

Infection due to *Penicillium marneffei*

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Abstract

Penicillium marneffei is endemic in Southeast Asia, the Guangxi province of China, and Hong Kong. Cases of patients infected with *P. marneffei* have been very rare, but the incidence has increased markedly during the past several years. This increase is exclusively due to infection among patients infected with human immunodeficiency virus (HIV). The patients usually presented with symptoms and signs similar to other patients with late HIV diseases. These included fever (99% of the patients), anaemia (78%), pronounced weight loss (76%), generalised lymphadenopathy (58%) and hepatomegaly (51%). Skin lesions were seen in 71% of our patients. These lesions were most commonly papules with central necrotic umbilication. It was easy to culture *P. marneffei* from various clinical specimens. Bone marrow culture was the most sensitive (100%), followed by culture of the specimen obtained from skin biopsy (90%) and blood culture (76%). The fungus was sensitive to amphotericin B, itraconazole, and ketoconazole. Our regimen is to give amphotericin B for 2 weeks, followed by itraconazole 400 mg/day orally for the next 10 weeks. After the initial treatment, the patient is given itraconazole 200 mg/day as secondary prophylaxis for life.

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Introduction

Penicillium marneffei is a dimorphic fungal pathogen, which can cause disseminated disease both in immunocompetent and immunocompromised human beings.¹ It is endemic in Southeast Asia, the Guangxi province of China and Hong Kong.¹⁻³ The prevalence of disseminated *P. marneffei* infection has increased markedly over the past few years.^{1,3-18} This increase is exclusively due to infection among patients infected with human immunodeficiency virus (HIV). Less than 40 cases were reported prior to the HIV epidemic in Southeast Asia,¹ whereas, between January 1991 and May 1996, 915 HIV-infected patients at Chiang Mai University Hospital were found to have *P. marneffei* infection (Fig. 1). In northern Thailand, infection with *P. marneffei* is the third most common opportunistic infection in late HIV disease after tuberculosis and cryptococcal meningitis.¹ As the HIV pandemic spreads across the endemic areas in Southeast Asia and China, this mycosis will become an even more important public health problem. In addition, cases of disseminated *P. marneffei* infection have been reported in HIV-infected individuals from the United States,⁴ the United Kingdom,⁵ the Netherlands,⁷ Italy,¹³ France,¹⁴ Germany,¹⁵ Switzerland,¹⁶ and Australia¹⁷ following visits to the endemic region. The clinical recognition and knowledge of management of this infection become

increasingly important in these days of global travel and immigration.

Epidemiology and Natural History

P. marneffei was first isolated from bamboo rats (*Rhizomys sinensis*) in Vietnam in 1956.^{19,20} The animals had been kept in captivity at the Pasteur Institute of Indochina in Vietnam. Some of the bamboo rats were observed to die spontaneously. The fungus isolated from the rats was sent to Paris to be studied. It was identified as a new species by Segretain and named *Penicillium marneffei*, in honour of Hubert Marneffe, director of the Pasteur Institute of Indochina. In the Guangxi province of China, the fungus has been isolated from the internal organs of more than 90% of another species of bamboo rats, *Rhizomys pruinosus*.^{21,22} In Thailand, *P. marneffei* was isolated from *R. pruinosus* and another species of bamboo rat, *Cannomys badius*, captured in the central part of Thailand.²³ In a recent study from northern Thailand, the fungus was isolated from yet another species of bamboo rat, *Rhizomys sumatrensis*.²⁴ Since the bamboo rats usually live near the forest and have limited contact with people, it is believed that both humans and bamboo rats are infected with *P. marneffei* from a common source, rather than the patients being infected from the rats. The route of entry of *P. marneffei*

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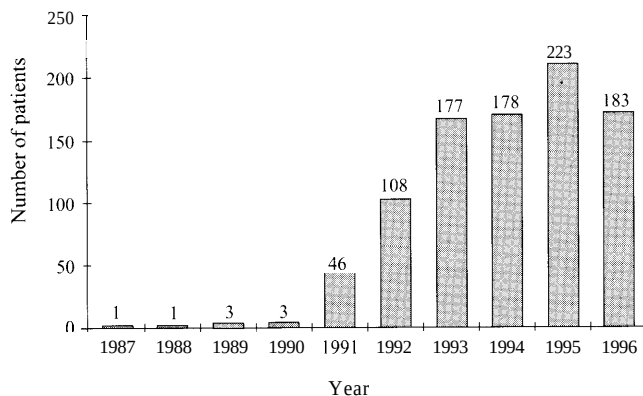


Fig. 1. Number of patients with *Penicillium marneffei* infection seen at Chiang Mai University Hospital and year of diagnosis.

is unknown. By analogy with other endemic systemic mycosis, such as histoplasmosis and coccidioidomycosis, it seems likely that *P. marneffei* conidia may be inhaled from a contaminated reservoir in the environment and subsequently disseminate from the lungs when the infected hosts experience immunosuppression. In a recent study, it was found that the disease was significantly more likely to occur in the rainy season, suggesting that there might be an expansion of the environmental reservoirs with favourable conditions for growth during these rainy months.²⁵ It is likely that in endemic areas such as northern Thailand, a certain proportion of the general population are infected, but remain asymptomatic. In the literature, patients have been reported with long periods of asymptomatic infection prior to presentation with disseminated disease.¹⁷ In other instances, the clinical appearance of disseminated infection occurred within a few weeks of exposure to the organism.^{4,26} Report of *P. marneffei* infection in HIV-infected infants also suggests that the duration between infection and clinical dissemination of the organism sometimes may be brief.²⁷

Mycology

P. marneffei, the only dimorphic fungus of the genus *Penicillium*, grows as mold at 25°C on Sabouraud's dextrose agar. In its mycelial form, the colony is greyish white and downy. During differentiation the colour of the colony turns to greyish pink. The reverse side becomes brownish red, as a soluble red pigment diffuse into the agar. Hyaline, septate branching hyphae with lateral and terminal conidiophores can be seen under microscopic examination. The conidiophores consist of basal stripes with terminal verticils of 3 to 5 metulae, each metula bearing 3 to 7 phialides. The conidia are oval, smooth-walled, measuring approximately 2 µm by 3 µm. They are formed basipetally in chains from each phialide. At 37°C on brain-heart infusion agar, rough, glabrous, tan-coloured colonies of yeast are seen within a few days. Microscopic examination of this growth

reveals unicellular, pleomorphic, ellipsoidal-to-rectangular yeast cells that divide by fission and not by budding.

Clinical Manifestation and Treatment

Segretain²⁸ reported the first infection in humans in 1959. He accidentally inoculated himself during an experimental study. He developed a nodule at the site of inoculation, lymphangitis, and lymphadenopathy. More than a decade later, the first natural human infection with *P. marneffei* was reported in a 61-year-old missionary with Hodgkin's disease who had had a splenectomy. He had been living in Southeast Asia.²⁶ The second reported case was in 1984 and was also from the USA.²⁹ Also in 1984, 5 patients were reported from Bangkok, Thailand.³⁰ They were between 6 and 50 years of age and diagnosed between 1972 and 1982. The first 8 Chinese cases were reported in 1985 from the Guangxi province of China.³¹ They were seen between 1964 and 1983. More cases were subsequently reported from the same area in southern China.^{2,32-34} Several patients with *P. marneffei* infection had also been reported from Hong Kong by 1990.³⁵⁻³⁸

The first case of disseminated *P. marneffei* infection in a HIV-infected patient in an endemic area was reported from Bangkok in 1989.⁶ In 1994, 86 more cases were reported from Chiang Mai.¹ We also reported 21 children with vertically transmitted HIV infection who developed systemic *P. marneffei* infection.²⁷ Outside Thailand, several cases of systemic *P. marneffei* infection in HIV-infected patients were reported from Hong Kong.^{8,9,12,39} More recently, one similar case was reported from Malaysia.⁴⁰

P. marneffei infection occurs late in the course of HIV infection. CD4+ cell count, determined within one month of the diagnosis of *P. marneffei* infection, was consistently less than 50 cells/µl.¹ Cases were reported in which *P. marneffei* infection occurred with other late HIV-related infections, such as cryptococcal meningitis, *Pneumocystis carinii* pneumonia, and cerebral toxoplasmosis.⁷ HIV-infected patients with disseminated *P. marneffei* presented with symptoms and signs seen in other patients with late HIV diseases.⁷ These included fever in 99% of the patients, anaemia (78%), pronounced weight loss (76%), generalised lymphadenopathy (58%) and hepatomegaly (51%). These were not specific for *P. marneffei* infection and could be caused by HIV or other HIV-related opportunistic infection. However, a more specific finding was skin lesions, which were seen in 71% of our patients. They were most commonly papules with central necrotic umbilication (Fig. 2). In 63% of our patients with disseminated *P. marneffei* infection, a presumptive diagnosis could be made several days before the results of fungal culture were available. This was done by microscopic examination of the Wright's-stained

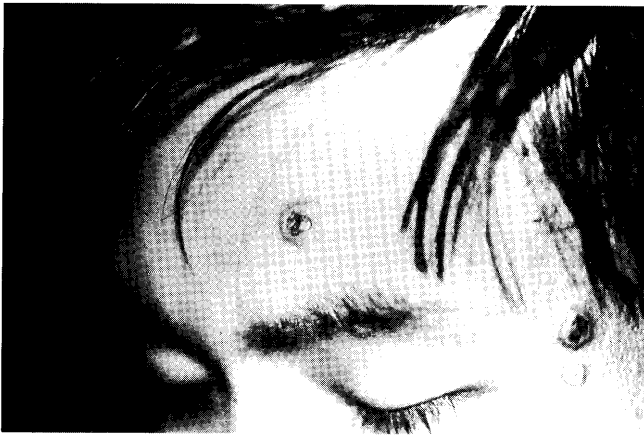


Fig. 2. Skin lesions of HIV-positive patient with *Penicillium marneffei* infection. They usually are papules with central necrosis.

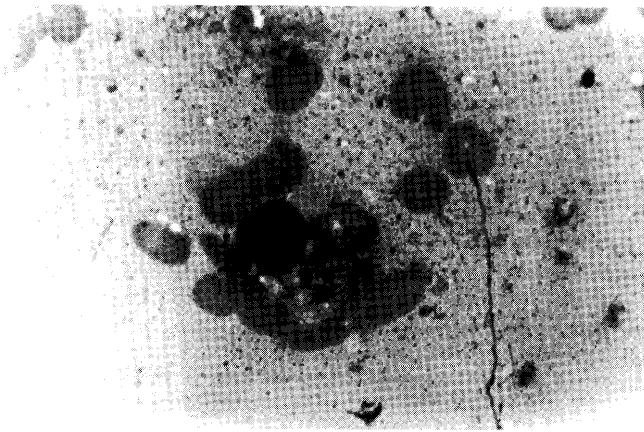


Fig. 3. Photomicrograph of Wright's-stained touch smear of skin-biopsy specimen from patient infected with HIV and *Penicillium marneffei* (magnification $\times 1000$). Note oval and elliptical yeast cells with clear central septation in a macrophage.

samples of bone-marrow aspirate, and/or touch smears of the skin-biopsy specimen, and/or the lymph-node biopsy specimen. Many intracellular and extracellular basophilic, spherical, oval, and elliptical yeast cells could be seen with this technique (3 to 8 μm in diameter). Some of these cells had clear central septation (Fig. 3), which is a characteristic feature of *P. marneffei*. It was easy to culture *P. marneffei* from various clinical specimens. Bone marrow culture was the most sensitive (100%), followed by culture of the specimen obtained from skin biopsy (90%), and blood culture (76%).¹

The mortality rate of patients with disseminated *P. marneffei* infection had been very high, regardless of whether the patient is concurrently infected with HIV^{2,12,30,31} or not. This was probably due to failure to make a timely diagnosis. In our experience, when the presumptive diagnosis was based on typical skin manifestation and microscopic finding and appropriate anti-fungal treatment was started early, the response to therapy was much better. The fungus was sensitive to amphotericin B, itraconazole, and ketoconazole.⁴¹ Our

current recommended treatment regimen for HIV-infected patients with disseminated *P. marneffei* infection is to give amphotericin B intravenously in the dose of 0.6 mg/kg/day for two weeks, followed by itraconazole 400 mg/day orally in two divided doses for the next 10 weeks. At Chiang Mai University Hospital, all 73 patients treated with this regimen responded well, with resolution of fever and skin lesions within the first 2 weeks. None of the 73 patients had to discontinue the treatment because of adverse drug reaction.

In one of our earlier studies,⁴¹ it was found that 12 out of 40 patients who responded to initial therapy relapsed within 6 months. Thus we recommend that after initial treatment, the patient should be given itraconazole 200 mg/day orally as secondary prophylaxis for life.

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