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Cryptococcosis in Patients with Nephrotic Syndrome: A Pooled Analysis of Cases

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Abstract Cryptococcosis is an infection that may be lethal in patients with nephrotic syndrome (NS). However, there is relatively limited epidemiological and clinical data about cryptococcosis in NS patients. We performed a pooled analysis to systemically summarize the epidemiology, risk factors, clinical and laboratory characteristics, treatments and outcomes of cryptococcosis in NS patients. Using data pooled from our hospital and studies identified via searches of three literature databases, 17 cases were identified for inclusion in this analysis. The prevalence of cryptococcosis in NS was 0.3%, with a higher rate in more recent years. Most patients were Asian (94%) and from upper-middle to high-income countries (76%). The median time interval from NS diagnosis to cryptococcosis diagnosis among the cryptococcosis patients was 16 months, and 46% of the identified cryptococcal infections were diagnosed within the first year of NS diagnosis. Cutaneous cryptococcosis was frequently diagnosed among the included patients (35%), 58% received an erroneous diagnosis and inappropriate treatment, 90% of whom had a cryptococcal infection mistaken for a bacterial infection. The mortality rate was 35%. Standard therapeutic strategies should be emphasized for both antifungal treatment and renal disease control. Further studies conducted in various medical centers are warranted to confirm our conclusions.

Keywords Cryptococcosis · Cryptococcal meningitis · Nephrotic syndrome · Pooled analysis

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Background

Cryptococcal disease is a systemic fungal infection that may be caused by seven newly recognized encapsulated yeast species belonging to the *Cryptococcus neoformans*/*C. gattii* species complex [1]. The meninges and lungs have been identified as the sites most frequently involved in cryptococcal infections, followed by the skin, blood, liver, bones, and other sites [2–4]. *Cryptococcus* tends to infect hosts with predisposing factors, including populations with underlying infections (i.e., HIV infection, tuberculosis, and hepatitis) and non-communicable diseases (NCDs) such as solid-organ transplants and systemic lupus erythematosus (SLE) [5–8]. According to Park et al. [9] in 2009, nearly 625 000 HIV/AIDS patients died within three months after cryptococcal infection, resulting in a mortality rate of 60%. However, a global decrease in cryptococcosis mortality among HIV-infected patients has been observed as a result of improved medical conditions in HIV-pandemic regions in the post-HAART (highly active antiretroviral therapy) era [10]. However, there is an increasing rate of cryptococcosis in NCD populations in middle- and high-income countries. For example, 84 and 80% of cryptococcal infections in China and the USA have been reported to be unrelated to HIV infection, respectively [11, 12].

Among the many NCDs are renal diseases, which have been suggested as having increased susceptibility to fungal infections [13, 14]. For example, the nephrotic syndrome (NS) accounted for approximate 23% of all renal disease cases in one study [15], and with an incidence of nine per 100 000 people identified in another [16]. Etiologically, NS is caused by primary (also called *idiopathic*) or secondary (such as SLE and diabetes mellitus) renal damage and is closely associated with immunoreaction abnormity. NS is characterized by heavy proteinuria (>3.5 g/day), hypoalbuminemia (<30 g/L), hyperlipemia and edema. Among NS patients, renal loss of plasma proteins (especially immunoglobulin), long-term administration of immunosuppressive agents and disruption of the skin barrier due to edema may be associated with increased susceptibility to infection [14, 17]. A previous study reported that nearly 20% of NS patients had experienced various infections, including mycoses [18]. Although rare, fungal infections in NS patients have frequently been reported in association with delayed or erroneous diagnoses and high lethality. Indeed, renal diseases rank sixth among the most important underlying diseases of cryptococcosis, and in NS populations, an increasing number of cryptococcal infections have been observed recently [19–28].

However, there is a relative lack of knowledge regarding this rare but fatal fungal infection among NS patients. The scarcity of coherent clinical data is impeding the development of effective prevention and treatment strategies. Hence, we performed a pooled analysis of patients from our hospital and those reported in the literature to summarize the epidemiological and clinical characteristics of NS patients with cryptococcosis.

Methods

Case Selection

The protocol for this research was approved by the Institutional Review Board of Shanghai Changzheng Hospital (Approval Number: 2016SL021). Cases included in the pooled analysis consisted of original cases from our hospital and published cases from electronic literature databases. The original cases with discharge diagnoses of "cryptococcosis" or "nephrotic syndrome" who were admitted to our hospital from 2005 to 2015 were identified in the inpatient medical record database. We further systematically reviewed cases published in three major electronic literature databases, PubMed, Embase and Google Scholar. The main search terms "cryptococcosis" and "nephrotic syndrome" were used as both MeSH terms and free text words, and the search strategy was not limited by language or publication date. A definitive diagnosis of cryptococcosis was defined as the identification of positive findings upon *Cryptococcus* culture, India ink staining, histology, or cryptococcal antigen (CrAg) tests. NS was defined based on the criteria described in a previous study [18].

Data Collection and Statistical Analysis

Demographic and clinical data were extracted independently by three authors using a pre-designed form and entered into EpiData (version 3.1, The EpiData Association, Odense, Denmark). The following data were extracted for (1) demographic and epidemiologic data, (2) clinical manifestations and laboratory test results, (3) mycological results, and (4) treatment

strategies and outcomes. The different types of steroids used for NS control were converted into prednisone equivalents via a free online tool prior to inclusion in the overall analysis (http://www.globalrph.com/steroid.cgi). SPSS (version 21, International Business Machines Corporation, New York, U.S.A.) and Graph Pad Prism (version 5, GraphPad Software, Inc. California, U.S.A.) were used for statistical analysis. Results are presented as the mean ± standard deviation (SD) for normal data.

Results

Demographic and Epidemiologic Profiles

The demographic and epidemiologic profiles of the 17 patients included in the pooled analysis are shown in Table 1. These include 11 from the literature and six in our medical records database. From 2005 to 2015, 1968 NS and 187 cryptococcosis patients were admitted to our hospital. The prevalence of cryptococcosis among NS patients was 0.3% (6/1968). In contrast, NS was more frequently reported as an underlying disease of cryptococcosis (3%, 6/187), accounting for 43% (6/14) of all renal damage-related cryptococcosis cases (including NS, renal failure, and glomerular nephritis as underlying diseases). Eleven cases [19–29] were identified in the systematically reviewed studies, of which nine were written in English, one was written in Chinese, and one was written in Japanese. Most (10/17, 59%) of the included cases were reported after 2010; however, five cases were reported during 2000–2009, and two cases were reported prior to 1999.

Males were predominant (65%, 11/17) among the included cases. The mean age of the cases was 36.41 ± 18.84 years, and 24% (4/17) were children below 16 years of age. The global distribution of the identified cases is shown in Fig. 1. All of the patients were from upper-middle to high-income countries (77%, 13/17) or medical center cities in countries with lower-middle income economies (classification based on World Bank data: http://data.worldbank.org/about/country-and-lending-groups). Except for one case from South America (Argentina), the remaining patients were from Asia (94%) [China ($n = 9$, including six original cases), Japan ($n = 3$), India ($n = 3$), and Pakistan ($n = 1$)]. Only seven cases (six from our hospital and one published case) had been reported as suspected *Cryptococcus* infections, and all except one patient were HIV seronegative. One child was diagnosed with concurrent *Cryptococcus* and *Plasmodium falciparum* infections. Another child was diagnosed with a granulocytosis caused by the use of high-dose corticosteroids and immunosuppressants for NS control just before infection.

NS State and Control

We analyzed the time interval from NS diagnosis to cryptococcosis diagnosis (Fig. 2). The median course of NS prior to the diagnosis of cryptococcosis was 16 months (ranging from 0.5 to 48 months), and nearly half of the cryptococcal infections (47%, 7/15) were diagnosed within the first year of NS diagnosis. Only two patients (12%) were diagnosed with NS secondary to SLE or rheumatoid arthritis (shown in Table 1). Of the 15 primary NS patients, eight were diagnosed via renal biopsy, for whom the most frequently identified pathological diagnosis was minimal change disease (4/8), followed by IgA nephropathy ($n = 1$), membranous glomerulonephritis ($n = 1$), focal segmental glomerulosclerosis ($n = 1$) and necrotizing glomerulonephritis ($n = 1$). The average 24-h urinary protein excretion rate was 2.37 ± 3.00 g/24 h (95% CI (0.07, 4.68 g/24 h)), and 33% patients ($n = 4$) presented as poor proteinuria control, defined as ≥3.5 g/24 h or +3 protein on the urine analysis (shown in Online Resource 1). Nine cases (9/12, 75%) had plasma albumin levels below the serum reference range (35–45 g/L). Five patients (83%, 5/6) had IgG levels below the serum reference range (IgG > 18 - years: 7.67–15.90 g/L). Fifteen patients received a corticosteroid to control NS. Six patients (55%, 6/11) received moderate to high doses of a prednisone equivalent (≥30 mg/day). The average daily prednisone equivalent dose was 31.93 mg/day (95% CI 15.90, 47.97 mg/day). Six patients also received immunosuppressants as part of a combined therapy.

Clinical Manifestations

Among the NS patients, the most common site of *Cryptococcus* infection was the brain ($n = 9$), followed by the skin ($n = 6$), lungs ($n = 4$), blood ($n = 3$) and bones ($n = 1$). Of the included patients, 35% (6/17) were diagnosed with a focal infection localized to the skin ($n = 3$) or lungs ($n = 3$). Although two of the patients presented neurological

Table 1 Demographic and epidemiologic characteristics of included cases

Case	Publication date	Gender	Age (years)	Pigeon contact	Cause of NS (primary/secondary)	Duration of NS (months)	HIV	Geographical location	Publishing language
1	2015	M	23	Neg	Primary (IgA nephropathy)	20	Neg	Jiangsu, China	English
2	2015	F	62	Neg	Primary	36	Neg	Shandong, China	Original data
3	2014	F	15	ND	Primary (focal segmental glomerulosclerosis)	ND	Neg	Kolkata, India	English
4	2014	M	42	Neg	Primary	24	Neg	Shaanxi, China	Original data
5	2013	M	34	ND	Primary (minimal change disease)	12	Neg	Beijing, China	English
6	2013	F	40	Neg	Primary	48	Neg	Hubei, China	Original data
7	2013	F	53	Pos	Primary (minimal change disease)	10	Neg	Shanghai, China	Original data
8	2011	M	56	ND	Primary (minimal change disease)	6	Neg	Zhejiang, China	Original data
9	2011	M	8	ND	Primary (necrotizing glomerulonephritis)	24	Neg	Mumbai, India	English
10	2010	F	58	Neg	Primary	4	Neg	Zhejiang, China	Original data
11	2006	M	37	ND	Primary (membranous glomerulonephritis)	24	Neg	Karachi, Pakistan	English
12	2005	M	68	ND	Secondary (rheumatoid arthritis)	0.5	Neg	Fukuoka, Japan	English
13	2005	M	26	ND	Primary (minimal change disease)	8	Neg	Kochi, Japan	English
14	2004	M	12	ND	Primary	2	Neg	Chongqing, China	Chinese
15	2001	M	24	ND	Secondary (systemic lupus erythematosus)	ND	Pos	Santa Fe, Argentina	English
16	1998	M	15	ND	Primary	36	Neg	New Delhi, India	English
17	1970	F	46	ND	Primary	16	Neg	Tokyo, Japan	Japanese

M male, *F* female, *NS* nephrotic syndrome, *HIV* human immunodeficiency virus infected, *Pos* positive, *Neg* negative, *ND* no data

symptoms, disseminated infections were not confirmed by mycological tests.

Cryptococcal Meningitis

Of the nine patients with cryptococcal meningitis, four patients presented with fever (38.2 ± 1.26 °C) as the earliest sign of infection (78%). Seven patients complained of mild (14%) to severe (86%) headaches, and in 71% of patients, headaches were the earliest symptom of infection. Nearly half (4/9, 44%) of the patients developed nausea and vomiting. Four patients had slight changes in mental state. Neck stiffness was less common (2/9, 22%), and no patient developed vision or hearing impairment.

Lumbar punctures were performed on nine patients. Turbid cerebrospinal fluid (CSF) was noted in two patients. The average intracranial pressure (ICP) was 215 mm H_2O (IQR 120, 260 mm H_2O), and high ICP (defined as ≥250 mm H_20 [30]) was found in two patients. The following findings were demonstrated upon CSF analysis: glucose, 33.5 mg/dl (IQR 21.5, 50.4 mg/dl); protein, 68.65 mg/dl (IQR 54.7, 86.5 mg/dl); chlorine, 126 mmol/L (IQR 124, 129 mg/dl); and white blood cells, 38/mm^3 (IQR 5, 232/mm^3).

Cutaneous Cryptococcosis

Three of the six cutaneous cryptococcosis patients had focal infections. The other three had disseminated infections with simultaneously diagnosed infections of the brain, blood, lung or bone marrow. The most frequently involved site was the leg ($n = 4$), followed by the trunk ($n = 2$), face ($n = 2$), hands ($n = 2$) and arms ($n = 1$). All of the six patients presented fever, four (4/6) of which had a high fever (>39 °C). Three patients reported the presence of painful skin lesions.

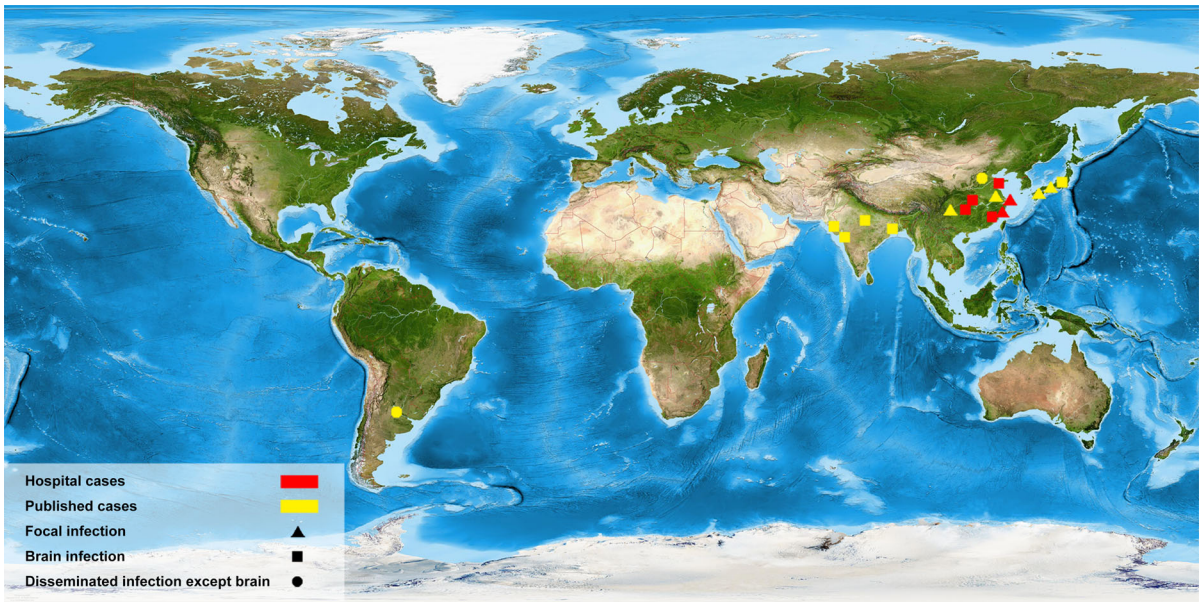

Fig. 1 Global distribution of cases

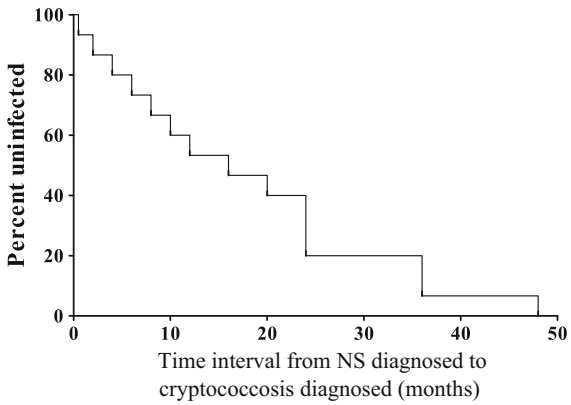

Fig. 2 Time interval from NS diagnosis to cryptococcosis diagnosis

Multiple types of skin lesions were identified, including edematous ($n = 5$), erythematous ($n = 3$), ulcerative ($n = 3$), nodular ($n = 2$) and papular ($n = 1$) lesions. Three patients also presented cryptococcal cellulitis, with one ultimately progressed to necrotizing fasciitis.

Pulmonary Cryptococcosis

Among the four patients diagnosed with pulmonary cryptococcosis (PC), three had focal infections. Half (2/4) of the patients were asymptomatic, and the remaining two cases presented symptoms of only cough and increased phlegm production. The imaging results indicated that the areas in which lesions were most frequently located in the lungs were the right (2/3, 67%) and upper (2/3, 67%) lobes.

Mycological Results

The results of the species identification and anti-fungal sensitivity tests are shown in Table 2. India ink staining was the most frequently used method of microscopic examination, and positive results were identified in 14 patients. Periodic acid-Schiff staining (PAS) was the most frequently used method of skin infection diagnosis (4/6). The average cryptococcal antigen (CrAg) titers were 1:366 in blood and 1:226 in CSF. All strains isolated from the 17 patients were *Cryptococcus neoformans*, among which eight were further identified as *C. neoformans var. neoformans.* Anti-fungal drug sensitivity results were available for eight patients; the majority of these strains demonstrated sensitivity to a wide spectrum of antifungal agents, except for one strain isolated from a skin lesion that showed resistance to fluconazole.

Therapeutic Strategies and Outcomes

Therapeutic details and outcomes reported for the included cases are presented in Online Resource 2. Of the 17 patients, 10 (59%) received erroneous diagnoses and inappropriate treatments. Specifically, nine cryptococcal infection cases were mistaken for bacterial infections, and the remaining patient was diagnosed with pneumocystis carinii and mycoplasma pneumonia. All misdiagnosed cases received antibacterial treatment.

Although the majority of the therapeutic strategies were based on guidelines, substandard therapies were also observed in some cases. Two of the patients underwent cryptococcal meningitis induction treatment with an insufficient dosage (<0.7 mg/kg) or duration (<4 weeks) of amphotericin B, and another patient received amphotericin B monotherapy without the prescription of flucytosine. Additionally, one PC patient only took 200 mg of fluconazole daily, whereas guidelines indicate that the standard dose should be 400 mg/day for HIV-negative patients with lung infections.

Six patients died of various causes (such as acute renal, respiratory or heart failure), resulting in a fatality rate of 35%.

Discussion

With the advent of HAART for HIV control in the late 1990s, a global decrease in the prevalence of cryptococcosis among the HIV-positive population has been observed. However, cryptococcosis continues to rank as one of the most common fungal diseases, and non-HIV cryptococcosis has recently been recognized as a neglected but increasingly important infection. Among non-HIV population, cases of cryptococcosis in NS patients have been continuously reported since the first case was identified in 1969 [24], and NS has now become one of the most important underlying diseases of cryptococcosis [11]. However, the epidemiologic profile of this disease remains extremely unclear. Our research represents the first and largest study so far with regard to epidemiology, risk factors, clinical and laboratory characteristics, treatment and outcomes of cryptococcal infections in NS patients.

We found that the prevalence of cryptococcosis in NS patients was 0.3%. A comparison of the prevalence of this condition between various medical centers was not possible because at present, this is the only study that has been conducted regarding the prevalence of cryptococcosis in this population. Among the 187 cryptococcosis patients admitted to our hospital, 7.5% had renal diseases (NS, renal failure, glomerular nephritis, etc.), of which NS (6/187) constituted a high proportion (42.9%). This result is consistent with that of a recent Chinese nationwide literature review, which reported that kidney disease (including NS) was the sixth most common underlying disease of cryptococcosis [11]. Previous findings indicated that renal diseases, especially NS, are important underlying diseases of cryptococcosis that warrant further study. Our study also demonstrated a recently increasing trend in the reporting of cryptococcosis cases among NS patients. For example, the number of cases reported after 2010 was twice that of the cases reported from 2000 to 2009 and five times that of the cases reported before 2000. We hypothesize that this increasing trend may be the result of changes in the epidemiology of host populations, increased availability of advanced diagnostic tools (such as the CrAg test) and improved awareness of cryptococcosis as a frequent fungal infection. We observed that 24% of the patients were children below the age of 16 years. This high proportion of pediatric patients may pose diagnostic and treatment challenges in clinical practice due to the subtle symptoms and side effects of antifungal agents that have been identified in this population [31].

The majority of the patients included in our study were from countries categorized as upper-middle to high-income (77%) according to the World Bank classification. Cryptococcosis continues to be highly prevalent in HIV-pandemic regions. However, in relatively higher-income counties such as Japan, America and China [3, 11, 32], non-HIV cryptococcosis is predominant. The prevalence of non-HIV cryptococcosis has raised numerous concerns, as the majority of existing clinical experience was gained in HIV-infected populations, which may somewhat limit the generalizability of previous findings to cryptococcosis cases with other backgrounds. Another interesting finding was that the majority of cases were identified in Asia (94%, 16/17). However, whether this Asian predominance was the result of differences in

Table 2 Results of species identification and anti-fungal sensitivity tests

Case	Position	Stain identification	Microscopic examination	Culture	Latex agglutination test	Drug sensitive test
1	Skin	*Cryptococcus neoformans*	PAS + (skin)	+(skin), −(blood)	1:32 (blood)	I (S), F (R)
2	Brain	*C. neoformans var. neoformans*	India ink + (brain)	+(brain)	1:2560 (blood); 1:320 (brain)	V (S), F (S), I (S), 5-FC (S), AmB (S)
3	Brain, blood	*Cryptococcus neoformans*	ND	+(brain, blood)	ND	F (S), K (S), 5-FC (S), AmB (S)
4	Brain	*C. neoformans var. neoformans*	India ink + (brain)	+(brain)	1:160 (brain); 1:1280 (blood)	V (S), F (S), I (S), 5-FC (S), AmB (S)
5	Skin, blood, lungs	*Cryptococcus neoformans*	PAS + (skin)	+(skin, blood, sputum)	1:1024 (blood)	ND
6	Brain	*C. neoformans var. neoformans*	India ink + (brain)	+(brain)	1:20 (blood); 1:40 (brain)	V (S), F (S), I (S), 5-FC (S), AmB (S)
7	Lungs	*C. neoformans var. neoformans*	India ink + (sputum), PAS + (lung)	+(sputum)	1:5120 (blood)	V (S), F (S), I (S), 5-FC (S), AmB (S)
8	Lungs	*C. neoformans var. neoformans*	India ink + (sputum)	+(lung)	1:80 (blood)	F (S), I (S), AmB (S), V (S)
9	Brain	*C. neoformans var. neoformans*	India ink + (brain)	+(brain)	ND	AmB (S)
10	Brain	*C. neoformans var. neoformans*	India ink + (brain, blood)	+(brain, blood)	1:1280 (brain)	V (S), F (S), I (S), 5-FC (S), AmB (S)
11	Brain, skin, bone	*Cryptococcus neoformans*	ND	+(skin, bone)	+(brain)	ND
12	Lungs	*Cryptococcus neoformans*	Biopsy specimen positive	ND	ND	ND
13	Skin	*Cryptococcus neoformans*	PAS + (skin)	ND	+(blood)	ND
14	Skin	*Cryptococcus neoformans*	India ink + (skin), PAS + (skin)	ND	ND	ND
15	Skin, blood	*C. neoformans var. neoformans*	India ink + (skin)	+(skin, blood)	+(blood)	ND
16	Brain	*Cryptococcus neoformans*	India ink + (brain)	+(brain)	+(brain)	ND
17	Brain	*Cryptococcus neoformans*	ND	+(brain, urine)	ND	ND

Strain identification: the species and/or variety names used here followed the traditional classifications as reported by the authors. Most of the literature was published before the seven-species framework was proposed for the *C. neoformans* and *C. gattii* species complex in 2015

PAS periodic acid-Schiff staining, *ND* no data, "+" positive, *I* itraconazole, *F* fluconazole, *V* voriconazole, *5-FC* flucytosine, *AmB* amphotericin B, *K* ketoconazole, *S* sensitive, *R* resistent

the susceptibilities for NS or cryptococcosis between Asian and non-Asian populations requires further exploration [33].

The treatment status and control of NS may be highly associated with the development of cryptococcosis. In the present study, nearly half of the cryptococcal infections developed within the first year after NS diagnosis. Nearly 33% patients were reported to have heavy proteinuria, and hypoalbuminemia and hypoimmunoglobulinemia were observed in most patients. The levels of immune-related proteins, such as IgG and its complements, may decrease in association with nephrotic-range proteinuria, leading to increased susceptibility to infection. Long-term and high-dose use of corticosteroids or immunosuppressants for NS control could also increase the risk for cryptococcal infection. Of the patients included in our study, 55% received moderate to high doses of

prednisone equivalents, with an average dose of 31.93 mg/day identified. Nearly half of our cases were pathologically diagnosed with the minimal change disease (MCD), a type of idiopathic NS, and the remaining cases were diagnosed with membranous glomerulonephritis, IgA nephropathy, focal segmental glomerulosclerosis, and other idiopathic NSs. This result is consistent with previous epidemiological findings suggesting that MCD (39%) was the most common form of idiopathic NS in Asia, followed by membranous nephropathy and lgA nephropathy [34].

Cryptococcosis is most frequently characterized by disseminated infection, and the brain and lungs have previously been identified as major sites of infection [2, 3]. However, an interesting finding of our study was that among the included NS patients, cutaneous cryptococcosis (35%) was observed much more frequently than pulmonary infection (24%). The skin of NS patients may be much thinner than that of members of the general population because of the presence of a high degree of edema. In addition, edema fluid in interstitial spaces is rich in protein, serving as a potentially favorable media for the growth of pathogenic microorganisms [20].

The cases included in this study were characterized by high rates of misdiagnosis, substandard therapy and case fatality. Of the NS patients, 59% had a cryptococcal infection mistaken for a non-fungal (mainly bacterial) infection or presentation of NS. The misdiagnosis rate was even higher among the deceased cases (66%). The implementation of appropriate interventions was, therefore, delayed; meanwhile, antibacterial agents were prescribed for all of the misdiagnosed cases. In addition to this diagnostic delay, substandard treatments were identified as another major problem. Insufficient amphotericin B dosage (<0.7 mg/kg), inadequate duration of treatment (<4 weeks) and the use of amphotericin B monotherapy without flucytosine were observed in the cases included in our study, which did not strictly follow the guideline for cryptococcosis [35]. Patients with renal diseases may require corticosteroids and immunosuppressants, which may undermine their immunologic function and lead to the requirement of longer and higher doses of antifungal agents. However, the possibility that patients with undermined renal function may be intolerant to anti-fungal agents may also negatively affect cryptococcosis control. Hence, adequate and appropriate antifungal durations and dosages may increase the probability of achieving cryptococcosis control, and organ function tests should be performed throughout the course of disease.

In conclusion, this is the first and largest study conducted to increase our knowledge regarding the epidemiological and clinical characteristics of cryptococcosis in NS patients. Further studies conducted in various medical centers are warranted to confirm our conclusions.

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Author Contributions WL, MC and WP were involved in study concept and design. WF, NH, and YL collected the data. JL and YL checked the data. WF and MC were involved in analysis and interpretation of data. WF drafted the manuscript. All authors contributed to the writing of the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declared that they have no conflicts of interest.

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