A 12-Case Series of Penicillium marneffei Pneumonia

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Background: *Penicillium marneffei, an endemic fungus in Southeast Asia and southern China, is the cause of opportunistic infection in HIV-infected patients who may present with symptoms and signs of the lungs, and abnormal chest radiographs. However, only a few cases of pulmonary infection from this organism have been reported.*

Objective: *To study the clinical manifestations of patients with Penicillium marneffei pneumonia diagnosed by sputum or bronchoalveolar lavage (BAL) fluid culture*

Material and Method: *Retrospective descriptive study of patients who were diagnosed with Penicillium marneffei pneumonia at Maharaj Nakorn Chiang Mai Hospital from September 1999 to July 2004.*

Results: *Twelve patients (eight males, four females) were included with mean age of 36.1 years. Nine cases were HIV-infected. Their presenting symptoms included fever, cough, dyspnea and weight loss. Skin lesions, hepatomegaly and lymphadenopathy were extrapulmonary signs. Chest radiographs revealed diffuse reticulonodular, diffuse reticular, localized alveolar, localized reticular infiltration, and cavitary lesion. The diagnosis was made by cultures from the sputum in five cases and BAL fluid in the others. Co-infections with Streptococcus pneumoniae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans, and Strongyloides stercoralis were found. Most of them were treated by intravenous amphotericin B followed by oral itraconazole, or oral itraconazole.*

Conclusion: *Penicillium marneffei pneumonia has non-specific clinical manifestations, it cannot be excluded from other infections and may have co-infections. Physicians should include this infection in their differential diagnosis especially in immunocompromised patients.*

Keywords: *Penicillium marneffei, Pneumonia, Chest radiography*

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Fungi are uncommon causes of pneumonia in the general population, but it is more prevalent in some patient groups such as immunocompromised hosts with HIV infection, solid organ or bone marrow transplantation, or neutropenia[1,2]. The lungs may be the primary site of infection or disseminated sites secondary to hematogenous spreading. From a retrospective study from 1988 to 1997, the most frequent pulmonary fungal infection was caused by *Aspergillus* spp. (57%), followed by *Cryptococcus* spp. (21%) and *Candida* spp. (14%)[3].

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Penicillium marneffei is a thermally dimorphic fungus and highly endemic in Southeast Asia and southern China. Although penicilliosis in humans is uncommon, it has been reported in both healthy and immunocompromised hosts[4], especially in HIV-infected patients[5,6]. Supparatpinyo et al[5] reported 21 cases of disseminated penicilliosis in which cough was observed in 11 cases and abnormal chest radiographs were present in six cases: diffuse reticulonodular infiltration (3 cases), localized interstitial infiltration (2 cases), and localized alveolar infiltration (1 case). While Pulmonary infection from *Penicillium marneffei* is common, only a few cases have been reported[7-9].

The present study was aimed to determine the clinical manifestations of patients with *Penicillium marneffei* pneumonia, diagnosed from sputum or bronchoalveolar lavage (BAL) fluid culture.

Material and Method

The authors collected the medical records of patients with *Penicillium marneffei* pneumonia diagnosed at Maharaj Nakorn Chiang Mai Hospital from September 1999 to July 2004, from sputum or BAL fluid culture which was done by incubating at 25°C on Sabouraud dextrose agar and then subculture on brain heart infusion agar and incubated at 37°C. The positive culture for *Penicillium marneffei* was characterized by a dimorphic fungus that grew as mold at 25°C and yeast at 37°C. [5]

The patients' clinical records were reviewed for demographic data (sex, age, and residence), underlying diseases, immune status, co-infections at diagnosis, symptoms and signs, chest radiographs, complete blood count, blood for liver function tests, sputum and/or BAL fluid culture, and treatment.

The present study was approved by the research ethics committee, Faculty of Medicine, Chiang Mai University.

Results

During the study period, the authors found 12 patients who were diagnosed with *Penicillium marneffei* pneumonia according to the criteria. There were eight males and four females. Their mean age was 36.1 years (range from 27-47 years). All patients lived in northern Thailand. Nine patients (75%) were infected with HIV, two of whom had a previous history of tuberculosis. The other two patients, who were not infected with HIV, had non-Hodgkin's lymphoma and non-tuberculous mycobacterium infection. HIV status was unknown in one patient. The details of clinical characteristics of these patients are summarized in Table 1.

Fever and cough were the most common presenting symptoms (10 cases), followed by dyspnea (9 cases), weight loss (3 cases), chest pain (2 cases), and hemoptysis (2 cases).

On examination, found crepitation (6 cases), wheezing (2 cases) and decreased breath sound (2 cases). Skin lesions (5 cases), hepatomegaly (5 cases), splenomegaly (2 cases) and lymphadenopathy (3 cases) were extrapulmonary signs. The chest radiographs revealed interstitial, alveolar, or mixed infiltration or a cavitary lesion as summarized in Table 2.

The complete blood counts of these patients showed a hemoglobin concentration of less than 10 g/dL in eight cases and a white blood cell count below 4,000 cells/ L in two cases, and more than 15,000 cells/ L in two cases. High bilirubin (more than 2 mg/dL), low albumin (less than 3 mg/dL), high transaminase (more than 5 times the upper limit), and high alkaline phosphatase level (more than 3 times the upper limit) were presented in three, eight, four and seven cases respectively.

The diagnosis was from sputum culture in five cases and BAL fluid culture in the others. Hemocultures were taken in nine patients, and positive in seven cases that were *Penicillium marneffei* (5 cases), *Cryptococcus neoformans* (1 case) and a mixture of *Penicillium marneffei* and *Cryptococcus neoformans* (1 case).

Six patients had co-infections with a diagnosis of *Penicillium marneffei* pneumonia, which were bacterial pneumonia from *Streptococcus pneumoniae* (1 case), *Klebsiella pneumoniae* and pulmonary tuberculosis (1 case), disseminated cryptococcosis (2 cases), skin cryptococcosis (1 case), and intestinal strongyloidiasis (1 case).

Ten patients with *Penicillium marneffei* pneumonia were treated: four patients with intravenous amphotericin B followed by oral itraconazole, four patients with oral itraconazole and the other two patients with intravenous amphotericin B.

Discussion

In general, the fungi, *Penicillium* spp., can be found ubiquitously in the environment, and contaminated in the clinical specimen. Although *Penicillium marneffei* infection is caused by a thermally dimorphic fungus and highly endemic in Southeast Asia and southern China. It is uncommon in humans. The infection can occur in both healthy and immunocompromised hosts, especially in HIV-infected patients. In northern Thailand, penicilliosis is the third most common opportunistic infection in HIV-infected patients after tuberculosis and cryptococcal meningitis[6].

Bamboo rats are the reservoir of *Penicillium marneffei* and the organism can be isolated from the organs of healthy bamboo rats and the soil containing feces around their burrows. Humans may receive the organism by inhalation of the conidia from an environmental source and this can cause the disease depending on the patients' immunity[10,11]. The first human case was reported by DiSalvo et al in 1973[12], which was a patient with Hodgkin's disease who underwent splenectomy. The organism was recovered by a culture from the spleen. In Thailand, the first report from Ramathibodi Hospital in 1984 described five cases presented with systemic *Penicillium marneffei* infection between 1974 and 1982[4], and 10 years later, there were two reports of 21 and 80 cases of disseminated

Table 1. The description of clinical characteristics of 12 patients with *Penicillium marneffei* pneumonia

No.	Age/Sex	Residence	Underlying diseases	Symptoms	Extrapulmonary signs	Chest x-ray	Diagnostic procedure of *P. marneffei* pneumonia	Co-existing diagnosis with *P. marneffei* pneumonia	Treatment of *P. marneffei* pneumonia
1.	27 / F	ChiangMai	HIV infection	Fever, productive cough, dyspnea, hemoptysis	Hepatosple-nomegaly, skin lesion	Diffuse reticular infiltration + cavity RLL	BALF , hemoculture	-	Itraconazole
2.	31 / M	ChiangMai	HIV infection, old pulmonary TB	Fever, productive cough, dyspnea, hemoptysis	-	Localized alveolar infiltration LLL + reticulonodular infiltration right lung + cavitary lesion left lung	BALF	*S. pneumoniae* pneumonia	N/A
3.	31 / M	ChiangMai	HIV infection, TB lymph node	Fever, cough, dyspnea	Cervical lymphadeno-pathy, skin lesion	Diffuse reticular infiltration	Sputum, hemoculture	-	Amphotericin B+ Itraconazole
4.	33 / F	ChiangMai	HIV infection	Nonproductive cough, dyspnea	Hepatomegaly	Diffuse reticulonodular infiltration	BALF	-	Itraconazole
5.	33 / M	ChiangMai	HIV infection	Fever	-	Diffuse reticulonodular infiltration	Sputum, hemoculture	Disseminated cryptococcosis	Amphotericin B
6.	37 / F	ChiangMai	HIV infection	Fever, dyspnea, cough	Skin lesion	Diffuse reticulonodular infiltration	Sputum, hemoculture	CMV retinitis, Disseminated cryptococcosis	Amphotericin B+ Itraconazole
7.	47 / M	ChiangMai	HIV infection	Fever, productive cough, dyspnea	Hepatomegaly, skin lesion	Localized reticular infiltration RUL	BALF, hemoculture	*K. pneumoniae* pneumonia, pulmonary TB	Itraconazole

Table 1. The description of clinical characteristics of 12 patients with *Penicillium marneffei* pneumonia (cont.)

No.	Age/Sex	Residence	Underlying diseases	Symptoms	Extrapulmonary signs	Chest x-ray	Diagnostic procedure of *P. marneffei* pneumonia	Co-existing diagnosis with *P. marneffei* pneumonia	Treatment of *P. marneffei* pneumonia
8.	30 / M	ChiangRai	HIV infection	Fever, productive cough	Hepatomegaly, skin lesion	Diffuse reticular infiltration	Sputum, hemoculture	Skin cryptococcosis	Amphotericin B
9.	40 / M	Lamphun	HIV infection	Fever, productive cough, chest pain	-	Localized alveolonodular infiltration RML	BALF, hemoculture, bone marrow aspiration	Strongyloides infestation	Amphotericin B+ Itraconazole
10.	35 / M	Payao	Nontuberculous mycobacterium lymphadeno-pathy	Fever, cough, dyspnea, neck mass, weight loss	Cervical lymphadeno-pathy	Localized alveolar infiltration RML	BALF	-	Amphotericin B+ Itraconazole
11.	45 / M	Payao	Non-Hodgkin's lymphoma	Cough, dyspnea, neck mass, weight loss	Cervical lymphadeno-pathy, hepatosple-nomegaly	Diffuse reticulonodular infiltration	BALF	-	Itraconazole
12.	44 / F	ChiangMai	N/A	Fever, chest pain, dyspnea, weight loss	-	Localized alveolar infiltration left lung	Sputum	-	N/A

BALF = bronchoalveolar lavage fluid, N/A = not applicable

Table 2. Chest radiographs of 12 patients with *Penicillium marneffei* pneumonia

Chest radiographs	Cases (%)
Diffuse reticulonodular infiltration	4 (33)
Diffuse reticular infiltration	2 (17)
Localized alveolar infiltration	2 (17)
Localized reticular infiltration	1 (8)
Localized alveolo-nodular infiltration	1 (8)
Diffuse reticular infiltration + cavitary lesion	1 (8)
Reticulonodular and alveolar infiltration + cavitary lesion	1 (8)

penicilliosis from Maharaj Nakorn Chiang Mai Hospital[5,6].

The present study reviewed 12 patients with *Penicillium marneffei* pneumonia, diagnosed from sputum or BAL fluid culture during a 5-year period. Most of them (75%) were men and all lived in northern Thailand. Nine patients were infected with HIV, the other two patients had non-Hodgkin's lymphoma and non-tuberculous mycobacterium infection. The authors believed that these two patients had some degree of cell-mediated immunity defect.

On examination, most of the patients presented with fever, cough, dyspnea and crepitation, which were not different from pneumonia caused by other organisms. In the present study, some patients were co-infected with tuberculosis and bacterial pneumonia. However, the clinical clues that suggested this infection were skin lesions, especially generalized papular rash on the face, pinnae, upper trunk and arms. Hepatomegaly, splenomegaly, and lymphadenopathy indicated disseminated infection. From a study by Supparatpinyo et al[6], most of the 80 HIV-infected patients with disseminated penicilliosis presented with fever, skin lesions, and diarrhea. Cough was found in 49%. Fever, weight loss, anemia, hepatomegaly, splenomegaly and skin lesions were revealed on examination, but lung signs were not mentioned.

The finding of chest radiographs in the present study were diffuse reticulonodular, diffuse reticular, localized alveolar and localized reticular infiltration, and a cavitary lesion, like the former study[6], which revealed abnormal chest radiographs in 30 cases: diffuse reticulonodular infiltration (13 cases), localized alveolar infiltration (12 cases), diffuse alveolar infiltration (3 cases), localized interstitital infiltration (1 case), and pleural effusion (1 case). These abnormal chest radiographs cannot be differentiated from other infections such as tuberculosis and fungal infections (histoplasmosis and cryptococcosis)[13].

The presented patients were co-infected with pulmonary tuberculosis, bacterial pneumonia, and disseminated cryptococcosis, which indicated a mixed infection. The study of Pothirat et al[14] showed that 50% of patients infected with both HIV and *Penicillium marneffei* had mixed pulmonary infection with the bacteria, *Pneumocystis jiroveci*, *Cryptococcus* spp., or cytomegalovirus.

Compared with other studies, Cheng et al[7] reported three cases of systemic *Penicillium marneffei* infection. All of them were HIV-infected and had traveled to Thailand. Fever and weight loss were found in all cases, skin lesion in two cases, cough in one case and hemoptysis in one case. All chest radiographs showed a cavitary lesion with a smooth or irregular thin wall. Two patients were diagnosed by sputum culture and the others by transthoracic needle aspiration of the cavity and bronchoscopic biopsy. *Pneumocystis jiroveci* was co-infected in one patient. After treatment with antifungal drugs, their clinical conditions improved, and the cavitary lesions on chest radiographs were resolved leaving chronic fibrotic and interstitial infiltration with pleural change. That report was similar to the study of Sekhon et al[8], which reported one patient with unknown HIV status from Canada who had lived in Thailand and presented with cough and dyspnea. A chest radiograph revealed bilateral pulmonary air fluid levels. The fungus was found from the sputum and BAL fluid culture.

McShane et al[9] reported an HIV-infected patient from England that had visited Hong Kong and southern China and presented with fever, chronic productive cough, dyspnea, generalized lymphadenopathy and skin lesion. There were no abnormal lung signs, but hypoxemia was detected. A chest radiograph and computed tomography revealed a 5 x 7.5 cm soft tissue mass at the right upper lobe and multiple lung nodules in both lung fields. A tumor-like lesion at the posterior wall of the trachea was revealed by a bronchoscope. The pathology and culture from the lung and skin lesion demonstrated *Penicillium marneffei*.

At present, treatment with intravenous amphotericin B at 0.6 mg/kg/day for 2 weeks followed by oral itraconazole at 400 mg/day for 10 weeks is suggested and was successful in 97.3% of HIV-infected patients with disseminated penicilliosis[15]. However, because of the high relapse rate (57%), lifelong secondary prophylaxis with oral itraconazole at 200 mg/day is suggested to prevent relapse[16].

Conclusion

Penicillium marneffei pneumonia is uncommon, but can be found in immunocompromised hosts, especially in HIV-infected patients who had lived or traveled to Southeast Asia and southern China. Its clinical manifestations are non-specific and co-infections can be encountered. Therefore, physicians should include this infection in the differential diagnosis especially in immunocompromised hosts for early diagnosis and proper management.

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ปอดอักเสบจากเชื้อ *Penicillium marneffei*: รายงานผู้ป่วย 12 ราย

อรรถวุฒิ ดีสมโชค, สุรัตน์ ตันประเวช

บทนำ: *เชื้อ Penicillium marneffei เป็นเชื้อราประจำถิ่นในเขตภูมิภาคเอเชียตะวันออกเฉียงใต้และภาคใต้ของประเทศสาธารณรัฐประชาชนจีน และ เป็นสาเหตุของการติดเชื้อฉวยโอกาสในผู้ป่วยที่ติดเชื้อ HIV โดยอาจพบอาการและอาการแสดงทางปอด รวมทั้งความผิดปกติของภาพรังสีทรวงอก แต่มีรายงานผู้ป่วยปอดอักเสบจากเชื้อนี้เป็นจำนวนน้อย*

วัตถุประสงค์: *เพื่อศึกษาลักษณะทางคลินิกของผู้ป่วยปอดอักเสบจากเชื้อ Penicillium marneffei ที่ได้รับการวินิจฉัยจากการเพาะเชื้อจากเสมหะหรือน้ำล้างปอด*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังแบบพรรณนา โดยรวบรวมผู้ป่วยปอดอักเสบจากเชื้อ Penicillium marneffei ที่ได้รับการวินิจฉัยที่โรงพยาบาลมหาราชนครเชียงใหม่ ระหว่างเดือนกันยายน พ.ศ. 2542 - กรกฎาคม พ.ศ. 2547*

ผลการศึกษา: *มีผู้ป่วย12 ราย (ชาย 8 ราย และ หญิง 4 ราย) อายุเฉลี่ย 36.1 ปี มีการติดเชื้อ HIV ร่วม 9 ราย อาการนำของผู้ป่วยได้แก่ ไข้ ไอ หอบเหนื่อย และ น้ำหนักลด อาการแสดงนอกปอดได้แก่ รอยโรคที่ผิวหนัง ตับโต และ ต่อมน้ำเหลืองโต ภาพรังสีทรวงอกพบลักษณะ diffuse reticulonodular, diffuse reticular, localized alveolar, localized reticular infiltration และ cavitary lesion การวินิจฉัยได้จากการเพาะเชื้อจากเสมหะ 5 ราย และที่เหลือจากน้ำล้างปอด พบมีการติดเชื้ออื่นร่วมได้แก่ Streptococcus pneumoniae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans และ Strongyloides stercoralis ผู้ป่วยส่วนใหญ่ได้รับการรักษาด้วย Amphotericin B ฉีดเข้าหลอดเลือดดำ ร่วมกับรับประทาน itraconazole หรือ รับประทาน itraconazole อย่างเดียว*

สรุป: *ปอดอักเสบจากเชื้อ Penicillium marneffei มีลักษณะทางคลินิกที่ไม่จำเพาะ ไม่สามารถที่จะแยกจากการติดเชื้ออื่นได้อย่างชัดเจน และยังสามารถพบการติดเชื้ออื่นร่วมได้ แพทย์ควรต้องนึกถึงการติดเชื้อนี้ไว้ในการวินิจฉัยแยกโรคโดยเฉพาะในผู้ป่วยที่มีภูมิคุ้มกันบกพร่อง*