Clinical Features of Pulmonary Aspergillosis Associated with Interstitial Pneumonia

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Abstract

Objective We retrospectively investigated the clinical features of pulmonary aspergillosis associated with interstitial pneumonia.

Methods We reviewed the medical records of all patients treated for interstitial pneumonia with or without pulmonary aspergillosis at our institution between April 2006 and August 2012 and evaluated the clinical features as well as risk and prognostic factors for pulmonary aspergillosis associated with interstitial pneumonia.

Results Among 539 patients with interstitial pneumonia, 15 who suffered from pulmonary aspergillosis were identified. The median age was 69.2±7.0 years, and fourteen patients were men. The subtypes of pulmonary aspergillosis were chronic pulmonary aspergillosis (n=14) and invasive pulmonary aspergillosis (n=1). The forms of interstitial pneumonia included idiopathic pulmonary fibrosis (n=9), rheumatoid arthritis-related interstitial pneumonia (n=4) and pleuroparenchymal fibroelastosis (n=2). The underlying conditions were emphysema (n=9) and a history of oral corticosteroid and/or immunosuppressive use (n=4). Home oxygen therapy (HOT) was administered in 11 patients. Following the diagnosis of pulmonary aspergillosis, all patients were treated with antifungal drugs. Ten patients (66.6%) died. A comparison of the interstitial pneumonia patients with and without pulmonary aspergillosis showed that the presence of emphysema, use of HOT and death were significantly associated with pulmonary aspergillosis.

Conclusion Pulmonary aspergillosis is one of the major complications of interstitial pneumonia and its prognosis is poor. Therefore, providing careful monitoring and proper treatment is extremely important.

Key words: pulmonary aspergillosis, interstitial pneumonia, emphysema, risk factors, outcome

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Introduction

Aspergillus is a mold spread by aerosols of spores. The organism is ubiquitous and saprophytic in nature, being commonly found in water, soil, and organic debris. Following inhalation, the conidia may be promptly destroyed by host defense mechanisms, colonize the conducting airways or cavities, or invade and destroy host tissues (1, 2). Pulmonary aspergillosis is classified into invasive pulmonary aspergillosis (IPA), chronic pulmonary aspergillosis (CPA) and allergic forms of aspergillosis (3). IPA occurs primarily in severely immunocompromised patients, including those with neutropenia, a history of hematopoietic stem-cell transplantation, solid-organ transplantation or prolonged and/or high-dose corticosteroid treatment. IPA rapidly progresses, and the mortality rate is high (2, 3). CPA is a locally invasive disease often found in patients with chronic lung disease or mild immunodeficiency. Affected patients usually have an underlying pulmonary disease involving the destruction of lung tissue. CPA may also occur in patients who are mildly immunocompromised due to diabetes mellitus, alcoholism, chronic liver disease or the use of low-dose corticosteroid therapy (2, 3). Common underlying pulmonary diseases include chronic obstructive pulmonary disease and previous pulmonary tuberculosis (4, 5). There is also a potential risk
for pulmonary aspergillosis in patients with interstitial pneumonia, although reports of these cases are few (6, 7). Therefore, we conducted a retrospective study of patients diagnosed with pulmonary aspergillosis associated with interstitial pneumonia over the last six years in order to investigate the clinical features of this condition.

**Materials and Methods**

We reviewed the medical records of all patients treated for interstitial pneumonia with or without pulmonary aspergillosis at our institution between April 2006 and August 2012 at Jichi Medical University. We classified interstitial pneumonia into two types: idiopathic interstitial pneumonia (IIP) and non-IIP. To diagnose IIP, we used the American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification (8). In patients with histological evidence, the diagnosis of interstitial pneumonia was dependent on pathological proof obtained from a respiratory sample (i.e., surgical specimens, necropsy or autopsy). In patients without histological evidence, the diagnosis was based on the findings of high-resolution computed tomography (HRCT) scans of the chest, medical history taking and physical examinations. Interstitial pneumonia was diagnosed based on the detection of bilateral honeycombing or reticular or ground-glass opacity predominantly in the peripheral, subpleural or bilateral lungs on CT images. The diagnosis of interstitial pneumonia was further confirmed by some of the authors prior to study commencement, and patients with sarcoidosis were excluded. Among the cases of pulmonary aspergillosis, the incidence of IPA and CPA was analyzed. IPA was diagnosed according to the European Organization for the Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria (9); proven IPA cases were included in this study. The diagnosis of CPA was made according to the following criteria (including probable disease) (2, 10, 11): (i) clinical symptoms lasting for >1 month caused by pulmonary aspergillosis (at least one of the following: fever, coughing, sputum production, hemoptysis and dyspnea) and elevated levels of inflammatory markers (the C-reactive protein level and white blood cell count); (ii) chest radiologic findings (cavitary lesions, fungus balls, consolidation, pleural thickening); and (iii) the isolation of *Aspergillus* species via culture or the presence of pathological proof obtained from a respiratory sample (i.e., sputum, samples obtained via bronchoscopy) and/or a positive serum *Aspergillus* precipitin test (Aspergillus-precipitating antibody test performed according to the Ouchterlony method and/or an *Aspergillus* galactomannan antigen test). The *Aspergillus*-precipitating antibody tests were performed by SRL, Inc. (Tokyo, Japan) using an *Aspergillus* immunodiffusion system (Microgen Bioproducts Ltd., Camberley, UK). The tests were judged to be positive if immunoelectrophoresis showed at least one distinct precipitation arc. *Aspergillus* galactomannan antigen tests were also performed by SRL, Inc. using the platelia *Aspergillus* enzyme-linked immunosorbent assay (ELISA) (Bio-Rad, Marnes-la-Coquette, France), with a cut-off index set at ≥1.0. Patients diagnosed with CPA satisfied all of the above criteria (i-iii), while those diagnosed with IPA, allergic forms of aspergillosis and simple aspergilloma were excluded.

We evaluated the clinical characteristics, laboratory findings, radiologic findings and pulmonary function test results. Laboratory tests included Krebs von den Lugen-6 (KL-6), surfactant protein D (SP-D) and (1→3) β-D glucan assays in addition to the *Aspergillus* precipitin test. The β-D glucan assay was carried out according to the MK method (20 pg/mL cut-off value; Nissui Seiyaku Co., Ltd., Tokyo, Japan). Radiologic examinations included chest radiography and CT. Treatment protocols and outcomes were also reviewed. In addition, we investigated risk and prognostic factors by comparing the cases of interstitial pneumonia with and without pulmonary aspergillosis. All data are expressed as the mean (±SD) or median (range). Categorical variables were compared using Fisher’s exact test or Student’s t-test. A p value of <0.05 was considered to indicate statistical significance. This study was approved by the ethics committee of Jichi Medical University Hospital. Informed consent was not required due to the retrospective study design.

**Results**

**Patient characteristics**

The patient characteristics are summarized in Table 1. Among the patients with interstitial pneumonia, we identified 320 cases of IIP (176 cases of idiopathic pulmonary fibrosis/usual interstitial pneumonia) and 219 cases of non-IIP (136 cases of collagen vascular disease-related interstitial pneumonia). A total of 15 patients suffered from pulmonary aspergillosis associated with interstitial pneumonia, with a median age of 69.2±7.0 years. Fourteen patients were men and one patient was a woman. All 15 patients were either current smokers or ex-smokers. The subtypes of pulmonary aspergillosis were as follows: 14 patients had CPA and one patient had IPA. Three forms of interstitial pneumonia were detected: nine patients had idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), four patients had rheumatoid arthritis-related interstitial pneumonia (RA-IP) and two patients had pleuroparenchymal fibroelastosis (PPFE). The period from the diagnosis of interstitial pneumonia to the detection of pulmonary aspergillosis was 44.0±37.8 months. As for underlying systemic conditions other than interstitial pneumonia or rheumatoid arthritis (RA), we detected emphysema in nine patients, a history of oral corticosteroid and/or immunosuppressive use in four patients, liver cirrhosis in two patients, diabetes mellitus in two patients, post-lobectomy of lung cancer in one patient and post-subtotal resection of stomach cancer in one patient. Of those who received steroids and/or immunosuppressive agents, three patients were treated for RA with a daily pred-
nisolone dose of 2 mg (over two years), 5 mg (over five years) and 7.5 mg (over three years), respectively, all of whom developed CPA. The remaining patient was also treated with 10 mg of cyclosporine daily in addition to 7.5 mg of prednisolone. On the other hand, one patient was treated with high doses of steroids and immunosuppressive agents due to the severity of IPF and developed IPA. The patient was administered 17.5 mg of prednisolone and 90 mg of cyclosporine per day for over eight months (the therapy began with steroid pulse treatment with subsequent oral prednisolone at a dose of 60 mg daily, which was gradually reduced to 17.5 mg daily). At the time of diagnosis, all patients presented with at least one of the following clinical symptoms: cough in 10 patients, sputum production in eight patients, dyspnea in seven patients, hemoptysis in five patients and fever in two patients.

**Laboratory findings**

Serum *Aspergillus*-precipitating antibody tests were performed in 14 patients (all with CPA), 12 of whom had positive results. *Aspergillus* galactomannan antigen tests were performed in all patients, three of whom exhibited a score above 1.0 (index). *Aspergillus* galactomannan antigen testing of the two CPA patients who tested negative on the *Aspergillus*-precipitating antibody test revealed scores of 1.1 and 2.4, respectively, and the one patient who did not receive an antibody test was diagnosed based on pathological proof at autopsy (proven IPA). β-D glucan assays were performed in 15 patients, four of whom exhibited results above 20 pg/mL. *Aspergillus* cultures and/or pathologic proof were positive in five patients: two patients were found to have *Aspergillus fumigatus*, while the details of *Aspergillus* species in the other three patients were unknown. The median KL-6 level (normal range, <500 U/mL) at 566±239 U/mL was elevated, as was that of SP-D (normal range, <110 ng/mL) at 138±84.8 ng/mL.

**Pulmonary function tests and the subjects’ respiratory condition**

Pulmonary function tests were performed in 13 patients,
six of whom were found to have a restrictive disorder (percent vital capacity <80%). In addition, home oxygen therapy (HOT) was initially administered in four patients, and followed by the addition of seven patients.

**Chest CT findings**

The CT findings are summarized in Table 2. The CT findings showed cavity lesions in 12 patients, pleural thickening in 10 patients, fungus balls in 10 patients and consolidation in nine patients. The shadows of *Aspergillus* infection included bullous and/or emphysematous lesions in eight patients (Fig. 1), honeycombing in four patients (Fig. 2) and upper lobe fibroelastosis in two patients with PPFE. A shadow of *Aspergillus* infection was found in the postoperative cavity in one patient. Nine patients had emphysema, in particular those with predominantly upper lobe emphysema, including bullous paraseptal changes distributed in the upper lobes. Of the nine patients with emphysema, upper lobe bullous infection with *Aspergillus* was detected in seven cases and honeycombing was detected in two cases. The site of *Aspergillus* infection was the upper lobe in nine patients, the lower lobe in four patients and both the upper and lower lobes in two patients.

**Treatments and outcomes**

The treatments and outcomes are summarized in Table 3. Following the diagnosis of pulmonary aspergillosis, all patients were treated with antifungal drugs. Oral itraconazole was administered in six patients (14.8±8.0 months), oral voriconazole was administered in five patients (6.4±5.5 months) and both were administered in three patients due to side effects (two patients were treated with itraconazole after voriconazole for approximately two months and 10 months, respectively, while one patient was treated vice versa for over five years). Meanwhile, intravenous micafungin was administered in one patient who had IPA (Fig. 3). At the end of therapy or follow-up, the conditions of six patients had improved, while those of eight patients had worsened and that of one patient did not change. Ten patients (66.6%) died. The cause of death in these 10 patients was as follows: pulmonary aspergillosis in four patients, bacterial pneumonia in two patients, gradual worsening of interstitial pneumonia in two patients, heart failure in one patient and acute respiratory failure in one patient. Since the patient with IPA died within one week, the mortality rate of CPA was 64.2% (9/14), with an observation period of 21.4±16.2 months. No patients were changed from oral to intravenous antifungal drugs. Surgical treatment was also not performed due to an impaired pulmonary function, hypoxic state or poor general status. In addition, a comparison between survivors and nonsurvivors showed that a higher proportion of patients who died had an increased KL-6 level and emphysema, whereas the type of antifungal drug and use of HOT were not significantly different between the two groups (Table 4).

**Risk and prognostic factors**

The results of the comparison of the cases of interstitial pneumonia with and without pulmonary aspergillosis, as summarized in Table 5, showed that the presence of emphysema, use of HOT and death were significantly associated with pulmonary aspergillosis, while the use of steroids and/or immunosuppressive agents was not.

**Discussion**

This study investigated the clinical features of 15 patients who suffered from pulmonary aspergillosis associated with interstitial pneumonia and evaluated risk and prognostic factors. In this study, of the 15 patients, 14 had CPA and one had IPA. The one patient with IPA was diagnosed based on an autopsy lung specimen showing lung parenchyma invasion with necrosis and pulmonary artery invasion due to *Aspergillus* hyphae. The diagnosis of CPA in this study was made according to criteria similar to those recommended by Kousha et al. (2), Denning et al. (10) and Kohno et al. (11). As for the serum *Aspergillus* precipitin tests, the *Aspergillus* antigen has been shown to be an excellent serum marker for diagnosing invasive aspergillosis (12). However, for the diagnosis of CPA, the *Aspergillus*-precipitating antibody test is

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**Table 2. Chest Computed Tomography Findings**

<table>
<thead>
<tr>
<th>Location of Aspergillus infection</th>
<th>Cavitary lesions</th>
<th>Pleural thickening</th>
<th>Fungus balls</th>
<th>Consolidation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullous and/or emphysematous lesions</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper lobe fibroelastosis</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative cavity</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequent lobe of <em>Aspergillus</em> infection</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

**Table 3. Treatments and Outcomes**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Imprved</th>
<th>Worsened</th>
<th>No change</th>
<th>Alive</th>
<th>Died</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral itraconazole</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pulmonary aspergillosis</td>
</tr>
<tr>
<td>Oral voriconazole</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>Oral voriconazole after itraconazole</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gradual worsening of interstitial pneumonia</td>
</tr>
<tr>
<td>Oral itraconazole after voriconazole</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart failure</td>
</tr>
<tr>
<td>Intravenous micafungin</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Prognosis</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Observation period of CPA, months, mean:SD</td>
<td></td>
<td></td>
<td></td>
<td>21.4±16.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CPA: Chronic pulmonary aspergillosis
more sensitive than the platelia Aspergillus EIA test (12). In this study, therefore, platelia Aspergillus EIA test results were added to the diagnostic criteria for diagnosing CPA in cases involving a negative Aspergillus antibody test. The cut-off level was set at an index of 1.0 in order to avoid false-positive results (11). In this study, only two CPA pa-

Figure 1. (a) Chest CT scan showing fungus balls in multiple cavities, localized consolidation, and irregular pleural thickening in the right upper lobe as well as a small fungus ball in the left upper lobe. The patient was a 70-year-old man with idiopathic pulmonary fibrosis (IPF) and emphysema, which was considered to be combined pulmonary fibrosis and emphysema (CPFE). (b) Chest CT scan about 2 years before showing upper-lobe emphysema including bullous, paraseptal and centriflobular changes, but absence of fungus ball, localized consolidation, and irregular pleural thickening.

Figure 2. (a) Chest CT scan showing a fungus ball in the cavitory lesion within honeycombing in the right lower lobe. The patient was a 72-year-old woman with rheumatoid arthritis-related interstitial pneumonia (RA-IP). She was treated with 5 mg prednisolone daily for over 5 years. (b) Neither fungus ball nor cavitory lesion was seen on chest CT scan 4 years before.

Figure 3. (a) Chest CT scan showing a fungus ball in the cavitory lesion within honeycombing in the right upper lobe. The patient was a 71-year-old man with idiopathic pulmonary fibrosis (IPF). He was treated with 17.5 mg prednisolone and 90 mg cyclosporine daily for over 8 months. (b) The lung specimen by autopsy showing lung parenchyma invasion with necrosis and pulmonary artery invasion due to Aspergillus hyphae (Elastica van Gieson staining, ×200).
In addition, the rate of positivity for both patients had both a negative Aspergillus-precipitating antibody test and positive platelet Aspergillus EIA test (see Results). In addition, the rate of positivity for both Aspergillus galactomannan antigens and β-D glucan was low. These results support the findings of a previous report showing low rates of positivity for both of these tests in CPA patients (13).

Emphysema was found in 9/15 patients; the radiologic findings on HRCT in these cases demonstrated upper lobe emphysema and lower lobe interstitial fibrotic changes. These characteristic radiologic findings are considered to reflect so-called combined pulmonary fibrosis and emphysema (CPFE), as proposed by Cottin et al. (14, 15). Of the patients diagnosed with CPFE, upper lobe bullous infection with Aspergillus was detected in more patients than honeycombing. In addition, a comparison of the cases of interstitial pneumonia with and without pulmonary aspergillosis showed the presence of emphysema to be a risk factor for pulmonary aspergillosis. The features of PPFE include subpleural upper lobe fibrosis without honeycombing and a slowly progressive clinical course similar to that of chronic idiopathic interstitial pneumonia (16, 17). PPFE is also called pulmonary apical fibrocystic disease (18) or idiopathic pulmonary upper lobe fibrosis (19). Bullous or emphysematous lesions, honeycombing and upper lobe fibroelastosis constitute destructive changes in lung tissue that are likely to result in infection with Aspergillus due to disturbed local clearance.

In the present study, steroid and/or immunosuppressive use was not found to be a significant risk factor for pulmonary aspergillosis. However, steroid therapy inhibits the killing of conidia and hyphae by macrophages and the migration of neutrophils around the fungus (1, 20, 21). Three CPA patients in this study were treated for long periods (over two years) with prednisolone, although the dose was low, under 7.5 mg daily. On the other hand, one IPA patient was treated with high doses of steroids and immunosuppressives. Therefore, patients treated with steroid therapy require special attention regarding the potential for Aspergillus infection.

Following the diagnosis of pulmonary aspergillosis, all patients were administered antifungal drugs. Treating IPA remains difficult, and the mortality rate continues to be high (2). For the primary treatment of IPA according to the guidelines of the Infectious Disease Society of America (IDSA), intravenous or oral voriconazole is recommended in most patients (3). Echinocandins, such as micafungin, can be considered as alternative or salvage therapy (3). Successful treatment of IPA depends on the ability to obtain an early diagnosis and provide prompt treatment, as any delay is associated with a high mortality rate (20). Therefore, treatment should be initiated empirically without waiting for a definitive diagnosis in patients suspected of having IPA. The IPA patient in this study was first treated empirically with micafungin once he was suspected of having pulmonary aspergillosis; however, the patient developed, resulting in death within one week due to IPA; thus, we should have considered voriconazole treatment earlier. As for the treatment of CPA according to the IDSA guidelines, CPA patients in this study were treated for long periods (over two years) with prednisolone, although the dose was low, under 7.5 mg daily. On the other hand, one IPA patient was treated with high doses of steroids and immunosuppressives. Therefore, patients treated with steroid therapy require special attention regarding the potential for Aspergillus infection.
guidelines, oral therapy with voriconazole or itraconazole is recommended as the primary treatment (3). In recent reports of CPA patients treated with voriconazole or itraconazole, the mortality rate was documented to be 51% by Nam et al. (22) and 50% by Ohba et al. (23). In the present study, the mortality rate of CPA was higher than that observed in the above two reports, and a diagnosis of pulmonary aspergillosis was shown to be a poor prognostic factor. The comparison of the survivors and non-survivors showed significant differences, not in the type of antifungal drugs administered, but rather in the KL-6 level and the presence of emphysema. Moreover, more patients received HOT, although this trend was not statistically significant and the use of HOT was found to be a risk factor for pulmonary aspergillosis; therefore, these patients’ respiratory condition was likely related to their poor prognosis. With regard to surgical treatment, none of the CPA patients underwent surgery due to an impaired pulmonary function, hypoxic state and/or poor general status. However, changing from oral to intravenous antifungal drugs should have been considered, as intravenous antifungal drugs have been reported to be more effective in CPA patients (3, 11).

There are some limitations to the present study, including the retrospective design and the small number of patients who suffered from pulmonary aspergillosis associated with interstitial pneumonia. In addition, the selection of treatment was based on the judgment of the treating physician. Moreover, the rate of positivity of mycological proof was low at 33.3% (5/15), although the diagnosis of pulmonary aspergillosis was made according to commonly used criteria.

In conclusion, in this study, among the patients with pulmonary aspergillosis associated with interstitial pneumonia, most had emphysema (9/15), which was considered to reflect CPFE, in which bullous and/or emphysematous lesions are more likely to be infected with Aspergillus and are related to a poor prognosis. Patients with RA and interstitial pneumonia are frequently treated with steroids and immunosuppressive agents, and we found that low-dose treatment with such drugs may have contributed to the development of Aspergillus infection in our study population. Moreover, we found that the patient who suffered from severe interstitial pneumonia and had been treated with high-dose steroids and immunosuppressive therapy developed IPA and died early. Despite the administration of antifungal treatment in all patients following the diagnosis of pulmonary aspergillosis, the prognoses were poor and the mortality rate was high. Pulmonary aspergillosis is a major complication of interstitial pneumonia, and it is extremely important to properly monitor and treat affected patients due to the poor prognosis of the disease.

The authors state that they have no Conflict of Interest (COI).

References

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http://www.naika.or.jp/imonline/index.html