Infection Due to *Penicillium marneffei*, an Emerging Pathogen: Review of 155 Reported Cases

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A disseminated and progressive infection, penicilliosis marneffei is the third most common opportunistic infection in human immunodeficiency virus (HIV)-infected patients in certain parts of Southeast Asia. *Penicillium marneffei* is endemic in Southeast Asia and the southern part of China. Cases have been reported from both Eastern and Western countries. This review discusses the history, epidemiology, mycology, clinical manifestations, diagnosis, and treatment of penicilliosis marneffei, on the basis of 155 cases of the infection. About 80% of the patients are immunocompromised. *P. marneffei* can infect various organs, particularly the lung, liver, and skin. The most common clinical features include fever, weight loss, and anemia. The organism has been isolated most commonly from skin, blood, and bone marrow. Immunologic identification of fungal isolates can be done with exoantigen tests and immunohistochemical methods. Treatment of disseminated penicilliosis marneffei in HIV-infected patients with parenteral amphotericin B and itraconazole is relatively effective and safe.

Penicilliosis marneffei is a disseminated and progressive infection caused by *Penicillium marneffei*, a facultative intracellular pathogen and the only thermally dimorphic fungus of the genus *Penicillium* [1–3]. It is the third most common opportunistic infection in HIV-infected patients in certain parts of Southeast Asia, following extrapulmonary tuberculosis and cryptococcosis [3]. Areas in which the organism is highly endemic include Southeast Asia [4–6] and the southern part of China [1, 7]. The infection has been widely suggested to be included in the list of indicator diseases for differential diagnosis of AIDS in HIV-infected patients who are visitors to or natives or residents of the areas of endemcity [2, 8–15].

Although most patients with penicilliosis marneffei are immunocompromised, some researchers have recommended that *P. marneffei* be considered as a primary pathogen in all humans, because in certain areas of endemcity most of the infections have occurred in persons with normal immunity [1, 16]. Without early diagnosis and proper treatment, the disease is associated with a high mortality rate, regardless of whether HIV infection is involved [1, 3, 5, 14, 16].

Many cases of penicilliosis marneffei have been misdiagnosed as tuberculosis, which is epidemic in regions where the fungal disease is prevalent [2, 5, 17–23]. Both infections have similar symptomology [5, 8, 15, 18, 23]. Unfortunately, antituberculosis agents are not effective against *P. marneffei* [5, 21, 22]. Because of similar clinical manifestations, penicilliosis marneffei in HIV-infected patients can be easily misdiagnosed as other fungal infections, such as histoplasmosis and cryptococcosis [1, 2, 8, 15, 17, 21, 24].

The incidence of penicilliosis marneffei has risen markedly during the past 5 years. From ~30 cases reported from 1973 to 1990, the number increased to a total of >160 by 1995. These figures, however, do not include cases reported in languages other than English. This review discusses the history, epidemiology, mycology, clinical manifestations, diagnosis, and treatment of penicilliosis marneffei, on the basis of 155 cases of the infection that have been described in the English-language literature. This review also introduces recent findings from research on serology for better diagnosis and from epidemiologic studies of penicilliosis marneffei.

History

Capponi et al. [4] first isolated *P. marneffei* in 1956 from the liver of a bamboo rat (*Rhizomys sinensis*) in Vietnam. Pathogenicity of the organism in mice, hamsters, and guinea pigs was established. The organism was named after Dr. Marneffe, director of the Institut Pasteur in Indochina and Paris [25].

In 1959, Segretain [6] reported the first infection in humans. After the researcher accidentally inoculated the fungi into his finger, auxiliary lymphadenopathy developed and a nodule appeared at the inoculated site 9 days later. *P. marneffei* was isolated from the nodule. Segretain successfully treated himself with oral nystatin—a drug other researchers later found to be ineffective in treating natural *P. marneffei* infection in humans [1].

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Fourteen years after the report of laboratory-acquired infection, DiSalvo and colleagues [25] reported the first natural infection of *P. marneffei* in a human. The patient was a 61-year-old man living in North Carolina. A minister who had worked in Vietnam and traveled in Southeast Asia, he had undergone radiation therapy and splenectomy for Hodgkin’s disease. *P. marneffei* was unexpectedly isolated from his enlarged and infarcted spleen. The isolate’s susceptibility to amphotericin B was tested, but the author did not mention whether the patient was treated with amphotericin B and, if so, whether the treatment was successful.

Deng and colleagues [1] claimed that they identified the first patient with penicilliosis marneffei in Guangxi, China, in 1964. However, they were unable to publish their findings until 1985 because of suppression of academic endeavors during the Cultural Revolution (1966–1976) [16].

When DiSalvo described the first case of penicilliosis marneffei, it was thought to be an isolated incident, until in 1984 Jayanetra et al. [5] reported on five cases in Bangkok, Thailand. Two of the patients had normal immunity. They were successfully treated with amphotericin B. The others had underlying conditions: tuberculosis, lymphoproliferative disorder, or pregnancy complicated by systemic lupus erythematosus. They died as a result of misdiagnosis of the condition as tuberculosis; isolates of *P. marneffei* from their tissues were discounted as contaminants.

In 1988, Pielh and colleagues [26] in the United States reported the first case of penicilliosis marneffei associated with HIV infection. Subsequently, additional cases of the opportunistic mycosis in persons with AIDS were reported. The most significant report of disseminated *P. marneffei* infection in AIDS patients was published in 1994 by Supparatpinyo and colleagues [3] in Chiang Mai, Thailand, where *P. marneffei* is endemic. Within 2 years, 86 patients with AIDS at one hospital were found to have the mycosis.

Recognizing the prevalence of the mycosis in patients with AIDS, the Thai Ministry of Public Health has allowed penicilliosis marneffei to be considered as an AIDS-indicating disease in Thailand since 1992, according to Imwidthaya [27]. A number of mycologists researching the fungal disease expect that finally. The verticils have 3–5 penicilli, which bear phialides in a verticillate fashion. The phialides give rise to curved chains of ellipsoidal and smooth-walled phialoconidia of 2–4 × 2–3 mm in size. The phialoconidia have prominent disjunctors. Spirals are occasionally present.

After 2 days’ incubation at 37°C, *P. marneffei* grows as a yeast on Sabouraud glucose agar, cotton-seed agar, blood agar, or brain-heart infusion agar medium. The colony surface has been described as cerebriform, convoluted, and smooth. No soluble, diffusing red pigment is produced. The colony is light tan, resembling the color of *Blastomyces dermatitidis* [25]. Microscopically, *P. marneffei* yeast cells are unicellular and 3–6 × 1.5–2 mm in size. The cells are mixed with hypha-like elements. Investigators have described them as round [25], ellipsoidal [1], or rectangular [5]. A unique characteristic of the yeastlike cells is that they divide by fission, not budding, and have an easily seen white central septum.

**Epidemiology**

More than 155 cases of penicilliosis marneffei have been described in the English-language literature. The organism’s ecological characteristics and geographic distribution are still unknown. The organism has been isolated from bamboo rats in various parts of Southeast Asia, particularly in Vietnam [6] and Thailand [27]. The organism is also endemic in Guangxi Province of China [1, 7] and in some areas of Hong Kong [14]. More than 90% of bamboo rats in Guangxi are infected with the fungus and carry it in their internal organs [7]. Information from the 155 reported cases indicates that infected patients have either visited or lived in Vietnam [6, 25], Laos [2, 33], Singapore [19, 22], Malaysia [2, 11], Burma [2, 8], Thailand [2, 3, 5, 9, 15, 20, 26, 34, 35], Indonesia [2], Guangxi [1, 16], or Hong Kong [13, 14, 19, 23].

Animal hosts for *P. marneffei* include humans and bamboo rats (*R. sinensis* and *Rhizomys pruinosus senex*) [4, 6, 7]. The organism has been isolated from the feces, liver, lungs, and spleen of bamboo rats [1, 7], as well as from soil from the rats’ burrows [1]. It is believed that both humans and bamboo...
rats are infected with *P. marneffei* from a common source, as opposed to humans being infected from the rats [1, 7].

No definitive route of transmission has been determined. It has been suggested that the organism is acquired via ingestion and inhalation [5, 27, 36]. Inoculation via skin can cause the infection as well [6]. In an interesting case, a 61-year-old immunocompetent patient from an area of nonendemicity in Hong Kong had *P. marneffei* infection without having ever been to an area where such infection is endemic [18]. However, the patient had daily working contact with Vietnamese refugees. Chan and Woo [18] speculate that *P. marneffei* was carried by these refugees or in their belongings and transmitted to the patient.

Approximately 90% of patients with penicilliosis marneffei have been male. Their ages have ranged from 3 months to 72 years. As a whole, >80% of the patients are immunocompromised. In their reports, Supparatpinyo et al. [3] and Sirisanthana [37] demonstrated a correlation between the increase in incidence of AIDS in northern Thailand and that of penicilliosis marneffei. Within two years, 86 cases of *P. marneffei* infection associated with AIDS were diagnosed at Chiang Mai University Hospital [3]. Among the first 400 patients with AIDS at the hospital, 140 cases of penicilliosis marneffei were identified [37]. (Not all of these case reports are published in English.) Many of these patients had no other opportunistic infection at the time of admission [3]. It is important to note that, as presented in figure 1, a small number of the patients were not HIV-positive.

In contrast to the Thai cases of *P. marneffei* infection, almost all of the cases (14 of 15) reported from Guangxi involved patients with normal immunity [1, 16, 31]. However, the reports did not mention whether malnutrition, which may be considered to be an immunocompromising factor, was involved. It is surprising that the mortality rate was very high (13 patients died). According to the authors, this was partially due to the lack of treatment and to incorrect diagnosis.

A number of cases of *P. marneffei* infection have involved individuals from Western countries such as Italy [15], Britain [32], Canada [33, 38], France [2], Netherlands [9, 39], Switzerland [17], and the United States [21, 25, 26]. All of these patients had traveled to various parts of Southeast Asia and southern China. It has been suggested that the HIV-infected patients in the United States who are at risk of penicilliosis marneffei include Southeast Asian immigrants, immigrants from southern China, Vietnam War veterans, and those who have traveled to Southeast Asia, Guangxi, and certain parts of Hong Kong [21].

**Pathology**

Histopathologically, penicilliosis marneffei can lead to three distinct tissue reactions [1]. The granulomatous reaction involves infection of the reticuloepithelial system, often seen in immunocompetent patients. The yeast cells invade macrophages and survive and multiply intracellularly. The cell-mediated response to the fungi leads to formation of granulomas. Multinucleated giant cells, lymphocytes, and neutrophils participate in the reaction. As a result, centers of the granuloma become necrotic and the yeast cells are released. The reaction can occur in any organs of the mononuclear phagocytic system [1, 14].

Commonly, a suppurative reaction occurs in immunocompetent patients with *P. marneffei* infection [1]. An inflammatory response invoking neutrophils and fibrin results in abscesses in various organs, especially the lung, skin, liver, and subcutaneous tissues.

An anergic and necrotizing reaction is often seen in patients with compromised immune function [1]. Organs involved include the lung, liver, and skin. Many of the reports indicate observation of diffuse infiltration of macrophages engorged with proliferating yeast cells in tissues [1, 2, 5, 12, 34].

![Figure 1](cid-1992-23.jpg)

**Figure 1.** Number of patients with *P. marneffei* infection seen at Chiang Mai University Hospital and time of diagnosis. The number of HIV-infected patients (open bars) and HIV-noninfected patients (solid bars) is indicated. (Reproduced with permission from [3].)
Table 1. Sites of culture-positive infection in the 155 reported cases of penicilliosis marneffei.

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. (%) of patients</th>
</tr>
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<tbody>
<tr>
<td>Skin</td>
<td>96 (61.9)</td>
</tr>
<tr>
<td>Blood</td>
<td>85 (54.8)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>44 (28.4)</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>35 (22.6)</td>
</tr>
<tr>
<td>Liver</td>
<td>26 (16.8)</td>
</tr>
<tr>
<td>Lung</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Bone</td>
<td>12 (7.7)</td>
</tr>
<tr>
<td>Spleen</td>
<td>8 (5.2)</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>5 (3.2)</td>
</tr>
<tr>
<td>Bowel</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Kidney</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Pericardium</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Finger*</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Meninges</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>

* Laboratory-acquired infection.

stage signals initiation of a progressive and disseminated infection with *P. marneffei* [1].

Immunocompromised patients have a greater chance of having disseminated penicilliosis marneffei [14] involving a number of organs as listed in table 1.

Clinical Manifestations

The most common clinical features observed in patients with penicilliosis marneffei include fever, weight loss, and anemia. Dissemination of the disease is characterized by skin lesions, most often on the face, upper trunk, pinnae, and arms [12, 27]. Many patients have painful, nonproductive cough [1, 27]. Generalized lymphadenopathy is commonly observed. Hepatosplenomegaly is noted in many patients, especially children with AIDS [28]. In some patients pulmonary infiltrates occur and can be evidenced on roentgenographs showing densities, abscesses, and cavitations [3]. Hilar node calcification is not commonly reported [5].

Many cases of penicilliosis marneffei also involve fungemia, diarrhea (especially in children with AIDS [28]), necrotic papules, and nodules or pustules of the skin and subcutaneous tissues [3, 12, 34]. In addition, bone marrow infection, leukocytosis [1, 21, 32], and genital ulcer [12] have been reported. Pericarditis [1, 5, 22] and pleurisy [31] have been observed in a few cases. Osteolytic lesions or osteomyelitis [18], arthritis [34], and retropharyngeal purulent abscess causing upper-airway obstruction [19] are rare.

The clinical manifestations observed in cases of penicilliosis marneffei may closely resemble those of other systemic fungal infections, such as histoplasmosis and cryptococcosis in HIV-infected patients [2, 9, 14, 17]. Moreover, cases of AIDS have been reported in which penicilliosis occurred with other opportunistic infections, such as salmonellal septicemia [12], *Pneumocystis carinii* infection [11], and cryptococcosis [27]. Its nonspecific symptoms and signs and great similarities to the manifestations of other HIV-related opportunistic infections may make diagnosis of *P. marneffei* infection more difficult [3, 9]. Common clinical findings in the 155 reported cases of penicilliosis marneffei are presented in table 2.

### Immunity

Because *P. marneffei* is a facultative intracellular pathogen, cell-mediated immunity is important in helping to eradicate the organism from a host [1, 2, 14, 20, 34]. This is consistent with the observation that dissemination of the infection is much more common in patients with AIDS. Formation of granulomas helps localize and prevent the dissemination of the infection. Although a humoral reaction may be induced by presence of the fungi, antibody-mediated immunity appears to be of little importance against the fungal infection. Yuen and colleagues [40] reported an increase in titer of IgG (specific for *P. marneffei* antigens originating from the germinating conidia and yeast hyphae) in patients with penicilliosis marneffei, as compared with the titer in healthy individuals. The information may be useful serologically for rapid detection of the fungal infection.

### Diagnosis

The first important step in diagnosis of penicilliosis marneffei involves determination of whether the patient has been to an area of endemcity [8, 9, 13, 22]. Chest roentgenography may be able to show cavities present in the lung [3]. A presumptive diagnosis can be established with use of any of a number of different staining/direct examination techniques, such as with Wright’s [3], Giemsa [2], hematoxylin and eosin [17], Grocott-Gomori methenamine-silver nitrate [1], and periodic acid–Schiff stains [1]. Samples for direct examination can

Table 2. Common clinical characteristics reported in the 155 reported cases of penicilliosis marneffei.

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>No. (%) of patients</th>
</tr>
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<tbody>
<tr>
<td>Fever</td>
<td>152 (98.0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>116 (74.8)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>111 (71.6)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>108 (69.7)</td>
</tr>
<tr>
<td>Fungemia</td>
<td>84 (54.2)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>81 (52.3)</td>
</tr>
<tr>
<td>Cough</td>
<td>77 (49.7)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>68 (43.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (23.2)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>21 (13.5)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>7 (4.5)</td>
</tr>
<tr>
<td>Osteolytic lesions</td>
<td>6 (3.9)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>6 (3.9)</td>
</tr>
</tbody>
</table>
be obtained from bone marrow aspirate [2, 3], lymph nodes [3], and skin scrapings [17, 34]. Intracellular and extracellular basophilic, elliptical yeastlike organisms can be seen in these specimens. P. marneffei yeasts have clear central septation. The organism can be cultured from specimens of blood, bone marrow, skin and palatal papule scrapings, liver tissue, draining abscesses, lymph nodes, sputum, and ulcers. Cultures of stool [2, 10, 13, 14, 22], urine [2, 9, 32], bronchial washings [17, 33], fluid from knee joints [5], and CSF [34] have been reported to yield P. marneffei colonies.

Differentiation between P. marneffei and Histoplasma capsulatum is important because of the great morphological resemblance between the two organisms [1, 2, 8, 15, 17, 21, 24]. Both are intracellular pathogens. However, H. capsulatum yeast divides by budding, not fission. Immunologic identification of P. marneffei by means of an immunohistochemical approach [41] and exoantigen tests [2] has been reported. More important, differentiation between tuberculosis and P. marneffei infection must be accurate for proper antifungal therapy [5].

Recently, Yuen and colleagues [40] experimented with serodiagnosis of penicilliosis marneffei. They used an indirect immunofluorescent antibody test to evaluate the increase in IgG titer, and they found that patients with P. marneffei infection have a much higher titer of antibody against antigens in yeast hyphae and germinating conidia than do control groups (healthy persons and patients with diseases of which the symptoms are similar to those of penicilliosis marneffei). The clinical utility of serodiagnosis on the basis of IgG titers remains to be proven.

LoBuglio and Taylor [24] developed oligonucleotide primers from nucleotide sequences unique to the fungus. They used the primers to selectively amplify DNA from six isolates of P. marneffei and exclude the other species tested, including Penicillium subgenus Biverticillium, Talaromyces species, Aspergillus fumigatus, Coccidioides immitis, H. capsulatum, and P. carinii. The researchers believe that these primers can be used to create a PCR identification system, potentially leading to faster diagnosis of P. marneffei.

Treatment

It is relatively effective and safe to treat disseminated penicilliosis marneffei in HIV-infected patients with parenteral amphotericin B (for 2 weeks) followed by itraconazole (for 6 weeks) [2, 27, 42]. Supparatpinyo and colleagues found that this combination did not lead to serious adverse effects in any of their patients with HIV infection who had culture-proven penicilliosis marneffei [42]. Clinical improvements were seen in all of them after 2 weeks. In immunocompetent patients, amphotericin B yields a very good outcome if the condition is diagnosed early.

Relapse can occur. In one of Supparatpinyo’s reports [3], the treatment-response rate was 59%. The conditions of 77% of patients responded well to amphotericin B; most responses to itraconazole and some to fluconazole were good.

Conclusions

In summary, P. marneffei has emerged as an opportunistic pathogen in immunocompromised patients. Immunocompetent persons living in areas of endemicity are also at risk of the fungal disease. Successful treatment of the disease requires early diagnosis and administration of the proper antifungal drugs. Diagnosis is difficult because of similarities between penicilliosis marneffei and tuberculosis and other AIDS-related opportunistic infections, such as histoplasmosis and cryptococcosis.

Currently, the environmental niche of P. marneffei is unknown. Serological tests, as well as epidemiologic investigations, may be useful for diagnosis. Given the increase in incidence of the mycosis in patients with AIDS in Southeast Asia, penicilliosis marneffei is a potential AIDS-indicating disease in this area.

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