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ORIGINAL ARTICLE

Characteristics and Prognosis of *Talaromyces marneffei* Infection in HIV-positive Children in Southern China

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Abstract Knowledge about the clinical characteristics and prognostic factors of *Talaromyces marneffei* infection in children is limited, especially in HIV-positive children. We performed a retrospective study of all HIV-positive pediatric inpatients with *T. marneffei* infection in a tertiary hospital in Southern China between 2014 and 2019 and analyzed the related risk factors of poor prognosis using logistic regression. Overall, 28 cases were enrolled and the prevalence of talaromycosis in AIDS children was 15.3% (28/183). The median age of the onset was 8 years (range: 1–14 years). The typical manifestation of skin lesion with central umbilication was not common (21.4%). All the children had very low $CD4^+$ cell counts (median 13.5 cells/μL, range: 3–137 cells/μL) on admission. 92.9% children were misdiagnosed and talaromycosis was only noted after positivity for HIV infection. 89.3% diagnoses of *T. marneffei* infections were based on positive blood cultures, with a long culture time (median 7 days, range from 3–14 days). The sensitivity of fungus 1,3-β-D-glucan assay was 63.2%. Amphotericin B was superior to itraconazole in the induction antifungal therapy of talaromycosis in HIV-positive children. A six-month follow-up revealed a 28.6% mortality. Lower ratio of $CD4^+$/$CD8^+$ and amphotericin B treatment not over 7 days predicted poor prognosis. Our retrospective study

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provided an overview and update on the current knowledge of talaromycosis in HIV-positive children. Pediatricians in endemic areas should be aware of mycoses to prevent misdiagnosis. 1,3-β-D-glucan assay did not show optimal sensitivity. Amphotericin B treatment over 7 days can improve poor prognosis.

Keywords HIV · AIDS · *Talaromyces marneffei* · Talaromycosis · Children · Penicilliosis

Introduction

Talaromyces (formerly *Penicillium*) *marneffei* is a dimorphic fungi endemic in Southeast Asia and Southern China [1, 2], which can cause life-threatening disseminated infections mainly in immunocompromised populations, such as those with HIV, organ transplantation, autoimmune diseases and hematological malignancies [3–5].With the increasing overseas travel, global warming and the growing use of chemotherapy and immunosuppression, talaromycosis presents a worldwide clinical challenge by disseminating to non-endemic areas [6, 7]. In 1988, talaromycosis was found to be present in HIV-positive patients [8–10] and became an pressing complication among those with HIV in Southeast Asia [11].

Common clinical manifestations of patients coinfected with *T. marneffei* and HIV were fever, lymphadenopathy, respiratory symptoms, weight loss, skin lesions and gastrointestinal complications [7]. However, since most of the clinical manifestations were nonspecific, and overlapping those HIV-positive patients or other opportunistic infections (OIs), talaromycosis has always been misdiagnosed, which potentially contributed to a high mortality rate due to the lack or delay of antifungal treatment [12]. Presumptive diagnosis of talaromycosis can be made based on microscopic findings of intramacrophage and extramacrophage yeast organisms in smears of clinical specimens. Definitive diagnosis is made by a positive culture of *T. marneffei*. Amphotericin B and itraconazole have been proved effectively for the treatment of disseminated *T. marneffei* infection [2].

Recently, endemic-systemic mycoses in children have attracted a significant attention, including talaromycosis. The children with immunodeficient disease are more susceptible to certain endemic mycoses [13]. However, studies exploring talaromycosis in children with HIV-positive have been scarce in the last decade [14–16], which has led to a limited knowledge about the clinical epidemiology and diagnostic and treatment strategies. Subsequently, there is a concern regarding the underestimation of this complication and poor clinical management of HIV-positive children with talaromycosis.

Guangxi province is in the south of China, with a relatively high burden of HIV/AIDS infection [17]. The cumulative number of HIV/AIDS cases in Guangxi was ranked third in China [18, 19]. It was reported that 42.8% of talaromycosis in China came from Guangxi [20]. Up to 16.1% of HIV-infected hospitalized patients were coinfected with *T. marneffei* in Guangxi [15]. As such the scope of the current study was to determine the epidemiological, clinical and laboratory findings, imaging results, misdiagnosis rates, treatments and prognostic factors of talaromycosis among HIV-positive children to enrich our knowledge which can potentially advances our awareness of this disease.

Materials and Methods

Study Design and Population

A retrospective study was conducted at the Fourth People's Hospital of Nanning, the largest infectious disease hospital as well as HIV/AIDS Clinical Treatment Center in Guangxi. There were more than 2500 HIV/AIDS inpatients admitted to the hospital each year [21]. We evaluated all hospitalized children infected with *T. marneffei* from January 2014 to December 2019. The inclusion criteria included: (1) HIV infection, (2) talaromycosis, and (3) children.

Diagnosis of Talaromycosis

The diagnosis of talaromycosis included a positive culture of *T. marneffei* from blood, bone marrow, and other clinical specimens on sabouraud dextrose agar according to standard culture techniques [22]. Identification was based upon the morphology of the colonies. *T. marneffei* grew as a mold form at 25 °C and a yeast form at 37 °C . At 25 °C, it produced a soluble red pigment that diffused into the agar. Under

the microscope, a typical broomstick with septal hyphae can be seen [7].

Definitions

HIV infection was determined by positive ELISA and western blot assays [21]. Tuberculosis was defined as having any tuberculosis symptom or tuberculosis with culture-positive sputum [7]. The diagnosis of pneumonia included bacterial pneumonia, mycoplasma pneumonia, pneumocystis pneumonia and pneumonia caused by other factors, except for tuberculosis pneumonia, which was classified as tuberculosis. Severe anemia were defined as hemoglobin < 60 g/L. Fungus 1,3-β-D-glucan (BDG) assay (Dynamiker Biotechnology (Tianjin) Co., Ltd, China) was used for the evaluation of invasive fungal infection. Values $<$ 70 pg/mL of BDG were considered negative, while values 70–94 pg/mL and > 94 pg/mL were classified as intermediate and positive, respectively [23].

Data Collection

The data were obtained from electronic medical records according to a standardized form, including epidemiology, personal history, laboratory and imaging data, treatment, clinical manifestations, diagnoses and misdiagnoses, and outcome scored as died or survived [24]. In order to comprehensively evaluating the survival status, all patients were followed up six months after therapy. For those with multiple admissions, data from the first admission were collected.

Review of the Literature

A literature search was performed in PubMed on July 7th, 2021 to further analyze the characteristics of HIV-associated talaromycosis in children. We screened using the key words ''*Talaromyces marneffei*'' or ''*Penicillium marneffei*'' or ''Penicilliosis'' or ''Talaromycosis''. Cases including *T. marneffei*-infected children with HIV-positive were included. Infant cases were excluded.

Statistical Analysis

SPSS software (version 22.0, SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analysis. The results were presented as number, frequency (%) or median (interquartile ranges). Student's t-test, $\chi 2$ test and Mann–Whitney U-test were applied for continuous variables conforming to a normal distribution, categorical variables and non-normally distributed data, respectively. Univariable and multivariable logistic regression analysis with forward stepwise selection were used to predict the risk factors of poor prognosis. Variables with a P-value < 0.10 from the univariable analysis were tested in multivariable models. A P-value of < 0.05 was applied for indicating statistical significance.

Results

Demographic and Epidemiological Characteristics

A total of 183 HIV/AID children were admitted to the Fourth People's Hospital of Nanning from January 2014 to December 2019. Among them, 28 children (15.3%) were diagnosed with *T. marneffei* infection, including 15 girls and 13 boys (Table 1). The proportion of HIV-infected talaromycosis children among total HIV-infected talaromycosis cases was 1.7%. The median age of talaromycosis children was 8 years (range: 1–14 years). None of them had a clear history of bamboo rat exposure. Twenty-two children had either one or both parents with AIDS. Five children had been diagnosed with HIV-positive before the onset of symptoms and three of them received antiretroviral therapy (ART).

Clinical, Laboratory and Radiographic Characteristics

Clinical, laboratory and radiographic characteristics of HIV-positive children coinfected with *T. marneffei* are presented in Table 2. Recurrent fever was the most common clinical manifestation (96.4%, average 39.6 °C), followed by cough (89.3%), hepatosplenomegaly (64.3%), and abdominal pain or diarrhea (64.3%). 21.4% patients presented the manifestation of papular skin lesion with central umbilication. Only two patients had underlying diseases, including glucose-6-phosphate dehydrogenase deficiency ($n = 1$) and thalassemia ($n = 1$). All patients had complications and pneumonia (92.9%) was the major presentation.

All the *T. marneffei* infection in the ch ildren occurred late in the course of HIV infection with very

Table 1 Demographic and epidemiological characteristics of HIV-positive children coinfected with *T. marneffei*

Case	Year	Gender	Age (years)	Bamboo rat contact	HIV of parents	HIV test before the onset	ART before admission
P1	2014	F	6	Neg	Pos	No	No
P2	2014	F	14	Neg	Neg	No	No
P3	2014	M	5	Neg	Pos	No	No
P4	2014	F	1	Neg	Pos	No	No
P5	2014	F	4	Neg	Pos	No	No
P6	2014	F	11	Neg	Pos	Yes	Yes (3 months)
P7	2015	F	7	Neg	Neg	No	No
P8	2015	F	13	Neg	Pos	No	No
P9	2015	M	8	Neg	Pos	No	No
P10	2016	M	8	Neg	Pos	Yes	No
P11	2016	M	8	Neg	Pos	No	No
P12	2016	M	2	Neg	Neg	No	No
P13	2016	M	3	Neg	Pos	No	No
P14	2016	M	2	Neg	Pos	No	No
P15	2016	F	6	Neg	Pos	No	No
P16	2017	F	6	Neg	Pos	Yes	Yes (4 days)
P17	2017	F	5	Neg	Pos	No	No
P18	2017	M	3	Neg	Neg	No	No
P19	2017	F	11	Neg	Pos	No	No
P20	2017	F	5	Neg	Pos	No	No
P21	2018	M	11	Neg	Neg	No	No
P22	2018	M	10	Neg	Pos	No	No
P23	2018	F	9	Neg	Pos	No	No
P24	2019	F	8	Neg	Pos	No	No
P25	2019	M	13	Neg	Pos	Yes	Yes (over 1 year)
P26	2019	M	11	Neg	Pos	No	No
P27	2019	M	14	Neg	Neg	No	No
P28	2019	F	13	Neg	Pos	Yes	No

P, patient; M, male; F, female; Pos, positive; Neg, negative; ART, antiretroviral therapy

low $CD4^+$ lymphocyte counts (median 13.5 cells/μL, range: 3–137 cells/μL) and ratio of $CD4^+/CD8^+$ lymphocyte (median 0.05, range: 0.01–0.11). However, only 64.3% cases presented decreasing lymphocytes counts and 50.0% cases presented decreasing leukocytes on admission. Other main laboratory abnormities included increased serum C-reactive protein levels (26/28, 92.9%), decreased hemoglobin levels (24/28, 85.7%), increased aspartate aminotransferase level (23/28, 82.1%), and thrombocytopenia (15/28, 53.6%).

Lungs and pleura were the major cumulative sites of talaromycosis coinfected with HIV, and only two children showed no obvious abnormality on plain CT scan of the chest. There was a high misdiagnosis rate of talaromycosis and 26 cases (92.9%) were misdiagnosed as pneumonia or bronchial pneumonia. Talaromycosis was only noted after positivity for HIV infection.

Etiological Diagnosis of Talaromycosis

Among the five specimen types used to diagnose *T. marneffei,* blood was the most common specimens (n = 28), followed by sputum (n = 10), pharyngeal swab (n = 14), feces (n = 9) and bone marrow (n = 4). Most patients (25/28, 89.3%) were confirmed of *T. marneffei* infection by blood culture, and three by sputum, bone marrow or pharyngeal swab culture. Six patients were confirmed by two and more kinds of specimens (Table 3). Fungi culture was relatively time-consuming. The median positive culture time of

Table 2 Clinical, laboratory and radiographic characteristics of HIV-positive children coinfected with *T. marneffei*

	Number of cases	Percentage (%, n = 28)
Symptoms and signs		
Fever	27	96.4
Cough	25	89.3
Hepatosplenomegaly	18	64.3
Abdominal pain or diarrhea	18	64.3
Oral mucosal injury	17	60.7
Malaise	13	46.4
Weight loss	12	42.9
Failure to thrive	8	28.6
Chills	7	25
Skin lesion	6	21.4
Superficial lymphadenopathy	6	21.4
Dyspnea	6	21.4
Lower limb edema	5	17.9
Hematochezia	4	14.3
Melaena	2	7.1
Adenoids	2	7.1
Underlying conditions		
G6PD deficiency	1	3.6
Thalassemia	1	3.6
Complications		
Pneumonia	26	92.9
Tuberculosis	15	53.6
Oral candidiasis	13	46.4
Severe anaemia	11	39.3
Cytomegalovirus infection	8	28.6
Septic shock	5	17.9
Enteritis	5	17.9
Herpesvirus infection	4	14.3
Electrolyte disturbances	4	14.3
Septicaemia	3	10.7
GIB	3	10.7
Heart failure	2	7.1
Hepatitis (B or C)	2	7.1
Non-tuberculous mycobacterial infections	1	3.6
IRIS	1	3.6
Pneumothorax	1	3.6
DIC	1	3.6
Circulatory failure	1	3.6
Respiratory failure	1	3.6
Laboratory tests		
Increased CRP	26	92.9
Decreased hemoglobin	24	85.7
Increased AST	23	82.1
Lymphocytopenia	18	64.3
Thrombocytopenia	15	53.6
Leukopenia	14	50.0
Increased ALT	10	35.7
Neutrocytosis	5	17.9
Thrombocytosis	3	10.7
Leukocytosis	3	10.7
$CD4^+$ cell counts, median (IQR)	13.5 (3–137)	
Ratio of $CD4^+/CD8^+$, median (IQR)	0.05 (0.01–0.11)	
Chest imaging abnormality	26	92.9
Misdiagnosis	26	92.9

G6PD, glucose-6-phosphate dehydrogenase; GIB, gastrointestinal bleeding; IRIS, immune reconstitution inflammatory syndrome; DIC, disseminated intravascular coagulation; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; IQR, interquartile ranges

T. marneffei was 7 days (range: 3–14 days). In addition to fungal culture, fungus BDG assay was conducted for the early diagnosis of invasive fungal infection. There was a sensitivity of 63.2% (12/19) in our study.

Treatment and Outcomes

Most patients (27/28, 96.4%) were treated with antifungal agents, including fluconazole for injection (Beijing Sihuan Kebao Pharmaceutical Co., Ltd., China) before confirmed talaromycosis, amphotericin B for injection (Huabei Pharmaceutical Co., Ltd., China) and itraconazole capsules (Chengdu Brilliant Pharmaceutical Co., Ltd., China). The details are available in Table 4. Fluconazole was applied on eleven patients and switched to amphotericin B ($n = 7$) or itraconazole ($n = 3$) when *T. marneffe*i infection was suspected or confirmed. One patient died before the switch. The patients infected with *T. marneffe*i received induction antifungal therapy with amphotericin B or itraconazole, followed by

consolidation and maintenance therapy with itraconazole [21]. Of the 17 patients who were treated with amphotericin B, three (17.6%) died during hospitalization and the rest survived during 6-month follow-up. Nine patients received induction therapy with itraconazole, of whom two died at home during the followed-up and one died on readmission. Only one patient didn't receive antifungal agents and was discharged for a deteriorative condition 24 h after admission. Adverse drug reactions (ADRs) of amphotericin B were present, including fever (n = 1) and hypokalemia (n = 1). The ADRs were relieved with symptomatic treatment after drug withdrawal. Other treatments included antibacterial therapy, anti-tuberculosis, ART, blood transfusions, anti-herpesvirus, and cotrimoxazole. ART was initiated when the condition of the patient was stabilized. Six patients didn't receive ART for the deteriorated condition. Twenty-two patients received ART and the median initiation time was 23 days after antifungal therapy (Table 4). The overall mortality rate was 28.6% (8/28), among whom five patients died for septic shock or circulatory failure during hospitalization. The other three patients discharged against medical advice for worsening conditions were found dead in follow-up. The mortality rate in those children was much higher than that in HIV-infected talaromycosis adults (15.3%, 227/1481). The median length of stay was 24 days (range: 1–73).

Prognostic Factors

Prognostic factors were investigated for the clinicians to better predict the outcome of HIV-positive children with *T. marneffei* infection. The patients were divided into two groups according to outcomes as the died and survived groups. Twenty-six factors related to clinical manifestations, laboratory tests, treatment were involved (Supplementary table). According to compare the two group, we found that the ratio of $CD4^+$/$CD8^+$ rather than $CD4^+$ cell counts showed statistically significant differences (P = 0.039). In addition, whether the patient received ART after antifungal therapy and was treated with amphotericin B for over 7 days also contributed to statistically significant differences.

Both the univariate and multivariate logistic regression analysis showed that the lower ratio of $CD4^+/CD8^+$ and amphotericin B treatment not over 7 days were risk factors for poor outcome (95% confidence interval [CI], $P < 0.05$).

Systematic Review of HIV-associated Talaromycosis in Children

For a better understanding of the characteristics of HIV-positive children coinfected with *T. marneffei*, a literature review was conducted in PubMed (Table 5). We found nine related articles, and one of which was abandoned for without the full text. As a result, a total of 11 cases with HIV-associated talaromycosis in children were analyzed (Table 5). Most of the cases were reported 10 years ago (9/11, 81.8%). The age of the patients ranged from 1 to 14 years. 63.6% (7/11) of the cases were from Thailand, and none was from China. Only three patients were treated with ART for a short period of time before confirmed *T. marneffei* infection. The common clinical manifestations included fever (10/11, 90.9%), skin lesion (9/11, 81.8%), lymphadenopathy (9/11, 81.8%), abdominal pain or diarrhea (6/11, 54.5%) and hepatosplenomegaly (6/11, 54.5%). $CD4^+$ cell counts were available in five cases, all of which were less than 200 cells/mm^3. All the patients were diagnosed by positive culture of *T. marneffei* and blood was the most common culture specimen (n = 8), followed by skin scraping (n = 6). Two patients did not receive antifungal treatment and died. Two patients died despite antifungal treatment.

Discussion

Despite seemingly causing a higher mortality rate among children, the talaromycosis has not been studied well among HIV-positive children [33] and the recent studies were almost conducted on HIV-negative children [15, 33–35]. By systemically reviewing the literatures, we found only two cases available in the last decade and none was from China. Herein, we conducted a retrospective study on HIV-positive children coinfected with *T. marneffei* in Southern China. To our knowledge, it is the largest number of cases in the existing literature. Our study provided a broader knowledge for the awareness of talaromycosis in children.

We found a high prevalence (15.3%) of talaromycosis among HIV admissions in children, which was in

Table 3 Laboratory examination of talaromycosis in children

Case	Culture					Positive culture time of *T. marneffei* (days)	1,3-β-D-glucan assay
	Blood	Sputum	BM	PS	Feces		
P1	Pos	ND	ND	Neg	ND	3	ND
P2	Pos	Neg	ND	Neg	Neg	13	ND
P3	Pos	ND	ND	Neg	ND	14	ND
P4	Pos	ND	ND	Neg	ND	14	ND
P5	Pos	ND	ND	ND	Neg	8	ND
P6	Pos	ND	Neg	Neg	ND	7	ND
P7	Pos	Neg	Pos	Neg	ND	5	ND
P8	Pos	Pos	Pos	ND	Neg	4	Pos
P9	Pos	ND	ND	ND	ND	5	Pos
P10	Pos	ND	ND	Neg	ND	5	Neg
P11	Neg	Pos	ND	ND	Neg	7	Neg
P12	Pos	ND	ND	Neg	Neg	5	ND
P13	Pos	ND	ND	ND	Neg	14	Neg
P14	Pos	ND	ND	ND	ND	5	Pos
P15	Pos	ND	ND	ND	ND	12	Neg
P16	Pos	Neg	ND	ND	ND	12	Pos
P17	Pos	Pos	ND	Neg	ND	7	Neg
P18	Pos	ND	ND	ND	ND	4	Pos
P19	Pos	Neg	ND	Neg	Neg	6	Pos
P20	Pos	ND	ND	ND	ND	14	ND
P21	Pos	Neg	ND	ND	ND	8	Pos
P22	Neg	ND	ND	Pos	ND	5	Pos
P23	Pos	Pos	ND	ND	ND	8	Neg
P24	Pos	Neg	ND	Pos	Neg	5	Pos
P25	Pos	ND	ND	Pos	ND	6	Pos
P26	Neg	ND	Pos	ND	Neg	10	Neg
P27	Pos	ND	ND	Neg	ND	7	Pos
P28	Pos	ND	ND	ND	ND	4	Pos

P, patient; BM, bone marrow; PS, pharyngeal swab; Pos, positive; Neg, negative; ND, not detected

line with that in adults [7]. However, the proportion (1.7%) of HIV-infected talaromycosis children among total HIV-infected talaromycosis cases was much lower than that (7.4%) of non-HIV-infected talaromycosis children among talaromycosis patients [15]. It indicates that the status of HIV-positive children in the field of children *T. marneffei* infection changes.

Although bamboo rats have been considered as nature reservoirs of *T. marneffei* [2], none of the patients had a history of contact with bamboo rats in our study. The infection route is still mysterious.

The common clinical manifestations of children HIV-associated talaromycosis included fever, cough, abdominal pain or diarrhea, oral mucosal injury, and hepatomegaly. They were nonspecific and could be shown in adult patients with HIV-positive or related OIs [7]. However, there were different laboratory findings between HIV-positive and HIV-negative talaromycosis children. On the one hand, HIV-positive talaromycosis children showed significant elevated levels of ALT and AST together with lymphocytopenia and leukopenia [15]. On the other hand, abnormal immunoglobulin findings (mainly decreased IgG or

Table 4 Treatment and outcome of HIV-positive children coinfected with *T. marneffei*

Case	Antifungal treatment	ART time (after antifungal therapy)	Length of stay	Outcome
P1	No	No	1	Died (follow-up)
P2	AmB 15 mg day^{-1} × 12 days + ITZ 0.1 g q12h	Day 51	52	Survived
P3	FCZ 0.08 g day^{-1} × 6 days + ITZ 0.1 g q12h	Day 13	12	Survived
P4	FCZ 0.04 g day^{-1} × 14 days + AmB 5 mg day^{-1} × 8 days	No	22	Died
P5	FCZ 0.08 g day^{-1} × 8 days + AmB 6 mg day^{-1} × 10 days + AmB 3 mg day^{-1} × 11 days	Day 30	29	Survived
P6	FCZ 0.1 g day^{-1} × 14 days + ITZ 0.1 g q12h	Day 28	27	Survived
P7	AmB 9 mg day^{-1} × 21 days + ITZ 0.1 g q12h	Day 18	26	Survived
P8	ITZ 0.1 g q12h × 15 days	Day 14	15	Survived
P9	AmB 10 mg day^{-1} × 18 days + ITZ 0.1 g q12h	Day 22	30	Survived
P10	ITZ 0.1 g q12h × 19 days	Day 33	19	Survived
P11	ITZ 0.1 g q12h × 12 days	Day 25	12	Survived
P12	FCZ 0.048 g day^{-1} × 7 days + ITZ 0.1 g q12h	Day 23	24	Died (readmission)
P13	AmB 6 mg day^{-1} × 14 days + ITZ 0.05 g q12h × 17 days	Day 18	31	Survived
P14	ITZ 0.05 g q12h × 35 days	Day 34	35	Died (follow-up)
P15	ITZ 0.1 g q12h × 56 days	No	57	Died (follow-up)
P16	FCZ 0.15 g day^{-1} × 11 days + AmB 10 mg day^{-1} × 11 days + ITZ 0.1 g q12h	Day 20	73	Survived
P17	ITZ 0.1 g q12h × 17 days	Day 12	17	Survived
P18	FCZ 0.1 g day^{-1} × 4 days + AmB 8 mg day^{-1} × 9 days + ITZ 0.1 g q12h	Day 17	19	Survived
P19	FCZ 0.1 g day^{-1} × 5 days + AmB 9 mg day^{-1} × 14 days + ITZ 0.05 g q12h	Day 33	39	Survived
P20	FCZ 0.06 g day^{-1} × 15 days	No	16	Died
P21	AmB 12 mg day^{-1} × 14 days + ITZ 0.1 g q12h	Day 23	25	Survived
P22	AmB 14 mg day^{-1} × 18 days + ITZ 0.2 g q12h	Day 35	28	Survived
P23	FCZ 0.2 g day^{-1} × 7 days + AmB 12 mg day^{-1} × 14 days + ITZ 0.1 g q12h	Day 21	28	Survived
P24	FCZ 0.12 g day^{-1} × 5 days + AmB 12 mg day^{-1} × 14 days + ITZ 0.1 g q12h	Day 24	24	Survived
P25	AmB 10 mg day^{-1} × 14 days + ITZ 0.1 g q12h	Day 16	20	Survived
P26	AmB 14 mg day^{-1} × 17 days + ITZ 0.2 g q12h	Day 27	23	Survived
P27	AmB 10 mg day^{-1} × 2 days	No	3	Died
P28	AmB 15 mg day^{-1} × 3 days	No	4	Died

P, patient; AmB, amphotericin B; ITZ, itraconazole; FCZ, fluconazole; ART, antiretroviral therapy

increased IgE) were considerable in HIV-negative talaromycosis children.

The occurrence of talaromycosis in HIV-positive children in Guangxi seemed to be associated with HIV untreated or treatment failure. ART can markedly increase CD4 counts in HIV-infected children and reduce AIDS-related OIs [36]. In our study, only three children received ART before the onset and they failed to response. All the children had very low $CD4^+$ cell counts (median 13.5 cells/μL, range: 3–137 cells/μL) on admission, which was probably the most important factor for *T. marneffei* infection in HIV-positive children. The same findings were present according to the literature review in our study (Table 5). In addition, ratio of $CD4^+/CD8^+$ plays an important role in the prognosis of HIV-associated children

Table 5 Characteristics of HIV-positive children coinfected with *T. marneffei:* Literature review

Author, reference	Year of publication	Age/ Gender	Country	ART before admission	Clinical manifestations	$CD4^{+}$T cell counts (cells/ mm^3)	Site(s) of positive culture	Antifungal treatment	Outcome
Sirisanthana et al. [25]	1993	1.5y/ NA	Thailand	No	Fever, skin lesion, lymphadenopathy, hepatosplenomegaly	NA	Skin scraping, blood	No	Died
Sirisanthana et al. [25]	1993	1y/NA	Thailand	No	Fever, skin lesion, lymphadenopathy, hepatosplenomegaly, osteolytic lesion	NA	Skin scraping, blood	FCZ + AmB	Died
Sirisanthana et al. [25]	1993	1.5y/ NA	Thailand	No	Fever, lymphadenopathy, thrush, hepatosplenomegaly	NA	Blood	No	Died
Sirisanthana et al. [25]	1993	3y/NA	Thailand	No	Fever, skin lesion, lymphadenopathy, hepatosplenomegaly, thrush	NA	Skin scraping, blood	AmB	Improved
Chokephaibulkit, et al. [26]	2001	1.5y/M	Thailand	No	Fever, Skin lesion, diarrhea, oral thrush, lymphadenopathy, hepatosplenomegaly	NA	Skin scraping, bone marrow	AmB + KCZ	Improved
Chaiwun, et al. [27]	2002	4y/F	Thailand	NA	Skin lesion, lymphadenopathy, hepatosplenomegaly, diarrhea	NA	Lymph node aspirate	Antifungal treatment	Improved
Othman, et al. [28]	2006	7y/M	Malaysia	No	Fever, lymphadenopathy, abdominal pain, weight loss	10	Blood	AmB + ITZ	Improved
Sharma, et al. [29]	2007	9/M	India	No	Fever, skin lesion, dry cough, weight loss, swelling of abdomen, lymphadenopathy	48	Skin scraping	FCZ	Improved
Saikia, et al. [30]	2009	12y/M	India	Yes (9 weeks)	Fever, skin lesion, lymphadenopathy, diarrhea, cough, weight loss, oral thrush	172	Blood	NA	NA
Sudjaritruk, et al. [31]	2012	14y/F	Thailand	Yes (4 weeks)	Fver, skin lesion, oral ulcer, multiple joint pain	51	Skin scraping, blood, bone marrow	AmB + ITZ	Cured
Sethuraman, et al. [32]	2020	3y/M	India	Yes (4 weeks)	Fever, skin lesion, diarrhea, vomiting, weight loss, shortness of breath	135	Blood, bone marrow	Liposomal AmB	Died

BDG, 1,3-β-D-glucan; FCZ, fluconazole; AmB, amphotericin B; KCZ, ketoconazole; ITZ, itraconazole; Pos, positive; Neg, negative; NA, not available

talaromycosis. A low ratio of $CD4^+/CD8^+$ provides a poor prognosis, which helps physicians to make a correct judgment of the patient's condition.

Rapid diagnostics of *T. marneffei* is still lacking. All the *T. marneffei* infections were confirmed according to a positive culture in the present study. Fungal culture is featured with high accuracy of diagnosis and wide applicability of various specimens. Blood was the most common specimen with high positive rates (89.3%) in our study. However, fungal culture is relatively time-consuming [37]. The longest culture time was 14 days, which was not conducive to improve treatment. BDG assay was used for the early diagnosis of invasive fungal infection. However, it was nonspecific and cannot determine the species recognition. The sensitivity of BDG assay was also not high, only 63.2% in our study. Therefore, a rapid diagnostic method with high sensitivity and specificity for *T. marneffei* is demanded.

Amphotericin B and itraconazole are effective drugs in the treatment of *T. marneffei* infection, both with low minimal inhibition concentrations [38]. However, efficacy evaluation of the two drugs in HIV-positive children with talaromycosis was few. Amphotericin B was superior to itraconazole in the induction antifungal therapy of HIV-associated talaromycosis in adults with respect to 6-month mortality [39]. In line with the results in adults, amphotericin B showed a lower mortality rate than itraconazole in children at 6-month follow-up in our study. In addition, the ADRs of amphotericin B can be relieved. Therefore, amphotericin B is more recommended than itraconazole for the induction antifungal treatment of talaromycosis in HIV-positive children. Notably, considering prognostic factors, the treatment course of amphotericin B should be over 7 days.

There was a relatively high mortality (28.6%) among talaromycosis in HIV-positive children. Although it was lower than the mortality of talaromycosis in HIV-negative children [34], but higher than that in HIV-positive adults [7]. In addition to antifungal agents, the high mortality was associated with the high misdiagnosis rate of talaromycosis [12]. Approximately 93% of our cases were misdiagnosed as pneumonia or bronchial pneumonia in our study. There was a similar result in HIV-negative children infected with *T. marneffei* [15]. Misdiagnosis was mainly concerned with the following reasons. Firstly, pediatricians were not well aware of mycosis. Talaromycosis was only noted after positivity for HIV infection. Secondly, the common clinical manifestations of talaromycosis were nonspecific, including fever, cough, hepatosplenomegaly, and abdominal pain or diarrhea. They could be shown in patients with HIV-positive or other OIs [7]. Finally, the most typical skin lesion manifestation of talaromycosis was not common in our cases (21.4%). The percentage was much lower than that in perinatally HIV-infected children (67%) [40], in HIV-positive adults (44.5%) [7], and in the literature review of our study (81.8%), which made diagnosis more difficult. The reason for the discrepancy is unclear. Therefore, in endemic areas, pediatricians should be alerted to the possibility of talaromycosis to avoid misdiagnosis.

For the current study, the main limitation was owing to its retrospective design in a single center. Nevertheless, this study may provide an overview and update on the current knowledge of HIV-associated talaromycosis in children.

In conclusion, our findings confirmed that there was a high prevalence and mortality among talaromycosis in HIV-positive children in Guangxi. The occurrence of talaromycosis was associated with HIV untreated or treatment failure. 1,3-β-D-glucan assay did not show optimal sensitivity. In order to prevent misdiagnosis, rapid diagnostic methods of *T. marneffei* infection still need to be explored and pediatricians in endemic regions should be alerted to the possibility of mycoses. Ratio of $CD4^+/CD8^+$ was useful to help physicians to make a correct judgment of the patient's condition. Induction therapy with amphotericin B over 7 days provide a good prognosis of children HIV-associated talaromycosis.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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