



Brief Report

Allergic bronchopulmonary aspergillosis (ABPA) sans asthma: A distinct subset of ABPA with a lesser risk of exacerbation

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Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is a complex immunological disorder complicating asthma. Uncommonly, ABPA presents without underlying asthma. Herein, we describe the outcomes of ABPA with and without asthma. Of the 530 subjects (median follow-up, 39 months), 37 (7%) were ABPA sans asthma. Bronchiectasis was more frequent (97.3% vs. 83.2%, $P = .02$), and the lung function was significantly better in ABPA sans asthma. The incidence-rate of ABPA exacerbation was higher in those with asthma than without (112 vs. 242 per 1000 person-years, $P = .0001$). ABPA sans asthma appears to be a distinct subset of ABPA, with a better lung function and fewer exacerbations.

Key words: aspergillosis, ABPM, asthma, allergy, bronchiectasis, *Aspergillus*.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder caused by reactions against the antigens of *Aspergillus fumigatus*.¹ ABPA is usually encountered in patients with asthma or cystic fibrosis (CF).² A subset of patients with ABPA, however, may present without underlying bronchial asthma.^{3–5} Although ABPA in the absence of asthma was described almost four decades ago,³ much remains unknown. We hypothesized that patients with ABPA sans asthma are likely to behave differently than those with ABPA complicating asthma. Herein, we compare ABPA subjects with and without a history of asthma, and describe their clinical, radiological, and immunological profile along with treatment outcomes.

We retrospectively reviewed our database to identify treatment-naïve subjects with ABPA, over a 10-year period (2007–2017). The Institute ethics committee approved the study

protocol and granted a consent waiver as this was a retrospective analysis of anonymized data. We have previously published the data of several participants included in the current study.^{6–8} ABPA was diagnosed, if five or more of the following was satisfied: (1) physician-diagnosed asthma; (2) elevated *A. fumigatus*-specific immunoglobulin E (IgE) (>0.35 kUA/l); (3) immediate cutaneous hypersensitivity (type I reaction) on *Aspergillus* skin test; (4) serum total IgE levels >1000 IU/ml; (5) serum precipitating antibodies against *A. fumigatus*; (6) peripheral blood eosinophil count >500 cells/ μ l; (7) consistent radiographic abnormalities on chest radiograph (fleeting or fixed); and/or, high resolution computed tomography (HRCT) of chest showing bronchiectasis or high attenuation mucus. None of the patients were evaluated for cystic fibrosis (CF). Subjects were labelled as “ABPA sans asthma” if they were asymptomatic for

asthma before the first presentation, lacked features to suggest atopy (allergic rhinitis, conjunctivitis, and/or atopic dermatitis), and there was absence of wheeze on physical examination. The remaining group was labelled as “ABPA complicating asthma.” The objectives of the study were to identify the proportion of ABPA sans asthma and compare their profile with ABPA complicating asthma.

We retrieved the clinical history and relevant physical examination of all the study participants. The commercially available fluorescent enzyme immunoassay (Phadia 100, Thermo Fisher Scientific, Uppsala, Sweden) was used to measure the serum *A. fumigatus*-specific IgE. Serum total IgE levels were measured using the quantitative enzyme-linked immunoassay (Demeditec diagnostics, GmbH, Kiel, Germany).⁹ Serum *Aspergillus* precipitins were measured using the double gel diffusion technique.¹⁰ HRCT of the chest was performed using a 16-row, multiple-detector scanner (LightSpeed plus, GE medical systems, Slough, UK) and was interpreted by a thoracic radiologist. We recorded the extent of bronchiectasis and the presence of high-attenuation mucus (HAM).^{6,11} Spirometry was performed at baseline, and the severity of obstruction was graded as mild, moderate or severe.¹²

ABPA was treated with either glucocorticoids or itraconazole for 4 months, as described previously.^{7,8} Chest radiograph and serum total IgE were performed every 6–8 weeks during follow-up. *Response* was defined as clinical and radiological resolution together with a decline in total IgE >25% from the baseline value. ABPA exacerbation was diagnosed, if the serum total IgE increased by >50% from the last recorded IgE, with clinical and/or radiologic worsening.¹³ We managed the first exacerbation of ABPA with oral prednisolone. The subsequent exacerbations were treated with a combination of prednisolone and itraconazole. Clinical worsening of symptoms in the absence of radiological or immunological worsening (total IgE) was labeled as asthma exacerbation and managed accordingly. Inhaled corticosteroids, long and short-acting beta-2 agonists, and montelukast were used in all patients for asthma control, at the discretion of the treating physician.

All statistical analyses were performed using the commercial statistical package SPSS for MS-Windows (version 22.0, IBM Inc., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as mean (standard deviation [SD]) or median with interquartile range (IQR), as applicable. The χ^2 test was used for comparing the categorical variables while the student *t* test (or the Mann-Whitney *U* test) was used for continuous variables. A *P* value <.05 was considered statistically significant. The incidence rate of ABPA exacerbation (sum of the number of exacerbations in each subject/sum of the number of years each subject was followed up, multiplied by 1000) was computed for ABPA subjects with and without asthma.

We included 530 subjects, of which 37 (7%) were ABPA sans asthma, while 493 (93%) were ABPA-complicating asthma (mean duration of asthma, 11.2 years). The mean (SD) age of the study population was 34.9 (13.5) years; majority were men (54.2%) and nonsmokers (Table 1). The clinical and immunological features were similar in ABPA subjects with or without asthma. Hemoptysis and expectoration of mucus plugs were seen in 32% and 28%, respectively. The median (IQR) total IgE was 7113 (3198–11617) IU/ml. Bronchiectasis was more common in ABPA sans asthma (97.3% vs. 83.2%, *P* = .02). However, the number of lobes and segments involved by bronchiectasis was similar in both the groups. Spirometry was available in 505 subjects (473 and 32 ABPA subjects with and without asthma, respectively). A normal spirometry was more frequently encountered in ABPA sans asthma than those with asthma (53.1% vs. 27.7%, *P* = .02). The FEV1, FVC and the FEV1/FVC values were significantly lower in subjects with ABPA complicating asthma. The median (IQR) duration of follow-up was 39 (24–68) months. Most of the subjects (83.2%) were treated with glucocorticoids, and this was similar in ABPA with and without asthma. A significantly larger proportion (44% vs. 21.6%) of subjects in the ABPA complicating asthma experienced ABPA exacerbations (Table 1). The incidence rate of ABPA exacerbation was also significantly higher in ABPA complicating asthma than ABPA sans asthma (242 vs. 114 per 1000 person-years, respectively; *P* = .0001).

In the present study, we have shown that ABPA sans asthma behaves differently from ABPA complicating asthma. As compared to ABPA complicating asthma, these subjects experienced fewer episodes of ABPA exacerbation, probably due to the better lung function observed in these individuals. To our knowledge, the current study is the largest report of ABPA sans asthma. Of the entire cohort of ABPA in the present study, 7% (37 subjects) were ABPA sans asthma. However, the true prevalence of ABPA sans asthma remains unknown as the current study was conducted at a tertiary referral center. The diagnosis of ABPA sans asthma is difficult, as these patients do not have underlying asthma, and they are often misdiagnosed as pulmonary tuberculosis, lung cancer or other respiratory disorders. The widespread use of HRCT chest has, however, greatly enhanced the diagnosis of this entity. In fact, in all these patients, it was the imaging findings, which led us to suspect ABPA.

Our study has certain limitations. The major drawback is the retrospective study design. We also do not have the information regarding the presenting symptoms of the cohort with ABPA sans asthma, which led to their referral. This knowledge could have provided useful insights for clinicians to suspect ABPA without asthma, in the future. Although none of the patients in our study had features suggestive of CF, we did not test for any genetic mutations. One may also question that we missed the diagnosis of asthma our cohort of ABPA sans asthma. The

Table 1. Baseline clinical features, investigations, treatment and follow-up details of the ABPA patients included in the current study.

Parameter	ABPA sans asthma (<i>n</i> = 37)	ABPA with asthma (<i>n</i> = 493)	Total (<i>n</i> = 530)	<i>P</i> value
Clinical features				
Age, in years*	37.3 (15.2)	34.7 (13.4)	34.9 (13.5)	.26
Male sex	26 (70.3)	261 (52.9)	287 (54.2)	.06
Duration of asthma, in years*	...	11.2 (9.6)	11.1 (9.6)	...
Nonsmokers	37 (100)	480 (97.4)	517 (97.5)	1.00
Hemoptysis	13 (35.1)	158 (32)	171 (32.3)	.72
Expectoration of BBMP	8 (21.6)	148 (28.8)	150 (28.3)	.45
History of ATT intake	15 (40.5)	172 (34.9)	187 (35.3)	.76
Height in cm*	166.4 (9.0)	163.1 (10.8)	163.4 (10.7)	.13
Weight in kg*	58.4 (12.6)	55.5 (12.9)	55.7 (12.9)	.24
Investigations				
# <i>A. fumigatus</i> specific IgE, kUA/l	12.5 (3.1–23)	17.4 (3.6–36.5)	16.6 (3.6–34.8)	.12
# Positive <i>Aspergillus</i> skin test	35 (94.6)	470 (95.3)	505 (95.3)	.69
# Total IgE, IU/ml	6198 (2835–14468)	7122 (3212–11562)	7113 (3198–11617)	.92
# Total eosinophil count, cells/ μ l	800 (321–1400)	773 (328–1317)	786 (326–1314)	.77
Positive serum <i>Aspergillus</i> precipitins	20 (54.1)	318 (64.5)	338 (63.8)	.22
Imaging				
Fleeting opacities on chest radiograph	17 (54.8)	173 (56)	190 (55.9)	1.00
Bronchiectasis	36 (97.3)	410 (83.2)	446 (84.2)	.02
Number of lobes involved [#]	3 (2–5)	3 (2–5)	3 (2–5)	.76
Number of segments involved [#]	5 (3–9)	6 (3–10)	6 (3–10)	.42
Presence of HAM	16 (43.2)	160 (32.5)	176 (33.3)	.21
€ Spirometry*				
FEV1, liters	2.56 (0.67)	1.97 (0.83)	2.01 (0.83)	.0001
FVC, liters	3.35 (0.79)	2.80 (0.91)	2.87 (0.91)	.004
FEV1/FVC	77.4 (10.3)	67.7 (13)	68.5 (13.1)	.001
€ Spirometry category				
Normal	17 (53.1)	131 (27.7)	148 (29.3)	.02
Mild obstruction	8 (25)	148 (31.3)	156 (30.9)	
Moderate	4 (12.5)	126 (26.6)	130 (25.7)	
Severe	3 (9.4)	68 (14.4)	71 (14.1)	
Treatment and follow-up				
# Follow-up duration, in months	47 (27–72)	37 (24–64)	39 (24–68)	.15
Dosage of ICS (BDPE), in μ g*	963 (650)	728 (457)	746 (476)	.12
Glucocorticoid therapy	28 (75.7)	413 (83.8)	441 (83.2)	.25
Itraconazole therapy	9 (24.3)	80 (16.2)	89 (16.8)	
Subjects with ABPA exacerbation	8 (21.6)	217 (44)	225 (42.5)	.009
Number of exacerbations per 1000 PY [¶]	114	242	232	.0001

ABPA, allergic bronchopulmonary aspergillosis; AEC, absolute eosinophil count; ATT, antitubercular therapy; Asp, *Aspergillus fumigatus*; BBMP, brownish black mucus plug; BDPE, beclomethasone dipropionate equivalent; ICS, inhaled corticosteroid; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; HAM, high-attenuation mucus; IgE, immunoglobulin E; PY, person-years.

All values are presented as numbers (percentages), unless otherwise mentioned as *mean (standard deviation) or #median (interquartile range).

€ Spirometry data was available for 505 subjects (473 and 32 subjects of ABPA with and without asthma, respectively).

¶ Number of exacerbations per 1000 person-years = (Sum of the number of exacerbations experienced by each participant/sum of the number years each participant was followed-up) $\times$ 1000.

presence of obstructive defect (43% subjects in our study) in these patients suggests that some of them could have been “poor perceivers” of asthma.¹⁴ However, none of the subjects with ABPA sans asthma were symptomatic prior to the diagnosis of ABPA. In fact, the presence of bronchodilator reversibility and airway hyperresponsiveness has also been previously documented in ABPA sans asthma.^{3,15} Finally, bronchiectasis per

se may explain the obstructive defect on spirometry in some patients of ABPA sans asthma. The large sample size and comparison with ABPA complicating asthma are the strengths of our study.

In conclusion, ABPA sans asthma appears to be a distinct disease subset with a different natural history. The study highlights the need for more research in this subset of ABPA.

Declaration of interest

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

References

1. Patterson KC, Strek ME. Diagnosis and treatment of pulmonary aspergillosis syndromes. *Chest*. 2014; 146: 1358–1368.
2. Agarwal R. Allergic bronchopulmonary aspergillosis. *Chest*. 2009; 135: 805–826.
3. Glancy JJ, Elder JL, McAleer R. Allergic bronchopulmonary fungal disease without clinical asthma. *Thorax*. 1981; 36: 345–349.
4. Koh WJ, Han J, Kim TS et al. Allergic bronchopulmonary aspergillosis coupled with broncholithiasis in a non-asthmatic patient. *J Korean Med Sci*. 2007; 22: 365–368.
5. Rosenberg M, Patterson R, Mintzer R et al. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med*. 1977; 86: 405–414.
6. Agarwal R, Gupta D, Aggarwal AN et al. Clinical significance of hyperattenuating mucoid impaction in allergic bronchopulmonary aspergillosis: an analysis of 155 patients. *Chest*. 2007; 132: 1183–1190.
7. Agarwal R, Aggarwal AN, Dhooria S et al. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J*. 2016; 47: 490–498.
8. Agarwal R, Dhooria S, Singh Sehgal I et al. A randomized trial of itraconazole vs prednisolone in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Chest*. 2018; 153: 656–664.
9. 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: 659–663.
10. Longbottom JL, Pepys J. Pulmonary aspergillosis: diagnostic and immunological significance of antigens and C-substance in *Aspergillus fumigatus*. *J Pathol Bacteriol*. 1964; 88: 141–151.
11. Agarwal R, Khan A, Gupta D et al. An alternate method of classifying allergic bronchopulmonary aspergillosis based on high-attenuation mucus. *PLoS One*. 2010; 5: e15346.
12. Aggarwal AN, Gupta D, Jindal SK. Development of a simple computer program for spirometry interpretation. *J Assoc Physicians India*. 2002; 50: 567–570.
13. Agarwal R, Chakrabarti A, Shah A et al. Allergic bronchopulmonary aspergillosis: review of literature and proposal of new diagnostic and classification criteria. *Clin Exp Allergy*. 2013; 43: 850–873.
14. Bijl-Hofland ID, Cloosterman SG, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax*. 1999; 54: 15–19.
15. Yoshida Y, Oosaki R, Fujishita T, Maruyama M, Kobayashi M. [Allergic bronchopulmonary aspergillosis in a patient with no symptoms of asthma until after bronchial lavage]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1997; 35: 784–789.