Journal of Microbiology, Immunology and Infection (2016) 49, 289–294

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CASE REPORT

# Simultaneous cryptococcal and tuberculous meningitis in a patient with systemic lupus erythematosus

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Received 19 March 2012; received in revised form 9 March 2013; accepted 25 April 2013
Available online 7 June 2013

**KEYWORDS**
*Cryptococcus*;
Intraventricular amphotericin B;
Meningitis;
Tuberculosis

Simultaneous central nervous system (CNS) infection with *Cryptococcus* and tuberculosis (TB) is very rare. Despite improved therapeutic options, treatment of CNS cryptococcosis is still difficult and needs invasive treatment modalities, such as intrathecal or intraventricular amphotericin B, in refractory cases. We describe a patient with systemic lupus erythematosus diagnosed with simultaneous cryptococcal and TB meningitis who had a poor response to intravenous liposomal amphotericin B and fluconazole, but was successfully treated with intraventricular amphotericin B, in addition to anti-TB therapy.


## Introduction

The etiology of central nervous system (CNS) infections in immunosuppressed patients varies widely. Opportunistic infections due to *Listeria monocytogenes*, *Mycobacterium tuberculosis*, or fungi such as *Cryptococcus* spp. should be considered in the differential diagnosis of meningitis in patients with systemic lupus erythematosus (SLE) receiving immunosuppressive agents.[1] Simultaneous CNS cryptococcosis and tuberculosis (TB) is a rare condition in immunosuppressed patients and even more rare in immunocompetent individuals.

Treatment of cryptococcosis has improved with the advent of polyene antifungal drugs. However, treatment may be difficult and invasive modalities may be needed in refractory cases of CNS cryptococcosis.[2] Here we present a rare case of CNS cryptococcal and TB infection.

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1684-1182/$36 
http://dx.doi.org/10.1016/j.jmii.2013.04.009

## Case report

A 45-year-old woman with SLE was admitted to our clinic with headache, fever, nausea, vomiting, incontinence, somnolence, and convulsions. She had been diagnosed with SLE 10 years before on presentation with a malar rash and polyarthritis. She had lupus involvement of the kidney, but no CNS involvement. She was taking steroids (10 years, approximately 16 mg methylprednisolone/day), hydroxychloroquine and methotrexate (for 1 year; stopped 1 year before admission), and non-steroidal anti-inflammatory drugs (as needed). She had been on methylprednisolone treatment (16 mg/day) for the last 2 years. Her SLE *disease activity index (*SLEDAI*)* score was 10 on admission. Headache, nausea, and vomiting were present for the previous 4 months. During the previous 2 months, fever, incontinence, somnolence, and convulsions were added to the clinical spectrum. The patient was conscious with limited cooperation; she had neck stiffness and dysarthric speech. The bilateral muscular strength of her lower extremities was 3/5 and her deep tendon reflexes were hypoactive. Cranial magnetic resonance imaging (MRI) demonstrated lesions in the basal ganglia and hydrocephalus. Laboratory results for whole blood were as follows: leukocytes, 6200 /mm$^3$; hemoglobin, 12 g/dL; platelets, 324,000 /mm$^3$; C-reactive protein (CRP), 170 mg/L (normal range 0—5); erythrocyte sedimentation rate, 100 mm/hour; and anti-HIV, negative. CSF results were as follows: leukocytes, 160 /mm$^3$ (80% lymphocytes); protein, 174 mg/L; and glucose, 20 mg/dL (simultaneous blood glucose, 144 mg/dL). Empirical anti-TB therapy (rifampin + isoniazid + pyrazinamide + ethambutol) was initiated for a probable diagnosis of TB meningitis. One week later, acid-fast bacilli were detected in a CSF sample inoculated into mycobacterium growth indicator and were identified as *M. tuberculosis* complex using polymerase chain reaction (PCR). The isolate was found to be sensitive to all of the major anti-TB drugs tested.

Although appropriate therapy was administered, the clinical state of the patient deteriorated. She lost consciousness during Week 2 of anti-TB therapy. Her Glasgow coma scale score was 10/15 and left hemiparesis developed. A repeat CSF examination on Day 15 of therapy revealed capsulated yeasts using Indian ink staining, and *Cryptococcus neoformans* was isolated. Although liposomal amphotericin B (5 mg/kg/day) was added to treat her cryptococcal meningitis, the patient became unresponsive to external stimuli by Week 3 of antifungal therapy. After progression of hydrocephalus was detected by cranial MRI, an external ventricular drain was applied to control CSF pressure and fluconazole was added to liposomal amphotericin B as flucytosine is not available in our country. Repeated CSF cultures became sterile on this combination therapy. The patient showed some improvement and recovered minimal consciousness after 1 month of combination antifungal therapy, and CSF cultures were negative; however, her fever persisted and MRI revealed ventriculitis (Fig. 1). Although it did not fulfill the definition of persistent infection, we decided to add intraventricular liposomal amphotericin B based on the insufficient clinical response to treatment. Following three doses of intraventricular liposomal amphotericin B (1 mg/day every 72 hours), her fever

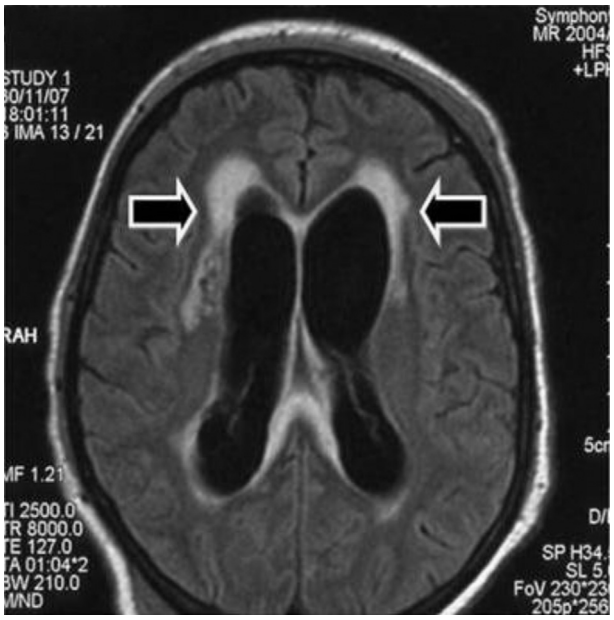


**Figure 1.** Magnetic resonance image demonstrating bilateral ventricular ependymal contrast enhancement indicative of ventriculitis (arrows).

subsided, CRP levels decreased, and radiological improvement (Fig. 2) was observed. Repeated HIV tests remained negative. Systemic liposomal amphotericin B was stopped in Week 14 and oral fluconazole was discontinued after 6 months of treatment. Anti-TB treatment was continued for 1 year. The patient was referred to a physical therapy unit for rehabilitation. Two years after completion of the therapy, she was mobile with support and had only residual speech impairment.

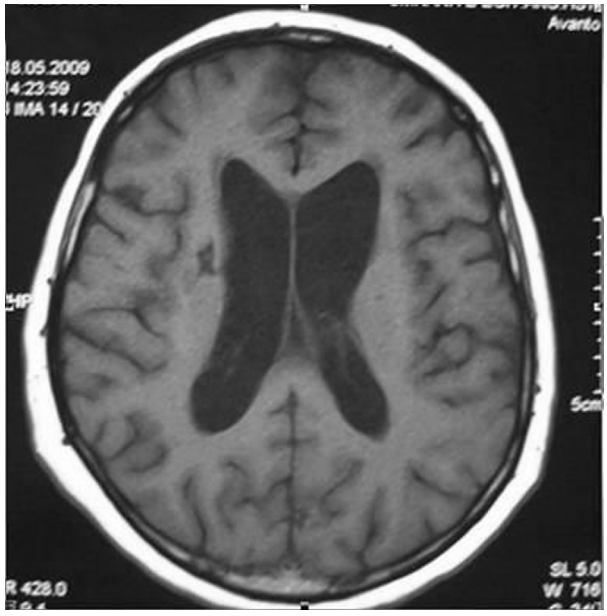


**Figure 2.** MRI demonstrating complete regression of ventriculitis after intraventricular amphotericin B.

**Table 1** Summary of seven reported cases and the present case of simultaneous cryptococcal and tuberculous meningitis

| Ref. | Age (y) | Sex | Clinical features | Underlying diseases | History of pulmonary TB | Microbiology | Treatment | **Outcome** |
|---|---|---|---|---|---|---|---|---|
| 13 | 10 | Male | Fever, headache, nausea, vomiting, neck stiffness comatose state | None | | CSF culture: *M. tuberculosis* +, *C. neoformans* + | SM + INH + promizole for TB; ethyl vanillate for *C. neoformans* | Discharged with some spasticity in left hand and wrist |
| 9 | 46 | Female | Fever, headache, irritability, progressive drowsiness, neck stiffness (meningitis 1 y after pulmonary TB treatment) | Reticulum cell sarcoma (radiotherapy) | + (Twice) | CSF culture: *M. tuberculosis* +, *C. neoformans* + | INH and prednisone for TB; sulfadiazine for *C. neoformans* (CSF TB culture was negative but cryptococci were detected) | Exitus (attributed to renal insufficiency and *E. coli* bacteremia) |
| 8 | 31 | Male | Fever, meningismus, convulsion, comatose state | HIV infection | Simultaneous | CSF culture: *M. tuberculosis* − (TB diagnosis based on radiological and clinical findings); CSF cryptococcal antigen + | RIF + INH + PZA + EMB; amphotericin B | Recovery |
| 12 | 51 | Male | Fever, neck stiffness, right epididymitis | Chronic epididymitis (biopsy culture *M. tuberculosis*) | | CSF culture: *M. tuberculosis* +, *C. neoformans* +; CSF cryptococcal antigen + | RIF + INH + PZA + EMB; amphotericin B + flucytosine | Recovery |
| 10 | 61 | Male | Fever, mild neck stiffness | Waldenstrom's macroglobulinemia (treated with fludarabine) | | CSF and blood cultures: *C. neoformans* +; CSF and serum cryptococcal antigen +; cerebral tissue culture: *M. tuberculosis* + | RIF + INH + PZA + EMB for intracranial tuberculoma; amphotericin B (4 wks) | Exitus (due to septicemia) |
| 11 | 25 | Female | Fever, cough, headache, vomiting, neck and lumbar stiffness | None | | CSF culture: *M. tuberculosis* +; *C. neoformans* +; CSF cryptococcal antigen + | RIF + INH + PZA + EMB + SM; intravenous fluconazole, followed by amphotericin B | Almost complete recovery |

(*continued on next page*)

**Table 1** (*continued*)

| Ref. | Age (y) | Sex | Clinical features | Underlying diseases | History of pulmonary TB | Microbiology | Treatment | **Outcome** |
|---|---|---|---|---|---|---|---|---|
| 14 | 43 | Male | Fever, confusion, incontinence | HIV | | CSF culture: *C. neoformans* +; CSF cryptococcal antigen +; CSF PCR for *M. tuberculosis* + | RIF + INH + PZA + EMB; amphotericin B | Recovery |
| Current report | 45 | Female | Fever, headache, nausea, vomiting, neck stiffness incontinence, somnolence, convulsions | SLE with steroid therapy | | CSF culture: *M. tuberculosis* +; *C. neoformans* + | RIF + INH + PZA + EMB; intravenous liposomal amphotericin B and fluconazole, intraventricular liposomal amphotericin B | Discharged (mobile with support and residual speech impairment) |

CSF = cerebrospinal fluid; EMB = ethambutol; HIV = human immunodeficiency virus; INH = isoniazid; PCR = polymerase chain reaction; PZA = pyrazinamide; RIF = rifampin; SLE = systemic lupus erythematosus; SM = streptomycin; TB = tuberculosis.

## Discussion

CNS TB is frequently encountered in regions where the incidence of TB is high. HIV infection, intravenous drug use, immunosuppression, immigration, and homelessness are risk factors for TB development. Anti-TB therapy should be initiated if clinical suspicion of CNS TB is high, as delayed treatment contributes to morbidity and mortality.[3]

In Turkey, TB is the most common etiological agent leading to chronic meningitis.[4] According to a 2009 WHO report, the TB prevalence rate is 25 per 100,000 in Turkey.[5] The resistance rate for isoniazid, rifampicin, isoniazid + rifampicin, ethambutol, and streptomycin is 13.1%, 6.5%, 5.1%, 4.7%, and 8.6%, respectively.[6] As TB is moderately endemic in our country and our patient had a history of extended corticosteroid use, empirical anti-TB therapy was started for a probable diagnosis of TB meningitis.

Besides *M. tuberculosis*, fungi are also among the microorganisms that can cause chronic meningitis. The incidence of infections caused by *C. neoformans* has markedly increased over the past 20 years because of the increase in the number of patients with HIV infection. Cryptococcal meningitis may also occur in patients with other types of immunosuppression and in immunocompetent patients.[7]

Simultaneous tuberculous and cryptococcal meningitis is very rare. Seven cases of meningitis due to simultaneous *C. neoformans* and *M. tuberculosis* infection have been reported in the English literature.[8–14] HIV infection, reticulum cell sarcoma, and Waldenstrom's macroglobulinemia treated with fludarabine were underlying conditions in four of these cases.[8–10,14] One patient was an immigrant from China.[11] The characteristics for these seven cases are summarized in Table 1. Our patient had received methylprednisolone treatment for SLE for the previous 2 years. Both corticosteroid therapy-related immunosuppression and SLE disease itself were thought to be underlying factors in the development of simultaneous CNS cryptococcosis and TB in our case. Although the coexistence of both infections has been reported to be rare in immunosuppressed hosts, this situation might lead to underdiagnosis. Since coinfection is so rare, the physician may diagnose either disease: if an immunosuppressive patient is admitted with clinical findings of CNS infection, any clue of TB or cryptococcal infection might be accepted as a satisfactory diagnostic finding. The accompanying second agent might be missed because of lack of a thorough search.

CSF cell counts and protein and glucose levels may be within the normal range in certain cases of TB or cryptococcal meningitis, particularly in immunosuppressed patients.[3,15] For immunosuppressed patients, the approach to CNS infection should include Indian ink and Erlich–Ziehl–Neelsen (EZN) staining and mycobacterial culture of CSF to exclude TB and cryptococcal meningitis. Baseline staining studies, such as with Indian ink and EZN, may be helpful in guiding empirical therapy.

Treatment of CNS cryptococcal infections used to be challenging.[16] Polyene antifungal drugs led to a dramatic improvement in the outcome for individuals with cryptococcal meningitis. The Infectious Diseases Society of America (IDSA) recently published a clinical practice guideline for the management of cryptococcal disease.[17] According to this guideline, for patients who are not infected with HIV and who have no history of transplantation, combination therapy of amphotericin B plus flucytosine for at least 4 weeks is followed by consolidation therapy with fluconazole for 8 weeks. After induction and consolidation therapy, maintenance therapy with fluconazole for 6–12 months is recommended.[17]

Combination therapy with amphotericin B and fluconazole for cryptococcal meningitis has mostly been limited to animal studies, with a few human cases reported; however, the new guideline recommends this as an alternative treatment modality for patients infected with HIV.[17] Barchiesi *et al* investigated the interaction between triazoles and amphotericin B against *C. neoformans*. Although they found antagonism between fluconazole and amphotericin B *in vitro*, this antagonism was not observed *in vivo*. They also suggested that the combination of triazoles and amphotericin B was significantly more active than either drug alone against *C. neoformans in vitro*.[18]

In our case, the patient became unresponsive to external stimuli by Week 3 of parenteral liposomal amphotericin B therapy. After progression of hydrocephalus was detected by cranial MRI, an external drain was applied and as flucytosine is not available in our country, fluconazole was added to liposomal amphotericin B.

Intraventricular administration of liposomal amphotericin B for cryptococcal meningitis is preferred for cases who are seriously ill or unresponsive to intravenous therapy.[17] With concerns regarding complications associated with multiple injections into the cisternal space via subcutaneous reservoirs,[19] its use is not routinely recommended by the IDSA.[17] Systemic antifungal treatment failed in our case but intraventricular administration of amphotericin B led to a clinical improvement within 1 week and no adverse events were observed during therapy.

In a study of 13 patients with cryptococcal meningitis, CSF was sterile in all six patients receiving intraventricular and systemic therapy, and in three of seven patients receiving only systemic therapy.[20] In our case, although the patient showed some improvement and recovered minimal consciousness after 1 month of systemic combination antifungal therapy, fever persisted and MRI revealed ventriculitis. However, following intraventricular liposomal amphotericin B therapy, a dramatic clinical and radiological response was obtained.

In conclusion, the simultaneous presence of TB and cryptococcal meningitis is a rare condition, but is deemed possible in immunosuppressed patients. A combination of amphotericin B and fluconazole and/or intraventricular amphotericin B may be considered as alternative therapy in patients with cryptoccocal meningitis refractory to standard therapy.

## Conflicts of interest

The authors declare no conflict of interest.

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