

COMORBIDITIES

Allergic bronchopulmonary aspergillosis: a clinico-serological correlation with radiologic profile

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Objective: To study the different types of radiological presentations of ABPA in a tertiary clinic in Northern India and analyze them with respect to serological profile and clinical characteristics. **Methods:** We performed a retrospective analysis of clinical, serological and radiological characteristics of ABPA patients registered at a unit of tertiary pulmonary care center in North India. The patients were classified based on radiological presentation into ABPA-S, ABPA-CB and ABPA-CB-ORF and the differences in these groups were studied. **Results:** There were 112 patients with ABPA between age 6 and 75 years. About 8.9% ($n = 10$) of patients had a history of smoking and 38.4% ($n = 43$) had a history of prior anti-tuberculosis treatment. The median duration of symptoms was longest in the ABPA-CB-ORF group (15 years) followed by ABPA-CB (7 years) and ABPA-S (5 years). Mean serum total IgE level in the ABPA-CB-ORF group was 14 330 IU/mL followed by the ABPA-CB (3700 IU/mL) and ABPA-S (1020 IU/mL) groups ($p < 0.0001$). The ABPA-CB-ORF group had the highest median specific anti-*Aspergillus fumigatus* IgE followed by ABPA-CB and ABPA-S groups (42.24 kU/L, 20.65 kU/L and 3.44 kU/L, respectively) ($p < 0.0001$). ABPA-CB-ORF group had the highest percentage of positive serum precipitins against *Aspergillus* spp. (92%) followed by ABPA-CB (79.6%) and ABPA-S (68%) ($p < 0.05$). **Conclusions:** The patients with more pronounced lung damage in the form of ABPA-CB and ABPA-CB-ORF had higher serological parameters suggestive of increased systemic inflammation. Hence, ABPA may be categorized as mild (ABPA-S), moderate (ABPA-CB) and severe (ABPA-CB-ORF) categories which oscillate between remission and exacerbation phases.

KeywordsABPA, ABPA-CB, ABPA-CB-ORF, ABPA-S, *Aspergillus*, bronchiectasis, hypersensitivity**History**

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Introduction

Complex hypersensitivity reaction to antigens of the fungus *Aspergillus* results in Allergic Bronchopulmonary Aspergillosis (ABPA), which is characterized by asthma, recurrent chest roentgenogram infiltrates, bronchiectasis and a state of systemic inflammation. ABPA was first described by Hinson et al. [1] in 1952. It has been found to occur in 1 to 2% of patients with persistent asthma and in 2 to 15% of patients with cystic fibrosis [2]. In India the prevalence has been reported to be about 16% amongst asthma patients [3]. Traditionally ABPA has been divided into two types, ABPA-S (seropositive) and ABPA-CB (central bronchiectasis) based on radiological criteria [4]. The presence of bronchiectasis is considered to be advanced disease implying permanent damage in the form of bronchiectasis. Kumar [5] has proposed another classification which includes ABPA-CB-ORF (ABPA-CB with Other Radiologic Features) along with the ABPA-S and ABPA-CB types.

It had also been hypothesized that ABPA-CB and ABPA-CB-ORF denote severe forms of ABPA [5]. The present work was planned to identify these different presentations of ABPA and study their characteristics based on various diagnostic criteria.

Methods

The study is a retrospective analysis of ABPA cases diagnosed in a unit of the Department of Respiratory Medicine at the Vallabhbhai Patel Chest Institute between 1997 and 2010. Ethical approval for the study was obtained from the Institutional ethical review board. All of the patients registered in one unit of Viswanathan Chest Hospital, V. P. Chest Institute, Delhi, between 1997 and 2010 were scrutinized. Details of clinical history like duration of illness, history of anti-tubercular therapy, family history of asthma and smoking history were noted from the records. Spirometry with bronchodilator reversibility parameters was studied and patients were categorized as mild, moderate and severe obstructive defects based on Indian asthma guidelines [6]. According to this classification patients were categorized as follows: FEV₁/FVC ratio $< 70\%$ and (a) FEV₁ $> 80\%$ predicted – mild obstruction, (b) FEV₁ = 60–80% predicted – moderate obstruction or (c) FEV₁ $< 60\%$ predicted – severe obstruction.

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The findings on chest X-ray and high-resolution computed tomography (HRCT) of the chest were recorded. The results of skin prick tests (SPT) to *Aspergillus* spp. in the form of both early and late phase reactions were analyzed from the records. The SPT were performed using *Aspergillus fumigatus* (*A. fumigatus*) antigen (All Cure Pharmaceuticals, Delhi, India) in a concentration of 1:10. A small drop of antigen solution was placed on the volar aspect of the forearm. This was followed by pricking in the center of the drop using a lancet, for at least one second without causing bleeding. The test was read for early phase reaction at 15 minutes. The largest diameter and perpendicular diameter of the wheal for each of the allergens was measured. Thereafter, size of wheal was calculated as:

$$\text{Size of wheal} = (\text{Largest diameter} + \text{perpendicular diameter})/2.$$

The test was labeled as positive if this calculated value was ≥ 3 mm. The late phase reaction was read after six hours and any amount of swelling (subcutaneous edema) was considered to be a positive result. The results of serological tests including serum *A. fumigatus* precipitating antibodies, total serum IgE, and serum *A. fumigatus* IgE and IgG were also recorded.

Inclusion criteria

Patients diagnosed with ABPA were included in the study if they had been diagnosed based on fulfillment of the following criteria:

- (1) History of bronchial asthma,
- (2) Central bronchiectasis (inner two thirds of chest CT field) (in ABPA-CB),
- (3) Immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus*,
- (4) Total serum IgE concentration >417 kU/L (1000 ng/mL),
- (5) Elevated serum *A. fumigatus* IgE,
- (6) Serum precipitating antibodies to *A. fumigatus* or elevated *A. fumigatus* IgG, With or without
- (7) Chest roentgenographic infiltrates (transient/fixed).

For the purpose of analyzing the characteristics of disease, the patients were first categorized into two groups based on Patterson et al. [4] as: Allergic Broncho Pulmonary Aspergillosis Seropositive (ABPA-S) and Allergic Broncho Pulmonary Aspergillosis with Central Bronchiectasis (ABPA-CB).

The cases were further reclassified based on HRCT chest into three groups as described earlier by Kumar [5]. These three groups were; Allergic Broncho Pulmonary Aspergillosis Seropositive (ABPA-S), Allergic Broncho Pulmonary Aspergillosis with Central Bronchiectasis (ABPA-CB) and ABPA-CB with Other Radiologic Features (ABPA-CB-ORF). ABPA-CB-ORF included patients diagnosed with ABPA based on the above mentioned criteria and who apart from central bronchiectasis had other radiologic features such as pulmonary fibrosis, bleb, bullae, pneumothorax, parenchymal scarring, emphysematous change, multiple cysts, fibrocavitary lesions, aspergilloma, ground-glass appearance, collapse, mediastinal lymph node, pleural effusion and pleural thickening.

The above groups were analyzed for the clinical and serological findings. The differences between the three groups with regard to various parameters were characterized and evaluated statistically.

The patients with incomplete records or not meeting the diagnostic criteria of ABPA (as above) were excluded from the study. The diagnosed patients were treated with oral steroids as per the following regimen: Prednisolone 0.75 mg/kg daily for 6 weeks, then 0.5 mg/kg daily for 6 weeks, then tapered by 5 mg daily every 6 weeks, for a total of 6–12 months.

Statistical analysis

Statistical analysis was performed using a statistical software package (SPSS for Microsoft Windows, package version 10; SPSS Inc; Chicago, IL). Mean (SD) or the median (range) were calculated for the descriptive data. The categorical variables were compared using the chi-squared (χ^2) test, while continuous variables were compared using the Mann–Whitney *U*-test or Kruskal–Wallis tests, as applicable. Statistical significance was taken at a *p* value of <0.05 .

Results

The 112 patients with ABPA who were evaluated ranged in age from 6 to 75 years, with duration of symptoms varying from 6 months to 50 years. The details of these patients are summarized in Table 1.

About 8.9% ($n=10$) of patients had a history of smoking and 38.4% ($n=43$) had a past history of anti-tuberculosis treatment. Family history of asthma was present in about 29% of the patients. Characteristics of the three groups divided by the Kumar [5] classification are depicted in Table 2. There were 38 (33.92%) patients in ABPA-CB-ORF group, 49 (43.75%) in ABPA-CB and 25 (22.32%) in ABPA-S groups. The duration of symptoms was longest in the ABPA-CB-ORF followed by ABPA-CB and ABPA-S group, respectively, although the difference was not statistically significant. The spirometry parameters revealed poorer lung functions in the ABPA-CB and ABPA-CB-ORF groups compared to the ABPA-S although this difference was not statistically significant either. On comparing the serological profile in the three groups, mean serum total IgE levels in ABPA-CB-ORF group were 14 330 IU/mL followed by ABPA-CB (3700 IU/mL) and ABPA-S (1020 IU/mL) groups ($p<0.0001$). The type I skin test reactivity against *Aspergillus* spp. was positive in all patients included in the study. In the case of type III skin test reactivity 28%, 59.2% and 47.4% had a positive reaction in ABPA-S, ABPA-CB and ABPA-CB-ORF groups respectively and the difference was statistically significant ($p<0.04$). There was also a statistically significant difference ($p<0.0001$) in specific *A. fumigatus* IgE between the three groups with the highest values in the ABPA-CB-ORF group followed by ABPA-CB and ABPA-S groups (42.24 kU/L, 20.65 kU/L and 3.44 kU/L, respectively). The ABPA-CB-ORF group had highest percentage of positive serum precipitins against *Aspergillus* spp. (92%) followed by ABPA-CB (79.6%) and ABPA-S (68%) and the difference was statistically significant ($p<0.05$).

Table 1. Baseline characteristics of 112 patients with ABPA.

Clinical characteristics	Results
Age (yr)	
Mean $\pm$ SD	34.05 $\pm$ (13.16)
(minimum – maximum)	(6–75)
Sex	
Male	60 (53.6%)
Female	52 (46.4%)
Duration of asthma (yr)	
Mean $\pm$ SD	12.68 $\pm$ 12.11
History of hemoptysis	29 (25.9%)
History of allergic rhinitis	65 (58%)
Family history of asthma	32 (28.6%)
History of expectoration	33 (29.5%)
of brownish-black mucus plugs	
History of anti-tuberculosis treatment	43 (38.4%)
Smoking history	10 (8.9%)
Crackles on clinical examination	30 (26.5%)
Presence of clubbing	25 (22.1%)
Spirometry findings	
Normal	26 (23%)
Mild obstruction ^a	20 (17.7%)
Moderate obstruction ^b	22 (19.6%)
Severe obstruction ^c	43 (38.4%)
Bronchodilator reversibility	45 (39.82%)
Restriction	1 (0.9%)
<i>Aspergillus</i> skin test	
Type 1	112 (100%)
Type 3	54 (48.2%)
Absolute eosinophil count, cells/mm ³	
Mean $\pm$ SD	1181 $\pm$ 1295
Median (range)	900 (10 270)
(minimum-maximum)	(9–10 280)
<i>Aspergillus</i> spp. precipitins positive	91 (81.3%)
Serum total IgE levels IU/mL	
Mean $\pm$ SD	7479.95 $\pm$ 7310.08
Median (range)	4683 (35 488)
(minimum-maximum)	(244–35 732)
Positive Specific IgG to <i>A. fumigatus</i>	94 (83.9%)
Specific IgE to <i>A. fumigatus</i> (kU/L)	
Mean $\pm$ SD	28.32 $\pm$ 24.47
Median (range)	21.68 (158.65)
(minimum-maximum)	(0.16–158.80)

^aMild: FEV₁/FVC ratio <70% and FEV₁ >80% predicted.

^bModerate: FEV₁ = 60–80% predicted.

^cSevere: FEV₁ <60% predicted.

The patients were further re-classified into two groups (ABPA-CB and ABPA-S) based on Patterson et al. [4]. The gender distribution and median duration of asthma was comparable in these two groups (Table 2). The different types of spirometry patterns observed are depicted in Table 2. The difference in spirometric patterns observed was not statistically significant. Similarly, difference in absolute eosinophil counts was not statistically significant between the two groups. On comparison of total serum IgE levels, a statistically significant difference was observed with mean levels of 1020 IU/mL in ABPA-S group and 7260 IU/mL in ABPA-CB group ($p < 0.0001$). Serum precipitins were positive in 68% of patient in the ABPA-S group and in 85.1% of patients in the ABPA-CB group ($p = 0.05$). As described above, type I hypersensitivity was demonstrated in all patients included in the study, but delayed type III skin test positivity was observed more frequently in the ABPA-CB group (54%) versus ABPA-S group (28%), ($p < 0.02$). There was no

statistically significant difference in rates of observed specific IgG against *A. fumigatus* between the two groups (80% in ABPA-S versus 85% in ABPA-CB). Mean levels of specific IgE against *A. fumigatus* in ABPA-S and ABPA-CB groups were 3.44 kU/L and 30.90 kU/L respectively ($p < 0.0001$).

Discussion

The first case of ABPA was described in India in 1971 [7] and since then there has been a gradual rise in reports of the disease. This may be attributed to increasing awareness of the disease amongst physicians. Still, in a country like India with a high prevalence of Tuberculosis (TB), ABPA remains an underdiagnosed disease [8,9]. This was evident in our study, as 38.4% ($n = 43$) of patients diagnosed with ABPA had a history of anti-tuberculosis treatment. ABPA is characterized by repeated episodes of exacerbations alternating with variable periods of remissions and if untreated may result in a fibrotic lung disease closely resembling the chronic fibrocavitary disease sequelae of pulmonary tuberculosis. This necessitates the early diagnosis and proper treatment of this disease.

Traditionally, ABPA has been divided into two groups as ABPA-S and ABPA-CB based on classification by Patterson R et al. [4]. ABPA-CB is considered a more severe form of the disease because of permanent damage to airways in the form of bronchiectasis. Further, bronchiectasis acts as a site for antigen-antibody reactions and increases susceptibility to infections, thus leading to a more rapid deteriorating course of the disease compared to the ABPA-S form [10]. The etiopathogenic factors responsible for development of bronchiectasis in some and continuing as ABPA-S in others remain elusive.

In 2003, Kumar [5] proposed another classification of ABPA as mild, moderate and severe which present as ABPA-S, ABPA-CB and ABPA-CB-ORF, respectively. The conclusion of the study was that ABPA should be treated in its early stage as ABPA-S, preventing progression to more severe forms of ABPA-CB and ABPA-CB-ORF. In the present study, we also studied these three categories of ABPA and found that patients with ABPA-CB-ORF had a longer duration of symptoms compared to those with ABPA-CB and ABPA-S. Also, all the serological parameters of ABPA (serum total IgE, serum precipitins against *Aspergillus* spp., specific IgE and IgG against *A. fumigatus*) were highly raised in the ABPA-CB-ORF group followed by the ABPA-CB and ABPA-S groups, respectively, and the differences were statistically significant. Thus, this study again confirms that ABPA-CB-ORF constitutes a severe phenotype of ABPA. In other words, it can be inferred that amongst individuals with ABPA, those having more severe hypersensitivity (as evidenced by higher values of serum total IgE, serum precipitins against *Aspergillus* spp., specific IgE and IgG against *Aspergillus* spp.) develop a more severe form of disease which presents as ABPA-CB and ABPA-CB-ORF. This sentiment is further supported by a study conducted by Kiely et al. [11] in which chest radiographic findings were correlated with immunological findings and found significant positive correlations between peak antibody to *A. fumigatus* titres (expressed as an index), peak eosinophil count and radiographic severity.

Table 2. Characteristics of ABPA patients in different classifications.^a

Characteristic	Classification of ABPA based on Kumar ^b				Classification of ABPA based on Patterson et al. ^c		
	ABPA-S (n = 25)	ABPA-CB (n = 49)	ABPA-ORF (n = 38)	p Value	ABPA-S (n = 25)	ABPA-CB (n = 87)	p Value
Sex (n)				NS			NS
Male	13	25	22		13	47	
Female	12	24	16		12	40	
Duration of asthma (years)	5 (1–50)	7 (0.5–47)	15 (1–50)	NS	5 (1–50)	10 (0.5–50)	NS
H/o hemoptysis, n (%)	6 (24%)	15 (30.6%)	8 (21.1%)	NS	6 (24%)	23 (26.4%)	NS
H/o anti-tubercular therapy, n (%)	8 (32%)	16 (32.7%)	19 (50%)	NS	8 (32%)	35 (40.2%)	NS
Family H/o asthma, n (%)	6 (24%)	16 (32.7%)	10 (26.3%)	NS	6 (24%)	26 (29.9%)	NS
H/o allergic rhinitis, n (%)	9 (36%)	32 (65.3%)	24 (63.2%)	<0.05	9 (36%)	56 (64.4%)	<0.03
PFT, n (% of total 112 patients)				NS			NS
Mild	5 (4.5)	9 (8)	6 (5.4)		5 (4.5)	15 (13.4)	
Moderate	6 (5.4)	5 (5.4)	11 (9.8)		6 (5.4)	16 (14.3)	
Severe	7 (6.3)	24 (21.4)	12 (10.7)		7 (6.3)	36 (32.1)	
Restrictive pattern		1 (0.9)				1 (0.9)	
Normal	7 (6.3)	10 (8.9)	9 (8)		7 (6.3)	19 (17)	
Absolute eosinophil count (cells/mm ³)	1000	800	860	NS	1000	820	NS
(100–2460)		(9–3900)	(11–10 280)		(100–2460)	(10–10 280)	
Total serum IgE levels (IU/mL) ^d	1020	3700	14 330	<0.0001	1020	7260	<0.0001
(244–1900) ^e		(1020–11 000) ^f	(6530–35 730) ^g		(244–1900)	(1020–35 730)	
S precipitins positive against <i>Aspergillus</i> spp, n (%)	17 (68)	39 (79.6)	35 (92)	<0.05	17 (68)	74 (85.1)	p = 0.055
Skin test type 3 positive against <i>Aspergillus</i> spp, n (%)	7 (28)	29 (59.2)	18 (47.4)	<0.04	7 (28)	47 (54)	<0.02
Specific IgG positive against <i>A. fumigatus</i> , n (%)	20 (80)	40 (81.6)	34 (89.5)	NS	20 (80)	74 (85.1)	NS
Specific IgE against <i>A. fumigatus</i> (kU/L) ^d	3.44	20.65	42.24	<0.0001	3.44	30.90	<0.0001
(0.16–12.60) ^e		(8.15–58.60) ^f	(18.20–158.80) ^g		(0.16–12.60)	(8.15–158.80)	

^aAll values are Median (minimum–maximum) except if otherwise indicated.^bFrom reference [5].^cFrom reference [4].^dVariation in superscript indicates significance of difference^(e,f,g).

They suggested that the peak *A. fumigatus* index and eosinophil counts correlate with the severity of radiographic stages in allergic bronchopulmonary aspergillosis.

An early diagnosis and initiation of systemic corticosteroid is essential to prevent irreversible damage [12]. The course of patients who present primarily with ABPA-S appears to be less severe than those who present with ABPA-CB. This was also observed in the study conducted by Kumar [5] in 18 patients with ABPA.

Patterson et al. [13] have proposed a five staging system for different presentations and progressions of ABPA which include: acute, remission, exacerbation, corticosteroid-dependent asthma and fibrotic. They also concluded that delayed diagnosis and non compliance to treatment results in an increased number of patients presenting in later stage (i.e. fibrotic stage) of ABPA. On a similar note, the patients in our study with more pronounced lung damage in form of ABPA-CB and ABPA-CB-ORF had higher serological parameters suggestive of increased systemic inflammation. Further, it is important to stress that patients with ABPA-CB-ORF had even higher serological parameters than those with ABPA-CB. Hence, it can be recommended that patients with ABPA should be diagnosed as early as possible with swift institution of treatment. Treatment compliance and regular follow up is imperative so as to prevent progression to later stages of disease involving permanent lung damage.

Another important aspect that requires mention is the similarity of radiological findings in pulmonary tuberculosis and ABPA-CB-ORF. In a country like India with a high prevalence of tuberculosis, misdiagnosis of ABPA as tuberculosis is quite common. In our study 38.4% of patients had a prior history of anti-tuberculosis treatment. Bilateral involvement in ABPA versus unilateral or bilateral involvement in cases of tuberculosis may be of some help in differentiating the two diseases radiologically. Still the radiologic findings in ABPA-CB-ORF mimic tuberculosis and a treating physician needs to utilize the history, serial chest X rays, sputum and serological findings to clinch the diagnosis.

We hereby reinforce the earlier proposed classification system for ABPA [5] on presentation to be done as: mild (ABPA-S), moderate (ABPA-CB) and severe (ABPA-CB-ORF); and further add that these three groups enter states of remission and exacerbation depending on clinical symptoms, serological and radiological worsening or improvement (Figure 1). This proposition of remission and exacerbation of mild, moderate and severe presentations of ABPA needs further validation by longitudinal follow up studies.

Conclusions

Patients with ABPA may present as ABPA-S (mild), ABPA-CB (moderate) or ABPA-CB-ORF (severe) types and these patients fluctuate between phases of remission

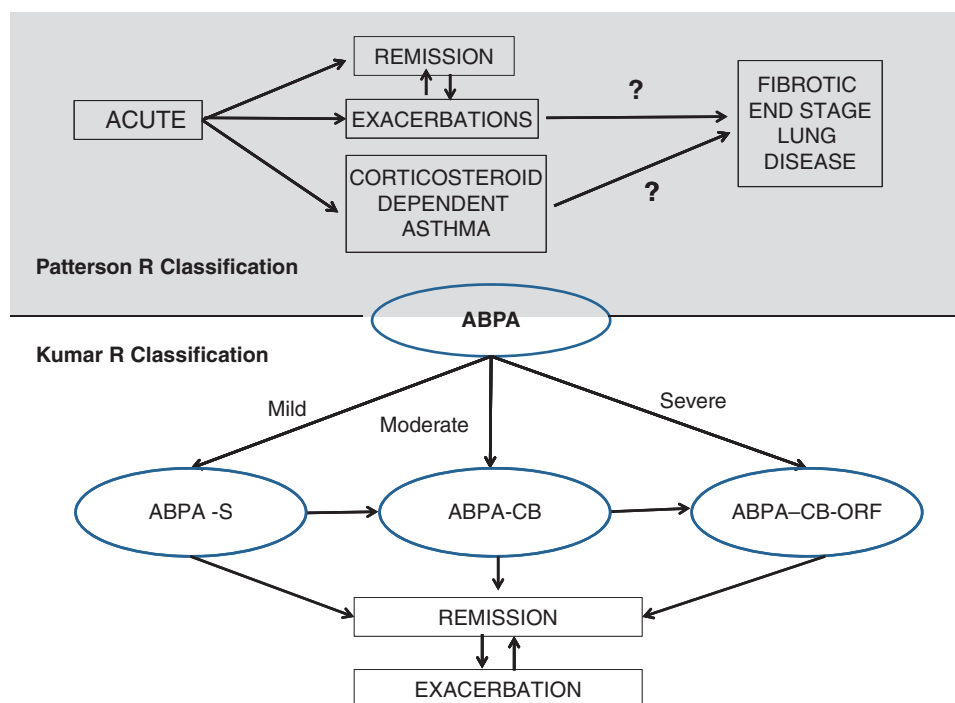


Figure 1. Kumar [5] and Patterson [4] classification for ABPA.

and exacerbation. Diagnosis and treatment should be instituted quickly so as to prevent progression to more severe forms of the disease (ABPA-CB and ABPA-CB-ORF).

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Declaration of interest

Dr. (Prof.) Raj Kumar has no conflicts of interest to declare
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