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Schizophyllum commune-induced allergic fungal rhinosinusitis and sinobronchial mycosis

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ABSTRACT

We present 32- and 38-year-old males with *Schizophyllum commune*-induced allergic fungal rhinosinusitis (AFRS). *S. commune*-induced AFRS was diagnosed by clinical and radiographic findings, positive specific IgE antibodies against *S. commune* as measured by the ImmunoCAP system, and sequencing analysis of the fungus. Our two cases with *S. commune*-induced AFRS for the first time showed evidence for type 1 hypersensitivity to *S. commune* as determined by using specific IgE antibodies against *S. commune*, and the fungus was identified by sequence analysis.

1. Introduction

Schizophyllum commune is a ubiquitous basidiomycetous fungus growing every continent except Antarctica. Although *S. commune* rarely causes human disease, recent evidence suggests that it occasionally causes respiratory disorder via sensitization to this fungus, including allergic fungal rhinosinusitis (AFRS) and allergic bronchopulmonary mycosis (ABPM) [1,2]. In the literature, few cases of *S. commune*-induced AFRS or ABPM have been reported because antigen or antibody of *S. commune* has not been available till recently, thereby lacking the convenient method that identifies sensitization to the fungus. So far, there is no report showing evidence for type 1 hypersensitivity to *S. commune* that causes AFRS. The presence of concomitant AFRS and ABPM in the same patient represents the same process of fungal hypersensitivity in the upper and lower airways [3]. This disease concept, termed *S. commune*-associated sinobronchial allergic mycosis (SAM) syndrome, an acronym for sinobronchial allergic mycosis, has recently been proposed [3,4]. Here, we for the first time describe two cases of *S. commune*-induced AFRS diagnosed by clinical and radiological findings, positive specific IgE antibodies against *S. commune,* as measured by the ImmunoCAP system and identification of the fungus by sequencing analysis. Evaluation of the lower airway revealed subclinical asthma in one patient, while no hypersensitivity in the lower airway in the other patient. Recognition of *S. commune*-associated SAM would help clinicians to evaluate function and hypersensitivity in the lower airway of the patients with AFRS caused by sensitization to *S. commune*.

2. Case

2.1. Case 1

A 32-year-old male with a half year history of allergic rhinitis, presenting the right side nasal obstruction and rhinorrhea, was referred to our hospital for the purpose of endoscopic sinus surgery (ESS) (day 0). The right nasal cavity was filled with nasal polyps. Computed tomography (CT) revealed opacification of the right maxillary and ethmoid sinuses, heterogeneous signal intensity in the maxillary sinus, and high signal intensity in central part of the sinus (Fig. 1). Under general anesthesia, the patient underwent the right side ESS (day 16), revealing thick, viscoid, and brown to green mucous with a peanut butter-like material in the maxillary sinus. Histologic examination showed the allergic

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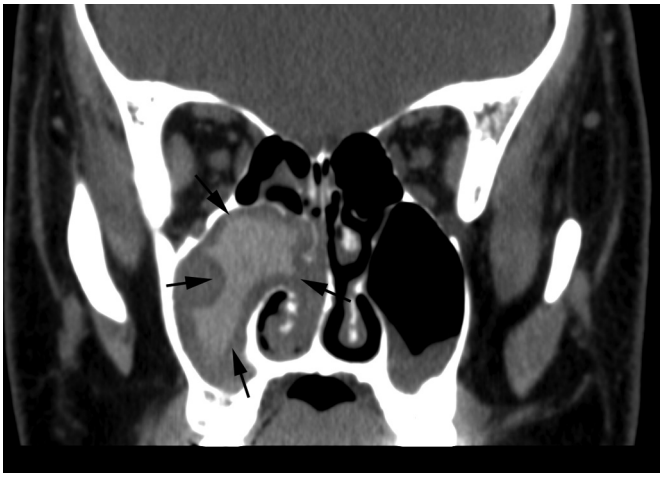

Fig. 1. Computed tomography coronal scan of case 1. Heterogeneous maxillary sinus opacification and allergic mucin with hyperdensity (arrows) are noted.

mucin, containing many eosinophils, necrotic tissue and fungal hyphae (Fig. 2). No invasion of hyphae into the mucous membrane was found. Cultures of the mucin from the maxillary sinus on Sabouraud's dextrose yielded the white colonies with a tart and bad smell. Microscopic examination of the colony using Parker ink-potassium hydroxide method showed fungal branched hyphae with spicules. Since it was difficult to identify the fungus by the morphological features, *S. commune* was identified by the 26S ribosomal (r)RNA (D1/D2 domains) sequence analysis [5].

Investigations revealed a white blood cell (WBC) count of 7930/mm^3 with 7.2% of eosinophils and high serum IgE levels (988 IU/ml). There was a positive specific IgE antibody against *S. commune*, which was measured using the ImmunoCAP system (Phadia Ltd, Uppsala, Sweden) as described in our previous studies [2,4,6]. Specific IgE antibody, as measured by the fluoroenzyme immunoassasy (FEIA, SRL Inc. Tokyo, Japan), against *Cladosporium* and *Trichophyton* were positive but negative for *Aspergillus*, *Penicillium* and *Candida*. This case was diagnosed as AFRS because it met all the major criteria of Bent and Kuhn diagnostic standard [7].

Chest CT revealed neither mucoid impaction nor significant bronchial wall thickening, which are often associated with ABPM. The pulmonary function test using the Collins DS system showed the values for FVC of 4.84 L (118.9% of predicted value), FEV1 of 3.35 L (89.1% of predicted value), and FEV1/FVC ratio of 69.2%. Administration of a bronchodilator slightly increased the values for FEV1 from the baseline of 3.35 L to 3.59 L. Methacholine (14.4 mg/ml) caused a 20% decrease from the baseline FEV1 (PC20), suggesting the presence of subclinical bronchial asthma. The patient received montelukast and nasal corticosteroid spray, whereas AFRS recurred (day 180). However, the symptoms disappeared after oral betamethasone (1 mg/day) therapy for 2 weeks. Subsequent clinical course was uneventful until day 900.

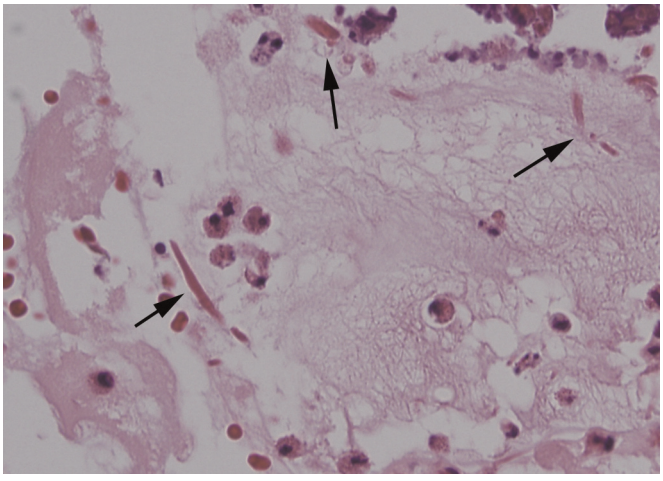

Fig. 2. Allergic mucin of case 1 stained with hematoxylin and eosin. Many eosinophils and fungal hyphae (arrows) are present.

2.2. Case 2

A 38-year-old male with a history of allergic rhinitis was referred to our hospital because of chronic sinusitis with purulent rhinorrhea despite the long-term therapy (day 0). CT scan showed opacification of bilateral sinuses and high signal density in the left side sphenoid sinus. He underwent bilateral ESS (day 47), revealing polyposis in the left nasal cavity. The left side sphenoid and maxillary sinuses were filled with mucoid secretions (allergic mucin). Histological examination showed fungal hyphae in the mucin but no invasion into the mucous membrane was found. Cultures of the mucin from the sphenoid sinus yielded the white wooly fungus. Microscopic examination of the mold showed hyphae with clamp connection and spicules (Fig. 3), suggesting that the fungus might be basidiomyctete. *S. commune* was identified by the rRNA sequencing analysis [5].

Investigations revealed a WBC count of 8820/mm^3 with 9.0% of eosinophils, and high serum IgE levels (958 IU/ml). Specific IgE antibodies against *S. commune*, *Aspergillus*, *Penicillium* and *Candida* were positive (2+ ~ 3+) but negative for *Cladosporium* and *Trichophyton*. This case fulfilled all the major criteria of AFRS standard [7]. Pulmonary function and other tests found no remarkable change in the lower airway. Although the patient was in good condition, his respiratory function has been periodically checked since sensitization to *S. commune* might be a future risk of asthma.

3. Discussion

To the best of our knowledge, 27 cases of sinusitis due to *S. commune* have been reported in the literature [1,5,8–14]. However, AFRS is associated with only 7 cases, including our cases [5,11–14]. Table 1 summarizes clinical characteristics of the patients with *S. commune*-induced AFRS. It occurs in both children and adults without gender preponderance. Our cases for the first time showed evidence for type 1 hypersensitivity to *S. commune* using

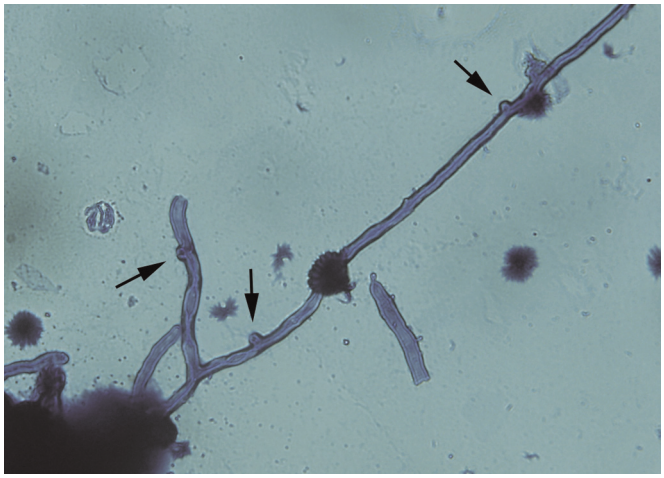

Fig. 3. The cultured fungus of allergic mucin in case 2 detected by Parker ink-potassium hydroxide method. Clamp connections (arrows) on hyphae are distinctive features of basidiomycete.

Table 1
Literature review of cases with *Schizophyllum Commune*-induced allergic fungal rhinosinusitis.

Reference	Sex/age	Type 1 hypersensitivity to *S. commune*	Lung disease	Other history	Identification of *S. commune*	Treatment	Recurrent AFRS
Clark et al. [11]	M/35	ND	NA	NA	Morphological	ESS	NA
Taguchi et al. [12]	F/55	ND	NA	Allergic rhinitis, food allergy	Morphological	ESS	No
Ahmed et al. [13]	F/57	ND	Aspirin sXensitive asthma	Rheumatoid arthritis, myasthenia gravis	Morphological	ESS Oral corticosteroids, oral itraconazole	Yes
Peric et al. [14]	F/32	ND	No	Allergic rhinitis	Morphological	ESS Oral itraconazole, topical corticosteroids	Yes
Won et al. [5]	F/14	ND	No	No	Sequence analysis	ESS Oral and topical corticosteroids	No
Case 1	M/32	2+[a]	Subclinical asthma	Allergic rhinitis	Sequence analysis	ESS Oral and topical corticosteroids, montelukast	Yes
Case 2	M/38	3+[a]	No	Allergic rhinitis	Sequence analysis	ESS Topical corticosteroids	No

AFRS: allergic fungal rhinosinusitis; ESS: endoscopic sinus surgery, NA: not available, ND: not done.
[a] Type 1 hypersensitivity to *S commune* was confirmed by the presence of specific IgE antibody against *S. commune*, as measured by using the immunoCAP system.

specific IgE antibody against *S. commune* and the fungus was identified by sequence analysis. Although the possibility that specific IgE antibody against *S. commune* used in our study crossreacts with *Cladosporium* or *Trichophyton* cannot be excluded, the usefulness of the measurement of this antibody for detection of *Schizophyllum* asthma has been reported in our previous studies [2,6]. The gene sequencing analysis is an additional valuable method for identification of *S. commune* [5] because the morphological identification is particularly difficult in the case of monokaryotic isolates. *S. commune* is the third most common causative antigen (11%) in 143 cases of ABPM caused by fungi other than *Aspergillus* [1]. *S. commune* has not been widely recognized as a pathogenic antigen for AFRS, since the method for detection of specific IgE antibody against *S. commune*, which confirms type 1 hypersensitivity to the fungus, and sequencing analysis for identification of the fungus have not been available till recently. Thus, the number of patients with AFRS caused by sensitization to *S. commune* may be underestimated.

Recent evidence suggests that sensitization to *S. commune* may develop asthma, similar to that caused by *Aspergillus*. The rate of sensitization to *S. commune* appeared to be higher in patients with severe asthma than in those with moderate or mild asthma and correlated with severity and exacerbation frequency of asthma, suggesting that sensitization to *S. commune* may be a future risk of lung dysfunction [2]. Venarske and deShazo contended that the presence of concomitant AFRS and allergic bronchopulmonary mycosis in the same patients represents the same process of fungal hypersensitivity in the upper and lower airways. They termed this condition the SAM syndrome. Patients with SAM syndrome have chronic sinusitis involving multiple sinuses, asthma, cutaneous hyperreactivity to fungal allergens, eosinophilia, high serum IgE levels, and radiographic evidence of bronchiectasis, mass lesions to diffuse pulmonary infiltrates, and even normal findings [3]. Each case with *S. commune*-induced AFRS developed aspirin-sensitive asthma [13] and subclinical asthma as in our case (Table 1), suggesting that sensitization to *S. commune* can also cause allergy in the lower airway. Thus, function and sensitivity of the lower airway should be carefully evaluated in patients with *S. commune*-induced AFRS. Ogawa et al. have proposed the following guidance for *S. commune*-associated SAM. Fundamental condition; (1) eosinophilic mucoid impaction of the bronchi with/without asthma, and/or (2) eosinophilic mucin involved in multiple sinuses with/without nasal polyposis. Major criteria; (1) positive culture for *S. commune* using bronchial or sinus specimens, and (2) positive results for *S. commune*-specific IgE and/or IgG. Supplemental findings; (1) eosinophilia and/or high serum IgE levels, and (2) positive radiographic evidence of ABPM and/or AFRS [4].

Regarding the treatment modalities for *S. commune*-induced AFRS, all patients underwent ESS to remove all obstructing allergic mucin and diseased/hypertrophic sinus mucosa [15] (Table 1). Failure of this process increases higher relapse rates and the need for additional surgical intervention. Recurrent AFRS was noted in a half of the patients reported. All but one patient received oral or topical corticosteroids to reduce disease activity and the need for further surgical intervention.

Systemic antifungal agents are a fundamental component in the treatment of invasive fungal sinusitis, but are not indicated for the treatment of the non-invasive sinusitis such as indolent fungus ball type [16]. The effect of systemic antifungal agents in the treatment of AFRS is controversial. A systematic review published in 2014 has revealed that systemic antifungal agents have no benefit in the treatment of AFRS caused by fungi other than *S. commune* when used with concurrent surgical intervention [17]. Another systematic review concluded that in cases of refractory AFRS, oral antifungal agents cannot be recommended because of insufficient clinical data for their benefit [18]. However, some

investigators proposed that oral itraconazole could be added to the regimen with ESS followed by corticosteroids in patients with *S. commune*-induced AFRS in whom frequent recurrences occur after debridement or when there is histological evidence of severe pressure erosion [11]. Additionally, in vitro antifungal susceptibility test against *S. commune* strains isolated from patients with respiratory disease revealed that isovuconazole, itraconazole, voriconazole, and amphotericin B showed low geometric minimum inhibitory concentrations (MICs), but fluconazole and flucytosine high MICs [19]. This study also described that 5 of the 8 patients in the study and the 8 patients reported in previous studies [see references in [19] with *S. commune*-induced ABPM receiving oral itraconazole responded favorably without recurrence during the follow-up period. Although the sample size is very small, these data suggest that itraconazole may be of benefit in patients with *S. commune*-induced ABPM. In terms of the benefit of itraconazole in patients with *S. commune*-induced AFRS, oral itraconazole, in combination with ESS and corticosteroids, showed improvement of nasal symptom in two cases [13,14] (Table 1). However, it is difficult to judge the benefit of itraconazole by itself since these cases received concurrent topical or systemic corticosteroids. In the present cases, subsequent clinical course was uneventful so that we did not use itraconazole therapy. Nonetheless, since few cases with *S. commune*-induced AFRS have been reported in the literature, accumulating data are necessary to determine which antifungal agents are useful for the treatment of these patents.

Conflict of interest

There are none.

Acknowledgments

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