Mycopathologia (2019) 184:735–745
https://doi.org/10.1007/s11046-019-00373-4

ORIGINAL ARTICLE

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

Jing Guo · Bing-Kun Li · Tian-Min Li · Fang-Lin Wei · Yu-Jiao Fu · Yan-Qing Zheng · Kai-Su Pan · Chun-Yang Huang · Cun-Wei Cao

Received: 12 April 2019 / Accepted: 16 August 2019 / Published online: 31 August 2019

Abstract Knowledge about the clinical and laboratory characteristics and prognosis of *Talaromyces marneffei* infection in children is limited. A retrospective study was conducted on pediatric patients with disseminated *T. marneffei* infection in a clinical setting. Extracted data included demographic information (age and sex), clinical features, laboratory findings, treatment, and prognosis. Eleven HIV-negative children were enrolled. The male/female ratio was 8:3. The median age of onset was 17.5 months (3.5–84 months). The mortality rate in these children was 36.36% (4/11). Seven children had underlying diseases. All of the children had multiple immunoglobulin abnormalities and immune cell decline. Ten children received voriconazole treatment, and most of the children (7/10) had a complete response to therapy at primary and long-term follow-up assessment; only three children died of talaromycosis. One patient recovered from talaromycosis but died of leukemia. The child who received itraconazole treatment also showed clinical improvement. No adverse events associated with antifungal therapies were recorded during and after the treatment. Talaromycosis is an indicator disease for undiagnosed severe immunodeficiencies in children. Awareness of mycoses in children by pediatricians may prompt diagnosis and timely treatment. Voriconazole is an effective, well-tolerated therapeutic option for disseminated *T. marneffei* infection in non-HIV-infected children.

Keywords *Talaromyces marneffei* · Non-HIV-infected · Children · Voriconazole · Misdiagnosis

Handling Editor: Vishnu Chaturvedi.

J. Guo · B.-K. Li · T.-M. Li · F.-L. Wei · Y.-J. Fu · Y.-Q. Zheng · K.-S. Pan · C.-Y. Huang · C.-W. Cao (✉)
Department of Dermatology and Venereology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, People's Republic of China
e-mail: caocunwei@yeah.net

C.-W. Cao
The Department of Dermatology, The First Affiliated Hospital of Guangxi Medical University, No 22, Shuang Yong Road, Nanning 530022, People's Republic of China

Introduction

Dimorphic fungal *Talaromyces* (*Penicillium*) *marneffei* is endemic in Southeast Asia and southern China. The pathogen can cause life-threatening disseminated infections in humans, mainly in immunocompromised hosts, such as those with HIV, autoimmune diseases, renal or hematopoietic stem cell transplantation [1], and hematological malignancies [2]. In recent years, the number of *T. marneffei* infections in non-HIV-infected individuals has increased [3]. However, the literature on the clinical features and medical data of *T. marneffei* infection in HIV-negative children is scarce,

and pediatricians in endemic regions are unfamiliar with the disease, which results in misdiagnosis and delay of treatment in many pediatric patients [4]. In addition, no recommended therapeutic guidelines for this infectious disease in children are available. Amphotericin B and liposomes have been recommended as the initial antifungal treatment for disseminated *T. marneffei* infection in adults and are generally effective [5]. Unfortunately, the adverse effects of amphotericin B, especially nephrotoxicity and hepatotoxicity, occur frequently and limit its clinical application in children [6]. Voriconazole is a triazole antifungal agent recommended as a first-line therapy for the treatment of invasive aspergillosis and candidiasis [7]. However, experience with voriconazole treatment for *T. marneffei*-infected children is limited. The mortality rate in children with *T. marneffei* is higher than that in adults [8]. To provide correct diagnoses, as well as effective and safe treatment for children with talaromycosis, we performed a retrospective study to analyze the epidemiological, clinical and laboratory findings, diagnosis and misdiagnosis rates, and treatment outcomes, including the long-term follow-up outcome, in *T. marneffei*-infected children in Guangxi, a major endemic region in southern China, and discussed specific management strategies for this particular at-risk group.

Materials and Methods

Ethics Statement

All study procedures were reviewed and approved by the institutional ethics review board at the First Affiliated Hospital of Guangxi Medical University. All of the patients and their caregivers provided written informed consent before participating in the study.

Study Design and Population

A retrospective cohort study was conducted from January 2013 to December 2018 at the First Affiliated Hospital of Guangxi Medical University, which has 2750 beds and is the largest tertiary care hospital in the Guangxi Autonomous Region in southern China. Among 147 confirmed cases, 11 children were enrolled in this study who presented with culture or histopathologically proven infections caused by *T. marneffei* and who were aged < 14 years. All data were collected using a standardized form that was based entirely on the medical reports of each patient. The data included demographic information (age and sex), domiciles, birth and development details, medical history, family history, clinical manifestations, laboratory data, imaging changes, diagnoses, misdiagnoses, treatments, and prognoses.

Mycological Methods

Blood samples were processed using the VersaTREK/REDOX (TREK Diagnostic System, Cleveland, OH, USA) continuous-monitoring blood culture system. Cultures of clinical specimens, including lymph node, tissue, and bone marrow samples, were performed on Sabouraud dextrose agar at 25 °C and brain–heart infusion agar at 37 °C. Positive cultures for *T. marneffei* were characterized by dimorphic fungi that grew as a mold at 25 °C and produced a soluble red pigment that diffused into the agar and grew as a yeast at 37 °C. All clinical strains were also identified as *T. marneffei* by PCR assays using specific primers based on the 18S rRNA gene as described in a previous study [9]. The isolated strains were subjected to in vitro activity tests of antifungal agents against the yeast form of *T. marneffei* and were also examined according to the guidelines of the Clinical and Laboratory Standards Institute microdilution method (M27-A3) [10].

Anti-interferon (IFN)-γ Autoantibody Detection

Serum samples from all 11 pediatric patients were tested for anti-IFN-γ autoantibodies using an indirect enzyme-linked immunosorbent assay (ELISA) [11]. Serially diluted serum (1:100, 1:500, 1:2500) from healthy donors and patients was added to IFN-γ-coated wells (100 μL/well). Regardless of dilution, sample with an optical density (O.D.) greater than 0.5 was classified as positive for antibodies against IFN-γ [12], which was further confirmed by inhibition assays and functional tests. The effect of anti-IFN-γ autoantibodies in patient serum on IFN-γ-induced HLA-DR

expression was utilized to assess autoantibody neutralization function.

Misdiagnosis

Both the initial and revised diagnoses of the enrolled patients were recorded to analyze the diagnosis and misdiagnosis rates.

Drug Administration and Efficacy Assessment

Among the 11 children, ten children (P1–P10) received voriconazole intravenously as the primary antifungal treatment. After the initial intravenous therapy, they received voriconazole orally as part of an extended treatment program at the discretion of the investigators according to the clinical and mycological responses of the patients. In the absence of guidelines for voriconazole dosing in *T. marneffei*-infected children, dosing and monitoring regimens were determined by the treating clinician. One pediatric patient (P11) was treated with oral itraconazole at 5 mg/kg, qd.

The primary efficacy variable was the global response evaluated at the end of treatment (EOT) or at 12 weeks for subjects continuing with long-term antifungal therapy at the discretion of the investigators [13]. The therapeutic evaluation was based on the overall clinical, mycological, radiological, and serological responses according to our previous description and was evaluated using the following scale: (1) complete response, defined as the resolution of all signs and symptoms and/or radiographic abnormalities attributable to fungal infection present at baseline, with a normal serological response (when appropriate) and mycological eradication (when obtainable); (2) partial response, defined as improvement in most signs and symptoms; and (3) failed response, defined as no clinical improvement, clinical condition deterioration, or death. When mycological assessments were undertaken, eradication was defined as the absence of the original fungal pathogen in a relevant clinical specimen. Presumed eradication was inferred in subjects with satisfactory clinical responses (including complete and partial responses) for whom relevant clinical specimens were not analyzed.

For subjects with a complete response or partial response at 12 weeks or the EOT, follow-up evaluations were performed at 6 months of therapy, as well as 1 year after the EOT. The responses (findings attributable to the fungal infection) were compared to those at 12 weeks or the EOT and were categorized as cured (continued resolution), improved (further improvement), relapsed (deterioration), or death.

All adverse events were recorded during treatment, and laboratory data were collected, including peripheral blood counts, liver function, renal function, and electrolyte tests.

Statistical Analysis

The SPSS statistical software package version 17.0 was used for the statistical analysis. Data are presented as the mean ± SD, frequency (%), or median (interquartile ranges).

Results

Patient Demographic and Clinical Characteristics

Eleven pediatric patients (7.48%) among 147 cases of talaromycosis were diagnosed between January 2013 and December 2018 (including 78 HIV-positive patients and 69 HIV-negative patients). None of the 11 children were infected with HIV. The ratio of males to females was 8:3. The median age of onset was 17.5 months (range 3.5–84 months). The patients resided in different regions across Guangxi. All children lived in urban areas and had no history of rodent contact. Disease onset mainly occurred during the spring, from January to April (n = 7, 63.64%), followed by autumn, from August to October (n = 4, 36.36%). The median time from symptom onset to diagnosis was 1.9 months (range 0.7–3.4 months). Among the 11 children, ten were infants and one was a preterm infant with a low birth weight (33 weeks, 1.8 kg).

Fever and cough were the most common clinical manifestations (n = 11, 100%), followed by anemia, fungemia, abdominal pain or diarrhea, weight loss, lymphadenopathy, and hepatosplenomegaly (90.91%, 82.80%, 72.70%, 63.64%, 63.64%, and 63.64%, respectively). All of the above patients exhibited

disseminated *T. marneffei* infections (Table 2). Nine cases (81.82%) were misdiagnosed as pneumonia or bronchial pneumonia. Seven patients (7/11, 63.63%) had various underlying diseases, including a congenital heart (ventricular septum) defect ($n = 1$); white matter demyelinating lesions ($n = 1$); Crohn's enteritis ($n = 1$); iron deficiency anemia ($n = 1$); congenital megacolon, gallstones, and leukemia ($n = 1$); severe malnutrition ($n = 1$); and G6PD deficiency (n = 1). Notably, one child was diagnosed with leukemia one year after *T. marneffei* infection. Seven patients also had other opportunistic infections ($n = 7$, 63.63%), and *Candida albicans* infection ($n = 4$, 36.36%) was the major coinfection (Table 1).

Laboratory Findings

We tested 11 patients for autoantibodies, syphilis antibody, and IFN-γ autoantibodies, and the results were all negative.

The results of laboratory tests in patients with acute infection showed that all patients had elevated serum C-reactive protein (CRP) levels ($n = 11$, 100%), including nine patients who had decreased hemoglobin and natural killer (NK) cells ($n = 9$, 81.8%); seven patients had leukocytosis and lymphocytosis and decreased IgA levels ($n = 7$, 63.60%); six patients had decreased IgM levels ($n = 6$, 54.50%); five patients had decreased CD4 + T cell and CD8 + T cell levels ($n = 5$, 45.50%); four patients had thrombocytopenia, neutropenia, decreased IgG levels, and increased IgM levels ($n = 4$, 36.40%); and three patients showed thrombocytopenia, lymphopenia, and leukopenia ($n = 3$, 27.30%) (Table 2).

T. marneffei was confirmed by pathology and culture in two patients (2/11). In eight patients (8/11), only the cultures of the secretions and tissues were positive. In one patient (1/11), only the pathology result was positive.

The fungal culture results indicated the proportion of positive results for different tissues (blood sample, $n = 9$, 81.8%; bone marrow, $n = 7$, 63.63%; liver tissue, $n = 1$, 9.1%; intestinal tissue, $n = 1$, 9.1%; sputum, $n = 2$, 18.2%) (Fig. 1).

The in vitro antifungal susceptibility tests showed that the *T. marneffei* isolates collected from these patients were highly susceptible to voriconazole and itraconazole, with minimum inhibitory concentrations (MICs) ranging from 0.0078 to 0.015 mg/L and 0.0039 to 0.03 mg/L, respectively.

Imaging Results

We performed CT examinations in 11 patients, and the lungs and pleura were the major cumulative sites of the disease. The imaging examination results showed that four patients had thickening of the lungs with flaky diffuse plaque, with or without pleural effusion ($n = 4$, 36.4%). Two patients had pneumonia accompanied by pneumothorax ($n = 2$, 18.2%). Two patients had high-density shadows in the left upper lung ($n = 2$, 18.2%). One patient had inflammation in the left lung and swelling of the left hilar lymph node ($n = 1$, 9.1%). A total of 9.1% of the patients showed diffuse hepatomegaly ($n = 1$, 9.1%), and one patient showed diffuse soft tissue inflammation of the upper jaw with cervical lymphadenopathy ($n = 1$, 9.1%) (Fig. 2).

Pathological Results

Three patients underwent histopathological examination of lymphoid, liver, and lung tissues. Chronic pyogenic granulomatous inflammation was the main pathological feature. Microscopic examination showed infiltration of lymphocytes, macrophages, and plasma cells in the tissue specimens. After periodic acid–Schiff (PAS) and diastase-PAS (D-PAS) staining, a large number of fungal spores were observed in the interstitial space and macrophages (Fig. 3).

Treatment and Prognosis

Among the ten children who were treated with voriconazole, the primary global response was assessed at week 12 or at the EOT. Seven children (7/10) had a complete response, one patient (1/10) had a partial response, and two patients (2/10) who were moribund were discharged and died after 1 month of voriconazole treatment, which was recorded as a failed response. The mycological evaluations at week 12 showed eradication in seven patients and presumed eradication in one patient.

Table 1 Clinical manifestations of 11 non-HIV children with *T. marneffei* infection

Patient	Age (months)	Gender	Domicile	HIV	Medical history	Concurrent infection	Clinical manifestations	Flowing time after diagnosis (day)
P1	4	M	Urban	–	Mycotic stomatitis; multiple cysts complicated liver; sepsis	HBV *E. coli* (multidrug resistance), *Pseudomonas aeruginosa*; *C. albicans*, *Klebsiella pneumoniae*	Erythema and papules on whole-body skin; recurrent fever; hepatosplenomegaly for 2 months	61
P2	3.5	F	Urban	–	Congenital heart diseases (ASD); mycotic stomatitis	*C. albicans*; HSV; human *Staphylococcus* subspecies	Cough for 2 months; dark red macules (ear, neck, chest); hepatosplenomegaly; recurrent fever	59
P3	10	M	Urban	–			Cough for 6 months; lymph node enlargement (armpit, mediastinal); recurrent fever	2037
P4	28	F	Urban	–	White matter demyelination; hydrocephalus	EBV; *Mycoplasma pneumoniae* (MP)	Swelling in lower limbs for 3 months; hemophagocytic syndrome; hepatosplenomegaly; recurrent fever, weight loss	723
P5	30	M	Urban	–	Crohn's disease	*Oidium tropioale*	Bellyache for 3 months; hepatosplenomegaly; lymph node enlargement (mesentery, neck, ear, armpit); recurrent fever, weight loss	403
P6	84	M	Urban	–	Iron deficiency anemia		Face pale for 8 months; hepatosplenomegaly for 3 months; lymph node enlargement (groin, mesentery); recurrent fever	514
P7	12	M	Urban	–	Cholecystolithiasis; JMML		Cough; cerebral hemorrhage; pneumorrhagia; upper gastrointestinal hemorrhage; hepatosplenomegaly; lymph node enlargement (mesentery) for 1 year; hemophagocytic syndrome; recurrent fever; weight loss	670

Table 1 continued

Patient	Age (months)	Gender	Domicile	HIV	Medical history	Concurrent infection	Clinical manifestations	Flowing time after diagnosis (day)
P8	19	M	Urban	–	Pyemia; chronic viral hepatitis B	HBV	Cough for 6 months; lymph node enlargement (neck, armpit and mediastinal); hemophagocytic syndrome; recurrent fever; weight loss	225
P9	34	F	Urban	–	Nasosinusitis		Oral pain for 6 months; oral cervical for 4 months; lymph node enlargement (neck); erythema on trunk and both lower extremities skin; recurrent fever; recurrent fever, weight loss	2157
P10	28	M	Urban	–	Severe malnutrition; mycotic stomatitis	*C. albicans*	Cough for 7 months; gasp for 1 month; aerothorax; empyema; recurrent fever; weight loss	425
P11	16	M	Urban	–	G6PD deficiency; perianal abscess		Anti-TB treatment; cough for 8 months; hepatosplenomegaly; lymph node enlargement (neck, submandibular, armpit, pulmonary hilar, supraclavicular, and mediastinal); hemophagocytic syndrome; recurrent fever; weight loss	2204

MP Mycoplasma pneumonia, *HBV* hepatitis B virus, *PA* Pseudomonas aeruginosa, *KP* Klebsiella pneumoniae, *JMML* juvenile myelomonocytic leukemia, *ASD* atrial septal defect, *G6PD* glucose-6-phosphate dehydrogenase, *NTM* non-tuberculosis mycobacteria

In the long-term follow-up assessment, one of the eight children died of talaromycosis after 6 months of therapy and the other seven children had a complete response. Five of the seven children were cured and had not relapsed at 6 months after the EOT. However, one of the five children (P7) died because of leukemia at 1 year after the end of voriconazole therapy. The remaining four children had not relapsed at 1 year after the EOT. Two patients were still undergoing voriconazole treatment and had a favorable response, and the mycological evaluations of all seven patients showed eradication (Table 3).

Among the ten children who were treated with voriconazole, P1–P7 received 6–7.8 mg/kg twice daily as intravenous treatment; the mean duration was 21.25 days (range 12–48 days), and the median duration was 24.28 days. After the intravenous treatment, they received 4.3–6.5 mg/kg twice daily orally as an extended treatment, and the mean duration of this therapy was 25.8 weeks (range 1–55 weeks) with a median of 18.1 weeks. P8–P10 received 9–10 mg/kg twice daily as intravenous treatment; the mean duration was 20 days (range 16–26 days), and the median duration was 18 days. After the intravenous treatment, they received 4.7–10 mg/kg twice daily orally as an extended treatment, and the mean duration of this therapy was 50 weeks (range 15–90 weeks) with a median of 45 weeks. The efficiency rates of voriconazole in the low-dose and high-dose groups were 71.42% and 66.67%, respectively.

P11 had a complete response to oral itraconazole (5 mg/kg/day) treatment and did not relapse during the follow-up assessment.

The mortality rate in the 11 pediatric patients was 36.4% (4/11).

Safety Evaluation of Antifungal Administration

We evaluated the adverse reactions of 11 pediatric patients at different time points during treatment or after the EOT. No significant adverse reactions

Table 2 Clinical features and laboratory findings of 11 non-HIV children with Talaromyces marneffei infection

Clinical features	Number of cases (n = 11)	Percentage (%)	Laboratory findings	Number of cases (n = 11)	Percentage (%)
Fever	11	100	CRP increase	11	100.00
Cough	11	100.00	Hemoglobin decrease	9	81.80
Anemia	10	90.90	NK cell decrease	9	81.80
Fungemia	9	82.80	Leukocytosis	7	63.60
Abdominal pain or diarrhea	8	72.70	Achroacytosis	7	63.60
Weight loss	7	63.30	IgA decrease	7	63.60
Lymphadenopathy	7	63.60	IgM decrease	6	54.50
Hepatomegaly	7	63.60	CD4 + T cells decrease	5	45.50
Splenomegaly	7	63.60	CD8 + T cells decrease	5	45.50
Malaise	6	54.50	Thrombocytopenia	4	36.40
Dyspnea	6	54.50	Neutropenia	4	36.40
Chest pain	5	45.50	IgG decrease	4	36.40
Osteomyelitis	5	45.50	IgM increase	4	36.40
Hemophagocytic syndrome	4	36.36	Thrombocytosis	3	27.30
Cutaneous or subcutaneous lesion	3	27.30	–	–	–

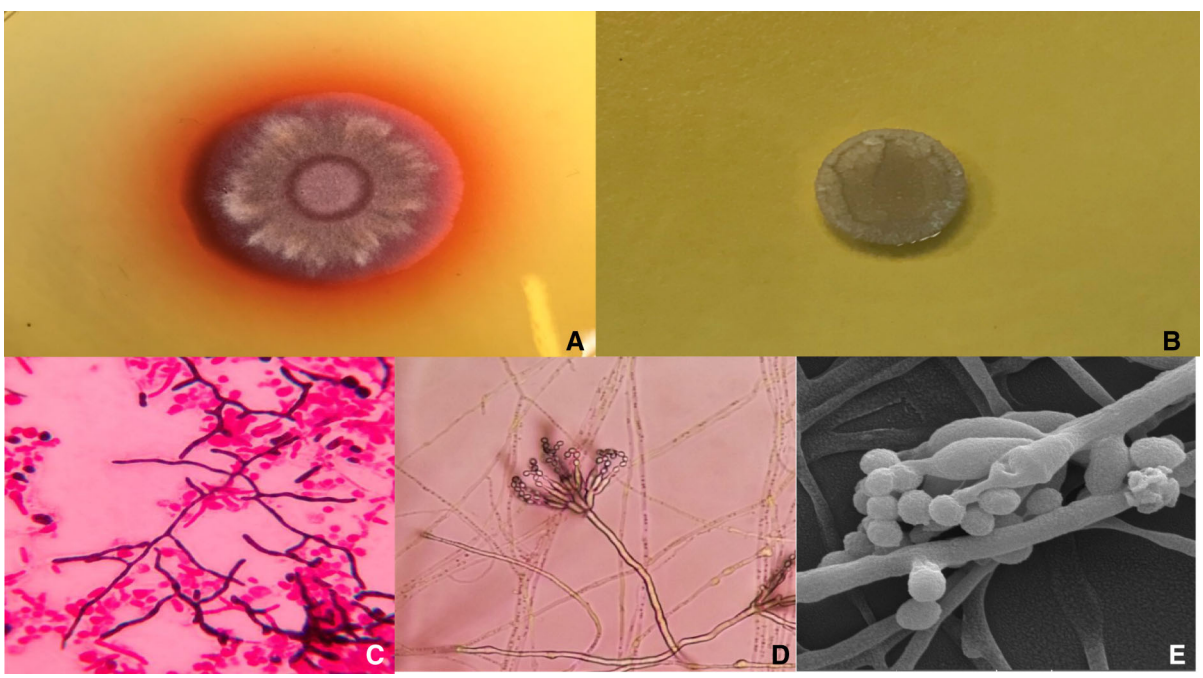

Fig. 1 **a** Culture at 25 °C. The medium was dyed red by T. marneffei. **b** *T. marneffei* cultured at 37 °C; no red pigments were produced. **c** Microscopically, blood culture smears (original magnification 400). **d**, **e** Culture at 25 °C, mycelial structure of *T. marneffei* (**d**: under the microscope, original magnification 400, **e**: under the electron microscope, original magnification 15,000). (Color figure online)

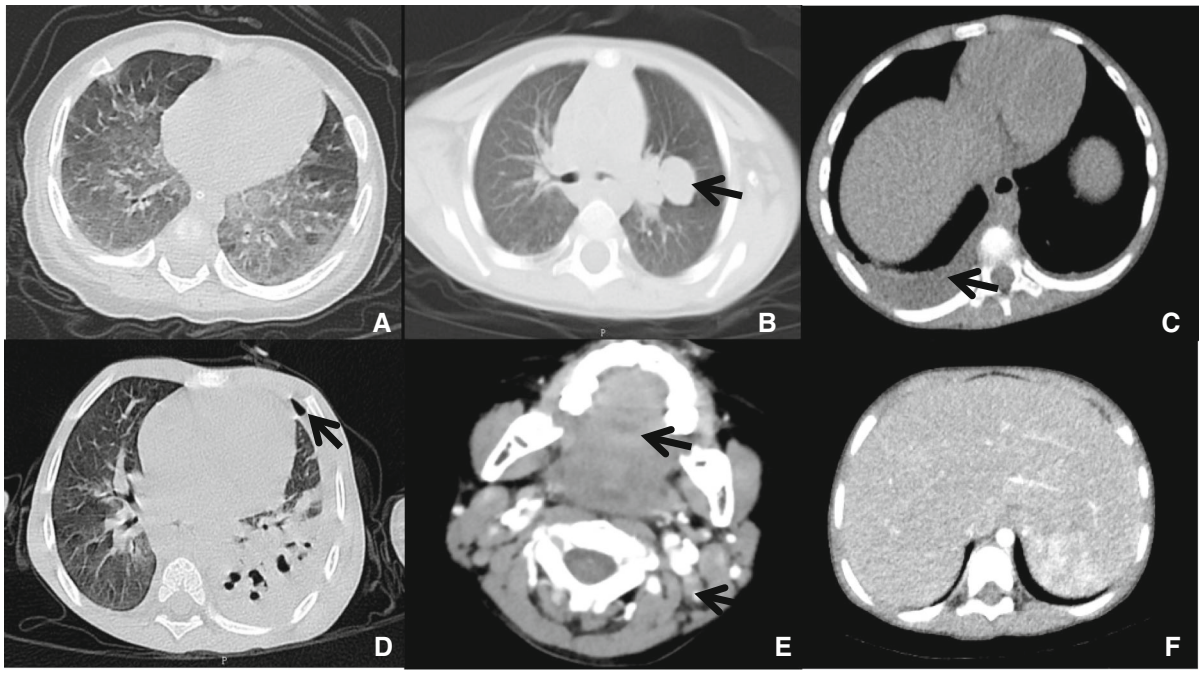

Fig. 2 Imaging manifestations of *T. marneffei* infection in non-HIV-infected children: **a** increased bronchovascular shadows, **b** left hilar lymphadenopathy, **c** pleural effusion, **d** increased bronchovascular shadows, left lung parenchymal lesions with bronchiectasis, pneumothorax, **e** upper palate soft tissue edema with cervical lymph node enlargement, **f** diffuse hepatomegaly

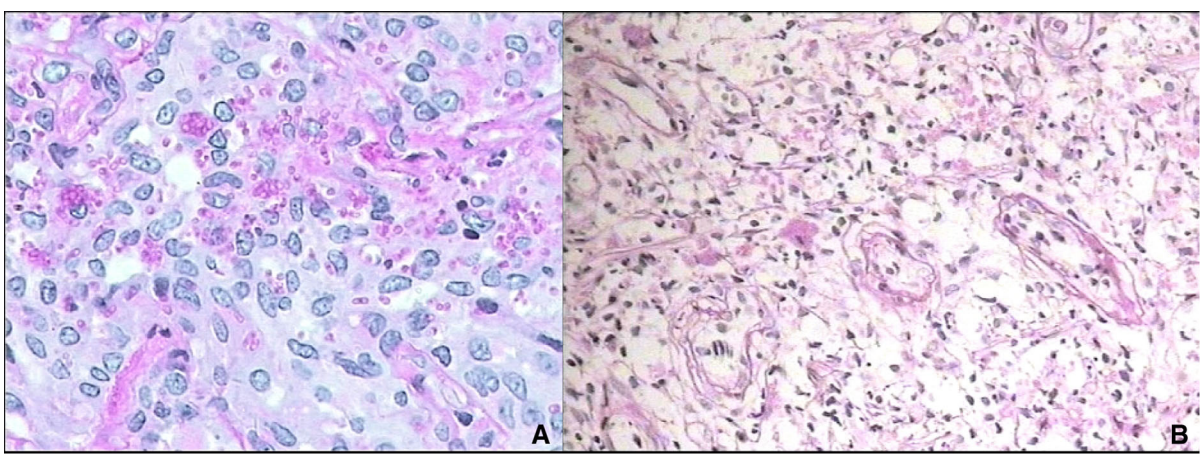

Fig. 3 Photomicrograph of pathology: **a** lung tissue, **b** liver tissue. Sausage-like yeast of *T. marneffei* can be observed in macrophages stained with PAS and D-PAS. Necrotizing granulomatous inflammation in tissue

occurred after treatment. Among the patients, P1, P2, and P4 had elevated alanine aminotransferase (ALT) levels before treatment, but they were still tolerant to voriconazole treatment. In addition, the ALT levels decreased to normal levels after their conditions stabilized. The elevation of ALT levels in these three children may have been caused by acute infection.

Discussion

In this study, the proportion of pediatric patients among talaromycosis patients was 7.4% (11/147). All of these children were HIV negative, which is similar to previous reports from China but is contrary to the results of a study in northern Thailand, in which 21 of

Table 3 Application and follow-up of voriconazole in ten non-HIV children with *T. marneffei* infection

Patient	Site(s) of positive culture	Treatment by voriconazole				Treatment by itraconazole (weeks)	Response at week 12		Response at follow-up		Side effects
		Intravenous dose (mg/kg, q12 h)	Intravenous (days)	Oral dose (mg/kg, q12 h)	Oral (weeks)		Mycological	Global response	6 months later	1 year later	
P1	Blood	6	12	6	3	–	Not eradicated	Failure	Death	–	No
P2	Blood	7	14	6.2	1.1	–	Not eradicated	Failure	Death	–	No
P3	Lung tissue	7	12	6	36	–	Eradicated	Complete response	Cured	Cured	No
P4	Bone marrow, blood	7	30	6.5	52	–	Eradicated	Complete response	Cured	Cured	No
P5	Bone marrow, blood, liver tissue Intestinal tissue	7.3	28	4.3	55	–	Eradicated	Complete response	N/A***	N/A***	No
P6	Bone marrow, blood	7.5	48	5	17.5	–	Eradicated	Complete response	Cured	Cured	No
P7	Bone marrow, blood sputum	7.8	26	6.2	18.1	–	Eradicated	Complete response	Cured	Death#	No
P8	Bone marrow blood	9	18	4.7	15	–	Eradicated	Complete response	N/A***	N/A***	No
P9	Sputum blood	10	26	9	90	–	Eradicated	Complete response	Cured	Cured	No
P10	Lung pathological	10	16	10	45	–	Presumed eradication	Partial response	Death	–	No
P11	Bone marrow, blood	–	–	–	–	132	Eradicated	Complete response	N/A***	N/A***	No

Ten children treated with voriconazole were divided into two groups (low-dose group: P1–P7; high-dose group: P8–P10)

#The patient did die not from *T. marneffei* infection but from other diseases

***When we finished this study and stopped follow-up, the patients did not receive the 6 months or 1 year after the end of treatment

23 pediatric patients were HIV infected. Although up to 16.1% of HIV-infected hospitalized patients are coinfected with *T. marneffei* in Guangxi, talaromycosis has not been reported in children with HIV in the region, suggesting that other immunocompromising conditions exist in these children [14].

Immunodeficiency due to anti-IFN-γ autoantibodies is an emerging adult-onset immunodeficiency syndrome associated with *T. marneffei* infection, which could explain the cases of *T. marneffei* infection among non-HIV-infected adult Asian patients who had no other comorbidities. In the current study, anti-IFN-γ autoantibodies were not detected in the pediatric patients, suggesting that anti-IFN-γ autoantibodies might not play a role in the pathogenesis of the disease in children [15].

Talaromycosis has been reported in children with various forms of immune-related underlying diseases and primary immunodeficiencies (PIDs), including leukemia, hyper-IgM syndrome, hyper-IgE syndrome, mutations in CYBB or CD40L, or gain-of-function mutations in STAT1/STAT3 [3, 8, 16]. In the present study, all of the children had abnormal immune functions at the time of infection, and a reduction in the number of T-lymphocytes or cellular immunity is probably the most important predisposing factor for *T. marneffei* infection. It is noteworthy that one child (P7) in the study was diagnosed with leukemia one year after he recovered from *T. marneffei* infection and died of hematological malignancies, which implied that *T. marneffei* infection should be regarded as an indicator disease for undiagnosed severe immunodeficiencies in children. However, the genetic susceptibility associated with *T. marneffei* infection in these children is currently unknown and requires further research.

Voriconazole is a broad-spectrum triazole that has been successful in the treatment of a variety of pediatric mycoses. However, voriconazole dosing for children is still challenging [13]. Multiple simulation studies have recommended initial dose ranges of 7–8 mg/kg administered intravenously twice daily in Caucasian children aged 2–12 years to achieve exposures comparable to those in adults [6, 10, 11]. The European Medical Association approved higher doses in younger children (2 to $<$ 12 years) consisting of 8 mg/kg intravenously twice daily (9 mg/kg day 1) and 9 mg/kg orally twice daily [17, 18]. In the present study, seven of ten children who received voriconazole treatment had a complete response during short-term follow-up assessment at week 12. Furthermore, long-term follow-up assessments performed after the EOT also showed encouraging results, with five of ten patients cured at 1 year after the EOT, although one child died of leukemia one year later. The efficacy of voriconazole with initial dose ranges of 7.0–8 mg/kg administered intravenously twice daily was similar to that of 9.0–10.0 mg/kg administered twice daily. Our data suggest that intravenous voriconazole doses of 7–8 mg/kg are suitable for *T. marneffei*-infected children in China. However, many factors, such as concomitant medications and polymorphisms in the cytochrome P450 (CYP450) genotype, could affect voriconazole concentrations in vivo. Thus, therapeutic drug monitoring (TDM)-guided individualized dosing adjustment should be routinely used in voriconazole administration for *T. marneffei*-infected children [19].

In the present study, 81.8% (9/11) of children were misdiagnosed with pneumonia or bronchial pneumonia because of unspecific clinical features associated with *T. marneffei* infection, which resulted in delayed treatment in these children. Considering the ubiquitous distribution of *T. marneffei* within the environment of endemic areas and that the route of infection is still enigmatic, pediatricians in endemic regions should be aware of this mycosis in children. Establishment of guidelines for the timely diagnosis and effective treatment of *T. marneffei*-infected children is urgently needed [20].

The study still has some limitations that should be considered. This is a retrospective analysis from a single institution with relatively few patients. The voriconazole plasma concentration was not routinely monitored, and the polymorphisms associated with voriconazole metabolism were not investigated in this study. In addition, it is unknown whether these children have PIDs. Nevertheless, this study may provide a valuable reference for the diagnosis and treatment of *T. marneffei* infection in children.

Acknowledgements We thank Ku C. L. and his team from Laboratory of Human Immunology and Infectious Diseases, Graduate Institute of Clinical Medical Sciences, Chang Gung University, Taiwan. This study was supported by grants from the National Natural Science Foundation of China (Nos. 81571971 and 81271804) and the Natural Science Foundation of Guangxi Province of China (2017GXNSFAA198004 and 18221017).

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions CC and JG designed the study. JG, B-KL, T-ML, F-LW, and Y-JF collected the data. JG and B-KL analyzed the data. Y-QZ, K-SP, and C-YH performed the fungal culture and data collection. JG drafted the manuscript. All of the authors have read and approved the final manuscript.

Availability of Data and Material The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

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

Consent for Publication All of the nine authors agree to submit the manuscript for possible publication in "Mycopathologia".

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