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A Retrospective Analysis of 7 Human Immunodeficiency Virus-Negative Infants Infected by *Penicillium marneffei*

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Abstract: Infection with *Penicillium marneffei* has rarely been reported in human immunodeficiency virus (HIV)-negative infants. We aimed to determine the epidemiological, clinical, pathological, and immunological characteristics of 7 HIV-negative infants infected by *P. marneffei*, and to provide insights into its diagnosis and treatment.

We retrospectively reviewed the cases of 7 HIV-negative infants infected by *P. marneffei* who presented to the First Affiliated Hospital of Guangxi Medical University between January 1, 2003 and December 1, 2014. The infants' median age was 23.43 months (SD = 8.34), and all lived in Guangxi Province in China, where *P. marneffei* is endemic. The median time from disease onset to diagnosis was 2.29 months (SD = 2.12). Of the cases studied, 5 (71.43%) had medical histories that included frequent pneumonia or bronchopneumonia, thrush, congenital megacolon, glucose-6-phosphate dehydrogenase deficiency, and hemophagocytic syndrome. The most common symptoms were fever, cough, and anemia, followed by lymphadenopathy, hepatosplenomegaly, and being underweight. Four patients had slightly elevated white blood cell counts. The lymphocyte and $CD4^+$ T-cell counts were normal. The $CD8^+$ T-cell counts, serum immunoglobulin (Ig) G titer, and serum IgA titer were low in 5 patients, and the serum IgM titers were high in 3 infants. Caseous necrosis was observed in 3 patients whose lymph nodes were affected. One case who received intravenous amphotericin B and 3 cases who received intravenous voriconazole improved, and these patients were cured after continual treatment with oral voriconazole for 6 or 12 months. The remaining patients died before they received antifungal treatment.

P. marneffei causes severe disease and disseminated infections, and it has high mortality rates in HIV-negative infants in endemic areas. *P. marneffei* susceptibility may be associated with immunodeficiencies or immune disorders. In endemic areas, clinicians should aware of disseminated *P. marneffei* infections when infants present with serious or recurrent infections, even if they are HIV negative. *P. marneffei* is highly susceptible to amphotericin B and voriconazole. Timely diagnosis and treatment can improve patients' prognoses. Intravenous voriconazole could be recommended as the initial antifungal agent for HIV-negative infants infected by *P. marneffei*, because of its low nephrotoxicity, high sensitivity, and high efficacy levels.

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Abbreviations: HIV = human immunodeficiency virus, Ig = immunoglobulin, SD = standard deviation, SDA = Sabouraud dextrose agar, WBC = white blood cell.

INTRODUCTION

Penicilliosis is an infectious disease that is caused by the fungus *Penicillium marneffei*. Primary penicilliosis has been reported among adult patients with acquired immunodeficiency syndrome, but few cases and studies of primary penicilliosis have been described in infants who are not infected by the human immunodeficiency virus (HIV).[1–3] Infants, whose scopes of activity are limited, are not typically exposed to rodents, which are the natural hosts of *P. marneffei* and have been confirmed as a risk factor for penicilliosis.[1] The reasons underlying the susceptibility of HIV-negative infants to *P. marneffei* infections and the risk factors associated with infection remain unclear.

This retrospective study of 7 HIV-negative infants who were infected by *P. marneffei* aimed to describe the epidemiological, clinical, pathological, and immunological characteristics of the disease and its treatment, to evaluate the outcomes from these patients, and to provide insights into its correct diagnosis and treatment.

METHODS

Study Population

The medical records of 126 patients who were diagnosed with *P. marneffei* infections between January 1, 2003 and December 31, 2014 at The First Affiliated Hospital of Guangxi

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Consent: Written informed consent was obtained from all of the patients' parent/guardians in relation to the publication of this report and any accompanying images. Copies of the written consents are available for review by the Editor of this journal. This study was approved by the ethics committee associated with the Faculty of Medicine at The First Affiliated Hospital of Guangxi Medical University.
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Medical University were reviewed. Seven HIV-negative infants who were infected with *P. marneffei* and who were younger than 3 years of age were retrospectively evaluated. The information gathered from the patients' medical records was summarized for the analysis, and it included data about the patients' demographics, namely, their sexes, ages, and domiciles, birth details and development, medical histories, auxiliary examination results, including their hematological test results, serological test results, immune statuses, imaging findings, and their clinical and pathogen test results, treatments, namely, the doses and durations of the treatments, and the patients' outcomes. Any HIV-positive individuals were excluded from the study.

This study was approved by the ethics committee associated with the Faculty of Medicine at The First Affiliated Hospital of Guangxi Medical University.

Methods Used to Diagnose *P. marneffei* Infection

Specimen Culture and Pathogen Examinations

Cultures of the clinical specimens that included blood, sputum, lymph node, mass secretion, tissue, bone, and bone marrow sample, were performed on Sabouraud dextrose agar (SDA) at 25 and 37°C. Positive cultures for *P. marneffei* were characterized by the dimorphic fungi that grew as mold at 25°C and as yeast at 37°C. A unique characteristic of the *P. marneffei* mold is the presence of a soluble red pigment that diffuses into the agar; subsequently, the reverse side of the culture plate looks either pink or red at 25°C.[2] The yeast form of *P. marneffei* was confirmed by cytological and histopathological assessments of tissue and secretion samples using Periodic Acid-Schiff staining or Wright stain, which reveal a characteristic morphology that includes numerous intracellular yeast-like or sausage-like cells that are 2 to 3 μm in diameter with transverse septa.[3]

Determination of HIV Status

Two enzyme-linked immunosorbent assays (Enzymun-Test, Anti-HIV 1 + 2, Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) were used to test the sera for the presence of anti-HIV antibodies. Any sera that were negative for anti-HIV antibodies underwent repeat testing at our hospital and at the Guangxi Center for Prevention and Control.

Interactions of the Drugs In Vitro

Etest® antimicrobial susceptibility test strips (bioMérieux, Marcy l'Etoile, France) were used to test the susceptibilities of the yeast and mold forms of the *P. marneffei* strains isolated from our 7 patients to amphotericin B, fluconazole, voriconazole, and itraconazole. Drug interactions were assessed using a microdilution chequerboard method, and we were also able to determine the minimum inhibitory concentration of each drug individually on the same plate using the Clinical and Laboratory Standards Institute guidelines that are presented in document M27-A2, with minor modifications.[4]

RESULTS

Patients' Demographic and Clinical Characteristics

During the 11-year study period, 7 HIV-negative cases of *P. marneffei* infection were evaluated at the hospital. All of the patients were younger than 3 years of age, they had a median age of 23.43 months (standard deviation [SD] = 8.34), (range: 12–33 months), and they comprised 2 females and 5 males. All of the infants and their parents lived in Guangxi Province in China. The median time from the onset of symptoms to a diagnosis was 2.29 months (SD = 2.12) (range: 0.5–6 months). The patients began to feel unwell in January (n = 2, 28.6%), March or April (n = 3, 42.9%), and June or July (n = 2, 28.6%). All of the infants had undergone full-term normal deliveries and flat growth. Five patients (71.43%) had medical histories that included oral thrush (n = 1), congenital megacolon (n = 1), glucose-6-phosphate dehydrogenase deficiency (n = 1), septicopyemia (n = 1), and frequent pneumonia or bronchopneumonia (n = 3). None of the patients or their parents had histories of contact with rodents.

All of the patients presented with fever and cough. In addition, 6 patients (85.72%) had generalized or cervical lymphadenopathy, 3 patients (42.86%) had hepatosplenomegaly and were underweight, 2 patients (28.57%) had oral thrush, and 1 patient exhibited papular lesions with central umbilications (Table 1).

Laboratory Test Results and Imaging Findings

Complete blood counts showed that the white blood cell (WBC) counts were elevated in 4 patients (57.14%), and the mean WBC count was 9.4×10^9 cells/L (SD = 3.8×10^9) (range: 3.6–12.9×10^9 cells/L). The mean neutrophil count was 3.7×10^9 cells/L (SD = 2.0×10^9) (range: 1.3–6.5×10^9 cells/L). The mean lymphocyte cell count was 3.7×10^9 cells/L (SD = 2.0×10^9) (range: 1.6–11.4×10^9 cells/L), and the lymphocyte cell count was elevated in 5 patients (71.43%). All patients showed reduced hemoglobin concentrations, and the mean hemoglobin concentration was 89.31 g/L (SD = 28.32) (range: 44.8–113 g/L). The serum immunoglobulin (Ig) G and IgA titers were reduced in 5 infants (71.43%). The mean IgG titer was 7.42 g/L (SD = 6.43) (range: 0.92–16.80 g/L). The mean IgA titer was 0.72 g/L (SD = 0.53) (range: 0.18–1.48 g/L). Three infants (42.86%) showed elevations in their serum IgM titers. The mean T-lymphocyte percentage was 57.42% (SD = 9.70) (range: 41.70–68.0%). Five out of 6 of the patients (83.33%) showed significant reductions in their $CD8^+$ T-cell levels, and the mean percentage of $CD8^+$ T lymphocytes was 14.95% (SD = 7.76) (range: 8.50–29.40%). The percentage of $CD4^+$ T cells was normal in all of the patients (6/6, 100%), and the mean percentage of $CD4^+$ T cells was 33.92% (SD = 7.30) (range: 22.20–40.60%). The mean serum albumin concentration was 27.3 g/L (SD = 6.6), which was below the normal range in all of the patients (range: 19.1–38.0 g/L). The erythrocyte sedimentation rate was higher in 5 patients (71.43%), and the mean rate was 39.29 mm/h (SD = 27.92) (range: 13–88 mm/h). The C-reactive protein levels were higher in 4 patients (range: 6.4–205 mg/L) (Table 2).

High-resolution computed tomography scans of the patients' chests indicated pulmonary involvement in 5 patients (71.43%), which included nodules in 2 cases (Figure 1A), infiltrates in 3 cases (Figure 1B), pleural effusion in 1 case, and the involvement of the pleural cavity in 1 case (Figure 1A).

Culture Results, Pathogen Morphology, and Histopathology

Bone marrow, blood, bronchoalveolar lavage fluid, and dermal secretion samples were inoculated onto SDA, and they were incubated at 37 and 25°C. *P. marneffei*-positive results were obtained from the blood (5/7, 71.43%), bone marrow (3/5, 60%), mass secretion (1/1, 100%), and dermal secretion (1/1, 100%; Figure 2A) samples. Staining with lactophenol

TABLE 1. Clinical Features of 7 Human Immunodeficiency Virus-Negative Infants With *Penicillium marneffei* Infections

Patient	Age (Months)	Gender	Endemic Area	Contact Rodents	Time From Disease Onset to Diagnosis (Months)	Medical History	Clinical Findings	Site(s) of Positive Culture/Histology
P1	29	Male	Yes	No	4	Oral thrush, frequent pneumonia	Fever, cough, weight loss, lymphadenopathy	BALF, lymph nodes
P2	27	Male	Yes	No	1	Frequent bronchopneumonia	Fever, cough, lymphadenopathy	Bone marrow, lymph node
P3	30	Male	Yes	No	0.5	History of sepsis and pneumonia	Fever, cough, weight loss, oral ulcers, lymphadenopathy	Blood, lymph node
P4	14	Male	Yes	No	1	G6PD deficiency	Fever, cough, weight loss, melena, edema, oliguria, hepatosplenomegaly, lymphadenopathy	Blood, bone marrow
P5	33	Female	Yes	No	6	Previously healthy	Fever, cough, right hard and soft palate mass and pain, umbilication papular, lymphadenopathy	Blood, mass, lymph node
P6	12	Male	Yes	No	0.5	Congenital megacolon	Fever, cough, oral thrush, hepatosplenomegaly, hemophagocytic syndrome, upper gastrointestinal and intracranial hematoma, shock	Blood, bone marrow dermal secretions
P7	19	Female	Yes	No	3	Previously healthy	Fever, cough, lymphadenopathy, hepatosplenomegaly, hemophagocytic syndrome	Blood

BALF = bronchoalveolar lavage fluid, G6PD = glucose-6-phosphate dehydrogenase.

TABLE 2. Laboratory Findings for 7 Human Immunodeficiency Virus-Negative Infants With *Penicillium marneffei* Infections

Patient	P1	P2	P3	P4	P5	P6	P7
Hb (g/L)	112.9	58	115	113	96.6	44.8	84.9
WBC ($\times 10^9$/L)	11.1	3.6	7.5	14.1	6.0	12.9	10.6
ANC ($\times 10^9$/L)	5.8	1.3	2.7	1.3	4.0	4.1	6.5
ALC ($\times 10^9$/L)	4.3	1.6	4.5	11.4	1.3	6.0	3.7
PLT ($\times 10^9$/L)	332	97	226	51	283.2	22.1	274.4
Albumin (g/L)	38	24	22.9	33	29.9	24.1	19.1
Globulin (g/L)	27	22	28.3	14	61.6	21.7	32.0
IgA (g/L)	0.44↓	0.42↓	0.18↓	0.87↓	0.27↓	1.48	1.39
IgG (g/L)	0.92↓	1.35↓	6.90↓	3.10↓	7.57↓	15.31	16.80
IgM (g/L)	1.82↑	1.52↑	1.33↑	0.47↓	0.15↓	0.87	3.76↑
T lymphocytes	63.9%↓	53.1%↓	68%	41.7%↓	–	54.1%↓	63.7%↓
$CD4^+$ T cells	31.5%	40.6%↑	40%↓	30.1%	–	22.2%↓	39.1%
$CD8^+$ cells	11.4%↓	8.5%↓	14.4%↓	9.1%↓	–	29.4%	16.9%↓
ESR (mm/H)	33	17	28	13	28	68	88
CRP (mg/L)	6.4	ND	205.00	ND	21.95	40.50	106.9

Data are presented as the numbers (%) or medians (interquartile ranges). Normal ranges: Immunoglobulin (Ig) A: 0.9–4 g/L; IgG: 8–18 g/L; IgM: 0.84–1.32 g/L; T lymphocytes: 64.2–78.5%; $CD4^+$ T cells: 30.1–40.4%; $CD8^+$ T cells: 20.7–29.4%; C-reactive protein: ≤10 mg/L; absolute lymphocyte count: $1.1–3.2 \times 10^9$/L; absolute neutrophil count: $1.8–6.3 \times 10^9$/L; erythrocyte sedimentation rate: ≤20 mm/hour. ALC = absolute lymphocyte count, ANC = absolute neutrophil count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, Hb = hemoglobin, IgA = serum immunoglobulin A, IgG = serum immunoglobulin G, IgM = serum immunoglobulin M, ND = not done, PLT = platelet, WBC = white white cell count, ↓ = reduced, ↑ = increased.

cotton blue revealed that the conidiophores of this mold were smooth and that they had 3 to 5 metulae, each of which had several phialides, and that they produced smooth, spherical conidia in chains (Figure 2B). Lymph-node biopsies from 3 out of 4 cases (75%) showed caseous necrosis (Figure 2C), and 1 out of 4 cases who had their lymph nodes biopsied (1/4, 25%) showed granuloma formation. Four patients were diagnosed with *P. marneffei* infections based on the histopathology of the lymph nodes (Figure 2D) or based on the cytological evaluations of the bone marrow specimens (Figure 2E).

Treatments and Outcomes

The Etest® antimicrobial susceptibility tests showed that the *P. marneffei* isolates were highly susceptible to amphotericin B and voriconazole. Three patients (3/7, 42.85%) died before they received antifungal treatment. One patient experienced a severe inflammatory reaction and died within 10 days, and 2 of the patients experienced septic shock and they succumbed to disseminated intravascular coagulation and multiple organ failure within 1 week. The remaining patients received treatment and all of them improved. Two patients (P1 and P3) were treated with intravenous amphotericin B (1 mg/kg/day) on the basis of the susceptibility tests and their good physical condition overall. After 1 week, P1 showed a significant improvement in the symptoms, but P3 had a fever and appeared to have renal dysfunction. Once P3 had been administered intravenous voriconazole (7 mg/kg every 12 hours) for 2 weeks, he showed a good response. Two patients (P5 and P6) were initially administered intravenous voriconazole (7 mg/kg every 12 hours) on the basis of the susceptibility tests, their poor physical condition, and the side effects of amphotericin B. Both patients improved after 2 weeks. One month later, all 4 patients began

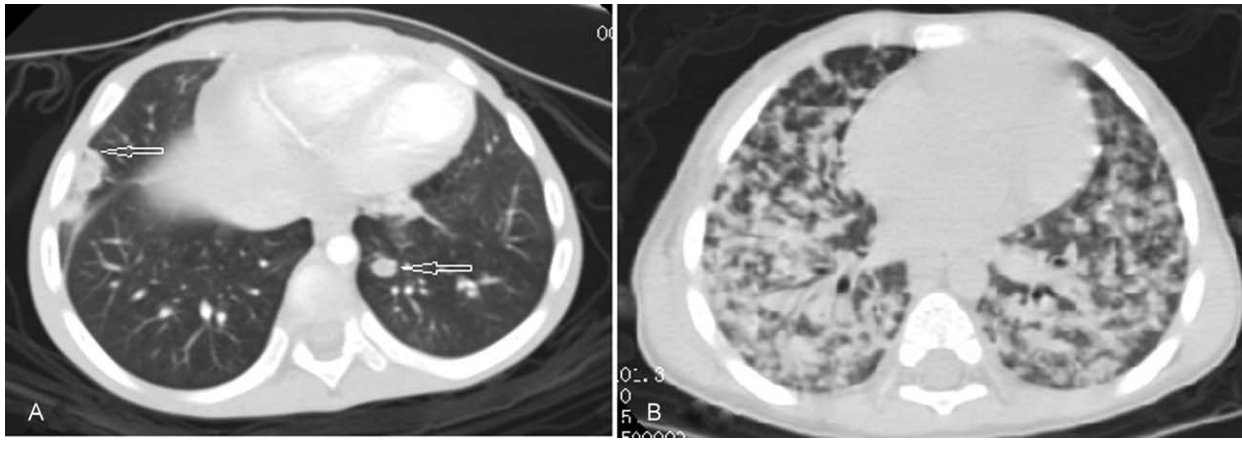

FIGURE 1. Images from the high-resolution computed tomography of the infants' chests indicated pulmonary involvement, which included (A) the pleural cavity and (B) nodular infiltrates.

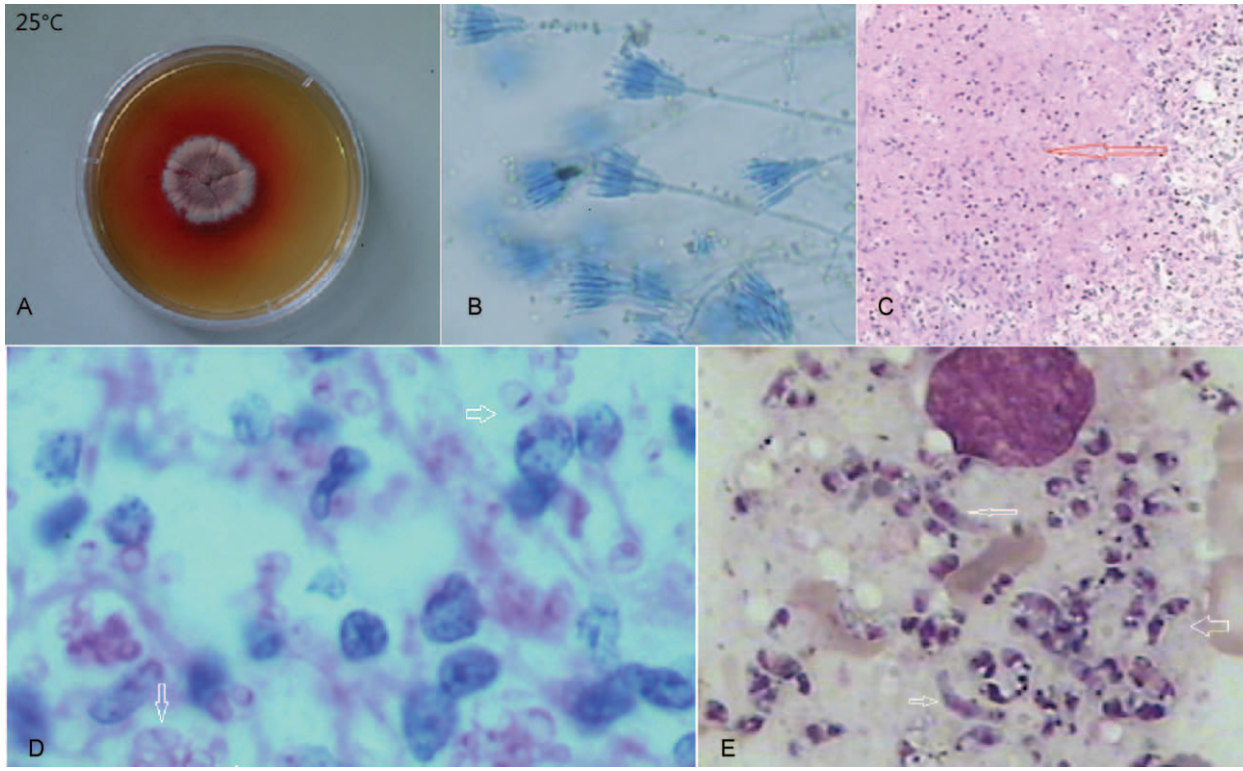

FIGURE 2. Positive cultures, pathogen morphology, and histopathology of the infants' clinical specimens indicated that (A) at 25°C on Sabouraud dextrose agar (SDA), the mold from cultured lymph nodes produced a red pigment on the SDA, (B) the mold was stained with lactophenol cotton blue, and the conidiophores of this mold were smooth and had 3 to 5 metulae, each of which had several phialides and produced smooth, spherical conidia in chains, (C) a pattern of necrosis was observed in lymph nodes stained with hematoxylin and eosin (×100), (D) the yeast form of *Penicillium marneffei* was confirmed by the histopathological analysis of the lymph nodes using Periodic Acid-Schiff staining (×400). The yeast showed a characteristic morphology, including a transverse septum, and (E) numerous intracellular yeast-like or sausage-like cells measuring 2 to 3 μm in diameter with a transverse septum were observed when specimens obtained from bone marrow were stained with the Wright stain (×1000).

receiving continual treatments with oral voriconazole (10 mg/kg/day) for 6 or 12 months. All of the patients were cured and there were no disease recurrences (Table 3).

DISCUSSION

P. marneffei infection causes a rare type of deep mycosis, and it is mainly found in southeast Asia and in southern China in patients with acquired immunodeficiency syndrome and in immunocompromised populations.[1] However, few cases and studies have been described that have involved infants who are not infected by the HIV.[3,4] The current knowledge gaps include the epidemiology of *P. marneffei* infections in children and the immune statuses of these children, the categories of the primary immunodeficiencies associated with *P. marneffei* infections, the long-term outcomes, and the relapse rates.

The 7 infants we have described all lived in Guangxi Province where *P. marneffei* is endemic. A review of the literature advised that *P. marneffei* infections are more likely to occur during the rainy season, which spans from May to October in endemic areas.[5] The inhalation of airborne conidia, and exposure to soil and bamboo rats have been proposed as the risk factors associated with infection by *P. marneffei*.[6] Guangxi Province in southern China is a subtropical region, and the rainy season spans from April to October. Our study data showed that 71.4% of the patients became sick during the rainy season, which concurs with the findings from previously reported studies.[5] These infants were limited with respect to their scopes of activity, they had few opportunities to come into contact with rodents, and their parents did not have histories of contact with rodents. These findings suggest that *P. marneffei* is ubiquitous within the environment in areas where it is endemic, and that is it present within the air and soil.

The most common clinical symptoms associated with the *P. marneffei* infections in the infants in this study were fever, cough, and anemia, which were followed by lymphadenopathy, hepatosplenomegaly, and being underweight. Findings from previous studies have suggested that HIV-negative adults infected by *P. marneffei* experience significant increases in the levels of leukocytes in the peripheral blood, especially neutrophil levels. Suppuration and granuloma formation are more common in HIV-negative adults infected by *P. marneffei*. Such characteristic findings suggest that this disease is characterized by a purulent infection.[7] Papular lesions with central umbilications have been observed in 67% of the children who are coinfected with the HIV, and specific patterns of necrosis are more often observed in HIV-infected adult patients who have *P. marneffei* infections.[7–9] The infants in the present study showed slight elevations in their leukocyte levels, and caseous necrosis was the most common pattern of pathology. Papular lesions with central umbilications were seen in 1 case. HIV-negative infants have the highest culture-positive rates, which

TABLE 3. Treatment Administered to 7 Human Immunodeficiency Virus-Negative Infants With *Penicillium marneffei* Infections

Patient	Initial Antifungal Therapeutic	Continual Antifungal Treatment	Outcome
P1	Intravenous amphotericin B for 1 month	Oral voriconazole for half year	Improved and cured
P2	None	None	Death
P3	Start with intravenous amphotericin B for 1 week (ineffective), then change to intravenous voriconazole for 1 month	Oral voriconazole for 1 year	Improved and cured
P4	None	None	None
P5	Intravenous voriconazole for 1 month	Oral voriconazole for half year	Improved and cured
P6	None	None	Death
P7	Intravenous voriconazole for 1 month	Oral voriconazole for 1 year	Improved and cured

are similar to those of HIV-coinfected adult patients, but they differ from adults who are not infected by the HIV.[9,10] These data indicate that there may be an association between *P. marneffei* infection and the immature immune system in infants. An inadequate immune response to *P. marneffei* invasion would cause difficulties when mounting a systemic immunopathological response. Indeed, the increases in the WBC and neutrophil counts were not significant in our patient cohort, and the infants showed less purulent changes compared with HIV-positive infants with *P. marneffei* infections.

Findings from previous studies have shown abnormal immunological profiles in HIV-negative children with penicilliosis. These reports have described HIV-negative children who had penicilliosis and primary immunodeficiencies, blood disorders, or abnormal immune functions, including severe combined immunodeficiencies, congenital neutropenia, common variable immunodeficiencies, hyperimmunoglobulin M syndrome, and hyperimmunoglobulin E syndrome. Furthermore, some of the children had heterozygous missense mutations in exon 12 of the *STAT3* gene.[4] In our cohort, 5 of the patients had histories of diseases that included oral thrush, congenital megacolon, glucose-6-phosphate dehydrogenase deficiency, septicopyemia, frequent pneumonia, and bronchopneumonia. The evaluation of the serum Ig and circulating lymphocyte levels determined that there were varying degrees of abnormalities in the cellular and humoral immune responses. For example, the serum IgG and IgA titers, and the percentages of circulating $CD8^+$ T cells were reduced in most of the cases, indicating that a reduction in the number of T lymphocytes and, hence, cellular immunity is probably the most important factor that predisposes HIV-uninfected infants to *P. marneffei* infections and reactivations.[4]

The patients' clinical manifestations and their hematological and pathological assessments revealed less purulent changes and aberrations in their cellular and humoral immune parameters. These characteristics suggest that some of these infants might have been immunodeficient or had immune disorders that had not been diagnosed; however, the evaluations of the statuses of the immune systems in the remaining patients were not available for the analyses. Thus, the HIV-uninfected infants in this study who lived in areas where *P. marneffei* is endemic may have underlying immunodeficiencies that render them genetically susceptible to fungal infections, and physicians should be aware of these potential underlying immunodeficiencies when they evaluate infants who present with *P. marneffei* infections, particularly those with serious and/or recurrent infections. When penicilliosis is present in HIV-negative infants and they do not have secondary immunodeficiencies, detailed histories should be taken to evaluate the patients' immune statuses, and these should include the patients' previous infections, families' disease histories, Ig profiles, lymphocyte subset levels, and any genetic factors that may underlie the clinical features and immunological characteristics.

P. marneffei infection is a severe disease that can lead to high mortality rates in children.[3,4] In our study, 3 out of the 7 children (42.85%) died before they received antifungal treatment, and the 4 patients who received treatment improved. These findings suggest that timely and effective antifungal therapy can improve patients' prognoses.

Since many of the organs in infants are immature, their physiologies differ from those of older children and adults. Thus, more caution must be exercised when selecting antifungal drugs and doses to treat *P. marneffei* infections in infants than when adults are being treated for *P. marneffei* infections. The findings from previous studies have shown that the *P. marneffei* isolates from Guangxi bamboo rats and clinical *P. marneffei* isolates are sensitive to voriconazole, itraconazole, terbinafine, amphotericin B, and fluconazole.[4,7,11–14] However, there are no criteria to guide the treatment of *P. marneffei* in HIV-uninfected infants. Currently, amphotericin B at a dose of 0.8–1.0 mg/kg/day is administered to infants and children, which can be increased to a maximum dose of 1.5 mg/kg/day in China. The duration of treatment can range from 1 to 2 months. Oral voriconazole at a dose of 10 mg/kg/day has also been used in a continuous treatment regimen for 3 months.[7,14] Relapses are common following *P. marneffei* infections, and consolidation therapy is recommended.[7,9] In this study, all of the in vitro susceptibility tests showed that all of the infants' isolates were highly susceptible to voriconazole and amphotericin B. One case who was administered intravenous amphotericin B and 3 cases who were administered intravenous voriconazole showed improvements. After a continual treatment regimen involving oral voriconazole (10 mg/kg/day) for 6 or 12 months, 2 of the patients did not show any evidence of disease recurrences. Thus, intravenous voriconazole could be recommended as the initial antifungal agent for infants, because of its low nephrotoxicity, its high sensitivity, and its high levels of efficacy.

This study evaluated data obtained from HIV-negative infants infected by *P. marneffei*. In this study, the patients had a median age of 23.43 months (SD = 8.34). Most of the patients were infected by *P. marneffei* during the rainy season that spans from April to October in Guangxi Province in southern China, where *P. marneffei* is endemic.[5] All of the patients in this study presented with fever, cough, and anemia, and some presented with lymphadenopathy, hepatosplenomegaly, or they were

underweight. Caseous necrosis was the most common pathological pattern. While *P. marneffei* infections can be associated with a high level of mortality among HIV-negative infants, timely and effective antifungal therapy can improve patients' prognoses. In endemic areas, clinicians should be aware of disseminated *P. marneffei* infections when infants present with serious or recurrent infections, even if they not infected by the HIV. Intravenous voriconazole could be recommended as the initial antifungal agent for infants, because of its low nephrotoxicity, its high sensitivity, and high efficacy levels.

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