Asymptomatic Meningitis and Lung Cavity in a Case of Cryptococcosis

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Patient: Male, 52
Final Diagnosis: Cryptococcosis
Symptoms: Forehead skin lesions and fever
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Cryptococcus neoformans (C. neoformans) infection is one of the most common opportunistic infections in AIDS patients. C. neoformans usually infects the central nervous system (CNS) and/or lungs with typical clinical manifestation.

Case Report: Here, we report the case of a 52-year-old HIV-1-infected man with disseminated cryptococcosis, including subacute meningitis, pulmonary, and cutaneous cryptococcosis, but only skin lesion served as the chief complaint. Moreover, the results of cerebrospinal fluid (CSF) tests and lung computed tomography (CT) scan were atypical.

Conclusions: We present the clinical characteristics of this case and discuss the diagnostic procedure, which will likely help clinicians in making a timely definitive diagnosis of this disease.

MeSH Keywords: Case Reports • Cryptococcosis • Cryptococcus neoformans

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Background

Cryptococcus neoformans (C. neoformans) infection, termed cryptococcosis, is one of the most common opportunistic infections in people infected with human immunodeficiency virus (HIV) with very low CD4 T lymphocyte counts. C. neoformans usually infects the central nervous system (CNS) and/or lungs [1,2]. Here, we report a case of disseminated cryptococcosis, including subacute meningitis, atypical pulmonary infection, and cutaneous cryptococcosis, but only skin lesion served as the chief complaint.

Case Report

A 52-year-old man complained of a 1-month history of a skin lesion on the forehead and a 1-week history of fever. One month ago, he initially found a fluid-filled blister about 5 cm×1.5 cm in diameter on his forehead skin (Figure 1A). One week later, the blister began to self-rupture and formed a skin ulcer with a cover of white pus moss. Another week later, the patient began to complain of an irregular fever with an axillary highest temperature of approximately 38.5°C, and the fever persisted 1 week. The patient complained of mild malaise, but had not chest tightness, dry cough, or exertional dyspnea. During the development of this case, he did not complain of neuropsychiatric symptoms or signs such as dizziness, headache, neck stiffness, photophobia, lethargy, altered mentation, personality changes, or memory loss. His past medical history included a 7-year history of hypertensive disease and a 5-year history of diabetes mellitus. Further, he had a 32-year history of sexual contact with men. On admission, except for the forehead skin ulcer, a physical examination did not reveal rales in his lungs or any positive sign in his CNS. Laboratory tests revealed that the patient was positive for serum anti-neoformans antigen and anti-HIV antibody with enzyme-linked immunosorbent assay (ELISA). Further Western blot analysis test confirmed his HIV infection. CD4 cell counts were 22 cells/μL. The results of laboratory tests taken on admission are shown in Table 1. Local skin biopsy was performed and the histology revealed Cryptococcus neoformans yeasts with clear mucoid capsule amid the background spindle cell proliferation. This finding was consistent with a diagnosis of confirmed skin cryptococcal infection. Because cryptococcosis

Figure 1. Morphological presentation of this case. (A) Cryptococcosis skin lesion. (B) Pathological morphology of the cutaneous biopsy. Cryptococcus neoformans yeasts with clear mucoid capsule are present amid the background spindle cell proliferation. (C) Cerebrospinal fluid light India ink staining. (D) Normal bronchial mucosa. (E) Cryptococcosis skin lesion after 20 days of anti-C. neoformans treatment. (F) Cryptococcosis skin lesion after 40 days of anti-C. neoformans treatment.
### Table 1. Laboratory test results on admission.

| Serum/plasma sample | Test value | Normal range | CSF/BALF sample | Test value | Normal range |
|---------------------|------------|--------------|-----------------|------------|--------------|
| White blood cell counts (10^9/L) | 5.51 | 3.5–9.5 | CSF pressure (mmHgO) | 85 | 80–180 |
| Neutrophils percentage (%) | 77.5 | 40–75 | CSF color and clarity | Clear/colorless | Clear/colorless |
| Lymphocyte percentage (%) | 11.3 | 20–50 | CSF total cell count (10^9/L) | 0.004 | <0.01 |
| Hemoglobin (g/L) | 110.0 | 120–140 | Mononuclear Cell count (10^9/L) | 0.001 | <0.01 |
| Platelets (10^9/L) | 247 | 125–350 | Multinuclear Cell count (10^9/L) | 0.003 | 0 |
| Blood urea nitrogen (mmol/L) | 3.05 | 2.29–7.0 | CSF protein (g/L) | 0.5 | 0.15–0.4 |
| Creatinine (μmol/L) | 78.6 | 53–106 | CSF glucose (mmol/L) | 4.18 | 2.8–4.5 |
| Albumin (g/L) | 36.6 | 40–55 | CSF Chloride (mmol/L) | 119.5 | 110–125 |
| Glutamic-oxalacetic transaminase (U/L) | 24.7 | 15–40 | CSF gram stain | Negative | Negative |
| Total bilirubin (μmol/L) | 11.2 | 5–20 | CSF acid fast stain | Negative | Negative |
| Direct bilirubin (μmol/L) | 3.2 | 1.7–10 | CSF light India ink stain | Positive | Negative |
| Lactate dehydrogenase (U/L) | 554.1 | 135–225 | Positive | Negative |
| C-reactive protein (mg/L) | 74.1 | 0–3 | Negative | Negative |
| High-sensitivity C-reactive protein (mg/L) | 96.0 | <15 | Negative | Negative |
| Procalcitonin (ng/ml) | 1.2 | <1.0 | Negative | Negative |
| Anti-human immunodeficiency virus antibody | Positive | Negative | Negative | Negative |
| Plasma (1,3) beta-D-glucan (pg/mL) | 10.0 | <60 | Negative | Negative |
| Galactomannan | Negative | Negative | CSF anti-EBV-VCA Ig M antibody | Negative | Negative |
| Anti-cryptococcal antigen | Positive | Negative | CSF anti-HIVB19 Ig M antibody | Negative | Negative |
| Anti-EBV-EA Ig M antibody | Negative | Negative | CSF Syphilis PCR fluorescence | Negative | Negative |
| Anti-EBV-VCA Ig M antibody | Negative | Negative | CSF EBV DNA (copies/ml) | <500 | <500 |
| Anti-Cryptomegalovirus Ig M antibody | Negative | Negative | CSF Syphilis rapid plasma reagin | Negative | Negative |
| Anti-HPVB19 Ig M antibody | Negative | Negative | CSF T. pallidum particle agglutination assay | Negative | Negative |
| Syphilis rapid plasma reagin | 1: 16 | Negative | Negative | Negative |
| T. pallidum particle agglutination assay | Positive | Negative | BALF gram stain | Negative | Negative |
| Anti-Mycoplasma immunoglobulin M antibody | Negative | Negative | BALF anaerobic bacteria culture | Negative | Negative |
| Anti-Chlamydia immunoglobulin M antibody | Negative | Negative | BALF aerobic bacteria culture | Negative | Negative |
| Anaerobic bacteria culture | Negative | Negative | BALF fungus culture | C. neoformans | Negative |
| Aerobic bacteria culture | Negative | Negative | BALF M. tuberculosis PCR fluorescence | Negative | Negative |
| Fungi culture | Negative | Negative | BALF Pneumocystis | Negative | Negative |

CSF – cerebrospinal fluid; BALF – bronchoalveolar lavage fluid; EBV – Epstein-Barr virus; EA – early antigen; VCA – viral capsid antigen; HPV-B19 – human parvovirus B19; IgM – immunoglobulin M; T. pallidum – Treponema pallidum; M. tuberculosis – Mycobacterium tuberculosis.
commonly presents as a subacute meningitis or meningoencephalitis, patients conventionally undergo lumbar puncture to collect cerebrospinal fluid (CSF) for testing, even if there are no neurological manifestations. Although the CSF pressure and cell count were normal, the positive anti-cryptococcal antigen and light India ink staining in CSF confirmed *C. neoformans* infection in the CNS (Figure 1C), but brain magnetic resonance imaging (MRI) did not reveal any local foci in the cerebral parenchyma. Furthermore, a thoracic CT scan presented with bilateral ground glass opacities (GGO) and focal consolidation, with 1 thin-walled cavity located in each lung (severe in the right lung) (Figure 2A, 2E, 2I, 2M). Therefore, the patient was suspected to have *Pneumocystis* pneumonia (PCP) and bronchoalveolar lavage (BAL) was performed (Figure 1D). *C. neoformans* growth was found in BAL fluid fungi culture, but BALF *Pneumocystis* immunofluorescent staining was negative (Table 1).

The patient first received 3 weeks of induction therapy for disseminated cryptococcosis, including amphotericin B formulation at a dose of 0.7 mg/kg daily and fluconazole 800 mg daily. Simultaneously, he received 21 days of trimethoprim-sulfamethoxazole (2800 mg/960 mg per day) anti-*Pneumocystis* therapy because negative BALF *Pneumocystis* immunofluorescent stain did not completely exclude PCP. Then, the

**Figure 2.** Thoracic CT scans of this case. Column denotes different parts of the lungs (lung window and mediastinal window) and row denotes different scan time. From I to L, the scan interval was about 15 days.
patient received 8 weeks of consolidation therapy with fluconazole 800 mg daily and 12 months of long-term maintenance therapy with fluconazole 800 mg daily. Two weeks after the end of induction therapy, the patient began to receive combined antiretroviral therapy, including tenofovir, lamivudine, and efavirenz. After 2 weeks of treatment, the patient presented the skin lesion and pulmonary GGO improvement (Figures 1A, 1E, 1F, 2A–2P), and a negative CSF culture after repeat lumbar puncture, but the 2 pulmonary cavities seemed not to change (Figure 2A–2P).

Discussion

Although any organ of the body can be involved, *C. neoformans* most commonly infects the CNS and presents as meningitis or meningoencephalitis in HIV-infected patients [3,4]. The incidence of cryptococcal meningitis ranges from 0.04% to 12% per year among HIV-infected persons, and Sub-Saharan Africa has the highest yearly burden, with two-thirds of patients dead within 3 months after infection [5]. Fever, malaise, and headache are most common symptoms of *C. neoformans* meningitis and meningoencephalitis [6]. Only one-third of patients experience meningeval symptoms and signs, and encephalopathic symptoms usually result from increased intracranial pressure [7,8]. In this case, although cryptococcal meningitis was confirmed with positive anti-cryptococcal antigen and light India ink staining in CSF, the patient did not present any neurological symptoms or signs.

Inhalation of desiccated yeast or infectious spores is the main route of *C. neoformans* infection in humans [9]; therefore, the lungs are also susceptible to *C. neoformans* infection, which can be asymptomatic, or manifest cough and dyspnea, and even acute respiratory distress syndrome [10]. Isolated pulmonary infection is relatively common and its typical chest radiograph is lobar consolidation and occasional nodular infiltration [11]. Interestingly, this case presented bilateral GGO and thin-walled cavities without significant respiratory symptoms, even with the confirmation of pulmonary *C. neoformans* infection.

Primary cutaneous cryptococcosis can occur in both immunocompetent [11] and immunocompromised people [12,13]. Only 10–15% of disseminated cryptococcal infection cases have cutaneous manifestations, and males seem to be more susceptible to cutaneous cryptococcosis [11]. Cryptococosis skin lesions may show myriad different manifestations, including pustules, papules, nodules, or ulcers [14]. Cutaneous cryptococcosis is often misdiagnosed as carcinoma and other skin diseases due to its non-specific symptoms and signs [15–17]. Therefore, etiology or pathology detection is required for the definitive diagnosis of cutaneous cryptococcosis.

Conclusions

The clinical characteristics and the diagnostic procedure we discussed in this case will likely help clinicians in making a timely definitive diagnosis of this disease.

Conflict of interest

None.

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