INTERNAL MEDICINE

□ CASE REPORT □

A Case of Sinobronchial Allergic Mycosis; Possibility of Basidiomycetous Fungi as a Causative Antigen

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Abstract

We herein report a case of sinobronchial allergic mycosis (SAM) caused by basidiomycetous (BM) fungi (probably *Phanerochaete velutina*). The patient with bronchial asthma that accompanied allergic fungal sinusitis (AFS) fulfilled all 6 criteria for diagnosing SAM. In this case, the BM fungus may act as an allergen, reacting continually in both the upper and lower respiratory tract. The antifungal drug (itraconazole 50 mg/day) seemed to achieve a partial response. Basidiomycetous fungi may attract attention because of the possibility as a causative antigen in this new clinical concept of SAM.

Key words: allergic fungal sinusitis, basidiomycetous fungi, allergic bronchopulmonary mycosis, allergic fungal cough, Sinobronchial allergic mycosis

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Introduction

Recently, allergic fungal respiratory diseases caused by basidiomycetous (BM) fungi (1), such as allergic bronchopulmonary mycosis (ABPM) (2), allergic fungal sinusitis (AFS) due to *Schizophyllum commune* (*S. commune*) (3), and allergic fungal cough (AFC) associated with *Bjerkandera adusta* (*B. adusta*) (4) have been reported.

The concomitant occurrence of allergic bronchopulmonary aspergillosis (ABPA) and allergic *Aspergillus* sinusitis (AAS) have gradually been recognized (5). It is therefore also likely that concomitant AFS and ABPM may sometimes exist in the same patient, thereby suggesting that the same process of fungal hypersensitivity occurs in the upper and lower airways. Venarske and deShazo termed this process SAM, an acronym for "sinobronchial allergic mycosis" (6). Patients with SAM have chronic sinusitis involving multiple sinuses, asthma, immediate cutaneous reactivity to fungal allergens, peripheral eosinophilia, and radiographic evidence of bronchiectasis. Total serum IgE levels are usually elevated as well. A variety of chest radiographic abnormalities may occur, ranging from mass lesions to diffuse pulmonary infiltrates and even normal findings on chest radiographs. We herein report a case of bronchial asthma that accompanied AFS probably caused by *Phanerochaete velutina* (a BM fungus), and discuss this case from the viewpoint of the diagnostic criteria of SAM.

Case Report

A 39-year-old man was admitted to our hospital in mid-November 2007 for the treatment of a productive cough, wheezing, and post nasal drip. Further questioning revealed that the patient had been diagnosed to have bronchial asthma at 37 years of age. Despite long-term therapy with topical nasal steroids, his symptoms of nasal obstruction and intermittent purulent discharge persisted for at least 7 years. Of particular note, he had suffered from expectoration of plugs and flecks for about 2 months. The patient worked at an insurance company and had no history of smoking.

A physical examination demonstrated the following: temperature, 36.5℃; blood pressure, 138/70 mmHg; heart rate, 85 beats/min; and bilateral wheezes were audible on auscul-

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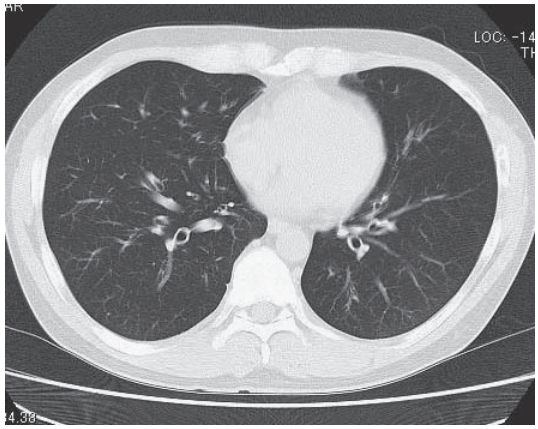

Figure 1. **A CT scan of the chest shows almost normal findings except for bilateral bronchial wall thickening of the lower lobes.**

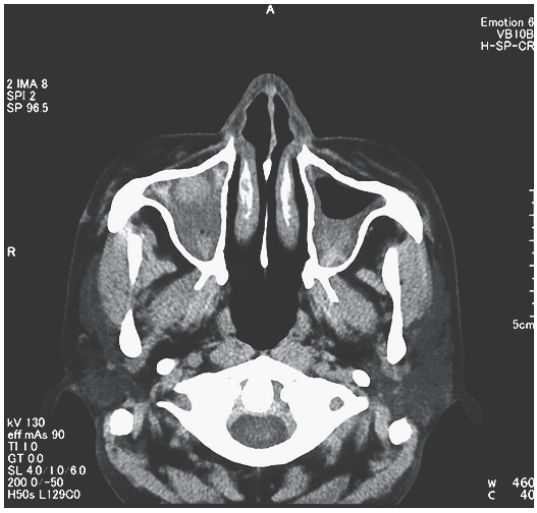

Figure 2. **A CT scan of the sinuses shows multiple soft-tissue densities causing partial obstruction of both nares and opacification of the right frontal, ethmoid, maxillary, and sphenoid sinuses, with occlusion of the osteomeatal complex.**

tation of the chest. Chest radiographs taken upon his admission showed almost normal findings. A CT scan of the chest revealed relatively normal findings except for bilateral bronchial wall thickening (Fig. 1). A CT scan of the sinuses (Fig. 2) revealed multiple soft-tissue densities causing partial obstruction of both nares and opacification of the right frontal, ethmoid, maxillary, and sphenoid sinuses, with occlusion of the osteomeatal complex.

Laboratory studies showed a white blood cell count of 8,000/μL with 28.9 percent eosinophils. No inflammatory reactions, as assessed by the C-reactive protein level and erythrocyte sedimentation rate, were observed. A radioimmunosorbent test revealed an elevated IgE level (553 U/mL), and results of a radioallergosorbent test for specific IgE antibodies against house dust, mite, *Aspergillus*, *Penicillium*, *Candida*, and *Alternaria* were all negative. The following laboratory findings were normal or negative: urinalysis, stools for ova and parasites, serum electrolytes, total protein, albumin, and bacterial and mycobacterial cultures of the sputum. A differential cell analysis of the sputum revealed marked eosinophilia (2% alveolar macrophages, 2% neutrophils, and 96% eosinophils).

Pulmonary function testing using the Collins DS system, which was performed according to the standards of the American Thoracic Society, revealed a forced vital capacity (FVC) of 5.22 L (127.9% of the predicted value), forced expiratory volume in 1 second (FEV_1) of 3.81 L (101.9% of the predicted value), and a FEV_1/FVC ratio of 72.9%.

To assess bronchial reversibility, spirometry was carried out before and 30 min after inhalation of 300 μg salbutamol sulfate. The FEV_1 values significantly increased after the bronchodilator therapy, namely from 3.33 to 3.90 L, thus indicating that his bronchomotor tone was increased. Bronchial responsiveness which was assessed as the provocative concentration of methacholine that caused a 20% decrease from the baseline FEV_1 (PC20) was 2.5 mg/mL.

The patient was then treated with dexamethasone at 12 mg/day for 4 days, 8 mg/day for 4 days, and 4 mg/day for 7 days, with aminophylline (250 mg/day) for 15 days, and erythromycin (500 mg/day) for 4 days. Since his symptoms disappeared while he was on these treatments, the patient was discharged on November 23rd. After being discharged from the hospital, the patient was maintained on 400 μg/day CFC-BDP, 450 mg/day pranlukast hydrate, and 40 μg/day clenbuterol hydrochloride for bronchial asthma, and 200 mg/day clarithromycin for sinobronchial syndrome.

In March, May, and August of 2008, the patient repeatedly experienced wheezing attacks with productive cough and post nasal drip. Because the fungal culture obtained from his sputum yielded basidiomycetous fungi, we prescribed low dose itraconazole (ITCZ; 50 mg/day) to the patient on the basis of our therapeutic experience of fungus-associated chronic cough (FACC) (7). The 3 weeks of antifungal drug therapy reduced his nasal symptoms, such as nasal obstruction and postnasal drip, and opacification of the left maxillary sinuses improved, but the right sinuses were still affected.

Functional endoscopic sinus surgery was performed in mid-October 2008 with a polypectomy, anterior and posterior ethmoidectomy, maxillary antrostomy, and frontal recess dissection. Large quantities of polypoid material were removed from the sinuses. A microscopic examination of material from the right maxillal sinus showed allergic mucin with layers of mucus, squamous epithelial cells, eosinophils, and an eosinophil-predominant mixed inflammatory cell infiltrate (Fig. 3). A culture of the material from the right maxillary sinuses grew basidiomycetous fungus on Sabouraud's dextrose agar plates.

The patient's immediate (15 min) skin reaction was 9×9/16×16 mm (positive) for the antigenic solution of *B. adusta* (1 mg/mL) (4). The serum anti-fungus antibody titers measured by the Ouchterlony method were negative. Later, using molecular biological analysis, the fungi cultured from

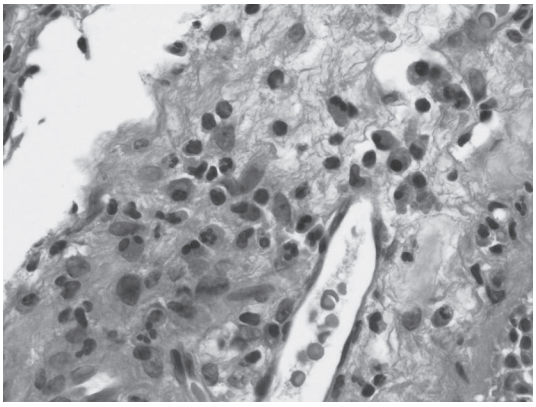

Figure 3. A microscopic examination of material from the right maxillal sinus showsallergic mucin with layers of mucus, squamous epithelial cells, eosinophils, and an eosinophil-predominant mixed inflammatory cell infiltrate.

the maxillary sinus fluid samples and expectorations were all revealed to be *Phanerochaete velutina* (a BM fungus).

Postoperatively, the patient was treated with low dose itraconazole (ITCZ) 50 mg daily for 1 month, topical nasal steroids, inhalation of CFC-BDP 400 μg/day, pranlukast hydrate 450 mg/day, and clenbuterol hydrochloride 40 μg/day. At two months after the surgery, the patient continues to do well while receiving these medications, and a CT scan of the sinuses revealed no problems.

Discussion

AFS was first reported by Miller et al (8) in 1981, and was named by Katzenstein et al (9) in 1983. The five criteria for AFS proposed by Bent and Kuhn (10) in 1994 are as follows: 1) CT findings of chronic paranasal sinusitis, 2) the presence of nasal polyps, 3) the occurrence of allergic mucin, in the absence of fungal invasion of the tissues, 4) demonstration of fungi in the paranasal sinus contents and 5) the presence of type I allergy on the basis of the past history, the results of skin tests or serological studies.

From the eighth to fourteenth day after cultivation, cultures of mucous in the maxilla sinus samples yielded white, felt-like colonies with a fluffy appearance on Sabouraud's dextrose agar plates; which were identified to be basidiomycetous fungi by specialists. Later the BM fungi obtained from the mucous samples and expectorations of this patient were identified to be *Phanerochaete velutina* (*P. velutina*) by using 28S rDNA (D1/D2) sequencing and analysis.

To estimate whether the detected unknown fungus is a probable etiologic antigen, allergological tests such as the skin reaction test or the serum anti-fungus antibody titers are helpful; however it seems to be difficult to prepare the antigenic solution for each detected fungus in an ordinary clinic.

Because it has been previously reported that when the result of the immediate subcutaneous reaction for *B. adusta* fungi was judged to be positive in a case of the longer axis of the flare beyond 10 mm at 15 minutes after the injection, the positive ratio in allergic airway diseases such as atopic cough (18.8%), cough variant asthma (26.9%), and cough predominant asthma (22.4%) are significantly higher than that in physically unimpaired persons (3.4%) (Sequentially, p=0.049, p=0.014, p=0.021) (4), in this case we decided to use the antigenic solution of *B. adusta* which is phylogenetically the same as *P. velutina* to accomplish allergological examination. On the basis of the positive result of allergological tests, all of the five criteria for AFS were satisfied

Venarske and deShazo recommended that the clinicians should routinely consider the diagnosis of SAM in patients who have either AFS or ABPM (6). In diagnosing ABPM which merged AFS, it is almost impossible to distinguish precisely the sputum samples from post nasal drip and to separate the allergological reactions that arise in the upper airways and lower airways. And it may also be difficult to make a definitive diagnosis of SAM even after the bronchoprovocation test or nasal provocation test. The new disease concept of SAM was proposed for clinical benefit and was not for the complicated nature of the diagnosis itself.

A variety of abnormalities on chest radiographs are described in SAM. Because the radiographic finding of bronchial wall thickening is often demonstrated in asthma patients, it is not specific criteria for diagnosing SAM but it is important in considering SAM. The present case fulfilled all 6 criteria for diagnosing SAM (6); chronic sinusitis involving multiple sinuses, asthma, immediate cutaneous reactivity to *B. adusta* as a substitute for the BM fungi obtained from the mucous samples and expectorations of this patient, peripheral eosinophilia, bronchial wall thickening, and elevated total serum IgE levels.

Thus, the diagnosis of SAM caused by BM fungi (highly suspected to be *P. velutina*) was made in the present case. As the direct examinations of allergological tests using *P. velutin* were not achieved, we could not demonstrate the causal relationship between the patient's SAM and this BM fungus; however the possibility that the BM fungus may be a causative antigen for SAM became clear. Investigation of the crossing-over (11) of the allergic response and the epitope of BM fungi will confirm the final diagnosis of this case.

P. velutina ("usukiirokawatake" in Japanese) is found throughout Japan, and is commonly found in dry logs, dead wood, and fallen trees. The phylum of *P. velutina* is Basidiomycota, and subclass of this fungus is Agaricomycetidae. Because the major species of BM fungi in the fields may change their profiles according to natural environmental factors such as global warming or other geographical characteristics, an epidemiological investigation of BM fungi will be necessary in the near future.

Recently, we have reported the efficacy of antifungal drugs for atopic cough induced by BM fungi (12, 13), fungus-associated chronic cough (FACC) (7), and allergic fungal cough (AFC) (4); however some controversy persists with regard to the use of antifungal therapy for chronic rhi-

nosinusitis (14). Most airborne fungal structures are spores or conidia, which are robust, hydrophobic structures, essentially devoid of allergenic proteins. The repetitive exposure to viable hyphal fragments, which contain numerous diffusible allergens, is sufficient to directly drive allergic responses on an ongoing basis, and exposure to fungal spores is irrelevant. Therefore, antifungal therapy may either reduce or even eradicate the effects of such antigen exposure (15). In the present case, the antifungal drug seems to have achieved a partial response.

The importance of *Aspergillus* (5) and *Alternaria* as causative eumycetes of AFS has been reported, but that of BM fungi has rarely been documented (3), and thus this case will add new information that BM fungi may attract attention because of the possibility as a causative antigen in this new clinical concept of SAM.

The authors state that they have no Conflict of Interest (COI).

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References

1. Helbling A, Brander KA, Horner WE, Lehrer SB. Allergy to basidiomycetes. Chem Immunol **81**: 28-47, 2002.
2. Kamei K, Unno H, Nagano K, Kuriyama T, Nishimura K, Miyaji M. Allergic bronchopulomonary mycosis caused by the basidiomycetous fungus *Schizophyllum commune*. Clin Infect Dis **18**: 305-309, 1994.
3. Ahmed MK, Ishino T, Takeno S, Hirakawa K. Bilateral allergic fungal rhinosinusitis caused by *Schizophillum commune* and *Aspergillus niger*. A case report. Rhinology **47**: 217-221, 2009.
4. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Is *Bjerkandera adusta* important to fungus-associated chronic cough (FACC) as an allergen? Eight cases' report. J Asthma **46**: 849-855, 2009.
5. Shah A, Panchal N, Agarwal AK. Concomitant allergic bronchopulmonary aspergillosis and allergic *Aspergillus sinusitis*: a review of an uncommon association. Clin Exp Allergy **31**: 1896-1905, 2001.
6. Venarske DL, deShazo RD. Sinobronchial allergic mycosis. Chest **121**: 1670-1676, 2002.
7. Ogawa H, Fujimura M, Takeuchi Y, Makimura K. Efficacy of itraconazole in the treatment of patients with chronic cough whose sputa yield basidiomycetous fungi—Fungus-associated chronic cough (FACC). J Asthma **46**: 407-411, 2009.
8. Millar JW, Johnston A, Lamb D. Allergic aspergillosis of the maxillary sinuses [abstract]. Thorax **36**: 710, 1981.
9. Katzenstein A, Sale SR, Greenberger PA. Allergic *Aspergillus sinusitis*: a newly recognized form of sinusitis. J Allergy Clin Immunol **72**: 89-93, 1983.
10. Bent JP III, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg **111**: 580-588, 1994.
11. Crameri R, Zeller S, Glaser AG, Vilhelmsson M, Rhyner C. Cross-reactivity among fungal allergens: a clinically relevant phenomenon? Mycoses **52**: 99-106, 2009.
12. Ogawa H, Fujimura M, Tofuku Y. Two cases of atopic cough successfully treated by oral cleansing with amphotericin B. *Basidiomycetes* detected from pharyngeal swab. Allergology International **53**: 193-196, 2004.
13. Ogawa H, Fujimura M, Tofuku Y. Treatment of atopic cough caused by *Basidiomycetes* antigen with low dose Itraconazol. Lung **182**: 279-284, 2004.
14. Rank MA, Adolphson CR, Kita H. Antifungal therapy for chronic rhinosinusitis: the controversy persists. Curr Opin Allergy Clin Immunol **9**: 67-72, 2009.
15. Denning DW, O'Driscoll BR, Powell G, et al. Randomized controlled trial of oral antifungal treatment for severe asthma with fungal sensitization. Am J Respir Crit Care Med **179**: 11-18, 2009.