Schizophyllum commune-induced allergic fungal rhinosinusitis and sinobronchial mycosis

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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 as determined by using specific IgE antibodies against S. commune, and the fungus was identified by sequence analysis.

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, viscid, and brown to green mucous with a peanut butter-like material in the maxillary sinus. Histologic examination showed the allergic

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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 rRNA (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 immunoassays (FEIA, SRL Inc. Tokyo, Japan), against Cladosporium and Trichophyton were positive (2+ or 3+) 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]. 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...
Table 1

| Reference                  | Sex/age | Type 1 hypersensitivity to S. commune | Severe asthma | Other history | Lung disease | Treatment | Recurrent AFRS |
|----------------------------|---------|--------------------------------------|---------------|--------------|-------------|-----------|----------------|
| Clark et al. [11]          | M/35    | NA                                   | No            | ND           | NA          | ESS       | Yes            |
| Taguchi et al. [12]        | F/55    | NA                                   | No            | NA           | NA          | ESS       | No             |
| Ahmed et al. [13]          | F/57    | No                                   | No            | ND           | ND          | ESS       | No             |
| Peric et al. [14]          | F/32    | No                                   | No            | Subclinical asthma | No     | ESS, Oral itraconazole, topical corticosteroids | No        |
| Won et al. [5]             | F/14    | No                                   | No            | NA           | NA          | ESS       | No             |
| T. Tsukatani et al. / Medical Mycology Case Reports 8 (2015) 10–13 | M/38    | 3+1                                  | 3+1           | ND           |             | ESS       |                |

AFRS: allergic fungal rhinosinusitis; ESS: endoscopic sinus surgery, NA: not available, ND: not done.

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* 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 polypsis. 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 ABPM 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. commute* 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 fluocytosine 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. commute*-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. commute*-induced ABPM. In terms of the benefit of itraconazole in patients with *S. commute*-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. commute*-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.

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