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 01, 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 obtaining informed consent was waived by the committee due to the retrospective nature of the study.

Diagnostic criteria

The diagnostic criteria [4,5] are outlined below.

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 C. neoformans involved were identified using the Rap ID Yeast Plus System [6].

Pathological diagnosis: The pathological tissues of the patient were collected in different ways, such as by lung needle biopsy or fine-needle aspiration, or by bronchoscopic-protected brushing. C. neoformans was then identified by different staining techniques.

Cryptococcal antigens: 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’ ages ranged from 26 to 81 years, with a median age of 51.5 years.

Patients’ medical history

Symptoms: Seven individuals were asymptomatic (36.8%), 8 subjects had a cough and expulsion of phlegm (42.1%), 9 had chest pain (47.4%), 3 had 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 pleural effusion (15.8%), and 1 subject had concurrent cryptococcal meningitis (5.3%).

Underlying diseases: Five patients had no underlying diseases (26.3%), 3 had AIDS (15.8%), 2 had diabetes (10.5%), 4 had tuberculosis (21.1%), 2 had undergone organ transplantation (10.5%), 1 had rheumatic autoimmune disease (5.3%), and 2 had 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. One subject with rheumatic autoimmune diseases had a history of long-term glucocorticoid intake. Two 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).

Computed tomography imaging

Of the 19 patients, CT imaging showed 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 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 (Figures 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 bronchoscopic 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 under high magnification indicated by the arrows in Figures 9-13 [7].

Etiology

**Culture and smear:** Among the 19 patients, *C. neoformans* 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 the Rap ID Yeast Plus System; examples of results are shown in 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 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;
entrance for alive. and the subject was cured of the cryptococcal infection and is still AIDS was treated for 12 months; the pulmonary foci were absorbed, 2 weeks and died of respiratory failure. The remaining subject with renal function, and the subject had a worsening lung infection after amphotericin B was switched to oral fluconazole due to the impaired condition associated with AIDS. For another of these subjects, (AIDS), 1 died after 4 weeks of treatment due to the deteriorating condition with the report by Ye et al. [13]. The non-specificity in the imaging finding of PC is one of the leading causes for the clinical misdiagnosis of PC.

The pathological features of C. neoformans are jelly-like lesions or noncaseating granulomatous lesions. Encapsulated C. neoformans can be observed inside macrophages under high magnification [5]. C. neoformans was found in the lung biopsy specimens obtained from the 19 patients reported here, and currently, pathological diagnosis is the main approach for the diagnosis of PC. Among the 19 patients described here, C. neoformans was cultured from the CSF, BALF, or the secretions collected using bronchoscopic-protected brushing in 31.6% of patients, only 1 patient showed a 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 the diverse imaging findings of PC, clinical misdiagnosis is common [14]. Most of the 19 PC cases collected in this study 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 [2,15] and non-AIDS patients [16,17], and infects both adults and children [18]. Among the 19 PC cases collected in this study, there were 3 AIDS patients (15.7%), and non-AIDS patients accounted for 84.3%. Among them were 1 patient with rheumatic autoimmune disease and 2 patients who had undergone organ transplantation and had received continuous glucocorticoid or immunosuppressive therapy; these patients all had impaired cellular immune function, which 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. 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

Outcome

All 16 non-AIDS patients completed the course of treatment, and the corresponding clinical symptoms disappeared. Chest CT lung scans were performed again, and revealed that the pulmonary foci had been absorbed, and the patients were cured or in a stable condition for more than 3 months. Of the 3 subjects with underlying diseases (AIDS), 1 died after 4 weeks of treatment due to the deteriorating condition associated with AIDS. For another of these subjects, amphotericin B was switched to oral fluconazole due to the impaired renal function, and the subject had a worsening lung infection after 2 weeks and died of respiratory failure. The remaining subject with AIDS was treated for 12 months; the pulmonary foci were absorbed, and the subject was cured of the cryptococcal infection and is still alive.

Discussion

C. neoformans can invade various organs. The lungs are the main entrance for C. neoformans invasion [9]. Generally, PC patients are asymptomatic or show mild symptoms; the main manifestations are cough, an expulsion of phlegm, and dull chest pain, and there is usually a large amount of bacteria in the phlegm [10,11]. The 19 patients presented in the present study had similar clinical symptoms as those described in the literature. The imaging findings of PC are non-specific [12]. Among the 19 patients presented in this paper, those with solitary or multiple mass shadows or nodular shadows, lung patchy shadows, diffuse miliary shadows, and acute interstitial pneumonia in their chest CT scans were present in 57.9%, 26.3%, 10.5%, and 5.3%, respectively. Localized foci were generally found in the lower lobes of the lung, which was consistent with the report by Ye et al. [13]. The non-specificity in the imaging finding of PC is one of the leading causes for the clinical misdiagnosis of PC.
were treated with fluconazole and were cured, but treatment required 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, and 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 approach can therefore be recommended. 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.

**Acknowledgements**

This study was funded as a social development project of the Science and Technology Department of Guangdong province (Grant No. 2014A020212531).

**References**