Aspergillus Sensitisation and Severe Asthma Clinical Outcomes

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Abstract

Fungal lung diseases represent a heterogenous group of conditions and the differing definitions are used to describe these relationships. Historically there has been the nomenclature evolution on the spectrum of lung diseases linked to sensitisation to *A. Fumigatus* including SAFS (severe asthma with fungal sensitisation) and ABPA/M (allergic bronchopulmonary aspergillosis/mycosis). It seems that AFAD (airway fungal airway disease) therefore represents an open definition of IgE sensitisation to thermotolerant fungi. It covers not only the most severe forms of the disease as SAFS and ABPA, but also milder forms of airway disease. It might represent a treatable trait which has to be seen, longitudinally observed, and treated and consequently preventing lung damage.

Keywords: allergic fungal airway disease, severe asthma, IgE sensibilisation

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Introduction

Fungal lung disease represents a heterogeneous group of conditions[1]. They can be divided into infective, toxic, or allergic in nature, although there is a degree of overlap. Some of them are connected and interact in patients with asthma and particularly in severe asthma. Its behaviour in interaction with fungi results in different clinical asthma outcomes, which are under recognised and represents a clinical and diagnostical challenge.

The differing nomenclatures are used to describe these relationships. A recent proposal of various clinical outcomes of airway colonisation with thermotolerant filamentous fungi e.g. *A. Fumigatus* (table 1) includes allergic group. This allergic group can again be broadly divided into two, both of which can be associated with severe asthma. The first type is an allergenic response to environmental fungi such as non-thermotolerant *Alternaria* and *Cladosporium* which act as seasonal aeroallergens, the symptoms of which are directly related to airborne concentrations of fungal material, and which can include acute severe exacerbations. The second type involves an allergic response to thermotolerant filamentous fungi such as species from the *Aspergillus* and *Penicillium* which can act as aeroallergens, and they have the additional property of being able to germinate in the airways. Consequently, they are colonising the lungs and causing a persistent allergenic stimulus that can lead to lung damage[2–4].

Historically the clinical and immunological variability in presentation of fungal allergy to thermotolerant fungi has developed into a separate differentiation/definition of two conditions: allergic bronchopulmonary aspergillosis/mycosis (ABPA/M) and severe asth-

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Table 1. Clinical outcomes of airway *colonisation* with thermotolerant filamentous fungi e.g., *A. Fumigatus (adapted from 1)*

	Basic Clinical manifestaton	Further subclasification
Upper airway	Allergic fungal sinusitis	
Lower airway	Cavitating lung disease	Aspergilloma
	Chronic Lung disease	Fungal allergy Chronic pulmonary aspergillosis Ekstrinsic allergy alveolitis
		Fungal bronchitis
	Immunocompromised host	Invasive aspergillosis

ma with fungal sensitisation (SAFS). Recent publications[1] support the idea that these presentations should not be strictly seen as a completely different entities since there is limited evidence that there are distinct mechanisms involved in the spectrum of thermotolerant fungal lung allergy. Consequently, recently an inclusive set of criteria which includes all presentations of the disease under the umbrella term allergic fungal airway disease (AFAD) is preferred[1,5].

Evolution of terminology toward AFAD

The fungi that play a role in asthma can be divided into two groups: those that can grow at body temperature, referred to as thermotolerant, which are capable of both infection and allergy, and those that cannot but can still act as allergens in IgE sensitised individuals. It is the thermotolerant group of filamentous fungi that cause AFAD[1,5]. The pathophysiology behind different clinical outcomes is the host response to airway colonising, allergenic, thermotolerant, filamentous fungi, with *A. fumigatus* as the major culprit[5].

Sensitisation ot *A. Fumigatus* has been associated with a spectrum of states including SAFS and ABPA/M. The descriptions of ABPA criteria have developed over time and the Petterson s criteria[6] were later further upgraded with the criteria proposed by the International

Society for Human & Animal Mycology (ISHAM)[7] which are more relaxed making them more relevant to clinical practice[5].

Proposed ABPA criteria includes:

1. the presence of asthma or cystic fibrosis,
2. evidence of specific IgE to *A. fumigatus* and total IgE above 1000 IU/ml
3. at least two of raised IgG antibodies to A. fumigatus, abnormal radiology consistent with ABPA and an eosinophil count (steroid-naive patients of greater than 0.5X109/l)

In an accompanying diagnostic algorithm, total IgE was central in distinguishing between ABPA and IgE sensitization without ABPA

This structure has been very recently further upgraded[8] with the work of the Japan ABPM research program, supported by the Japan Medical Research and Development Organization. They developed new ten-component diagnostic criteria for ABPA/ABPM in non-cystic fibrosis patients (table 2) where they compared the sensitivity and specificity of the new and conventional criteria to discriminate pathological and physician-diagnosed ABPA/ABPM from related diseases, including fungus-negative mucoid impaction in bronchi, chronic eosinophilic pneumonia, fungus-sensitized severe asthma, and chronic pulmonary aspergillosis. The new diagnostic criteria, compared with existing criteria, showed better sensitivity and specificity for diagnosing ABPA/ABPM; The sensitivity for pathological ABPM with Rosenberg-Patterson criteria, ISHAM criteria, and these new criteria were 25.3%, 77.2%, and 96.2%, respectively. The sensitivity for physician diagnosed ABPA/ABPM were 49.2%, 82.7%, and 94.4%, respectively. The areas under the curve for the receiver operating characteristic curves were 0.85, 0.90, and 0.98, respectively[7].

Table 2. Clinical diagnostic criteria for allergic bronchopulmonary mycosis in patients without cystic fibrosis (adapted from 7)

1. Current or previous history of asthma or asthmatic symptoms
2. Peripheral blood eosinophilia (≥ 500 cells/mm3)
3. Elevated total serum immunoglobulin E levels (IgE ≥ 417 IU/mL)
4. Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
5. Presence of precipitins or specific IgG for filamentous fungi
6. Filamentous fungal growth in sputum cultures or bronchial lavage fluid
7. Presence of fungal hyphae in bronchial mucus plugs
8. Central bronchiectasis on computed tomography (CT)
9. Presence of mucus plugs in central bronchi, based on CT/ bronchoscopy or mucus plug expectoration history
10. High attenuation mucus in the bronchi on CT

Filamentous fungi in 4-6 should be identical. Patients that meet 6 or more of these criteria are diagnosed with ABPM.

Many fungal sensitised individuals with severe asthma do not fulfil the criteria for ABPA, so in 2006 the term SAFS was introduced. Denning and colleagues thus proposed the term severe asthma with fungal sensitisation (SAFS) to describe this aspect of troublesome asthma and used criteria in opposition to the ABPA criteria by including an IgE of 1000 IU/L[8]. However, SAFS includes asthmatics with sensitisation to any fungus.

It seems that AFAD therefore represent an open definition of IgE sensitisation to thermotolerant fungi, therefore a treatable trait which has to be seen, longitudinally observed and treated as appropriate. It covers not only the most severe forms of the disease as SAFS and ABPA, but also milder forms of airway disease. It is important to stress that many patients with clinically significant fungal allergy do not have severe asthma. Nevertheless, all patients with IgE sensitisation to thermotolerant fungi in the context of asthma and other airway disease are at risk of progressive lung damage, and as such should be monitored closely irrespective of a diagnosis of ABPM[7].

The terminus AFAD reminds a clinician, that the disease might progress in other forms including lung damage and that »watch and see« strategy might be not enough.

Pathophysiological abnormalities and clinical outcomes related to airway fungal allergy

Basic immunology

Fungal sensitisation occurs in about 3–10% of the general population[9] and 7–20% of asthmatics. The prevalence is higher in patients with severe asthma (rates between 35–75%)[10]. The hallmark of AFAD is exaggerated T2 immunity causing IgE sensitisation to filamentous fungi and eosinophilic inflammation[7]. Airway epithelium is exposed to proteolytic enzymes from fungi following deposition of the spores/hyphae or smaller particles on the surface. Those enzymes augment the permeability of the epithelial layer by digesting the proteins of tight junctions, destroying the integrity of epithelial cells and by digesting the structural proteins of the basement membrane. Selective production of TSLP, IL-25, and IL-23 by epithelial cells and inhibition of IL-12 production by dendritic cells (DCs) may be responsible for the shift toward Th2 responses[11]. In the study of Balenga and co-workers they have shown that a major *A. fumigatus* allergen, Asp f13, which is a serine protease, alkaline protease 1 (Alp1), promotes airway hyper-responsiveness by infiltrating the bronchial submucosa and disrupting airway smooth muscle (ASM) cell-extracellular matrix (ECM) interactions[12]. The group later demonstrated that Alp1 quantities were significantly higher in sputum from patients with Af sensitivity than those without, regardless of clinical severity of the disease. But the amount of Alp1 in the lower airways of asthmatics correlated with severity of disease and interestingly with sputum neutrophil, but not eosinophil counts. They suggested that it is proteolytic destruction of lung tissue, which could promote influx of neutrophils into the airway lumen[13].

Mucus impaction

Mucus impaction in AFAD is most strikingly evident in those patients who present with lobar collapse due to inspissated mucus but is also seen in the smaller airways on CT scans[7]. The precise pathway by which IgE sensitisation to thermotolerant filamentous fungi may cause production of viscid mucus is not clear but could be related to excess production of MUC5AC by goblet cells because of vigorous T2 hyperimmune stimulation[7,14]. Evolution of mucin synthesis is complex and include activated eosinophils as well since there is evidence that they induce mucin synthesis in human airway epithelial cells via EGFR (epidermal growth factor receptor)[15].

Immaging, functional impairment and comorbidities

Aspergillus fumigatus sensitization defined by a specific IgE of 0.35 kU/L or greater was associated with functional and radiological abnormalities: 83.4% had an abnormal HRCT with bronchial wall thickening (41.3%), bronchiectasis (35.3%), air trapping (20.3%) and bronchial dilatation (16.5%). Radiological evidence of airway disease was also associated with more obstructive spirometry. *A. fumigatus* sensitization was associated with a 2.01 increased hazard ratio of bronchiectasis and more obstructive spirometry. They suggested that patients with *A. fumigatus* sensitization had variable clinical and radiological characteristics that frequently did not conform to the conventional diagnostic criteria for ABPA[16].

All patients with IgE sensitisation to *A. fumigatus* are at risk of lung damage irrespective of whether they meet the criteria for ABPA[17]. A large cohort (n = 431) of asthmatics enriched for IgE sensitisation to fungi were recruited in a cross-sectional study to determine the relationship between immunological biomarkers of fungal allergy and evidence of lung damage in asthma[17]. The patients with AFAD had higher rates of early-onset disease and as a result almost twice the duration of asthma. Those with AFAD had overall about a 10% deficit in FEV1 which was not related to atopy and not seen in patients sensitised to non- thermotolerant or non-filamentous fungi. Significant differences in radiological appearances between those sensitised and non-sensitised to fungi included bronchiectasis (50% versus 29%), tree-in-bud (17% vs 4%) and collapse/ consolidation (35% vs 21%). Authors suggested that IgE sensitisation to thermotolerant filamentous fungi, in particular *A. fumigatus* but not total IgE, is associated with fixed airflow obstruction and several radiological abnormalities in moderate to severe asthma.

The group of Kurukulaaratchy[18] reported that *A. fumigatus* sensitisation in patients with difficult asthma identifies a more severe form of disease associated with older age, male sex, longer duration of disease, lung function impairment, bronchiectasis, higher inflammatory parameters, greater treatment needs but less psychophysiologic comorbidities.

Fungal bronchitis

Fungal bronchitis describes chronic purulent sputum production due to non-invasive infection with thermotolerant fungi in the context of a relatively immunocompetent host. It is not widely used in the medical literature. A positive sputum culture for thermotolerant fungi is critical for the diagnosis of fungal bronchitis. In a recent report[19] the group of Wardlaw and co-workers have recognised a clinical presentations of often chronic exacerbations of airway disease which were unresponsive to standard treatment with broad spectrum antibiotics or high dose oral corticosteroids, in which sputum culture was positive for either *A. fumigatus* or *Candida spp.* Usually the sputum was white/creamy or brown rather than the green associated with bacterial infection, and was very mucoid or rubbery in consistency[19].

Management of AFAD

To a large extent management of AFAD is similar to the management of the underlying airway disease with personalised approach. An approach toward treatment of T2 treatable trait (eosinophilic pattern of disease) includes inhaled corticosteroids. They are a cornerstone of therapy. There exist a theoretical risk of augmentation od fungal colonisation, but with the approach toward using the lowest dose of inhaled corticosteroids to achieve a control of disease this might not be serious problem in clinical practice. In severe cases low dose continuous or intermittent oral corticosteroids (OCS) are necessary to achieve control.

Since OCS are seen as a last resort in asthma therapeutic algorithms, anti-T2 biological therapy is a possible option in AFAD treatment. Evidence on omalizumab, but also mepolizumab, benralizumab and dupilumab are based mostly on case series and reports. Favourable reported responses include significant reduction in OCS burden, reduction in acute exacerbations, improvement in lung function and improvement in patients outcomes[120–23].

The place of antifungal therapy in AFAD remains uncertain. Whilst open studies have often reported a benefit, placebo controlled, blinded studies have shown either no benefit or a modest improvement at best compared to standard of care, which these days probably includes biological therapy. Clinical practice would suggest that in the majority of patients with AFAD the benefits of azole therapy are not outweighed by side effects. However, where fungal bronchitis is present, particularly in the context of difficult to treat exacerbations, they are an important adjunct to therapy and can lead to a dramatic improvement in symptoms in relatively short time. Positive sputum fungal culture seems to be a useful biomarker of a response to antifungal therapy even in the case of *Candida* species if it is persistent[5]. There are no definitive guidelines on how long a course should be, but clinical recommendation from the group of Wardlav[1] recommends that three months is necessary and usually sufficient. Repeated courses are sometimes necessary.

Conclusions

The term AFAD has a liberal definition, based on the presence of IgE sensitisation to thermotolerant fungi and evidence of fungal-related lung damage[23]. As such it is more inclusive than ABPA or SAFS, not being focused on total IgE and not restricted to severe asthmatics only. The recommendation supports close patient s follow up due to detecting and preventing long term lung damage[17].

Furthermore, unlike SAFS, AFAD distinguishes between sensitisation to thermotolerant and non-thermotolerant fungi[5].

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