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【 CASE REPORT 】

Allergic Bronchopulmonary Mycosis Caused by *Schizophyllum commune*: A Special Interest in Positive Culture of Other Basidiomycetes Fungi

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Abstract:
A 42-year-old man with asthma presented in 2007 with chest infiltration and productive cough. *Pycnoporus sanguineus* and *Perenniporia tephropora* were repeatedly isolated from sputum and bronchial washing fluids. Because we lacked immunologic evidence, we could not diagnose him with allergic bronchopulmonary mycosis (ABPM) due to these basidiomycetous fungi. At that time, serum-specific IgE and IgG against *Schizophyllum commune* findings were negative. Inhaled beclomethasone/salmeterol improved his condition. Seven years later, mucous plugs obtained via bronchoscopy at a relapse were compatible with allergic mucin. Because *S. commune* was isolated from mucous plugs and serum-specific IgG against *S. commune* turned positive, we diagnosed the patient with ABPM due to *S. commune*.

Key words: allergic bronchopulmonary mycosis, mucoid impaction of bronchi, *Perenniporia tephropora*, *Pycnoporus sanguineus*, *Schizophyllum commune*

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Introduction

Allergic bronchopulmonary mycosis (ABPM) is an immunologic disorder caused by a hyperimmune response to the endobronchial growth of certain fungi and occurs most commonly in atopic patients with asthma. Although there have been several reports of ABPM due to *Schizophyllum commune*, only two cases in which other fungi were isolated or also causative have been reported (1, 2).

We experienced a patient with ABPM due to *S. commune*. Seven years before the isolation of the *S. commune*, the patient had already developed radiologic and laboratory findings compatible with ABPM. *Pycnoporus sanguineus* and *Perenniporia tephropora,* which are both basidiomycetous fungi, as is *S. commune*, were repeatedly isolated from the patient's airways, but they disappeared when *S. commune* was isolated from the patient. We report this case considering the significance of these fungi.

Case Report

An asthmatic 42-year-old man presented to the Saitama Cardiovascular and Respiratory Center in Japan in August 2007 for the further evaluation of chronic cough and sputum production.

He had developed a productive cough as an initial symptom one year earlier. Several months before presentation, he expectorated brownish sputum. He was an ex-smoker (330 pack-years). A physical examination showed bilateral rhonchi and wheezes. Laboratory tests revealed a white blood cell count of 6600/μL with increased eosinophils of 670/μL. Serum immunoglobulin E (IgE) was within normal range (42 IU/mL), and specific IgE antibodies against *Aspergillus* spp., *S. commune, Cladosporium* spp., *Penicillium* spp., and *Alternaria* spp. were all negative. Serum immunoglobulin G (IgG) antibodies against *Aspergillus* spp. and *S. commune* were also negative. Pulmonary function testing (%predicted)

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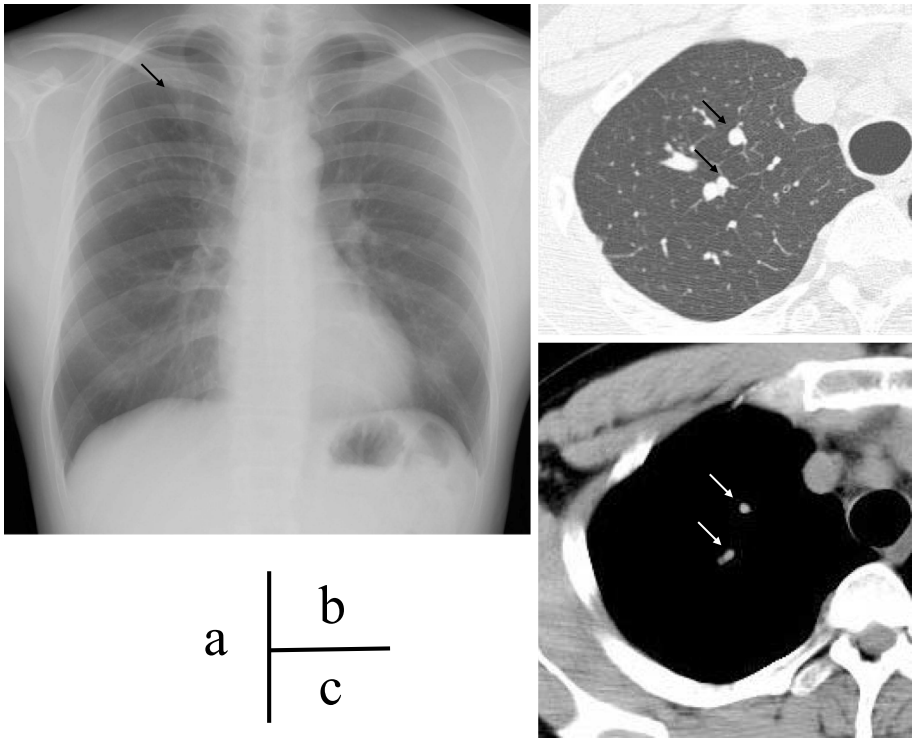

Figure 1. Chest X-ray and computed tomography images obtained at the development of allergic bronchopulmonary mycosis in 2007. Mucoid impaction was shown by chest X-ray in the right upper lung field (a) and by chest computed tomography in the right upper lobe (b, c) (arrow).

showed a vital capacity of 3.30 L (72.7%), a forced expiratory volume in 1 second (FEV_1) of 2.0 L (57.2%), and FEV_1/forced vital capacity ratio of 66.0%. An arterial blood gas analysis under ambient air showed a pH of 7.39, $PaCO_2$ of 45.4 Torr, and PaO_2 of 93.1 Torr.

Chest X-ray showed linear shadows in the right upper lung field. Computed tomography (CT) showed mucoid impaction (high-attenuation mucus) within ectatic bronchi in the right upper lobe (Fig. 1). We performed bronchoscopy but detected no mucous plugs. Bronchial washing fluids obtained from the anterior segment of the right upper lobe where mucous plugs were detected by CT showed an increased number of eosinophils and yielded *Pycnoporus sanguineus* and *Perenniporia tephropora*, which were identified by gene analyses of the D1/D2 region of the large subunit and the internal transcribed spacer region of the ribosomal RNA gene. These fungi were repeatedly isolated from sputum expectorated on separate days.

Although we suspected the patient of having bronchial asthma and ABPM due to these fungi, the diagnostic criteria (3) were not met. Specific IgE and precipitating antibodies against these fungi could not be evaluated because of technical limitations. We started beclomethasone [an inhaled corticosteroid (ICS)], and salmeterol [a long-acting β2 agonist (LABA)], which gradually improved his symptoms, and the mucoid impaction disappeared.

In November 2014, his productive cough recurred despite his continuing inhalation therapy. Peripheral blood eosinophils were increased to 1700/μL, but the serum total IgE value was 69 IU/mL. Chest X-ray showed gloved finger shadows in the left lower lung fields. CT showed central bronchiectasis in a posterior segmental bronchus of the right upper lobe and a posterior basal bronchus along with infiltration in the right posterior segment of the right upper lobe, posterior segment of the right lower lobe, superior segment of the left lingula, and the left lower lobes (Fig. 2a, b). We performed bronchoscopy again and found mucous plugs in the medial bronchus of the right middle lobe and left anteromedial bronchus of the left lower lobe (Fig. 2c). Pathologically, infiltrated eosinophils and Charcot-Leyden crystals were observed in the mucous plugs, although fungal hyphae were not observed by Grocott's staining. Bronchial aspirates and bronchial washing fluid yielded colonies with a white and fluffy appearance that were identified as *S. commune* by analyzing the rRNA gene, as described earlier. Specific IgE against *S. commune* was negative, but IgG against *S. commune* was positive, so we diagnosed the patient with ABPM due to *S. commune* (3).

The patient was treated with itraconazole (ITCZ) oral solution 200 mg daily, and his symptoms improved; however, he developed a relapse with symptoms of wheezing 3 months later while taking ITCZ. Chest infiltrates were also present, so we started prednisolone 40 mg daily, which improved his symptoms and chest infiltrates. He has since been followed on an outpatient basis and has not experienced a relapse of ABPM for four years. The serum total IgE value at his final follow-up (December 2018) was within the normal range (103 IU/mL) under treatment with daily predniso-

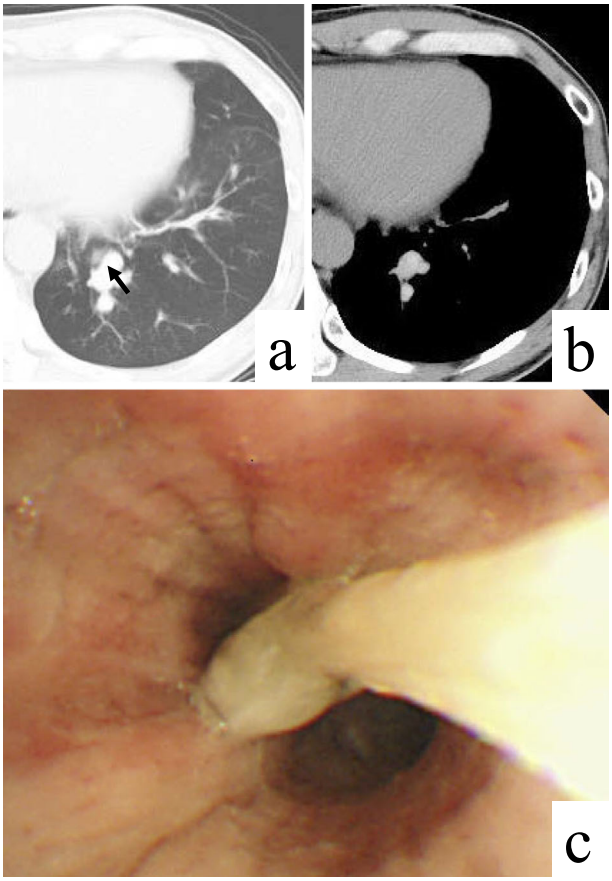

Figure 2. Chest computed tomography findings from 2014. Chest computed tomography at relapse of allergic bronchopulmonary mycosis showed mucoid impaction of the left lower lobe (a, b). Bronchoscopic findings and a mucous plug. Bronchoscopy showed mucous plugs embolized in a lower-lobe bronchus (c).

lone 2 mg and ITCZ 200 mg.

Discussion

The present patient was diagnosed with ABPM based on comprehensive diagnostic criteria (4). A previous study suggested that fungi can be regarded as causative of ABPM when two or more of the following three criteria are satisfied (4): (i) fungi are repeatedly isolated from sputum or other respiratory samples, (ii) positive for specific IgE antibody, and (iii) positive for precipitating antibody or IgG antibody. Our patient satisfied these criteria in 2014, and we were therefore able to diagnose him with ABPM due to *S. commune*. To date, 26 cases of ABPM due to *S. commune*, including our own, have been reported. All but two of these cases (5, 6) were reported from Japan. *S. commune* is the second leading cause of ABPM in Japan (7).

However, the significance of the two other fungi isolated in 2007, *Pycnoporus sanguineus* and *Perenniporia tephropora*, requires some discussion. In the present case, *S. commune* was not isolated from respiratory samples, and serum-specific antibodies against *S. commune* were negative in 2007, when the patient had already developed characteristic findings of ABPM. At that time, both fungi were repeatedly isolated from sputum and bronchial washing fluid obtained from the bronchus where mucous plugs were detected by CT in this patient. In addition, these fungi have not been isolated from other patients in our hospital since 1998, which suggests the isolation of these fungi may not be simple contamination.

S. commune, Pycnoporus sanguineus, and *Perenniporia tephropora* are basidiomycetous fungi. A case of fungal ball due to *Perenniporia tephropora* in humans has been reported (8), which indicates the ability of *Perenniporia tephropora* to colonize the lung. Basidiomycetous fungi, to which allergic reaction is not uncommon (9, 10), share some antigens among members (11). There have been no reports of ABPM due to *Pycnoporus sanguineus* and *Perenniporia tephropora*, and we were unable to measure the specific IgE and IgG antibodies against either fungus and were therefore unable to designate either as the cause of ABPM in this patient. However, it is possible that allergic reactions against these two fungi caused the development of mucous plugs similar to those developed due to *S. commune*. There have been reports of cases showing changes in causative fungi of allergic bronchopulmonary aspergillosis (ABPA) over the clinical course (12). Specific IgG antibodies against *S. commune* in the present case turned positive in 2014; thus, it may be possible that the fungi causing ABPM in our patient in 2007 were *Pycnoporus sanguineus* and *Perenniporia tephropora* initially, with the causative fungus changing to *S. commune* thereafter.

Systemic corticosteroids are the mainstay of ABPA treatment. Combination therapies of antifungal agents with corticosteroids are also listed in the guidelines because of the efficacy of antifungal agents for ABPA (13). However, a consensus concerning the treatment of ABPM due to *S. commune* and other fungi has not yet been reached. Among 26 reported cases of ABPM due to *S. commune*, 16 were treated with antifungal agents: 6 with antifungal agents alone and 10 with combination therapies of antifungal agents with systemic and/or ICSs; the efficacy of each treatment type was 4 of 6 (66.7%) and 10 of 10 (100%), respectively. Chowdhary et al. assessed the antifungal sensitivity in 30 cases of infectious disease caused by *S. commune* in an *in vitro* experiment, and both ITCZ and voriconazole were shown to have high susceptibility. Indeed, we have experienced two patients with ABPM due to *S. commune* who were successfully treated with ITCZ alone (14, 15), and we administered ITCZ to the present patient. However, our current patient required systemic steroids in addition to ITCZ. Further studies are needed to establish a treatment consensus for ABPM due to *S. commune*.

Our patient's condition improved after starting ICS therapy, and he showed no relapse for seven years (until 2014) under ICS and LABA therapy. ICS and LABA are not recognized as an effective treatment option for ABPA. As such, the efficacy of ICS for ABPM due to fungi other than *As-*

pergillus sp. also needs to be confirmed.

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

References

1. Ishiguro T, Takayanagi N, Saito A, et al. Allergic bronchopulmonary mycosis due to *Schizophyllum commune* and *Aspergillus fumigatus*. Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc) **49**: 612-618, 2011 (in Japanese, Abstract in English).
2. Itou Y, Sasaki S, Watanabe S, et al. A case of mucoid impaction of bronchi (MIB) due to *Schizophyllum commune*. Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc) **39**: 266-270, 2001 (in Japanese, Abstract in English).
3. Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Int Med **86**: 405-414, 1977.
4. Ishiguro T, Takayanagi N, Uozumi R, et al. Diagnostic criteria that can most accurately differentiate allergic bronchopulmonary mycosis from other eosinophilic lung diseases: a retrospective, single-center study. Respir Investig **54**: 264-271, 2016.
5. Shen Q, Yao YK, Yang Q, Zhou JY. *Schizophyllum commune*-induced pulmonary mycosis. Chin Med J **129**: 2141-2142, 2016.
6. Chowdhary A, Randhawa HS, Gaur SN, et al. *Schizophyllum commune* as an emerging fungal pathogen: a review and report of two cases. Mycoses **56**: 1-10, 2013.
7. Oguma T, Taniguchi M, Shimoda T, et al. Allergic bronchopulmonary aspergillosis in Japan: a nationwide survey. Allergol Int **67**: 79-84, 2018.
8. Chowdhary A, Agarwal K, Kathuria S, et al. First human case of pulmonary fungal ball due to a *Perenniporia* species (a basidiomycete). J Clin Microbiol **50**: 3786-3791, 2012.
9. Lehrer SB, Lopez M, Butcher BT, Olson J, Reed M, Salvaggio JE. Basidiomycete mycelia and spore-allergen extracts: skin test reactivity in adults with symptoms of respiratory allergy. J Allergy Clin Immunol **78** (Pt): 478-485, 1986.
10. O'Neil CE, Horner WE, Reed MA, Lopez M, Lehrer SB. Evaluation of Basidiomycete and Deuteromycete (Fungi Imperfecti) extracts for shared allergenic determinants. Clin Exp Allergy **20**: 533-538, 1990.
11. Lopez M, Salvaggio J, Butcher B. Allergenicity and immunogenicity of Basidiomycetes. J Allergy Clin Immunol **57**: 480-488, 1976.
12. Yamamoto K, Abe M, Inoue Y, Yokoyama A, Kohno N, Hiwada K. Development of infection with *Aspergillus flavus* in woman being treated for allergic bronchopulmonary aspergillosis caused by *Aspergillus fumigatus*. Nihon Kyobu Shikkan Gakkai Zasshi (Jpn J Thorac Dis) **33**: 1099-1104, 1995 (in Japanese, Abstract in English).
13. Walsh TJ, Anaissie EJ, Denning DW, et al.; Infectious Diseases Society of America. Treatment of aspergillosis; clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis **46**: 327-360, 2008.
14. Ishiguro T, Takayanagi N, Tokunaga D, et al. Pulmonary Schizophyllum commune infection developing mucoid impaction of the bronchi. Yale J Biol Med **80**: 105-111, 2007.
15. Ishiguro T, Takayanagi N, Harasaw K, et al. Mucoid impaction of the bronchi caused by Schizophyllum commune which developed after discontinuation of itraconazole administration. Nihon Kokyuki Gakkai Zasshi (J Jpn Respir Soc) **47**: 296-303, 2009 (in Japanese, Abstract in English).

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