A Study of 19 Pulmonary Cryptococcosis Cases

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Abstract

Background: Pulmonary cryptococcosis (PC) has recently become more frequent.

Methods: We collected and analyzed data from 19 cryptococcal pneumonia cases that had been treated in our hospital over the past 10 years and analyzed the clinical features, underlying diseases, past medication and auxiliary examinations of the patients.

Results: The patients demonstrated various symptoms and underlying diseases, but most of the latter involved diseases associated with immune deficiency. More than half of the patients had no history of exposure to bird droppings or soil. Chest computed tomography scans of the 19 patients revealed single or multiple pulmonary nodular shadows in 11 subjects. Initial misdiagnosis was common. Because of the long course of treatment for PC and the high costs of fluconazole and itraconazole, as long as the renal functions in these patients are normal, the more cost-effective drug amphotericin B can be used as an alternative treatment for PC.

Conclusions: This study provides a summary of the characteristics of pulmonary cryptococcosis as a basis for future clinical diagnosis and treatment of pulmonary cryptococcosis.

Keywords: Acquired immune deficiency syndrome; Cryptococcus neoformans; Diagnosis; Disseminated cryptococcal infection; Imaging; Pathology; Pulmonary cryptococcosis

Introduction

Pulmonary cryptococcosis (PC) is a subacute or chronic visceral fungal disease caused by Cryptococcus neoformans infection [1]. In recent years, the incidence of cryptococcal infection has shown an apparent upward trend [2,3]. Because of the atypical clinical manifestations of pulmonary cryptococcosis, clinical diagnosis is difficult, we have collected 19 cryptococcal pneumonia cases that had been treated in our hospital over the past 10 years, and analyzed the corresponding data. We hope to help clinicians improve their understanding of pulmonary cryptococcosis.

Materials and Methods

Source of Subjects

From January 1, 2006, to December 31, 2015, 19 patients in total were diagnosed with cryptococcal pneumonia in our hospital, and pertinent information, including general information, medical history, laboratory data, and treatments were collected, analyzed, and summarized. The study was approved by the Ethics Committee of Clinical Medical Research at The Third Affiliated Hospital, Sun Yat-sen University (Approval No. [2016]2-114). The requirement for obtained informed consent was waived by the committee due to the retrospective nature of the study.

Diagnostic Criteria [5]

Pathogenic examination: Traditional microscopy and culture methods were used to identify C. neoformans from the patients’ phlegm, broncho-alveolar lavage fluid (BALF), or cerebrospinal fluid (CSF). The strains of Cryptococcus neoformans were identified using RapID Yeast Plus System [6].

Pathologic diagnosis: The pathological tissues of the patient were collected by different ways, such as by lung needle biopsy or fine-needle aspiration, or by bronchoscopic-protected brushing. C. neoformans can be found by different staining.

Cryptococcal antigen: The latex agglutination test was used to detect the capsular polysaccharide antigen of C. neoformans from patients’ serum, BALF, or excessive pleural fluid.

Results

General Information

Of the 19 patients, 11 were male and 8 were female. Patients’ age ranged from 26 to 81 years, with a median age of 51.5 years.

Patients’ Medical History

Symptoms: Seven were asymptomatic (36.8%), 8 subjects had a cough and expulsion of phlegm (42.1%), 9 had chest pain (47.4%), 3 had a fever (15.8%), and 3 had dyspnea and hypoxemia (15.8%). Ten subjects had fatigue and weight loss (52.6%), 4 subjects had hemoptysis (21.1%), 3 had a pleural effusion (15.8%), and 1 subject had concurrent cryptococcal meningitis (5.3%).

Underlying diseases: Five with no underlying diseases (26.3%), 3 subjects with AIDS (15.8%), 2 subjects with diabetes (10.5%), 4 subjects with tuberculosis (21.1%), 2 subjects who had undergone organ transplantation (10.5%), 1 subject with rheumatic autoimmune disease (5.3%), and 2 subjects with tumors (10.5%).

Exposure history: Two patients (10.5%) had a history of raising chickens, 4 patients (21.1%) had a history of soil exposure, and the remaining patients (68.4%) were not occupationally exposed to bird droppings and/or soil.

Previous medication history: Five subjects without underlying disease and 3 subjects with AIDS had no medication history; the 2 subjects who had undergone organ transplantation had a 0.5- to 3-year history of taking anti-rejection drugs; 1 subject with rheumatic autoimmune diseases had a history of long-term glucocorticoid intake; 2 cancer subjects had received more than 2 courses of chemotherapy.

Hematology

No patients underwent galactomannan testing, as it was not yet available in our hospital at the time of the study. We detected CD3 and CD4 in the blood of all patients (Table 1).

Imaging (CT)

19 patients revealed single or multiple pulmonary nodular shadows in 11 subjects (57.9%), of which 7 cases had cavity formation and 5 subjects had a “halo sign.” Lung patchy shadows

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were found in 5 subjects (26.3%), 2 subjects (10.5%) had diffuse miliary shadows, and 1 subject (5.3%) had acute interstitial pneumonia. Mild mediastinal lymph node enlargement was observed in 12 subjects. Localized foci were generally found in the lower lobes of the lung (Figure 1-6, foci indicated by arrows).

Pathology

The diagnoses of the 19 patients were confirmed by pathological examinations. *C. neoformans* was found in 15 subjects using CT-guided percutaneous needle biopsy of the lung, in 3 subjects by using thoracoscopic lung biopsy, and in 1 subject using bronchosopic lung biopsy. Granuloma formation (Figure 7) or jelly-like lesions (Figure 8) were observed under low magnification. *C. neoformans* with capsules could be observed inside macrophages at high magnification (indicated by the arrows in Figures 9-13) [7].

Etiology

**Culture and smear:** Among the 19 patients, *C. neoformans*

<table>
<thead>
<tr>
<th>Subject</th>
<th>CD4⁺/T (%)</th>
<th>CD8⁺/T (%)</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.6</td>
<td>25.3</td>
<td>0.74</td>
</tr>
<tr>
<td>2</td>
<td>16.8</td>
<td>24.3</td>
<td>0.69</td>
</tr>
<tr>
<td>3</td>
<td>21.5</td>
<td>28.3</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>20.7</td>
<td>30.1</td>
<td>0.54</td>
</tr>
<tr>
<td>5</td>
<td>21.6</td>
<td>32.5</td>
<td>0.66</td>
</tr>
<tr>
<td>6</td>
<td>19.5</td>
<td>35.2</td>
<td>0.55</td>
</tr>
<tr>
<td>7</td>
<td>28.4</td>
<td>32.8</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>23.6</td>
<td>39.8</td>
<td>0.59</td>
</tr>
<tr>
<td>9</td>
<td>14.3</td>
<td>21.8</td>
<td>0.66</td>
</tr>
<tr>
<td>10</td>
<td>19.2</td>
<td>29.3</td>
<td>0.66</td>
</tr>
<tr>
<td>11</td>
<td>28.1</td>
<td>40.3</td>
<td>0.70</td>
</tr>
<tr>
<td>12</td>
<td>21.8</td>
<td>38.4</td>
<td>0.57</td>
</tr>
<tr>
<td>13</td>
<td>14.3</td>
<td>25.1</td>
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<td>14</td>
<td>19.6</td>
<td>31.6</td>
<td>0.62</td>
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<tr>
<td>15</td>
<td>25.3</td>
<td>41.7</td>
<td>0.61</td>
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<tr>
<td>16</td>
<td>15.3</td>
<td>28.6</td>
<td>0.53</td>
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<tr>
<td>17</td>
<td>24.7</td>
<td>38.5</td>
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<tr>
<td>18</td>
<td>21.4</td>
<td>30.2</td>
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</tr>
<tr>
<td>19</td>
<td>18.6</td>
<td>25.8</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 1: Values for CD4⁺ and CD8⁺ T lymphocytes in the 19 patients. (Normal reference values used in our hospital: CD4⁺ T lymphocytes/T lymphocytes (T/T) 28–58%, CD8⁺ T/T: 19–48%, CD4⁺/CD8⁺: 0.9–2.0).

Figure 1: The white arrow is pointing at the solitary pulmonary nodule.

Figure 2: The white arrow is pointing at the solitary pulmonary nodule with halo signs.

Figure 3: The white arrow is pointing at the solitary pulmonary nodule with cavities.

Figure 4: The white arrow is pointing at the solitary pulmonary nodule with cavities.
was isolated from only 6 subjects. One subject had a positive CSF direct ink smear, while BALF culture and culture of the secretions collected using bronchoscopic-protected brushing were positive.
in the other 4 and 1 subjects, respectively. The smear and culture results of *C. neoformans* are shown in figures 14–19.

**Identification of strains:** *C. neoformans* were identified using RapID Yeast Plus System. (Figures 20, 21)

**Diagnosis and Treatment**

All 19 patients were diagnosed with *C. neoformans* infection.
All patients had received some form of misdiagnosis. Four patients were misdiagnosed with tuberculosis, and diagnostic anti-tuberculosis treatment that had been administered for 2–4 weeks was ineffective. Five subjects were misdiagnosed with lung cancer and were subsequently diagnosed with *C. neoformans* infection based on CT-guided percutaneous needle biopsy of the lung. Three subjects with patchy shadows in their chest CT scans were misdiagnosed with pneumonia, and a 2-week antibiotic treatment was ineffective. Three subjects with underlying diseases (AIDS) were misdiagnosed with viral infection or *Pneumocystis carinii* infection, because the bilateral lung lesions involved diffuse pulmonary infiltrates, and a 2-week ganciclovir or caspofungin therapy was not effective.

After receiving the correct diagnosis, 16 patients with localized PC were administered fluconazole (0.4 g/day) intravenously for 2–4 weeks and were then given fluconazole (0.4 g/day) orally for 3–6 consecutive months. One patient who also had central nervous system infection received fluconazole (0.4 g/day) orally for 12 months. The 3 subjects with underlying diseases (AIDS) had disseminated cryptococcosis; for these patients, amphotericin B was administered for 6–8 weeks (starting from 5 mg/day, and
The pathological type of C. neoformans is jelly-like lesions or noncaseating granulomatous lesions and C. neoformans with capsules can be observed inside macrophages under high magnification [5]. C. neoformans was found in the lung biopsy specimens obtained from the 19 patients of this paper, and currently, pathological diagnosis is the main approach for the diagnosis of PC.

Among the 19 patients in this paper, C. neoformans was cultured from the CSE BALF or the secretions collected using bronchoscopic-protected brushing in 31.6% of patients, only 1 patient showed the positive result in the CSF cryptococcal capsular polysaccharide antigen test, and C. neoformans could not be isolated from 63.2% of patients. This result is related to minimal or absent phlegm in most patients and the localized nature of the foci.

Because of diversified imaging findings of PC, clinical misdiagnosis is common [14]. Most of the 19 PC cases collected in this paper were first misdiagnosed, and the average time from the onset to diagnosis was 21 days. Based on our experience, we suggest that for patients with a lung mass or nodular lesions, the possibility of PC should be considered, and corresponding diagnostic tests should be conducted. For patients with pulmonary inflammation or with disseminated disease, the possibility of C. neoformans infection should be considered when antimicrobial therapy is not efficacious, particularly in patients with immunodeficiency or those receiving immunosuppressive therapy. Early percutaneous lung biopsy, transbronchial lung biopsy, or even surgical thoracoscopic lung biopsy is the key to accurate diagnosis of PC.

C. neoformans infects both AIDS patients [15,16] and non-AIDS patients [17,18], and infects both adults and children [19]. Among the 19 PC cases collected in this study, there were 3 AIDS patients (15.7%), non-AIDS patients accounted for 84.3%. Among them, 1 patient with rheumatic autoimmune diseases and 2 patients who underwent organ transplantation and had received continuous glucocorticoid or immunosuppressive therapy, which causes impaired cellular immune function, which in turn is the root cause for C. neoformans infection. Three patients with malignant tumors received earlier induction chemotherapy, and their humoral and cellular immune functions were suppressed, which is also related to C. neoformans infection. The primary diseases in the 2 diabetic patients and 4 tuberculosis patients were not well controlled and they had a long-term medication history, and the changes in their own immune function are one of the causes for C. neoformans infection.
infection. The reason for the *C. neoformans* infection in the other 5 PC patients without underlying diseases was not clear, but the CD4+ and CD8+ T lymphocyte counts were low. This indicated that, despite the absence of underlying disease in these patients, their cellular immune functions decreased, which is probably the main reason for their susceptibility.

In this study, 15 non-AIDS patients with localized PC were treated with fluconazole and cured, but treatment needs 5-10 weeks. For the 3 subjects with underlying AIDS, the pulmonary manifestation involved disseminated cryptococcosis; amphotericin B treatment was administered for 6-8 weeks, fluconazole was given orally for 6-12 consecutive months. The mortality rate was only 10.5%, and the cure rate was 89.5%. All patients were followed up for 2 years, without recurrence. Our treatment can be replicated.

As long as the renal functions in these patients are normal, the more cost-effective drug amphotericin B can be used as an alternative treatment for PC.

References


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