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Case Report

A Case of Allergic Bronchopulmonary Aspergillosis Following Active Pulmonary Tuberculosis

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Summary. Allergic bronchopulmonary aspergillosis usually occurs in children with underlying airway disease such as asthma and cystic fibrosis. While the colonization and infection of pre-existing tuberculosis lesions by aspergillus species is well known, occurrence of allergic bronchopulmonary aspergillosis following pulmonary tuberculosis in children has not been reported yet. Here, an 11-year-old girl who developed allergic bronchopulmonary aspergillosis following active pulmonary tuberculosis is reported and the mechanisms of causality are also speculated. **Pediatr Pulmonol. 2009; 44:86–89.** © 2008 Wiley-Liss, Inc.

Key words: allergic bronchopulmonary aspergillosis; tuberculosis.

INTRODUCTION

Mycobacterium tuberculosis (MTB) is one of the most common causes of chronic lung infection that occur in children. Pulmonary infection in children is usually due to contact with an infected adult, most commonly a member of the family. Aspergillus fumigatus (AF) is a dimorphic fungus that is found ubiquitously, particularly in soil. After colonization of respiratory mucosa, different clinical patterns may occur from airway colonization to invasive disease.

In the lungs, the clinical consequences of both micro-organisms are different depends upon microbiological factors or host immunity.[1,2] Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder induced by Aspergillus fumigatus that occurs generally in patients with asthma or cystic fibrosis (CF).[2–4] Herein, we report a child who developed ABPA following active pulmonary tuberculosis infection. To our knowledge this association has not been reported yet in children.

CASE REPORT

An 11-year old girl was admitted to the hospital with a 2 years history of progressive cough, dyspnea, and bloody sputum expectoration despite many broad spectrum anti-bacterial therapies.

On arrival she was anorexic, mildly dyspnoeic and had basal crackles. Her weight was 26 kg (below 3rd percentile) and height was 140 cm (25th percentile). Laboratory evaluation on admission revealed hemoglobin 13.6 g/dl, white blood cell count 12,200/mm^3 with 51% segmented neutrophils, 29% lymphocytes, and 20% monocytes. Erythrocyte sedimentation rate was 81 mm/hr and C-reactive protein was 4.04 mg/dl (normal $<$ 0.5 mg/dl). Serum immunoglobulin results included IgG, 1,500 mg/dl; IgM, 190 mg/dl; IgA, 83 mg/dl; IgE, 10 kIU/L (normal $<$ 100 kIU/L). Sweat test was 43 mmol/L, cystic fibrosis transmembrane conductance regulator

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Fig. 1. Computed tomography shows multiple nodules and cavitary lesion located in posterior segment of the right upper lobe.

(CFTR) mutation was negative and electron microscopic evaluation of cilia morphology was normal. Chest radiography showed nodular infiltrate at the right upper zone. High resolution computed tomography (HRCT) documented multiple cavitary nodules in the posterior segment of the right upper lobe (Fig. 1). Radiologic picture was compatible with pulmonary tuberculosis.

Direct microscopy of her sputum after Ziehl-Neelsen staining showed acid-fast bacteria, and culture of the sputum was positive for MTB. A tuberculin skin test reaction was negative. Two previous BCG vaccination scars were seen. The family members were healthy. There had been no signs of tuberculosis in her parents or siblings. However there was history of past tuberculosis in her uncle 2 years ago. Because of cavitary lesions, treatment was started with four antituberculosis drugs (isoniazid, rifampin, pyrazinamide, and ethambutol). During the first 2 months of treatment the general clinical response was good. She started to gain weight and the cough and dyspnea disappeared. Ethambutol and pyrazinamide were stopped and isoniazid and rifampin were continued for 4 months. At the end of 6 months antituberculous therapy was stopped. After a remission period for a year she was admitted for dyspnea, wheeze, increased cough and sputum production. Her oxygen saturation was 94% in room air. She had bilateral expiratory wheeze with basal crackles. White blood cell count was 14,600/mm^3 (neutrophils, 55%; lymphocytes 25%; monocytes 7%; eosinophil 12%). Erythrocyte sedimentation rate was 45 mm/hr. Pulmonary function tests showed FEV1: 24% of predicted, FVC: 25% of predicted, PEF: 49% of predicted. There was 45% increase in FEV1 and 38% increase in FVC after salbutamol use (early reversibility). Repeated spirometry tests at different times showed airflow obstruction and acute response to salbutamol. Repeated sputum smears and cultures were negative for MTB. Sputum cultures isolated Streptococcus pneumonia. The mycoplasma IgM test result was negative. Chest roentgenograph on admission showed multiple small nodules at right upper zone and right paracardiac infiltration. HRCT demonstrated bilateral apical acinar and centrilobular nodules mainly on the right lung. There were bronchial thickening mostly prominent at basal segments and centrilobular nodules, bronchiectasis and mucus plugs in the right medial segment. Cavitary lesion and nodules in previous HRCT were totally disappeared, no residual cavity and bronchiectasis were detected in the posterior segment of the right upper lobe (area of tuberculosis infection) after tuberculosis treatment. She was treated with nebulized salbutamol, inhaled steroid and ceftriaxone for 10 days according to antibiogram results.

At follow-up the patient did not have adequate clinical and radiological improvement despite treatment. Fiberoptic flexible bronchoscopy was performed and showed only purulent secretions. She underwent a HRCT which showed mucus plugs in left upper lobe, bronchiectasis at the medial segment of the right lower lobe, ground glass infiltration and patchy consolidation at middle lobe and bilateral basal segments. There were geographic pattern consistent with small airway disease (Fig. 2). Total serum IgE titre was 1,404 kIU/L (normal range, 0–100 kIU/L), skin prick test was positive for AF antigen. Specific IgG and IgE antibodies to AF were positive. The diagnosis of ABPA was made based on the clinical, radiological and laboratory findings.[2] Oral methylprednisolone was started at a dose of 1 mg/kg/day. After 4 weeks of therapy, her symptoms, clinical and radiologic findings improved. However she became cushingoid, gained 10 kg in weight and oral moniliazis developed. The steroid dose was tapered to 1 mg/kg every other day. Within 6 months her spirometry results returned to normal (FEV1: 104% of

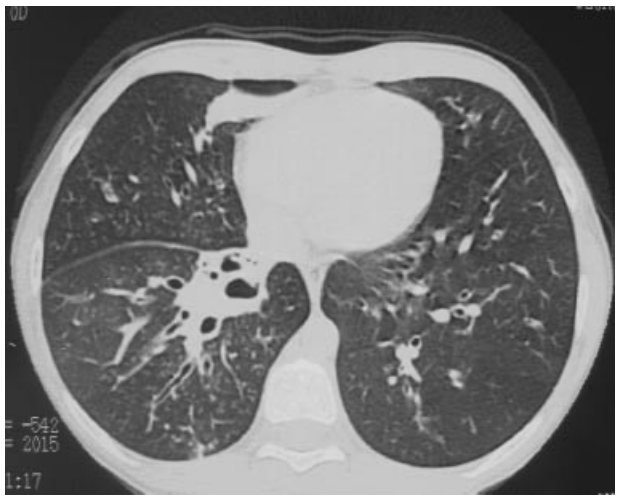


Fig. 2. High resolution computed tomography shows bronchiectasis and multiple centrilobular nodules in right lower lobe and peribronchial thickening in basal segments.

predicted) and serum IgE level was 643 kIU/L. Repeated sputum cultures for AF and MTB were negative. She was weaned from corticosteroid therapy. She was well within 2 months after discontinuation of steroid therapy. After a remission period of 2 months, an exacerbation of ABPA was observed with increased total IgE levels (982 kIU/L), decreased respiratory functions (FEV1: 45% of predicted) and clinical and radiological findings. Although sputum cultures negative for AF and MTB, AF antigen was positive in sputum sample. Oral prednisolone was started with itraconazole (200 mg twice daily) to decrease antigenic burden. She received itraconazole and decreasing doses oral corticosteroids over 6 months. Her respiratory status gradually improved during follow up.

DISCUSSION

Although the pathophysiology of the different pulmonary manifestations related to Aspergillus infection remains complex, the severity of them seems to depend on the quantity and virulence of the inhaled Aspergillus and immune status of the host. Airway colonization usually occurs in patients with underlying chronic airway disease such as asthma, chronic obstructive pulmonary disease, bronchiectasis and CF.[2–4] The airway sequels in chronic airway disease such as cellular debris, increased mucus, cavity and ectatic bronchus are important to trap aspergillus spores. Pulmonary aspergillosis mainly manifests as aspergilloma or as invasive or allergic disease. While aspergillomas occur in patients with pre-existing lung cavities, invasive aspergillosis affects immunocompromised individuals. Whereas ABPA is a hypersensitivity reaction to the aspergillus spores manifesting as chronic wheeze, pulmonary infiltrates and systemic immune activation that results in elevated IgE, IgA, and IgG levels. Although ABPA is not an invasive disease, bronchial wall damage occurs and this gives rise to bronchiectasis and fibrosis Chronic necrotizing pulmonary aspergillosis (CNPA) is another form of pulmonary aspergillosis that can be also defined as ''semi-invasive pulmonary aspergillosis'' and generally seen in adult age. CNPA is a discrete clinical entity with different CT scan findings.[2,5,6]

Tuberculosis remains one of the major diseases which is an important cause of morbidity and mortality in children. A variety of sequels and complications such as parenchymal destruction and bronchiectasis may occur in the lung in treated or untreated patients. Destroyed lung parenchyma and pulmonary cavities are the sites for microbial colonization including fungi. In children natural history of pulmonary tuberculosis depends upon the age at infection and immune response. Preschool children develop immediate clinical and radiologic manifestations. Whereas children infected in preadolescence or adolescence tend to developing severe adult-type pulmonary tuberculosis.[1,7]

Almost half of the patients with ABPA are initially misdiagnosed as having pulmonary tuberculosis and many of them had received antitubercular therapy in the past. Fleeting pulmonary infiltrates, the characteristic radiological finding of ABPA, is often confused with pulmonary tuberculosis.[2,5] However, central bronchiectasis on computed tomography is considered to be the hallmark of the ABPA. In our case once pulmonary tuberculosis was confirmed by clinical, microbiological and radiological findings she was well responded to antituberculous therapy. Following a remission period for a year she developed ABPA with typical findings.

The colonization and infection of pre-existing tuberculosis lesions by aspergillus species is well known; however development of ABPA following pulmonary tuberculosis in children has not been reported yet. In our patient, pulmonary sequels due to tuberculosis may favor Aspergillus colonization and then development of ABPA.

ABPA is a Th2 CD4+ T-cell response to Aspergillus fumigatus antigens that occur in approximately 1–2% of asthmatic and 7–10% of CF patients. The pathogenesis remains complex and confusing. It is reported that ABPA develops in genetically susceptible patients due to increased activity of specific Th2 CD4+ T-cells and to HLA-DR restriction.[2–4] Our patient's human leukocyte antigen haplotype study was positive for DR 16, which has been shown to be associated with ABPA. The abnormal airway functions and architecture allow increased Aspergillus colonization within the bronchial airway of asthma and CF patients, and in a genetically susceptible individual, stimulate a Th2 T-cell response and subsequent asthma. Similarly, pulmonary sequels and tendency to aspergillus colonization in pulmonary tuberculosis may favor development of ABPA in genetically susceptible patients. In our case although we do not know asthma diagnosis before admission to our hospital, CF was excluded by both clinical and laboratory findings.

Long-term systemic corticosteroid treatment as various dosage schemes have been proposed but the best option has not been defined yet. Many studies show that bronchial inflammation sensitive to systemic corticosteroids is not enough to achieve optimal control of the disease. Initial daily doses of 1–2 mg/kg/day prednisolon have been shown to be adequate and should be followed by a slow and gradual reduction according to the remission of symptoms and of the pulmonary infiltrates with a minimum duration of treatment of at least 3 months.[2,8] Because our patient had undergone pulmonary tuberculosis, we tried to keep systemic steroid dose as low as possible. During follow-up period repeated sputum cultures were negative for MTB. Fungal colonization of bronchus is another factor in the disease pathogenesis justifying the use of antifungal therapies. Itraconazole is a

systemic antifungal agent that can be administered orally and has shown to suppress the proliferation of A. fumigatus and limit bronchial inflammation in ABPA.[8]

In conclusion, pulmonary tuberculosis with its pathological consequences may be a risk factor for development of ABPA. Children who underwent pulmonary tuberculosis should be followed for ABPA and other Aspergillus related diseases.

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