Allergic bronchopulmonary aspergillosis: radiological and microbiological profile of patients presented in an outpatient pulmonary clinic in a developing country

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Key words: asthma, ABPA, microbiology, radiology.

Contributions: NI, MI, MBAZ, MA, KJ, made contributions to conception and design, interpretation of data, drafting the manuscript and revising it critically for important intellectual content; SA, contributed to the statistical analysis and interpretation of data; ABSZ, made contributions to conception and design and revised the manuscript critically for important intellectual content. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: the study protocol was approved by the Ethical Review Committee of the Aga Khan University Hospital. ERC number assigned 2019-0901-2239.

Informed consent: the study is a retrospective chart review that does not require informed consent. The manuscript does not contain any individual person's data in any form.

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Funding: none.

Received: 7 October 2023.
Accepted: 9 November 2023.
Early view: 7 December 2023.

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Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2024; 94:2803
doi: 10.4081/monaldi.2023.2803

Abstract

There is limited data available about allergic bronchopulmonary aspergillosis (ABPA) in Pakistan. The aim of the study was to describe the radiological and microbiological profile of ABPA patients presenting to the outpatient pulmonary clinic of a tertiary care hospital in Karachi, Pakistan. A retrospective study was conducted on ABPA patients who presented to the pulmonary outpatient clinic at Aga Khan University Hospital, Karachi, Pakistan, from January 2017 to December 2019. Data was collected on microbiology and radiology features on a predesigned proforma. A total of 7759 asthmatic patients presented at the outpatient pulmonology clinic during the study period. Of the 245 patients labeled as ABPA, 167 fulfilled the inclusion criteria, and 91 (54.5%) were female (mean age 41.9±13.0 years). A high-resolution computed tomography scan of the chest was available for 126 patients. Of these, 104 (82.5%) patients had bronchiectasis. Central bronchiectasis was noted in 98 (94.2%) patients, mucus plugging in 71 (56.3%), and hyperinflation was seen in 30 (23.4%). Microbiological testing was available in 103/167 (61.7%) patients. The most common bacterial pathogen was *Pseudomonas aeruginosa* 32 (31.1%), followed by *Hemophilus influenzae* 16 (15.5%), and *Moraxella catarrhalis* 7 (9.7%). *Aspergillus fumigatus* 17 (23.6%) was the most common mold, followed by *Aspergillus flavus* 16 (22.2%) and *Aspergillus niger* 11 (15.3%). Co-infection (bacterial and fungal) was found in 18 (17.45%) patients. Bronchiectasis was frequently observed in our cohort of patients with ABPA. *P. aeruginosa* was found to be common among bacterial pathogens. Isolation of fungus is not uncommon in these patients.

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disease caused by an immunological reaction to the *Aspergillus* species, with *Aspergillus fumigatus* being the most implicated pathogen [1]. The occurrence of ABPA is commonly seen among asthma and cystic fibrosis patients, with a prevalence of 12.9% and 8.9%, respectively [1].

ABPA is generally diagnosed *via* a combination of clinical, serological, and radiographic findings [2-4]. Previous diagnostic criteria have been modified by the International Society of Human and Animal Mycology (ISHAM) [2-4] since APBA may be present without bronchiectasis and all criteria previously proposed are not required to establish the diagnosis of ABPA. Radiological findings

of ABPA vary and include, fleeting pulmonary infiltrates, centrilobular nodules characterizing dilated and opacified bronchioles, bronchiectasis, and mucoid impaction leading to bronchocoele formation (the finger in glove sign) [5]. ABPA is often misdiagnosed as tuberculosis (TB) or pneumonia, due to similar radiological presentations [6,7], leading to a considerable delay in the provision of appropriate treatment especially in a TB-endemic country like Pakistan.

Clinically ABPA is divided into five stages, stage I with acute flare while stage V is advanced fibrotic disease. It is further classified into two categories, according to Patterson *et al*., namely ABPA-S called seropositive only in the absence of bronchiectasis, and ABPA-CB (central bronchiectasis) if bronchiectasis is present. ABPA-CB is the more aggravated form of the disease [8].

A Japanese study found the isolation of *Aspergillus* spp. in sputum in 59% of patients, including *A. fumigatus* (33%), *A. niger* (6%), *A. terreus* (4%), unspecified *Aspergillus* spp. (16%) and *Schizophyllum commune* identified in 6% [9]. Sputum microscopy and culture were positive in 63% of patients in the Indian study, but overall data is limited on microbiology for both fungi and bacterial pathogens among patients with ABPA [10]. However, the most frequently isolated organisms reported in patients with non-cystic fibrosis bronchiectasis are *Hemophilus influenzae, Pseudomonas aeruginosa,* and *Moraxella catarrhalis* while *P. aeruginosa* was reported with more advanced bronchiectasis [11]. Another complication of ABPA is the development of chronic pulmonary aspergillosis (CPA), which has an estimated burden of 411,000 patients, out of 4,837,000 ABPA patients. CPA is associated with significant morbidities, including potentially fatal hemoptysis [12].

A study estimated that, annually, 1661 cases of ABPA develop in the Pakistani population, but data on the radiological and microbiological profile of these patients are very limited [13]. The objective of this study is to determine the microbiological and radiographic profile of ABPA patients. We believe that an understanding of radiological and microbiological patterns among ABPA patients in a TB-endemic country may considerably improve diagnosis and prognosis in these patients.

Materials and Methods

This retrospective study was conducted on patients diagnosed with ABPA at the adult outpatient pulmonary clinic of Aga Khan University Hospital, (AKUH) Karachi, Pakistan from January 2017 to December 2019. AKUH is one of the largest tertiary care facilities in Karachi with 650 beds, and the largest outpatient department that receives patients from wide socio-economic backgrounds from all over the city and outside from different cities of Pakistan as well. The study was approved by the Ethical Review Committee of AKUH.

The patients of ABPA were initially identified through the outpatient pulmonary clinic database. Medical records of all patients who were labeled as ABPA in the database were reviewed. Those patients who fulfilled the inclusion criteria were then recruited for the study.

The inclusion criteria for ABPS were adopted from ISHAM 2013 [4], and included: i) age ≥18 years with underlying asthma; ii) serum immunoglobulin E (IgE) level ≥1000 IU/mL; iii) peripheral eosinophilia ≥500 cells/μL in steroid naïve patients; iv) radiographic pulmonary opacities consistent with ABPA; v) a positive type I *Aspergillus* skin test (immediate cutaneous hypersensitivity to *Aspergillus* antigen); vi) active TB and other infections were ruled out by sputum microscopy, culture and Xpert MTB/Rif. We did not use the *Aspergillus* skin test in all of our patients.

The exclusion criteria were: i) age <18 years; and ii) patients with an incomplete record.

We classified patients into five stages: stage 1 – patients with acute flare; stage 2 – patients who underwent remission after treatment and remain asymptomatic; stage 3 – patients with recurrent exacerbations; stage 4 – patients who were steroids dependent; and stage 5 – patients with advanced fibrotic lung disease. Sputum results were obtained during exacerbations and worsening of symptoms. Chest imaging was reviewed by two independent pulmonologists and imaging reports issued by the radiologist were also reviewed. Data was collected on a predesigned proforma that included demographics, co-morbid, duration of asthma and ABPA, stages of ABPA, presenting clinical symptoms, smoking status, serum IgE and eosinophilia levels, and radiological and microbiology findings.

Statistical analysis

SPSS V.19.0 (IBM, Armonk, NY, USA) was used for data analysis. Descriptive statistics were done, and results are presented as the mean and standard deviation for continuous variables and the number and percentages for categorical variables. Numbers and percentages were reported of all radiological and microbiological features of patients with ABPA.

Results

A total of 7759 asthmatic patients presented at the outpatient pulmonology clinic during the study period, 245 (3.15%) were labeled as ABPA, and 167/245(68.16%) patients fulfilled the inclusion criteria. The mean age of patients was 41.9±13.0 years, and 91 (54.5%) were females. All patients had a long-standing history of asthma, with a mean duration of 17.7±13.1 years before they were diagnosed with ABPA. Out of 167 patients, 104 (62.3%) had ABPA-CB and 63/167 (37.2%) had ABPA-S. All five stages of ABPA were observed among the patients and 87 (52.1%) had stage 3. Cough (78.4%), dyspnea (56.9%), wheezing (25.1%), chest pain (25.1%), and hemoptysis (18.6%) were the predominant presenting symptoms at the clinic. All patients received systemic and inhaled corticosteroids, while 135 (80.8%) patients were on itraconazole (Table 1).

The radiographic images available for these patients included chest X-ray in 167/167 (100%) and high-resolution computed tomography (HRCT) in 126/167 (75.44%). Table 2 describes the radiological pattern of the study population. Bilateral involvement on X-rays was found in 84.4%. The common X-ray findings were hyperinflation in 91 (54.5%) patients and fleeting infiltrations in 84 (50.3%). HRCT was available for 126/167 (75.44%) patients, with bilateral involvement in 92% and bronchiectasis being the most observed finding, present in 104/126 (82.5%) patients (Table 2).

Sputum culture results were available in 103 (61.7%) patients with bacterial growth in 66 (64.1%) of the cases. The microbiological profile is presented in Table 3. The common pathogens identified were *P. aeruginosa* (31.1%) and *H. influenzae* (15.5%). One or more fungi were isolated in 46 (44.6%) cases. *A. fumigatus* (23.6%) followed by *A. flavus* (22.2%) were commonly isolated fungi. A fungal-bacterial co-infection was seen in 18 patients. Microorganism isolations are more common in ABPA-CB (n=81/103, 78.64%) as compared to ABPA-S (n=22/103, 21.36%). Among the bacterial pathogens, a greater percentage of patients with *P. aeruginosa* (33.3%) *and H. influenzae* (17.2%) were isolated from ABPA-CB than with ABPA-S, while *H. parainfluenzae* (9%) and *Klebsiella pneumonia* (18.8%) were frequently isolated with ABPA-S.

Discussion

This is the first study from Pakistan that has highlighted the radiographic and microbiological features associated with ABPA. We have found hyperinflation on chest X-ray and central bronchiectasis on HRCT to be the most common radiological findings. Microbiologically, we found *P. aeruginosa* to be the most common bacterial infection among ABPA-CB patients. Isolation of fungi, such as *A. fumigatus*, was also seen in patients with ABPA.

In our study, more patients had ABPA-CB than ABPA-S, which is in concordance with another study conducted in India where patients with more pronounced lung damage were seen in the form of ABPA-CB [14]. On radiological evaluation, bilateral chest x-ray and HRCT observations were noted in 84.4% and 92.1% of the patients, respectively. The most common HRCT observation was bronchiectasis which was seen in 77.8% of the patients. This observation was found to be consistent with similar studies carried out in China and India, which also reported bronchiectasis as the most common observation [15,16]. Agarwal *et al*. reported 36.6% of patients with a normal HRCT whereas in our study none of the patients had normal HRCT this may be due to delayed diagnosis leading to advanced disease due to poor diagnostic facilities in primary care centers or referral bias of a tertiary care hospital as there is no insurance system and patients pay from their own pocket [15]. Additionally, patients with minimal disease did not undergo chest HRCT: HRCT is performed when underlying parenchymal abnormality is suspected. We suggest early chest HRCT in all patients with ABPA. On the other hand, a study from China reported central bronchiectasis as a common computed tomography finding [16]. However, hyperinflation, consolidation, and tree-in-bud appearance were not reported as seen in our study. The study also described the presenting clinical symptoms of cough, dyspnea, sputum, wheezing, chest pain, fever, and hemoptysis in the diagnosed patients consistent with our study.

Chest X-ray findings associated with ABPA are variable, during early stages, chest X-ray images are usually normal or mimicking asthma [5]. In our study, X-rays showed fleeting filtrations and hyperinflation to be present in more than half of the patients while lung consolidations, cavitation, fibrosis, nodules, and cystic changes were also seen.

Laboratory testing showed an increase in mean serum IgE which was comparable with published data [17]. Normally a blood eosinophil level >1000 cells/mm^3 is used as a diagnostic criterion [18]. However, 25% of ABPA patients are also reported to have an absolute eosinophil count of <500 cells/mm^3 [17], which may possibly be attributed to the use of drugs prior to diagnosis, which may have reduced blood eosinophil levels. Agarwal *et al*. reported that peripheral eosinophilia has limited utility in the diagnosis of ABPA [19]. In our study, we measured the differential eosinophil count which was found to have a mean value of 11.2±7.7%. The concept of the five stages of ABPA was first proposed by Patterson *et al.*

Table 1. Characteristics of study population (n=167).

Variables	n (%) or ± SD
Age, in years	41.9±13.0
Gender	
Male	76 (45.5)
Female	91 (54.5)
Duration of asthma	17.7±13.1
Duration of ABPA	4.8±5.0
ABPA	
ABPA-S*	63 (37.2)
ABPA-CB*	104 (62.3)
Stage of ABPA	
1	15 (9.0)
2	39 (23.4)
3	87 (52.1)
4	24 (14.4)
5	2 (1.2)
Mean serum IgE IU/mL	2455±1600.3
Mean eosinophil count %	11.2±7.7
Smoking status	
Current	1 (0.6)
Non-smoker	159 (95.2)
Ex-smoker	7 (4.2)
Symptoms	
Cough	131 (78.4)
Dyspnea	95 (56.9)
Wheezing	42 (25.1)
Chest pain	42 (25.1)
Fever	37 (22.2)
Weight loss	36 (21.6)
Hemoptysis	31 (18.6)
Pallet of sputum	31 (18.6)
Exacerbation in 12 months	120 (71.9)
Treatment Itraconazole	135 (80.8)
Systemic steroids	167 (100)

SD, standard deviation; ABPA-S, allergic bronchopulmonary aspergillosis seropositive; ABPA-CB, allergic bronchopulmonary aspergillosis central bronchiectasis; IgE, immunoglobulin E.

Table 2. Radiographic features in patients with allergic bronchopulmonary aspergillosis.

Variables	n (%)
Chest X-ray; n=167/167	
Unilateral	26 (15.6)
Bilateral	141 (84.4)
Consolidation	29 (17.4)
Nodules	47 (28.1)
Cavitation	22 (13.2)
Fleeting filtration	84 (50.3)
Fibrosis	16 (9.6)
Hyperinflation	91 (54.5)
Cystic changes	47 (28.1)
HRCT; n=126/167	
Unilateral	10 (7.9)
Bilateral	116 (92.1)
Bronchiectasis	104 (82.5)
Central bronchiectasis	98/104 (77.8)
Non-central bronchiectasis	6/104 (4.7)
Mucus plugging	71 (56.3)
Hyperinflation/emphysema	30 (23.8)
Tree-in-bud appearance	12 (9.5)
Consolidation	11 (8.7)
Collapse	11 (8.7)
Fibrosis	7 (5.5)
Aspergilloma	7 (5.5)

HRCT, high-resolution computed tomography.

Table 3. Microbiological features in patients with allergic bronchopulmonary aspergillosis.

	n (%)	
Sputum culture available	103/167 (61.7)	
Bacteria isolated	66 (64.1)	
Pseudomonas aeruginosa	32 (31.1)	
Haemophilus influenzae	16 (15.5)	
Haemophilus parainfluenzae	3 (2.9)	
Klebsiella pneumoniae	8 (7.8)	
Moraxella catarrhalis	7 (9.7)	
Fungi isolated	46 (44.6)	
Aspergillus fumigatus	17 (23.6)	
Aspergillus niger	11 (15.3)	
Aspergillus flavus	16 (22.2)	
Aspergillus terus	2 (2.8)	
Fungal bacterial co-infection	18 (17.5)	
Organisms identified, n (%)	**ABPA-S (n=22/103)**	**ABPA-CB (n=81/103)**
Pseudomonas aeruginosa	5 (22.7)	27 (33.3)
Haemophilus influenzae	2 (9.0)	14 (17.2)
Haemophilus parainfluenzae	2 (9.0)	1 (1.2)
Klebsiella pneumoniae	4 (18.8)	4 (4.9)
Moraxella catarrhalis	0	7 (8.6)
Aspergillus fumigatus	1 (4.5)	16 (19.7)
Aspergillus niger	4 (18.8)	7 (8.6)
Aspergillus flavus	5 (22.7)	11 (13.5)
Aspergillus terreus	1 (4.5)	1 (1.2)

ABPA-S, allergic bronchopulmonary aspergillosis seropositive, ABPA-CB, allergic bronchopulmonary aspergillosis central bronchiectasis.

[20]. The fibrotic stage represents the most advanced stage of the disease with complications and a poor disease prognosis. It has been reported by Greenberger *et al*. that patients frequently present in stage 3 or the exacerbation stage of the disease which is characterized by the presence of chest infiltrates on radiography [21]. Furthermore, the same study reported that the total serum IgE concentration in stage 3 patients is normally two times as high as the baseline IgE levels, while in the remainder of the stages, the IgE levels may be elevated or even normal [21]. More than half (52%) of our patients were also presented in stage 3 of the disease, while 50% of the patients were seen to have fleeting infiltrates on radiography. The total mean serum IgE levels in our study were elevated most likely because most patients were in stage 3 of ABPA.

The fungal isolation in ABPA is known to act as both the infecting organism as well as an allergen, both of which are responsible for eliciting the symptoms of ABPA [22]. These allergens lead to an immune response only in already immunocompromised patients. Furthermore, fungal hyphae are responsible for the release of chemicals that further trigger the secretion of mediators such as certain interleukins and cytokines, and inflammatory cells, including eosinophils [17]. *Aspergillus* species have been previously reported in other studies, like the one by Shah *et al*., to be a major cause of ABPA [23]; however, data on the bacterial spectrum in ABPA patients is not available.

Limitations

A few limitations of our study included the small sample size that was taken into account and the fact that the ABPA patients from only one tertiary care hospital were included, which might have created a referral bias in our results. Therefore, we suggest a large-scale study involving multiple hospitals throughout the country to be conducted. Moreover, chest HRCT was not done in all patients and was only done where the suspicion of bronchiectasis was high, so the percentage of bronchiectasis may be underreported. Lastly, we did not use *Aspergillus* skin test or precipitating and IgG antibodies to *Aspergillus* in all of our patients due to limited availability.

Conclusions

Hyperinflation and fleeting infiltrates on chest X-rays and bronchiectasis on HRCT were the most common radiological findings in our ABPA patients. *P. aeruginosa* and *A. fumigatus* were identified as the most common bacterial and fungal pathogens isolated respectively on sputum samples during exacerbation, particularly with ABPA-CB. We suggest that both radiographic evaluation and microbiological profile should be identified early to reduce the extent of lung damage.

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