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Update on disseminated cryptococcosis in non-HIV infected children

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Abstract

Background Disseminated cryptococcosis is a rare disease in children, especially in children with normal immunity. The understanding of this disease needs to be improved. This study aims to update the global situation of disseminated cryptococcosis in non-HIV infected children for the first time.

Methods The clinical data of a child with disseminated cryptococcosis was retrospectively analyzed, and disseminated cryptococcosis clinical features of published studies were summarized. Electronic databases were searched in February 2025. Clinical studies that meet the criteria were included in the present study.

Results Totally 116 cases were analyzed in this study, including 1 case in our center and 115 cases from 45 studies. The cohort included 82 males (70.7%) and 34 females (29.3%), with ages ranging from 10 months to 18 years. The main clinical manifestations were fever (79.3%), respiratory symptoms (41.4%), and neurological symptoms (39.7%), followed by hepatosplenomegaly (35.3%), rash (27.6%), lymphadenopathy (18.1%), and gastrointestinal symptoms (16.4%). *The most commonly affected organs were the lungs (77.6%), central nervous system (53.4%), and lymph nodes (51.7%).* Immunodeficiency was present in 12.9% of children (3.4% domestic cases vs. 9.5% foreign cases). Elevated eosinophils were observed in 43 patients (37.1%), and elevated IgE levels in 35 patients (30.2%). The most common pathogen-positive specimens were cerebrospinal fluid (54 cases, 46.6%), blood cultures (49 cases, 42.2%), lymph node biopsies (26 cases, 22.4%), bone marrow (18 cases, 15.5%), and skin samples (8 cases, 6.9%). Combination therapy was administered to 89 patients (76.7%), while 21 patients (18.1%) received monotherapy. Clinical improvement occurred in 94 patients (81.0%), with 15 fatal cases.

Conclusions Disseminated cryptococcosis in children often presents with fever, respiratory and neurological symptoms, *with the lungs, central nervous system, and lymph nodes being the most frequently involved organs.* Most cases do not have immunodeficiency or underlying diseases, and blood tests often reveal eosinophilia and elevated IgE levels. The positive detection rates of pathogens are relatively high in blood cultures, cerebrospinal fluid, bone marrow cultures, and lymph node biopsies. The majority of patients achieved favorable therapeutic outcomes with combination therapy.

Keywords Disseminated cryptococcosis, Immunocompetent, Children

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Introduction

Cryptococcus neoformans was listed as a top fungal priority pathogen by WHO in 2022 [1]. It was previously believed that disseminated cryptococcosis is uncommon in healthy children. However, an increasing number of studies indicate that this condition can occur in immunocompetent pediatric patients [2, 3]. Currently, disseminated cryptococcosis is mostly reported as sporadic cases, and the global incidence and overall profile remain unclear. This study retrospectively analyzes case of disseminated cryptococcosis in children from our center and, for the first time, summarizes globally reported cases of disseminated cryptococcosis in non-HIV-infected children. By utilizing large-sample data, it comprehensively describes the clinical characteristics, diagnosis, treatment, and therapeutic outcomes of disseminated cryptococcosis in children, aiming to enhance healthcare professionals' understanding and management of this disease.

Methods

Inclusion and exclusion criteria

The inclusion criteria were cases of children with disseminated cryptococcosis, cases with complete medical records. The diagnostic criteria for disseminated cryptococcosis were defined as the spread of cryptococcus to two or more organs [4]. The exclusion criteria were cases with HIV infection, cases without immune function testing.

Patient

A patient diagnosed with disseminated cryptococcosis in the First Affiliated Hospital of Guangxi Medical University was enrolled in this study.

Clinical data collection

Demographic characteristics (gender, age of onset), clinical manifestations (fever, cough, sputum production, abdominal pain, skin lesions, etc.), physical examination findings, auxiliary examination (blood routine examination, chest CT, etc.), immune function (immunoglobulins, T-cell subsets, complement levels), treatment were collected for the enrolled patient. Follow-up information included response to antifungals and prognosis.

Information sources of review

We searched the databases (CNKI, Wan Fang, Medline, Embase, and Pubmed) for data up to February 2025 and included pediatric cases diagnosed with disseminated cryptococcosis. These cases had relatively complete data, encompassing information on gender, age, primary manifestations, positive physical examinations, laboratory tests, medications, and treatment efficacy. We have summarized the gender, age, primary manifestations, immune status, underlying diseases, auxiliary examinations (including eosinophil count, IgE levels, and pathogenetic tests), antifungal treatment medications, and therapeutic outcomes of disseminated cryptococcosis in children as reported in China and outside of China. A comparison of the clinical characteristics of disseminated cryptococcosis in children between domestic and international cases has been conducted, including age, clinical manifestations, treatment, and outcomes.

Statistical analysis

Statistical analysis was performed using SPSS 22.0 software. Categorical data were expressed as number (percentage) [n (%)], and intergroup comparisons were analyzed using the Chi-square test. Non-normally distributed continuous data were presented as median (25th percentile, 75th percentile) [M (P25, P75)], with intergroup differences assessed by the Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

Results

Case presentation

A 5 years and 4 months old male was admitted to the hospital due to recurrent fever for over a month. The fever was mainly moderate to high, accompanied by cough, sputum production, abdominal pain, and rash. Tests from an external hospital showed elevated eosinophils (23.2%, 4.91*10^9/L); CT scan suggested bilateral lung infection with multiple calcifications in the right upper lobe and hilar lymph nodes. Diagnosed with tuberculosis, eosinophilia. The patient was treated with anti-infective and anti-tuberculosis therapies, resulting in improvement in cough and abdominal pain, but the fever persisted. Past medical history: At the age of 3, the patient was diagnosed with right lung abscess due to cough for 6 days and underwent right empyema and right upper lobectomy. Personal history is unremarkable, with no contact history in epidemic areas, and no history of exposure to bird droppings. Family history: Chest X-ray of his grandmother suggesting tuberculosis, but no further diagnosis or treatment was pursued.

Physical Examination: One ulcer is visible on the right occipital region and behind the right ear, scattered red papules are visible on the forehead, and three old dark red rashes are seen at the root of the right thigh, protruding from the skin surface. Scattered old rashes are observed on the trunk and both lower limbs. Subcutaneous nodules are palpable on the left frontoparietal region, right occipital region, lower back, and lower abdomen, with the largest one on the left lower back measuring approximately 2*3 cm, soft in texture, with clear boundaries and no tenderness. Several enlarged lymph nodes are palpable in the bilateral neck, armpits, and groin, soft in texture, with clear boundaries and no tenderness upon

pressure, with the largest lymph node in the right neck measuring approximately 2*3 cm. No rales were heard on lung auscultation, and no abnormalities were found on physical examination of the heart, abdomen, and nervous system.

Ancillary Investigations: Blood Routine: WBC 21.13×10^9/L, Hb 90.9 g/L, PLT 784.8×10^9/L, Neutrophils 53.3%, Eosinophils 16.5% (3.49×10^9/L); CRP 72.84 mg/L, PCT 0.895 ng/mL; Immunoglobulin Panel: IgG: 10.12 g/L, IgA: 1.77 g/L, IgM: 1.38 g/L, IgE: 2327.0 IU/mL(Reference: <90 IU/mL); Lymphocyte Subset Analysis: Total T cells: 59.17%, CD4 + T cells: 29.68%, CD8 + T cells: 23.14%, CD4/CD8 ratio: 1.28, Double-positive T cell subset: 0.35%, Double-negative T cell subset: 6.70%, T cell absolute count: 4016 cells/μL, CD4 + T cell absolute count: 2014 cells/μL, CD8 + T cell absolute count: 1570 cells/μL, B cells (CD19+): 18.18%, NK cells: 21.59%, B cell absolute count: 1194 cells/μL, NK cell absolute count: 1419 cells/μL; Complement Levels: C3: 1.041 g/L, C4: 0.18 g/L. Serum Galactomannan Test: Positive (1.427); (1,3)-β-D-glucan test: Negative. Cryptococcal Capsular Antigen: Positive (1:5). Bone Marrow Cytology: Reactive bone marrow morphology with proliferative anemia and mild eosinophilia (E = 23%). Bone Marrow Culture: Cryptococcus neoformans infection. CSF Analysis: normal. Superficial Ultrasound: Multiple hypoechoic masses in bilateral cervical regions, lumbar regions, axillae, and retroauricular areas. Neck CT: Multiple enlarged lymph nodes with liquefactive necrosis in bilateral cervical, retroauricular, occipital, parotid, supraclavicular, and axillary regions, suggestive of infectious etiology. Chest CT: Bilateral pulmonary infectious lesions. BAL Fluid: GM test (+) 0.686, G test (-); BAL smear/culture (-); BAL metagenomics: Aspergillus spp. (6.78 copies). Pathology: Right Supraclavicular Lymph Node: Chronic granulomatous inflammation consistent with fungal infection, fungal spores morphologically consistent with Cryptococcus. Right Axillary Abscess: Chronic suppurative inflammation with microabscess formation, showing acute/chronic inflammatory cell infiltration. Metagenomic Pathogen Detection (Neck Lymph Node Necrotic Pus): Cryptococcus neoformans (1539 sequence reads).

The preschool-aged patient presented with fever, cough, abdominal pain, rash, and multi-site lymphadenopathy as the main symptoms. The cryptococcal capsular antigen test was positive, Cryptococcus neoformans was cultured from bone marrow fluid, and metagenomic testing of necrotic fluid from a cervical lymph node also detected Cryptococcus neoformans. The diagnosis was disseminated cryptococcosis. The patient was initially treated with voriconazole, followed by liposomal amphotericin B and fluconazole for induction therapy, and consolidation and maintenance therapy with voriconazole tablets. After discharge, the patient was followed up every 1 to 2 months. During this period, the patient self-discontinued the medication, leading to an increase in the size and number of cervical lymph nodes and recurrent rashes. The symptoms improved after resuming oral voriconazole. The patient underwent regular antifungal treatment for approximately 10 months, achieving a near-complete resolution of clinical symptoms. The last follow-up was on October 11, 2021, at which point Voriconazole had been discontinued for about two months, with no clinical symptoms. A repeat chest CT scan revealed marked resolution of the inflammatory lesions in both lungs and a reduction in the size of the lymph nodes compared to previous findings.

Article review

Totally 115 cases from 45 studies were included in this research, comprising 18 studies from China and 27 studies from outside of China. The cohort included 82 males (70.7%) and 34 females (29.3%), with ages ranging from 10 months to 18 years. The main clinical manifestations were fever (79.3%), respiratory symptoms (41.4%), and neurological symptoms (39.7%), followed by hepatosplenomegaly (35.3%), rash (27.6%), lymphadenopathy (18.1%), and gastrointestinal symptoms (16.4%). Hepatosplenomegaly was more common in Chinese cases ($P < 0.05$). Immunodeficiency was present in 12.9% of children (3.4% domestic cases vs. 9.5% foreign cases). The most commonly affected organs were the lungs (77.6%), central nervous system (53.4%), and lymph nodes (51.7%), followed by the liver (48.3%), spleen (37.9%), and skin (21.6%). Pulmonary involvement was more common among domestic pediatric patients ($P < 0.05$). Elevated eosinophils were observed in 43 patients (37.1%), and elevated IgE levels in 35 patients (30.2%). The most common pathogen-positive specimens were cerebrospinal fluid (54 cases, 46.6%), blood cultures (49 cases, 42.2%), lymph node biopsies (26 cases, 22.4%), bone marrow (18 cases, 15.5%), and skin samples (8 cases, 6.9%). Combination therapy was administered to 89 patients (76.7%), while 21 patients (18.1%) received monotherapy. Clinical improvement occurred in 94 patients (81.0%), with 15 fatal cases. (Table 1)

The reported cases in China were predominantly male, totaling 62 cases (71.3%), with ages ranging from 10 months to 16 years. The main clinical manifestations included fever (80.5%), respiratory symptoms (43.7%) such as cough and chest pain, hepatosplenomegaly (43.7%), neurological symptoms (41.3%) including headache, vomiting, and convulsions, skin lesions (26.4%), and lymphadenopathy (21.8%). Some cases also presented with abdominal pain, jaundice, and weight loss. The most commonly affected organs were the lungs (85.1%), lymph nodes (55.2%), and central nervous system (54.0%), followed by the liver (48.3%), spleen (40.2%),

Table 1 Clinical characteristics of disseminated cryptococcus in 116 patients [M(P25,P75), n(%)]

Characteristics	Total	China	Other countries	χ^2/Z	*P*-value
Gender, M(F)	82(34)	62(25)	20(9)	0.550	0.814
Age (y)	5(4.00,9.00)	6(4.65,9.40)	5(3.25,9.00)	-0.599	0.549
Symptoms					
Fever	92(79.3%)	70(80.5%)	22(75.9%)	0.099	0.753
Cough/chest pain	48(41.4%)	38(43.7%)	10(34.5%)	0.280	0.597
Headache/vomiting/convulsions	46(39.7%)	36(41.3%)	10(34.5%)	0.432	0.511
Abdominal pain/distension	19(16.4%)	10(11.5%)	9(31.0%)	6.063	0.014
Skin lesions	32(27.6%)	23(26.4%)	9(31.0%)	0.230	0.631
Jaundice	9(7.8%)	9(10.3%)	0	0.322	0.763
Lymphadenopathy	21(18.1%)	19(21.8%)	3(10.3%)	1.197	0.274
Hepatosplenomegaly	41(35.3%)	38(43.7%)	3(10.3%)	9.167	0.020
Weight loss	5(4.3%)	2(2.3%)	3(10.3%)	1.742	0.187
Joint pain	1(0.9%)	0	1(3.4%)	3.000	0.083
Invaded organs					
Central nervous system	62(53.4%)	47(54.0%)	15(51.7%)	0.046	0.830
Lung	90(77.6%)	74(85.1%)	16(55.2%)	11.17	0.010
Liver	56(48.3%)	42(48.3%)	14(48.3%)	0.000	1.000
Spleen	44(37.9%)	35(40.2%)	9(31.0%)	0.781	0.377
Lymph nodes	60(51.7%)	48(55.2%)	12(41.4%)	1.657	0.198
Skin	25(21.6%)	20(23.0%)	5(17.2%)	0.364	0.546
Blood	24(20.7%)	16(18.4%)	8(27.6%)	1.121	0.290
Bone	11(9.5%)	6(6.9%)	5(17.2%)	2.712	0.100
kidneys	2(1.7%)	1(1.1%)	1(3.4%)	0.000	1.000
Pancreas	2(1.7%)	0	2(6.8%)	6.053	0.014
Joints	1(0.9%)	0	1(3.4%)	3.000	0.083
Immuno-deficiency					
No	101(87.1%)	83(95.4%)	16(55.2%)	28.144	0.000
Yes	15(12.9%)	4(4.6%)	13(44.8%)	28.144	0.000
Blood test					
Eosinophilia	43(37.1%)	38(43.7%)	5(17.2%)	6.516	0.011
IgE	35(30.2%)	32(36.8%)	3(10.3%)	6.015	0.014
Microbiological findings					
Blood culture	49(42.2%)	39(44.8%)	10(34.5%)	0.954	0.329
Cerebrospinal fluid	54(46.6%)	38(43.7%)	16(55.2%)	1.155	0.283
Lymph node biopsy	26(22.4%)	14(16.1%)	12(41.4%)	7.998	0.005
Bone marrow culture	18(15.5%)	10(11.5%)	8(27.6%)	4.296	0.038
Skin	8(6.9%)	4(4.6%)	4(13.8%)	1.611	0.204
Sputum	5(4.3%)	3(3.4%)	2(6.9%)	0.070	0.792
Liver biopsy	5(4.3%)	2(2.3%)	3(10.3%)	1.742	0.187
Lung/BALF	6(5.2%)	2(2.3%)	4(13.8%)	3.749	0.050
Urine culture	5(4.3%)	2(2.3%)	3(10.3%)	1.742	0.187
Ascites culture	2(1.7%)	2(2.3%)	0	0.345	0.557
Treatment					
Monotherapy	21(18.1%)	19(21.8%)	2(6.9%)	2.345	0.126
Combination therapy	89(76.7%)	64(73.6%)	25(86.2%)	1.303	0.254
Mortality					
Improved	94(81.0%)	74(85.1%)	20(69.0%)	3.665	0.056
Died	15(12.9%)	8(9.2%)	7(24.1%)	4.313	0.038

M: male; F: female. BALF: Broncho alveolar lavage fluid

and skin (23.0%). Four children had immunodeficiency or underlying diseases (Hodgkin's disease, decreased $CD4^+$ T lymphocytes, neutrophil dysfunction, and postoperative chemotherapy and hormone treatment for yolk sac tumor), while the majority of cases (95.4%) had normal immune function. Eosinophilia and elevated IgE levels were observed in 43.7% (38/87) and 36.8% (32/87) of the children, respectively. The highest pathogen-positive rate was found in blood cultures (39, 44.8%), followed by cerebrospinal fluid (38, 43.7%), lymph node biopsies (14, 16.1%), and bone marrow cultures (10, 11.5%). Treatment with a combination of liposomal amphotericin B, fluconazole, and flucytosine was administered in 73.6% (64/87) of the cases, with 85.1% of the cases showing symptomatic improvement. (Table 2)

The cases reported outside of China are also predominantly male, totaling 20 cases (69.0%), with ages ranging from 34 months to 18 years. The main clinical manifestations include fever (75.9%), respiratory symptoms (34.5%), neurological symptoms (34.5%), abdominal pain and distension (31.0%), and skin lesions (26.4%). A minority of cases presented with hepatosplenomegaly, lymphadenopathy, weight loss, and arthralgia. The most commonly affected organs were the lungs (55.2%), central nervous system (51.7%), and liver (48.3%), followed by the lymph nodes(41.4%) and spleen (31.0%). Compared to cases reported in China, there is a higher proportion of cases with immunodeficiency or underlying diseases (44.8%, 13/29), including 5 cases of Hyper-IgM syndrome, 1 case of Hyperimmunoglobulinemia E, 1 case post-liver transplantation, 1 case of IgG subclass deficiency, 1 case of hypogammaglobulinemia, 2 cases of leukemia, 1 case of Idiopathic CD4 + T-lymphocytopenia, and 1 case on steroids with severe malnutrition. The proportions of children with elevated eosinophils (43.7%, 38/87) and elevated IgE (36.8%, 32/87) are lower than those reported in China, at 17.2% and 10.3% respectively. The highest rates of positive pathogen detection were found in cerebrospinal fluid (16, 55.2%), lymph node biopsies (12, 41.4%), and blood cultures (10, 34.5%), followed by bone marrow cultures (8, 27.6%) and skin samples (4, 13.8%). 86.2% (25/29) of the cases were treated with a combination of two or more antifungal drugs, with 69.0% showing symptomatic improvement. Among the cases with underlying diseases, 4 resulted in death (4/13, 30.8%). (Table 3)

Evaluation and treatment process for disseminated cryptococcosis

Through case analysis and literature review, we attempted to outline the evaluation and treatment process for disseminated cryptococcosis in children. For high-risk children presenting with symptoms such as fever, respiratory symptoms, neurological symptoms, and skin lesions, and exhibiting signs like hepatosplenomegaly, lymphadenopathy, and rash during physical examination, cryptococcal infection should be highly suspected if laboratory tests reveal elevated eosinophils and IgE levels. Active efforts should be made to identify the pathogen. If the infection involves two or more organs and is confirmed to be caused by cryptococcus, a diagnosis of disseminated cryptococcosis can be made. Treatment should follow the induction, consolidation, and maintenance therapy protocols (Fig. 1).

Discussion

Disseminated cryptococcosis is a deep-seated fungal infection caused by hematogenous dissemination of Cryptococcus neoformans, leading to multi-organ involvement including the central nervous system, lungs, and brain [1]. Systemic disseminated cryptococcosis is primarily caused by Cryptococcus neoformans and Cryptococcus gattii, characterized by non-contiguous lesions in two or more sites throughout the body. The clinical manifestations and auxiliary examinations of this condition are non-specific, and the disease course can be protracted.

The pediatric patient in our center presented with recurrent moderate to high fever as the primary manifestation, accompanied by cough, expectoration, abdominal pain, rash, lymphadenopathy, elevated eosinophils, and increased IgE levels. The cryptococcal capsular antigen test was positive. Chest CT revealed infectious lesions in both lungs. Bone marrow culture identified an infection with Cryptococcus neoformans. Pathological examination of the right supraclavicular lymph node indicated chronic granulomatous inflammation and cryptococcal infection. Cryptococcus neoformans was also identified in the necrotic tissue of a right axillary abscess.

Both domestic and international literature indicate that fever is the most common manifestation of disseminated cryptococcosis, occurring in approximately 80% of affected children. This is followed by respiratory symptoms such as cough, sputum production, and chest pain. Neurological symptoms, including headache, vomiting, and seizures, are also frequently observed. In addition to the lungs and central nervous system, which are commonly affected sites in disseminated cryptococcosis, the reticuloendothelial system, including the liver, spleen, and lymph nodes, can also be involved. This often manifests as hepatosplenomegaly and lymphadenopathy. In severe cases, liver dysfunction and jaundice may occur [11]. In this case, the patient also presented with multiple sites of lymphadenopathy, along with abdominal pain and skin rash. Current studies suggest that approximately 11.5-16.4% of affected children exhibit abdominal symptoms, while 26.4-27.6% develop a skin lesion which is similar to previously report [49]. In this case, the child

Table 2 Clinical characteristics of disseminated cryptococcosis in China

Author	Year	Gender	Age	Main symptoms	Skin lesions	Invaded organs	EOS %	IgE IU/mL	Immuno-deficiency	Etiology detected	Antifungal	Mortality
Wu [5]	1990	M	10y	Fever, weight loss, LA, HSM	-	CNS, blood, LD, BM, liver, spleen	-	-	Hodgkin's disease	Blood, CSF, LD, BM and urine	AMB + 5-FC	Improved
Liu [6]	1994	F	6y	Fever, cough/ chest pain, rash, joint pain, convulsions	Papules, purulent discharge	Skin, LD, lung, bone, brain	-	-	No	Sputum, BM, LD	FZ	Treatment withdrawal
Xin [7]	2005	F	4y	Fever, cough, HSM	-	CNS, lung, blood, liver, spleen	-	-	No	CSF, blood	FZ	Improved
Chen [8]	2005	M	5y	Fever, headache, vomiting	-	CNS, blood, lung	60%	-	No	BM, blood	AMB + 5-FC	Improved
Xu [9]	2005	M	5y	Fever, cough, HSM	Miliary eruption	CNS, lung, blood, LD	25%		Decreased $CD4^+T$ lymphocytes	BM, CSF, sputum, LD, urine	AMB + FZ	Improved
Ji [10]	2006	M	6y	Rash, fever, cough, abdominal distension	Papulonodular eruptio, ulcerocrustous	Blood, lung, liver, spleen, LD	-	-	N0	BM, skin	-	Treatment withdrawal
Zhu [11]	2009	F	8y10m	Fever, cough, rash, HSM, jaundice	Herpetiform eruption	Blood, lung, LD, skin, brain	31%	2718	Neutrophil dysfunction	Skin, LD, blood, CSF	AMB + 5-FC	Improved
Chen [12]	2010	M	3y8m	Fever, HSM	-	lung, liver, spleen	78%	-	N0	BM, blood	AMB	Treatment withdrawal
Tan [13]	2011	F	11y	Cutaneous eruption cough, fever	Erythematous nodules, central umbilication	lung, skin	-	-	No	Skin	AMB + 5-FC	Improved
Wang [14]	2014	M	5y	Fever, weight loss, abdominal distension, jaundice	-	LD, liver, spleen, abdomen	Increase	-	No	Liver, LD, ascites	AMB + 5-FC	Improved
Xie [15]	2015	5 M, 3 F	Average6. 1y	Fever, HSM, jaundice, cough, cutaneous eruption	Ulceration	Blood, lung, skin	5 cases increase	3 896.5	No	Blood, skin, CSF, liver	AMB + 5-FC/FZ	Improved
Luo [16]	2015	10 M,1 F	3–14y	Fever, HSM, rash, cough, LA	-	CNS, lung, LD, liver, spleen, skin	5/11	-	-	CSF, blood, BM, LD	5 FZ, 1 AMB, 3AMB + 5-FC,1 AMB + FZ,1 FZ + 5-FC	2 Cured 7 Improved 2 Dead
Ql [17]	2016	M	5y	Fever, cough, sputum	-	Lung, liver, spleen, ALD	34.9%	-	No	ALD	AMB	Improved
Gao [18]	2017	38 M, 14 F	Average4.3(1.3–11y)	Fever, cough, HM, Headache, LA	6/52	Lung, CNS, LD, liver, spleen, skin	22/52	27/52	-	CSF, blood, BM	22AMB + 5-FC + FZ,9FZ,6 FZ + 5-FC,5AMB + FZ,5AMB + 5-FC,1 AMB	6 Died 45 Improved

Table 2 (continued)

Author	Year	Gender	Age	Main symptoms	Skin lesions	Invaded organs	EOS %	IgE IU/mL	Immuno-deficiency	Etiology detected	Antifungal	Mortality
Liu [19]	2017	F	16y	Cough, fever	-	CNS, BM, blood, lung	-	-	Steroids, tumor	CSF, blood, BM	AMB + 5-FC + FZ	Improved
Chen [20]	2019	F	7y	Cough, fever	-	lung, LD	-	-	No	LD	AMB + VC	Improved
Cai [21]	2019	M	14y	Fever	-	CNS, lung	10.5%	-	No	Blood, CSF, BM, LP	AMB + 5-FC	Improved
Zhang [22]	2020	F	2y4m	Fever	-	Blood, LD, lung	28.2%	2023	No	Blood, ALD, LP	AMB + 5-FC + FZ	Improved

M: male; F: female. LA: lymphadenopathy, HM: hepatomegaly, HSM: hepatosplenomegaly. CNS: central nervous system; BM: bone marrow; EOS: eosinophils; CSF: cerebrospinal fluid; LD: lymph node. ALD: Abdominal LD. LP: lung puncture. LAMB: Liposomal amphotericin B. AMB: amphotericin-B. 5-FC:5-flucytosine. FC: flucytosine. FZ: fluconazole. VC: voriconazole

presented with skin lesions characterized by ulcers and papules, involving the forehead, occipital region, postauricular area, trunk, and lower extremities. Consistent with previous literature reports, disseminated cryptococcosis can manifest with skin lesions that affect the entire body, typically appear as pedunculated, dome-shaped papules with an umbilicated centre, also presenting as miliary macules, vesicles, ulcers, nodules, cutaneous ulcers with raised edges, eczematous skin rash, erythematous skin lesions, pruritic skin lesions, skin papules with central umbilication [37], as well as cutaneous cellulitis [50].

Disseminated cryptococcosis is commonly observed in immunocompromised children. However, an increasing number of cases have been reported in children without apparent underlying immunodeficiencies [18, 47]. This study excludes cases of HIV infection. Among the enrolled cases, 87.1% of the children did not exhibit immune dysfunction or underlying diseases, indicating that the possibility of disseminated cryptococcosis should also be considered in children without underlying conditions. Among the children with underlying diseases, four cases were reported in China, including two cases of neoplastic diseases and one case of CD4 + T lymphocyte [9] and neutrophil dysfunction [11]. Internationally, a higher proportion (44.8%) of children had underlying conditions, with 10 cases of primary immunodeficiency (including 5 cases of hyper-IgM syndrome [25, 26, 39, 40, 44]. Special attention should be paid to cryptococcosis infection in children with immunodeficiencies, particularly those with hyper-IgM syndrome.

In this study, more than 30% of the cases exhibited elevated eosinophils and IgE levels, with the percentage of eosinophils ranging from 10.5 to 78% [12]. The research demonstrated that patients with cryptococcosis had increased peripheral blood eosinophil counts and serum IgE levels. In these cases, following systemic antifungal treatment, both serum IgE levels and peripheral blood eosinophil counts returned to normal as clinical symptoms improved [15]. Elevated serum IgE levels and significantly increased peripheral blood eosinophil counts are considered distinctive features of disseminated cryptococcosis. The mechanism of eosinophils elevation may be related to certain specific components of the Cryptococcus neoformans capsule inducing a type I hypersensitivity reaction. For children presenting with recurrent fever, respiratory, and neurological symptoms, elevated eosinophils and high serum IgE levels should raise suspicion for possible cryptococcal infection.

In this case, the etiological evidence of Cryptococcus infection in the child includes: positive Cryptococcus neoformans capsular antigen, positive bone marrow culture, identification of Cryptococcus in lymph node biopsy, and detection of Cryptococcus neoformans in

Table 3 Clinical characteristics of disseminated cryptococcosis in other countries

Author	Year	Gender	Age	Main symptoms	Skin lesions	Invaded organs	EOS %	IgE	Immuno-deficiency	Etiology detected	Antifungal	Mortality
Fusner [23]	1979	M	9y	Fever, weight loss	-	LD, liver	4	-	No	LD	5-FC	Improved
Stone [24]	1990	M	3y	Headache, abdominal pain	-	CNS, blood	-	37,250	HIE syndrome	Blood, BM, CSF	AMB + 5-FC	Improved
Iseki [25]	1994	M	34 m	Fever	-	HSM, LA	-	-	Hyper-IgM syndrome	CSF, BM, LD	AMB + 5-FC + FZ	Died
Tabone [26]	1994	M	3y	fever	-	LD, liver	3	-	Hyper-IgM syndrome	LD	AMB + 5-FC	Improved
Goenka [27]	1995	M	7y	Fever, LA	Cutaneous ulcers with raised edges	CNS, liver, LD, lungs, blood	-	-	No	Liver, LD, blood, CSF, urine	AMB + 5-FC	Improved
Lascari [28]	1997	M	5.5y	Abdominal pain	-	CNS, lungs, heart, kidneys, pancreas	-	-	Leukemia, chemotherapy and radiotherapy	Brain, lungs, heart, kidneys, pancreas	-	Died
Menon [29]	1998	F	4.5y	Rash, fever, weight loss	Eczematous skin rash	lungs, liver, LD, bones	-	-	Idiopathic CD4 + T-lymphocytopenia	BM	AMB + 5-FC + FZ	Died
Chaudhary [30]	2005	F	8y	Fever, cough, headache, LA, HSM, cutaneous lesions	cutaneous lesions	CNS, lung, LD, liver, spleen, skin	-	-	No	CSF, sputum, urine	AMB + 5-FC + FZ	Improved
Godbole [31]	2007	M	7.5y	fever, cough, breathlessness, weight loss	-	CSF, BM, blood, liver, LD	-	-	No	CSF, BM, blood, liver, LD	AMB + 5-FC	Improved
Swe Han [32]	2008	M	4y	fever, meningism, skin lesions	Erythematous skin lesions	CNS, blood, lung, skin	-	-	No	Skin, CSF	AMB + FZ	Improved
Heath [33]	2012	M	9y	Fever, headache, respiratory distress	-	Lung, CNS, blood	-	-	Acute lymphoblastic leukemia	CSF, blood	AMB + 5-FC	Improved
Bothra [34]	2014	M	5y	Fever, abdominal distension, fast breathing	-	Lung, HM, LD	66%	-	No	LD	AMB + FZ	Improved
Kaur [35]	2015	F	11y	Epigastrium pain, fever, vomiting	-	Lung, CNS, blood, LD, liver, spleen	-	-	No	CSF, blood, LD	AMB + 5-FC	Died
Saeed [36]	2016	F	2.5y	fever, abdominal lump	-	LA, HSM, BM	48%	-	No	BM, LD	AMB	Died
Jain [37]	2017	M	7y	Fever, headache, vomiting, irritability	-	CNS	54%	1175	No	Skin, CSF, blood	AMB + FZ	Improved
Gupta [38]	2017	M	2y	Fever, cough, irritability	-	Lung, CNS, liver, spleen	-	-	-	BALF, BM, CSF	AMB + 5-FC	Improved
Saini [39]	2018	M	4y	Fever, abdominal pain, skin eruptions	pruritic, umbilicated, papular	Skin, liver, spleen, LD	-	-	Hyper-IgM syndrome	LD	AMB + 5-FC	Improved
Mohanty [40]	2018	M	3y	Fever	maculopapular skin lesions	Blood, lung, LD, CSF	-	-	Hyper-IgM syndrome	Blood, urine, sputum, LD, CSF	AMB + FZ	Improved
Aldemir [41]	2018	F	12y	Headache, cough	-	CNS, lung	-	-	Transient hypogammaglobulinemia	CSF	AMB + 5-FC + FZ	Improved
Ismail [42]	2018	F	5y	Fever, cough, abdominal distension	-	CSF, lung, liver	-	-	No	CSF, BALF, Lung, liver	AMB + 5-FC	Died
Kaushik [43]	2019	M	18y	Ulcerated papule	cutaneous ulcer	Skin, brain	1%	-	IgG subclass deficiency	CSF, Skin	LAMB + 5-FC	Improved

Table 3 (continued)

Author	Year	Gender	Age	Main symptoms	Skin lesions	Invaded organs	EOS %	IgE	Immuno-deficiency	Etiology detected	Antifungal	Mortality
Pacharn [44]	2021	M	12y 8y	Fever, headache	-	CNS, blood	-	-	Hyper-IgM syndrome	Blood, CSF	AMB + FZ	Improved
Kalasekhar [3]	2021	F	11y	Fever, abdominal pain	-	Lung, HSM, LA	-	-	No	LD	AMB + 5-FC + FZ	Improved
Huan [45]	2023	F	5y	Fever, cough, fatigue.	-	Lung, blood, BM	-	-	No	Blood, BM	AMB + 5-FC +FZ	Improved
Barut [46]	2024	M	15y	Fever, hypertension, sacroiliac joint pain	-	Pancreas, gastrointestinal bleeding, lung	-	-	Liver transplantation	Blood	AMB + 5-FC + FZ	Died
Singh [47]	2024	F	4y	Fever, abdominal pain, HSM	-	BM, HSM	-	444	No	BM	AMB + 5-FC	Improved
Paul [48]	2024	M	3y	Occiput swelling	Ulcerated scalp swelling	Skin, lung	12%	-	Steroids, severe malnutrition	Aspirated fluid from the swelling	LAMB + FZ	Improved

M: male; F: female. LA: lymphadenopathy, HM: hepatomegaly, HSM: hepatosplenomegaly. CNS: central nervous system; BM: bone marrow; BALF: broncho alveolar lavage fluid; EOS: eosinophils; LD: lymph node. ALD: Abdominal LD. LP: lung puncture. HIE syndrome: Hyperimmunoglobulinemia E. LAMB: Liposomal amphotericin B. AMB: amphotericin-B. 5-FC:5-flucytosine. FC: flucytosine. FZ: fluconazole. VC: voriconazole

lymph node necrotic fluid. Among the cases enrolled in this study, the positive rate of etiological detection was ranked as follows: cerebrospinal fluid, blood culture, lymph node biopsy, and bone marrow culture. The highest positive rates of pathogen detection in Chinese and foreign cases were blood culture and cerebrospinal fluid, respectively. For suspected cases, it is recommended to perform etiological examinations of the relevant areas to assist in the diagnosis of the underlying cause.

The pediatric patient showed improvement after treatment with liposomal amphotericin B combined with voriconazole, followed by maintenance therapy with voriconazole for over 10 months. Follow-up at 1 year revealed significant clinical improvement. Among the included cases, the majority received combination therapy, with 76.7% of the children treated with a combination of liposomal amphotericin B, flucytosine, and fluconazole, achieving an improvement rate of 81.0%. The latest Global Guideline for the Diagnosis and Management of Cryptococcosis, published in 2024, provides recommendations for the treatment of pediatric cryptococcosis. For disseminated cryptococcosis, the induction phase involves the use of amphotericin B 1 mg/kg daily or liposomal amphotericin B 3–4 mg/kg daily plus flucytosine (100–150 mg/kg daily in 4 divided doses) for 2 weeks. The consolidation phase includes fluconazole 12 mg/kg (maximum 800 mg) daily for 8 weeks, and the maintenance phase consists of fluconazole 6 mg/kg daily for 6–12 months. For pediatric disseminated cryptococcosis, standardized treatment based on the guidelines can be implemented to achieve clinical benefits.

The prevention strategies for disseminated cryptococcosis in children should be formulated based on susceptible populations and high-risk factors. For children, especially those with compromised immune systems (such as those receiving immunosuppressive therapy, suffering from chronic diseases, or having congenital immunodeficiency), exposure to potential sources of infection should be avoided. If symptoms such as fever, cough, rash, or lymphadenopathy with hepatosplenomegaly occur, the possibility of disseminated cryptococcosis should be considered, and appropriate laboratory tests should be conducted to assist in diagnosis.

Conclusions

Disseminated cryptococcosis in children often presents with fever, respiratory and neurological symptoms, and may be accompanied by hepatosplenomegaly, lymphadenopathy, and skin lesions. Most cases do not have immunodeficiency or underlying diseases, and blood tests often reveal eosinophilia and elevated IgE levels. The positive detection rates of pathogens are relatively high in blood cultures, cerebrospinal fluid, bone marrow cultures, and lymph node biopsies. The majority of patients

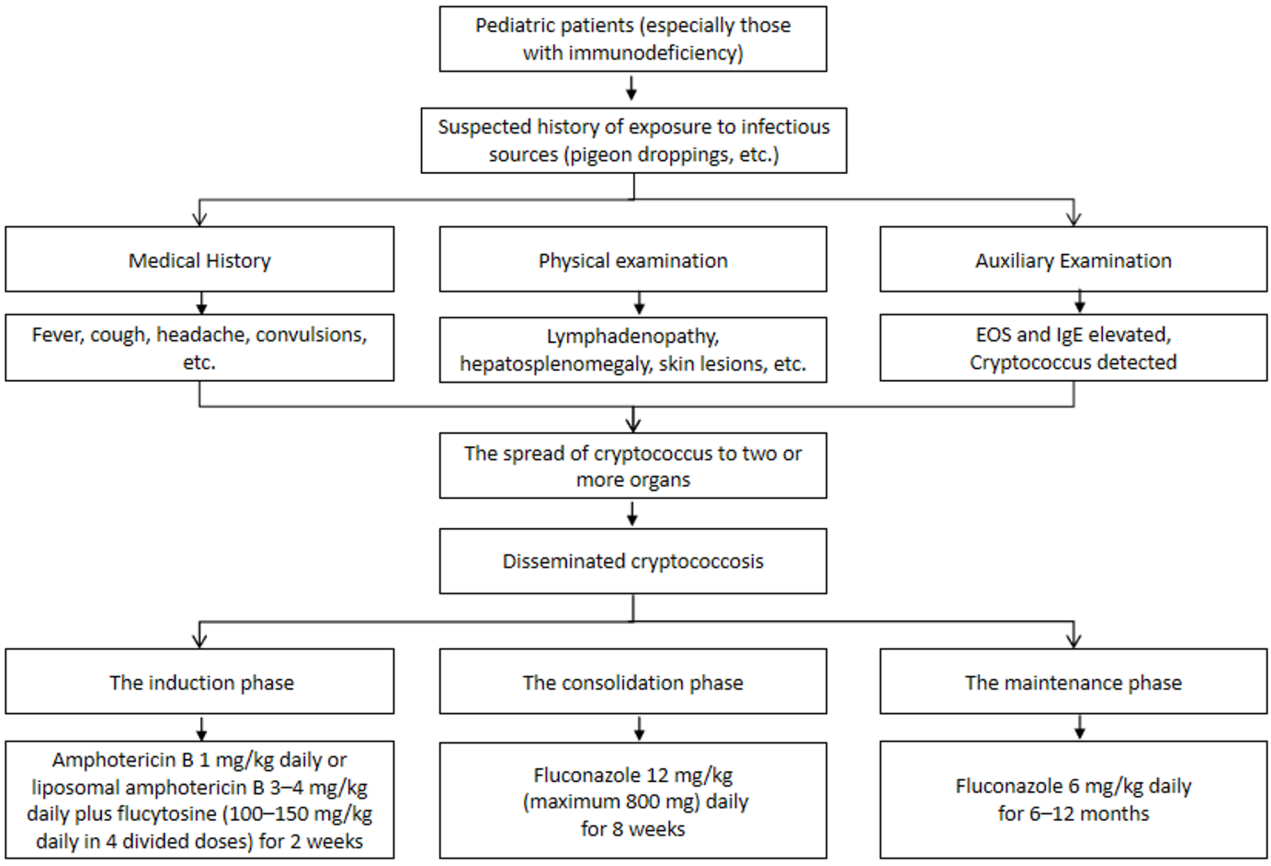

Fig. 1 Diagnosis and Treatment Flowchart for Disseminated Cryptococcosis in Children

achieved favorable therapeutic outcomes with combination therapy.

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Author contributions
ZXB collected and analyzed the data, as well as prepared the manuscript; LHY and WX collected the data and provided an interpretation of data; NGM contributed to the conception of this study and overall supervision.

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Data availability
All data in this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The present study was approved by The Medical Ethics Committee of First Affiliated Hospital of Guangxi Medical University [approval no. 2025-E0164].

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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