Critical Reviews in Microbiology

http://informahealthcare.com/mcb
ISSN: 1040-841X (print), 1549-7828 (electronic)

Crit Rev Microbiol, Early Online: 1–19
 DOI: 10.3109/1040841X.2012.754401

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REVIEW ARTICLE

Allergic bronchopulmonary mycosis due to fungi other than *Aspergillus*: a global overview

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Abstract

Allergic bronchopulmonary mycosis (ABPM) is a hypersensitivity-mediated disease of worldwide distribution. We reviewed 143 reported global cases of ABPM due to fungi other than aspergilli. The commonest etiologic agent was *Candida albicans*, reported in 60% of the cases, followed by *Bipolaris* species (13%), *Schizophyllum commune* (11%), *Curvularia* species (8%), *Pseudallescheria boydii* species complex (3%) and rarely, *Alternaria alternata*, *Fusarium vasinfectum*, *Penicillium* species, *Cladosporium cladosporioides*, *Stemphylium languinosum*, *Rhizopus oryzae*, *C. glabrata*, *Saccharomyces cerevisiae* and *Trichosporon beigelii*. India accounted for about 47% of the globally reported cases of ABPM, attributed predominantly to *C. albicans*, followed by Japan (16%) where *S. commune* predominates, and the remaining one-third from the USA, Australia and Europe. Notably, bronchial asthma was present in only 32% of ABPM cases whereas its association with development of allergic bronchopulmonary aspergillosis (ABPA) is known to be much more frequent. The cases reviewed herein revealed a median IgE value threefold higher than that of ABPA, suggesting that the etiologic agents of ABPM incite a stronger immunological response than that by aspergilli in ABPA. ABPM is currently underdiagnosed, warranting comprehensive basic and clinical studies in order to elucidate its epidemiology and to devise a more effective therapy.

Keywords

Allergic bronchopulmonary mycosis, *Candida albicans*, India, moulds, yeasts

History

Received 5 October 2012
Revised 21 November 2012
Accepted 27 November 2012
Published online 5 February 2013

Introduction

Allergic bronchopulmonary mycosis (ABPM) is a hypersensitivity-mediated disease of the lower airways caused by environmental fungi, the most common being *Aspergillus fumigatus*. The other etiologic agents include *Candida albicans*, *Schizophyllum commune*, species of *Alternaria*, *Bipolaris*, *Cladosporium*, *Curvularia*, *Fusarium*, *Penicillium*, *Pseudallescheria*, *Rhizopus*, *Saccharomyces*, *Stemphylium* and *Trichosporon*. The disease was first recognized by Hinson et al. (1952) in the UK who described it in asthmatics with recurrent pulmonary infiltrates, peripheral blood eosinophilia and sputum culture positive for *A. fumigatus*. While allergic bronchopulmonary aspergillosis (ABPA) has been extensively studied worldwide, there is paucity of information on ABPM due to other fungi. This review aims to provide an update on the work done globally on ABPM, excluding ABPA. As stated above, numerous fungi have been implicated in the etiology of ABPM. Our literature search done through PubMed covered the period up to July 2012; the search words used were allergic, bronchopulmonary, mycosis, mycoses, candidiasis, helminthosporiosis, curvulariosis, penicilliosis, mucormycosis, *Schizophyllum*, *Bipolaris*, *Alternaria*, *Curvularia*, *Cladosporium*, *Stemphylium* and *Penicillium* etc. Additionally, the references not listed in PubMed but cited in published articles were included. Altogether 159 cases of ABPM were compiled. Of these, 143 cases published in English have been analyzed in detail.

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Historical

Historically, the association of molds with allergic respiratory disorders spans over three centuries. The first case linking molds to an exacerbation of asthma appeared in 1698; the patient had experienced an ''asthmatic attack'' when he came into contact with fermenting wine (Floyer, 1698). Further observations supporting the allergenic role of molds and their association with asthma accumulated over the nineteenth and twentieth centuries. A definitive evidence of fungi causing asthma was first brought out in 1924 by Cadham (Cadham, 1924) who showed that *Puccinia graminis*, a plant pathogenic fungus, incited asthma. Later in the same decade, *Alternaria* (Hopkins et al., 1930), *Aspergillus* (Bernton, 1930) and *Trichophyton* (Ramirez, 1930) were incriminated in the causation of asthma. The triad of asthma, pulmonary infiltrates and eosinophilia was linked to *Aspergillus* species

and the term allergic bronchopulmonary aspergillosis was coined in 1952 by Hinson, Moon and Plummer from the UK (Hinson et al., 1952). The pioneering work on ABPA done in the UK led to the recognition of this disease as an important mycosis with a worldwide distribution. Subsequently, in the 1970s series of well-documented ABPA cases, some of whom had been masquerading as pulmonary tuberculosis not responding to anti-tubercular therapy were reported from the V. P. Chest Institute, Delhi, India (Khan et al., 1976; Khan & Sandhu, 1978; Pamra et al., 1972; Radha & Viswanathan, 1978; Sandhu et al., 1972; Sandhu et al., 1978; Sandhu et al., 1979; Subramanian & Viswanathan, 1972). For further information pertaining to ABPA, reference may be made to several reviews (Agarwal, 2009; Agarwal et al., 2009b; Agarwal et al., 2012; Burnie, 1995; Hogan & Denning, 2011; Knutsen & Slavin, 2011; Mahdavinia & Grammer, 2012; Patterson & Strek, 2010; Shah, 2008; Tillie-Leblond & Tonnel, 2005). The role of molds other than *Aspergillus*, and of yeasts, as etiologic agents of ABPM came to light much later as described below.

Diagnostic criteria

ABPM is a complex disease that is diagnosed by a combination of clinical, mycoserologic and radiological features. The most commonly accepted criteria are those proposed by Rosenberg et al. (1977) and Patterson et al. (1986) as listed in Table 1. Subsequently, the minimal essential diagnostic criteria were proposed (Greenberger, 2002; Schwartz & Greenberger, 1991; Stevens et al., 2003). This simplified version excluded eosinophilia and demonstration of precipitating antibodies as diagnostic criteria. The exclusion of precipitating antibodies was done on the ground that they are prone to be false negative in patients receiving corticosteroid therapy or during remission of the disease. However, controversy regarding the essential diagnostic criteria continues due to lack of their specificity. For example, although asthma is an important diagnostic criterion, many cases of ABPM (Chowdhary et al., 2012; Gendry et al., 2006; Glancy et al., 1981; Halloran, 1983; Hamilton et al., 2006; Hendrick et al., 1982; Ishiguro et al., 2007; Ishiguro et al., 2011; Itou et al., 2001; Kamei et al., 1994; Lake et al., 1991; McAleer et al., 1981; Mroueh & Spock, 1992; Muscat et al., 1988; Ogawa et al., 2004; Ogawa et al., 2012; Patterson et al., 1982b; Sahn & Lakshminarayan, 1973; Tajima et al., 2000; Tomita et al., 1996; Travis et al., 1991) as well as ABPA (Agarwal et al., 2009a; Amin & Mahmood, 2008; Berkin et al., 1982; Bondue et al., 2005; Glancy et al., 1981; Gupta et al., 2012; Hinson et al., 1952; Hoshino et al., 1999; Koh et al., 2007; Shah et al., 2004; Yoshida et al., 1992) have been diagnosed in non-asthmatics. Likewise, false positive and negative results for serum precipitins are not uncommon in ABPM cases (Chowdhary et al., 2012; Darke et al., 1976; Longbottom & Pepys, 1964; Vlahakis & Aksamit, 2001; Zacharisen & Fink, 2005). The presence of serum precipitins against an antigen should be taken as indicative of a previous exposure to it and not necessarily a sign of active disease (Darke et al., 1976).

Table 1. Diagnostic criteria for allergic bronchopulmonary mycosis (Patterson et al., 1986; Rosenberg et al., 1977).

Major criteria	
Clinical	Asthma
Serological	*In vivo*
	Type I hypersensitivity reaction
	In vitro
	Total IgE (>1000 ng/ml)
	Serum fungus-specific IgE/IgG
	Serum precipitins
Radiological	Fleeting pulmonary opacities
	Central bronchiectasis
Hematological	Eosinophilia
Minor criteria	
Clinical	Expectoration of mucus plugs
Serological	Delayed/type III (Arthus) reaction
Mycological	Culture of fungus

The country-wise distribution and the fungi implicated in a total of 159 cases of ABPM are shown in Table 2 and depicted in Figures 1 and 2. It is noteworthy that only 16 of 143 ABPM cases (11%) analyzed and summarized in Tables 3–5 fulfilled the Rosenberg–Patterson criteria. The data pertaining to individual diagnostic parameters were as follows: total IgE reported in 81.1% (116/143) cases, increase in eosinophil count in 47% (67/143), culture of fungus in 46.8% (67/143), type I skin test in 38.5% (55/143), precipitins in 30% (43/143) and fungus-specific IgE/IgG antibodies in 27% (39/143). Asthma which figured prominently in the discussion was present in only 32% of the cases (Table 6). Actually, a majority of the published cases lacked data on all the diagnostic parameters. Consequently, their diagnosis as ABPM would be better regarded as probable and not unequivocally proven. Table 6 provides a synopsis of clinical and laboratory diagnostic profiles of 143 reported ABPM cases. The highest positivity of 94.5% (52/55 cases) was found for type I skin hypersensitivity to the etiologic fungus, followed by eosinophilia in 92.5% (62/67 cases), precipitating antibody in 90.7% (39/43), fungal isolation in 89.6% (60/67), increased serum total IgE in 86.2% (100/116), pulmonary infiltrates in 66.2% (43/65) and central bronchiectasis in 32.3% (21/65).

Clinical features

The majority of ABPM patients reviewed were middle-aged with a mean of 42 years, and there was no gender predilection (Table 6). This is in consonance with the observations on ABPA by Agarwal (2009). The symptomatology of the cases reported was similar to that of poorly controlled asthma, that is the predominant complaints were cough, dyspnea and expectoration of mucus plugs (Tables 3–5). Generally other non-specific symptoms such as fever, malaise, chest pain and hemoptysis may be present (Agarwal, 2009; Tillie-Leblond & Tonnel, 2005). Often a detailed history reveals past episodes of these symptoms in association with radiologic but not bacteriologic evidence of pneumonia. Also, careful examination of past serial radiographs of the patients may reveal the presence of fleeting pulmonary opacities, which should alert the clinician about the presence of ABPM. As discussed above, up to 70% of ABPM cases occur without asthma. Therefore, patients in whom no tangible cause for their radiologic abnormalities is

Table 2. Geographical distribution of 159 globally reported cases of allergic bronchopulmonary mycosis due to various fungi.

Fungus	Country	No. of cases	References
C. albicans ($n=94$)	India	72	Mehta, 1981; Mehta & Sandhu, 1980; Sandhu et al., 1979
	Japan	7	Inoue et al., 1992; Iwahashi et al., 1993; Miyagawa et al., 1992; Matsumoto et al., 2000; Takabatake et al., 1997; Tajima et al., 2000; Yuasa, 1997
	Ireland	5	Donnelly et al., 1991
	France	3	Gendry et al., 2006; Voisin et al., 1976; Lahoute et al., 1983
	The USA	3	Akiyama et al., 1984; Lee et al., 1987; Patterson et al., 1982b*
	Belgium	1	Pinson & van der Straeten, 1991
	Spain	1	de Olano et al., 2009
	Poland	1	Krakowka et al., 1971
	The UK	1	Muscat et al., 1988†
Bipolaris spp. ($n=20$)	Australia	10	Glancy et al., 1981‡; Lake et al., 1991; Matthiesson, 1981; McAleer et al., 1981‡
	The USA	8	Adam et al., 1986; Dolan et al., 1970; Dyer et al., 2008; Halloran, 1983; Hamilton et al., 2006; Hendrick et al., 1982; Saenz et al., 2000
	France	1	Lahoute et al., 1983
	India	1	Chowdhary et al., 2011
S. commune ($n=17$)	Japan	16	Amemiya et al., 2009; Amitani et al., 1996; Ikushima, 1997; Ishiguro et al., 2007; Ishiguro et al., 2011; Itou et al., 2001; Kamei et al., 1994; Kamei et al., 1999; Kawano et al., 2003; Masunaga et al., 2010; Ogawa et al., 2012; Tomita et al., 1996; Yamashina, 1997; Yamasaki et al., 2002
	India	1	Chowdhary et al., 2013
Curvularia spp. ($n=6$)	Australia	1	Lake et al., 1991; McAleer et al., 1981
	The USA	4	Halwig et al., 1985; Mroueh & Spock, 1992; Travis et al., 1991
	France	1	Lahoute et al., 1983
P. boydii species complex ($n=5$)	The USA	2	Miller et al., 1993
	France	2	Cimon et al., 2000
	Australia	1	Lake et al., 1990
Penicillium spp. ($n=3$)	The USA	2	Sahn & Lakshminarayan, 1973; Akarian et al., 2012
	France	1	Lahoute et al., 1983
A. alternata ($n=2$)	India	1	Chowdhary et al., 2012
	The UK	1	Singh & Denning, 2012
F. vasinfectum ($n=2$)	The USA	2	Backman et al., 1995; Saini et al., 1998
Cladosporium spp. ($n=2$)	Spain	1	Moreno-Ancillo et al., 1996
	Japan	1	Fujimoto et al., 1994¶
Stemphylium spp. ($n=2$)	South Africa	1	Benatar et al., 1980
	France	1	Lahoute et al., 1983
Mucor-like fungus($n=1$)	Japan	1	Kino et al., 1983
Rhizopus sp. ($n=1$)	France	1	Lirsac et al., 1986
Trichosporon sp. ($n=1$)	The USA	1	Gondor et al., 1998
S. cerevisiae ($n=1$)	Japan	1	Ogawa et al., 2004
Paecilomyces sp. ($n=1$)	Russia	1	Akhunova, 1991
Geotrichum sp. ($n=1$)	France	1	Lahoute et al., 1983

*Includes a single case of *C. glabrata.*
†Includes ABPM due to *Rhizopus* sp. and *C. albicans* as etiologic agents but counted under *C. albicans* only.
‡Include seven cases of ABPM with dual etiology *Bipolaris* spp. and *Curvularia* spp. but not counted under *Curvularia* spp.
¶Both *Cladosporium* spp. and *Penicillium* spp. were etiologic agents but counted under *Cladosporium* spp. only.

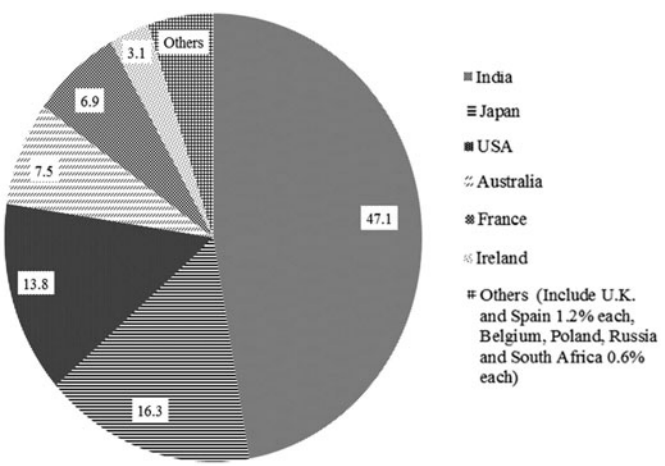

Figure 1. Geographic distribution (%) of 159 reported cases of allergic bronchopulmonary mycosis.

apparent should be investigated for ABPM. Additionally, considering that ABPM is associated with atopy, the patients may have allergic manifestations elsewhere in the body such as rhinosinusitis, conjunctivitis, atopic dermatitis and food allergies. In the ABPM cases reviewed (Table 6), 41% had other allergic manifestations, such as allergic rhinosinusitis, atopic dermatitis and urticaria. General physical examination is often unremarkable but digital clubbing can occur rarely. Likewise, examination of the chest is unrewarding except during periods of acute exacerbations or in patients with fibrosis when coarse crackles may be heard (Tillie-Leblond & Tonnel, 2005). Occasionally, endobronchial impaction of mucus in the airways may give rise to atelectasis (Dolan et al., 1970; Kamei et al., 1994; Tomita et al., 1996). Since physical diagnostic examination is often unrewarding, the diagnosis of ABPM depends on laboratory investigations.

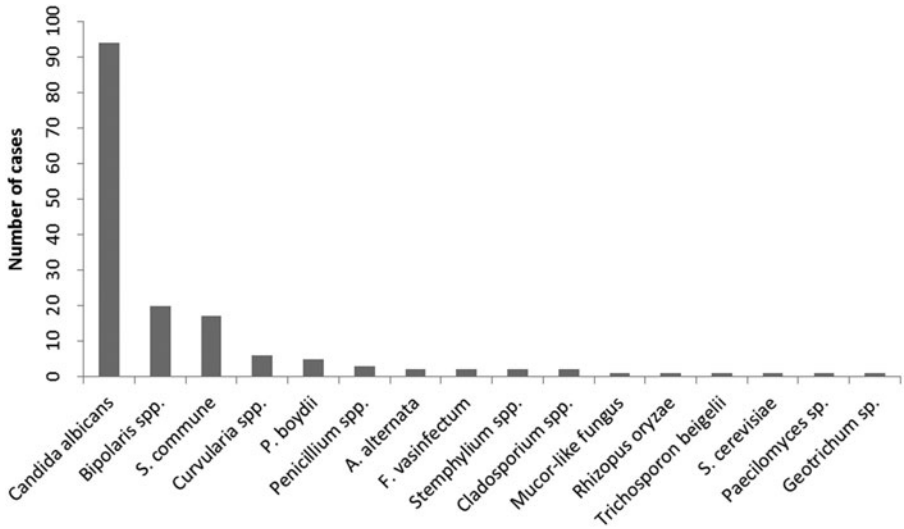

Figure 2. Prevalence of fungi other than *Aspergillus* species reported as etiologic agents of allergic bronchopulmonary mycosis ($n = 159$).

Laboratory diagnostic features

A summary of the various clinical and laboratory diagnostic features of ABPM cases reviewed are presented in Tables 3–6 and briefly discussed below.

Skin tests: Type I cutaneous hypersensitivity to antigens of the etiologic fungus is an essential diagnostic feature of ABPM. The test was found positive in 52 (94.5%) of 55 cases in which it was done (Table 6). By employing skin tests, the humoral immune response is assessed in two sequential phases, namely the immediate/early/type I cutaneous hypersensitivity response and the delayed/late/type III cutaneous hypersensitivity response mediated through IgE and IgG antibodies, respectively (Janeway et al., 2001; Platts-Mills, 2001). The skin test is best performed with commercially available, standardized fungal antigens to avoid false negative reactions. However, not all of the antigens are commercially available. Most consensus guidelines place a skin prick test (SPT) superior to an intradermal test because of the former's high sensitivity, specificity, concerns with time, patient comfort and safety (Bousquet et al., 2012; Cox et al., 2008). The accuracy of SPTs for positive results is reported in the range of 50–60%. The variable results are attributed to quality of the reagent such as its potency and to interpretation of the test. The negative predictive value has an accuracy of 95% (Knutsen et al., 2012). The SPT is usually performed on the volar aspect of the forearm, with the antigens being placed 3 cm from each other (5 cm in the case of the intradermal test). The concentration of the antigen used in a prick test is 1:10 or 1:20 w/v while in case of the intradermal test it is significantly lower, 1:500 w/v. The reaction to the antigen is assessed 15–20 min later by the presence of a wheal. A test is read as positive if the mean of two perpendicular diameters exceeds 3 cm (Gaur et al., 2009). A positive skin test should be followed up to six hours. A reaction that develops soon after performing the test and subsides within 1–2 hours is termed as the type I reaction, mediated by IgE antibodies whereas a reaction that develops after six hours and persists for 24–48 hours is the immune-complex mediated type III reaction.

Specific fungal IgE and IgG antibodies: Demonstration of IgE and/or IgG antibodies specific for fungi is an important requirement for the diagnosis of ABPM (Chowdhary et al., 2012; Patterson et al., 1986; Rosenberg et al., 1977). The most common *in vitro* tests for detection of allergen-specific IgE are the radioallergosorbent test (RAST) and enzyme-linked immunosorbent assay (ELISA). The radioactive counts and optical density values directly correlate with allergen-specific IgE in the sera of patients. However, RAST and ELISA can be adapted to obtain quantitative and semiquantitative immunoglobulin estimation. Activities of allergens and their specificity can also be compared by competitive inhibition. Fifty percent inhibition in binding of the patient's IgE to the reference allergen is taken as a measure of the potency of the test allergen (Dhyani et al., 2006). Standardized antigen kits for ELISA are available commercially though not for all fungi incriminated in ABPM. SPTs are reportedly more sensitive but less specific than serum IgE tests in diagnosing allergic sensitization in allergic subjects (Bousquet et al., 2007). Although the criteria proposed by Rosenberg et al. (1977) require positivity of specific IgE, the same may also be found in a case of simple mold-sensitization and thus it does not pinpoint the diagnosis of ABPM. However, the elevation of specific IgE to a level twice as much as that in pooled sera of patients with fungal sensitization can be indicative of ABPM (Wang et al., 1978).

Serum precipitins: The most commonly employed method for the demonstration of precipitins in serum is a solid-phase immunodiffusion method (Ouchterlony, 1958). The antigens employed in this method are often crude extracts which can be prepared in the laboratory (Khan et al., 2000). Also, serum precipitins can be present in other respiratory diseases (Darke et al., 1976; Longbottom & Pepys, 1964; Vlahakis & Aksamit, 2001) or could be masked by concomitant corticosteroid intake (Chowdhary et al., 2012; Zacharisen & Fink, 2005).

Serum total IgE: Measurement of the serum levels of IgE is one of the essential criteria for diagnosing ABPM. An IgE level of >200 IU/ml measured by ELISA defines atopy. The IgE value of >1000 ng/ml (equivalent to 417 IU/ml) is considered significant to diagnose ABPM in relation to *Aspergillus* species (Greenberger, 2002), but such cutoffs are not universally accepted. Some researchers have used values

DOI: 10.3109/1040841X.2012.754401

Table 3. Clinical and laboratory diagnostic profiles of 89 globally reported cases of allergic bronchopulmonary mycosis due to yeasts.

Fungus	Country (no. of cases)	Sex/Age (years)	Past history	Culture (source)	Eosinophilia*	Total serum IgE*	Specific IgE antibodies	Precipitins against the etiologic fungus	Skin test, type I	Radiology	Therapy and outcome	Ref
C. albicans ($n = 86$)	India (59)	NI	Pulmonary infiltrates	+(Sputum)	+	NI	NI	+	+	Pulmonary infiltrates	NI	Sandhu et al., 1979; Mehta, 1981
	India (13)	M/11, F/2	History of pulmonary tuberculosis in 8 subjects	+ (Sputum)	+	NI	NI	+	+	Pulmonary infiltrates	NI	Mehta & Sandhu, 1980; Mehta, 1981
	Japan (6)	M/77	Asthma with persistent pneumonia	+ (Sputum)	NI	NI	+	+	+	Pulmonary infiltrates	Inhalation of AmB; resolution	Inoue et al., 1992
		F/49	Asthma	NI	+	+	+	NI	NI	Inhomogeneous shadows	Steroids and inhaled AmB; relapse managed by inhaled steroids	Iwahashi et al., 1993
		F/66	Asthma, fleeting radiographic shadows	+ (Sputum)	+	+	+	+	NI	Fleeting infiltrates	NI	Miyagawa et al., 1992
		M/84	Asthma, radiographic changes	NI	+	+	+	NI	NI	CB, ground-glass opacities, dense patches	Steroids and FLU	Takabatake et al., 1997
		M/61	Steroid-dependent asthma, brownish mucous plugs, Churg–Strauss syndrome	+ (Sputum)	+	1400 IU/ml	+	NI	+	Central bronchiectasis	Steroids, inhaled AMB for a year; patient died of respiratory failure on 203rd hospital day	Matsumoto et al., 2000
		M/61	Acute cough, no asthma, hepatomegaly, ascites, gastritis with ulceration	− (Sputum)	+	6700 IU/ml	+	NI	+	Right pleural effusion and emphysema without atelectasis, fleeting pulmonary infiltrates	Steroids total IgE level and eosinophil count declined and hepatomegaly resolved	Tajima et al., 2000
	Ireland (3)	F/29	Asthma	+ (Sputum)	+	125 IU/ml	+	NI	−	Nil	NI	Donnelly et al., 1991
		F/74	Asthma	+ (Sputum)	+	1200 IU/ml	+	NI	−	Fibrosis	NI	Donnelly et al., 1991
		F/47	Asthma	+ (Sputum)	+	450 IU/ml	+	NI	+	Nil	NI	Donnelly et al., 1991
	The USA (2)	F/54	Asthma	+ (Sputum)	NI	5120 ng/ml	+	+	+	Fleeting pulmonary infiltrates	Steroids	Akiyama et al., 1984
		F/16		+ (BAL)	−	5745 ng/ml	+	+	+	Atelectasis	Steroids	Lee et. al., 1987

(continued)

Table 3. Continued

Fungus	Country (no. of cases)	Sex/Age (years)	Past history	Culture (source)	Eosinophilia*	Total serum IgE*	Specific IgE antibodies	Precipitins against the etiologic fungus	Skin test, type I	Radiology	Therapy and outcome	Ref
	France (1)	M/58	Asthmatic, wheezing, chest pain COPD, productive cough, inhaling marijuana, oral candidiasis	+ (BAL)	+	4343 IU/ml	+	−	+	Bronchiectasis, bronchial wall thickening, distal MI, segmental atelectasis	FLU and steroids	Gendry et al., 2006
	Belgium (1)	M/42	Recurrent hemoptysis, dyspnea, wheezing	+ (Sputum, BAL)	+	146 IU/ml	−	+	+	Fleeting pulmonary infiltrates, central bronchiectasis	NI	Pinson et al., 1991
	Spain (1)	M/59	Dyspnea, wheezing, steroid-dependent asthma	+ (Induced sputum)	+	531 IU/ml	+	+	+	Infiltrates, peripheral bronchiectasis	Steroids for 3 months, omalizumab	de Olano et al., 2009
C. glabrata ($n=1$)	The USA (1)	F/66	Cough, fever, no asthma	+ (Sputum)	−	7000 ng/ml	+ (IgG)	−	NI	Infiltrates	Steroids	Patterson et al., 1982
S. cerevisiae ($n=1$)	Japan (1)	F/25	Non-atopic, cough, fever, pulmonary infiltrates	+ (Sputum)	−	230 IU/ml	NI	+	+	Consolidation	Inhaled steroids	Ogawa et al., 2004
T. beigelii ($n=1$)	The USA (1)	M/11	Cystic fibrosis; cough, wheezing	+ (BAL)	+	4888 IU/ml	+	+	NI	NI	AMB, steroids, remission	Gondor et al., 1998

NI, no information; ''+'' positive; ''−'' negative; BAL, bronchoalveolar lavage; CB, central bronchiectasis; COPD, chronic obstructive pulmonary disease; MI, mucoid impaction; AMB, amphotericin B; FLU, fluconazole.

Only the cases published in English and those with an abstract in English are included. The data were compiled, using PubMed as the search portal with combinations of words such as allergic, bronchopulmonary, mycosis, mycoses, candidiasis etc. Additionally, those references that were cited in published articles were included.

*Normal eosinophil count <500 cells/μl; normal value of total serum IgE <200 IU/ml.

Table 4. Clinical and laboratory diagnostic profiles of 39 globally reported cases of allergic bronchopulmonary mycosis due to molds.

Fungus	Country (no. of cases)	Sex/age (years)	Past history	Culture (clinical specimen)	Eosinophilia*	Total serum IgE*	Specific IgE antibodies	Precipitins	Skin test, type I	Radiology	Therapy and outcome	Ref
ASCOMYCOTA (29)												
Bipolaris spp. ($n=12$)	The USA (8)	M/41	Asthmatic, necrotizing pneumonia, black sputum plugs	*B. hawaiiensis* (sputum plugs, bronchial washings, endobronchial biopsies)	+	4307 KU/L	NI	NI	NI	Cavitary consolidation	Steroids, ITC, Improved	Saenz et al., 2000
		M/40	Asthma with rhinitis, chronic back pain	*B. australiensis* (transbronchial brushings/biopsies and BAL)	+	118 IU/ml	NI	+	+	Lung mass	Steroids, improved	Dyer et al., 2008
		M/48	Chronic cough and hemoptysis; no asthma	*B. spicifera* (bronchial washings)	+	406 ng/ml	NI	NI	+	Lobar collapse/mass, due to MI, CB, mediastinal LAP	Steroids, nebulized albuterol, remissions achieved	Hamilton et al., 2006
		M/30	No asthma, family history of asthma, short-pneumonitis like illness with sputum plugs	*Bipolaris* sp. (sputum)	+	90 µg/ml	NI	NI	+	Fleeting shadows, CB	Steroids, exacerbations on follow-up	Hendrick et al., 1982
		M/21	Marine, exertional dyspnea, cough um, no asthma, pulmonary HP suggestive of ABPM	*Bipolaris* sp. (sputum)	+	NI	NI	NI	NI	Multiple rounded infiltrates	Steroids, remission	Halloran et al., 1983
		M/40	Asthma, wheezing, productive cough, hemoptysis; recurrent infections; HP suggestive of ABPM	*Bipolaris* sp. (surgical specimen)	NI	NI	NI	NI	NI	Lung mass, nodules	Lung resection	Dolan et al., 1970
		M/23	Asthmatic, indeterminate lesion in right upper lobe; HP suggestive of ABPM	*Bipolaris* sp. (surgical specimens)	NI	NI	NI	NI	NI	Indeterminate lesion-right lung apex	Lung resection	Dolan et al., 1970
		M/58	Chronic cough, wheezing and sputum plugs	*Bipolaris* sp. (bronchial secretions)	+	87 IU/ml	NI	NI	NI	Finger-in-glove shadows	Steroids, improved	Adam et al., 1986
	Australia (3)	F/36	Allergic rhinitis, no asthma	*B. hawaiiensis* (sputum)	+	650 IU/ml	NI	NI	+	MI	Steroids, improved	McAleer et al., 1981; Glancy et al., 1981‡
		M/29	Asthma	*Bipolaris* sp. (mucus plugs)	+	NI	NI	NI	NI	MI	Not given	Matthiesson, 1981
		F/33	No asthma	–	+	1440 IU/ml	NI	+	NI	Infiltrates, CB	Steroids, no follow-up	Lake et al., 1991
	India (1)	F/6	Chronic cough and wheeze	*B. hawaiiensis* (BAL, sputum)	+	1051.3 IU /ml	NI	+	+	Collapse-consolidation, air-fluid levels in CB, localized mosaic-perfusion	Oral ITC, for 12 weeks, iv AMB, for 1 month, repeated suctioning and local instillation of VRC by	Chowdhary et al., 2011

(continued)

Table 4. Continued

Fungus	Country (no. of cases)	Sex/age (years)	Past history	Culture (clinical specimen)	Eosinophilia*	Total serum IgE*	Specific IgE antibodies	Precipitins	Skin test, type I	Radiology	Therapy and outcome	Ref
											bronchoscopy followed by oral steroids	
P. boydii species complex ($n=3$)	France (2)	M/20	Cystic fibrosis; bronchoconstriction, infiltrates	*P. boydii* (sputum)	+	1400 IU/ml	NI	+	NI	Infiltrates	Steroids, ITC, remissions,	Cimon et al., 2000
		M/18	Cystic fibrosis; bronchoconstriction, infiltrates	*P. boydii* (sputum)	+	80 IU/L	NI	+	NI	Bilateral interstitial infiltrates	Steroids, ITC, remissions, subsequent exacerbation	Cimon et al., 2000
	The USA (1)	F/48	Childhood asthma	*P. boydii* (sputum)	+	2602 ng/ml	−	+	NI	Infiltrates	Chest physiotherapy. Spontaneous remission	Miller et al., 1993
C. lunata ($n=3$)												
	The USA (2)	M/36	Asthma, atopic dermatitis, spontaneous pneumothoraxes	*C. lunata* (bronchial washings, sputum)	+	2565 IU/ml	+	+	+	Recurrent infiltrates, bronchiectasis, MI	Steroids, good response	Halwig et al., 1985
		F/48	Ex-smoker, Allergic fungal sinusitis, cerebrosinusoidal mycosis HP showed impaction with allergic mucin	*C. lunata* (frontal sinus aspirate, lung specimen)	+	794 IU/ml	NI	NI	NI	Pulmonary nodule	Surgical debridement, AMB, TERB,† KTC†	Travis et al., 1991
	Australia (1)	F/33	History of measles pneumonia, recurrent bronchitis HP showed necrotizing and obliterative bronchiolitis and granulomata	*C. lunata* (sputum and sputum plugs)	+	NI	NI	NI	NI	Pseudohilar shadows	Segmental resection; exacerbation treated by Sodium cromoglycate and salbutamol	McAleer et al., 1981
Curvularia senegalensis ($n=2$)	The USA (2)	M/16	Asthma, nasal congestion. HP revealed bronchocentric granulomatosis	*C. senegalensis* (sinus material)	−	785 IU/ml	NI	NI	+	Infiltrates	Surgical debridement	Travis et al., 1991
		F/10	Allergic rhinitis treated with ITC; sudden cough and wheeze since 4 months	*C. senegalensis* (sputum plugs, bronchial aspirate)	+	800 IU/ml	NI	+	+	RUL collapse	Steroids, remissions for five years	Mroueh & Spock, 1992
A. alternata ($n=2$)	India (1)	F/36	Urticaria, no asthma; HP consistent with ABPM	A. *alternata* (sputum, BAL)	+	4007 IU/ml	+	+	+	Consolidation	Steroids, ITC, surgical resection	Chowdhary et al., 2012
	The UK (1)	M/21	Asthma, rhinitis, hay fever, eczema	−	+	3800 IU/ml	+	NI	+	Consolidation	Steroids, ITC, remissions	Singh & Denning, 2012
F. vasinfectum ($n=2$)	The USA (2)	M/46	Allergic rhinitis with polyposis, asthma	NI	+	2614 ng/ml	+	+	+	Infiltrates, CB	Steroids, remissions	Backman et al., 1995
		M/12	Eczema, recurrent pneumonias	NI	+	2252 ng/ml	+	+	+	Fleeting shadows, atelectasis	Steroids, inhaled cromolyn, albuterol, steroids; clinical improvement	Saini et al., 1998
Penicillium spp. ($n=2$)	The USA (2)	M/73	Nasal polyposis, no asthma		+	NI	+ (IgG)	+	+	Fleeting shadows, CB		Sahn et al., 1973

				P. rubrum (sputum)							Bronchial hygiene, clearance of sputum	
		M/53	Ex-smoker, asthma, mucus plugs	NI	+	623 IU/ml	+	NI	+ (*P. notatum*)	Bronchiectasis	Steroids and ITC	Zakarian et al., 2012
C. cladosporioides (*n* = 1)	Spain (1)	M/6	Asthma, sputum plugs	−	+	1771 ng/ml	+	+	+	CB	Steroids; remissions	Moreno-Ancillo et al., 1996
S. languinosum (*n* = 1)	South Africa (1)	M/35	Asthma, persistent shadows on X- rays	*S. languinosum* (bronchial aspirate)	+	NI	NI	+	+	Gloved-fingers	Steroids; remissions	Benatar et al., 1980
BASIDIOMYCOTA (*n* = 10)												
S. commune (*n* = 10)	Japan (9)	F / 57	Allergic rhinosinusitis, no asthma	*S. commune* (bronchial aspirate)	+	4286 IU/ml	+	NI	NI	Fleeting shadows; CB	No relief with ITC, spontaneous remission	Kamei et al., 1994
		F/72	Recurrent atelectasis	*S. commune* (bronchial aspirate)	+	NI	+	NI	NI	Fleeting shadows, atelectasis	Relief with 5FC, & nebulized AMB; exacerbation later	Tomita et al., 1996†
		F/27, F/33	Bronchial asthma	*S. commune*	+	+	+	NI	NI	Fleeting shadows	Steroids; relief	Yamashina , 1997†
		M/55	Asthma	*S. commune* (mucus plug)	+	+	+	NI	NI	Fleeting shadows, consolidation, MI	Steroids and ITC; improvement	Amemiya et al., 2009†
		F/58	Productive cough; no asthma	*S. commune* (sputum, bronchial aspirates)	+	805 IU/L	+	−	+	MI, consolidation, fleeting shadows, PB and CB	Bronchoscopic removal of sputum plugs, Environmental modification; remission	Ogawa et al., 2012
		F/67	Asthma,	*S. commune* (mucus plugs, sputum, bronchial aspirates)	+	NI	−	−	−	Y densities, left pseudohilar consolidation	Repeated bronchoscopies, inhaled procaterol; recurrence treated by	Amitani et al., 1996
		F/51	Productive cough	*S. commune* (mucus plugs)	+	NI	NI	NI	NI	LUL atelectasis	ITC 200 mg OD	Itou et al., 2001§
		F/54	Productive cough; no asthma	*S. commune* (sputum, mucus plugs, bronchial washings)	+	−	NI	NI	NI	Band shadows, atelectasis	Bronchoscopic removal, ITC; remissions till 3 yrs	Ishiguro et al., 2007§
	India (1)	F/ 35	Asthma	*S. commune* (sputum)	+	2248 IU/L	+	+	+	Gloved fingers, CB, HAM	Steroids, remissions	Chowdhary et al., 2013
MUCORMYCOTINA (*n* = 1)												
R. oryzae (*n* = 1)	France (1)	M/44	Late-onset asthma, sinusitis	*R. oryzae* (sputum plug)	+	380 IU/ml	+	+	NI	Infiltrates	Steroids, inhaled β agonists	Lirsac et al., 1986

Abbreviations used: HP, histopathology; ''−'' negative; ''+'' positive; BAL, bronchoalveolar lavage; NI, no information; CB, central bronchiectasis; MI, mucoid impaction; LAP, Lympadenopathy; R/LUL, right/left upper lobe; PB, peripheral bronchiectasis; HAM, high attenuating mucous; ITC, itraconazole; 5FC, flucytosine; AMB, amphotericin B; VRC, voriconazole; TERB, terbinafine; KTC, ketoconazole

Only the cases published in English and those with an abstract in English are included. The data were compiled, using PubMed as the search portal with combinations of words such as allergic, bronchopulmonary, mycosis, mycoses, curvulariosis, helminthosporiosis, penicilliosis etc. Additionally, those references that were cited in published articles were included.

*Normal eosinophil count <500 cells/μl; normal value of total serum IgE <200 IU/ml.

†Articles published in Japanese; details taken from the English abstracts available on PubMed.

‡Includes two mutually inclusive publications on ABPM due to *Bipolaris* spp.

§Published as cases of bronchial mucoid impaction but meet the criteria for ABPM due to the presence of allergic mucin.

Table 5. Clinical and laboratory diagnostic profiles of 15 allergic bronchopulmonary mycosis cases with more than one etiologic agent.

Fungi	Country (no. of cases)	Sex/Age (years)	Past history	Culture (source)	Eosinophilia*	Total serum IgE*	Specific IgE antibodies	Precipitins against the etiologic fungi	Skin test, type I	Radiology	Therapy and outcome	Ref
S. commune and *A. fumigatus*	Japan (1)	M/53	Asthma	*S. commune*, *A. fumigatus* (sputum, bronchial washings, mucus plugs)	NI	NI	+ *A. fumigatus* NI on *S. commune*	+ *A. fumigatus* + *S. commune*	NI	Infiltrates	Inhaled steroids + β agonists, ITC; clinical and radiologic resolution	Ishiguro et al., 2011
S. commune and *C. albicans*	Japan (1)	F/70	Productive cough, fever; no asthma	*S. commune*, *C. albicans* (bronchial aspirates) sputum,	+	797 IU/L	+ *S. commune,* NI on *C. albicans*	+ for *C. albicans* NI against *S. commune*	+ for *S. commune* and *C. albicans*	Pulmonary infiltrates, HAM	ITC; exacerbation treated with bronchoscopic flushing	Ogawa et al., 2012
B. hawaiiensis and *C. lunata*	Australia (7)	M/35	Sudden hemoptysis, shoulder pain	*B. hawaiiensis* and/or *C. lunata* (sputum)	+	8400 IU/ml	NI	+ *B. hawaiiensis* + *C. lunata*	+ *B. hawaiiensis* - *C. lunata*	Lingular consolidation, CB	-Steroids and potassium iodide, responded well	McAleer et al., 1981; Glancy et al., 1981
		F/52	Asthma	*B. hawaiiensis* and/or *C. lunata* (sputum)	+	3800 IU/ml	NI	+	+	Infiltrates	Steroids; no follow-up	Lake et al., 1991
		M/30	Asthma	*B. hawaiiensis* and/or *C. lunata* (sputum)	+	3200 IU/ml	NI	+	NI	Infiltrates, CB	-do-	Lake et al., 1991
		F/17	Asthma	*B. hawaiiensis* and/or *C. lunata* (sputum)	+	3800 IU/ml	NI	+	+	Infiltrates, CB	-do-	Lake et al., 1991
		M/17	Asthma	*B. hawaiiensis* and/or *C. lunata* (sputum)	+	7500 IU/ml	NI	+	+	Infiltrates	-do-	Lake et al., 1991
		F/43	Asthma	–	+	2500 IU/ml	NI	+	+	Infiltrates, CB	-do-	Lake et al., 1991
		M/27	Asthma	(sputum)	+	560 IU/ml	NI	+	NI	Infiltrates	-do-	Lake et al., 1991
C. albicans and *A. fumigatus*	Ireland (2)	F/65	Asthma	*C. albicans* (sputum)	+	1240 IU/ml	+ *C. albicans* + *A. fumigatus*	NI	+ *A. fumigatus*	Fibrosis	NI	Donnelly et al., 1991
		F/49	Asthma	*C. albicans* (sputum)	+	1500 IU/ml	+ *C. albicans* + *A. fumigatus*	NI	+ *A. fumigatus*	Fibrosis	NI	Donnelly et al., 1991
Penicillium, Cladosporium spp. and *A. fumigatus*	Japan (1)	M/36	Asthma, abnormal radiographic shadows	*A. fumigatus*, *Penicillium* spp., *Cladosporium* spp. (sputum)	+	7800 IU/ml	+ *A. fumigatus* + *P. luteum* + *C. cladosporioides*	*A. fumigatus* + *P. luteum* + *C. cladosporioides*	*A. fumigatus* + *P. luteum* + *C. cladosporioides*	Patchy shadows, consolidation	NI	Moreno-Ancillo et al., 1996
P. boydii species complex and *Aspergillus* spp.	Australia (1)	F/24	Asthma	*P. boydii* species complex, *A. terreus* (bronchoscopy specimen, sputum)	+	>4000 IU/ml	NI	+ *P. boydii* species complex + *A. fumigatus, A. terreus, A. flavus*	+ *P. boydii* species complex + *A. terreus, A. fumigatus, A. niger, A. nidulans*	Fleeting infiltrates, hilar shadows	Systemic steroids; remission	Lake et al., 1990
	The USA (1)	F/33	Asthma	*A. fumigatus*, *P. boydii* species complex (sputum plug)	+	23 092 ng/ml	–	+	NI	Infiltrates	Steroids, recurrent exacerbations	Miller et al., 1993
Rhizopus spp. and *C. albicans*	The UK (1)	M/62	Farmer; no asthma	*C. albicans* only (sputum)	–	NI	NI	+ *Candida* + *Rhizopus*	NI	Infiltrates	Steroids, AMB; clinical improvement	Muscat et al., 1988

breviations used: ''–'' negative; ''+'' positive; NI, no information; HAM, high attenuating mucus; CB, central bronchiectasis; ITC, itraconazole; AMB, amphotericin B.
ormal eosinophil count <500 cells/μl; normal value of total serum IgE <200 IU/ml.

Table 6. Synopsis of clinical and laboratory diagnostic profiles of allergic bronchopulmonary mycosis cases reported in English ($n = 143$).

Characteristics investigated	Results
Mean age ± SD (years; range)	41.70 ± 18.97 (6–84, $n = 71$)
Sex distribution (male:female)	1.33:1
History of asthma	46/143* (32.1%)
History of allergic disorders	51/143 (35.6%)
Raised total IgE	100/116 (86.2%)
Median total IgE (IU/ml; range)	1400 (80–37, 530, $n = 63$)
Eosinophilia	62/67 (92.5%)
Precipitins	39/43 (90.6%)
Specific (IgE/IgG) antibodies	35/39 (89.7%)
Type I skin test	52/55 (94.5%)
Pulmonary infiltrates	43/65 (66.1%)
Central bronchiectasis	21/65 (32.3%)
Isolation of fungus	60/67 (89.5%)

*Numerator denotes the number positive and denominator the number reported.

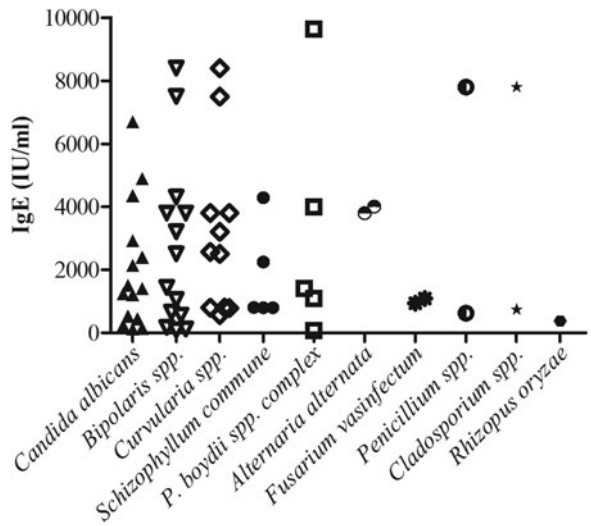

Figure 3. Distribution of total IgE levels in 57 reported cases of allergic bronchopulmonary mycosis (an outlier with value of >30 000 IU/ml of total IgE value in *Bipolaris* sp. is not shown).

ranging from 400 to 1000 IU/ml for diagnosis of ABPA (Eaton et al., 2000; Kumar & Gaur, 2000; Patterson et al., 1982a; Patterson et al., 1986). However, it may be pointed out that using the cutoff of 1000 ng/ml for IgE estimation may result in overdiagnosis of ABPM as this level may also be found in the cases of fungal sensitization without ABPM (Agarwal, 2009). In the cases of ABPM reviewed here, we found an average total IgE almost three times higher than that recommended for ABPA. The median value of total IgE derived from 63 published cases of ABPM is 1400 IU/ml (Table 6, Figure 3). In the discussion below on the pathogen factors, it is pointed out that some fungi causing ABPM, especially *Alternaria* and *Cladosporium*, are associated with a severe form of asthma (Bush & Prochnau, 2004; Pulimood et al., 2007). Thus, it is likely that these fungi elicit a stronger immunological response than *Aspergillus*. Apart from the role in diagnosis, serum total IgE is important as a marker of disease activity/response to treatment. A decline or increase in baseline values is taken as a marker of remission or exacerbation of the disease (Fink, 2000). Elevation of IgE may precede clinical or radiological worsening during exacerbation, and isolated increase in severity of bronchoconstriction does not amount to exacerbation. Although the majority of excerbations are accompanied by increased symptoms, the absence of the latter does not preclude an exacerbation. About one-third of the patients with radiographic infiltrates may be asymptomatic and thus progressive lung damage may remain unrecognized. Total serum IgE levels should be monitored every four to eight weeks for at least a year following diagnosis (Chupp & Rochester, 2008).

Blood eosinophilia: The presence of >1000 eosinophils/mm^3 in blood is taken as another qualifying criterion for the diagnosis of ABPM. However, it is not specific for ABPM as eosinophilia may also occur in other conditions such as Churg–Strauss syndrome, tropical pulmonary eosinophilia, worm infestations and corticosteroid intake (Schulman & Sporn, 2008).

Radiology: Radiological investigations often provide the first clue to the diagnosis of ABPM. As stated by Hinson et al. (1952) in their first case report on ABPA, a single X-ray examination is inadequate in the diagnosis. Instead serial radiographs are needed to show the progressive changes of lobar or segmental collapse and consolidation in different parts of the lung. Imaging techniques discussed below have an important role in diagnosing and assessing the prognosis of the disease.

Chest X-ray: Pulmonary infiltrates have been reported in a majority (66%) of the ABPM cases reviewed herein (Table 6). Classically described in ABPA as ''fleeting'', these non-specific opacities are highly suggestive of the underlying disorder and represent an inflammatory infiltrate in the lung (Shah, 2008; Thompson et al., 1995). The changes seen can be classified as ''transient'' or ''permanent'' and represent an affliction of the parenchyma, airways and pleura at different stages in the disease process (Shah, 2005). The transient pulmonary infiltrates, an important marker of the disease activity, may be observed on and off. Subsequently, these may recur at the same site, developing as ''recurrent fixed shadows'' (Shah, 2008). With the passage of time as inflammation gives way to scarring, these changes become ''fixed'' and tend to persist for life. Additionally, a patient with ABPM may demonstrate a spectrum of non-specific opacities on the X-ray (Table 7) because of which the disease may be misdiagnosed as tuberculosis, especially in countries with high endemicity (Chowdhary et al., 2012).

Computed tomography (CT): The high resolution CT scan is the investigation of choice for demonstration of central bronchiectasis with peripherally tapering bronchi, which is a hallmark of ABPM (Angus et al., 1994; Greenberger & Patterson, 1987; Panchal et al., 1994). However, one needs to guard against the possibility of overdiagnosing ABPM based exclusively on this finding which may also occur in asthmatics without ABPM (Angus et al., 1994; Neeld et al., 1990; Paganin et al., 1992). In addition, cases of ABPM can have peripheral bronchiectasis (Agarwal et al., 2006; Scadding, 1967) and the presence of impacted high-attenuating mucus (HAM) in the airways that is more radiodense than the paraspinal muscles. The presence of HAM correlates with a poorly controlled course of ABPA and has been reported in 21–28% of ABPA cases (Agarwal et al., 2007; Agarwal et al.,

Table 7. Synopsis of radiologic manifestations in reported cases of allergic bronchopulmonary mycosis.

	Transient	Permanent
Parenchymal	Consolidation	Fibrosis with or without cavitation
	Pseudohilar opacities	Local emphysema
	Miliary shadows	Fungal ball
	Pulmonary masses	
Airways	Infiltrates: toothpaste, finger-in-glove and wine-glass shadows	Central bronchiectasis
	''Tramline'' shadows	Ring shadows or parallel-line shadows
	Lobar/segmental collapse	
	Air-fluid levels	
Pleura	Pleural effusions	Pleural thickening
	Pneumothorax	

2010; Logan & Muller, 1996). This pathognomonic finding has also been reported recently in two cases of ABPM due to *S. commune* (Chowdhary et al., 2013; Ogawa et al., 2012).

Fungal culture: Isolation of the etiologic fungus from bronchial secretions/sputum aids in the diagnosis of ABPM but it is not diagnostic by itself. Also, repeatedly negative cultures need to be interpreted cautiously.

Spectrum of etiologic fungi: There is a wide spectrum of molds and yeasts incriminated in the etiology of ABPM (Tables 2–5, Figure 2). *Candida albicans*, a major etiological agent, was responsible for 60% of ABPM cases, followed by *Bipolaris* species in 13% (20/159), *S. commune* in 11% (17/159), *Curvularia* species in 8% (7/159) and *Pseudallescheria boydii* species complex in 3% (5/159). Other less reported fungi include *A. alternata*, *Fusarium vasinfectum*, *Penicillium* species, *Cladosporium cladosporioides* and *Stemphylium languinosum*, *Rhizopus oryzae*, *C. glabrata*, *Saccharomyces cerevisiae* and *Trichosporon beigelii*. India accounted for nearly half (47%) of the globally reported cases of ABPM, attributed predominantly to *C. albicans*, followed by Japan (16%) where *S. commune* was the most commonly reported agent. The remaining one-third of the reported cases was from the USA, Australia and Europe. Additionally, 9% of the ABPM cases reviewed had more than two fungi as possible etiologic agents (Table 5). Of these, 47% were due to *Bipolaris hawaiiensis* and *Curvularia lunata*.

Histopathology: ABPM is a disease with diverse histological manifestations which differ not only from individual to individual but also in different parts of the lung in the same individual (Chan-Yeung et al., 1971; Slavin et al., 1988). The large airways are frequently dilated, filled with mucus plugs, consisting of macrophages, eosinophils and Charcot-Leyden crystals and occasionally, hyphal fragments (Dolan et al., 1970; Jelihovsky, 1983; Travis et al., 1991). The walls of the bronchi exhibit an inflammatory infiltrate, comprising of eosinophils associated with thickening of the basement membrane (Chan-Yeung et al., 1971; Dolan et al., 1970). It is not uncommon to find granuloma formation in the bronchial walls (bronchocentric granulomatosis) or exudative bronchiolitis, obliterative bronchiolitis or granulomatous bronchiolitis in the peribronchial tissue and pulmonary parenchyma (Chowdhary et al., 2012; Travis et al., 1991). Also, microabscesses with fungal hyphae have been observed in the parenchyma, which may be indicative of a progression to an invasive disease as a complication of ABPM (Ganassini & Cazzadori, 1995; Tillie-Leblond & Tonnel, 2005). It is noteworthy that some histological features of ABPM overlap those seen in other pulmonary disorders or with invasive mycoses. Eosinophilic infiltration, for example, is common in ABPM (Hamilton et al., 2006) but also seen in eosinophilic pneumonia (Halloran, 1983; Chamilos & Kontoyiannis, 2008). Similarly, bronchocentric granulomatosis, that is airway-centered non-necrotizing, eosinophilic granulomas with multinucleate giant cells, though seen in ABPM, are non-specific for the same as they may also occur in association with tuberculosis and autoimmune diseases afflicting the lung (Berendsen et al., 1985; Katzenstein et al., 1975; Koss et al., 1981). Since the diagnosis of ABPM relies on clinical, radiological and mycoserological parameters, a histological examination is often unnecessary.

Pathogenesis

The pathological processes underlying ABPM are essentially the same as those of ABPA. As mentioned earlier, ABPM develops in only a minority of the asthmatics who are constitutionally ''predisposed'' to it. Genetic studies have shown that asthmatics with alterations in the cystic fibrosis trans-membrane conductance regulator (CFTR) gene (Marchand et al., 2001) and collagen region of the surfactant protein A2 (Saxena et al., 2003) are predisposed to develop ABPA. In patients who already have defective mucociliary clearance as that seen in cystic fibrosis, fungal spores multiply, resulting in colonization of the airways. Since germinating molds possess protease antigens, they penetrate through the mucociliary barrier and epithelial membrane of the lung and activate the epithelial cells through cell-surface receptors to initiate an immune response through the release of cytokines (Agarwal, 2009; Denning et al., 2006; Tillie-Leblond & Tonnel, 2005). The inflammatory cascade engages both the humoral and cell-mediated immune pathways. Once captured, an antigen is processed and presented by the antigen presenting cells to the T lymphocytes of which the Th2 response predominates over the Th1 response (Knutsen et al., 2002; Schuyler, 1998). This activation of T-cells and the subsequent release of interleukins lead to mast cell proliferation and eosinophilic inflammation. The same is also responsible for the production of IgE, IgA and IgG antibodies, thereby indicating the activation of B-cells (Schuyler, 1998). Mold-specific IgE and IgA antibodies have been shown to be present in a higher concentration in broncho-alveolar fluid than in blood, whereas IgG concentrations in both fluids are equal. Therefore, it is likely that the production of mold-specific IgE and IgA antibodies is a local phenomenon (Greenberger et al., 1988; Tillie-Leblond & Tonnel, 2005). Upon contact with fungal antigens, mast cells bound to IgE antibodies degranulate, releasing histamine and producing vascular leakage in the pulmonary bed, thus facilitating influx of IgG antibodies from the blood which in turn form antigen–antibody complexes with these antigens and activate the complement pathways culminating in tissue damage (Chamilos & Kontoyiannis, 2008). The resulting constant

inflammation results in the destruction of the bronchial wall, producing the bronchiectasis characteristic of ABPM. With the onset of bronchiectasis, a vicious cycle of infection and inflammation ensues which leads to progressive lung damage.

The predisposing factors in ABPM remain unclear. The host immune responses and direct fungal injury lead to airway damage and fibrosis. The manifestations of fungal allergy in an individual depend on the characteristics of the host more than that of the fungus per se. The prevalence of ABPM due to various fungi is currently unknown whereas it has been estimated that 1–2% asthmatics and 1–15% patients with cystic fibrosis have ABPA (Geller et al., 1999; Greenberger, 2003; Moss, 2002; Stevens et al., 2003). The multiple factors impacting the prevalence are as follows:

Host factors: Asthma and cystic fibrosis remain the two most important underlying conditions that are associated with ABPM. As evident from Table 7, asthma and other allergic disorders were present in 35.6% of ABPM cases. It is noteworthy that among all the cases of ABPM reviewed asthma was lacking in 70% of cases (Chowdhary et al., 2012; Gendry et al., 2006; Glancy et al., 1981; Halloran, 1983; Hamilton et al., 2006; Hendrick et al., 1982; Ishiguro et al., 2007; Ishiguro et al., 2011; Itou et al., 2001; Kamei et al., 1994; Lake et al., 1991; McAleer et al., 1981; Mroueh & Spock, 1992; Muscat et al., 1988; Ogawa et al., 2004; Ogawa et al., 2012; Patterson et al., 1982b; Sahn & Lakshminarayan, 1973; Tajima et al., 2000; Tomita et al., 1996; Travis et al., 1991) which is in stark contrast to ABPA in which the majority of cases, with the exception of 37 cases, reported so far had an asthmatic background (Agarwal et al., 2009a; Amin & Mahmood, 2008; Berkin et al., 1982; Bondue et al., 2005; Glancy et al., 1981; Gupta et al., 2012; Hinson et al., 1952; Hoshino et al., 1999; Koh et al., 2007; Shah et al., 2004; Yoshida et al., 1992;). Thus ABPM due to non-*Aspergillus* fungi afflicts a greater number of patients without asthma than does ABPA. It is well known that atopy is a heritable trait and thus ABPM is likely to be the consequence of genetic interplay. It has been reported that certain genotypes of the HLA molecules such as HLA-DR2 and HLA-DR5 occur with a higher frequency in ABPA (Chauhan et al., 1997) whereas HLA-DQ2 is associated with resistance to ABPA (Tillie-Leblond & Tonnel, 2005). Rarely, sporadic reports of the familial occurrence of ABPA are found in the literature (Shah et al., 2008). However, the association of HLA genotypes and familial occurrence of ABPM cases due to non-*Aspergillus* species has not been reported to date.

Pathogen factors: Although fungi are ubiquitous and respiratory exposure to airborne spores of molds is common, it is not known why certain fungal allergens produce more severe airway disease than other common aero-allergens. However, fungi differ from other allergens in that their spores can germinate and propagate, thereby bathing the respiratory tract with allergens which in turn stimulate the host to mount an inflammatory response (Denning et al., 2006). The causative role of yeasts such as *C. albicans* in severe asthma may also be due to long-term colonization of airways, sinuses, skin and nails in atopic individuals. Thus exposure to these fungi may provide a chronic source of allergen exposure. As indicated by the literature review, *C. albicans*, a major etiological agent of ABPM, was responsible for 60% of the reviewed ABPM cases. It has been reported that up to 10% patients with mild stable asthma and 33% with severe asthma show sensitization to *Candida* (O'Driscoll et al., 2005). Similarly, the dermatophyte *Trichophyton* that causes skin infections has been reported in association with asthma (Agarwal, 2009; O'Driscoll et al., 2009). However, improvement of such patients with antifungal treatment (Chishimba et al., 2012; Denning et al., 2009; Pasqualotto et al., 2009; Vicencio et al., 2010) suggests a possible link between chronic infection and asthma.

Table 8. Fungal allergens implicated in the etiology of allergic bronchopulmonary mycosis, their molecular size and biological activity.

Fungal species	Allergen* (molecular size kDa)	Biological activity
A. alternata	Alt a (16.4/15.3)	
	Alt a 3 (−)	Heat Shock Protein 70
	Alt a 4 (57)	Disulfide isomerase
	Alt a 5(11)	Ribosomal protein P2
	Alt a 6 (45)	Enolase
	Alt a 7 (22)	YCP4 protein
	Alt a 8 (29)	Mannitol dehydrogenase
	Alt a 10 (53)	Aldehyde dehydrogenase
	Alt a 12 (11)	Acid ribosomal protein P1
	Alt a 13 (26)	Glutathione-S-transferase
C. albicans	Cand a 1 (40)	Alcohol dehydrogenase
	Cand a 3 (20)	Peroxysomal protein
C. cladosporioides	Cla c 9 (36)	Vacuolar serine protease
	Cla c14 (36.5)	Transaldolase
C. lunata	Cur l 1 (31)	Serine protease
	Cur l 2 (48)	Enolase
	Cur l 3 (12)	Cytochrome c
	Cur l 4 (54)	Vacuolar serine protease
P. chrysogenum	Pen ch 13 (34)	Alkaline serine protease
	Pen ch 18 (32)	Vacuolar serine protease
	Pen ch 20 (68)	*N*-acetyl-glucosaminidase
	Pen ch 31	Calreticulin
	Pen ch 33 (16)	
	Pen ch 35 (36.5)	Transaldolase
S. commune	Sch c1 (61)	Glucoamylase

*Available on www.allergen.org

Fungal allergens: Fungal allergens are a diverse group of molecules, ranging from secreted products of metabolism to constitutive components of the cell (Knutsen et al., 2012). They can be grouped into five principal categories, namely, proteases, glycosidases, components of protein production, oxidative stress response proteins and enzymes involved in gluconeogenesis or the pentose phosphate shunt (Denning et al., 2006). The Allergen Nomenclature Sub-committee of the International Union of Immunological Societies (IUIS) has recognized fungal allergens including isoallergens and variants belonging to 25 species of the phyla Ascomycota and Basidiomycota. A catalog of fungal allergens of non-*Aspergillus* and yeast species is accessible on www.allergen.-org, and those implicated in ABPM cases reviewed in this report are listed in Table 8. It is important that intergenus and interspecies allergenic cross-reactivity be differentiated from individual sensitization to multiple fungi.

It is believed that protease antigens probably play the role of initiators in the inflammatory cascade. Though this mechanism is not clear, it is likely that proteases of fungal origin either injure the epithelium through protease-activated cell receptors or by degrading the epithelial membrane,

thereby facilitating antigen access to the subepithelium (Denning et al., 2006). It has been further reported that proteases are vital in producing eosinophilic airway inflammation (Kheradmand et al., 2002). Through the mechanisms postulated above, it seems probable that proteases modify other allergens in such a way that they become more potent antigens. Apart from proteases, the fungi possess glycosidases and stress–response molecules. Although the role of the former is not known for sure, it is postulated that they act on the cell wall and bring about innate immune responses whereas in the case of the latter, one may assume that the role they play is to protect the germinating spores from the immune attack mounted by the host. Considering the observation that stress–response molecules of fungi bear homology to their human counterparts, it is likely that when the host mounts an immune attack on germinating spores, damage is suffered by the host as well (Denning et al., 2006).

Environmental factors: It has been reported that asthmatics sensitive to *Alternaria* or *Cladosporium* species tend to suffer from a more severe form of the disease when these fungi sporulate during the late summer and early autumn (Bush & Prochnau, 2004; Pulimood et al., 2007). Exposure to fungi can occur in both the indoor and the outdoor environment. The molds, *Alternaria*, *Penicillium*, *Cladosporium* and *Fusarium*, implicated in ABPM are known to be prevalent in the indoor environment (Richardson et al., 2005; Sharma et al., 2012; Singh & Deval, 2005). The worsening of asthma symptoms concurrent with thunderstorms has also been reported. That is attributed to climatic influences such as high winds and increased humidity which favor sporulation and dissemination of fungi such as *Didymella exitialis*, *Sporobolomyces* (Packe & Ayres, 1985) and *A. alternata* (Dales et al., 2003; Durham, 1938; O'Hollaren et al., 1991). It is noteworthy that although all the asthmatics are exposed to the molds, not all of them culminate into ABPM. Thus, it may be inferred that environmental factors do not play a central role in the pathogenesis of ABPM (Agarwal, 2009).

Treatment

Being primarily a hypersensitivity disease resulting from exposure of the respiratory tract to the offending fungus, treatment of ABPM has the following objectives: (a) suppression of the immune response and prevention/eradication of fungal colonization in the airways, (b) control of eosinophilic bronchitis caused by fungal exposure, (c) removal of any bronchial mucus plugs and (d) identification and elimination or management of the etiologic fungus from the patient's environment (Ogawa et al., 2012; Tillie-Leblond & Tonnell, 2005). Systemic steroids are the mainstay of treatment of ABPM but that may not entirely prevent exacerbations or a decline in lung functions as seen in ABPA (Wark et al., 2004). No specific guidelines exist on the dosing schedule of oral steroids; variable doses and dosing regimens have been described (Agarwal et al., 2006; Patterson et al., 1986; Vlahakis & Aksamit, 2001). The goal of systemic steroid therapy is to achieve a reduction in total IgE concentration by 35–50% over a period of 6–8 months (Chupp & Rochester, 2008; Rosenberg et al., 1978). In general, prednisolone (or other steroids) is given in daily doses of 0.5 mg/kg for the first two weeks, tapered for the next three months, followed by gradual withdrawal if the subsequent three months are unremarkable (Agarwal, 2009; Greenberger & Patterson, 1986; Safirstein et al., 1973; Shah, 2008). Should the patient show resolution of pulmonary infiltrates and decline in IgE by the desired factor for six months, it may be inferred that remission has been achieved (Tillie-Leblond & Tonnel, 2005). Further management then depends on serial radiographs and serum IgE level measurements in follow-up. The later stages of ABPM often require prolonged steroid administration though long-term treatment with steroids is controversial (Sethi & Singhal, 2008) and generally not recommended due to the systemic adverse effects (Tillie-Leblond & Tonnel, 2005).

Administration of appropriate antifungal therapy may be required for prevention/eradication of fungal colonization of the airways of ABPM patients and to guard against the risk of dissemination or recurrence of the disease (Clark et al., 1996; Denning et al., 2009; Ogawa et al., 2004; Ogawa et al., 2009; Shaw et al., 2000; Sigler et al., 1997; Roh et al., 2005). Currently, experience with antifungal therapy in ABPM is limited and no definite guidelines exist regarding choice of drug, dosage and duration of treatment. However, the etiologic agents of ABPM are susceptible *in vitro* to a number of antifungal drugs, such as amphotericin B, itraconazole, voriconazole, fluconazole, posaconazole, micafungin, caspofungin and anidulafungin, and therefore anyone of these may be used depending upon their availability and efficacy against a particular etiologic agent (Chowdhary et al., 2011; Chowdhary et al., 2012; Chowdhary et al., 2013; Gonzalez et al., 2001). Also, usage of antifungals in ABPM cases has been reported (Amemiya et al., 2009; Chowdhary et al., 2011; Chowdhary et al., 2012; Cimon et al., 2000; Ishiguro et al., 2007; Itou et al., 2001; Saenz et al., 2000; Singh & Denning, 2012; Travis et al., 1991; Tomita et al., 1996). It is pertinent to mention here that low dose itraconazole therapy prevented relapse of the disease upon environmental re-exposure of the patient in one of the ABPM cases investigated by Ogawa et al. (2012). Attention may also be called here to studies done on ABPA using itraconazole, which brought about significant reduction in the total IgE (Denning et al., 1991; Germaud, 1995; Pasqualotto et al., 2009; Santos et al., 2009; Stevens et al., 2000b) and eosinophil counts of the patients (Germaud, 1995; Pasqualotto et al., 2009). These studies have also shown azoles to have a steroid-sparing effect (Stevens et al., 2000a; Stevens et al., 2000b). A Cochrane review on the efficacy of itraconazole in ABPA concluded that itraconazole had the potential to modify the inflammatory process underlying ABPA and thus is a promising alternative to steroids (Wark et al., 2004). Likewise, a randomized trial of efficacy of itraconazole and other antifungals vis-à-vis corticosteroids in patients with ABPM is warranted for a more efficacious therapy. For patients with bronchial mucoid impaction, bronchoscopic suctioning (Chowdhary et al., 2011) and flushing as a mechanical treatment has been utilized beneficially. Considering that oral drugs are seemingly more difficult to deliver to the fungus in mucus plugs, favorable

results have been reported in ABPA patients with inhalation of antifungal drugs (Henderson & Pearson, 1968; Sandhu et al., 1972; Slavin et al., 1969; Stark, 1967). Similarly, cases of ABPM where inhalational antifungal therapy has been instituted are known (Inoue et al., 1992; Iwahashi et al., 1993; Matsumoto et al., 2000; Tomita et al., 1996). It would be therefore desirable to evaluate the use of nebulized antifungal therapy in a larger group of ABPM patients.

Epilogue

ABPM has emerged as an important respiratory mycosis in atopic individuals. The etiologic agents include a heterogeneous group of molds and yeasts, predominantly belonging to the Ascomycota or Basidiomycota, and rarely Mucorales. This review underscores the worldwide distribution of this rarely reported disease and reveals that the yeast *C. albicans*, a frequent resident colonizer of the oropharynx, is responsible for causing 60% of the cases. Furthermore, an overwhelming number of these cases were from India whereas scattered reports originated from Japan, the USA and Europe. Concerning the ABPM cases due to molds, Japan and the USA accounted for 19 cases each, followed by 12 from Australia and few isolated reports from other parts of the world. It is not clear how far this wide divergence in geographic distribution of ABPM cases is due to greater awareness and better laboratory diagnostic facilities/mycological expertise in some countries than in others. Among the most common molds inciting ABPM were species of *Bipolaris*, commonest being *B. hawaiiensis* and *S. commune*. It is noteworthy that association of bronchial asthma with ABPM was found much less frequently than it is known with ABPA, although the two diseases share many clinical and radiologic features and have the same diagnostic criteria. Also, the cases reviewed herein demonstrated a threefold higher IgE level than that of ABPA (417 IU/ml), suggesting that the fungi causing ABPM incite a stronger immunological response than done by aspergilli in ABPA.

The epidemiology of ABPM is currently not fully understood because it is likely to be underdiagnosed due to an inadequate clinical awareness and paucity of mycoserologic laboratory diagnostic facilities, especially in the many developing countries. Considering that the patient's immune response appears to be the most significant factor, studies are indicated for elucidating the mechanism of innate host responses to the fungi causing ABPM. It is anticipated that the list of fungi causing ABPM will likely expand with further studies. Investigations on a wider variety of fungal allergens and diagnostic modalities promise to reveal the true prevalence of ABPM. In order to achieve this goal, investigations aimed at standardization of fungal allergens are warranted to ensure the accuracy and reproducibility of skin testing and *in vitro* hypersensitivity results. Furthermore, the association of ABPM with asthma needs to be critically investigated to ascertain their interrelationship. Finally, apart from the well-established role of corticosteroids, the relevance of other therapeutic agents such as antifungal drugs, monoclonal antibodies and allergen-specific immunotherapy in the management of ABPM needs to be carefully evaluated.

Acknowledgement

H.S.R. acknowledges the award of an Honorary Scientist position by the Indian National Science Academy, New Delhi.

Declaration of interest

J.F.M received grants from Astellas, Merck, Pfizer, Schering-Plough, Gilead and Janssen Pharmaceutica. He has been a consultant to Basilea and Merck and received speakers fees from Merck, Pfizer, Schering-Plough, Gilead and Janssen Pharmaceutica.

All other authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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