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The Clinical Characteristics of Allergic Bronchopulmonary Mycosis Differ Among Pathogenic Fungi

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ABSTRACT

Background Allergic bronchopulmonary mycosis (ABPM) occurs with fungi, other than *Aspergillus fumigatus*. However, the clinical characteristics of ABPM caused by non-*Aspergillus* species are unspecified.

Methods We retrospectively reviewed all patients with ABPM who visited to our hospital between April 2005 and December 2020. The causative fungi and clinical characteristics were analyzed. Patients were divided into the *Aspergillus* group and the non-*Aspergillus* group.

Results Fourteen patients and five patients were included in the *Aspergillus* group and the non-*Aspergillus* group, respectively. Compared to the *Aspergillus* group, the non-*Aspergillus* group had a significantly low serum immunoglobulin E level and low forced vital capacity. In addition, the non-*Aspergillus* group had a lower rate of the requirement for oral corticosteroid treatment and a low frequency of recurrence.

Conclusion Patients with non-*Aspergillus* ABPM had lower type 2 inflammation than did patients with allergic bronchopulmonary aspergillosis.

Key words allergic bronchopulmonary aspergillosis; allergic bronchopulmonary mycosis; characteristics; fungus; recurrence

Allergic bronchopulmonary mycosis (ABPM) is an immunological disease induced by type I and III hypersensitivity reactions to fungi that colonize in the lower airways. In 1952, Hinson et al. first reported this disease and described the clinical characteristics of asthma, peripheral blood eosinophils, pulmonary infiltration, bronchiectasis, mucus plug, and sputum containing *Aspergillus fumigatus*.[1] The clinical characteristics of this disease are increased peripheral blood eosinophils, increased levels of serum immunoglobulin E, pulmonary infiltration, mucus plug, and bronchiectasis.[2, 3] The most common etiologic fungus is *Aspergillus fumigatus*, although other fungi such as *Schizophyllum commune* and species of *Bipolaris*, *Curvularia*, and *Penicillium* have been implicated in ABPM.[4]

In 1977, the clinical diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) were first proposed.[5] Greenberger and Patterson, added serum antibody in this criteria,[6] and the International Society for Human and Animal Mycology (ISHAM) proposed new diagnostic criteria in 2013.[3] However, these diagnostic criteria were not intended for ABPM caused by non-*Aspergillus* species. In 2021, Asano et al. proposed new diagnostic criteria for ABPM.[7] These criteria are the first to be applied to ABPM caused by non-*Aspergillus* fungi. To date, the clinical characteristics of ABPM caused by non-*Aspergillus* species have not been described. Chowdhary et al. described only 32% of patients as having complicated asthma for non-*Aspergillus* ABPM.[4] Asthma is an allergic disease characterized as a type 2 immunological response. Therefore, non-*Aspergillus* ABPM might be considered a lower immunological response than ABPA. In addition to that, antifungal susceptibility differs among fungal species. It is necessary to identify fungal species for antifungal therapy. Thus, the aim of this study was to analyze the clinical characteristics of ABPM that is induced by fungi other than *Aspergillus* spp. and to compare its clinical characteristics with those of ABPA.

SUBJECTS AND METHODS

Patients

We conducted a retrospective review of the medical records of all patients who visited to our hospital because of ABPM during a 15-year period from April 1, 2005 to December 31, 2020. In this study, we included patients with ABPM who had probable ABPM or definite ABPM, based on the new diagnostic criteria for ABPM recommended by the Japan ABPM Research Program. The causative fungi were identified and isolated from mucus plugs or specimens obtained by bronchoscopy

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Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; CT, computed tomography; FVC, forced vital capacity; HAM, high-attenuation mucus; IgE, immunoglobulin E; ISHAM, International Society for Human and Animal Mycology; OCS, oral corticosteroid

Table 1. Clinical characteristics of patients with non-Aspergillus ABPM

Patient	1	2	3	4	5
Age, y	84	46	47	75	63
Sex	Female	Male	Male	Female	Female
Fungi	*Penicillium* sp.	*Fulvifomes inermis*	Unknown	Filamentous fungus	Unknown
Asthma	+	+	+	+	+
Eosinophil count, /μL	92	1088	616	2522	638
Serum IgE levels, IU/mL	101	1266	411	106	99
Specific IgE for Aspergillus	-	+	-	+	-
Specific IgG for Aspergillus	-	NE	-	-	-
Specific IgE for isolated fungi	+	NE	NE	NE	NE
Specific IgG for isolated fungi	NE	NE	NE	NE	NE
Skin prick test for isolated fungi	NE	NE	NE	NE	NE
Central Bronchiectasis	+	-	-	+	-
Mucoid Impaction	+	+	+	+	+
High attenuation mucus	-	-	+	+	+
Infiltration	+	-	+	+	+

IgE, immunoglobulin E; IgG, immunoglobulin G; NE, not evaluated (patient did not received the test); y, year(s).

or sputum culture. We performed bronchoscopy when ABPM was suspected by imaging findings and informed consent for bronchoscopy was obtained from the patients. If the culture results were negative, the causative fungi were identified by a positive reaction for immunoglobulin G (IgG) (i.e., precipitating antibodies) and immunoglobulin E (IgE). Total IgE and fungus specific IgE were measured by fluorescence enzyme immunoassay. *Aspergillus fumigatus* (*A. fumigatus)*-specific IgG antibodies were measured instead of serum precipitated antibody to *Aspergillus* antigen. Recurrence was defined as a positive result for two of the following three criteria: (1) symptoms worsened, (2) radiographic findings worsened, and (3) a 50% increase in the serum IgE levels or the clinical condition worsened and required a change in therapy. We divided ABPM patients into two groups: the *Aspergillus* group and the non-*Aspergillus* group. We compared the clinical characteristics of both groups.

This observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by the ethical review board of the Tottori University Hospital (Tottori, Japan; registration number, 20A132). The need to obtain written informed consent was waived due to the retrospective nature of the analysis.

Statistical analysis

Descriptive statistics included the mean (SD), as appropriate, for continuous variables and the frequency (percentage) for categorical variables. Parameters were analyzed by using Fisher's exact test for comparing categorical variables. To compare continuous variables between the *Aspergillus* group and the non-*Aspergillus* group, the Mann–Whitney *U* test was used for parameters with a non-normal distribution. All *P* values were two-tailed. A value of $P < 0.05$ was statistically significant. SPSS software version 24 (SPSS Japan, Tokyo, Japan) was used for analyzing the data.

RESULTS

Clinical characteristics

Nineteen patients with a diagnosis of ABPM were analyzed in this study. Fourteen patients were placed into the *Aspergillus* group, and five patients were placed into the non-*Aspergillus* group. In non-*Aspergillus* group, isolated fungi are shown in Table 1. Significant fungi were not isolated in two cases. These cases had typical clinical picture of ABPM and high attenuation mucus (HAM) in the thoracic computed tomography (CT) which is a specific CT finding of ABPM. The demographic data and clinical features of all 19 patients are shown in Table 2. The mean age at the onset of ABPM was 59 years. Seventeen (89.5%) patients had been diagnosed with asthma by a physician before the diagnosis of ABPM. Six (31.6%) patients had complications with allergic rhinitis and 1 (5.3%) patient had complications with atopic dermatitis. The mean total serum

Table 2. Differences in clinical characteristics according to causative fungi

Characteristics	Total	Aspergillus	non-Aspergillus	*P* value
n	19	14 (73.7%)	5 (26.3%)	
Age, y	59 ± 13	57 ± 11	63 ± 17	0.622
Female	11 (57.9%)	8 (57.1%)	3 (60%)	0.664
Asthma	17 (89.5%)	12 (85.7%)	5 (100%)	0.532
Allergic rhinitis	6 (31.6%)	4 (28.6%)	2 (40%)	0.520
Atopic dermatitis	1 (5.3%)	1 (7.1%)	0 (0%)	0.737
current or ex smoker	6 (31.6%)	6 (42.9%)	0 (0%)	0.111
Duration of follow up, day	1558 ± 1516	1753 ± 1676	1014 ± 845	0.444
Laboratory data				
Serum IgE levels, IU/mL	3135 ± 4358	4113 ± 4722	397 ± 504	0.010*
Eosinophil count, /μL	1699 ± 1445	1952 ± 1538	991 ± 926	0.156
IgG for *A. fumigatus*	9 (47.4%)	9 (64.3%)	0 (0%)	0.029*
IgE for *A. fumigatus*	15 (78.9%)	13 (92.9%)	2 (40%)	0.037*
Thoracic CT findings				
Infiltration	17 (89.5%)	13 (92.9%)	4 (80%)	0.468
Mucoid impaction	18 (94.7%)	13 (92.9%)	5 (100%)	0.737
Central bronchiectasis	8 (42.1%)	6 (42.9%)	2 (40%)	0.664
High attenuation mucus	11 (57.9%)	8 (57.1%)	3 (60%)	0.664
Lung function				
FVC % predicted	94.6 ± 12.4	98.4 ± 10.7	84.7 ± 11.6	0.046*
FEV_1 % predicted	81.8 ± 17.0	82.6 ± 19.6	79.9 ± 8.9	0.849
FEV_1/FVC ratio	70.5 ± 14.3	69.5 ± 15.2	73.3 ± 12.7	0.849
Therapy				
Inhaled corticosteroid	17 (89.5%)	13 (92.9%)	4 (80%)	0.468
Oral corticosteroid	12 (63.2%)	11 (78.6%)	1 (20%)	0.038*
Anti-fungal drugs	11 (57.9%)	10 (71.4%)	1 (20%)	0.071
Biological agents	1 (5.3%)	1 (7.1%)	0 (0%)	0.737
Frequency of recurrence	0.4 ± 0.5	1.0 ± 1.1	0.0 ± 0.0	0.070

CT, computed tomography; FEV_1, forced expiratory volume 1; FVC, forced vital capacity; IgE, immunoglobulin E; y, year(s). The data are presented as the mean ± SD or as the number (%). The *P* values were determined by using Fisher's exact test for categorical variables and the Mann–Whitney *U* test for continuous variables. *$P < 0.05$.

IgE level was 3135 IU/mL, and the mean peripheral blood eosinophil count was 1699 cells/μL. The thoracic CT findings revealed that 17 (89.5%) patients had pulmonary infiltration, 18 (94.7%) patients had mucoid impaction, 8 (42.1%) patients had central bronchiectasis, and 11 patients (57.9%) had HAM. After the patients were diagnosed with ABPM, 17 (89.5%) patients were administered inhaled corticosteroid (ICS) treatment for asthma, 12 (63.2%) patients were administered oral corticosteroid (OCS) treatment, and 11 (57.9%) patients were administered antifungal drugs for ABPM.

Comparison of the clinical characteristics of the *Aspergillus* group and the non-*Aspergillus* group

We compared the clinical characteristics of the *Aspergillus* group and non-*Aspergillus* group (Table 2). The detection rates of fungal culture were 9 patients (64.3%) in the *Aspergillus* group and 3 patients (60%) in the non-*Aspergillus* group. The mean total serum IgE levels were significantly lower in the non-*Aspergillus* group than in the *Aspergillus* group (397 IU/mL vs. 4113 IU/mL; $P = 0.010$). The mean peripheral blood eosinophil count tended to be lower in the non-*Aspergillus* group than in the *Aspergillus* group (991 cells/μL vs.

1952 cells/μL; $P = 0.156$). The mean percent predicted forced vital capacity (FVC) was significantly lower in the non-*Aspergillus* group than in the *Aspergillus* group (84.7% vs. 98.4%; $P = 0.046$). After the diagnosis, the rate of requiring OCS treatment was higher in the *Aspergillus* group than in the non-*Aspergillus* group (78.6% vs. 20%; $P=0.038$) and the rate of requiring antifungal treatment tended to be higher in the *Aspergillus* group than in the non-*Aspergillus* group (71.4% vs. 20%; $P = 0.071$). No significant differences existed between the *Aspergillus* group and non-*Aspergillus* group with regard to age, sex, smoking history, coexisting asthma, thoracic CT findings (i.e., infiltration, mucoid impaction, central bronchiectasis, and HAM), percent predicted forced expiratory volume 1 (FEV_1), FEV_1/FVC ratio, and the requirement for ICS and biological agent treatment. During treatment, the frequency of recurrence was 57.1% in the *Aspergillus* group and 0% in the non-*Aspergillus* group. The mean frequency of recurrence was 1.0 in the *Aspergillus* group and 0 in the non-*Aspergillus* group, and there is no significant difference. The rate of recurrence was significantly different between the two groups ($P = 0.040$).

DISCUSSION

In this retrospective single-center analysis of ABPM, we found differences in laboratory findings, pulmonary function, and OCS treatment between the *Aspergillus* group and the non-*Aspergillus* group. Especially, type 2 inflammation was lower in non-*Aspergillus* group than in *Aspergillus* group. The frequency of non-*Aspergillus* ABPM constitutes approximately 30%–40% of all cases of ABPM, and it differs, depending on geographical area. Oguma et al. reported the fungi identified among of patients with ABPM from whom sputum cultures had been obtained: patients *Aspergillus* spp were identified among 126 (59%) of 213.[8] Ishiguro et al. reported the causative fungi among 42 patients with ABPM: the causative fungi among 26 (61.9%) of 42 patients was *Aspergillus* spp.[9] Prasad et al. reported 30 (71.4%) of 42 patients with ABPM had *Aspergillus*-specific IgE and IgG.[10] In our study, *Aspergillus* spp. were identified among 14 (73.7%) of 19 patients. Thus, the frequency of *Aspergillus* spp. in our study was slightly higher than that reported in previous studies in Japan.

The reason *A. fumigatus* was more likely to develop into ABPM is related to the characteristics of *A. fumigatus*. Asano et al. described three important characteristic factors.[11] The first factor is the size of the conidia. The conidia of *Aspergillus* spp. are smaller (approximately 2–3.5 μm) than that of other fungi and spherical. These species consequently can easily reach the lower airway. The second factor is that the thermophilicity of *Aspergillus* spp. are suitable for germinating, even at human body temperatures. Common fungi can germinate at room temperature, and the optimal temperature is 18°C–22°C. However, *A. fumigatus* can germinate at 37°C–42°C[12]; thus, it can easily germinate in the human lower airway. The third factor is high serine protease activity, which induces mucus production. Mucus production helps to create a suitable environment for fungal colonization and germination.

The serum IgE levels were significantly lower in the non-*Aspergillus* group than in the *Aspergillus* group. The levels of IgE in patients with ABPA differ between countries. Several reports from East Asian countries demonstrate lower serum IgE in patients with ABPA: Tanimoto et al. showed the median IgE level was 1170 IU/m among Japanese patients; Kim et al. showed the median IgE level was 927 IU/mL in Korean patients; Zhang et al. showed the median level was 2629 IU/mL in Chinese patients; and Oguma et al. showed the IgE level was 1913 IU/mL.[8, 13–15] Ishiguro et al. reported the mean level of serum IgE in patients with biopsy-proven ABPM due to non-*Aspergillus* spp. was 4754 IU/mL.[16] However, Ishiguro collected previous reports of patients with ABPM caused by *S. commune* and described elevated serum IgE levels (> 1000 kU/L) in 14 of 21 patients. The median age of ABPA patients in these studies was from 49 to 62.5 years. ABPA patients, especially in Japan, China, and Korea, were older than the other countries. Muthu et al. reported the IgE levels were significantly lower in elderly ABPA patients than in non-elderly ABPA patients.[17] Therefore, low serum IgE of East Asian ABPA might be due to old age. However, the mean age at the onset of *Aspergillus* ABPM was 57 years and non-*Aspergillus* ABPM was 63 years, and the difference in age was not significant in this study. The reason for low IgE levels in the non-*Aspergillus* group might be because the non-*Aspergillus* ABPM induced low type 2 inflammation.

In this study, 6 patients (31.6%) had complications with allergic rhinitis and 1 patient (5.3%) had with atopic dermatitis. Like asthma, allergic rhinitis and atopic dermatitis are allergic diseases which involve type 2 immune reactions. However, elevated levels of serum IgE is shown in some patients with allergic rhinitis and atopic dermatitis, and the frequencies of allergic rhinitis and atopic dermatitis in two groups showed no significant differences. Therefore, low IgE levels in the non-*Aspergillus* group was not associated with the complications of allergic rhinitis and atopic dermatitis.

No study has compared the levels of serum IgE or peripheral eosinophils. Percier et al. showed that

A. fumigatus but not *Cladosporium sphaerospermum* induced eosinophil recruitment, based on findings in the bronchoalveolar lavage fluid and Th2 cytokine production in mice sensitized with MyD88$^{-/-}$ bone marrow-derived dendritic cells.[18] Fritzsching et al. revealed that reduced mucus clearance exacerbated the Stat6-dependent secretion of Th2 cytokines and airway eosinophilia in juvenile Scnn1b-Tg mice.[19] Knight et al. reported that proteinases secreted by filamentous fungi promote the type 2 immune response.[20] *A. fumigatus* specifically induce the expression of the mucin gene *Muc5ac* and mucus production because of the high serine protease activity.[21] These data suggest that *A. fumigatus* likely induces type 2 inflammation, compared to other fungi. Furthermore, the rate of the requirement for OCS treatment was lower in the non-*Aspergillus* group in this study. The induction of low type 2 inflammation by non-*Aspergillus* fungi may reduce the necessity for glucocorticoid therapy.

Predicted FVC was significantly lower in the non-*Aspergillus* group than in the *Aspergillus* group. However, FVC was improved after treatment in both group, and there was no significant difference. Therefore, the reason why predicted FVC was lower in non-*Aspergillus* group might be the effect of pulmonary involvement, such as pulmonary infiltration which could be improved and did not cause fibrotic change.

In this study, we used the new diagnostic criteria proposed by the Japan ABPM Research Program.[7] The classical diagnostic criteria proposed by Rosenberg et al. has low sensitivity, as previously described.[5] The criteria proposed by the ISHAM have higher sensitivity than the criteria proposed by Rosenberg. However, Asano et al. demonstrated that the sensitivity of the criteria by Rosenberg was poor for cases of non-*Aspergillus* ABPM.[7] The reason is that serum tests for pathogens of non-*Aspergillus* are lacking. Asano et al. showed the sensitivity of new diagnostic criteria for pathological ABPM was 96.2%, even in the situation of a culture positive for non-*Aspergillus* fungi (91.3%).[7]

This study had some limitations. First, our study was retrospective and was conducted in a single center. Thus, selection bias may exist. Second, this study had a small number of patients. Therefore, the results of this study may not apply other patients. Third, conducting a complete diagnostic workup for every patient was not possible. Bronchoscopy could not be conducted for every patient. Fourth, the decision of the treatment was determined by each patient's physician. Fifth, the data of our study was collected over 15 years period. The decision of therapeutic strategy by each physician might be affected by the change of therapeutic policy for asthma and ABPM.

In conclusion, the patients with non-*Aspergillus* ABPM might have clinical feature of low type 2 inflammation. The characteristics of ABPM may differ, depending on whether the causative fungi are *Aspergillus* spp. Larger studies are needed to establish the phenotype of non-*Aspergillus* ABPM.

The authors declare no conflict of interests.

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