Different Forms of Allergic Bronchopulmonary Aspergillosis Encountered in Two Patients: ABPA-seropositive and ABPA-central Bronchiectasis

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Abstract

Two female patients, aged 30 and 46 years, with allergic bronchopulmonary *aspergillosis* (ABPA) are presented. Both patients had asthma. In the first patient, the diagnosis of ABPA-seropositive was made at an early stage. The diagnosis was based on a positive *Aspergillus* skin prick test, positivity for *Aspergillus fumigatus* IgG, IgE antibodies, presence of *Aspergillus* precipitating antibody and increased total serum IgE (>4000 IU/ml). There were no signs of pulmonary infiltration or bronchiectasis and corticosteroid therapy was initiated in this early phase. In the second patient, a diagnosis of ABPA-central bronchiectasis was made upon finding that the *Aspergillus* skin prick test and *Aspergillus fumigatus* IgE antibody test were positive and upon locating central bronchiectasis on high-resolution CT scans. Total serum IgE (2643 IU/ml) was also increased and peripheral eosinophilia (1570/mm^3) was present. Corticosteroid therapy was started at this relatively advanced stage.

It was stressed that to exclude ABPA, the *Aspergillus* skin prick test should be applied in patients with asthma if peripheral eosinophilia is prominent or total IgE > 1000 ng/ml is present. Patients with positive *Aspergillus fumigatus* skin prick tests must be investigated for a diagnosis of ABPA-seropositive. Damage in the airways and end-stage lung disease may be prevented with appropriate treatment of patients with ABPA in the early stage.

Turkish Respiratory Journal, 2004;5:(3):189-92

Keywords: *asthma, prick test,* Aspergillus fumigatus, *ABPA-seropositive, ABPA-central bronchiectasis*

Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a disease in which the fungus A. *fumigatus* colonizes in the sputum plugs of the bronchi in asthmatic patients, with little or no tissue invasion. An appropriate approach to the diagnosis of ABPA entails the exclusion of the disease in every patient with asthma or cystic fibrosis (1). Withholding therapy until the development of clinical symptoms and of bronchiectasis may lead to irreversible pulmonary damage (2).

In the classification of ABPA patients, the term "ABPA-S (seropositive)" is used to define patients in whom the serological tests are positive, but who do not have central bronchiectasis. The term "ABPA-CB (central bronchiectasis)" is used for patients with central bronchiectasis (1-3). In this paper we present two ABPA cases with early and late diagnoses.

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Case Report

Case 1

A 46-year-old woman was admitted to our hospital with a history of cough and dyspnea which had started in the past 19 months. Following several dyspnea attacks in the past three months, the patient was started on inhaler therapy with corticosteroids and bronchodilators. She applied to our hospital because her complaints persisted despite treatment and because she also started expectorating a mucopurulant sputum.

The patient's past history and family history were unremarkable. Her axillary temperature was 36.4°C, her pulse rate was 74/minute, her respiratory rate 12/minute, and her blood pressure was 110/60 mmHg. Physical examination was normal. Laboratory results were: hemoglobin: 13.4g/dl, leukocyte count: 4900/mm^3, peripheral blood eosinophilia: 3.7%, total eosinophilia: 150/mm^3, erythrocyte sedimentation rate: 12 mm/hour. total serum IgE>4000 IU/ml. The skin prick test for *Aspergillus* was positive (10x6 mm). IgE and IgG antibodies for *Aspergillus fumigatus* measured by ELISA were positive [respectively, 5.10 kUA/I and 4.97 kUA/I (<0,35 kUA/I normal range)]. In addition, *Aspergillus* precipitant antibody measured by haemagglutination assay was also found to be positive.

Radiography and high-resolution CT scan of the chest were assessed as normal (Figure 1). Results of pulmonary function tests were: FEV_1: 87%, FVC: 98%, PEF: 96%, FEV_1/FVC: 80%, DLCO: 84% and DLCO/VA: 94%. Bronchoscopy could not be performed because the patient refused to give her consent. CT examination of the paranasal sinuses were normal and by consultation with the otorhinolaryngology department, allergic *Aspergillus* sinusitis was eliminated. The sputum was negative for acid-fast bacilli as well as for fungi. The stool examination revealed no parasites. c-ANCA, p-ANCA and HIV were also negative.

Based on a background of asthma, absence of any clinical and radiological findings, a positive skin prick test for *Aspergillosis* and ABPA-seropositivity, a diagnosis of allergic bronchopulmonary aspergillosis was made and the patient was started on prednisone treatment 40 mg/day (0.5 mg/kg/day). In the first follow-up visit one month later, the patient had improved. Total serum IgE was 3412 IU/ml. The prednisone dose was decreased to 30 mg/day. In the second monthly visit, there were again no complaints and total serum IgE was 2887 IU/ml. The prednisone dose was decreased to 20 mg/day. In the third visit the stable condition was found to continue and the total serum IgE level had decreased to 2630 IU/ml. The corticosteroid dose was decreased to 10 mg, taken on alternate days. On week 14, the total serum IgE level was 2575 IU/ml and had reached a plateau. Corticosteroid treatment was stopped. The patient was again seen 9 months after the initiation of treatment. The patient had no complaints and total serum IgE was 2082 IU/ml.

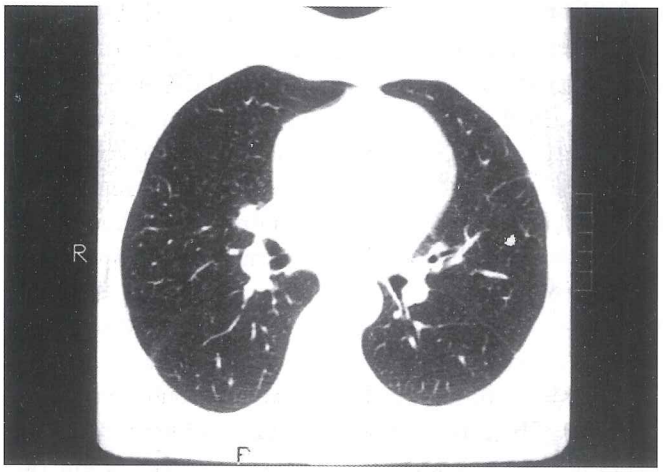

Figure 1. *Normal high-resolution CT of the first patient.*

Case 2

A 30-year-old female patient presented with the complaints of cough and dyspnea. The cough had started three years ago and the dyspnea 18 months ago. She also complained of expectorating and the sputum was yellow-brown in color. She would wake up in the middle of the night coughing and had suffered several episodes of haemoptysis. The physicians to whom she applied with these complaints prescribed antibiotics, antihistaminics, inhaler corticosteroid and bronchodilator therapy, but her complaints continued.

Except for widespread wheezing in both lungs, physical examination findings were unremarkable. Personal and family history were also noncontributory. Her temperature was 37.2°C, pulse 108/minute, respiratory rate 15/minute and her blood pressure was 120/70 mmHg. Laboratory results were: hemoglobin: 12.8 g/dl, leukocyte count: 8230/mm^3, peripheral blood eosinophilia: 19%, total eosinophilia: 1570/mm^3, erythrocyte sedimentation rate: 37 mm/hour. Total serum IgE level was 2643 IU/ml. *Aspergillus* skin prick test was positive (5x4 mm). *Aspergillus fumigatus* IgE antibody was positive, but close to normal (0.35 kUA/I), Aspergillus precipitant antibody was detected as negative. Chest x-ray revealed bilateral hilar enlargement and reticular infiltrates and cystic changes in the middle and lower zones of both lungs (Figure 2). In high-resolution CT scans, central bronchiectasis was detected in the segments of the middle and lower lobes on the right side and in the lingual on the left (Figure 3). Allergic aspergillus sinusitis was eliminated by CT and by consultation with the otorhinolaryngology department. Results of pulmonary function tests were: FEV_1: 93%, FVC: 98%, PEF: 92%, FEV_1/FVC: 83%, FEF_{25-35}: 83%. In the bronchoscopic examination; all the segments were open in both bronchial systems and bilateral intense mucopurulent secretion was observed. No growth occurred in the cultures made from sputum and the bronchial lavage samples for acid-fast bacilli, fungi and other microorganisms. No parasites were detected in the stools. HIV tests were negative.

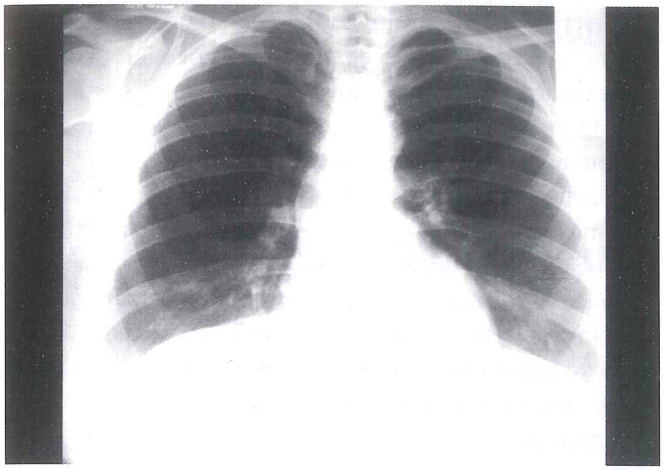

Figure 2. *Chest radiograph of the second patient showing bilateral hilar enlargement, reticular infiltrates and cystic changes in the middle and lower zones of both lungs.*

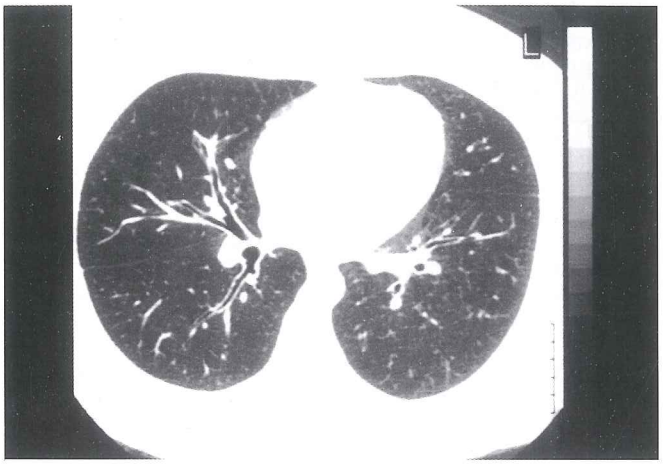

Figure 3. *High resolution CT showing extensive proximal bronchiectasis in the second patient.*

Based on the asthmatic background of the patient, a positive aspergillus skin prick test, an increase in total serum IgE, blood eosinophilia, presence of yellow-brown mucus plugs, positive Aspergillus fumigatus IgE antibody, and detection of central cystic bronchiectasis in high-resolution CT scans, a diagnosis ABPA-CB was made. Prednisone treatment in a dose of 40 mg/day (0.5 mg/kg/day) was started. In the first monthly follow-up visit, the patient was found to be much improved and free of complaints. Total serum IgE level had decreased to 2267 IU/ml, peripheral blood eosinophilia was 1.3%. Prednisone was decreased to 30 mg/day. In the second monthly visit, there were again no complaints and the total serum IgE was 1288 IU/ml. The prednisone dose was decreased to 20 mg/day. In the third monthly follow-up, it was noted that the patient's stable condition was maintained. Total serum IgE level had decreased to 851 IU/ml and the corticosteroid dose was decreased to 10 mg on alternate-days. In the fourth month, total serum IgE level was 617 IU/ml and had reached a plateau level. Corticostreoid treatment was stopped. In the fifth monthly control, there were no complaints and total serum IgE was 750 IU/ml.

Discussion

ABPA is often indolent and may be present for years before diagnosis. When the diagnosis is made sufficiently early, irreversible lung damage can be prevented. Although asthma is a common diagnosis, ABPA is diagnosed infrequently, with the exact prevalence remaining uncertain (4).

Patients with asthma should be investigated for ABPA if the clinical course is unresponsive to treatment, if peripheral eosinophilia is prominent or the total serum IgE level is over 1000 ng/mL. We became suspicious of ABPA in our first patient with asthma upon finding that total serum IgE level was very high and as a first step we performed an *Aspergillus* skin prick test. ABPA is eliminated in patients with a negative skin test, but serological examinations should be made in patients with a positive test result. Essential diagnostic criteria for ABPA include asthma, skin prick test positivity to *Aspergillus fumigatus* (AF), elevated levels of serum total IgE, elevated levels of serum Aspergillus fumigatus specific IgE, and either pulmonary infiltrates on chest radiography or central brochiectasis. Minor supporting criteria include positive precipitins and serum eosinophilia (2,4-7). In order to be able to make a diagnosis of ABPA, total serum IgE, precipitation test, *Aspergillus fumigatus* IgE and IgG antibody levels should also be taken into consideration. A diagnosis of ABPA-seropositive was made in a patient with asthma who had skin prick test positivity to AF and serological tests were found positive, while the other features of ABPA were lacking (1,2). In our first case, positive results in the skin prick test to AF, positive *Aspergillus fumigatus* IgG and IgE antibodies, a total serum IgE over 4000 IU/ml and positive *aspergillus* precipitant antibody levels, the diagnosis of ABPA-seropositive was made in the early stage before any damage occurred in the lung and oral corticosteroid therapy could be started also at an early stage. Prognosis for patients with ABPA-seropositive is not clearly described, but it is possible that active ABPA development risk is higher in these patients (1). Information about the optimal treatment of patients with ABPA-seropositive is also limited. It is recommended that these patients should be considered stage 1 and 0,5 mg/kg/day prednisone treatment should be applied and continued until the total IgE level decreases and reaches a plateau, without necessarily going down to the normal level (1,8). We followed these recommendations in our first case and the treatment was adjusted according to the decrease in total serum IgE level. Attempts to normalize IgE may lead to significant side effects as a result of long term steroid use. The total IgE level is important in treating and monitoring the disease. Also, a normal IgE level in untreated symptomatic patients is a highly specific finding for excluding the diagnosis of ABPA (5).

In the second case we were suspicious of ABPA since the patient appeared to be unresponsive to asthma treatment and had peripheral blood eosinophilia. Aspergillus skin prick test and *Aspergillus fumigatus* IgE antibody were positive. Central bronchiectasis was detected in high-resolution CT and prednisone therapy was started. In contrast to the first case, the diagnosis was made only after permanent lesions had occured in the airways in this patient. The progression of the disease might have been prevented if the treatment had been initiated at an earlier stage. The clinical criteria for the diagnosis of ABPA established by Rosenberg, et al (6) continue to be challenged and modified. These modifications aim at earlier identification of the patients and early institution of treatment in an attempt to prevent progression of the disease (5). Chest x-ray is not a sensitive and specific method in detecting central bronchiectasis (9). Pulmonary infiltrates may be suppressed by the corticosteroid therapy given for the treatment of the asthma or missed because chest radiographs are seldom repeated in asthmatic patients. Central bronchiectasis can be detected in the early stage by a routine thorax high resolution CT examination in patients whose *Aspergillus* skin prick test is positive (10,11). If cystic fibrosis is eliminated, the central bronchiectasis is pathognomonic for ABPA (7).

The underdiagnosis of ABPA may be ascribed to a lack of routine skin testing in most asthma clinics. The *aspergillus* skin test can be found positive in 20% of the patients with asthma. Nevertheless, ABPA should be considered in all patients with positive skin results (4).

The precipitant antibodies are reported to be positive in 60-70% of patients with a diagnosis of ABPA, but the rate of positive results can be as high as 90% when the serum is concentrated (12). However, the precipitant antibodies are found to be positive between 1% and 10% of normal individuals (12). Therefore, the serum precipitant antibodies are not sensitive and specific for ABPA diagnosis (4,7). The serum precipitant antibodies were found to be negative in our second case. It was reported that allergic *aspergillus* sinusitis (AAS) can be seen simultaneously with ABPA (13). No AAS was detected in either of our cases.

Although antifungal agents are generally ineffective in controlling ABPA, itraconazole was reported to have steroid-sparing effects in patients with ABPA (14,15). We did not apply itraconazole treatment to our patients due to lack of enough data and controlled studies on this treatment, the necessity of monitoring the drug level, and due to its having side effects and interactions with various medicines. Our patients had no contraindication for oral corticosteroid treatment and it would have been the first time for itraconazole to be applied together with corticosteroid treatment. Although not generally advocated, inhaled corticosteroiods have occasionally been used as primary therapy and as steroid-sparing agents for the treatment of symptomatic exacerbations and pulmonary infiltrates (1).

In conclusion, we would like to stress that indolent ABPA with mild asthma and a normal chest radiograph may be overlooked unless every patient with asthma is evaluated to exclude ABPA. In patients with a positive *Aspergillus fumigatus* skin prick test, the appropriate serological studies must be made for the diagnosis of ABPA-seropositive. Thus, damage in the airways and end-stage lung disease may be prevented with appropriate treatment of the patients with ABPA in the early stage.

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