Cryptococcal meningitis and SLE: a diagnostic and therapeutic challenge

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ABSTRACT

Cryptococcal meningitis is a rare occurrence in systemic lupus erythematosus (SLE). The risk factors of developing this infection are duration of SLE, intensity of glucocorticoid use, and SLE-related intrinsic immune abnormalities. Early recognition and prompt initiation of antifungals can prevent complications and improve survival. There is a dearth of evidence with regards to optimal treatment of cryptococcosis in non-HIV infected and non-transplant patients. The general consensus is to follow treatment guidelines for HIV-positive patients with cryptococcal meningitis. We describe a girl with active SLE and cryptococcal meningitis, and discuss the diagnostic and therapeutic challenges faced in this case.

Keywords: Cryptococcal meningitis; Systemic Lupus Erythematosus;

INTRODUCTION

Approximately 20-55% of patients with SLE die from serious infections during the course of their illness[1]. Genetic and intrinsic immunological abnormalities, as well as the use of immunosuppressive agents increase the susceptibility to common and opportunistic infections. Cryptococcal meningitis is a rare infection in SLE patients. The presenting symptoms and signs can mimic central nervous system (CNS) lupus, which could delay the diagnosis. Although cryptococcal meningitis is curable, it is associated with high morbidity and mortality if antifungals are not initiated promptly. Here we describe the case of a young girl with active SLE and cryptococcal meningitis.

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CASE REPORT

A previously healthy 13-year-old girl was diagnosed with SLE in May 2012 when she presented with alopecia, malar rash, arthralgia in the hand and knee joints, hypocomplementaemia, positive antinuclear antibody and a highly positive anti-dsDNA (1141 IU/ml). She achieved rapid improvement with 25 mg of oral prednisolone (0.5mg/kg/day) and 200 mg of hydroxychloroquine (HCQ) daily (3.5mg/kg/day). Five months later when her prednisolone was tapered to 10 mg daily, she developed bilateral lower limb oedema and frothy urine. During hospitalisation, investigations revealed significant proteinuria (5.31g/24hr) and WHO class IVa lupus nephritis. She received 500 mg of intravenous (IV) methylprednisolone daily for three days and was then maintained on 25 mg of prednisolone daily (0.5 mg/kg/day).

Her admission was uneventful until day-7 when she developed fever and cough. She received fourteen days of piperacillin/tazobactam for presumed hospital acquired pneumonia. Prednisolone and HCQ were continued during this period. Additional investigations were performed because of persistent fever. Urine, blood and stool cultures were negative. Echocardiogram and CT scan of brain, thorax, abdomen, and pelvis were normal.

A few days later, the patient complained of dull headache, nausea, neck stiffness and double vision. She was found to have a new left sixth nerve palsy. Due to strong personal beliefs, the parents of the patient did not consent for a lumbar puncture (LP). MRI of the brain showed multiple recent lacunar infarcts with increased left temporal leptomeningeal enhancement (Figure 1) which suggested either CNS lupus or active infection. Taking into consideration that her SLE was active with other organ involvement, the clinical team diagnosed CNS lupus. Daily 500 mg of mycophenolate mofetil (MMF), a lower than standard starting dose, was introduced.

Her fever continued despite receiving oral prednisolone, MMF, and two weeks of antibacterial antibiotics.

Parental consent for LP was finally obtained. The opening pressure was 23 cmH_2O and the cerebrospinal fluid (CSF) findings were consistent with meningitis caused by *Cryptococcus neoformans* (Table I). Blood cultures were negative for Cryptococcus, and there was no obvious lung or skin involvement. Her HIV antibody was negative. The patient was treated with daily 35mg (0.7 mg/kg/day) IV amphotericin B (AMP-B). Flucytosine was not available in Malaysia. Mycophenolate mofetil was temporarily withheld, with the plan to reintroduce it when the induction phase of antifungals was completed. Prednisolone was also tapered at a faster rate compared to patients without active infection. An LP on day-10 of antifungals showed significant improvement in opening pressure (13 cmH_20), normal CSF glucose and protein levels, and negative fungal stain, cryptococcal antigen and fungal culture (Table I). Despite the improvement in CSF findings, her headache did not resolve. A change of her antifungal regime was made by adding fluconazole 800 mg daily to the induction phase therapy. The combination of IV AMP-B and oral fluconazole was to be continued for a total of four weeks (new induction phase).

Unfortunately the patient developed right-sided hemiparesis on day-17 of antifungal treatment. MRI brain established the presence of new infarcts at the left thalamus and caudate nucleus (Figure 2a and 2b). MR angiography showed narrowing at the posterior circulation arteries (Figure 3). There was no abscess or meningeal enhancement. The MRI findings posed another diagnostic challenge as it could represent either a sequelae of SLE or cryptococcal infection. At the time of the neurological deficit, she was on 10 mg of prednisolone and 200 mg (3.5mg/kg/day) of HCQ daily. As the CSF had demonstrated a significant improvement a week prior to the neurological event, and the stroke occurred during a recent reduction of steroid dosage, we believed active SLE was very likely, although cryptococcal-related brain infarction could not be confidently ruled out. The patient was pulsed with another course of IV methylprednisolone at 250 mg daily for three days. She was restarted on 500 mg of MMF daily, much earlier than originally planned. Compared to standard dosing, both medications were given at a lower dose. In addition, she was maintained at 25 mg (0.5 mg/kg) of prednisolone and 200 mg of HCQ daily. She completed four weeks of daily IV AMP-B at 0.7mg/kg/day and daily oral fluconazole at 800mg. The plan was to administer an additional eight weeks of 800 mg of fluconazole daily (consolidation phase) and then to begin a maintenance dose of 600--800 mg, depending on tolerability, clinical response and degree of immunosuppression.

Over the next few weeks, the patient made a remarkable recovery with only minimal residual right-sided weakness. Her SLE was inactive. Her cryptococcal infection was under control as evidenced by absence of symptoms, normal opening pressure during the third LP with normal protein level and glucose in the CSF (Table I). During her last clinic review in March 2013,

TABLE I. SUMMARY OF CSF RESULTS FROM THREE LUMBAR PUNCTURES

CSF	14/12/12	28/12/12	18/1/13
Opening pressure (cmH20)	23	14	16
Appearance	Clear	Clear	Clear
Erythrocytes (/uL)	20	120	Negative
Leucocytes (/uL)	40	20	36
Polymorph (%)	100	100	38
Lymphocyte (%)	0	0	62
CSF glucose (mmol/L)	0.7	1.6	3.2
Serum glucose (mmol/L)	4.9	8.8	Not done
Protein (g/L)	0.85	0.65	0.42
Gram stain and culture	Negative	Negative	Negative
India Ink Stain	Capsulated yeast not seen	Capsulated yeast not seen	Capsulated yeast not seen
Culture	Cryptococcus neoformans*	No growth	No growth
Cryptococcus neoformans antigen	Positive 1:2	Negative	Not done

* sensitive to flucytosine, fluconazole, itraconazole, voriconazole

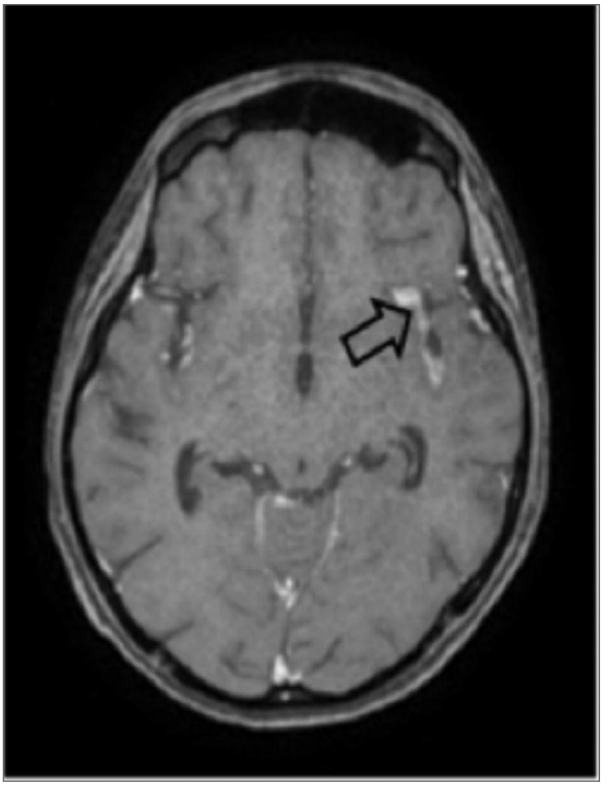

FIGURE 1. Increased left temporal leptomeningeal enhancement at the sylvian fissure

there was no evidence of infection. We adjusted her SLE regime with an increment of MMF from 500 mg to 1 g daily, HCQ from 200 mg to 400 mg daily, and a reduction of prednisolone from 25 mg to 20 mg daily. The fluconazole was reduced from 800 mg to 600 mg daily.

DISCUSSION

Cryptococcal meningitis is an opportunistic infection commonly identified as an AIDS-defining illness, especially in Southeast Asia and Africa. *Cryptococcus neoformans* is found in soil that is contaminated with bird excreta and causes infection in immunosuppressed patients[2]. Infection is acquired by inhalation of the yeast spores and can affect any organ in the body with a preference for the lungs and the CNS[2]. The most common manifestation is meningo-encephalitis with patients complaining of headache, fever, lethargy and confusion. Occasional signs include meningism, papilloedema, cranial nerve palsies and reduced levels of consciousness[2]. The signs and symptoms can often lead to a misdiagnosis of CNS lupus, especially when there is evidence of SLE flare in other organs[3].

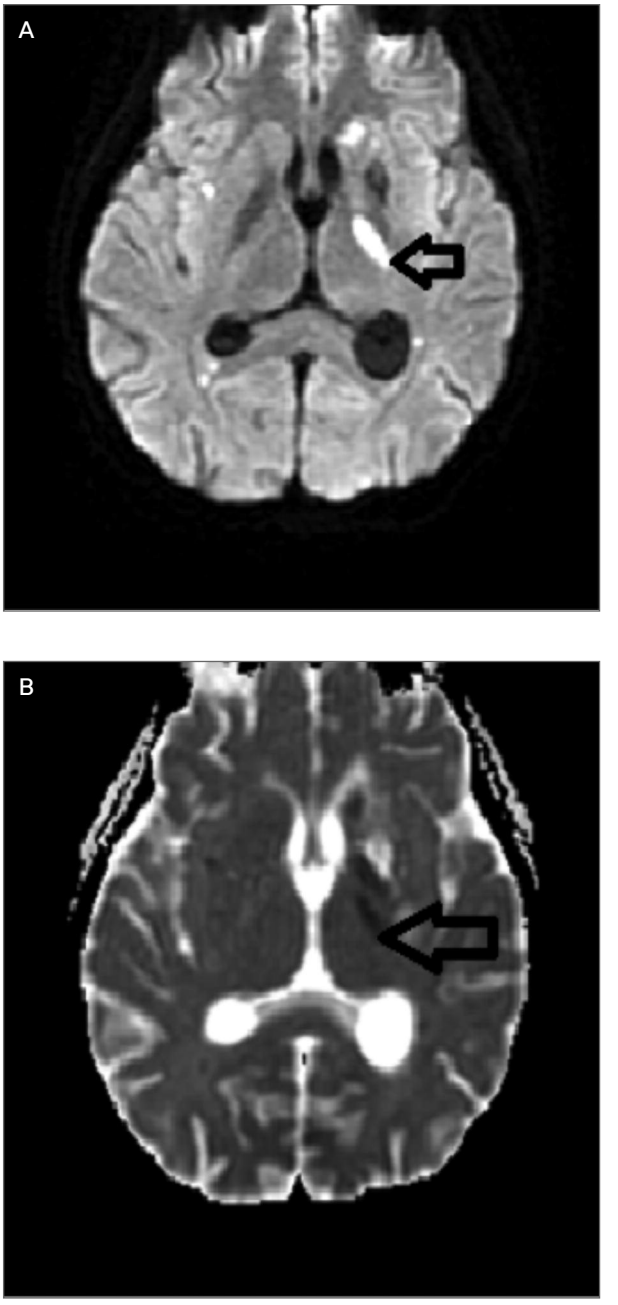

FIGURE 2. New infarct at left thalamus. **(A)** Hyperintensity at left thalamus (diffusion weighted imaging); **(B)** Hypointensity at left thalamus (apparent diffusion coefficient)

Corticosteroids, immunosuppressants, and SLE disease activity predispose patients to infections[1,3,4]. In addition, intrinsic defects in immune system also play an important role. Data from HIV-negative patients

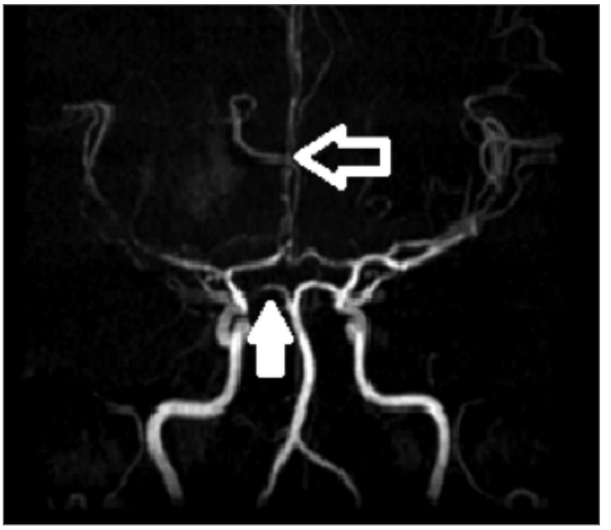

FIGURE 3. Beaded appearance of both ACAs(black arrow) and left PCA

with cryptococcosis revealed approximately a quarter of patients had previous glucocorticoid therapy while only a tenth had rheumatic disorders[5]. Glucocorticoids are widely used in SLE to control disease activity. One of the undesirable side effects of long-term and/or high intensity glucocorticoids is alteration in the immune system with an increased susceptibility to fungal infections[6]. Active lupus itself is also a risk factor for this opportunistic infection. There are case reports that described SLE patients with cryptococcosis without any previous exposure to immunosuppressants[7-9]. These cases supported the hypothesis that intrinsic immunological abnormalities may also contribute to the pathogenesis.

Cerebrovascular disease (CVD) is relatively uncommon in SLE, occurring in only 5-20% of cases[10]. In addition to traditional risk factors, vasculitis and antiphospholipid antibodies play an important role in CVD among patients with SLE[10]. The typical appearance of vasculitis in MRI is multiple infarcts in the cortical and subcortical areas with a predilection for the middle cerebral artery territory[11]. One of the diagnostic challenges in this case was the presence of cerebral infarction. The infarction could be related to SLE, or an early or late complication of cryptococcal meningitis which could occur in approximately one in three patients[12]. The most common areas affected in cryptococcosis are the basal ganglia, internal capsule and thalamus[12].

We also faced a dilemma in therapeutic choice. Due to lack of data from randomised control trials (RCTs) in non-HIV and non-transplant patients, the treatment of cryptococcal meningitis follows that of HIV-positive patients[12,13]. The US guidelines recommend the use of IV AMP-B (0.7-1.0 mg/kg/day) and oral flucytosine (100 mg/kg/day in four divided doses) as induction therapy for at least 4 weeks, consolidation therapy with oral fluconazole (400 mg/day) for 8 weeks, followed by maintenance phase with oral fluconazole (200 mg/day) for a further 6 to 12 months[14]. A recent landmark RCT concluded the efficacy of induction treatment with AMP-B and flucytosine. This combination improved survival, demonstrated faster cryptococcal clearance from CSF and reduced rate of complications, when compared to AMP-B alone or combination of AMP-B and fluconazole[15]. No similar RCT has been performed in non-HIV immunocompromised subjects.

Unfortunately, flucytosine is not readily available in many countries, including Malaysia, mainly due to concerns about costs and potential side effects[16]. Hence an alternative regime was recommended - induction therapy either with AMP-B monotherapy (1 mg/kg/day IV) or AMP-B (0.7 mg/kg/day IV) and fluconazole (800 mg/day orally), both for 2 weeks followed by consolidation therapy with fluconazole (800 mg/day orally) for 8 weeks[14]. However, combination therapy with amphotericin B and fluconazole had no survival benefit in HIV-positive patients in a recent RCT[15], although it was proven to be efficacious in the past[17,18]. The rationale of initial AMP-B monotherapy, and not combination of AMP-B and fluconazole in our patient was the concern of a potential drug interaction between prednisolone and fluconazole that might cause an undesired elevation in glucocorticoid levels. There was also published evidence of an antagonistic reaction between AMP-B and fluconazole, although such finding was only reported when fluconazole was administered at 400 mg daily[17].

After induction and consolidation phase, most experts recommend lifelong treatment if the patients have significant ongoing immunosuppression or persistent disease[5,13]. This is also partly due to the high relapse rate in approximately 15-20% of patients without maintenance therapy[13]. Our patient is likely to receive long term fluconazole in view of the chronic nature of her SLE.

CONCLUSION

Cryptococcal meningitis should be considered in patients with SLE with or without glucocorticoid thera-

py who present with neurological symptoms and signs. As the disease is related to the intensity of glucocorticoid therapy and SLE disease activity, lowest glucocorticoid dose should be given in active SLE for the shortest duration to achieve remission. Cerebral infarction in patients with SLE may be part of CNS lupus or secondary to cryptococcal meningitis. Early detection of the infection and initiation of AMP-B and flucytosine significantly reduce mortality and complications of this potentially curable disease. The combination of amphotericin B and fluconazole is an alternative but lacking mortality data. Because of high relapse rate, long term fluconazole is recommended during chronic immunosuppression for SLE.

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