



Patient Report

Allergic bronchopulmonary aspergillosis in children

Yunlian Zhou, Dan Xu, Yuanyuan Zhang, Yuanjian Sheng, Xiaoyou Chen and Zhimin Chen

Children's Hospital, Zhejiang University School of Medicine, Hangzhou, China

Abstract Allergic bronchopulmonary aspergillosis (ABPA) is a disease of the lungs resulting from a hypersensitivity reaction to spores of *Aspergillus fumigatus*. Here we report the case of a 13-year-old girl with ABPA who presented with productive cough, bronchiectasis and decline in lung function, and review the clinical features and treatment for pediatric ABPA.

Key words allergic bronchopulmonary aspergillosis, child, *Aspergillus fumigatus*, itraconazole, methylprednisolone.

Allergic bronchopulmonary aspergillosis (ABPA) is a disease of the lungs resulting from a hypersensitivity reaction to spores of *Aspergillus fumigatus*. It is characterized by wheeze, productive cough and pulmonary infiltrates associated with a decline in lung function. The prevalence of ABPA is estimated to be approximately 1–2% in adult patients with asthma and 2–15% in patients with cystic fibrosis (CF).¹ In children, the incidence of ABPA is unknown. Here we report the case of a 13-year-old girl with ABPA who presented with productive cough, bronchiectasis and decline in lung function. The clinical features and treatment for pediatric ABPA are also reviewed.

Case report

A 13-year-old girl was admitted to hospital with a 1 month history of productive cough and chest tightness. She complained of a 7 year history of asthma. The girl was first diagnosed with pneumonia, and treated with ceftriaxone for 6 days and discharged after improving. The illness, however, was aggravated days later. Further investigation was done and the laboratory results were as follows: elevated eosinophils (11%), total immunoglobulin E (IgE; 556 IU/mL), and erythrocyte sedimentation rate (71 mm/h). Serum *Aspergillus*-specific IgG and IgE were both detected using ImmunoCAP system (Phadia, Uppsala, Sweden). *Aspergillus*-specific IgG and IgE were 46.9 mg/L (positive, >44 mg/L) and 38.1 kUA/L (positive, >0.35 kUA/L), respectively. *Aspergillus* skin prick test was positive and immediate. The wheal diameter was 4 mm (positive, >3 mm). Chest high-resolution computed tomography (HRCT) showed infiltration and central bronchiectasis in the left lower lobe and lingula (Fig. 1a). *CF transmembrane conductance regulator* (*CFTR*) sequencing found a mutation at 99C>T, which has not previously been reported. Lung function test showed severe restrictive ventilatory functional disturbance (FEV1: forced expiratory volume in one second 32.7% predicted; vital capacity

31.5% predicted). On flexible bronchoscopy a large amount of purulent material and brownish sputum plugs within the dilated left lobe airways were seen (Fig. 2). Filamentous fungi were cultured from bronchoalveolar lavage (BAL), although no positive results were found in sputum or BAL on microscopy. Tests for other possible pathogens including cultures and/or stains of blood and sputum for viruses, fungi, acid-fast bacilli and bacteria were negative. All tumor markers and antinuclear antibodies were negative. The diagnosis of ABPA was considered. Given that the parents refused corticosteroid therapy due to the side-effects, only fluconazole was prescribed. During the next 3 months, the symptoms persisted and imaging worsened (Fig. 1b). Finally, corticosteroid (methylprednisolone 0.5 mg/kg/day) plus itraconazole was initiated. The girl responded well to the therapy. Two weeks later, she was free of symptoms. Lung function improved to normal. One month later, her condition stabilized. Peripheral eosinophil percentage and IgE decreased to 1.3% and 404 IU/L, respectively. Chest CT showed improvement in pulmonary infiltration (Fig. 1c). Oral itraconazole was stopped 3 months later and corticosteroids were tapered over 5 months. On her last visit to hospital in late July 2013, methylprednisolone tablets were given at a dose of 0.15 mg/kg/day.

Literature review

We performed a search on MEDLINE using the key word “ABPA” with the filter “child: birth-18 years”. The search was limited to human studies published in English and Chinese between January 1970 and August 2013. The abstracts of all articles were used to confirm the target population and the corresponding full text articles were reviewed. Two investigators independently identified the eligible studies. Predefined variables were collected including year of publication and number of patients included, and any inconsistencies between the two investigators in interpretation of data were resolved by consensus. A quality assessment of the included studies was performed independently by two of the authors using SPSS 16.0 (SPSS, Chicago, IL, USA).

Seventy-seven cases were collected. Thirty-three involved girls and 44 involved boys. Mean patient age was 9.9 years. Thirty-two were confirmed as having CF previously while 35 had

Correspondence: Zhimin Chen, MD, Children's Hospital of Zhejiang University School of Medicine, 57 Zhugan Xiang, Hangzhou 310003, China. Email: 17932846@qq.com

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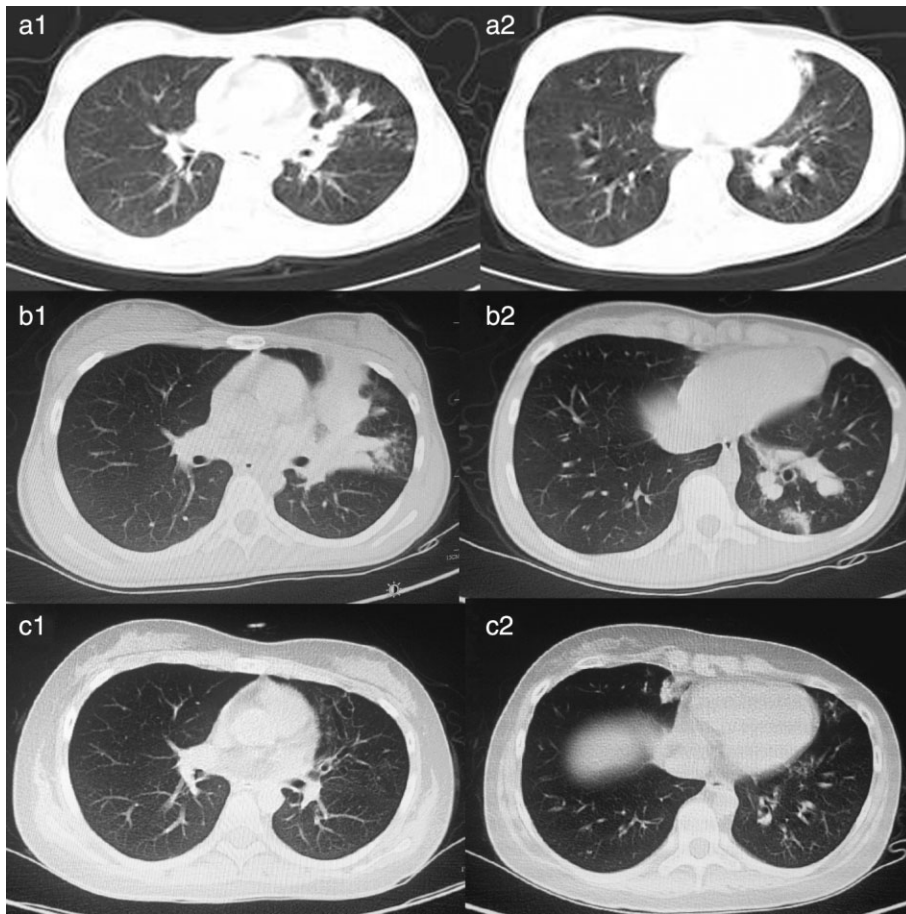


Fig. 1 Chest high-resolution computed tomography: (a) infiltration and central bronchiectasis in the left lower lobe and lingula on 6 December 2012 (before therapy); (b) infiltrates and central bronchiectasis in the left lung on 25 February 2013 (before corticosteroid therapy); (c) improvement of the lung lesion on 7 May 2013 (after corticosteroid and itraconazole therapy). 1–2, different scan levels.

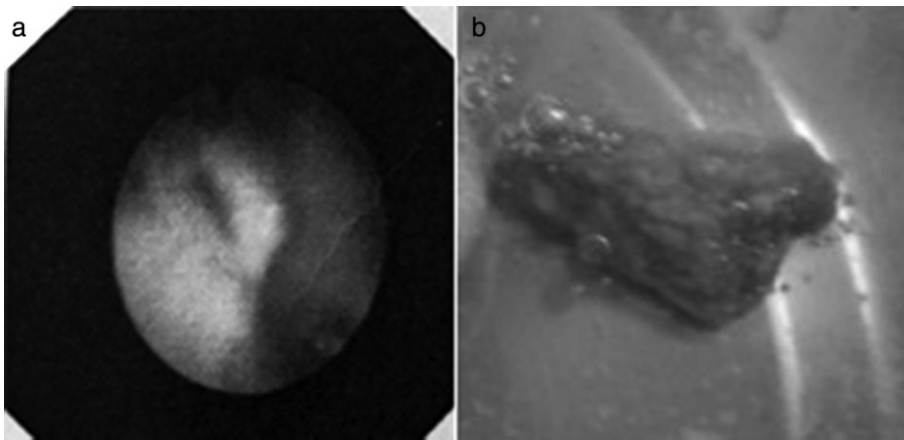


Fig. 2 (a) Bronchoscopy showed a large amount of purulent material and brownish sputum plugs within the left lobe airways. (b) Brownish sputum plugs removed from the left lobe airways on bronchoscopy.

asthma. Other underlying diseases were tuberculosis ($n = 1$) and dysregulation, polyendocrinopathy, enteropathy, and X-linked (IPEX; $n = 1$). Other important information is listed in Table 1.

After treatment, 84.2% of patients had improved, while 12.3% had relapsed. Two patients (3.5%) died despite corticosteroid therapy.

Discussion

Allergic bronchopulmonary aspergillosis was first described by Hinson *et al.* in 1952 in the UK.² It is primarily the result of an

abnormal host immune response to *Aspergillus* antigens. Host immunologic responses are central to the pathogenesis of ABPA, which is defined as a hypersensitivity disorder induced by *Aspergillus* species.³ This disease could happen in more than one family member. It was proposed that ABPA developed in genetically susceptible patients because of increased frequency and/or activity of fumigatus-specific T-helper 2 (Th2) CD4+ cells. The Th2 cytokines lead to total and fumigatus-specific IgE synthesis, mast cell degranulation, and promotion of a strong eosinophilic response.¹ The common pathological findings are persistent

Table 1 Reported cases of ABPA in children

	Positive, n (%)	Total [†]
Signs and symptoms		
Wheeze	43 (81.1)	53
Cough	33 (63.5)	52
Fever	13 (25.0)	52
Dyspnea	14 (25.9)	54
Chest tightness	4 (7.5)	53
Imaging results		
Bronchiectasis	43 (64.2)	67
Lab results		
Elevated total IgE	62 (98.4)	63
Elevated <i>Aspergillus</i> -specific IgE	47 (95.9)	49
Elevated eosinophils	33 (82.5)	40
Positive skin test	36 (90.0)	40
Therapy		
Systemic corticosteroids	52 (92.9)	56
Antifungal medicines	20 (35.7)	56
Omalizumab	9 (15.3)	59
Outcome		
Improved	48 (84.2)	57
Relapsed	7 (12.3)	57
Died	2 (3.5)	57

[†]No. cases described. ABPA, allergic bronchopulmonary aspergillosis.

airway inflammation and fibrosis with destruction of bronchial structural elements leading to mucous plugging and bronchiectasis. If left untreated, end-stage lung disease manifesting as pulmonary fibrosis can result.

In diagnosis, the classic Rosenberg–Patterson criteria are most often used.⁴ The diagnosis of ABPA remains a challenge. First, ABPA is a rare and complicated disease. The second major problem is the lack of standardized allergens mentioned in diagnosis criteria. The present case satisfied seven primary and one secondary criteria. The differential diagnosis of ABPA includes hypereosinophilic syndrome, neoplastic disorders (particularly lymphomas) and so on. The accurate diagnosis of ABPA requires the presence of a constellation of findings that may have presented and evolved over a period of years.

Allergic bronchopulmonary aspergillosis develops almost exclusively in atopic patients with asthma or CF. In the 77 cases we reviewed, 32 were confirmed as CF while 35 involved asthma. Several host characteristics have been identified to explain the specific population who are prone to develop ABPA. The colonization of the airways of CF patients with *Aspergillus*, probably a consequence of disrupted mucociliary clearance, leads to heavy allergen load on the epithelial surface. Both allergic asthma and ABPA are characterized by a Th2 immune response to *Aspergillus*.⁵ In the present case, the patient had a history of asthma. Although she had a novel mutation in *CFTR*, there was only one point mutation. Regretfully, the patient did not undergo sweat chloride concentration test. The diagnosis of CF was not established.

In the acute phase, pulmonary infiltrates, consolidation, and macronodular densities could be found on chest X-ray or computed tomography (CT). Bronchiectasis represents a common

final end-stage of different lung diseases and is typically considered irreversible.¹ In the cases we collected, 64.2% of patients had bronchiectasis on X-ray or CT. In children, some potential for reversibility of prebronchiectasis may exist when treatment starts early. Thus, rapid evaluation, diagnosis and treatment are essential to preserve lung function and stop the vicious cycle of inflammation, infection and bronchial-wall destruction seen in bronchiectasis. Although not specific, central bronchiectasis affecting three or more lobes, centrilobular nodules, and mucoid impaction are highly suggestive of ABPA.⁶

The treatment of ABPA focuses on controlling acute inflammation and preventing progression of lung injury. The Infectious Diseases Society of America proposed clinical practice guidelines on aspergillosis.⁷ The treatment of ABPA should consist of a combination of corticosteroids and itraconazole. The use of corticosteroids is the most common and effective therapy. Corticosteroids could improve pulmonary function and decrease episodes of recurrent consolidation. Due to the side-effect of corticosteroids, however, other approaches to manage ABPA are also used, such as antifungal medicine. The mechanism is to diminish the fungal burden. Itraconazole is often prescribed. The benefits of adding itraconazole include reduction of corticosteroid dose, increased interval between corticosteroid courses, and improvement in eosinophilic inflammatory parameters, IgE concentration, exercise tolerance, and pulmonary function. Other forms of antifungal medicine, such as amphotericin by inhalation, have also been reported.⁸ The side effects of combination of antifungal and corticosteroid are less severe than those of higher doses of corticosteroid. In the present case, the combination of methylprednisolone and itraconazole was used. The patient remained stable without signs of relapse or side-effects at the time of writing.

Since 2007, omalizumab has been used in patients with ABPA and CF.⁹ Omalizumab is an anti-IgE antibody, which can reduce unbound IgE concentration and downregulate IgE receptors, decreasing exacerbation in severe allergic asthma. Omalizumab effectively improved glycemic control in ABPA patients by tapering off systemic corticosteroids.⁹ In several cases, corticosteroid was ceased and single-use omalizumab was effective, suggesting that omalizumab may be an alternative therapy in CF patients with ABPA.¹⁰

Conclusion

The present case emphasizes the importance of considering the diagnosis of ABPA in children with uncontrolled pneumonia, hypereosinophilia, and bronchiectasis with a previous history of asthma or CF. Early diagnosis and initiation of systemic corticosteroids are essential to prevent irreversible damage. Omalizumab may be an alternative therapy.

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