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Severe asthma with fungal sensitization

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Abstract

Bronchial asthma is an inflammatory disease of the airways, which may be worsened due to many extrinsic factors. The most common trigger is the continuous exposure to allergens, of which fungal agents are important factors. A new phenotype of asthma called severe asthma with fungal sensitization (SAFS) has been described. It is diagnosed by the presence of severe asthma, fungal sensitization, and absence of allergic bronchopulmonary aspergillosis. SAFS is more of a diagnosis of exclusion. Treatment of SAFS initially should be similar to that of severe asthma including humanized anti-IgE monoclonal antibody and other biologics. These patients usually do not have their symptoms relieved with conventional treatment of severe asthma, i.e. high-dose inhaled corticosteroids and long-acting bronchodilators. Prolonged use of oral corticosteroids and pulse high-dose intravenous corticosteroid is effective. There are some evidence implicating the role of antifungal agents including itraconazole, but its use as a specific therapy requires further studies.

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Full Text

Introduction

Asthma is a heterogenous disease usually characterized by chronic airway inflammation and is defined by the history of respiratory symptoms such as chest tightness, shortness of breath, cough and wheeze that varies over time, and intensity together with variable airflow limitation.[1] It is a serious public health problem affecting people of all ages throughout the world. Asthma can lead to severe limitation of activities in daily life and can even be fatal. Severe asthma is defined as asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite adequate therapy.[2] It is estimated that 5%–10% of asthmatics have poorly controlled disease.[3] One-third to one-half of these severe asthmatics have atopic

sensitization to filamentous fungi, especially to *Aspergillus fumigatus*. There are enough evidence that fungal sensitization is associated with more severe asthma phenotypes. Thus, an important subgroup of asthma termed as severe asthma with fungal sensitization (SAFS) has emerged. SAFS mimics allergic bronchopulmonary aspergillosis (ABPA). SAFS and ABPA can be hypothesized as different states of fungal sensitization, which differs in terms of immune response with asthma at one end of the spectrum and ABPA at the other. The term SAFS was introduced in 2006 and is defined as the presence of immediate cutaneous hyperreactivity to fungal antigen or increase in specific IgE antibodies to a particular fungus. Fungal sensitization may or may not be associated with severe asthma. The present study aims to review the current understanding of pathogenesis, diagnosis, and treatment of SAFS.

Fungi and Severe Asthma

Worsening asthma control with inhalation of fungal spores is similar as a foreign particle is being inhaled into the lung. Fungi interact directly with the human host in many ways. Many fungi have been associated with SAFS. The first evidence of the link between fungal sensitization and asthma was published in 1978, when *Aspergillus* sensitization was found to be involved in the severity of airway obstruction in 193 asthmatics.[4] Relation between *Alternaria* species sensitivity and increased risk of respiratory disease was shown in 11 asthmatics.[5] Subsequently, a correlation between sensitization to various fungi (e.g. *Alternaria*, *Aspergillus*, *Aureobasidium*, *Cladosporium*, *Helminthosporium*, and *Trichophyton* species) and severe asthma has been noticed.[6],[7],[8],[9],[10],[11],[12],[13],[14],[15] The Respiratory Health Survey in European Community was conducted, which showed that asthma severity was associated with *Alternaria* or *Cladosporium* species sensitivity in 1132 adult asthmatics.[16] It is a matter of inquisitiveness that whether all the fungi really cause SAFS or it is just a random association, as most of these fungi are rarely capable of growing in the human host to cause infection in the lung. The fungi have to grow at body temperature and this property is restricted to narrow range of fungi, particularly yeasts and member of *Aspergillus* and *Penicillium*. Only *Aspergillus* species can grow at 37°C. Small fungal spores of the mold *A. fumigatus*, which is abundant in environment, can easily reach the lower airways and alveoli through inhalation. Only with *A. fumigatus*, two extreme types of immune phenomenon, the *Aspergillus*-sensitized asthma and ABPA, are reported.[17],[18],[19],[20]

Prevalence of SAFS

The prevalence of SAFS remains highly variable because it is a newly described entity. The World Health Organization estimated worldwide asthma prevalence to be roughly around 339 million cases with the possibility of up to 33.9 million of these falling into the SAFS category. Many studies have evaluated the prevalence of *Aspergillus* sensitization in bronchial asthma,[21] which can be used to determine the prevalence of SAFS. In a systematic review and meta-analysis of 20 observational studies that included more than 5000 asthmatics, it was demonstrated the prevalence of *Aspergillus* sensitization in bronchial asthma to be ranging from 15% to 48%, with a pooled prevalence of 28%.[22] Similar frequency of *Aspergillus* sensitization has been documented even in other studies.[12],[14] In a study conducted by Prasad et al., the prevalence of *Aspergillus* sensitization was found out to be 30.3% in 244 patients of bronchial asthma.[23]

Pathogenesis of SAFS

The mechanism by which fungal allergens induce the hypersensitivity reaction is still an area of research. Fungal allergens are implicated in severe asthma compared with other aeroallergens because many allergens cause only a limited airway inflammation on inhalation.[24],[25] However, fungi such as *Aspergillus* species can elicit a profound immune response even without prior exposure.[26] Fungal spores are ubiquitous in the environment and, thus, gain access to the respiratory tract via the inhalational route. SAFS is proposed as the occurrence of fungal sensitization with no and/or low levels of colonization. ABPA occurs in asthmatics who are genetically predisposed[27] and SAFS being closely related to ABPA has the same genetic predisposition. The polymorphic major histocompatibility complex Class II molecules on antigen-presenting cells plays an important role in restricting antigen-specific T-cell activation. Fungi are known to produce a wide range of allergens that can be broadly classified into cell wall components such as β (1 $\rightarrow$ 3)-glucans, secreted products such as proteinases and glycosidases, and enzymes.[28] Of these, the proteinases are presumed to be the most important agents. It may well be hypothesized that SAFS occurs due to an immune response against larger amounts of fungal proteinases. The antigens are further processed by the antigen-presenting cells and presented to T cells, which are then in turn activated. This immune-mediated inflammatory response leads to airway inflammation and worsening asthma control.

Diagnosis of SAFS

Fungal sensitization is defined as the presence of immediate cutaneous hyperreactivity to fungal antigen(s) or an increase in specific IgE antibodies to a particular fungus. Skin tests employ crude antigens and thus are more sensitive but less specific than fungus-specific serum IgE tests to diagnose fungal sensitization. Studies have compared skin testing with specific IgE levels, with conflicting results. The specific IgE levels were found to be better than skin prick test (SPT), which is in contrast to the findings of another study in which intradermal skin testing was superior to the measurement of specific IgE levels.[29],[30] Although theoretically both intradermal tests and SPT should perform in an identical manner, intradermal tests generally have been found to be more sensitive than SPT.[31] SAFS is currently more of a diagnosis of exclusion. Criteria for the diagnosis of severe asthma with fungal sensitivity (SAFS) include history of poorly controlled asthma with the use of >500 µg/day of fluticasone or the equivalent, near continuous oral corticosteroids (OCS) use for >6 months, or >2 oral steroid tapers per year, total serum IgE <1000 IU/mL, positive immediate skin test reactivity to *A. fumigatus* or elevated specific serum IgE to *A. fumigatus*, absence of serum precipitins by gel diffusion or elevated specific serum IgG to *A. fumigatus*, and no radiographic evidence of bronchiectasis or infiltrates.[2]

Treatment of SAFS

The important clinical question is whether patients with SAFS should be managed differently from other patients with severe asthma without fungal sensitization. The initial management of asthma with fungal sensitization should be on the same basis as those without fungal sensitization. The combination of long-acting beta-2 agonist (LABA) and ICS delivered using the SMART approach achieves better control of asthma than a high dose of ICS or ICS-LABA combination in poorly controlled asthmatics.[32] Additional controller medications such as theophylline and leukotriene receptor antagonists should be added routinely. Omalizumab and itraconazole should be considered when the response is partial or lacking.

Anti-IgE

Omalizumab is a monoclonal antibody to IgE that prevents allergen-induced IgE-mediated signaling of the classic allergic inflammatory cascade. In a study where 205 patients who received omalizumab were analyzed to see change in 5-item Asthma Control Questionnaire (ACQ-5) score, the exacerbation frequency, and OCS dosage over a 24 month period revealed that omalizumab is an effective therapy in SAFS, leading to sustained improvements in symptoms and exacerbations.[33]

Corticosteroids

A conventional high-dose ICS is insufficient to control SAFS. ICS useful for asthma management in patients with SAFS do not control the pathophysiology or clinical manifestations of SAFS.[34],[35],[36],[37],[38] Use of chronic recurrent OCS carries a troublesome toxicity profile. Pulse steroid therapy 10–20 mg/kg/day, i.v. methylprednisolone infused on three consecutive days every 3–4 weeks have been found to be safe and effective in two open-labelled series of 13 steroid-dependent ABPA patients selected for this treatment because they were either not well controlled or had severe corticosteroid side effects on conventional oral prednisone treatment. Pulse i.v. steroid therapy was well tolerated, with disease control allowing discontinuation of pulse therapy after 6–12 months.[39],[40]

Antifungal therapy

The alternatives to long-term oral steroids are the use of antifungal agents as a primary treatment of SAFS. Antifungal treatment of SAFS rests upon an assumption that allergic inflammatory responses arise in part from noninvasive airway fungal infection. Antifungal therapy for SAFS has been directed against the main fungal pathogen, *A. fumigatus*. Pacheco et al. showed that itraconazole reduced specific IgG titers in patients.[41] Germaud and Tuchsais showed effectiveness of itraconazole in 11 out of 12 treated patients, including prevention of exacerbations in six patients who were successfully weaned off oral steroids.[42] An antifungal agent, itraconazole, has also been used in SAFS in Fungal Asthma Sensitization Trial study.[43] It was a randomized, placebo-controlled investigation assessing the effects of itraconazole, 200 mg twice daily till 8 months. The primary endpoint was change in the Asthma Quality of Life Questionnaire (AQLQ) score. The secondary endpoints were rhinitis score, decline in total IgE levels, and pulmonary function. The study enrolled 58 patients, only 41 of whom completed 32 weeks of therapy. At the end of 32 weeks, there was an improvement in the AQLQ. Modest degrees of improvement were also noted in the secondary endpoints. The apparent benefit of itraconazole is also confounded by the fact that itraconazole can increase the levels of certain inhaled steroids, thereby potentiating the effect of steroids.[44],[45],[46]

However, the optimal dose and therapy of antifungal remains unknown. Finally, azoles themselves have direct and profound immunologic effects.[47],[48],[49],[50],[51],[52],[53] Hence, it is not definite that was it the antifungal action of azoles or the anti-inflammatory property of the drug that led to improvement in patients with SAFS. Newer oral triazoles with excellent anti-*Aspergillus* activity have also been reported as beneficial in the treatment of SAFS. Voriconazole has the advantage of excellent oral bioavailability. Amphotericin deoxycholate has been frequently used via inhalational route in the treatment of pulmonary fungal infection, primarily in the setting of cancer treatment and lung transplantation. There have been no published reports of inhaled amphotericin use in SAFS. The role of itraconazole and other antifungal agents in the treatment of SAFS requires further studies.

Conclusion

Fungal sensitization has been associated with increased asthma severity and mortality.

A variety of fungi are related to SAFS; however, this association has been more extensively studied for *Aspergillus* species. Diagnosis of SAFS should carefully be made as there is a significant overlap with ABPA, especially ABPA-S. Patients with SAFS should be initially managed on a similar line as those with severe asthma. Corticosteroids remain the validated mainstay pharmacological treatment in SAFS. The role of itraconazole and other antifungal agents in the treatment of SAFS requires further study. Further studies are required to define the exact place of SAFS as a separate subtype of asthma.

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Conflicts of interest

There are no conflicts of interest.

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