Allergic bronchopulmonary aspergillosis: a review

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Introduction

Aspergillus, generally of the species *fumigatus*, can cause a number of lung diseases. *A. fumigatus* spores can act as triggers for asthma in sensitized atopic individuals, inhalation of high concentrations of *A. clavatus* can lead to allergic alveolitis, people with pre-existing lung damage are susceptible to colonization of cavities with fungal balls (aspergillomas) or to a chronic necrotizing pneumonia usually affecting the upper lobes. Immunocompromised individuals are at risk of developing invasive, systemic aspergillosis. One of the commoner syndromes associated with aspergillus is allergic bronchopulmonary aspergillosis (ABPA) characterized by asthma, pulmonary eosinophilia, and an allergic type immune response in the bronchi and proximal bronchiectasis. Although *A. fumigatus* is by far the commonest cause of ABPA other *Aspergillus* species such as *A. niger*, *A. flavus* and *A. terreus* can lead to an identical disease as can other fungi[1,2].

In this paper, our current understanding of the clinical aspects and pathogenesis of ABPA will be reviewed, in particular focusing on how the immune response in ABPA compares with that in uncomplicated asthma in the light of recent advances in our understanding of the pathogenesis of asthma.

Clinical aspects

The first report of ABPA was in 1952 when three patients with recurrent episodes of wheezy bronchitis, peripheral blood eosinophilia, fever, sputum production and chest X-ray shadowing were described. Sputum culture grew *A. fumigatus*[3]. This was followed by a number of series of patients with a similar syndrome[4-6]. Since then ABPA has been described in many countries and is universally recognized as being a complication of several obstructive lung diseases, in particular asthma and cystic fibrosis. ABPA can present acutely either as fleeting pulmonary eosinophilia or with symptoms and signs due to mucus impaction of a proximal airway. The acute illness often occurs as an exacerbation of a chronic pattern of disease characterized by proximal bronchiectasis. It is generally assumed, firstly that the chronic form follows the acute, and secondly that the chronic lung damage can be prevented by corticosteroid treatment. The two acute forms present with wheezy breathlessness, malaise often with fever, and cough sometimes producing brown mucus plugs. In chronic ABPA the acute episodes are superimposed on a background of chronic cough and sputum. The bronchiectasis can then dominate the clinical picture with clubbing and fixed radiographic abnormalities. Chest X-ray changes include hyperinflation with, in the acute forms, either fleeting alveolar infiltrates due to eosinophilic pneumonia, or a combination of mucus plugging with segmental, lobar or even whole lung collapse. When collateral air drift prevents collapse the impacted bronchus may be clearly outlined and show a 'toothpaste', 'gloved finger' or rabbit's ear appearance. Chronic changes usually favour the upper lobes with proximal saccular bronchiectasis and a combination of tramline and ring shadows sometimes merging into more generalized lung fibrosis. Bronchiectasis may be present in the absence of chest X-ray evidence and is better demonstrated by narrow section (3 mm) computerized tomograms[7]. Bronchography has now been supplanted by this technique. Lung function testing usually reveals airways obstruction although in severe end stage cases in which lung fibrosis has occurred a restrictive or mixed obstructive and restrictive picture may occur.

The laboratory features of acute ABPA include (i) peripheral blood and sputum eosinophilia, (ii) immediate, IgE type, hypersensitivity to *A. fumigatus* as defined by a positive immediate skin prick test and a positive RAST to *Aspergillus* antigens, (iii) a very high total IgE level (ie greater than 2500 ng/ml), (iv) IgG (precipitating)) antibodies to *Aspergillus*, (v) *Aspergillus* hyphae in the sputum and positive sputum cultures for *Aspergillus*. As well as an immediate type, wheal and flare, reaction to skin testing with aspergillus antigen; a delayed type reaction has been described to intradermal testing which has been ascribed to an Arthus type reaction. However this is more likely to represent a late response to allergen challenge readily seen in atopic individuals with a vigorous type 1 immune response[8]. None of the clinical, radiological or laboratory features are specific for ABPA and the diagnostic criteria for ABPA remain undefined. In Britain the criteria have been asthma (although ABPA patients without asthma is well recognized[9,10]), pulmonary eosinophilia (ie fleeting shadowing on the chest X-ray in association with a peripheral blood or airway eosinophilia) and a positive immediate skin prick test to *A. fumigatus*[11]. Chapman *et al.* recently suggested that this should be modified to include positive precipitins to *A. fumigatus* or positive sputum cultures[12]. In the USA stricter rules are applied demanding in addition to the above criteria a raised serum total IgE concentration and the identification of proximal bronchiectasis for a definite diagnosis[13]. The characteristic features of ABPA and their frequency are shown in Table 1. A simple skin prick test to detect immediate hypersensitivity to *A. fumigatus* is a useful screening test as ABPA is very unlikely with a negative reaction.

Table 1. Diagnostic criteria for ABPA

Parameters	*ABPA*	*Pulmonary eosinophilia*	*Atopic asthma*	*Cystic fibrosis (no ABPA)*
Immediate skin prick (*Aspergillus* extract)	100	25	35-50	35
Total IgE >1000 ng/ml	80-100	30	50	20
IgG precipitins	70-95	0	10-20	35
+ve sputum culture	60-80	10	NR	NR
Eosinophilia	100	100	40	20
Shadowing on CXR	100	100	0	100
Asthma	75-95	80	100	25
Bronchiectasis	60	20	0	100

NR: not reported

Clinical course

The spectrum of disease severity varies widely from the mild asthmatic with occasional episodes of pulmonary eosinophilia without evidence of bronchiectasis at one end to progressive lung damage and respiratory failure at the other. Greenberger and Patterson have suggested a clinical classification for patients with ABPA and bronchiectasis consisting of five stages. Stage 1 acute (first) episode of ABPA which is rarely in practice identified, stage II=remission, stage III=exacerbation, stage IV=corticosteroid dependant, stage V=fibrotic. Patients without bronchiectasis but with a clinical and immunological profile suggestive of ABPA they classify as ABPA-S (S=seropositive). They regard each stage as having a distinctive immunological profile most clearly differentiated by fluctuations in total IgE[14]. Treatment has two aims: first to control the acute episodes, and second to limit progressive lung damage. Corticosteroids (eg prednisolone 30-40 mg/day) rapidly clear the eosinophilic infiltrates and the associated symptoms but are less effective at treating mucus impaction. If this impaction and the associated distal lung collapse persists for more than a week in spite of corticosteroids then bronchoscopy should be performed to confirm the diagnosis and to attempt to remove the mucus plugs. When the acute episode has resolved corticosteroids can be tailed off over the next month.

Chronic treatment with corticosteroids is more controversial. In the first place only a minority of patients with ABPA are at risk of progressive lung damage and so to expose all patients to the risks of long term side effects from treatment would be wrong; secondly the relationship between the acute episodes and lung damage is unclear and it may be that chronic low grade inflammation is also important[15]; third the required dose of prednisolone is not certain and acute exacerbations may continue while the patient is taking 5-15 mg/day[16,17] and finally a balance must be struck between the beneficial effects of steroids on airways inflammation and their theoretical disadvantage in the face of chronic bacterial colonization of the associated bronchiectasis. Probably the best compromise is to treat two groups of patients with long term corticosteroids: those with frequent symptomatic attacks, and those with evidence of progressive lung damage[18].

Inhaled corticosteroids help to control the symptoms of asthma but do not prevent the epidoses of eosinophilic infiltration or mucus impaction, and are not thought to have any influence on progressive lung damage. Anti-fungal agents have been tried on many occasions but have never been shown to be beneficial in clinical trials[19-21].

ABPA in cystic fibrosis

ABPA is a well recognized complication of cystic fibrosis with the reported incidence varying between 0.6% and 11%[22,23]. Diagnosis may be difficult because of the relatively high prevalence of atopy, including high IgE levels, and wheeze in these patients. In addition a third have specific IgE and IgG precipitins to aspergillus and a peripheral blood eosinophilia is not uncommon as are fleeting lung shadows due to infection[24-26]. The approach of one group was to regard a diagnosis of ABPA likely if a new pulmonary infiltrate persisted after an appropriate course of antibiotics, in the presence of an immunological profile suggestive of ABPA. If the shadowing cleared after a course of corticosteroids the diagnosis was regarded as confirmed. Using this approach they identified 6% of their cystic fibrosis patients as having ABPA[27].

Aspergillus

Aspergillus are a genus of spore forming fungi with several species of which only *A. fumigatus* and *A. niger* occur with any frequency in Britain. The spores are 3 microns in diameter, are dispersed by wind and have an optimum temperature for growth of 37°C which may be one reason why they so readily colonize human airways. They also have an array of strategems to counter host defences which one author suggested may have been designed to fend off amoebae[28]. They grow rapidly on mycological media and are recognized by septate branching hyphae which are 7-10 μm in diameter and have characteristic swollen condiphores[29]. Their natural habitat is rotting vegetation particularly fallen leaves and spore counts are highest in the autumn and winter which may explain the possible increase in the number of exacerbations of ABPA in these seasons[30,31]. *Aspergillus* can be identified in tissue by routine haematoxylin and eosin staining, although periodic acid-Schiff and silver staining are better[32].

ABPA and the immune response

ABPA is characterized by a vigorous polyclonal antibody response as well as a less well characterized cellular immune response. Serum levels of *A. fumigatus* specific IgE, IgA and IgG are all increased. A study measuring immunoglobulin concentrations in BAL

from 8 patients with ABPA, suggested that local production of specific IgA and IgE (though not total IgE or specific IgG) in the airways was responsible for the increase[33]. Extracts of *A. fumigatus* contain a complex mixture of antigenic proteins which appear to be mainly derived from the hyphae rather than the spores[34]. The antigenic mix can vary between batches. This lack of standardization has led to some variability in results from different laboratories. Longbottom *et al.* identified four major proteins as contributing to a large part of the antigenicity of *Aspergillus* extracts. These include two lectin binding, cytoplasmic antigens of 150–200 kDa and 70 kDa which provoked an IgG response and a heat labile, 24 kDa by gel filtration (18 kDa by SDS-PAGE), allergen (IgE response)[35]. In contrast Leung *et al.*[31] reported several IgG reacting protein bands with a molecular weight ranging between 30 and 110 kDa with the major allergen having a molecular weight of 70 kDa. T cell clones to *A. fumigatus* recognized an 18 kDA antigen[36]. The antigenic profile depends both on the individual and the stage of the disease. Baur *et al.*[37] investigated the specific IgG and IgG response to *A. fumigatus* in 28 patients with different stages of ABPA and demonstrated that stage II disease was characterized by a very poor IgE reaction whereas numerous distinct IgE bands were seen in stage III. Immunoreactivity to the higher molecular weight proteins was lost in those patients treated with long term corticosteroids, stage IV, whereas stage V gave a mixed picture. The more informative IgE response is mirrored by the tendency of total serum IgE levels to reflect exacerbations. Thus Bernstein *et al.*[38] found that exacerbations of ABPA, which were often clinically silent, were characterized by marked increases in serum total IgE levels. Indeed total concentrations of total IgE are regarded as a useful marker of disease activity in the USA with a 2-fold increase suggesting the prodrome of an exacerbation[39]. Total serum IgA was also found to increase both before and during an exacerbation in five out of seven patients with ABPA[40]. A likely explanation for the increase in total IgE is that exacerbations of ABPA are characterized by the release into the airways of IL-4 from T lymphocytes and possibly mast cells. IL-4 is an interleukin that promotes the synthesis of IgE by B cells. The subgroup of T cells that produce IL-4 also produce IL-5, the interleukin responsible for eosinophil differentiation, which explains the eosinophilia found in ABPA.

Pathology of ABPA

There are few studies of the pathology of ABPA and those reported have involved small numbers of patients[41-43]. Macroscopically the most prominent features are obstruction of major bronchi with thick tenacious mucus and findings consistent with proximal bronchiectasis. Microscopically the findings are those of asthma with plugging of the bronchial lumen, with mucus containing Charcot-Leyden crystals and fungal hyphae which do not invade the bronchial wall. Epithelial damage and a prominent eosinophilic and mononuclear infiltrate in the bronchial submucosa are characteristic together with a thickened collagen layer beneath the epithelial basement. The inflammatory pattern extends into the small airways and alveoli to give a similar pathological appearance to eosinophilic pneumonia. It is the alveolar infiltrate which is thought to be responsible for the fleeting shadows on CXR which are characteristic of the disease. The inflammatory response seen in ABPA is due to a combination of type I and type III immune responses[44]. While there is some evidence from animal models that both IgE and IgG antibodies are necessary for the development of the disease[45], there is little evidence that mast cells or immune complex deposition are important. Mast cells were not noted to be increased in the airways in ABPA and the eosinophilia in ABPA, as in asthma, may be more reliant on T cell than mast cell activation. In addition there is no evidence for immune complex deposition, vasculitis, complement activation or involvement of neutrophils, (in the absence of bacterial infection due to bronchiectasis) which would be expected with a type III 'Arthus response'.

Bronchocentric granulomatosis (BCG)

This is an unusual clinical entity consisting of chronic symptoms of malaise, cough, fever, breathlessness, chest pain and haemoptysis associated with a focal lesion on CXR which has the appearance of a tumour. About one-third of patients are asthmatic. The characteristic pathological feature is a necrotizing granulomatous reaction centred around airways with peripherally necrotic lesions within collapsed and consolidated lung. In asthmatics eosinophilic infiltration occurs. The relationship to ABPA is uncertain. *Aspergillus* hyphae were seen in 18 of 24 patients who had BCG and asthma but only 6 out of 21 who did not have asthma. Out of 19 patients with BCG but no asthma none had precipitating antibodies against *Aspergillus*. The evidence that *Aspergillus* is central to the pathogenesis of BCG is therefore inconclusive[46].

Pathogenesis of ABPA

The patterns of immune response described above are not specific and are likely to occur in atopic asthma without ABPA. The relationship between asthma and ABPA is interesting. Most, though not all patients with ABPA have asthma which almost invariably predates the onset of ABPA by many years, a mean of 19 years in one study 12. Many of the features of ABPA, such as variable airflow obstruction with periods of remission and exacerbation, eosinophilic inflammation of the airways and a good response to corticosteroids are shared with uncomplicated asthma. A striking feature of chronic asthma is that despite decades of intense inflammation permanent structural damage to the airways is unusual. Indeed, in general, eosinophilic inflammation of the lungs does not involve irreparable tissue destruction. Why does this occur in ABPA? One explanation is that the colonization of the airways by *A. fumigatus*

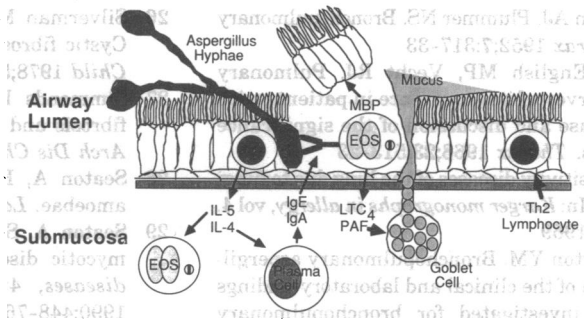

Figure 1. Pathogenesis of allergic bronchopulmonary aspergillosis: a review

leads to a persistent antigenic stimulus which results in a more vigorous and amplified immune response than seen in asthma. This in turn could lead to a more marked inflammatory reaction involving the production of large amounts of mucus and cellular debris. The high concentrations of specific immunoglobulin in the airways in combination with the fungal spores and surface of the hyphae could act as an effective trigger for eosinophils with subsequent mediator release and mucus secretion. This could lead to a more prolonged and complete bronchial obstruction than is generally seen in asthma, resulting in bronchiectasis (Figure 1). Thus chronic, indolent obstruction in untreated ABPA may be the primary cause of the bronchiectasis rather than the initial inflammatory response to the fungus. Why only a subset of individuals should respond to *A. fumigatus* in this manner is not clear. *A. fumigatus* spores are widespread and increased environmental exposure is not generally a factor in the development of ABPA, although some reports have suggested a link[47]. In addition some normal individuals have substantial amounts of specific IgG to *A. fumigatus* and mononuclear cells from normal individuals proliferate in response to *A. fumigatus* antigens[40]. The most likely explanation is a genetically determined T lymphocyte response to *Aspergillus* that results in the generation of IL-5 and IL-4 together with some feature of the airways in ABPA patients that either renders them susceptible to colonization by *A. fumigatus*.

Conclusion

ABPA is a not uncommon condition affecting mainly chronic asthmatics and patients with cystic fibrosis. It can result in severe bronchiectasis and fibrosis causing respiratory failure. Corticosteroid treatment should be given to treat acute episodes and probably has an additional role in preventing progressive lung damage. At present the subset of individuals with ABPA at risk of developing progressive respiratory impairment cannot be identified and so close monitoring is needed. The pathogenesis of ABPA has not been fully determined but is likely to be due to a vigorous T lymphocyte/eosinophil mediated inflammatory response in the airways directed against the colonizing aspergillus.

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