

## Case Report

# A case series of cutaneous *Penicillium marneffe* infection with dissemination

## 皮膚馬爾尼菲青黴菌感染與播散的病例系列

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Penicilliosis is an infection caused by *Penicillium marneffe*, which is an opportunistic fungal pathogen endemic in areas such as Southeast Asia. It is usually found in patients infected with human immunodeficiency virus (HIV). *P. marneffe* is present in soil and is also associated with bamboo rats. Patients with AIDS are particularly susceptible to infection. Thus, penicilliosis is an important differential diagnosis in immunocompromised patients with an acneiform eruption. Early detection and diagnosis can improve the outcome for these patients. We report a case series of two HIV patients with disseminated *P. marneffe*, who presented with acneiform eruptions, and discuss the relevant literature.

青黴菌病是一種由馬爾尼菲青黴菌引起的感染，該真菌為機會性真菌病原體，流行地區包括東南亞國家，並常見於愛滋病病毒感染者。馬爾尼菲青黴菌一般存在於土壤中，竹鼠體內亦有發現。愛滋病患者特別容易受其感染，所以在免疫功能低下患者的痤瘡狀發疹中，青黴菌病是一個重要的鑑別診斷。透過早期的檢測和診斷，患者病情可得到理想改善。我們報告一系列兩名愛滋病病毒感染者併發播散性馬爾尼菲青黴菌感染，表現為痤瘡狀發疹，並討論相關文獻。

**Keywords:** Acneiform eruptions, AIDS, human immunodeficiency virus, infection, *Penicillium marneffe*

**關鍵詞：**痤瘡狀發疹、愛滋病、人類免疫力缺乏病毒、感染、馬爾尼菲青黴菌

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## Introduction

*Penicillium marneffe* is an infectious pathogen that is usually found in patients with human immunodeficiency virus (HIV). Multiple skin-coloured or erythematous papules with central necrosis over the face are the most common clinical presentation of cutaneous penicilliosis, and dissemination may be life-threatening. Early detection in laboratory tests and early treatment can improve patient outcomes. Systemic amphotericin B is the most effective treatment agent for dissemination of *P. marneffe*.

## Case 1

The first case was a 48-year-old single cook, who had had sexual intercourse with different partners for several years. He presented with poor appetite, weight loss (15 kg in 2 months) and an intermittent low-grade fever, which he had had for two months. He denied drug abuse, smoking, alcohol, or betel nut use. He also denied any medical systemic disorders. He went to a local hospital where panendoscopy revealed oesophageal candidiasis and gastric ulcers. In addition, an HIV antibody test was positive. He was then transferred to a medical centre in central Taiwan for further survey and management, where laboratory data showed HIV positivity on Western blot test, reactive rapid plasma reagin (RPR) 1:4 dilution, and *Treponema pallidum* haemagglutination (TPHA) 1:80. Though leucopenia was not noted, the level of CD4-helper/inducer cells was only 3% (42 cells/cumm (23.1-51.0%)), the level of CD8-suppressor/cytotoxic cells was 85% (1150 cells/mm<sup>3</sup> (17.9-47.5%)), and the CD4/CD8 ratio was 0.036 (0.5-1.8), which were indicative of AIDS infection. A few days later, bilateral lower limb weakness developed. Laboratory results showed positivity for cytomegalovirus (CMV) PCR, with a high suspicion of CMV neuropathy and myopathy. The patient was then transferred to our medical centre where he received an 18-day course of valganciclovir, after which his symptoms of limb weakness subsided. Five days prior to this admission, multiple acneiform lesions developed over his whole face. A dermatologist was consulted, and physical examination revealed multiple asymptomatic pink to reddish papules (3-5 mm) with central necrotic dark-reddish craters over the whole face which were preceded by intact tiny reddish papules (Figure 1a). As the patient was immunocompromised, the clinical differential diagnosis included *Molluscum contagiosum* infection, cryptococcosis, penicilliosis, histoplasmosis, and coccidioidomycosis. A skin biopsy was performed, with fungal culture done for one of the skin lesions. The histopathological examination revealed mixed cell

granulomatous inflammation with focal necrosis. There were many foamy histiocytes with basaloid inclusions, which contained nuclei and binary fissures (Figures 2a & 2c). Periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) stains revealed microorganisms with binary fission (Figures 3a & 3b). Three sets of fungal cultures of blood yielded *P. marneffeii*, which was consistent with the colony morphology on Sabouraud dextrose agar and the hyphae morphology on slide cultures stained with lactophenol blue (Figures 4a-c). A fungal culture of the skin biopsy yielded *P. marneffeii*. Sputum and blood tuberculosis (TB) cultures were negative. After confirming the diagnosis of AIDS with disseminated *P. marneffeii* infection, amphotericin B at 0.6 mg/kg/day intravenously for two weeks was prescribed and highly active antiretroviral therapy (HAART) was initiated. The patient was discharged after successful treatment and given oral itraconazole at 400 mg/day for 10 weeks. He has had no recurrence of skin lesions since then.

## Case 2

The second case was a 48-year-old man with a past medical history of hypertension which was under medical control. He presented with poor appetite and weight loss (17 kg in six months), nights, general weakness, sour taste, mild dry cough, mild chest discomfort and dysphagia. A chest radiograph revealed increased infiltration with miliary nodules over bilateral lung fields, and chest computed tomography showed mediastinal lymphadenopathy, multiple nodules, and tree-in-bud-like lesions in bilateral lungs. The patient was newly diagnosed with AIDS (CD4 count 15/mm<sup>3</sup> and virus load 396,000 copies/mL and syphilis (TPHA 1:2560, RPR 1:32 dilution), and he was admitted for treatment of pneumonia a few days later. He received wedge resection of the lung, and the pathology report showed *Pneumocystis jirovecii* pneumonia and CMV pneumonitis. The intravenous form of ganciclovir was given for three weeks, and was then changed to oral

valganciclovir. However, an intermittent fever with multiple asymptomatic pea-sized erythematous papules and pustules with central umbilication over his face were noted (Figure 1b). A skin biopsy revealed ulceration of the epidermis and frothy exudates in the dermis admixed with neutrophils and PAS-positive yeast (Figure 2b). Fungal cultures of the lung tissue, skin biopsy and a blood culture yielded *P. marneffe*. Under the impression of fungaemia with *P. marneffe*, he was treated with the intravenous form of amphotericin B for two

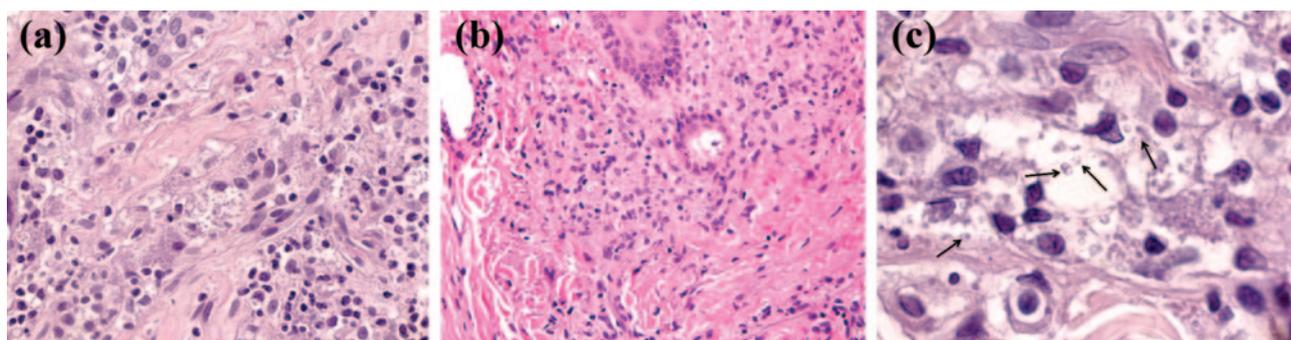
weeks and started on HAART, after which his skin condition improved. After successful treatment, he was discharged and given oral itraconazole 200 mg b.i.d. for about 10 weeks.

## Discussion

Penicilliosis, which is caused by the fungal pathogen *P. marneffe*, has emerged as the third most common opportunistic infection worldwide,



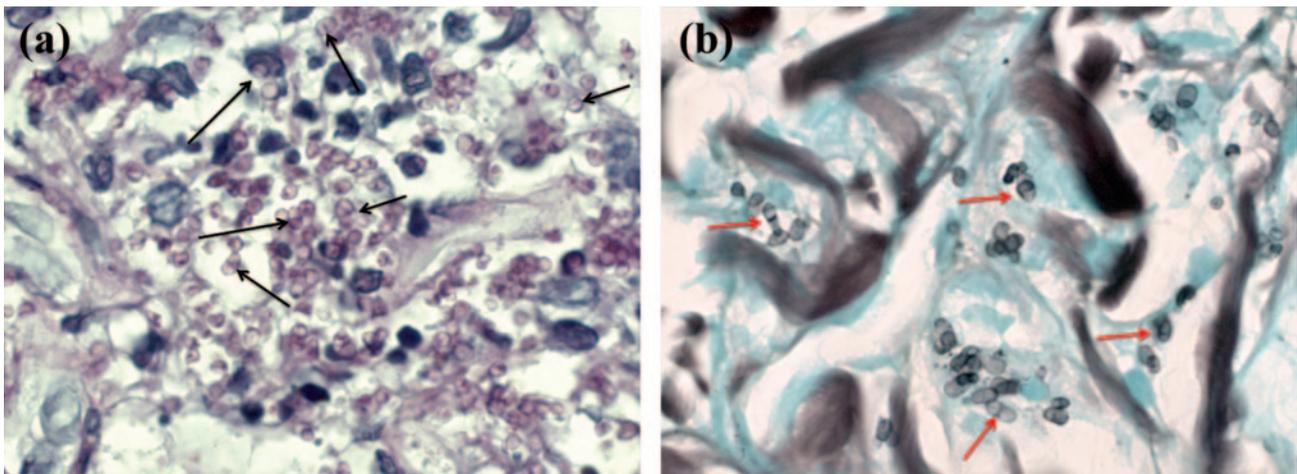
**Figure 1.** Multiple asymptomatic variable-sized (2-5 mm) pink to reddish papules with central necrotic dark-reddish craters over the whole face (preceded by intact tiny reddish papules) (a) Case one, (b) Case two.



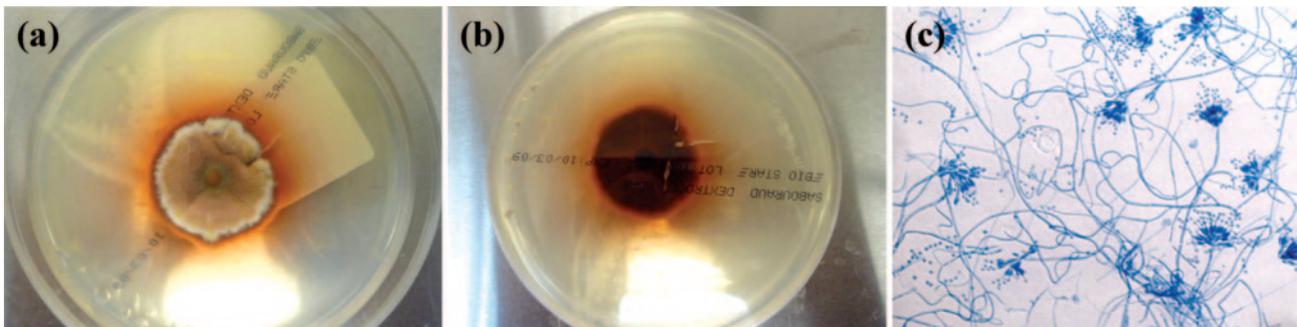
**Figure 2.** (a) Case one; many foamy histiocytes with basaloid inclusions, which contained nuclei and were admixed with neutrophils in the dermis (H&E original magnification, x400). (b) Case two; frothy exudates in the dermis admixed with many microorganisms and neutrophils (H&E original magnification, x400). (c) Binary fission features in a high power field (H&E original magnification, x600).

after extrapulmonary tuberculosis and cryptococcosis in AIDS patients. People with CD4 cell count  $<100$  cells/ $\mu\text{L}$  are at particular risk in Southeast Asia.<sup>1</sup> The endemic areas include Thailand, northern India, Vietnam, Hong Kong, southern China and Taiwan.<sup>2</sup> A study in Thailand reported that 3% of 3054 AIDS patients had *P. marneffei* infection.<sup>3</sup> *P. marneffei* is usually transmitted by inhalation of conidia from environmental sources, such as soil, into the lungs, followed by localised or disseminated pulmonary infection leading to fever, anaemia, weight loss, fungaemia and generalised lymphadenopathy. Previous studies showed that HIV infection was the most common underlying disease of *P. marneffei* infection (87.72%) and penicilliosis occurred rarely in otherwise healthy persons. A

detailed history of the immunological status of patients with penicilliosis is needed, including previous infections, autoimmune manifestations, family history, even a basic panel of immunological evaluations for patients with penicilliosis, including immunoglobulin patterns (IgG, IgA, IgM, and IgE), a lymphocyte subset, nitroblue tetrazolium test or dihydrorhodamine test, and interferon- $\gamma$  autoantibody test.<sup>2,4</sup> Penicilliosis occurs in patients with immunodeficiency secondary to diabetes mellitus, immunosuppressive therapy, solid organ or haematopoietic stem cell transplant, and primary immunodeficiency disorders, including severe combined immunodeficiency, common variable immunodeficiency, hyper-IgM syndrome, hyper-IgE syndrome, and congenital neutropaenia.<sup>4</sup>



**Figure 3.** (a) PAS stain (original magnification, x600). (b) GMS stain (original magnification, x600).



**Figure 4.** (a) Colony morphology on Sabouraud dextrose agar, obverse. (b) Colony morphology on Sabouraud dextrose agar, reverse. (c) Hyphae morphology on a slide culture stained with lactophenol blue (original magnification x400).

Moreover, STAT1 gene mutations, which mediate signalling in innate immune defense against *P. marneffe*, were recently identified in patients with penicilliosis.<sup>4</sup> More than 50% of AIDS patients with this infection have been reported to have multiple umbilicated papules (which may be enlarged with central ulceration) that are similar to cryptococcosis or histoplasmosis.<sup>5,6</sup> Approximately 70% of infected patients present with typical skin lesions, papules with central umbilication resembling molluscum contagiosum. Other presentations include Sweet's syndrome, which is more common in HIV negative patients, pustular psoriasis, chronic ulcer, subcutaneous nodules, subcutaneous abscess and panniculitis.<sup>6</sup> Some case reports have also described rare atypical presentations such as verrucous lesions and generalised skin rash.<sup>7,8</sup> *P. marneffe* can disseminate into organs as intracellular yeasts from the reticuloendothelial system.<sup>2</sup> It is usually widespread on the face and trunk, and can even affect the lungs, spleen, liver, lymph nodes and bone marrow.<sup>9</sup> It remains an important cause of morbidity and mortality in patients with HIV. According to one study, there were 24 cases of penicilliosis diagnosed in Taiwan between 1987 and 1998, of which 67% occurred in patients with AIDS and 83% cases had dissemination. The majority (63%) of cases were considered to be indigenous. The number of cases increased markedly in the last two years of the study period, with 17 of the 24 cases diagnosed between 1996 to 1998, implying that it is an emerging pathogen in Taiwan.<sup>10</sup> According to a literature review, which documented 125 cases between 1984 and 2009, penicilliosis is increasing exponentially.<sup>2</sup> With regard to histology, a granulomatous response is minimal or absent. Necrosis with perivascular inflammatory cell infiltration is occasionally found. *P. marneffe* is a dimorphic pathogen, which grows filamentously at room temperature (25°C) (mold phase) and in a uninucleate yeast form, that reproduces by fission at body temperature (37°C).<sup>11</sup> Its small spores (2~4 µm) are seen most clearly under GMS stain, and a distinct finding is that the spores divide by binary fission (transverse

septum).<sup>12</sup> These characteristics can be used to differentiate it from *Histoplasma* infection, which exhibits narrow-necked unequal budding with a clear halo (pseudocapsule) in histopathology, and from *Leishmania* infection which exhibits kinetoplasts distinctly seen under Giemsa and GMS staining, but negative under PAS staining.<sup>12</sup> The colony cultured on Sabouraud dextrose agar at 25-27°C for 14 days is initially white and pannaose, gradually turning in colour from yellow to yellow-green diffused with a deep red pigment produced by *Penicillium* conidiophores. The conidial heads are divergent, and the chains of conidia are formed from phialides.<sup>13</sup> The colony on brain-heart infusion agar at 35°C for seven days has a greyish white, membranous yeast-like form with fine plicae.<sup>12</sup> In treatment of severe cases, systemic intravenous amphotericin B 0.6 mg/kg/day for two weeks and oral itraconazole 400 mg/day for 10 weeks should be used.<sup>14</sup> There was no significant difference in the rates of favourable outcome between patients treated with intravenous amphotericin, oral itraconazole, or intravenous amphotericin followed by oral itraconazole.<sup>2</sup> Supparatpinyo et al. reported that the failure rate of treatment, which was defined as a lack of clinical response or persistent fungemia, was 22.8% for amphotericin B, 63.6% for fluconazole, 25% for itraconazole, and 100% for no treatment.<sup>15</sup> In a survey in mainland China, 569 cases who received antifungal therapy had a mortality of 24.3% and 99 cases who had not received antifungal therapy had a mortality of 50.6%.<sup>2</sup> For early detection of penicilliosis by immunological methods, the double-antigen sandwich ELISA shows a high specificity in detecting Mp1p-specific antibody. Simultaneous detection of Mp1p antigen and antibody increases the diagnostic sensitivity for penicilliosis.<sup>16</sup>

## Conclusion

In conclusion, persistent high fever uncontrolled by antibiotics in immunocompromised patients in

endemic areas should alert physicians to the possibility of *P. marneffe* infection. In our two middle-aged immunocompromised patients, the skin presentations were similar with acneiform eruptions on the face, even though they were of a different size; however, different clinical courses revealed the same infectious pathogen, *P. marneffe*. For dermatologists, *P. marneffe* infection should be considered in the differential diagnosis of patients with these similar symptoms. Both patients were treated successfully, most likely due to early recognition of the pathogen and sufficient treatment. It is important for clinicians to keep in mind that *P. marneffe* is an increasingly prevalent causative agent in immunocompromised patients. Early detection and early initiation of treatment may be life-saving.

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