

## Current Review



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# Allergic bronchopulmonary mycosis – pathophysiology, histology, diagnosis, and treatment

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## ABSTRACT

Allergic bronchopulmonary mycosis (ABPM) develops mainly in patients with asthma or cystic fibrosis via types I and III hypersensitivity reactions to filamentous fungi. *Aspergillus* spp., especially *Aspergillus fumigatus*, is the major causative fungus because of its small conidia, thermophilic hyphae, and ability to secrete serine proteases. The cardinal histological feature of ABPM is allergic (eosinophilic) mucin-harboring hyphae in the bronchi, for which the formation of extracellular DNA trap cell death (ETosis) of eosinophils induced by viable fungi is essential. Clinically, ABPM is characterized by peripheral blood eosinophilia, increased IgE levels in the serum, IgE and IgG antibodies specific for fungi, and characteristic radiographic findings; however, there are substantial differences in the clinical features of this disease between East and South Asian populations. Systemic corticosteroids and/or antifungal drugs effectively control acute diseases, but recurrences are quite common, and development of novel treatments are warranted to avoid adverse effects and emergence of drug-resistance due to prolonged treatment with corticosteroids and/or antifungal drugs.

**Keywords:** Fungus; *Aspergillus fumigatus*; Eosinophils; Allergy

## INTRODUCTION

Allergic bronchopulmonary mycosis (ABPM) is a disease first recognized by Hinson et al. [1] as bronchopulmonary aspergillosis in 1952. Four cases have been reported, demonstrating the clinical characteristics typical for allergic bronchopulmonary aspergillosis (ABPA), including bronchitis (possible asthma), eosinophilia, bronchiectasis and/or mucus plugs, and isolation of *Aspergillus fumigatus* in lung tissue.

ABPM develops mainly in adult patients with asthma or in adult/pediatric patients with cystic fibrosis. Reports from South Africa, Ireland, New Zealand, Saudi Arabia, and China suggest that 2.5% (range, 0.7%–3.5%) of adult patients with asthma suffer from ABPA, whereas the prevalence is higher (>5%) in South Asia, especially in India [2]. Pathophysiologically, the disease is closely associated with types I and III hypersensitivity reactions to filamentous fungi inhaled as conidia (spores) and germinated in the respiratory tract. Clinically, ABPM is characterized by peripheral blood eosinophilia, high IgE levels in serum, positive fungus-

specific IgE and/or IgG antibodies, immediate and/or delayed skin reactions to fungal antigen, and radiographic findings including pulmonary opacities, central bronchiectasis, and mucus plugs [3-5]. Although treatment with corticosteroids and/or antifungal drugs are effective in most cases, recurrence is common and occurs repeatedly [6, 7]. Patients that are untreated or inadequately treated may develop cystic and fibrotic changes in the lungs, resulting in respiratory failure [8].

## PATHOPHYSIOLOGY OF ABPM

In contrast to conidia that are immunologically silent, fungal hyphae express and release various proteases and pathogen-associated molecular patterns [9-11]. For example,  $\beta$ -glucan, a major fungus-specific pathogen-associated molecular pattern, is not accessible in resting conidia but expressed on the surface of swollen conidia and hyphae, and activates dendritic cells via the type-C lectin receptor Dectin-1 [12]. Therefore, repeated exposures to airborne fungal fragments, either dead or alive, can induce various immune responses related with various respiratory diseases such as asthma and hypersensitivity pneumonitis.

In contrast, for the development of ABPM, it is essential that viable fungi, but not their fragments, are inhaled into the lower airways. There are several steps for the inhaled fungi to induce ABPM pathology; the first step is that conidia, but not hyphae, are inhaled into the lower airways because of their small size. In the second step, the conidia germinate and form hyphae, which activates the immune system of the host. Unlike fungal infections, hyphae do not penetrate the lung tissues but stay in the mucus plugs of the bronchi. Then, eosinophilic mucus plugs containing fungal hyphae are formed in the respiratory tracts, which plays a major role in the pathophysiology of ABPM.

## CAUSATIVE FUNGI OF ABPM

*A. fumigatus* is the major causative fungus, but other *Aspergillus* spp. such as *A. flavus*, *A. niger*, and *A. oryzae* can result in ABPA, although less frequently. In contrast, there have been few studies on the causative fungal species other than *Aspergillus* spp. Chowdhary et al. [13] reviewed 143 cases of non-*Aspergillus* ABPM published worldwide, and reported that the top three species, *Candida albicans*, *Bipolaris* spp., and *Shizophyllum commune* accounts for 84% of the reported cases of ABPM. However, care must be taken in the interpretation of these data. Firstly, the diagnostic criteria currently used are specific for ABPA, and no criteria are available to diagnose ABPM caused by other fungi. Secondly, *C. albicans*, reported as the most common pathogen to cause non-*Aspergillus* ABPM, is a yeast-like fungus that is unlikely to induce an ABPM-like pathology. *C. albicans* is often colonized in the upper airway and is expectorated frequently in the sputum, whereas *C. albicans*-specific IgE, IgG, and precipitins can be positive even in healthy individuals. Therefore, it can be easily misdiagnosed as a causative fungus when the true causative fungi could not be identified serologically or microbiologically. If the cases associated with *C. albicans* are excluded, *Bipolaris* spp. (31%), *S. commune* (28%), and *Curvularia* spp. (9%) might be the major causative fungi of non-*Aspergillus* ABPM. *Penicillium* spp. are also found in a substantial number of cases [14], whereas *Alternaria* spp. and *Cladosporium* spp., although common as airborne fungi, rarely causes ABPM.

## CHARACTERISTICS OF CAUSATIVE FUNGI

Atopic sensitization to fungi occurs proportionally to the amount of airborne fungi; for example, in patients with severe asthma, the sensitization rates to *Aspergillus* spp. (36%) were the highest, followed by *Penicillium* spp. (21%), *Alternaria* spp. (19%), and *Cladosporium* spp. (15%) [15]. In sharp contrast, there was significant disproportionality in the frequency of fungi causing ABPM as previously mentioned [13].

This can be explained to some extent by the difference in the size of fungal conidia. Conidia of *Alternaria* are as large as  $25\text{--}60 \times 3\text{--}3.5 \mu\text{m}$ , and conidia of *Cladosporium* are generally  $15\text{--}25 \times 7\text{--}10 \mu\text{m}$ . However, conidia of *Aspergillus* and *Penicillium* are spherical and smaller in size, approximately  $3\text{--}6 \mu\text{m}$ , and therefore can easily reach the lower airways. The conidial size of *S. commune* is as small as  $3\text{--}4 \times 1\text{--}1.5 \mu\text{m}$ .

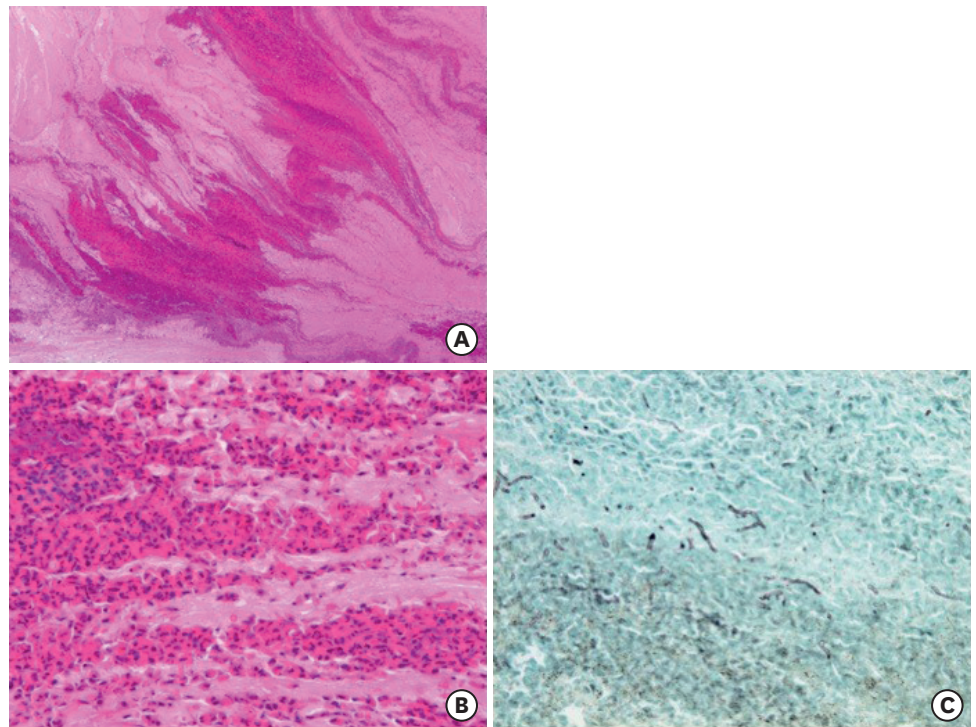
Another important factor for the causative fungus of ABPM is thermophilicity, which can allow the fungi to germinate even at human body temperatures. The optimum germination temperature for common fungi is  $18^{\circ}\text{C}\text{--}22^{\circ}\text{C}$ , which is close to room temperature, and the optimum germination temperature for *A. niger* is approximately  $30^{\circ}\text{C}$ . On the other hand, the optimum germination temperature of *A. fumigatus* is  $37^{\circ}\text{C}\text{--}42^{\circ}\text{C}$  [16], which is approximately the same as that of the human body; therefore, it can easily germinate in the lower airway and form hyphae. The optimum germination temperature of *S. commune* is  $30^{\circ}\text{C}\text{--}35^{\circ}\text{C}$  as well [17].

There are also important differences in the fungus-host interaction according to the type of fungi. When gene expression profiles were examined in the bronchial epithelial cells stimulated with extracts of *A. fumigatus*, *Penicillium notatum*, or *Alternaria alternata*, the mucin gene *Muc5ac* was specifically induced by *A. fumigatus* [18]. Induction of *Muc5ac* and mucus production were dependent on the serine protease activity of *A. fumigatus*, which activates a tumor necrosis factor  $\alpha$ -converting enzyme on the epithelial cell membrane, cleaves membrane-bound transforming growth factor- $\alpha$ , and activates epidermal growth factor receptors. Compared to *A. fumigatus*, other fungi such as *P. notatum* and *A. alternata* have lower serine protease activity [18]. Among *Aspergillus* spp., serine protease activity was highest in *A. fumigatus*, followed by *A. flavus*, and the lowest in *A. niger* [19]. Mucus production promoted by *A. fumigatus* may be helpful to create a suitable environment for fungal colonization and germination.

## HISTOPATHOLOGY OF ABPM (Fig. 1)

Morphologically, ABPM is characterized by (1) allergic (eosinophilic) mucin in the bronchi (mucoïd impaction of bronchi), (2) expansion of the bronchi with mucus plug (central bronchiectasis), and (3) bronchocentric granulomatosis with tissue eosinophilia, eosinophilic pneumonia, and organized pneumonia in the peripheral lungs [20]. In 1988, Bosken et al. [21] proposed pathological diagnostic criteria for ABPM based on observations in surgically-resected lung specimen. In their criteria, the presence of (1) eosinophilic mucus plugs or bronchocentric granulomatosis with advanced eosinophil infiltration, and (2) fungal hyphae in these lesions without tissue invasion suggest the diagnosis of ABPM.

Hebisawa et al. [22] examined the pathology of ABPM in the specimens obtained by lobectomy including central bronchi, and found that (1) the oldest lesions were eosinophilic mucus plugs in the bronchi, (2) central bronchiectasis was formed secondarily because of the expansion of



**Fig. 1.** Histology of allergic (eosinophilic) mucin in the bronchi. Mucus plugs packed in the bronchi of surgically-resected lungs from a patient with allergic bronchopulmonary mycosis demonstrate a fir tree-like structure (A: H&E, x5), which contain many eosinophils, Charcot-Leyden crystals, and fibrin exudates (B: H&E, x40). (C) Hyphae of fungi are sparsely found in mucus plugs (Grocott staining, x40).

mucus plugs stretching the airway wall, which has already been weakened by severe eosinophilic inflammation, and (3) the peripheral lung lesions were caused by the transmural spreading of fungal components from the eosinophilic mucus plugs in the central bronchi. Based on these observations, they concluded that the primary lesions of ABPM were eosinophilic plasmacytoid/lymphocytic mucus plugs but not central bronchiectasis or pulmonary infiltration as often cited in the diagnostic criteria [22, 23]. Another example of eosinophilic mucus plugs deviating anatomical structures has been reported in cases of allergic fungal rhinosinusitis, in which eosinophilic mucus plugs deflect the paranasal sinus bony structures [24, 25].

Mucus plugs in ABPM contain many eosinophils, Charcot-Leyden crystals, and fibrin exudates, and are packed in the bronchi, forming a fir tree-like structure [23], suggesting a dehydration process. Filamentous fungi are found in mucus plugs without gathering densely as seen in chronic pulmonary mycoses. Neutrophils are sometimes observed on the periphery of eosinophilic mucus plugs, but the number is much smaller compared to eosinophils. In comparison to the mucus plugs in resected lungs, mucus plugs in sputum or collected by bronchoscopy were softer, and less often accompanied by fir tree-like structures [22].

## CHARACTERISTICS OF EOSINOPHIL MUCUS PLUGS IN ABPM

Extracellular DNA trap cell death (ETosis) of eosinophils has been suggested as a mechanism for the formation of eosinophilic mucus plugs in various diseases [26, 27]. ETosis was originally reported in neutrophils, which release granular proteins together with nuclear

chromatin DNA (neutrophil extracellular traps [NETs]) to exert bactericidal activity [28]. Fungi cause ETosis of neutrophils, but recent studies have revealed that NETs have no fungicidal action [29].

Cells other than neutrophils can also cause ETosis and release chromatin DNA and eosinophils as well. Ueki et al. [30] investigated eosinophilic ETosis and demonstrated that the extracellular DNA trap released by eosinophils was more aggregated in structure and more stable than the extracellular DNA trap produced by neutrophils. Although NETs are viscous owing to the physical properties of DNA, the extracellular DNA trap derived from eosinophils exhibits greater viscosity. We and other researchers have demonstrated that eosinophilic mucus plugs of ABPA, eosinophilic sinusitis, and eosinophilic otitis media have a net-like structure with DNA and citrullinated histones suggesting the extracellular DNA traps [30-32].

## CLINICAL CHARACTERISTICS OF ABPA IN EAST AND SOUTH ASIA

**Table 1** summarizes the clinical characteristics of ABPA/ABPM in cohort studies reported from Japan, Korea, China, and India [6, 7, 33-41]. The inclusion criteria for each study were different; the presence of asthma was indispensable in the studies by Agarwal et al. [6, 33], and central bronchodilation or mucous plugs were required for the study by Oguma et al. [7]. However, there were obvious differences in the clinical characteristics of ABPA/ABPM between East Asian countries such as Japan, Korea, and China versus India.

### Age and age at onset

There was a significant difference in the age of the recruited patients with ABPA between the studies in Japan and Korea versus those in India. It has been suggested that ABPA mostly develops in patients aged 30–40 years old, which is in agreement with the cases in India [6, 33-35, 38]. Meanwhile, the median age of patients with ABPA in Japan and Korea was 50–70 years [7, 36, 37, 39], and that of Chinese patients was 40–50 years [40, 41]. Two studies in Japan and Korea that examined the age of onset for ABPA demonstrated that the median age at disease onset was 50–60 years [7, 37]. Two-thirds of cases developed ABPA at 50 years or older as reported in a Japanese nation-wide survey of this disease [7].

There are 3 possible reasons that might explain the difference in age distribution. The first possibility involves genetic predisposition, but little is known about this except for the cases with *CFTR* mutation in patients with cystic fibrosis. The second possibility is the difference in the age structure of populations in East Asian countries versus India. The elderly population aged 55 years or older makes up less than 15% of the total population in India, whereas it accounts for 22%, 30%, and 40% of the population in China, Korea and Japan, respectively (<https://www.cia.gov/library/publications/the-world-factbook/fields/2010.html>). These differences in the age structure may have skewed the age distribution of the patients to younger generation in India, and to older population in Japan and South Korea. We performed a cluster analysis using a Japanese nationwide survey data and identified three clusters with different ages of onset, with the median age of onset being 30–40, 50–60, and 60–70 years, respectively (Oguma T and Asano K, unpublished data), suggesting that there are multiple phenotypes of ABPA with different ages of onset. One phenotype of Japanese ABPA had a median age at onset of 37 years, compatible with that of Indian ABPA.

**Table 1.** Clinical characteristics of allergic bronchopulmonary aspergillosis (ABPA) in East and South Asia

Characteristic	East Asia					South Asia				
	Japan	Korea	China	India						
Study										
Author [reference number]	Tanimoto [39]	Oguma [7]	Ye [40]	Behera [34]	Chakrabarti [35]	Prasad [38]	Agarwal [6]	Agarwal [33]		
Publication year	2015	2018	2009	1994	2002	2009	2010	2018		
No. of cases	53	358	57	35	89	42	234	131		
Age (yr)	57	64	41	34	36	31	34	37		
Women	42%	57%	42%	60%	39%	36%	47%	47%		
Asthma	79%	81%	-	94%	80%	100%	100%	100%		
Duration between onset of asthma and ABPA (yr)	31	14	-	11	12	12	6	12		
Peripheral blood eosinophil counts ( $\mu$ L)	580	1,075	-	-	-	-	847	1,271		
Serum IgE levels (IU/mL)	1,170	1,913	-	-	-	-	5,015	10,540		
Serum IgE levels > 1,000 IU/mL	-	68%	-	-	-	-	-	100%		
Specific IgE or immediate skin reaction to <i>Aspergillus</i> antigen	100%	100%	-	51%	82%	98%	100%	95%		
Precipitins for <i>Aspergillus</i> antigen	-	73%	-	77%	72%	100%	83%	50%		
Culture-positive for <i>Aspergillus</i> spp.	-	59%	-	-	63%	69%	-	-		
Radiographic findings	-	-	-	-	-	-	-	-		
Pulmonary opacities	-	88%	56%	-	43%	95%	-	66%		
Central bronchiectasis	-	89%	44%	71%	69%	100%	77%	93%		
High attenuation mucus	-	41%	-	-	-	-	21%	41%		

Therefore, a classic, early onset phenotype of ABPA was also present in Japan as in India, but later-onset phenotype(s) may dominate in these populations. Importantly, there are no substantial differences in the duration between the onset of asthma and ABPA in Indians and East Asians, suggesting that the age of onset for asthma may be higher in the latter population. The third possibility is that greater exposure to environmental fungi in India, possibly because of higher burden of airborne fungi in the hot and humid environments, accelerates the sensitization and development of ABPA in younger age. This hypothesis is supported by the remarkably high incidence of ABPA in India compared to other areas of the world [2, 42].

ABPA rarely develops during childhood in patients with asthma, with some exception in India [43]. This trend matches well with the findings among other eosinophilic diseases in the upper and lower airways, such as rhinosinusitis with nasal polyps, eosinophilic otitis media, aspirin-exacerbated respiratory diseases, and chronic eosinophilic pneumonia, suggesting a common pathology underlying these adult-onset eosinophilic airway diseases [44].

### Predisposing condition

Cystic fibrosis, a major predisposing condition of ABPM in Europe and the United States, is rare in Asians, for whom the major predisposing disease of ABPM is asthma. Asthma was included as one of the essential components in the current diagnostic criteria for ABPA. However, there have been reports of cases with ABPA that were not accompanied by asthma [45]. In a study of pathologically diagnosed cases of ABPM, 7 of 17 patients (41%) reported that they did not have asthma nor cystic fibrosis [46]. Among 453 Japanese patients with ABPM, approximately 20% (93 patients) did not present with asthma [7,36,39]. In contrast, only 5% (20 patients) of 400 Indian patients with ABPA did not have asthma [6, 34, 35, 38]. This difference in the incidence of asthma among patients with ABPA may be due to the difference in the diagnostic criteria used in these studies, or may reflect the presence of a specific phenotype without asthma among Japanese ABPA.

### Serum levels of total IgE

Increased levels of total IgE in serum are characteristic of ABPA, and are useful not only for its diagnosis but also for monitoring disease activity. However, different cutoff values, such as >417 IU/mL or >1,000 IU/mL, have been used depending on the diagnostic criteria [3, 47, 48]. A survey of the members of the American Academy of Allergy Asthma Immunology reported that 44.9% used the cutoff value of 417 IU/mL whereas 42% used 1,000 IU/mL [49]. The diagnostic criteria proposed by the International Society for Human Animal Mycology (ISHAM) in 2013 emphasize the usefulness of higher cutoff values, such as 1,000 IU/mL, to distinguish ABPA from severe asthma with fungal sensitization [3]. A recent Indian study recommends even higher cutoff value, 2,347 IU/mL [50]. However, we should be cautious not to exclude patients with relatively low levels of total IgE in serum, because its levels in East Asian patients were lower than in Indian patients, and 20%–50% of the patients showed IgE < 1,000 IU/mL [7, 36, 37, 41].

### Fungal culture

Although the efficacy to detect filamentous fungi with culture methods may vary depending on culture conditions such as media, duration, and temperature [51], most of the previous studies demonstrate the detection rate of *Aspergillus* spp. between 60%–70% [7, 35, 36, 38]. What was unique in Japanese studies was the presence of *S. commune* in 6%–14% [7, 36]. *S. commune* was the most common filamentous basidiomycetes of mushroom that causes human airway diseases

**Table 2.** Comparison of diagnostic criteria

Diagnostic criteria	Rosenberg-Patterson 1977	Greenberger-Patterson 1986	ISHAM 2013
Asthma or cystic fibrosis	●	●	●
Peripheral blood eosinophilia	●		○
Increased levels of IgE in serum	●	●	●
Immediate skin reaction to <i>Aspergillus</i> antigen	●	●	●
Specific IgE to <i>Aspergillus fumigatus</i>		●	●
Specific IgG to <i>Aspergillus fumigatus</i>		●	○
Precipitin to <i>Aspergillus fumigatus</i>	●		○
Pulmonary opacities	●		○
Central bronchiectasis	●	●	○
Positive sputum culture of <i>Aspergillus fumigatus</i>	△		
Expectoration of brownish mucous plugs	△		
Arthus-type skin reaction to <i>Aspergillus</i> antigen	△		

Closed circles are mandatory components. In International Society for Human Animal Mycology (ISHAM) criteria, 2 out of 3 components (open circles) should also be fulfilled. Triangles are secondary components, further supporting the diagnosis of allergic bronchopulmonary aspergillosis.

[52], commonly found on the rotten wood of trees worldwide. The difference in the incidence of *S. commune*-induced ABPM between Japan and other countries may be because of the difficulty in identifying this fungus in the laboratory, which grows as a nonsporulating white mold.

## DIAGNOSTIC CRITERIA FOR ABPA/ABPM

ABPM should be suspected, and more detailed diagnostic tests should be performed when peripheral blood eosinophil counts or serum IgE levels were increased in patients with asthma sensitized to fungal antigens, or when pulmonary opacities, central bronchiectasis, or mucus plugs were accompanied by peripheral blood eosinophilia even in the absence of asthma.

The classic diagnostic criteria were proposed in 1977 by Rosenberg, Patterson, and their colleagues [48] based on the clinical characteristics of 20 cases suspected of ABPA; which included 7 primary components: asthma, peripheral blood eosinophilia, positive immediate skin reaction to *Aspergillus* antigen, presence of precipitating antibody to *Aspergillus* antigen, increased serum total IgE levels, transient or fixed pulmonary opacities, and central bronchiectasis. Agarwal et al. [53] examined these criteria with an additional component, the presence of *A. fumigatus*-specific IgE, and demonstrated that the specificity and sensitivity were high when 6 components were satisfied, but its sensitivity decreased to 39% when 7 components were needed to be satisfied as originally proposed.

In 1988, Greenberger and Patterson [47] added a new disease concept, ABPA-seropositive, which refers to cases that lack central bronchiectasis, but satisfy other criteria including serological tests. In 2013, ISHAM proposed new diagnostic criteria [3], which defines asthma or cystic fibrosis as predisposing conditions and proposes 2 obligatory criteria that must be met, immediate cutaneous hypersensitivity to *Aspergillus* antigen or elevated IgE levels against *A. fumigatus*, and elevated total IgE levels > 1,000 IU/mL. In addition, at least two of the following three criteria should be satisfied for the diagnosis of ABPA, which include the presence of precipitating or IgG antibodies against *A. fumigatus* in serum, radiographic features in the lungs consistent with ABPA, and total eosinophil count > 500 cells/ $\mu$ L. A comparison of these diagnostic criteria is summarized in **Table 2**.

However, these diagnostic criteria are specific to ABPA caused by *A. fumigatus*. The ABPM research program supported by the Japan Medical Research and Development Organization



are developing new diagnostic criteria for ABPM. Based on the preliminary results, the new diagnostic criteria may improve sensitivity and specificity for ABPA/ABPM.

## TREATMENT

### Corticosteroids

Systemic corticosteroids improve symptoms such as wheezing, as well as laboratory and radiographic abnormalities such as high IgE levels in the serum and pulmonary opacities during the acute phase of ABPA. There are 2 standard protocols for systemic corticosteroid treatment: the administration of high-dose prednisolone (0.75 mg/kg/day) for 6 weeks, followed by 0.5 mg/kg/day for 6 weeks, and then tapered by 5 mg per week for 6–12 months; and 2 weeks of moderate-dose prednisolone (0.5 mg/kg/day), followed by the same dose administered every other day for 8 weeks, and then tapered by 5 to 10 mg per every 2 weeks. Randomized controlled trials comparing these 2 protocols were performed in 92 patients with ABPA that were previously untreated [54]. There was no significant difference between the 2 protocols in the relapse rate after treatment, which was 46% for each group. The rate of clinical improvement based on symptoms, serum IgE levels, and radiographic findings after the 6-week-treatment was 100% in the high-dose corticosteroid group and 88% in the middle-dose group, but the number of patients that experienced side effects due to corticosteroid treatment was 80% in the high-dose protocol compared to 29% in the middle-dose protocol [54].

Treatment efficacy can be evaluated by a radiographic improvement, with serum IgE levels decreased by 20%–25% or more from the baseline [3, 55]. The recurrence rate was high after decreasing/stopping corticosteroids regardless of the initial dose or treatment period, and often continuous administration of low dose corticosteroids is required [7, 54]. Long-term corticosteroid administration in the presence of bronchiectasis may be complicated with chronic lower respiratory tract infections with *Pseudomonas aeruginosa* or nontuberculous mycobacteria [56].

Inhaled corticosteroids may be useful to control asthmatic symptoms, but there has been no large-scale trial showing its effectiveness as a therapeutic agent for ABPA. A small, single-arm study demonstrated that a combination of inhaled high-dose corticosteroids with the long-acting  $\beta$ -agonist formoterol/budesonide (24/1,600  $\mu$ g/day) for 6 months resulted in subjective improvements, but did not decrease the levels of IgE [57], suggesting a failure to suppress the disease activity of ABPA.

### Antifungal drugs

The latest systematic review on the treatment of ABPA with antifungal drugs, which summarizes 38 observational studies and 4 randomized controlled trials, confirms that antifungal drugs might improve symptoms, pulmonary function, and radiographic findings, and reduce the exacerbation rate and dose of corticosteroids, but the evidence is not robust because of the lack of controlled studies and heterogeneity of study design [58]. Therefore, there are some differences in the positioning of antifungal drugs among the guidelines. In the clinical practice guidelines from the Infectious Diseases Society of America [59], oral itraconazole therapy is recommended when asthmatic patients with bronchiectasis or mucoid impaction are symptomatic despite oral or inhaled corticosteroid therapy. Meanwhile, the Japanese guidelines for management of deep-seated mycosis [60]

recommend a more cautious approach for using antifungal drugs; the identification of the causative fungi in culture and short-term treatment (16 weeks) is recommended to avoid the induction of azol-resistance. However, in more than half of the cases with ABPM in Japan, antifungal drugs were used for more than a year [7].

In an open-labeled study, 131 patients with ABPA complicating asthma were randomly assigned to the treatment groups with either itraconazole or systemic corticosteroids [33]. In 6 weeks, 88% and 100% of the subjects receiving itraconazole and systemic corticosteroids, respectively, showed partial/total improvement in symptoms and radiographic findings, with serum IgE levels having decreased by 25% or more. Although the corticosteroid group showed quicker responses, both treatment groups show 100% treatment response within 3 months [33].

### Anti-IgE antibody

An anti-IgE antibody (omalizumab) was effective in patients with severe asthma in improving symptoms and reducing the frequency of exacerbation. There is an increasing number of reported cases demonstrating the effectiveness of omalizumab in patients with ABPM, but only a few studies have examined the effect of omalizumab prospectively. Tillie-Leblond et al. [61] performed a single-arm study in 16 cases with ABPA, and omalizumab significantly reduced the exacerbation rate and dose of systemic corticosteroids. Additionally, Voskamp et al. [62] performed a randomized, placebo-controlled study in cases, revealing a decrease in the exacerbation rate and fraction of exhaled nitric oxide, but not in pulmonary functions.

## CONCLUSIONS

It has been more than 65 years since ABPA was first reported; however, there are still several unsolved problems for ABPA/ABPM. First, the current diagnostic criteria do not necessarily cover the whole spectrum of this complex disease, and there is a substantial number of patients who are misdiagnosed. Secondly, systemic corticosteroids and/or antifungal drugs were effective for improving the acute-phase symptoms, but recurrences are quite common, and side effects of the drugs and emergence of azol-resistant fungi are problematic.

Histopathological and biological approaches are now being used to elucidate the pathophysiology of this condition for subsequent development of new therapies.

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