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The utility of galactomannan antigen in the bronchial washing and serum for diagnosing pulmonary aspergillosis

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KEYWORDS
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Summary
Background: The diagnosis of pulmonary aspergillosis is difficult because the sensitivity of the conventional methods for the detection of *Aspergillus* such as culture and cytology, is poor. To improve the sensitivity for *Aspergillus* detection, the detection of galactomannan antigen has been investigated. The serum galactomannan (GM) antigen has been recognized to be a useful tool for the diagnosis of invasive pulmonary aspergillosis. However, the utility of the galactomannan antigen for the diagnosis of pulmonary aspergillosis other than invasive pulmonary aspergillosis (IPA) has been unclear.
Methods: The GM antigen using serum and bronchial washing (BW) using bronchofiberscopy for the diagnosis of pulmonary aspergillosis other than IPA were measured.
Results: In 45 enrolled patients, 7 patients had pulmonary aspergillosis, 5 of these patients had chronic necrotizing pulmonary aspergillosis and 2 patients had allergic bronchopulmonary aspergillosis. The area under the receiver operating characteristic (ROC) curve was 0.89 for the BW GM antigen detection test, and 0.41 for the serum GM antigen detection test, suggesting that the BW GM antigen detection test exhibits a better diagnostic performance than the serum GM antigen detection test. The BW GM antigen detection test had a sensitivity of 85.7% and a specificity of 76.3% at a cut-off level of $\geq$0.5, which was the optimal cut-off level obtained by the ROC curve.

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Conclusion: The BW GM antigen detection test is thought to be a promising test for the diagnosis of pulmonary aspergillosis other than IPA.

Introduction

Aspergillus species are ubiquitous fungi isolated from the various environments such as the soil, foods, plant debris and the indoor environment.[1] Although there are approximately *Aspergillus* 200 species, the pathogenic species which cause pulmonary aspergillosis are limited. Among these, the most common pathogenic species is *A. fumigatus*, followed by *A. flavus*, *A. niger* and *A. terreus*.[1,2]

Pulmonary aspergillosis involves a variety of clinical entities. Invasive pulmonary aspergillosis (IPA) is a rapidly progressive, fatal disease, and usually occurs in severely immunocompromised patients.[3] Allergic bronchopulmonary aspergillosis (ABPA) is caused by an exaggerated immune response to *Aspergillus*.[4] Aspergilloma is a fungus ball that develops in a pre-existing cavity in the lung parenchyma.[5] Chronic necrotizing pulmonary aspergillosis (CNPA) is an indolent, cavitary, infectious disease that occurs secondary to local invasion by *Aspergillus*.[6] Most patients with CNPA have prior pulmonary disease, such as a healed tuberculosis cavity.[2]

In every entity of pulmonary aspergillosis, the detection of *Aspergillus* from respiratory tract samples is very important for reaching a precise diagnosis. However, the roles of conventional diagnostic tools, such as cultures obtained from respiratory tract samples, are limited by their low sensitivity. According to the previous reports, the culture sensitivity using respiratory tract samples was reported to be 40% for IPA, and 17.9% for chronic pulmonary aspergillsis (CPA).[7,8] To improve the sensitivity for *Aspergillus* detection, the detection of galactomannan (GM) antigen has been investigated.[9,10] GM is a polysaccharide fungal cell wall component released during hyphal growth in tissues and that can be detected in body fluids. The serum GM antigen detection test has been widely used as a useful tool for the diagnosis of IPA.[10] In addition, the detection of GM antigen in respiratory tract samples, such as bronchoalveolar lavage (BAL) and bronchial washing (BW), has also been investigated recently, and the GM antigen detection test using the respiratory tract samples was reported to be a good diagnostic tool using these samples.[11–15] The detection of GM antigen was reported to be more successful in the BAL compared with in serum.[11] However, the study population in that report comprised primarily patients with IPA. Thus, the utility of the GM antigen detection test has been unclear for pulmonary aspergillosis other than IPA.

Therefore, to evaluate the utility of the GM antigen detection test for the diagnosis of pulmonary aspergillosis other than IPA, we investigated the diagnostic performance of the GM antigen detection test using the BW and serum.

Materials and methods

Patients

Patients at Tokyo Medical University Hospital who were clinically suspected to have pulmonary aspergillosis between April 2008 and October 2011 were enrolled in this study. Eligible patients displayed at least one of following features: 1) a nodular shadow or cavity formation on chest CT and an elevated C-reactive protein (CRP) level; 2) asthma with bronchiectasis and mucoid impaction; 3) pulmonary infiltrates on chest CT refractory to antibiotics. Informed consent was obtained from each patient, and this study was approved by the ethics committee of Tokyo Medical University.

Detection of *Aspergillus* species

After finishing the routine procedures associated with fiberoptic bronchoscopy, BW was obtained by the instillation of 50 mL of 0.9% sterile saline into the segment which showed an abnormal shadow on the chest CT, and then recovered as much of the saline as possible as BW. The lung specimens obtained by transbronchial lung biopsy (TBLB) were obtained from the same lesion as that which underwent BW. The Platelia *Aspergillus* enzyme immunoassay (EIA) (Bio-Rad Laboratories, Hercules, CA, USA) was performed by SRL, Inc. (Tokyo, Japan) to measure the BW and serum GM antigen levels. The serum sampling for the GM was obtained on the same day as the performance of bronchoscopy. The BW samples which were obtained for the GM antigen detection test were used also for the fungal and bacterial culture and cytology examinations. When a diagnosis could not be made despite performing these examinations, then the *Aspergillus* precipitin test was performed in the patients who agreed to be checked for the presence of precipitant antibody. Next, *Aspergillus* precipitin tests were performed by SRL, Inc. using a double-gel diffusion Ouchterlony assay (Mercia Diagnostics, Camberley, UK).

Case definitions

The diagnostic criteria for CNPA and ABPA are shown in Table 1. The diagnosis of proven CNPA was made by the presence of at least one of the compatible symptoms such as a persistent productive cough, at least one of the compatible chest radiological images such as cavity formation, and a positive serum *Aspergillus* precipitin test or the positive isolation of *Aspergillus* species from respiratory tract samples by culture. Even if the existence of an *Aspergillus* species could not be confirmed, the diagnosis of possible CNPA was made when antibacterial therapy was