Review

Disseminated *Penicillium marneffei* Infection in Patients with Acquired Immunodeficiency Syndrome

Thira Sirisanthana, MD.

Department of Medicine, Faculty of Medicine, Chiang Mai
University, Chiang Mai 50200, THAILAND

Abstract

The fungal pathogen *Penicillium marneffei* is endemic in Southeast Asia and China. The prevalence of disseminated *Penicillium marneffei* infection has increased markedly over the past few years. This increase is exclusively due to infection among patients infected with human immunodeficiency virus (HIV). In northern Thailand disseminated *Penicillium marneffei* infection is the third most common opportunistic infection in late HIV disease, after tuberculosis and cryptococcosis. As of early 1995, 550 cases of disseminated *Penicillium marneffei* in HIV-infected patients had been diagnosed at Chiang Mai University Hospital alone. Signs and symptoms of these patients were fever, marked weight loss, skin lesions, anemia, lymphadenopathy and hepatomegaly. Skin lesions were commonly necrotic papules resembling molluscum contagiosum. They could not be differentiated from skin lesions in AIDS patients with disseminated cryptococcosis or histoplasmosis. Diagnosis of disseminated *Penicillium marneffei* infection could be made by culture of the blood, skin lesions, or bone marrow and by microscopic examination of Wright's-stained skin smears or bone marrow aspirates. Most patients responded to treatment with amphotericin B and itraconazole. Maintenance therapy with itraconazole should be given in patients who responded initially. With the expected epidemic of HIV infection in southern China and Southeast Asian countries other than Thailand, *Penicillium marneffei* is potentially an organism of great public health importance in the future. Many critical features of the epidemiology and natural history of *Penicillium marneffei* infection remain unknown and need further elucidation.

Key words : *Penicillium marneffei*, AIDS, HIV, fungal infection, Southeast Asia, Thailand

Introduction

Penicillium marneffei is a dimorphic fungal pathogen, which can cause disseminated disease both in immunocompetent and immunocompromised human beings¹⁾. It is endemic in Southeast Asia and China^{2,3)}. The prevalence of disseminated *Penicillium marneffei* infection has increased markedly over the past few years⁴⁻¹⁷⁾. This increase is exclusively due to infection among patients infected with human immunodeficiency virus (HIV)^{1,7,12)}. In northern Thailand, disseminated *Penicillium marneffei* infection is the third most common HIV-related opportunistic infection, after tuberculosis and cryptococcosis¹⁾. As of early 1995, 550 cases of disseminated *Penicillium marneffei* infection in HIV-infected patients had been diagnosed at Chiang Mai University Hospital alone. Many more cases were diagnosed at district

hospitals in Chiang Mai as well as hospitals in other provinces in northern Thailand. The rare occurrence of *Penicillium marneffei* disease in the past and the recent rapid increase coincides with the explosive outbreak of HIV infection and acquired immunodeficiency syndrome (AIDS) in northern Thailand¹⁸⁾. Also, in a few patients whose T-lymphocyte subsets were determined, CD4 counts were consistently below 100/ μ l¹⁾. Thus, it has been suggested that *Penicillium marneffei* infection should be regarded as another AIDS-defining illness^{7,10,12)}.

History

Penicillium 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 from a fungal pathogen. 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 honor of Hubert Marneffe, director of the Pasteur Institute of Indochina^{19,20}.

Segretain accidentally inoculated himself during an experimental study²¹. He developed a nodule at the site of inoculation, lymphangitis, and lymph node enlargement. The infection seemed to respond to high dose of oral nystatin. More than a decade later, the first natural human infection with *Penicillium marneffei* was reported in a 61-year-old missionary with Hodgkin's disease who had had a splenectomy: he had been living in Southeast Asia²². The second reported case was in 1984 and was also from the USA²³. The patient was a 59-year-old man who had travelled in the Far East. He had recurrent episodes of hemoptysis thought to be caused by bronchiectasis. A pneumonectomy revealed granuloma; tissue sections showed yeast-like cell of *Penicillium marneffei*, and the culture grew *Penicillium marneffei*. Also in 1984, 5 patients were reported from Bangkok, Thailand². They were aged between 6 and 50 years and diagnosed between 1972 and 1982. The first 8 Chinese patients were reported in 1985 from the Guangxi Province of China²⁴. They were seen between 1964 and 1983. Several more cases were subsequently reported from the same area in southern China^{3,25-27}. Up to 6 cases of patients with *Penicillium marneffei* infection had also been reported from Hong Kong²⁸⁻³³.

From 1988, many HIV-infected patients with disseminated *Penicillium marneffei* disease were reported for the first time, including patients from USA⁴, UK⁵, the Netherlands⁸, Australia¹⁴, Italy¹⁵, and France¹⁶. All the patients had travelled to Southeast Asia or southern China. In some cases, *Penicillium marneffei* infection was the indicator of HIV infection upon returning from

the trip.

The first case of disseminated *Penicillium marneffei* infection in HIV-infected native of Southeast Asia was reported from Bangkok, Thailand in 1989⁷. In 1994, 86 more cases were reported from Chiang Mai¹. We also reported 5 children aged 9 to 36 months with vertically transmitted HIV infection who developed systemic *Penicillium marneffei* infection³⁴. Outside Thailand, 4 cases of systemic *Penicillium marneffei* in HIV-infected patients had been reported from Hong Kong^{10,13,35}.

Clinical features

HIV-infected patients with disseminated *Penicillium marneffei* usually presented with symptoms and signs seen in other patients with late HIV diseases¹. These included fever in 99% of the patients, anemia (78%), pronounced weight loss (76%), generalized lymphadenopathy (58%) and hepatomegaly (51%). They were not specific for *Penicillium marneffei* infection and could be caused by HIV or other HIV-related opportunistic infection. However, a more specific finding was the skin lesion, which were seen in 71% of our patients. They were most commonly papules with central necrotic umbilication. In Chiang Mai, similar skin lesions had been seen in AIDS patients with disseminated cryptococcosis or histoplasmosis. In 63% of our patients with disseminated *Penicillium 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 samples of bone-marrow aspirate, and/or touch smears of the skin-biopsy specimen, and/or the lymph-node biopsy specimen. These procedures were also very helpful in diagnosing disseminated cryptococcosis and disseminated histoplasmosis (Table 1). It was relatively easy to culture *Penicillium marneffei* from various clinical

Table 1. Characteristics of the fungal pathogens seen in microscopic examination of clinical specimens stained by Wright's stain

	<i>P. marneffei</i>	<i>C. neoformans</i>	<i>H. capsulatum</i>
Diameter	1-8 μ	3-10 μ	2-5 μ
Capsule	thin	thick	thin
Staining of capsule	no	no	no
Shape	round to ovoid, "sausage" cells, width: length = 1:3-1:4	round to ovoid	round to ovoid, more uniform, width: length = 1:2
Division	binary fission, cross-walls are formed before separation	budding, broad neck, seen more frequent than in <i>H. capsulatum</i>	budding, narrow neck

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 mortality rate of patients with disseminated *Penicillium marneffei* infection is very high, regardless of whether the patient is concurrently infected with HIV^{2,3,13,24}. This is 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 antifungal treatment was started early, the response to therapy was much better at 59%. The fungus was sensitive to amphotericin B, itraconazole, and ketoconazole³⁶. Our current recommended treatment regimen for HIV-infected patients with disseminated *Penicillium marneffei* infection is to give amphotericin B intravenously in the dose of 0.6mg/kg/day for two weeks, followed by itraconazole 400mg/day orally in 2 divided doses for the next 10 weeks. Then the patient is given itraconazole 200mg/day orally as secondary prophylaxis for life.

Mode of transmission

Thirty years after the discovery of *Penicillium marneffei* in bamboo rat (*Rhizomys sinensis*) in Vietnam, the fungus was cultured in southern China from another species of bamboo rat, *Rhizomys pruinosus*^{37,38}. Later, another member of the family Rhizomyidae in Thailand, *Cannomys badius*, was found as a host of *Penicillium marneffei*³⁹. In Chiang Mai we have cultured *Penicillium marneffei* from yet another species of bamboo rat, namely *Rhizomys sumatrensis*. Despite these several isolations of the fungus from bamboo rats, it is not clear whether human beings contact *Penicillium marneffei* disease from them. They usually live near the forest, and the majority of our patients did not remember coming in contact with them. In fact, most of our patients have never seen a bamboo rat before in their life.

The mode of transmission is also unknown. Our hypothesis is that the fungus is transmitted via the respiratory route, as is the case in other endemic systemic mycosis, namely histoplasmosis, coccidioidomycosis, and blastomycosis. It is likely that in the endemic area such as northern Thailand, a certain proportion of the general population have already been infected, but are asymptomatic. In the literature, lengthy asymptomatic infection before immunosuppression and reactivation has been described, as well as clinically active infection within 4 to 5 weeks of

exposure in an endemic area^{4,14,22}. Clearly, more information is needed about the epidemiology, natural history, and pathogenesis of this important emerging AIDS-related pathogen.

References

- 1) Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T: Disseminated *Penicillium marneffei* infection in Southeast Asia. *Lancet* **344**:110-113, 1994.
- 2) Jayanetra P, Nitiyanant P, Ajello L, et al: Penicilliosis marneffei in Thailand: report of five human cases. *Am J Trop Med Hyg* **33**:637-644, 1984.
- 3) Deng Z, Ribas JL, Gibson DW, Connor DH: Infection caused by *P. marneffei* in China and Southeast Asia: review of eighteen published cases and report of four more Chinese cases. *Rev Infect Dis* **10**:640-652, 1988.
- 4) Piehl MR, Kaplan RL, Haber MH: Disseminated penicilliosis in a patient with acquired immunodeficiency syndrome. *Arch Pathol Lab Med* **112**:1262-1264, 1988.
- 5) Peto TEA, Bull R, Millard PR, et al: Systemic mycosis due to *Penicillium marneffei* in a patient with antibody to human immunodeficiency virus. *J Infect* **16**:285-290, 1988.
- 6) Tsang DN, Chan JKC, Lau YT, Lim W, Tse CH, Chan NK: *Penicillium marneffei* infection: an underdiagnosed disease? *Histopathology* **13**:311-318, 1988.
- 7) Sathapatayavongs B, Damrongkitchaiporn S, Saengditha P, Kiatboonsri S, Jayanetra P: Disseminated penicilliosis associated with HIV infection [letter]. *J Infect* **19**:84-85, 1989.
- 8) Hulshof CMJ, Van Zanten RAA, Sluiter JF, et al: *Penicillium marneffei* infection in an AIDS patient [letter]. *Eur J Clin Microbiol Infect Dis* **9**:370, 1990.
- 9) Ma KF, Tsui MS, Tsang DN: Fine needle aspiration diagnosis of *Penicillium marneffei* infection. *Acta Cytol* **35**:557-559, 1991.
- 10) Tsang DN, Li PCK, Tsui MS, Lau YT, Ma KF, Yeoh EK: *Penicillium marneffei*: another pathogen to consider in patient infected with human immunodeficiency virus [letter]. *Rev Infect Dis* **13**:766-767, 1991.
- 11) Chiewchanvit S, Mahanupab P, Hirunsri P, Vanittanakom N: Cutaneous manifestations of disseminated *Penicillium marneffei* mycosis in five HIV-infected patients. *Mycoses* **34**:245-249, 1991.
- 12) Supparatpinyo K, Chiewchanvit S, Hirunsri P, Uthammachai C, Nelson KE, Sirisanthana T: *Penicillium marneffei* infection in patients infected with human immunodeficiency virus. *Clin Infect Dis* **14**:871-874, 1992.
- 13) Tsui WN, Ma KF, Tsang DN: Disseminated *Penicillium marneffei* infection in HIV-infected subject. *Histopathology* **20**:287-293, 1992.

- 14) Jones PD, See J: *Penicillium marneffei* infection in patients infected with human immunodeficiency virus: late presentation in an area of nonendemicity [letter]. Clin Infect Dis 15:744, 1992.
- 15) Viviani MA, Tortorano AM, Rizzardini G, et al: Treatment and serological studies of an Italian case of penicilliosis marneffei contracted in Thailand by a drug addict infected with the human immunodeficiency virus. Eur J Epidemiol 9:79-85, 1993.
- 16) Hilmarsdottir I, Meynard JL, Rogeaux O, et al: Disseminated *Penicillium marneffei* infection associated with human immunodeficiency virus: a report of two cases and a review of 35 published cases. J Acquir Immune Defic Synd 6:466-471, 1993.
- 17) Dupont B, Denning DW, Marriott D, Sugar A, Viviani MA, Sirisanthana T: Mycoses in AIDS patients. J Med Vet Mycol 32 (suppl 1):65-77, 1994.
- 18) Sirisanthana T: AIDS in Thailand. Antibiotics and Chemotherapy (Japan) 11:657-667, 1995.
- 19) Capponi M, Sureau P, Segretain G: Pénicilliose de *Rhizomys sinensis*. Bull Soc Pathol Exot 49:418-421, 1956.
- 20) Segretain G: Description d'une nouvelle espèce de *Penicillium*: *Penicillium marneffei* n. sp. Bull Soc Mycol Fr 75:412-416, 1959.
- 21) Segretain G: *Penicillium marneffei* in. sp., agent d'une mycose du système réticulo-endothélial. Mycopathol Mycol Appl 11:327-353, 1959.
- 22) Disalvo AF, Fickling AM, Ajello L: Infection caused by *Penicillium marneffei*: a description of first natural infection in man. Am J Clin Pathol 60:259-263, 1973.
- 23) Pautler KB, Padhye AA, Ajello L: Imported penicilliosis marneffei in the United States: report of a second human infection. Sabouraudia 22:433-438, 1984.
- 24) Deng Z, Connor DH: Progressive disseminated penicilliosis caused by *Penicillium marneffei*: report of eight cases and differentiation of the causative organism from *Histoplasma capsulatum*. Am J Clin Pathol 84:323-327, 1985.
- 25) Li JS, Pan Q, Deng ZL, Wang ZJ, Yoo CL: A case report on *Penicillium marneffei*. J Clin Dermatol (China) 14:24-26, 1985.
- 26) Li PC, Pan LQ, Wu SS, Su SX, Su SB, Shan LY: Disseminated penicilliosis marneffei in China. Report of three cases. Chin Med J 104:247-251, 1991.
- 27) Wang IL, Yeh HP, Chang SC, Chen JS: Penicilliosis due to *Penicillium marneffei*. A case report. Derm Sinica 7:19-22, 1989.
- 28) Chan JKC, Tsang DN, Wong KK: *Penicillium marneffei* in bronchoalveolar lavage fluid. Acta Cytol 33:523-526, 1989.
- 29) Chan JKC, Tsang DNC: *Penicillium marneffei* infection: an update (correspondence). Am J Clin Pathol 92:709, 1989.
- 30) Chan YF, Woo KC: *Penicillium marneffei* osteomyelitis. J Bone Joint Surg [Br] 72B:500-503, 1990.
- 31) Chan YF, Chow TC: Ultrastructural observations on *Penicillium marneffei* in natural human infection. Ultrastructural Pathol 14:439-452, 1990.
- 32) So SY, Chau YF, Jones BM, et al: A case of invasive penicilliosis in Hong Kong with immunologic evaluation. Am Rev Respir Dis 131:662-665, 1985.
- 33) Yuen WC, Chan YF, Loke SL, Seto WH, Poon GP, Wong KK: Chronic lymphadenopathy caused by *Penicillium marneffei*: a condition mimicking tuberculous lymphadenopathy. Br J Surg 73:1007-1008, 1986.
- 34) Sirisanthana V, Sirisanthana T: *Penicillium marneffei* infection in children infected with human immunodeficiency virus. Pediatr Infect Dis 12:1021-1025, 1993.
- 35) Li PC, Tsui MS, Ma KF: *Penicillium marneffei*: indicator disease for AIDS in South East Asia (letter). AIDS 6:240-241, 1992.
- 36) Supparatpinoy K, Nelson KE, Merz WG, et al: Response to antifungal therapy by human immunodeficiency virus-infected patients with disseminated *Penicillium marneffei* infections and in vitro susceptibilities of isolates from clinical specimens. Antimicrob Agents Chemother 37:2407-2411, 1993.
- 37) Deng ZL, Yun M, Ajello L: Human penicilliosis marneffei and its relation to the bamboo rat (*Rhizomys pruinosus*). J Med Vet Mycol 24:383-389, 1986.
- 38) Li JC, Pan LQ, Wu SX: Mycologic investigation on *Rhizomys pruinosus* senex in Guangxi as natural carrier with *Penicillium marneffei*. Chin Med J 102:477-485, 1989.
- 39) Viviani MA, Hill JO, Dixon DM: *Penicillium marneffei*: dimorphism and treatment. In: Dimorphic fungi in biology and medicine. Edited by H. Vanden Bossche, F. Odds, D. Kerridge. New York: London, pp.413-422, 1993.