

Allergic bronchopulmonary fungal disease without clinical asthma

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ABSTRACT During a retrospective survey of patients with pulmonary shadows and blood eosinophilia between the years 1965 and 1980, 42 patients were found with allergic bronchopulmonary fungal disease. Eleven of these had no clinical evidence of asthma. Three of these 11 had hypersensitivity to fungi other than *Aspergillus sp.* In the absence of asthma there was some difficulty in making a diagnosis, particularly where collapse of the upper lobe occurred in middle-aged or elderly patients and bronchogenic carcinoma was presumed responsible. We suggest that the term allergic bronchopulmonary aspergillosis be replaced by allergic bronchopulmonary fungal disease, the diagnosis be considered in patients with lung disease and blood eosinophilia even in the absence of asthma, and a wider range of fungal allergens be used for skin and precipitin tests.

The increasing frequency with which the diagnosis of allergic bronchopulmonary aspergillosis is being made is probably the result of increasing recognition of the disease entity,¹⁻³ and perhaps some liberalisation of the criteria required for diagnosis. The list of criteria usually required begins with asthma and includes blood eosinophilia and transient pulmonary infiltrates. Immediate positive skin tests to *Aspergillus sp.*, precipitating antibody against *Aspergillus sp.*, elevated IgE concentrations, and where possible, proximal bronchiectasis are required in the USA.^{1 3-5} British criteria require the presence of asthma, blood eosinophilia, transient infiltrates, and a positive prick test to the fungus.^{2 6-9} Previous reports have, however, included isolated instances in which the patient did not have asthma.^{5 8 10}

Thirty-one cases of allergic bronchopulmonary aspergillosis diagnosed by the above criteria have been seen at Sir Charles Gairdner Hospital. Eleven additional patients conforming to the above criteria but with no history of asthma as defined clinically by episodes of wheezing or dyspnoea, and no clinical evidence of airflow obstruction at the time of diagnosis form the basis of this paper.

Methods

During a retrospective survey of patients with lung opacities and blood eosinophilia seen at the Sir

Charles Gairdner Hospital between 1965 and 1980, 31 cases of allergic bronchopulmonary aspergillosis conforming to the usual criteria were found. In addition there were 11 patients with similar findings but with no history of asthma—that is, no history of wheezing or dyspnoea and no clinical evidence of airflow obstruction at the time of the diagnosis.

Criteria for diagnosis centred mainly on a positive prick test¹¹ to extracts of *Aspergillus fumigatus* or *A terreus* and in two patients to an extract of the fungus *Helminthosporium sp.* A wheal greater than 3 mm within 15 minutes was considered positive. Atopy or an immediate type I sensitivity was determined by means of prick tests to 19 common allergens using Commonwealth Serum Laboratories antigen. Total IgE estimation was performed in eight but specific IgE by means of a RAST test in only three patients. Blood was examined for eosinophils and serum was examined for precipitins to *Aspergillus* by Ouchterlony agar gel double diffusion in all patients.

Early morning sputa, collected after first rinsing out the mouth with water, were examined by the mycology laboratory for mycelium and were cultured on appropriate media at both 26°C and 37°C.

All patients had chest radiography on several occasions. All patients had ventilatory function tests on more than one occasion, and eight had ventilatory function tests performed before and after the inhalation of two puffs of sympathomimetic bronchodilator aerosol. Two patients had lobectomies and one a segmental resection before a diagnosis was made.

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Results

All 11 patients, whose ages ranged from 15 to 65 years, denied a history of asthma and none had clinical evidence of generalised airway obstruction at the time of diagnosis. Five admitted to a previous history of rhinitis or hayfever. Eight patients had ventilatory function tests before and after bronchodilators. Six showed a change of less than 9%. Case 10 exhibited a change of 17% and case 9, 34% (table 1).

Eight patients had a positive prick test to *Aspergillus* and two to *Helminthosporium*. Three had a negative prick skin test to all 19 antigens and in one the test was equivocal. Of these three the total IgE was normal in only one (case 2). A summary of results is given in table 2.

All patients had a raised blood eosinophil count which ranged from 8% of 8900 WBC (801 mm³) to 34% of 13700 (4685 mm³). Eight patients had an excess of eosinophils in the sputum and one other had Curshman's spirals.

Mycological investigations on specimens from these patients gave the following results. Cases 1, 4, and 9 had septate branching mycelium in the sputum and *Aspergillus fumigatus* was cultured. Their serum contained antibody to *A fumigatus*. Case 3, also with mycelium in the sputum, grew various combinations of *A terreus*, *A fumigatus*, *A niger*, and *A flavus*. Precipitins were positive to all four species but were strongly positive for *A terreus* and *A fumigatus* which each showed four bands. Cases 2 and 5, in whose sputum no mycelium was found, grew *A fumigatus* from at least two sputum specimens and had positive precipitins for *A fumigatus*. One patient (case 7) had masses of septate branching mycelium similar to that of *Aspergillus* in a plug from a bronchoscopy specimen but the fungus failed to grow. Precipitins were positive for *A fumigatus*. Cases 8, 10, and 11 all had mycelium on microscopy of sputum. Case 8 grew *D hawaiiensis* from six sputum samples. This fungus is closely related to and cross reacts

with *Helminthosporium*. Case 10 grew *C lunata* from five sputa and the resected specimen. Case 11 grew both *D hawaiiensis* and *C lunata* from several specimens. Precipitins to aspergilli were negative in all three cases but positive to both *D hawaiiensis* and *C lunata* in case 11. Suitable extracts of these fungi were not available at the time of diagnosis of cases 8 and 10. These latter three cases are discussed in the accompanying paper.¹²

The radiological characteristics of this series of patients did not vary significantly from previously reported series,^{8 13 14} but perhaps varied quantitatively. Five had lobar collapse at one time or another and one had lobar consolidation. Three had classical branching bronchoceles in the upper lobes and two in the right lower lobe. Fleeting opacities were seen at some time in only six of these patients and on some occasions occurred after the diagnosis had been made. Bronchial wall thickening and bronchiectasis were present on the plain films of several patients. Six patients had bronchograms but only two exhibited classical central bronchiectasis. One other with a bronchocele showed no filling of the segmental bronchus to that area. In the other, contrast outlined the head of the mucus plug in the proximal portion of the segmental bronchus.

Discussion

Hinson *et al*⁶ stated that Renon in 1879 first associated *Aspergillus sp* with asthma. Asthma is the first criterion for a diagnosis of allergic bronchopulmonary aspergillosis in all reported series. However some important series do include occasional cases who did not have clinical asthma.^{5 8 10} It is difficult to determine the exact number but a thorough search of the literature indicates that approximately 10 patients with allergic bronchopulmonary aspergillosis without asthma have previously been reported.

In 42 patients in whom a diagnosis of allergic bronchopulmonary fungal disease was made there were 11 who conformed to the accepted criteria for

Table 1 Pulmonary function tests before and after bronchodilator inhalation

Case	Vital capacity			FEV ₁		
	Before	After	Predicted	Before	After	Predicted
1	3.16	Not done	3.61	1.82	Not done	2.58
2	2.77	2.58	2.49	1.88	1.60	1.94
3	1.79	1.79	2.30	1.37	1.40	2.00
4	2.87	Not done	2.70	1.81	Not done	2.15
5	4.87	4.98	5.12	3.40	3.61	4.24
6	3.29	Not done	4.40	2.63	Not done	3.39
7	2.65	2.77	4.50	1.55	1.68	3.29
8	3.10	3.00	3.20	2.70	2.65	2.70
9	1.70	2.12	2.25	0.98	1.32	1.85
10	3.68	3.78	3.36	2.34	2.75	2.80
11	6.20	6.30	5.6	4.32	4.56	4.4

Table 2. Clinical summary

Case	History of allergy	Blood eosinophilia	Sputum eosinophilia	Prick tests			Total IgE	Microscopy of sputum	Culture	Comments	
				*C	F	T					
1	Allergic rhinitis	2178	Yes	0	3 mm	8 mm	Pos	Not done	Septate hyphae	<i>A fumig</i> × 1	1978. collapse RUL. Plug removed at bronchoscopy
2	No	1500	60%	2 mm	5 mm	7 mm	Pos	210	Neg	<i>A fumig</i> × 2	1974 RUL, RML collapse. 1975 bronchocele. Recurrent opacities
3	No	712	Not done	2 mm	3 mm	6 mm	Pos	1750	Septate hyphae	<i>A fumi</i> and <i>terreus</i> × 4	Multiple opacities. Bronchiectasis. Recurrent opacities since
4	Hayfever	1886	15%	0	5 mm	2 mm	Pos	Not done	Septate hyphae	<i>A fumig</i> × 7 after resection	Pre 1961 Recurrent opacities. 1961 collapse LUL and lobectomy. Subsequent LLL collapse × 2
5	Hayfever and recurrent infections childhood	2860	Eosinoph predominant	3 mm	8 mm	8 mm	Pos	3800	Neg	<i>A fumig</i> × 4	1961 collapse lingula. 1962 bronchiectasis. 1966 LLL collapse. 1967 developed asthma
6	Hayfever	1782	Abundant eosinoph	0	5 mm	0	Neg	2500	Not done	Not done	R axillary pneumonia. Brown plugs in sputum. Cleared on steroids
7	No	1500	Negative but Curshman spirals	0	5 mm	3 mm	Pos	740	Branching septate hyphae in plugs 1971	No growth	1962 lobectomy for collapse LUL. 1971 segmental collapse. 1975 developed asthma. Fleeting opacities since
8	Hayfever	4568	Yes	0	3 mm	0	Neg	650	Septate hyphae	<i>D haw</i> × 6	Bilateral bronchoceles. Cleared on steroids
9	No	2057	No	0	6 mm	9 mm	Pos	4000	Septate hyphae	<i>A fumig</i> × 1	Recurrent opacities. 1972 bronchocele. 1977 collapse LLL. Cleared on steroids
10	Bronchitis	1080	70%	0	3 mm	0	Neg	Not done	Septate hyphae	<i>C lunata</i> × 5	1972 pulmonary opacity. Bronchocele. Bronchogram segmental obstruction. Segmental resection. 1974 developed asthma
11	No	1007	Abundant eosinoph	0	3 mm	3 mm	Neg <i>A fumig</i> Pos <i>C lun</i> Pos <i>D haw</i>	4800	Septate hyphae	<i>C lun</i> × 4 <i>D haw</i> × 6	1977 haemoptysis and consol lingula. 1977 bronchogram pos on review. 1979 bronchocele LLL. Cleared on steroids

*C=control; F=*A fumigatus*; T=*A terreus*; †Normal = <210

diagnosis except for the absence of clinical asthma. Their ages ranged from 15–65 years. This suggests that in 26% of patients with this syndrome the diagnosis will be missed if clinical asthma is considered essential for diagnosis.

Three patients developed asthma years after diagnosis—case 5 10 years; case 7 four years, and case 10 two years after. Steroids used for the treatment of the syndrome may have masked the development of asthma in cases 1, 3, 4, and 8 but case 2 has only had occasional brief courses of steroids when opacities have appeared on chest radiographs, and has not developed asthma in the four years since diagnosis. Case 11 was first seen four years ago with haemoptysis and lingular consolidation. He was undiagnosed, untreated, and non-asthmatic even on laboratory testing. He is now on steroids. Case 6 has been lost to follow-up. Case 9 was a heavy smoker with a history of occasional episodes of bronchitis. She was not considered to have asthma by her general practitioner or a physician she had attended for some years. Pulmonary function tests were performed after recurrent opacities on serial chest radiographs suggested the diagnosis of allergic bronchopulmonary fungal disease. These tests showed reversible obstruction diagnostic of asthma (table 1). Case 10 was considered to have recurrent bronchitis after measles pneumonia at the age of 12 years and was treated with antibiotics. On admission to this hospital at 32 years of age she had no clinical evidence of asthma but she did have wheezes localised to the right chest and her FEV₁ improved by 17% after bronchodilator, which is suggestive but not diagnostic of asthma. A bronchogram showed obstruction to the superior segment of the right lower lobe. Two years after surgery she developed clinical asthma.

Difficulty in recognising the nature of the disease process in the absence of asthma did occur in some patients. Cases 4 and 7 had an upper lobectomy and case 10 a segmental resection before diagnosis. A fourth patient (case 1) had collapse of the right upper lobe with a presumptive diagnosis of carcinoma; a preoperative bronchoscopy revealed an obstructing mucous plug. Case 3, a boy of 15 years, had previously been considered to have cystic fibrosis, although sweat electrolyte concentrations were not elevated. Despite a positive bronchogram four years ago, case 11 remained undiagnosed and untreated because of the absence of asthma even on laboratory testing.

Three patients had fungi other than *Aspergillus* as a cause of their pulmonary disease, case 8 *Drech-slera hawaiiensis*, case 10 *Curvularia lunata*, and case 11 both of these fungi. In view of these three cases in which fungi other than *Aspergillus* have caused

this syndrome and a previous report¹⁵ of two similar patients of bronchopulmonary *Helminthosporium* and the possible incrimination of *Candida* by Pepys,¹⁶ we suggest that the more usual term, allergic bronchopulmonary aspergillosis be widened to allergic bronchopulmonary fungal disease. In cases of mucoid impaction with negative tests to *Aspergillus* or cryptogenic pulmonary eosinophilia a wider range of fungal allergens should be used for skin and precipitin testing.

Addendum

Since this paper was accepted for publication, a single case of allergic bronchopulmonary fungal disease with asthma caused by *Stemphylium lanuginosum* has been reported from South Africa.¹⁷

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References

- 1 Slavin RG, Stanczyk DJ, Lonigro AJ, Broun GO. Allergic bronchopulmonary aspergillosis—a North American rarity. Clinical and immunologic characteristics. *Am J Med* 1969; **47**:306–13.
- 2 Editorial. Diagnosing allergic bronchopulmonary aspergillosis. *Br Med J* 1977; **2**:1439–40.
- 3 Hoehne J, Reed C, Dickie H. Allergic bronchopulmonary aspergillosis is not rare. *J Lab Clin Med* 1971; **78**:1007–8.
- 4 Khan ZU, Sandhu RS, Randhawa HS, Menon MPS, Dusa JIS. Allergic bronchopulmonary aspergillosis: a study of 46 cases with special reference to laboratory aspects. *Scand J Respir Dis* 1976; **57**:73–87.
- 5 Rosenberg M, Patterson R, Mintzer R, Cooper BJ, Roberts M, Harris KE. Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. *Ann Intern Med* 1977; **86**:405–14.
- 6 Hinson KFW, Moon AJ, Plummer NS. Bronchopulmonary aspergillosis: a review and a report of eight new cases. *Thorax* 1952; **7**:317–33.
- 7 Henderson AH. Allergic aspergillosis: review of 32 cases. *Thorax* 1968; **23**:501–12.
- 8 McCarthy DS, Simon G, Hargreave FE. The radiological appearances in allergic bronchopulmonary aspergillosis. *Clin Radiol* 1970; **21**:366–75.
- 9 Malo JL, Hawkins R, Pepys J. Studies in chronic allergic bronchopulmonary aspergillosis. 1. Clinical and physiological findings. *Thorax* 1977; **32**:254–61.
- 10 Elder JL, Smyth JT. Allergic bronchopulmonary aspergillosis. *Med J Aust* 1967; **1**:231–2.
- 11 Longbottom JL, Pepys J. Pulmonary aspergillosis: diagnostic and immunological significance of antigens of c-substances in *Aspergillus fumigatus*. *J Path Bact* 1964; **88**:141–51.
- 12 McAleer R, Kroenert DB, Elder JL, Froudust JH. Allergic bronchopulmonary disease caused by

- Curvalaria lunata* and *Drechslera hawaiiensis*. *Thorax*. 1981; **36**:338-44.
- 13 Malo JL, Pepys J, Simon G. Studies in chronic allergic bronchopulmonary aspergillosis. 2. Radiological findings. *Thorax* 1977; **32**:262-8.
- 14 Mintzer RA, Rogers LF, Kruglik GD, Rosenberg M, Neiman HL, Patterson R. The spectrum of radiologic findings in allergic bronchopulmonary aspergillosis. *Radiology* 1978; **127**:301-7.
- 15 Dolan CT, Weed LA, Dines DE. Bronchopulmonary helminthosporiosis. *Am J Clin Path* 1970; **53**:235-42.
- 16 Pepys J. Hypersensitivity disease of the lungs due to fungi and organic dusts. *Monogr Allergy* 1969; **4**:63-8.
- 17 Benatar SR, Allan B, Hewitson RP, Dou PA. Allergic bronchopulmonary stemphyliosis. *Thorax* 1980; **35**:515-8.