

Itraconazole, an Effective Adjunctive Treatment for Allergic Bronchopulmonary Aspergillosis

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■ Abstract

We report the case of a 21-year old man with a long-standing history of severe asthma and allergic rhinosinusitis who developed progressive worsening of dyspnea, wheezing, productive cough, and nasal obstruction, with little response to antibiotics and repeated short courses of oral corticosteroids. A diagnosis of allergic bronchopulmonary aspergillosis was made on the basis of a combination of clinical, laboratory and radiographic findings. Treatment with oral methylprednisolone and itraconazole resulted in an improvement in symptoms, lung function and computed tomography results, as well as in a decrease in total serum immunoglobulin E. This case report highlights the importance of a high degree of clinical suspicion in order to diagnose and treat allergic bronchopulmonary aspergillosis in patients with a long-standing history of severe asthma as early as possible as this has a major impact on prognosis. It also highlights the effectiveness of itraconazole as adjunctive therapy to systemic corticosteroids in this condition.

Key words: Allergic bronchopulmonary aspergillosis. *Aspergillus*. Asthma. Bronchiectasis. Itraconazole.

■ Resumen

Comunicamos un caso de un hombre de 21 años con una historia de larga evolución de asma grave y rinosinusitis alérgica que desarrolló un progresivo empeoramiento de la disnea, sibilancias, tos productiva, y obstrucción nasal, con pobre respuesta a antibióticos y tandas cortas de corticoides orales. Se realizó el diagnóstico de aspergilosis broncopulmonar alérgica en base a la combinación de los hallazgos clínicos, radiográficos y de laboratorio. EL tratamiento con Metilprednisolona oral e Itraconazol resultó en una mejora de los síntomas, de la función pulmonar, y de los resultados de la tomografía computarizada, así como un descenso en la IgE sérica total. Este caso resalta la importancia de un alto grado de sospecha clínica para diagnosticar y tratar la aspergilosis broncopulmonar alérgica en pacientes con una historia de larga evolución de asma grave tan pronto como sea posible ya que el diagnóstico precoz tiene un gran impacto en el pronóstico.

También destaca la efectividad del Itraconazol como tratamiento adyuvante a los corticoides sistémicos en esta condición.

Palabras clave: Aspergilosis broncopulmonar alérgica. *Aspergillus*. Asma. Bronquiectasias. Itraconazol.

Introduction

In allergic bronchopulmonary aspergillosis (ABPA), the inhalation of fungal spores and airway colonization by *Aspergillus* species can give rise to type I, type III, and possibly type IV hypersensitivity reactions, resulting in damage to bronchi and surrounding lung parenchyma such as bronchiectasis and pulmonary atelectasis [1,2].

ABPA is most common in young adults, although it has been reported at both extremes of life, with pre-existing obstructive lung disease (namely asthma and cystic fibrosis). The prevalence of ABPA in patients with asthma ranges from 0.25% to 28% [3-5]. Diagnosis is based on a combination of clinical, laboratory, and radiographic findings, and a set of specific diagnostic criteria has been defined for patients with asthma [2]. In the absence of typical proximal bronchiectasis,

the condition is designated ABPA-seropositive as opposed to ABPA-central bronchiectasis [6].

Delayed recognition of ABPA is not uncommon and can have important implications for long-term prognosis. ABPA progresses in 5 stages [7] and adequate treatment depends on the stage of disease [1,2]. The cornerstone of ABPA treatment is systemic corticosteroid therapy, although antifungal agents such as itraconazole are playing an emerging role in adjunctive therapy.

We report the case of a young man with a long-standing history of severe allergic asthma who developed progressive worsening of respiratory symptoms that did not respond to the usual rescue medication or repeated courses of antibiotics and systemic corticosteroids.

Case Description

We describe the case of a 21-year-old Caucasian student who had had allergic asthma and rhinosinusitis since the age of 2 years. Despite regular preventive treatment, he had experienced frequent asthma exacerbations during childhood, requiring systemic corticosteroids and admission to hospital. The respiratory symptoms were usually triggered by upper tract respiratory infections and exposure to house dust and grass pollen. Skin prick testing at the time was positive to different species of house dust mites and grass pollen allergen extracts. He underwent subcutaneous immunotherapy to treat house dust mite allergy for 5 years, leading to a clear improvement in symptoms and respiratory function, which was maintained throughout adolescence. Despite clinical and functional stability (forced expiratory volume in 1 second [FEV₁], 97.8%; FEV₁/forced vital capacity [FVC], 88.8%; midexpiratory flow at 50% of vital capacity [MEF₅₀], 66.7%; MEF₂₅₋₇₅, 63.7%), he was admitted to hospital for spontaneous pneumothorax and pneumomediastinum when he was 18 years old. This episode

developed out of the context of an asthma exacerbation and had no bearing on the course of disease.

At the age of 21 years, the patient started to develop recurrent episodes of dyspnea, exercise intolerance, productive cough, worsening of nasal obstruction, and purulent sputum and nasal discharge. He was prescribed antibiotics and oral corticosteroids, in addition to his usual inhaled therapy (salbutamol on an as-needed basis, fluticasone 500 µg twice a day and salmeterol 50 µg twice a day), but there was little improvement.

Although the patient had a poor perception of symptoms, on clinical examination he presented nasal intonation and mouth breathing, increased anteroposterior thoracic diameter, and wheezing on pulmonary auscultation. Markedly inferior turbinate hypertrophy was also observed. Peak expiratory flow was 330 L/min (59% of predicted for his gender, age, height, and weight) and nasal inspiratory flow was 50 L/min.

At this point, further investigations were performed. A full blood count revealed an increased eosinophil count (7.6%, 1026/µL). Lymphocyte subsets, erythrocyte sedimentation rate, liver and renal function tests, as well as serum C-reactive protein, immunoglobulins (Ig A, G, and M, IgG subclasses, and complement fractions were within normal limits. Total IgE was 1460 U/mL (previously 1200 U/mL). Antineutrophil cytoplasmic antibodies were negative. The sweat test result was unremarkable, as were results for serum α-1-antitrypsin, thyroid function, and serological studies (including HIV-1 and HIV-2 analyses). Arterial blood gas analysis showed hypoxemia (pO₂, 79 mm Hg). Skin prick and intradermal testing were positive for *Aspergillus fumigatus* (5 mm and 20 mm wheal diameter after 20 minutes, respectively, with a positive control of 5 mm and a negative control of 0 mm). Previous skin prick testing had been negative for molds. Specific IgE to *A fumigatus* was elevated (34.7 kU/L) and specific IgG to the same mold was within the normal range (26.9 mgA/L). *A fumigatus* was identified in a bronchial aspirate culture

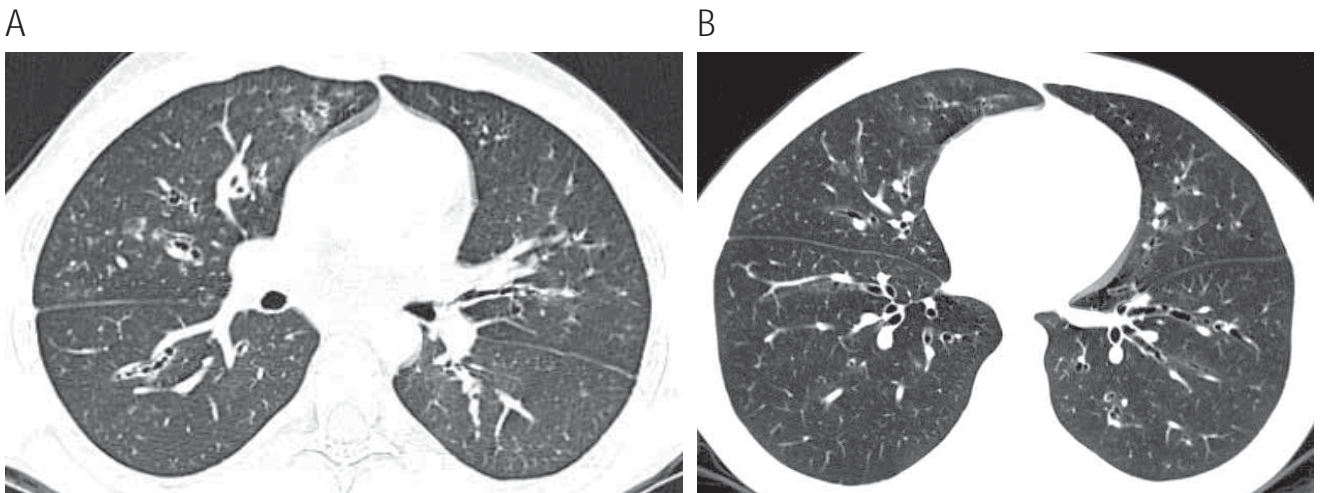
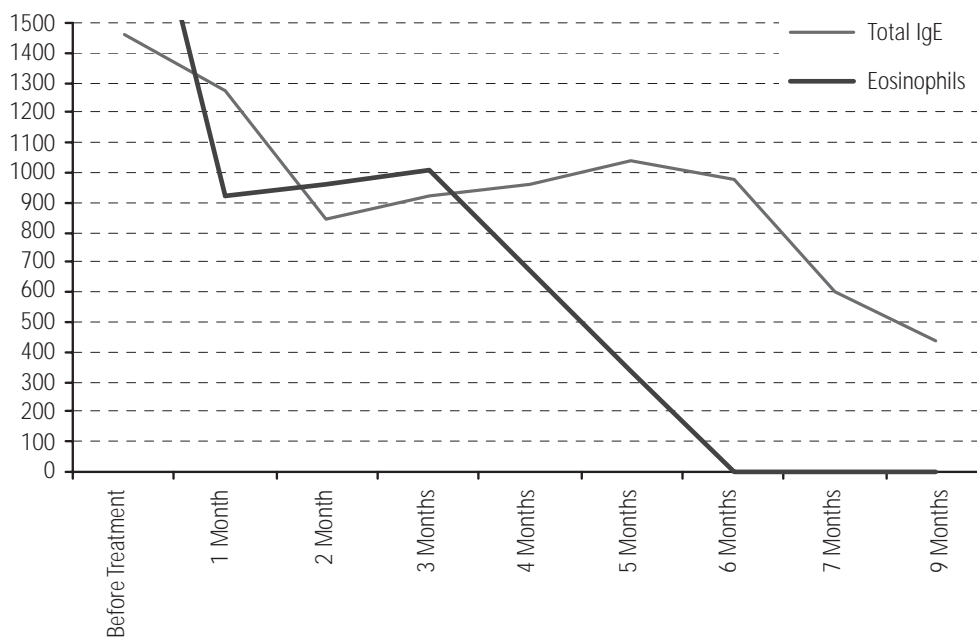


Figure 1. High-resolution pulmonary computed tomography scan. A, cystic and cylindrical bronchiectasis, micronodular and tree-in-bud images are seen bilaterally. B, evident signs of improvement 1 year after initiation of treatment despite the persistence of bronchiectasis.



Total IgE	Before Treatment	4 Months	6 Months	9 Months	12 Months
FVC	75.0%	85.8%	76.8%	96.1%	97.8%
FEV ₁	50.4%	58.0%	51.4%	88.5%	86.3%
FEV ₁ /FVC	57.8%	58.0%	57.4%	79.1%	75.9%
MEF ₂₅₋₇₅	17.4%	18.5%	15.0%	56.3%	54.9%
R	139.9%	144%	131%	161%	63.4%
RV	202.2%	135%	117%	NP	171.4%
BD (change in FEV ₁)	4.9%	6.73%	1.68%	-1.1%	2.9%
CO Diffusion	Normal	Normal	NP	Normal	NP

Figure 2. Evaluation of total serum immunoglobulin (Ig) E, blood eosinophil count, and lung function before and after initiation of treatment (6 months of oral methylprednisolone including weaning doses and 4 months of itraconazole). FVC indicates forced vital capacity; FEV₁, forced expiratory volume in 1 second; MEF₂₅₋₇₅, midexpiratory flow between 25% and 75% of FVC; R, airway resistance; RV, residual volume; BD, bronchodilation test; CO, carbon monoxide; NP, not performed.

performed after bronchial endoscopy. Lung function testing revealed severe bronchial obstruction (FEV₁, 50.4%; FEV₁/FVC, 57.8%; MEF₅₀, 21.1%; MEF₂₅₋₇₅, 17.4%) and an increase in FEV₁ after 200 µg of inhaled salbutamol of 4.9%. Carbon monoxide diffusing capacity was normal. Chest radiography revealed signs of hyperinflation (previous radiographs had been unremarkable), and a high-resolution computed tomography (CT) scan revealed central cylindrical and cystic bronchiectasis bilaterally (Figure 1). A nasal-sinus CT scan showed inferior and medium turbinate hypertrophy, ostiomeatal complex obstruction, and frontal and maxillary chronic sinusitis.

The patient was prescribed oral methylprednisolone (1 mg/kg/day) and itraconazole (200 mg/day), with no change to asthma and rhinitis treatments. Two weeks later, the

methylprednisolone was progressively tapered down over the following 3 months until a dose of 10 mg was reached; this was then taken on alternate days for an additional 6 months. During this time, antifungal therapy was continued until 4 months of treatment were completed.

Close monitoring of the disease was performed throughout the treatment. Clinical improvement was evident with a reduction in dyspnea, wheezing, cough, and nasal obstruction, and improved exercise tolerance. This was accompanied by a reduction in total IgE and blood eosinophil count and an improvement in lung function parameters (Figure 2). Recovery was also noticeable on the CT scan 1 year after diagnosis (Figure 1). There was no clinical or laboratory evidence of adverse therapy-related effects.

Discussion

We report the case of ABPA in a young adult with previously controlled severe asthma who developed an exacerbation of respiratory symptoms that did not respond to oral corticosteroids and in which oral itraconazole led to considerable clinical and functional improvement. This case highlights the role of antifungal agents in the treatment of ABPA. Treatment should not only target the hypersensitivity reaction (with systemic corticosteroids) but also aim to eradicate *Aspergillus* from the airways (using an antifungal agent such as itraconazole) [1]. Early diagnosis of ABPA is essential for the prevention of recurrent exacerbations and progression to lung fibrosis [2,6]. However, it is not uncommon to diagnose ABPA at late stages of the disease [8]. In long-standing poorly-controlled and/or severe asthma, sometimes in association with pre-existing bronchiectasis, ABPA can be particularly difficult to detect and an extensive differential diagnosis has to be considered [9].

In the reported case, the deterioration of respiratory symptoms and lung function parameters in a patient with previously controlled severe asthma could have been explained by several conditions. Nonadherence to therapy was denied by the patient and his inhalation technique was good. Bacterial infection of asthma-induced bronchiectasis and/or exacerbation of chronic rhinosinusitis seemed not to be the only issue, as there was no response to appropriate antibiotic treatment. Other conditions which can either mimic or occur simultaneously with uncontrolled asthma were also excluded based on history, clinical examination, and lung function findings. These included chronic obstructive pulmonary disease, vocal cord dysfunction, psychological disturbances, chronic heart failure, gastro-oesophageal reflux and occupational and drug-induced respiratory diseases. Cystic fibrosis, primary ciliary dyskinesia, α -1-antitrypsin deficiency, thyroid disease and Churg-Strauss syndrome were ruled out based on laboratory testing, as were primary immunodeficiencies (namely antibody deficiencies) and secondary immunodeficiencies such as HIV infection. The detection of impaired immunity is important not only as a differential diagnosis per se but also within the context of *Aspergillus*-induced diseases, as ABPA occurs in immunocompetent hosts, in whom the response of polymorphonuclear leucocytes and alveolar macrophages is not defective [1,2]. On the contrary, immunodeficient patients are more likely to have invasive aspergillosis [10,11].

The presence of asthma, central bronchiectasis on the CT scan, positive skin prick and intradermal tests to *A fumigatus*, increased total serum IgE and specific IgE to *A fumigatus*, combined with pulmonary infiltrates in chest radiography, peripheral blood eosinophilia and a positive sputum culture for *A fumigatus* enabled the diagnosis of ABPA to be made as a complication of pre-existing controlled severe allergic asthma.

As clearly demonstrated by the clinical improvement observed, the decrease in serum total IgE, and the improvement in CT and lung function results, the patient responded well to treatment with oral itraconazole and methylprednisolone following failure to respond to repeated courses of oral corticosteroids in the same dose range. In fact, oral itraconazole has been shown to be effective as an adjunctive therapy for ABPA, allowing a

reduction in the need for corticosteroids [12-14]. This therapy has been seen to reduce exacerbations, improve laboratory and lung function parameters, and prevent disease progression [15]. It has an antiinflammatory effect, which reduces eosinophilic airway inflammation and systemic immune activation [16]. However, there are concerns regarding this treatment in relation to resistance, cost, drug interactions, and toxicity (such as rhabdomyolysis, adrenal insufficiency, and hepatitis). Moreover, the long-term effect of itraconazole on lung function is still unknown [17]. In our patient, no adverse events had developed at the time of writing and different laboratory parameters reflecting immunological mechanisms of ABPA, such as total and specific IgE, eosinophil count and cutaneous reactivity to *Aspergillus*, decreased with this treatment. Corticosteroids are the first-line therapy for ABPA, reducing the immune response mounted to the presence of *Aspergillus* in the airways. Nevertheless, long-term systemic corticosteroid therapy is not recommended as there is no evidence that it prevents the progression of lung destruction [18] and it may be ineffective in end-stage fibrosis.

In the future, our patient will continue to be monitored for clinical deterioration as relapses in ABPA are common, despite initial response to therapy. The most useful tools, used in combination, to monitor the course of disease, assess response to therapy, and identify exacerbations and relapses are the evaluation of symptoms, chest radiography or high resolution CT [19], total serum IgE, and lung function tests [1].

References

1. Tillie-Leblond I, Tonnel AB. Allergic bronchopulmonary aspergillosis. *Allergy*. 2005;8:1004-13.
2. Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol*. 2002;5:685-92.
3. Kumar R, Gaur SN. Prevalence of allergic bronchopulmonary aspergillosis in patients with bronchial asthma. *Asian Pac J Allergy Immunol*. 2000;4:181-5.
4. Novey J. Epidemiology of allergic bronchopulmonary aspergillosis. *Immunol Allergy Clin North Am*. 1998;641-53.
5. Schwartz HJ, Greenberger PA. The prevalence of allergic bronchopulmonary aspergillosis in patients with asthma, determined by serologic and radiologic criteria in patients at risk. *J Lab Clin Med*. 1991;2:138-42.
6. Greenberger PA, Miller TP, Roberts M, Smith LL. Allergic bronchopulmonary aspergillosis in patients with and without evidence of bronchiectasis. *Ann Allergy*. 1993;4:333-8.
7. Patterson R, Greenberger PA, Radin RC, Roberts M. Allergic bronchopulmonary aspergillosis: staging as an aid to management. *Ann Intern Med*. 1982;3:286-91.
8. Lee TM, Greenberger PA, Patterson R, Roberts M, Liotta JL. Stage V (fibrotic) allergic bronchopulmonary aspergillosis. A review of 17 cases followed from diagnosis. *Arch Intern Med*. 1987;2:319-23.
9. Polosa R. An overview of chronic severe asthma. *Intern Med J*. 2008;3:190-8.
10. Rivera A, Hohl T, Pamer EG. Immune responses to *Aspergillus fumigatus* infections. *Biol Blood Marrow Transplant*. 2006;1 Suppl 1:47-9.

11. Chignard M, Balloy V, Sallenave JM, Si-Tahar M. Role of Toll-like receptors in lung innate defense against invasive aspergillosis. Distinct impact in immunocompetent and immunocompromized hosts. *Clin Immunol.* 2007;3:238-43.
12. Salez F, Briche A, Desurmont S, Grosbois JM, Wallaert B, Tonnel AB. Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. *Chest.* 1999;6:1665-8.
13. Wark P, Wilson AW, Gibson PG. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst Rev.* 2001;4:CD001108.
14. Stevens DA, Schwartz HJ, Lee JY, Moskovitz BL, Jerome DC, Catanzaro A, Bamberger DM, Weinmann AJ, Tuazon CU, Judson MA, Platts-Mills TA, DeGraff AC Jr. A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. *N Engl J Med.* 2000;11:756-62.
15. Wark PA, Gibson PG, Wilson AJ. Azoles for allergic bronchopulmonary aspergillosis associated with asthma. *Cochrane Database Syst Rev.* 2004;3:CD001108.
16. Wark PA, Hensley MJ, Saltos N, Boyle MJ, Toneguzzi RC, Epid GD, Simpson JL, McElduff P, Gibson PG. Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. *J Allergy Clin Immunol.* 2003;5:952-7.
17. Wark P. Pathogenesis of allergic bronchopulmonary aspergillosis and an evidence-based review of azoles in treatment. *Respir Med.* 2004;10:915-23.
18. Capewell S, Chapman BJ, Alexander F, Greening AP, Crompton GK. Corticosteroid treatment and prognosis in pulmonary eosinophilia. *Thorax.* 1989;11:925-9.
19. Angus RM, Davies ML, Cowan MD, McSharry C, Thomson NC. Computed tomographic scanning of the lung in patients with allergic bronchopulmonary aspergillosis and in asthmatic patients with a positive skin test to *Aspergillus fumigatus*. *Thorax.* 1994;6:586-9.

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