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BRIEF REPORT

Cryptococcal meningitis in patients with lupus nephritis

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Abstract

Objective Cryptococcal meningitis (CM) is a rare condition in patients with lupus nephritis (LN). Here, we describe the clinical characteristics, possible risk factors, and outcomes of LN patients with CM.

Methods A systematic review of medical records from16 LN patients with CM admitted to our hospital was performed. A total of 32 cases were randomly selected as controls from LN patients without infection during the same period.

Results The mean age of patients with CM at presentation was 35.1 years, and the female-to-male ratio was 15:1.The most common clinical manifestation was headache (93.7%); patients with CM had a significantly higher prednisone dose at the time of hospitalization, a higher SLE Disease Activity Index (SLEDAI), a higher urine protein/creatinine ratio, and a lower CD4+ T cells count than those without infection ($p < 0.05$). Patients with CM also had significantly higher activity index and more moderate and severe mesangial proliferation than those without infections ($p < 0.001$ and $p = 0.025$, respectively).

Conclusion Serious renal pathological changes, mass proteinuria, higher SLEDAI, higher prednisone dose, and a decline in CD4+ T cells could be risk factors for CM in patients with LN.

Key Points

- *LN patients with CM had more serious renal pathological changes than those without infections; serious renal pathological changes could be a major risk factor for CM in patients with LN.*

Keywords Cryptococcal meningitis · Lupus nephritis · Renal pathology

Introduction

Cryptococcus neoformans is a common cause of opportunistic infections in immunocompromised patients, and the central nervous system (CNS) is a common site for cryptococcal infection which usually presents as cryptococcal meningitis (CM) [1, 2]. The host's immune status plays a crucial role in combating infections, which is especially apparent in patients with defective cell-mediated immunity, such as that seen in patients with acquired immunodeficiency syndrome or those receiving immunosuppressive drug therapy, which is common in patients with systemic lupus erythematosus (SLE) [3, 4]. The clinical manifestations are usually nonspecific and frequently confused with lupus flare or neuropsychiatric lupus. Therefore, the diagnosis is often delayed, which leads to progression of the infection and neurological complications [5].

Previous studies have found that CM is a rare but a fatal complication in SLE patients [6, 7]. Increasing immunological activity, particularly renal involvement, has been considered an independent risk factor for the development of infectious complications [6, 7]. The aim of this study is to describe the clinical and pathological features and prognostic and risk factors of patients with lupus nephritis (LN) who developed CM in a single center.

Patients and methods

Patients hospitalized in the First Affiliated Hospital of Wenzhou University during April 2003 to April 2018 were selected for this retrospective study. All patients met the

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criteria for SLE revised by the American Rheumatism Association in 1997 [8] and showed the clinical manifestations of LN. A renal biopsy was obtained in all patients. The diagnosis of CM was based isolation of *C. neoformans* from cerebrospinal fluid (CSF) or positive CSF India ink staining. In addition to CM patients, 32 LN patients without infection were randomly selected and used as controls to identify possible risk factors for the development of CM.

For each patient, the following data were obtained: demographic information, LN duration, SLE disease activity according to the SLE Disease Activity Index (SLEDAI) [9], neurologic manifestations that occurred at the time of CM diagnosis, glucocorticoid and/or other immunosuppressive therapy, laboratory data, including hematuria, urine protein/creatinine ratio, serum creatinine, serum albumin, serum hemoglobin (Hb), white blood cells (WBC) and platelets, serum C3, serum C4, immunoglobulinG (IgG), and results of CSF analyses, magnetic resonance imaging (MRI), and patient outcomes.

Renal biopsies were interpreted and reported by one special pathologist according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of LN [10]. The following data were obtained: activity index, chronicity index, classification, mesangial proliferation, endothelial proliferation, crescent, loop necrosis, microthrombus, and ratio of chronic renal tubular interstitial inflammation. The intensity of glomerular immunofluorescence staining for IgG, IgM, IgA, C3, C4, and C1q was semiquantitatively scored on a scale of 0 to 3, where 0 = no glomerular staining, 1 = mild glomerular staining, 2 = moderate glomerular staining, and 3 = intense glomerular staining[11].

Statistical analysis

Variables are described as the mean plus the standard deviation or proportion. Differences between patients with and without CM were compared by the independent sample t-test or chi-square test. Binary logistic regression was used to determine the independent clinical variables associated with CM. A *p*-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17 (IBM, Cary NC, USA).

Results

A total of 16 LN patients with concurrent CM were enrolled in this study. India ink staining of CSF for cryptococcal organisms was positive for all patients. The CSF culture was positive for *C. neoformans* in 11 patients (68.7%). The mean age at presentation was 35.1 years (range: 21.4–42.2), and the female-to-male ratio was 15:1. The most common clinical manifestation was headache in 15 patients (93.7%), followed by fever in 14 patients (87.5%) and vomiting in 12 patients (75%). Meningeal signs (i.e., neck stiffness) were present in six patients (37.5%) (Table 1).

Table 1 The neurologic manifestations of LN patients with CM (n=16)

Variables	Number	Percentage (%)
Headache	15	93.7
Fever	14	87.5
Vomiting	12	75.0
Seizures	3	18.7
Confusion	4	25.0
Coma	1	6.2
Hemiparesis	2	12.5
Paraparesis	2	12.5
Neck stiffness	6	37.5

LN, lupus nephritis ; CM, Cryptococcal meningitis

The interval between symptom onset and establishment of the diagnosis was 8.4 days (range1 − 18 days). Patients with CM were receiving a significantly higher prednisone dose at the time of hospitalization and had a higher SLEDAI than those without infections ($p < 0.001$ for both). There were no differences in LN duration, cumulative dose over the preceding year, methylprednisolone pulse therapy, or immunosuppressive therapy over the preceding year (Table 2).

Compared to patients without infections, those with CM had a significantly higher urine protein/creatinine ratio and a lower CD4+ cell count ($p < 0.05$ for both). Although patients with CM had a higher serum creatinine level, lower albumin and IgG level, and more hematuria than those without infections, there were no significant differences between the groups. CSF examination revealed a higher opening pressure, higher protein level, lower glucose, and higher WBC in those with CM compared to controls (Table 2).

The renal pathological differences between LN patients with or without CM are compared in Table 3. Patients with CM had a significantly higher activity index and more moderate and severe mesangial proliferation than those without infection ($p < 0.001$ and $p = 0.025$, respectively). However, there were no significant differences in ISN/RPS classification, endothelial proliferation, crescent, loops necrosis, microthrombus, ratio of chronic renal tubular interstitial inflammation, and the intensity of glomerular immunofluorescence staining between the two groups.

Patients with cryptococcal infection were treated with systemic antifungal agents, either amphotericin B with 5-flucytosine (5-FC) or fluconazole, and were then switched to oral fluconazole. The mean duration of systemic combination therapy and oral fluconazole therapy was 8.7 ± 5.2 weeks and 21.5 ± 10.4 weeks, respectively. The doses were reduced if patients had renal insufficiency. The death rate was 25% in patients with CM.

We also analyzed possible factors associated with mortality between survival CM patients and died CM patients with LN

Table 2 Clinical characteristics of LN patients with and without CM infection

Variables	CM(n=16)	No infection (n=32)	P value
Gender (F:M)	15:1	30:2	1.000
Age (years)	35.1±7.2	34.9±6.5	1.000
LN duration (months)	15.5(4-100)	19.2(0-120)	0.241
Interval between symptom onset and establishment of the diagnosis(days)	8.4(1-18)		
Prednisone dose at the time of hospitalization (mg/day)	27.5±10.2	15.5±7.8	<0.001*
Cumulative dose of prednisone over the preceding year (g)	3.85±1.42	3.25±1.81	0.324
Methylprednisolone pulse therapy over the preceding year (n %)	4(25)	2(6.25)	0.086
[a]Other immunosuppressive therapy over the preceding year (n %)	16(100)	31(96.8)	1.000
SLEDAI	15.6±4.3	7.2±2.1	<0.001*
Albumin (g/L)	25.8±9.4	27.8±5.2	0.354
IgG(g/L)	14.6±3.6	15.9±2.7	0.665
Serum creatinine(μmol/l)	116.4±35.2	89.2±30.4	0.076
Urine P/C ratio (g/g)	3.8±2.1	2.4±1.2	0.023*
Hematuria (n, %)	10(62.5)	16(50)	0.542
Serum C3(mg/dl)	47.0±16.1	53.7±22.7	0.245
Serum C4(mg/dl)	7.8±5.2	10.3±2.1	0.125
Anti-dsDNA (n, %)	16(100)	31(96.8)	1.000
Hemoglobin (g/dl)	100.2±24.5	104.9±27.3	0.895
WBC(10^9/l)	5.4±2.1	6.2±3.2	0.563
Platelet (10^9/l)	159.2±61.2	174.9±71.3	0.242
ESR (mm/h)	65.2±24.1	59.3±26.2	0.436
CRP (mg/l)	86.3±36.4	27.1±10.2	<0.001*
$CD4^+$ cell count (cells/mm^3)	152.8±30.4	252.4±35.4	0.037*
NK cell count (cells/mm^3)	94.6±21.8	101.7±27.5	0.147
CSF opening pressure (cmH_2O)	26.4±3.0		
CSF WBC (cell/mm^3)	192.2±48.4		
CSF protein(g/l)	2.41±0.27		
CSF glucose, mmol/l	1.61±0.44		
MRI abnormality (n, %)	8(50)		
Died (%)	4(25)		

LN, lupus nephritis; CM, Cryptococcal meningitis; SLEDAI: SLE Disease Activity Index; P/C: protein to creatinine; WBC, white blood cell; ESR,erythrocyte sedimentation rate; CRP, Creactive protein; NK cell: Natural killer cell; CSF: cerebrospinal fluid; MRI: Magnetic Resonance Imaging

[a] Including cyclophosphamide, mycophenolatemofetil, cyclosporine A and azathioprine

Data are shown as the Mean±SD (standard deviation) or the percentages

*p<0.05

(Table 4). We found that the mortality was associated with low serum albumin levels and high cumulative doses of prednisolone used in the previous year (both $p < 0.05$). Other factors such as age, sex, duration of LN, interval between symptom onset and establishment of the diagnosis, prednisone dose at the time of hospitalization, SLEDAI, and CD4+ cell count were not associated with mortality.

Discussion

Infection is estimated to be responsible for 20–55% of the cases of morbidity and mortality in patients with SLE [12]. *C. neoformans* is an important opportunistic pathogen that commonly infects immunosuppressed individuals [13]. Among HIV-negative patients with cryptococcal infection, studies have found that 41–61% of the patients received immunosuppressive drugs and most had SLE [4, 14].

In this study, we found that patients with CM were receiving a significantly higher prednisone dose at the time of hospitalization and had a higher SLEDAI than those without infections. The duration of LN in patients with CM ranged from 4 months to 8 years but was 4–10 months in most patients (68.7%). Two patients had duration of more than 5 years, but they relapsed at 6 and 8 months, respectively, before infection. These findings indicate that CM was more likely to appear in

Table 3 Pathological data of LN patients with or without CM infection.

Variables	CM (n=16)	No infection (n=32)	p value
ISN/RPS classification			0.260
II (n, %)	0(0)	4(12.5)	
III (n, %)	5(31.2)	7(21.8)	
IV (n, %)	10(62.5)	15(46.8)	
V (n, %)	1(6.2)	6(18.7)	
Activity index	6.9±2.1	3.5±1.9	<0.001*
Chronicity index	2.0±1.4	2.4±2.0	0.384
Mesangial proliferation			0.025*
Mild (n, %)	4(25)	21(65.6)	
Moderate (n, %)	10(63.5)	10(31.2)	
Severe (n, %)	2(12.5)	1(3.1)	
Endothelial proliferation (n, %)	10(63.5)	12(37.5)	0.131
Crescent (n, %)			0.642
Cellular crescent (n, %)	6(37.5)	3(9.3)	0.109
Fibrous crescent (n, %)	1(6.3)	6(18.7)	
Hybrid crescent (n, %)	3(18.7)	7(21.8)	
Loops necrosis (n, %)	5(31.2)	3(9.3)	0.097
Micro-thrombosis(n, %)	5(31.2)	3(9.3)	0.097
Ratio of chronic renal tubular interstitial inflammation (%)	12.3±7.5	17.6±14.1	0.288
IgG deposition (n, %)	13(81.2)	22(68.7)	0.497
IgA deposition (n, %)	11(68.7)	22(68.7)	1.000
IgM deposition(n, %)	14(87.5)	30(83.3)	0.592
C3 deposition (n, %)	16(100)	30(93.7)	0.546
C4 deposition (n, %)	11(68.7)	24(75.0)	0.735
C1q deposition (n, %)	14(87.5)	29(90.6)	1.000

LN: lupus nephritis;CM, Cryptococcal meningitis; ISN/RPS: WHO: renal biopsy findings according to the International Society of Nephrology/Renal Pathology Society

Data are shown as mean± SD (standard deviation) or percentages

*p<0.05

Table 4 Possible risk factors associated with mortality between survival CM patients and died CM patients with LN

Variables	Survival patients (n = 12)	Died patients (n = 4)	p value
Gender (F:M)	11:1	4:0	0.551
Age (years)	35.3 ± 7.4	34.8 ± 6.9	0.784
LN duration (months)	15.2 (4–100)	16.3 (6–36)	0.442
Interval between symptom onset and establishment of the diagnosis (days)	7.7 (1–18)	10.4 (6–14)	0.137
Prednisone dose at the time of hospitalization (mg/day)	25.9 ± 9.7	32.3 ± 17.5	0.326
Cumulative dose of prednisone over the preceding year (g)	3.6 ± 1.3	4.5 ± 2.2	0.046*
SLEDAI	15.4 ± 4.3	16.2 ± 4.5	0.245
Albumin (g/L)	27 ± 9.2	22.1 ± 10.5	0.041*
IgG (g/L)	15.3 ± 3.4	12.3 ± 4.8	0.061
Serum creatinine (μmol/l)	115.3 ± 35.4	119.5 ± 33.6	0.237
Urine P/C ratio (g/g)	3.9 ± 2.1	3.6 ± 2.2	0.328
CD4+ cell count (cells/mm^3)	149.2 ± 30.2	163.4 ± 34.5	0.236

CM, cryptococcal meningitis; LN, lupus nephritis; SLEDAI, SLE Disease Activity Index; P/C, protein to creatinine

Data are shown as the mean ± SD (standard deviation) or the percentages

*$p < 0.05$

the duration of 4–10 months, when patients did not achieve a complete remission and were still receiving large doses of prednisone.

The results of renal pathological examinations showed that patients with CM had a significantly higher activity index and more moderate and severe mesangial proliferation than those without infection. The CM group also had more proliferative lesions (class III and IV), more endothelial proliferation, more cellular crescent, more loops necrosis, and more microthrombus than the other group, although there were no significant differences. Overall, patients with CM had more serious pathological changes, which may have resulted in a higher prednisone dose for a longer time.

The predisposition of patients with SLE to infection varies, and disease activity is highly associated with infection. It has been reported that an SLEDAI of 4 or higher in outpatients and greater than 8 in hospitalized patients is a significant prognostic factor for the development of infection [9, 15, 16]. In this study, patients with CM had a higher SLEDAI and more complement consumption, which were mainly attributed to nephritis, than those without infections. Complement deficiencies, decreased phagocytosis, reduced production of interleukin by polymorph nuclear cells, and defective chemotaxis, membrane recognition, and attachment to microorganisms are known to predispose SLE patients to infection [17, 18].

SLE patients are more vulnerable to infections because both the disease itself and the immunosuppressive treatments weaken the immune system. In this study, we found that patients with CM had significantly higher prednisone dose and lower CD4+ counts than patients without infection and patients with CM also had lower IgG and albumin than patients without infection. These findings suggest that immunocompromised host caused by immunosuppressive drug therapy may play an important role in *C. neoformans* infection in patients with LN. Yang et al. described 38 SLE cases with CNS infection and found that higher doses of prednisone and low levels of serum albumin were important risk factors for the development of CNS infections in SLE patients [19]. Vargas et al. studied 23 SLE patients with CNS infection and found that moderate- to high-dose steroids and other immunosuppressants like cyclophosphamide were risk factors for CNS infections in SLE patients [20]. Previous studies have shown that successful host resistance to *C. neoformans* depends primarily on cell-mediated immunity [21, 22]. Glucocorticoids could cause rapid redistribution of lymphocytes from the circulation depleting circulating CD4 + T cells and to a lesser extent CD8 + T cells [23]. Different studies have demonstrated that steroid therapy increases the susceptibility to infections because of impairment of cellular immunity [24–26].

In summary, we described the clinical characteristics of CM in a cohort of Chinese SLE patients and identified possible risk factors associated with infection. The main findings were that LN patients with CM had more serious renal pathological changes and a higher SLEDAI and were receiving a higher prednisone dose than those without infections. CD4+ T cells were lower in the CM group than in the control group because of immunosuppressive effects of glucocorticoids or other immunosuppressors. Therefore, serious renal pathological changes, a higher SLEDAI, a higher prednisone dose, and a decline in CD4+ T cells could be risk factors for CM in patients with LN.

Compliance with ethical standards

Disclosures None.

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