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Clinical features and high-resolution CT findings of pulmonary cryptococcosis in non-AIDS patients

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Summary The objective of this study was to clarify clinical and high-resolution computed tomography (HRCT) characteristics in non-AIDS patients with pulmonary cryptococcosis. We analyzed the medical records and HRCT scans in 22 patients with pulmonary cryptococcosis from 1988 to 2003. Thirteen patients (59%) were immunocompetent and nine (41%) were immunosuppressed, seven of whom had diabetes mellitus. No patients exhibited extrapulmonary involvement. Nineteen patients (86%) were asymptomatic. Radiography revealed incidental chest abnormality in all but two patients. The typical HRCT findings were solitary or multiple nodules in the subpleural area. Cavitation was present in 30% of the patients who had nodules. The most frequently applied and reliable diagnostic procedure was video-assisted thoracoscopic surgery (VATS). Treatment included antifungal therapy alone in 11 patients, surgery alone in eight including four treated by VATS, surgery plus antifungal therapy in two and none in one. Patients who underwent surgery alone did not develop any relapse. The majority of non-AIDS patients with pulmonary cryptococcosis present with incidental chest radiographic abnormalities. The most common HRCT findings are solitary or multiple nodules with or without cavitation in the subpleural areas of the lung. VATS is a useful tool for both diagnosis and treatment of isolated pulmonary cryptococcosis.

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Introduction

Cryptococcosis is an illness caused by infection with the encapsulated fungus, *Cryptococccus neoformans*, an organism with a worldwide distribution.[1] Inhalation of organisms is the usual route of infection that may remain isolated to the lungs or undergo hematogenous spread to involve the central nervous system (CNS), bones, and skin, depending on the host immune status.

Cryptococcal infection can occur in individuals with normal immunity but is most common in the immunocompromised host.[1,2] Predisposing factors include acquired immunodeficiency syndrome (AIDS), hematologic malignancies, organ transplantation, corticosteroid therapy, diabetes mellitus, and other conditions that impair T-cell mediated immunity. In particular, cryptococcosis is most prevalently associated with AIDS patients.[3]

The clinical features and computed tomography (CT) findings of pulmonary cryptococcosis in non-AIDS individuals have not been well described because cryptococcal infections among these subjects are quite rare. The most common radiographic characteristics are known as solitary or multiple pulmonary nodules or masses.[4–6] Other less frequent radiographic features may include segmental or lobar pneumonia, cavitation, lymphadenopathy or pleural effusion. However, there is only a limited number of studies focusing on CT findings of pulmonary cryptococcosis in non-AIDS individuals.[7–9] In immunocompromised patients, pulmonary cryptococcosis should be treated with antifungal therapy.[10] In contrast, there are several therapeutic options such as follow-up observation, antifungal therapy or surgical resection of the lesion in immunocompetent patients.[2,4,10–13]

In Japan, because of mass screening or the widespread use of chest CT, the number of detected patients with pulmonary cryptococcosis is increasing.[14] The histologic diagnosis of pulmonary cryptococcosis can be made more easily than ever by the recent development of video-assisted thoracoscopic surgery (VATS). The aim of this study was to clarify clinical features and high-resolution CT (HRCT) findings in non-AIDS individuals with pulmonary cryptococcosis.

Materials and methods

We reviewed 22 individuals with pulmonary cryptococcosis in a non-AIDS condition who were treated in Toranomon Hospital from June 1988 through October 2003. The diagnosis of pulmonary cryptococcosis was confirmed by histologic presence of the organism in a lung biopsy specimen or a positive finding from culturing respiratory specimens or positive result of the serum cryptococcal antigen test with a radiographic evidence of pulmonary disease.

The medical charts, HRCT images and histologic specimens were reviewed. From the medical charts, the following data were abstracted: age, sex, smoking history, underlying disease, respiratory symptoms, serum cryptococcal antigen, data for cerebrospinal fluid (CSF), and finally, treatment and follow-up information.

CT scans were performed on CT 9800 scanner or High Speed Advantage scanner (GE Medical Systems, Milwaukee, USA). Routine scanning of the entire lung was carried out with 10-mm section thickness. Additional HRCT scans with 1–3 mm collimation were acquired through areas of interest with a bone algorithm using fixed window settings (lung center, −500 HU and width, 1800 HU) from all patients.

A consensus reading of the HRCT images was conducted by two observers (A.K., K.K.). CT findings were divided into two categories: nodules or consolidation. Nodules were classified according to predominant size (1–5, 6–10, 11–29 mm), number (1, 2–4, 5–10, or >10), margination (smooth, irregular, well defined, ill defined, lobulation, spiculation, convergency of peripheral bronchi and vessels, or pleural indentation) and internal characteristics (cavitation, air-bronchogram, or calcification).

The lobar distribution of parenchymal lesions was evaluated and the locations were also categorized into a central or a peripheral type by an imaginary line of 3 cm apart from the pleura.

All resected specimens were stained with hematoxylin–eosin, Grocott, and periodic acid-Schiff, and reviewed by one pulmonary pathologist (N.M.).

Results

Clinical characteristics of 22 patients with pulmonary cryptococcosis are summarized in Table 1. Seventeen individuals were male and five were female, with a mean age of 54.5 years. Sixteen patients (73%) were non-smokers. Four were past and two were current smokers, with a mean of 21 pack-years. Only one patient had a close contact with pigeons that frequently flew to the veranda of his residence. Thirteen patients were immunocompetent and nine were immunosuppressed. Seven of nine immunocompromised patients had diabetes mellitus. Three patients were receiving

Table 1 Clinical characteristics of 22 patients with pulmonary cryptococcosis.

Characteristics	Subjects (%)
Age, yr	
Mean	54.5
Range	24–85
Gender	
Male	17 (77)
Female	5 (23)
Host status	
Immunocompetent	13 (59)
Immunocompromised	9 (41)
Immunocompromising conditions	
Diabetes mellitus	6
Diabetes mellitus+bronchial asthma	1
Autoimmune pancreatitis	1
Non-Hodgkin's lymphoma	1
Corticosteroid therapy	3
Symptoms	
None	19 (86)
Cough and fever	1
Cough	1
General fatigue	1
Mode of detection	
Mass screening	15 (68)
Routine follow-up of other diseases	5 (23)
Subjective symptoms	2 (9)

Table 2 HRCT findings of pulmonary nodules in 20 patients of pulmonary cryptococcosis.

Characteristics	Subjects (%)
Number of nodules	
Solitary	12 (60)
Multiple	8 (40)
5–10	3 (15)
>10	5 (25)
Nodular margin	
Well defined	17 (85)
Poorly defined	5 (15)
Irregular	12 (70)
Smooth	6 (30)
Spiculation	6 (30)
Lobulation	7 (35)
Convergence of peripheral vessels and bronchi	10 (50)
Pleural indentation	10 (50)
Internal characteristics	
Cavity	6 (30)
Air-bronchogram	7 (35)

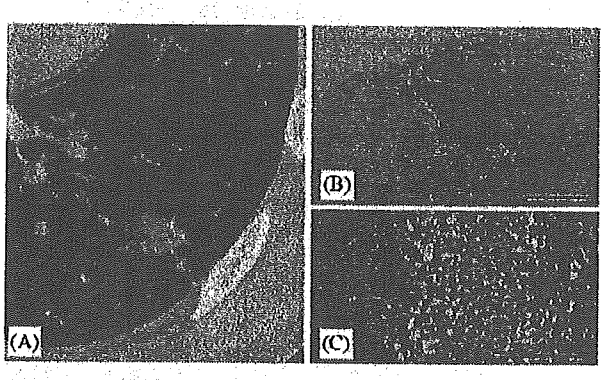

Figure 1 An immunocompetent patient with pulmonary cryptococcosis. (A) HRCT scan shows a spiculated nodule with pleural indentation resembling well-differentiated adenocarcinoma. (B) Photomicrograph of the lower magnification shows a cluster of granulomas with irregular margin (hematoxylin–eosin stain). The bar indicates 5 mm. (C) Photomicrograph of the higher magnification reveals caseous epithelioid cell granuloma (hematoxylin–eosin stain). The bar indicates 100 μm.

corticosteroid therapy. Nineteen patients (86%) were asymptomatic. As the mode of detection, 15 patients were incidentally detected an abnormal radiographic findings on mass screening. All patients had pulmonary cryptococcosis without any extrapulmonary involvement, and no progressive dissemination occurred during the follow-up period.

CSF was examined in five patients (23%), and the findings of Indian ink and culture were all negative. Five of 14 patients (36%) revealed positive for the serum cryptococcal antigen. According to the host status, the serum cryptococcal antigen was positive in two of six immunocompetent patients (33%) and three of eight immunocompromised patients (38%).

HRCT patterns included pulmonary nodules in 20 of 22 patients (91%) (Table 2) and consolidation in two patients, respectively. The number of nodules in each case was one in 12 patients, 5–10 in three, and more than 10 in five (Figs. 1 and 2). The diameter ranges of the multiple pulmonary nodules were less than 6 mm in four patients, 6–10 mm in two, and more than 10 mm in two. Margination of nodules in each patient was well defined in 17 (85%), irregular in 12 (60%), and spiculated in six (30%), respectively. Cavitation was seen in six patients (30%). According to the host status, cavitation was present in 2 of 12 immunocompetent patients (17%) and in four of eight immunocompromised patients (50%) (Fig. 2). Ground-glass opacities were found as an associated finding with nodules in three patients. Consolidation was identified as the predominant CT finding in two patients

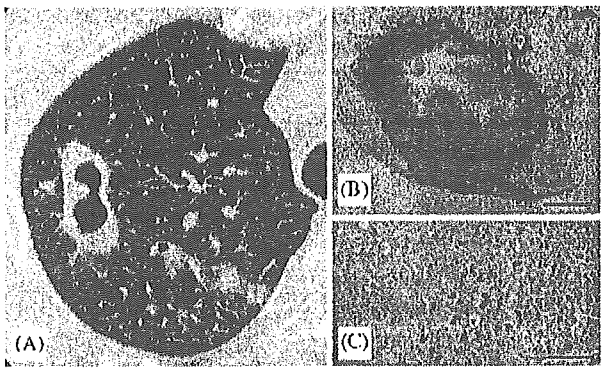

Figure 2 A diabetic patient with pulmonary cryptococcosis. (A) HRCT scan shows well demarcated mass with cavitation and small nodules mimicking tuberculosis. (B) Photomicrograph of the lower magnification reveals encapsulated epithelioid cell granuloma with central cavitation (hematoxylin–eosin stain). The bar indicates 5 mm. (C) Cryptococci are found in the necrotic tissue (Grocott stain). The bar indicates 100 μm.

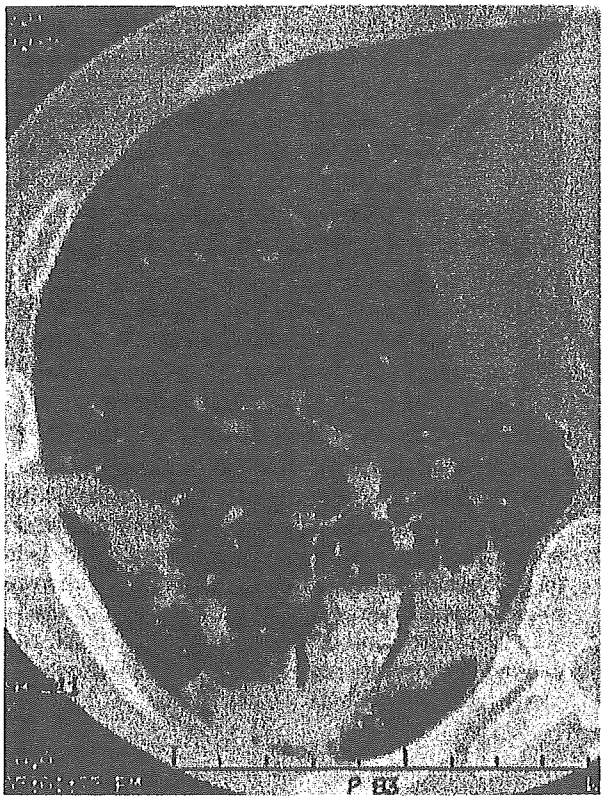

Figure 3 Chest CT scan of a symptomatic patient with pulmonary cryptococcosis who had no underlying disease. Note the patchy areas of air-space consolidation with air-bronchograms, and adjacent ground-glass opacities in the subpleural region in the right lower lobe.

(one immunocompetent and one immunocompromised) with ground-glass opacities (Fig. 3). Lower lobes were involved in 14 patients (64%) and upper lobes in four (18%). Diffuse nodular lesions were found in four patients (18%). Parenchymal lesions were located in the peripheral portion in 20 patients (91%), 14 of which had contact with the pleura.

The diagnosis of pulmonary cryptococcosis was made by direct tissue examination in 18 patients (surgery in 13, percutaneus needle biopsy in four, and transbronchial biopsy in one), and by culture of the organism from bronchial lavage fluid in two and a percutaneus needle biopsy specimen in one. An immunocompetent patient presented with cough was diagnosed as having pulmonary cryptococcosis based on a positive cryptococcal antigen titer and histologic findings of epithelioid cell granuloma formation (Fig. 3). Among 13 patients who underwent surgery, thoracoscopic excisional biopsy was performed in nine patients (41%).

Treatment included antifungal therapy alone in 11 patients, surgery alone in eight patients, surgery plus antifungal therapy in two and none in one. Of 11 patients (five immunocompetent and six immunocompromised) treated with an antifungal agent alone, itraconazole was prescribed in eight patients, fluconazole in two and amphotericin B syrup plus 5-flucytosine in one. The duration of treatment ranged from 1.8 to 27.5 months with a median of 5.1 months for five immunocompetent patients, and 6.0 to 24.3 months with a median of 9.3 months for six immunocompromised patients. Radiographic findings showed improvement in all patients. The follow-up period after antifungal therapy ranged from 2.4 to 172.5 months, with a median of 8.7 months. CT findings revealed deterioration in an immunocompetent patient who had multiple cavitary nodules 22 months after discontinuation of itraconazole. The patient was re-treated with itraconazole for 10 months and multiple nodules improved one more time.

Eight patients including seven immunocompetent ones underwent surgical resection because the diagnosis had not been confirmed preoperatively. Open lung surgery was performed in four patients and VATS in four. The procedure of surgery was wedge resection in seven and lobectomy in one. The follow-up period after surgery ranged 10.1 to 177.7 months, with a median of 42.4 months. No relapse was seen after surgery.

Two patients received both antifungal therapy and surgical resection. One individual underwent wedge resection after antifungal therapy, and no recurrence has been observed for 23.3 months. Another patient who had both diabetes mellitus and bronchial asthma was treated with amphotericin B plus 5-flucytocine for 2 months and surgery was performed. Subsequently, fluconazole was

administered for 10 months, but pulmonary cryptococcosis relapsed thereafter. Fluconazole was re-administered for 13 months, followed by itraconazole for 45 months. Antifungal therapy lasted long because the patient eventually developed pulmonary infiltration with eosinophilia and was treated with corticosteroid therapy. Fortunately, no relapse occurred for 5 years after antifungal therapy.

One patient was followed up without any therapy for 3 months because of spontaneous resolution of the radiographic findings.

Discussion

Clinical description regarding pulmonary cryptococcosis with non-AIDS individuals is rather limited because of the rarity of the disease itself. In general, men are involved more frequently than women.[2] Likewise, in the present study, the disease was overwhelmingly predominant in males. As has been reported in a recent study, about one-third of immunocompetent patients with pulmonary cryptococcosis were asymptomatic.[13] Most of our patients were also asymptomatic and incidentally detected on chest radiographs taken at mass screening or on the routine follow-up of other diseases. About 40% of the patients were immunosuppressed, and diabetes mellitus was the most common underlying disease.

Although the radiographic characteristics of pulmonary cryptococcosis have been well described, there are only a few studies evaluating the CT findings in non-AIDS individuals thus far.[7–9] Zinck et al.[7] demonstrated that the most common CT finding was solitary or multiple pulmonary nodules without cavitation in 10 (91%) of 11 cases. The margination of nodules was smooth in five cases. Similarly, our study demonstrated that pulmonary nodules were the most frequent HRCT findings of pulmonary cryptococcosis. However, irregular margin and spiculation were observed in 70% and 30% of the patients who had nodules, respectively. Cavitation inside the nodule has been reported to be a less common radiographic finding and limited to immunocompromised patients.[5,15] In the present study, cavitation was found in 30% of the patients with nodular lesions, especially in half of the immunocompromised patients. In this context, it may be quite difficult to distinguish a spiculated nodule from lung cancer and a cavitary nodule from tuberculosis. Lindell et al.[9] examined CT findings of pulmonary cryptococcosis in 10 immunocompetent patients recently and, as in our study, found that pulmonary nodules were the most common CT findings, although the majority of their patients had multiple nodules as oppose to those in our study. Similar to the findings about the size of multiple nodules in our study, the nodules were most commonly less than 10 mm in diameter. In contrast to our observations, the majority of nodules was well defined with smooth margins, and area of cavitation occurred less frequently in their study

Regarding the distribution of the lesions of pulmonary cryptococcosis, no particular lobar predilection of the disease has been noted,[2,5,7,8] although Hatcher et al.[4] demonstrated the predominance in the lower lobes. Likewise, in the present study, the lower lobes were affected more frequently than the upper lobes. In addition, the nodules were usually located in the subpleural regions, as described in the previous reports.[6,8]

The treatment of pulmonary cryptococcosis depends on the hosts' immune status and the anatomical sites of involvement. Practical guidelines for the management of cryptococcal disease by Saag et al.[10] recommended observation alone for immunocompetent hosts with isolated pulmonary cryptococcosis and antifungal therapy for those with symptomatic infection. Preferred treatment regimens are oral azol therapy (fluconazole or itraconazole) for 6–12 months. HIV-negative, immunocompromised patients with the non-CNS pulmonary and extrapulmonary disease are recommended to be treated with amphotericin B plus flucytosine for 6–10 weeks as patients with the CNS disease.

We hence treated immunocompetent as well as immunocompromised patients of proven pulmonary cryptococcosis with antifungal therapy if there was no radiographic resolution after a 1–2-month period of close observation. Radiographic findings revealed improvement in all patients treated with oral azole antifungal agents alone without side effects, even in the immunocompromised hosts.

For focal pulmonary cryptococcosis, surgical resection is a choice of treatment if preoperative diagnosis cannot be confirmed.[4,13] Recently, small peripheral nodules have frequently been detected by CT scans, and VATS is used to make precise diagnosis for such lesions.[16,17] To our knowledge, however, no studies have proved the efficacy of VATS in the diagnosis and treatment of pulmonary cryptococcosis. In the present study with the use of VATS, nine patients were diagnosed as having pulmonary cryptococcosis, and four patients underwent wedge resection under VATS. No relapse occurred. Because the lesions of pulmonary cryptococcosis are usually located in the subpleural area of the lung and are of a benign nature, wedge resection under VATS could be a reasonable and a possibly ideal option for non-AIDS patients with isolated pulmonary cryptococcosis.

In summary, the majority of non-AIDS patients with pulmonary cryptococcosis are males. They are commonly asymptomatic and are found to have incidental chest radiographic abnormalities. The most common HRCT findings are solitary or multiple nodules with or without cavitation in the subpleural areas of the lung. The nodules so often resemble lung cancer or tuberculosis, that histologic confirmation is required. In this regard, VATS is a useful tool for both diagnosis and treatment of isolated pulmonary cryptococcosis.

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