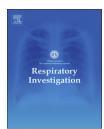
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Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv



Original article

Diagnostic criteria that can most accurately differentiate allergic bronchopulmonary mycosis from other eosinophilic lung diseases: A retrospective, single-center study



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ARTICLE INFO

Article history: Received 6 August 2015 Received in revised form 20 November 2015 Accepted 27 January 2016 Available online 24 March 2016

Keywords: Allergic bronchopulmonary mycosis Aspergillosis Diagnosis Classification criteria Eosinophilic lung diseases

ABSTRACT

Background: Several diagnostic criteria have been proposed to differentiate allergic bronchopulmonary mycosis (ABPM) from asthma, but there have been no studies to establish diagnostic criteria to classify ABPM differently from other eosinophilic lung diseases.

Methods: We retrospectively investigated both patients with ABPM (n=42) diagnosed by clinical (Rosenberg–Patterson criteria modified to apply to fungi other than Aspergillus spp., with consideration of computed tomography and bronchoscopy findings) or pathological criteria and those with other eosinophilic lung diseases (n=118) to establish elaborate diagnostic criteria for ABPM.

Results: Etiologies of ABPM included fungi other than Aspergillus spp. or unidentified pathogens in 16 patients. Fourteen patients (33.3%) did not have asthma. When the diagnostic cutoff line was set to satisfy six or more primary plus secondary modified Rosenberg–Patterson criteria, ABPM could be diagnosed with good sensitivity, specificity, and positive/negative predictive values (97.6%, 98.3%, 95.3%, and 99.1%, respectively). When the diagnostic criteria were combined with pathological criteria, the values further improved to 100%, 98.3%, 95.5%, and 100%, respectively. *Conclusions*: Our results suggest that these novel criteria offer good sensitivity, specificity, and positive/negative predictive values for the diagnosis and classification of ABPM.

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http://dx.doi.org/10.1016/j.resinv.2016.01.004

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; ABPM, allergic bronchopulmonary mycosis; CT, computed tomography; HAM, hyperattenuating mucous; IgE, immunoglobulin E; IgG, immunoglobulin G *Corresponding author. Tel.: +81 48 536 9900; fax: +81 48 536 9920.

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1. Introduction

Allergic bronchopulmonary mycosis (ABPM) is an immunological disorder caused by a hyperimmune response to the endobronchial growth of certain fungi and is considered to occur most commonly in atopic patients with asthma. If the disease is not adequately treated, irreversible damage occurs to the airways and lungs. In 1977, clinical diagnostic criteria comprising seven primary and three secondary criteria were suggested by Rosenberg, Patterson, et al. (Rosenberg–Patterson criteria) [1]. Since that time, several other diagnostic criteria have been proposed, but there has been no general consensus on which criteria are acceptable for the comprehensive diagnosis of ABPM.

The Rosenberg-Patterson criteria [1] consider allergic bronchopulmonary aspergillosis (ABPA) to be probable when six primary criteria are satisfied and definite when seven criteria are satisfied. Other criteria, which stipulate that the presence of bronchial asthma is "essential" for the diagnosis, have also been proposed [2]. In a recent report on ABPA, patients with asthma were screened for ABPA with a positive skin test for Aspergillus species antigens or a positive specific immunoglobulin E (IgE) antibody against Aspergillus spp., and the characteristics of ABPA were evaluated [3]. Furthermore, recently proposed diagnostic criteria [4-6] are based on the diagnosis of ABPA that was discovered in patients with asthma. However, reports of patients with ABPM but without asthma have been increasing [7,8]. Hinson et al. [9], who were the first to report a case of ABPA, remarked that ABPA resembles to some extent the condition described under the term "pulmonary eosinophilia." In clinical settings, ABPM should be differentiated from both eosinophilic lung diseases and bronchial asthma. In a previous study [4], the sensitivity and specificity of diagnostic criteria to differentiate ABPA from asthma were investigated; however, diagnostic criteria to differentiate ABPM from other eosinophilic lung diseases have not been investigated. In the present study, we therefore investigated patients with ABPM and suggest novel diagnostic and classification criteria based on the results of this investigation.

2. Patients and methods

We conducted a retrospective study that evaluated patients with ABPM (n=42) and other eosinophilic lung diseases (n=118; acute eosinophilic pneumonia in 11, chronic eosinophilic pneumonia in 73, eosinophilic granulomatosis with polyangiitis in 15, drug-induced lung disease in 15, Löffler syndrome in 3, eosinophilic pneumonia due to paragonimiasis in 1, eosinophilic pneumonia accompanied by rheumatoid arthritis [suspected drug-induced pneumonia] in 1, and eosinophilic bronchiolitis in 1) who presented to our hospital and

underwent laboratory and radiological testing from 1998 to 2014. This study was approved by the institutional review board of Saitama Cardiovascular and Respiratory Center (2015004, approved on May 27, 2015).

A diagnosis of ABPM was made when (1) at least six of the primary diagnostic Rosenberg-Patterson criteria [1] were satisfied, or (2) there was adequate pathologic evidence of allergic mucin containing fungal hyphae, a definite histologic finding of ABPM as suggested by Bosken et al. [10] and Katzenstein [11]. Diagnoses of other eosinophilic lung diseases (acute eosinophilic pneumonia [12], chronic eosinophilic pneumonia [13], eosinophilic granulomatosis with polyangiitis [14]), drug-induced lung diseases, Löffler syndrome, and others (eosinophilic pneumonia due to paragonimiasis, eosinophilic pneumonia accompanied by rheumatoid arthritis [suspected drug-induced pneumonia], and eosinophilic bronchiolitis) were established by consensus among clinicians, radiologists, and pathologists based on the diagnostic criteria for each disorder or on clinical courses, laboratory findings, and histologic findings obtained via bronchoscopic or thoracoscopic lung biopsy [12–16].

Sabouraud dextrose agar was used for fungal culture. The serum-specific IgE antibody was routinely measured for Aspergillus spp., Candida spp., Penicillium spp., Cladosporium spp., and Alternaria spp. by the radioallergosorbent test. From 2010, serum IgE for Schizophyllum commune was measured by enzyme-linked immunoassay. Precipitating antibody was measured for A. fumigatus, A. niger, A. versicolor, A. terreus, A. flavus, A. pullulans, A. clavatus, A. restrictus, A. nidulans, P. digitatum, P. glaucum, P. luteum, C. albicans, Cephalosporium acremonium, and Cryptococcus neoformans. Immunoglobulin G (IgG) antibody was measured by the complement fixation method [17] or enzyme-linked immunoassay. Fungi were regarded as causative when two or more of the following three criteria were satisfied: (1) fungi were isolated from sputum repeatedly or from other respiratory samples, (2) tests revealed positive specific IgE antibody, and (3) tests revealed positive precipitating antibody or immunoglobulin G (IgG) antibody. However, Candida sp., which is a colonizing fungus in the human oral cavity, was regarded as significant when it was isolated from mucus plugs or samples obtained from bronchial washings. In two of our previously reported cases of ABPM due to S. commune [18,19], specific IgE or IgG antibody could not be measured at the time, and because S. commune was isolated from mucus plugs, we regarded S. commune as the causative fungus.

We then compiled comprehensive diagnostic criteria for ABPM modified to apply to fungi other than Aspergillus spp., taking into consideration computed tomography (CT) and bronchoscopy findings (Table 1), and the number of criteria satisfied was counted. Results of specific IgE or IgG antibody tests were sometimes used as an alternative to each skin test or precipitating antibody result, as reported previously [4]. In

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