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Severe Asthma With Fungal Sensitization in a Child: Response to Itraconazole Therapy

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KEY WORDS

fungal, inflammation, airway

ABBREVIATIONS

ABPA—allergic bronchopulmonary aspergillosis

SAFS—severe asthma with fungal sensitization

PFT—pulmonary-function test

FVC—forced vital capacity

FEV₁—forced expiratory volume in 1 second

FEF_{25%-75%}—forced expiratory flow, midexpiratory phase

IgE—immunoglobulin E

CF—cystic fibrosis

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abstract

People with severe asthma with fungal sensitization may represent an underdiagnosed subset of patients with refractory disease. It is important to know that such patients may benefit from adjunct treatment with antifungal agents. We describe here the case of a child with refractory asthma, persistent airway obstruction, a serum immunoglobulin E level of >20 000 IU/mL, and severe eosinophilic airway infiltration. Although he did not meet diagnostic criteria for allergic bronchopulmonary aspergillosis, he demonstrated evidence of sensitization to several fungi and responded dramatically to the addition of itraconazole therapy. We also discuss emerging hypotheses regarding fungal-induced asthma. *Pediatrics* 2010;125:e1255–e1258

Fungi are important allergens for patients (especially children) with asthma.^{1,2} In addition, severity of disease has been linked to fungal sensitization in some studies.^{3,4} The generally accepted paradigm is that fungal sensitization results from recurrent, transient environmental exposures. However, sensitization in the context of fungal infection or colonization has also been described and is increasingly appreciated.⁵⁻⁷ The most widely recognized example of this condition is allergic bronchopulmonary aspergillosis (ABPA). Exacerbation of asthma symptoms has also been described with fungal colonization of the sinuses (ie, allergic fungal sinusitis)⁸ and fungal infection outside the respiratory tract. For example, antifungal treatment of some asthmatic patients with dermatophytic infections improves respiratory symptoms.^{9,10} Recently, Denning et al¹⁵ identified and studied a cohort of patients with severe asthma and fungal sensitization (SAFS) who did not meet diagnostic criteria for ABPA but demonstrated sustained improvements in asthma symptoms with itraconazole therapy. The improvement of asthma symptoms associated with antifungal treatment led the authors to hypothesize that unrecognized fungal infection was partly responsible for ongoing allergen exposure and sensitization (as opposed to limited exacerbations that coincide with transient exposures). The following case highlights the potential importance of SAFS and fungal infection in childhood asthma.

CASE REPORT

A 10-year-old boy with severe persistent asthma and atopic dermatitis present since early childhood was referred to our pediatric pulmonology service for management. He was raised in the Bronx, New York, and for the past several years the family had lived in the same apartment, in which

mold was often visible. Results of pulmonary-function tests (PFTs) at baseline (ie, no perceived deterioration in daily symptoms) confirmed obstruction with reversibility after bronchodilator therapy (representative prebronchodilator values: forced vital capacity [FVC], 99% predicted; forced expiratory volume in 1 second [FEV₁], 75% predicted; FEV₁/FVC, 69; forced expiratory flow, midexpiratory phase [FEF_{25%-75%}], 44% predicted; and post-bronchodilator values: FVC, 97% predicted; FEV₁, 89% predicted; FEV₁/FVC, 85; FEF_{25%-75%}, 91% predicted). Results of a sweat test were negative. He was treated in a stepwise fashion and eventually required high-dose inhaled corticosteroids, long-acting β agonists, and leukotriene receptor antagonists. Despite the addition of antireflux medications and antihistamines, the patient continued to exhibit daily symptoms and require frequent bursts of high-dose systemic steroids. He was eventually maintained on low-dose prednisone (5 mg daily) for several months, but results of PFTs run during his routine visits continued to show small-airway obstruction. His serum immunoglobulin E (IgE) level rose from 4778 IU/mL to a peak of 24 760 IU/mL, coinciding with a peak blood eosinophilia of 24% (absolute value: 2300/ μ L) without any apparent environmental changes. He was evaluated for possible ABPA and numerous environmental allergies. Results of skin testing were positive for histamine, birch, and oak but negative for *Aspergillus*. Serum precipitins to *Aspergillus* were negative, and a chest computed-tomography scan demonstrated bronchial wall thickening without bronchiectasis. Although the patient demonstrated elevated levels of *Aspergillus*-specific IgE (5.39 kU/L [class 3]), he did not fulfill minimum diagnostic criteria for ABPA (see "Discussion").

Extensive rheumatologic and infectious-disease evaluations identified no alternate diagnoses, and hypereosinophilic syndromes and malignancies were excluded. Because of previous episodes of recurrent right lower lobe atelectasis interspersed with hyperinflation, the patient underwent flexible bronchoscopy with bronchoalveolar lavage; endobronchial biopsies were also obtained from the right basilar bronchus to evaluate for the presence of submucosal granulomas or other evidence of localized vasculitic disease. Test results from bronchoalveolar lavage fluid were negative for organisms or hemosiderin-laden macrophages, and a differential cell count demonstrated 15% eosinophils. Results of an endobronchial biopsy showed no granulomas, but the biopsy demonstrated marked thickening of the basement membrane (Fig 1, arrows) and extensive eosinophilic inflammation in the submucosa (Fig 1, arrowheads).

Because radioallergosorbent testing results were positive for *Alternaria* (10.6 kU/L [class 3]), *Cladosporium* (1.35 kU/L [class 2]), and *Penicillium* (0.8 kU/L [class 2]) in addition to *Aspergillus* (5.39 kU/L [class 3]), a decision was made to start the patient on 100 mg of itraconazole by mouth twice per day. Within 1 month of initiating itraconazole treatment, his IgE levels decreased to 1862 IU/mL (pretreatment IgE level: 6275 IU/mL), PFT results normalized for the first time in 2 years, and the patient reported complete resolution of symptoms (Table 1). The patient was maintained on itraconazole for a total of 6 months. Systemic steroids were weaned within the first 2 to 3 weeks, and he was maintained on inhaled corticosteroids, long-acting β agonists, and leukotriene receptor antagonists. Throughout the 6-month treatment period, he experienced only 1 exacerbation after acquiring an upper respiratory infection and was

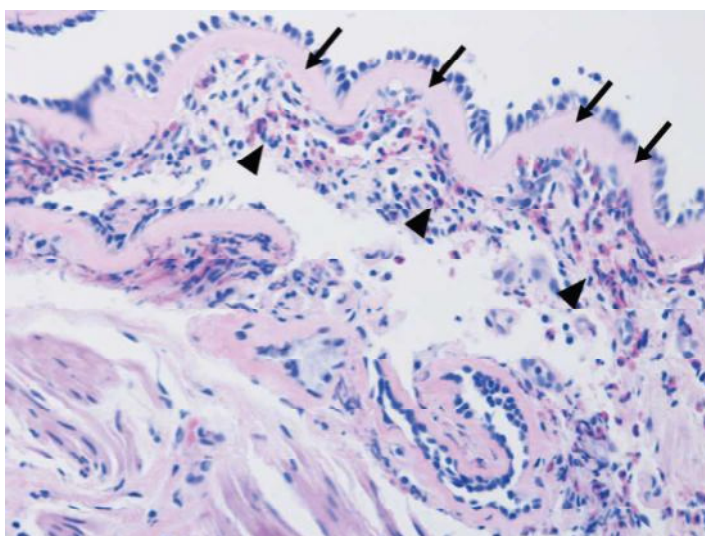


FIGURE 1
Endobronchial biopsy obtained from a segmental carina of the right basilar bronchus demonstrates markedly thickened basement membrane (arrows) and significant eosinophilia in the submucosa (arrowheads). No submucosal granulomas or evidence of vasculitic disease can be seen.

TABLE 1 Pre- and Posttreatment PFTs and IgE

	Average Values for Preceding 2 y	Values After 1 mo of Itraconazole Treatment
FEV ₁ , % predicted	72	99
FEV ₁ /FVC	75	80
FEF _{25%-75%} , % predicted	51	91
Serum IgE, IU/mL	23 221	1862

treated as an outpatient. Although his serum IgE level never fully normalized during itraconazole therapy, the values remained relatively stable (2236 and 2149 IU/mL) and did not approach pretreatment levels. However, 3 months after discontinuation of itraconazole, the patient was again hospitalized for an exacerbation. His serum IgE level at that time, drawn after 3 days of systemic steroids, had risen to 3060 IU/mL. Efforts to address the mold problems in the apartment have been unsuccessful thus far, and the family is attempting to relocate to a different building.

DISCUSSION

Although not standard practice in our clinic, we initiated antifungal therapy

for this patient after failure to identify other comorbid conditions or diseases, including ABPA. In some clinical conditions, most notably cystic fibrosis (CF), a diagnosis of ABPA is sometimes reached with less stringent adherence to general recommendations than those used for patients without CF.¹¹ Our patient did not have a positive skin-test result for *Aspergillus* or *Aspergillus* precipitins and, thus, did not fit minimum diagnostic criteria with either CF or non-CF guidelines.^{12–14} Omalizumab was not considered for this patient, because his IgE levels were significantly outside of standard dosing regimens.

The addition of itraconazole resulted in notable improvements in our patient's pulmonary function, serum IgE levels, and symptoms, all of which had been poorly responsive to aggressive therapy over the preceding 2 years. Although Denning et al⁵ also demonstrated beneficial effects with the addition of itraconazole in patients with SAFS, the overall responses in that investigation were not as dramatic as those seen in our patient. It should be noted, however, that their

investigation excluded patients with extremely high IgE levels and did not include children. In a previous review article, the same authors recommended applying the term SAFS specifically to adults, because the increased prevalence of fungal sensitization in children may simply reflect immaturity of the immune system.¹⁵ However, given the severity of our patient's signs and symptoms, the extensive evaluation revealing no alternate disease, and failure of aggressive therapy, our group felt that it was prudent to initiate treatment with close observation.

Equally relevant to our patient's positive response to therapy was the return of symptoms and elevation of serum IgE level after discontinuation of itraconazole. A similar phenomenon was observed in the Denning et al study, which highlights the difficulties in controlling environmental exposures to fungi or other allergens.⁵ It is unfortunate that many families in our urban community do not possess the resources to address these issues by way of home-remodeling or relocation (personal observation).

Our patient demonstrated sensitization to several fungal organisms that are common in most environments. However, there is emerging evidence that exposure to or infection with other endemic fungi may partly explain geographic variations in asthma severity. *Cryptococcus neoformans* is a unique fungal pathogen that is able to colonize pigeon droppings and cause persistent subclinical pulmonary infection in humans.^{16–18} The results of serologic studies have suggested a high prevalence of cryptococcosis among residents of the Bronx, a New York City borough with an extraordinarily high rate of severe asthma.^{19,20} In a study of 185 children seen in our emergency department, 70% had evidence of *C neoformans* infection, which is in stark contrast to children

from outside the Bronx.^{19,21} Although this organism is not widely considered to be associated with asthma, experimental, subclinical pulmonary cryptococcosis results in airway hyperreactivity, T helper 2 inflammation and goblet-cell hyperplasia in rats.²² Experimental pulmonary infection also produces a sustained induction of chitinases, which were recently implicated as critical mediators of asthma.^{23,24} Particularly interesting is that we found that the patient in this case report had serologic evidence of crypto-

coccal infection by using a previously described immunoblot assay^{19,25} (note that the patient's serum was collected under an ongoing institutional review board–approved protocol, and results were known only after the initiation of therapy). Although the significance of cryptococcal infection in this specific context remains to be determined, the patient's dramatic response to itraconazole brings to light interesting points for speculation regarding both SAFS and unsuspected fungal infection in children.

CONCLUSIONS

Our case highlights the potential importance of SAFS and fungal infection in pediatric asthma. Development of new diagnostic techniques and identification of novel biomarkers are required to further characterize the underlying mechanisms of fungal-mediated respiratory disease (including the potential differences between sensitization and active infection), particularly in the pediatric age group.

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