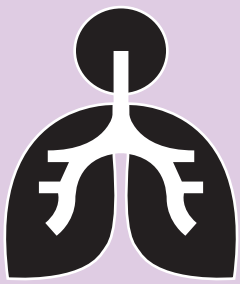
Vol. 11 No. 1 April-June' 15

Asthma Focus

Key Points



- Fungi cause lung disease by acting as aeroallergens or by colonizing the lung.
- A more liberal term is needed to encompass the spectrum of lung disease caused by fungi.
- The emphasis should be on detecting and preventing long-term lung damage.

Allergic fungal airway disease: pathophysiologic and diagnostic considerations

Fungi can act as aeroallergens in those that are Immunoglobulin E (IgE)-sensitized and can cause a range of airway diseases by colonizing the lung. Allergen exposure to fungal spores, such as Alternaria alternata during the late summer and autumn months, has been associated with acute bronchospasm, asthma admissions and deaths. Most fungi that act as aeroallergens do not grow at body temperature and so cannot germinate in the airway. Adverse events are therefore related to the level of spore exposure. However, thermotolerant fungi including some saprophytes that are important in vegetation decomposition, such as Aspergillus fumigatus, grow at body temperature, enabling them to colonize the lung. Depending on the host airway response, fungal colonization can exacerbate asthma or cause chronic sinusitis, fungal bronchitis, chronic necrotizing pneumonia, fungal empyema, allergic alveolitis or, in people with pre-existing lung cavities, the development of a fungal ball (aspergilloma) (Fig. 1). Lastly, severely immunocompromised individuals can develop systemic infection. This review will focus on the clinical aspects of the involvement of thermotolerant fungi in allergic airway disease.

What is allergic fungal airway disease?

Thermotolerant fungi are implicated in several different presentations of airway disease and there is no good term that encompasses them all (Fig. 2). Allergic bronchopulmonary aspergillosis (ABPA), the most common form of allergic bronchopulmonary mycosis (ABPM), originally described in patients with asthma who were IgE-sensitized to A. fumigatus and presented with fleeting lung shadows, eosinophilic airway inflammation, and progressive lung damage with lung fibrosis, proximal bronchiectasis and fixed airflow obstruction. A set of criteria based on clinical experience was developed to try and define this syndrome. These were fleeting lung shadows, eosinophilia, evidence of IgE sensitization to A. fumigatus, total IgE of above 417 IU/ml (although 1000 IU/ml is said to offer greater specificity), precipitating antibodies to A. fumigatus (usually measured as specific IgG) and proximal bronchiectasis. Evidence of colonization was not part of the major criteria even though it is thought to be the underlying cause of the condition. It is unusual for someone with asthma who is IgE-sensitized to A. fumigatus to fulfil all these criteria. Some people do not have good evidence of variable airflow obstruction and fleeting shadows are now unusual, due to the widespread use of highdose inhaled steroids reducing large airway inflammation. Total IgE may be below 417 IU/ml and precipitating antibodies to A. fumigatus, usually measured as specific IgG, are frequently not raised. Bronchiectasis, when present, is often not proximal and is a common feature of severe asthma without evidence of fungal sensitization. Therefore, only about 10% of people with asthma associated with IgE sensitization to Aspergillus fulfil all the standard criteria for ABPA. ABPA is, thus, considered unusual, although sensitization to fungi, particularly in severe asthma, is common.

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The diagnostic criteria for ABPA, at present, are unsatisfactory. Recently, the International Society of Human and Animal Mycology (ISHAM) proposed to revise these criteria to include the presence of asthma or cystic fibrosis, evidence of specific IgE to A. fumigatus and total IgE above 1000 IU/ml and at least two of raised IgG antibodies to A. fumigatus, abnormal radiology consistent with ABPA and an eosinophil count in steroid-naive patients of greater than 0.5 109/l. In an accompanying diagnostic algorithm, total IgE was central in distinguishing between ABPA and IgE sensitization without ABPA. Although

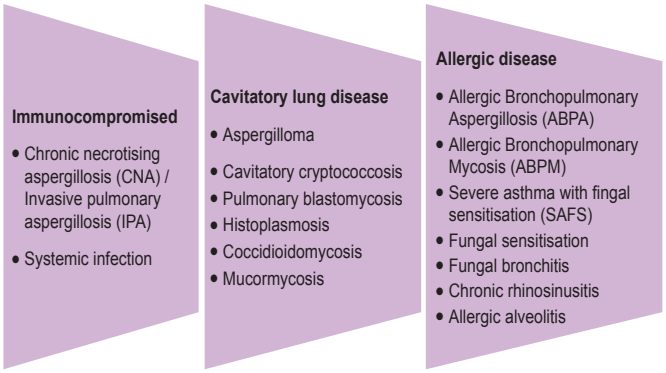

FIGURE 1. The spectrum of lung disease caused by fungi is dependent on the presence of pre-existing lung conditions and on whether the host is immunocompetent.

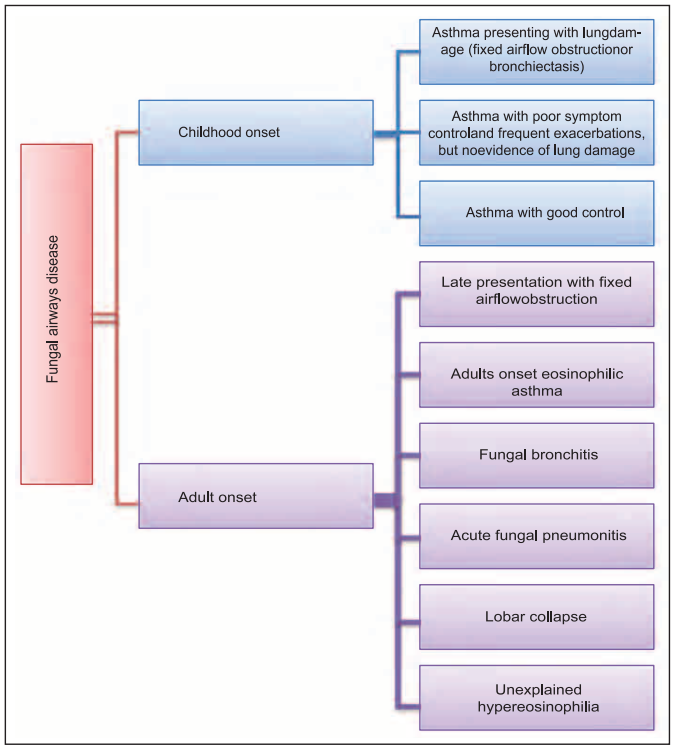

FIGURE 2. The different presentations of allergic fungal airways disease (AFAD).

less restrictive than the previous criteria, there is still no gold standard for the diagnosis of ABPA against which to test the specificity and sensitivity of biomarkers. Ideally, the immunological and radiological biomarkers should be tested against a fungal-specific outcome measure, but there are no features of fungal disease which are sufficiently specific compared to asthma without fungal sensitization. There is limited evidence that the strength of the Th2 response, denoted by high total IgE and marked eosinophilia, correlates with disease severity in fungal asthma, nor that these markers are able to guide management and improve outcomes. A similar problem occurs with the label of severe asthma with fungal sensitization (SAFS) which is largely separated from ABPA by using a total IgE of less than 1000 IU/ml as a cut-off. A more liberal diagnostic term to describe allergic fungal airway disease (AFAD) that would favour sensitivity over specificity would be more clinically useful than restrictive terms such as these. One solution is to describe anyone with airways disease and IgE sensitization to colonizing fungi as having ABPA, grading them according to the degree of fungal-related lung damage and symptom control. However, it may not be possible to reassign such a historically well established label which relates to the florid end of the spectrum of fungal airway disease. Alternatively, a term such as AFAD could be coined, which could be divided into mild, moderate and severe, and the term ABPA phased out or limited to patients with severe patients. Overall, the emphasis should be on determining which biomarkers of AFAD predict prognosis (particularly the risk of lung damage) and treatment response.

Presentation of allergic fungal airway disease.

Variable airflow obstruction caused by airway smooth muscle (ASM) contraction is pathognomic of asthma. However, this is just one of the five pathophysiological endotypes that occur in asthma as well as other airway diseases, each with distinct pathologies, clinical presentation and response to treatment [17]. Heterogeneity exists within these presentations and these endotypes can coexist within the same patient or occur independently. This is also true for fungal-associated disease which can be a complication of a number of asthma endotypes and could be regarded as an endotype in its own right (Fig. 2). Fungal IgE sensitization is most commonly seen in 'classical' early-onset atopic eosinophilic asthma. It is likely that sensitization occurs in childhood, whereas in adults, it is associated with more severe disease. Many patients with adult-onset asthma are nonatopic, but a proportion is atopic, a minority of whom are sensitized to thermotolerant fungi. Fixed airflow obstruction can be seen in patients presenting in their 6th decade. This may be due to subclinical fungal colonization causing progressive loss of lung function. Clinical presentations of AFAD vary, including those presenting with lobar collapse due to mucus impaction with a peripheral blood eosinophilia pointing towards an allergic cause; and fungal pneumonitis caused by exposure to high levels of fungal spores – often in

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the context of gardening – leading to acute respiratory illness with pneumonic shadowing. Heavy colonization with filamentous fungi or yeasts can lead to a fungal bronchitis in patients with underlying airway disease, characterized by a heavy growth of fungi in the sputum and a good response to triazole antifungals. This presentation can occur in the absence of fungal IgE sensitization. Lastly, occult fungal IgE sensitization is a common cause of a marked eosinophilia and can present in patients with unexplained eosinophilia.

Which fungi are involved?

The fungal kingdom could contain as many as 1.5–3 million species. There are 8–10 phyla within the kingdom and fungal pathogens have evolved independently and repeatedly throughout. Any fungi can be allergenic; however, the most common fungal allergens are those present in high levels either outdoors or in an occupational or residential setting. Most are mesophilic (unable to grow at body temperature, with optimum growth occurring at 18–228C) and thrive in temperate climates. Thermophilic fungi can grow at body temperature, but are unable to grow below 208C, so are not present in the environment and are rarely associated with human infections. Thermotolerant fungi grow in the environment and at body temperature and are thus associated with human disease, including AFAD.

Studies looking at fungal colonization of the airways have mainly focused on cystic fibrosis patients, with few studies on ABPA or asthma. Many have not looked for fungi other than A. fumigatus; an exception being our study looking at 126 patients with moderate to severe asthma. A good review of non-Aspergillus fungi associated with ABPM has recently been published. More than 600 fungal species have been recovered from human infections, with a core 200 seen regularly. In contrast, the number associated with the respiratory system is far lower. The two fungi regularly seen are both Ascomycota (A. fumigatus and Candida albicans); however, fungi from the Ascomycota, Basidiomycota and the group formerly referred to as the Zygomycota have all been implicated (Table 1). Species from 22 fungal genera representing 14 families have been detected so far, and whilst not all of them have been shown to induce allergies, due in part to a lack of reagents with which to test, it is highly probable that most of them would be able to cause AFAD.

Fungal culture is still the main way in which fungal agents are identified in the clinic; however, culture from respiratory samples, particularly sputum, could indicate colonization of the airways or an upper airway contaminant. Culture is notorious for being insensitive and biased towards the faster growing members of the less than 10% of the fungal kingdom able to grow on general growth media. The use of selective media increases the number of fungi that can be detected; however, it is the use of molecular culture-free tests that is likely to result in the greatest leap forward in our understanding of the fungi associated with AFAD.

How important is exposure in causing allergic fungal airway disease?

Epidemiological studies have associated dampness in the home with poor respiratory health and newonset asthma. However, whether the microbial content in the home is responsible for this is less clear-cut. Some studies have demonstrated a relationship with fungal exposure; others have not. A case-control study found no relationship between increased fungal exposure [as measured by fungal culture or concentrations of ergosterol and (1-3,1-6) beta-D-glucan in dust] and asthma in

Table 1. Fungi cultured from respiratory samples of individuals with allergic bronchopulmonary mycosis, allergic bronchopulmonary aspergillosis, asthma, Chronic obstructive pulmonary disease or cystic fibrosis

Phyla	Order	Family	Genus	Species (if determined)
Ascomycota	Eurotiales	Trichocomaceae	*Aspergillus*	*A. fumigatus, A. niger, A. flavus, A. nidulans, A. oryzae, A. glaucus, A. versicolor, A. terreus*
			Tallaromyces	*T. piceae (was Penicillium piceum), T. verruculosus (was P. verruculosum). T. marneffei (was P. marneffei)*
			Penicillium	*P. citrinum, P. chrysogenum, P. brasilianum, P. diversum, P. capsulatum, P. citreonigrum*
			Paecilomyces	
	Pleosporales	Massarinaceae	*Helminthosporium*	
		Pleosporaceae	*Ulocladium*	*U. lanuginosum (was Stemphylium lanuginosum)*
			Curvularia	*C. hawaiiensis (was Drechslera hawaiiensis), C. senegalensis, C. lunata,*
			Bipolaris	
			Alternaria	*A. alternata*
	Nectriaceae	Hypocreales	*Fusarium*	*F. oxysporum (was F. vasinfectum)*
			Microdochium	*M. dimerum (was Fusarium dimerum)*
	Microascales	Microascaceae	*Pseudallescheria*	*P. boydii (was Scedosporium apiospermum)*
			Scedosporium	*S. aurantiacum, S. prolificans,*
	Saccharomycetales	Incertae sedis	*Candida*	*C. albicans, C. glabrata, C. dubliniensis, C. parapsilosis*
		Saccharomycetaceae	*Saccharomyces*	*S. cerevisiae*
	Capnodiales	Cladosporiaceae	*Cladosporium*	*C. cladosporioides*
	Dothideales	Dothioraceae	*Aureobasidium*	*A. pullulans*
	Herpotrichiellaceae	Chaetothyriales	*Exophiala*	*E. dermatitidis*
Basidiomycota	Agaricales	Schizophyllaceae	*Schizophyllum*	*S. commune*
	Sporidiobolales	Incertae sedis	Rhodotorula	
	Tremellales	Trichosporonaceae	*Trichosporon*	
Zygomycotaa	Mucorales	Rhizopodaceae	*Rhizopus*	*R. arrhizus (was R. oryzae)*

Only fungi that have been isolated in the absence of A. fumigatus have been included from the asthma and COPD studies. Not a currently recognised phyla, taxonomic placement is under review.

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children, although levels of fungal exposure were relatively low. Furthermore, high levels of yeast exposure in infancy have been shown to be protective for later development of asthma.

Increased airborne levels of A. fumigatus have been associated with a positive sputum culture, but not IgE sensitization to *A. fumigatus* in asthma, despite spore concentrations being within the normal range for noncomplaint housing. The reasons for the lack of a consistent message may be due to the complexity of the relationship between fungal exposure and health outcomes. Intervention studies are required to determine if reducing exposure to thermotolerant fungi benefits respiratory health.

Biomarkers for the diagnosis of allergic fungal airway disease.

Biomarkers, whether used for diagnosis or prognosis, should be related directly to a disease process or pattern of response to treatment and be useful in predicting, preventing or reversing disease outcomes. In the context of current asthma management, where potent inhaled steroids have reduced the risk of severe exacerbations, the most common abnormalities associated with AFAD are fixed airflow obstruction and bronchiectasis. These develop over many years making direct links to biomarkers difficult.

Specific IgE

The most useful biomarker for the diagnosis of AFAD is the presence of specific IgE to a thermotolerant fungus, particularly *A. fumigatus*. Skin prick test (SPT) and in-vitro tests (such as ImmunoCap) are used to measure sensitization to fungi; however, discordance exists between the two tests. Cross-reactivity with clinically benign determinants may account for some of the discordance. In addition, fungal extracts are not standardized and are of variable quality.

Considerable cross-reactivity exists between fungal allergens even between distantly related genera. *Penicillium* species are commonly cultured from sputum. However, positive specific IgE to *Penicillium chrysogenum* without positive IgE to *A. fumigatus* only occurs in around 5% of patients. About 15% of patients with fungal sensitization to thermotolerant yeasts (*C. albicans, Malazzesia* species and *Trichophyton* spp.) are not sensitized to *A. fumigatus* (personal observation). However, the relevance of these fungi to allergic airway disease is uncertain, although yeasts, in particular, *C. albicans*, are almost invariably cultured from sputum in asthma. A positive specific IgE to *A. fumigatus* is

Antifungals in severe asthma

Purpose of review

Despite guideline-based treatment, many patients with severe asthma continue to have uncontrolled disease. Fungal allergy is being increasingly recognized in the pathogenesis of severe asthma. Limited data exist on the approach to treatment of fungal asthma. This review summarizes existing evidence on the use of antifungal agents in allergic bronchopulmonary aspergillosis (ABPA) and severe asthma with fungal sensitization (SAFS), and highlights needed areas of future investigation.

Recent findings

Recent studies evaluating oral triazole therapy in ABPA appear to support triazole use in a carefully considered clinical setting, whereas studies assessing triazole use in SAFS have yielded mixed results. Despite early encouraging findings that oral triazole use may improve asthma symptoms, stabilize lung function, decrease inhaled and systemic corticosteroid requirements, and alter serum biomarkers, overall data are limited. Appropriate patient selection, as well as choice of the optimal drug, dose, frequency and duration of therapy, remains poorly defined.

Summary

The role of antifungal therapy in severe asthma remains unclear. Early studies have suggested a possible benefit of some antifungal agents, such as oral triazoles in ABPA and SAFS; however, routine clinical use of these agents in severe asthma without ABPA is not currently recommended. Further research is needed to better delineate the potential utility of antifungal medications in severe asthma and identify the asthma populations who benefit from such treatment.

Keywords

antifungals, azoles, fungal asthma, severe asthma, triazoles

Source: www.com-pulmonarymedicine.com Vo. 21 No 1 Jan 2015

Antifungal therapy in severe asthma with fungal sensitization

The first randomized control trial of oral antifungal treatment in SAFS was performed by Denning et al.. The Fungal Asthma Sensitization Trial (FAST) randomized 58 patients with severe asthma and sensitization to at least one of the seven fungi to receive either oral itraconazole 200mg twice daily or matched placebo for 32 weeks. The primary endpoint was change in Asthma Quality of Life Questionnaire (AQLQ). In all, 60% of the patients treated with itraconazole showed substantial improvement in their AQLQ score compared with the placebo group (?0.85 vs. 0.01; P1/40.014). This improvement in AQLQ was larger than the minimally important difference of 0.5. Secondary endpoints showed an improvement in rhinitis score and serum IgE level in the treatment group. At 4-month follow-up, after discontinuation of therapy, AQLQ scores had returned to near prestudy values. Whereas no severe adverse events were observed, adverse events led to discontinuation in five patients in the antifungal group and two patients in the placebo group. In a subsequent retrospective study, Pasqualotto et al. evaluated the effects of antifungal therapy on SAFS (n1/422) and ABPA (n1/411). Patients receiving 6 months of itraconazole therapy had improved lung function, decreased serum total IgE and A. fumigates-specific IgE, and reduced blood eosinophils when compared to the pretreatment levels. There was also a reduction in both total oral corticosteroid dosage and courses of systemic corticosteroids. Three patients were switched to oral voriconazole due to adverse effects, low itraconazole levels, or clinical deterioration. Interestingly, the benefit of antifungal therapy was less profound after 12 months of treatment, but only 17 patients were evaluated for 12-month endpoints, making statistically significant differences difficult to show. The recently published randomized controlled effectiveness of voriconazole in the treatment of Aspergillus fumigatus–associated asthma (EVITA3) study sought to evaluate the effectiveness of voriconazole in the treatment of A. fumigatus-associated asthma [50&&]. Sixty-five patients with asthma who were IgE-sensitized to A. fumigatus and had a history of at least two severe asthma exacerbations in the prior 12 months were randomized to receive oral voriconazole 200mg twice daily or placebo for 3 months, followed by observation for 9 months. Patients were using an equivalent of 2000 mg of inhaled beclomethasone per day and about 30% were on maintenance oral prednisolone. Treatment with voriconazole did not result in a reduction in the number of severe exacerbations per patient per year compared with placebo. Additionally, no improvement in quality of life, measure by AQLQ, was seen. The negative results of this trial contrast the results seen in the FAST trial. Direct comparisons may be difficult as the duration of treatment was significantly shorter in the EVITA3 study compared to the FAST trial (12 vs. 32 weeks, respectively). It is also possible that compared to voriconazole, itraconazole may have a stronger effect on increasing corticosteroid levels or may have more potent immunosuppressive properties. Whereas early data have shown some promise, there is still insufficient evidence to support the routine use of triazole antifungals in the treatment of SAFS. This is reflected in recent European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines on severe asthma that do not recommend the use of antifungal agents in severe asthma without ABPA irrespective of sensitization to fungi. Additional investigation is warranted prior to routine clinical use of antifungal agents for SAFS.

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associated with fixed airflow obstruction and bronchiectasis when compared with nonsensitized asthmatic patients of the same severity and is considered to be clinically relevant in isolation, as well as a criterion for ABPA. The use of recombinant proteins of fungal extracts might offer a better correlation with markers of disease activity, although at present, only Asp F1-6 are commercially available. Differences in the geographical prevalence of fungal sensitization, the extent to which it is sought [as seen in the US severe asthma research programme (SARP)] and differences in asthma phenotypes may explain the low rates of fungal sensitization found in Europe (~10% in the European Network For Understanding Mechanisms Of Severe Asthma cohort) and the variable rates of *A. fumigatus* sensitization found between centres found in the UK-based British Thoracic Society severe asthma cohort. For a comprehensive fungal assessment, a panel for SPT and specific IgE consisting of *A. fumigatus, P. chrysogenum, C. albicans, Malassezia species, Trichophyton species, A. alternata* and *Cladosporium herbarum* should be undertaken.

Total Immunoglobulin E

Total IgE has been used extensively as a biomarker to define ABPA. A raised total IgE is almost invariably observed in AFAD and is reduced to a modest degree by oral steroids and possibly antifungal agents. However, there is little evidence that precise levels and repeated measurements relate sufficiently closely to be of value in assessing disease severity or activity. A high total IgE is a feature of atopic dermatitis due to sensitization to Malassezia spp. and other skin fungi which can confound the interpretation of total IgE in asthma.

Specific Immunoglobulin G

Current practice measures total A. fumigatus IgG rather than precipitating antibodies. This is relatively nonspecific and may represent increased environmental exposure or colonization. There is no evidence it provides additional information to specific IgE in the diagnosis of AFAD.

Blood and sputum eosinophil count

The peripheral blood eosinophil count is usually raised in fungal allergy, which is one of the commoner causes of hypereosinophilia. It is, however, nonspecific, with blood eosinophilia not correlating well with disease activity. A mixed Th2/Th1-17 immune response is suggested by lower values of sputum eosinophils in comparison to higher values of neutrophils found in people with

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refractory asthma who were sensitized to *A. fumigatus*, despite comparable blood eosinophilia. Thus, sputum eosinophil values do not seem of significance in AFAD.

Detection of fungi in airway secretions

Fungal colonization is thought to be the underlying event that leads to AFAD and thus fungal identification is a useful biomarker for its diagnosis.

Culture and quantitative PCR

There are no guidelines for processing respiratory samples for fungal detection. Methods using higher concentrations of sputa, and thus increasing the amount of clinical material available for culture, have higher rates of fungal growth than methods used by the UK National Health Service clinical laboratories, with lower rates from healthy individuals, suggesting good sensitivity and specificity. This technique has demonstrated a link between impaired lung function and higher culture rates for fungi in IgE-sensitized asthmatic patients, and shown increased fungal diversity, detecting 27 species of thermotolerant fungi. During a 12-month clinical trial of voriconazole in asthma, 80% of *A. fumigatus* IgEsensitized asthmatic patients had at least one positive fungal culture. However, fungal culture is not very quantitative. Quantitative PCR (qPCR) is an alternative means to detect Aspergillus spp. whichhas been used mainly for the diagnosis of invasive aspergillosis. It is very sensitive and potentially more quantitative compared with culture; however, assays are not available for all fungi that may be clinically relevant. The extent to which a positive qPCR relates to a clinically relevant outcome of AFAD has not yet been established.

Cell wall components

Galactomannan is a carbohydrate component of the cell wall of Aspergillus spp. and other fungi, and is used as a blood test to aid in the diagnosis of invasive fungal infection in neutropaenic individuals. Galactomannan assays of bronchial alveolar lavage samples and antibody-based Aspergillus assays both provide reasonable sensitivity and specificity for the diagnosis of invasive pulmonary aspergillosis; whereas culture has been found to be insensitive and a 1,3, beta-D-glucan assay nonspecific. There is little information on the value of these assays in AFAD.

Cytology and immunohistology

Fungal spores seen in sputum cytospins often represent contaminants. Fungal elements are rarely seen in bronchial biopsies; even in florid situations of fungal allergic responses, hyphae can be difficult to detect. Other approaches such as measurement of fungal toxins, enzymes or volatile organic compounds in exhaled air have potential as sensitive, specific and quantitative biomarkers for the presence of fungal growth in the lung, but for the moment, they remain in the realm of research.

Radiological abnormalities in allergic fungal airway disease.

A normal high-resolution computed tomography (HRCT) scan is unusual in AFAD and a wide range of radiological abnormalities exist (reviewed in [14&&]). No features are absolutely specific, however, high attenuation mucus has been suggested to be characteristic, central or proximal bronchiectasis was an original defining characteristic of ABPA and is a specific, albeit insensitive marker of AFAD. Upper lobe fibrosis is a feature which is often apparent on the chest X-ray and is commonly associated with severe fixed airflow obstruction. HRCT scanning has revealed that minor degrees of bronchiectasis are common in severe asthma and COPD. In two series, there was about a two-fold increase in the rate of bronchiectasis in patients with AFAD compared to asthmatic patients of matched severity without fungal sensitization. The extent to which the presence and pattern of bronchiectasis relates to the immunological criteria for AFADis not clear. Tree in bud shadowing and nodularity are under-appreciated, but are relatively common features of AFAD.

Conclusion

Fungi can cause lung disease either by acting as simple aeroallergens in IgE-sensitized individuals or by colonizing the lung, a property largely restricted to yeasts and Aspergillus and Penicillium spp., particularly A. fumigatus. Colonization with filamentous fungi is associated with a number of distinct patterns of airway disease, and the focus on trying to define ABPA, which represents the florid end of what is a spectrum of lung disease, has in our opinion outlived its usefulness. We recommend a more liberal definition of AFAD, based solely on the presence of IgE sensitization to fungi and evidence of fungal-related lung damage. Management of AFAD is similar to that of asthma without fungal sensitization and depends on the individual pattern of presentation. The emphasis should be on detecting and preventing long-term lung damage which is the most characteristic feature of AFAD. A priority for research is to standardize and improve the methods for detection of noninvasive fungal growth in the lung and to determine the natural history of AFAD to ascertain whether fungal colonization and sensitization are truly causal or a by-product of lung damage.

Acknowledgements

None.

Financial support and sponsorship

Research from our group quoted in this study was supported by Asthma UK, Pfizer, the Midlands Asthma and Allergy Research Association and the National Institute for Health Research Leicester Respiratory Biomedical Research Unit.

Conflicts of interest

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Ref: www.co-pulmonarymedicine.com. Vol. 21 No. 1 Jan 2015

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Editorial Note

Dear Doctor,

We are happy to present you the 1st issue of "Asthma Focus" Newsletter, 2015. In this issue we have concentrated 'allergic fungal airway disease: pathophysiologic and diagnostic considerations'. We hope you will enjoy reading the publication!

We appreciate your comments and queries.

Please participate in Quiz competition & win prizes.

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