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Serum galactomannan antigen test for the diagnosis of chronic pulmonary aspergillosis

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Summary *Background:* A serum galactomannan (GM) antigen test has been widely used to diagnose invasive pulmonary aspergillosis. However, there are limited data on the use of the serum GM antigen test for the serologic diagnosis of chronic pulmonary aspergillosis (CPA).
Methods: Data were collected from all consecutive patients with a clinical suspicion of CPA who underwent a serum GM antigen test.
Results: In total, 334 patients who were suspected to have CPA were eligible for this study and 168 (50%) patients were finally diagnosed with CPA. The serum GM antigen test was positive in 38 (23%) patients with CPA and in 25 (15%) patients without CPA. The sensitivity of the serum GM antigen test was 23% (95% confidence interval [CI], 17–30%), and its specificity was 85% (95% CI, 79–90%), with positive and negative predictive values of 60% (95% CI, 47–72%) and 52% (95% CI, 46–58%), respectively. The accuracy of the test was 54%. The area under the receiver operating characteristic curve was 0.538 (95% CI, 0.496–0.580).
Conclusion: The serum GM antigen test could not be used for the serologic diagnosis of CPA.

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Introduction

The chronic forms of pulmonary aspergillosis are simple aspergilloma, chronic cavitary pulmonary aspergillosis (CCPA), and chronic necrotizing pulmonary aspergillosis (CNPA).[1] Although certain authors distinguish chronic fibrosing pulmonary aspergillosis (CFPA) from CCPA,[2] many investigators have described CCPA, CFPA, and CNPA as chronic pulmonary aspergillosis (CPA) in the recent literature.[3–5]

The diagnosis of CPA is difficult and is generally based on a constellation of clinical signs and symptoms, radiologic manifestations, and microbiological evidence, including the positive isolation of *Aspergillus* species from respiratory tract samples.[6–9] However, in patients with CPA, the role of conventional culture is limited by low sensitivity and relatively delayed results.[10] Therefore, a serum *Aspergillus* precipitin antibody test has been widely used for the serologic diagnosis of CPA.[6–8,10]

Galactomannan (GM) is a component of the *Aspergillus* species cell wall and is released into the surrounding environment during fungal growth or tissue invasion.[11] A serum GM antigen test has been widely used to diagnose invasive pulmonary aspergillosis.[12] However, there are limited data on the use of the serum GM antigen test in patients with CPA.[4,10,13,14] Therefore, we investigated the diagnostic performance of the serum GM antigen test to evaluate the utility of the test for the serologic diagnosis of CPA.

Patients and methods

Data were collected from all consecutive patients with a clinical suspicion of CPA who underwent a serum GM antigen test at the Samsung Medical Center (a 1961-bed, university-affiliated, tertiary referral hospital in Seoul, South Korea) between January 2010 and December 2012 and were retrospectively analyzed. A portion of the clinical data from these patients was included in an article published in 2013.[9] Immunocompromised patients, such as those with neutropenia, hematological malignancy, or organ transplantation, were excluded. The institutional review board of the Samsung Medical Center approved the review and publication of information obtained from the patients' records. Informed consent was waived because of the retrospective nature of the study.

Diagnosis of CPA

During the study period, a diagnosis of CPA was considered certain when it was associated with the following: (1) compatible chronic pulmonary or systemic symptoms, including at least weight loss, productive cough, or hemoptysis; (2) compatible chest radiological findings, including cavitary pulmonary lesion with evidence of paracavitary infiltrates, new cavity formation, or expansion of cavity size over time; and (3) a positive serum *Aspergillus* precipitin antibody test or the positive isolation of *Aspergillus* species from a respiratory sample (i.e., sputum, transtracheal aspirate, or bronchial aspiration fluid).[6–9] Radiological findings including chest computed tomography (CT) were retrospectively reviewed by two of the authors (B. Shin and K. Jeon). Differences in observed findings were resolved by consensus. Simple aspergilloma was excluded from the diagnosis of CPA.[6]

Serum GM antigen test

During the study period, a serum *Aspergillus* precipitin antibody test and a fungal culture with respiratory samples were performed for the laboratory diagnosis of all patients suspected to have CPA based on a constellation of clinical and radiological findings. Simultaneously, serum GM was measured using an enzyme-linked immunosorbent assay-based kit (Platelia *Aspergillus*; Bio-Rad Laboratories, Hercules, CA), following the manufacturer's instructions. An optical density of 0.5 or greater was considered to be a positive result.[11]

Statistical analysis

The data are presented as medians and interquartile ranges for continuous variables and as numbers (percentages) for categorical variables. To evaluate diagnostic performance, we estimated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for a preset cut-off point. The discriminatory power of the test was assessed by calculating the area under the receiver operating characteristic (ROC) curve. The data were compared using the Mann–Whitney *U* test for the continuous variables and Pearson's Chi-square test or Fisher's exact test for the categorical variables. We used STATA 12 (STATA Corp., College Station, TX) for all analyses and considered a two-sided P of <0.05 to be statistically significant.

Results

During the study period, a total of 334 patients who were suspected to have CPA were eligible for this study. The clinical characteristics of the patients are presented in Table 1. Most patients had underlying lung disease, such as previous tuberculosis ($n = 254$, 76%), bronchiectasis ($n = 181$, 54%), or nontuberculous mycobacterial lung disease ($n = 120$, 36%). All patients presented with at least one of the following chest CT findings: cavity ($n = 301$, 90%), consolidation ($n = 214$, 64%), mycetoma ($n = 95$, 28%), or paracavitary infiltration including pleural thickening ($n = 68$, 20%). Based on the criteria described above, 168 (50%) patients were finally diagnosed with CPA. Of the 166 patients who did not meet the diagnostic criteria of CPA, 131 patients showed negative results for laboratory tests. In remaining 35 patients, although the results of laboratory tests were positive (positive serum *Aspergillus* precipitin antibody in 33 patients and *Aspergillus* culture in 2 patients), chest CT findings were incompatible with CPA on the basis of the review by two of the authors in 33 patients or chronic pulmonary or systemic symptoms were resolved following anti-bacterial treatment in 12 patients.

In patients with CPA, a microbiological diagnosis of CPA was made based on a positive serum *Aspergillus* precipitin antibody test (in 164 [98%] patients) or the positive isolation of *Aspergillus* species (in 19 [11%] patients). The serum GM antigen test was positive in 38 (23%) patients with CPA