Clinical characteristics and prognosis of chronic pulmonary aspergillosis

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KEYWORDS
Chronic pulmonary aspergillosis;
Chronic necrotizing pulmonary aspergillosis;
Chronic cavitary pulmonary aspergillosis

Summary
Background: The details of the clinical characteristics of patients with chronic pulmonary aspergillosis (CPA) have not been fully understood.
Method: One hundred twenty-nine consecutive patients with isolation of Aspergillus species by culture from respiratory specimens who attended our hospital between October 2001 and September 2009 were enrolled. Patients diagnosed with chronic pulmonary aspergillosis (CPA) were retrospectively reviewed for clinical characteristics and prognosis, compared with patients with Aspergillus species colonization.
Results: Forty-two (32.6%) were diagnosed with CPA, whereas 87 (67.4%) with colonization. Aspergillus fumigatus was significantly more frequently detected in the CPA group than in the colonization group. Regarding underlying diseases, CPA patients had a significantly higher prevalence of a history of pulmonary tuberculosis and diabetes mellitus than colonization patients. There were no significant differences between the CPA and colonization group in Aspergillus antigen titers. Positivity for Aspergillus precipitating antibody was 74.3% in CPA and 15.8% in colonization, respectively. Sensitivity and specificity of Aspergillus precipitating antibody for the determination of CPA was 74.4% and 84.1%, respectively. Patients with CPA had significantly shorter survival than patients with colonization (mortality rate 50.0% vs. 13.8%, observation periods: 28.7±26.6 months) (p<0.0001). Multivariable analysis revealed that BMI was an independent predictor of prognosis (Odds Ratio, 1.973; p=0.0223).
Conclusions: CPA is a disease with a poor prognosis, which shows distinct clinical characteristics from colonization.

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Introduction

Aspergillus species are ubiquitous, saprophytic fungi commonly found in humid soil, water, and decaying organic material of various climatic conditions. Aspergillus species can reach the respiratory tract by airborne transmission, causing various pulmonary diseases. Although the pathogenesis of Aspergillus infection has been incompletely understood, it is thought that the quantity and virulence of inhaled organisms and the adequacy of host defense are important factors for disease development. In intact host defense, namely healthy persons, the spores are eliminated by mucociliary clearance and by pulmonary macrophages and neutrophils, resulting in limitation of the proliferation and spread of Aspergillus organisms; however, impaired host defense by underlying pulmonary disease or decreased immune function can cause several forms of clinical conditions, including disease (i.e., pulmonary aspergillosis) and colonization. Pulmonary aspergillosis is categorized into invasive aspergillosis, chronic forms of aspergillosis, and allergic forms of aspergillosis (i.e., allergic bronchopulmonary aspergillosis [ABPA]). The definition of chronic pulmonary aspergillosis (CPA) has been not clearly defined and has been described with a variety of names because of a wide range of clinical, radiologic, and anatomicopathologic entities. Recently, it has been accepted that CPA mainly consists of chronic necrotizing pulmonary aspergillosis (CNPA) and chronic cavitary pulmonary aspergillosis (CCPA). CPA causes progressive destruction of the lung, while CCPA causes multiple cavities, with or without aspergilloma, accompanied by pulmonary and systemic symptoms. Although there have been many reports on invasive and allergic types, there are few reports of the chronic type. In this study, based on the isolation of Aspergillus species, we evaluated the clinical characteristics and prognosis of patients with CPA.

Materials and methods

Patients

We retrospectively collected consecutive patients with isolation of Aspergillus species by culture from respiratory specimens (sputum or samples obtained by bronchoscopy) who attended Tenryu Hospital, National Hospital Organization between October 2001 and September 2009. Respiratory specimens were cultured on potato-dextrose agar, and selected colonies were identified as Aspergillus by standard morphological procedures. The present study was conducted according to hospital ethics committee approval and informed consent was obtained according to the hospital’s guidelines.

Diagnosis

Chronic pulmonary aspergillosis (CPA), such as chronic necrotizing pulmonary aspergillosis (CNPA) and chronic cavitary pulmonary aspergillosis (CCPA), was diagnosed according to the following criteria (4): 1) Clinical symptoms: fever, cough, sputum production, and weight loss of 1–6 months’ duration. 2) Radiologic findings showing cavitary pulmonary lesion with evidence of paracavitary infiltrates and adjacent pleural thickening with/without fungal ball. 3) Isolation of Aspergillus species by culture from sputum or samples obtained by bronchoscopy. 4) Exclusion of similar presentations caused by active tuberculosis, other mycoses, neoplasm, abscess, Wegener’s granulomatosis etc. and 5) Exclusion of invasive pulmonary aspergillosis, allergic forms of aspergillosis, and simple aspergilloma. Colonization was defined as isolation of Aspergillus species with clinical or radiographic evidence that was consistent with the possibility that Aspergillus species were part of their flora, moreover, had neither radiological nor clinical CPA findings.

Aspergillus serological examination

Aspergillus galactomannan antigen tests were performed using the platelia Aspergillus enzyme-linked immunoassay (ELA) (Bio-Rad, Marnes-la-Coquette, France). Aspergillus precipitating antibody tests were performed by the Ouchterlony method (Merica Diagnostics, Camberley, Surrey, UK). The (1→3) β-D glucan assay was carried out by the MK method (Seikagaku Corporation, Tokyo, Japan). Healthy volunteers free from respiratory disease were included as normal controls.

Statistical analysis

The values are expressed as the mean ± SD. For nonparametric statistical evaluation of differences between the two groups, Fisher’s exact probability test or the Mann-Whitney U test was used. Survival was analyzed using Kaplan-Meier analysis and the log rank test. Prognostic factors were determined by univariate and multivariate analysis. Data was analysed using Statview v5.0 (SAS) software. p values < 0.05 were considered significant.

Results

Patients characteristics

The patient’s characteristics are summarized in Table 1. Of 129 enrolled patients (82 males and 47 females; 73.2 ± 12.0 years old), 42 (32.6%) (31 males and 11 females; 75.1 ± 11.3 years old) were diagnosed with chronic pulmonary aspergillosis (CPA), whereas 87 (67.4%) (51 males and 36 females; 72.3 ± 12.2 years) were diagnosed with colonization. CPA patients had a significantly lower body mass index (BMI) than colonization patients (17.1 ± 2.8 vs. 20.2 ± 2.9 kg/m²; p < 0.0001). Consistent with previous reports, most underlying diseases were sequelae of mycobacterium such as tuberculosis and non-tuberculous mycobacterium in both groups. CPA patients had a significantly higher prevalence of pulmonary tuberculosis (50.0 vs. 17.2%; p = 0.0003) and diabetes mellitus (23.8 vs. 5.7%; p = 0.0061) than colonization patients.

Isolation of Aspergillus species

As shown in Table 2, 187 Aspergillus species were isolated from 129 patients. Of 187 Aspergillus species, 90 were Aspergillus fumigatus (48.1%), 56 were Aspergillus niger (30.0%), 12 were Aspergillus flavus (6.4%), and 29 were...
As shown in Fig. 1A, Aspergillus antigen titers in the CPA group were significantly higher than in the colonization group (0.92 ± 1.09 vs. 0.39 ± 0.28; p = 0.0056), but there was no significant difference between the CPA and colonization groups (0.92 ± 1.09 vs. 0.61 ± 0.58). Since the area under curve (AUC) of the receiver-operating characteristic (ROC) for discriminating between CPA and colonization groups was 0.574 (Fig. 1B), we could not find an optimal cut-off point of Aspergillus antigen titers. Positivity for Aspergillus precipitating antibody was 74.3% (29/39) in the CPA, 15.8% (10/63) in the colonization, and 0% (0/39) in the control group, respectively (Fig. 1C). Sensitivity and specificity of Aspergillus precipitating antibody for the determination of CPA were 74.4% and 84.1%, respectively.

Prognosis

The observation period was 28.7 ± 26.6 months. There were 21 (50.0%) deaths in 42 CPA patients and 12 (13.8%) deaths in 87 colonization patients. In CPA patients, 18 (85.7%) were CPA-related deaths, while 3 (14.3%) were lung cancer-related deaths. In Kaplan–Meier survival analysis from the time of diagnosis of CPA and colonization, patients with CPA had significantly shorter survival than patients with colonization (p < 0.0001, log rank test) (Fig. 2).

Prognostic factor in patients with CPA

By univariate analysis, BMI (Odds Ratio, 1.858; p = 0.0142) and serum albumin (Odds Ratio, 6.515; p = 0.0165) were predictors of prognosis in CPA patients (Table 3A). Furthermore, multivariate analysis revealed that BMI was an independent predictor of prognosis (Odds Ratio, 1.973; p = 0.0223) (Table 3B). In the CPA patients, 32 (76.1%) underwent anti-fungal therapy, including 22 (69%) itraconazole, 12 (38%) micafungin, 8 (25%) voriconazole and 3 (9.4%) intracavitary instillation of Amphotericin B at the discretion of the participating physicians. Neither univariate nor multivariate analysis indicated that anti-fungal therapy significantly affected survival.

Discussion

The present long-term follow-up study, based on Aspergillus species isolation from respiratory samples, demonstrated that CPA is a high mortality disease. In addition, patients with CPA were distinct from colonization regarding the type of species, underlying disease, precipitating antibody sensitivity, and prognosis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients characteristics.</th>
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<tbody>
<tr>
<td></td>
<td>CPA</td>
</tr>
<tr>
<td>(n = 42)</td>
<td>(n = 87)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>75.1 ± 11.3</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>31/11</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>17.1 ± 2.8</td>
</tr>
<tr>
<td>Underlying disease</td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>21 (50.0%)</td>
</tr>
<tr>
<td>NTM</td>
<td>15 (35.7%)</td>
</tr>
<tr>
<td>COPD</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>Interstitial pneumonia</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (4.8%)</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>3 (7.1%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10 (23.8%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>13 (30.9%)</td>
</tr>
<tr>
<td>Chronic hepatitis</td>
<td>6 (14.3%)</td>
</tr>
<tr>
<td>Steroid therapy</td>
<td>1 (2.4%)</td>
</tr>
</tbody>
</table>

CPA; chronic pulmonary aspergillosis, BMI; body mass index, TB; tuberculosis, NTM; non-tuberculous mycobacterium, COPD; chronic obstructive pulmonary disease, N.S.; not significant.

unidentified Aspergillus (i.e. Aspergillus sp.) (15.5%). A. fumigatus was significantly more frequently detected in the CPA group than in the colonization group (68.0 vs. 34.8%; p < 0.0001), whereas A. niger was significantly less detected in the CPA group than the colonization group (14.7 vs. 40.2%; p = 0.0002).

Laboratory findings

Serum C-reactive protein (CRP) (4.01 ± 5.18 vs. 2.26 ± 4.47 mg/ml; p = 0.0011) and (1→3) β-D glucan (26.7 ± 44.2 vs. 6.86 ± 10.7 pg/ml; p = 0.0023) in the CPA group were statistically higher than in the colonization group. Serum albumin in the CPA group was significantly lower than in the colonization group (3.32 ± 0.54 vs. 3.81 ± 0.48 g/dl; p < 0.0001). There were no significant differences in white blood cell count (7183 ± 2938 vs. 6462 ± 3136/mm³) and serum total protein (7.14 ± 0.84 vs. 6.68 ± 0.66 g/dl) between the two groups.

Aspergillus serological antigen and antibody test

As shown in Fig. 1A, Aspergillus antigen titers in the CPA group were significantly higher than in the control group (0.92 ± 1.09 vs. 0.39 ± 0.28; p = 0.0056), but there was no significant difference between the CPA and colonization groups (0.92 ± 1.09 vs. 0.61 ± 0.58). Since the area under curve (AUC) of the receiver-operating characteristic (ROC) for discriminating between CPA and colonization groups was 0.574 (Fig. 1B), we could not find an optimal cut-off point of Aspergillus antigen titers. Positivity for Aspergillus precipitating antibody was 74.3% (29/39) in the CPA, 15.8% (10/63) in the colonization, and 0% (0/39) in the control group, respectively (Fig. 1C). Sensitivity and specificity of Aspergillus precipitating antibody for the determination of CPA were 74.4% and 84.1%, respectively.

Prognosis

The observation period was 28.7 ± 26.6 months. There were 21 (50.0%) deaths in 42 CPA patients and 12 (13.8%) deaths in 87 colonization patients. In CPA patients, 18 (85.7%) were CPA-related deaths, while 3 (14.3%) were lung cancer-related deaths. In Kaplan–Meier survival analysis from the time of diagnosis of CPA and colonization, patients with CPA had significantly shorter survival than patients with colonization (p < 0.0001, log rank test) (Fig. 2).

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Discussion

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<table>
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<tr>
<th>Table 2</th>
<th>Isolation of Aspergillus species.</th>
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<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>(n = 187)</td>
<td>(n = 75)</td>
</tr>
<tr>
<td>Aspergillus fumigatus</td>
<td>90 (48.1%)</td>
</tr>
<tr>
<td>Aspergillus niger</td>
<td>56 (30.0%)</td>
</tr>
<tr>
<td>Aspergillus flavus</td>
<td>12 (6.4%)</td>
</tr>
<tr>
<td>Aspergillus sp.</td>
<td>29 (15.5%)</td>
</tr>
</tbody>
</table>

CPA; chronic pulmonary aspergillosis, N.S.; not significant.
The prognosis of patients with CPA remains to be well documented. The first review report by Binder and coworkers\(^8\) showed that the mortality rate was 19% with a median follow-up time of 15 months. Camuset and coworkers\(^6\) reported that the mortality rate was 8% with a median follow-up time of 10 months. In contrast, our study showed a high mortality rate (50%) with a follow-up time of 28.7\(^{\pm}26.6\) months. Consistent with our study, a report by Nam and coworkers,\(^9\) including 43 CNPA patients with a median follow-up of 15 months, showed that the mortality rate was 51%. The reported prognosis of CPA patients may vary due to various follow-up periods, severity of underlying disease, delayed diagnosis, and/or the initiation of effective therapy.

Since CPA is a progressive lung destruction disease, systemic treatment with anti-fungal agents could be taken into consideration.\(^10,11\) The Infectious Diseases Society of America (IDSA) recommended the use of orally administered itraconazole or voriconazol for CPA.\(^2\) Dupont reported that in 14 patients treated with itraconazole, 57% (8/14) were cured and 35% (5/14) were stabilized with a follow-up time of 11 months.\(^12\) Similarly, De Beule and coworkers reported that in 44 patients treated with itraconazole, 66% (29/44) showed marked improvement or cure.\(^13\) Regarding voriconazole treatment, Camuset and coworkers\(^6\) observed

![Figure 1](image1.png)

**Figure 1** Aspergillus serological test. (A) Aspergillus antigen titer levels in CPA, colonization, and control group. Aspergillus antigen titer levels are significantly higher in the CPA group than in the control group (\(p = 0.0056\)), while there are no significant difference between the CPA and the colonization group, the colonization and the control group, respectively. (B) Receiver-operating characteristic (ROC) curve analysis of Aspergillus antigen titer levels to discriminate between CPA and colonization patients. Area under curve (AUC) of ROC is 0.574. (C) Aspergillus precipitating antibody test in CPA, colonization, and control group. Antibody-positive is 74.3% (29/39) in the CPA, 15.8% (10/63) in the colonization, and 0% (0/39) in the control group, respectively.

![Figure 2](image2.png)

**Figure 2** Kaplan–Meier curves of survival probability from the time of diagnosis of CPA (\(n = 42\)) and colonization (\(n = 87\)). CPA patients show significantly shorter survival than colonization patients (\(p < 0.0001\), log rank test).

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<table>
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<tr>
<th>Table 3A</th>
<th>Mortality predictive factors in patients with CPA using univariable analysis.</th>
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<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Sex(male)</td>
<td>0.455</td>
</tr>
<tr>
<td>Age</td>
<td>0.999</td>
</tr>
<tr>
<td>Body mass index</td>
<td>1.858</td>
</tr>
<tr>
<td>TB</td>
<td>1.833</td>
</tr>
<tr>
<td>NTM</td>
<td>0.952</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>0.876</td>
</tr>
<tr>
<td>Albumin</td>
<td>6.515</td>
</tr>
<tr>
<td>β-D glucan</td>
<td>0.990</td>
</tr>
<tr>
<td>Aspergillus antigen</td>
<td>1.284</td>
</tr>
<tr>
<td>Therapy (Yes)</td>
<td>0.237</td>
</tr>
</tbody>
</table>

CPA; chronic pulmonary aspergillosis, TB; tuberculosis, NTM; non-tuberculous mycobacterium.
clinicroadiological improvement in 70% (17 of 24 patients) after a median follow-up time of 10 months. Sambatakou and coworkers in a prospective study found an 80% response rate; however, they were a small number of nonrandomized or open-label studies. Recently, Kohno and coworkers in a prospective, randomized, open-label study reported that intravenous micafungin was as effective as intravenous voriconazole and significantly safer than as an initial treatment of CPA. Notably, our study showed that intravenous voriconazole was equal or better than micafungin after a median follow-up time of 10 months. Sambatakou et al.14 in a prospective study found an 80% (54/68; 95% CI 72.8–93.6%) sensitivity to the cut-off value was low in CPA (13.3% (5/38; 95% CI 4.6–29.9%) patients were consistently positive, further confirming that CPA patients were basically consistent with the previous report, whereas in our colonization patients, A. niger (40.2%) was detected more than A. fumigatus (34.8%). The reason for this might depend on the number of colonization samples (our study: 112; previous study: 735).

Aspergillus antibody and/or antigen have been often measured for the serodiagnosis of pulmonary aspergillosis. For invasive pulmonary aspergillosis (IPA), the cut-off index of Aspergillus galactomannan antigen (≥1.5 or ≥ 0.5) has been determined by several studies and is useful for diagnosis, however, since it was reported that the sensitivity to the cut-off value was low in CPA (13.3–50%).6,20 the usefulness of Aspergillus galactomannan antigen for CPA remains to be clarified. In our study, there were no significant differences between CPA and colonization. Furthermore, by ROC analysis, we could not find an appropriate cut-off point to discriminate between CPA and colonization. In contrast, it was accepted that the Aspergillus participating test was suitable for the diagnosis of chronic forms of aspergillosis.1 Similar to a previous report,20 our study showed high sensitivity and specificity for CPA, and no reaction to the normal control. Thus, the Aspergillus participating test appears to be a more helpful tool than galactomannan antigen test for the diagnosis of CPA.

The present study had several limitations. First, it was retrospective; in particular, systemic anti-fungal therapy was performed at the discretion of the participating physicians. Second, since it was based on the isolation of Aspergillus species, probable CPA patients who had typical radiographic findings and a positive Aspergillus participating test without isolation of Aspergillus species might have been excluded; however, we believe that the present study revealed the principles of the CPA condition.

In conclusion, the clinical characteristics and prognosis of patients with CPA were different from colonization. Since our study demonstrated that CPA has a poor prognosis, the long-term effects of systemic therapy, as well as the involvement of Aspergillus species in the development of a poor condition, need to be further investigated.

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Conflict of interest

All authors have no conflict of interest.

References