Successful Treatment of Cryptococcal Meningitis with Amphotericin B in a Patient with Systemic Lupus Erythematosus

S Jiang, T-C Lei, S-Z Xu

ABSTRACT

Patients with systemic lupus erythematosus (SLE) have an increased susceptibility to bacterial, viral, fungal and parasitic infections. Cryptococcal infection of the central nervous system (CNS) is a rare but often fatal complication of SLE. Here, we describe a case of cryptococcal meningitis in a female patient with active SLE, who was successfully treated with amphotericin B. This case suggests that the clinical findings of SLE patients with cryptococcal meningitis are non-specific and misleading, and early use of amphotericin B has a good response.

Keywords: Amphotericin B, cryptococcal meningitis, *Cryptococcus neoformans*, systemic lupus erythematosus

Tratamiento Exitoso de la Meningitis Criptocócica con Anfotericina B en un Paciente con Lupus Eritematoso Sistémico

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RESUMEN

Los pacientes con lupus eritematoso sistémico (LES) tienen una mayor susceptibilidad a las infecciones bacterianas, virales, fúngicas y parasitarias. La infección criptocócica del sistema nervioso central (SNC) es una complicación rara, pero a menudo fatal de LES. Aquí, describimos un caso de meningitis criptocócica en un paciente femenino con LES activo, que fue tratada con éxito con anfotericina B. Este caso sugiere que los resultados clínicos de pacientes de LES con meningitis criptocócica son no específicos y engañosos, y el uso temprano de la anfotericina B tiene una buena respuesta.

Palabras claves: Anfotericina B, meningitis criptocócica, Cryptococcus neoformans, lupus eritematoso sistémico

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune, connective-tissue disorder with a broad range of clinical presentations (1). Patients with SLE have an increased susceptibility to bacterial, viral, fungal and parasitic infections, either from disease-related immunologic dysfunction or the effects of immunosuppressive therapies on the immune system (2). Cryptococcal infection of the central nervous system (CNS) is a rare but often fatal complication of SLE (3). Herein, we describe a case of cryptococcal meningitis in a female patient with active SLE, who was successfully treated with amphotericin B.

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CASE REPORT

A 37-year old woman was admitted with headache, fever and joint pain for 15 days. Five years previously, she was diagnosed with SLE at a local hospital with initial presentation of polyarthralgia, malar rash, leukopenia, positive anti-dsDNA antibody and positive antinuclear antibodies (ANA) titres. Therapy with methylprednisolone (60 mg/day) was initiated. The patient's condition improved and the dosage of glucocorticoids was reduced gradually to prednisone 30 mg/day. During the 15 days preceding admission, she had intermittent low grade fever and dull generalized headache with joint pain.

On admission, her body temperature was 37.7 °C, with pulse rate 112 beats per minute, blood pressure 130/80 mmHg and normal respiratory rate. On physical examination, there was a malar rash and telangiectasia on the fingers. Both legs showed mild oedema. But papilloedema and meningeal irritation signs were absent. There were no focal neurological signs. Laboratory evaluation showed leukopenia (total white

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cell count 1620 mm^{-3}). Complement C3 was 0.328 mg ml^{-1} (normal range, 0.81~1.6 mg ml^{-1}), ANA titre was 1:160 (normal range, ≤ 1:40) and anti-dsDNA antibody was positive. Examination by echocardiography showed mild pericardial effusion. Computed tomography (CT) of the head showed no abnormal finding. Other laboratory findings were unremarkable. The patient was diagnosed with "active systemic lupus erythematosus" (Systematic Lupus Erythematosus Disease Activity Index [SLEDIA] scores = 15) and treated with methylprednisolone at a dose of 80 mg/d (1.5 mg/kg.d).

After therapy, her body temperature became normal, ANA titre was decreased to 1:40, the level of complement C3 was increased to 0.735 mg mL^{-1} and pericardial effusion gradually disappeared. Methylprednisolone was gradually tapered to the dose of 40 mg/d, but she still complained of a headache without neck stiffness. Magnetic resonance imaging (MRI) and CT of the head showed no abnormal finding. The patient refused lumbar puncture because of fear.

Four weeks later, she developed mental confusion and slight neck rigidity, followed by seizures within days. Lumbar puncture was therefore performed as a necessary examination. Cerebrospinal fluid (CSF) analysis showed a pressure of 220 mmH_2O, white blood cell (WBC) count 30 mm^{-3} (neutrophils 23%, lymphocytes 77%), red blood cell (RBC) 0 mm^{-3}, elevated protein level (60 mg dL^{-1}) and a reduced CSF glucose level (32 mg dL^{-1}, serum glucose 120 mg dL^{-1}). Gram stain showed many yeast cells, which on staining with India ink resembled *Cryptococcus neoformans* (Fig. 1). Cerebrospinal fluid culture yielded *Cryptococcus neoformans* (Fig. 2). Drug susceptibility testing showed it was susceptible to amphotericin B, fluconazole, itraconazole and terbinafine (Fig. 3). Antibodies to cryptococcal antigen were detected in a dilution titre of 1:128.

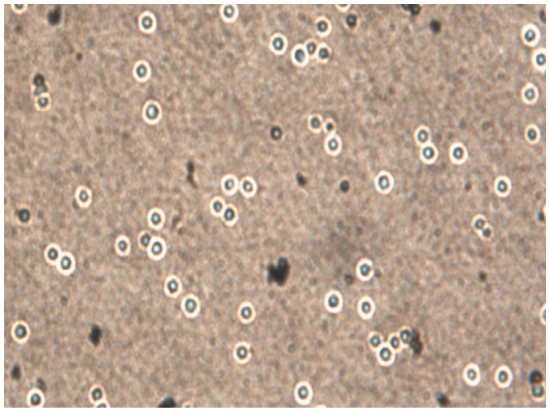

Fig. 1: Indian ink examination shows capsulated cryptococci under dark-field microscope. Around the round glistening thalli, there is a transparent incrassate capsule.

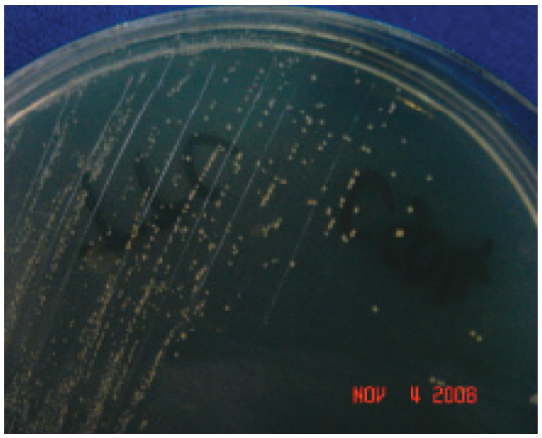

Fig. 2: Sabouraud dextrose agar with small yellow colonies. *Cryptococcus neoformans* was confirmed by France bioMerieux ATB fungus kit.

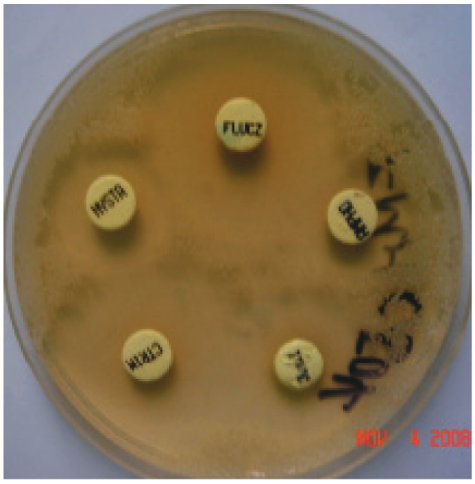

Fig. 3: Drug susceptibility testing showed that *C neoformans* were susceptible to amphotericin B, fluconazole, itraconazole and terbinafine.

Amphotericin B was started at 1 mg (0.3 mg kg^{-1} day^{-1}) and gradually increased to 1 mg kg^{-1} day^{-1} in 10 days with an accumulative dose of 1200 mg. Headache and psychiatric symptoms subsided after one week. After 30 days of treatment, the CSF data reverted to normal and CSF culture was negative. Therapy of amphotericin B was substituted by fluconazole 200 mg day^{-1} for four weeks. Laboratory findings improved in tandem with the patient's clinical progress. Prednisone was gradually tapered to 10 mg day^{-1} and there were no neurological sequelae.

DISCUSSION

Systematic lupus erythematosus is a chronic inflammatory autoimmune disease of unknown aetiology that involves various organ systems. Early studies revealed a 50% survival in four years. More recent papers, however, have shown that nearly 90% of SLE patients survive at least 10 years after diagnosis

(4). Such a survival increase has been attributed to early diagnosis and more effective treatment. Infections are very common among these patients due to aggressive immunosuppressive treatment and the intrinsic immunological defects associated with the disease. As a result, infection becomes a major cause of morbidity and mortality in SLE. Lung and skin are the most common sites of infection (4). The central nervous system is an uncommon site, constituting only about 3% of infection in SLE patients. But in these patients, cryptococcal meningitis is the most common cause of CNS infection (5). Thus, cryptococcal meningitis is a recognized complication of SLE, with high mortality rates, particularly in those treated with immunosuppressive agents (6).

Cryptococcus neoformans is an environmental saprophyte. Infection is probably acquired by the inhalation of small yeast cells or, possibly, basidiospores. The primary pulmonary infection is frequently asymptomatic and may be eradicated or contained within granulomata. However, depending on host factors, inoculum, and possibly isolate virulence, the organism may disseminate either acutely or after a period of latency to extrapulmonary sites, with a particular predilection for the brain (7). Cryptococcal meningitis is a common opportunistic infection in patients with late-stage HIV-infection, particularly in southeast Asia and southern and east Africa. Cryptococcal meningitis in non-HIV patients is commonly associated with an underlying immunocompromised condition, but can also occur in otherwise immunocompetent individuals. In a recent study, the most commonly associated conditions included immunosuppressive drug treatment (41%), SLE (16%), malignancy (16%) and diabetes mellitus [14%] (8).

Cryptococcal meningitis in patients with SLE usually has an insidious onset. It is difficult to diagnose unless it is suspected. Cryptococcal meningitis should always be included in the differential diagnosis of chronic or subacute meningoencephalitis, since its clinical features are not specific. Patients usually present with: headache, fever, malaise and altered mental status over several weeks. Signs are often absent, but may include: meningism, papilloedema, cranial nerve palsies and other focal neurological deficit and depressed conscious level (7). The index patient presented initially with intermit-tent headache and vomiting, and there were no clinical meningeal signs and no brain abnormalities on MRI or CT. These presentations were easily confused with CNS manifes-tations of active SLE. However, her headache could not be improved after therapy of larger doses of steroids and she pre-sented with altered mental status which suggested possible in-fection of CNS.

Diagnosis of cryptococcal meningitis must depend on microscopy and culture of CSF and detection of the cryptococcal polysaccharide antigen in body fluids by latex agglutination tests or enzyme immunoassay. Microscopy and culture of CSF are the most useful methods in diagnosis of cryptococcal meningitis. The CSF white cell count is raised, with a predominance of lymphocytes, in non-HIV-associated infection; CSF protein is usually elevated and CSF glucose may be low. Indian ink examination is positive in 50% of non-AIDS patients (7). A positive fungal culture is the gold standard for diagnosis of cryptococcal infection and CSF samples show fungal growth in almost all the cases (9). In our case, microscopy of CSF was consistent with abnormality of cryptococcal meningitis. Indian ink examination was also positive and the culture of CSF yielded *Cryptococcus neoformans*.

Untreated cryptococcal meningitis is uniformly fatal, although survival can range from years in those without apparent immunocompromise to only a few weeks in HIV-associated infection (10). Amphotericin B, a fungicidal agent that binds to ergosterol in the fungal plasma membrane, remains the best treatment for cryptococcal meningitis. According to the practical guidelines for the management of cryptococcal disease proposed by an eight-person subcommittee of the National Institute of Allergy and Infectious Diseases Mycoses Study Group, the recommendation for CNS disease in HIV-negative, but immunosuppressed patients, is amphotericin B (0.7–1 mg/kg.d) for two weeks, followed by 8–10 weeks of fluconazole (400–800 mg/d), then 6–12 months of suppressive therapy with a lower dose of fluconazole (200 mg/d). For those patients receiving long-term prednisone therapy, reduction of the prednisone dosage (or its equivalent) to 10 mg/day, if possible, may result in improved outcome to antifungal therapy (11). In our case, we achieved a good and quick response after therapy of amphotericin B alone for 10 days. After 30 days of treatment, the CSF data reverted to normal and CSF culture was negative. Amphotericin B was then substituted by fluconazole (200 mg/day). During the period of treatment, the dosage of steroids was gradually reduced according to the activity of lupus.

In summary, we report a case of cryptococcal meningitis in a female patient with active SLE, which was successfully treated with amphotericin B. Because the clinical findings of SLE patients with cryptococcal meningitis are non-specific and misleading, the diagnosis is often overlooked or delayed (12). We should be alert to the early signs and symptoms such as fever and headache. A lumbar puncture is the necessary diagnostic procedure and must be carried out in all cases of suspected cryptococcal meningitis. Once the diagnosis is established, early use of amphotericin B with prolonged fluconazole suppressive therapy is effective in SLE patients with cryptococcal meningitis.

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