

Research article

Radiological features of AIDS complicated by pulmonary cryptococcosis: Literature review and a report of 10 cases

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Received 20 October 2015; revised 17 November 2015; accepted 21 December 2015

Available online 7 January 2016

Abstract

Purpose: To retrospectively analyze the clinical data and radiological features of AIDS complicated by pulmonary cryptococcosis (PC) for more knowledge about the condition and its diagnosis.

Methods: A total of 10 cases with AIDS complicated by pulmonary cryptococcosis was recruited as the subject of the study, and all the clinical and radiological data were collected. The patients included 6 males and 4 females, aged 40–58 years. The CD4⁺ T cell count was below 100/μl in 8 cases. All of them were pathologically or etiologically diagnosed with AIDS complicated by PC, and received digital radiography (DR) and CT examination. All the radiological images were retrospectively analyzed by two senior radiologists who knew nothing about the patients.

Results: The radiological findings were categorized into 3 types: (1) multiple miliary nodules in 2 cases (20%), which distributed in bilateral lung apex and dorsal segment of lower lobe, being 2–3 mm–2 cm in diameter, with “halo sign” around the larger lesion; (2) singular nodule or mass in 3 cases (30%), which was located in the peripheral region of lung, also with “halo sign” around the lesion; (3) cavity in 5 cases (50%), which was singular or multiple, with uneven thickness of the cavity wall and inner-wall nodule. In a few cases, enlarged mediastinal lymph node and pleural effusion accompanied.

Conclusion: The radiological signs featured AIDS complicated by pulmonary cryptococcosis such as singular or multiple nodules with cavity and “halo sign” can facilitate its diagnosis. But the diagnosis should be made in combination to the clinical history.

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Keywords: AIDS; HIV; Pulmonary cryptococcosis (PC); Lung; Halo sign; Cavity; Nodule

1. Introduction

Fungal infection is the most common opportunistic infection in patients with HIV/AIDS, whose pathogen is the most commonly candida, followed by pneumocystis carinii and cryptococcus [1–3]. Pulmonary cryptococcosis (PC) is mainly caused by inhaled aerosols containing new cryptococcus and

its variants, which further lead to subacute or chronic pulmonary disease. Lung is the second most common target of the fungus, following the brain [4]. Recently, the incidence rate of PC sees an obvious increase due to the prevalence of AIDS, which demands more knowledge and accurate diagnosis of its pathogenic microorganism.

The onset of PC is mild, with non-specific clinical symptoms and routine laboratory findings. In addition to the greatly diversified radiological demonstrations due to different levels of immunity, the disease tends to be misdiagnosed. In recent years, many studies about radiological features of PC have been conducted in patients with normal immunity. However, radiological features of HIV/AIDS complicated by PC have been rarely reported. In order to increase the clinical

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Peer review under responsibility of Beijing You'an Hospital affiliated to Capital Medical University.

understanding about HIV/AIDS complicated by PC, 10 cases of HIV/AIDS complicated by PC were retrospectively analyzed. By analyzing the clinical manifestations, CD4⁺ T cell count and radiological features, we intended to further improve the diagnostic accuracy of the diseases for early appropriate intervention.

2. Materials and methods

2.1. Subjects

All the cases were clinically diagnosed with AIDS, with HIV positive. The whole research protocol was approved by the ethics committee of our institution. Six cases were recruited from Zhongnan Hospital of Wuhan University during Nov. 2012 to Jul. 2014, 2 cases from Beijing Youan Hospital, and 2 cases from the Shenzhen 3rd People's Hospital. The subjects include 6 males and 4 females, aged 40–58 years with a mean of 47.7 ± 7.1 years. Nine cases had a history of cough, sputum or chest pain, 4 cases had fever, 1 case had epilepsy symptom, 3 cases had symptoms of central nervous system, headache and nausea. Epidemiological investigation showed no history of close contact to pigeon or other poultries. Of all the cases, 4 were diagnosed by CT guided percutaneous fine needle lung puncture for biopsy with PC, 1 case was pathologically defined after surgery, 2 cases by multiple sputum cultures, and the other 3 cases experienced symptoms of central nervous system which were confirmatively diagnosed by cerebrospinal fluid with *Cryptococcus neoformans* positive. The lung lesions were cured by using amphotericin B and fluconazole therapy. CD4⁺ T cell count and three times consecutive sputum tests showed mycobacterium tuberculosis negative and tuberculin test negative.

2.2. Equipment for radiological examination and statistical analysis

All cases received chest X-ray (GE Healthcare Definition 6000 DR) and CT scan (SIEMENS SOMATOM Definition 64). Routine chest CT scan was performed from the lung apices through the bases. Transverse thin-section CT scans were performed with the following parameters: tube voltage 120–140kVp, tube current 200–250 mA, slice thickness 2–5 mm, distance 2–5 mm 1.5 mm coronal and sagittal multi-planar reconstructions were achieved for the interested lesions in the lung. Six cases received contrast CT scan with high pressure injector using iodinated contrast agent 70–100 ml (iohexol 300 mg/ml) at a flow rate of 3.0–3.5 ml/s.

All the radiological images were retrospectively and blindly analyzed by two experienced radiologists. Scans were evaluated for the location, size, contour, margin and density of the lesions as well as their surrounding tissue changes, such as pleura, mediastinum, hilar lymph node of lung. The enhancement was also evaluated for the changes before and after contrast scans. For the cases receiving re-examination, dynamic changes before and after treatment were paid focused attention, including the changes of lesion size and quantity et al.

3. Results

3.1. Demographic and clinical data

Ten cases were analyzed in this study, including 6 male cases and 4 female cases with a male-female ratio of 3:2. Their age ranged from 40 to 58 years, with a mean of 47.7 ± 7.1 years. Clinically, 1 case was asymptomatic, and 9 experienced nonspecific respiratory symptoms and other symptoms. All the 10 cases were confirmatively diagnosed with pulmonary Cryptococcosis, and all of them received laboratory test for serum CD4 T cell count. The demographic and clinical data were listed in Table 1.

3.2. Radiological demonstrations

Chest radiology demonstrated that the 10 cases of AIDS complicated by PC can be categorized into the following 3 types:

3.2.1. Multiple miliary nodules

Multiple miliary nodules were demonstrated in 2 cases (20%), with scattering multiple miliary nodules at both lungs that mainly distributed at the lung apex and dorsal segments of lower lung lobe, ranging from 2–3 mm–2 cm in diameter. The lesions were shown with high density and favorably defined boundary. For the large nodules (with a diameter of above 1 cm), the central density was homogeneously high, and the surrounding manifested as ground glass opacity, known as the halo sign (Fig. 1).

3.2.2. Singular nodule/mass

Singular nodule/mass was shown at the lung in 3 cases (30%), which progressively increased in size if inappropriately

Table 1
Demographic and clinical data of the 10 cases.

N	10
Age (years old)	47.7 ± 7.1 (40–58)
Gender	
Male	6 (60%)
Female	4 (40%)
Clinical data	
Asymptomatic	1 (10%)
Cough and sputum	7 (70%)
Chest pain	5 (50%)
Epilepsy	1 (10%)
Headache	3 (30%)
Fever	4 (40%)
Diagnostic examination	
CT guided percutaneous needle lung biopsy	4 (40%)
Surgery	1 (10%)
Sputum culture	2 (20%)
Clinical confirmed	3 (30%)
CD4 ⁺ T lymphocyte cell count	53.8 (21–153)
Concurrent infection	
Tuberculosis	0
Cryptococcus meningitis	4 (40%)
Spore bacterium pneumonia	1 (10%)

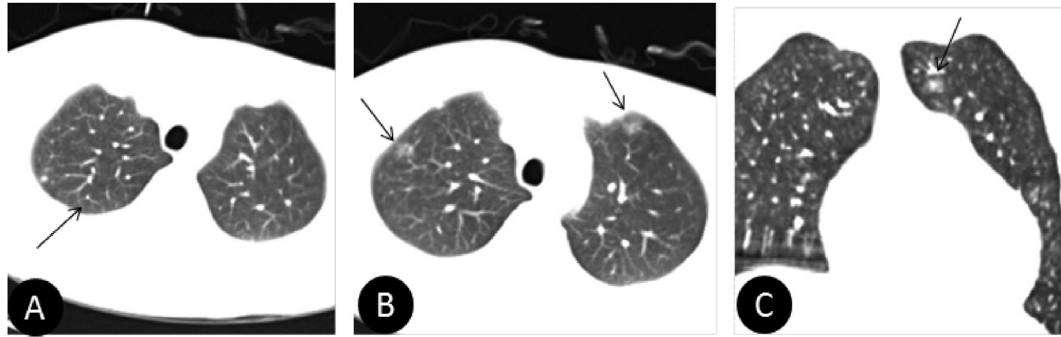


Fig. 1. Chest CT showed multiple miliary nodules and small nodules in both lung apices (arrows in A and B). Coronal reconstruction showed halo sign at the left upper lung (arrow in C). The images were from a 40-year-old man who complained of fever and headache for 1 week with a CD4 T cell count of 39 cells/ μ L.

treated. The lesion in all the 3 cases grew near pleura, with homogeneous density and favorably defined margin, and the larger lesion was lobulated. All the lesions showed long and coarse spikes and pleural reaction (Fig. 2). Meanwhile, the large lesion showed bubble sign within the mass, and halo sign around the mass.

3.2.3. Cavity

Cavity was shown in 5 cases (50%), manifested as singular or multiple nodules or masses with cavity. Only one case showed with singular cavity at the lesion, and the other 4 cases showed with multiple cavities at the lesion, which were ipsilaterally or bilaterally distributed. The lesions had different sizes, uneven thickness of cavity wall and inner-wall nodule. The inner wall was smooth, and was shown to be slightly enhanced by contrast scan (Fig. 3). In 1 case, the lesion was shown with shrinkage in size after amphotericin B and fluorine cytosine treatment was administered for 1 month (Fig. 4). The follow-up examination demonstrated shrinkage of the lesion in size after 1 year treatment, with no cavity shown (Fig. 5).

In addition to the above radiological findings, mediastinal lymphadenectasis was also shown in 2 cases, with 1–2 enlarged lymph nodes in the middle mediastinum, and bilateral pleural effusion in 1 case during treatment. The

radiological finding of cryptococcal meningitis in 4 cases was not illustrated in our research.

4. Discussion

Studies have demonstrated that PC is one of the most common opportunistic fungal infections in patients with AIDS/HIV in the United States, and 5–10% patients with AIDS/HIV in Europe died from PC [5–7]. The incidence rate of PC in patients with AIDS/HIV decreased in 2000 compared to that in 1990s in the United States. And African American patients with AIDS/HIV are more susceptible to PC than Caucasian, which may be related to the wider use of highly active antiretroviral therapy in African American patients [8]. The incidence ratio of AIDS complicated by PC in males to females is about 5:1–11:1, with the occurring age ranging from 30 to 60 years [9], which are in consistency with the data of our present research. Due to the comparatively low incidence of AIDS complicated by PC, large sampling studies on radiological features of PC in HIV/AIDS patients have been rarely reported.

Clinically, HIV/AIDS complicated by PC was characterized by cough, sputum, chest pain, fever, and other respiratory symptoms in our study, which were non-specific. In

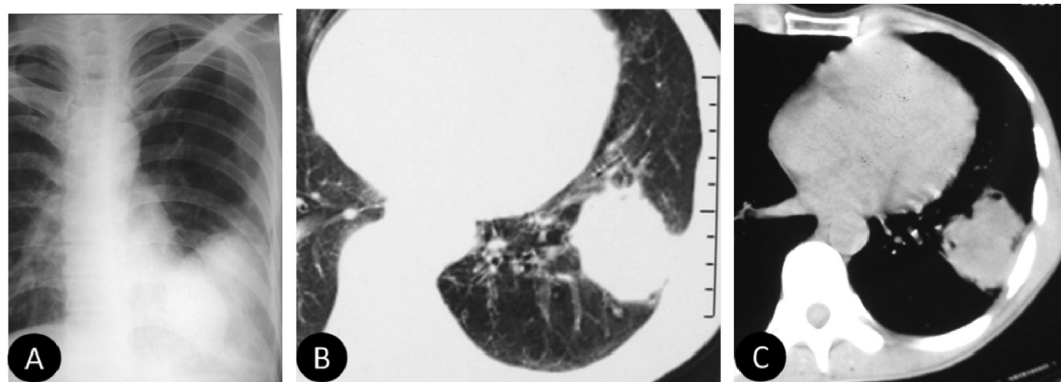


Fig. 2. Chest X-ray showed high density opacity at the left lower lobe, with well defined margin (A). Chest CT showed round like high density lesion at the left lower lobe near the pleura in the lung window. The mass was lobulated with coarse spikes (B). Mediastinum window showed the lesion with homogeneous density and bubble sign (C). The images were from a 54-year-old woman who complained of repeated fever and headache for 10 days, with a CD4 T cell count of 153 cells/ μ L.

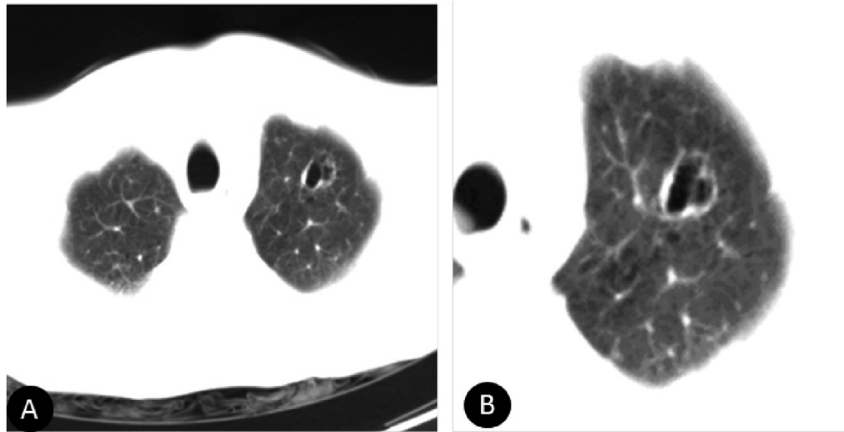


Fig. 3. Chest CT showed singular cavity at the left lung apex, with well defined margin (A). Amplification of local lesion showed uneven thickness of the cavity wall, septum and inner wall nodule within the lesion (B). The images were from a 40-year-old man who complained of blurry vision and fever for 2 months, with a CD4⁺ T cell count of 21 cells/ μ L.

some rare cases, the patients were asymptomatic or experienced slight symptom but with serious chest radiological lesions. Other research has shown that a few patients may experience serious clinical symptom, which may further develop into acute respiratory distress syndrome (ARDS) or even death [10].

A study by Benito N showed that [11] AIDS related PC is more serious than other pulmonary fungal infections, and its severity and range with lesions are negatively related with CD4 T cell count. Patients with HIV/AIDS complicated by PC and a CD4 T cell count of lower than 100 cells/ μ L are symptomatic. In our research, 9 cases were symptomatic,

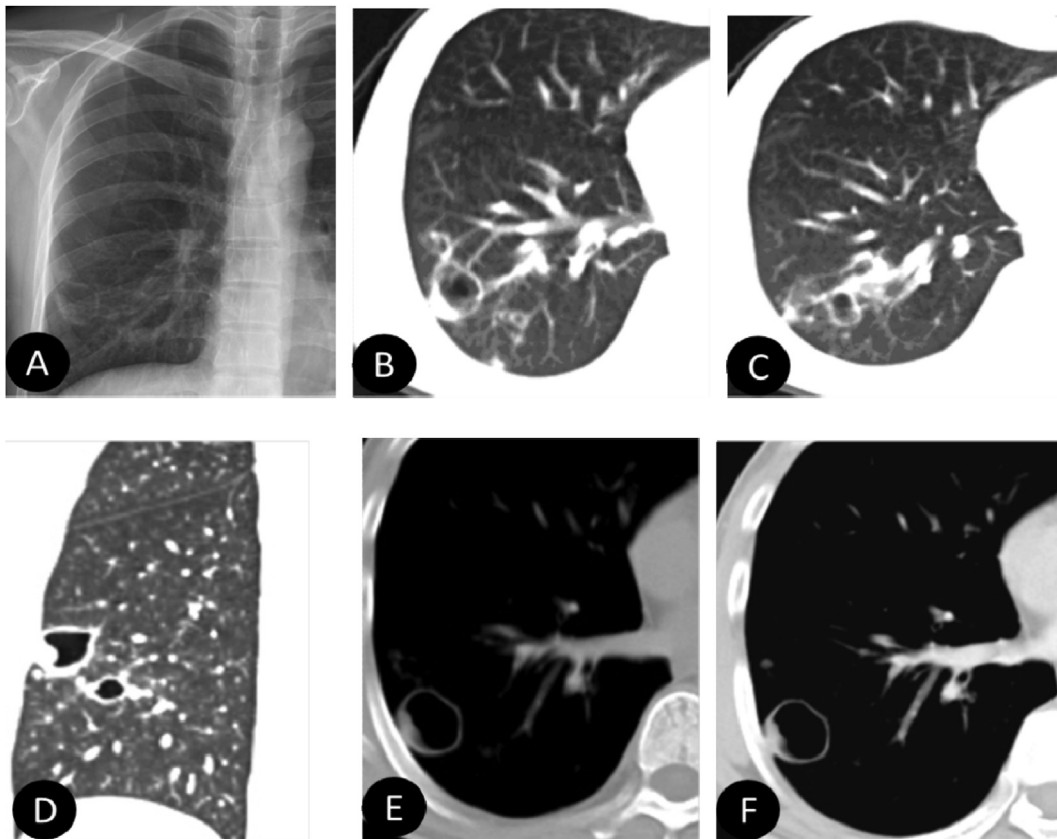


Fig. 4. Chest X-ray showed multiple thin-wall cavity lesions at the right lower lung lobe (A). Plain Chest CT showed two thin-wall cavity lesions with surrounding nodule at the right lower lung lobe, with a size of 2.3 cm \times 2.6 cm and 1.2 cm \times 1.9 cm, separately (B,C). Coronal reconstruction showed inner-wall nodule in the large cavity (D). By contrast scan, the cavity wall and inner-wall nodules were shown to be slightly enhanced, with CT values of 28Hu and 43Hu separately (E,F). The images were from a 41-year-old man who complained of cough and headache for 8 days, with a CD4 T cell count of 55 cells/ μ L.

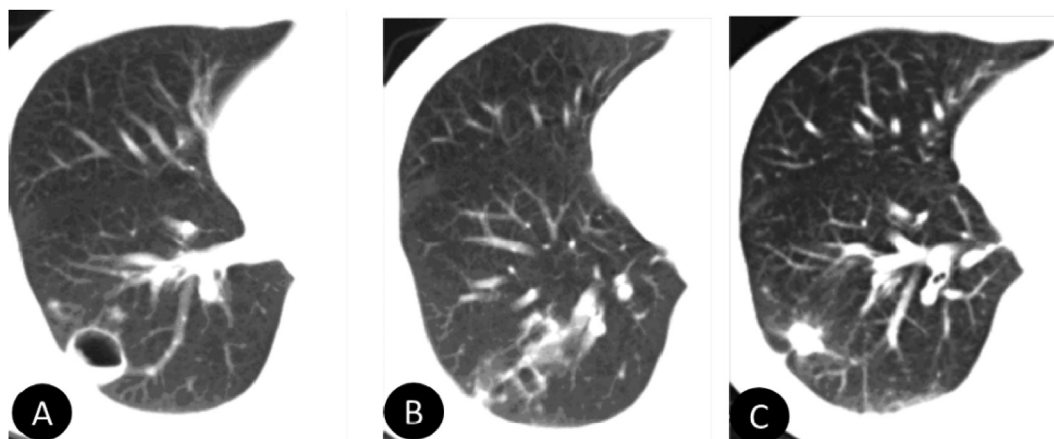


Fig. 5. The same case as Fig. 4 showed shrinkage of the cavity after 1 month treatment (A,B). Follow-up examination after 1 year showed no large cavity but an irregular dense nodule instead (C).

among which 8 cases had a CD4 T cell count of lower than 100 cells/ μL , and the patient with the lowest CD4 T cell count experienced cryptococcus encephalitis, cranial nerve dysfunction, and PCP in the advanced stage of AIDS, all of which were consistent with the literature reports. In addition, a CD4 T cell count of <50 cells/ μL was shown in 70% of the concerned cases, indicating that such patients are more vulnerable to PC infection.

Research has shown that HIV/AIDS complicated by PC is radiologically characterized by diffuse interstitial infiltrates in both lungs, which resemble to PCP [11–13]. In addition, unilateral pulmonary interstitial infiltrates, focal consolidation, nodules, cavity, pleural effusion as well as mediastinal and hilar lymphadenectasis may also be demonstrated. However, these lesions may be induced by other concurrent opportunistic infections, therefore, are non-specific. The chest radiological manifestations of 10 cases AIDS complicated by PC can be categorized into 3 types: multiple miliary nodules, singular nodule/mass and cavity, among which the cavity type accounts for 50%, and the singular nodule/mass type for 30%. The lesions mainly distribute in double lung apices and lower lobe that are closed to the pleura; and the multiple lesions are in different sizes, with or with no cavity at the nodule or mass. Although HIV/AIDS complicated by PC radiologically resembles to PC in patients with normal immunity [14,15], the location of lesions as well as multiple lesions in different sizes can facilitate its diagnosis. And multiple cavities with wall in uneven thickness, inner-wall nodule, and smooth cavity wall are characteristically signs of HIV/AIDS complicated by PC. In addition, the halo sign is common in these cases (40%), showing as ground glass opacity around the large nodule ($d > 1.0$ cm) or mass, with bubble or cavity within the mass but no surrounding calcification or satellite lesion. Zinck reported that 40% of the PC cases show the halo sign, especially in the immune-compromised patients, which is pathologically based on granulomatous inflammation [16]. In addition, 2 cases showed mediastinal lymphadenectasis and pleural effusion in our study, the other 4 cases showed cryptococcal meningitis.

HIV/AIDS complicated by PC should be differentiated from tuberculosis (TB). According to the data from WHO, the risk of TB infection in HIV positive patients can be several times higher than those in HIV negative population, and the risk of TB infection in patients with AIDS is even much higher [17]. And the lesions of AIDS complicated by TB are radiologically diversified, being non-typical and non-specific [18–20]. The most common lesions are multiple miliary nodules as well as lobe distributed infiltrates and consolidation, with poorly defined margin. And as the CD4 T cell count decreases, the condition is more likely to develop into hematogenous disseminated tuberculosis, manifested as diffusely distributed lung nodules in the medial region of both lower lung lobes, with a diameter of lower than 1 cm. Some of its lesions show consolidation without cavity [19]. Mediastinal lymphadenectasis, pleural effusion, and pericardial effusion are characteristic radiological signs of AIDS complicated by TB. In some cases, extra-pulmonary TB lesions can be found. In addition, the death rate from AIDS complicated by lung cancer is higher than that in HIV negative population [21,22]. The onset age of lung cancer is younger in AIDS patients compared to that in HIV negative population, especially in males with habitual smoking. CD4 T cell count is not shown to be related to lung cancer [23,24]. PC manifested as singular nodule/mass should be differentiated from lung cancer, but the key points for the differential diagnosis between PC and lung cancer are to be defined [25,26]. No obvious shape difference has been found between AIDS related lung cancer and the other types of lung cancer, but the halo sign around the lesion can facilitate the differential diagnosis. If primary lesions are to be located, pleural lesions or pleural effusion can facilitate the diagnosis. PC is more likely to be accompanied by mediastinal lymphadenectasis and pleural effusion, and metastasis sign is also helpful for differential diagnosis. In addition to the radiological findings, CT guided percutaneous lung puncture for biopsy, sputum culture and follow-ups after treatment are all helpful for differential diagnosis.

The incidence of AIDS complicated by PC has been increasing these years, and we should gain more knowledge

about its radiological manifestations. The radiological finding of the 10 cases HIV/AIDS complicated by PC can be categorized into 3 types, and nodule with cavity is the most common. The radiological signs of cavity and the halo sign around the lesion are helpful for the diagnosis of PC. Our findings can improve the understandings about HIV/AIDS complicated by PC, and therefore, improve the accuracy of clinical diagnosis.

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