Central Nervous System Infections in Patients with Systemic Lupus Erythematosus

JENG-JUH HUNG, LIANG-SHIOU OU, WEN-I LEE, and JING-LONG HUANG

ABSTRACT. ***Objective.*** To evaluate the clinical profiles of patients with systemic lupus erythematosus (SLE) with central nervous system (CNS) infections.

Method. We retrospectively reviewed patients with SLE with CNS infections from January 1983 to June 2003. The clinical features, laboratory data, and prognoses of these patients were recorded.

Results. During the 20-year review period, 17 SLE patients with CNS infections were identified. The mean age at CNS infection was 29.6 ± 15.3 years. Cryptococcal infection was identified in 10 patients and bacterial meningitis in 7. Most patients (94%) had active SLE at the time of CNS infection. Fifteen patients received corticosteroid therapy and of these, 7 received it in conjunction with immunosuppressive agents. The most common presentation was headache, fever, and vomiting. The mortality rate among the 17 patients was high (41.2%).

Conclusion. Cryptococcal meningitis played the major role in CNS infection of patients with SLE, and it cannot be ruled out even when the cerebrospinal fluid (CSF) white blood cell count is within normal range. CSF India ink and latex agglutination testing for cryptococcal antigen should be performed and are effective screening tools to establish an early diagnosis. (J Rheumatol 2005;32:40–3)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS BRAIN ABSCESS
MENINGITIS CRYPTOCOCCUS LISTERIA

Infections are responsible for 30% to 50% of the morbidity and mortality in patients with systemic lupus erythematosus (SLE)[1–3]. The risk factors for infection include immunosuppressive and cytotoxic medications[4]. A relationship between disease activity and the presence of infection has been suggested in some studies[5,6]. The sites of infection often include lungs, skin, and genitourinary tract[6,7]. Central nervous system (CNS) infection in patients with SLE is rare, constituting only up to 3% of all infections in such patients[6-9]. Significant mortality is noted unless an accurate diagnosis is quickly made and appropriate therapy is administered as soon as possible. We evaluated the clinical profiles of patients with SLE with CNS infections.

MATERIALS AND METHODS

We retrospectively reviewed the clinical charts of patients with SLE with proven CNS infections admitted to one medical center in Taiwan between January 1983 and June 2003. All cases fulfilled the requirement of the 1982 American Rheumatism Association revised classification criteria for SLE[10]. A definitive diagnosis of CNS infection was made by isolation of a bacterial or fungal organism from cerebrospinal fluid (CSF) or brain abscess. SLE disease activity was calculated according to the SLE Disease Activity Index (SLEDAI)[11]. Patients were divided into 2 groups based on the type of infection: cryptococcal or bacterial. Clinical features and laboratory data were recorded. All cases were followed for at least 12 months after the diagnosis of CNS infection. We used the nonparametric Mann-Whitney U test and chi-square test to compare the demographic features, laboratory data, and mortality rates between both groups. A p value of 0.05 or less was considered statistically significant.

RESULTS

From a total of 10,462 inpatient records of 3165 patients with SLE, there were 17 patients with proven CNS infections during the 20-year review period. The ratio of female to male was 14:3. Three patients were adolescents (< 18 years of age) and 14 patients were adults (mean age 29.6 ± 15.3 years). The interval between onset of SLE and CNS infection ranged from 0 to 15 years (mean 25.0 ± 43.6 mo). *Cryptococcus neoformans* was identified in 10 patients (59%), *Listeria monocytogenes* in 4 (23%), *Enterobacter aerogenes* in one (6%), and *Streptococcus pneumoniae* in 2 (12%). Detailed data for these patients are shown in Table 1. The case of meningitis due to *E. aerogenes* was a nosocomial infection, while the others were community acquired. One patient with cryptococcal infection presented as brain abscess and the others as meningitis. All patients with bacterial infection presented as meningitis. Patients were divided into 2 groups: those with cryptococcal (n = 10) and those with bacterial infection (n = 7). No significant difference was noted between the 2 groups regarding age of SLE onset, age at CNS infection, and time interval between SLE onset

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Table 1. Culture results, India ink stain, cryptococcal antigen latex agglutination test, antifungal therapy, and outcomes of 17 patients with SLE.

Patient	Age/Sex (years)	SLEDAI	CSF Culture	Blood Culture	CSF/blood Cryptococcal Antigen Titer	Antifungal Agents	Steroid and Immunosuppressive Agents	Outcome
1	50/F	10	Enterobacter aerogenes	Listeria monocytogenes	N/ND		Nil	S
2	29/F	4	L. monocytogenes	N	N/N		P+C	S
3	24/F	12	L. monocytogenes	N	N/N		P	E
4	22/F	10	L. monocytogenes	L. monocytogenes	ND/ND		P+H	E
5	30/F	6	N	S. pneumoniae	N/N		P	S
6	22/M	4	L. monocytogenes	N	N/N		P+H	S
7	11/M	10	Streptococcus pneumoniae	N	ND/N		P	S
8	25/M	4	Cryptococcus neoformans	C. neoformans	1:8192/1:16384	AMB/Flu	P+C	E
9	17/F	4	C. neoformans	N	1:8/1:128	AMB/5-FC, Flu	P+H	S
10	19/F	0	C. neoformans	C. neoformans	1:1024/1:2048	AMB/Flu	P	E
11	42/F	7	C. neoformans	C. neoformans Sallmonella enteritidis B	1:4096/ND	AMB/Flu	P+A	E
12	37/M	5	C. neoformans	N	1:64/1:64	AMB/Flu	P	S
13	56/F	7	C. neoformans	C. neoformans	1:256/ND	AMB/Flu	Nil	E
14	19/F	4	C. neoformans	C. neoformans	1:64/1:2048	AMB/Flu	P+H+A+C	S
15	17/F	4	C. neoformans (brain abscess culture)	C. neoformans	ND/1:512	AMB/5-FC, Flu	P	S
16	65F	4	C. neoformans	N	1:128/ND	AMB/5-FC, Flu	P	R
17	19/F	4	C. neoformans	N	ND/ND	AMB/Flu	P	E

N: negative; ND: not done; AMB: amphotericin B; 5-FC: flucytosine; FLU: fluconazole; P: prednisolone; H: hydroxychloroquine; C: cyclophosphamide; A: azathioprine; S: survived; E: expired; R: relapse.

and CNS infection (Table 2). The time interval between symptom onset and diagnosis was significantly longer in the cryptococcal infection group than in the bacterial infection group ($p = 0.004$).

Most patients (94%) had active SLE (SLEDAI $\geq$ 4) at the time of CNS infection, except one patient with cryptococcal meningitis. Fifteen patients received corticosteroid treatment in the 6 months before onset of CNS infection, except for 2 patients in whom the CNS infections were detected at the first SLE presentation. In addition, 7 patients received corticosteroid therapy in conjunction with immunosuppressive agents such as cyclophosphamide, azathioprine, or hydroxychloroquine.

The most common presentation of CNS infection in patients with SLE was headache (100%), followed by fever (82%), vomiting (65%), seizure (53%), consciousness disturbance (41%), neck stiffness (29%), and diplopia (12%). CSF analysis was performed in all but one patient, who had a culture-proven cryptococcal brain abscess. Twelve of the 16 patients had pleocytosis in the CSF, except 4 patients

Table 2. Demographic features, systemic lupus erythematosus (SLE) disease activity (SLEDAI), laboratory data, and mortality rate in patients with CNS infections.

	Total n = 17	Bacterial Infection n = 7	Cryptococcal Infection n = 10	p
Age at CNS infection, yr	29.6 ± 15.3	26.9 ± 12.0	31.6 ± 17.6	1.000
Age at SLE onset, yr	27.7 ± 14.9	25.9 ± 16.7	29 ± 16.8	0.922
Interval between SLE onset and CNS infection, mos	25.9 ± 43.6	2.6 ± 21.3	30.2 ± 54.2	0.378
SLEDAI at infection	5.9 ± 3.0	8.0 ± 3.3	4.5 ± 1.7	0.042
Interval between symptom onset and diagnosis established, days	10.6 ± 3.9	7.6 ± 1.7	12.8 ± 3.5	0.004
Prednisolone dose, daily, mg	30.7 ± 14.7	35.0 ± 18.1	27.8 ± 12.3	0.369
CRP, mg/l	60.9 ± 75.4	119.3 ± 81.1	16.5 ± 14.1	0.038
CSF WBC, /µl	794.3 ± 2305.0	1390.7 ± 3350.1	19.2 ± 18.9	0.001
CSF protein, mg/dl	117.7 ± 111.1	175.4 ± 148.5	72.9 ± 38.1	0.023
Mortality rate, %	41.2	28.6	50	0.377

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with cryptococcal meningitis. A raised serum C-reactive protein (CRP) was noted in 94% of patients and was significantly higher in the bacterial infection group than in the cryptococcal infection group. In addition, the CSF white blood cell (WBC) counts and protein level were significantly higher in the bacterial infection group compared to the cryptococcal infection group (Table 2). Of the patients with cryptococcal infection, the CSF India ink stain was positive for all patients tested. Latex agglutination test for cryptococcal antigen in CSF or blood was positive for all of the 9 patients tested. Six patients with cryptococcal meningitis received repeat CSF analysis and 4 of them had sterile CSF after treatment. The median duration of antifungal treatment to determination of sterile CSF was 23.5 (16–32) days. The 2 patients who continued to have cryptococcal antigen present in their CSF died 41 and 32 days after diagnosis, respectively. The other 3 fatalities died within 2 weeks of diagnosis and no second lumbar puncture was performed. Concomitant cryptococcemia was found in 6 patients with cryptococcal meningitis. Computed tomography (CT) of the brain was performed in 13 patients and magnetic resonance imaging (MRI) in 7. There was no specific finding, except one patient showed multiple brain abscesses.

Patients with cryptococcal infection were treated with antifungal regimens consisting of amphotericin B with 5-flucytosine (5-FC) or fluconazole, which were then switched to oral fluconazole. The mean duration of combination therapy was 6.2 ± 1.8 weeks and fluconazole therapy was 17.6 ± 5.5 weeks. Five patients (50%) in the cryptococcal infection group died and of them, 3 had cryptococcemia and one had cryptococcemia with *Salmonella enteritidis B* bacteremia (Table 1). Two patients (28.6%) in the bacterial infection group died. The mortality rate did not differ significantly between the 2 groups (Table 1). No neurological deficit was mentioned among the survivors during followup period. A 65-year-old woman who received 7 weeks of combination therapy and 14 weeks of fluconazole therapy had a relapse of cryptococcal meningitis 3 months after oral fluconazole was discontinued. The duration of antifungal treatment to determination of sterile CSF in this patient was 32 days, but the titer of blood latex agglutination testing for cryptococcal antigen remained 1:8 at the end of fluconazole treatment. She received an additional course of amphotericin B and 5-FC for 8 weeks, until the CSF cryptococcal antigen was negative, and oral fluconazole for 45 weeks.

DISCUSSION

The most striking finding in this study was that *C. neoformans* played the major role in patients with SLE with CNS infection. As reported, the annual incidence rate of cryptococcal meningitis in non-HIV-infected patients was 1.75 episodes per 10,000 discharges in Taiwan[12]. Host resistance to *C. neoformans* depends primarily on cell-mediated immunity. CD4 cells, cytotoxic lymphocytes, natural killer cells, activated macrophages, interleukin 12 (IL-12), and gamma interferon are implicated in successful host responses to *C. neoformans*[13]. Abnormalities of cell-mediated immunity have been shown in SLE and in association with immunosuppressive drug therapy, making patients with SLE prone to cryptococcal infection. Among the 10 patients we studied with cryptococcal infection, 9 had received corticosteroids before the infection developed. The remaining patient had cryptococcal meningitis concurrent with initial diagnosis of SLE. Therefore, intrinsic immunological defects in SLE may predispose SLE patients to opportunistic fungal infections, even without administration of immunosuppressive agents.

Clinical symptoms and signs were variable in patients with SLE with CNS infection. Not all patients were febrile and meningeal signs were not prominent in some patients. It made early diagnosis difficult according to clinical presentation, especially in patients with cryptococcal meningitis. Cryptococcal meningitis cannot be ruled out in patients with SLE even if the CSF WBC count is within normal range, as 4 of our patients had normal CSF WBC counts. The high positive rate for India ink staining and cryptococcal antigen among our patients resulted in early diagnoses, and antifungal agents were initiated before the culture results were available. Therefore, CSF India ink and latex agglutination testing for cryptococcal antigen should be performed and are effective screening tools to establish an early diagnosis.

Currently, suggested regimens for antifungal therapy for cryptococcal meningitis are amphotericin B with or without 5-FC, and switching to fluconazole. The optimum duration of therapy is uncertain in patients with SLE. Of the 5 surviving patients in our study, duration of therapy depended on the physician and repeat lumbar puncture results or serum cryptococcal antigen titer. One patient had a satisfactory response to treatment but the titer of blood latex agglutination testing for cryptococcal antigen remained 1:8 at the end of fluconazole treatment. She suffered a relapse of cryptococcal meningitis 3 months after fluconazole was discontinued. Whether chronic suppressive fluconazole therapy is necessary in SLE patients with cryptococcal meningitis remains controversial. We suggest that fluconazole therapy should continue unless the CSF culture and CSF and blood latex agglutination tests are all negative.

The mortality rate was higher in our patients with SLE with cryptococcal meningitis than in the general population. The mortality rate was 50% among our patients and Zimmermann, *et al* reported a mortality rate of 40% in the antifungal era[14]. Shih, *et al* analyzed 94 patients negative for HIV with cryptococcal meningitis and the mortality rate was 19.1%[12]. Eighty percent of the fatalities in our study had concomitant cryptococcemia. Two of the 6 patients who received repeat CSF analysis failed to achieve sterile CSF and died thereafter. Repeatedly positive CFS cultures and

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concomitant cryptococcemia appear to indicate risk of mortality in patients with SLE.

The second most common pathogen of CNS infections in SLE patients was *L. monocytogenes*, an intracellular pathogen capable of spreading directly from cell to cell without exposure to the extracellular humoral immune system[15]. Resistance to infection with *L. monocytogenes* is predominantly cell-mediated[16] and depletion of CD4 T cells could play a role in the pathogenesis of *L. monocytogenes* infections[17]. Patients with SLE often receive immunosuppressive agents and have abnormal cell-mediated immunity, and are therefore susceptible to *L. monocytogenes* infections. Their prognoses are also poor, as seen in our review: 2 of the 4 patients died despite appropriate antibiotic therapy.

Other pathogens in the bacterial meningitis group included *S. pneumoniae* and *E. aerogenes*. Although Salmonella species are among the most common opportunistic bacterial infections seen in fatal SLE[2], no salmonella meningitis was identified among our patients. Salmonella meningitis is an unusual complication of Salmonella sepsis and occurs almost exclusively in infants and young children. It is very rare in adults, even in patients with SLE.

Based on our findings, we suggest that once a patient presents with symptoms of CNS infection and signs of elevated CRP, CSF analysis should be performed as soon as possible because an accurate diagnosis is crucial to survival of the patient. Because of the prevalence of cryptococcal meningitis, an India ink stain and cryptococcal antigen test should be performed on the initial CSF specimen in every patient to ensure the earliest diagnosis possible. Patients with high cryptococcal latex agglutination titers and concomitant cryptococcemia appear to be prone to death. The duration of antifungal therapy remains controversial in patients with SLE and further study is needed to optimize therapy.

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