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LETTER TO THE EDITOR

Disseminated Pulmonary Cryptococcosis Complicated with Cryptococcemia in an AIDS Patient

Cryptococcosis is a potentially fatal fungal disease. Its risk factors include lymphomas, sarcoidosis, liver cirrhosis, long-term corticosteroid therapy, and AIDS. The prevalence of cryptococcosis has been increasing over the past 20 years due to increases in the incidence of human immunodeficiency virus (HIV) infections and the use of immunosuppressive drugs. The most common opportunistic infection of lungs in AIDS patients is *Pneumocystis jiroveci* pneumonia (PJP). Here, we report a newly diagnosed AIDS patient who suffered from disseminated pulmonary cryptococcosis complicated with cryptococcemia as initial pulmonary opportunistic infections.

A 21-year-old male homosexual patient presented himself to our clinic with intermittent fever, dry cough, body weight loss, and general malaise for 1 month. On admission, his vital signs were as follows: body temperature 39.2°C, pulse rate 137 beats/minute, and respiratory rate 20 breaths/minute. The findings of physical examination showed clear consciousness and no evidence of neck stiffness, and Kernig or Brudzinskin sign. However, he had rhonchus breathing sounds in the bilateral lungs and severe oropharyngeal candidiasis. Chest X-ray revealed the findings of interstitial infiltrations of bilateral lower lobes of lungs (Figure 1A). Results of laboratory tests included the following: white blood cell count 3450/mL, neutrophil 69%, lymphocyte 20%, hemoglobin 11.5 g/dL, and platelet 135,000/μL. The serum biochemical study revealed blood urea nitrogen 6 mg/dL, creatinine 1.07 mg/dL, alanine aminotransferase 16 U/L, and aspartate aminotransferase 17 U/L. The result of serology tests showed a high titer of anti-HIV antigen 1:1024× (enzyme-linked immunosorbent assay test) and confirmed HIV infection by Western blot test (positive P34/pol, P52/pol, P55/gag, and P68/pol). The CD4/CD8 ratio was 0.092, CD4 absolute count 32, and HIV viral load 2,689,776 (copy/mL).

Laboratory data also revealed a high titer of *Mycoplasma pneumoniae*, immunoglobulin G (IgG 1:320×) and *Cryptococcus* Ag (1:1024×). The patient received initially empirical antibiotic therapy with a daily intravenous administration of levofloxacin 750 mg and fluconazole 400 mg. He also received 80 mg trimethoprim/400 mg sulfamethoxazole orally twice daily for prophylaxis of PJP. His clinical condition was improved transiently, but his fever flared up again 3 days later. Blood culture for *Cryptococcus neoformans* was reported on the following day. Brain computed tomography (CT) scan images revealed faint leptomeningeal enhancement of bilateral cerebral hemispheres (Figure 1B), suggesting congested pia vessel or meningitis. He underwent a lumbar puncture examination with an open pressure of 11 cmH_2O. Results of the cerebral spinal fluid study revealed the following: glucose 51 mg/dL (blood glucose 97 mg/dL), protein 39 mg/dL, white blood cell count 1/μL, mononuclear cell 100%, and negative finding for India ink stain of cerebrospinal fluid (CSF). However, the CSF cryptococcal antigen was positive (1:4×). Therefore, he was highly suspected to have septic encephalopathy due to cryptococcemia. Cryptococcemia still persisted, as revealed by a blood culture, even after a 10-day course of fluconazole treatment. Moreover, the treatment regimen was adjusted to daily intravenous administration of fluconazole 600 mg and amphotericin B 40 mg. A chest CT scan showed the findings of multiple small nodules of bilateral lung fields, being compatible with disseminated cryptococcosis (Figure 1B). The findings of blood culture were negative after complete therapy with a 25-day fluconazole and a 14-day amphotericin B regimen. The patient continued to receive oral fluconazole 400 mg/d at our clinic for 3 months, and he maintained in stable condition.

This typical patient lived in an area full of pigeons. This is an important environmental risk factor for infection. *Cryptococcus* is believed to enter the body through the respiratory tract, causing pulmonary disease and infection of the central nervous system.[1] *C. neoformans* is found frequently in soils contaminated with avian excreta and can easily be recovered from shaded and humid soils contaminated with pigeon excreta. The polysaccharide capsule, which is a surrounding membrane, is a major virulence factor for *Cryptococcus*. AIDS patients are especially susceptible to cryptococcal infection due to their immunocompromised status.[2,3] Over 80% of cryptococcal infection occurs in HIV-infected patients.[2,3] About 60–70% of patients with cryptococcosis infection are manifested clinically with fever and weight loss. Cryptococcosis most commonly involves the central nervous system (83.7%). Headache and vomiting are the most frequent symptoms.[2,3] The second most common presentation is respiratory manifestation (50%), and a few patients have cutaneous skin lesions. In our patient, the initial presentations were high fever, weight loss, oropharyngeal candidiasis, cough, and dyspnea on exertion, which may lead the clinician to suspect PJP infection and miss the differential diagnosis of pulmonary cryptococcal infections.

A definitive diagnosis of cryptococcosis requires the demonstration of yeast cells in normally sterile tissues, e.g., blood or CSF.[1,2] A positive cryptococcal antigen test can provide strong evidence for cryptococcosis. India ink stain of the CSF is a useful, rapid diagnostic technique.[1] Cryptococcal cells in India ink have a distinctive appearance because their capsules exclude ink particles. However, the CSF India ink examination may yield negative results in patients with a low fungal burden. In cryptococcal meningitis, CSF examination usually shows evidence of chronic meningitis with mononuclear cell pleocytosis and increased protein levels. We excluded CNS as the primary infection in our patient, because *C. neoformans* was

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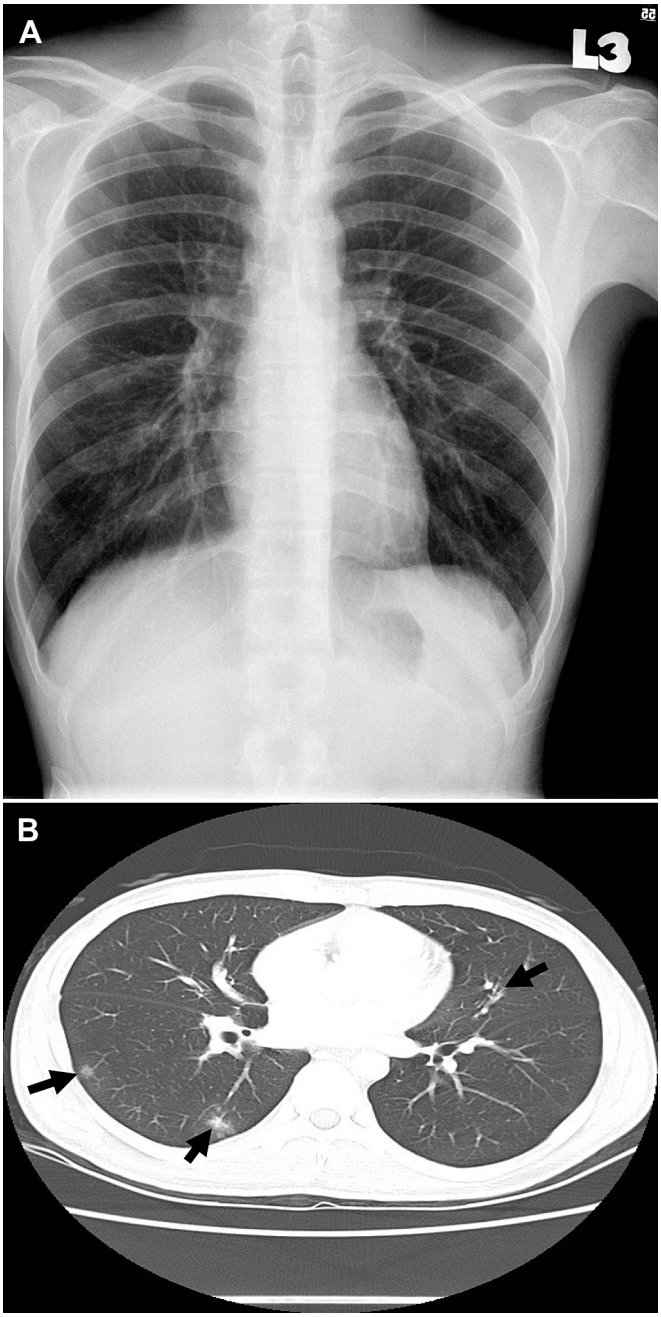

Figure 1 (A) Chest X-ray showed interstitial infiltration of bilateral lower lobes of lungs. (B) Chest computed tomography scan revealed multiple small nodules of bilateral lung fields.

isolated from the blood culture, he did not have pleocytosis, and he had negative CSF India ink stain and fungal culture. However, the chest CT scan picture revealed bilateral multiple cryptococcoma, and he had a high serum to CSF cryptococcal antigen titer ratio (1:1024/1:4). All those findings suggest that disseminated cryptococcosis in our patient was originated from the lungs with septic encephalopathy.

The treatment of choice for cryptococcosis is a 2-week induction course of intravenous amphotericin B and oral flucytosine (5FC).[4–6] Results of three randomized controlled trials of combined regimens have demonstrated increased fungal clearance and reduced risk of relapse compared to amphotericin B alone.[4–7] However, another study has shown that a high dose of fluconazole (800–1200 mg/d) should be used with amphotericin B for severe cryptococcosis.[8,9] Our patient having disseminated pulmonary cryptococcosis complicated with cryptococcemia was treated successfully with a combined therapy of amphotericin B and a high dose of fluconazole. This combination regimen may be an alternative choice.

In summary, PJP is the most common pulmonary infection among AIDS patients. However, our patient had an unusual clinical picture of disseminated pulmonary cryptococcosis, with cryptococcemia manifested initially as a pulmonary opportunistic infection. Based on our experience of this case and the findings of the published papers, we suggest that clinicians should be aware of cryptococcal infection being the initial pulmonary infection in AIDS patients.

References

1. Sabiiti W, May RC. Mechanisms of infection by the human fungal pathogen *Cryptococcus neoformans*. *Future Microbiol* 2012;**7**:1297–313.
2. Lindenberg AS, Chang MR, Paniago AM, Lazéra Mdos S, Moncada PM, Bonfim GF, Nogueira SA, et al. Clinical and epidemiological features of 123 cases of cryptococcosis in Mato Grosso do Sul, Brazil. *Rev Inst Med Trop* 2008;**50**:75–8.
3. Lee WS, Hsieh TC, Ou TY, Teng SO, Chen FL, Wang FD. Breakthrough disseminated cryptococcosis during micafungin therapy. *J Microbiol Immunol Infect* 2013 Apr 27. pii: S1684-1182.
4. Vander CM, Saag MS, Cloud GA, Hamill RJ, Graybill JR. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. *N Engl J Med* 1997;**337**:15–21.
5. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O. Major role for amphotericin B and flucytosine combination in severe cryptococcosis. *PLoS ONE* 2008;**3**:2870–8.
6. Day JN, Chau TTH, Dung NT, Mai PP, Phu NH. *Combination antifungal therapy for HIV associated cryptococcal meningitis*. 51st Interscience Conference on Antimicrobial Agents and Chemotherapy; 17–20 September 2011. Chicago, IL, United States.
7. Brouwer AE, Rajanuwong A, Chierakul W, Griffin GE, Larsen RA. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* 2004;**363**:1764–7.
8. Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. *PLoS Med* 2012;**9**. e1001316.
9. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, Sobel JD, et al. Practice guidelines for the management of cryptococcal disease. *Clin Infect Dis* 2000;**30**:710–8.

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