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

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 neutropenia1,2. 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.

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 hosts4, especially in HIV-infected patients5,6. Supparatpinyo et al7 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 reported7-9.

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. (9)

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 (13), 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

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


<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Sex</th>
<th>Residence</th>
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<th>Treatment of <em>P. marneffei</em> pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>30 / M</td>
<td>ChiangRai</td>
<td>HIV infection</td>
<td>Fever, productive cough</td>
<td>Hepatomegaly, skin lesion</td>
<td>Diffuse reticular infiltration</td>
<td>Sputum, hemoculture</td>
<td>Skin cryptococcosis</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>9.</td>
<td>40 / M</td>
<td>Lamphun</td>
<td>HIV infection</td>
<td>Fever, productive cough, chest pain</td>
<td>-</td>
<td>Localized alveolnodular infiltration RML</td>
<td>BALF, hemoculture, Strongyloides infestation</td>
<td>Amphotericin B+ Itraconazole</td>
<td></td>
</tr>
<tr>
<td>10.</td>
<td>35 / M</td>
<td>Payao</td>
<td>Nontuberculous mycobacterium lymphadenopathy</td>
<td>Fever, cough, dyspea, neck mass, weight loss</td>
<td>Cervical lymphadenopathy</td>
<td>Localized alveolar infiltration RML</td>
<td>BALF</td>
<td>-</td>
<td>Amphotericin B+ Itraconazole</td>
</tr>
<tr>
<td>11.</td>
<td>45 / M</td>
<td>Payao</td>
<td>Non-Hodgkin's lymphoma</td>
<td>Cough, dyspea, neck mass, weight loss</td>
<td>Cervical lymphadenopathy, hepatosple-nomegaly</td>
<td>Diffuse reticulonodular infiltration</td>
<td>BALF</td>
<td>-</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>12.</td>
<td>44 / F</td>
<td>ChiangMai</td>
<td>N/A</td>
<td>Fever, chest pain, dyspea, weight loss</td>
<td>-</td>
<td>Localized alveolar infiltration left lung</td>
<td>Sputum</td>
<td>-</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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

Acknowledgements

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References

ปอดอักเสบจากเชื้อ Penicillium marneffei: รายงานผู้ป่วย 12 ราย

อรรถวุฒิ ดีสมโชค, สุรัตน์ ตันประเวช

บทนำ: เชื้อ Penicillium marneffei เป็นเชื้อราประจำถิ่นในเขตภูมิภาคเอเชียตะวันออกเฉียงใต้และภาคใต้ของประเทศสาธารณรัฐประชาชนจีน และเป็นสาเหตุของการติดเชื้อโดยโอกาสในผู้ป่วยที่ติดเชื้อ HIV โดยอาทาห์อาการและการแสดงทางปอด รวมทั้งความผิดปกติทางภาพรังสีทรวงอก แต่มีรายงานผู้ป่วยปอดอักเสบจากเชื้อรินี้เป็นจำนวนน้อย

วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิกของผู้ป่วยปอดอักเสบจากเชื้อ Penicillium marneffei ที่ได้รับการวินิจฉัยจากการตรวจเชื้อ

วัสดุและวิธีการ: เป็นการศึกษาข้อมูลผู้ป่วยที่ได้รับการวินิจฉัยจากเชื้อ Penicillium marneffei ที่ได้รับการวินิจฉัยจากโรงพยาบาลมหาวิทยาลัยนเรนทร์ (พ.ศ. 2542 - 2547)

ผลการศึกษา: มีผู้ป่วย 12 ราย (ชาย 8 ราย และหญิง 4 ราย) อายุเฉลี่ย 36.1 ปี มีการติดเชื้อ HIV ร่วม 9 ราย อาการนำของผู้ป่วยได้แก่ไข้, ไอ, หอบเหนื่อย และน้ำหนักลด อาการแสดงทางปอดได้แก่ รอยโรคที่ผิวหนัง, ตับโต และต่อมน้ำเหลืองโต เลือกของภาพรังสีทรวงอกพบมีลักษณะ diffuse reticulonodular, diffuse reticular, localized alveolar, localized reticuloid infiltration และ cavitary lesion

การวินิจฉัยได้จากการเพาะเชื้อจากเสมหะ 5 ราย และที่เหลือจากการเพาะเชื้อจากน้ำล้างปอด พบมีการติดเชื้อร่วมกันในเชื้อ Streptococcus pneumoniae, Klebsiella pneumoniae, Mycobacterium tuberculosis, Cryptococcus neoformans และ Strongyloides stercoralis ผู้ป่วยส่วนใหญ่ได้รับการรักษาด้วย Amphotericin B ซึ่งมีการเพิ่มDefaultValue ร่วมกับยาitraconazole หรือยาitraconazole อย่างเดียว

สรุป: ปอดอักเสบจากเชื้อ Penicillium marneffei มีลักษณะทางคลินิกที่ไม่ซ้ำกัน ในบางกรณีอาจแยกจากการติดเชื้อไวรัส HIV ได้ แพทย์ควรจะต้องมีการติดตามอาการติดเชื้อในกรณีนี้ในการวินิจฉัยแยกโรคโดยเฉพาะในผู้ป่วยที่มีภูมิคุ้มกันบกพร่อง