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Which came first, allergic bronchopulmonary aspergillosis or asthma?

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Abstract

Aspergillosis includes a group of disorders caused by Aspergillus species that affect the respiratory system most commonly. The clinical spectrum of respiratory aspergillosis is divergent. Allergic bronchopulmonary aspergillosis is a result of hypersensitivity to Aspergillus antigens. Although it is known for many years, pathogenesis is not entirely clarified and there are no exact diagnostic criteria. The results are diagnostic delay, incompletely known management that can cause serious disability.

Keywords: allergic; bronchopulmonary; aspergilosis; asthma.

Introduction

Aspergillosis includes a group of diseases caused by Aspergillus species, among which *A.fumigatus* is the most common causative agent [1,2].

The clinical spectrum of respiratory aspergillosis varies, allergic disorders include Aspergillus-induced asthma, extrinsic allergic alveolitis, allergic Aspergillus sinusitis, and Allergic Bronchopulmonary Aspergillosis (ABPA) [1].

The diagnosis of ABPA requires clinical, laboratory, and radiological criteria to be fulfilled [2]. The most accepted criteria are those from the International Society for Human and Animal Mycology (ISHAM) which include predisposing factors (asthma, cystic fibrosis), obligatory criteria (positive type I skin test or elevated specific IgE levels and total IgE levels, >1,000 IU/ml) and other criteria of which at least two should be present (precipitating or IgG, radiological changes compatible with ABPA, total eosinophil count >500 cells/µL in steroid naive patients) [2,3].

Symptoms include cough, usually with expectoration of dark mucus plugs, dyspnea, fever, malaise, hemoptysis, weight loss, chest pain [4,5].

Radiological findings are perihilar infiltrates, consolidation, dilatated bronchi, segmental or lobar collapse, or signs of mucoid impaction, bronchiectasis, cavitation, lung fibrosis [4]. Central bronchiectasis without peripheral bronchial changes is considered as a hallmark of APBA [4].

One of the major criteria is positive allergy skin tests, eosinophilia is not pathognomonic but is considered to be an important finding [4]. ABPA has several stages that are not strictly or

chronologically separated. The acute phase is manifested with symptoms and the above mentioned findings [5]. Remission is characterized by IgE level fall for more than 35% over 6 weeks, radiological and clinical improvement. In exacerbation, there are radiological worsening, eosinophilia, and a rise in IgE levels for >50% from remission values [4,5]. In the corticosteroid-dependent phase, oral glucocorticoids are needed for asthma control. The final phase is the fibrotic phase when serological tests are usually negative [4,5].

The main stay of ABPA treatment is corticosteroids, although there are no controlled studies and the exact dosing and the duration of therapy are not defined [6,7]. For steroid-dependent and steroid-resistant patients, antifungal therapy can be added [6,7].

Here we present a case of APBA that occurred before asthma.

Case report

A 70-year old meteorologist presented to the emergency department with a two-month history of productive cough (dense, green sputum), intermittent wheeze, and a one-day history of fever. The patient did not have stenocardia, dyspnea, and hemoptysis. Physical examination was unremarkable. Medical history revealed hypertension and hyperlipidemia. For the last five years, the patient was hospitalized several times due to migratory lung infiltrates, initially no blood in the bronchi nor lung eosinophilia were detected. The microbiological analysis did not reveal significant pathogens. Two years ago blood eosinophilia was detected (30%), allergological tests and parasite analysis were negative. Spirometry was performed on several occasions, results were within the normal limits with negative bronchodilatation and methacholine test. A year ago mild obstructive pattern was detected and the bronchodilatation test was positive, asthma was diagnosed and inhaled corticosteroid therapy was initiated.

On admission now, a chest roentgenogram revealed right upper and middle lobe lung infiltrates, blood eosinophilia (29%), inflammatory markers were within the normal limits. The total IgE level was elevated (1210 kIU/L), and specific IgE against *A.fumigatus* was >100 kU/L. Sputum analysis revealed neutrophils and eosinophils, bacterial and M.tuberculosis testing was negative, but A.fumigatus 105 CFU/ml was detected. Chest Computed Tomography (CT) revealed diffuse peripheral bronchiectasis with mucoid impactions, consolidation, centrilobular nodules, and tree-in-bud pattern. Fibrobronchoscopy was performed; the purulent, thick plug was seen in the right upper lobe, cytological analysis of mini lavage revealed neutrophils, eosinophils, and fungal hyphae. Given the above, prednisolone and itraconazole were initiated. Five months later, the patient has no symptoms, radiographically there is a complete regression of lung infiltrates, without blood eosinophilia and total IgE levels are reduced by 54%.

Discussion

Although APBA is first described 68 years ago, exact diagnostic criteria and optimal therapy are not entirely clarified, due to unknown pathogenesis [3]. CF and asthma are considered crucial criteria, however, ABPA can occur in healthy individuals and patients with other comorbidities [4]. Our case is a rare presentation of ABPA before the diagnosis of asthma. Symptoms of ABPA arose before diagnostic elements for asthma were present. Initially, lung function (including methacholine test), and allergy tests were negative. The question remains, whether the patient had asthma that was worsened by untreated ABPA and then detected by the tests.

The problem is that some of the proposed, obligatory, criteria do not have to be present at the same time. If the patient was taking corticosteroid therapy recently, eosinophilia may not be detected or a skin prick test, which is in all criteria considered as a major factor, could be negative. Our patient did not have a positive skin prick test, but, when put all together, the patient has asthma, migratory pulmonary infiltrates, blood and lung eosinophilia, elevated total, and specific IgE. According to today's diagnostic protocols, the patient would not fulfill all criteria for ABPA. Furthermore, migratory lung infiltrates are not considered to be essential by most criteria. In our case chest CT did not reveal central bronchiectasis, however, in the later course of a disease, only peripheral lung changes can be present.

It is debatable whether there should be cut-off values for IgE levels and blood eosinophilia, especially since IgE values >1000 kIU/L are accepted as relevant. If a patient has other criteria fulfilled and elevated total IgE, but not >1000 kIU/L, should he be excluded from the diagnosis and not given the therapy?

The role of antifungals is unknown and it is confusing when to start with this therapy. In our case, prednisolone and itraconazole were inducted simultaneously with very good clinical and laboratory responses. Since *Aspergillus* can be found everywhere in the environment, some authors propose decreasing exposure to molds as a therapeutic option, especially in the context of professional disease [9].

Considering all mentioned, ABPA is rare but can cause serious lung damage and a patient's disability. Upgrading of diagnostic criteria is mandatory to enable faster diagnosis establishment, complications reduction, and better quality of life for the patients.

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