Allergic bronchopulmonary aspergillosis in two patients with cystic fibrosis

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SUMMARY: Anadol D, Özçelik U, Kiper N, Göçmen A. Allergic bronchopulmonary aspergillosis in two patients with cystic fibrosis. Turk J Pediatr 2000; 42: 68-71.

Allergic bronchopulmonary aspergillosis (ABPA) is hypersensitivity to Aspergillus fumigatus which manifests as episodic wheezing, usually refractory to bronchodilator therapy, with fixed and transient pulmonary infiltrates, central bronchiectasis, blood eosinophilia, elevated serum IgE level, immediate skin reactivity to an A. fumigatus antigen and precipitating antibodies to A. fumigatus. It is an unusual complication of asthma and cystic fibrosis (CF). We present two cystic fibrosis patients with ABPA treated successfully with prednisone and, in Case 1 also with itraconazole. The physician should be alert to the possibility of ABPA whenever CF patients present with the new infiltrates, high serum total IgE and other positive parameters of A. fumigatus sensitization. Treatment with systemic steroids should be started in order to prevent irreversible lung damage.

Key words: allergic bronchopulmonary aspergillosis, cystic fibrosis.

Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitive reaction to Aspergillus fumigatus which was first described by Hinson et al. in 1952[1]. It is an unusual complication of asthma, cystic fibrosis (CF) and other bronchitic pulmonary diseases, and is a relatively uncommon pulmonary disease in childhood[2]. It manifests clinically as episodic wheezing, usually refractory to bronchodilator therapy. Its diagnostic features include fixed and transient infiltrates, central bronchiectasis, blood eosinophilia, elevated serum IgE level, immediate skin reactivity to an A. fumigatus antigen and precipitating antibodies to A. fumigatus[3]. Here, we report two cystic fibrosis patients with allergic bronchopulmonary aspergillosis.

Case Reports

Case 1

A seven-year-old boy who was the third child of nonconsanguineous parents was admitted to our hospital because of failure to thrive, chronic cough and recurrent sinusitis. On physical examination, his weight was 19.5 kg (< 5th percentile) and his height was 127 cm (10th percentile). Clubbing of the fingers, bilateral crackles and rhonchi on auscultation were prominent findings. Chest x-ray showed bilateral bronchiectatic changes and paracardiac infiltration (Fig. 1). Laboratory findings showed normal serum biochemical values, but the sputum culture revealed Staphylococcus aureus and Pseudomonas aeruginosa. As his sweat chloride concentration was 74 mEq/L, he was diagnosed with cystic fibrosis. He was delta F508 heterozygous in mutation analysis. His pulmonary function test revealed obstructive pattern unresponsive to bronchodilator as well as restrictive pattern on spirometry (VC: 50%, FVC: 49%, FEV1: 40%, FEV1/FVC: 75%, FEF25-75: 25%). He had an IgE level of 893 IU/ml in blood and positive A. fumigatus specific IgE and was therefore diagnosed with ABPA. He had no skin reactivity to A. fumigatus antigen. he was treated with intravenous antibiotics (ceftazidime, amikacin), inhaled tobramycin, pancreatic enzymes, multivitamins, inhaled human DNA'se and prednisone (1 mg/kg/day orally). The prednisone dose was tapered to 0.5 mg/kg on alternate days in four months as his clinical status improved. On his follow-up, the serum total IgE level was 2000 IU/ml, so the prednisone dose was increased to 1 mg/kg/alternate day, but as the IgE levels were

no longer decreasing, itraconazole was added to his therapy. His prednisone was tapered to 0.25 mg/kg/alternate day with this therapy. He has been taking prednisone for 22 months and itraconazole for 12 months; no side effects have been noted with this therapy to date.

Case 2

A 15-year-old boy whose parents were second cousins presented with chronic diarrhea when he was three years old and was diagnosed to have cystic fibrosis, as his sweat chloride concentration was 118 mEq/L. Staphylococcus aureus and Pseudomonas aeruginosa were cultured from his sputum. He was 621+1 G-T homozygous in mutation analysis. He was treated with pancreatic enzymes, multivitamins and antibiotics.

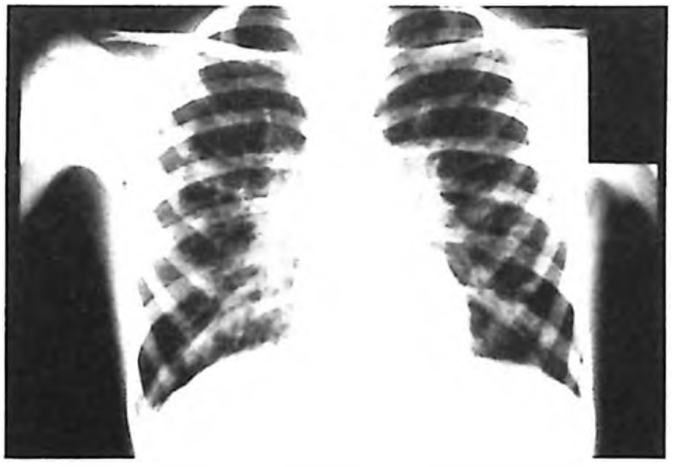

Fig. 1. Chest x-ray of Case 1 showing bilateral bronchiectatic changes and paracardiac infiltration.

When he was 13 years old, a lobectomy was performed for cystic bronchiectasis which was noticed at the right upper lobe in thoracal computerized tomography. On his clinical follow-up, at the age of 15, he complained of chronic productive cough, his chest x-rays revealed fixed infiltrates (Fig. 2) and pulmonary function tests revealed an obstructive pattern unresponsive to bronchodilator as well as a restrictive pattern on spirometry (VC. 54%, FVC: 49%, FEV1: 40%, FEV1/FVC: 75%, FEF25-75: 37%). He was diagnosed to have ABPA as his total blood IgE level was 2761 IU/ml and skin reactivity to A. fumigatus antigen was positive. Treatment with prednisone (1 mg/kg/day) was started. the prednisone dose was gradually tapered to 0.8 mg/kg/alternate day in five months and he is still being followed in our department.

Discussion

Allergic bronchopulmonary aspergillosis (ABPA) lung disease resulting from hypersensitivity induced in predisposed individuals by the ubiquitous fungus, Aspergillus fumigatus[4]. There is no clear consensus concerning the mechanisms of the lung disease in ABPA. However, it is apparent that both reaginic antibodies (IgE) and precipitating antibodies (IgG) are involved. An

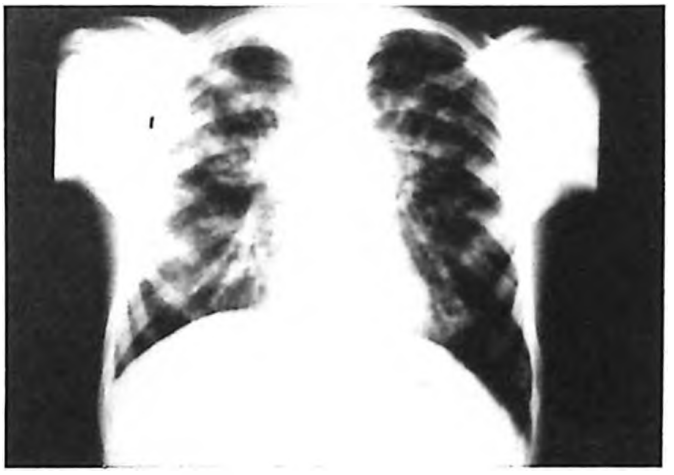

Fig. 2. Bilateral infiltrates and bronchiectatic changes in the chest x-ray of Case 2.

important component of the disease is persistent colonization of the airway with A. fumigatus and failure to clear the organism. That would explain the predilection of the disease for patients with asthma and cystic fibrosis (CF)[2]. This entity was documented as occurring in up to 22 percent of asthmatic patients in England[5] and in 9 percent in North America[6]. ABPA was reported in two patients with CF in 1965 by Mearns et al.[7]. It has since become a serious complication of CF but its prevalence is disputed, ranging from 0 to 11 percent, in the published literature[8-11].

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by wheezing, which is usually unresponsive to bronchodilator therapy, and recurrent pneumonia[3]. Chest roentgenograms usually show homogeneous consolidation, bronchiectatic changes, contracted upper lobes with honeycomb lung, and branching shadows of mucus impaction with "tramline" shadows of thickened bronchial walls. The laboratory criteria for the diagnosis include sputum eosinophilia, peripheral blood eosinophilia, a positive immediate response to the skin prick test, a positive delayed reaction to intradermal testing, the presence of precipitating antibodies to A.

fumigatus, an increased serum IgE value and a positive specific reaction to A. fumigatus on an IgE antibody test (RAST)[2].

The diagnosis of ABPA in patients with CF is frequent overlooked because the signs and symptoms of each disease mimic each other. Therefore, with a high index of suspicion, the physician should be alert for ABPA in the presence of clinical and laboratory findings described above. Prick or intradermal skin testing with A. fumigatus antigen provides a screening test for ABPA, but confirmation requires other evidence of the disease[3]. An elevated level of total serum IgE is an important immunological finding in the diagnosis of ABPA in CF. A four-fold rise in total IgE, particularly to above 500 IU/ml, is strongly suggestive of the diagnosis of ABPA in children with CF[12]. The presence of high IgE and positive Aspergillus precipitins in conjunction with clinical deterioration and new radiological shadowing allow simplification of the diagnosis of ABPA in CF[12]. Both of our patients were suspected to have ABPA as they had persistent infiltrates and an obstructive pattern unresponsive to bronchodilator therapy on spirometry. Their elevated serum IgE led to the diagnosis, and specific IgE levels in Case 1 and positive skin test to A. fumigatus in Case 2 established the final diagnosis of ABPA.

The objective treatment fo ABPA in CF patients is to control acute exacerbation and to prevent lung damage. The first treatment choice is systemic corticosteroids; inhaled corticosteroids have been found to be ineffective[3]. Oral corticosteroids decrease the likelihood of permanent damage by suppressing the allergic response and inflammation associated with the colonization of A. fumigatus in the airways[13]. We aministered an initial dose of 1 mg/kg/day prednisone to both patients and reduced the dosage according to the clinical status of each. Corticosteroids usually produce a satisfactory clinical and immunologic response. However, such therapy is frequently associated with the well known long-term side effects of systemic corticosteroids. Itraconazole, a new orally administered azole antifungal agent of low toxicity, has an activity against Aspergillus spp. in vitro as well as in vivo. It has been shown to be useful in reducing corticosteroid requirements, reducing serum IgE concentrations and improving pulmonary functions in some patients with ABPA[13,14]. Treatment with prednisone was not so effective in our first case, so itraconazole was added to his therapy. With the administration of this drug, his IgE levels started to fall and the corticosteroid requirement was decreased. no side effects due to therapy were determined in the patient.

In conclusion, ABPA is a common complication of CF that may be difficult to identify. Its diagnosis requires a high index of suspicion. the physician should be alert to the possibility of ABPA whenever CF patients present with the new infiltrates, high serum total IgE and other positive parameters of A. fumigatus sensitization. Once the diagnosis is established, treatment with systemic steroids should be started in order to prevent irreversible lung damage. Patients should be followed-up for a long period, as relapses are seen, and a prolonged period of treatment is generally needed.

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