

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

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**Two cases of Schizophyllum asthma; is this a new clinical entity or
a precursor of ABPM?**

Haruhiko Ogawa, M.D.

Division of Pulmonary Medicine, Ishikawa-ken Saiseikai Kanazawa Hospital

Kanazawa, Japan 920-0353

E-mail saiseikh@po3.nsknet.or.jp

Tel +81-76-266-1060 Fax +81-76-266-1070

Masaki Fujimura, M.D.

Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University

Graduate School of Medical Sciences, Kanazawa, Japan

E-mail fujimura@med3.m.kanazawa-u.ac.jp

Yasuo Takeuchi, M.D., Ph.D.

Division of Respiratory Medicine and Clinical Allergy, Fujita Health University,

Toyoake, Japan

E-mail yasuotakeuchi2001@yahoo.co.jp

Koichi Makimura, M.D., Ph.D.

Department of Molecular Biology and Gene Diagnosis, Institute of Medical
Mycology and Genome Research Center, Graduate School of Medical Science,
Teikyo University Hachioji, Japan

makimura@main.teikyo-u.ac.jp

Corresponding author. Haruhiko Ogawa, M.D.

The Division of Pulmonary Medicine,

Ishikawa-ken Saiseikai Kanazawa Hospital,

Ni-13-6 Akatsuchi-machi, Kanazawa 920-0353, Japan.

TEL: +81-76-266-1060 e-mail : saiseikh@po3.nsknet.or.jp

Conflict of interest

The all authors declare that they have no competing interests that might be perceived to influence the results and discussion reported in the present manuscript.

Abstract

(Background) There is a close link between fungal sensitization and asthma severity. Though *Schizophyllum commune* (*S. commune*, called “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 the asthma is unclear. (Methods) The bronchial provocation test using *S. commune* antigen was performed in two asthmatics who had demonstrated positive skin reaction to *S. commune* antigen, and low dose of itraconazole (50 mg/day) for 2 weeks was prescribed as an adjunctive therapy. The allergological features and clinical manifestations of them were 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 reaction 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. Though 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 here were diagnosed to have bronchial asthma caused by *S. commune*; so-called Schizophyllum asthma. *S.*

commune may be a causative fungal antigen of bronchial asthma.

Key words

allergic bronchopulmonary mycosis

allergic fungal cough

allergic fungal sinusitis

Schizophyllum asthma

Schizophyllum commune

Abbreviation

Asthma Control Test (ACT)

allergic bronchopulmonary aspergillosis (ABPA)

allergic bronchopulmonary mycosis (ABPM)

allergic fungal cough (AFC)

allergic fungal respiratory diseases (AFRD)

allergic fungal sinusitis (AFS)

basidiomycetous (BM)

Bjerkandera adusta (*B.adusta*)

forced expiratory volume in 1 second (FEV1)

forced vital capacity (FVC)

Global Initiative for Asthma (GINA)

itraconazole (ITCZ)

mucoid impaction of bronchi (MIB)

polymerase chain reaction (PCR)

Sabouraud's Dextrose Agar (SDA)

Schizophyllum commune (*S. commune*)

sinobronchial allergic mycosis (SAM)

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 treatment should include not only such routine investigation 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 disease [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], it still remains unclear whether this fungus really causes or triggers asthma symptoms similar to *Aspergillus* species [14] or not.

This report describes two patients with bronchial asthma caused by *S. commune*; so-called *Schizophyllum* asthma. Except for the criteria of the pulmonary involvement, such as central bronchiectasis and mucoid impaction, both cases met the criteria of

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 instead is a precursor of ABPM caused by *S. commune*.

Material and Method

Preparation of the antigenic solution

S. commune: One liter of Sabouraud's dextrose broth in 3 liter 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 the 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.

Allergological tests

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 minutes and at 8 hour 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.

Lymphocyte stimulation test

The lymphocyte stimulation test [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.

Bronchoprovocation test

After obtaining informed consent, a 2 ml dose of culture-filtrate antigen solution at the concentration (maximum at 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 PaO₂ significantly decreased (more than 20%), patients developed asthma attacks with 20% decrease in PEF and/ or FEV 1.0, laboratory findings such as WBC and CRP significantly elevated, and/or patients developed cough attacks with a significant increase in the cough reflex sensitivity to inhaled capsaicin, which was measured prior to and 24 hours after the provocation test.

A statement of 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 the two patients.

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 a chest discomfort and dyspnea. Her cough and wheezing 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* and *Trichophyton* were all negative. A differential cell analysis of 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 a FVC of 2.94 L (133.0% of predicted value), a FEV₁ of 1.35 L (84.9% of predicted value), and an FEV₁/FVC ratio of 45.9%. The bronchodilator therapy revealed slight increase in FEV₁ values (from 1.35 to 1.37 L).

The immediate (15 min) skin reaction (1 mg/ml) was 0 x 0/0 x 0 mm for *Aspergillus*, 4 x 4/0 x 0 mm for *Alternaria*, 5 x 5/0 x 0 mm for *Candida*, 4 x 4/0 x 0 mm for *Bjerkandera adusta* (*B.adusta*), and 10 x 10/0 x 0 mm for *S. commune*. The late skin reactions were positive for only *S. commune* (10 x 10/ 0 x 0 mm).

Because she was suspected to be sensitized to *S. commune*, the closer examination was performed. Though the bronchoprovocation test using *Aspergillus* antigen was negative, the results of the bronchoprovocation test using *S. commune* at the concentration of 10⁻¹ mg/mL was graded as positive due to the development of a coughing symptom and significant decreases in PEF (from 200 to 130 L/min), 10 hrs

after the inhalation challenging. These symptoms spontaneously disappeared 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. The score of the Asthma Control Test (ACT) showed a slight increase from 13 to 16 (Table.2).

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), transdermal tulobuterol patch (2 mg/day) and inhaled beclomethasone dipropionate (400 µg/day) on a basis of a diagnosis of asthma 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 x 20/68 x 74 mm). He was a non-smoker. Physical examination revealed the following: his temperature was 36.2 °C, blood pressure 131/79 mmHg, and heart rate 68 beats per minute. Auscultation did not

reveal any abnormalities except forced late expiratory wheezes.

Laboratory studies showed a white blood cell count of 5,000 per μl with 2.0% eosinophils. No inflammatory reactions were observed as assessed by C-reactive protein level and erythrocyte sedimentation rate. Radioimmunosorbent tests revealed normal level of IgE (114 U/ml), and the results of radioallergosorbent test for specific IgE antibodies against *Aspergillus* was 0.57 (UA/mL), and negative for *Penicillium*, *Candida*, *Cladosporium*, *Alternaria*, house dust or mites. Differential cell analysis of sputum revealed eosinophilia (88% alveolar macrophages, 10% neutrophils, and 2% eosinophils).

Chest radiographs and computed tomography of the chest and sinus taken upon admission showed normal findings. A pulmonary function test revealed a FVC of 3.02 L (91.0% of predicted value), a FEV₁ in 1 second of 1.73 L (70.3% of predicted value), and a FEV₁/FVC ratio of 57.3%. The bronchodilator therapy revealed a small increase in the FEV₁ value (from 1.73 to 1.84 L).

The immediate (15 min) skin reaction was 9 x 8/40 x 40 mm for *Aspergillus* and 0 x 0/4 x 4 mm for *Alternaria* and *Candida*. The result of prick test for *S. commune* (10^{-10} mg/ml) examined before the intradermal skin test was 5x5/0x0 mm. Additional examinations of the immediate (15 min) skin reaction for *S. commune* produced the

following findings: 8 x 6/28 x 22, 8 x 5/0 x 0, 5 x 5/0 x 0, 3 x 3/0 x 0, 4 x 4/0 x 0, 4 x 4/0 x 0, and 5 x 5/0x 0 mm at concentrations of 2×10^{-4} , 10^{-4} , 10^{-5} , 10^{-6} , 10^{-7} , 10^{-8} , 10^{-9} and 10^{-10} mg/ml, respectively.

The bronchoprovocation test using *Aspergillus* antigen was negative; however, the test using *S. commune* antigen at the concentration of 10^{-4} mg/ml was graded as positive due to the development of a wheezing attack, decreases in PEF (from 440 to 340 L/min) 3hr after the provocation. These symptoms spontaneously disappeared next day after the challenge without any additional therapy (Table. 1b).

He was discharged on August 27 and treated with ITCZ (50 mg/day) for 2 weeks as an adjunctive therapy. The FEV₁ values showed a slight increase from 1.67 to 1.75 L accompanied with decrease of the specific IgG for *S. commune* (from 8.10 to 7.28 mg A/L; Table.2).

Discussion

It is important to elucidate the etiological agents and the exacerbating factors in allergic fungal respiratory diseases (AFRD) [7]. In particular, there has been increasing interest in the association between severe asthma and fungal sensitization [1-3].

Recently, it is stated in Global Initiative for Asthma (GINA) 2009 that describing

patients as having allergic asthma is usually of little benefit, unless a single specific trigger agent can be identified [21]. However, different from occupational asthma, an environmental fungus cannot be the only etiological factor that causes asthma symptoms. Even if asthmatics have positive intradermal reaction against some fungus, it does not necessarily mean that the concern fungus is a causative antigen of the asthmatics. Therefore, the finding that the concern fungi can cause asthma symptoms is itself important.

Because there was no history of pulmonary infiltrates and no history of any expectoration of either brown plugs or flecks, and because there was no central bronchiectasis and no sinusoidal findings, the two patients were diagnosed to have bronchial asthma caused by *S. commune*, which is so-called Schizophillum asthma, instead of being diagnosed to have AFS or ABPM due to *S. commune*. Subsequently, this report has proved that *S. commune* is an environmental factor which causes asthma symptoms.

We recently found that specific IgE for *S. commune* was negative in most of patients with MIB who were not sensitized by *S. commune*, and in a large number of patients with bronchial asthma who were sensitized to *S. commune* (Details of this report will be shown in another manuscript), it may be considered that the positive titer is one of

reliable items for making a diagnosis of ABPM caused by *S. commune*. The positive results of the serum IgE and IgG to *S. commune* titer suggest that Case 2 may be a precursor of ABPM allergologically.

We have previously reported that the positive ratios for the immediate cutaneous reaction and the lymphocyte stimulation test to *Bjerkandera adusta* (*B. adusta*) were found to be significantly higher in the allergic fungal cough (AFC) sensitized to *B. adusta* group than in that non-sensitized group [22]. [The lymphocyte response to *S.*](#)

[commune may also play a part of important role in immunological systems in](#)

[Schizophyllum asthma.\(結果まちです\)](#)

There is evidence of a close link between fungal sensitization and asthma severity [3]. Denning et al. reported that the results of a randomized controlled trial (FAST study) that showed a significant quality of life benefit, a fall in IgE, and a modest improvement in rhinitis and morning PEF, but not FEV1, after oral antifungal therapy in patients with severe asthma sensitized to one of several common fungi [23]. Gonzalez GM et al. reported that *S. commune* was susceptible *in vitro* to ITCZ, amphotericin B, and voriconazole, with MIC values of 0.06, 0.5, and 0.5 µg/ml, respectively [24]. Therefore, such antifungal therapy may have some advantages [9, 22, 25, and 26] in either reducing or eradicating such antigen exposure [23]. **Though the efficacy of ITCZ**

(50 mg/day for 2 weeks) 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.

It is necessary to determine whether the quantity of the daily dose of ITCZ and the duration of the therapy are appropriate. The efficacy of antifungal drugs for this condition is worth being investigated also from another aspect such as the potential of preventing the development of ABPM.

We have previously accomplished bronchoprovocation test using *S. commune* antigen for the definitive diagnosis of ABPM, the inhalation test was graded as positive due to the development of a coughing attack and a ticklish throat, significant decrease in PaO₂, and increase in the serum CRP, but the patient did not experience asthma attack in the examination. Thus, even if there is some overlap between the eosinophilic bronchitis of *Schizophyllum* asthma and that of ABPM caused by *S. commune*, it is considered that *Schizophyllum* asthma is not always a precursor of ABPM.

Both *B. adusta* and *S. commune* are BM fungi that colonize rotting wood and are distributed throughout the world. They are whitish in color when young and become darker shades of gray at maturity; *B. adusta* causes allergic fungal cough (“Yakeirotake cough” in Japanese) [27] but not bronchial asthma nor ABPM. The difference of the clinical manifestation (AFC, ABPM or asthma) evoked by such BM fungi may depend

on the allergological characteristics of each fungus.

This report presented two patients with Schizophyllum asthma (“Suehirotake asthma” in Japanese). The results of [these cases suggest](#) that *S. commune* is a potential causative fungal antigen of bronchial asthma similar to Trichophyton. Further studies are required to determine whether environmental fungi such as *S. commune*, which are easily deposited within the airway, may enhance the clinical symptoms of bronchial asthma. It is also important to follow such patients carefully to estimate whether the sensitization to *S. commune* may become the risk factor for the onset of ABPM or SAM.

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Tables

Table 1a, 1b Results of bronchoprovocation test

Table 2 Effect of the adjunctive therapies

		pre	15 min	30 min	6 hr	10 hr	24 hr
<i>S. commune</i>	BT	36.6	36.6	36.9	36.9	36.9	36.4
	Wheezes	(-)	(-)	(-)	(-)	(±)	(-)
	SpO2 %	97	97	98	96	95	97
	PEF L/min	200	200	200	190	130	180
	FEV1.0 L	1.25					1.24
	PaO2 mmHg	94.1				81.7	87.9
<i>Aspergillus</i>	BT	36.7	36.7	36.6	36.8	36.5	36.2
	Wheezes	(-)	(-)	(-)	(-)	(-)	(-)
	SpO2 %	96	97	97	96	97	96
	PEF L/min	200	190	190	210	200	200
	FEV1.0 L	1.11					1.18

		pre	15min	30min	3hr	8hr	24hr
<i>S.communis</i>	BT	36.2	36.9	36.4	35.8	36.3	36.1
	Wheezes	(-)	(-)	(-)	(±)	(-)	(-)
	SpO2 %	98	96	96	96	97	97
	PEF L/min	440	410	400	340	420	420
	FEV1 L	1.77				1.73	1.73
	PaO2 mmHg	86.9				85	88.2
<i>Aspergillus</i>	BT	35.7	36.2	36.5	36.4	36.2	36
	Wheezes	(-)	(-)	(-)	(-)	(-)	(-)
	SpO2 %	97	96				97
	PEF L/min	450	460	430	460	450	450
	FEV1 L	1.72					1.77
	PaO2 mmHg	93.1					95

Case 1	run in	pre-itraconazole	post-itraconazole
ACT	19	13	16
FEV1 (l)	1.34	1.27	1.3
MMF (l/s)	0.37	0.3	0.27
Specific IgG- for <i>S. commune</i> (mgA/l)	< 2		
Specific IgE- for <i>S. commune</i> (mgA/l)	< 0.35		

Case 2	run in	pre-itraconazole	post-itraconazole
ACT	19	22	23
FEV1 (l)	1.82	1.67	1.75
MMF (l/s)	0.56	0.56	0.4
Specific IgG- for <i>S. commune</i> (mgA/l)	9.57	8.1	7.28
Specific IgE- for <i>S. commune</i> (mgA/l)	2.8		