

Allergic Bronchopulmonary Aspergillosis in Patient with Cystic Fibrosis - a Case Report

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ABSTRACT

Asthma with allergic bronchopulmonary aspergillosis (ABPA), a hypersensitivity disease of the lungs due to an immune response to Aspergillus fumigatus (Af) antigens, is rarely seen in children, other than complicating cystic fibrosis. We present the case of a 14 – year- old female teenager with cystic fibrosis (CF), admitted in our hospital with respiratory failure and persistent cyanosis. Chest X-ray showed perihilar and upper lobes pulmonary infiltrates. Her airway cultures were positive for methicillin resistant staphylococcus aureus (MRSA) and non-mucoid Pseudomonas aeruginosa. She was prescribed intravenous antibiotherapy with ceftazidime and vancomycine (to which MRSA and Pseudomonas aeruginosa were susceptible). Pulmonary function testing (PFT) revealed severe obstructive lung disease. After ten days of intravenous antibiotics and first five days of corticosteroid, the patient's FEV1 was 68% of predicted. Total serum IgE and IgE antibodies to Aspergillus fumigatus were elevated. These results raised the possibility of allergic bronchopulmonary aspergillosis (ABPA).

The possibility of ABPA should be considered in all pulmonary exacerbation and in order to determine if ABPA is developing or if an exacerbation is occurring, a serial monitoring of IgE levels should be performed.

INTRODUCTION

ABPA is a hypersensitivity disease of the lungs due to an immune response to Aspergillus fumigatus (Af) antigens. Unlike in adults where asthma with allergic bronchopulmonary aspergillosis (ABPA) is common, ABPA is rarely seen in children, other than complicating cystic fibrosis (1).

The prevalence of ABPA is difficult to determine due to the use of different diagnostic criteria and different indices of suspicion.

The European Cystic Fibrosis Society Registry reported a peak for ABPA between 13-18 years with the disease being rare below the age of 6. The prevalence varied from 1.4% to 17.9%. ABPA was associated with a poorer general clinical condition. There was an association with bacterial infection (*Pseudomonas*

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aeruginosa, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Haemophilus influenzae*), pneumothorax and massive hemoptysis. Atopy is an important risk factor, ABPA occurring in 22% of atopic CF patients (1-3).

Common symptoms seen in patients with ABPA include: wheezing, dyspnea, cough with increased mucus production, and expectoration of mucus with brown to black plugs. Other symptoms that may be present include anorexia, malaise, fever, an influenza-like syndrome, hemoptysis (2,4,5).

Lung function is reduced with an obstructive pattern on the flow-volume curve. The chest radiograph shows new infiltrates that tend to disappear with systemic corticosteroid therapy. Fleeting pulmonary infiltrates represent a characteristic feature of the disease that tend to appear in the upper lobe and are central in location (3).

Chest high resolution computer tomography (HRCT) is helpful in defining bronchiectasis and is also more sensitive in demonstrating the above changes.

Typically, total serum IgE is elevated, usually >1,000 UI/ml. According to the ABPA in CF consensus criteria, serum IgE >500 UI/ml is considered diagnostic (4). Immediate skin test reactivity to Af antigens and elevated levels of specific IgE, IgG antibodies to Af are usually documented (1-7). Peripheral blood eosinophilia was one of the major diagnostic criteria, but now it is considered only "other" criteria.

Treatment of ABPA aims to treat acute exacerbations of the disease and limit the evolution towards progressive lung disease and bronchiectasis. Oral corticosteroids are the main treatment for ABPA. They suppress the hypersensitivity and inflammatory response provoked by Af, rather than eradicating the organism. Oral antifungal agents are also used considering that it is beneficial to combat the airway fungal infection and thus reduce the antigenic burden (2,6).

Several studies have been done on the utility of the antifungal agent itraconazole in the management of patient with ABPA. Recently, voriconazole has also been tried in the treatment of ABPA and showed a favorable therapeutic response (2-5).

Some of these patients have recurrent relapses, and are steroid-dependent (often with significant adverse effects, particularly impaired glucose metabolism). ■

CASE REPORT

A 14-year-old, female teenager, with cystic fibrosis, was admitted in our hospital with respiratory failure and persistent generalized cyanosis.

She was diagnosed at 6 month of age, after prolonged respiratory symptoms following a viral respiratory infection in association with abnormal stools. The sweat test confirmed the diagnosis with an elevated sweat chloride level, 106 mmol/l. Genetic analysis highlighted the most common mutation known as $\Delta F508$. Her current treatment regimen consisted of airway clearance, rh-DNAse by aerosol once a day, hypertonic saline (6%) 4 ml by aerosol twice a day, pancreatic enzymes and vitamins.

Her airway cultures were positive for methicillin resistant *Staphylococcus aureus* (MRSA) for the past few years, but no *Pseudomonas*.

She recently developed a cough in association with a viral respiratory infection. She was prescribed levofloxacin (to which her MRSA was susceptible), but her cough worsened and her forced expiratory volume in 1 second (FEV1) was 70% of predicted.

Clinical picture on admission: weight - 42 kg (the 25th percentile), height - 153 cm (the 25th percentile), productive cough with mucopurulent and brown sputum, respiratory distress with dyspnea, tachypnea (respiratory rate 40/min), and wheezing.

She accused chest pain, easy fatigability and physical examination showed nasal flaring, deep retraction, accessory muscle use and cyanosis. Pulmonary auscultation revealed rhonchi and crackles. Heart rate (HR) was 120 b/min, blood pressure (BP) was normal and oxygen saturation was 86%.

Laboratory results: Hb=14.3 g/dl, Ht=42, WBC=15,800/mm³, with neutrophils 68%, lymphocytes = 18%, monocytes = 8%, eosinophils = 5%, basophils = 1%, CRP = 45 mg/dl, AST = 28 U/l, ALT = 30 U/l, IgE total = 380 ui/ml (normal <90 ui/ml), PaO₂ = 58 mmHg, PaCO₂ = 47 mmHg.

Pulmonary function testing (PFT) revealed severe obstructive lung disease with a forced expiratory volume in 1 second (FEV1) of 41% of predicted, which improved to 60% of predicted after bronchodilator treatment.

Chest X-ray showed perihilar and upper lobes pulmonary infiltrates (Figure 1).

The airway cultures were positive for MRSA and non-mucoid *Pseudomonas aeruginosa*.

nosa. She was prescribed intravenous antibiotics associated to her current treatment. After ten days of intravenous antibiotherapy (Ceftazidim, Vancomicyne) and corticoid therapy – medrol (in the first five days), her clinical status improved, but her FEV1 was 68 % of predicted.

Then we repeated the measurement of total serum IgE and found it to be elevated at 905 ui/ml; specific IgE for *Aspergillus fumigatus* were positive at 16 ku/l (normal <0,35). Chest X-ray showed other pulmonary infiltrates (Figure 2) and pulmonary HRCT scan confirmed the presence of central bronchiectasis (Figure 3).

These results raised the possibility of allergic bronchopulmonary aspergillosis. We continued the antibiotic therapy and started steroids at 2 mg/kg/day for two weeks, followed by a slow, prolonged tapering period over two months. Voriconazole was added to her regimen and the evolution was good. After three weeks, FEV1 was 80% of predicted and two months later the FEV1 was 98%. □

DISCUSSION AND CONCLUSION

Af is ubiquitous in the environment. Two of its features particularly favour the infection of human lower airway. The first is that the spores have a mass median diameter in the range of 2-5 μm , which is the ideal size for impacting in the lower airways and the second is that they grow at 37°C, the body temperature (1).

The inhaled spores are trapped in airways mucus, then germinate and form mycelia which release allergens. The bronchus-associated lymphoid tissue (BALT) may be exposed to high level of these allergens. This is followed by type I and type III immune responses with production of specific IgE and IgG antibodies. This is accompanied by an exaggerated T helper type 2 lymphocyte response leading to the release of cytokines associated with allergy interleukin 4, 5, 13 (IL4), (IL5), (IL13) (2-4).

The Af is not efficiently killed by monocytic and eosinophilic infiltrates, thus resulting in chronic airway inflammation. When the inflammation extends into the small airways and alveoli, it resembles eosinophilic pneumonia; the alveolar infiltration is thought to cause the fleeting shadows seen on the chest radiograph, which is characteristic in ABPA (3).

ABPA is a pulmonary disease resulting from hypersensitivity to *Aspergillus* antigens, mostly



FIGURE 1. Frontal chest X-ray: diffuse interstitial disease, pulmonary infiltrates, bronchiectasis and nodular opacities in the bilateral lower lobe.



FIGURE 2. Chest X-ray after 10 days showing extension and the appearance of the new infiltrates; confluent alveolar nodular opacities in the left lower lobe.

due to Af. In the case of cystic fibrosis, 1-15% of patients may develop ABPA. In the context of CF, ABPA is difficult to diagnose because it mimics CF lung disease. Thus, the most important thing for the clinician is to have a high index of suspicion (2,6).

Clinical picture may vary. First, the patient may present with wheezing, dyspnea, chest

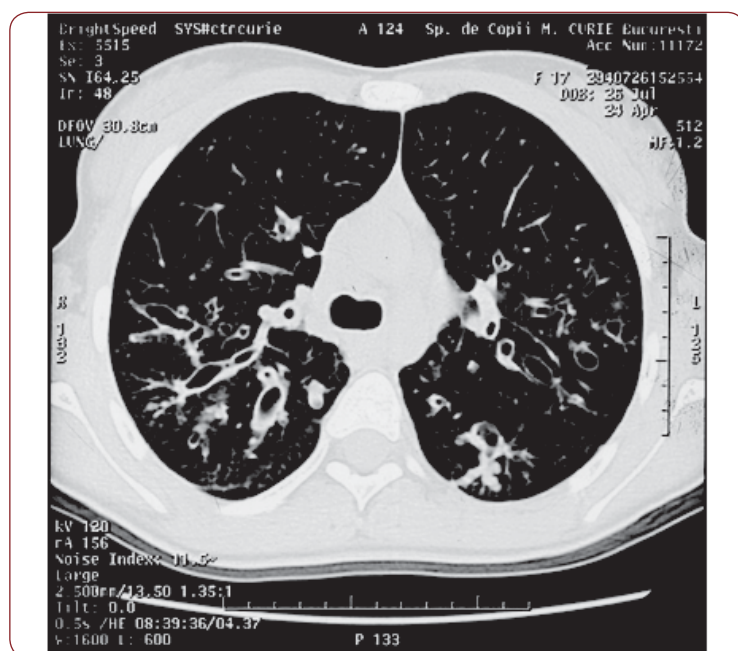


FIGURE 3. MDCT-axial view at the tracheal bifurcation level: bronchial wall and peribronchial interstitial thickening; cylindrical bronchiectasis; mucoid impaction in periphery of the left Fowler segment.

pain and plugs of sputum with brown or black flecks. In some cases fever, myalgia or an influenza-like syndrome may be present (1-3). Our patient presented at the hospital with respiratory distress, but she began to cough two weeks before when she was thought to have a viral respiratory infection. With antibiotic treatment her cough worsened and her FEV1 was 70% of predicted. The PFT revealed severe obstructive lung disease with FEV1 41% of predicted which improved to 60% after bronhodilator treatment.

Laboratory results showed leukocytosis, neutrophilia, moderate eosinophilia, elevated CRP. Her airway culture was positive for MRSA and non mucoid *Pseudomonas aeruginosa*; in that moment the treatment consisted in intravenous antibiotic. Because the response to treatment was poor, the serum IgE measurement with determination of specific IgE for Af was repeated (first value was <500 ui/ml). The results were elevated total IgE (905 UI/ml) and positive specific IgE for Af.

Diagnostic criteria for ABPA in our case were: acute clinical deterioration with poor response to treatment, total IgE >500UI/ml, specific IgE for Af positive and recent abnormalities (chest X-ray) not clearing with standard therapy (Figure 1, Figure 2).

After the treatment with corticosteroid and antifungal was started, the evolution of our patient was favourable.

The classical case is easy to diagnose. There have been proposed major and minor criteria for ABPA, but atypical cases may not meet these classical criteria.

An annual measurement of total IgE is recommended, with further investigation if IgE is >500 UI/ml or 200-500 UI/ml and the index of suspicion is high (2,4,6).

ABPA may easily be confused with an exacerbation. The possibility of ABPA should be considered in all exacerbations, in particular if there are fresh chest radiographic infiltrate and there is a poor response to treatment.

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