Clinical Neurology and Neurosurgery 131 (2015) 59–63

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Cryptococcal meningitis in Chinese patients with systemic lupus erythematosus

Yuhua Zhong[a], Min Li[a], Jia Liu[a], Weixi Zhang[b,*], Fuhua Peng[a,*]

[a] Multiple Sclerosis Center, Department of Neurology, The Third Affiliated Hospital of Sun Yat-Sen University, No. 600, Tianhe Road, Guangzhou, Guangdong 510630, China
[b] Department of Neurology, The First Affiliated Hospital Sun Yat-sen University, No. 58, Zhongshan 2nd Road, Guangzhou, Guangdong 510080, China

ARTICLE INFO

Article history:
Received 22 April 2014
Received in revised form 8 January 2015
Accepted 23 January 2015
Available online 2 February 2015

Keywords:
Cryptococcal meningitis
Systemic lupus erythematosus
Chinese

ABSTRACT

Objective: Systemic lupus erythematosus (SLE) is a chronic immunologic disorder that can affect multiple organ systems and makes the patient susceptible to infection. Cryptococcal meningitis (CM) is a rare but often fatal complication of SLE.
Design: In this study, 6 patients with CM were identified among 631 patients with SLE. The demographic, clinical, laboratory profiles, serological features and outcomes of these 6 SLE patients with CM were retrospectively analyzed.
Results: The mean age of these patients was 24.1 years (range 12–42) at the time of SLE diagnosis, and 27.1 years (range 14–42) at the time of *Cryptococcus neoformans* infection, with mean disease duration of 37 months (range 3–72). Four patients had active SLE. All patients were receiving glucocorticoids therapy (mean prednisone dose of 20.5 (5.0–36.0) mg/day) at the onset of infection. Five patients had received other immunosuppressive drugs. The most common presentations of CM were headache and fever and 4 of the 6 patients were normal on physical examination. The cerebrospinal fluid (CSF) indices (protein and glucose) were normal in 4 cases, whereas they were mildly abnormal in the other 2 patients. White counts in the CSF ranged from 8 to 240 cells/mm. *C. neoformans* were isolated from CSF of 4 patients. The isolation of crytococci from extraneural sites, including blood and lungs, was found in 2 patients. Results of the head computed tomography scan were unremarkable in 5 of the patients. The infection was completely resolved in 5 patients, and it was resolved with serious sequelae in one patient.
Conclusions: In conclusion, the key to a rapid diagnosis of CM in patients with SLE is to maintain a high degree of awareness which will help avoid delays in treatment. This is mainly due to the fact that the clinical presentation and laboratory results from routine hematological, biochemical and CSF analyses of CM in patients with SLE are mostly non-specific.

1. Introduction

Cryptococcus neoformans, as one of the most common pathogenic species worldwide, can cause infection disease in humans [1]. The central nervous system (CNS) is a common site for cryptococcal infection which usually presents cryptococcal meningitis (CM) [2]. Systemic lupus erythematosus (SLE) is an autoimmune disease with myriad of presentations and is characterized by the immune dysregulation in its pathogenesis [3]. Therefore, SLE patients are susceptible to infection because of their disease-related immunological defect or concomitant immunosuppressive therapies [4]. The CNS, which is an uncommon site, constitutes only about 3%of the infections in SLE patients.

CM is the most common cause of CNS infection with a high mortality rate in patients with SLE [5]. The clinical features of CM may be non-specific which may lead to a missed diagnosis or delayed treatment, especially in patients receiving immunosuppressive therapy [6]. However, neuropsychiatric systemic lupus erythematosus (NPSLE) encompasses highly diverse clinical manifestations and may occur at any time in SLE [7]. Therefore, CM in patients with SLE can be misdiagnosed as NPLSE or an activation of SLE. In this retrospective study, we described the demographic characteristics, clinical histories, laboratory profiles, serological features and outcomes of 6 SLE patients with CM.

2. Patients and methods

2.1. Definitions

We retrospectively reviewed the inpatients medical records of patients with SLE from January 2008 to June 2013 admitted to the

* Corresponding authors. Tel.: +86 18922102909.
E-mail address: pfh93@163.com (F. Peng).

http://dx.doi.org/10.1016/j.clineuro.2015.01.023
0303-8467/

Table 1
Clinical and serological features of SLE.

	Patient					
Parameter	1	2	3	4	5	6
Gender	Female	Female	Female	Female	Female	Female
Age at SLE diagnosis (years)	24	26	42	24	17	12
Age at onset of CM (years)	31	32	42	24	20	14
Interval between diagnosis of SLE and CM (months)	84	72	3	3	36	25
SLEDAI when suffering from Cryptococcus infection	8	8	28	12	2	1
Active renal disease	No	Yes	Yes	Yes	No	No
Medications before the diagnosis of CM	P, HCQ, AZA	P, AZA	IVMP	IVMP, CTX, HCQ	P, MTX, AZA, HCQ	IVMP, AZA, MTX
Glucocorticoids dose at the time of infection diagnosis (mg/day)	Prednisolone 5	Prednisolone 15	Methylprednisolone 25	Methylprednisolone 45	Prednisolone 15	Methylprednisolone 40
Clinical features of SLE	Arthritis, malar rash	Vasculitis, cerebral hemorrhage, nephritis	Fever, arthritis, malar rash, baldness, oral ulcer, nephritis, altered mental status	Fever, fatigue	Arthritis, malar rash	Fever, dropsy
Serologic feature of SLE	AnuA 24 U/ml, AHA 36 U/ml, ANA1:1000, anti-RNP+, anti-Sm+	ANA1:100, CCP 9 U/ml, anti-SSA+, anti-SSB+	ANA1:160, anti-RNP+, anti-Sm+, anti-SSA+, anti-SSB+	ANA1:100	ANA1:100, anti-SSA+	ANA1:3200, anti-dsDNA1:320, AnuA115 U/ml, AHA131 U/ml

Abbreviations: SLE: systemic lupus erythematosus; CM: cryptococcal meningitis; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; P: prednisolone; IVMP: methylprednisolone; HCQ: hydroxychloroquine; AZA: azathioprine; CTX: cyclophosphamide; MTX: methotrexate.

Third Affiliated Hospital of Sun Yat-Sen University in Guangzhou, China. Of these patients, 6 patients with CM were identified. All patients fulfilled the 1982 American College of Rheumatology (ACR) classification criteria for SLE [8]. Cryptococcal antigen test was not available at the Third Affiliated Hospital of Sun Yat-Sen University, so CM was defined as clinical features of meningitis along with isolation of *C. neoformans* in CSF cultures or a positive CSF India ink stain. A standardized case collection form was used to record gender, age at SLE diagnosis and at the time of CM diagnosis, interval between SLE diagnosis and CM diagnosis, lupus clinical and serological manifestations prior or at cryptococcal infection onset, CM clinical manifestations, disease activity, glucocorticoids and immunosuppressors administered prior to and at infection diagnosis, prednisolone dose, at the time of infection, cytotoxic agents, prior to infection, active renal disease, HIV testing, laboratory data, 24-h urine total protein, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum complement levels (C3 and C4), initial cerebrospinal fluid findings, extra-CNS involvement, antifungal agents used, and outcomes. Disease activity was calculated using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and considered active if scores were $\geq$4. The time from the initial observation of symptoms to the time of definite diagnosis was considered as the symptom duration. The interval from positive CSF India ink for the first time to negative CSF India ink for the third time were considered as the time to sterile CSF.

This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-Sen University (200733) and in compliance with the Helsinki Declaration. All subjects provided informed consents to participate in this study.

2.2. Statistical analysis

Descriptive statistical data are presented as mean (range) values for continuous variables and as frequencies and percentages for categorical variables. Analyses were performed using the SPSS software version 13.0.

3. Results

From January 2008 to June 2013, 631 patients with SLE were identified. Of these 631 patients, six patients developed cryptococcal infection. All of these 6 patients were female, with mean age of 24.1 years (range 12–42) at SLE diagnosis, and 27.1 years (range 14–42) at the time of *C. neoformans* infection, with mean disease duration of 37 months (range 3–72). Four patients (patients 1–4) had active SLE (SLEDAI score $\geq$ 4) at the time when CM was diagnosed. All patients were tested negative for anti-HIV antibodies. All but 1 patient (patient 3) had no underlying diseases and had not used antibiotics use prior to cryptococcal infection. Patient 3 had hypertension and received a short course of cefminox sodium (3–4 days) prior to cryptococcal infection. All of these patients were receiving glucocorticoids therapy (mean prednisone dose of 20.5 (5.0–36.0) mg/day) at the onset of infection before the onset of CM. There was concomitant use of other immunosuppressants in 5 patients, including hydroxychloroquine (patient 1), azathioprine (patients 1, 2, 5, and 6), cyclophosphamide (patient 4), methotrexate (patients 5 and 6). Characteristics of patients with cryptococcal meningitis are shown in Table 1.

Headache and fever were the most common symptoms of CM, displayed by all of the patients, followed by vomiting (n = 3). Other initial presentations included altered mental status and seizure. On neurological examination, 4 of the 6 patients displayed normal characteristics, including papilloedema and meningeal irritation. The average time from the appearance of initial symptoms to diagnosis was 25 days (range 4–103) (Table 2).

There was no record of hemolytic anemia in any of the patients. However, lymphopenia ($<1.5 \times 10^3/mm^3$) associated with disease activity was observed in all patients, C-reactive protein (CRP) (>6 mg/L) was observed in 2 patients but platelets and leukocytes