

Case study

***Alternaria*-induced asthma**Robert K. Bush, MD, and Jay J. Prochnau, MD *Madison, Wis*

Acute, severe asthma attacks can be precipitated by a variety of stimuli including exposure to aeroallergens, viral respiratory infections, pollutants, and occupational chemicals. *Alternaria* is a major aeroallergen in many parts of the world. Sensitivity to *Alternaria* has been increasingly recognized as a risk factor for the development and persistence of asthma, asthma severity, and potentially fatal asthma exacerbations. We present the case of a patient with IgE-mediated sensitivity to *Alternaria* who developed an acute, life-threatening asthma attack during the peak *Alternaria* season. We describe the aerobiology, pathophysiology, diagnosis, and treatment options for patients with *Alternaria*-induced asthma. (*J Allergy Clin Immunol* 2004;113:227-34.)

Key words: *Alternaria*, asthma, allergens, aerobiology

CASE PRESENTATION

A previously healthy 9-year-old boy presented to the University of Wisconsin emergency department in September 2003 with wheezing, severe shortness of breath, and cough of 2 days' duration. He denied any prodromal symptoms of an upper respiratory infection; his mother stated that the patient had complained of clear rhinorrhea and nasal congestion for 2 to 3 days before the onset of cough and shortness of breath. He denied any sick contacts. He described the cough as nonproductive and did not complain of headache, postnasal drip, fever, or heartburn. Because the weather had been unusually warm for late September in Wisconsin, the patient had slept with his window open for 2 to 3 nights before admission.

His history was significant for intermittent dyspnea with exertion, although he did not have a formal diagnosis of asthma or exercise-induced bronchospasm. He had never used an inhaled bronchodilator. He had been treated with oral cetirizine in the past for symptoms of allergic rhinitis, which had helped his complaints of rhinorrhea, sneezing, and nasal itching. His mother stated that his symptoms of allergic rhinitis were usually worse in the spring and fall. The patient also had a diagnosis of attention deficit hyperactivity disorder, for which he was being treated with combination amphetamine/dextroamphetamine. He had undergone a tonsillectomy with ade-

Abbreviations used

FEF₂₅₋₇₅: Forced expiratory flow rate between 25% and 75% of vital capacity

Heliox 70/30: Helium 70%, oxygen 30%

NaCl-HSA: Sodium chloride-human serum albumin

noideotomy in the remote past. His mother specifically denied the recent use of any other medications including nonsteroidal anti-inflammatory drugs or aspirin.

Social history was significant in that both of the patient's parents smoked. He lived with his mother, who admitted to smoking in the house. He spent occasional weekends with his father, who also smoked. The house had wall-to-wall carpeting with the exception of the bedrooms, which were hardwood floors covered with throw rugs. There was no central air-conditioning in the home, although there was 1 window air conditioner unit in the living room. A pet cat had been removed from the home approximately 3 weeks before admission. A pet hamster was also present in the patient's house.

Family history was significant for intermittent asthma in the patient's mother. The patient also had an older brother who had been diagnosed with allergic rhinitis and atopic dermatitis. The older brother was specifically allergic to cat, and this had prompted the cat's removal from the home.

Initial physical examination showed an afebrile patient in moderate respiratory distress. Nasal examination showed pale, boggy nasal turbinates with clear discharge present in the bilateral nasal cavity. Cardiac examination was unremarkable. Chest examination showed diffuse inspiratory and expiratory wheezes with a prolonged expiratory phase. Extremities were without cyanosis or clubbing.

Pulse oximetry showed an oxygen saturation of 90% on room air. A chest radiograph showed hyperinflation and atelectasis of the right lower lobe of the lung. No infiltrate or pleural effusion was appreciated.

The patient was immediately placed on 6 L of oxygen via nasal cannula, and he was treated with albuterol and ipratropium bromide via nebulization every 20 minutes in the emergency department. When he failed to respond to inhaled bronchodilators, he was placed on helium 70%, oxygen 30% (Heliox 70/30) and continuous albuterol by nebulization. Intravenous methylprednisolone was initiated and continued every 6 hours, and the patient was transferred to the pediatric intensive care unit for further management and close monitoring. His condition improved during the following 3 to 4 days, and he was switched from Heliox to oxygen via

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nasal cannula. The patient was discharged to home with an oral prednisone taper, combination fluticasone 250 μ g, and salmeterol 50 μ g via dry powder inhaler twice daily, and an albuterol metered dose inhaler to use on an as-needed basis.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses in this case included the causes of status asthmaticus or acute severe asthma. Causes of severe exacerbations of asthma include viral upper respiratory infections, particularly with rhinovirus, aeroallergen exposure, exposure to environmental irritants such as cigarette smoke, medications, particularly nonsteroidal anti-inflammatory drugs and aspirin, gastroesophageal reflux, and acute bacterial rhinosinusitis. Although the patient did not complain of any prodromal symptoms consistent with an upper respiratory infection, his mother thought that he had an increase in rhinorrhea and nasal congestion before the start of his asthma exacerbation, possibly consistent with an acute viral upper respiratory infection. These symptoms are also consistent with seasonal allergic rhinitis, which might have preceded an acute exacerbation of allergic asthma. Both parents also admitted to smoking indoors around the patient.

TESTING PROCEDURES

The patient presented to our pediatric allergy clinic 2 weeks after discharge from the hospital. His condition had continued to improve after discharge, and he believed that he was back to his baseline condition when we saw him in clinic. He had completed his course of prednisone and was tolerating the combination inhaled steroid and long-acting β -agonist without difficulty. He had used his albuterol inhaler twice in the 2 weeks since discharge.

Spirometry showed a forced vital capacity of 2.85 L, 120% of predicted. FEV₁ was 2.40 L, 120% of predicted. FEV₁/forced vital capacity ratio was 0.84. Peak expiratory flow rate was 5.55 L/s, 123% of predicted. Forced expiratory flow rate between 25% and 75% of vital capacity (FEF₂₅₋₇₅) was 3.01 L/s, 121% of predicted. The shape of the flow volume loop was normal. These were interpreted as normal pulmonary function test results.

Skin testing with a panel of aeroallergens (1:20 w/v in 50% glycerine; Greer Laboratories, Lenoir, NC) was performed by using the modified prick technique. This showed the results indicated in Table I.

FINAL DIAGNOSIS/PATHOGENESIS OF SEVERE ASTHMA

The patient was diagnosed with seasonal allergic rhinitis and mild intermittent, allergen-induced asthma. It was suspected that his acute severe asthma exacerbation had been caused by exposure to airborne *Alternaria* spores, given the patient's positive skin test results and timing of the exacerbation. *Alternaria* is one of the most common atmospheric mold spores in the United States,

and the highest concentrations of spores are seen in grain-growing areas such as the Midwest.¹

Asthma is characterized by reversible airway obstruction resulting from airway inflammation and edema, airway smooth muscle contraction, and mucous plugging.² This inflammatory process is multicellular and involves a panoply of cells including lymphocytes, eosinophils, mast cells, macrophages, neutrophils, and dendritic cells.³ Pro-inflammatory cytokines and other inflammatory mediators such as histamine and leukotrienes contribute to destruction of the airway epithelium, which ultimately results in an irritable or hyperresponsive airway.² Acute obstruction of this chronically inflamed airway can be induced by any number of triggers (Table II). Exposure to aeroallergens can result in chronic airway inflammation via T_H2-driven IgE-mediated mechanisms.⁴ Stimulation of goblet cells and mucus glands in the airway can then subsequently lead to hypersecretion of mucus into the airway, resulting in bronchial cast formation.⁵

In addition to IgE-mediated responses that drive the inflammatory process in asthma, recent studies in animal models demonstrated that fungal proteases might play an important role in the development of allergic airway inflammation. Kheradmand et al⁶ demonstrated that intrinsic protease activity of the fungal allergens from *Aspergillus fumigatus* promoted chronic eosinophilic inflammation in the airways of mice exposed to these allergens. In contrast, aerosol exposure to allergens that lack intrinsic protease activity (ovalbumin) led to a state of tolerance. When a purified fungal protease was added to the ovalbumin, sensitized animals exposed to these aerosols demonstrated persistent allergic inflammatory changes. Many human allergens contain intrinsic protease activity.^{7,8} In addition, many fungal allergens contain intrinsic protease activity, including *Alternaria*, which could result in an adjuvant effect leading to a prolonged T_H2 type of response.

In addition, protease activity of fungal extracts also has demonstrated ability to induce morphologic changes and cytokine production in airway epithelial cells. Kauffman et al⁹ found that *Alternaria* extracts induced cell shrinkage and desquamation when applied to cultured airway epithelial cells in vitro. This was accompanied by enhanced production of IL-6 and IL-18 at high concentrations of the *Alternaria* extract. These effects were due to intrinsic protease activity in the extracts because they were abrogated by the addition of protease inhibitors. Potentially, fungal proteases could activate epithelial cells through protease-activated receptor type-2 mechanisms. This might lead to airway epithelial desquamation and heightened airway responsiveness as a result of the exposure of airway irritant receptors.

The treatment of acute severe asthma has been reviewed elsewhere.¹⁰ The treatment of patients with allergic sensitivity to *Alternaria* is analogous to the treatment of any other environmental allergen and would include avoidance of the allergen, treatment with antiasthmatic medications, and immunotherapy vaccines. Avoidance of exposure to outdoor fungal allergens, although difficult if not impossi-

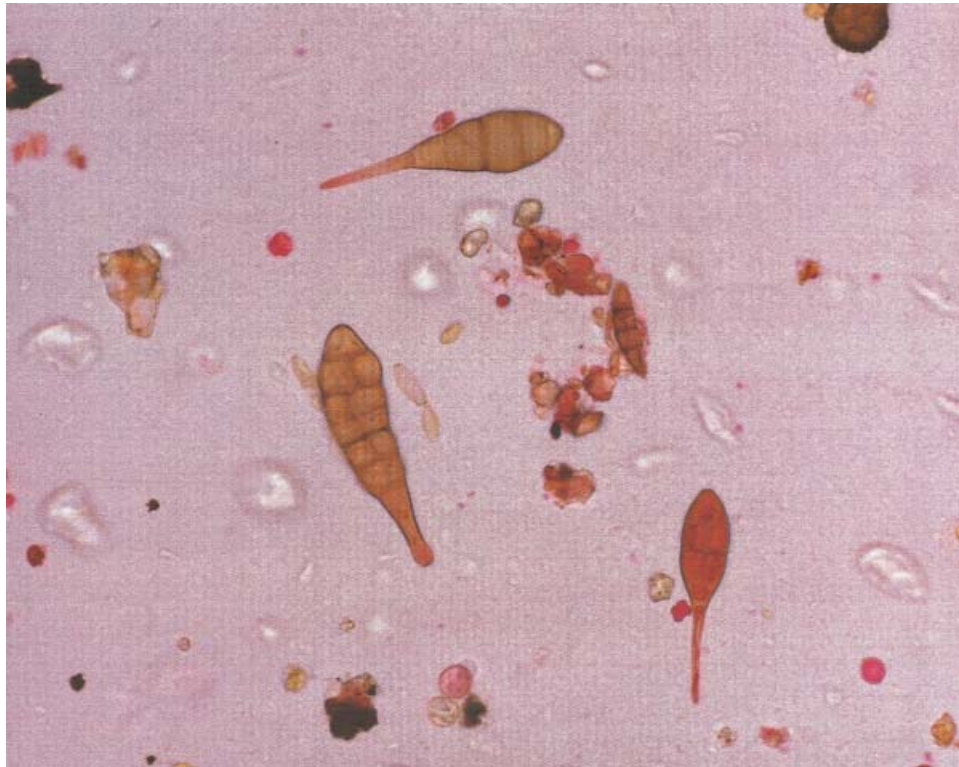


FIG 1. Photomicrograph of typical septate, beaked spores of *Alternaria alternata* (original magnification, $\times 40$). Courtesy of Rose Vrtis.

ble to achieve completely, can be reduced by several methods (Table III).^{11,12} However, controlled trials demonstrating the effectiveness of these measures for the treatment of *Alternaria*-induced asthma have not been conducted.

There are only a few studies that have evaluated the efficacy of specific immunotherapy with *Alternaria* extracts in patients with respiratory allergy. In a study from Italy, 39 children with *Alternaria*-induced asthma or rhinitis were treated with specific *Alternaria* immunotherapy and were monitored for 3 years.¹³ The investigators concluded that immunotherapy with *Alternaria* was successful in reducing symptoms and medication scores in 80% of the children receiving cumulative doses of 80,000 protein nitrogen units or more, when compared with placebo. In a more recent study Horst et al¹⁴ showed that specific immunotherapy with a standardized *Alternaria* extract resulted in lower symptom-medication scores, increased the mean provocative dose of *Alternaria* necessary for a positive nasal challenge, and reduced skin test reactivity. Another recent study has also shown similar effectiveness of sublingual immunotherapy compared with conventional immunotherapy in patients treated with *Alternaria alternata* extracts.¹⁵

The mAb to IgE, omalizumab, has been shown to be effective in the treatment of allergic rhinitis^{16,17} and allergic asthma,¹⁸⁻²¹ and it is currently approved for use in the treatment of moderate to severe allergic asthma in patients older than the age of 12 years. Omalizumab has been shown to reduce serum free IgE, reduce FCER1 receptors,

and improve asthma control in both adults and children. It has been shown to reduce the need for corticosteroids and rescue medications, reduce exacerbations, reduce hospitalizations, medical visits, and emergency department use, as well as enhance quality of life. To date, no studies have been performed with omalizumab specifically for the treatment of *Alternaria* hypersensitivity.

SUMMARY

Aerobiology of *Alternaria*

In the life cycle of fungi, the organisms typically produce both sexual and asexual spores that are morphologically distinguishable. These are termed *perfect* and *imperfect* stages, respectively.²² Often, the reproductive forms require different growth conditions, and they might not exist together, although in certain instances they might coexist. As a consequence, the life cycle stages might be named as separate organisms when, in fact, they might be the same.²² Typically, clinicians recognize the asexual stage spores of *Alternaria* because these are the most common spores encountered in airborne samples (Fig 1). Newer molecular biology techniques might allow for allergenic fungi to be connected to their corresponding sexual stages and integrated into more understandable taxonomic relationships. The teleomorph (sexual stages) and anamorph (asexual stages) develop at different times and on different substrates.²² In many cases, each stage of the organism was described as a species in total ignorance of the other stage in the life

TABLE I. Aeroallergen skin test results

Reagent	Wheal (mm)	Flare (mm)
Phenol—0.9% NaCl-HSA diluent	0	0
Histamine hydrochloride, 1 mg/mL	5	15
Eastern tree mix	7	20
Seven-grass mix	7	20
<i>Cladosporium herbarium</i>	5	15
<i>Aspergillus fumigatus</i>	3	10
<i>Penicillium chrysogenum (notatum)</i>	5	15
Short ragweed	3	10
Cat dander	3	10
<i>Dermatophagoides farinae</i>	3	10
<i>Alternaria alternata (tenius)</i>	13	30

TABLE II. Triggers of acute asthma exacerbations

Aeroallergens
Respiratory infections
Irritants/pollutants
Occupational exposures
Drug sensitivity, eg, nonsteroidal anti-inflammatory drugs
Sulfites
Exercise (rarely life threatening)

TABLE III. Fungal allergen control measures

Indoors
Keep windows closed in warm months; use air-conditioning
Maintain relative humidity at <50%
Clean washable surfaces with 5% bleach and detergent solution
Outdoors
Avoid heavy exposure to moldy vegetation
Use a well-fitted particulate mask when working with moldy material
Use air-conditioned vehicles

cycle. The term *Deuteromycetes* has been applied to the anamorphs that are widely recognized as common allergenic fungi.²² The form class Fungi imperfecti or Deuteromycetes is one example.

All fungi that do not have a known connection with any ascomycetous or basidiomycetous form are included in the broad artificial group of Deuteromycetes. This group is recognized as the second largest group of fungi after the Ascomycota.²² Monioiales represent 1 of the 4 form orders and, by far, are the largest and most important group of Deuteromycetes that contain most of the recognized and suspected allergenic fungi.²²

Fungi are easily adaptable to a variety of growth conditions but require oxygen and an organic nitrogen source. Traces of carbohydrates are also essential. Most fungi grow best between 18°C and 32°C.²² Dispersion of *Alternaria* spores occurs during dry weather periods. These are accompanied by higher wind velocity and lower relative humidity, which results in peak levels during sunny afternoon periods. The organism, *Alternaria alternata*, is a cosmopolitan organism that is typically isolated in outdoor environments in which it grows on

dead vegetation and is recovered from soil samples. Typically, higher levels of *Alternaria* are found in cultivated areas in which grasslands and grain growing predominate. In North America, fungal spores are found at peak levels in late summer or early autumn (Fig 2). Where snow cover occurs and colder temperatures prevail, spores of *Alternaria* are no longer detectable.

Thus, it would appear that the predominant exposure to *Alternaria* allergens occurs principally in the outdoor environment. Nonetheless, exposure to *Alternaria* allergens can occur in the indoor environment. In the first reported case of sensitivity to *Alternaria*, the patient was found to have sensitivity to *Alternaria* species growing in his basement.²³ Aerosampling data conducted at a time when *Alternaria* spores are prevalent in the outdoor environment indicate that spores can also infiltrate the indoor environment. Outdoor spore counts of up to 7500 spores per cubic meter of air were associated with indoor spore counts between 0 and 280 per cubic meter.²⁴

Exposure to fungi (and presumably to fungal allergens) has been traditionally assessed by microscopically identifying and measuring the number of fungal spores in air samples or by using semiquantitative cultures obtained from air or settled dust samples. Because of the morphologic distinctiveness of *Alternaria* spores, they can be assessed microscopically after collection by using volumetric samplers such as the Rotorod (Sampling Technologies, St Louis Park, Minn), Burkard Sampler (Burkard Manufacturing, Brackmenschworth, United Kingdom), and Sampler Mark MK-3 (Allergenco/Bluestone Press, San Antonio, Texas). In general, samplers that use a suction device are more efficient over broad range of particle size compared with impaction samplers.²⁴

A variety of techniques have been developed in an attempt to quantitate indoor fungal exposure, although these have not been fully characterized or developed as have sampling measures for other indoor allergens (eg, house dust mites, cat dander). Allergen-specific immunoassays that use mAbs to specific allergens have been used to quantitate indoor allergen exposure to *Alternaria* allergens^{25,26}; however, these assays have not yet achieved the same reliability as have similar assays for other allergens.

It should be noted that although the spore counts are used to measure fungal exposure, allergenic activity is distributed on other components of the fungal organisms including mycelial fragments. Allergens might also be eluted off of spores or mycelia and carried on dust particles. Thus, more reliable techniques to assess fungal allergen exposure are needed.

Characterization of *Alternaria* allergens

Studies of *Alternaria* asthma have been limited because of the fact that commercially available fungal allergen extracts are complex and variable and lack standardization. *Alternaria* extracts are crude mixtures, and the quantity of clinically relevant allergens they contain is unknown. In addition, *Alternaria* strains produce variable quantities of allergens depending on the growth conditions.²⁷

Advances in molecular biology have led to a better understanding of fungal allergens and their relationship to allergic disease. Several major allergens have been identified and characterized from *Alternaria* (Table IV). Alt a 1 is a major allergen with a molecular weight of 29 to 30 kd. The allergen appears to be two-chain dimer. Ninety percent of individuals with *Alternaria* allergy have IgE antibodies to this protein.²⁴ Its biologic function has not been elucidated. The allergic context of Alt a 1 has been measured in *Alternaria* extracts, but, to date, it has not been used as a method of standardization.¹¹

Alt a 2 is another major *Alternaria* allergen that has been molecularly cloned.²⁸ It has a molecular weight of 25 kd. Approximately 60% of individuals with *Alternaria* sensitivity have IgE directed against this protein. Sequence homology demonstrated similarity to a common transposable region to mouse RNA-dependent eukaryotic initiation factor-2 α -kinase.

Enolase is a conserved protein isolated from *Alternaria* and *Cladosporium* and other fungi. Enolases have molecular weights ranging from 46 to 48 kd.²⁹ Several other minor *Alternaria* allergens have been identified.³⁰ Alt a 3 is heat shock 70 protein; Alt a 6 is a P₂ ribosomal protein; Alt a 7 is homologous with YCP4 yeast protein; and Alt a 10 is an alcohol dehydrogenase. These proteins appear to be cytoplasmic housekeeping proteins that are conserved among several fungal species.

A 70-kd glycoprotein has been described.³¹ It accounts for 13% of the dry weight of *Alternaria* extracts and elicits positive skin test results in 87% of patients with *Alternaria* sensitivity who were tested with it. This protein might be distinct from Alt a 1, because substantial discrepancies were observed over time when these allergens were measured in air samples, which suggests that these glycoproteins are released under different conditions.²⁶

Epidemiology of *Alternaria* asthma

An association between fungal exposure and asthma has been long recognized.³² An accumulating body of evidence suggests that sensitivity to fungi, particularly *Alternaria*, is associated with asthma.

Allergy to fungi is generally demonstrated by skin testing or by in vitro assays. Although the presence of IgE antibodies does not necessarily reflect disease, it is one way of determining the frequency of sensitization and its relationship to respiratory symptoms. Because fungal extracts are nonstandardized, variability in epidemiologic studies will result. Estimates of the true prevalence of sensitization to *Alternaria* and other fungi will therefore be difficult to establish. Nonetheless, studies in various parts of the world indicate that fungal sensitivity is common, particularly among asthmatic patients and especially in younger patients.

In a study of more than 17,000 US citizens, positive skin test responses to *Alternaria* occurred in 3.6% of the population.³³ Up to 70% of patients with fungal allergy have skin test reactivity to *Alternaria*. In the United States up to 80% of subjects with confirmed asthma have demonstrated positive reactions to 1 or more fungi.³⁴ In

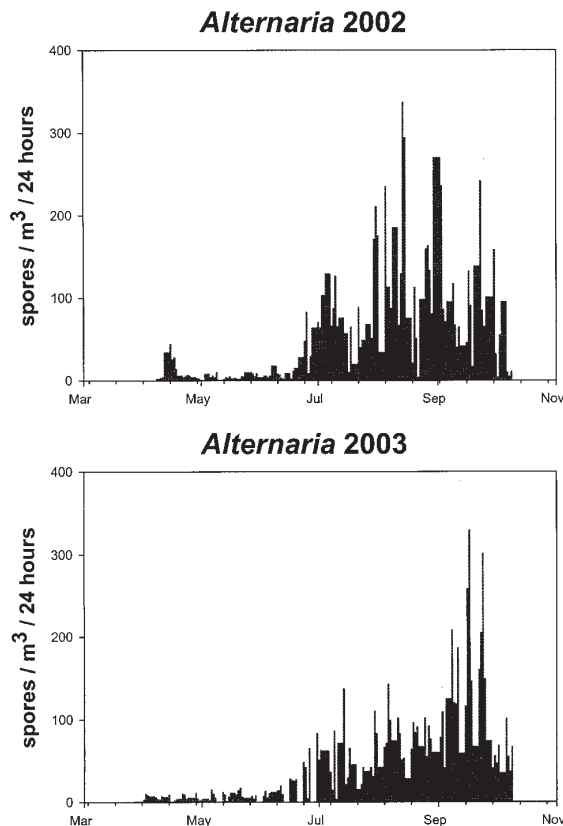


FIG 2. Atmospheric *Alternaria* spore counts obtained by an impaction sampler in Madison, Wis during 2002 and 2003. Courtesy of Rose Vrtis.

a large-scale study of children with asthma residing in US inner cities, 38.3% of the 12,086 asthmatic children had positive skin test reactions to *Alternaria* species.³⁵ In European studies approximately 3% of patients in Portugal and 20% of patients in Spain with allergic respiratory symptoms had a positive skin test reaction to either *Alternaria* or *Cladosporium* species.³⁶

Gergen and Turkeltaub³⁷ reported that in individuals with *Alternaria* sensitivity, the adjusted odds ratio for a person with self-reported asthma was 2.3 (range, 1.5 to 3.4; $P = .05$). Peat et al³⁸ examined sensitivity to *Alternaria* in different climatic regions of Australia. In the less humid interior portion of the country, sensitivity to *Alternaria* was more likely to be associated with asthma than sensitivity to house dust mites.

In a study of children residing in the desert southwest of the United States, skin test reactivity to *Alternaria* at age 6 years was associated with the presence of asthma and new onset of asthma.³⁹ Similarly, Henderson et al⁴⁰ demonstrated that sensitivity to *Alternaria* in school-age children in North Carolina was associated with recurrent wheezing. Perzanowski et al⁴¹ conducted a similar study in school-age children residing in Los Alamos, New Mexico and Charlottesville, Virginia; they found a positive association between presence of asthma and *Alternaria* sensitivity. Children with *Alternaria* sensitiv-

TABLE IV. Purified *Alternaria* allergens

Allergen designation	Molecular size (kd)	Sequence homology/comments
Alt a 1	29-31	Unknown. Major allergen
Alt a 2	25	Mouse RNA dependent, eukaryote initiation. Factor-2 α -kinase. Major allergen
Alt a 3	20	Heat shock 70 protein
Alt a 4	57	Protein disulfide isomerase
Alt a 6	11	P ₂ ribosomal protein
Alt a 7	22	YCP4 yeast protein (1,4-benzoquinone reductase)
Alt a 10	53	Alcohol dehydrogenase
Alt a 11	46-48	Enolase conserved allergic protein in several fungal species
Alt a 12	12	P ₁ ribosomal protein
GP70	70	Major allergen

TABLE V. Clinical pearls

Alternaria sensitivity is a risk factor for:

- Development of asthma
- Persistence of asthma
- Severity of asthma

Patients with severe, acute asthma attacks should be evaluated for *Alternaria* sensitivity.

Lack of standardized allergenic extracts and vaccines hamper the diagnosis and treatment of *Alternaria* sensitivity.

ity have also been shown to have heightened airway responsiveness to methacholine.⁴²

It has been difficult to causally relate exposure to *Alternaria* spores with the development of asthma symptoms in sensitized individuals. Nonetheless, Bruce et al⁴³ demonstrated that 50% of subjects with *Alternaria* sensitivity by skin testing had asthma symptoms that were correlated with the level of *Alternaria* spores in the air. A study of children residing in San Diego, California demonstrated that increasing spore counts in the atmosphere were associated with increased use of bronchodilator medication and asthma symptoms.⁴⁴ Interestingly, there was better correlation of increments in non-skin testable fungi spore counts compared with fungi to which the patients demonstrated positive test responses. This study points out our inability to accurately assess fungal allergen exposure and that we are limited in our ability to test for relevant strains.

Sensitivity and exposure to *Alternaria* have also been observed to be associated with emergency department visits for asthma. Nelson et al⁴⁵ reported an association between emergency department visits for asthma in children who exhibited sensitivity to a variety of allergens including *Alternaria*. Dales et al⁴⁶ also have demonstrated the influence of ambient *Alternaria* spores on emergency department visits for children with acute asthma exacerbations.

Several epidemiologic studies have linked *Alternaria* sensitivity not only to persistence of asthma, but also to severe and potentially fatal asthma. Halonen et al⁴⁷ found that in children with *Alternaria* sensitivity, asthma was likely to persist beyond age 11 years compared with individuals who had negative skin test responses to *Alternaria*. Two studies^{48,49} have demonstrated an association

between *Alternaria* sensitivity and the severity of asthma. Individuals who are sensitized to *Alternaria* appear to be more at risk for developing severe asthma than those with other allergen sensitivities.

With regard to our case presentation, a study in children and young adults demonstrated that patients with respiratory arrest caused by asthma were associated with sensitivity to *Alternaria*.¹ Ten of 11 patients with *Alternaria* sensitivity experienced severe episodes of asthma during the peak of the *Alternaria* season in the upper Midwest. The adjusted odds ratio was 189 (95% CI, 6.5 to 5535.8) for a severe, potentially fatal attack of asthma in these patients with *Alternaria* sensitivity. The risk of death from asthma has also been correlated with the presence of fungal spores in the atmosphere. In a study of death certificates conducted in Chicago, the adjusted odds ratio for an asthma death on a day when the fungal spore counts exceeded 1000 per cubic meter was 2.3 times higher than when the counts were less than 1000.⁵⁰ Similar reports have indicated that sensitivity to fungal allergens is a significant risk factor for life-threatening asthma.⁵¹

CONCLUSIONS

Alternaria alternata is a major allergen in many parts of the world. The precise prevalence of *Alternaria* sensitivity is unknown. However, allergic sensitization to *Alternaria* has been linked to airway hyperresponsiveness in children, has been identified as a risk factor for the development and persistence of asthma, and is associated with severe and life-threatening episodes of asthma.

Diagnostic and therapeutic reagents for *Alternaria* sensitivity are not standardized. Recent developments suggest that molecular cloning of allergens might make standardization of these reagents possible.

Fungal allergens, including *Alternaria*, have been shown to induce IgE-mediated hypersensitivity. In addition to the effect of IgE-mediated mechanisms, fungi might also produce chronic inflammatory changes through a variety of other mechanisms. Fungal exposure differs from pollen exposure in quantity in that fungal spore counts are often 1000-fold or greater than pollen counts. Furthermore, fungal exposure occurs for months, whereas pollen exposure occurs for a few weeks. The

protracted exposure to *Alternaria* mimics that of indoor allergens that have been associated with asthma such as cat dander and dust mites and likely contributes to asthma severity and chronicity in individuals with *Alternaria* sensitivity. Moreover, proteases produced by fungi might act as adjuvants to promote T_H2 types of responses. The proteases might also directly act on airway epithelium, causing its disruption, and, thereby, heighten airway hyperresponsiveness.

Much remains to be learned about the sources (outdoor versus indoor) and quantity of allergen exposure to *Alternaria* and other fungi. Environmental controls for *Alternaria* are limited because it appears to be chiefly an outdoor exposure. Reducing exposure times and possibly wearing masks when exposure levels tend to be high, while theoretically helpful, are impractical. Indoor exposure to *Alternaria* can occur on occasion and can be reduced by proper environmental control measures, although such situations are rare. Although pharmacologic agents are available for improving asthma control, individuals with *Alternaria* sensitivity appear to be at increased risk for potentially fatal asthma attacks. The precise role of immunotherapy and anti-IgE treatment to prevent these episodes has yet to be demonstrated.

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