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<td>Author(s)</td>
<td>Matsumura, Masami; Kawamura, Rika; Inoue, Ryo; Kawano, Mitsuhiro; Yamagishi, Masakazu</td>
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<tr>
<td>Citation</td>
<td>Modern Rheumatology, 21(3): 305-308</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2011-06</td>
</tr>
<tr>
<td>Type</td>
<td>Journal Article</td>
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<td>URL</td>
<td><a href="http://hdl.handle.net/2297/29569">http://hdl.handle.net/2297/29569</a></td>
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Cryptococcal meningitis is a recognized complication of systemic lupus erythematosus (SLE), with high mortality rates, particularly in those treated with immunosuppressive agents. We describe a patient diagnosed simultaneously with cryptococcal meningoencephalitis and SLE and reviewed four similar cases reported in the literature. In our case, profound low CD4 lymphocyte count and low complement levels were observed. The patient was treated with prednisolone, fluconazole, and 5-flucytosine and evinced good clinical improvement. This case suggests that intrinsic immunological abnormality related to SLE predisposed to opportunistic infections. © 2010 Japan College of Rheumatology. |
Case report

Concurrent presentation of cryptococcal meningoencephalitis and systemic lupus erythematosus

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The numbers of text pages and figure legends are 10 and 1, respectively.
The numbers of figures is one.

Keywords Cryptococcal meningoencephalitis, Intrinsic immunological abnormality, Systemic lupus erythematosus,
Abstract
Cryptococcal meningitis is recognized complication of systemic lupus erythematosus with high mortality, particularly those treated with immunosuppressive agents. We describe a patient with cryptococcal meningoencephalitis at the diagnosis of systemic lupus erythematosus and reviewed four similar cases reported in the literature. In our case, profound low CD4 lymphocyte count and low complement level were observed. The patient was treated with prednisolone, fluconazole, and 5-flucytosine and evinced good clinical improvement. This case suggests that intrinsic immunological abnormality of systemic lupus erythematosus predisposed to opportunistic infections.
**Introduction**

Despite a significant increase in the survival of patients with systemic lupus erythematosus (SLE), infection is a significant cause of morbidity and mortality [1]. The risk factors of infections include immunosuppressive therapies and some manifestations of active SLE itself [2-4]. Central nervous system (CNS) is rare organ system of infections [3] and cryptococcal meningoencephalitis has been described as one of life-threatening cause of CNS infection in patients with SLE [5, 6].

We describe a rare case of simultaneous presentation of cryptococcal meningoencephalitis and SLE. Opportunistic infections can present concurrently with new-onset of SLE.

**Case report**

A 47-year-old man was admitted with a 2-week history of fever, headache, general malaise, and anorexia. He had been well until 10 months before admission when he began to have wrist, knee and ankle arthritis, which persisted for 4 months and resolved spontaneously. Two weeks earlier, fever of 37 to 37.8°C in the evening was noted. He lost 2 kg in weight in past two weeks. On physical examination, his temperature was 37.2°C, blood pressure was 112/62 mmHg, and pulse was 60 beats per minute. Skin rash or oral ulcer was not noted. His chest was clear. There were no murmurs or rubs. No abdominal tenderness was present, and the liver and spleen could not be felt. Arthritis was not observed. Meningismus was absent. Other neurological examination was normal. Laboratory values were as follows: leukocyte count 3,000/μl; lymphocytes 249/μl; platelet count 205,000/μl; serum IgG 2,520 mg/dl; IgA 140 mg/dl; IgM 60 mg/dl; total functional hemolytic complement (CH50) 14 U/ml (normal 32-47 U/ml); C3 56 mg/dl (normal 65-135 mg/dl); and C4 5 mg/dl (normal 13-35 mg/dl). Liver enzymes, blood urea nitrogen, serum creatinine, serum electrolytes, and urinalysis were all normal. Serum antinuclear antibodies were positive at a titer of 1:2,560, with peripheral pattern. Serum antibodies to double-stranded DNA titer was markedly elevated at 165 IU/ml (normal < 12 IU/ml). SLE was diagnosed. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [7] was 5. Low complement, increased DNA binding, and leukopenia were descriptors.

On hospital day 1, loxoprofen sodium (120 mg daily) was prescribed for headache and was somewhat effective. He had been afebrile after admission, but anorexia persisted. On hospital day 8, he complained of neck pain. The next day, hallucination, apraxia, and agnosia appeared. Meningismus was noted. MRI of the brain with gadolinium contrast showed interhemispheric and occipital meningeal enhancement suggesting adjacent meningitis (Fig. 1). Examination of the cerebrospinal fluid (CSF) showed 212 white blood cells/μl (neutrophils 2, lymphocytes 210, and unclassified 29), glucose of 60 mg/dl, and protein of...
146 mg/dl. An India-ink preparation of the CSF revealed mucinous capsule of cryptococcus as a translucent halo surrounding budding yeast. A latex-agglutination test of the CSF was positive for cryptococcal antigen at a dilution of 1:2,048 and CFS culture grew *Cryptococcus neoformans*. Cryptococcal meningoencephalitis was diagnosed based on clinical manifestations, MRI finding, and result of CSF examinations. His human immunodeficiency virus (HIV) serology was negative, but lymphocyte and CD4 lymphocyte count was 200/μl and 33/μl, respectively. CD4/CD8 was 0.47 (normal 0.69-1.74). He was treated with intravenous fluconazole (800 mg daily) and oral 5-flucytosine (8,000 mg daily). Prednisolone (30 mg daily) was administered concomitantly for treatment of SLE. On hospital day 15, headache, neck pain, hallucination, apraxia, agnosia, and meningismus had disappeared completely. After the eight weeks course of intravenous fluconazole, fluconazole was changed to oral administration (400 mg daily). On hospital day 100, examination of the CSF showed 89 white blood cells/μl (neutrophils 1, lymphocytes 88, and unclassified 1). Cryptoccocus was still positive India-ink staining. However, CFS culture did not grow *Cryptococcus neoformans*. His lymphocyte, CD4 lymphocyte count, CH50, C3, and C4 had recovered at 1,100/μl, 176/μl, 42 U/ml, 99 mg/dl, and 14 mg/dl, respectively. On hospital day 106, he was discharged the hospital with good clinical improvement. Oral 5-flucytosine was discontinued at the time of discharge. Prednisolone had been tapered to 10 mg daily. He continued taking oral fluconazole (400 mg daily) as maintenance therapy for 12 months. He remains well more than three years without relapses.

**Discussion**

The spectrum of infections reported in patients with SLE has varied. Gram-positive cocci, gram-negative bacilli, *Mycobacterium tuberculosis*, *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis jirovecii*, cytomegalovirus, Epstein-Barr virus, and herpes virus have all been implicated [2-6, 8]. Use of steroids ever [3] and disease activity [2, 4] were significantly associated with infections. SLEDAl [7] score of 4 or higher in outpatients and greater than 8 in hospitalized patients were significant predicting factors for development of infections [2, 4]. Death in which infection was the primary cause was significantly associated with the peak corticosteroid dose received [9]. The major organ systems of infections often include skin, genitourinary, and lung [2-4]. CNS is rare organ system of infections in patients with SLE. Gladman et al. [3] reported that CNS infections consisted 4 (2.7%) of 148 infection episodes in 93 patients with SLE. Clinical manifestations of CNS infections including headache, cognitive disorder, acute confusional state, and seizure can mimic manifestations of CNS lupus. We should carefully exclude CNS infections when a patient with SLE discloses CNS manifestations even prior to the initiation of
Cryptococcal meningoencephalitis had been described as a rare complication of SLE [5]. However, Hung et al. [6] reported that cryptococcal meningoencephalitis played the major role in CNS infections of patients with SLE. They retrospectively reviewed 17 cases of CNS infections during a 20-year follow up of 3,165 patients with SLE and 10 (59%) of 17 patients had been diagnosed with cryptococcal meningoencephalitis. The average of SLEDAI scores in these 10 patients was 4.3. Kim et al. [10] reported 4 cases of cryptococcus meningoencephalitis during a 15-year follow up of 1,155 patients with SLE. SLEDAI scores of these 4 cases were 8 or higher. The outcome of these patients with cryptococcal meningoencephalitis was uniformly poor. Mortality rates were as high as 40-50% despite of antifungal therapy [5, 6]. Headache, fever, diplopia, nausea, and vomiting were symptoms for nonimmunosuppressed patients with CNS cryptococcosis at presentation [11, 12]. Sivalingam et al. [13] reported that the normal neurological examination and CSF examination did not exclude cryptococcal meningoencephalitis in a patient with SLE. Cryptococcal meningoencephalitis should be considered as one of differentials in SLE patients presenting even non-specific symptoms of headaches, fevers, nausea, or vomiting.

Most of the patients previously reported with cryptococcal meningoencephalitis had received corticosteroid administration when cryptococcal meningoencephalitis was diagnosed [5]. To our knowledge, there have been four previous reports of a patient who developed cryptococcal meningoencephalitis simultaneously with the diagnosis of SLE or prior to immunosuppressive therapy (Table 1) [6, 14-16]. Mok et al. [14] reported that the first case of cryptococcal meningoencephalitis complicating SLE without immunosuppressive therapy. Their case revealed normal CD4 lymphocyte count and low complement levels. The second reported case showed profound hypocomplementemia and lupus nephritis [15]. Hung et al. [6] mentioned that 1 of 10 patients had cryptococcus meningoencephalitis simultaneously with initial diagnosis of SLE. Chen et al. [16] reported 15 cases with invasive fungal infection in SLE. Their case series included one case of cryptococcal meningoencephalitis complicating SLE without prednisolone administration. All cases were women and SLEDAI score in three cases was 4, 7, and 11, respectively (Table 1). Mortality rate was high at 50%.

It is difficult to identify the intrinsic immunological abnormality as the risk for development of cryptococcal meningoencephalitis in SLE patients other than immunosuppressive therapy. Host resistance to Cryptococcus neoformans depends primarily on cell-mediated immunity. CD4 lymphocytes, cytotoxic lymphocytes, natural killer cells, activated macrophages, and various cytokines including interleukin 12, granulocyte-macrophage colony-stimulating factor, and interferon-γ are implicated in successful host
responses to *C. neoformans* [17]. Decreased CD4 lymphocyte count, natural killer cell activity, and T-cell cytotoxicity are related to clinical activity of SLE [18]. In this case, immunosuppressive agents were not administered at the diagnosis of cryptococcal meningoencephalitis, despite which his CD4 lymphocyte count and complement levels were low. The profound, progressive loss of CD4 lymphocyte in HIV patients correlates with the appearance of cryptococcal meningoencephalitis with the highest risk found when CD4 lymphocyte counts fall below 100/µl [17]. However, CD4 lymphocyte count was normal in first case report of a patient who developed cryptococcal meningoencephalitis simultaneously with the diagnosis of SLE (Table 1) [14]. Godeau et al. [8] reported that 2 of 6 patients had *Pneumocystis jiroveci* pneumonia in patients with SLE prior to corticosteroid administration. Lymphocyte count of one of these 2 patients was low at 180/µl. However, the other patient was not lymphocytopenic. Ecevit et al [11] described 9 nonimmunosuppressed patients with CNS cryptococcosis. Pappas et al [19] reported that 47 of 157 patients had cryptococcus meningoencephalitis in HIV-negative patients without underlying conditions. Zonios et al [12] reviewed 53 patients with cryptococcosis and idiopathic CD4 lymphocytopenia. Idiopathic CD4 lymphocytopenia is a syndrome defined by the repeated presence of a CD4 lymphocyte count of fewer than 300/µl or of less than 20% of total T cells with no evidence of HIV infection and no condition that might cause low CD4. Selective defect in lymphocyte responsiveness to *Cryptococcus neoformans* might explain cryptococcus meningoencephalitis in otherwise normal hosts. CD4 lymphocyte count should be measured in patients with cryptococcus meningoencephalitis in patients without underlying conditions. Complement levels in two previous case reports and in our case were low (Table 1) [14, 15]. Complement has been shown to be an opsonic requirement for *in vitro* phagocytosis of *C. neoformans* by rat macrophages [20]. Shapiro S et al. [21] mentioned that the importance of C3 in defense against cryptococcus infection by demonstrating increased susceptibility for genetically deficient C3 knockout mice. Low CD4 lymphocyte count and/or low complement levels might contribute to developing opportunistic fungal infection in patients with SLE even prior to immunosuppressive therapy. The recommended therapy for cryptococcal meningoencephalitis in HIV-negative and nontransplant patients includes induction therapy with amphotericin B deoxycholate (0.7-1.0 mg/kg daily) plus flucytosine (100 mg/kg daily) for at least four weeks, followed by a consolidation therapy with fluconazole (400-800 mg daily) for eight weeks and another six to twelve months of reduced dose of fluconazole (200 mg daily) for maintenance therapy [22]. Nussbaum et al [23] reported that combination flucytosine and high-dose fluconazole was optimal regimen for the treatment of cryptococcal meningitis in HIV-seropositive patients. In this case, fluconazole plus flucytosine administration was successful. In case of presenting toxic side effect of amphotericin B, fluconazole plus flucytosine regimen might be
considered.

Our case represents the fifth case report of a patient diagnosed with cryptococcal meningoencephalitis concurrently at the diagnosis of SLE. Intrinsic immunological abnormality of SLE itself can predispose to opportunistic infections, even in the absence of immunosuppressive therapies. However, additional case experience is required to confirm this relationship.

Acknowledgment
We would like to thank John Gelblum for his critical reading of the manuscript.

Conflict of interest statement None.
References


Figure legends

Fig. 1 Brain MRI (FLAIR sequences). Post-contrast enhancement showing enhancement of the interhemispheric and occipital meninges.