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Molds as a cause of asthma and exacerbations

Abstract

Molds are often found in patients with pre-existing asthma, when they can be the cause of worsening asthma and even death. However, they can also represent a risk factor for the development of asthma in a previously healthy person. The most allergenic molds causing respiratory diseases are: *Aspergillus, Alternaria, Penicillium* and *Cladosporium* with an emphasis on *Aspergillus* in patients with asthma. In order to be inhaled their spores must be ≤5 µm in size. Germination of inhaled mold spores in the lungs is related to Th2 and Th17 pathways, as well as activation of the innate immune system, but also could promote sensitization to allergens of other mushrooms, as well as allergy to pollens and dust mites. Sensitization rates in asthma patients range from 5-50% of patients. Molds can act as internal or external sources of respiratory allergens depending on the climatic conditions. The diagnosis of fungal allergy is complicated by the fact that patients with mold allergy are often polysensitized to pollen as well. Therefore, a good allergic anamnesis and clinical picture play a key role. Regarding diagnostic procedures, the most important are serum fungal-specific IgE or precipitins, total IgE, IgG against suspected fungus, peripheral blood eosinophils and fungal-specific skin prick tests. The role of antifungal therapy in severe asthma remains unclear. Further research is needed to better define the potential utility of antifungal drugs in patients with asthma and mold sensitization or allergy to identify drugs and populations of patients who would benefit from such treatment. There is also insufficient evidence for the safety and efficacy of allergen immunotherapy in mold-sensitive patients. About 70% of patients with severe eosinophilic asthma with sensitization or allergy to *Aspergillus* and *Penicillium* could benefit with Mepolizumab therapy. On the other side, measures to avoid mold still remain key factor in therapy.

Keywords: molds, sensitization, allergy, asthma, diagnostic, therapy

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Abbreviations: IL, interleukin; TNF-α, tumour necrosis factor alpha; SAFS, severe asthma with fungal sensitization; ABPA, allergic bronchopulmonary aspergillosis; AFAD, allergic fungal airway disease; ABPA-S, serological allergic bronchopulmonary aspergillosis; ABPA-B, bronchopulmonary aspergillosis with bronchiectasis; Ig, immunoglobulin; sIg, specific immunoglobulin; AF, Aspergillus fumigatus; PCR, polymerase chain reaction; HRCT, high-resolution computed tomography; PEF, peak expiratory flow; FEV1, forced expiratory flow in the first second; GINA, Global Initiative for Asthma; SIT, specific immunotherapy; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy, AIT, allergen immunotherapy; SGRQ, St George's respiratory questionnaire score; ACQ-5, asthma control questionnaire; MCID, minimum clinically important difference

Introduction

Molds are only one of the structures of certain fungi, as not all fungi create molds. On the other hand, over 100.000 taxonomically different types of mold have been recognized. The most common genera are: *Aspergillus, Alternaria, Penicillium, Cladosporium, Mucor, Acremonium, Fusarium, Rhizopus, Stachybortys, Trichoderma, Tricgophyton* and *Candida*. The most allergenic in causing of respiratory diseases are: *Aspergillus, Alternaria, Penicillium* and *Cladosporium*, and the most common isolated mold in patients with asthma is *Aspergillus fumigatus*.[1]

Immunology and pathobiology in asthma

In order to be inhaled and consequently cause an allergic reaction in the respiratory system, their spores must be ≤5 µm in size.[2]

The mechanism involves germination of inhaled mold spores in the lungs, leading to IgE sensitization and eosinophilic inflammation with release of IL-4, IL-5, IL-13, IL-33 and TNF-α (Th2 pathway) with release of mold proteases, but also activation of Th17 pathway. Interestingly, molds could also activate the innate immune system and could increase inflammation caused by other allergens (eg grass pollen). It is important to note that molds can act both as internal (living and working spaces) and as external allergens (time of storms, harvests, ...) allergens.[3]

The association of mold with asthma and asthma exacerbations

16 studies (11 cohort and 5 incident case-control studies) showed that dampness, visible mold, and even odor in the home are determinants of developing asthma.[4] In addition to that molds represent a risk factor for development of asthma.[5] They are also represent a risk factor for asthma exacerbations,[4] multiple hospital admissions and even death.[6]

Rates of mold sensitization in patients with asthma range from 5-20%,[4] and up to 50% in severe asthma.[7] However, a minority of these patients develop a true allergic reaction.[4]

Acute exacerbations of asthma to external mold allergens depend on polysensitization, time of year and atmospheric conditions

The highest number of acute exacerbations of asthma in patients polysensitized to fungi and pollen is in the period of extreme weather conditions (high temperature, high air humidity and high atmospheric pressure) and maximum pollination of the responsible pollen. In monosensitized patients to mold, they are positively correlated with relative humidity, atmospheric pressure and temperature.[7,8]

Fungal lung disease represents a heterogeneous group of conditions

Allergy to mold's colonization of the airways leads to a marked eosinophilic endotype of severe lung disease. Numerous entities are

recognized: severe asthma with fungal sensitization (SAFS), allergic bronchopulmonary aspergillosis (ABPA), allergic fungal airway disease (AFAD), as well as other terms.[3]

Diagnosis of sensitization and allergy

The diagnosis of mold allergy is complicated by the fact that patients with mold allergy are most often polysensitized to pollen as well. Therefore, a good allergological history and clinical picture (eg nasal polyposis, immunocompromise, ...) play a key role.[5]

If suspected on indoor allergens, it is advisable to visit the patient's living or working area and take mold samples. On the other hand, if external allergens are suspected, the daily concentration of molds in the air should be monitored through local meteorological stations (if such data are available), and the results are correlated with the clinical picture.

Regarding the diagnostic procedure, the most important are: 1. fungal-specific IgE (sIgE) and/or serum precipitins (high levels best describe mold sensitivity; although sIgE levels <0.35 IU/L may be relevant for AFAD), 2 total IgE (for fungal IgE-sensitized asthma: 500-1000 IU/L: for SAFS>1000 IU/L), 3. IgG against suspected mold, 4. peripheral blood eosinophils (usually <500 cells/μL), and 4. mold-specific skin prick tests (SPT) (a cutoff ≥3 mm than the diluent).[3,5,8]

In addition, it is possible to perform, according to the individual approach to the patient, a swab of the throat and nose, and in unclear situations, bronchoalveolar lavage (culture or PCR), then spirometry (most often fixed airflow obstruction in non-smokers, which occurs in late middle age in severe asthma with mold's sensitization, and if necessary, X-ray and/or high-resolution computed tomography of the chest.[9]

Algorithmic approach to the diagnosis of various manifestations of fungal asthma

(Figure 1).

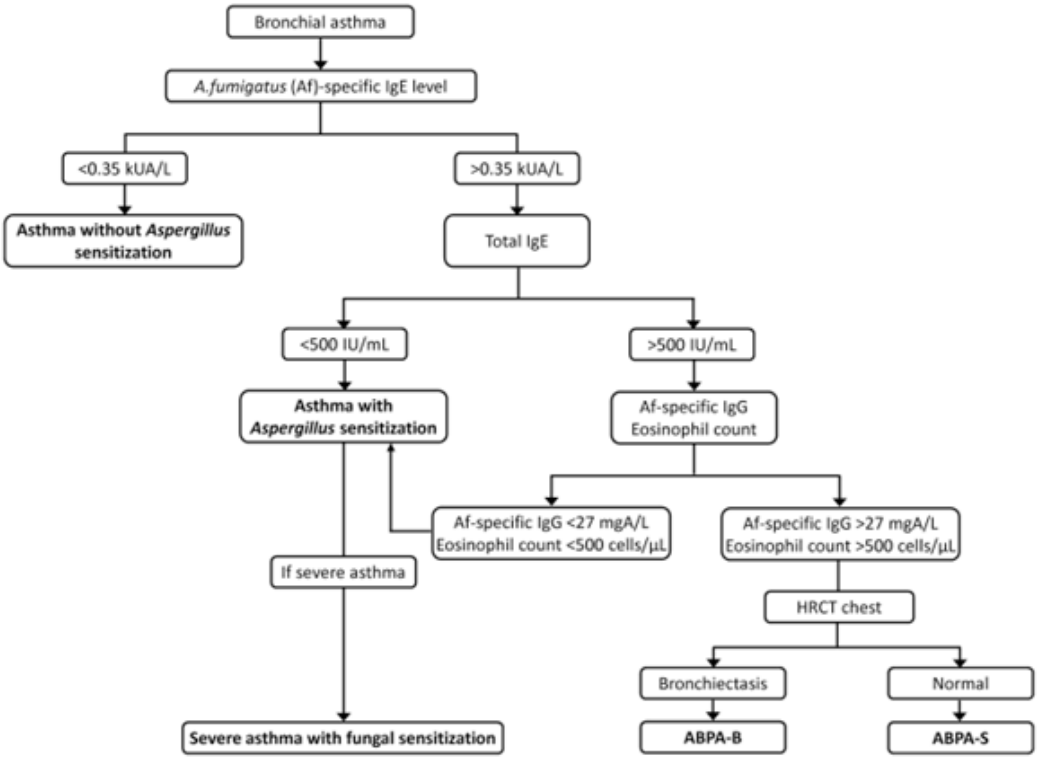

Figure 1 Algorithmic approach to the diagnosis of various manifestations of fungal asthma.

ABPA-S, serological allergic bronchopulmonary aspergillosis; ABPA-B: bronchopulmonary aspergillosis with bronchiectasis.

The *Aspergillus fumigatus* IgE and IgG are assayed using the fluorescent enzyme immunoassay method (Phadia). In patients with bronchopulmonary mycossi, the specific IgE and IgG against the fungus in question (e.g., *Aspergillus flavus*) is used, instead of *Aspergillus fumigatus*.

Source: *Agarwal R, Sehgal IS, Dhooria S, et al.* Challenging cases in fungal asthma. *Med Mycol. 2019*;57(2):S110–S117.[9]

Therapy

Antifungal therapy, immunotherapy and therapy with biological drugs could be possible,[8,10] but still not recommended for rutine use.[11] However, avoiding mold and removing it from the living or working space still remains the key of therapy.[8,12,13]

Antifungal therapy

In SAFS, up to 50% of adult patients with asthma, the severity of asthma can be reduced with antifungal therapy (Fluconazole, Itraconazole, Voriconazole, Posaconazole, Amphotericin B) in 30-60% of patients.[8]

Randomized control study of patients with SAFS sensitized to at least one of 7 molds (*Aspergillus fumigatus, Cladosporium herbarum, Penicillium chrysogenum (notatum), Candida albicans, Trichophyton mentagrophytes, Alternaria pricinerea, Alternaria alternata*), who had previously undergone SPT or specific IgE was performed on 58 patients. They were treated with Itraconazole (200 mg twice daily) or placebo for 32 weeks, with follow-up every 16 weeks. The results

showed that about 60% of SAFS patients treated with Itraconazole had a significant improvement in quality of life, a decrease in IgE and a moderate improvement in morning peak expiratory flow (PEF), but forced expiratory flow in the first second (FEV1) did not improve.[10]

Case presentation

A 54-year-old woman, on immunosuppressive therapy due to a kidney transplant, and with a diagnosis of asthma for the last 20 years, treated with Budesonide + Formoterol (800+24 µg/day) + Montelukast 10 mg/day, complains of hemoptysis for the past 3 weeks.

Chest X-ray was normal. Chest CT showed mucosal plaques. Sputum culture for bacteria, fungi and tuberculosis remained sterile. Analysis of the bronchoscopic aspirate showed acute inflammation with numerous eosinophils. Anti-neutrophil cytoplasmic antibodies and *Aspergillus fumigatus* (AF) SPT were negative. However, other parameters were elevated, namely: AF specific IgE (sIgE): 1.75 kUA/l, total IgE: 403 IU/ml, AF sIgG: 22 mgA/l and peripheral blood eosinophil count: 280 cells/µl. A diagnosis of asthma with AF (severe form, due to hemoptysis) was made. Itraconazole 400 mg/day per os was prescribed for 4 months. The results were satisfactory. Namely, AF sIgE decreased over time (1.34 to 0.2 kUA/l), and hemoptysis stopped already after 1 week. After 4 weeks, the patient felt completely fine.

Limitations of antifungal therapy

Despite encouraging findings that antifungal therapy can improve asthma symptoms in patients with mold's allergy, stabilize lung function, reduce inhaled and systemic corticosteroid requirements, and alter serum biomarkers, overall data from the literature are limited. Namely, the appropriate selection of patients, as well as the choice of the optimal drug, its dosage, and the regimen and duration of therapy, are poorly defined. Therefore, the role of antifungal therapy in severe asthma with mold's sensitization or allergy remains unclear. Further researchs are needed to better define the potential utility of antifungal drugs and to identify patient's populations that would benefit from such treatment.[12]

Immunotherapy against mold allergens

Immunotherapy against mold's allergens is still not recommended for routine use due to inconsistency of study results, which may be due to the rapid genetic variability of molds, but also the standardization of allergen doses, and possibly other reasons.[13]

One study showed that in patients with asthma sensitized to *Alternaria*, specific immunotherapy (SIT) had resulted in improvement of the bronchial response to methacholine, the level of specific IgE, as well as the number of eosinophils in sputum.[14] Another study documented that three years long of sublingual immunotherapy (SLIT) had resulted in reduced use of inhaled β2 agonists, as well as inhaled and oral corticosteroids.[15] Furthermore, subcutaneous immunotherapy (SCIT) of recombinant antigen Alt a 1 in asthmatic mice sensitized to *Alternaria* could alleviate the progression of asthma, but also have a regulatory effect on Tfh and Breg cells.[16]

On the other hand, 9 randomized allergen immunotherapy trials (AIT) comparing AIT with placebo (168 children and 99 adults) showed evidence of low power in the therapeutic effect of mold's (*Alternaria* and *Cladosporium*)-induced respiratory allergies.[17]

Therefore, the 2022 GINA states that there is still insufficient evidence for the safety and efficacy of immunotherapy in mold-susceptible patients.[13]

Mepolizubam and fungal sensitization – a review of the MENSA study

MENSA is a double-blind, phase III trial (GSK ID: 115588; NCT01691521), that was done on 576 patients with severe eosinophilic asthma. Patients were randomized (1:1:1) to receive mepolizumab 75 mg intravenously or 100 mg subcutaneously, or placebo, every 4 weeks for 32 weeks plus standard of care. All treatment groups were pooled and patients were stratified into subgroups based on their sensitization to fungal and/or perennial/seasonal allergens for the analysis of baseline characteristics and all end-points. Patients were also stratified for selected end-points based on their fungal allergen combined specific immunoglobulin Ig-E level percentile (0-≤50th, >50th-≤75th, 75-≤90th or >90th percentile) and IgE-sensitivity to *Aspergillus fumigatus* and/or *Penicillium chrysogenum* (selected because these thermotolerant filamentous fungi are known to colonize the airways and are associated with lung damage in severe asthma), 5 other fungal or no fungal sensitization. Allergen sensitization was defined as serum IgE level ≥0.35 kU/L. End-points assessed included the prevalence of fungal and/or perennial/seasonal allergen sensitization and response to mepolizumab at Week 32.

Mepolizumab response was determined according to the annual rate of clinically significant exacerbations, change from baseline in pre-bronchodilator forced expiratory volume in 1 second (FEV1), St George's Respiratory Questionnaire (SGRQ) score, Asthma Control Questionnaire (ACQ-5) score and change from baseline in blood eosinophil count. Changes from baseline in eosinophil granule proteins were assessed in patients receiving mepolizumab 100 mg subcutaneously or placebo.

61% of patients were sensitized to allergens (fungal: 33%, perennial: 46%, or seasonal: 29%). The most common fungal allergens associated with sensitization were *Candida albicans, Aspergillus fumigatus, Malassezia species* and *Penicillium chrysogenum*. In particular, 15% patients were sensitized to *Aspergillus fumigatus* and 10% to *Penicillium chrysogenum*. Overall, 9% patients were sensitized to fungal allergens only, 29% to perennial/seasonal allergens only and 23% to both fungal and perennial/seasonal allergens. 34% patients were not sensitized to allergens.

A trend for reductions in the annual rate of clinically significant exacerbations with mepolizumab *vs* placebo was observed in patients sensitized to *Aspergillus* and/or *Penicillium* (70%) and those not sensitized to fungal allergens (52%). Although a numerical reduction in exacerbation rate was also observed with mepolizumab vs placebo in patients sensitized to other fungal allergens (44%), this was not as pronounced.

Mepolizumab *vs* placebo was associated with a numerical trend for improved pre-bronchodilator FEV1 from baseline in all patients except those with fungal sensitization only, although this may be due to the small sample size (n=51) for this group. There was also a trend for improvement in FEV1 from baseline with mepolizumab *vs* placebo in patients sensitized to *Aspergillus* and/or *Penicillium*, but no treatment difference in patients sensitized to other fungal allergens. SGRQ and ACQ-5 scores also showed a trend for improvement with mepolizumab *vs* placebo in all groups; the improvement from baseline with mepolizumab exceeded the minimum clinically important difference (MCID) of 4-points for SGRQ total score and 0.5-points for ACQ-5 score in all groups. In addition, mepolizumab *vs* placebo reduced blood eosinophil counts from baseline by 80%-87% and reduced eosinophil cationic protein and eosinophil-derived neurotoxin levels in all groups.

In conclusion, patients with severe eosinophilic asthma are likely to benefit from mepolizumab treatment. Based on the results from this study of those with IgE-sensitization, individuals sensitized to *Aspergillus* and/or *Penicillium* may demonstrate the greatest response, although further investigations of this effect are required.[18]

Measures to avoid mold

Measures to avoid mold still remain a key factor in therapy. They include:

A. Using high-efficiency air filters and ionizers – reduce airborne mould.

B. Ensuring adequate natural ventilation.

C. Removing visible mould by cleaning (moulds are not always visible!).

D. Sealing leaks in bathrooms and roofs.

E. Clearing overflowing gutters and blocked under floor vents.

F. Removing indoor pot plants.

G. Drying or removing wet carpets.

H. Treating rising damp as soon as it is detected.

I. Avoiding the use of organic mulches, and compost heaps.[8,12,13]

Conslusions

a. Molds are often found in patients with pre-existing asthma, when they can be the cause of worsening asthma and even death. However, they can also represent a risk factor for the development of asthma in a previously healthy person.

b. Germination of inhaled mold spores in the lungs is related to Th2 and Th17 pathways, as well as activation of the innate immune system.

c. Mold sensitization rates in asthma patients range from 5% to 50% of patients.

d. Molds can act as internal and external sources of respiratory allergens depending on the climatic conditions, which complicates the diagnosis due to the very frequent simultaneous polysensitization with pollens in most patients with asthma.

e. Allergy to mold colonization of the airways leads to a distinct eosinophilic endotype of severe lung disease and numerous entities have been recognized, such as severe asthma with fungal sensitization (SAFS), allergic bronchopulmonary aspergillosis (ABPA), allergic fungal airway disease (AFAD), and others

f. The diagnosis of fungal allergy is complicated by the fact that patients with mold allergy are often polysensitized to pollen as well. Therefore, a good allergic anamnesis and clinical picture play a key role (eg nasal polyposis, immunocompromised, ...).

g. If indoor mold allergens are suspected, it is advisable to visit the patient's living or work area and collect mold samples. On the other hand, if external allergens are suspected, it is preferable to monitor their concentration in the air through meteorological station reports, and then correlate these results with the clinical picture.

h. Regarding diagnostic procedures, the most important are serum fungal-specific IgE or precipitins, total IgE, IgG against suspected fungus, peripheral blood eosinophils (usually <500 cells/μL), and fungal-specific skin prick tests. Other diagnostic procedures are also possible, depending on the individual presentation of the patient.

i. The role of antifungal therapy in severe asthma remains unclear. Further research is needed to better define the potential utility of antifungal drugs in asthma with mold sensitization or allergy, and to identify populations of patients with asthma who would benefit from such treatment.

j. There is insufficient evidence for the safety and efficacy of allergen immunotherapy in mold-sensitive patients

k. Mepolizumab could, in great majority of patients with severe eosinophilic asthma with sensitization or allergy to *Aspergillus* and *Penicillium*, improve annual exacerbation rates, lung function, SGRQ and ACQ-5, but also the number of blood eosinophils, eosinophil cationic protein, and neurotoxins produced from eosinophils.

l. Measures to avoid mold still remain a key factor in therapy.

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Conflicts of interest

I declare that I have no conflict of interest.

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