

ORIGINAL ARTICLE

Clinical characteristics of allergic bronchopulmonary aspergillosis

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Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease caused by a hypersensitivity reaction to *Aspergillus* colony in the airways. Due to the diversity of disease manifestations and physicians' incomplete knowledge of ABPA, patients with ABPA are often misdiagnosed and given poor prognosis.

Objectives: To investigate the clinical characteristics, treatment and prognosis status among patients with ABPA.

Methods: We retrospectively analyzed 75 patients diagnosed as ABPA in Zhongshan Hospital, Fudan University between October 2008 and June 2018.

Results: Among 75 patients, 28% had asthma as the predisposing condition and 69% suffered from misdiagnosis before ABPA diagnosis was made, among which 21% were misdiagnosed as tuberculosis. About 34% of patients had eosinophil count below 500 cells/ μ L and 25% had total serum IgE level <1000 IU/mL. Nearly half of patients did not meet the diagnostic criteria of ABPA and all the patients who overlapped with invasive pulmonary aspergillosis (IPA) did not meet the diagnostic criteria of standard ABPA. Patients who did not fully meet the diagnostic criteria were more likely treated with inhaled corticosteroids (ICS) and antibiotics, but more difficult to attain response and remission and easier to develop advanced ABPA.

Conclusions: This study demonstrates an unsatisfactory situation of diagnosis, treatment and prognosis of ABPA, including a high misdiagnosis rate, uncertainty in the diagnosis of ABPA, lack of standardization in treatment and relatively poor prognosis.

KEYWORDS

allergic bronchopulmonary aspergillosis, diagnosis, eosinophils, immunoglobulin E, treatment

1 | INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder caused by a hypersensitivity reaction to airway colonization of *Aspergillus* species, which predominantly affects patients with asthma and cystic fibrosis (CF).¹ A positive type I hypersensitivity reaction to *Aspergillus fumigatus*, increasing levels of serum immunoglobulin E (IgE)

and peripheral blood eosinophils, evidence of pulmonary infiltration, airway mucus plugging and bronchiectasis on chest computerized tomography (CT) are critical diagnostic basis for ABPA.²

After Hinson et al first described ABPA in 1952, it was found that ABPA was presented in 2.5% (range 0.72%-3.5%) of asthma patients and 7%-9% of CF patients.³ Recently, Denning et al estimate that a total of 4837 thousand ABPA

patients are presented worldwide, of which 491 thousand are diagnosed in China.⁴ Despite nearly seven decade of research, ABPA is still a complicated disorder with common misdiagnosis, high recurrence rate and poor outcome. It is reported that more than two-thirds of ABPA/allergic bronchopulmonary mycosis (ABPM) patients are misdiagnosed or undiagnosed worldwide⁵ with recurrence rates high up to 48% in Japan and 46% in India.^{6,7}

The unsatisfactory management of ABPA is mainly attributed to a lack of complete recognition of the disease and there are no formally validated diagnostic criteria and standardized treatment protocol so far.⁸⁻¹⁰ Although many cases of ABPA have been reported, a comprehensive description of clinical characteristics, diagnosis and prognostic perspective of ABPA is still lacking. This article retrospectively analyzed a total of 75 patients with ABPA diagnosed by physicians in Zhongshan Hospital, Fudan University in the past decade. We demonstrated the real-world management of ABPA in China, which will help researchers comprehensively understand and recognize ABPA toward better diagnosis and treatment of the debilitating diseases.

2 | MATERIALS AND METHODS

2.1 | Study design

A total of 75 patients were included in the study. All cases were diagnosed and hospitalized as ABPA in the Department of Respiratory Medicine and Infectious Disease of Zhongshan Hospital, Fudan University between October 2008 and June 2018. The study was approved by the Local Ethics Committee (B2016-047). Written consent was waived by the Local Ethics Committee due to the retrospective nature of the study.

2.2 | Patients

Because the study was designed to investigate the real-world management of ABPA, we included all 75 patients clinically diagnosed with ABPA. In consideration of some cases did not fully meet the diagnosis criteria of ABPA,¹¹ we also analyzed 39 cases out of 75 patients who fully met the diagnostic criteria recommended by the ABPA work-group of the International Society for Human and Animal Mycology (ISHAM) to better validate the statistical analysis.

2.3 | Data collection

The clinical details of all patients were collected from the medical records, including demographic data, pulmonary

comorbidities, clinical symptom and sign, laboratory examinations, thoracic CT findings, diagnosis, treatment courses and prognosis status.

In this study, basic lung diseases were defined as the history of other pulmonary disorders, such as tuberculosis, chronic obstructive pulmonary disease (COPD), pulmonary abscess, lung cancer, lung surgery or trauma. We collected prognosis information including evaluation of treatment response, remission, recurrence and advanced ABPA.¹¹ After 8 weeks of treatment, patients were thought responsive if there were evidence of clinical-radiological improvement and the decline of IgE levels by at least 25%. Patients were further evaluated 6 months after the end of treatment and patients were in remission if there was no manifestation of recurrence. Recurrence was considered when clinical and/or radiological worsen, accompanied by 50% increases in IgE levels. Advanced ABPA was manifested as type 2 respiratory failure and/or pulmonary heart disease, along with diffuse bronchiectasis and/or fibrosis.

2.4 | Statistical analysis

Statistical analyses were performed using SPSS version 20. Continuous variables were presented as median and interquartile range (IQR). Categorical data were presented as number/percentage. Continuous variables were compared using the Mann–Whitney *U* test. For categorical data, comparisons were made using Fisher's exact test. Statistical significance was set at $P < .01$ (two-tailed).

3 | RESULTS

3.1 | Clinical characteristics

A total of 75 patients with a clinical diagnosis of ABPA were analyzed in this study. Serum *A fumigatus*-specific IgE (sIgE) was detected in 61 patients, among which 58 were positive, one patient with negative sIgE was diagnosed with ABPA in another hospital 6 years ago, one was receiving chemoradiotherapy for lung cancer before sIgE detection and another one had a positive skin test for *Aspergillus* antigen. All patients underwent total IgE levels test and chest CT scan. About 70 cases received peripheral blood eosinophil count and 33 patients performed lung function tests. According to the diagnostic test results, 39 patients fully met the obligatory criteria for ABPA.

Table 1 presents demographic data and clinical features of all 75 patients and the differences of clinical characteristics between the patients who fully met the diagnostic criteria of ABPA ($n = 39$) and those who did not ($n = 36$). Median (IQR) age at onset of all patients was 45 (IQR 32–60), while

TABLE 1 Demographic and clinical data of the patients

Characteristics	All patients <i>n</i> = 75	Age at onset of ABPA, y		Meet diagnostic standard	
		<50 <i>n</i> = 46	≥50 <i>n</i> = 29	Yes <i>n</i> = 39	No <i>n</i> = 36
Age, y	49 (38-62)	41 (31-49)	63 (58-72)*	49 (40-61)	54 (32-65)
Women	29 (39%)	23 (50%)	6 (21%)*	15 (38%)	14 (39%)
Physician-diagnosed asthma	21 (28%)	12 (26%)	9 (31%)	10 (26%)	11 (31%)
Lung basic diseases	31 (41%)	16 (35%)	15 (52%)	17 (44%)	16 (44%)
Misdiagnosis	52 (69%)	36 (78%)	16 (55%)	28 (72%)	24 (67%)
Misdiagnosed as tuberculosis	16 (21%)	13 (28%)	3 (10%)	8 (21%)	8 (22%)
Age at onset of ABPA, y	45 (32-60)	35 (26-43)	63 (57-70)*	46 (34-57)	45 (26-64)
Laboratory data					
Eosinophil count, ^a cells/μL	780 (180-1312)	710 (330-1670)	850 (140-1190)	1130 (780-1825)	180 (45-720)*
Total IgE, IU/mL	2629 (952-5547)	3049 (1068-6605)	1880 (808-3523)	4169 (2528-6786)	926 (370-2885)*
Lung function					
FEV ₁ % predicted	73 (49-85)	63 (46-82)	82 (69-85)	69 (49-83)	80 (56-85)
FEV ₁ /FVC ratio	70 (55-81)	64 (53-80)	75 (66-81)	69 (54-80)	75 (54-83)
Thoracic CT findings					
Central bronchiectasis	62 (83%)	39 (85%)	23 (79%)	33 (85%)	29 (81%)
Mucoid impaction	35 (47%)	21 (46%)	14 (48%)	22 (56%)	13 (36%)
Chronic pleuropulmonary fibrosis	32 (43%)	16 (35%)	16 (55%)	15 (38%)	17 (47%)
IPA	7 (9%)	6 (13%)	1 (3%)	0 (0%)	7 (19%)*
CPA	7 (9%)	3 (7%)	4 (14%)	3 (8%)	4 (11%)

Note: Values are medians (interquartile range) or number (proportion). *n* of all patients = 75, except for ^a*n* = 70.

Abbreviations: CPA, chronic pulmonary aspergillosis; CT, computed tomography; FEV₁% predicted, percentage of predicted forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IPA, invasive pulmonary aspergillosis.

**P* < .01; age at onset of ABPA <50 versus >50, or patients meeting diagnostic standard versus patients not meeting diagnostic standard.

the median age for men was 49 (IQR 38-63), older than women with 37 (IQR 31-48) (*P* < .01). 21 (28%) patients had been diagnosed by a physician as asthma before diagnosis as ABPA in our hospital. More than two-thirds of patients (*n* = 52, 69%) were misdiagnosed before being diagnosed with ABPA (Table 1), among which 34 patients (45%) were misdiagnosed as infectious pneumonia, 16 patients (21%) were tuberculosis, 14 patients received anti-tuberculosis therapy and others were misdiagnosed as bronchitis, eosinophilic pneumonia, hypersensitivity pneumonitis and lung cancer. In addition, the time between symptom onset and the correct diagnosis was more than 1 year in 41 patients (55%), and >10 years in 13 patients (17%).

The median (IQR) eosinophil count was 780 (180-1312) cells/μL (Table 1; Figure 1) of all patients but was only 180 (45-720) cells/μL in the 36 patients who did not meet the diagnostic standard (*P* < .001). The median total IgE levels (IQR) was 2629 (952-5547) IU/mL of 75 patients but was 926 (370-2885) in those who did not meet diagnostic criteria (*P* < .001). Total IgE levels were observed >417 IU/mL in 66 patients (88%) and >1000 IU/mL in 56 patients (75%),

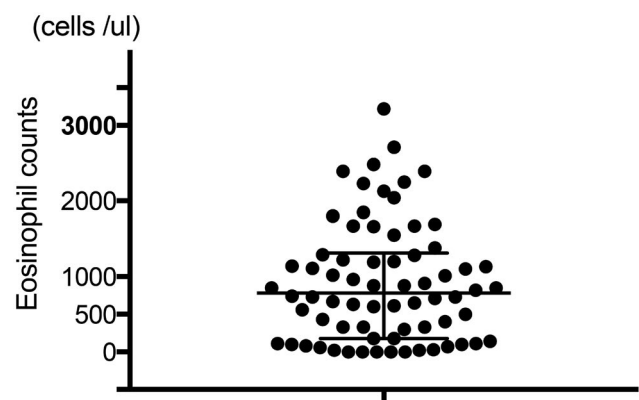


FIGURE 1 Peripheral blood eosinophil counts of 70 patients. The bar indicates the median value and interquartile range

respectively (Table 1; Figure 2). About 7 of 36 patients insufficient to meet diagnostic criteria, were overlapped with invasive pulmonary aspergillosis (IPA) while no IPA-overlap patient was found among the 39 patients adequately diagnosed as ABPA (*P* = .004).

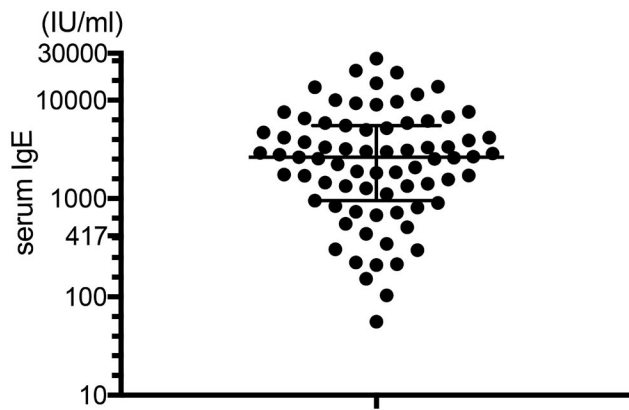


FIGURE 2 Total IgE levels in serum of 75 patients. The bar indicates the median value and interquartile range

Table 2 shows the differences in clinical features between 25 (34%) patients with eosinophil count < 500 cells/ μ L and 45 (66%) patients with eosinophil count $\geq$ 500 cells/ μ L. Median total IgE levels (IQR) was 1840 (408-2990) IU/mL in patients with eosinophil count < 500 cells/ μ L and 3098 (1342-6219) IU/mL in patients with eosinophil counts $\geq$ 500 cells/ μ L. The patients overlapping with IPA had lower eosinophil count ($P = .007$) while complicated with chronic pulmonary aspergillosis (CPA) did not (Table 2).

3.2 | Treatment

Table 3 demonstrates remedy applications of all 75 patients and the differences in treatments between the patients who fully met the diagnostic criteria of ABPA ($n = 39$) and those patients who did not ($n = 36$). The patients applied with systemic steroids, anti-fungal drugs or systemic steroids plus anti-fungal drugs accounted for 95%, 71% and 67%, respectively. The two drugs are used in similar proportions in both groups (Table 3). Inhaled corticosteroids (ICS) were applied in 26% of patients who fulfilled diagnosis standard and 50% of patients who inadequately met diagnostic criteria, while antibiotics were used in 38% and 69% of the two groups, respectively (Table 3).

3.3 | Prognosis

After 8 weeks of treatment, 48 patients were reviewed with clinical-radiological conditions and total IgE levels for response evaluation, among which 38 (79%) of them were proved to respond to treatments. The improvement rates were 92% in patients meeting diagnostic criteria and 65% in patients insufficient to diagnosis (Table 4). About 42 patients were further assessed for remission 6 months after the end of treatment. About 31 (74%) patients went into remission, in which remission rates of the two groups were 91% and

TABLE 2 Differences in clinical characteristics according to peripheral blood eosinophil level

Characteristics	Eosinophil count, cells/ μ L		<i>P</i> value
	<500 <i>n</i> = 25	$\geq$ 500 <i>n</i> = 45	
Age, y	52 (38-68)	49 (39-62)	.755
Women	11 (44)	17 (38)	.621
Physician-diagnosed asthma	6 (24)	14 (31)	.591
Lung basic diseases	11 (44)	18 (40)	.803
Misdiagnosis	15 (60)	33 (73)	.290
Age at onset of ABPA, y	44 (30-65)	47 (33-59)	.849
Laboratory data			
Eosinophil count, cells/ μ L	100 (20-315)	1140 (835-1745)	.000
Total IgE, IU/mL	1840 (408-2990)	3098 (1342-6219)	.048
Lung function			
FEV ₁ % predicted	64 (41-84)	78 (55-86)	.287
FEV ₁ /FVC ratio	66 (52-82)	70 (56-81)	.553
Thoracic CT findings			
Central bronchiectasis	21 (84)	39 (87)	.737
Mucoid impaction	8 (32)	26 (58)	.037
Chronic pleuropulmonary fibrosis	12 (48)	18 (40)	.616
IPA	6 (24)	1 (2)	.007
CPA	4 (16)	3 (7)	.239

Note: Values are medians (interquartile range) or number (proportion). *n* of all patients with eosinophil count = 70.

Abbreviations: CPA, chronic pulmonary; CT, computed tomography; FEV₁% predicted, percentage of predicted forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; IPA, invasive pulmonary aspergillosis.

55%, respectively (Table 4). Up to the day of data collection, 26 (67%) patients suffered from recurrences after responses and 4 (12%) patients developed advanced ABPA (Table 4). Noticeably, the four advanced patients all belonged to the group insufficient to diagnosis criteria.

4 | DISCUSSION

This is a retrospective study to investigate the clinical characteristics and real-world management of ABPA in China and help to improve present diagnostic and therapeutic status.

It is commonly known that ABPA usually occurs in patients with asthma or CF. The rates for patients complicated

TABLE 3 Treatments of the patients

Treatment	All patients	Meet diagnostic standard		
	<i>n</i> = 75	Yes (<i>n</i> = 39)	No (<i>n</i> = 36)	<i>P</i> value
Systemic steroids (SS)	71 (95%)	38 (97%)	33 (92%)	.345
Anti-fungal drugs (AFD)	53 (71%)	29 (74%)	24 (67%)	.612
SS + AFD	50 (67%)	28 (72%)	22 (61%)	.341
Inhaled corticosteroids	28 (37%)	10 (26%)	18 (50%)	.035
Antibiotics	40 (53%)	15 (38%)	25 (69%)	.011

Note: Values are shown as number (proportion). *n* of all patients = 75.

TABLE 4 Prognosis of the patients

Prognosis	All patients	Meet diagnostic standard		
		Yes	No	<i>P</i> value
Response ^a	38 (79%)	23 (92%)	15 (65%)	.033
Remission ^b	31 (74%)	20 (91%)	11 (55%)	.013
Recurrence ^c	26 (67%)	15 (68%)	11 (65%)	1.000
Advanced ABPA ^d	4 (12%)	0 (0%)	4 (29%)	.024

Note: Values are shown as number (proportion).

Abbreviation: ABPA, allergic bronchopulmonary aspergillosis.

^a*n* = 48.

^b*n* = 42.

^c*n* = 39.

^d*n* = 33.

with asthma are reported as 81%, 100% and 100% in Japan, Korea and India, respectively. However, our study finds that only 28% of patients have been diagnosed with asthma before being diagnosed as ABPA. This is probably because of the relatively low diagnostic and treatment rate of asthma in China in the past,¹² which may also contribute to the misdiagnosis of ABPA.

Aspergillus overlap syndromes (AOS) are defined as simultaneous or sequential occurrence of more than one form of aspergillus disease in a single patient, which usually accompanied by atypical clinical manifestations.^{13,14} In this study, there are seven ABPA patients overlapped with IPA and seven patients overlapped with CPA. Intriguingly, we find that all patients with ABPA overlapping with IPA do not meet diagnostic criteria and six of them have eosinophil counts below 500 cells/ μ L, while the patients overlapped with CPA have no distinct differences with simple ABPA patients. We infer that the potent immunosuppressed state of IPA patients may account for the lower eosinophil counts and atypical clinical characteristics. Although overlapping with IPA is rare among ABPA patients, they are faced with high risk of misdiagnosis and death.¹³ So, physicians should be cautious of IPA overlapping especially among patients with suspicious ABPA and atypical clinical manifestations.

It has been 5 years since Mou et al⁵ reported the delayed diagnosis of ABPA in our hospital. However, we find that the

situation remained grim. Diagnostic errors and delays happen to most patients, and they were commonly misdiagnosed as pneumonia and tuberculosis. There are three possible reasons for ABPA misdiagnosis¹⁵: the first one is the diverse clinical presentations of ABPA; second, some patients lack the history of asthma, and even have no symptom of airflow obstruction at the time of diagnosis; the third reason is the similar symptoms and radiological findings between ABPA and pulmonary tuberculosis. And the high prevalence of tuberculosis in China¹⁶ often leads to misdiagnosis of ABPA as tuberculosis. Such a high rate of misdiagnosis no doubt poses patients at risk of severe lung damage. Hence, it is imperative to adopt screening tests of higher sensitivity among those patients with potential ABPA.

The newest management guideline for ABPA suggests >500 cells/ μ L of peripheral blood eosinophil count as one of the diagnostic criteria.¹¹ However, many ABPA patients have eosinophil counts lower than 500 cells/ μ L because of receiving oral steroids or at the relatively stable stage of the disease.¹⁷ Even a previous study showed that blood eosinophilia was not presented in all ABPA patients.¹⁸ Agarwal et al reported that 23.9% of patients had less than 500 cells/ μ L with median (IQR) eosinophil count of 850 (510-1541) cells/ μ L. Similarly, Kumar et al showed that the absolute eosinophil count was >500 cells/ μ L only in 53% of patients.¹⁹ In addition, total IgE in a quarter of patients is less than 1000 IU/mL in our study when total IgE level > 1000 IU/mL

is considered as an essential criterion in the diagnosis of ABPA.¹¹ Several studies reported that total IgE levels were < 1000 IU/mL among many ABPA patients in Korea and Japan.^{6,20,21} As total IgE of 1000 IU/mL is a new standard cut-off line published in 2013, there is a wide variation of IgE concentrations in ABPA patients,²² most of the physicians will not diagnose ABPA strictly based on the diagnostic standard of total IgE. Due to the two major factors above, 48% of patients analyzed in our study do not meet diagnostic criteria of ABPA, although they have been diagnosed as ABPA, accepted some treatments and follow-ups according to the clinical guidelines. More investigations are required to determine whether those patients insufficient to diagnostic criteria suffered from excessive medical treatment or whether the diagnostic standards of ABPA lack sensitivity.

In our study, systemic steroids, anti-fungal drugs, ICS and antibiotics are the four main medicines applied in ABPA patients. It has been reported that on the premise of possible rapid recognition and treatment of acute exacerbations, continuous treatment with ICS will reduce the episode number and severity of relapses.²³ Probably because secondary infections or misdiagnosis as pneumonia are prevalent among ABPA patients in this study, over half of the patients receive antibiotics during initial therapy. Noticeably, we observe that physicians incline to use ICS and antibiotics on patients who do not meet diagnostic standards. However, prognostic analyses show that the patients inadequate to the diagnostic standard poorly obtain response and remission after the treatments, but are easier to advance into severe ABPA. Actually, there is controversy over the efficacy of ICS in treating ABPA. A double-blind, multicenter, placebo-controlled trial proves no benefit by using ICS over placebo and the other study finds that median IgE levels increase by 99% after 6 month-treatment of ICS.^{24,25} In addition, long-term use of broad-spectrum antibiotics may alter the local microbiota and cause the development of antibiotics resistance, which may ultimately influence the short-term outcome. Therefore, whether applications of ICS and antibiotics affect the outcomes of ABPA patients may need further research. Furthermore, it remains questionable whether those patients who do not meet the diagnostic standard are qualified for the diagnosis of ABPA. If they do qualify, it will be worth exploring whether they require a more reasonable treatment course. Due to a lack of statistical significance, we believe that more subjects are required to verify these results.

In conclusion, our study demonstrates the real-world management condition of ABPA in China. The results in our study expose several problems in the diagnosis and treatment of ABPA, including a high misdiagnosis rate, part of ABPA patients inadequate to diagnostic criteria and poorer prognosis of them. Because this is a single-center retrospective study and the sample size was relatively small, additional studies may be necessary to confirm our results.

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CONFLICT OF INTEREST

No conflict exists for the all authors.

AUTHOR CONTRIBUTIONS

Designed the study: Shao

Collected and analyzed the data, wrote the paper: Zhang

Contributed to the review of the manuscript: Jiang and Shao

ETHICS

The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University. And the written consent was waived for this type of study.

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