

Case Report

Allergic Bronchopulmonary Aspergillosis with Normal Serum IgE in a Child with Cystic Fibrosis

DANIELLE DORSANEO, M.D.,¹ DRUCY BOROWITZ, M.D.,¹ JACK SHARP, M.D.,¹
and RICHARD MOSS, M.D.²

ABSTRACT

Diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA) in patients with cystic fibrosis have required an absolute increase in total serum immunoglobulin E (IgE) to >1000 IU/mL (2400 ng/mL). Current guidelines recommend in depth evaluation for those with IgE >500 IU/mL (1200 ng/mL), or even for those with lower values if there is clinical suspicion for ABPA. We present a case of a patient who met all criteria for ABPA with the exception of elevation of IgE above the diagnostic level. An increase in serum IgE from the baseline level, but not >1000 IU/mL, and subsequent return to baseline corresponded to a clinical exacerbation and resolution of presumptive ABPA. (Pediatr Asthma Allergy Immunol 2004; 17[2]:146–150.)

INTRODUCTION

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA) is a hypersensitivity reaction to *Aspergillus fumigatus* (Af) that occurs in 1–15% of cystic fibrosis (CF) patients.^{1,2} Marked elevation of *Aspergillus*-specific immunoglobulin E (IgE) antibodies, nonspecific elevation of total serum IgE, and increased levels of IgA and IgG *Aspergillus*-specific antibodies were seen.^{2,3} In June, 2001, new diagnostic criteria were developed by a Cystic Fibrosis Foundation (CFF)-sponsored Consensus Conference panel to aid in the diagnosis of ABPA in patients with CF. The minimal criteria for diagnosis include the following: (1) clinical deterioration; (2) total serum IgE >1000 IU/mL (2400 ng/mL); (3) immediate cutaneous reactivity to Af or Af-specific IgE antibodies, in addition to either precipitins to Af/Af-specific IgG antibodies or abnormal chest radiograph/change from previous examination.^{4,5}

The pathogenesis of ABPA involves the colonization of Af spores within mucus plugs in the bronchial tree and impaired mucociliary clearance of these spores, resulting in mycelial growth and release of cytoplasmic antigens, eosinophilic and lymphocytic infiltrates, and a local and systemic humoral immune response. Marked elevation of *Aspergillus*-specific IgE antibodies, nonspecific elevation of total serum IgE, and increased levels of IgA and IgG *Aspergillus*-specific antibodies are seen.^{2,3} The immune response to

¹Department of Pediatrics, University at Buffalo School of Medicine and Biomedical Sciences, Buffalo, NY 14222.

²Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA 94304.

ABPA demonstrates increased levels of Af-reactive CD4⁺ TH2 cells that secrete interleukin-4 (IL-4). It has been hypothesized that some CF patients may have increased baseline levels of Af-reactive TH2 CD4⁺ cells, predisposing these patients to ABPA.⁶ Furthermore, there may be certain HLA alleles that make CF patients susceptible to ABPA, including HLA DR2 and DR5 versus alleles that may protect against ABPA, such as HLA DQ2.²

Previously published diagnostic criteria of ABPA in CF required an absolute increase in total serum IgE to >1000 IU/mL,^{5,7} and the current guidelines recommend in-depth evaluation for those with IgE >500 IU/mL (1200 ng/mL), and even for those with lower values if there is clinical suspicion. We present a case in which an increase in serum IgE from the patient's baseline level, rather than an absolute increase in serum IgE, corresponded to clinical ABPA. This case illustrates the potential presence of ABPA in CF patients, even when total serum IgE levels remain substantially below 500 IU/mL.

CASE

A Caucasian female was evaluated at age 15 months because of chronic cough and severe maxillary sinusitis. A chest radiograph demonstrated right lower lobe streaky linear infiltrates. A chest CT scan demonstrated air trapping and mildly dilated airways with thickened walls. The patient had evaluations for common allergies and immune deficiency, gastroesophageal reflux, and ciliary dyskinesia, all of which were negative. Sweat chloride levels were 33 and 36 mEq/L and were not considered diagnostic of CF. Four months after her presentation, the patient underwent sinus surgery and bronchoscopy; cultures revealed *Pseudomonas aeruginosa*. The diagnosis of CF was made when genetic analysis revealed the 621 + 1G-T/3849 + 10 kbC-T genotype. Both components of the genotype are known mutations causing CF and can result in normal sweat tests and milder pulmonary disease compared to the more common Δ F508 mutation. These components affect the level of mRNA and CFTR protein required for normal function.⁸ Calculation of the coefficient of fat absorption indicated that the patient was pancreatic sufficient. The patient began chest physical therapy and nebulized tobramycin after her diagnosis with good resolution of her cough.

The patient remained clinically stable until the age of 4 years. At that time, her cough increased and did not respond readily to DNase, airway clearance, nebulized tobramycin, or oral antibiotics. She was admitted to the hospital for intravenous (i.v.) antibiotics. A chest CT was dramatically different from the previous exam performed around the time of her diagnosis, and demonstrated extensive mucus plugging and bronchiectasis (Fig. 1A). At this time, the patient had a serum IgE level of 150 IU/mL (Table 1).

Three months later, she was readmitted to the hospital she but did not improve despite aggressive airway clearance and i.v. antibiotics. Her total serum IgE at that time was 281 IU/mL (Table 1). Cultures obtained during bronchoscopy were significant for growth of *Aspergillus* species. The cell count revealed 82% neutrophils and 2% eosinophils. In light of her clinical symptoms, marked mucus plugging and bronchiectasis on chest CT, a positive skin test to *Aspergillus*, and elevated serum IgE and *Aspergillus*-specific IgE and IgG, she was diagnosed presumptively with ABPA and placed on prednisone and itraconazole. Two weeks after starting this treatment, the patient's symptoms improved. Her total serum IgE decreased to 73 IU/mL. Three months after treatment was started, the patient's cough remained under good control and her total serum IgE was 15 IU/mL (Table 1). A repeat chest CT 5 months after her treatment began showed significant improvement (Fig. 1B).

DISCUSSION

This patient met all of the minimal criteria for ABPA defined in the recent CFF Consensus Conference, except for an absolute increase in IgE to >1,000 IU/mL. Specifically, she had a clinical deterioration, immediate cutaneous reactivity to *Aspergillus*, elevation of both *Aspergillus*-specific IgE and IgG antibodies, and change in the chest CT from baseline examination, including vast mucus plugging. However, the elevation of her *Aspergillus*-specific IgE was not dramatic, and total IgE level was only moderately elevated above normal limits for her age.

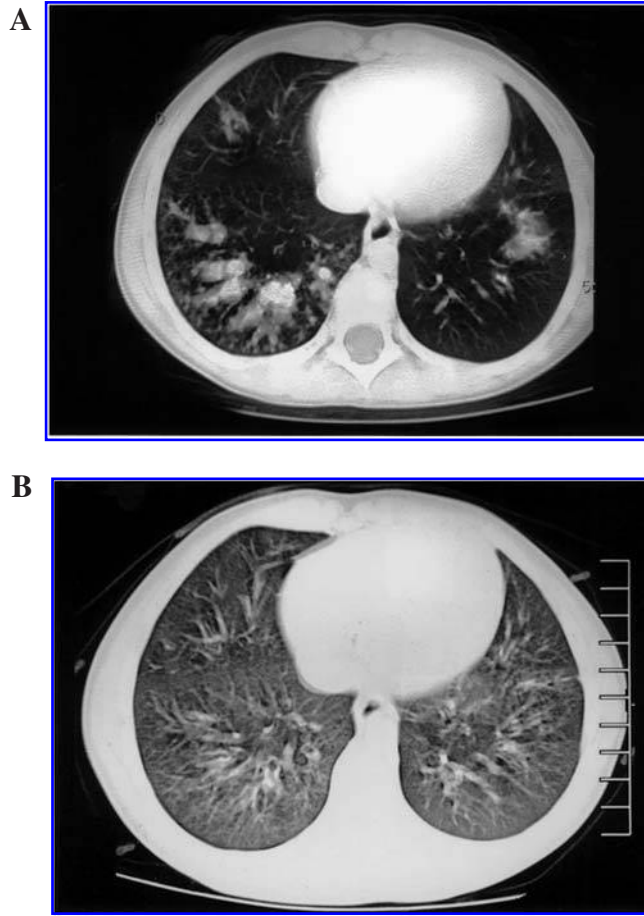


FIG. 1. The patient's chest CT (A) at the onset of symptoms and (B) following treatment for allergic bronchopulmonary aspergillosis. Slices are at approximately the same level, but different equipment and techniques were employed.

TABLE 1. LABORATORY VALUES

<i>Date</i>	<i>% Eosinophils</i>	<i>Total serum IgE (IU/ml)</i>	<i>Aspergillus-specific IgE (KU/L)</i>	<i>Aspergillus-specific IgG (UG/ml)</i>	<i>Comments</i>
10/19/1999	1	22			
10/23/2000	1	8			
10/1/2001	8	150			
1/9/2002	8	281	2.95	>200	Prednisone and Itraconazole treatment instituted
3/19/2002	0	73			
5/13/2002	1	15	<0.11		
6/26/2002	1	16	0.72	27	Prednisone and Itraconazole treatment stopped
9/17/2002	3	20	<0.05 IU/mL ^a		

^aPatient's insurance required using a different reference lab for *Aspergillus*-specific antibodies.

Atopy has been associated with ABPA.^{1,9,10} Sensitization to non-*Aspergillus* antigens could also account for a modest rise in serum IgE. However, this patient had skin testing and was not found to be sensitive to common aeroallergens. Although the patient did not have an absolute rise in serum IgE to greater than 1,000 IU/mL, she did have a rise from her baseline level of between 8–22 IU/mL to 281 IU/mL. In light of the 10-fold increase of IgE from baseline and the presence of the other diagnostic criteria, corticosteroid treatment was instituted, resulting in a significant clinical, biochemical, and radiologic improvement. The drop in total IgE immediately following start of prednisone therapy strongly supports the diagnosis of ABPA.¹ Maiz *et al.* described a child with CF and ABPA who had a serum IgE <500 IU/mL.¹¹ However, that patient's IgE did not decrease substantially after treatment with prednisone. Marchant *et al.* reported 12 children with CF diagnosed with ABPA, including one child with maximum total IgE of 341 IU/mL. Those children had at least four-fold rises in total IgE from baseline during an ABPA exacerbation. They further noted that, with the exception of one child who died during the acute exacerbation, all had a substantial reduction in total IgE with systemic corticosteroid therapy.¹² Hutcheson *et al.* have reported that CF patients have variable baseline laboratory values, including serum IgE and IgG to Af, total serum IgE, skin test, and precipitating antibody test to Af.¹³ This emphasizes the necessity of examining the clinical picture as well as the relative increase in serum IgE compared to the patient's own baseline value.

The 3849 + 10 kb C-T mutation has been associated with CF in which patients have normal sweat tests, milder lung disease, and pancreatic sufficiency.⁸ There are several possible reasons for the observed discrepancy between this patient's genotype and her apparently severe pulmonary phenotype. The immune response to ABPA demonstrates increased levels of Af-reactive CD4⁺ TH2 cells that secrete IL-4. It has been hypothesized that some CF patients may have increased baseline levels of Af-reactive TH2 CD4⁺ cells, predisposing these patients to ABPA.⁶ Perhaps the presence of HLA alleles that are associated with ABPA susceptibility or modifier genes that increase the TH2 response may have made the patient more likely to have ABPA than one might predict from her CFTR genotype.^{6,14} Studies have suggested that HLA-DR2 and DR5 are more frequently observed in CF patients with ABPA than with other CF patients or healthy controls, which may contribute to susceptibility while HLA-DQ2 was observed more frequently in patients without ABPA, suggesting an element of protection.¹⁴ One may hypothesize that eventually the ABPA diagnostic criteria could be extended to include information on HLA typing once this relationship is further elucidated.

This patient's pulmonary involvement is also notable in light of the fact that she is pancreatic sufficient. Kerem *et al.* demonstrated that pulmonary function is significantly better in pancreatic-sufficient patients as compared to pancreatic-insufficient patients.¹⁵ The discordance between the expected and observed degree of lung involvement in our patient contributed to a higher index of suspicion for ABPA.

This case emphasizes the importance of obtaining baseline total IgE levels in patients with CF, maintaining a high level of suspicion for ABPA if there is a marked change from baseline levels, and the importance of documenting a decrease in serum IgE when a patient is being treated presumptively for ABPA but the diagnosis is not clear-cut. The recent CFF Consensus Conference on ABPA recommended obtaining annual total serum IgE levels in CF patients.⁴ ABPA should be considered in an individual who has a relative, but not an absolute, rise in total serum IgE if other diagnostic criteria for ABPA are met.

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Address reprint requests to:

Drucy Borowitz, M.D.

Division of Pediatric Pulmonology

Women and Children's Hospital of Buffalo

219 Bryant Street

Buffalo, NY 14222

E-mail: dborowitz@upa.chob.edu

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