Cryptococcal pleuritis with pleural effusion as the only clinical presentation in a patient with hepatic cirrhosis

A case report and literature review

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Abstract

**Rationale:** Cryptococcosis is a significant life-threatening fungal infection in worldwide, mainly reported in immunocompromised patients. Pleural effusion presentation of cryptococcal infection as the only clinical presentation is rarely seen in pulmonary cryptococcosis, which may lead to be misdiagnosed, and the study on this subject will provide further insights.

**Patient concerns:** A 64-year-old man was hospitalized in our department and diagnosed as hepatic B cirrhosis. A computed tomography (CT) of the thorax showed a massive right pleural effusion without pulmonary parenchymal abnormalities. He was started on empirical treatment for pleural tuberculosis (TB). However, during his hospitalization, a right pleural effusion developed and fever was not controlled.

**Diagnoses:** On day 14 admission, pleural fluid cultured positive for *Cryptococcus neoformans*. The *C neoformans* isolate belonged to ST5 and molecular type VNI (var. grubii).

**Interventions:** The patient was diagnosed with cryptococcal pleuritis, then amphotericin B and fluconazole were administrated.

**Outcomes:** Finally, the patient was improved and discharged from our hospital.

**Lessons:** Similar cases in cryptococcal pleuritis patients with pleural effusion as the only clinical presentation in the literature are also reviewed. Through literature review, we recommend that pleural effusion cryptococcal antigen test should be used to diagnose cryptococcal pleuritis to reduce misdiagnosis. The early administration of antifungal drug with activity to *Cryptococcus* seemed beneficial in preventing dissemination of cryptococcosis.

**Abbreviations:** CT = computed tomography, HIV = human immunodeficiency virus, HTLV-1 = human T-cell lymphotropic virus type 1, MIC = minimum inhibitory concentration, PCT = procalcitonin, TB = tuberculosis.

**Keywords:** cryptococcosis, *Cryptococcus neoformans*, hepatic cirrhosis, multilocus sequence typing (MLST), pleuritis

1. Introduction

Cryptococcosis is a significant invasive fungal infection including cryptococcal meningitis, cryptococcosis, pulmonary cryptococcosis, disseminated cryptococcosis and so on, primarily caused by *Cryptococcus neoformans* and *Cryptococcus gattii*.\textsuperscript{1,2} Cryptococcosis may occur in healthy hosts, the majority of infections occur in patients with impaired cellular immune function, such as immunodeficiency virus (HIV) infection, diabetes mellitus, hepatic cirrhosis, haematologic malignancies, solid organ and stem cell transplantation, corticosteroid therapy, and immunosuppressive medications.\textsuperscript{3–7} However, pleural presentation of cryptococcal infection is rarely seen, especially as the only clinical manifestation without other lesions.

In this study, we reported a case of *C neoformans* pleural effusion as the only clinical presentation in a patient who was diagnosed with hepatitis B cirrhosis, and relevant literatures were reviewed and analyzed. Recognizing the clinical features of these patients may improve diagnosis and promote timely treatment.

2. Case report

A 64-year-old male was admitted for repeated fatigue and fever for 3 months and 1-week duration of right-sided chest pain in 2014. The patient was a farmer who was originated from a rural
area in Zhejiang Province, China. He had past medical history of hepatitis B for about 20 years but did not receive any antivirus therapy. He did not keep any pets. He had a 7-years history of smoking and drinking but had given up these habits for 20 years. Physical examination revealed decreased breath sounds over the right lung base, and his temperature was 38°C to 39°C.

During admission, the liver ultrasound finding suggested chronic liver disease. For further examination, liver biopsy was performed and the result showed a trend of chronic moderate hepatitis B with cirrhosis (G3S4), HBS(+), and HBC(+).

On admission, the patient’s blood cultures were negative. HIV test was negative and the CD4+ count was normal. The full blood count showed a normal white blood cell (WBC) count of 4.2 × 10^9/L with neutropenia (2.4 × 10^9/L) and lymphocytosis (1.4 × 10^9/L). He had a moderately increased C-reactive protein (CRP) level of 30 (normal, <8) mg/L and a normal procalcitonin (PCT) level of 0.29 ng/mL (Table 1). A computed tomography (CT) of the thorax showed a moderate right pleural effusion. Biapenem, a kind of carbapenems, was empirically administrated for anti-infection. But the patient felt breathless and remained fever.

On day 7 admission, a CT of the thorax was repeated and it showed a worsening right pleural effusion without apparent pulmonary parenchymal abnormalities (Fig. 1). A right thoracentesis was carried out, and pleural fluid studies revealed a lymphocytic exudative pleural effusion and raised protein level (Table 1). Pleural fluid acid-fast stain was negative for acid-fast bacilli, and no tumor cell was detected in pleural fluid. While the result of T-SPOT tuberculosis (TB) blood test was positive. He was started on empirical treatment for pleural TB with rifampicin 450 mg, isoniazid 300 mg, ethambutol 750 mg, and pyrazinamide 1500mg daily. However, the temperature of the patient was still 45°C and he remained breathlessness. He underwent repeat pleural drainage, and pleural fluid studies showed a lymphocytic effusion (Table 1).

On day 14 admission, the culture of the pleural fluid was performed and his cerebrospinal fluid (CSF) studies did not reveal any evidence of cryptococcal meningitis. As cryptococcal infections tend to occur in those immunocompromised, this patient was hepatic cirrhosis. So he was started on intravenous amphotericin B 40 mg daily and intravenous fluconazole 400 mg daily. Because the patient had liver disease, flucytosine was not used for its side effect of liver dysfunction.

On day 23 admission, the patient was improved and discharged from our hospital. The he admitted in the local hospital for continue treatment of cryptococcal infection. Culture for Mycobacterium tuberculosis in the pleural effusion was negative. Since then, the patient has remained well.

The Cryptococcal isolate from this patient was stored for further research. It was identified as C. neoformans by internal transcribed spacer (ITS) sequencing and by 2 matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) systems. The isolate was susceptible to all of the 5 antifungal agents (amphotericin B minimum inhibitory concentration [MIC] 0.5 mg/L, fluconazole MIC 1 mg/L, fluconazole MIC 4 mg/L, itraconazole MIC 0.125 mg/L, and voriconazole MIC 0.06 mg/L). Multilocus sequence typing (MLST) was used to verify species variaty and to designate molecular types. It revealed that the C. neoformans isolate belonged to ST5 and molecular type VNI (var. grubii).

We obtained an exempt status from the Institutional Review Board of the First Affiliated Hospital, College of Medicine, Zhejiang University to use these data.

3. Discussion

C. neoformans infection usually presents as meningitis and is increasingly being recognized in immunocompromised patients. While, pleural diseases due to fungi are rare,[8] and more than half of the patients have moderate to severe underlying diseases such as HIV infection, leukemia and lymphoma, as previously reported.[9-11] Our patient was a 64-year-old man with hepatic B cirrhosis. The incidence of hepatic B cirrhosis has been high in

| Table 1 |
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| Results of blood tests and pleural effusion. |
| Blood tests | Normal reference range | PCT, ng/mL | ESR, mm/h |
| CRP, mg/L | 30 | 0–8 | 32 | 0–20 |
| WBC, 10⁹/L | 4.2 | 4.0–10.0 | Blood culture: bacteria negative |
| Neutrophil percentage, % | 56.6 | 50.0–70.0 | HBV DNA, IU/mL 1.56 × 10⁵ |
| Lymphocyte percentage, % | 32.2 | 20.0–40.0 | Tspot positive |
| Eosinophil, 10⁹/L | 1.70 | 0.02–0.50 |
| Hb, g/L | 119 | 131–172 |
| Platelet count, 10⁹/L | 149 | 83–303 |
| BUN, mmol/L | 6.0 | 2.9–8.2 |
| Creatinine, μmol/L | 92 | 59–104 |
| Albumin, g/dL | 26.8 | 35.0–55.0 |
| ALT, U/L | 15 | 5–35 |
| AST, U/L | 22 | 8–40 |
| TB, μmol/L | 26 | 0–21 |
| Sodium, mmol/L | 138 | 136–145 |
| Potassium, mmol/L | 4.12 | 3.50–5.20 |
| INR | 1.21 | 0.85–1.15 |
| PT, s | 14.0 | 10.0–13.5 |
| Fibrinogen level, g/L | 2.9 | 2.0–4.0 |
| D-dimer, μg/L | 1679 | 0–700 |

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Hb = haemoglobin concentration, INR = international normalized ratio, PCT = procalcitonin, PT = prothrombin time, RBC = red blood cell, TB = total bilirubin, WBC = white blood cell.
China. However, cryptococcal pleuritis still remains uncommon. Hence, misdiagnosis and delay of therapy will lead to the cryptococcal dissemination and increase of mortality.

Cryptococcal pleuritis with pleural effusion as the only clinical presentation is rarely reported. We performed a literature search using the terms “cryptococcal pleural infection”, “cryptococcal pleuritis”, “empyema caused by cryptococcus”, “Pleural cryptococcosis”, and “cryptococcal empyema” on PubMed. Papers in English were included. Cryptococcal pleuritis cases with pleural effusion as the only clinical presentation were included. Several relevant reports in Spanish, French or Japanese were not included. Disseminated cryptococcosis cases with cryptococcal pleuritis were excluded. Cryptococcal pleuritis cases with apparent pulmonary parenchymal abnormalities were also excluded. Only reports on cryptococcal pleuritis with pleural effusion as the only clinical presentation including the main clinical and biological data and the survival status were taken into account. In total 11 studies (11 cases) met the inclusion criteria (Table 2). Most of the studies (7/11) were from Asia including Japan (5 cases), Singapore (1 case), and India (1 case), while no relevant report in English from China. All of the 11 patients were immunocompromised, with underlying diseases including HIV, human T-cell lymphotropic virus type 1 (HTLV-1) carriers, renal failure, transplantation, acute myeloid leukemia (AML), lymphoma, and rheumatoid arthritis (RA) with corticosteroids usage. Impaired cell-mediated immunity associated with HIV infection, blood disease, cancer and corticosteroid treatment are risk factors for cryptococcosis including cryptococcal pleuritis. Our patient had the underlying disease of hepatic B cirrhosis. Patients with hepatic cirrhosis were also immunocompromised, and decompensated liver cirrhosis was confirmed as 1 of the risk factors of invasive C. neoformans diseases.

Among patients with hepatic cirrhosis, cryptococcal meningitis was frequently reported, while several cases of cryptococcal peritonitis were reported, and cases of cryptococcal pleuritis were rarely reported especially as the only manifestation.

![Computed tomography of the chest.](image)

### Table 2

Reported cases of cryptococcal pleuritis with pleural effusion as the only clinical presentation.

| Reference          | Age (y) | Gender | Country       | Underlying disease | Percentage of lymphocyte (%) | ADA (IU/L) | Culture for cryptococcus | Cryptococcal antigen test | Serum Cryptococcal antigen test | Anti-fungal agents | Outcome |
|--------------------|---------|--------|---------------|--------------------|-----------------------------|------------|--------------------------|--------------------------|--------------------------|---------------------|---------|
| Taguchi H et al     | 70/F    | Japan  | HTLV-1        | Lymphocyte predominant | ND                       | C. neoformans | + | – | 5-FC, ITC | Survived |
| Fukuchi M et al     | 52/M    | Japan  | HIV, chronic renal failure | Lymphocyte predominant | 29 | C. neoformans | + | – | AMPH, 5-FC, FCZ | Survived |
| Ramanathan Y et al | 49/M    | USA    | Renal-pancreas transplantation, immunosuppressive agent | ND | ND | – | ND | + | 5-FC, FCZ | Survived |
| Yoshino Y et al     | 51/M    | Japan  | HIV           | ND                 | 86 | C. neoformans | ND | + | AMPH, FCZ | Survived |
| Kusmartoko EB et al | 28/M    | USA    | HIV           | ND                 | 37 | C. neoformans | + | + | AMPH, FCZ | Died |
| Wee ACR et al       | 38/M    | Singapore | AML           | 81                  | ND | C. neoformans | + | + | AMPH, 5-FC, FCZ | Survived |
| Kinjo K et al       | 64/M    | Japan  | HIV, chronic renal failure, hemodialysis | 94 | 33.2 | C. neoformans | – | – | AMPH, 5-FC, FCZ | Survived |
| Swan CD et al       | 79/M    | Australia | Lymphoma, chemotherapy | normal | ND | C. neoformans | + | + | AMPH, FCZ | Survived |
| Cartwright EM et al | 51/M    | USA    | HIV           | Lymphocyte predominant | ND | C. neoformans | + | + | FCZ | Survived |
| Shanker EM et al    | 35/F    | India  | HIV, diabetes | ND                 | ND | C. laurenti | ND | ND | FCZ | Survived |

5-FC = flucytosine, ADA = adenosine deaminase, AML = acute myeloid leukemia, AMPH = amphotericin B, F = female, FCZ = fluconazole, HIV = human immunodeficiency virus, HTLV-1 = human T-cell lymphotropic virus type 1, ITD = itraconazole, M = male, ND = not described, RA = rheumatoid arthritis, VRC = voriconazole.

* Died from aspiration pneumonia 5 months after the transfer.
Cryptococcal pleuritis with pleural effusion as the only clinical presentation had better prognosis than cryptococcal meningitis or disseminated cryptococcosis. After antifungal treatment, 10 of the 11 patients with cryptococcal pleuritis were survived, and the only 1 patient was died from aspiration pneumonia 5 months after discharge.

All of the 11 cryptococcal pleuritis cases without apparent pulmonary parenchymal abnormalities showed a right or left side of pleural effusion. Pleural effusion cultures for cryptococcus were positive in 10 of 11 patients including 9 patients infected with *C. neoformans* and 1 patient with *Cryptococcus laurentii*. Pleural fluid examination results showed lymphocyte predominance in 6 cases, which was similar with our patient. Adenosine deaminase (ADA) was high in pleural fluid in previous reports of cryptococcal pleuritis, which was also similar with the pleural fluid characteristic of tuberculous pleuritis. Hence, only according to the pleural fluid characteristic, cryptococcus and tuberculous pleuritis were difficult to be distinguished. Even rarely, cryptococcal pleuritis could be coincident with pulmonary tuberculosis.

The sensitivity of cryptococcal antigen testing in disseminated disease was confirmed higher than that of blood culture, so serum and cerebrospinal fluid antigen tests were recommended to diagnose disseminated or cryptococcal meningitis by the European Conference on Infections in Leukemia. In contrast, among non-HIV infected patients with pulmonary cryptococcosis, the sensitivity of serum cryptococcal antigen tests was only 56%. The sensitivity of serum cryptococcal antigen tests in the patients with only cryptococcal pleuritis was unclear. Although cryptococcal antigen test was not examined in our patient, serum or pleural effusion cryptococcal antigen test was examined in reviewed previous reports. In the 11 patients, 3 patients were serum cryptococcal antigen test negative, but pleural effusion cryptococcal antigen test was done in 2 of the 3 patients showing positive. These findings suggest that pleural effusion cryptococcal antigen test had higher sensitivity than serum cryptococcal antigen test in cryptococcal pleuritis patients with pleural effusion as the only clinical presentation. Since pleural effusions cultures have low sensitivity for both cryptococcus and tuberculous pleuritis, pleural effusion cryptococcal antigen test should be recommended to be used in clinic for diagnosing cryptococcal pleuritis.

4. Conclusions
In conclusion, pleural presentation of cryptococcal infection as the only clinical presentation is rare, which may lead to be misdiagnosed, while delay in diagnosis may lead to treatment failure. Through study on clinical characteristics of our cryptococcal pleuritis case and previous relevant reports, it will helpful to be familiar with cryptococcal pleuritis and pleural effusion cryptococcal antigen test should be recommended to diagnose cryptococcal pleuritis. Reduction of misdiagnosis and the early administration of antifungal drug with activity to *Cryptococcus* seemed beneficial in preventing dissemination of cryptococcosis.

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