Cutaneous penicilliosis due to penicillium marneffei infection in human immunodeficiency virus infected patients

F A Karo, T Kembaren, R Saragih, E Sembiring, F Ginting, and Y Ginting

1Division of Tropical Medicine and Infectious Diseases, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
2Haji Adam Malik General Hospital, Medan, Indonesia
3Dr. Pirngadi General Hospital, Medan, Indonesia

Corresponding author: fitri_armanti@yahoo.co.id

Abstract. *Penicillium marneffei* is an important cause of morbidity and mortality in HIV-infected and other immunosuppressed. The diagnosis of penicilliosis should be considered in patients who live in or are from Southeast Asia who present with fever, weight loss, nonproductive cough, skin lesions, hepatosplenomegaly, and/or generalized lymphadenopathy. Cutaneous penicilliosis lesions commonly appear on the face, ears, extremities, and occasionally the genitalia and are most commonly papules with central necrotic umbilication. We reported a 25-year-old male patient in Adam Malik General Hospital on April 26th 2017 with of recurrent episodes of coughing and fever for 1 month. The patient had multiple papules in his skin which began to appear 3 months ago, which were soft, flocculating and tender, and yellow-whitish fluid oozed out when the papules became ulcerated. No specific allergic history or recent medication were reported. He had been diagnosed with HIV and Tuberculosis, and had received anti-retroviral and anti-tuberculosis therapy. Physical examination: multiple generalised subcutaneous nodules were seen on the face, ear, chest, abdomen and the extremities with purulent secretions. Laboratory examination: CD4+ T lymphocytes 64 cells/μL. Biopsy of the skin lesions confirmed penicilliosis, with the culture showing *Penicillium marneffei*. The patient completely recovered after being prescribed Itraconazole.

1. Introduction

Penicilliosis marneffei is a lethal form of systemic fungiosis due to *Penicillium marneffei*. With its recent upright trend in incidence, the disease has emerged as a serious public health concern in Southeast Asia and its incidence has reached 12.3% in some regions in China. Penicilliosis marneffei is more common in immunocompromised hosts; in Thailand, it ranks third in opportunistic infections behind tuberculosis and cryptococcosis in patients with acquired immunodeficiency syndrome (AIDS).[1]

Most cases of penicilliosis are observed in patients who have CD4 T lymphocyte (CD4) cell counts <100 cells/μL. The infection is associated with a high mortality rate if timely treatment with appropriate antifungal drugs is not administered.[2]

No data are available on acquisition and transmission of penicilliosis. However, like histoplasmosis, it is believed to be acquired by inhalation of microconidia from the mycelial phase of the organism. Reactivation of a silent focus of infection that was acquired years earlier can occur when cellular immunity wanes and it is the presumed mechanism for disease occurrence in...
nonendemic areas. Evidence exists for seasonality in penicilliosis infections; increased cases have been noted during the rainy months.[1,2]

However, it is extremely rare to find Cutaneous penisilliosis due to penicillium marneffei infections. Here we report on the case of Penisilliosis in HIV-infected who had been living in the endemic area. The infection was confirmed as penicilliosis through fungal culture.

2. Findings
We reported a 25-year-old male patient was admitted to Adam Malik General Hospital on april 26th 2017 because of recurrent episodes of coughing and fever for 1 month. The cough, which started 1 month ago, was irritating and nonproductive. The body temperature reached as high as 39°C. This is experience by patients since 2 weeks before entering the hospital. History of fever before was found since 3 months ago. The patient toldthat he had multiple papules in his all of skin began to appear 3 months ago, which were soft, flocculating and tender, and yellow-whitish fluid oozed out when the papules became ulcerated. Multiple papules firstly appeared on the chest, abdomen and the extremities and spread to all skin. No specific allergic history or recent medication were reported. He had been diagnosed with HIV in 1 year and Tuberculosis in 2 months, and received anti-retroviral and anti-tuberculosis therapy at other hospitals before admission to our hospital, but showed no clearly improvement with his complaint. His body weight decreased 15 kg in 3 months. He denied drug use and contact with pets or rats. He denied about his any history of homosexual contact.

On Physical examination findings were as follows: sensorium alert, blood pressure 130/80 mmHg, pulse 92 times/min, regular, respiration, 22 times/min, body temperature, 38.4°C. Multiple generalised papules were seen on the face, ear, chest, abdomen and the extremities with purulent secretions. Pale conjunctiva and icteric sclera was not found. Increased of jugular vein pressure was not found. There was no palpable lymphadenopathy, his chest was clear and his abdomen was soft and non-tender with no organomegaly. The heart and liver were normal. From extremities : multiple papules was seen, oedema pretibial was not found on both leg.

From electrocardiographic examination shows sinus tachycard. Examination of chest Xray with normal chest. Upon laboratory examination, his complete blood cell counts were:hemoglobin 13.0 g/dL, white blood cell count 9420/µL (neutrophil 64.40%, lymphocytes 21.10%), and platelet 382,000/µL, Ureum: 30mg/dL ; Creatinine: 1.04 mg/dL. Natrium: 134 mEq/L; Kalium: 4.4 mEq/L; Cloride: 101 mEq/L; Peripheral CD4+ T lymphocyte count were 64 cells/µL. AST: 57 U/L; ALT: 50 U/L; HbsAg and Anti HCV: non reactive, respectively. Considering the typical skin lesions and fungal organisms in the biopsy, a Penisillium marneffei infection was suspected.

We started oralItrakonazole for 400mg/day, antiretroviral including tenofovir, lamivudine and evafirenz and anti-tuberculosis medications including isoniazid, rifampin, ethambutol and pyrazinamide, antipiretic including paracetamol, and for the cough used N-acetyl systein.

After 5 days oral Itraconazole administration, the patient exhibited clinical improvement in his skin. The patient go home without complaint and continue therapy at home.
Figure 1. Skin lesion of a HIV-infected patient with *Penicillium marneffei* infection.

3. Discussion

*P. marneffei* was first isolated from the bamboo rat (*Rhizomys sinensis*) in Vietnam in 1956. Most patients have constitutional symptoms with fever, weight loss and malaise. Skin manifestation such as subcutaneous abscesses and papule-like ulcers may be present.\[3,4\] Molluscum-contagiosum-like lesion is not infrequent. It is common to have signs and symptoms reflecting involvement of reticuloendothelial system including anaemia, hepatosplenomegaly and lymphadenopathy. Respiratory involvement is often present, with productive cough, dyspnoea and haemoptyisis. Chest X-ray may show diffuse reticular infiltration, localized alveolar infiltrates or cavitary lesion.\[4\] Diarrhoea is not
uncommon and sometimes may be bloody. The infection may rarely present as acute abdomen.[5] Other presenting symptoms include osteoarthritis, genital ulcers and oral lesions.[6]

In this case, the 25 years old man complaint recurrent episodes of coughing and fever for 1 month, weight loss, and general skin papules.

*P. marneffei* mainly affects people with impaired cellular immunity (i.e. HIV-infected patients) [8] and the severity and clinical manifestations depend on the patient’s immunity.[9] In patients with normal immunity, *P. marneffei* mostly causes mild and localized infections, but it can cause severe disseminated infections with generalized lymphadenopathy and persistent fever in immunocompromised HIV-infected patients.[7] It is known that the prognosis of penicilliosis can be improved if immunity could be recovered during the antifungal treatment in immunocompromised patients.[9,10]

Skin lesions present as multiple fleshcolored, dome-shaped papules in the early stage, similar to molluscum contagiosum.[13] However, simple papules observed on the face, trunk, neck and extremities frequently ulcerate over time and change with central necrotic umbilication.[11,12] Molluscum contagiosum resolves by itself in six months to two years in HIV-infected patients in accordance with immune function improvement after ART. But skin lesions of *P. marneffei* are not expected to improve without active antifungal treatment.

In this case, The HIV infected patient had multiple papules in his all of skin, which were soft, floculating and tender, and yellow-whitish fluid oozed out when the papules became ulcerated. Multiple papules firstly appeared on the chest, abdomen and the extremities and spread to all skin. There was no palpable lymphadenopathy, his chest was clear and his abdomen was soft and non-tender with no organomegaly. He had mild and localized infections.

Penicilliosis is mostly seen in late HIV infection with CD4+ count less than 100/uL. Up to 80% or more of the cases have CD4+ count below 50/uL.[8]

In this Case, on laboratory examination, the average number of CD4+ T lymphocytes at presentation is 64 cells/uL.

The gold standard for diagnosis of penicilliosis marneffei is identification of *P. marneffei* by fungal culture by culture of the fungus from blood, skin biopsy, bone marrow, or lymph nodes. However, given the need for early treatment, a presumptive diagnosis can be made by demonstrating the characteristic morphologic findings of this fungus in biopsy material or in blood smears of patients with fungemia.[14,15] *P. marneffei* appear as oval or elongated yeast-like organisms with a clearly defined central septum. The presence of a centrally located transverse septum (eg, "cross wall") differentiates *P. marneffei* from *Histoplasma capsulatum*.[8] The definitive diagnosis of penicilliosis is based on isolation of organisms from cultures of blood or other clinical specimens or by histopathologic demonstration of organisms in biopsy material. *P. marneffei* exhibits dimorphic growth in culture. At 25°C, the fungus grows as a mold, demonstrating characteristic colonies that include a flat green surface and underlying deep red coloring. At 37°C the fungus grows as white colonies of yeast.[7,14]

In this case, biopsy of the skin lesions confirmed penicilliosis, with the culture showing *P. marneffei*.

For the recommended treatment is liposomal amphotericin B, 0.3 to 0.5 mg/kg body weight/day intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. Patients with mild disease can be initially treated with oral itraconazole 400mg/day for 8 weeks, followed by 200mg/day for prevention of recurrence. Itraconazole capsule is better absorbed when taken with or immediately after a meal. Itraconazole oral solution can be taken on an empty stomach. The alternative drug for primary treatment in the hospital is IV voriconazole, 6 mg/kg every 12 hours on day 1 and then 4 mg/kg every 12 hours for at least 3 days, followed by oral voriconazole, 200mg twice daily for a maximum of 12 weeks. Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day 1, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.[8,10]
In this case, treatment for mild penicilliosis used itraconazole 400mg/day. After 5 days, patient shows improvement.

A double-blind, placebo-controlled study from Chiang Mai, Thailand, demonstrated that oral itraconazole 200 mg daily for secondary prophylaxis in AIDS patients, reduced the relapse rate for *P. marneffei* from 57% to 0% (P<0.001).[15] It shows that HIV patients with CD4+ count less than 100/uL should be considered to get the prophylaxis treatment.

4. Conclusion

It was reported a 25-year-old male patient with penicilliosis. The patient was treatment with itraconazole. However, it is extremely rare to find cutaneous *Penicillium marneffei* infections.

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