An atypical acute exacerbation of COPD due to *Aspergillus fumigatus*

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**Abstract**

A 64-year-old male with a history of stable chronic obstructive pulmonary disease (COPD) presented with increasing dyspnea and sputum for the last two months. Complete blood count showed WBC 14x10³/ml, Hgb: 14.2 g/dL and eosinophilia. Blood biochemistry was normal. Chest x-ray showed hyperluency while thorax computed tomography (CT) revealed obstructive lung disease and bronchiectasis. Pulmonary function tests demonstrated severe obstructive lung disease and a negative bronchoreversibility with a moderately reduced diffusing capacity/alveolar volume (DLCO/VA). ABG gases revealed significant hypoxemia. Sputum culture was negative. Total IgE was 1140 ng/ml. Aspergillus RAST, precipitins and aspergillus-galactomannan antigen were positive. CF genetic screening tests gave negative results. Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction that occurs due to bronchial aspergillus colonization. It is most common in patients with asthma and cystic fibrosis. We present a COPD case with an acute exacerbation due to *Aspergillus fumigatus* that lead to an aberrant clinical profile unresponsive to conventional treatment. Clinicians should consider Aspergillus fumigatus as an etiologic agent in an atypical and severe COPD exacerbation.

**Introduction**

Allergic bronchopulmonary aspergillosis (ABPA) is a chronic pulmonary eosinophilic hypersensitivity reaction that leads to airflow obstruction and bronchiectasis. Disease results from an exaggerated allergic response to several fungal species, particularly *Aspergillus fumigatus*, which accounts for nearly 90% of the cases. The exact mechanism of ABPA is unknown. Several host factors and specific IgE-mediated type-I, IgG-mediated type-III and cell-mediated type-IV hypersensitivity reactions play a role in the pathogenesis of this disorder [1-6]. First described by Hinson *et al.*., ABPA exclusively occurs in patients with underlying asthma [7,8]. While asthma is the most common and best understood contributing factor, ABPA may occur among those with cystic fibrosis and other underlying obstructive lung diseases. Although majority of patients with ABPA are associated with difficult asthma or cystic fibrosis, chronic obstructive pulmonary disease has been recognized recently as a risk factor for invasive aspergillosis. Airway colonization by Aspergillus species may occur as a common feature of chronic pulmonary diseases [9-12]. The lack of consensus regarding the diagnostic criteria may contribute to the difficulty for identifying this disorder and establishing its true prevalence among chronic obstructive pulmonary disease (COPD) patients. These underlying etiologies are crucial to identify since steroid treatment may lead to invasive fungal infection [13].

We present a case of severe exacerbation of a COPD patient in whom the etiologic agent for the acute exacerbation was identified as *Aspergillus fumigatus*. The case was a diagnostic dilemma as the symptoms of COPD and ABPA overlapped while the patient did not respond to conventional bronchodilator and antibiotic treatment in the long term with significant deterioration of his COPD profile. The only clue to the diagnosis was the appearance of recent blood eosinophilia followed by a high serum IgE level and positive immunologic markers thereafter. Clinicians should bear in mind that ABPA may be the etiologic factor in a patient with an aberrant acute COPD exacerbation that does not respond to conventional treatment.
Case Report

A 64-year-old stable COPD patient was admitted for progressive dyspnea, sputum, treatment failure and continuously worsening symptoms. The patient was an ex-smoker of 10 years with a 60 pack-year smoking history. Personal history consisted of COPD for six years without any other significant disease in the family history. On physical examination, there were rales in both lung bases. Blood pressure was 120/70 mm Hg with normal heart sounds and a tachycardia of 114/minute. Full blood count demonstrated a WBC: 11.4x10^3/µl, eosinophilia 7.8x10^3/µl, PLT 272x10^3/µl and Hgb 12.8 g/dL. The previous blood count three months before showed a normal eosinophil count (3.6x10^3/µl). Serum biochemistry revealed CRP: 42.9 mg/ml, creatinine: 0.38 mg/ml, BUN: 14 mg/dL, total protein: 5.2 gr/dL, albumin: 3.2 gr/dL, AST: 13 IU/L, ALT: 16.7 IU/L, LDH: 204 IU/L, GGT: 24 IU/L and CK: 18 IU/L. ECG demonstrated a sinus tachycardia of 112/min and rare ventricular premature beats. Chest x-ray showed hyperlucency, fibrotic changes, bronchiectasis and minimal inflammatory infiltrations (Figure 1). Thorax CT revealed infiltrative lesions, fibrotic changes, proximal bronchiectasis, centrilobular emphysema and emphysematous bullae (Figures 1-3). Cystic fibrosis (CF) genetic screening was negative. Pulmonary function tests established severe obstructive lung disease revealing a FEV1: 1.83 (45%), a FEV1/FVC: 48% and MEF 25-75%: 0.36 (11%). DLCO [Diffusing capacity (DLCO)] was 13.35 mL/mmHg/min (51%) and DLCO/VA [Diffusing capacity/alveolar volume (DLCO/VA)] was 15.28 mL/mmHg/min/L (58%). Bronchoreversibility was negative as FEV1, FVC and MEF 25-75% revealed only 4%, 6% and 5% increase after 4x100 µg salbutamol inhalation. There was also no significant change of the lung function test values following one month of oral 32 mg oral methylprednisolone treatment that justified the diagnosis of COPD. Arterial blood gases (ABG) exhibited a pO2 of 50 mm Hg, a pCO2 of 48 mm Hg and a pH of 7.32 on room air. Sputum cytology and culture were negative. The patient had received brief courses of antibiotics and a long term combined inhaled steroid and long-acting beta agonist, ipratropium bromide and oral theophylline 600 mg/day which lead to a brief response for his symptoms but the treatment was unsuccessful while the clinical manifestations continued to deteriorate. Complete blood count, quantitative immune globulin measurements and skin testing for delayed hypersensitivity were normal ruling out immunodeficiency. Serum total IgE was 1140 ng/ml. This high above nor-
A mal value suggested that a hypersensitivity reaction was responsible for the deterioration of the patient’s symptoms. Aspergillus radioallergosorbent test (RAST) and precipitins and aspergillus-galactomannan antigen were positive. The final diagnosis was an acute exacerbation of COPD due to Aspergillus fumigatus colonization. The patient was commenced on methylprednisolone 32 mg/day, a combined inhaled steroid and long-acting beta agonist, ipratropium bromide and oral theophylline 600 mg/day with 4 L/min O2 nasal oxygen. Following treatment, the pO2 increased to 62 mm Hg and the patient had complete resolution of symptoms. The only symptom was dyspnea during prolonged exertion. He is under follow-up with the same treatment protocol and the steroid dose was reduced to 24 mg/day without any exacerbation of his symptoms for the last six months.

Discussion

ABPA is a complex hypersensitivity reaction that occurs in response to colonization of the airways with Aspergillus fumigatus. It occurs almost exclusively in patients with asthma or cystic fibrosis [1-4]. Repeated episodes of bronchial obstruction, inflammation, and mucoid impaction can lead to bronchiectasis, fibrosis, airflow obstruction and respiratory compromise. Proteolytic enzymes released by Aspergillus contribute to the development of bronchiectasis by damaging the walls of the airways [5,6]. The chronic pulmonary eosinophilic hypersensitivity reaction of ABPA leads to airflow obstruction and bronchiectasis in the long term. Disease results from an exaggerated allergic response to several fungal species, particularly the Aspergillus fumigatus, which accounts for approximately 90% of the cases. The exact pathologic mechanism for this complex hypersensitivity reaction is unknown. Specific IgE-mediated type-I, type-III and cell-mediated type-IV hypersensitivity reactions are thought to contribute to the pathogenesis of this disorder [1-4]. ABPA is a disease that exclusively emerges in those with underlying obstructive airways disorders such as asthma or cystic fibrosis. Novey has reported in a recent epidemiologic study that ABPA occurs between 0.25 and 11% in asthma while the incidence may be greater than 20% among poorly controlled asthma patients [14]. ABPA is a disease exclusively seen in those with underlying obstructive disorders while it is not a common pathogen in the COPD patients and its real incidence in this group is unknown [11,12]. We present this case as the presence of ABPA may cause an acute exacerbation of COPD that usually arises due to bacterial pathogens. The second crucial point is the overlap of clinical manifestations in both disorders with the same profile that may lead to a significant delay in diagnosis.

The difficulty in establishing the diagnosis of ABPA is likely multifactorial. Clinical presentations are inconsistent and are non-specific. Symptoms may present in childhood while others may remain asymptomatic for decades with no real age distribution and disease may present more commonly in the fifth and sixth decades [6]. Most of the patients experience long-standing and often difficult asthma profile while others may experience mild symptoms or remain relatively asymptomatic [8]. The lack of consensus regarding the diagnostic criteria contributes to the difficulty in identifying ABPA. Coexistence of an obstructive disease further beclouds the diagnosis of ABPA, as it could not be clear whether the deterioration of clinical manifestations is caused by the underlying obstructive disorder or by the ABPA itself, which was the case in our patient. Another crucial point is that if two diseases coexist, they will further potentiate the deterioration of the clinical picture. The only clue to the diagnosis of ABPA was the recently emerging eosinophilia followed by the established presence positive RAST and galactomannan tests thereafter. Tong et al. has revealed that Aspergillus colonization in the lower respiratory tract of the COPD patients affected their clinical outcome and lead to clinical treatment dilemma. Bao has also referred to the fact that a reliable diagnosis was required for the diagnosis of Aspergillus in COPD patients to improve the prognosis [15,16]. Clinicians should be notified that Aspergillus fumigatus may be the etiologic agent for an aberrant exacerbation of a COPD patient. An unresponsive conventional treatment response for an acute exacerbation of COPD...
may also be the evidence for *Aspergillus fumigatus* as the pathologic agent in a chronic obstructive pulmonary disease patient. The recent development of eosinophilia in this COPD patient lead to ABPA suspicion while the subsequent RAST and galactomannan positivity confirmed the diagnosis of ABPA. The patient did not have asthma as verified by the lack of early or late bronchoreversibility and patient history revealed a smoking history with permanent dyspnea without acute dyspnea attacks dyspnea that may be relevant to asthma. A possible immunodeficiency status was ruled out by the presence of normal laboratory findings for the specific components of the immune system. Another crucial point relevant to this case was the absence of any significant radiologic infiltration implying infection despite the serious clinical manifestations and the critical COPD exacerbation. Absence of notable radiological findings in a patient presenting with such a severe and noteworthy clinical profile may point out to the presence of a probable Aspergillus infection.

Conclusions

ABPA is a chronic, progressive disorder affecting patients with airflow obstruction. Among patients with poorly controlled COPD, a diagnosis of ABPA should be considered. The prevalence of ABPA among COPD patients is unknown. Although the clinical manifestations are often nonspecific and usually overlap, several diagnostic criteria may be used to distinguish ABPA from obstructive diseases. The lack of definitive criteria for diagnosis and the overlap of the symptoms of the underlying primary disease with ABPA may lead to a significant delay in the detection of *Aspergillus fumigatus* as the responsible agent for the acute exacerbation of the primary obstructive disease. An aberrant acute exacerbation unresponsive to conventional treatment in a previously stable COPD patient with a recently emerging eosinophilia should raise the likelihood Aspergillus as an etiologic agent. Absolutely disproportionate or absent infiltrative radiologic manifestations in a case presenting with such a severe clinical picture may also indicate an Aspergillus infection.

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