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ORIGINAL PAPER

Comparison of Clinical Features and Prognostic Factors of Cryptococcal Meningitis Caused by *Cryptococcus neoformans* in Patients With and Without Pulmonary Nodules

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Abstract Whether the clinical features of cryptococcal meningitis (CM) patients vary with the coexistence of pulmonary nodules is not clear. This study aimed to compare the clinical features of CM in patients with and without pulmonary nodules detected by chest computed tomography (CT). The medical records of CM patients hospitalized in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 1, 2010, to December 31, 2016, were retrospectively reviewed. Baseline demographics, laboratory and radiographic findings, clinical managements, and outcomes were analyzed. A total of 90 CM patients were enrolled. Forty (44.4%) patients had pulmonary nodules (PN-positive), and 50 (55.6%) patients had no pulmonary nodules (PN-negative). Compared with PN-negative patients, PN-positive patients had higher cerebrospinal fluid (CSF)/serum albumin ratios, higher rates of CSF protein > 1000 mg/L, CSF glucose < 2.5 mmol/L, worse overall treatment response, higher rates of abnormal head CT and magnetic resonance imaging manifestations, and more unfavorable clinical outcomes. Multivariate analysis showed that immunocompromise ($p = 0.037$) and CSF glucose < 2.5 mmol/L ($p = 0.044$) indicated poor outcome in PN-positive patients, while CSF glucose < 2.5 mmol/L ($p = 0.025$) also indicated poor outcome in PN-negative patients. Amphotericin B in the initial therapy was a protective factor for PN-negative patients ($p = 0.008$). Certain clinical features showed significant differences between CM patients with and without pulmonary nodules, and several independent contributing factors impacted the clinical outcomes for CM patients. Future studies should be performed to further examine these factors.

Keywords Cryptococcal meningitis · Pulmonary nodules · Chest CT · Unfavorable clinical outcomes

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Introduction

Cryptococcus neoformans is an uncommon human fungal pathogen that can infect both apparently normal hosts and immunocompromised individuals, especially patients with human immunodeficiency (HIV) infection. While the infection site could be anywhere in the human body, *C. neoformans* mainly causes pulmonary cryptococcosis (PC) and cryptococcal meningitis (CM) [1–3]. *C. neoformans* is usually acquired by inhalation and then exhibits a propensity to disseminate to the brain, causing CM, the most severe form of cryptococcosis, after a period of latency within pulmonary lymph nodes [4–6].

PC may cause vague symptoms including fever, dyspnea, or cough. When asymptomatic, it may be discovered incidentally on radiological imaging. The most common presentation of PC on chest computed tomography (CT) is pulmonary nodules, both in HIV-infected and in HIV-uninfected patients [7–9]. Although the common route of cryptococcal infection was considered to be Cryptococcus inhalation into the lung, it mainly affects the central nervous system, causing fever, headache, and other symptoms, while symptomatic pulmonary infection is uncommon.

Various clinical features of CM in patients with HIV (or hepatitis B virus) and in uninfected patients have been reported [10, 11]. However, few studies have investigated the clinical features of concurrent pulmonary and neurological cryptococcosis, since concomitant PC is often not identified in most CM patients. Although some case series reported clinical features of disseminated cryptococcosis [12–14], the differential diagnosis of CM with a coexisting PC could be difficult. Baddley et al. [15] identified several factors (including weight loss, fever, altered mental status, high-dose corticosteroid administration) that may help distinguish patients with PC alone from patients with coexisting PC and disseminated complications such as meningitis.

In addition, the management of CM in the presence of PC was not described in the 2010 Infectious Diseases Society of America guidelines [16]. It is essential to identify several features that could help recognize the difference between patients with CM alone and patients who had pulmonary plus neurological cryptococcosis, guiding the diagnostic and treatment evaluation.

In this study, we hypothesized that CM patients may have latent PC if pulmonary nodules are detected by chest CT. We aimed to compare the various clinical features of CM in patients with and without pulmonary nodules (PN-positive and PN-negative) detected by chest CT and to identify the independent contributing factors to clinical outcomes for CM patients.

Materials and Methods

Study Population

The study was approved by the Ethics Committee of Tongji Hospital. Informed consent was obtained from all participants. The medical records of CM patients hospitalized in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from January 1, 2010, to December 31, 2016, were reviewed. Patients were excluded from the study for the following reasons: (1) if the medical records were incomplete; (2) if the age was under 16 years old; (3) if the pulmonary nodules were confirmed or highly suspected to be cancer or an entity other than cryptococcosis by the attending physician; and (4) if the size of nodules was larger than 3 cm. Patients with pulmonary nodules were defined as patients who obtained a chest CT scan between the onset of symptoms and the date of diagnosis, with detection of pulmonary nodules by two radiologists regardless of number (solitary or multiple), location, border characteristics (well-defined with smooth margins or poorly defined with irregular margins). For all patients, no chest CT scan was performed, or the absence of a nodule was once demonstrated by chest CT before enrollment in the current study. CM was diagnosed by a positive fungal culture for Cryptococcus from cerebrospinal fluid (CSF) or by positive CSF India ink staining [4].

Laboratory Data

Baseline demographic characteristics (including gender, age, smoking history), coexisting baseline conditions (measured using the Charlson Comorbidity Index [17]), clinical manifestations (including admission history, initial symptoms, physical and neurological examination and Glasgow Coma Scale [18]), findings of head CT and magnetic resonance imaging

(MRI), results of laboratory tests including CSF and serum examination, and management decisions were recorded. The CSF/serum albumin ratio and CSF/serum glucose ratio were calculated.

Neurological abnormalities on head CT or MRI were defined as any parenchymal abnormality (including meningeal enhancement, bleeding, and strokes).

Treatment Strategies and Outcome

Patients diagnosed with CM were recommended to be treated with amphotericin B, and the treatment response was evaluated at week 2 based on clinical and mycological criteria [19, 20]. In this study, the initial therapy including amphotericin B (Amp-B) means treatment with Amp-B for at least 7 days after diagnosis with CM [20].

The primary study endpoint was an unfavorable outcome measured using Glasgow Outcome Scale score when patients were discharged [21]. Score of 1–4, which indicates death, vegetative status, severe and moderate disability, was considered unfavorable clinical outcomes [21].

Statistical Analysis

Categorical data were described as numbers (percentage) and were analyzed using the Chi-square test or Fisher's exact test. Continuous data were described as median (range) or mean ± SD and were analyzed using the Mann–Whitney *U* test or an independent *t* test. Risk factors for adverse clinical outcome were analyzed using a logistical regression model. All variables were initially examined by univariate analysis, and those with a p value < 0.1 were examined by multivariate analysis. A 2-tailed p value < 0.05 was considered significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows (version 21.0; IBM Corp, NY, USA).

Results

Patients' Characteristics

A total of 90 CM patients were enrolled in this study. The pathogenic agents included 90 *C. neoformans* isolates. No *Cryptococcus gattii* isolates were identified. The baseline demographics and clinical manifestations of CM patients are listed in Table 1. Of these, 40 (44.4%) were identified as PN-positive patients, and 50 were PN-negative. The median age of the two groups was 43 ± 13 and 39 ± 14 years old, respectively. The most common symptoms were headache (82/90, 91.1%), nausea or vomiting (41/90, 45.6%), and fever (58/90, 64.4%). There were no significant differences between the two groups in terms of age, gender, smoking history, symptoms, signs, underlying conditions, and duration of symptoms from presentation to hospitalization.

Laboratory Results

Laboratory data are listed in Table 2. There were no significant differences in white blood cell counts and serum C-reactive protein levels between the two groups. However, PN-positive patients were more likely to have CSF protein > 1000 mg/L ($p = 0.021$), CSF glucose < 2.5 mmol/L ($p = 0.016$), and higher CSF/serum albumin ratios ($p = 0.029$). In addition, PN-positive patients had higher rates of abnormal head CT (62.1 vs. 33.3%, $p = 0.021$) and higher rates of abnormal head MRI manifestations (93.8 vs. 75%, $p = 0.034$). There were no significant differences in the rates of positive blood and CSF culture results, India ink staining, or cryptococcal antigen between the two groups.

Management and Clinical Outcomes

As listed in Table 3, there were no significant differences between the two groups in terms of average length of hospitalization, rates of ICU admission, amphotericin B in the initial therapy, or empirical use of antibiotics. However, PN-positive patients were less likely to show overall treatment response at week 2 than were PN-negative patients (27.5 vs. 56%, $p = 0.007$). A total of 53 (58.9%) participants had unfavorable clinical outcome. PN-positive patients had significant higher rates of unfavorable outcome (72.5 vs. 48%, $p = 0.019$).

Contributing Factors of Adverse Clinical Outcomes

The univariate analysis revealed several potential factors contributing to the unfavorable clinical

Table 1 Demographic and clinical characteristics of CM patients

Variables	PN-positive (n = 40)	PN-negative (n = 50)	p value
Age, median ± SD	43 ± 13	39 ± 14	0.221
Gender (male), n (%)	25 (62.5%)	37 (74%)	0.242
Smoking history, n (%)	16 (40%)	23 (46%)	0.568
Coexisting baseline conditions			
Charlson Comorbidity Index score, median ± SD	1.9 ± 2.1	1.5 ± 2.1	0.49
Charlson Comorbidity Index score ≥ 1, n (%)	27 (67.5%)	27 (54%)	0.194
Immunocompromised[a], n (%)	14 (35%)	16 (32%)	0.764
HIV, n (%)	6 (15%)	7 (14%)	0.893
Duration from symptoms presentation to hospitalization, median (range) (days)	39 (2–180)	37 (5–210)	0.768
Presenting symptoms, n (%)			
Headache	36 (90%)	46 (92%)	0.74
Nausea	19 (47.5%)	22 (44%)	0.74
Fever	23 (57.5%)	35 (70%)	0.218
Disorders of consciousness	5 (12.5%)	7 (14%)	0.835
Physical signs, n (%)			
Nuchal rigidity	17 (42.5%)	16 (32%)	0.304
Abnormal neurological examination[b]	8 (20%)	12 (24%)	0.65

[a]Patients with HIV, organ transplantation, long time of steroid use and other conditions affecting immune status

[b]GCS score < 15, seizure, cranial nerve abnormality, blurred vision and so on

outcome of CM patients (Table 4). Multivariate analysis showed that immunocompromise (OR = 16.27; 95% CI = 1.19–223.36; p = 0.037) and CSF glucose < 2.5 mmol/L (OR = 34.60; 95% CI = 1.11–1083.89; p = 0.044) indicated poor outcome in PN-positive CM patients, while CSF glucose < 2.5 mmol/L (OR = 4.64; 95% CI = 1.22–17.71; p = 0.025) also indicated poor outcome in PN-negative patients (Table 5). Amphotericin B in the initial therapy (OR = 0.149; 95% CI = 0.036–0.61; p = 0.008) was a protective factor for PN-negative patients.

Discussion

Cryptococcosis has been described as an uncommon opportunistic infection in both immunocompromised and immunocompetent individuals. It most often involves the lung and central nervous system [1]. Of the 90 patients identified with CM in the present study, only 13 (14.4%) were documented as HIV-positive. This was lower than rates reported in other regions such as Europe (68%) and the USA (84%) [22] but was similar to the data from China, where CM occurred most frequently in HIV-negative patients [10, 20].

Although less typical clinical manifestations of CM patients were reported previously, the most common symptoms of the 90 patients in the present study were headache, fever, nausea or vomiting, partly consistent with data reported by Chen et al. [23]. No significant differences in the above-mentioned symptoms between the two groups in our study were found.

In this study, male predominance was shown in the two groups (62.5 and 74%, respectively), which was in accordance with a previous study [22]. That proposed several possible contributing factors, including increased environmental exposure, hormonal effects, and/or genetic predisposition. However, the specific reason for these phenomena is not fully understood.

Poor prognostic factors for CM in previous findings included CSF protein > 1000 mg/L, CSF glucose < 2.5 mmol/L, and decreased CSF/serum glucose ratio. Zheng et al. [24] insisted that a decreased CSF

Table 2 Laboratory results of CM patients

Variables	PN-positive (n = 40)	PN-negative (n = 50)	p value
WBC count, $*10^9$/L, mean ± SD	8.6 ± 3.2	7.7 ± 3.6	0.219
WBC > 12 or < 4, $*10^9$/L, n (%)	10 (25%)	18 (36%)	0.263
N, $*10^9$/L, mean ± SD	6.7 ± 3.0	5.9 ± 3.4	0.276
L, $*10^9$/L, mean ± SD	1.18 ± 0.61	1.17 ± 0.72	0.906
M, $*10^9$/L, mean ± SD	0.64 ± 0.48	0.51 ± 0.28	0.14
CRP, median (range)	26.8 (0.1–301)	15.7 (0.2–183.9)	0.354
CSF leukocyte count, $*10^6$/L, median (range)	146.1 (0–2000)	164.2 (0–1230)	0.772
CSF protein, mg/L, median (range)	1040.9 (300–6470)	1111.6 (200–13,100)	0.838
CSF protein > 1000 mg/L, n (%)	17 (42.5%)	10 (20%)	0.021*
CSF/serum albumin ratio, $*10^{-3}$, median (range)	24.9 (4.6–173.5)	14.5 (2–63.4)	0.029*
CSF glucose, mmol/L, median (range)	1.9 (0.13–8.25)	2.1 (0.28–4.23)	0.531
CSF/blood glucose ratio, median (range)	0.29 (0.02–0.93)	0.36 (0.04–0.85)	0.176
CSF glucose < 2.5 mmol/L, n (%)	27 (67.5%)	21 (42%)	0.016*
CSF chloride, mean ± SD	118.7 ± 7.3	120.7 ± 6.3	0.183
Positive blood culture, n (%)	4 (10%)	3 (6%)	0.481
Positive CSF culture, n (%)	28 (36)	38 (42)	0.121
CSF fungal spore, n (%)	15 (36)	13 (42)	0.325
India ink staining, n (%)	29 (72.5%)	36 (72%)	0.958
Cryptococcal antigen, n/N (%)	14 (30)	21 (37)	0.411
Abnormal head CT, n (%)	18/29 (62.1%)	12/36 (33.3%)	0.021*
Abnormal head MRI, n (%)	30/32 (93.8%)	30/40 (75%)	0.034*

WBC white blood cell; *N* neutrophil count; *L* lymphocyte count; *M* monocyte count; *CSF* cerebral spinal fluid

*$p < 0.05$ for patients with versus without pulmonary nodules

Table 3 Management and clinical outcomes of CM patients

Variables	PN-positive (n = 40)	PN-negative (n = 50)	p value
Length of hospitalization, median (range) (days)	30 (2–130)	33 (2–180)	0.727
ICU admission, n (%)	9 (22.5%)	10 (20%)	0.773
Amphotericin B in the initial therapy, n (%)	30 (75%)	35 (70%)	0.599
Empirical use of antibiotics, n (%)	25 (62.5%)	29 (58%)	0.665
Treatment response at week 2, n (%)	11 (27.5%)	28 (56%)	0.007*
Unfavorable clinical outcomes, n (%)	29 (72.5%)	24 (48%)	0.019*

ICU intensive care unit

*$p < 0.05$ for patients with versus without pulmonary nodules

glucose level was associated with high Cryptococcus titer and weakened immunity. The CSF/serum albumin ratio has been recognized as an indicator of blood–CSF barrier (BCB) function [25]. Our study revealed some laboratory data differences between the two cohorts. PN-positive patients more often had CSF protein > 1000 mg/L, CSF glucose < 2.5 mmol/L, and a higher CSF/serum albumin ratio.

Thus, our results showed that PN-positive patients might have more serious BCB dysfunction and weak immune function. A previous study showed that the CSF/serum albumin ratio in patients with tuberculous

Table 4 Univariate analysis of factors associated with an unfavorable clinical outcome in CM patients with and without nodules on chest CT

Variables	PN-positive			PN-negative		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age ≥ 50	0.848	0.175–4.103	0.838	3.158	0.746–13.359	0.118
Male	0.935	0.222–3.944	0.927	0.82	0.225–2.989	0.764
Smoking history	0.733	0.18–2.986	0.665	0.894	0.29–2.757	0.845
Charlson Comorbidity Index score ≥ 1	0.733	0.18–2.986	0.665	0.894	0.29–2.757	0.845
Immunocompromise	8.125	0.917–72.021	0.06	4.875	1.173–20.261	0.029
HIV	–	–	–	6.364	0.719–56.353	0.096
Duration from symptoms presentation to hospitalization (days)	4.821	0.884–26.3	0.069	0.419	0.129–1.366	0.149
Headache	0.867	0.08–9.343	0.906	–	–	–
Nausea or vomiting	1.875	0.45–7.821	0.388	0.556	0.178–1.734	0.312
Fever	0.081	0.009–0.72	0.024	0.889	0.26–3.044	0.851
Disorder of consciousness	1.6	0.159–16.131	0.69	5.217	0.578–47.096	0.141
Nuchal rigidity	2.857	0.629–12.981	0.174	0.424	0.126–1.426	0.166
Abnormal neurological examination	3.182	0.344–29.432	0.308	2.7	0.631–11.551	0.18
WBC	0.457	0.1–2.091	0.313	4.544	1.228–16.881	0.023
CSF protein > 1000 mg/L	1.235	0.295–5.181	0.773	4.275	0.816–22.390	0.086
CSF glucose < 2.5 mmol/L	5.76	1.249–26.566	0.025	4.091	1.222–13.690	0.022
CSF/blood glucose ratio	4.594	1.052–20.057	0.043	5.236	1.495–18.339	0.01
Positive blood culture result	1.154	0.107–12.44	0.906	–	–	–
Cryptococcal antigen	3.176	0.58–17.406	0.183	1.32	0.42–4.149	0.634
ICU admission	–	–	–	3.619	0.682–19.208	0.131
Amphotericin B in the initial therapy	0.238	0.044–1.299	0.097	0.166	0.045–0.619	0.008
Empirical use of antibiotics	0.263	0.029–2.395	0.236	1.119	0.363–3.452	0.845

OR odds ratio; *CI* confidence interval

Table 5 Multivariate analysis of factors associated with an unfavorable clinical outcome in CM patients with and without nodules on chest CT

Variables	PN-positive			PN-negative		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Immunocompromise	16.27	1.19–223.36	0.037*	–	–	–
CSF glucose < 2.5 mmol/L	34.6	1.11–1083.89	0.044*	4.64	1.22–17.71	0.025*
Amphotericin B in the initial therapy	–	–	–	0.149	0.036–0.61	0.008*

OR odds ratio; *CI* confidence interval

*$p < 0.05$

meningitis who recovered was higher than that in patients who experienced a progress of illness, which may have been caused by weakening of the treatment effect due to hindrance of the drug delivery by the BCB [26]. Our observations showed that PN-positive CM patients experienced worse treatment response at week 2 and were more likely to have unfavorable clinical outcome. Therefore, evaluation of altered BCB function will help achieve a better treatment

response since clinicians can determine when to implement intrathecal injection for CM patients.

In our series, PN-positive patients had higher rates of abnormal head CT and MRI scanning than those of PN-negative patients. This might indicate different disease severity, a result similar to that of a previous study by Rodrigo et al [27]. In addition, we showed that immunocompromise and CSF glucose < 2.5 mmol/L independently contributed to unfavorable clinical outcome for PN-positive patients. CSF glucose < 2.5 mmol/L was also independently associated with unfavorable clinical outcome for PN-negative patients. These findings were consistent with a prior study, showing that low CSF glucose usually indicated weak host immune state [24, 25]. These studies also suggested that a decreased ratio of CSF/blood glucose was a contributing factor of worse prognosis and comparatively shorter survival. This ratio was not associated with prognosis in our patients. This finding might be due to the small number of cases in the present study. In addition, recent guidelines suggested that amphotericin B should be used in the initial therapy to improve treatment response [19]. This might explain why amphotericin B in the initial therapy was a protective factor for PN-negative patients in this study.

The reasons for the differences between the two cohorts remain unknown. One possibility is that the nodules in the lung may have represented a presentation of PC that was not determined because we excluded patients with pulmonary nodules that were confirmed to be or were highly suspicious for cancer, or that were suspected to be granuloma or any other entity other than cryptococcosis. The presence of PC had a detrimental influence on CM patients, and the resolution of PC with antifungal therapy had a beneficial influence on the recovery from CM.

There are several limitations of this study. First, this was a retrospective study performed in a single hospital, and some medical records were inevitably missing. Second, some patients in the current study only stayed several days undergoing treatment for CM before they were sent to specialized hospital for HIV treatment. This was far from enough time to show an effect, possibly exerting an influence on our results. Third, the number of CM patients in our study was small, which may have led to an underestimation of the significant factors. We could only pay attention to the existence of pulmonary nodules on chest CT without analyzing the effect of different characteristics including nodule number, location, size, border, while ignoring other radiological features such as pleural effusion. Therefore, we were not able to perform a subgroup analysis. Nodules only represent indirect evidence for the existence of PC, and therefore, they are not reliable diagnostic indicators. Fourth, no case of *C. gattii* isolate was found in our study, and thus, we could not compare different clinical features between CM patients with *C. neoformans* infections and *C. gattii* infections.

In summary, our study demonstrated that CM patients with pulmonary nodules differ significantly from patients without nodules with respect to laboratory tests, management, and disease severity. In addition, we identified several clinical features associated with unfavorable clinical outcomes in both groups of patients. Our study indicated that CM patients with pulmonary nodules experienced poorer outcomes than patients with CM alone. Therefore, we suggest that all CM patients are essential to be examined by chest CT to exclude pulmonary involvement. Future studies are expected to elucidate the mechanisms for this effect of PC on the clinical features of CM patients. Such studies would be important from both a research and public health perspective.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

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