

Allergic Bronchopulmonary Aspergillosis due to *Aspergillus niger* without Bronchial Asthma

Hideaki Hoshino^{a,b} Shigeru Tagaki^a Hayato Kon^{a,b} Takashi Shibusa^{a,b}
Hirosugu Takabatake^a Akihisa Fujita^a Kyuichiroh Sekine^a Shosaku Abe^b

^aDepartment of Respiratory Medicine, Hokkaido Keiaikai Minami Ichijyo Hospital, and

^bThird Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan

Key Words

Allergic bronchopulmonary aspergillosis · *Aspergillus fumigatus* · *Aspergillus niger* · Bronchial asthma

Abstract

A 65-year-old woman was admitted to our hospital with a dry cough and pulmonary infiltrates. Chest radiograph and CT revealed mucoid impaction and consolidations. Peripheral blood eosinophilia and elevated serum IgE were observed. *Aspergillus niger* was cultured repeatedly from her sputum, but *A. fumigatus* was not detected. Immediate skin test and specific IgE (RAST) to *Aspergillus* antigen were positive. Precipitating antibodies were confirmed against *A. niger* antigen, but not against *A. fumigatus* antigen. She had no asthmatic symptoms, and showed no bronchial hyperreactivity to methacholine. Thus, this case was diagnosed as allergic bronchopulmonary aspergillosis (ABPA) without bronchial asthma due to *A. niger*, an organism rarely found in ABPA. The administration of prednisone improved the symptoms and corrected the abnormal laboratory findings.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a lung disease caused by hypersensitivity reactions to antigens of *Aspergillus* species, which is characterized by bronchial asthma, pulmonary infiltrates and eosinophilia [1]. Bronchial asthma has been considered an essential diagnostic criterion and to play an important role in the development of the disease [2]. However, several cases have been reported without bronchial asthma [3–6], but in those reports, some patients were included who were in the pre-asthmatic state and who ultimately developed bronchial asthma. On the other hand, it is certain that there are patients, who never develop bronchial asthma. The natural course of ABPA is not known in detail, but a diagnostic criterion which is absent at the time of the diagnosis can develop during follow-up [7, 8]. Clinical symptoms of airway obstructions are, as Safirstein et al. [9] put it, not a reliable indication of early episodes of consolidation. From these points of view, bronchial asthma is not necessarily considered as an essential factor for the diagnosis of ABPA, especially in the early stage.

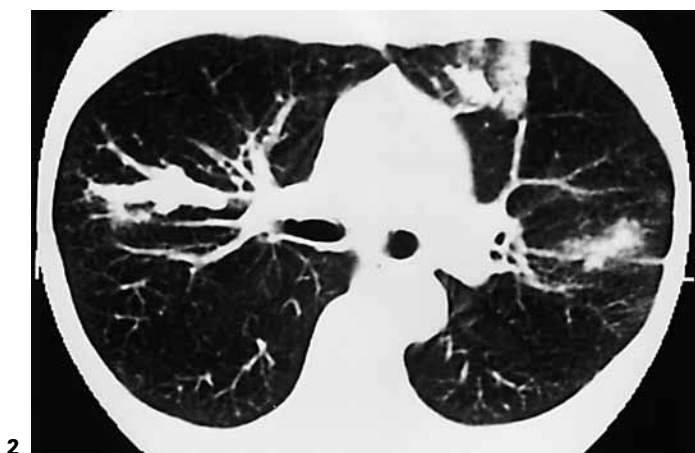
ABPA is mostly caused by *Aspergillus fumigatus*. In the present case, the causative organism was *A. niger*, which is rarely encountered in ABPA, especially in Japan.



1



3



2



4

Fig. 1. Chest radiograph on admission showed consolidations in both lung fields and band-like shadow in the right upper lung field.

Fig. 2. Chest CT on admission showed the image of mucoid impaction in the right upper lobe bronchus and consolidations in the left lung fields.

Fig. 3. Microscopic view of *A. niger* isolated from the patient's sputum, showing a characteristic spherical conidial head of this species.

Fig. 4. Close-up view of agar gel double diffusion test. A = The serum of our patient; B = *A. niger* antigen of another patient; C = the serum of another patient with *A. niger*; D = *A. niger* antigen of our patient; E = saline; F = *A. fumigatus* antigen. This test demonstrated precipitating antibodies appearing against *A. niger* antigen (A-B, C-D), but not against *A. fumigatus* antigen (A-F).

Case Report

A 65-year-old woman visited her physician with 2-week symptoms of a non-productive cough in mid-December 1991. The chest radiograph showed bilateral infiltrates, and she was referred to our hospital on January 9, 1992. She was a non-smoker and had no previous disease except an operation for gastric ulcer at age 45. She was a housewife and had lived in a condominium for about 8 years. On admission, she only complained of a non-productive cough. She was afebrile and her chest was clear to auscultation. Other physical examinations showed no abnormal findings.

Laboratory findings on admission included a red blood cell count of $321 \times 10^4/\text{mm}^3$, hemoglobin value of 10.1 g/dl, a white blood cell count of $7,800/\text{mm}^3$ with 45% neutrophils, 26% lymphocytes, 26% eosinophils, and 3% basophils, an erythrocyte sedimentation rate of 70 mm/h and a C-reactive protein value of 1.7 mg/dl. Her serum IgE level was 5,449 IU/ml (normal, 0–500 IU/ml). Other blood chemistry values were all within normal limits. Pulmonary function test on admission revealed vital capacity of 3,060 ml, percent vital capacity of 134.8%, forced expiratory volume in 1 s of 2,200 ml and 71.9%, pulmonary diffusing capacity for carbon monoxide (DL_{CO}) of 9.73 ml/min/mm Hg and % DL_{CO} of 52.5%. A decrease in DL_{CO} was found.

The chest radiograph and chest CT on admission showed consolidations in both lung fields and the image of a mucoid impaction in the right upper bronchus (fig. 1, 2). *Aspergillus* species were cultured from both sputum and mucus aspirated by fiberoptic bronchoscopy, and these were identified as *A. niger* (fig. 3). Culture for *A. fumigatus* was negative. Intradermal skin test to extracts of *A. fumigatus* and *Candida* showed immediate wheal and flare reactions, but no late reactions, respectively. Specific IgE (RAST) was positive to *Aspergillus*, *Candida*, *Penicillium*, *Cladosporium*, *Mucor* and *Alternaria*. An agar gel double diffusion test demonstrated precipitating antibodies against *A. niger* antigen, but not against *A. fumigatus* antigen (fig. 4).

Thus, a provisional diagnosis of ABPA caused by *A. niger* was made. The patient fulfilled all the primary criteria, except bronchial asthma and central bronchiectasis, and two of the secondary criteria by Rosenberg et al. [1]. Next we examined her airway hyperresponsiveness. The methacholine inhalation test disclosed that respiratory resistance (Rrs) at baseline was 3.6 cm H₂O/l/s and Rrs did not increase, even though the concentration of methacholine increased. Rrs at end concentration (25.0 mg/ml) was 4.4 cm H₂O/l/s. Thus, hyperresponsiveness of the bronchus was absent.

During the hospital stay, increase in consolidations was confirmed, but there were no symptoms of bronchial asthma. She was treated with prednisone 40 mg daily from January 31, 1992. Consolidations improved gradually, and the dose of prednisone was tapered to 10 mg daily. On March 5, the chest radiograph showed marked improvement in consolidations and laboratory data showed a white blood cell count of 5,800/mm³ with 3% eosinophils, a C-reactive protein value of 0 mg/dl and serum IgE level of 2,661 IU/ml and 2 days later she was discharged. When the dose had been tapered to 5 mg every other day 6 months after the discharge, a non-productive cough and consolidations on a chest radiograph recurred and the dose was increased to 20 mg daily on December 8. The dose was then tapered to 10 mg daily. Although over 6 years have passed since the diagnosis, she has remained well with prednisone from 5 to 10 mg daily and there has been no appearance of bronchial asthma.

Discussion

ABPA is a disease of the lung caused by hypersensitivity reactions to antigens of *Aspergillus* species, mostly *A. fumigatus*. For establishing the diagnosis of ABPA, the criteria of Rosenberg et al. [1] have generally been adopted. Our patient fulfilled five of the seven primary criteria, and two of the three secondary criteria. She had no airway hyperresponsiveness. Therefore, the diagnosis of ABPA with a lack of bronchial asthma was appropriate.

The mechanism of ABPA has been considered as follows [2]. In atopic patients, the repeated inhalation of *Aspergillus* spores lead to the production IgE antibody and bronchial asthma appears by the type 1 allergy of Gell and Coombs. Furthermore, spores are trapped and colonize the bronchus for the viscous sputum, acting as the antigen and leads to the appearance of precipitating antibodies by the type 3 allergy. Based on this theory, bron-

chial asthma is important for spores to colonize. In fact, it has been regarded as an essential criterion by Henderson [10] in 1968.

However, several cases without bronchial asthma have been reported [3–6]. Above all, Glancy et al. [3] reported that 11 of 42 patients with allergic bronchopulmonary fungal disease had no evidence of asthma. But in those cases, some patients were included who had showed airway hyperresponsiveness [6], and who had developed bronchial asthma [3]. These facts suggest that those patients might have been in a stage preceding bronchial asthma. Greenberger and Patterson [7] and Greenberger [8] considered that patients can be classified into five stages, namely: acute stage, remission, exacerbation, corticosteroid-dependent asthma and fibrotic end stage, and each diagnostic criterion could occur in different stages. From this point of view, it is probable that bronchial asthma may appear later.

It is considered that the role of bronchial asthma in the development of ABPA is to make excretion of *Aspergillus* difficult and colonization easy by the viscous sputum. Recently, Amitani et al. [11, 12] demonstrated experimentally that *Aspergillus* species produced substances which slowed ciliary beat frequency and damaged respiratory epithelium. This fact suggested that those substances could deteriorate mucociliary clearance and could lead to the process of the colonization of the airways. In conclusion, bronchial asthma was suspected to be the accelerating factor in the development of ABPA, but not the premise or an essential factor.

ABPA is mostly caused by *A. fumigatus*, and other *Aspergillus* species are rather rarely the cause of this disease. There are several reports due to *A. oryzae*, *A. terreus*, *A. niger* and *A. flavus*. Also, there are some reports without bronchial asthma due to *Aspergillus* species other than *A. fumigatus* [3], but to our knowledge, never due to *A. niger* alone.

We report a rare case of ABPA due to *A. niger* without bronchial asthma. We suspect that bronchial asthma is not an essential factor for the diagnosis of ABPA.

Acknowledgment

The authors wish to thank Dr. K. Takahashi for the preparation of the agar gel precipitin test and helpful comments regarding *A. niger*.

References

- 1 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.
- 2 Slavin RG, Fischer VW, Levine EA, Tsai CC, Winzenburger P: A primary model of allergic bronchopulmonary aspergillosis. *Int Arch Allergy Appl Immunol* 1978;56:325–333.
- 3 Glancy JJ, Elder JL, McAleer R: Allergic bronchopulmonary fungal disease without clinical asthma. *Thorax* 1981;36:345–349.
- 4 Berkin KE, Vernon DRH, Kerr JW: Lung collapse caused by allergic bronchopulmonary aspergillosis in non-asthmatic patients. *Br Med J* 1982;285:552–553.
- 5 McCarthy DS, Simon G, Hargreave FE: The radiological appearances in allergic bronchopulmonary aspergillosis. *Clin Radiol* 1970;21:366–375.
- 6 Yoshida N, Suguro H, Kohara F, Akiyama Y, Katoh H, Hashimoto N, Majima T, Yamaguchi M, Horie T, Kawabata Y: A case of allergic bronchopulmonary aspergillosis with no history of bronchial asthma. *Nippon Kyobu Shikkan Gakkai Zasshi* 1992;30:2123–2127.
- 7 Greenberger PA, Patterson R: Allergic bronchopulmonary aspergillosis and the evaluation of the patient with asthma. *J Allergy Clin Immunol* 1988;81:646–650.
- 8 Greenberger PA: Diagnosis and management of allergic bronchopulmonary aspergillosis. *Allergy Proc* 1994;15:335–339.
- 9 Safirstein BH, D'Souza MF, Simon G, Tai E H-C, Pepys J: Five-year follow-up of allergic bronchopulmonary aspergillosis. *Am Rev Respir Dis* 1973;108:450–459.
- 10 Henderson AH: Allergic aspergillosis: Review of 32 cases. *Thorax* 1968;23:501–512.
- 11 Amitani R, Murayama T, Nawada R, Lee WJ, Niimi A, Suzuki K, Tanaka E, Kuze F: Aspergillus culture filtrates and sputum sols from patients with pulmonary aspergillosis cause damage to human respiratory ciliated epithelium in vitro. *Eur Respir J* 1995;8:1681–1687.
- 12 Amitani R, Taylor G, Elezis E-N, Llewellyn-Jones C, Mitchell J, Kuze F, Cole PJ, Wilson R: Purification and characterization of factors produced by *Aspergillus fumigatus* which affect human ciliated respiratory epithelium. *Infect Immun* 1995;63:3266–3271.