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Case Report

Allergic Bronchopulmonary Aspergillosis (ABPA) in a Middle Aged Man camouflaged by Atopic Chronic Persistent Bronchial Asthma

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Abstract

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic pulmonary disease characterized by an exaggerated immune response (a hypersensitivity response) to the fungus Aspergillus (most commonly Aspergillus fumigatus) with a variable radiographic appearance. ABPA most commonly affects patients with steroid-dependent asthma (1 - 2%) and patients with cystic fibrosis (5 - 15%). ABPA is very rarely diagnosed in non-asthmatics. Clinical features of ABPA are wheezing, mucoid impaction, and pulmonary infiltrates. Oral corticosteroids and anti-fungal agents are standard therapy for ABPA. ABPA causes airway inflammation that if left untreated can lead to bronchiectasis (an abnormal dilation of the airways) due to the immune system and fungal spores damaging sensitive lung tissues and ultimately leading to scarring. We report a case of ABPA in a 40-year-old male initially evaluated for poorly controlled chronic persistent bronchial asthma. After the diagnostic investigation was complete, the diagnosis of ABPA was established and appropriate treatment was instituted leading to clinical, radiological, and serological improvement.

Keywords: *Aspergillus Fumigates; Hypersensitivity; Steroid-Dependent Asthma; Wheezing; Bronchiectasis*

Introduction

Allergic bronchopulmonary aspergillosis is an eosinophilic pulmonary disorder caused by a hypersensitivity reaction to a fungal species known as Aspergillus fumigatus that is almost seen exclusively in patients with asthma and cystic fibrosis. Only a minority of the population develop this condition after the aspergillus hypersensitivity (which is defined as the presence of cutaneous hypersensitivity to the above-mentioned fungus) [1,2]. ABPA was first described in 1952 by Hinson., *et al* [3]. The prevalence of this disease among patients with asthma is approximately 1 - 2% but slightly higher in patients that suffer from cystic fibrosis being about 2 - 9% [1,4]. For those that are corticosteroids-dependent asthmatics, the prevalence is 7 - 14% [5]. There are no gender predilections noted and the global burden for this disease potentially exceeds 4.8 million people [4,6]. This disease can also be seen in recipients of a lung transplant and people that suffer from bronchiectasis, chronic granulomatous disease or hyper IgE syndrome, but it is very rare among those individuals [2]. There are debates about the predisposing factors that can lead to ABPA, but they are thought to include atopy, immunogenic HLA- restricted phenotypes, mutations in the CFTR gene that causes cystic fibrosis, polymorphisms of the collagen region of the surfactant protein A2, psychochemical characteristics of respiratory secretions and environmental exposure history [7].

The International Society for Human and Animal Mycology (ISHAM) provides a proposed set of diagnostic criteria for ABPA (Table 1) [8] These criteria are divided into three groupings: predisposing conditions, obligatory criteria, and other criteria. One of the following predisposing conditions must be present: asthma or cystic fibrosis. ABPA characteristically presents with poorly controlled bronchial asthma, eosinophilia, elevated serum IgE levels, and radiological findings such as with the most common findings being atelectasis, transient pulmonary infiltrates, proximal bronchiectasis, and signs of mucoid impaction [9]. The mainstream and most effective therapeutic options for ABPA include comprises a combination of systemic corticosteroids (to attenuate allergic inflammation) and anti-fungal agents (to reduce the fungal load). However, patients usually experience exacerbations after these treatments. Furthermore, long-term systemic glucocorticoid use, which is necessary for patients with refractory ABPA, may cause serious adverse effects including infections and osteoporosis and so on [10]. Since a systemic corticosteroid-sparing agent is required, recent case reports and several studies have shown the efficacy of Th2 inflammatory cascade inhibitors, such as omalizumab, mepolizumab, and benralizumab, for the treatment of ABPA.

Predisposing conditions	Requirements: 1of 2, rarely none are present Bronchial Asthma Cystic Fibrosis
Obligatory criteria	Requirements: 2of 2 Elevated serum IgE (> 1000IU/>417 IU/ml)) Elevated IgE or IgG against A. fumigatus OR Aspergillus skin prick test positivity
Other criteria	Requirements: 2of 3 Serum eosinophil count > 500/mcL Radiographic changes consistent with ABPA Precipitating serum antibodies to A. fumigates OR elevated aspergillus fumigates specific IgG level (>27mg/L)

Table 1: *ISHAM criteria for diagnosis of ABPA*

Case Report

A 40-year-old non smoker businessman, not known to have diabetes mellitus, hypertension or coronary artery disease but with a history of bronchial asthma of five years duration came to our hospital for evaluation of poorly controlled asthma. Since his diagnosis, he was started with on demand inhaled short acting β-agonists and anti muscarinic combination followed by combination of inhaled long acting β-agonists and steroid on a regular basis. Not long after, montelukast, doxophylline and anti histamine were added to the treatment because of persistent asthma consisting of a persistent cough, shortness of breath and wheezes that were not responding to the treatment previously prescribed. He also was prescribed steroids as needed for relapses which happened frequently. For that he had to be hospitalized twice in last 6 months. On query he has been suffering from allergic rhinitis since child hood and he is allergic to cold and dust. His mother and younger brother is also asthmatic.

He sought help by multiple pulmonologists and internists, because it was interfering with his life activities, who prescribed him the same treatment and would put him on oral steroids which would improve the patient's condition partially but not completely. Frequent exacerbations were noticed but since he was already taking the maximal optimal dose for asthma medications, nothing else could be done.

In our hospital, the patient was reevaluated with a detailed history focusing on the place of residence, degree of ventilation of his house (which was well ventilated) and exposure to animals at home. But when searching for mold exposure in the patient's medical history, we discovered his gardening activities and that he had multiple indoor plants at his house. There was no history of NSAIDs or β-blockers use and no heart burn. He did however mention brownish colored sputum with a plug like consistency and multiple courses of antibiotics.

He also mentioned that his brother is an avid smoker but not in front of him and his past medical and surgical history was unremarkable despite the asthma. He affirmed to be compliant with his medication but still suffering from frequent exacerbations that were partially relived by oral or IV steroids. This led to the suspicion of allergic bronchopulmonary aspergillosis and thus further investigations were done. A chest X-ray (face and profile, figure 1) showed a left hilo-axillary linear opacity with retraction signs evoking atelectasis. Her blood tests didn't show a biological inflammatory syndrome (CRP= 06 mg/l; white blood cells= 8340/mm^3, eosionphil- 1392/mm^3). Chest computed tomography (CT) confirmed the diagnosis of atelectasis and proximal bronchiectasis with no parenchymatous lesion (Figure 2).

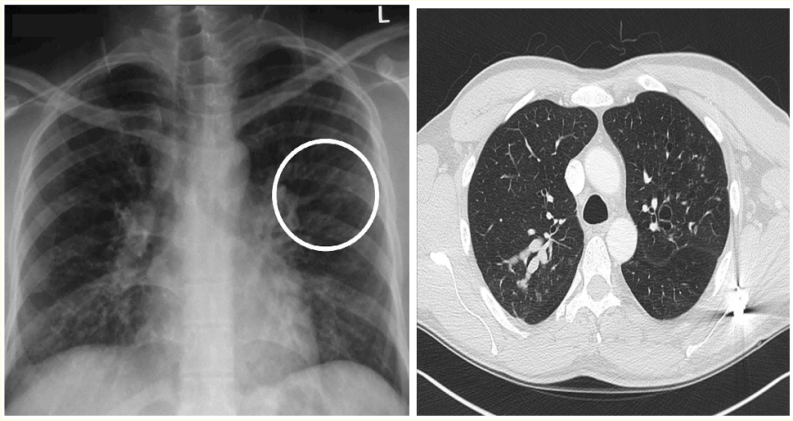

Figure 1: *Chest X ray showing hilo-axillary linear opacity with retraction signs and*
Figure 2: *CT chest showing left proximal bronchiectasis.*

Bacterial culture of sputum revealed growth of acinetobacter and the patient received consequently an antibiotherapy associating Levofloxacin and Ceftazidime for two weeks, with partial improvement in respiratory symptoms. Aspergillus serology (IgG) was positive at 33.6 U/L (positive > 12 U/L). Total IgE count was 1610 IU/ml. Aspergillus fumigatus specific IgE and Aspergillus skin testing, flexible bronchoscopy and pulmonary function tests, mycological culture were not done. The diagnosis of ABPA associated to asthma was established. The patient was started prednisolone at the dosage of 0.5 mg/kg/day and oral itraconazole 400 mg twice daily along with his usual asthma medications In addition to medical treatment, it was recommended that the patient should remove all the indoor plants. The evolution has been marked by the disappearance of respiratory symptoms and of the atelectasis on chest x-rays and the decrease in the eosinophil count (262/mm^3) on follow up after 4 weeks. There is plan to taper the oral steroid dose over next 6 months and to continue itraconazole for at least 6 months.

Discussion

Aspergillus is a common mould which accounts for 0.1 - 22% of all fungal spores in air samples. Although about 250 species of this fungus have been described so far, only some of them are human pathogens, e.g. Aspergillus fumigatus (90%), Aspergillus flavus, Aspergillus

niger. commonly Aspergillus fumigatus. Spores are commonly airborne in the environment yet rarely cause disease in immunocompetent patients. Depending on the individual's immune status, the diseases caused by Aspergillus may be saprophytic (aspergilloma), allergic (ABPA, allergic aspergillosis of the paranasal sinuses, allergic alveolitis) or invasive (invasive aspergillosis) [9].

ABPA is a disease caused by hypersensitivity to antigens of moulds, most commonly to antigens of Aspergillus fumigatus, which usually develops in patients suffering from asthma or cystic fibrosis, usually in the presence of atopy. The increased viscosity of the mucus in the respiratory tract in some of the patients with asthma and cystic fibrosis combined with impaired mucociliary clearance in cystic fibrosis disrupts the process of effective removal of the fungal spores from the bronchi. Exposure to large numbers of conidia may cause ABPA [8,11], but not all asthmatics develop ABPA despite being exposed to the same environmental factors. This means that other factors play a role in the pathogenesis of ABPA [8]. In a genetically predisposed individuals, inhaled conidia of Aspergillus fumigatus germinate into hyphae with release antigens that activate the innate and adaptive immune responses (Th2 CD4+ T cell responses) of the lung [8,11]. Five stages of the disease, which may develop in various orders, are distinguished: stage I (acute), stage II (remission), stage III (exacerbation), stage IV (steroid dependent), and stage V (fibrotic). The disease may be insidious with periods of exacerbation and periods of remission, and early diagnosis may prevent the progression of the disease, damage to the pulmonary interstitium, and pulmonary function deterioration [12].

The condition has a variable pathophysiology that is still largely unknown. Some papers define it as an immediate hypersensitivity (type 1) response, some as an antigen-antibody complexes (type 3) response and some as an eosinophil-rich inflammatory cell response (type 4b) [6,7]. The reason why asthmatic patients are susceptible to this disease is not fully understood, but some authors have reported that exposure to large concentrations of the A fumigatus spores may be the cause [8]. Environmental factors are not considered one of the main pathogenic factors because not all asthmatic patients develop ABPA even if they had been exposed to the same environmental factors [9]. The fungus persists and germinate into hyphae in a genetically predisposed individual, which causes the release of antigens that compromise the mucociliary clearance, stimulate and breach the airway epithelial barrier and activate the innate immunity of the lungs. This causes an influx from the inflammatory cells and a resultant early and late phase inflammatory reaction [9]. In recent years, it has been discovered that the fungus attaches to the lung epithelial cells resulting in the release of pro-inflammatory mediators and the influx of granulocytes which cause an intense Th2 CD4 T- cell immune response. The Th2 cytokines (interleukin [IL]-4, IL-5, and IL-13) lead to total and A fumigatus-specific IgE synthesis, mast cell degranulation, and promotion of a strong eosinophilic response [13,14]. Mucus plugs contain Charcot–Leyden crystals and eosinophils. Culture of these plugsmay or may not grow the Aspergillus fungus [16]. A combination of these events can also be the cause for the development of progressive fibrosis and bronchiectasis. Although traditional treatment has focused on suppressing the immune reaction to these phenomena, with high-dose corticosteroids, the presence of viable organisms driving this process makes the option of antifungal chemotherapy an attractive adjunct [9,15].

ABPA is due to an inflammatory pulmonary disorder which often causes non specific symptoms such aschronic cough, wheezing and recurrent pulmonary infiltration [9]. It may be associated to other symptoms such as fever, weight loss, deterioration of general condition, hemoptysis, chest pain and night sweats [17]. Expectoration of yellowish-green lumps of mucus is characteristic of ABPA and can be observed in half of the cases [9].

A characteristic feature of ABPA is the variable radiographic appearance. The chest X-ray may be normal in the early stages of the disease. The most common X-ray features include transient pulmonary infiltrates (mainly in the upper and lower lobes), atelectasis, band-like opacities (the gloved finger sign), bronchiectasis, "Tramline shadows which are temporary patterns corresponding to bronchial wall edema and thickening, ; "Toothpaste shadows" which are also transient and indicate mucus plugs within bronchi; "parallel line shadows" which appear when the mucus plugs are expectorated [18,19] and - less frequently areas of poor vascular pattern, cavities, and signs of fibrosis. The most common findings on chest CT include: bronchiectasis with a predominance of proximal changes, signs of atelectasis, mucoid impaction, local areas of consolidation and - less frequently - changes of an air trap nature, cavities, fibrosis, and pleural thicken-

ing [20]. Flexible bronchoscopy has an important place particularly in patients with atelectasis to rule out malignant etiologies. It also allows bacteriological and mycological samples. Sputum or bronchial fl uid cultures are positive for Aspergillus in nearly 40 - 60% of cases [19,21]. The presence of Aspergillus fumigates in the sputum culture is not sufficient to confirm the diagnosis of ABPA as this fungus is human saprophyte and can be present in other pulmonary diseases [8,11].

When the diagnosis of ABPA is suspected, some biological investigations are used for the diagnosis and monitoring of ABPA. The relevant tests are eosinophil count, total serum IgE level, serum IgE antibodies specific to Aspergillus fumigatus and serum precipitins or specific IgG against Aspergillus fumigatus [8,18]. First, blood eosinophil count should be checked and a level over 500 cell/L can help to establish the diagnosis. Our patient had an elevated eosinophilic count (1392/mm^3). However, high eosinophil counts can be detected in many other diseases and normal levels are reported in patients with ABPA receiving corticosteroids [18]. It is known that the pulmonary eosinophilia is far greater than in peripheral blood; thus, a low eosinophil count does not exclude ABPA [8,22]. The measurement of the serum total IgE level is an accurate and important test for the diagnosis and the follow-up of ABPA[11]. Active ABPA is generally excluded when serum IgE is normal [8,11]. For the cut-off value of IgE level that should be used in the diagnosis of ABPA, there is no consensus, and it remains uncertain [8]. In addition, the reported IgE values in different units (IU/mL, ng/mL) could lead to false interpretation [8]. Some laboratories employ 417 IU/mL as a cut-off value, while others use a value of 1000 IU/mL [23]. So, a validation of the IgE cut off value across all populations is required since it could be influenced by both risk of exposure to Aspergillus antigens and ethnicity [8,18]. Despite this, the most sensitive investigation in the diagnosis of ABPA is currently the detection of high levels of serum IgE antibodies specific to Aspergillus fumigatus (> 0.35 kUA/l). This test is also considered the preferred one for screening asthmatic patients for ABPA [8,11,24]. Although the detection of IgE antibodies specific to Aspergillus fumigatus is useful for the diagnosis, it is less helpful in the follow up of patients[11]. In addition, serum precipitins or specific IgG against Aspergillus fumigatus are detected in 69 - 90% of cases of ABPA [8,25]. In fact, double gel diffusion technique for the detection of Aspergillus fumigatus-specific IgG has a limited sensitivity (27%) in the diagnosis of ABPA, whereas, commercial enzyme immunoassays have a sensitivity exceeding 90% [11,25].

Different therapeutics have shown their efficiency in the treatment of ABPA. Glucocorticoids are the first molecules to be used. A randomized trial showed that the medium-dose regimen and high-dose regimen are both effective against ABPA with less side effects for the medium-dose regimen [24]. In the medium dose regimen, prednisolone is prescribed in monotherapy for a total duration of three to five months (0.5 mg/kg/day for two weeks, then on alternate days for eight weeks, then 5 mg less every two weeks) [11]. When a patient is on glucocorticoids and still has recurrent exacerbations or worsening pulmonary function test or become glucocorticoid-dependent, antifungal therapy could be added [11,26]. In our case, the patient presented a severe complication of glucocorticoid treatment which is aseptic osteonecrosis of both femoral heads requiring surgery. Itraconazole is usually used with or without glucocorticoids for at least six months, at a dose of 200 mg twice a day [26]. It requires frequent liver enzymes level monitoring because of its toxicity [26]. In fact, itraconazole can cause liver toxicity which was the case of our patient. Other oral azoles such as voriconzaole and posaconazole are also effective in ABPA and can be used when itraconzaole is toxic or contraindicated [27]. However, when there is a drug toxicity due to one molecule of azole, there is a risk of a cross-azole toxicity. So alternative approaches to antifungal treatment, in ABPA, that avoid systemic effects were tested and inhaled amphotericin B has been explored with varying results in uncontrolled studies [28,29]. In our case, inhaled amphotericin B was not available and itraconazole was used without a cross-azole toxicity. It led to remission without relapse after discontinuation of antifungal therapy.

The Th2 inflammatory response along with IgE and eosinophils is considered as the pathogenesis of ABPA. Interleukin-5 (IL-5) is a cytokine mediator that induces eosinophil development, activation, and proliferation. Eosinophils are activated by IL-5 and form mucoid impactions that damage the bronchial wall. However, recent studies have shown the efficacy of Th2 inflammatory cascade inhibitors. Specifically, omalizumab, (a monoclonal antibody against IgE), mepolizumab, (a monoclonal antibody against IL-5), and benralizumab, (an anti-IL-5 receptor alpha monoclonal antibody), are used for the treatment of ABPA as systemic glucocorticoid-sparing agents. A system-

atic review reported that omalizumab treatment used in ABPA patients resulted in a significant reduction in serum IgE levels, exacerbation rates, and steroid requirement, while it also improved pulmonary function [30]. Another review presented eight ABPA cases, treated successfully with mepolizumab. Mepolizumab improved pulmonary function, radiological findings, and quality of life [31]. Only four cases have been described for the use of benralizumab [32-34].

In the case of acute lung collapse, broncho-alveolar lavage during rigid or flexible bronchoscopy helps the lung re-expansion and significant improvement of ABPA symptoms [35,36]. For patients with thick sputum, chest physiotherapy and nebulized hypertonic saline solution improve the symptoms [37,38]. Patients should be examined every two months with chest radiography and total serum IgE levels until remission [8]. Exacerbation is confirmed when the baseline total IgE levels doubles with clinical or radiological deterioration [8]. Response to therapy is defined by a minimum of 25% decrease in total IgE levels with clinical and radiological improvement and remission is confirmed when the patient has no exacerbations for at least six months after stopping all therapeutics [8]. However, it has not been demonstrated that there are benefits of treating ABPA diagnosed on routine investigation in asymptomatic patients with well controlled asthma.

Long-term prognosis of patients with ABPA is still not clear[39]. But early detection of the disease and prescription of treatments lead to a good prognosis[40]. Untreated patients progress to irreversible lung fibrosis and respiratory failure [41].

Conclusion

In conclusion, it should be emphasized that ABPA is a frequently under diagnosed condition associated exclusively with the presence of asthma or cystic fibrosis. Also, not all the diagnostic criteria are always fulfilled, which makes establishment of the final diagnosis difficult. We should always keep ABPA in mind as a possible condition in asthmatic patients and patients with cystic fibrosis specially if In addition, if the commonly used medications for a disease do not improve the patient's condition. However, the disease should be detected as soon as possible because prompt initiation of treatment may prevent irreversible pulmonary fibrosis and disability.

Conflict of Interest

None declared.

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