Penicilliosis marneffei Infection in Non-HIV-Infected Patients

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INTRODUCTION

Penicillium marneffei is a thermally dimorphic fungus endemic in Southeast Asia. Penicilliosis marneffei is one of the commonest opportunistic infections in AIDS patients in Thailand. Most patients present with chronic course of fever, lymphadenopathy, hepatosplenomegaly, and cutaneous lesions. Even though P. marneffei infection in non-HIV-infected patients is rarely reported, the incidence has constantly increased especially those living in North Thailand since 1990. This review thus aims to describe P. marneffei infection in non-HIV-infected patients regarding the epidemiology, clinical manifestations, diagnosis, treatment, and outcomes, in comparison with that in HIV-infected patients.

EPIDEMIOLOGY

P. marneffei was first isolated from the lesions in the liver of a bamboo rat, Rhizomys sinensis, at the Pasteur Institute of Indochina, Dalat, South Vietnam, in 1956.1 The fungus was named in honor of Hubert Marneffe, a director of the Pasteur Institute of Indochina. Three years later, in 1959, the first patient with Penicilliosis marneffei was reported as a laboratory-acquired infection due to a needle stick injury. Until 1973, the first natural infection in man was described in a 61-year-old American man with Hodgkin’s lymphoma undergoing splenectomy.2 Before the HIV era, there were fewer than 30 patients from the endemic area including Thailand, Guangxi region in South China, and Hong Kong.3,4 The incidence of human Penicilliosis marneffei has markedly increased due to expansion of the AIDS epidemic in Southeast Asia.5

The incidence of P. marneffei infection in Thailand among AIDS patients is 2.4 percent-4.2 percent. In the North, it is as high as 6.8 percent.6 Even though, the high incidence is noted in AIDS patients, the infection in non-HIV-infected patients remains sporadic.5

The only known non-human host of P. marneffei is the bamboo rat. P. marneffei has been isolated from the organs of the bamboo rats including hoary bamboo rat (Rhizomys pruinosus), Chinese bamboo rat (Rhizomys sinensis), large bamboo rat (Rhizomys
sumatrensis), and bay bamboo rat (Cannomys badidus) as well as the soil around their burrows. The role of these bamboo rats in human infection is unknown. In a case-control study of 80 AIDS patients with *Penicilliosis marneffei*, an association between the infection and a recent history of occupational or other exposure to the soil especially during the rainy season [odds ratio (OR) = 1.91, 95% CI = 1.04-3.52] was observed. However, a history of exposure to or consumption of bamboo rats was not a risk factor for infection in this study. Chaiyalertsak and colleagues have shown that the infection occurred more commonly during the rainy season in North Thailand, probably due to the inhalation of fungal conidia from the environmental source including the soil.

**CLINICAL MANIFESTATIONS**

There is something different regarding the clinical manifestations between HIV and non-HIV-infected patients. Five non-HIV-infected patients with the age ranging from 6 to 50 years were reported from Ramathibodi Hospital, Bangkok, Thailand in 1984.

Three patients had associated conditions including tuberculosis, systemic lupus erythematosus, and lymphoproliferative disorder. The other two patients were non-immunocompromised. The common manifestations included fever, generalized lymphadenopathy, and cutaneous lesions characteristic as nodules or abscesses. The osteolytic lesions of the flat and long bones were noted in two patients. The pulmonary involvement was a common feature in this study. In addition, the poor clinical outcome was observed despite appropriate antifungal treatment by amphotericin B, likely due to the delayed diagnosis in most patients.

Another study was retrospectively carried out by Wortman and colleagues in 28 non-HIV-infected patients, in comparison with 38 HIV-infected patients. From 1994 to 1999, a study in Hong Kong by Wong and colleagues compared the clinical manifestations of *P. marneffei* infection in non-HIV- and HIV-infected patients. They showed that HIV-infected patients had a higher frequency of fungemia than non-HIV-infected patients, consistent with a previous study by Wortman and colleagues mentioned above.

In addition, the
delayed diagnosis was more frequently observed in non-HIV-infected patients than HIV-infected patients (the median duration of illness before diagnosis was 5.5 and 1 week among non-HIV- and HIV-infected patients, respectively). Approximately 85 percent of non-HIV-infected patients in this study had predisposing conditions including hematologic malignancies, corticosteroid use, and immunosuppressive drug use.

A recent study in Thailand described the unique clinical syndrome in non-HIV-infected patients with acquired cell-mediated immunity defects who were susceptible to opportunistic infections caused by Salmonella, P. marneffei, Cryptococcus neoformans, Histoplasma capsulatum, and nontuberculous mycobacteria. The syndrome comprised the clinical manifestations of opportunistic infections mostly involving the lymph nodes and the lungs as well as reactive skin diseases like Sweet’s syndrome, pustular psoriasis, and acute generalized exanthematous pustulosis.

As mentioned earlier, the osteoarticular involvement was more commonly noted in non-HIV-infected patients than HIV-infected patients. The affected bones and joints include the ribs, skull, scapula, long bones, lumbar vertebrae, and temporomandibular joints. Arthritis commonly involves both peripheral large and small joints of the fingers. A recent study by Louthrenoo and colleagues has shown that non-HIV-infected patients had the delayed time to diagnosis of osteoarticular penicilliosis, compared to HIV-infected patients (11.75 ± 7.76 months and 15.75 ± 9.01 days in non-HIV- and HIV-infected patients, respectively). In addition, they found that patients with osteomyelitis usually had associated subcutaneous abscesses or chronic ulcers overlying the corresponding osteolytic lesions. In this study, the radiographic abnormalities included periarticular soft tissue swelling, periarticular osteopenia with the narrowing joint spaces, and multiple osteolytic lesions and minimal sclerotic margins without periosteal reaction. However, these findings are not specific for P. marneffei osteomyelitis since the infections caused by Mycobacterium, Histoplasma, Cryptococcus, Blastomyces, and Coccidioides can give these radiologic abnormalities.

**DIAGNOSIS**

The diagnosis is based on the identification of the organism on microscopy with the confirmation by the culture method. P. marneffei has the unique feature among the Penicillium species of being thermally dimorphic. At 25°C it grows as the mycelium form (similar to Aspergillus), but at 37°C it grows as the yeast form. Microscopic examination of all clinical specimens reveals the yeast cells (2 × 2 to 3 × 6.5 μm in size) with a transverse septum per each yeast cell (asexual fission for schizogony), present both within and outside the macrophages. The cultivation at 37°C, the fungal colonies appear to have soluble red pigment around them and diffused into the agar medium. Several serodiagnosis and molecular methods have been developed, but these have not yet entered to the routine clinical practice due to their relatively low sensitivity and specificity. Interestingly, the currently available galactomannan test for Aspergillus antigen may assist in the diagnosis of P. marneffei infection. A recent study has shown that the sera from 11 of 15 HIV-infected patients with P. marneffei infection were positive (optimal density index of > 0.5) for galactomannan antigen test. However, the serum samples from 9 percent of HIV-infected patients without P. marneffei infection were apparent to be falsely positive.

The differential diagnosis of P. marneffei infection includes other fungal infections like
Histoplasmosis and cryptococcosis. In a retrospective study in Thailand, Mootsikapun and colleagues found that histoplasmosis and *Penicilliosis marneffei* had shared similar clinical presentations, laboratory investigations, and radiologic appearance. The most common clinical findings in both infections included chronic fever, weight loss, cough, anemia, lymphadenopathy, hepatomegaly, and splenomegaly. The occurrence of skin lesions was noted with the same frequency in both fungal infections. The most common findings of chest X-ray in both infections was bilateral interstitial infiltrations. Table 1 demonstrates the difference and similarity among the 3 important yeasts causing human infection including *P. marneffei*, *H. capsulatum*, and *C. neoformans*.

**TREATMENT**

Therapeutic intervention of *P. marneffei* infection has to be timely and optimally appropriate. The delayed diagnosis is associated with the increased mortality and morbidity. Amphotericin B and itraconazole is the drug of first choice for treatment of *P. marneffei* infection. The approach to initial treatment depends on the disease’s severity and the patient’s ability to tolerate the oral therapy. For HIV-infected patients with severe disseminated disease, the intravenous therapy with amphotericin B (0.6 mg/kg daily) for two weeks followed by oral itraconazole (200 mg twice daily) for 10 weeks is the preferred regimen. However, the duration for non-HIV-infected patients remains unclear, perhaps for years. The patients treated with amphotericin B should be monitored for the infusion-related adverse reactions, nephrotoxicity, and electrolyte disturbances. The new triazoles including voriconazole and posaconazole are also effective and well-tolerated but the clinical studies are limited.

**OUTCOMES**

The mortality is very high in disseminated *P. marneffei* infection unless the early diagnosis is made and appropriate treatment is promptly instituted. The response rate ranging from 59

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<th>Table 1. The characteristics of <em>Penicillium marneffei</em>, <em>Cryptococcus neoformans</em>, and <em>Histoplasma capsulatum</em> on the histopathology.</th>
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<tbody>
<tr>
<td><strong>P. marneffei</strong></td>
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<tr>
<td>Size (μ)</td>
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<tr>
<td>Capsule</td>
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<td>Staining of capsule</td>
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<td>Shape</td>
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<td>Inflammatory cells</td>
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percent to 77 percent in early studies has increased to approximately 90 percent in recent studies. 19

CONCLUSIONS

In conclusion, non-HIV-infected patients with P. marneffei infection have the different and similar clinical manifestations, compared to HIV-infected patients. The clinical features vary from the localized infection to the severe disseminated infection. Localized infection is more commonly noted in non-HIV-infected patients than in HIV-infected patients. The unique skin lesion like abscesses and ulcers as well as osteoarticular involvement are frequently observed in non-HIV-infected patients. The under-recognition of Penicilliosis marneffei in non-HIV-infected patients may cause the delayed diagnosis and will lead to the increased mortality and morbidity rates. Even though P. marneffei infection in non-HIV-infected patients is not uncommon, we urge all clinicians to raise the awareness of this infection in their daily clinical practice.

References

cases reported in HIV infected patients during the last 5 years compared to 44 cases of non AIDS patients reported over 20 years. J Mycol Med 1993;4:195-224.


