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Review Article

Clinical analysis of pulmonary cryptococcosis in non-HIV patients in south China

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Abstract: Aims: The aim of this study was to investigate the clinical characteristics of pulmonary cryptococcosis occurring in non-HIV patients, and to develop early diagnosis of pulmonary cryptococcosis in immunocompetent cases as well. Methods: We retrospectively reviewed the clinical data of 41 non-HIV infected patients with pulmonary cryptococcosis who were admitted to the First Affiliated Hospital of Wenzhou Medical University from January 2006 to April 2014. Results: The study included a total of 41 patients (23 males and 18 females) with mean age of 47 years. 12.19% of patients had a history of direct exposure to pigeon droppings; 31.70% of the patients' working or living environments were potentially contaminated by fungal spores. Almost one-third of the patients involved into the study were asymptomatic. The most common clinical manifestations were cough, expectoration and hemoptysis. The most common radiological manifestation was single node or mass in lung, which was described as untypical. Of all cases, 11 patients were diagnosed by CT-guided percutaneous cutting needle biopsy (PCNB), 5 patients were diagnosed by operation, and Crytococcus spore was found in 7 patients' cerebrospinal fluid. 8 patients' blood Cryptococcus Neoformans capsular polysaccharide antigens latex agglutination tests were positive. 36 patients received antifungal therapy. 5 patients underwent surgical resection. During 6 to 24 months follow-up, 40 cases showed total recovery and 1 cases showed improvement. Conclusions: Pulmonary cryptococcosis in non-HIV subjects might be related to fungus-contaminated environmental exposure. The great variations and protean manifestations of its clinical features often lead to misdiagnosis. Recognition and invasive examination of non-HIV infected patients' pulmonary cryptococcosis in the early stage may help with improvement of its diagnosis and prognosis.

Keywords: Pulmonary cryptococcosis, non-HIV patients, clinical characteristics, radiographic features, diagnosis

Introduction

Cryptococcosis, which occurs sporadically worldwide, is a potentially serious fungal disease [1]. Pulmonary infection results from inhalation of the organism from an environmental source and the organism has a propensity to metastasize to the central nervous system (CNS) [2, 3]. In past decades, most studies of pulmonary cryptococcosis have focused on immunecompromized hosts. Only a few reports or small-scale studies of pulmonary cryptococcosis in immunocompetent patients have been published. Compared with C.neoformans, C.gattiiis are more inclined to cause disease in healthy people [5]. C. gattii infections have drawn increased attention since 2002 [6], with cases reported in Papua New Guinea and Northern Australia, India, Brazil, Vancouver Island in Canada, and Washington State and Oregon in the USA.

Pulmonary cryptococcosis is not rare in mainland China. Currently, our understanding of pulmonary cryptococcosis is mostly limited to typical clinical manifestations and radiological presentations. Pulmonary cryptococcosis does not have specific clinical manifestation and image findings, and it is difficult to be differentiated from lung cancer, tuberculosis, or pneumonia. The great variations and protean manifestations of its clinical features often lead to misdiagnosis. Our study was to provide an updated review and to characterize the clinical and radiological characteristics, as well as diagnosis and treatment of pulmonary cryptococcosis in non-HIV patients in the region of south China.

Table 1. Characteristics of patients with pulmonary cryptococcosis in non-HIV patients (n=41)

Variable	Patients with PC (%) (n=41)
Gender	
Female	18 (43.90)
Male	23 (56.09)
Median Age (years)	47
Occupation	
Workers	10 (24.39)
Staff	6 (14.63)
Housewives	5 (12.19)
Farmers	5 (12.19)
Businessman	5 (12.19)
Medical staff	3 (7.31)
Catering industry	3 (7.31)
Greengrocer	2 (4.87)
Teachers	1 (2.43)
Unemployed	1 (2.43)
Disease history	
Healthy	19 (46.34)
Chronic disease	13 (31.70)
Use of immunosuppressive drugs	6 (14.63)
Malignancy	3 (7.31)
Occupational environment exposure history	
History of exposure to pigeon droppings	5 (12.19)
History of keeping cats, dogs or poultry	13 (31.70)
No exposure history	23 (56.09)

Methods

Patients

This study retrospectively analyzed the data of 41 non-HIV infected patients with pulmonary cryptococcosis, who were admitted to the First Affiliated Hospital of Wenzhou Medical University from January 2006 to April 2014. The patients' database was established to collect demographics, underlying diseases, admission history, respiratory symptoms, physical examination results, and laboratory tests, immune status studies, imaging data, pathology data, treatment and outcome. The relevant follow-up patient information was obtained on regular clinic visits and by telephone follow-up. The last follow-up was performed on April 30, 2014. The study plan had been approved by the Ethics Committee of First Affiliated Hospital of Wenzhou Medical University, and all participating subjects had signed informed consents prior to entering the study.

Results

Immune function

In a total of the 41 patients, 19 patients (46.34%) were previously healthy and 22 patients (53.65%) had a history of hypertension and severe diabetes mellitus with organ damage (13, 31.70%), using immunosuppressive drugs (6, 14.63%), and hematological malignancy (3, 7.31%) (**Table 1**). All the patients were human immunodeficiency virus antibody (HIV-Ab) negative.

Environmental exposures

In term of environmental factors, 12.19% of patients (5 out of 41) had a history of direct exposure to pigeon droppings. Another 31.70% of the patients (13 out of 41), whose working or living environment were potentially contaminated by fungal spores, were recorded (**Table 1**).

Clinical features

All the medical records of 41 (23 male and 18 females) patients with pulmonary cryptococcasis were studied (mean age 47 years; range 22-80 years). Their occupations were classificated as follows: workers (10, 24.39%), staff (6, 14.63%), housewives (5, 12.19%), farmers (5, 12.19%), businessman (5, 12.19%), medical staff (3, 7.31%), catering industry (3, 7.31%), greengrocer (2, 4.87%), teachers (1, 2.43%), unemployed (1, 2.43%). 41.46% patients (17 out of 41) were asymptomatic, and pulmonary nodules or masses were just found in them by means of radiological examination. Most common clinical manifestations of pulmonary cryptococcasis were cough (18, 43.90%), expectoration (11, 26.83%), hemoptysis (5, 12.20%), and chest tightness (2, 4.88%) (**Table 2**).

Laboratory tests

All the reviewed sputum cultures of 41 patients were negative. Both serum cryptococcal antigen (SCRAG) test and blood Cryptococcus cap-

Table 2. Clinical features of pulmonary cryptococcosis in non-HIV patients (n=41)

Variable	Patients with pc (%) (n=41)
Symptoms	
No symptoms	17 (41.46)
Cough	18 (43.90)
Expectoration	11 (26.83)
Hemoptysis	5 (12.20)
Chest tightness	2 (4.87)
Laboratory tests	
Sputum cultures	41
Positive	0
Negative	41 (100)
Latex agglutination test	18
Positive	18 (100)
Negative	0
Cerebrospinal fluid	16
Positive	7 (43.75)
Negative	9 (56.25)
Alveolar lavage fluid brush	4
Positive	0
Negative	4 (100)

sular polysaccharide antigens latex agglutination test performed in 18 patients (43.90%) were showed positive (titre 1:100-1:1280 vs titre 1:80-1:1280). Cerebrospinal fluid examination was performed in 16 patients and fungal spores were found in 7 cases (17.07%). The result from 4 patients who took alveolar lavage fluid and protective brush showed negative (**Table 2**).

Histological pathology

5 patients underwent a thoracoscopic surgery or an open lung biopsy. 11 patients were diagnosed by CT-guided percutaneous cutting needle biopsy (PCNB). All lung tissue sections were stained with haematoxylin-eosin (HE) and histochemically stained with periodic acid-Schiff (PAS), mucus card Red (Mc) and Grocott's methenamine silver (GMS) [11]. In these 16 cases, Cryptococcal pathogens were fund in lung tissue sections by means of microscope.

Radiological assessment

All pulmonary cryptococcosis patients underwent CT scan. However, the radiographic features of pulmonary cryptococcosis varied in lesions' shape, which showed single (14, 34.14%) or multiple nodules (18, 43.90%), pneumonic infiltrates (9, 21.95%) or both (mixed) (**Figure 1**). In 9 cases (21.95%), lesions were observed only in left lungs, 14 (34.14%) in right lungs and bilateral lung lesions were seen in 18 cases (43.91%) (**Table 3**). Most of lung lesions were located in the peripheral lung fields (outer third of the lung), closed to the pleura, where 31.70% of lesions occurred in the lower lobe [13], and 26.83% in the upper lobe. More lesions (17, 41.46%) were characterized by patchy consolidations (**Table 3**). The cavity lesions were found in 3 patients (7.32%). Calcification or pleural effusion was not found in chest radiograph in all the patients involved in study.

In brief, the radiographic features of pulmonary cryptococcosis varied in lung lesions. Lung lesions occur mostly in the outer lung fields, varying in shape. Nodular lung masses were relatively common in people with normal immune functions.

Diagnosis

Diagnosis is based on environmental exposure history, coupled with appropriate clinical symptoms or radiological findings, and ideally, histopathological evidence of tissue invasion [5]. The time from clinical presentation to final tissue diagnosis ranged from 17 days to 10 months. Of all 41 cases, cryptococcal infection was considered in only 6 patients (14.63%) who were admitted for the first time. Most of the patients (85.37%) were initially misdiagnosed: 15 patients (36.59%) were diagnosed with pneumonia, 13 patients (31.70%) were diagnosed with lung cancer and 7 patients (17.07%) were diagnosed with tuberculosis when they were admitted (**Table 4**).

Treatment

5 patients underwent surgical resection, 3 patients were treated with surgery alone, and 2 patients were treated with surgery and postsurgical medication (itraconazole). 36 patients were treated with antifungal drugs; the lesions of lung were reduced remarkably in all patients (**Figure 2**).

Discussion

In the past, many of the reports of cryptococcal infection have been in the human immunodeficiency virus (HIV)-positive population, and little

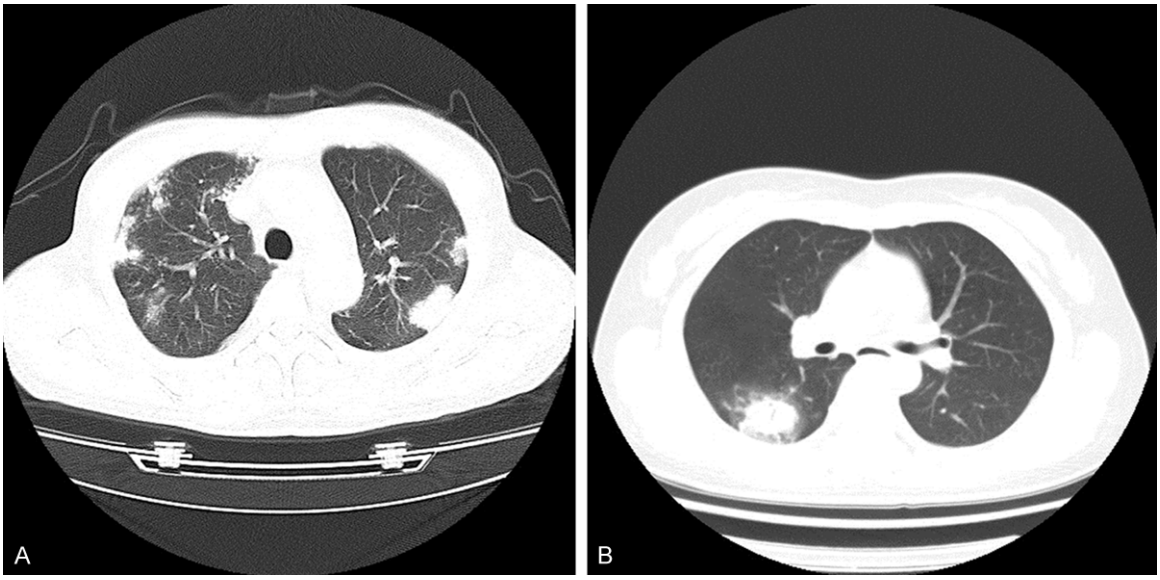

Figure 1. Pulmonary Cryptococcosis with scattered nodular pattern in 68-year-old man who had diabetes mellitus (A), Pulmonary Cryptococcosis of solitary pulmonary nodular in 48-year-old man who had no systematic disease (B).

Table 3. Radiography of pulmonary cryptococcosis in non-HIV patients (n=41)

Variable	Patients with pc (%) (n=41)
Image feature	
Single nodule	14 (34.14)
Multiple nodule	18 (43.90)
Diffuse infiltrates	9 (21.95)
Lesion lung	
Right lung	14 (34.14)
Left lung	9 (21.95)
Combination	18 (43.90)
Lesion area	
Upper lobe	11 (26.83)
Lower lobe	13 (31.70)
Combination	17 (41.46)

Table 4. Diagnosis and treatment of pulmonary cryptococcosis in non-HIV patients (n=41)

Variable	Patients with pc (%) (n=41)
Admitting diagnosis	
Misdiagnosis	35 (85.36)
Pneumonia	15 (36.58)
Lung cancer	13 (31.70)
Tuberculosis	7 (17.07)
Diagnosis	6 (14.63)
Pulmonary Cryptococcosis	6 (14.63)
Discharge diagnosis	
Proven diagnosis	23 (56.09)
PCNB*	11 (26.83)
Operation	5 (12.20)
Cerebrospinal fluid	7 (17.07)
Probable diagnosis	18
Latex agglutination test	18 (43.90)
Possible diagnosis	0
Treatment	
Surgical	3 (7.31)
Antifungal therapy	36 (87.80)
Both	2 (4.88)

*PCNB CT-guided percutaneous cutting needle biopsy (PCNB).

is reported of the disease in non-HIV patients, particularly pulmonary involvement [7]. Recent data shows that the incidence of pulmonary cryptococcosis is increasing despite the report that the incidence of people with HIV infection is stable. Thus, the increased incidence is mainly due to non-HIV patients [8]. Cryptococcosis is an important issue in non-HIV patients, including patients with underlying medical conditions or predisposing factors. As has been reported in a recent study, about one-third of immunocompetent patients with pulmonary cryptococcosis were asymptomatic [9]. An underlying immunosuppressed condition was identified in 14.63% (6 out of 41) of our patients. Other predisposing conditions associated with cryptococcosis in immunocompetent

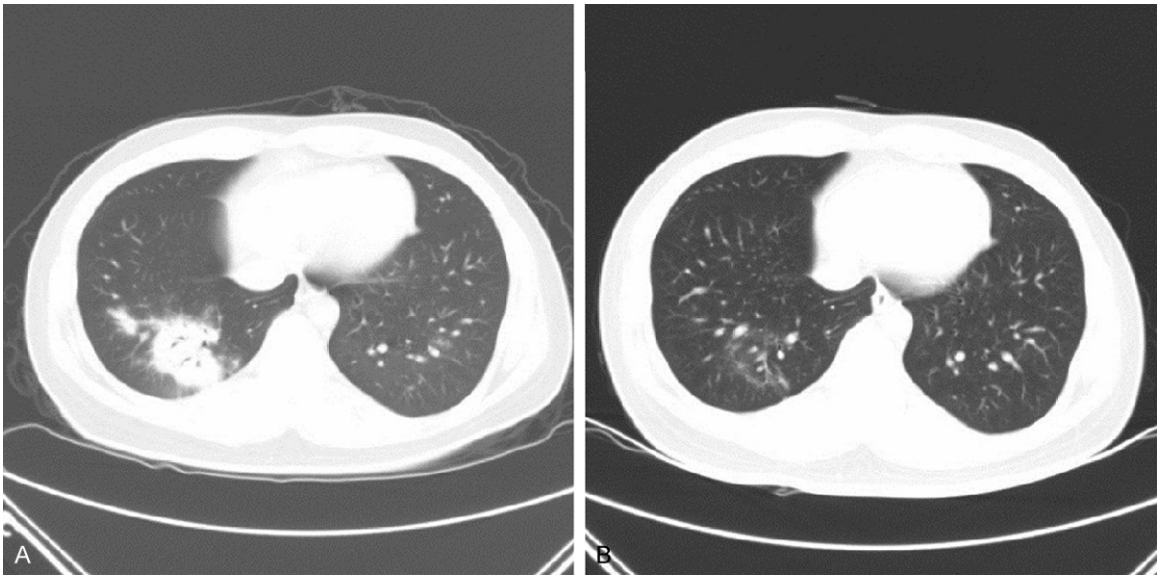

Figure 2. Chest CT scan showed mass in right lower lobe (A) before treatment, lesions significantly absorbed after treatment (B).

patients have been reported, such as chronic leukemia, tumour, or diabetes, 35 (85.37%) of our patients had unknown underlying medical conditions [9, 10]. It is worthy of paying more attention to pulmonary cryptococcosis in non-HIV patients whose symptoms are untypical. In addition to the host immune factors, pulmonary cryptococcosis could also be related to environmental exposure to contaminated airspace, including close contact with animals, green plants or other natural sources contaminated by fungi. Cryptococcosis is mainly caused by the yeast Cryptococcus neoformans, which has been recovered from soil contaminated with avian excreta, especially pigeon droppings [10]. Fungal contamination can occur not only in the living area or office environment but also in automobiles, trains and other modern means of transportation. In this study, 12.19% (5 out of 41) of patients had a history of direct exposure to pigeon droppings. About 31.70% (13 out of 41) patients' working or living environments have potential risk of fungal spores' contamination. 43.90% (18 out of 41) of pulmonary cryptococcosis patients had direct or potential environmental exposure history. The data suggests that we should pay more attention to the details of occupation and potential exposure risk factors of fungal spores.

In this study, 41.46% patients who had no symptoms and pulmonary indications were only found to have nodules in lung or have other lung diffused changes via routine annual imaging examination. Disease manifestations ranged from asymptomatic pulmonary nodules to fulminant respiratory failure with diffuse infiltrates and acute respiratory distress syndrome depending on host immune response [11, 12]. The radiographic features of the pulmonary cryptococcosis varied and are influenced by the immune status of the patient. Findings could be broadly categorized into pulmonary nodules or mass (**Figure 1**); segmental or lobar consolidation; diffuse infiltrates (**Figure 1**). In non-HIV patients, solitary or multiple pulmonary nodules were seen on approximately 78% of chest radiographs in our study. Data in this group showed that the symptoms and signs did not match with the image manifestation of the lung in pulmonary cryptococcosis patients. The symptoms and signs were always untypical, even absent, but lesions in lung with CT scan were often obviously. Both clinical and imaging findings of patients should be considered for diagnosis. If the infiltration could not be absorbed after anti-inflammatory or anti-tuberculosis treatment, the possibility of pulmonary cryptococcosis should be considered. If lung lesion can not be diagnosed with any other definite disease, the possibility of pulmonary cryptococcosis should also be considered, especially in immunocompromised patient.

Clinical symptoms and signs of pulmonary cryptococcosis were unspecific, even sometimes

asymptomatic, and its chest imaging findings are varied. Thus early diagnosis is difficult. In this group, (35 out of 41) patients were misdiagnosed when admitted, the rate of misdiagnosis is 85.37%. 15 patients (36.59%) were misdiagnosed with pneumonia, 13 cases (31.70%) were misdiagnosed with lung cancer, 7 cases (17.07%) were misdiagnosed with tuberculosis. It is crucial to get all kinds of invasive biopsy specimens and find Cryptococcus spores in patients' blood, CSF and pleural effusion at the early phase of diagnosis. Some noninvasive diagnostic tests, such as the SCRAG test is also considered as an effective diagnostic tool, which is convenient and cheap. Histological evidence is golden standard for confirming pulmonary cryptococcosis. It is important to get an early biopsy of pulmonary specimen through bronchoscope or transbronchial lung biopsy (TBLB), even surgical resection and all kinds of invasive techniques.

Conclusions

Pulmonary cryptococcosis cases in non-HIV infection have been increased rapidly in recent years. This might be related to fungus-contaminated environmental exposure. Radiographic features of pulmonary cryptococcosis were varied. Lung lesions occurred mostly in the outer lung fields, varying in shape. Nodular lung masses were relatively common in non-HIV patients. The great variations and protean manifestations of its clinical features often led to misdiagnosis. Recognition and invasive examination of non-HIV infected patients' pulmonary cryptococcosis in the early stage may help with improvement of diagnosis and prognosis.

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Disclosure of conflict of interest

None.

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