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Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan

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ABSTRACT

Objective: To clarify the clinical features of pulmonary cryptococcosis in Japanese non-HIV population.
Methods: Retrospective investigation of 151 pulmonary cryptococcosis cases between 1977 and 2012 was executed. The underlying disease (UDs), aggravating factors, radiological characteristics, and treatment were examined.
Results: Sixty-seven patients (44.4%) had no UDs. The common UDs were diabetes (32.1%) followed by hematologic disease (22.6%), and collagen disease (22.6%). Peripherally distributed pulmonary nodules/masses were most commonly seen. Lesions in the right middle lobe ($p = 0.01$) and air bronchogram ($P = 0.05$) were significantly more frequent, respectively, in patients with UDs than patients without them. Azoles were mainly selected for the patients without meningoencephalitis. Mean treatment duration for patients with and without UDs was 6.64 and 2.87 months, respectively. Patients whose pulmonary nodules improved after treatment continued to experience gradual reduction of cryptococcosis antigen titers, even if antigen titers were positive at the time of treatment cessation. The average time for antigen titers to become negative after treatment cessation was 13.1 and 10.7 months for patients with and without UDs, respectively. When groups were compared according to the presence of meningoencephalitis complications, deaths, and survivals, factors contributing to cryptococcosis prognosis included higher age, hypoproteinemia, hypoalbuminemia, steroid use, high C-reactive protein levels, and meningoencephalitis complications.
Conclusions: It is crucial to consider the presence of UDs and meningoencephalitis for the choice of antifungals and treatment duration for cryptococcosis in non-HIV patients. Three- and six months-administration of azoles for pulmonary cryptococcosis with or without UDs, respectively is reasonable.

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1. Introduction

Cryptococcus neoformans is a nonmycelial, budding encapsulated yeast-like fungus found in soil contaminated with pigeon and chicken excreta [1–4]. Inhalation of cryptococcal particles from contaminated soil into the lung is considered the usual route of human infection [2,3]. The organism may cause isolated pulmonary infection or hematogenous dissemination involving the central nervous system (CNS), bones, and skin, mostly depending on the host immunity [2,3]. Although cryptococcal infection can occur in individuals with normal immunity, it most commonly occurs in immunocompromised hosts. Predisposing factors are acquired immune deficiency syndrome (AIDS) and other causes of impaired T cell–mediated immunity, e.g., transplant-related immunosuppression, hematological malignancies, corticosteroid administration, and diabetes mellitus [4–6].

Although the clinical characteristics and natural history of cryptococcosis in HIV patients have been described elsewhere due to its large number, those in non-HIV patients have rarely been reported [7]. To date, few studies have reported comparative data regarding the clinical manifestations, laboratory findings, radiographic findings and survival of patients with pulmonary cryptococcosis in Japan [8]. Additionally, very few research comparing clinical manifestation of cryptococcosis between HIV and non-HIV patients [9–11].

In Japan, the number of HIV/AIDS patients is relatively lower compared to those of other countries. However, it is increasing recently and over 20,000 of the cumulative patients are registered in Japanese government database to date (http://www.nih.go.jp/niid/ja/aids-m/aids-iasrd/2274-kj3888.html). Hence, the study of clinical manifestation of cryptococcal diseases in non-HIV background possess high impact. We reviewed 151 cryptococcal cases among non-HIV background and investigated the clinical features, including clinical manifestations, underlying conditions, laboratory findings, radiological features, treatment, survival, and outcomes.

2. Materials and methods

2.1. Patients

A retrospective cohort study was conducted by reviewing the medical records of patients who had been diagnosed with pulmonary cryptococcosis at Nagasaki University Hospital and its affiliated hospitals during the 35-year period between 1977 and 2012. The patients were grouped into 2 populations based on positivity of underlying diseases. Definite case of pulmonary cryptococcosis requires isolation or detection of *Cryptococcus* by lung specimen culture and/or by histopathological examination, and only definite cases are recruited in this study. This retrospective study including analysis and release of clinical data was approved by the ethical committee of Nagasaki University Hospital.

2.2. Clinical data

All available patient records were reviewed from the time of cryptococcal diagnosis until the patients died or were lost to follow up.

The data included clinical manifestations, underlying conditions, laboratory findings (age, lymphocyte count, neutrophil count, immunoglobulin, serum protein, serum albumin, CD4/8 ratio, CD4 count, C-reactive protein [CRP], cryptococcal serum antigen titers) at the timing of diagnosis, radiological findings, treatment, survival, and outcome were recorded.

Eiken Latex® (Eiken Kagaku Co., Tokyo, Japan) was used for the qualitative and semi-quantitative detection of the *C. neoformans* capsular polysaccharide antigen in serum and CSF according to the manufacturer's instructions.

2.3. Interpretation of chest CT scans

The findings of chest CT scans were assessed for 1) the presence and distribution of parenchymal lesions, including nodules, masses, and consolidation; 2) the characteristics of nodules and masses; and 3) related thoracic abnormalities such as pleural effusion and lymphadenopathy according to previous reports [12]. Based on the predominant parenchymal findings from the CT scans, the morphological characteristics were classified as solitary nodule/mass (type I), multiple nodules/masses (type II), and consolidation (type III). In addition, type II was subdivided into distribution in a single lobe (type IIa) and distribution in multiple lobes (type IIb).

2.4. Statistical analysis

We used FREQ, NPAR1WAY, and ANOVA in SAS. The chi-square test was used to compare the frequency of categorical variables (e.g., underlying disease, steroid usage). Wilcoxon's test was used to compare age, lymphocyte count, neutrophil count, serum protein, serum albumin, CD4/8 ratio, CD4 count, CRP, and cryptococcal serum antigen titers. The Eiken Latex® latex agglutination test was used to detect cryptococcal polysaccharide. Antigen titers were transformed to the logarithm to the base 2 ($\mathrm{Log}_2[\mathrm{Ag}+1]$). Ag (cryptococcal antigen titer) is expressed as 0, 1, 2, 4, … as powers of 2 and Ag + 1 was expressed as $\mathrm{Log}_2(0+1)=0$.

For radiographic analysis, a chi-square test was employed to compare the presence and distribution of parenchymal lesions, nodule and mass characteristics except their number, and related thoracic abnormalities between the 2 groups. A Cochran–Armitage test was used to analyze the differences among 4 groups based on the number of nodules and masses, and among 4 morphological types based on the CT classification between the 2 patient populations. For all statistical tests, $p < 0.05$ indicated a significant difference.

3. Results

3.1. Patients

One hundred fifty-one patients were diagnosed with pulmonary cryptococcosis during the 35-year period between 1977 and 2012. Sixty-seven (44.4%) occurred in the patients without underlying diseases. Forty-two were men and 25 were women. Eighty-four cases (56.6%) were the patients with underlying disease. Thirty-eight were men and 46 were women.

3.2. Underlying diseases

Among 84 patients with underlying diseases, diabetes mellitus was most dominant (32.1%) followed by hematological diseases including human T-cell leukemia virus type-I carrier (22.6%), collagen disease including systemic lupus erythematosus, rheumatoid arthritis and others (22.6%), renal failure (16.7%), solid tumor (13.1%), chronic lung diseases including bronchiectasis, sequel pulmonary tuberculosis, and interstitial pneumonia (13.1%), liver disease including cirrhosis or hepatitis (9.5%), renal transplantation (2.4%), and other diseases (9.5%). Treatment with glucocorticoids (5–40 mg/day or pulse therapy) were recorded in 31 (37.0%) patients. Total of 5 patients were administrated glucocorticoids concomitantly with immunosuppressant such as cyclosporine and azathioprine.