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 megaloclon, 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 cases. 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 be 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.

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). In 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. 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 Medical University were reviewed. Of the 126 patients, 7 were HIV-negative infants with infections caused by P. marneffei. Five patients were males and 2 were females, with ages ranging from 11 to 36 months (median age, 23.43 months).

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

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ISSN: 0025-7974
DOI: 10.1097/MD.0000000000001439
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 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 checkerboard 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 megalocornea (n = 1), glucose-6-phosphate dehydrogenase deficiency (n = 1), septi- copypemia (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 × 10⁹ cells/L (SD = 3.8 × 10⁹) (range: 3.6–12.9 × 10⁹ cells/L). The mean neutrophil count was 3.7 × 10⁹ cells/L (SD = 2.0 × 10⁹) (range: 1.3–6.5 × 10⁹ cells/L). All of the patients (range: 0.53–1.48 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 CD8⁰ 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.
cotton blue revealed that the conidioles 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

| Patient | P1  | P2  | P3  | P4  | P5  | P6  | P7  |
|---------|-----|-----|-----|-----|-----|-----|-----|
| Hb (g/L) | 112.9 | 58  | 115 | 113 | 96.6 | 44.8 | 84.9 |
| WBC (×10⁹/L) | 11.1 | 3.6 | 7.5 | 14.1 | 6.0 | 12.9 | 10.6 |
| ANC (×10⁹/L) | 5.8 | 1.3 | 2.7 | 1.3 | 4.0 | 4.1 | 6.5 |
| PLT (×10⁹/L) | 4.3 | 1.6 | 4.5 | 11.4 | 1.3 | 6.0 | 3.7 |
| Albumin (g/L) | 27 | 22 | 28.3 | 14 | 61.6 | 21.7 | 32.0 |
| Globulin (g/L) | 38 | 24 | 22.9 | 33 | 29.9 | 24.1 | 19.1 |
| 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⁺ T 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: 1.1–3.2×10⁹/L; absolute neutrophil count: 1.8–6.3×10⁹/L; erythrocyte sedimentation rate: ≤20 mm/hour. 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 cell count, ↓ = reduced, ↑ = increased.

**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.
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. However, few cases and studies have been described that have involved infants who are not infected by the HIV. 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 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.

![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 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).](image-url)
are similar to those of HIV-coinfected adult patients, but they differ from adults who are not infected by the HIV. These data indicate that there may be an association between \textit{P. marneffei} infection and the immature immune system in infants. An inadequate immune response to \textit{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 \textit{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 \textit{STAT3} gene. In our cohort, 5 of the patients had histories of diseases that included oral thrush, congenital malacoc, glucose-6-phosphate dehydrogenase deficiency, septicemia, 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 \textit{P. marneffei} infections and reactivations.

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 \textit{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 \textit{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.

\textit{P. marneffei} infection is a severe disease that can lead to high mortality rates in children. 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 \textit{P. marneffei} infections in infants than when adults are being treated for \textit{P. marneffei} infections. The findings from previous studies have shown that the \textit{P. marneffei} isolates from Guangxi bamboo rats and clinical \textit{P. marneffei} isolates are sensitive to voriconazole, itraconazole, terbinafine, amphotericin B, and fluconazole. However, there are no criteria to guide the treatment of \textit{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. Relapses are common following \textit{P. marneffei} infections, and consolidation therapy is recommended. 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 \textit{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 \textit{P. marneffei} during the rainy season that spans from April to October in Guangxi Province in southern China, where \textit{P. marneffei} is endemic. All of the patients in this study presented with fever, cough, and anemia, and some presented with lymphadenopathy, hepatosplenomegaly, or they were...

| 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 | Death |
| P5 | Intravenous voriconazole for 1 month | Oral voriconazole for half year | Improved and cured |
| P6 | None | None | None |
| P7 | Intravenous voriconazole for 1 month | Oral voriconazole for 1 year | Improved and cured |

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

**ACKNOWLEDGMENT**

The authors thank Zhenbo Feng, Professor of Pathology, Department of Pathology, The First Affiliated Hospital of Guangxi Medical University.

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