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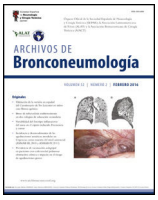

Editorial

Allergic Bronchopulmonary Aspergillosis: A Disease that Raises Many Questions☆

Aspergilosis broncopulmonar alérgica: una enfermedad con muchos interrogantes

Aspergillus is an ubiquitous, saprophytic fungus that produces a wide spectrum of lung diseases, including allergic bronchopulmonary aspergillosis (ABPA).[1]

Respiratory exposure to *Aspergillus* conidia is unavoidable. In the healthy host, these spores are eliminated quickly. However, in susceptible subjects, a hypersensitivity reaction occurs due to the defective elimination of these conidia from the airways, associated with innate and adaptive immunity defects, causing an inflammatory reaction with mast cell degranulation, recruitment of a large number of inflammatory cells (neutrophils and eosinophils), and IgE synthesis (total and specific).[1] Its pathogenesis, then, is characterized in immunological terms by immediate hypersensitivity (type-I), antigen–antibody complexes (type-III), and response by inflammatory cells such as eosinophils (type-IVb). Although ABPA was first described in 1952,[2] proper diagnosis and treatment still depend on scant information, as there are few controlled trials (most publications are case series) that address these knowledge gaps.

ABPA mainly affects patients with cystic fibrosis (CF) and asthma, and although genetic predisposition appears to be a factor, the reasons why some subjects are susceptible and others not remain to be clarified. Approximately 9% of CF patients have ABPA,[3] compared to 0.7%–3.5% of asthmatics (approximately 4.8 million cases worldwide).[4] Despite this high prevalence, ABPA is still underdiagnosed, partly because clinical suspicion in CF is complicated, as symptoms and radiological and functional findings that support an ABPA diagnosis are often common in this condition, and asthma patients also have overlapping symptoms. Moreover, the disease is sometimes asymptomatic. In recent decades, however, the number of cases reported has increased, probably indicating a greater awareness among professionals.

The ABPA diagnostic criteria proposed by Rosenberg[5] in 1977, which require a combination of clinical, radiological and immunological findings (8 major and 3 minor criteria), remain in force. However, these criteria have several limitations, including the lack of consensus on the number of major and minor criteria required and the cut-off values of the various immunological tests. Indeed, several groups have proposed different ways of diagnosing ABPA in asthma and CF,[1,6,7] and there are still no clearly standardized and validated diagnostic criteria. The ISHAM group,[1] for example, published a set of highly practical recommendations that contain easily obtained variables, i.e., the existence of a predisposing disease (asthma, COPD, cystic fibrosis, etc.) together with 2 mandatory analytical criteria, and another 2 of 3 additional criteria (analytical and radiological), with well-established cut-off points, so they are very useful in routine clinical practice. However, the lack of standardization means that the disease is not correctly diagnosed in many countries (in developing countries up to one third of cases are misdiagnosed as pulmonary tuberculosis), and diagnosis is also often late, with a diagnostic delay of up to 10 years. It is therefore recommended to rule out ABPA in any patient with CF or asthma, regardless of severity or level of control.[1]

It is important to recognize ABPA in order to establish early diagnosis and treatment to improve symptoms and prevent or delay the development of bronchiectasis and pulmonary fibrosis, which are manifestations of permanent lung damage associated with worse health outcomes.

Treatment objectives include reduction of inflammation, control of symptoms, prevention of exacerbations, and mitigation of onset or progression to chronic lesions. The natural history of ABPA is characterized by repeated exacerbations, so most patients require long-term treatment.[1]

Treatment of ABPA includes anti-inflammatory drugs (glucocorticoids) to suppress the immune hyperresponse, and antifungal agents to attenuate (or eliminate) the fungal burden in the airways. Oral glucocorticoids are currently the first line of treatment, as they are the most effective therapy, although there is no clear agreement on dosing protocols and duration. However, their significant side effects mean that they must be used judiciously. By reducing the fungal burden, antifungal agents reduce the antigenic stimulus and can act as steroid-sparing agents, so they are positioned as second-line treatment. Itraconazole 400 mg/day is usually recommended, although itraconazole doses have never actually been standardized in the treatment of ABPA, and lower doses (200 mg/day) have also been found to be clinically effective. Several reviews have also emphasized the weakness of evidence on the safety and efficacy of the azoles,[8,9] and the duration of treatment, when they should be started, and the best protocol are all still unclear.

In the search for more effective and safe treatments, taking into account that the response to *Aspergillus* is mainly mediated by a T2 response that generates IL-5 and IgE, trials of new

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biological treatments for asthma such as omalizumab (anti-IgE) or anti-IL5/antieosinophils have shown very promising results.

In fact, several case series with omalizumab have been published,[10] but currently only 1 randomized, placebo-controlled study is available, which is limited by its small sample size (13 patients) and single-center, open-label design.[11] A clinical trial did begin,[12] but ended earlier than expected due to adverse events probably caused by an unrealistic design that involved the administration of a daily dose of omalizumab. In the published cases using omalizumab in ABPA, a significant reduction in exacerbations and use of oral corticosteroids was detected,[10,11] and the doses used in asthma appear to be sufficient despite these patients' higher IgE levels.

Case series with mepolizumab and benralizumab as monotherapy for ABPA have also shown good results.[13,14] Furthermore, given the eosinophilia and increased IgE characteristic of ABPA, omalizumab has been used synergically in combination with an anti-IL5.[15] These new treatments appear to be a good alternative, especially as corticosteroid-sparing agents or in patients who refuse steroid treatment. However, due to the lack of clinical trials, the ideal dose, length of treatment, and the medium to long-term side effects remain to be determined.

Although almost 70 years have passed since the first description of a patient with ABPA, there are still large gaps in our knowledge, and evidence on epidemiology, pathogenesis, diagnosis, and treatment is limited. More effective and less toxic treatments are needed for the management of this complex disorder. Given the results of case studies with the newly available drugs and the lack of controlled trials, a greater commitment to research is needed to help answer the questions raised.

Conflict of Interests

Alicia Padilla Galo has participated in scientific papers and/or scientific consultancy with the following companies: ALK-Abelló, Astra-Zeneca, Boehringer, Chiesi, Grifols, GSK, Menarini, Mundipharma, Novartis, Orion, Pfizer, Praxis, Teva, and Zambon.

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