Successful treatment of AIDS-associated talaromycosis with low-dose itraconazole

Satiti Retno Pudjiati, MD, Sunardi Radiono, MD, Hardyanto Soebono, MD, Agnes Sri Siswati, MD, Yohanes Widodo Wirohadidjojo, MD, and Carolina Kurniawati, MD
Yogyakarta, Indonesia

Key words: HIV; itraconazole; *Talaromyces marneffei*; talaromycosis.

INTRODUCTION

Talaromycosis, formerly known as penicilliosis, is caused by *Talaromyces marneffei* (previously known as *Penicillium marneffei*), an opportunistic fungus that typically infects immunocompromised individuals in Southeast Asia, especially Thailand and Vietnam.[1] The clinical presentation and symptoms of this fungal infection are highly variable; the most common symptoms are fever, fatigue, and characteristic skin lesions. Umbilicated papules with central necrosis are the most common skin lesions observed,[2,3] which appear as rashes resembling molluscum contagiosum. Other lesions that develop during talaromycosis include subcutaneous nodules, subcutaneous ulcers, cutaneous masses, multiple abscesses, and central necrosis. However, the pathogenesis of *T marneffei* infection is unclear. Talaromycosis disseminates via the reticuloendothelial system in immunosuppressed individuals, and its severity depends on the degree of immunosuppression.[4,5] Here, we report a case of talaromycosis in an HIV+ patient with atypical clinical findings which may be a result of immune reconstitution inflammatory syndrome.

Abbreviations used:

ART: antiretroviral therapy
CD4: cluster of differentiation 4

CASE REPORT

A 41-year-old Indonesian man diagnosed with HIV infection and having unknown cluster of differentiation (CD) 4 count and viral load was started on antiretroviral therapy (ART) with lamivudine, tenofovir, and efavirenz. He did not take other prescribed medications, vitamins, herbal supplements, or homeopathic remedies. Two months later, he developed asymptomatic erythematous papules all over the face. Within a month, the lesions increased in number, and some lesions on the arms and legs coalesced into plaques without central necrosis. The lesions further increased in number, while the previous lesions persisted. His nails and scalp were unaffected (Fig 1, *A*). At this point, he presented at the Dermatology and Venereology Outpatient Department at Sardjito Public Hospital (Yogyakarta, Indonesia). Upon examination, the patient appeared healthy, with a CD4 count of 5 cells/μL, and did not have fever, fatigue, or cough. He reported daily adherence to ART and did not take other prescribed medications, vitamins, herbal supplements, or homeopathic remedies. Laboratory evaluation and chest X-ray results were unremarkable. A skin biopsy from the lower portion of the patient's left arm revealed the presence of a granulomatous reaction, with numerous foreign body giant cells and round fungal structures observed using periodic acid–Schiff stain (Fig 2). A fungal culture from the skin biopsy revealed the presence of *T marneffei* (Fig 3) whereas bacterial and mycobacterial cultures yielded negative results.

From the Dermatology and Venerology Department, Dr. Sardjito General Public Hospital/Gadjah Mada University Yogyakarta, Indonesia.
Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
Correspondence to: Satiti Retno Pudjiati, MD, Perum Casa Grande Cluster Andalusia No. 248, Maguwoharjo, Depok Sub-District, Sleman Regency, Yogyakarta 55281, Indonesia. E-mail: satiti_rp@yahoo.com, satiti_rp@ugm.ac.id.

JAAD Case Reports 2020;6:1278-80.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.09.015

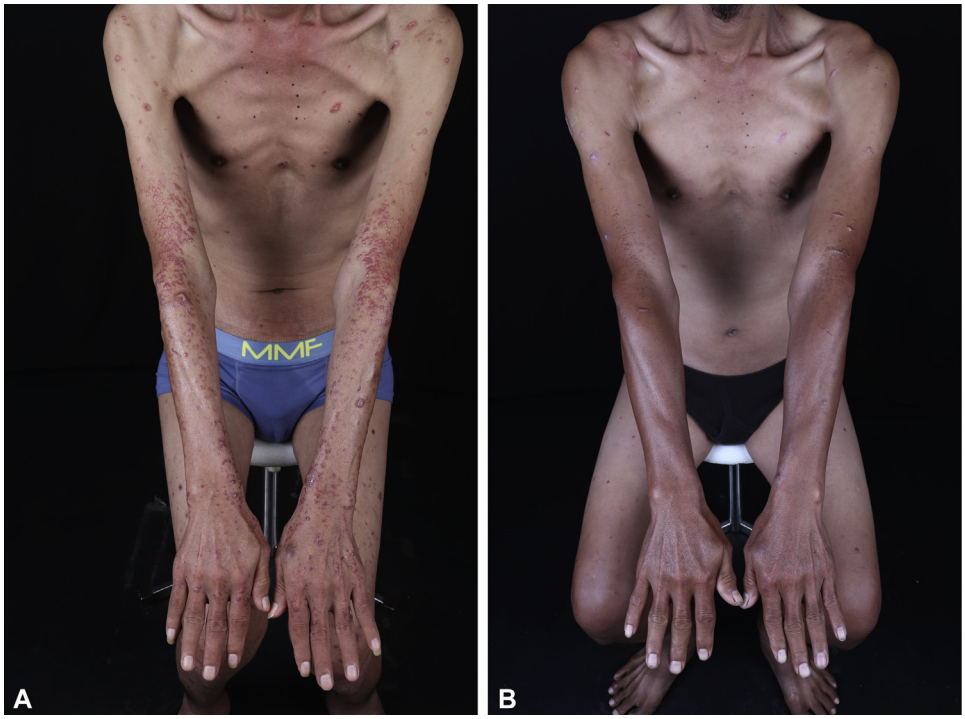

Fig 1. Skin lesions of AIDS-associated talaromycosis visualized with periodic acid–Schiff stain (**A**) before and (**B**) after low-dose itraconazole monotherapy. (©Dermatology and Venerology Department, Dr. Sardjito General Public Hospital/Gadjah Mada University Yogyakarta)

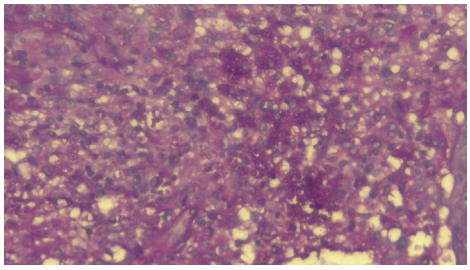

Fig 2. Histopathology of skin lesions. (©Dermatology and Venerology Department, Dr. Sardjito General Public Hospital/Gadjah Mada University Yogyakarta)

Moreover, a fungal sensitivity test of the skin samples revealed itraconazole sensitivity. The patient was prescribed 100 mg of itraconazole twice daily and was continued on ART. The treatment was continued at the same dosage for 16 weeks, and he was followed up at our department every month. The treatment was well tolerated, and the skin lesions decreased during the treatment course (Fig 1, *B*). The treatment efficacy was evaluated after 16 weeks by performing a biopsy, which yielded unremarkable results, with no fungal structures observed with the periodic acid–Schiff stain. Furthermore, the fungal culture tested negative for *T marneffei*.

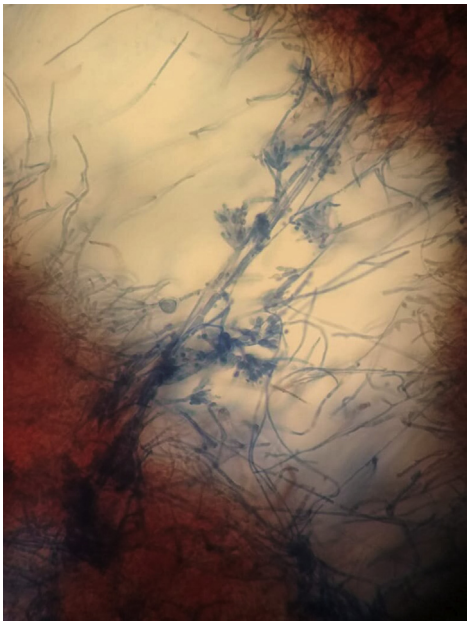

Fig 3. Tissue culture of skin samples from the patient. (©Dermatology and Venerology Department, Dr. Sardjito General Public Hospital/Gadjah Mada University Yogyakarta)

DISCUSSION

After tuberculosis and cryptococcosis, talaromycosis is the third most important opportunistic

infection in HIV+ patients in Southeast Asia. Its causative organism, *T marneffei*, is the only thermally dimorphic pathogenic species among over 200 species of *Talaromyces*. Although *T marneffei* infection can be diagnosed by identifying the fungus in a variety of specimens using microscopy and culture, a definitive diagnosis using a fungal culture from skin biopsy has been reported to have 90% sensitivity.[2] Thus, skin biopsy should be routinely performed in patients suspected of having talaromycosis.[6] Immune reconstitution inflammatory syndrome is a pathologic immune response associated with bacterial, fungal, and viral pathogens following the initiation of ART. It is described as the unmasking of previously undiagnosed infections or worsening of existing infections. Our case may be classified as immune reconstitution inflammatory syndrome because of the lack of clinical evidence regarding active *T marneffei* infection before ART initiation.[7]

Most patients with *T marneffei* infection have been reported to have a CD4 count of <100 cells/μL. On the day of the examination, our patient had a CD4 count of 5 cells/μL. Without treatment, *T marneffei* infection is fatal in HIV+ patients.[5] Currently, the recommended treatment for talaromycosis in HIV+ patients includes amphotericin B (0.6-1 mg/kg/day for 2 weeks), followed by oral itraconazole (400 mg/day for 8-10 weeks). According to the current guidelines, patients with intolerance to amphotericin B should be treated with intravenous voriconazole (400 mg every 12 hours on day 1, followed by 200 mg every 12 hours for at least 3 days) followed by oral voriconazole (200 mg twice daily for 12 weeks).[8] It is also important to consider the potential drug-drug interactions between itraconazole/voriconazole and antiretroviral drugs. Itraconazole must not be coadministered with efavirenz and lopinavir/ritonavir as these combinations would synergistically increase the itraconazole levels in the blood. Therefore, high doses of itraconazole should be avoided.[3] In the present case, because of the unavailability of amphotericin B and voriconazole at our institution, itraconazole was the sole therapy initiated at doses much lower than those recommended by the current guidelines. Hence, we successfully treated the patient with 100 mg of itraconazole twice daily for 16 weeks. We report a case of talaromycosis with atypical skin lesions caused by *T. marneffei* which showed regression with low dose itraconazole monotherapy. Given the increase in the prevalence of HIV infection, talaromycosis is expected to become more prevalent. Therefore, we hope that this treatment option will be beneficial, considering its potential drug-drug interactions with antiretroviral drugs.

REFERENCES

1. Duong TA. Infections due to *Penicillium marneffei,* an emerging pathogen: review of 155 reported cases. *Clin Infect Dis*. 1996; 23(1):125-130.
2. Cao C, Xi L, Chaturvedi V. Talaromycosis (penicilliosis) due to *Talaromyces (Penicillium) marneffei:* insights into the clinical trends of a major fungal disease 60 years after the discovery of the pathogen. *Mycopathologia*. 2019;184(6):709-720.
3. Chen J, Zhang R, Shen Y, et al. Clinical characteristics and prognosis of penicilliosis among human immunodeficiency virus-infected patients in Eastern China. *Am J Trop Med Hyg*. 2017;96(6):1350-1354.
4. Castro-Lainez MT, Sierra-Hoffman M, LLompart-Zeno J, et al. *Talaromyces marneffei* infection in a non-HIV non-endemic population. *IDCases*. 2018;12:21-24.
5. Guiguemde KT, Sawadogo PM, Zida A, Cisse M, Sangare I, Bamba S. First case report of *Talaromyces marneffei* infection in HIV-infected patient in the city of Ouagadougou (Burkina Faso). *Med Mycol Case Rep*. 2019;26:10-12.
6. Vanittanakom N, Cooper CR Jr, Fisher MC, Sirisanthana T. *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. *Clin Microbiol Rev*. 2006;19(1):95-110.
7. Hall C, Hajjawi R, Barlow G, Thaker H, Adams K, Moss P. *Penicillium marneffei* presenting as an immune reconstitution inflammatory syndrome in a patient with advanced HIV. *BMJ Case Rep*. 2013;2013:bcr2012007555.
8. Ge Y, Xu Z, Hu Y, Huang M. Successful voriconazole treatment of *Talaromyces marneffei* infection in an HIV-negative patient with osteolytic lesions. *J Infect Chemother*. 2019;25(3):204-207.