

COMMENTARY

Nonsystemic allergic bronchopulmonary aspergillosis in cystic fibrosis: A suggested paradigm for the evolution from topical to systemic disease

Carolina Miranda¹ | Monica Cardenas¹ | Mariana Bedoya¹ | George Retsch-Bogart² | Andrew A. Colin¹ 

¹Division of Pediatric Pulmonology, Miller School of Medicine, University of Miami, Miami, Florida

²Division of Pediatric Pulmonology, University of North Carolina, Chapel Hill, North Carolina

Correspondence

Andrew A. Colin, Division of Pediatric Pulmonology, 1580 NW 10th Ave, Miami, FL 33136.

Email: acolin@med.miami.edu

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1 | INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a well-established diagnosis and represents an entity in the ill-defined spectrum of fungal disease in patients with cystic fibrosis (CF). We are describing a case of a child with a unique presentation of recurrent eosinophilic inflammation of the airways with *Aspergillus* and diffuse airway obstruction with severe morbidity. He had positive immunoglobulin E (IgE) specific for *Aspergillus fumigatus* (AF), however, the conventional systemic markers of ABPA; notably increased total IgE, specific immunoglobulin G (IgG) for AF, and the skin testing were negative. We proposed to define this as localized *Aspergillus*-related airway eosinophilic inflammation and speculate this unique presentation of *Aspergillus* bronchitis, which may be the precursor of ABPA.

2 | CASE REPORT

A 7-year-old boy presented with a lifetime diagnosis of CF, pancreatic insufficiency, chronic sinusitis (S/P four sinus surgeries), and hypogammaglobulinemia (on weekly subcutaneous immunoglobulin therapy). The child underwent multiple bronchoscopies predominantly for surveillance when he had endotracheal intubation for sinus surgery or performed to manage recurrent episodes of

atelectasis. The bronchoalveolar lavage (BAL) fluid samples obtained from different lung segments in repeated bronchoscopies were negative for bacteria, except once when *Haemophilus influenzae* (O1 May 2015) was isolated, treated, and subsequently resolved. The culture and cytologic analyses of bronchoscopies over the period 2015-2017 are shown in Table 1. Total serum IgE was followed routinely and was always within the normal range. Specific AF IgE was positive (1.3 kU/L), yet specific AF IgG and skin testing for *Aspergillus* were negative. He had intermittent eosinophilia in peripheral blood ranging from 9% to 15%.

During 2015, he had two episodes of right middle lobe (RML) opacification consistent with atelectasis. He underwent bronchoscopy on the first occasion (September 2015) revealing RML bronchial mucosal erythema and scant secretions. Both events resolved with intensification of chest physical therapy (CPT), enhanced lung clearance, antibiotic therapy, bronchodilator inhalation, and systemic corticosteroids. During these events, he complained of chest tenderness over the right anterior chest during his routine CPT and his mother reported nocturnal sweating, both of which resolved as the radiographic abnormalities improved.

In August 2016, he presented with sinus tenderness, increasing cough, and again complained of right chest tenderness with CPT. After failing to improve with 2 weeks of oral antibiotic therapy, he was admitted for treatment of acute CF pulmonary exacerbation and acute worsening of chronic sinusitis. He was treated with intravenous antibiotic therapy targeting the bacterial pathogens previously isolated from his sinuses; *Pseudomonas aeruginosa* and *Methicillin-sensitive Staphylococcus aureus*.

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AF, *Aspergillus fumigatus*; BAL, bronchoalveolar lavage; CF, cystic fibrosis; CPT, chest physiotherapy; RML, right middle lobe.

Miranda and Cardenas have contributed equally to this work.

TABLE 1 Timeline of bronchoalveolar lavages with cytology and microbiology cultures

Date	Cytology, %		Bacterial culture	Fungal smear/culture	
	Right	Left		Right	Left
06/02/2017	M25, N56, L4, E15	M65, N27, L7, E1	Negative	Rare hyphal elements <i>Aspergillus fumigatus</i>	Negative
11/10/2016	M80, N18, L2, E0	M94, N4, L2, E0	Negative	Negative	Negative
08/19/2016 (UNC)	M7, N41, L13, E22, other 17 Mucous plugs with degenerating eosinophils and Charcot-Leyden crystals with admixed fungal microorganisms, consistent with ABPA	M21, N44, L2, E4, other 29	Negative	GMS stain positive for fungal microorganisms	Negative
04/29/2016	M62, N38, L0, E0	M42, N57, L1, E0	Negative	Negative	Negative
09/14/2015	M80, N20, L0, E0	M84, N11, L0, E0	Negative	Negative	Negative
05/01/2015	M59, L37, L2, E2	M53, N43, L3, E1	<i>Haemophilus influenzae</i>	Negative	Negative

Abbreviations: E, eosinophils; GMS, Grocott-Gomori's methenamine silver stain; L, lymphocytes; M, macrophages; N, neutrophils; UNC, University of North Carolina.

Lung examination on admission revealed few crackles and minimally decreased aeration over the RML. Chest radiography was delayed awaiting PICC line placement given his unchanged physical examination and complete resolution of the crackles was noted on admission. Decreased aeration over the right lower lobe (RLL) was noted by day 3 of admission and the radiograph revealed RLL and RML atelectasis (Figure 1A). On day 5, he was discharged to continue IV antibiotic therapy (ceftazidime, tobramycin, and clindamycin), prednisone for 5 days, dornase alfa twice-daily, hypertonic saline twice-daily, Vibralung treatments, and aggressive CPT by his home respiratory therapist. At home, he had decreased exercise tolerance and intermittent episodes of oxyhemoglobin desaturation to 90%, which improved with CPT. One week after discharge, his lung examination worsened. Repeated chest X-ray showed interval worsening with RML and RLL collapse and mediastinal shift to the right (Figure 1B).

Flexible bronchoscopy performed after 9 days of antibiotic treatment showed thick and tenacious mucus obstructing all

segments of the right lung (Figure 2) only sparing the right upper lobe. The rubbery nature of the secretions required prolonged suctioning to obtain full patency of the airways. Pathologic analysis of the tenacious mucus revealed fungal elements with eosinophils (Figure 3). BAL cytology from RML revealed 22% eosinophils. BAL fluid cultures were negative for bacteria, virus, and fungi. The patient responded to prolonged corticosteroid therapy, with rapid and complete resolution of the radiological changes, and clinical wellness (Figure 1C). Three months later, in November 2016, a month after discontinuation of all steroid therapies, he underwent diagnostic bronchoscopy in conjunction with an elective surgical procedure. Visual inspection revealed no abnormality of the bronchial airway mucosa, normal patency of all orifices, no bacterial or fungal growth, and no eosinophils on BAL (Table 1). The following 6 months, he had repeated minor complaints of cough, and in April 2017, his cough increased, he developed low-grade fever, worsening sinus complaints, and again vague complaints of tenderness to right-sided CPT and night sweating. Repeated chest radiographs in the interim revealed

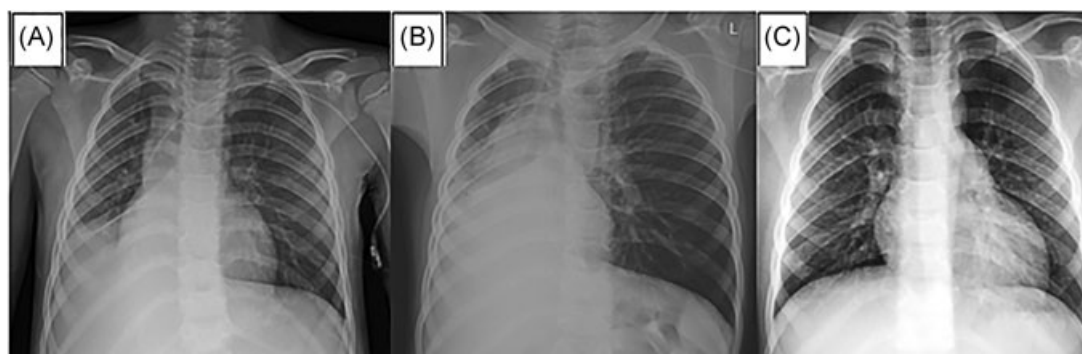


FIGURE 1 A, Atelectasis/collapse affecting right lower lobe and right middle lobe and mediastinal shift. B, Follow-up chest radiograph at 1 week: Interval worsening of right middle/lower lobe collapse. C, Normal chest X-ray 2 weeks post bronchoscopy with complete resolution of right middle lobe collapse

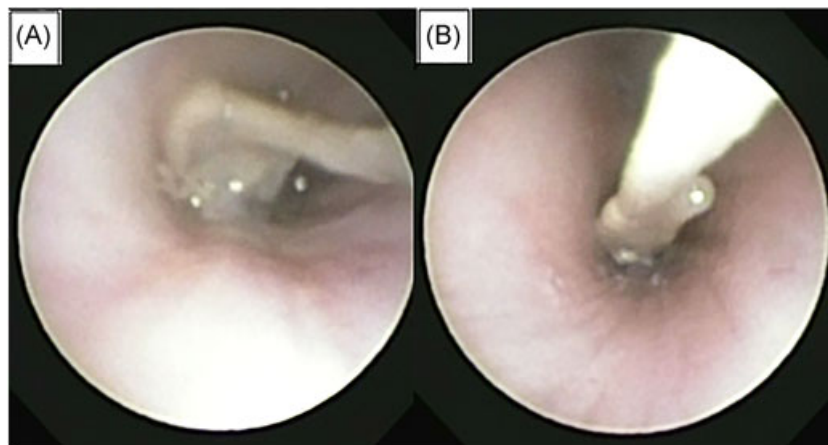


FIGURE 2 A, Bronchoscopic view of right middle lobe bronchus completely obstructed by thick secretions. B, Bronchoscopic view of tenacious “cast-like” mucus removal [Color figure can be viewed at wileyonlinelibrary.com]

no abnormalities such as atelectasis, specifically no change in the RML. As his sinus findings worsened he was taken to his fourth sinus surgery in June 2017. Again, a surveillance bronchoscopy was undertaken while intubated; diffuse erythema of the left-sided bronchial tree was noted, and the medial segment of the RML was mostly obstructed by thick sputum, reminiscent of the bronchoscopy almost a year prior. BAL cytology (Table 1) again revealed increased eosinophils, direct smear revealed *Aspergillus* hyphae, but bacterial and fungal cultures remained negative.

3 | DISCUSSION

This patient presented in August 2016 with severe acute lung involvement, including atelectasis of multiple right lung segments, caused by mucoid impaction of most large bronchi of the right lung, on the background of mild clinical CF lung disease, except two episodes of atelectasis of the RML in the prior year. Curiously, he complained of chest tenderness to physical therapy over the chest wall region corresponding to the RML on all these episodes. Failing medical intervention, bronchoscopy revealed tenacious airway impaction that mandated physical bronchoscopic removal. All cultures of the removed obstructing plugs and BAL were negative, but direct smear revealed fungal elements and 22% eosinophils on BAL.

What should be highlighted in this case is the presence of typical allergic inflammatory airway markers, namely eosinophils, in a CF patient without a previous finding of eosinophils in the airway and lacking features of asthma to suspect CF with allergic asthma. In addition, the airway eosinophils occurred in the presence of fungal elements, assumed to be *Aspergillus*.

Asthma is by far the most common entity associated with airway eosinophils, association with tenacious secretions with airways obstruction is not uncommon. Asthma diagnosis is usually made in patients with CF based on airway reactivity and response to bronchodilator, but not on the basis of eosinophilia, bronchial, or systemic. In our case, this child had no clinical history of asthma, and his prior bronchoscopies were without eosinophils. Rarer conditions such as eosinophilic pneumonias and connective tissue diseases are highly unlikely in this child's presentation. Rare entities related to bronchial impaction known as cast/plastic bronchitis while not phenotypically suggestive in our case, cannot be conclusively ruled out and were found to be associated with rare eosinophils and *Aspergillus* in BAL in one series.¹

The pathogenicity of fungi in CF, specifically the role of *Aspergillus*, is not well characterized. Invasive pulmonary fungal infections, predominantly *Aspergillus* in CF, are diagnosed based on the persistent clinical decline, radiographic changes, and failure of antibiotic therapy for conventional colonizing bacteria, fungal culture positivity, and response to antifungal therapy.² More

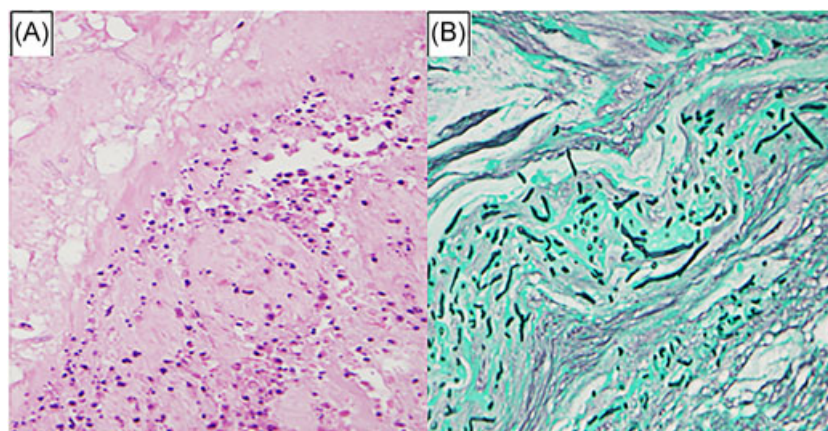


FIGURE 3 A, Photomicrograph of mucus plug showing abundant eosinophils and Charcot-Leydin crystals, modified Wright stain. B, Photomicrograph of mucus plug showing fungal hyphae, Grocott-Gomori's methenamine-silver nitrate stain [Color figure can be viewed at wileyonlinelibrary.com]

important, these are severely ill patients without significant eosinophilia.

ABPA is by far the predominant fungal morbidity in CF, but we found this case unusual enough to report it under the title "Nonsystemic Allergic Bronchopulmonary Aspergillosis (ABPA) in cystic fibrosis".³ We argued that his presentation was reminiscent of cast bronchitis although secretions did not form frank casts. We commented that the findings were consistent with an allergic response to fungi as would be expected in ABPA. However, this child who had intermittent blood eosinophilia (ranging from 9% to 15%), did not present with the conventional parameters for diagnosis of ABPA⁴; having normal serum total IgE, negative IgG to AF, negative skin test to AF, albeit positive IgE to AF on two occasions. He failed intravenous antibiotic therapy and aggressive clearance interventions but unequivocally responded to physical removal of the airway secretions followed by systemic corticosteroid therapy typical for ABPA. A short course of itraconazole was discontinued due to side effects.

A case reminiscent to ours; of tenacious mucus causing severe atelectasis that was difficult to remove by flexible bronchoscopy in a child with CF who was also diagnosed as having ABPA was reported by Cakir et al.⁵ A phenotypically similar description termed "plastic bronchitis" in a 2-year-old patient with CF was suggestive; however, without eosinophils or fungal elements.⁶

A proposed separate clinical entity is that of "*Aspergillus* bronchitis," which is less well defined than APBA, and largely diagnosed on the basis of response to treatment. It is, however, scant in radiologic or bronchoscopic data.⁷ Baxter et al⁸ have proposed a new classification of aspergillosis in adults with CF using established serological markers with the addition of sputum galactomannan and real-time polymerase chain reaction. Further studies on these markers and how the classification system relates to clinical response to treatment have not been completed. This novel classification does support the idea that *Aspergillus* disease in CF may, in fact, present a broader spectrum than the currently defined APBA, and less well defined pulmonary aspergillosis, and raises the question of significance of the presence of *Aspergillus* that is often viewed as a benign colonizer of airways.

We hypothesize that an allergic response to fungi (likely *Aspergillus*) can present with localized involvement in large bronchi, reminiscent of ABPA, which also responds to treatment of ABPA, yet lacks its systemic markers. Follow-up over subsequent months for our case revealed response to steroids (clinically and bronchoscopically); however, some 10 months later, the clinical and bronchoscopic findings, as well as the BAL findings of *Aspergillus* and eosinophils recurred. One could speculate that this represents a *forme fruste* of ABPA, but we submit that our observations suggest that the early presentation of ABPA can be initially limited to a portion of the lung, and that the process may eventually blossom to ABPA; namely, evolution to the broader systemic involvement with the serologic conversion. And, therefore, this may represent a

continuum that starts with this local inflammation and progresses over time to full-blown ABPA with its systemic markers. Whether this child, if left untreated, would progress to ABPA at this point subject to future observation.

This paper is not intended to untangle the broader and complex discussion of the interplay between *Aspergillus* detection and measures of immunologic response, which is attempted by the publication by Baxter et al.⁸ Our case, however, appears to be different from "*Aspergillus* Bronchitis" as discussed by Shoseyov et al,⁷ in the sense that the classification into this entity of their six cases, was lacking in unifying clinical details including information on the bronchial disease via bronchoscopy. The diagnosis was based on persistent positive cultures and response to antifungal medication, neither of which was the case in our patient.

The purpose of this report is to alert others involved in the management of patients with CF to our observations, which we view as different from conventional mucus plugging in CF. We hope that with contribution of other observers we will be able to better characterize the evolution of such cases, and whether they indeed herald the development of ABPA. The pernicious combination of ABPA and CF has long been pointed out,⁹ and the potential to thwart the undesired transition from what we speculate as the presystemic stage to a systemic disease would ultimately be the goal.

ORCID

Andrew A. Colin  <http://orcid.org/0000-0002-2693-2733>

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