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General overview of fungal allergic asthma

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Abstract:

Asthma is a complicated disorder, whose prevalence has increased over the past few decades. Asthma is characterized by infiltration of inflammatory leukocytes along with enhanced proinflammatory cytokines and chemokines. Fungi are now far more widely being considered as the dominant extrinsic trigger for asthma. Fungi are linked to the severity of asthma in many ways. Some differences between studies can be partly attributed to difficulties in the standardization of mould allergen extracts for skin-testing techniques. Allergy to fungi is associated with increased asthma symptoms and severity, increased asthma risk, and even death. These fungi are zoonosis; pet animals could be the main source of pathogenic fungi and infection and treatment of pets and periodic checking with a veterinarian could help avoid fungi-allergic asthma. Attention therefore needs to be paid to fungi infection in allergic reactions, especially in asthma.

Keywords: Asthma, fungi, allergic reactions.

Introduction

Allergic asthma is a multifaceted disorder, which over the past few decades has increased noticeably in prevalence. Cells involved in this pathway, mostly allergic asthma in genetically predisposed children or adults, are typically Th2- and eosinophil-dominant. Recently, some researchers showed that NK-T cells play a role in allergic asthma as well (Umetsu, 2010). However, some studies have also suggested that asthma in older patients may be under epigenetic control, may be exacerbated by viral and bacterial pathogens instead of allergens, and may involve Th1 cells and exhibit neutrophil dominance (Nakamura, 2005). Allergic asthma is characterized by the infiltration of inflammatory leukocytes including eosinophils with an enhanced lung expression of proinflammatory cytokines and chemokines, with a possible link to the activation of STAT6 (signal transducer and activator of transcription 6), where the STAT6 pathway plays an important role in inflammatory cytokines pathway and the beginning of allergic reactions. Furthermore, some previous studies have revealed that gastrointestinal tract colonization by *Candida* spp enhances allergic airway responses (Cowan, 2010: Platts-Mills et al., 2010). Allergic asthma is a genetic predisposition to produce immunoglobulin E antibodies from B cells as a reaction to everyday exposures that is associated with Th2 responses, characterized by increased levels of type-2 cytokines and increased levels of total and allergen-specific antibodies (Malerba et al., 2008; Wenzel et al., 2008).

Clinical symptoms of asthma are airway hyper-responsiveness, coughing, breath construction and wheezing. It represents an important public health problem, with more than 300 million affected individuals. Numerous environmental factors are involved in the initiation and continuation of asthma (Reed, 2010).

Thus, recognition of environmental triggers is fundamental in attempts to prevent allergic asthma. Fungal spores are also an important problem for asthmatic patients in buildings with damp (Becker, 2008). The role of fungal allergens as the primary extrinsic factor and a dominant factor in asthma severity has been incompletely explored. Fungi

can be linked to the severity of asthma such as through inhalation of fungal spores, fungal sensitization or causation of allergic bronchopulmonary mycosis and respiratory system damage (Bateman et al., 2008; O'Driscoll, 2005). Some studies have shown that exposure to environmental fungi increased the risk of death from asthma. However, fungal sensitization seems to be more prevalent in populations of patients with severe asthma. In older adults, asthma mortality and hospital admissions are more common during the winter, and in younger adult population in periods of high ambient allergen load: [the cause of] asthma in younger adults is usually allergic and in older adults is usually non-allergic' (Denning, 2006).

Up to age 13, in children allergic bronchopulmonary aspergillosis is very rare. In allergic asthma dendritic cells orchestrate a Th2 response and eosinophils, which play a main role in relation to allergens (Targonski, 1995; Fahy et al., 1993).

There are three distinct forms of exposure to fungal allergens which have been associated with severe asthma: 1. Fungal colonization of the lungs has been related to immediate hypersensitivity to the relevant fungus. 2. Inhalation of fungal allergens or hyphae acting in the same way as other inhaled allergens. 3. Fungal infection outside the respiratory tract again associated with immediate hypersensitivity (Maurya et al., 2005; Dales et al., 2003).

Here, we intend to review the diversity of fungi affecting asthma and the role of fungal infections in exacerbation of asthma.

Inhalation of fungal allergens

Aspergillus and *Malassezia* spp: The fungal spores are between 2-20 μm in diameter and particles less than 5 μm in diameter; these descend into the lower respiratory airways and lead to allergic asthma symptoms. Therefore, fungal spores are the main allergen in asthmatic patients. Storm asthma was correlated to a two-fold increase in the number of fungal spores in the air (Fairs et al., 2010; Agarwal et al., 2009).

Allergic bronchopulmonary aspergillosis is the main fungal problem in allergic asthma (Agarwal et al., 2010).

The classical forms of allergic bronchopulmonary mycosis include: increased severity of asthma, transient infiltrates in the lungs, large amount of sputum production, increased total IgE, immediate hypersensitivity reactions to *Aspergillus* spp, and eosinophilia (Agarwal et al., 2011; Khosravi et al., 2007). Thioredoxin is an allergenic protein from the mould *Aspergillus fumigatus*, the aetiologic agent identified in the majority of *Aspergillus*-related asthma, and from *Malassezia sympodialis*, a skin-colonizing yeast involved in the pathophysiology of asthma and atopic eczema. Spores of *Malassezia* could be a trigger of asthma in atopic people (Limacher et al., 2007).

***Alternaria, Cladosporium, Penicillium* and *Aspergillus* spp:** *Alternaria* spp has a major role in the establishment of allergic asthma. Occasionally other inhaled fungi such as *Cladosporium* spp or *Penicillium* spp appear to play an important role in severe allergic asthma (Kilic et al., 2010).

Alternaria and *Cladosporium* spp spores are the most common airborne particles of fungal origin. Their threshold concentration in the air for creation of allergic symptoms has been estimated to be 100 and 3,000 spores/m3, respectively. *Alternaria* spp is the most important fungal species belonging to the class Deuteromycetes that causes allergic respiratory diseases (Bush, 2004).

The unique and potent Th2 adjuvant, identified for *Alternaria* spp, which is partially mediated through dendritic cells, may explain the strong association between *Alternaria* spp and allergic asthma. *Alternaria*-induced Th2 development in the airways in vivo may be due to the synergistic effects of *Alternaria* spp on dendritic cells and on other airway cells, including eosinophils, Mast cells, and NKT cells (Gioulekas, 2004).

In atopic patients, *Alternaria* spp spores can decrease respiratory functions and development of allergic asthma symptoms. The presence, persistence and severity of asthma have been

strongly associated with sensitization and exposure to *Alternaria* spp (Knutsen et al., 2010).

It has been suggested that fungal exposure may promote adjuvant effects on allergic immune responses. Fungal proteases may also interact directly with airway epithelium. Recent studies showed that proteases present in *Alternaria* spp extracts induced morphological changes, cell desquamation, and production of proinflammatory cytokines and chemokines and active Th2 pathway (Niedoszytko et al., 2002; Sakiyan, 2003).

Inhalant fungal allergens induce the development of allergic asthma indoors and outdoors. Significant fungi responsible for allergic asthma are *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus* spp. Environmental fungi are particularly important allergens and could have a serious effect on health (Proesmans et al., 2010).

Sensitivity tests to *Alternaria* and *Cladosporium* spp and implications of these allergies for respiratory illness have not been well characterized. There is evidence of a specific relation with airway responsiveness in children sensitized to *Cladosporium* spp. Association between *Alternaria* spp spore concentrations and airway responsiveness can be attributed to fungal exposure. The frequency of sensitization to *Alternaria* or *Cladosporium* spp, or both, was a strong risk factor for severe asthma in adults (Mitakakis, 2001; Knutsen, 2011).

Patients with Aspergillosis had more frequent nocturnal symptoms and poorer lung function. Other fungi, like *Cladosporium* spp, *Epicoccum* spp, *Helminthosporium* spp and others have also been implicated in severe asthma, recurrent hospital admissions and ICU admissions. Studies have demonstrated that *Aureobasidium* spp, *Helminthosporium* spp and *Trichophyton* spp sensitivity does not mean sensitivity to other fungi, and is associated with asthma severity and hospitalizations (Patterson, 2000).

Dermatophytes: There have been many reports on the association between *Trichophyton* spp sensitivity and asthma; studies have also shown a connection between higher titers of IgE antibodies and *Trichophyton* spp and severity of asthma. This can be compared to the better-known case of dermatophyte infection in severe asthma (Denning et al., 2009; Zureik et al., 2002).

Saccharomyces cerevisiae: Zymosan, a cell wall formation and a mixture of beta-glucan and mannan residues from the fungus Saccharomyces cerevisiae, is known to induce the production of proinflammatory cytokines and chemokines that attract inflammatory cells. Beta-glucan has various biological activities, such as production of inflammatory mediators including leukotrienes and tumour necrosis factor-alfa. Therefore, this fungus could be the main allergen in asthmatic patients (Savolainen, 1995).

***Candida* spp:** *Candida albicans*, commensal yeast, is the most common opportunistic fungal pathogen, which causes a disseminated systemic infection in immunocompromised hosts. *Candida* spp has been been examined as a possible allergen in allergic asthma (Gumowski et al., 1987).

Candida spp may induce allergic airway inflammation, and activate Th2 (IL-13) dominant response and enhanced phosphorylation of STAT6 (signal transducer and activator of transcription 6), one of the pivotal transcriptional factors in the Th2 microenvironment in lung, beginning an allergic reaction that leads to asthma (Inoue et al., 2009).

***Fusarium* spp:** Airborne spores of the *Fusarium* species are also widely dispersed and common in many environments. They cause systemic infections in immunocompromised hosts. *Fusarium* species play the most important role in IgE-mediated allergic reactions in patients with asthma, and are important in atopic patients (Noverr et al., 2004).

Discussion

Asthma is a major problem in public health and common in industrialized and developed countries; over the past two decades, its prevalence, severity, and incidence have been increasing. Allergic asthma responses are mediated by CD4+ T cells polarized to a Th2 cell phenotype. Type-2 cytokines, such as IL-4, IL-5

and IL-13, derive the pathological features of asthma, with airway hyper-responsiveness and eosinophilia, elevated IgE, excessive production of mucus, and airway remodelling. The immunopathogenesis of allergic asthma is complex and multifactorial. Allergic inflammation of the bronchial airways highlights the pathogenesis. Many genetic risk factors including inflammatory pathways, with polymorphisms of IL-4, IL-10, IL-13, and CD14, have been described but are not present in the majority of patients. CD86+ B cells are the subpopulation of B cells that secrete IgE, which correlates with the increased total IgE seen in patients with severe fungal asthma (Athari, 2013a).

Asthma may represent exaggerated immune responses to chitin-containing fungi. Aetiology of human asthma is complex and multifactorial, and it likely involves interactions between genetic factors and environmental stimuli (Chupp et al., 2007).

Because allergic disorders are dependent on environmental and genetic factors, immune responses to allergens may be independent of population and race. Therefore, standardization of fungal extracts is imperative to improve the diagnosis of fungal sensitization in atopic patients (Kiliç et al., 2011).

Fungal spores are the main respiratory allergens. However, the role of fungi in the development of asthma has not yet been fully investigated. Lung fungal infection has been associated with an increased risk of respiratory arrest in asthmatic patients and fungi can occasionally cause allergic asthma (Athari, 2013b).

Exposure to environmental fungal spores has been associated with worsening asthma symptoms, hospital admissions and asthma related with deaths. Establishing whether severe asthma is actually caused by fungal sensitization, and demonstration of effectiveness of antifungal therapy for asthma could also implicate fungal exposure in the pathogenesis of asthma (Athari, 2013c).

However, the diagnosis of asthma tends to be made on a history of recurrent or episodic attacks of chest tightness, breathlessness and cough with documented wheeze on auscultation of the chest and obstructive defect on spirometry. In immunological attention, asthma is characterized by pulmonary infiltrates, eosinophilia, increased levels of total IgE, and increased levels of anti-fungal specific IgE, IgG and IgA antibody levels. Treatment of patients with fungal asthma with antifungals results in improved situation in these patients, decreased IgE levels, and increased peak flow. The current medication regimen of inhaled corticosteroids, leukotriene antagonists, and long-acting beta-2 agonists is usually inadequate to control severe asthma (Athari, 2013d).

Fungi proteases (for example in *Alternaria* and *Cladosporium* spp) had a direct effect on the bronchial epithelia causing pro-inflammatory cytokine synthesis and desquamation similar to *Aspergillus* proteases; however, *Aspergillus* proteases were more potent in initiation of immune response and triggering of allergic reaction (Platts-Mills, 2009). Thus, more attention needs to be paid to other pathologic factors of fungi. Sometimes fungi products are more important than the fungi themselves, especially when these products are the main allergens causing asthma.

Conclusions

Allergy is a major feature of asthma presenting to the hospital; in particular, it is a dominant feature of exercise-induced bronchospasm, which can be severe. Allergy to fungi is associated with increased asthma symptoms and severity, increased asthma admissions and even death.

Recent data suggest strongly that the titer of IgE antibodies is relevant to severe allergic asthma and that specific antibodies against fungi are important in diagnosis of fungi-allergic asthma. Strong and specific attention needs to be given to fungal allergens in asthmatic patients and could prevent hospitalization and deaths.

Because fungi are present in air and are indoor and outdoor allergens, prevention of allergic reactions to fungi and spores is difficult. In houses

with atopic people, reduction of heat and moisture to prevent growth of spores is important. Domestic animals could act as allergy inducers. The best and most effective management of a domestic animal allergy is to avoid contact with the relevant pet. Some preventive steps, especially at home, may help to control growth of moulds. Specific immunotherapy may be indicated for both household pets and fungal (mould) allergies in certain circumstances. Clinical relevance, however, needs to be demonstrated by accurate allergological assessment.

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