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Case Report

Successful treatment with inhaled corticosteroid/long-acting β_2-agonist in a case of allergic bronchopulmonary mycosis caused by *Schizophyllum commune*

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ABSTRACT

Allergic bronchopulmonary mycosis (ABPM) is a chronic immune-mediated pulmonary disease, which is caused by fungal infection of the airways. *Aspergillus* species are the main causative fungi and standard treatment typically comprises systemic corticosteroid therapy with or without adjunct antifungal agents. We describe our experience with a case of ABPM caused by *Schizophyllum commune* (*S. commune*), with satisfactory response to treatment with a combination of an inhaled corticosteroid and a long-acting β 2-agonist. The patient was a 61-year-old man who was referred to our hospital with dry cough and abnormal findings on chest radiography. He had peripheral blood eosinophilia and elevated levels of total serum IgE. High-resolution CT showed multiple areas of patchy consolidation with high-attenuation mucus plugs in the right upper lobe. Bronchoscopy revealed mucus plug impaction in the bronchial lumen, and Grocott's staining of the mucus detected fungal hyphae. Bronchioalveolar lavage fluid culture yielded white woolly colonies, which was subsequently identified as *S. commune* by MALDI-TOF MS and gene sequencing. Serology was positive for *S. commune*-specific IgE and IgG. We made a definitive diagnosis of ABPM caused by *S. commune*. Symptoms and chest CT findings improved considerably with inhaled combined fluticasone furoate/vilanterol trifenatate therapy, without the use of systemic corticosteroids or antifungal agents.

1. Introduction

Allergic bronchopulmonary mycosis (ABPM) is a chronic airway disease caused by fungal infection of the airways, which induces type I and type III hypersensitivity reactions. The main causative fungi are *Aspergillus fumigatus* and other *Aspergillus* species, which are together considered causative agents of allergic bronchopulmonary aspergillosis (ABPA).

In a nationwide survey of ABPM in Japan, *Schizophyllum commune* (*S. commune*) was reported to be the most common culprit fungus apart from *Aspergillus* species [1]. ABPM caused by *S. commune* has since been reported in Japan after the first report by Kamei et al., in 1994 [2]. Identification of *S. commune* in infectious disease is difficult, and so the diagnosis is often missed. Further, there is no fully established optimal treatment modality for ABPM caused by *S. commune*. Here, we report on a case of ABPM with *S. commune*

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identified as the causative fungus, which was successfully treated with inhaled corticosteroid/long acting β2 agonist (ICS/LABA) therapy.

2. Case presentation

A 61-year-old Japanese male was referred to our hospital for evaluation of dry cough of one month duration and chest radiography abnormalities. He had a history of childhood asthma that resolved spontaneously in adolescence. He lived in a 20-year-old wooden house in an urban area and had smoked for 30 pack-years. Physical examination showed normal breath sounds. Laboratory tests revealed a white blood cell count of 7500/μL with eosinophilia of 945/μL. Serum total IgE level was elevated to 199 U/mL. Allergen-specific IgE antibodies for house dust and *Candida* species were positive, but *Aspergillus*-specific IgE and IgG antibodies were negative. Pulmonary function test results showed that both lung vital capacity and forced expiratory volume in 1 s were normal. Fractional exhaled nitric oxide level was high at 81 ppb. Chest radiography showed a central consolidation with band-like infiltrate in the right middle lung field (Fig. 1A). High-resolution CT (HRCT) of the chest demonstrated bronchiectatic cavities with mucus plugs in the S^3 segment of the right upper lobe, with consolidation (Fig. 1B). The mediastinal windows showed some plugs with a CT value of 110 Hounsfield units deemed high-attenuation mucus (HAM) (Fig. 1C) typical of ABPM. Bronchoscopy revealed endobronchial changes with erythema, luminal edema in the right B^3 (Fig. 2A), and an impacted yellowish-white mucus plug (Fig. 2B). Histopathology of the mucus plug showed numerous eosinophils (Fig. 3A); Grocott's stain revealed a few hypahe (Fig. 3B). White woolly colonies were observed on bronchoalveolar lavage fluid (BAL) culture in Sabouraud glucose agar medium (Fig. 3C). Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI-TOF MS) showed a log score of 1.96 for *S. commune*, suggesting the possibility of *S. commune* infection.

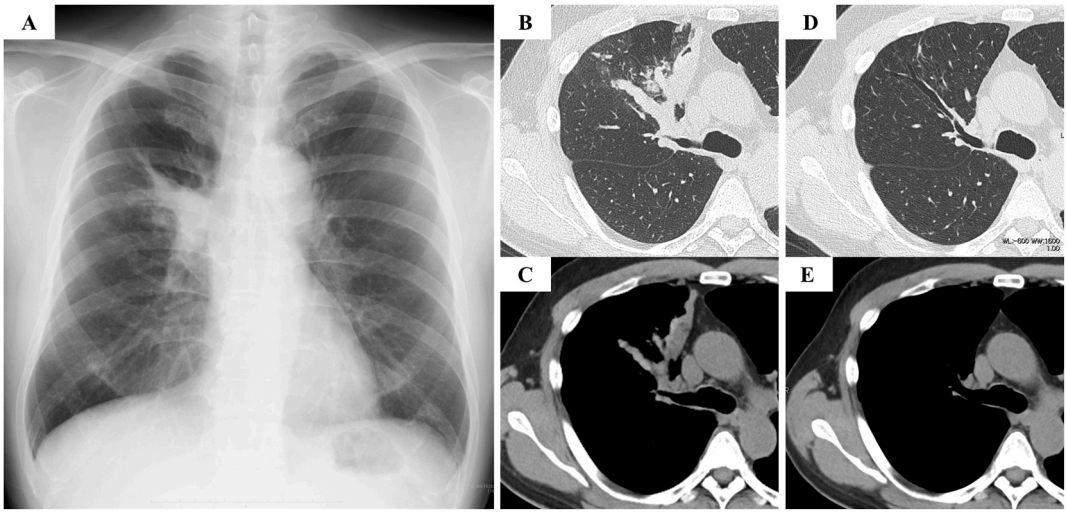

Fig. 1. Chest imaging findings. Chest X-ray showing central consolidation with band-like infiltrate in the right middle lung field (A). High-resolution CT showing mucus plugs with HAM and concomitant peripheral consolidation in the S^3 segment of the right upper lobe (B, C). Resolved mucus plug and consolidation leaving residual central bronchiectasis at eight months after ICS/LABA treatment (D, E).

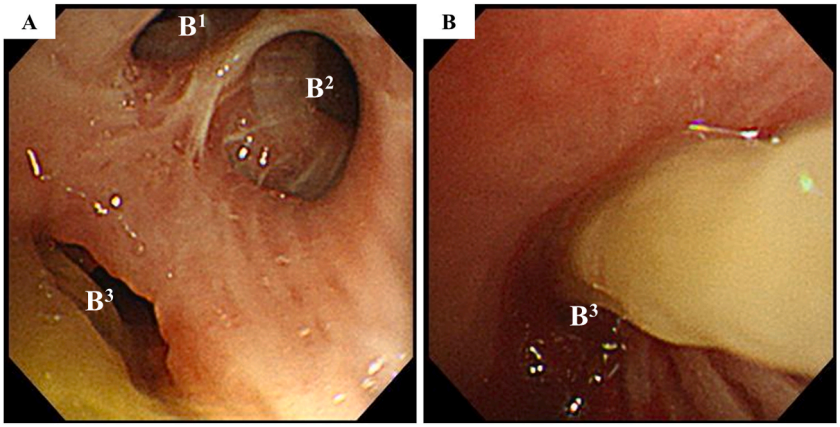

Fig. 2. Bronchoscopy findings. Right B^3 erythema with edema and obstruction by an impacted yellowish-white mucus plug (A, B).

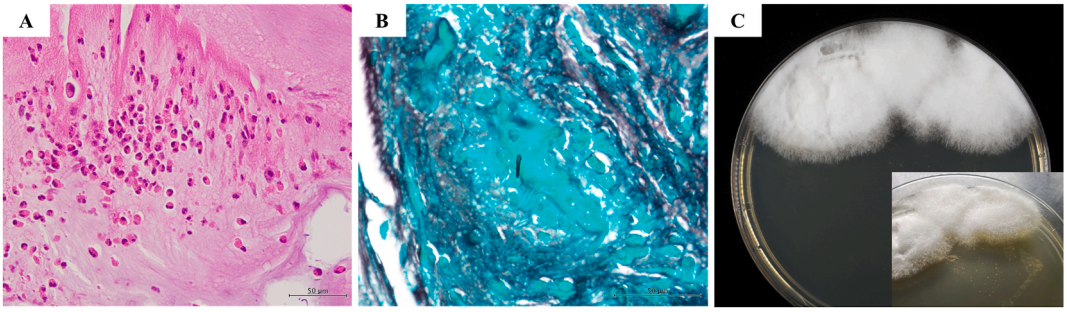

Fig. 3. Histopathological findings. Mucus plug specimen showing infiltration of eosinophils on Hematoxylin and Eosin staining (A). A few hyphae were evident on Grocott's staining (B). White woolly, non-characteristic colonies grew when cultured in Sabouraud glucose agar medium (C).

Serum *S. commune*-specific IgE and IgG were determined by enzyme-linked immunosorbent assay (ELISA) [3], which were both strongly positive. We made identification of the isolated fungus based on sequencing of 26S ribosomal DNA by performing a BLAST search in GenBank and confirmed that the isolate was *S. commune*. He was diagnosed as having ABPM due to *S. commune* based on the Japan ABPM research program clinical diagnostic criteria [4]. After bronchoscopy, the dry cough and mucous plugs on HRCT did not improve. Because of the severe dry cough and untreated bronchial asthma, we started treating him with inhaled fluticasone furoate/vilanterol trifenatate (FF/VI). The dry cough disappeared and peripheral blood eosinophil count and serum total IgE levels promptly decreased to within normal range. Three months later, the mucus plugs disappeared on HRCT, although the consolidation remained. Eight months later, the consolidation also resolved but with residual central bronchiectasis (Fig. 2D). The patient has been relapse-free on maintenance treatment with only inhalation FF/VI since then.

3. Discussion

The diagnosis of ABPM caused by *S. commune* is challenging for clinicians, and the optimal treatment remains unknown partly due to the rarity of confirmed cases. To our knowledge, 53 cases have been reported so far the majority of which are from Japan [2,5–15]. We identified *S. commune* as the causative fungus of ABPM by using mass spectrometry and gene sequencing in this case, which was successfully treated with inhaled corticosteroid/inhaled long-acting β_2-agonist (ICS/LABA) combination therapy.

Several methods have been used to identify the causative fungus in ABPM, including morphological identification, gene sequencing, and mass spectrometry. *Aspergillus* species are easily identified morphologically because they easily show the characteristic morphology in culture. Conversely, *S. commune*, which is a true basidiomycete, is difficult to identify morphologically because it forms white, featureless colonies in culture and rarely forms its characteristic fruiting bodies. Gene sequencing is the most reliable method of identification, but is not practical as a routine examination. Identification using mass spectrometry has recently been put to practical use with the widespread availability of mass spectrometers. However, there is currently no established methodology and database for filamentous fungi. In this case, white colonies were formed in culture, and no fruiting bodies were observed. Mass spectrometry results gave a high index of suspicion for *S. commune*. Hence, we performed gene sequencing and identified the causative agent as *S. commune*. Both mass spectrometry and gene sequencing are useful in identifying fungi for which morphological identification is difficult or indeterminate.

The standard treatment for ABPA is oral corticosteroids (OCS) [16]. Short-term antifungals such as azoles are also recommended as ancillary treatment [17]. According to Agarwal et al., ICS alone has no role in the management of ABPA and should be used only for additional control of asthma in patients receiving OCS for ABPA [18].

Nevertheless, there is no concrete evidence for the use of OCS or antifungal therapy in non-aspergillus ABPM. Most reported cases of ABPM with *S. commune* demonstrated the efficacy of OCS or antifungal treatment [2,6–10,12,13,15]. In one case, ABPM due to *S. commune* could not be controlled by ICS alone [13]. Further study is thus needed to clarify the effectiveness of ICS for ABPM with *S. commune*. In addition, three cases of successful treatment with removal of mucus plugs by bronchoscopy with or without ICS have been reported [19–21]. In our case, the mucus plug could not be completely removed by bronchoscopy. However, partial removal of the mucus plug by bronchoscopy may have ultimately facilitated drainage of the airway.

4. Conclusion

- We have presented a case of ABPM with *S. commune* identified as the causative fungus, which was successfully treated by using ICS/LABA therapy and not the standard systemic corticosteroids or antifungals.
- This treatment modality facilitates an OCS-sparing effect and prevents potential unwanted side effects of OCS. Thus, ICS/LABA could be a viable therapeutic option for untreated patients with ABPM caused by *S. commune* who have coexisting asthma.

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Declaration of competing interest

The authors have no conflict of interest to declare.

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