Clinical Characteristics of Biopsy-proven Allergic Bronchopulmonary Mycosis: Variety in Causative Fungi and Laboratory Findings

Takashi Ishiguro¹, Noboru Takayanagi¹, Naho Kagiyama¹, Yoshihiko Shimizu², Tsutomu Yanagisawa¹ and Yutaka Sugita¹

Abstract

Objective  The diagnosis of allergic bronchopulmonary mycosis (ABPM) has traditionally relied widely on Rosenberg’s criteria, which emphasize immunologic responses while overlooking the investigation of mucous plugs as a primary criterion. Therefore, the characteristics of biopsy-proven ABPM require further elucidation. The aim of this study was to analyze the clinical characteristics of biopsy-proven ABPM and address whether full compliance with clinical criteria, such as the presence of asthma, and certain laboratory findings is necessary to establish a diagnosis of ABPM.

Methods  We retrospectively analyzed 17 patients with biopsy-proven ABPM focusing on causative fungi and laboratory findings.

Results  Causative fungi included *Aspergillus* sp. in seven patients, *Schizophyllum commune* in four patients, *Penicillium* sp. in two patients and unknown in five patients. Bronchial asthma was observed in 10 patients, eosinophilia was observed in 10 patients and an increased serum immunoglobulin (Ig) E level was observed in 14 of the 17 patients. IgG for *Aspergillus* sp. was positive in six of the seven patients with ABPM due to *Aspergillus* and turned positive in the remaining patient during follow-up. Technological limitations prevented the measurement of specific IgE for *S. commune* and IgG for *S. commune* and *Penicillium* sp. in most patients. Computed tomography revealed central bronchiectasis, pulmonary infiltration and mucous plugs in all patients.

Conclusion  Causative fungi other than *Aspergillus* sp. are not uncommon, and immunological tests for other fungi should be popularized. Asthma and characteristic laboratory findings, such as peripheral blood eosinophilia, increased serum IgE and precipitating antibodies, may not always be required to diagnose ABPM. The importance of typical pathologic findings of mucous plugs for diagnosing ABPM requires re-evaluation. Further studies are needed to establish more elaborate diagnostic criteria for ABPM.

Key words: allergic bronchopulmonary mycosis, *Schizophyllum commune*, Aspergillosis, biopsy

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Introduction

Allergic bronchopulmonary mycosis (ABPM) is an immunologic disorder caused by a hyperimmunologic response to the endobronchial growth of certain fungi. ABPM caused by *Aspergillus* sp. (ABPA) was first reported in 1952 by Hinson et al. (1) who described three patients, two with severe asthma and one with wheezing, presenting with recurrent fever, pulmonary infiltrates, peripheral blood eosinophilia and sputum containing *Aspergillus fumigatus*. In 1975, Katzenstein reported four characteristic findings of ABPA: eosinophilic pneumonia, mucoid impaction of the bronchi (MIB) containing numerous eosinophils and fungus hyphae, micro-

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granulomatous lesions and bronchocentric granulomatosis (2). Clinical diagnostic criteria for ABPA (Rosenberg’s criteria) that emphasize immunologic responses, including tests for precipitating antibodies, skin tests and assays for serum-specific immunoglobulin E (IgE), were proposed in 1977 (3) and remain well accepted to date. Other guidelines and diagnostic criteria have since been proposed, and the presence of asthma and/or cystic fibrosis is now required as a predisposing condition (4). A. fumigatus is regarded to be the most common causative organism; however, other species of Aspergillus (5) as well as other fungi can cause a similar syndrome, prompting a change in the terminology of ABPM.

To date, we have experienced several patients with biopsy-proven ABPM caused by non-Aspergillus fungi (6, 7) who did not satisfy the clinical criteria (3) due to the absence of asthma, eosinophilia or an increased serum IgE level and/or the technical limitations of immunological investigations. The objectives of this study were to analyze causative fungi and clinical characteristics in cases of biopsy-proven ABPM and examine the need to fully meet clinical criteria, such as the presence of asthma and certain laboratory findings, when diagnosing ABPM.

**Materials and Methods**

We conducted a retrospective study to analyze patients with biopsy-proven ABPM who were admitted to our institution between April 1992 and April 2013. Biopsy-proven ABPM was defined as the presence of MIB or bronchocentric granulomatosis with eosinophil infiltration into the tissue with the recognition of fungal hyphae in the mucous plug (2). Fungi were considered causative when isolated from mucous plugs or bronchial washings or from sputum culture only and found to be positive for immunoglobulin G (IgG) (precipitating antibodies) and IgE. IgG antibodies were measured using complement fixation test in most cases. Specific IgE for Aspergillus was measured using a radioallergosorbent assay and that for Schizophyllum commune was measured according to the Phadia CAP system (Phadia Ltd., Uppsala, Sweden) (8). The study protocol was approved by the Ethics Committee of Saitama Cardiovascular and Respiratory Center (No. 2013019).

**Results**

This study comprised 41 patients who physicians diagnosed as having ABPM based on clinical and radiologic findings. All subjects underwent bronchoscopy, 15 of whom were found to have biopsy-proven ABPM. The pathological specimens in the other two patients were obtained via lobectomy. The characteristics of these 17 patients [seven men, 10 women; median age, 60 (range, 24-76) years] at the time of ABPM diagnosis are listed in Table 1.

Ten patients had experienced periodic paroxysms of dyspnea interspersed with intervals of complete or nearly complete remission and/or airflow limitations on pulmonary function testing, suggesting bronchial asthma. One patient (Case 10) did not have asthma at the time of diagnosis, although this patient later developed the condition 12 years af-

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**Table 1. Characteristics of 17 Patients with Biopsy-proven Allergic Bronchopulmonary Mycosis**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/Sex</th>
<th>Fungi</th>
<th>Smoking history</th>
<th>Asthma</th>
<th>Treatment of asthma</th>
<th>Eo/mm³</th>
<th>Serum IgE</th>
<th>Specific IgE for Aspergillus sp.</th>
<th>IgE for isolated fungi other than Aspergillus sp.</th>
<th>IgG for Aspergillus sp.</th>
<th>IgG for isolated fungi other than Aspergillus sp.</th>
<th>Skin prick test for Aspergillus sp.</th>
<th>C. B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 60/F</td>
<td></td>
<td>A. fumigatus</td>
<td>Yes</td>
<td>Yes</td>
<td>FP/SM</td>
<td>2,400</td>
<td>1,956</td>
<td>+</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>2. 34/M</td>
<td></td>
<td>A. fumigatus</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>700</td>
<td>268</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3. 53/M</td>
<td></td>
<td>A. fumigatus</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>3,000</td>
<td>2,278</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4. 64/F</td>
<td></td>
<td>A. niger</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>400</td>
<td>671</td>
<td>+</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>5. 64/F</td>
<td></td>
<td>A. flavus</td>
<td>No</td>
<td>No</td>
<td>-</td>
<td>1,500</td>
<td>13,372</td>
<td>+</td>
<td>-→+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>6. 62/M</td>
<td></td>
<td>Aspergillus sp.</td>
<td>Yes</td>
<td>Yes</td>
<td>BDP-HFA</td>
<td>3,100</td>
<td>7,505</td>
<td>+</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>7. 53/M</td>
<td></td>
<td>A. fumigatus,</td>
<td>Yes</td>
<td>Yes</td>
<td>BUD</td>
<td>319</td>
<td>5,428</td>
<td>+</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>8. 62/F</td>
<td></td>
<td>S. commune</td>
<td>No</td>
<td>-</td>
<td>300</td>
<td>1,363</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N.E.</td>
<td>-</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>9. 75/F</td>
<td></td>
<td>S. commune</td>
<td>No</td>
<td>-</td>
<td>300</td>
<td>3,376</td>
<td>+</td>
<td>N.E.</td>
<td>-</td>
<td>N.E.</td>
<td>-</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>10. 56/F</td>
<td></td>
<td>S. commune</td>
<td>No</td>
<td>-</td>
<td>500</td>
<td>52</td>
<td>-</td>
<td>N.E.</td>
<td>-</td>
<td>N.E.</td>
<td>-</td>
<td>N.E.</td>
<td>+</td>
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<tr>
<td>11. 45/F</td>
<td></td>
<td>Penicillium sp.</td>
<td>Yes</td>
<td>No</td>
<td>-</td>
<td>300</td>
<td>3,755</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N.E.</td>
<td>N.E.</td>
<td>+</td>
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<tr>
<td>12. 57/F</td>
<td></td>
<td>Penicillium sp.</td>
<td>No</td>
<td>Yes</td>
<td>FP</td>
<td>1,200</td>
<td>7,282</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N.E.</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>13. 76/F</td>
<td></td>
<td>Unknown</td>
<td>No</td>
<td>-</td>
<td>2,300</td>
<td>1,450</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14. 71/M</td>
<td></td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>1,140</td>
<td>22,030</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15. 25/F</td>
<td></td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>900</td>
<td>1,983</td>
<td>+</td>
<td>-</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
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<tr>
<td>16. 24/M</td>
<td></td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>400</td>
<td>3,925</td>
<td>+</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>+</td>
</tr>
<tr>
<td>17. 62/F</td>
<td></td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
<td>PSL+FP</td>
<td>386.4</td>
<td>2,329</td>
<td>+</td>
<td>-</td>
<td>N.E.</td>
<td>+</td>
<td>N.E.</td>
<td>-</td>
</tr>
</tbody>
</table>

Eo: eosinophils, C. B.: central bronchectasis, A.: Aspergillus, S.: Schizophyllum, FP: fluticasone propionate, SM: salmeterol, BDP-HFA: beclomethasone-dipropionate, BUD: budesonide, PSL: prednisolone, N.E.: not evaluated (patient did not received the test), -: patient received the test but the result was negative.
ter the diagnosis of biopsy-proven ABPM. The treatments for bronchial asthma in the 10 patients diagnosed with ABPA included systemic corticosteroid administration in one patient (prednisolone, 20 mg daily), corticosteroid inhalation in five patients and short-acting β-stimulants for attacks only in five patients.

The causative fungi included Aspergillus sp. in seven cases, S. commune in four cases, Penicillium sp. in two cases and unknown in five cases. Four of these cases have been previously reported (6, 7, 9, 10). Two patients yielded A. fumigatus (9) and A. niger (10) from the sputum only; serum precipitating antibodies and specific IgE for each fungus were positive in these patients, and each fungus was regarded as causative. Significant fungi were not isolated in the other patients.

In accordance with Rosenberg’s criteria (3), bronchial asthma was detected in 10 patients, eosinophilia (≥1,000/mm³) was detected in 10 patients and an elevated serum IgE level (≥1,000 kU/L) was detected in 14 of the 17 patients. Among the seven patients with ABPA, specific IgE for Aspergillus was positive in all seven patients. IgG antibodies for Aspergillus were positive in six of the seven patients at the time of diagnosis of ABPM, while IgG antibodies turned positive later in the remaining one patient (Case 5). Serum-specific IgE was positive in two patients in whom Penicillium sp. was isolated, while that for S. commune was measured and found to be positive in one of the four patients in whom S. commune was isolated. Serum IgG (precipitating antibodies) was not measured in most patients whose causative fungi were other than Aspergillus. Central bronchiectasis, pulmonary infiltration and mucous plugs were found in all patients on computed tomography (Figure).

Discussion

We analyzed patients with biopsy-proven ABPM and found a variety of causative fungi and laboratory findings. The major causative agents of ABPM and MIB were A. fumigatus and other Aspergillus sp., whereas causative fungi other than Aspergillus sp. were present in six of 12 patients in whom causative fungi were identified. The causative fungi in these six patients included S. commune and Penicillium sp. Chowdhary et al. (11) reviewed 143 reported global cases of ABPM caused by fungi other than Aspergillus and found a variety of causative fungi: Candida albicans in 60% of cases, Bipolaris sp. in 13% of cases, S. commune in 11% of cases, Curvularia sp. in 8% of cases, Pseudallescheria boydii sp. in 3% of cases and other species in 5% of cases. They also found that the most reported fungus other than Aspergillus from Japan was S. commune, which is compatible with our findings.

S. commune is a basidiomycetes fungus found throughout Japan. ABPM caused by S. commune was first reported in 1993 (12), and to our knowledge, 21 cases of ABPM due to S. commune have been reported (6, 7, 10, 12-25) (Table 2). Some patients without bronchial asthma have been reported to have MIB, although they could also be diagnosed as having ABPM based on the reported pathological findings. All but one (13) of the patients with ABPM/MIB caused by S. commune were Japanese, including three patients from our institution (6, 7, 10). We do not know whether these results are due to geographic divergence in causative fungi; however, we speculate that other reasons underlying this finding may be that the pathogenic significance of S. commune is not well understood in other countries and that isolating and identifying the pathogen is difficult (26). This fungus appears in a clavate form in smears and is difficult to discriminate morphologically from filamentous fungi; S. commune has been morphologically misidentified as Aspergillus in previous reports (12, 15, 27). Because cross-reaction between S. commune and A. fumigatus is contradictory to the findings of our previous report (5), the presence of S. commune should be investigated, at least in cases of ABPM/MIB in Japan in which antibodies for Aspergillus sp. are negative or Aspergillus sp. is not detected in the sputum or specimens obtained from the patient’s airway.

Current clinical criteria (3) define mucous plugs as secondary lesions due to the low frequency of expectoration of mucous plugs; however, this concept is contradictory to the pathogenesis of ABPM. Both recent studies and the present study have reported mucous plugs at a high frequency radiologically (28-30). In the past, Katzenstein (2) and Jelihovsky (31) emphasized the importance of mucous plugs in

**Figure.** Computed tomography in patients with allergic bronchopulmonary mycosis. Computed tomography in the patients from reference (10) showed central bronchiectasis in the right upper lobe (a) (arrowheads) and hyperattenuated mucoid impaction in the right lower lobe (b, c) (arrows).
the diagnosis of ABPM. A previous study analyzing resected lung specimens (32) in five patients with biopsy-proven ABPM concluded that peripheral lung lesions and/or bronchiectasis occur secondarily to the formation of mucous plugs and that considering the pathogenesis of ABPM, mucous plugs themselves are the primary lesions of ABPM. Our report includes patients who did not expectorate mucous plugs but in whom mucous plugs were suspected based on chest imaging findings and proven via bronchoscopy, which may be used to establish a diagnosis of ABPM before results of characteristic immunologic findings are obtained. Therefore, the importance of mucous plugs for diagnosing ABPM should be reconsidered. Our study indicates that, with an aggressive investigation of mucous plugs, some patients can be diagnosed as having ABPM before serum immunological tests turn positive (33). However, typical pathologic findings were detected in 17 of the 41 patients in the present study, which indicates that the use of other investigational methods is required.

The clinical criteria (3) regard immunological tests as critical, defining them as a primary criterion. A previous study concluded that the detection of a normal serum IgE level excludes a diagnosis of ABPA (34); however, two patients had normal serum IgE levels in our study. One of our patients with ABPA was initially negative IgG for *Aspergillus* and subsequently turned positive during follow-up. Agarwal et al. (34) reported that serum precipitins for *Aspergillus* are positive in 86.5% of ABPA cases. These findings suggest that the serum immunological response varies, and that the detection of a positive titer of IgG for *Aspergillus* is not essential for making a diagnosis of ABPA. Previous reports (6, 7, 10, 12-25) of patients with ABPM caused by *S. commune* documented eosinophilia (≥1,000/mm³) in 11 patients and elevated serum IgE levels (≥1,000 kU/L) in 14 of 21 patients, suggesting that the results of laboratory tests in patients with ABPM caused by *S. commune* also vary (Table 2). In addition, these findings suggest that the presence of characteristic laboratory findings, such as peripheral blood eosinophilia, an increased serum IgE level and precipitating antibodies, is not always required to diagnose ABPM. In addition, specific immunological tests for causative fungi other than *Aspergillus* have not been popularized and cannot be performed practically due to technological limitations. For example, in patients with ABPM caused by *S. commune*, specific IgG (precipitating antibodies) and specific IgE were tested in only 15 and four of 21 patients, respectively (6, 7, 10, 12-25). These tests may suggest causative fungi or serve to confirm isolated fungi as causative; therefore, a method for detecting fungi that are known to frequently cause ABPM should be prepared.

Bronchial asthma is also considered to be an essential diagnostic criterion (3, 4, 35). However, Glancy et al. (36) reported 11 patients without bronchial asthma in whom some patients were in a pre-asthmatic state and ultimately developed bronchial asthma. Seven patients in the present study did not have bronchial asthma when ABPM was diagnosed based on histological findings, and one patient developed bronchial asthma at a later date. Therefore, some patients with biopsy-proven ABPM may not be diagnosed as having ABPM if bronchial asthma is considered essential for the diagnosis of ABPM. From this point of view, bronchial asthma should not necessarily be considered an essential factor for diagnosing ABPM.

The present study has several limitations. First, it was not possible to perform a complete diagnostic workup in every patient. Second, the number of patients was small. Third, we did not evaluate whether ABPA and ABPM differed with respect to clinical findings, including immunologic test results and the frequency of asthma. Table 2 suggests that ABPM caused by *S. commune* differs from typical ABPA in the frequency of an increased serum IgE level and bronchial asthma (34); however, these results cannot be directly compared due to the differences in patient populations between ours and previous studies (6, 7, 10, 12-25). Finally, we did not describe the treatment of ABPM. The management of ABPM includes systemic glucocorticoids and antifungal agents to control asthma and prevent irreversible damage (37). Therefore, we speculate that ABPM patients without bronchial asthma require treatment. Future stratified studies conducted over the long term are needed to clarify these issues.

In conclusion, ABPM presents with a variety of characteristics. Causative fungi other than *Aspergillus* sp. are not uncommon, and immunological tests for other causative fungi should be popularized. This study also suggests that patients with ABPM without evident asthma or characteristic laboratory findings, such as peripheral blood eosinophilia, an increased serum IgE level or precipitating antibodies, truly exist, and these criteria do not necessarily need to be fully met in order to diagnose the disease. Furthermore, the importance of typical pathologic findings of mucous plugs for diagnosing ABPM should be reevaluated. Further studies are needed to establish more elaborate diagnostic criteria for ABPM.

### Table 2. Characteristics of Reported Cases of ABPM/MIB Caused by *Schizophyllum commune*(n=21)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number/tested or mean ± SD</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>57 ± 14.8</td>
<td>9.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>2/21</td>
<td>52.4</td>
</tr>
<tr>
<td>Blood eosinophilia</td>
<td>(≥1,000/mm³)</td>
<td>14/21 66.7</td>
</tr>
<tr>
<td>Increased serum IgE</td>
<td>(≥1,000 kU/L)</td>
<td>11/21 52.4</td>
</tr>
<tr>
<td>Asthma</td>
<td>4/4</td>
<td>100</td>
</tr>
<tr>
<td><em>S. commune</em> IgE antibody</td>
<td>14/15</td>
<td>93.3</td>
</tr>
</tbody>
</table>


Cases cited in the previous literature [6, 7, 10, 12-25]

IgG antibody measured by ELISA method or precipitating antibodies

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

References