ORIGINAL ARTICLE

Clinical presentations and outcomes of *Penicillium marneffei* infections: a series from 1994 to 2004

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Objectives To describe the clinical presentation, management, and outcomes of patients with *Penicillium marneffei* infections in a regional hospital in Hong Kong.

Design Retrospective study.

Setting A regional and tertiary human immunodeficiency virus–referral hospital in Hong Kong.

Patients Those who had penicilliosis during the inclusive period January 1994 to February 2004.

Results Forty-seven immunocompromised patients (44 being human immunodeficiency virus–positive) with penicilliosis were retrospectively studied. Fever, malaise, and anaemia were the commonest presentations. Most diagnoses were obtained from blood cultures (83%) and lymph node biopsies (34%). Five (11%) died, death being attributable to penicilliosis; four (9%) of them had received no specific antifungal treatment due to late presentation and late diagnosis. The CD4 count of human immunodeficiency virus–infected patients upon diagnosis of penicilliosis was low (median, 20.0 cells/mm^3). Most (70%) patients received amphotericin B as an induction treatment, followed by oral itraconazole, although a smaller proportion (21%) received oral itraconazole only. All surviving human immunodeficiency virus–infected patients took highly active antiretroviral treatment and oral itraconazole as secondary prophylaxis after treatment of penicilliosis. The prognosis appeared satisfactory with early diagnosis and administration of appropriate antifungal therapy. Relapse ensued in two (4%) of the patients only.

Conclusion *Penicillium marneffei* infection in immunocompromised patients is a serious disease with significant mortality if not diagnosed early and treated with appropriate antifungal drugs. Simple investigations like blood culture enable the diagnosis in the majority of cases. Immunocompromised patients who have been successfully treated should receive oral itraconazole as a maintenance therapy to prevent relapse.

Key words
AIDS-related opportunistic infections; HIV infections; Immunocompromised host; Itraconazole; Penicillium

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Introduction

After the first report of the natural human infection in 1973,[1] *Penicillium marneffei* had been reported as an emerging pathogen for human immunodeficiency virus (HIV)–infected persons living in South-East Asia, including Thailand, Southern China, and Hong Kong.[2-5] Disseminated *P marneffei* infection has been classified as an AIDS-defining illness in Hong Kong,[6,7] and its incidence has increased in recent years,[5] ranking just after *Pneumocystis jiroveci* pneumonia (PCP) and tuberculosis.[8] It is also a common opportunistic infection in patients with advanced HIV disease in Thailand.[3] A recent history of exposure to soil, especially during the rainy season, was common, while exposure to bamboo rats has not been confirmed as a risk factor for the infection, although the fungus can also be isolated from these animals.[9] This infection has also been described in immunocompromised patients other than AIDS,[10] as well as in immunocompetent patients.[2] While amphotericin B followed by oral itraconazole is reported to be effective treatment,[11] up to 50% of AIDS patients had disease relapse after discontinuation of the antifungal therapy.[12] Although relapse can be prevented by secondary prophylaxis with oral itraconazole,[13] the possibility and timing for discontinuation for such treatment is not yet known. This retrospective study

青黴菌感染的臨床表徵及治療效果：1994至2004年的回顧研究

目的 描述香港一所分區醫院內，病人感染青黴菌後的臨床表徵、治療及治療效果。

設計 回顧研究。

安排 香港一所分區醫院及愛滋病轉介治療中心。

患者 從1994年1月至2004年2月期間，患有青黴菌感染的病人。

結果 分析了47名患有青黴菌感染的免疫缺乏病人的病歷，當中44名為愛滋病毒感染病人。研究結果顯示，最普遍的表徵是發燒、不適、貧血。大部份病人(83%)經血液培養診斷病原，另外34%病人經淋巴結活組織檢查斷症。當中5名病人(11%)死於青黴菌病，其中4人(9%)因遲發性表徵以致延遲診治及未能接受抗黴菌藥物治療。調查發現，愛滋病毒感染病人在確診感染青黴菌期間，CD4的讀數偏低（中位數為20.0/mm³）。治療方面，除21%病人只接受口服伊曲康唑（itraconazole）作為單一治療外，其餘大部份病人(70%)先接受兩性黴素(amphotericin B)作為抗黴菌藥療（誘導期的藥療），接着口服伊曲康唑。所有存活的愛滋病毒感染病人在接受青黴菌病治療後，再接受高活性抗逆轉錄病毒治療(HARRT)及口服伊曲康唑作為預防性藥療。研究發現，早期診斷及給予適當的抗黴菌藥療，只有兩個復發的病例(4%)，效果令人滿意。

結論 免疫缺乏的病人在感染青黴菌後，若未能及早診斷，給予適當治療，此病會是一種可致命的疾病。簡單的檢查如血液培養，可以確診大部份病患，另外，有免疫缺乏的病人在治療成功後，須繼續接受口服伊曲康唑作為長期預防性治療。

described the clinical presentation, management, and outcomes of patients with *P marneffei* infections in a regional hospital in Hong Kong.

Patients and methods

This 10-year retrospective review (from January 1994 to February 2004 inclusive) was conducted at the Queen Elizabeth Hospital (QEH), a 1700-bed regional hospital and tertiary referral centre for HIV-infected patients in Hong Kong. It also provides autologous bone marrow and renal transplantations. Cases of *P marneffei* infections were identified from the database of the Microbiology Laboratory in QEH and the Clinical Data Analysis and Reporting System of the Hong Kong Hospital Authority using the International Classification of Disease code of 118 (opportunistic mycoses). The clinical records of these patients were retrieved from the records office and analysed. Only cases with culture and/or pathological proof of *P marneffei* were included; cases with only a positive galactomannan antigen test (ie Pastorex Aspergillus test [BioRad, France]) were excluded. The Pastorex Aspergillus test is an agglutination test, which was originally designed to detect circulating galactomannan in patients with invasive aspergillosis.[14,15] A cross-reaction with *P marneffei* was observed due to common cell wall antigens with *Aspergillus fumigatus*.[16]

The following clinical information was obtained: demographic data; immune status; causes of immunosuppression if present; presenting symptoms; investigation results including CD4 cell count, microbiological and histopathological studies; choice and duration of antifungal therapy; clinical outcomes such as mortality, relapse, and length of hospital stay; the use and response to highly active antiretroviral treatment (HAART) in HIV-infected cases; as well as the use of secondary prophylaxis after treatment of the infection. Outcome of treatment was defined according to the classification used by Supparatpinyo et al.[17] Clinical response was defined as resolution of fever, skin lesions, and other symptoms and signs of *P marneffei* infection and absence of fungal growth in follow-up cultures. Failure was defined as no clinical improvement or deterioration of symptoms and signs of the infection and/or persistence of fungaemia during the course of treatment. Relapse of penicilliosis was defined as recurrence of symptoms and signs of the infection with isolation of the fungus after an initial clinical and microbiological response. Mortality was attributable to penicilliosis if death occurred within 14 days of diagnosis or if there were persistent positive fungal cultures at the time of death. An adverse outcome was defined as either the occurrence of death or relapse of the disease.

Penicilliosis was generally treated with intravenous amphotericin B, followed by oral itraconazole when conditions were stabilised. Sometimes oral itraconazole only was prescribed, mainly in patients who were stable and could be managed on an ambulatory basis. Discontinuation of secondary antifungal prophylaxis was considered in AIDS patients when their CD4 cell count rose and was persistently above 100 cells/mm³ and galactomannan serology became negative.[18,19]

Statistical analysis

Continuous data were expressed as mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical data were reported as numbers and percentages. Categorical variables were analysed by the Chi squared test or Fisher's exact test. Continuous variables were analysed by Mann-Whitney *U* tests. All statistical tests were two-sided, unless otherwise stated. P values of less than 0.05 were defined as significant. Data were processed with the Statistical

TABLE 1. Clinical manifestations in patients infected with *Penicillium marneffei* (n=47)

Symptom/sign	Patients No. (%)
Fever	45 (96)
Malaise	43 (91)
Anaemia	37 (79)
Lymphadenopathy	29 (62)
Cough	19 (40)
Hepatomegaly	13 (28)
Skin lesions	13 (28)
Diarrhoea	7 (15)
Splenomegaly	7 (15)

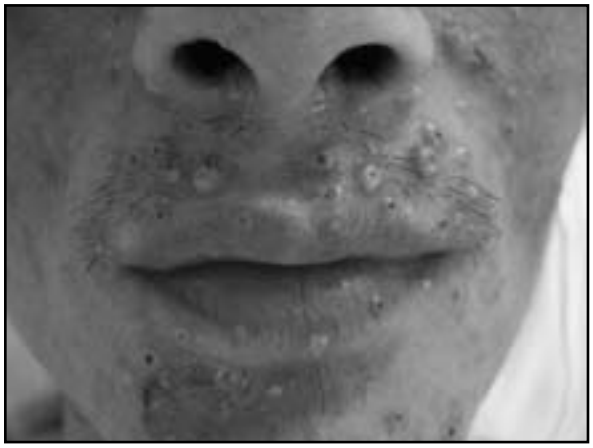

FIG. Papular skin lesions with central umbilication seen in a patient with penicilliosis

Package for the Social Sciences (Windows version 11.0; SPSS Inc, Chicago [IL], US).

Results

Forty-seven patients with *P marneffei* infections were identified from 1 January 1994 to 28 February 2004 inclusive. Twenty-nine patients were diagnosed in QEH, while the other 18 were diagnosed in other hospitals and referred to us for subsequent management. Most (96%) were males, 45 were Chinese and the remaining two were Thai and Nepalese. The mean age was 43 (SD, 12) years. All except one patient had a definite underlying immunocompromising condition. Forty-four (94%) were HIV-infected, while two (4%) were renal transplant recipients. The remaining patient had chronic hepatitis B infection with a very low absolute lymphocyte count upon admission (0.5 x 10^9 /L). HIV-antibody testing was not performed on this patient as he died shortly after admission and before the *P marneffei*–positive blood culture result was available. Thirty-four (77%) HIV-infected patients were first diagnosed to have HIV infection at the time of diagnosis of penicilliosis. The median duration of follow-up was 46 (IQR, 22.0-79.5) months. The median CD4 cell count of the HIV-infected patients when *P marneffei* infection was diagnosed was 20.0 cells/mm³ (IQR, 8.0-43.5 cells/mm³); 81% had counts lower than 50 cells/mm³ (reference range, 292-1366 cells/mm³). Only six (14%) of these patients were receiving HAART at diagnosis and all had therapy started for a few months only. Patients infected with HIV, who were not in receipt of HAART, were started on such therapy.

The commonest presenting features were fever (96%) and malaise (91%) [Table 1]. Anaemia was noted in 79% of patients; nearly half (43%) received blood transfusions because of severe symptomatic anaemia. The characteristic papular skin lesion with central umbilication was only seen in 28% of the patients (Fig), while lymphadenopathy was a common finding (62%). Radiographic abnormalities of the chest were noted in 21 (45%) of the patients; 17 had one abnormality and four had more than one (Table 2). In all, 57% of these immunosuppressed patients developed concurrent infections (Table 3); seven had more than one concurrent infection (4 had two and 3 had three). The mean haemoglobin level was 94 g/L (range, 42-149 g/L), the mean white cell count was 4.3 x 10^9/L (range, 0.6-10.4 x 10^9/L), and the mean lymphocyte count was 0.4 x 10^9/L (range, 0.1-1.0 x 10^9/L). The lactate dehydrogenase level was markedly elevated in most patients with a mean of 1599.4 IU/L (range, 263-18 720 IU/L) [normal range, 100-

TABLE 2. Radiographic abnormalities of the chest (n=21)

Radiographic findings	Patients No. (%)
Consolidation	8 (38)
Pleural effusion	6 (29)
Mediastinal lymphadenopathy	5 (24)
Nodules	4 (19)
Diffuse alveolar shadows	3 (14)

TABLE 3. Concurrent infections (n=27)

Concurrent infection	Patients No. (%)
Oral candidiasis	10 (37)
Tuberculosis	7 (26)
Herpes zoster	6 (22)
Pneumocystis jiroveci pneumonia	3 (11)
Oesophageal candidiasis	3 (11)
Cytomegalovirus infections	3 (11)
Salmonella bacteraemia	2 (7)
Cryptococcal infection	1 (4)
Cyclospora infection	1 (4)

TABLE 4. Sites of *Penicillium marneffei* isolation

Site of isolation	Patients No. (%)
Blood culture	39 (83)
Lymph node biopsy	16 (34)
Bone marrow aspiration	8 (17)
Respiratory specimens	5 (11)
Skin biopsy	3 (6)
Colon biopsy	2 (4)
Peritoneal fluid	1 (2)
Urine	1 (2)
Nasopharyngeal	1 (2)

190 IU/L]. Seventeen (36%) of patients had deranged liver function, with a mean alanine aminotransferase level of 54 IU/L (SD, 36 IU/L).

In most cases (39 patients, 83%) the diagnosis was obtained from blood cultures, followed by lymph node biopsy (16 patients, 34%) and bone marrow aspiration (8 patients, 17%) [Table 4]. The organism was isolated from more than one source in 26 (55%) of the patients. Among the 34 patients who had blood tested for galactomannan antigen, 27 (79%) had positive results with a median titre of 1:8 (range, 1:1-1:1280).

Clinical response was observed in all of the 43 patients given antifungal treatment. The remaining four (9%), including two HIV-infected and two non-HIV–infected patients, had not received any antifungal therapy, since they died before the diagnosis of *P marneffei* infection was made. While most (33 patients, 70%) received intravenous amphotericin B as the induction therapy (amphotericin B group), 10 (21%) patients received only oral itraconazole as treatment (itraconazole group). The mean duration of amphotericin B therapy was 14 (SD, 7; range, 1-29) days. There were no important differences in the clinical characteristics and outcomes between the two treatment groups except that the itraconazole group had slightly higher median baseline CD4 cell counts and a significantly shorter hospital stay than the amphotericin B group (P=0.029) [Table 5]. All surviving patients who received amphotericin B as an induction therapy were subsequently switched to oral itraconazole as the maintenance therapy. Secondary prophylaxis with oral itraconazole was given to all patients after successful initial treatment.

Six patients died, including four (9%) of 44 patients who were HIV-infected and two of the remaining three. Five of these deaths were attributable to *P marneffei* infection; four died shortly after admission and hence only one had received antifungal therapy. The death of the sixth patient was due to the disseminated *Mycobacterium avium complex* infection acquired a few years after the diagnosis of *P marneffei* infection. Two (4%) patients presented with relapse of the infection after successful initial treatment. One had repeated relapses after switching to oral itraconazole, despite initial success with intravenous amphotericin B. Poor drug compliance was subsequently identified as the underlying reason. The other suffered from disease relapse 5 years after discontinuation of itraconazole prophylaxis, when his CD4 count rose after institution of HAART.

Discussion

Penicillium marneffei mainly affects patients with impaired cellular immunity, particularly those with HIV infection. It has also been reported in those with

TABLE 5. Comparison of clinical characteristics and outcomes between patients who received amphotericin B followed by itraconazole and those who received itraconazole only

Characteristic/outcome	Amphotericin B (n=33)	Itraconazole (n=10)	P value
No. of male	33 (100%)	9 (90%)	0.23
HIV/Non-HIV*	32/1	10/0	1.00
Mean (SD) age (years)	44 (12)	36 (9)	0.06
No. with fungaemia	27 (82%)	8 (80%)	1.00
Mean (SD) haemoglobin level (g/L)	95 (23)	94 (27)	0.94
Mean (SD) total white cell count (x 10^9/L)	4.0 (2.6)	4.0 (2.26)	0.99
Mean (SD) lymphocyte count (x 10^9/L)	0.4 (0.3)	0.5 (0.2)	0.19
Mean (SD) lactate dehydrogenase (IU/L)	915 (768)	915 (242)	0.99
Mean (SD) alanine aminotransferase (IU/L)	56 (37)	57 (37)	0.94
Median (IQR) baseline CD4 count (/mm^3)	13 (8-28)	39 (18-60)	0.038
Deaths attributable to infection	2 (6%)	0	1.00
Disease relapse	2 (6%)	0	1.00
Mean hospital stay (days)	26	12	0.029

* HIV denotes human immunodeficiency virus

other immunocompromised states, such as those with haematological malignancies and diabetes mellitus.[10] In HIV-infected patients, it usually occurs at the advanced stage, when the CD4 cell count falls below 100 cells/mm³.[13] This also happened in our patients, although one of them had a CD4 cell count of 190 cells/mm³ at presentation.

As in other series,[2,3] many presenting symptoms of our patients such as fever, cough, and malaise were non-specific. Although skin papules with central necrotic umbilications had been described to be characteristic in almost 80% of patients with disseminated disease in Thailand and India,[3,20] such lesions were found in less than one third in our series. The extent of dissemination of the disease could not explain this observed difference, as our patients had a very high incidence of fungaemia and most had *P marneffei* isolated at more than one site. Ethnic and geographical differences could possibly account for the variations noted in the mucocutaneous manifestations noted in HIV infection.[21] However, in this retrospective study, limitations such as suboptimal documentation in the case notes might have confounded the reliability of our findings and underestimated the true incidence of such lesions. Culture[3,11] or direct fungal staining[22] of skin scrapings have been demonstrated to offer very high diagnostic yields of *P marneffei*. As with the other studies,[3] respiratory symptoms and abnormal chest radiographs were commonly encountered in our patients. Reported radiographical abnormalities are quite variable; apart from localised infiltrates, reticulonodular and diffuse alveolar shadows, pleural effusions,[3] and lung mass have been reported as presenting radiological features.[23] However, as in those who are immunocompromised, the possibility of concurrent pulmonary infections such as bacterial pneumonia, pulmonary tuberculosis or PCP should also be considered. In HIV-infected patients, a variety of lower respiratory disorders can be present, which could be affected by different HIV-disease stages and transmission categories.[24] Recognition of the common clinical presentations in an immunocompromised patient should alert clinicians to the existence of *P marneffei* infection and prompt investigations accordingly.

Almost half of our patients received blood transfusions because of severe symptomatic anaemia. Transfusions are typically given to those with a haemoglobin level below 7 g/L, while they might also be considered for anaemic symptoms in those with higher levels (7 to 10 g/L). A high incidence of anaemia was also consistent with the results of another series of 155 patients.[2] Bone marrow involvement may partly explain why severe anaemia was frequently observed in patients with disseminated infection,[25] consistent with the claim that bone marrow aspiration was the most sensitive means of diagnosis.[3] However, less than half (8/18 patients, 44%) of our patients who had undergone bone marrow aspiration were bone marrow–positive. Nor did marrow aspiration aid in the diagnosis in another series with negative blood cultures.[26] In our patients, the lymph node was found to be another useful source for arriving at a diagnosis, presumably because lymphadenopathy is a common clinical presentation in *P marneffei* infections and fine needle aspiration has been shown to be a simple yet useful diagnostic tool.[27]

Almost 80% of our HIV-infected patients had positive results from Pastorex Aspergillus testing. A cross-reacting monoclonal antibody (EB-A2) employed in the kit reacts with common cell wall antigens of *A fumigatus* and *P marneffei*.[16] As a result, false-positive results can be obtained in patients suffering from invasive aspergillosis.[28] Fortunately, invasive aspergillosis is infrequently found in HIV-infected patients.[28,29] By contrast, an antigenic cell wall mannoprotein (Mp1p) of *P marneffei* appears to be a promising focus of diagnosis,[30] offering good sensitivity and specificity in the detection of the infection.[31] An enzyme-linked immunosorbent assay (ELISA)–based antibody test with Mp1p has also been developed, and in HIV-infected patients, it has a sensitivity of 82% and specificity of 100%.[32] The combined antibody and antigen tests provide a sensitivity of 88%, a positive predictive value of 100%, and a negative predictive value of 96%. In addition, the Mp1p antigen–based ELISA can offer quantitative results, which might be useful in monitoring the fungal load and the host's ability to clear the fungal antigen. Modification of the test to provide a more convenient diagnostic kit could be useful for the rapid diagnosis of *P marneffei*.

The reported mortality rates of disseminated penicilliosis had been high[33,34]; about 75% in those whose diagnosis and treatment was delayed.[3] All of our patients who succumbed had not received timely antifungal therapy due to delayed presentation or diagnosis. On the contrary, outcomes appeared satisfactory in those who could be diagnosed sufficiently before death to receive appropriate antifungal therapy. The same reason might explain the seemingly better treatment responses in our patients, compared to results reported by Supparatpinyo et al[3] despite the similar baseline CD4 cell counts in the two study populations. A high clinical suspicion and timely ordering of appropriate investigations such as blood cultures and galactomannan antigen testing can enable clinicians to make an early diagnosis and achieve a better outcome with early and appropriate antifungal therapy.

Although susceptibility testing to antifungal agents is not standardised for the dimorphic fungus, some studies have demonstrated very good in-vitro susceptibilities of *P marneffei* isolates towards 5-flucytosine, miconazole, ketoconazole, and

itraconazole.[17] While fluconazole was the least active and should not be used in treatment, amphotericin B showed intermediate antifungal activity. Itraconazole should be considered as the drug of choice in mild to moderately severe *P marneffei* infections, while intravenous amphotericin B may be required for seriously ill patients.[17] Two weeks of intravenous amphotericin B (0.6 mg/kg/day) followed by 10 weeks of oral itraconazole 200 mg twice daily has been used in disseminated infections in AIDS patients, giving a response rate of 97%.[11] Fever and clinical parameters resolved within the first 2 weeks and no serious adverse drug effects were observed. This was also the treatment approach in most of our patients. Although oral itraconazole alone therapy has also been used with some success,[12] only one quarter of our patients were managed with this regimen. Apart from having a shorter hospital stay in those who received itraconazole alone, there was no significant difference between our two treatment groups, in terms of mortality and relapse rates. However, it is possible that patients with more severe infections who received amphotericin B would have required longer hospital stay due to the gravity of their illnesses. As it has been noted that a good in-vitro and in-vivo response ensues with the use of itraconazole,[17] use of this agent alone without amphotericin B seems a logical alternative. Our study was limited by small patient numbers in each group. Thus, the fact that no statistically significant difference in outcomes may be misleading. In future, randomised controlled studies would be conducted to compare the effectiveness of these two regimens.

Up to 57% of HIV-infected patients with initially successful treatment had a relapse within 6 months of discontinuing the antifungal therapy.[12,13] In a double-blind trial of 71 HIV-infected patients, none of the 36 patients who received itraconazole as a maintenance therapy experienced a relapse of *P marneffei* infection within 1 year, whereas 57% of those in the placebo arm developed a relapse.[13] It is therefore recommended that HIV-infected patients with penicilliosis should receive long-term secondary prophylaxis with oral itraconazole at a dose of 200 mg once daily,[13,19] which was also the practice in all of our HIV-infected patients.

Conclusion

Penicillium marneffei infection in immunocompromised patients is a serious disease with significant mortality if the diagnosis is not made early and timely appropriate antifungal therapy is not given. Many of the presenting features are relatively non-specific. While simple investigations like blood culture enable diagnosis in the majority of cases, the development of specific antigen or antibody tests could be helpful, if methodology could be modified into more convenient diagnostic kits. In general, either amphotericin B or oral itraconazole can be used as induction agents for the treatment of disseminated *P marneffei* infection, although the former should be considered in the critically ill. Clinically stable patients can be treated with oral itraconazole and managed in out-patient settings. Immunocompromised patients who have been successfully treated should receive oral itraconazole as the maintenance therapy to prevent relapse.

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