



REVISTA MÉDICA DEL
HOSPITAL GENERAL
DE MÉXICO

www.elsevier.es/hgmx



CLINICAL CASE

Allergic bronchopulmonary aspergillosis in teenager with bronchial asthma



C.I. Urquiza-Ramírez*, G.A. Eliosa-Alvarado, S. González-Flores,
J.C. Fernández de Córdova-Aguirre, A.A. Velasco-Medina, G. Velázquez-Sámamo

Servicio de Alergia e Inmunología Clínica, Hospital General de México "Dr. Eduardo Liceaga", Mexico City, Mexico

Received 13 February 2017; accepted 8 May 2017
Available online 27 June 2017

KEYWORDS

Allergic
bronchopulmonary
aspergillosis;
Hypersensitivity
mechanisms;
Asthma;
Bronchiectasis

Abstract Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by hypersensitivity mechanisms against antigens released by *Aspergillus* species, colonizing the airways.

We present the case of a 16-year-old male with a history of asthma and allergic rhinoconjunctivitis with a history of 15 months of cough with purulent sputum, intermittent fever and dyspnea. Thoracic tomography showed bronchiectasis accompanied by mucus impaction. He was treated with different antibiotics and steroid regimens, without a favorable clinical response. The presence of eosinophilia in the peripheral blood, immunoglobulin E Total, skin tests for *Aspergillus* positive guided the diagnosis of ABPA. Treatment with prednisone plus itraconazole was started, with remission of symptoms.

ABPA should be suspected in patients with asthma with poor response to treatment and alteration in radiologic studies. Treatment includes systemic steroids and avoiding exposure to *Aspergillus*.

© 2017 Sociedad Médica del Hospital General de México. Published by Masson Doyma México S.A. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALABRAS CLAVE

Aspergilosis
broncopulmonar
alérgica;
Mecanismos de
hipersensibilidad;
Asma;
Bronquiectasias

Aspergilosis broncopulmonar alérgica en adolescente con asma bronquial

Resumen La aspergilosis broncopulmonar alérgica (ABPA) es un trastorno pulmonar causado por mecanismos de hipersensibilidad contra antígenos liberados por especies de *Aspergillus*, que colonizan las vías respiratorias.

Presentamos el caso de un varón de 16 años con antecedentes de asma y rinoconjunctivitis alérgica con historia de 15 meses de tos con esputo purulento, fiebre intermitente y disnea. La tomografía torácica reporto bronquiectasias acompañadas de impactación de moco. Se le trató con diferentes regímenes de antibióticos y esteroides, sin tener una respuesta clínica favorable.

* Corresponding author at: Dr. Balmis 148, Cuauhtémoc, Doctores, 06726 Mexico City, Mexico.
E-mail address: dr.urquizaramirez@gmail.com (C.I. Urquiza-Ramírez).

La presencia de eosinofilia en la sangre periférica, inmunoglobulina E Total elevada y pruebas cutáneas para *Aspergillus* positivo guiaron el diagnóstico de ABPA. Se inició tratamiento con prednisona más itraconazol, con remisión de los síntomas.

Debe sospecharse ABPA en pacientes con asma con mala respuesta al tratamiento y alteración en los estudios radiológicos. El tratamiento incluye esteroides sistémicos y evitar la exposición a *Aspergillus*.

© 2017 Sociedad Médica del Hospital General de México. Publicado por Masson Doyma México S.A. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by a hypersensitivity mechanisms type I, III and IV against antigens released by *Aspergillus* species, colonizing the airways of patients mainly with asthma and cystic fibrosis (CF).^{1,2}

In predisposed individuals, disease occurs following colonization of the bronchi by *Aspergillus* conidia. The fungal hyphae extend, and allergens are released, leading to persistent airway inflammation resulting in excessive viscous mucous production and impaired mucociliary function. ABPA is clinically characterized by poorly controlled asthma, recurrent pulmonary infiltrates, and bronchiectasis, in some cases can leading to pulmonary fibrosis.³

In Mexico, its prevalence is unknown, however different case reports have been published.⁴ It is estimated that ABPA affects 12.9% (2–32%) of the asthmatic population; in steroid-dependent asthmatics the prevalence is thought to be 7–14%.^{5,6} It occurs with equal frequency in both sexes. Most patients are less than 35 years old at the time of diagnosis.⁷

Clinical case presentation

A 16 year old male patient with a previous diagnosis of asthma and allergic rhinoconjunctivitis since he was 6 years old, is evaluated in our department of allergy and immunology having history of 15 months of cough with purulent sputum, intermittent fever, progressive dyspnea and acrocyanosis. Six months after onset of symptoms he was hospitalized in pediatric unit for 2 months with diagnosis of pneumonia, treated with different antibiotics. The chest X-rays showed a reticular pattern accompanied by images suggesting bronchiectasis, computed tomography of the lungs confirmed central bronchiectasis, accompanied by mucoid impaction and reticular infiltrates (see Figs. 1–3).

Due to poor response to treatment, were performed multiple studies among them: sputum smear microscopy in 3 determinations negative, tuberculin test negative, Chlorine test in the sweat (Chlorimetry and conductivity) two determinations negative, the flow cytometry and the nitroblue tetrazolium test were within normal limits, the immunoglobulins were not compatible with some pattern of Immunodeficiency, so it was ruled out that it was pulmonary



Figure 1 X-ray chest shows right posterior basal segmental atelectasis, the lungs present diffuse interstitial reticulum infiltrates, inflammatory infiltrates in the left lung base, bronchiectasis in principal and segmental bronchi, associated right pleural effusion. In addition, right subdiaphragmatic intestinal loops (Chilaiditi syndrome).

tuberculosis, cystic fibrosis or some primary immunodeficiency.

An attempt was made to perform fiberoptic bronchoscopy but patient presented significant desaturation during the procedure, which impeded the conclusion of the procedure and take samples.

He was discharged with mild clinical improvement and oxygen dependence, Nine months after discharge was evaluated in our service of allergy and immunology, were performed the following studies: Blood peripheral eosinophils 9.1% (absolut # 700), total IgE: 455 IU/mL (NV: <150), specific IgG for *Aspergillus fumigatus* 4.19 mgA/L (NV: <2.0), sputum cytology studies reported polymorphonuclear cells 3+, eosinophils 3+, negative sputum culture for fungi, positive skin prick tests for *Aspergillus fumigatus*,



Figure 2 Computed tomography of the chest, axial section with a window for pulmonary parenchyma in which atelectasis with mucus impaction is observed in the lower right lobe (segments 7, 8 and 10). Cystic bronchiectasis with mucus impaction in the left lower lobe (segments 9 and 10).



Figure 3 Coronal reconstruction with window for pulmonary parenchyma in which consolidation is observed in the right upper lobe and parenchymal bands. Atelectasis with mucus impaction in the right lower lobe. In the lower left lobe there is consolidation, thickening of the wall of the main bronchus.

Chenopodium album, *Prosopis* spp., *Fraxinus americana*, *Dermatophagoides* spp.

Respiratory Functional Tests demonstrated a very severe flow obstruction without response to bronchodilator (Albuterol) with data suggesting pulmonary distention and increased resistance and severely decreased diffusion. With the clinical and laboratory data, we concluded that the patient had allergic bronchopulmonary aspergillosis stage 1. Treatment was started with prednisone at 1 mg/kg/day for

2 weeks then 0.5 mg/kg/day for 12 weeks and tritrated to 5 mg/day.

He was kept with prednisone 5 mg/day for a year, combined with itraconazole 200 mg/day for 6 months, salmeterol/fluticasone 50/500 µg bid. The patient was evaluated in a month and then every 2 months, at 6 months follow-up had significant clinical improvement. He had suspended supplemental oxygen and returned to normal activities at home and at school.

Discussion

ABPA should be suspected in patients with asthma who have a poor response to usual treatment since an appropriate management can cause an impact on quality of life because ABPA symptoms may be severe and leading to pulmonary fibrosis.

Aspergillus-related pulmonary disorders may be classified into four clinical categories depending on whether the host is atopic, non-atopic or immunosuppressed (see Table 1),⁷ Invasive aspergillosis (IA) is seen in patients with severe neutropenia, allogeneic bone marrow transplantation, prolonged use of systemic steroids, treatment with immunosuppressants and primary immunodeficiency, our patient did not have any of these conditions.⁸

ABPA is commonly caused by *A. fumigatus*, an ubiquitous mold common in indoors and frequently found around farm buildings and compost heaps. It is a Th2 hypersensitivity lung disease caused by bronchial colonization with *A. fumigatus*, characterized by asthma exacerbations, recurrent transient chest radiographic infiltrates, peripheral and pulmonary eosinophilia, especially during an exacerbation. Diagnosis is based on clinical and immunologic criteria for ABPA, standardized by Greenberger and Patterson: (1) asthma or CF with deterioration in lung function, (2) *Aspergillus* species immediate skin test reactivity, (3) total serum IgE level of 1000 ng/mL (417 IU/mL) or greater, (4) increased specific IgE and IgG antibodies for *Aspergillus* species-, and (5) chest radiographic infiltrates. Additional criteria modified might include peripheral blood eosinophilia, *Aspergillus* species serum precipitating antibodies, central bronchiectasis, and *Aspergillus* species-containing mucus plugs⁹⁻¹¹ (see Table 2). The case that we presented complied with the 5 criteria according to original criteria of Greenberger and Patterson, complying for both central bronchiectasis and for seropositive ABPA.

Galactomannan (GM) detection contributes to the diagnosis of IA, even form part of the diagnostic criteria, however for ABPA Agarwal et al. suggest that serum GM estimation has a limited role in the diagnostic workup.^{8,12}

ABPA can be divided into five stages, each stage representing a different category of presentation (Table 3). Determining the stage in which the patient is important for treatment and prognosis.¹³ Our patient was in stage 1 of the disease.

The aim of treatment in ABPA is to reduce episodic acute inflammation, thus limiting disease progression with resultant airway destruction and both parenchymal and airway fibrosis. To achieve this, a dual treatment approach is required: corticosteroids to control immunological activity and antifungal azole agents to suppress *Aspergillus*

Table 1 Pulmonary aspergillosis clinical syndromes.

Invasive aspergillosis	Allergic or hypersensitivity reactions	Saprophytic colonization	Mycotoxicosis
- <i>Generalized or disseminated</i>	- Allergic asthma	Aspergilloma (mycetoma or fungus ball)	Chemical pneumonitis
a. Aspergillosis pneumonia	- Allergic bronchopulmonary aspergillosis		
b. Angioinvasive aspergillosis	- Extrinsic allergic alveolitis		
c. Lung abscess and multiple cavities	- Bronchocentric granulomatosis		
d. Aspergillosis bronchitis/tracheobronchitis			
e. Infarction			
f. Pleural effusion and empyema			
- <i>Localized or limited</i>			
a. Chronic necrotizing pulmonary aspergillosis			

Table 2 Criteria for the diagnosis of ABPA in patients with asthma.

	Minimal essential criteria
<i>Criteria for ABPA-central bronchiectasis</i>	
1. Asthma	Yes
2. Central bronchiectasis	Yes
3. Immediate cutaneous reactivity to <i>Aspergillus</i> species	Yes
4. Total serum IgE concentration > 417 kU/L (1000 ng/mL)	Yes
5. Elevated serum IgE and or IgG to <i>A. fumigatus</i>	Yes
6. Chest roentgenographic infiltrates	No
7. Serum precipitating antibodies to <i>A. fumigatus</i>	No
<i>Criteria for the diagnosis of ABPA-seropositive</i>	
1. Asthma	Yes
2. Immediate cutaneous reactivity to <i>Aspergillus</i> species	Yes
3. Total serum IgE concentration > 417 kU/L (1000 ng/mL)	Yes
4. Elevated serum IgE and or IgG to <i>A. fumigatus</i>	Yes
5. Chest roentgenographic infiltrates	No

CT, computed tomography.

Table 3 Stages of ABPA.

Stage	Description	Radiographic infiltrates	Total serum IgE
I	Acute	Upper lobes or middle lobe	Sharply elevated
II	Remission	No infiltrate and patient off prednisone for >6 mo	Elevated or normal
III	Exacerbation	Upper lobes or middle lobe	Sharply elevated
IV	Corticosteroid-dependent	Asthma Often without infiltrates, but intermittent infiltrates might occur	Elevated or normal
V	End stage	Fibrotic, bullous, or cavitaries lesions	Might be normal

colonization and proliferation, which reduce antigenic stimulation, limiting further inflammation. However, reviews have emphasized the weakness of the evidence for safety and efficacy of azoles, with only two small, short-term, randomized, double-blind, placebo-controlled trials in asthmatic ABPA, and none in cystic fibrosis ABPA. There are potential alternative approaches to antifungal treatment that avoid systemic effects, azole resistance and drug interactions; Inhaled amphotericin B has been explored as an ABPA treatment with varying results in uncontrolled studies. Finally, the success of omalizumab (anti-IgE monoclonal antibody) in improving control of moderate-severe allergic asthma has led to great interest and rapidly increasing usage in ABPA, usually undertaken as a steroid-sparing agent, with virtually unanimous reporting of reduced steroid requirements and exacerbations in published uncontrolled studies.¹⁴⁻²⁰

Our patient had a good response with combined treatment with prednisone and itraconazole, with clinical improvement. He stopped using supplemental oxygen and six months later of start treatment was able to return to previous physical activities. On last visit, we were able to stop prednisone and was only using inhaled same-terol/fluticasone 50/250 µg bid.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Funding

No funding was received for this study.

Conflict of interest

The authors have no conflict of interests to declare.

References

- Bains S, Judson M. Allergic bronchopulmonary aspergillosis. *Clin Chest Med.* 2012;33:265-81.
- Matsuoka H, Uzu T, Koyama M, et al. Allergic bronchopulmonary aspergillosis presenting with cough variant asthma with spontaneous remission. *Respir Med CME.* 2011;4:175-7.
- Hogan C, Denning D. Allergic bronchopulmonary Aspergillosis and related allergic syndromes. *Semin Respir Crit Care Med.* 2011;32:682-92.
- Fernández de Córdova-Aguirre JC, Velasco-Medina AA, Cariño-Cartagena DA, et al. Aspergillosis broncopulmonar alérgica. *Rev Alerg México.* 2014;61:121-6.
- Agarwal R, Aggarwal AN, Gupta D, et al. Aspergillus hypersensitivity and allergic bronchopulmonary aspergillosis in patients with bronchial asthma: systematic review and meta-analysis. *Int J Tuberc Lung Dis.* 2009;13:936-44.
- Tillie-Leblond I, Tonnel AB. Allergic bronchopulmonary aspergillosis. *Allergy.* 2005;60:1004-13.
- Amchentsev A, Kurugundla N, Saleh A. Aspergillus-related lung disease. *Respir Med CME.* 2008;1:205-15.
- Fortún J, Meije Y, Fresco G, et al. Aspergilosis. Formas clínicas y tratamiento. *Enferm Infecc Microbiol Clin.* 2012;30:201-8.
- Knutsen A, Bush R, Demain J, et al. Fungi and allergic lower respiratory tract diseases. *J Allergy Clin Immunol.* 2012;129:280-91.
- Agarwal R, Maskey D, Aggarwal AN, et al. Diagnostic performance of various tests and criteria employed in allergic bronchopulmonary Aspergillosis: a latent class analysis. *PLoS ONE.* 2013;8:e61105.
- Schulze J, Zissler U, Martin Christmann M. Allergic bronchopulmonary aspergillosis (ABPA) an IgE mediated disease? *Respir Med CME.* 2011;4:33-4.
- Agarwal R, Aggarwal AN, Sehgal IS, et al. Performance of serum galactomannan in patients with allergic bronchopulmonary aspergillosis. *Mycoses.* 2015;58:408-12.
- Greenberger PA. Allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol.* 2002;110:685-92.
- Patterson R, Greenberger PA, Radin RC, et al. Allergic bronchopulmonary aspergillosis: staging as an aid to management. *Ann Intern Med.* 1982;96:286-91.
- Agarwal R, Aggarwal AN, Dhooria S, et al. A randomised trial of glucocorticoids in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J.* 2016;47:490-8.
- Tucker RM, Haq Y, Denning DW, et al. Adverse events associated with itraconazole in 189 patients on chronic therapy. *J Antimicrob Chemother.* 1990;26:561-6.
- Chishimba L, Niven RM, Cooley J, et al. Voriconazole and posaconazole improve asthma severity in allergic bronchopulmonary Aspergillosis and severe asthma with fungal sensitization. *J Asthma.* 2012;49:423-33.
- Chishimba L, Langridge P, Powell G, et al. Efficacy and safety of nebulised amphotericin B (NAB) in severe asthma with fungal sensitisation (SAFS) and allergic bronchopulmonary aspergillosis (ABPA). *J Asthma.* 2015;52:289-95.
- Godet C, Meurice JC, Roblot F, et al. Efficacy of nebulised liposomal amphotericin B in the attack and maintenance treatment of ABPA. *Eur Respir J.* 2012;39:1261-3.
- Voskamp AL, Gillman A, Symons K, et al. Clinical efficacy and immunologic effects of omalizumab in allergic bronchopulmonary aspergillosis. *J Allergy Clin Immunol Pract.* 2015;3:192-9.