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Asymptomatic Meningitis and Lung Cavity in a Case of Cryptococcosis

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Data Collection B
Statistical Analysis C
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Manuscript Preparation E
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Conflict of interest: None declared

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

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/905905

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, admixed with aggregates of foamy histocytes (Figure 1B). This finding was consistent with a diagnosis of confirmed skin cryptococcal infection. Because cryptococcosis

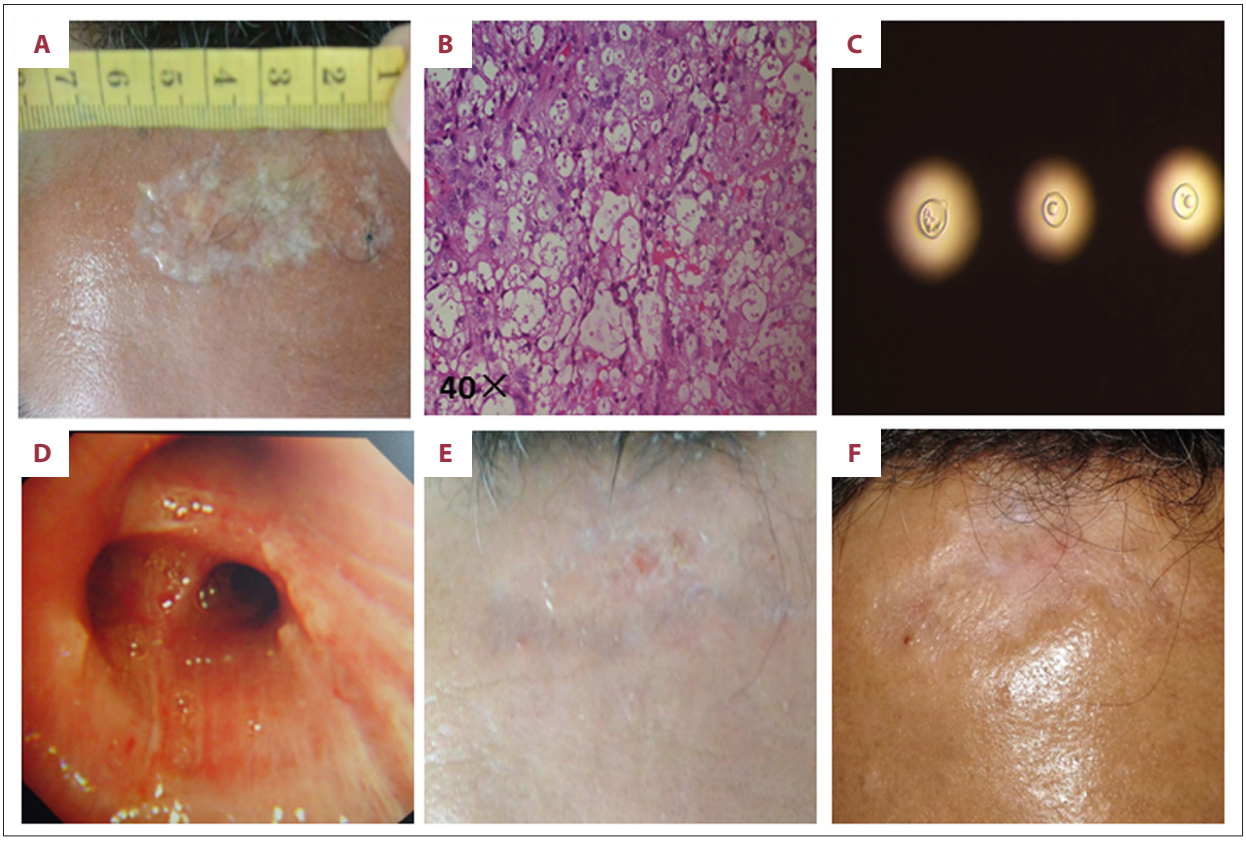

Figure 1. Morphological presentation of this case. (**A**) Cryptococcosis skin lesion. (**B**) Pathological morphology of the cutaneous biopsy. *Cryptococcus neoformans* yeasts with clear mucoid capsule are present amid the background spindle cell proliferation. (**C**) Cerebrospinal fluid light India 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 (mmH_2O)	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 (109/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
Alanine transarninase (U/L)	22.0	9–50	CSF Chloride (mmol/L)	119.5	110–125
Glutamic-oxal acetic 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
Albumin (g/L)	36.6	40–55	CSF anti-cryptococcal antigen	Positive	Negative
Lactate dehydrogenase (U/L)	554.1	135–225	CSF anaerobic bacteria culture	Negative	Negative
CD4 cell counts (cells/μL)	22.0	600–800	CSF aerobic bacteria culture	Negative	Negative
Erythrocyte sedimentation rate (mm/hr)	96.0	<15	CSF fungi culture	*C. neoformans*	Negative
High-sensitivity C-reactive protein (mg/L)	74.1	0–3	CSF *M. tuberculosis* PCR fluorescence	Negative	Negative
Procalcitonin (ng/ml)	1.2	<1.0	CSF anti-Toxoplasma Ig M antibody	Negative	Negative
Anti-human immunodeficiency virus antibody	Positive	Negative	CSF anti-Cytomegalovirus Ig M antibody	Negative	Negative
Plasma (1,3) beta-D-glucan (pg/mL)	10.0	<60	CSF anti-EBV-EA Ig M antibody	Negative	Negative
Galactomannan	Negative	Negative	CSF anti-EBV-VCA Ig M antibody	Negative	Negative
Anti-cryptococcal antigen	Positive	Negative	CSF anti-HPVB19 Ig M antibody	Negative	Negative
Anti-EBV-EA Ig M antibody	Negative	Negative	CSF Cytomegalovirus DNA (copies/ml)	<500	<500
Anti-EBV-VCA Ig M antibody	Negative	Negative	CSF EBV DNA (copies/ml)	<500	<500
Anti-Cytomegalovirus 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	BALF gram stain	Negative	Negative
T. pallidum particle agglutination assay	Positive	Negative	BALF anaerobic bacteria culture	Negative	Negative
Anti-Mycoplasma immunoglobulin M antibody	Negative	Negative	BALF aerobic bacteria culture	Negative	Negative
Anti-Chlamydia immunoglobulin M antibody	Negative	Negative	BALF fungi culture	*C. neoformans*	Negative
Anaerobic bacteria culture	Negative	Negative	BALF acid fast stain	Negative	Negative
Aerobic bacteria culture	Negative	Negative	BALF *M. tuberculosis* PCR fluorescence	Negative	Negative
Fungi culture	Negative	Negative	BALF Pneumocystis immunofluorescent stain	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*.

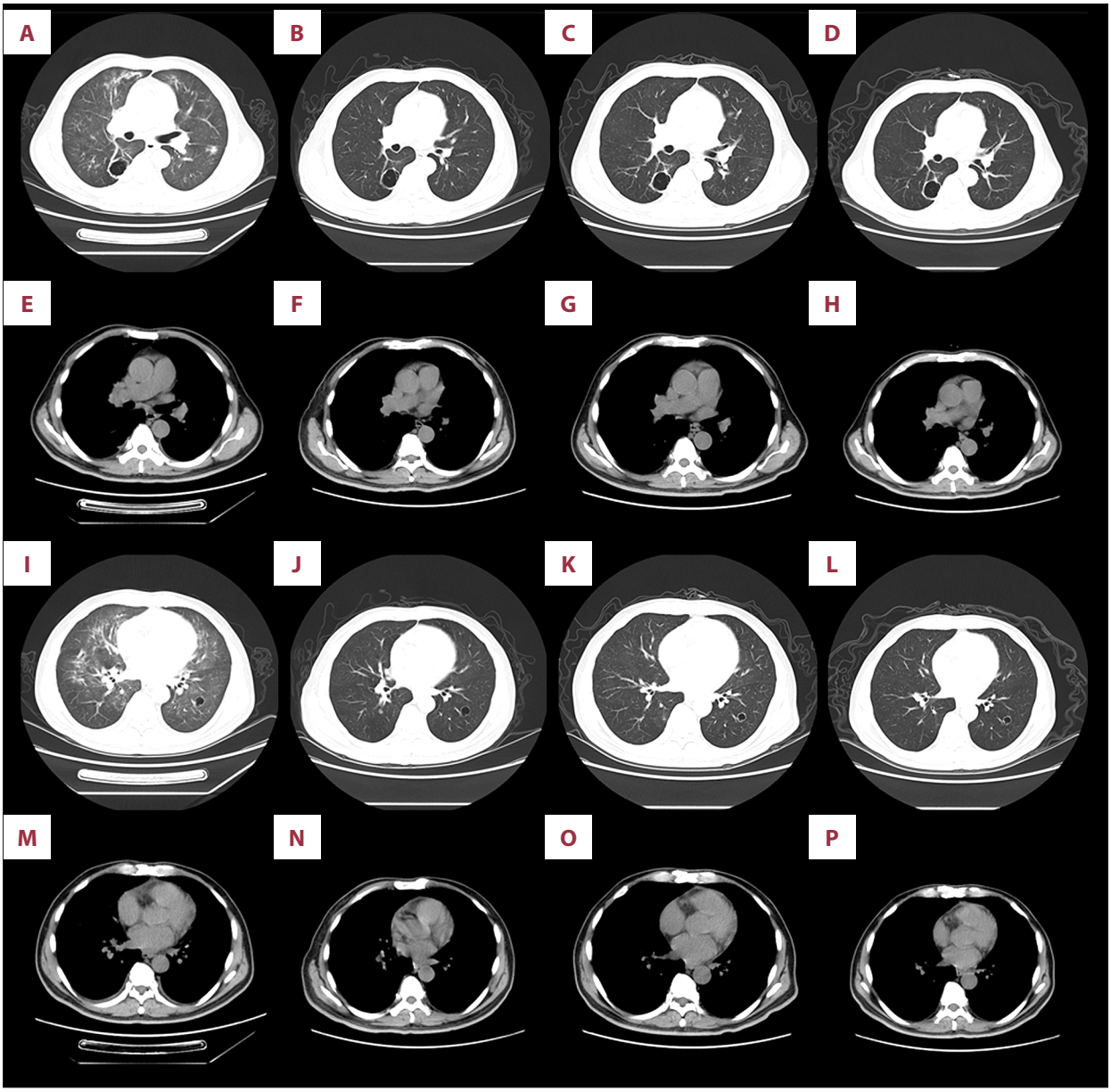

Figure 2. Thoracic CT scans of this case. Column denotes different parts of the lungs (lung window and mediastinal window) and row denotes different scan time. From I to L, the scan interval was about 15 days.

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

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 meningeal 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]. Cryptococcosis 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.

References:

1. Sabiiti W, Robertson E, Beale MA et al: Efficient phagocytosis and laccase activity affect the outcome of HIV-associated cryptococcosis. J Clin Invest, 2014; 124: 2000–8
2. Foong KS, Lee A, Vasquez G: Cryptococcal infection of the ventriculoperitoneal shunt in an immunocompetent patient. Am J Case Rep, 2016; 17: 31–34
3. Tintelnot K, de Hoog GS, Haase G: [Fungal infections of the central nervous system in the immunocompetent host]. Pathologe, 2013; 34: 534–39 [in German]
4. Mihret W, Zenebe G, Bekele A et al: Chronic meningitis in immunocompromised adult Ethiopians visiting Tikur Anbessa Teaching Hospital and Ye'huleshet Clinic from 2003–2004. Ethiop Med J, 2014; Suppl 1: 43–48
5. Park BJ, Wannemuehler KA, Marston BJ et al: Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS, 2009; 23: 525–30
6. Franco-Paredes C, Womack T, Bohlmeyer T et al: Management of Cryptococcus gattii meningoencephalitis. Lancet Infect Dis, 2015; 15: 348–55
7. Masur H, Brooks JT, Benson CA et al: Prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Updated Guidelines from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis, 2014; 58: 1308–11
8. de Vedia L, Arechavala A, Calderon MI et al: Relevance of intracranial hypertension control in the management of Cryptococcus neoformans meningitis related to AIDS. Infection, 2013; 41: 1073–77
9. McQuiston TJ, Williamson PR: Paradoxical roles of alveolar macrophages in the host response to Cryptococcus neoformans. J Infect Chemother, 2012; 18: 1–9
10. Huang L, Crothers K: HIV-associated opportunistic pneumonias. Respirology, 2009; 14: 474–85
11. Du L, Yang Y, Gu J et al: Systemic review of published reports on primary cutaneous cryptococcosis in immunocompetent patients. Mycopathologia, 2015; 180: 19–25
12. Liu Y, Qunpeng H, Shutian X, Honglang X: Fatal primary cutaneous cryptococcosis: Case report and review of published literature. Ir J Med Sci, 2016; 185(4): 959–63
13. Valente ES, Lazzarin MC, Koech BL et al: Disseminated Cryptococcosis presenting as cutaneous cellulitis in an adolescent with systemic lupus erythematosus. Infect Dis Rep, 2015; 7: 5743
14. Srivastava GN, Tilak R, Yadav J, Bansal M: Cutaneous Cryptococcus: Marker for disseminated infection. BMJ Case Rep, 2015; 2015: pii: bcr2015210898
15. Pena ZG, Byers HR, Lehmer LM et al: Mixed Pneumocystis and Cryptococcus cutaneous infection histologically mimicking xanthoma. Am J Dermatopathol, 2013; 35: e6–10
16. Atarguine H, Hocar O, Abbad F et al: [Cutaneous cryptococcosis mimicking basal cell carcinoma and revealing systemic involvement in acquired immunodeficiency]. J Mycol Med, 2015; 25: 163–68
17. Kikuchi N, Hiraiwa T, Ishikawa M et al: Cutaneous Cryptococcosis mimicking pyoderma gangrenosum: A report of four cases. Acta Derm Venereol, 2016; 96(1): 116–17