Case Reports

Allergic bronchopulmonary aspergillosis mimicking pulmonary Tuberculosis

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ABSTRACT

Allergic bronchopulmonary aspergillosis is an uncommon disease in which cystic bronchiectasis is a common feature. The presence of central bronchiectasis with constitutional symptoms of cough, fever, weight loss, and pulmonary infiltration in patients with allergic bronchopulmonary aspergillosis has been misdiagnosed as cavitating pulmonary tuberculosis. Herein, we report 2 cases of allergic bronchopulmonary aspergillosis that were misdiagnosed as pulmonary tuberculosis and treated with antituberculous therapy. They all have negative sputum and bronchoalveolar lavage for acid-fast bacillus as well as their tuberculin tests. The diagnosis of pulmonary tuberculosis was based on the presence of symptoms and radiological changes. In both cases the presence of long standing asthma, high peripheral eosinophilic counts and wide spread of central bronchiectasis besides the poor response of antituberculous therapy has drawn our attention towards the diagnosis of allergic bronchopulmonary aspergillosis. This was confirmed by the presence of high immunoglobulin E level, positive skin prick test and positive specific serum immunoglobulin E to *aspergillus fumigatus*. Therefore, a high index of clinical suspicion with appropriate laboratory tests is required to identify such cases.

Keywords: Allergic bronchopulmonary aspergillosis, tuberculosis, bronchial asthma.

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Allergic bronchopulmonary aspergillosis (ABPA) is an uncommon disease with variable prevalence of 5 to 15%.[1-7] It is found mainly in patients with asthma and cystic fibrosis.[1-7] It results from exposure of the asthmatic bronchial tree to *Aspergillus Fumigatus* (AF). This may lead to hypersensitivity reaction involving eosinophilic infiltration of the bronchial wall and mucoid impaction or granulomatous inflammation.[8,9] Repeated episodes of bronchial obstruction, inflammation and mucoid impaction can lead to bronchiectasis, fibrosis and respiratory impairment.[10] Patients with ABPA usually have long standing asthma and present with recurrent attacks of fever, malaise, hemoptysis, bronchial obstruction, expectoration of brownish mucous plugs and peripheral eosinophilia.[11,12] Therefore, with such a clinical presentation, and in the presence of radiological cavitating lesions due to bronchiectasis and as pulmonary tuberculosis is much more common than ABPA, some patients with ABPA have been misdiagnosed and treated as pulmonary tuberculosis. In one series from India almost one 3rd of the 35 patients with ABPA were misdiagnosed as pulmonary tuberculosis and treated with antituberculous therapy for varying periods of time.[13] The aim of this study is to report 2 cases of ABPA misdiagnosed and treated as pulmonary tuberculosis and to define the major differences between these 2 conditions.

Case Report.

Patient 1. A 42-year-old housewife was diagnosed to have pulmonary tuberculosis in April 1997. Since then she was placed on antituberculous therapy until her presentation at our institution. At that time, Ziehl-Neelsen staining for acid fast bacilli (AFB) in sputum and bronchial lavage were negative

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as well as her tuberculin test. The diagnosis of pulmonary tuberculosis was based mainly on radiological findings. She was a known asthmatic for 20 years. Her asthma was fairly controlled by beclomethasone and salbutamol inhalation, except in the past 2 years where her asthma was worse and she became more symptomatic. She was referred to our institution in July 1997 due to poor control of asthma and failure of antituberculous therapy. She presented with cough, shortness of breath, greenish sputum, wheezes and fever. On examination, she looked pale and underweight. Her height was 156 cm, weight was 38 kg, pulse rate was 85 beat/min. Blood pressure was 110/80 mmHg. Temperature was 38.5°C. Peak expiratory flow rate (PEFR) was 180l/min. She had no cyanosis or clubbing of the fingers. She had no palpable lymph nodes. Examinations of the head and neck were normal. Examination of cardiovascular system (CVS) was normal. Examination of the chest showed harsh vesicular breathing with prolonged expiration, occasional scattered crackles and rhonchi. Examinations of the abdomen and central nervous system (CNS) were unremarkable. Chest radiograph on presentation (Figure 1) showed chronic lung changes of both upper lobes with linear strands and loss of volume. The left upper lobe also showed ill defined opacity with irregular thickened wall cavity. There was also multiple different sized and shape cavities scattered on both lung fields. The radiological diagnosis (reported by 2 senior radiologists) was consistent with an active tuberculosis. She was hospitalized and underwent the following investigations: WBC 11 $x10^3$ per mm^3, Hb 12.2 g/dl, Eosinophils count $1.2x10^3$cells/mm^3 (n=00-0.73x103 cell/mm3), ESR 92. The high peripheral eosinophilic count in this lady has raised the possibility of pulmonary eosinophilia in which ABPA was among the differential diagnosis. So immunoglobulin E (IgE) level was measured and surprisingly it was very high 17802 IU/ml (n=0-195 IU/ml). Specific IgE was highly positive for AF as well as skin prick test. Sputum fungal culture grew AF. Ziehl-Neelsen staining of sputum was negative for AFB, and culture was negative for *Mycobacterium tuberculosis*. A repeated tuberculin test was also negative. Stool analysis was negative for parasites. High resolution computerized tomography (CT) scan of the chest showed cylindrical bronchiectasis and thickened bronchial wall affecting all lobes with central bronchiectatic changes (Figure 2). Arterial blood gases showed pH 7.4, PCO_2=5.2 mmol/l, PO_2=12.1 mmol/l, oxygen saturation was 97% on room air. Pulmonary function tests showed combined obstructive and restrictive disease. On the basis of the above findings ABPA was considered to be the diagnosis. So antituberculous drugs were stopped and 40 mg/day of prednisone therapy was started. After the first week of therapy her cough and dyspnea have subsided. She

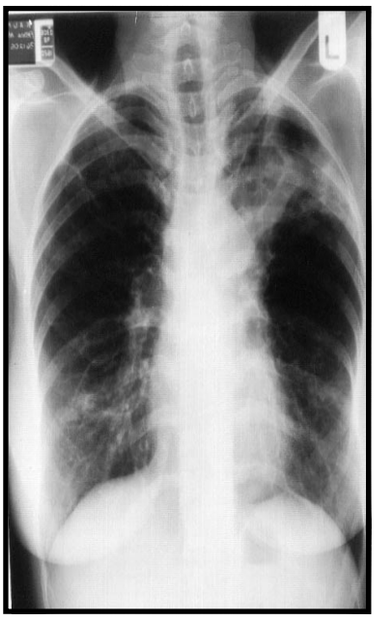

Figure 1 - Patient 1 - Chest radiograph showed ill defined opacity with irregular thickened wall cavity affecting left upper zone. There is right apical infiltration and multiple different sized and shape cavities on both lung fields.

was kept on 40 mg/day prednisone for one month. This was tapered gradually once her symptoms, IgE level and chest radiograph improved. Currently she is on 10 mg prednisone/day orally. Her last IgE level had decreased to 1243 IU/ml as well as her eosinophilic count to $0.073x10^3$ cells/mm^3. Recent chest radiograph showed complete resolution of lung opacities (Figure 3). Peak expiratory flow rate has risen to 330L per minute.

Patient 2. A 27-year-old gentleman was diagnosed to have pulmonary tuberculosis in June 1998. He was referred to our institution in September

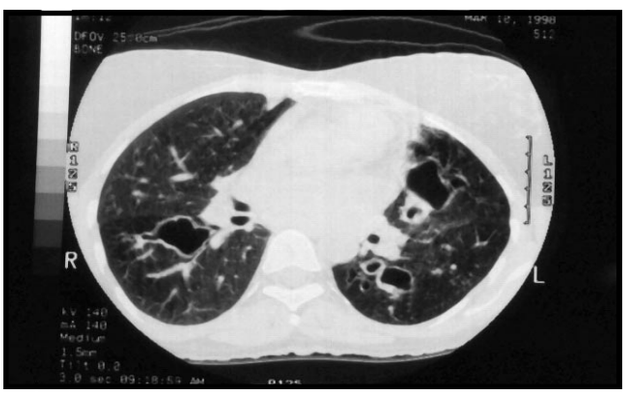

Figure 2 - Patient 1 - High resolution computed tomography (HRCT) scan of the chest showed central bronchiectatic changes of cylindical type affecting both lungs.

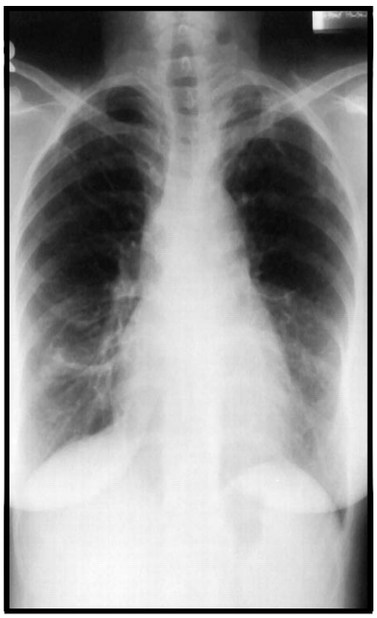

Figure 3 - Patient 1 - Chest radiograph showed complete resolution of lung opacities after corticosteroids therapy.

1998 due to a poor response to antituberculous therapy as well as for the control of his asthma. The diagnosis of pulmonary tuberculosis was based only on the presence of radiological cystic bronchiectatic changes affecting mainly the apical zone of the right lung. As at that time, his Ziehl-Neelsen stain for AFB was negative in the sputum and in the bronchial lavage as well as his tuberculin test. He was known asthmatic for almost 20 years. His asthma was poorly controlled on inhaled Ventolin therapy. In the past 2 years he became more symptomatic and visited the emergency room regularly. At our institution he presented with shortness of breath, cough, productive greenish sputum, wheezes and right sided chest pain.

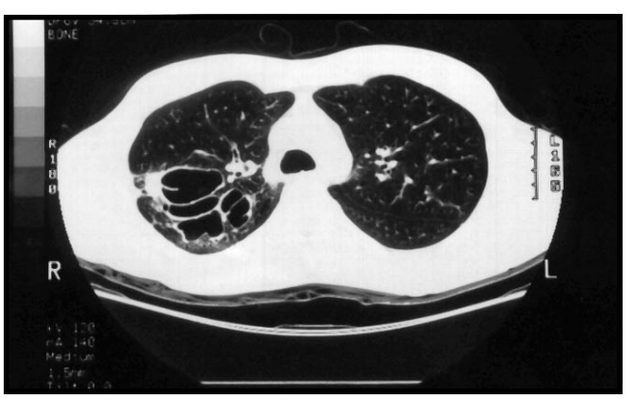

Figure 4 - Patient 2 - Chest radiograph showed well defined thin cystic bronchiectatic changes surrounded by mild parenchymal infiltrates at the right upper lobe.

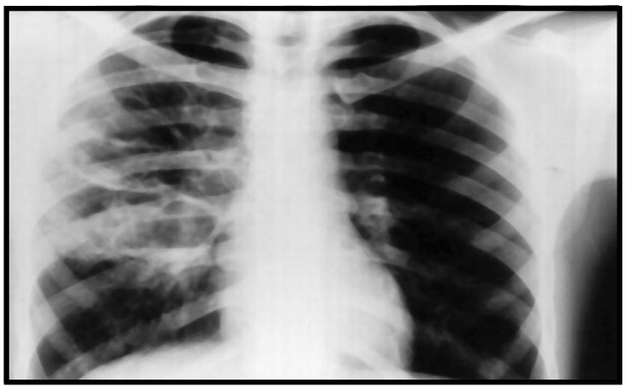

Figure 5 - Patient 2 - High resolution computed tomography (HRCT) scan of the chest showed wide spread central bronchiectasis affecting the posterior and the apical segments of the right upper lobe.

On examination, he was tall and underweight. His weight was 48.5 kg, height was 174 cm. There was no clubbing of the fingers or palpable lymph nodes. Examinations of his head and neck were normal. Examination of CVS was normal. Examination of the chest showed bronchial breathing in the right middle and lower zones of the lung with coarse crackles. There was bilateral expiratory rhonchi of the chest. Examinations of the abdomen and CNS were normal. He was hospitalized and underwent the following investigations. White blood cell count was $4.9x10^3$ per mm^3, Hb 14.3 g/dl, Eosinophils $15.3x10^3$ per mm^3. Erythrocyte sedimentation rate was 14. His PEFR was 280 L per minute. Measurement of IgE was 1752 IU/ml. Specific IgE was positive and high for AF. Skin prick test was also positive for AF. Fungal culture for aspergillus was negative. Ziehl-Neelsen stain for sputum was negative for AFB and culture for *Mycobacterium tuberculosis*. A repeated Tuberculin test was also negative. Chest radiograph revealed well-defined thin walled cystic structure surrounded by mild parenchymal infiltrates at the posterior segment of the right upper lobe (Figure 4). High resolution CT scan of the chest showed wide spread central bronchiectasis affecting the posterior and the apical segments of the right upper and lower lobes as well as the posterior segment of the left lower lobe (Figure 5). Stool analysis was negative for intestinal parasites. On the basis of the above findings, ABPA rather than pulmonary tuberculosis was considered to be the diagnosis. So, antituberculous therapy was stopped and oral prednisone 40 mg per day was started and then tapered gradually with the improvement of his condition. Currently he is on 10 mg/day of oral prednisone. His cough, shortness of breath and wheeze have subsided. His PEFR has risen to 410L per minute. His chest x-ray in December 1998 revealed significant reduction of the linear strand

from the hilum to the periphery involving the right upper lobe and apical segment of the lower lobe. Eosinophilic count dropped to $6.41x10^3$ per mm^3. IgE level dropped to 283 IU/ml.

Discussion. Allergic bronchopulmonary aspergillosis is an uncommon disease in which central bronchiectasis is a common feature.[12-14] It results from colonization of the asthmatic bronchial tree with (AF). Aspergillus fumigatus spores enter the respiratory airways by inhalation and due to their larger size (3-5 um) they tend to impact in the larger bronchi which is the same site of central bronchiectasis lesions.[15] It rarely behaves as a pathogen in healthy individuals, but may cause asthmatic reaction in atopic subjects.[16] Aspergillus colonization of the asthmatic airway leads to vigorous IgE and IgG mediated immune responses.[17] The occurrence of bronchiectasis in ABPA may result from the damage of the lung tissue by the proteolytic enzyme proteases released by both fungi and degranulating eosinophils.[15] The diagnostic criteria of ABPA is based on satisfying most of the major criteria with supporting evidence from 3 minor criteria. The major criteria for diagnosis should include; a history of asthma, immediate skin reactivity of AF antigen, precipitating serum antibodies to AF, total serum IgE level >1000 IU/ml, peripheral blood eosinophilia $>500/mm^3$, history of pulmonary infiltrate, central bronchiectasis, elevated serum IgE/IgG specific to AF. The minor criteria for diagnosis, AF in sputum by smear or culture, history of expectorating brown plugs and late skin reactivity (Arhus type) to AF.[18] Although, the pattern of bronchiectatic changes in ABPA is different from that in pulmonary tuberculosis misdiagnosis has been reported.[19] In this study, 2 patients with ABPA were misdiagnosed as pulmonary tuberculosis due to failure to recognize these differences. The bronchiectatic changes in ABPA are characterized by the tendency to involve the proximal segments of bronchi rather than the distal ones that results in what's so called proximal or central bronchiectasis.[20] While in pulmonary tuberculosis the bronchiectatic changes tend to affect the distal segments rather than the proximal ones and commonly affect the upper lobes and results in what's so called dry bronchiectasis.[20,21] In ABPA the bronchiectatic changes result from an immunological process while in pulmonary tuberculosis it results mainly from an infectious process that causes damage of the lung parenchyma with replacement of alveoli by fibrous tissue. Consequently, this may lead to parenchymal retraction and secondary bronchial dilatation.[20,21] Among the other factors that may also lead to misdiagnosis is the similarity of the clinical presentation between ABPA and pulmonary tuberculosis. As both conditions may present with increased cough, hemoptysis, fever, weight loss, plueritic pain, wheezing and dyspnea. Therefore, searching for additional clues may help to make the true diagnosis. In our patients the presence of long standing asthma, and peripheral eosinophilia and high IgE levels have drawn our attention towards the correct diagnosis. In these patients the misdiagnosis of pulmonary tuberculosis has occurred initially due to the presence of the pulmonary cavitating lesions (bronchiectasis) besides the presence of constitutional symptoms although their sputum and bronchial lavage were negative for AFB as well as their tuberculin tests. This has taken place as pulmonary tuberculosis is much more common than ABPA in our country and therefore, our physicians are more familial with tuberculosis rather than ABPA. Besides the wrong concept of practice that considers any pulmonary cavitating lesion in patients with fever, loss of weight, cough and hemoptysis is diagnostic of pulmonary tuberculosis. However, without the presence of AFB in the sputum, or in the bronchoalveolar lavage and with negative tuberculin tests, and in the presence of poor response to antituberculous therapy the possibility of an other underlying cause should always be considered. The differential diagnosis of a cavitating pulmonary lesion should include a wide range of underlying causes such as pneumonias, bronchogenic carcinoma, wegener's granulomatosis, cystic bronchiectasis, lung abscess, septic emboli and ABPA, besides tuberculosis.[21] In the literature few cases of ABPA have been misdiagnosed as pulmonary tuberculosis and treated with antituberculous therapy. Agarwal et al has reported a 47-year-old gentleman who presented with chronic fibrocavitary pulmonary disease, who had received 3 courses of antituberculous therapy over a period of 17 years before the final diagnosis of ABPA was reached.[19] In another study from India Behera et al has reported 12 out of 35 patients with ABPA who were misdiagnosed as pulmonary tuberculosis and were treated with antituberculous therapy for varying times, although in all cases the chest radiographs revealed the characteristic central/proximal bronchiectasis and fleeting shadows or both.[13] The radiological features of pulmonary tuberculosis and ABPA are quite distinct. The recognition of these differences will reduce the risk of misdiagnosing these two conditions. In pulmonary tuberculosis the cavitating lesions usually occur in the apical and posterior segments of the upper lobes (80%-90% of the patients) followed in frequency by the apical segment of the lower lobes. It tends to be of moderate thickness while the inner lining is generally smooth and less commonly may be associated with cavities and visible air-fluid.[22] In ABPA, the chest radiograph may show homogenous, finger like shadows of unit density in a precise bronchial distribution, usually affecting the upper lobes and almost always in

proximal bronchi rather than the distal ones. These bifurcating opacities have been variously described, according to their presentation on the radiograph, as having a gloved-finger, inverted Y or V, or cluster-of grapes appearance.[23] The shadows tend to be transient but may persist unchanged for weeks or months or may enlarge. They tend to recur in the same segmental bronchi.[23] Resolution of the mucoid impaction may reveal cylindrical or sacular bronchiectasis. Some of them may contain fluid level or occasionally true aspergilloma.[24] High resolution CT scan of the chest is more sensitive than chest radiograph in diagnosing both conditions and may help to differentiate ABPA from pulmonary TB. In ABPA, it may show widespread proximal bronchiectasis affecting 3 or more lobes, centrilobular nodules, and mucoid impaction.[14] In pulmonary tuberculosis it may show smaller cavitating lesion located at the apex of the lung as well as it may show the characteristic centrilobular lesions, nodules and branching linear densities sometimes giving what is so called a "tree in bud" appearance that could not be detected by chest radiograph.[25] Although central bronchiectasis is often seen in ABPA, it is not a specific finding. In one series CT failed to differentiate bronchiectasis caused by ABPA from that due to hypogammaglobulinemia, ciliary dysfunction, cystic fibrosis, or idiopathic causes.[10] However, the bronchiectatic changes in ABPA were found to be more widespread, with varicose and cystic types and the presence of peripheral eosinophilia may also help to differentiate ABPA from pulmonary tuberculosis especially in the presence of pulmonary infiltration in asthmatic patients. However, such findings should also prompt consideration of other diagnoses, including; acute or chronic eosinophilic pneumonia, drug-induced eosinophilic pneumonia, Churg-Strauss syndrome, hypereosinophilic syndrome, tropical eosinophilic pneumonia, loffler's pneumonia, auto immune diseases, sarcoidosis and complications of crack-cocaine abuse.[26] However, peripheral eosinophilia may not be present in each patient with ABPA but it could be the only clue to the diagnosis.

In conclusion, pulmonary tuberculosis is much more common than ABPA in the Kingdom of Saudi Arabia. Because of the similarity of the clinical, and radiological presentation some patients with ABPA have been misdiagnosed and treated as pulmonary tuberculosis. Therefore, a search for additional clues is important for making the final diagnosis. This will be supported by high index of clinical suspicion associated with appropriate radiological and laboratory tests.

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