aeroallergens including *A. fumigatus*, *A. flavus*, *A. niger*, *Trichosporon cutaneum*, and *T. asahii* when measured by the Ouchterlony method.

Five days after admission, the patient's cough gradually subsided naturally and a chest radiograph revealed further improvement. Environmental causes were investigated since the patient experienced a recrudescence a day after returning home on May 22. The recurrence of dry cough, decrease in PaO₂ values (from 86.7 to 75.2 mmHg) suggested the existence of etiological agents in his house. Sterile Petri dishes containing Sabouraud's agar medium supplemented with antibiotics were exposed for one hour on the floor of his bedroom with closed windows, and *A. niger* was isolated on these plates.

Although his coughing and chest infiltrations had not disappeared for 7 days after the environmental provocation test, the patient's condition showed immediate improvement on 10 mg/day prednisolone administration; the corticosteroid therapy was tapered and discontinued on July 7.

On July 28, the patient was re-admitted for a follow-up bronchoalveolar lavage and for antigen bronchoprovocation testing (20) using *A. niger* and *A. alternata* antigens. Differential cell analysis of the BALF performed during the follow-up revealed 85% alveolar macrophages, 14% lymphocytes, 1% neutrophils, 0% eosinophils, and a total cell count of 0.3×10^6 cells/mL. No fungus, including *A. niger*, was cultured from either his pharyngeal swab or BALF. After obtaining informed consent, a 2-mL dose of the culture-filtrate antigen solution (1 mg/mL) was inhaled by tidal mouth breathing from a Devilbiss 646 nebulizer (Devilbiss Co, Somerset, Pennsylvania, USA), which was operated by compressed air at a flow rate of 5 L/min. The bronchoprovocation test using *A. alternata*

antigen was negative; however, using *A. niger* antigen was considered positive due to the development of dry cough, significant decreases in PaO₂ (from 84.7 to 69 mmHg) and DLco values (from 72.3 to 59.4 mL/min/mmHg), and increases in the serum CRP (from 0.0 to 1.1 mg/dl) and surfactant protein D values (SPD) (from 82.7 to 126 ng/mL) on the day following the provocation. These symptoms disappeared within 3 days after the challenge and he was discharged on August 7.

Based on these results, we advised the patient to clean his bedroom and his condition was followed carefully. However, after approximately 2 months, a recrudescence of severe dry cough without wheezing occurred on September 9. Physical examination including auscultation of the lungs revealed almost normal findings, and laboratory studies revealed that the WBC count was 11300/ μ L and the differential count was as follows: 77.7% segmented neutrophils, 13.3% lymphocytes, 7.3% monocytes, and 0.9% eosinophils. The CRP value was 0.40 mg/dL; the IgE level, 81 U/mL; and SPD value, 64.1 ng/mL. Chest radiographs taken on September 13 showed normal findings without any interstitial shadows. To assess bronchial reversibility, spirometry was carried out before and 30 minutes after inhalation of 300 μ g salbutamol sulfate. The bronchodilator therapy did not increase FEV₁ values (from 3.14 to 3.14 l), indicating that his bronchomotor tone was not increased. Bronchial responsiveness to methacholine was measured according to the method described by Cockcroft et al. (21). The provocative concentration of methacholine that caused a 20% decrease from the baseline FEV₁ (PC20) was 20 mg/mL. Capsaicin cough threshold measured by our previously reported method (22) was 1.95 μ M. The patient was treated with the histamine H₁-antagonist cetirizine hydrochloride (10 mg/day) and fluticasone propionate (Flutide 400 μ g/day) for approximately 8 days, but his cough did not improve by this treatment and *A. niger* was detected again in his pharyngeal swab. The findings were indicative of subclinical allergic pneumonitis associated with the same fungal antigen; oral cleansing was performed using 300 mg/day amphotericin B. The allergic symptoms subsided within 2 weeks and the capsaicin cough threshold increased to 250 μ M. No fungal growth was observed on culturing the pharyngeal swab obtained after oral cleansing with amphotericin B. Due to oral cleansing with 100 mg/day amphotericin B, the patient has been healthy without any recurrence of the symptoms during the following year.

DISCUSSION

ABPM is usually diagnosed based on the following clinical and serological criteria (23): (1) asthma, (2) a history of infiltrates observed on the chest radiographs, (3) peripheral blood eosinophilia, (4) elevated total serum IgE, (5) immediate cutaneous reactivity to the fungus in question, (6) elevated specific IgE and IgG antibodies to the fungal antigen, and (7) presence or absence of central bronchiectasis. Our patient satisfied only three of the abovementioned criteria 2, 3, and 5. The diagnosis of eosinophilic pneumonia was confirmed by BALF examination and TBLB.

The detection of causative antigen is very important in not only eosinophilic pneumonia (3, 4) and ABPF (12–14) but also severe atopic cough (7–11). The conclusion that eosinophilic pneumonia in our patient was caused by *A. niger* was made based on the following evidence: (1) *A. niger* was

morphologically identified and isolated from the patient's pharyngeal swab and BALF; (2) the immediate (15 min) and delayed (48 h) skin reactions were positive for *A. niger*; and (3) an inhalation bronchoprovocation test using the *A. niger* antigen was positive.

Although the patient's condition improved immediately on 10 mg/day prednisolone administration, a recrudescence of severe dry cough occurred approximately 2 months after the completion of the corticosteroid therapy. He was treated with histamine H₁-antagonist cetirizine hydrochloride and fluticasone propionate inhalation, but his cough did not improve by this treatment, and *A. niger* was detected again in his pharyngeal swab. These findings were indicative of subclinical allergic pneumonitis associated with the same fungal antigen.

Based on our experience of successfully treating some cases of atopic cough caused by the Basidiomycetes antigen with oral cleansing using amphotericin B [10], oral cleansing was performed on the patient using 300 mg/day amphotericin B, and the severe cough disappeared within 2 weeks. Furthermore, the patient has been healthy without any recurrence of symptoms during the following year due to 100 mg/day amphotericin B administration.

Based on the results of this study, we hypothesize that *A. niger* colonizing the pharyngeal mucosa acts as an etiologic antigen of eosinophilic pneumonia. Oral cleansing with an antifungal drug, which is well-known to be effective in the treatment of oral candidiasis (24) and gastroesophageal candidiasis (25), could remove the fungus from the pharynx, successfully preventing the relapse of the allergic disorder.

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 it should be dropped directly on the tongue with the calibrated dropper. Patients should be directed to hold the suspension in the mouth for as long as possible before swallowing it.

In conclusion, we reported a case of eosinophilic pneumonia in which *A. niger* was detected in patient's pharyngeal swab, and treatment by oral cleansing with amphotericin B successfully relieved his coughing. We propose that oral cleansing with amphotericin B can be used to treat eosinophilic pneumonia caused by allergic reaction to a fungal antigen, when the fungus colonizes the pharyngeal mucosa. The treatment may be efficacious in preventing the relapse of such allergic diseases.

ACKNOWLEDGMENT

The authors wish to thank Dr. Masakatsu Seo (Seo Laboratory) for identification of the fungal species and Dr. Yasuo Takeuchi (Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagami National Hospital) for detecting the precipitating antibody against *A. niger*.

REFERENCES

1. Ricker DH, Taylor SR, Gartner JC Jr, Kurland G. Fatal pulmonary aspergillosis presenting as acute eosinophilic pneumonia in a previously healthy child. *Chest* 1991; 100:875–877.
2. Licorish K, Novey HS, Kozak P, Fairshier RD, Wilson AF. Role of Alternaria and Penicillium spores in the pathogenesis of asthma. *J Allergy Clin Immunol* 1985; 76:819–825.

3. Liebow AA, Carrington CB. The eosinophilic pneumonias. *Medicine* 1969; 48:251–285.
4. Ogawa H, Fujimura M, Amaike S, Matsumoto Y, Kitagawa M, Matsuda T. Eosinophilic pneumonia caused by *Alternaria alternata*. *Allergy* 1997; 52:1005–1008.
5. Ogawa H, Fujimura M, Myou S, Kitagawa M, Matsuda T. Eosinophilic tracheobronchitis with cough hypersensitivity caused by *Streptomyces albus* antigen. *Allergology International* 2000; 49:83–87.
6. Ogawa H, Fujimura M, Amaike S, Nishiura Y, Nakagawa-Yoshida K, Suga M, Ando M, Matsuda T. Seasonal chronic cough with sputum eosinophilia caused by *Trichosporon cutaneum* (*Trichosporon asahii*). *Int Arch Allergy Immunol* 1998; 116:162–165.
7. Fujimura M, Ogawa H, Yasui M, Matsuda T. Eosinophilic tracheobronchitis and airway cough hypersensitivity in chronic non-productive cough. *Clin Exp Allergy* 2000; 30:41–47.
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; 37:209–213.
9. 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; 39:331–336.
10. Ogawa H, Fujimura M, Tofuku Y. Two cases of atopic cough successfully treated by oral cleansing with amphotericin B relation to *Basidiomycetes* detected from pharyngeal swab. *Allergology International* 2004; 53:193–196.
11. Ogawa H, Fujimura M, Tofuku Y. Treatment of atopic cough caused by *Basidiomycetes* antigen with low dose Itraconazol. *LUNG* 2004; 182:279–284.
12. Mikker MA, Greenberger PA, Amerian R, Toogood JH, Noskin GA, Roberts M, Patterson R. Allergic bronchopulmonary mycosis caused by *Pseudallescheria boydii*. *Am Rev Respir Dis* 1993; 148:810–812.
13. Backman KS, Robert M, Patterson R. Allergic bronchopulmonary mycosis caused by *Fusarium vasinfectum*. *Am J Respir Crit Care Med* 1995; 152:1379–1381.
14. Ogawa H, Fujimura M, Tofuku Y. Allergic bronchopulmonary fungal disease caused by *Saccharomyces cerevisiae*. *J Asthma* 2004; 41:223–228.
15. Miyazaki H, Gemma H, Uemura K, Ono T, Masuda M, Sano T, Sato M, Koshimizu N, Suda T, Chida K. Hypersensitivity pneumonitis induced by *Aspergillus niger*. *Nihon Kokyuki Gakkai Zasshi* 2004; 42:676–681 (in Japanese).
16. Yamaguchi M, Nishiya H, Mano K, Kunii O, Miyashita H. Chronic necrotising pulmonary aspergillosis caused by *Aspergillus niger* in a mildly immunocompromised host. *Thorax* 1992; 47:570–571.
17. Kimmerling J, Fedrick JA, Tenholder MF. Invasive *Aspergillus niger* with fatal pulmonary oxalosis in chronic obstructive pulmonary disease. *Chest* 1992; 101:870–872.
18. Hoshino H, Takagi S, Kon H, Shibusa T, Takabatake H, Fujita A, Sekine K, Abe S. Allergic Bronchopulmonary Aspergillosis due to *Aspergillus niger* without bronchial asthma. *Respiration* 1999; 66:369–372.
19. American Thoracic Society: Standardization of spirometry-1987 update. *Am Rev Respir Dis* 1987; 136:1285–1298.
20. Hendrick DJ, Marshall R, Faux JA, Krall JM. Positive “alveolar” responses to antigen inhalation provocation tests: their validity and recognition. *Thorax* 1980; 35:415–427.
21. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen-induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977; 7:503–513.
22. Fujimura M, Sakamoto S, Kamio Y, Matsuda T. Cough receptor sensitivity and bronchial responsiveness in normal and asthmatic subjects. *Eur Respir J* 1992; 5:291–295.
23. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; 86:405–414.
24. Kutscher AH, Zegarelli EV, Herlands RE, Silvers HF. Amphotericin B in the treatment of oral monilial infections. *Oral Surg Oral Med Oral Pathol* 1964; 17:31–35.
25. Kotsi BE, Wickremesinghe PC, Kozinn PJ, Iswara K, Goldberg PK. Candida esophagitis, a prospective study of 27 cases. *Gastroenterol* 1976; 71:715–719.