Allergology International 65 (2016) 30–36

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Review article

Serological diagnosis of allergic bronchopulmonary mycosis: Progress and challenges

Yuma Fukutomi*, Hidenori Tanimoto, Hiroshi Yasueda, Masami Taniguchi

Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, Kanagawa, Japan

ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form
19 August 2015
Accepted 21 August 2015
Available online 26 September 2015

Keywords:
Allergic bronchopulmonary mycosis
Allergy
Aspergillus fumigatus
Fungi
Molecular-based allergy diagnostics

Abbreviation:
ABPM, allergic bronchopulmonary mycosis; Abs, antibodies; ABPA, allergic bronchopulmonary aspergillosis; MnSOD, manganese superoxide dismutase; AD, atopic dermatitis; MA, molecular-based allergy; WHO/IUIS, World Health Organization and International Union of Immunological Societies; ABPC, allergic bronchopulmonary candidiasis

ABSTRACT

Prompt diagnosis of allergic bronchopulmonary mycosis (ABPM) is an important clinical issue in preventing irreversible lung damage. Therefore, a good serological marker for the diagnosis of ABPM is desired in clinical practice.

The measurement of IgE antibody to crude *Aspergillus fumigatus* allergen is considered the first step in screening asthmatic patients for allergic bronchopulmonary aspergillosis (ABPA). However, presence of IgE to *A. fumigatus* does not always indicate genuine sensitization to *A. fumigatus* because of cross-reactivity between crude extracts from different fungal sources. The application of molecular-based allergy diagnosis can solve this problem. The specificity of testing can be greatly improved by measuring the IgE antibody to Asp f 1 and f 2, specific allergen components for genuine *A. fumigatus* allergy.

The problem of cross-reactivity between crude fungal extracts is also true for the identification of genuine causal fungi in each ABPM patient. Some patients with ABPM induced by fungi other than *Aspergillus* may be consistent with ABPA diagnostic criteria because current criteria depend on IgE/IgG reactivity to crude extracts. Accurate identification of genuine causal fungi for ABPM is of clinical importance, considering that clinical presentation, anti-fungal treatment strategies and disease prognosis can be influenced by different causal fungi. The diagnosis of causal fungi can be robustly validated by the confirmation of genuine sensitization to fungi after measuring IgE to specific allergen components, as well as repeated microbiological isolation of the fungi from their airway.

Introduction

Allergic bronchopulmonary mycosis (ABPM) is a pulmonary hypersensitivity disease characterized by sensitization to fungi, recurrent transient radiographic infiltrate, peripheral and pulmonary eosinophilia, and bronchiectasis.[1–5] The diagnosis of ABPM is an important clinical issue because ABPM may lead to ongoing decline in lung function, lung fibrosis, and early treatment is essential to prevent long-term tissue damage.[6] The diagnosis of ABPM is not difficult if patients exhibit all diagnostic criteria of ABPM including central bronchiectasis and lung infiltration. However, ABPM should ideally be diagnosed before bronchiectasis occurs, to prevent irreversible lung damage. Therefore, good serological markers for the early diagnosis of ABPM are desired. This review discusses the recent progress and challenges in serological diagnosis of ABPM.

Pathogenesis and causal fungal species of ABPM

The pathogenesis of ABPM is characterized by colonization of fungi in the airways and a strong humoral and cellular response to the fungi and its secreted proteolytic enzymes,[7,8] resulting in increased levels of serum IgE and IgG antibodies (Abs) to these fungal allergens.[9] A common feature of fungi which can induce ABPM includes thermotolerance,[10] which enables these microbes to grow at human body temperature. *Aspergillus fumigatus* is the most common causal pathogen for ABPM, whereas *Aspergillus flavus*, *Aspergillus niger*,[11–13] *Candida albicans*,[14–16] *Bipolaris* spp.,[17] and *Schizophyllum commune*[18–23] are also reported to induce similar clinical conditions.

* Corresponding author. Clinical Research Center for Allergy and Rheumatology, Sagamihara National Hospital, 18-1 Sakuradai, Minami-ku, Sagamihara, Kanagawa 252-0392, Japan.
E-mail address: y-fukutomi@sagamihara-hosp.gr.jp (Y. Fukutomi).
Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2015.08.004

The diagnostic criteria for ABPA and ABPM

There are no universally accepted set of criteria for the diagnosis of ABPM. However, it is generally accepted that the diagnosis of ABPM can be performed using the diagnostic criteria of allergic bronchopulmonary aspergillosis (ABPA) by replacing *A. fumigatus* with another fungus.[4,5] ABPA is a subset of ABPM induced by *Aspergillus* species, first described in 1952 by Hinson *et al.*[24] As *A. fumigatus* is the most common fungal agent to cause ABPA, the diagnostic criteria for ABPA have been based on the patient's immunological reactivity to crude extracts of *A. fumigatus* in combination with radiological or clinical findings. Although its clinical presentations have been well described in the literature,[3,25–28] there are no universally accepted diagnostic criteria for ABPA as yet.[29] The diagnostic criteria most widely accepted are those proposed by Rosenberg and Patterson,[25] which include 7 primary criteria. These include 1) asthma, 2) peripheral blood eosinophilia, 3) immediate skin reactivity to *Aspergillus* antigen, 4) precipitating Ab against *Aspergillus* antigen, 5) elevated total IgE, 6) history of pulmonary infiltrate, and 7) central bronchiectasis. Criteria 1), 3), 5) and "elevated serum IgE Ab to *A. fumigatus*" are also minimal essential criteria for seropositive ABPA, proposed by Greenberger.[2] The International Society for Human and Animal Mycology (ISHAM) working group has recently proposed new diagnostic criteria for ABPA,[3] in which each criterion is divided into "obligatory" and "other" status. These newly proposed criteria also regard positive immediate cutaneous hypersensitivity to *Aspergillus* antigen or elevated IgE levels against *A. fumigatus* as "obligatory" criteria and the presence of precipitating or IgG Abs against *A. fumigatus* in serum as "other" criteria.

It should be stressed that both the Rosenberg–Patterson (modified by Greenberger) and ISHAM working group criteria uses the elevation of IgE Abs to crude extracts of *A. fumigatus* as an essential requirement for ABPA. Furthermore, both criteria do not include the isolation of *A. fumigatus* from sputum as an essential requirement, which relates to the major challenges in the diagnosis of ABPM discussed in this paper. Since it is known that there is cross-reactivity between allergens from crude extracts of different fungi,[30] identification of IgE and/or IgG responses to *A. fumigatus* do not always indicate genuine sensitization to *A. fumigatus*. Therefore, those patients meeting current diagnostic criteria include patients with fungal allergy induced by fungi other than *A. fumigatus* (Fig. 1). In other words, current diagnostic criteria do not guarantee *A. fumigatus* colonization in the airway nor genuine antigen-specific IgE reactivity to *A. fumigatus*. These problems also apply for the diagnosis of ABPM induced by fungi other than *A. fumigatus*.

Isolation of fungi for the diagnosis and identification of causal pathogens of ABPM

Culture of *A. fumigatus* from sputum supports the diagnosis of ABPA, which is included as secondary criteria in the Rosenberg–Patterson criteria.[25] However the results of sputum culture have not been included in the primary criteria for the diagnosis of ABPA[25] because of its low sensitivity and specificity. The frequency of isolation of *A. fumigatus* from sputum of ABPA patients is not particularly high (63% in one report[31]) and can be influenced by the number of specimens examined and processing procedures.[3,32,33] In addition, the pathogen is frequently isolated from the respiratory tract of asthmatic patients without ABPA,[34,35] and also from patients with cystic fibrosis,[36] chronic obstructive pulmonary disease,[37] tuberculosis-related fibrocavity disease,[38,39] and healthy individuals.[35] Identification of more than two fungal species from one specimen is relatively common.[22,34,40] In addition, isolated fungi from a patient may vary by time of sampling, thus transient findings in sputum culture may not reflect the long-term history of fungal colonization. In contrast, the production of IgE Abs usually reflects long-term historical exposure to the fungal allergens thus serological findings may be superior to laboratory culture for the identification of genuine causal fungi. More recently, a study

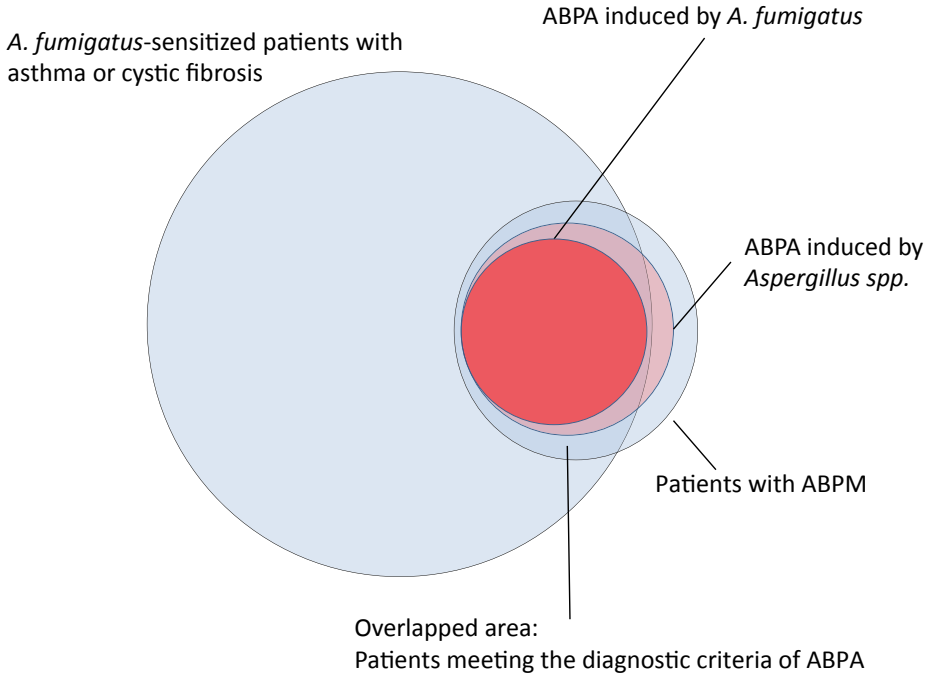

Fig. 1. The Venn diagram showing the relationship between patients meeting diagnostic criteria of ABPA and patients with ABPA genuinely induced by *Aspergillus fumigatus* or other *Aspergillus*. The patients meeting the current diagnostic criteria of ABPA (Rosenberg–Patterson or ISHAM working group) can theoretically include patients with ABPM induced by fungi other than the genus *Aspergillus* because of cross-reactivity to crude fungal allergen extracts.