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Two cases of Schizophyllum asthma: Is this a new clinical entity or a precursor of ABPM?

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ABSTRACT

Background: There is a close link between fungal sensitization and asthma severity. Although *Schizophyllum commune* (*S. commune*, "suehirotake" in Japanese), one of the basidiomycetous (BM) fungi, is a fungus that can cause allergic bronchopulmonary mycosis (ABPM) and allergic fungal sinusitis (AFS), whether the fungus causes or sensitizes subjects to asthma is unclear.
Methods: The bronchial provocation test using *S. commune* antigen was performed in two asthmatics who had demonstrated positive skin reactions to the *S. commune* antigen, and low dose of itraconazole (50 mg/day) was prescribed as an adjunctive therapy for 2 weeks. The allergological features and clinical manifestations of these patients are herein evaluated and discussed.
Results: Case 1 was a 71-year-old female, and case 2 was a 69-year-old male. Both patients demonstrated positive reactions to the inhalation test. A diagnosis of AFS or ABPM was excluded in both patients because of the lack of a history of pulmonary infiltrates, central bronchiectasis, a history of expectoration of brown plugs or flecks, or sinusoidal findings. Although the efficacy of itraconazole in our cases was unclear, the elevated titer of the specific IgG-for *S. commune* in case 2 gradually decreased during the period of antifungal therapy.
Conclusions: The two patients described herein were diagnosed to have bronchial asthma caused by *S. commune*; so-called *Schizophyllum* asthma. *S. commune* may also be a causative fungal antigen of bronchial asthma.

1. Introduction

There has been increasing interest in the relationship between severe asthma and fungal sensitization [1–3]. Therefore, testing in adults with asthma that does not respond to first-line treatments should include not only such routine investigations as lung function, sinus CT scanning, sensitization to common inhalant allergens or evaluation of evidence for allergic bronchopulmonary aspergillosis (ABPA) [4], but should also include an evaluation for evidence of colonization with a range of fungi, including *Alternaria*, *Candida*, and *Trichophyton*, as well as *Aspergillus* species [5].

Recent research has focused on the possible role of basidiomycetous (BM) fungi as a fungal aeroallergen [6], and allergic fungal respiratory diseases [7] caused by BM fungi have been increasingly reported [8–10]. Although it is well-known that *Schizophyllum commune* (*S. commune*), one of the BM fungi, causes mucoid impaction of bronchi (MIB) [11], allergic bronchopulmonary mycosis (ABPM) [12] and allergic fungal sinusitis (AFS) [13], however, it remains unclear whether this fungus really causes or triggers asthma symptoms similar to *Aspergillus* species [14].

This report describes two patients with bronchial asthma caused by *S. commune*; so-called *Schizophyllum* asthma. Except for

Abbreviations: ACT, asthma control test; ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; AFC, allergic fungal cough; AFRD, allergic fungal respiratory diseases; AFS, allergic fungal sinusitis; BM, basidiomycetous; *B. adusta*, *Bjerkandera adusta*; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GINA, global initiative for asthma; ITCZ, itraconazole; MIB, mucoid impaction of bronchi; PCR, polymerase chain reaction; SDA, Sabouraud's dextrose agar; *S. commune*, *Schizophyllum commune*; SAM, sinobronchial allergic mycosis.

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the criteria of pulmonary involvement, such as central bronchiectasis and mucoid impaction, both cases met the criteria for ABPM caused by *S. commune*. Therefore, it was difficult to distinguish Schizophyllum asthma from eosinophilic bronchitis involved in ABPM caused by *S. commune.*

This raises the question of whether the proposed Schizophyllum asthma is actually a new clinical entity similar to both Trichophyton asthma [15,16] and Candida asthma [17], or is instead a precursor of ABPM caused by *S. commune*.

2. Material and methods

2.1. Preparation of the antigenic solution of S. commune

One liter of Sabouraud's dextrose broth in 3 L flasks was sterilized. Five milliliters of a *S. commune* spore suspension (10^5 spores per ml) in sterile physiological saline from 14 day-old Sabouraud's dextrose agar culture were used to inoculate a flask. The flask was shaken at 25 °C at 150 rpm in a rotary shaker incubator for 14 days. Mycelia were separated by filtration, and centrifuged. The supernatants were dialyzed against 5 mM ammonium bicarbonate and lyophilized.

2.2. Allergological tests

2.2.1. Intradermal skin test and serological test

The antigenic solution (polysaccharide) was injected intradermally using a tuberculin syringe (0.02 mL, 1 mg/mL) to assess the skin response to the solution. The results of the immediate-type and the late-type responses were judged to be positive in a case of the longer axis of the flare beyond 10 mm at 15 min and at 8 h after the injection, respectively. The Phadia (previously Pharmacia) CAP system was used to quantify specific IgG and IgE levels (Phadia Ltd, Uppsala, Sweden) [18]. A positive test was taken as a measurement >2.00 (mgA/L) and >0.35 (UA/mL), respectively.

2.2.2. Lymphocyte stimulation test

The lymphocyte stimulation test (LST) [19] was performed using the antigenic solution with the Lymphoprep system. The results were considered to be positive when the magnitude of the response to *S. commune* was beyond 200% in comparison to the controls using PHA.

2.2.3. Bronchoprovocation test

After obtaining informed consent from both patients, a 2 ml dose of culture-filtrate antigen solution at a concentration (maximum: 1 mg/mL), which was determined based on the threshold of the weakest positive immediate skin reaction, 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 responses were assessed to be positive when the PaO_2 decreased significantly (more than 20%), or when patients developed asthma attacks with a 20% decrease in PEF and/or FEV_1.

2.3. IRB approval

This case study was approved by the institutional review boards (the IRB committee of Saiseikai Kanazawa Hospital; reference number 2009006) and informed consent was obtained from both patients.

2.4. Case report 1

A 71-year-old female long-term asthmatic patient was admitted to the hospital on October 4, 2010 for the treatment of chest discomfort and dyspnea. Her cough and wheezing had developed in September 2010 and had not improved. She was a non-smoker. A physical examination revealed a body temperature of 36.8 °C and a heart rate of 72 beats per minute. Auscultation revealed wheezes and rhonchi.

Laboratory tests revealed a white blood cell count of 8500 per μl with 0.7% eosinophils. C-reactive protein was present at 0.01 mg/dL. A radioimmunosorbent test revealed a normal level of IgE (35 U/mL), and the radioallergosorbent test for specific IgE antibodies against *Aspergillus, Penicillium, Candida, Cladosporium*, *Alternaria*, *Trichophyton* were all negative. Both the specific IgG and IgE levels for *S. commune* were revealed to be negative. The differential cell analysis of the sputum was as follows: 15% alveolar macrophages, 82% neutrophils, and 3% eosinophils.

Chest radiographs and computed tomography of the chest and sinus taken upon admission showed normal findings. A pulmonary function test using the Collins DS system [20] revealed an FVC of 2.94 L (133.0% of predicted value), a FEV_1 of 1.35 L (84.9% of predicted value), and an FEV_1/FVC ratio of 45.9%. The bronchodilator therapy revealed a slight increase in FEV_1 values (from 1.35 to 1.37 L).

The immediate (15 min) skin reaction (1 mg/ml) was 0 × 0/0 × 0 mm for *Aspergillus*, 4 × 4/0 × 0 mm for *Alternaria*, 5 × 5/0 × 0 mm for *Candida*, 4 × 4/0 × 0 mm for *Bjerkandera adusta (B. adusta)*, and 10 × 10/0 × 0 mm for *S. commune*. In addition, the result of the LST for *S. commune* was 800 cpm (533%).

Because she was suspected of being sensitized to *S. commune*, a closer examination was performed. Although the bronchoprovocation test using the *Aspergillus* antigen was negative, the results of the bronchoprovocation test using *S. commune* at a concentration of 10^{-1} mg/mL was graded as positive due to the development of a cough and significant decreases in PEF (from 200 to 130 L/min) 10 h after the inhalation challenge. These symptoms spontaneously disappeared the next day (Table 1a).

She was treated with the leukotriene receptor antagonist montelukast sodium (10 mg/day), theophylline (200 mg/day), transdermal tulobuterol patch (2 mg/day), inhaled budesonide/formoterol (2 puffs/day), and inhaled tiotropium bromide hydrate (18 μg/day). She was treated with itraconazole (ITCZ) (50 mg/day) for 2 weeks as an adjunctive therapy. Her Asthma Control Test (ACT) score showed a slight increase from 13 to 16 after the two-week therapeutic regimen (Table 2).

2.5. Case report 2

A 69-year-old male asthmatic patient was admitted to the hospital on August 24, 2010 for closer examination of fungal sensitization of asthma. He was administered montelukast sodium (10 mg/day), a transdermal tulobuterol patch (2 mg/day) and inhaled beclomethasone dipropionate (400 μg/day) on the basis of a diagnosis of asthma that had been present for about 5 years. He was suspected to be sensitized to *S. commune* because his intradermal skin test to this fungus revealed a strong positive finding (20 × 20/68 × 74 mm). He was a non-smoker. Physical examination revealed the following: his temperature was 36.2 °C, blood pressure was 131/79 mmHg, and his heart rate was 68 beats per minute. Auscultation did not reveal any abnormalities except forced late expiratory wheezes.

Laboratory studies showed a white blood cell count of 5000 per μl with 2.0% eosinophils. No inflammatory reactions were observed as assessed by the C-reactive protein level and erythrocyte