



Clinical Characteristics of Allergic Bronchopulmonary Aspergillosis in Patients with and without Bronchiectasis

Sijiao Wang, Jun Zhang, Cuiping Zhang & Changzhou Shao

To cite this article: Sijiao Wang, Jun Zhang, Cuiping Zhang & Changzhou Shao (2021): Clinical Characteristics of Allergic Bronchopulmonary Aspergillosis in Patients with and without Bronchiectasis, Journal of Asthma, DOI: [10.1080/02770903.2021.1904979](https://doi.org/10.1080/02770903.2021.1904979)

To link to this article: <https://doi.org/10.1080/02770903.2021.1904979>



Accepted author version posted online: 17 Mar 2021.



Submit your article to this journal [↗](#)



Article views: 3



View related articles [↗](#)



View Crossmark data [↗](#)

Running head: Characteristics of ABPA-CB and ABPA-S.

Clinical Characteristics of Allergic Bronchopulmonary Aspergillosis in Patients with and without Bronchiectasis

Sijiao Wang^a, Jun Zhang^a, Cuiping Zhang^a, and Changzhou Shao^{a,b*}

^a *Department of Pulmonary Medicine, Shanghai Respiratory Research Institute, Zhongshan Hospital, Fudan University, Shanghai 200032, China;*

^b *Department of Pulmonary Medicine, Xiamen Branch, Zhongshan Hospital, Fudan University, Xiamen 361015, China*

*Corresponding Author: Changzhou Shao, MD, Department of Pulmonary Medicine, Xiamen Branch, Zhongshan Hospital, Fudan University, Xiamen 361015, China. E-mail: sczzhongshan@126.com. Telephone: 08621-64041990 Fax: 08621-64187165

Objective: Allergic bronchopulmonary aspergillosis (ABPA) is classified radiologically as serologic ABPA (ABPA-S) or ABPA with central bronchiectasis (ABPA-CB). This retrospective case series study aimed to describe and compare the clinical characteristics of both forms of ABPA. **Methods:** Patients with ABPA treated in the hospital between February 2011 and June 2019 were enrolled and were divided into ABPA-S and ABPA-CB groups based on whether their cases were complicated with central bronchiectasis. Demographic data, symptoms, laboratory values, comorbidities, and image findings were collected. ABPA-S patients were followed up retrospectively through medical records. **Results:** Ninety-three (93) patients were enrolled, including 74 ABPA-CB patients and 19 ABPA-S patients. The most common predisposing condition was asthma (36.6%), with a median course of 30 years (IQR 13-42.5) prior to ABPA diagnosis. 54.8% of patients had been misdiagnosed, with ABPA-S more likely than ABPA-CB to have been misdiagnosed as asthma ($p < 0.01$). Obstructive ventilation dysfunction and mixed ventilation dysfunction were found in 21 patients (22.6%) and 18 patients (19.4%), respectively. Compared with ABPA-S, ABPA-CB had a higher median blood eosinophil count [880 vs. 700 cells/ μ l], serum IgE [2,957 vs. 2,616 IU/ml], and *Aspergillus fumigatus* specific-IgE [20.6 vs. 7.31 kUA/L], although these findings were not statistically significant. Three ABPA-S patients developed bronchiectasis during follow-up and experienced relapses more than twice. **Conclusions:** Our findings suggested that the clinical characteristics between ABPA-CB and ABPA-S were mostly similar. ABPA-S had a relatively lower immunological activity level than ABPA-CB, but was still immunologically active and could develop bronchiectasis.

Keywords: Allergic Bronchopulmonary Aspergillosis; Bronchiectasis; *Aspergillus*; Misdiagnosis

Introduction

Since the first report of allergic bronchopulmonary aspergillosis (ABPA) in 1952, ABPA has gradually become recognized across the globe (1). ABPA is a complicated pulmonary disorder caused by the allergic immune response to *Aspergillus fumigatus* (*A. fumigatus*), clinically manifesting as chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis (2). The global burden of ABPA is an estimated 4.8 million people (3), and accounts for approximately 2.5% of asthmatic patients, and 8.9% of cystic fibrosis (CF) sufferers (3, 4). According to radiologic

characteristics, ABPA can be generally classified as either serologic ABPA (ABPA-S), or ABPA with central bronchiectasis (ABPA-CB) (5, 6).

Due to the atypical manifestations of ABPA, such as expectoration and hemoptysis (7), it can easily be underdiagnosed or misdiagnosed for many years, resulting in irreversible lung damage, namely bronchiectasis or lung fibrosis (2, 7-9). Consequently, early and prompt diagnosis and treatment for ABPA are important for preventing poor prognosis. Unfortunately, at present, there are no defined international criteria or standardized treatment protocol for ABPA (10). A key first step was taken by the International Society for Human and Animal Mycology (ISHAM) working group in 2013, when it proposed criteria for diagnosis and treatments for ABPA (5). Later, Agarwal et al. proposed newly revised criteria based on ISHAM criteria and more evidence from studies in 2016 (11).

There are several differences between ABPA-S and ABPA-CB (8, 12-15). ABPA-S presents as meeting the ISHAM criteria for ABPA without bronchiectasis, whereas ABPA-CB has central bronchiectasis (13, 16, 17). In addition, as compared to ABPA-CB, ABPA-S has less immunological activity and a milder clinical course due to its lower level of total serum IgE and *A. fumigatus*-specific IgE (sIgE). ABPA-S also has fewer exacerbated symptoms (8, 12), and the frequency of exacerbation has been shown to be significantly lower than in patients with ABPA-CB (13, 14). Moreover, a study by Agarwal et al. found that with early diagnosis and treatment, patients with ABPA-S had a good long-term outcome, and did not progress into bronchiectasis (14). It is worth noting, however, that most of these studies had a limited sample size, so more evidence is required to elucidate the difference between ABPA-S and ABPA-CB.

In our study, we collected and analyzed data from patients with ABPA who had been hospitalized, aiming to describe and compare the clinical characteristics of patients with ABPA-S versus ABPA-CB.

Methods

Study design

Patients diagnosed with ABPA and hospitalized in the Department of Respiratory Medicine of Zhongshan Hospital at Fudan University (Shanghai, China) between February 2011 and June 2019 were enrolled. Based on their medical records, patients categorized as ABPA-S were retrospectively followed up until March 2020. Given the retrospective nature of the study, written consents were waived.

Patients

Based on the modified ISHAM 2013 criteria proposed in 2016 (11), the inclusion criteria for the patients were: [1] Diagnosis of bronchial asthma, CF, or other pulmonary diseases; [2] Elevated sIgE (anti-*Aspergillus fumigatus*) levels > 0.35 kUA/L (those diagnosed clinically, but without the data could also be included if they met all other criteria); total IgE levels > 1,000 IU/mL (or <1,000 IU/mL if all other criteria are met); [3] At least two of the following three additional criteria: IgG antibodies against *A. fumigatus* in serum > 27 mg/L; thoracic radiographic opacities consistent with ABPA (transient or permanent); or total eosinophil count > 500 cells/ μ L in oral steroid-naïve patients. The exclusion criteria were as follows: [1] Not meeting inclusion criteria mentioned above; [2] Combinations of other allergic diseases, except respiratory diseases.

If patients had central bronchiectasis on the initial chest computed tomography (CT) at the first diagnosis of ABPA, they were classified as ABPA-CB. Otherwise, they were classified as ABPA-S, and were included in the follow up part of the study. If located at the medial two-thirds or medial

half of the lung and at a point midway between the hilum and the chest wall, the bronchiectasis can be classified as CB by an experienced professional radiologist (5).

Data collection

All patient data were collected from electronic medical records in the hospital, including chief complaint, demographics; pulmonary comorbidities; symptoms at onset; pulmonary function tests; laboratory findings, such as eosinophil count, total serum IgE, and sIgE; microbiological tests; chest CT findings; and treatments. The information related to misdiagnosis was extracted from the medical history. Mild, moderate, and severe ventilation dysfunction were defined as $60\% \leq \text{FEV1\% pre} < 80\%$, $40\% \leq \text{FEV1\% pre} < 60\%$, $\text{FEV1\% pre} < 40\%$, respectively. Specific IgE values for twenty cases were not available because they were tested and diagnosed in other hospitals.

The five stages of ABPA at first admission were defined as follows (18, 19): Stage I (acute), Stage II (clinical and serological remission), Stage III (recurrence), Stage IV (chronic, steroid-dependent asthma or ABPA), and Stage V (fibro-cavity manifestation secondary to progressive inflammation and airway dilation). Clinical staging classification was evaluated based on their overall condition at the first visit to Zhongshan Hospital. According to WHO IgE reference standard 75/502, sIgE levels were divided into seven grades (20): grade 0, less than 0.35 kUA/L; grade 1, 0.35 - 0.7 kUA/L; grade 2, 0.70 - 3.5 kUA/L; grade 3, 3.6 - 17.5 kUA/L; grade 4, 17.5 - 50 kUA/L; grade 5, 50 - 100 kUA/L; and grade 6, greater than 100 kUA/L. Furthermore, patients with ABPA-S were followed up retrospectively, and their clinical manifestations, chest CT findings, and serum IgE were obtained from medical records. Relapse was defined as doubled baseline total serum IgE levels together with clinical symptoms or image findings worsening. Remission was defined as serum IgE levels that declined by 25% -35% with clinical improvement in two months.

Statistical analysis

Continuous variables were presented as the mean (SD) or median (interquartile range, IQR), and categorical data were presented as a number (percentage). Statistical comparison of continuous variables was performed using the Mann-Whitney U test between ABPA-CB and ABPA-S, or using the Kruskal-Wallis test among the five stages. Chi-square or Fisher's exact test was conducted for categorical data. A $p < 0.05$ (two-tailed) was considered statistically significant. IBM SPSS 22 was employed for all analyses.

Ethical considerations

The present study was conducted with the approval of Local Ethics Committee of Zhongshan Hospital (Approval no. B2016-047).

Results

Clinical characteristics

A total of 93 patients hospitalized due to acute wheezing dyspnea, hemoptysis, asthma exacerbation, discovery of unknown pulmonary shadows, and re-examination were enrolled, including 74 cases with ABPA-CB and 19 cases with ABPA-S. As shown in Table 1, the mean age at onset was 52.4 years old, and no significant differences were observed between the two groups in age, sex proportion, and smoking history. Asthma was the most common pulmonary comorbidity (36.6%), with a median history of 30 (IQR 13-42.5) years. Seven patients (7.5%) had chronic pulmonary aspergillosis (CPA). The symptoms in the ABPA-CB and ABPA-S groups showed little difference

except for hemoptysis ($p = 0.019$). Of 46 patients (49.5%) with lung function tests, obstructive ventilation dysfunction was found in 21 patients, and mixed ventilation dysfunction in 16. Initially, 39 patients (41.9%) received systemic corticosteroid treatment, and 54 patients (58.1%) were administered both antifungal agents and systemic corticosteroids.

Table 2 illustrates that 54.8% of the patients had been misdiagnosed. Pneumonia (31.2%) and tuberculosis (19.4%) were the two most commonly misdiagnosed diseases. Moreover, one ABPA-CB patient and four ABPA-S patients were misdiagnosed with asthma, one of whom was misdiagnosed as cough variant asthma. The finding that ABPA-S was more likely than ABPA-CB to be misdiagnosed as asthma was statistically significant ($p = 0.006$).

The duration from the first hospital visit to eventual confirmation varied remarkably, ranging from 20 days to 30 years. Approximately 23.5% of patients were misdiagnosed for more than one year. Of four patients diagnosed ten years later, one 37 year old patient was misdiagnosed with tuberculosis and had received long term anti-tuberculosis treatments. The other three patients aged over 55 at diagnosis, and had a history of tuberculosis that had been cured thoroughly. No difference was found in the duration of misdiagnosis between ABPA-CB and ABPA-S.

Laboratory and radiological findings

For all patients, the median eosinophil count was 865 (530-1,492) cells/ μ l, and the median total serum IgE was 2915 (1,637-6,481) IU/ml (Table 3). ABPA-CB patients had higher median blood eosinophil counts [880 vs. 700 cells/ μ l] and higher serum IgE than ABPA-S [2,957 vs. 2,616 IU/ml], even though the difference was not statistically significant [Figure 1(a) and Figure 1(b)]. In addition, 73 patients had available sIgE data, 35 of whom had an exact value for sIgE with mean level of 18.4 kUA/L. Additionally, 33.3% of patients with increased sIgE levels had elevated level of Penicillium specific IgE as well.

Regarding microbiological tests, bronchoalveolar lavage fluid (BALF) or sputum culture was tested for fungus in 57 patients (61.2%). Culture results showed that eight were positive for *A. fumigatus*, six for *Aspergillus flavus*, and four for both fungi. In addition, mucus plugging in bronchus was found during bronchofibroscopy in 26 patients (27.9%). Also, two common chest CT findings in ABPA patients were inflammation (80.6%) manifesting as infiltrates or consolidation that display patchy or shaggy cloudy shadows on CT images, bronchiectasis (79.5%) manifesting as typical characteristics such as signet ring or string of pearl appearance. Muroid impaction (17.2%), pleural thickening (16.1%), pulmonary fibro-cavity (8.6%) and lung fibrosis (5.4%) were observed as well. Although airway muroid plugging in ABPA is generally hypodense (5, 11), we found that high-attenuation mucus (HAM) impaction, the important radiological feature to distinguish ABPA from other causes of bronchiectasis, was presented in eight ABPA-CB patients. Except for bronchiectasis, all other radiological characteristics showed no difference between ABPA-CB and ABPA-S.

As noted in Table 4, most patients (69.9%) were in Stage I (acute) when confirmed in our hospital. Blood eosinophil count ($p = 0.308$) and total serum IgE level ($p = 0.078$) did not differ significantly among the five stages. Stages I and stage III (recurrence) demonstrated the much higher level of eosinophils and total IgE than other stages. No ABPA-S patients were classified in Stage V which tended to have typical image findings, such as bronchial dilation and fibro-cavity. Besides, two patients (3.1%) of Stage I exhibited the pulmonary cavity ever caused by lung squamous carcinoma and tuberculosis, respectively.

Follow-up of ABPA-S patients

Based on medical records in our hospital, 14 of 19 patients with ABPA-S had retrospective and continuous follow-ups. Furthermore, the duration of those retrospective follow-ups ranged from 2 months to 66 months. In two patients, clinical outcome could not be judged due to a short follow-up period. Nine patients attained clinical remission, and the remaining three patients developed bronchiectasis within 36, 43, and 66 months, respectively. Of these three patients, one relapsed three times, and two experienced two relapses with evident bronchiectasis on chest CT images (Figure 2).

Discussion

In the present study, our results showed that among hospitalized patients, clinical characteristics between ABPA-CB and ABPA-S were mostly similar. Yet there was one noteworthy difference in level of immunological activity. Specifically, ABPA-S patients had a relatively lower level of immunological activity than ABPA-CB patients, manifesting as a low level of blood eosinophils, serum IgE, and sIgE, a finding consistent with previous studies (13, 16). Importantly, we noticed that patients with ABPA-S could develop bronchiectasis, implying that this form was not immunologically inactive, but rather a milder form of ABPA.

Currently, an international standard consensus on the number of major and minor criteria required for the diagnosis of ABPA has not been defined. As a follow-up to the original ISHAM criteria (5), the 2016 version added COPD and post-tuberculous fibro-cavitary disease as predisposing conditions (11). Our findings consistently showed that in addition to asthma, COPD and tuberculosis were susceptible conditions for ABPA. A recent study by Asano et al. found that the incidence of asthma in ABPA was as high as 77% (10), while the incidence was only 37% in our cohort. In our study, there are two possible reasons for the relatively lower incidence of asthma in patients with ABPA: the underdiagnosis of asthma in the real world, and the fact that nearly 30% of patients in the cohort were complicated with COPD or tuberculosis, both of which have become highly prevalent in China in recent years (21, 22). In addition, we found seven patients had both ABPA-CB and CPA, which is so called aspergillus overlap syndromes (AOS) that had two more forms of aspergillus-related lung diseases(23).

Given the similarities in symptoms and imaging characteristics of ABPA and other diseases, such as pneumonia (7), recognizing and diagnosing ABPA remain difficult. Studies reported that half of the ABPA cases in India were misdiagnosed as tuberculosis, and in our hospital, the most common misdiagnosed diseases were pneumonia and tuberculosis (9, 12). Consequently, when a patient fails to improve or relapses after a course of antibiotics for pneumonia or tuberculosis, the physician should be prudent to consider a differential diagnosis for ABPA. We also found that ABPA-S was more likely to be misdiagnosed as asthma than ABPA-CB, implying the close relation between asthma and ABPA-S.

The features of ABPA-S, such as increased total and sIgE levels, evidence of fungal sensitization, and responsiveness to antifungal therapy, were also observed in severe asthma with fungal sensitization (SAFS), a specific asthma phenotype first introduced in 2006 (24, 25), posing a clinical challenge to differentiate SAFS from ABPA-S. One single-center retrospective study by Agarwal et al. revealed that the best cut-off value of *A. fumigatus* IgE was 1.9 kUA/L for distinguishing ABPA from asthma (26). Research suggests that sensitization to *A. fumigatus* has been unequivocally associated with reduced lung function and radiological abnormalities among asthmatic patients, regardless of SAFS or ABPA (27, 28), so the test for Aspergillus-specific IgE with high sensitivity should be used to screen asthmatic patients (11).

To our knowledge, since 13 cases of ABPA without bronchiectasis were first described in 1986, only a handful of reports investigated the difference between ABPA-S and ABPA-CB (13-16). Although ABPA-S was believed to be the earliest stage of the disease, studies showed that the condition could

remain immunologically active and progress as corticosteroid-dependent asthma (29). Our data showed that three ABPA-S patients developed bronchiectasis and experienced two or more relapses, suggesting ABPA-S was still an active form and required close and long-term monitoring. The relationship between relapse and the emergence of bronchiectasis deserves further research, especially since a long delay in ABPA diagnosis can cause irreversible lung damage. This highlights the need to elevate the diagnosis rate of ABPA for an improved prognosis, especially in patients with ABPA-S. Additionally, Stages I and III had highest level of eosinophils and total IgE, implying the immunologically active status when ABPA newly occurred or relapsed.

Our study also showed that *A. fumigatus* and *A. flavus* were the two most common fungi in BALF and sputum cultures in both ABPA-CB and ABPA-S patients. *A. fumigatus* has been identified as the most common fungus to cause lung infections and allergy (25), and *A. flavus* has resulted in a high occurrence of sensitization in subjects with ABPA (4). Although culture results are not the diagnostic standard for ABPA, fungi colonization was critical for antifungal drug administration, as there can be a disassociation between sensitizing and airway colonizing fungi in definitive ABPA (30). In addition, mucoid impaction is a classic finding in ABPA, which has mucoid secretions filled in the dilated and destroyed airway (31). Mucoid impaction is typically depicted as tubular or branching opacities radiating from the hilum toward the periphery of the lung on chest CT, and could form a finger-in-glove sign (32). Moreover, recent one meta-analysis demonstrated that hyperattenuating mucus on CT had a specificity of 92%, making it as a good biomarker for the diagnosis of (33).

This study also has several limitations. First, the number of patients with ABPA-CB and ABPA-S differed significantly, making comparisons less valid. Second, because of the retrospective nature of the study, some patients lacked essential data, such as sIgE, thereby impacting the quality of data. Third, without data on type III hypersensitivity to *A. fumigatus* including precipitating antibodies or *A. fumigatus* specific IgG, the subgroup ABPA-S was not defined rigorously enough. Finally, only a portion of ABPA-S patients was followed up based on available medical records, making the follow up non-comprehensive.

Conclusions

Clinical characteristics between ABPA-CB and ABPA-S were generally similar. However, ABPA-S had a relatively lower level of immunological activity, but could still develop bronchiectasis, suggesting that this form of ABPA is immunologically active, and needs early diagnosis and intervention.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

1. Hinson KF, Moon AJ, Plummer NS. Broncho-pulmonary aspergillosis; a review and a report of eight new cases. Thorax. 1952;7(4):317-33. doi: 10.1136/thx.7.4.317.
2. Agarwal R. Allergic bronchopulmonary aspergillosis. Chest. 2009;135(3):805-26. doi: 10.1378/chest.08-2586.

3. Denning DW, Pleuvry A, Cole DC. Global burden of allergic bronchopulmonary aspergillosis with asthma and its complication chronic pulmonary aspergillosis in adults. *Med Mycol*. 2013;51(4):361-70. doi: 10.3109/13693786.2012.738312.
4. Maturu VN, Agarwal R. Prevalence of *Aspergillus* sensitization and allergic bronchopulmonary aspergillosis in cystic fibrosis: systematic review and meta-analysis. *Clin Exp Allergy*. 2015;45(12):1765-78. doi: 10.1111/cea.12595.
5. Agarwal R, Chakrabarti A, Shah A, Gupta D, Meis JF, Guleria R, Moss R, Denning DW, group AcaIw. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013;43(8):850-73. doi: 10.1111/cea.12141.
6. Knutsen AP. Allergic bronchopulmonary aspergillosis. *Clin Exp Allergy*. 2015;45(2):298-9. doi: 10.1111/cea.12459.
7. Kim Y, Lee HY, Gu KM, Lee JY, Yoon SW, Park TY, Choi JC, Kim JY, Park IW, Shin JW, Choi BW, Jung JW. Delayed diagnosis of allergic bronchopulmonary aspergillosis due to absence of asthmatic symptoms. *Asia Pacific allergy*. 2016;6(3):187-91. doi: 10.5415/apallergy.2016.6.3.187.
8. Patterson K, Strek ME. Allergic bronchopulmonary aspergillosis. *Proc Am Thorac Soc*. 2010;7(3):237-44.
9. Mou Y, Ye L, Ye M, Yang D, Jin M. A retrospective study of patients with a delayed diagnosis of allergic bronchopulmonary aspergillosis/allergic bronchopulmonary mycosis. *Allergy Asthma Proc*. 2014;35(2):e21-6. doi: 10.2500/aap.2014.35.3731.
10. Asano K, Hebisawa A, Ishiguro T, Takayanagi N, Nakamura Y, Suzuki J, Okada N, Tanaka J, Fukutomi Y, Ueki S, Fukunaga K, Konno S, Matsuse H, Kamei K, Taniguchi M, Shimoda T, Oguma T. New Clinical Diagnostic Criteria for Allergic Bronchopulmonary Aspergillosis/Mycosis and its Validation. *The Journal of allergy and clinical immunology*. 2020. doi: 10.1016/j.jaci.2020.08.029.
11. Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med*. 2016;10(12):1317-34. doi: 10.1080/17476348.2016.1249853.
12. Agarwal R, Gupta D, Aggarwal AN, Behera D, Jindal SK. Allergic bronchopulmonary aspergillosis: lessons from 126 patients attending a chest clinic in north India. *Chest*. 2006;130(2):442-8. doi: 10.1378/chest.130.2.442.
13. Rajkumar DC. Evaluation of allergic bronchopulmonary aspergillosis in patients with and without central bronchiectasis. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2002;39(6):473-7. doi: 10.1081/jas-120004905.

14. Agarwal R, Garg M, Aggarwal AN, Saikia B, Gupta D, Chakrabarti A. Serologic allergic bronchopulmonary aspergillosis (ABPA-S): long-term outcomes. *Respir Med*. 2012;106(7):942-7. doi: 10.1016/j.rmed.2012.03.001.
15. Greenberger PA, Miller TP, Roberts M, Smith LL. Allergic bronchopulmonary aspergillosis in patients with and without evidence of bronchiectasis. *Ann Allergy*. 1993;70(4):333-8.
16. Kumar R. Mild, moderate, and severe forms of allergic bronchopulmonary aspergillosis: a clinical and serologic evaluation. *Chest*. 2003;124(3):890-2. doi: 10.1378/chest.124.3.890.
17. Rodrigues J, Caruthers C, Azmeh R, Dykewicz MS, Slavin RG, Knutsen AP. The spectrum of allergic fungal diseases of the upper and lower airways. *Expert Rev Clin Immunol*. 2016;12(5):531-50. doi: 10.1586/1744666X.2016.1142874.
18. Greenberger PA, Bush RK, Demain JG, Luong A, Slavin RG, Knutsen AP. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract*. 2014;2(6):703-8. doi: 10.1016/j.jaip.2014.08.007.
19. Patterson R, Greenberger PA, C.Radin R, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. *Annals of internal medicine*. 1982;96(3):286-91. doi: 10.7326/0003-4819-96-3-286.
20. Goikoetxea MJ, Sanz ML, García BE, Mayorga C, Longo N, Gamboa PM, Barber D, Caballero Molina T, A dlCT, Escribano Mora L, García Martínez JM, Labrador M, López Hoyos M, Martínez Quesada J, Monteseirín Mateo J. Recommendations for the use of in vitro methods to detect specific immunoglobulin E: are they comparable? *Journal of investigational allergology & clinical immunology*. 2013;23(7):448-54; quiz 2 p preceding 55.
21. Liu MY, Li QH, Zhang YJ, Ma Y, Liu Y, Feng W, Hou CB, Amsalu E, Li X, Wang W, Li WM, Guo XH. Spatial and temporal clustering analysis of tuberculosis in the mainland of China at the prefecture level, 2005-2015. *Infectious diseases of poverty*. 2018;7(1):106. Epub 2018/10/21. doi: 10.1186/s40249-018-0490-8.
22. Wang C, Xu J, Yang L, Xu Y, Zhang X, Bai C, Kang J, Ran P, Shen H, Wen F, Huang K, Yao W, Sun T, Shan G, Yang T, Lin Y, Wu S, Zhu J, Wang R, Shi Z, Zhao J, Ye X, Song Y, Wang Q, Zhou Y, Ding L, Yang T, Chen Y, Guo Y, Xiao F, Lu Y, Peng X, Zhang B, Xiao D, Chen CS, Wang Z, Zhang H, Bu X, Zhang X, An L, Zhang S, Cao Z, Zhan Q, Yang Y, Cao B, Dai H, Liang L, He J. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. *Lancet*. 2018;391(10131):1706-17. Epub 2018/04/14. doi: 10.1016/s0140-6736(18)30841-9.
23. Li L, Jiang Z, Shao C. Pulmonary Aspergillus Overlap Syndromes. *Mycopathologia*. 2018;183(2):431-8. doi: 10.1007/s11046-017-0212-y.

24. Wang Y, Li D, Ma G, Li W, Wu J, Lai T, Huang D, Zhao X, Lv Q, Chen M, Wu B. Increases in peripheral SIRT1: A new biological characteristic of asthma. *Respirology (Carlton, Vic)*. 2015;20(7):1066-72. doi: 10.1111/resp.12558.
25. Denning DW, Pashley C, Hartl D, Wardlaw A, Godet C, Giacco SD, Delhaes L, Sergejeva S. Fungal allergy in asthma-state of the art and research needs. *Clinical and translational allergy*. 2014;4:14. doi: 10.1186/2045-7022-4-14.
26. Agarwal R, Aggarwal AN, Garg M, Saikia B, Chakrabarti A. Cut-off values of serum IgE (total and *A. fumigatus* -specific) and eosinophil count in differentiating allergic bronchopulmonary aspergillosis from asthma. *Mycoses*. 2014;57(11):659-63. doi: 10.1111/myc.12214.
27. Woolnough KF, Richardson M, Newby C, Craner M, Bourne M, Monteiro W, Siddiqui S, Bradding P, Pashley CH, Wardlaw AJ. The relationship between biomarkers of fungal allergy and lung damage in asthma. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*. 2017;47(1):48-56. doi: 10.1111/cea.12848.
28. Pashley CH. Fungal culture and sensitisation in asthma, cystic fibrosis and chronic obstructive pulmonary disorder: what does it tell us? *Mycopathologia*. 2014;178:457-63. doi: 10.1007/s11046-014-9804-y.
29. Patterson R, Greenberger PA, Halwig JM, Liotta JL, Roberts M. Allergic bronchopulmonary aspergillosis. Natural history and classification of early disease by serologic and roentgenographic studies. *Archives of internal medicine*. 1986;146(5):916-8. doi: 10.1001/archinte.146.5.916.
29. Matsuse H, Tsuchida T, Fukahori S, Tetsuya Kawano, Nishino T, Fukushima C, Kohno S. Dissociation between sensitizing and colonizing fungi in patients with allergic bronchopulmonary aspergillosis. *Annals of allergy, asthma & immunology*. 2013;111(3):190-3. doi: 10.1016/j.anai.2013.06.022. 31.
30. Kaur M, Sudan DS. Allergic Bronchopulmonary Aspergillosis (ABPA)-The High Resolution Computed Tomography (HRCT) Chest Imaging Scenario. *J Clin Diagn Res*. 2014;8(6):RC05-RC7. doi: 10.7860/JCDR/2014/8255.4423.
32. Martinez S, Heyneman LE, McAdams HP, Rossi SE, Restrepo CS, Eraso A. Mucoid impactions: finger-in-glove sign and other CT and radiographic features. *Radiographics*. 2008;28(5):1369-82. doi: 10.1148/rg.285075212.
33. Li BCM, Huh SM, Prieto MD, Hong G, Schwarz C, Moss RB, Quon BS. Biomarkers for the Diagnosis of Allergic Bronchopulmonary Aspergillosis in Cystic Fibrosis: A Systematic Review and Meta-Analysis. *The journal of allergy and clinical immunology In practice*. 2021. doi: 10.1016/j.jaip.2020.12.064.

Table 1. Demographic, clinical characteristics, and treatments of ABPA patients

Characteristics	All (n= 93)	ABPA-CB (n=74)	ABPA-S (n=19)	p-value
Age at onset, years	52.4 (13.3)	52.0 (13.4)	53.8 (12.7)	0.591
Male	55 (59.1)	46 (62.2)	9 (47.4)	0.242
Smoking history	14 (15.1)	9 (12.2)	5 (26.3)	0.152
Pulmonary comorbidities				
Asthma	34 (36.6)	24 (32.4)	10 (52.6)	0.103
Asthma history, years	30 (13-42.5)	30 (12.5-43.5)	18 (13-33)	0.339
Bronchiectasis	18 (19.4)	18 (24.3)	0	0.019*
Chronic obstructive disease	17 (18.3)	16 (21.6)	1(5.3)	0.180
Tuberculosis	11 (11.8)	9 (12.2)	2 (10.5)	0.844
Chronic pulmonary aspergillosis	7 (7.5)	7 (9.5)	0	0.338
Symptoms				
Productive cough	84 (90.3)	67 (90.5)	17 (89.5)	0.888
Wheezing	34 (36.6)	24 (32.4)	10 (52.6)	0.103
Fever	25 (26.9)	18 (24.3)	7 (36.8)	0.272
Hemoptysis	20 (21.5)	19 (25.7)	1 (5.3)	0.064
Fatigue	9 (9.7)	8 (10.8)	1(5.3)	0.680
Ventilation dysfunction ^a				
Normal/Mild/ Moderate/ Severe type	8/23/7/8	4/18/7/6	4/5/0/2	0.154
Obstructive / Restrictive/ Mixed type	21/1/16	16/1/14	5/0/2	0.605
Treatments				0.987
Systemic corticosteroid	39 (41.9)	32 (43.2)	7 (36.8)	
Both of systemic corticosteroid and antifungal agents	54 (58.1)	43 (58.1)	11 (57.9)	

Data are shown as mean (SD), median (IQR), or n (%).

ABPA = allergic bronchopulmonary aspergillosis; CB= central bronchiectasis; ABPA-S = serologic ABPA

* $p < 0.05$

Table 2. Misdiagnoses of patients with ABPA-CB and ABPA-S

	All (n= 93)	ABPA-CB (n=74)	ABPA-S (n=19)	<i>p</i> -value
Number of misdiagnosed patients	51 (54.8)	40 (53.3)	11 (51.9)	0.764
Misdiagnosed diseases				
Pneumonia	29 (31.2)	22 (29.3)	7 (31.8)	0.551
Tuberculosis	18 (19.4)	16 (21.3)	3 (13.6)	0.348
Asthma	5 (5.4)	1 (1.3)	4 (18.2)	0.006*
Bronchitis	4 (4.3)	3 (4.0)	1 (4.5)	0.817
Bronchiectasis	4 (4.3)	4 (5.3)	0	0.578
Lung cancer	1 (1.1)	1 (1.3)	0	1.000
Duration of misdiagnosis, year				0.310
0-1	29 (31.2)	23 (31.1)	6 (27.3)	
1-10	18 (19.4)	13 (17.6)	5 (26.3)	
>10	4 (4.1)	4 (5.4)	0	

Data are shown as n (%).

* $p < 0.05$

Table 3. Laboratory data and chest CT findings of patients with ABPA-CB and ABPA-S

Laboratory data	All (n=93)	ABPA-CB (n=74)	ABPA-S (n=19)
Blood eosinophils, cells/ μ L ^a	865 (530-1,492)	880 (550-1,485)	700 (530-1,555)
Total IgE, IU/ml	3,000 (1,637-6,481)	2,957 (1,640-7,116)	3033 (1,220-5,547)
sIgE, kUA/L ^b	18.4 (4.4-47.64)	20.6 (7.05-52.06)	7.31 (1.42-20.2)
Grade of sIgE ^c			
Grade 1	5 (5.4)	5 (6.8)	0
Grade 2	18 (19.4)	12 (16.2)	6 (31.6)
Grade 3	23 (24.7)	17 (23.0)	6 (31.6)
Grade 4	13 (14.0)	11 (14.9)	2 (10.5)
Grade 5	10 (10.8)	8 (10.8)	2 (10.5)
Grade 6	4 (4.3)	4 (5.4)	0
Positive for Penicillium allergen	31 (33.3)	24 (32.4)	7 (36.8)
Culture of sputum or BALF			
<i>A. fumigatus</i>	7 (7.5)	6 (8.1)	1 (5.3)
<i>A. flavus</i>	6 (6.5)	4 (5.4)	2 (10.5)
Both of above fungi	2 (2.2)	2 (2.7)	0
Unidentified aspergillus	12 (12.9)	8 (10.8)	4 (21.1)
<i>Candida albicans</i>	3 (3.2)	1 (1.4)	2 (10.5)
Mucus plugging in bronchus	25 (26.9)	18 (24.3)	7 (36.8)
Chest CT findings			
Inflammation	75 (80.6)	59 (79.7)	16 (84.2)
Central bronchiectasis	74 (79.5)	75 (100)	0
Mucoid impaction	16 (17.2)	16 (21.6)	0
Pleural thickening	15 (16.1)	13 (17.6)	2 (10.5)
Pulmonary cavity	8 (8.6)	8 (10.8)	0
Lung fibrosis	5 (5.4)	3 (4.1)	2 (10.5)

Data are shown as median (IQR) or n (%).

^a n of patients = 92

^b n of patients with the exact number of sIgE = 35 with 30 ABPA-CB cases

^c n of patients with the available data of sIgE = 73 with 57 ABPA-CB cases

BALF = bronchoalveolar lavage fluid

Table 4. Differences in immunological and radiological features of patients among five stages

Stage	I	II	III	IV	V	<i>p</i> - value
Number of patients	65	7	11	3	7	
Blood eosinophils, (cells/ μ L),	885 (602-2062)	600 (470-780)	850 (190-1500)	787 (640)	880 (110-1150)	0.308
Total IgE (IU/ml)	3918 (1878-8625)	1880 (868-2818)	2880 (1291-5931)	2127 (324)	2049 (1383-3000)	0.078
ABPA-CB ^a	49 (75.4)	5 (71.4)	10 (9.9)	3 (100)	7 (100)	0.352
ABPA-S ^b	16 (24.6)	2 (28.6)	1 (9.1)	0	0	
Pulmonary cavity ^c	2 (3.1)	0	0	0	7 (100)	0.000*

Data are shown as median (IQR), mean (SD) or n (%).

^{a b c} data of three lines meaning the number and percentage of patients with ABPA-S, ABPS-CB, or pulmonary cavity of each stage.

* $p < 0.05$

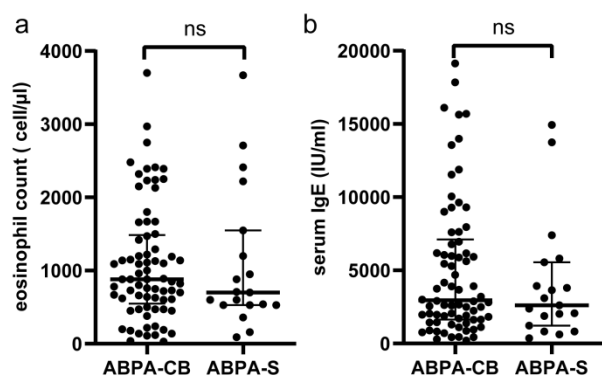


Figure 1. Blood eosinophil counts and total serum IgE level of patients. (a) Blood eosinophil counts, and (b) serum IgE level of patients with ABPA-CB and ABPA-S. The bars indicate the median and interquartile range. ns means no significance.

Accepted Manuscript

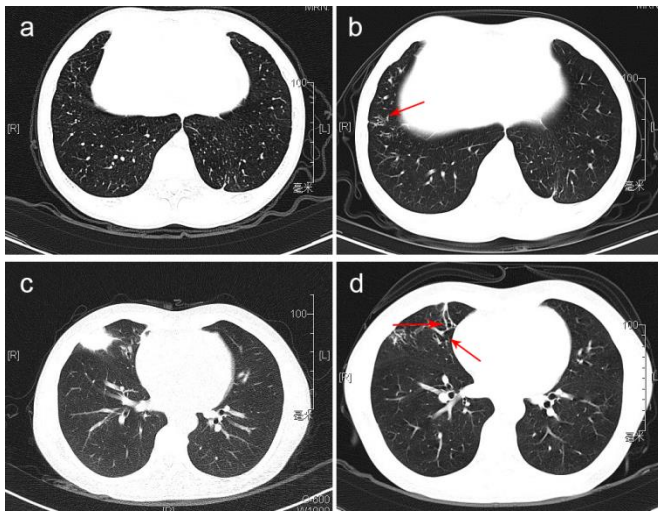


Figure 2. Chest computed tomography images of two ABPA-S patients who developed bronchiectasis. Case 1: (a) high-resolution CT image taken in January 2016 showing bilateral mottling high-density shadows with blurred edges and (b) plain CT taken in December 2019 presenting mild bronchiectasis, especially in the right lung. Case 2: (c) plain CT image taken in November 2015 showing patchy shadows at right upper lobes and (d) taken in April 2019 presenting columnar bronchiectasis at the same lobe. Red arrows indicate sites of bronchiectasis.