A retrospective study of patients with a delayed diagnosis of allergic bronchopulmonary aspergillosis/allergic bronchopulmonary mycosis

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ABSTRACT

This study was designed to aid health care providers in better understanding the need for earlier recognition of allergic bronchopulmonary aspergillosis/allergic bronchopulmonary mycosis (ABPA/ABPM). Patients with a confirmed diagnosis of ABPA/ABPM after evaluation in the Department of Respiratory Medicine of Zhongshan Hospital affiliated to Fudan University between March 2003 and January 2013 were analyzed retrospectively. Clinical signs and symptoms, previous diagnoses and potential diagnostic errors, serologic tests and chest computed tomography (CT) were reviewed and compiled. Seventy patients were diagnosed with ABPA/ABPM in which 52 were misdiagnosed or underdiagnosed. The median total serum IgE level was 2574 IU/mL, ranging from 338 to 31527 IU/mL. Fifty-eight of the 70 patients were tested for specific IgE (sp-IgE) in which 57 were positive to Aspergillus fumigatus *and 48 were positive to* Penicillium*. Twelve of the 70 patients did not undergo sp-IgE testing but allergy skin test, and all were positive to* A. fumigatus*. The two most common abnormalities found on chest CT exams were central bronchiectasis (CB) and mucus plugs in 48 and 20 patients, respectively. The time from first hospital visit to confirmation of diagnosis for ABPA/ABPM-CB (48/70) was longer than that of ABPA/ABPM-seropositive type (S; 22/70; 30.8 ± 9.81 m versus 9.3 ± 3.55 m; $p = 0.044$). Prior diagnoses antecedent to our diagnostic conformation included 13 patients with bronchial asthma, 12 with bronchiectasis, and 19 with pneumonia. Only 18 patients were correctly first diagnosed with ABPA/ABPM. ABPA/ABPM is not an uncommon complication accompanying underlying chronic diseases, most notably bronchial asthma and cystic fibrosis. Patients who present with poorly controlled disease, especially with recurrent pulmonary infiltrates, demand the attention of a specialist, the sooner the better to minimize the likelihood of more severe, persistent, and ultimately irreversible pathological changes in large airways. Early treatment of oral corticosteroid with or without antifungal therapy can improve the prognosis. Early testing for ABPA/ABPM along with careful ongoing follow-up is imperative and necessary to prevent or forestall significant future morbidity.*

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Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* clinically manifesting as uncontrolled asthma, expectoration of mucus plugs, fleeting pulmonary infiltrates, and central bronchiectasis (CB).[1–3] Occasionally, patients can develop a syndrome similar to ABPA but it is caused by fungi other than *A. fumigatus* and is called allergic bronchopulmonary mycosis (ABPM).[4] ABPA was first described by Hinson in 1952 in the United Kingdom.[5] Since then, the number of published scientific and clinical articles number in the hundreds, including a variety of journals from numerous countries throughout the world as recorded in recent comprehensive reviews.[6,7] ABPA/ABPM is an airway disorder affecting primarily patients with bronchial asthma (BA) and cystic fibrosis (CF) at an estimated percentage of 0.7–3.5% and 7–9%, respectively.[8–11]

The issue of lack of early diagnosis of ABPA/ABPM appears to be multinational in scope and the mean latency in diagnostic delay is as long as 10 years in patients who are eventually correctly diagnosed.[12] Making an early diagnosis does require a heightened awareness of ABPA/ABPM along with sufficient time for the practitioner to consider the need for further evaluation, in particular, those patients who present with early clinical and radiographic evidence of what may be ABPA-seropositive type (ABPA-S) or ABPA-CB type, with the former being more amenable to therapy.[13–16]

This article is a report of a relatively large series of ABPA/ABPM patients who have suffered a fate, *i.e.*, long duration of illness, many physician encounters, and delays in correct diagnosis. Unfortunately, when the correct diagnosis is finally made, for some patients the disease is at the irreversible stage. Here, 70 patients who came to the attention of the Department of Respi-

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ratory Medicine, Zhongshan Hospital affiliated with Fudan University were retrospectively analyzed regarding prior diagnoses, clinical presentations, and laboratory and radiological evaluations leading to the final diagnosis. The intent of this study was to alert medical practitioners to the not uncommon disease entity of ABPA/ABPM, especially in the high-risk groups of patients with BA or CF. Once these patients have received a high index of suspicion in the course of their disease, they should be referred to a knowledgeable allergist or pulmonologist for further evaluation and follow-up if confirmed with the diagnosis. This will, hopefully, result in improved care and outcomes.

MATERIALS AND METHODS

Patients

Seventy patients who presented to our hospital between March 2003 and January 2013 were analyzed retrospectively if they met any six of the following diagnostic criteria for ABPA/ABPM[17]: (1) asthma history, (2) immediate cutaneous hyperreactivity to *A. fumigatus* (or other potential fungal organism), (3) elevated total serum IgE (>417 IU/mL), (4) elevated serum *A. fumigatus*–specific IgE (sp-IgE; >0.35 kUA/L), (5) precipitating antibodies (IgG) in serum against *A. fumigatus* (*Penicillium* also included in this series), (6) increased eosinophils in the peripheral blood (absolute eosinophil count of >1000 cells/μL) (7) chest computed tomography (CT) evidence of CB, and (8) transient or fixed pulmonary opacities. Depending on the presence or absence of CB, ABPA/ABPM can be subdivided into early stages designated as ABPA/ABPM-S or late stages of ABPA/ABPM-CB.[15,16]

Methods

Demographic data, pertinent laboratory results, and chest imaging findings were recorded in detail. Clinical data were analyzed retrospectively.

Allergy skin test was performed from 2003 to 2010 in 12 of the 70 patients with the remainder from 2010 to 2013 tested by sp-IgE.

The allergy skin test was performed using a skin-prick test (SPT). The allergens were provided by Merck (Darmstadt, Germany) and 20 allergens were tested. SPT was performed by placing a drop of allergen solution on the inner side of forearm. The solution was allowed to enter the skin using a needle. Saline and histamine phosphate (10 mg/mL) were used as negative and positive controls, respectively. The skin response was measured at 15 minutes after pricking. The degrees of the positivity in SPT were assessed and graded on a scale of 0, 1+, 2+, and 3+, by comparing the size of wheal (mean wheal diameter [MWD]) induced by allergen with that induced by 10 mg/mL of histamine solution.[18,19] Grade 0 = the the allergen-induced MWD (aiMWD) and is smaller than ½ of the positive control–induced MWD (pciMWD); grade 1 (1+) = aiMWD and is ≥½ but smaller than ⅔ of pciMWD; grade 2 (2+) = aiMWD and is ≥⅔ but smaller than pciMWD; grade 3 (3+) = aiMWD and is equal or greater than pciMWD. In this study, grade 0 was judged as negative, and grades 1–3 were judged as positive.

Table 1 **The main chest CT manifestations of the 70 ABPA/ABPM patients**

Radiological Manifestations	Number of Cases (*n*)	Percentage (%)
CB	48	68.57
Mucus plug	20	28.57
Mediastinal adenopathy	12	17.14
Patch and stripe shadows	10	11.76
Pulmonary bulla	5	7.14
Fibrosis	2	2.86
Consolidation	2	2.86
Pulmonary atelectasis	1	1.43

ABPA = allergic bronchopulmonary aspergillosis; ABPM = allergic bronchopulmonary mycosis; CT = computed tomography; CB = central bronchiectasis.

The sp-IgE test system originated from FOOKE GmbH (Neuss, Germany) using the sp-IgE antibody kit using the ELISA methodology. Twenty major allergens were selected for testing; grade 0 = sp-IgE < 0.35KUA/L, grade 1 = 0.35 kUA/L <sp-IgE <0.7 kUA/L, grade 2 = 0.7 kUA/L <sp-IgE <3.5 kUA/L, grade 3 = 3.5 kUA/L <sp-IgE <17.5 kUA/L, grade 4 = 17.5 kUA/L<sp-IgE <50 kUA/L, grade 5 = 50 kUA/L <sp-IgE <100 kUA/L, and grade 6 = >100 kUA/L. In this study, grade 0 was judged as negative, and grades 1–6 were judged as positive.

Chest CT scans were evaluated by two radiologists in the Department of Radiology, Zhongshan Hospital affiliated to Fudan University and Shanghai Medical Imaging Institute. ABPA-CB/ABPM-CB was diagnosed by both radiologists when they agreed that centrolobular bronchiectasis was present (see Table 1). The study was approved by the Institutional Review Board of Zhongshan Hospital affiliated to Fudan University, and the requirement for informed consent was waived because of the noninterventional nature of this study.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 16.0 software (SPSS for Microsoft Windows, package Version 16.0; SPSS, Inc., Chicago, IL) was used for data analysis. Normal data were expressed in $\bar{x} \pm s_x$. Independent sample *t*-test was used in the test. A value of $p < 0.05$ is considered statistically significant.

NO PHOTOCOPY

RESULTS

General Information

Of the 70 patients, 43 (61.43%) were male and 27 (38.57%) were female patients, with an age range at the time of diagnosis from 16 to 80 years and a median age of 55.5 years. All were asthma patients and the median duration of asthma was 20.0 years with a range of 1.0–55.0 years. The total serum IgE value ranged from 338 to 31,527 IU/mL with a median value of 2574 IU/mL. One patient was underdiagnosed with poorly controlled asthma and was on oral glucocorticoid therapy at 10 mg/day at the time of testing, which could explain the relatively low IgE level of 338 IU/mL.

Clinical Features

Cough (66/70), especially coughing up brown mucoid sputum (56/70), and wheezing (50/70) were the most common symptoms. Less common symptoms were fever (24/70), chest pain (10/70), and hemoptysis (8/70). The majority of patients (50/70) had poorly controlled and recurrent asthma symptoms. Thirteen patients (13/70) with asthma reported taking above step 4 therapy according to the Global Initiative for Asthma and were given glucocorticoid therapy (5–10 mg/day).

Radiological Manifestations

Various chest CT abnormalities were noted in our patients as indicated in Table 1. As might be expected, CB (68.57%) and mucus plugs (28.57%) were the most common. Of the 70 patients, 48 were classified as ABPA/ABPM-CB, leaving 22 in the ABPA/ABPM-S group.

Allergic Conditions

Of the 70 patients, 12 underwent allergy skin test, and all were positive to *A. fumigatus*. Fifty-eight were tested for sp-IgE, in which 10 were only *A. fumigatus* sp-IgE$^+$ (17.24%), 1 was only *Penicillium* sp-IgE$^+$ (1.73%), and 47 were both *A. fumigatus* and *Penicillium* sp-IgE$^+$ (81.03%).

The levels of *A. fumigatus* sp-IgE ranged from 0.67 to 100 kUA/L, with a median value of 10.31 kUA/L, and the levels of *Penicillium* sp-IgE ranged from 0.35 to 15.67 kUA/L, with a median value of 1.07 kUA/L (Table 2).

Diagnostic Errors before Final Diagnosis

For the 70 patients, the time of first hospital visit to final diagnosis ranged from as short as 1 month to a period of 32 years with a median time of 6 months. The time from first hospital visit to confirmation of diagnosis for ABPA/ABPM-CB (48/70) was longer than that of ABPA/ABPM-S (22/70; 30.8 ± 9.81 m versus 9.3 ± 3.55 m; $p = 0.044$).

Table 2 **Allergy skin test and sp-IgE test of the 70 ABPA/ABPM patients**

Immunological Findings	Allergy Status	Grade	No. of Cases (*n*)
sp-IgE	*A. fumigatus*	Grade 2	13
		Grade 3	24
		Grade 4	13
		Grade 5	4
		Grade 6	3
	Penicillium	Grade 1	13
		Grade 2	26
		Grade 3	8

ABPA = allergic bronchopulmonary aspergillosis; ABPM = allergic bronchopulmonary mycosis; sp-IgE = specific IgE.

Table 3 **Misdiagnoses of the ABPA/ABPM patients**

Misdiagnosed Disease	No. of Cases (*n*)	Percentage (%)
Pneumonia	19	27.14
Bronchiectasis	12	17.14
Tuberculosis	6	8.57
Bronchitis	3	4.29
Lung cancer	2	2.86
Lung abscess	1	1.43
Bronchogenic cyst	1	1.43

ABPA = allergic bronchopulmonary aspergillosis; ABPM = allergic bronchopulmonary mycosis.

A majority of cases (44/70) were misdiagnosed or underdiagnosed as seen in Table 3. Not including asthma as a stand-alone diagnosis in 13 patients, the other patients in the top 3 included pneumonia-unspecified, bronchiectasis-unspecified, and tuberculosis in 19, 12, and 6 cases, respectively. Only 18 (26%) were correctly diagnosed without delay.

Two Case Studies Illustrating Miscues in Diagnoses prior to Final Diagnosis

Case 1. A 64-year-old man presented with a daily cough of 3 years associated with expectorated mucus. One month before specialty evaluation, he had a chest CT scan revealing a space-occupying lesion in the left lower perihilar area and inflammatory changes along with bronchiectasis in the left lower lung region along with mediastinal adenopathy. Before specialty evaluation the patient was diagnosed with a "left lower lobe cancer and obstructive pneumonia" and surgery was advised. However, after admission to our hospital,

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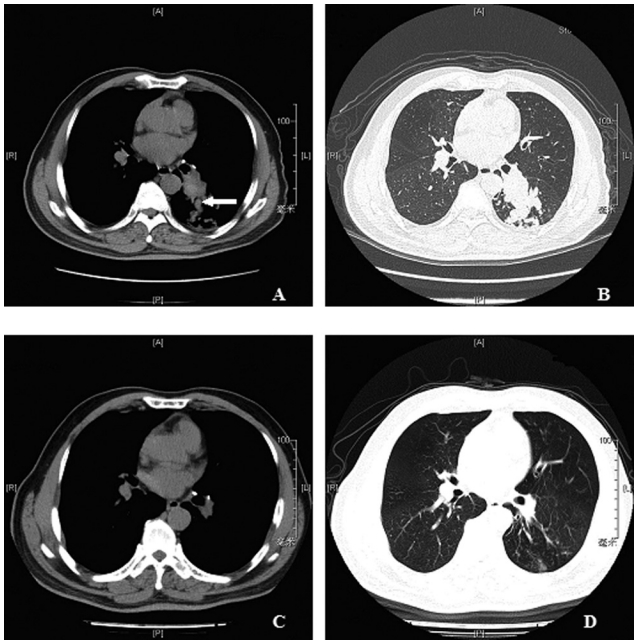


Figure 1. *Radiological changes of misdiagnosed case 1. (A and B) Mediastinal and lung windows before treatment. The arrow indicates the mucus plug. (C and D) Mediastinal and lung windows after treatment. The original lesions were significantly reduced after treatment.*

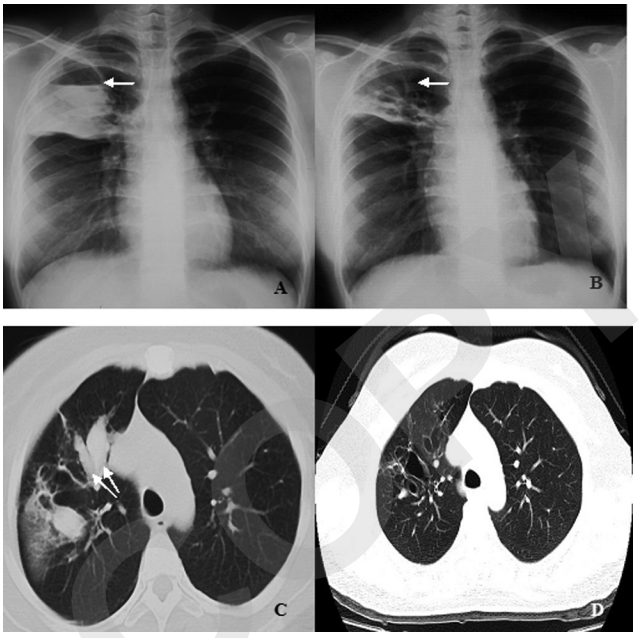


Figure 2. *Radiological changes of misdiagnosed case 2. (A) Chest x ray from the patient's first visit. The arrow indicates a thin-wall cavity containing the liquid–gas surface. (B) Chest x ray after anti-infective therapy. The original consolidation shadow was significantly reduced. The arrow indicates that the thin-wall cavity was smaller and the liquid–gas surface disappeared. (C) Lung window of the chest computed tomography (CT) scan taken at the same time as that shown in panel B. The arrow indicates a fingertip sign-like shadow. (D) Lung window of the chest CT scan taken after glucocorticoid and itraconazole treatment. The original mucus plugs disappeared, while the bronchiectasis-like changes remained.*

mucus plugs with bronchiectatic changes were noted in the left lower lung on his chest CT scan. Subsequently, he was diagnosed with asthma of 20 years duration. A routine blood test revealed increased eosinophils (1080 cells/μL). The total serum IgE was elevated at 1445 IU/mL and both *A. fumigatus* and *Penicillium* sp-IgE were positive. *A. fumigatus* sp-IgE was 6.82 kUA/L and *Penicillium* sp-IgE was 7.6 kUA/L, both positive at the grade of level 3. Fiberoptic bronchoscopy confirmed the presence of mucus plugs as seen on the chest CT scan. A transbronchial lung biopsy from the bronchus leading to the left lower lung revealed pathological evidence of inflammatory cell infiltration, mainly eosinophils and neutrophils. The aforementioned "space-occupying lesion" was believed to be mucus plugs. After confirming the diagnosis of ABPA/ABPM, he started on a course of prednisone and itraconazole therapy. Shortly thereafter he expectorated a large amount of sputum containing brown–black mucus plugs. The patient had another chest CT scan 10 days later, which revealed significant clearing in the left lower lung as seen in Fig. 1, *A–D*.

Case 2. A 27-year-old woman presented with repeated cough and expectoration for 4 years with an increase in symptoms over 3 months. Three months before further evaluation, a chest x ray revealed a consolidation-type shadow with a thin-walled cavity in the right upper lung wherein a liquid–gas interface was observed (Fig. 2 *A*). She was diagnosed with "lung abscess" and was given antibiotic and expectorant therapy. Recurrent sputum smear and sputum culture showed acid-fast bacilli negative, fungal spores negative, and fungal hyphae negative. After 1 week of therapy a repeat chest x ray showed a significant reduction of lung consolidation in the right upper lung and the thin-walled cavity was noted to be smaller along with disappearance of the liquid–gas interface (Fig. 2 *B*). Before specialty evaluation a chest CT scan showed multiple space-occupying lesions in the right upper lung in addition to bronchovascular bundles with bronchiectatic changes (Fig. 2 *C*).

The patient was subsequently evaluated by a specialist and further review of the chest CT scan confirmed the presence of fingertip sign-like changes, mucus plugs, and CB in the right upper lung. She had a positive history of allergic rhinitis and was diagnosed with asthma. Subsequent tests showed total serum IgE elevated at 1561 IU/mL and both *A. fumigatus* and *Penicillium* sp-IgE were positive. *A. fumigatus* sp-IgE was 14 kUA/L with a grade of level 3 and *Penicillium* sp-IgE was 0.7 kUA/L with a grade of level 2. Fiberoptic bronchoscopy revealed multiple mucus plugs.

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The patient was then diagnosed with ABPA and the treatment was initiated with prednisone and itraconazole for a period of 3 months. A follow-up chest CT scan revealed disappearance of the mucus plugs with residual bronchiectatic changes (Fig. 2 *D*).

DISCUSSION

ABPA/ABPM is a well-recognized and not uncommon relapsing chronic inflammatory airway disorder found primarily in patients with BA and CF. Since its first report in 1952,[5] there have been hundreds of published reports including many large series of patients with this disorder.[13,20–22] In the initial stages of this disorder, inhalation of certain species of fungal spores by the susceptible hosts who have been sensitized by previous exposure eventually sets off a complex inflammatory cascade that if left undiagnosed and improperly treated inevitably results in irreversible changes in the large airways. The most common fungal organism involved in this disorder is *A. fumigatus*.

Today, perhaps the most troubling aspect in dealing with ABPA/ABPM relates to a lack of early recognition in a disorder that has received so much attention in the medical and scientific literature in the past 60 years. Despite all of that, numerous reports of patients with ABPA/ABPM continue to be published. Many patients with significant morbidity related to irreversible large airway changes have gone unrecognized and undiagnosed for years.[23–28] One patient in our report was believed to be undiagnosed for 32 years.

There are many reasons for the misdiagnosis and underdiagnosis. Considering that ABPA/ABPM is relatively uncommon and even rare outside of the diagnosis of BA and CF, it could easily go unrecognized. Furthermore, because some practitioners may not recognize the signs and symptoms of this disease and if patients do not seek health care early, the diagnosis of ABPA/ABPM can be delayed.[29] In addition, early recognition of ABPA/ABPM is not a problem isolated to one country. If one looks at mainland China, where ABPA/ABPM has been considered to be a rare disorder, a literature review from January 1991 to March 2008 revealed reports of only 57 patients diagnosed with ABPA/ABPM.[30] This might appear to be extremely low and could represent underrecognition and/or underreporting. A recent systematic review and meta-analysis of patients with asthma revealed that 15–48% of patients diagnosed with asthma were skin test positive to *Aspergillus* with a total frequency of skin test positivity to *Aspergillus* at 28% and ABPA at 12.9%. Among those patients with asthma who were skin test positive to *Aspergillus*, an estimated 40% met the diagnostic criteria for ABPA/ABPM.[31] Our study showed that the percentage was as high as 60%.[32] As mentioned previously, the morbidity of ABPA/ABPM had been long underestimated in mainland China. However, the number of ABPA/ABPM patients diagnosed in our research center in the last 10 years had been as high as 70. Fifty-eight were diagnosed after the year 2010. We believe that this is because of a deeper understanding of ABPA/ABPM, along with an increased reliance on total serum IgE and sp-IgE test.

The information gleaned from the articles[30,33–35] of ABPA/ABPM should be very helpful in some health care settings, lending itself to targeting populations in a certain age range with a diagnosis of asthma and testing them for allergic sensitivity to *A. fumigatus*, the most common ABPA/ABPM culprit. Where a disease population management approach is possible and practical through an Electronic Medical Record database, *e.g.*, with BA and CF patients, there is potential for targeting and intervention of patients who could be identified as at risk for ABPA/ABPM. Once identified, a facilitated referral to an appropriate specialist could be made. Where disease population management does not exist, the issue of obtaining a greater yield of early (ABPA/ABPM-S) versus late (ABPA/ABPM-CB) diagnosis becomes a bigger challenge. In the latter more prevalent health care environment and clinical settings that lack easy access to large medical databases, consideration could be given by the appropriate specialists in an area to develop a periodic outreach program to their associate health care providers on the frontline informing them of what type of high-risk patients to target for basic screening tests looking for earlier diagnosis of ABPA/ABPM. Positive results could then be sent to the predesignated knowledgeable specialist for consideration regarding referral.

We believe that it is time to start considering the development of programs that target the majority of patients with ABPA/ABPM, those with BA or CF who can relatively easily be screened with total serum IgE and sp-IgE looking for early evidence of this disorder. ABPA/ABPM should be considered in any patient with asthma who has unexplained worsening of symptoms or significant increase in use of asthma medications.[36] Once a diagnosis of ABPA/ABPM is made, oral glucocorticoid with or without antifungal therapy are initiated, and it is imperative for a knowledgeable and experienced practitioner to assume the ongoing management and follow-up of these patients to minimize the likelihood of progressive bronchiectatic changes.

CONCLUSIONS

ABPA/ABPM is not a rare disease. Thus, physician awareness of ABPA/ABPM should be heightened. Once the diagnosis has been confirmed by a specialist according to established criteria for the diagnosis of ABPA/ABPM, treatment should be initiated and on-

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going follow-up continued throughout the course of this chronic lung disorder.[17]

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