



# Misinterpretation of allergic bronchopulmonary aspergillosis/ allergic bronchopulmonary mycosis due to diverse characteristics in different clinical stages

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**Background:** Allergic bronchopulmonary mycosis (ABPM) is a complex pulmonary disorder caused by a hyperimmune response to the endobronchial growth of certain fungi. This study aims to aid physicians in better understanding the need for earlier recognition of ABPM.

**Methods:** Patients with a confirmed diagnosis of ABPM after evaluation were analyzed retrospectively. Clinical features, previous diagnoses and potential diagnostic errors, laboratory findings were reviewed and compiled.

**Results:** Fifty-seven patients were diagnosed with ABPM in which 22 were misdiagnosed. Eosinophilia was observed in 11 patients and an elevated total serum Ig E level greater than 1,000 kU/L was detected in 25 of the 57 patients. All of the patients were tested for specific Ig E in which positive to different fungi. The two most common abnormalities found on chest high-resolution computed tomography (HRCT) exams were central bronchiectasis and mucus plugs. A mild to moderate obstructive pattern of lung function was observed in 32 cases. By bronchofiberscopic observation, bronchial lumen was seen to have significant inflammation in 12 patients. After 3 weeks of treatment, a decreased serum total Ig E value was observed.

**Conclusions:** This study highlights the importance of increasing awareness and understanding of non-Aspergillus-ABPM among physicians and draws attention to the need for establishing more elaborate diagnostic criteria for non-Aspergillus-ABPM, which is a rare kind of disease.

**Keywords:** Allergic bronchopulmonary mycosis (ABPM); allergic bronchopulmonary aspergillosis (ABPA); diagnosis

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## Introduction

Allergic bronchopulmonary mycosis (ABPM) is a pulmonary hypersensitivity-mediated disease, which was characterized by sensitization to environmental fungi, central bronchiectasis, peripheral and pulmonary eosinophilia, and recurrent fleeting radiographic infiltrate (1-3). This disease was first described as allergic bronchopulmonary aspergillosis (ABPA) by Hinson *et al.* in the United Kingdom who recognized it in asthmatics with uncontrolled asthma, peripheral blood eosinophilia, recurrent pulmonary infiltrates and sputum culture positive for *Aspergillus fumigatus* (4). Since then, a growing number of studies found that several different fungi have also been implicated in causing a syndrome similar to ABPA, including *Aspergillus flavus* (5), *Aspergillus niger* (6), *Bipolaris spp* (7), *Candida albicans* (8), *Curvularia lunata*, *Drechslera hawaiiensis* (9) and *Schizophyllum commune* (10). The complex disease is an airway disorder, which is associated with two most important underlying conditions including asthma and cystic fibrosis in primarily patients (11,12).

The ISHAM Working Group has proposed a latest clinical staging of ABPA, which has identified ABPA into seven clinical stages including stage 0 (diagnosed as ABPA but has no signs and symptoms), stage 1 (acute, 1a: with mucoid impaction, 1b: without mucoid impaction), stage 2 (response), stage 3 (exacerbation), stage 4 (remission), stage 5 (5a: treatment dependent ABPA, 5b: glucocorticoid dependent asthma), stage 6 (advanced ABPA). Several studies indicated that many patients with stage 1, stage 2, stage 3 and stage 4 can enter complete remission, while stage 5 and stage 6 may lead to lung fibrosis and irreversible lung damage (13). Therefore, early diagnosis and treatment is essential to lower the risk of advancement to stage 5 or stage 6, which could prevent long-term lung tissue damage (14). However, previous studies showed that the mean latency of diagnostic delay was as long as 10 years in patients with ABPM, which was correctly diagnosed at later stages eventually (15,16). Thus, the early diagnosis of ABPM is an important clinical issue.

Hence, a call was made to alert medical practitioners to identify this disease entity of ABPM as early as possible, especially in the high-risk patients with asthma or cystic fibrosis. In this study, we reported a relatively large series of ABPM patients who have suffered long duration of this disease, and even some of whom were at the irreversible stage when the correct diagnosis was made finally. Further, the clinical information of these patients was retrospectively

analyzed regarding clinical presentation, laboratory and radiological evaluations. This will improve the early diagnosis and outcomes for ABPM patients hopefully.

## Methods

This was a single-center retrospective study from the department of respiratory and critical care medicine using the clinical information system. The data of all patients diagnosed as ABPM from Dec 2015 to Dec 2017 were collected. Patients were excluded if they met any of the following criteria: (I) a history of pulmonary surgery; (II) previous diagnosis of advanced cancer or other severe diseases; (III) pregnancy; (IV) any immunosuppressive diseases (including: chronic renal failure, uncontrolled diabetes mellitus, chronic liver failure and cytotoxic therapy) or intake of systemic corticosteroids within 4 weeks; (V) mental or cognitive disorder.

Rosenberg-Patterson (R-P)-criteria was used to diagnose ABPA, including major criteria and minor criteria. Major Criteria: (I) asthma; (II) presence of fleeting or fixed pulmonary opacities on chest radiograph; (III) immediate cutaneous hypersensitivity reaction to *Aspergillus fumigatus*; (IV) total serum Ig E elevated, more than 1,000 IU/mL; (V) precipitating antibodies against *Aspergillus fumigatus*; (VI) peripheral blood eosinophilia; (VII) central or proximal bronchiectasis with normal tapering of distal bronchi. Minor criteria: (I) golden brown sputum plugs in expectorant; (II) positive sputum culture for *Aspergillus* species; (III) late (arthus-type) skin reactivity to *Aspergillus fumigatus*. The diagnosis of ABPM was made by a multidisciplinary team (pulmonary physician, radiologist, microbiologist) when at least 6 of the primary diagnostic R-P criteria were met (17). Apart from detailed demographic data, clinical history and physical examination, all subjects underwent the following investigations to achieve a definite diagnosis of ABPM: peripheral blood eosinophil count, total serum Ig E levels, fungus-specific Ig E levels, sputum microscopy and culture for fungus, high-resolution computed tomography (HRCT) of the chest. Lung function test and bronchofiberscopy were also performed in some patients. The indications included recurrent cough and sputum with invasion in lungs (nontypical imaging of ABPA), and non-response to empirical anti-infective therapy.

### *Total eosinophil count*

The total leucocyte count was initially determined using

an auto-analyzer (LH-750; Beckman Coulter, Mumbai, India). The percentage of differential leucocyte count was measured by counting and classifying 100 white blood cells on a peripheral blood smear. The total eosinophil count was obtained by multiplying the percentage with the total leucocyte count.

### *Serum total Ig E and fungus-specific Ig E levels*

The total Ig E levels were assessed using quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany), while the fungus-specific Ig E levels were assayed using fluorescent enzyme immunoassay (UniCap Systems; Phadia, Stockholm, Sweden).

### *Sputum culture*

Sputum samples were examined (smear and culture) for any pathogenic fungus in 57 patients. All the sputum samples were treated with N-acetyl-cysteine (NALC) and were examined for fungal hyphae using calcofluor dye with potassium hydroxide and cultured using Sabouraud glucose agar medium. Further, mycelial fungi were identified using a slide culture technique.

### *HRCT of the chest*

HRCT was performed using a multiple-detector CT scanner (LightSpeed Plus; GE Medical Systems; Slough, UK) with a matrix size of 512×512. The diagnosis of bronchiectasis and high-attenuation mucus on HRCT chest was made using the previously described criteria (18).

### *Pulmonary function test*

Pulmonary function test was performed on a dry rolling seal spirometer (Spiroflow; PK Morgan Ltd.; Kent, UK) to determine the lung function measurements as previously described (19). Age, gender, height and spirometry data were recorded for the patients.

### *Bronchofiberscopy*

Bronchofiberscopy was performed within 2 weeks of presentation and after stabilization of symptoms. During bronchofiberscopy, bronchial washings were obtained and cultured for growth of fungi. Further, 50 mL aliquots

of sterile 0.9% saline were infused into the right middle lobe or lingula, gently suctioned, and then processed for cell counts and differentials. The mucosal specimens were also obtained by bronchofiberscopy, and then fixed in 10% formalin and routinely processed for staining with hematoxylin and eosin (HE). In addition, bronchofiberscopy was not performed in those patients, who met Rosenberg's criteria, had expectoration of mucus plugs, or rejected bronchofiberscopy due to concern of exacerbation of asthmatic symptoms.

### *Treatment*

The patients were treated with glucocorticoids, itraconazole or glucocorticoid and itraconazole. The glucocorticoid was used as the following regimen: prednisolone 0.5 mg/kg for 4 weeks, 0.25 mg/kg for 4 weeks, 0.125 mg/kg for 4 weeks; then tapered by 5 mg every week to continue for a total duration of at least 4 months. Antifungal agent itraconazole was used as a dose of 200 mg twice a day for 4 months. The patients were followed up with history and physical examination, chest radiograph, serum total Ig E level and the number of eosinophil count every 4 weeks.

### *Statistical analysis*

The data were presented in a descriptive fashion as number (percentage), or median (interquartile range), as required. The differences between continuous variables were analyzed using Kruskal-Wallis test, while the categorical variables were compared using Chi-square test. Differences with a P value of lower than or equal to 0.05 were considered to be statistically significant.

## **Results**

In total, 57 patients were included in the study; of these, 29 (50.88%) were male and 28 (49.12%) were female patients, with a median age of 55.9 years (range, 24–90 years). Of the 57 patients, 9 were presented with recurrent asthma symptoms. The baseline characteristics of these patients with regards to clinical features are shown in *Table 1*. With Cough (57/57), expectoration (57/57) and wheezing (57/57) were the most common symptoms. Less common symptoms were chest tightness (35/57), fever (25/57), fatigue (21/57), haemoptysis (13/57) and headache (6/57). The clinical stages of these 57 patients are shown in *Table 1*.

For the 57 patients, the time of first hospital visit to final

**Table 1** The clinical features, stages, Ig E test and radiologic manifestation of the 57 ABPM patients

Characteristics	No. of patients (n)	Percentage (%)
<b>Symptoms/signs</b>		
Cough	57/57	100.0
Expectoration	57/57	100.0
Wheezing	57/57	100.0
Chest tightness	35/57	61.4
Fever	25/57	43.9
Fatigue	21/57	36.8
Haemoptysis	13/57	22.8
Headache	6/57	10.5
wheezes	37/57	64.9
crackles	28/57	49.1
<b>Clinical stage</b>		
Glucocorticoid dependent asthma [5]	26/57	45.6
Exacerbation [3]	18/57	31.6
Remission [4]	9/57	15.8
advanced [6]	2/57	3.5
Acute [1]	2/57	3.5
<b>Specific Ig E test</b>		
<i>A. fumigatus</i>	39/57	68.4
Polyvalent fungus	26/57	45.6
<i>Candida albicans</i>	20/57	35.1
<i>A. fumigatus</i> + Polyvalent	15/57	26.3
<i>A. fumigatus</i> + <i>Candida albicans</i>		
<i>A. fumigatus</i> + Polyvalent fungus	7/57	12.3
<i>A. fumigatus</i> + <i>Candida albicans</i>	2/57	3.5
<b>Radiological manifestations</b>		
Central bronchiectasis	33/57	57.9
Mucus plug	16/57	28.1
Mediastinal adenopathy	14/57	24.6
Patch and stripe shadows	14/57	24.6
Aspergilloma	10/57	17.5
Fibrosis	7/57	12.3
Pulmonary bulla	2/57	3.5
Consolidation	1/57	1.8

ABPM, allergic bronchopulmonary mycosis.

**Table 2** Misdiagnoses of the ABPM patients

Misdiagnosed disease	No. of patients (n)	Percentage (%)
COPD	10/22	45.5
Bronchiectasis	6/22	27.3
Pneumonia	3/22	13.6
DPB	1/22	4.5
Lung cancer	1/22	4.5
Tuberculosis	1/22	4.5

ABPM, allergic bronchopulmonary mycosis; COPD, chronic obstructive pulmonary disease; DPB, diffuse panbronchiolitis.

diagnosis ranged from as short as 24 days to a period of 40 years (average  $137.37 \pm 117.39$  months). A majority of cases (22/57) were misdiagnosed or underdiagnosed as seen in Table 2. Not including asthma as a stand-alone diagnosis in 9 patients, the other patients in the top 3 included chronic obstructive pulmonary disease (COPD), bronchiectasis and pneumonia in 10, 6 and 3 cases respectively. Only 26 (45.6%) were correctly diagnosed without delay.

Out of 57 patients, eosinophilia ( $\geq 1,000/\text{mm}^3$ ) was detected in 11 patients (19.3%). An elevated total serum Ig E level ( $\geq 1,000$  kU/L) was detected in 25 of the 57 patients (43.9%). All of the patients were tested for specific Ig E (sp-Ig E), in which 39 were only *Aspergillus fumigatus* sp-Ig E<sup>+</sup> (68.4%), 26 were only polyvalent fungus (*Penicillium notatum*, *Cladosporium*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Helminthosporium carbonum*) sp-Ig E<sup>+</sup> (45.6%), 20 were only *Candida albicans* sp-Ig E<sup>+</sup> (35.1%), 15 were *Aspergillus fumigatus*, polyvalent fungus and *Candida albicans* sp-Ig E<sup>+</sup> (26.3%), 7 were both *Aspergillus fumigatus* and Polyvalent fungus sp-Ig E<sup>+</sup> (12.3%), 2 were both *Aspergillus fumigatus*, and *Candida albicans* sp-Ig E<sup>+</sup> (3.5%) (Table 1). In addition, 40 patients were positive by sputum microscopy and culture. Sputum was positive for *Aspergillus* species in 31.6% (18 of 57 cases), while positive for *Candida* species in 38.6% (22 of 57 cases) (Table 3).

Various chest CT abnormalities were noted in our patients as indicated in Table 1. Central bronchiectasis was seen in 33 patients. As might be expected, central bronchiectasis (57.9%) and mucus plug (28.1%) were the most common manifestations. Aspergillomas, which moved to dependent positions on prone scans, were noted in dilated bronchiectatic cavities in 10 patients (17.5%).

Lung function was also tested in 34 patients. A mild to moderate obstructive pattern was observed in 32 cases.

**Table 3** The sputum cultures for fungus of the 57 ABPM patients

Sputum cultures for fungus	No. of patients (n)	Percentage (%)
<i>Candida</i>	22/57	38.6
<i>Candida albicans</i>	19/57	33.3
<i>Krusei</i>	2/57	3.5
<i>Candida glabrata</i>	1/57	1.8
<i>Aspergillus</i>	18/57	31.6
<i>Aspergillus fumigatus</i>	12/57	21.1
<i>Aspergillus flavus</i>	2/57	3.5
<i>Aspergillus terreus</i>	2/57	3.5
<i>Aspergillus niger</i>	1/57	1.8
<i>Aspergillus versicolor</i>	1/57	1.8

ABPM, allergic bronchopulmonary mycosis.

Additionally, bronchofiberscopy was performed in 14 patients. By bronchofiberscopic observation, bronchial lumen was seen to have significant inflammation in 12 patients, corresponding to an eosinophilic infiltration to the bronchial walls in pathologic findings of bronchial biopsy specimens. The mean number of cells per bronchoalveolar lavage fluid (BALF) in 6 patients was approximately 1.8 to 5 ( $\times 10^6$ ). The predominant cell type was neutrophil (65–90%), followed by macrophage (10–20%), lymphocyte (3–9%) and eosinophil (2–7%).

After 3 weeks of treatment, clinical and radiological improvement was observed in all the patients. The total Ig E level at baseline was 1,148.0 KU·L<sup>-1</sup>, after treatment with glucocorticoid, itraconazole or glucocorticoid and itraconazole, the mean absolute decline in total Ig E value was 316,325 and 316 respectively (Table 4). On the other hand, the trend of the number of total eosinophil count cells was inconsistent. The mean number of total eosinophil count cells at baseline was 0.215  $\mu\text{L}^{-1}$ , and after treatment with glucocorticoid, itraconazole or glucocorticoid and itraconazole, the mean number of total eosinophil count cells was 0.20, 1.06 and 0.125 respectively (Table 4).

## Discussion

ABPM is an allergic pulmonary disease caused by a hyperimmune response to the certain environmental fungi. It was first reported in 1952 by Hinson *et al.*, which was caused by *Aspergillus fumigatus* (4). Since then, hundreds of patients with this disorder were reported, who were

caused by *A. flavus*, *A. niger*, *Candida albicans*, *Penicillium* or *Schizophyllum commune*, other than *Aspergillus fumigatus* (20,21). However, several patients who presented to the hospital were diagnosed delay as long as more than 10 years (22). In our present study, 1 patient was believed to be undiagnosed for 40 years. Thus, the most troubling aspect in dealing with ABPM may be related to early recognition of this disorder.

There may be many reasons for the underdiagnosis of ABPM. Firstly, ABPM is usually described in patients with pre-existing asthma or cystic fibrosis, however, it is not absolutely essential (23). In the current study, preexisting asthma was only present in 9 patients and 48 patients were nonasthmatic, while preexisting cystic fibrosis was not present in total patients. Thus, ABPM is not a common disease even rare outside of the diagnosis of asthma or cystic fibrosis, which could easily go unrecognized.

Secondly, it is well-known that patients with ABPA were classified in to 7 stages (24). A previous study showed that peripheral blood eosinophilia is usually not present and pulmonary infiltrates are absent in the remission stage. Moreover, precipitating antibodies against fungus species may not be present in stages other than acute stage (23). Therefore, the patients in some stages of ABPM could be missed, who did not satisfy the clinical criteria due to the absence of eosinophilia and/or the technical limitations of immunological investigations (24).

Thirdly, some practitioners may not recognize the signs or symptoms of this disease, as a result of misdiagnosis. In our present study, nearly a half of cases (22/57) were misdiagnosed, while only 35 (61.4%) were correctly diagnosed without delay. A similar observation was recorded by other authors; a majority of cases (44/70) were misdiagnosed, while Only 18 (26%) were correctly diagnosed as ABPM (22). Thus, a deeper awareness or understanding of ABPM should be heightened and paid more attention in physicians.

One of the important findings in the present report was that 10 patients had been treated with bronchodilator drugs before coming to this hospital as they had been diagnosed as cases of COPD. Few patients with ABPM have been reported in clinical conditions such as COPD, other than asthma or cystic fibrosis. To date, only 3 reports documented the presence of ABPM concomitant with COPD in patients (25–27). Agarwal *et al.* reported the first report of such an association, who presented with an exacerbation of COPD due to co-existent ABPM (26). There is a pathophysiological plausibility of a link between



**Table 4** The total-Ig E level of the ABPM patients before and after treatment

Immunological findings	Before treatment (n=57)	After 3 months treatment (n=48)		
		Glucocorticoid (n=14)	Itraconazole (n=6)	Glucocorticoid + Itraconazole (n=28)
Total Ig E levels KU·L <sup>-1</sup>	1,148.0 (10.5–5,920)	316.0 (78.6–4,371)*	325.0 (10–5,850)*	316.0 (25–5,000)*
Total eosinophil count cells·μL <sup>-1</sup>	0.215 (0–17.8)	0.20 (0–0.64)	1.06 (0.01–1.32)	0.125 (0–14.3)

All the values are expressed as mean (95% confidence intervals). \*, P value ≤0.05 statistically significant after 3 months treatment compared to before treatment. ABPM, allergic bronchopulmonary mycosis.

ABPM and COPD, as the patients with COPD have mucus hypersecretion and impaired mucociliary clearance, where fungus could be trapped in and then germinate to form hyphae (28). Thus, COPD may be a predisposing factor for ABPM, which could develop the co-existence of COPD and ABPM. Therefore, co-existent ABPM should be considered in patients with exacerbation of COPD who are unresponsive to routine therapies, and these patients should do further examination as soon as possible.

The most important changes of HRCT chest in our present study showed central bronchiectasis and mucus plug, which is considered as highly suggestive of ABPM (29,30). Spirometry showed mild to moderate obstruction mostly, which may be due to bronchiectasis at presentation in most patients in the present study. The lung function test could not reveal any specific pattern to help in the diagnosis of ABPM, but could be used in the assessment of the severity of impairment of lung function (29). With help from radiographic findings, 14 patients also underwent bronchoscopy and showed similar results, providing support that discharge of mucus plugs is not a valid diagnostic criterion for ABPM (31,32) but could relieve uncomfortable symptoms such as wheezing and chest tightness.

*Aspergillus fumigatus* is regarded to be the most common organism implicated in the causation of ABPM, however, *Candida albicans* was also commonly isolated in the present series. The positive for *Candida albicans* species in sputum was observed in 33.3% of cases as compared to positive for *Aspergillus fumigatus* which were found in 31.6% cases. In addition, the positive for *Candida albicans* sp-Ig E was measured in 35.1% of cases, while the positive for *Aspergillus fumigatus* sp-Ig E was detected in 68.4% cases. In the study, the culture was made with bronchoscopic gained material or sputum. All sputum samples were collected with standard method and quality control to avoid the oral contamination. The diagnosis of candida-ABPM was made based on results of BALF or at least three-times positive

sputum culture. Therefore, *Candida albicans* is also frequent causative mycoses of ABPM, which is present greatly in the mouth of normal people. Before visiting our hospital, most patients have sought medical service for a long time and many kinds of antibiotics have been used, which inhibit normal bacteria flora and cause flora imbalance. This maybe one reason for high frequency of *Candida* in this study.

Furthermore, we also detected the level of total Ig E and the number of total eosinophil count cells during follow-up and found that a total Ig E value significantly decreased while eosinophilia in the peripheral blood did not change regularly after 3 weeks of treatment. Therefore, the serum total Ig E is a useful investigation either in the initial diagnostic workup or during follow-up, while the total peripheral blood eosinophil count is not a good screening test for ABPM (29).

## Conclusions

In conclusion, ABPM due to fungi other than aspergilli is not common and currently underdiagnosed, thus, comprehensive basic and clinical studies are needed to establish more elaborate diagnostic criteria for patients with ABPM. Increased awareness among physicians is also required to prevent misdiagnosis of cases, especially in those patients with exacerbation of COPD. Furthermore, once the diagnosis has been confirmed, treatment should be initiated, and ongoing follow-up continued with detecting total Ig E level throughout the course of this chronic lung disorder.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This is a retrospective study and ethical approval is not required.

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