Talaromycosis clinically and histopathologically mimicking histoplasmosis in an immunocompromised patient

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Abstract

Talaromycosis is caused by the dimorphic fungus *Talaromyces marneffei* (formerly *Penicillium marneffei*) endemic in South and Southeast Asia. Its clinical similarity with other dimorphic fungal infections (sometimes) make the diagnosis challenging. We report an immunocompromised patient with talaromycosis mimicking histoplamosis. A 26-year-old HIV-positive man had suffered from rashes over the face, trunk, and extremities for three months. His physical examination showed centrally necrotic, ulcerated papules and nodules. A biopsied papule revealed granulomas containing numerous oval, yeast-like cells, some displaying central septation. Saboraud agar culture grew mold with diffuse red pigment consistent with *T. marneffei*. Careful histopathological examination and microbiological culture are important for the accurate diagnosis of fungal infections.

Keywords: talaromycosis, histoplasmosis, immunocompromised, human immunodeficiency virus, diagnosis, Talaromyces marneffei, Penicillium marneffei

Introduction

Talaromycosis (formerly penicilliosis) is a systemic mycosis caused by *Talaromyces marneffei* (formerly *Penicillium marneffei*), a thermally dimorphic pathogenic fungus. *Talaromyces marneffei* is endemic in South and Southeast Asia and mostly affects immunocompromised hosts, including people with human immunodeficiency virus (HIV). HIV-positive individuals with CD4 cell count <100/µL have a higher risk of this opportunistic infection [1,2]. The clinical presentations are nonspecific and may mimic other dimorphic fungal infections such as histoplasmosis, making its diagnosis challenging. Histoplasmosis is caused by *Histoplasma capsulatum* and is an important opportunistic infection among HIV individuals in endemic areas. Both infections are serious opportunistic infections and have similar clinical presentations and laboratory findings. Skin lesions are more common in talaromycosis but are not pathognomonic for either infection [3].

Case Synopsis

A 26-year-old HIV-positive man, without history of antiretroviral treatment came to the dermatology-venereology outpatient clinic with multiple, small, crusted bumps and patches over the face, trunk, and extremities of three-months' duration. The papules and nodules were asymptomatic and appeared first on the chest and neck before spreading to all body surfaces except the palms and soles in one week. Some papules and nodules enlarged, broke down, and secreted pus. The patient also experienced fever, weight loss, mouth sores, night sweats, dry cough, and loss of appetite. He looked severely weak and

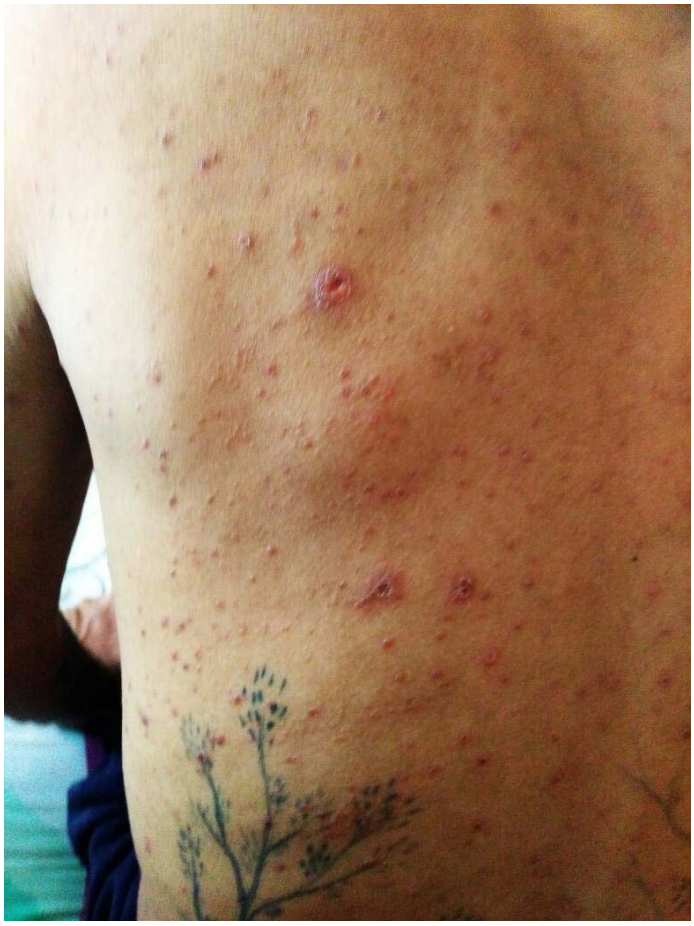

Figure 1. *Papules with central-necrotic ulceration on the back.*

malnourished. Aside from rhonchi from the upper part of the chest, there were no significant other physical findings. The cutaneous lesions included papules with centrally-necrotic ulceration, nodules, and hypopigmented and erythematous patches (**Figure 1**). The patient was sent for biopsy with provisional diagnoses of histoplasmosis and cryptococcosis. Specimens were taken for histopathologic examination, and microbial and fungal cultures .

A sample from an umbilicated papule showed granulomas containing numerous oval, yeast-like cells, in the absence of gelatinous capsules, suggesting histoplasmosis (**Figure 2A)**. However, once stained with Grocott-Gomori methenamine silver (GMS), it revealed numerous intra and extracellular, round-to-oval, thin-walled yeast-like organisms, some of which had central septation instead of budding, which is more consistent with talaromycosis (**Figure 2B)**. Fungal culture at 25°C on Sabouraud agar grew into a mold with diffused red pigment within 7 days, consistent with a *T. marneffei* colony. Fungal culture and microscopic examination are shown in **Figure 3**. The patient was treated with oral itraconazole 200mg twice daily for four weeks.

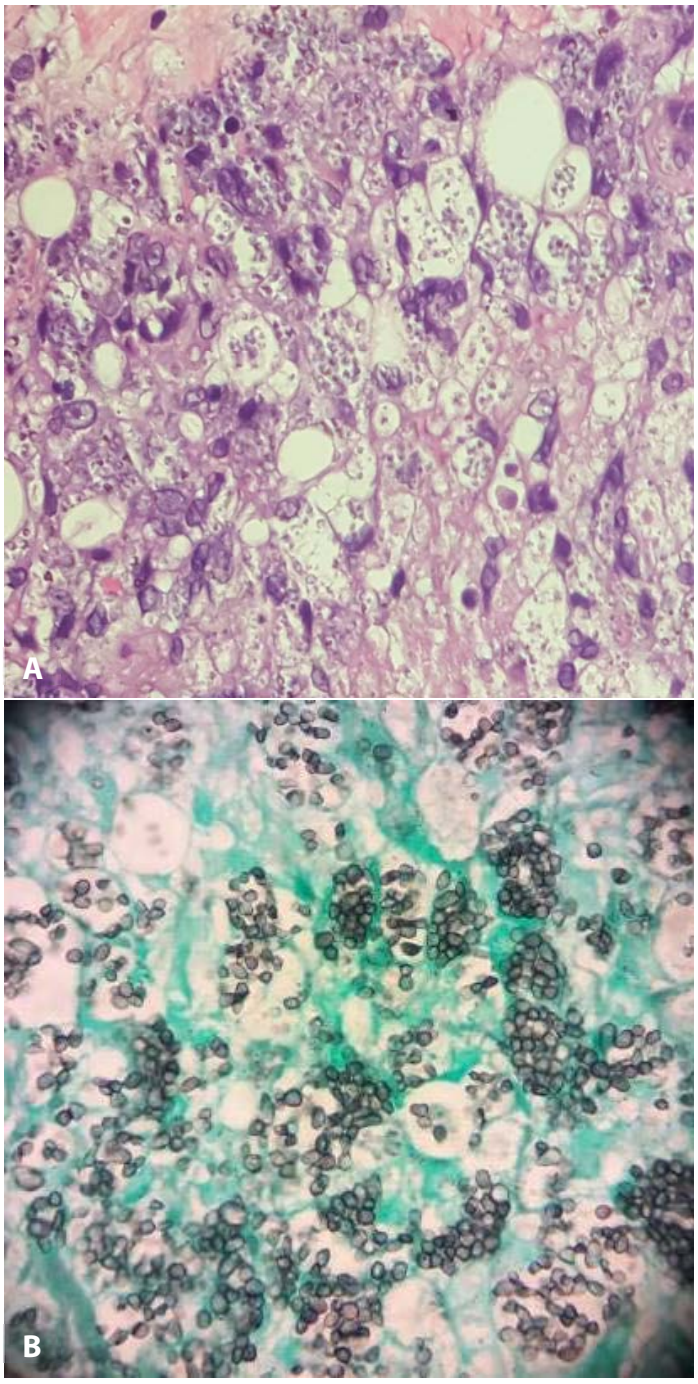

Figure 2. ***A)*** *Hematoxylin and eosin staining* ***B)*** *Grocott-Gomori methenamine silver (GMS) revealed numerous intra and extracellular, round to oval, thin-walled yeast-like organisms. Central septation was more easily demonstrated with GMS staining.*

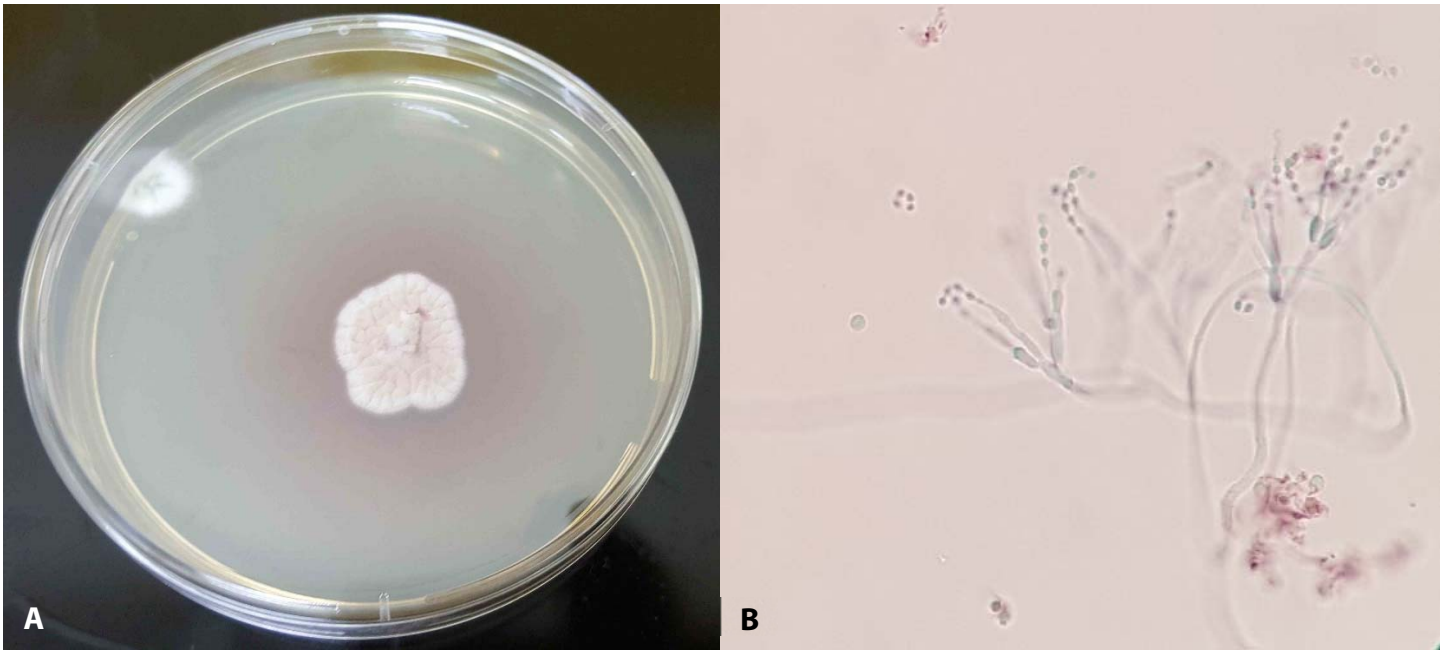

Figure 3. ***A)*** *Fungal culture on Sabouraud agar grew into a white mold with diffused red pigment.* ***B)*** *Microscopic examination showed filamentous hyphae with conidiophores and conidia.*

The cutaneous eruption resolved completely. Medication was continued for 12 months.

Case Discussion

Talaromycosis is caused by the dimorphic fungus *T. marneffei* (formerly *P. marneffei*), which is endemic in South and Southeast Asia [1,4]. In this region, talaromycosis is considered to be an Acquired Immunodeficiency Syndrome (AIDS)-defining illness, which usually occurs with CD4 cells <100/µL [1]. Talaromycosis is also reported in HIV-negative patients with different clinical presentations than in HIV-positive ones [1,5,6].

Constitutional symptoms are common such as fever, anemia, weight loss, malaise, respiratory involvement, and skin manifestations [7]. However, these are not specific and can be found in other dimorphic fungal infections such as histoplasmosis caused by *H. capsulatum*. Mucocutaneous lesions are present in nearly 20% of HIV-infected patients with disseminated histoplasmosis [8]. In countries where two pathogens have been reported in immunocompromised patients such as Indonesia, differentiating both pathogens is challenging [6,9-11]. Oral manifestations can occur in talaromycosis; these include erosions or ulcers covered with slough that can extend into the oropharynx [12]. Oral manifestations of histoplasmosis occur less frequently in HIV-positive patients [8]. Umbilicated crusted papules are more common in talaromycosis whereas erythematous plaques are more common in histoplasmosis [3]. Cohen et al. reported that the most commonly observed lesions of disseminated histoplasmosis in HIV-infected patients were papules, nodules, macules and patches, and ulcers, both oral and skin. More than half the patients exhibited more than one morphology and involvement was usually located on the face, arms, trunk, and legs [13]. Nevertheless, skin lesions are not specific and not pathognomonic in either disease [3,9]. The different clinical features of histoplasmosis and talaromycosis are shown in **Table 1.**

On histopathological examination, the characteristics of *T. marneffei* are sausage-shaped yeast with a central clear septum similar to cells which undergo binary fission [3]. Meanwhile, *Histoplasma* characteristics are oval or round budding yeasts intracellularly and extracellularly. However, since both fungi are organized in clusters and overcrowded in tissues along with phagocytic cells, it is hard to distinguish these forms based on histopathological examination alone [3]. It seems

Table 1. *Comparation of the features of HIV-associated talaromycosis and histoplasmosis [14-18].*

Feature	Talaromycosis	Histoplasmosis
Lesion morphology	Central necrotic papules, umbilicated papules. Other morphology such as papules, pustules, nodules, subcutaneous abcesses, cysts or ulcers can also occur.	Papules, nodules, macules, patches, oral and skin ulcers. Less frequent: pustules, fistulae, folliculitis, herpes-like.
H&E staining	Focal necrosis surrounded by distended histiocytes containing proliferating fungi	Intracellular and/or extracellular oval structures
Grocott-Gomori methenamine silver (GMS) or periodic-acid Schiff (PAS) staining	Sausage-shaped yeasts with a central clear septum, resembling cells undergoing binary fission	Intracellular and/or extracellular budding yeast
Fungal culture appearance	At 25-30ºC: yellow-green colonies with sulcate folds and diffuse red pigment in the media At 32-37ºC: tan colonies without red pigment	White to light tan colony
Microscopic examination	Mycelial form: filamentous hyphae with conidiophores and conidia Yeast form: sausage-shaped cells	Mycelial form: hyphae with tuberculated macroconidia and smooth-walled spherical, pyriciform or cigar shaped microconidia. Yeast form: ovoid thick-walled cells
Treatment	Liposomal amphotericin B 3-5mg/kg body weight or deoxycholate amphotericin B 0.7mg/kg body weight/day, IV for 2 weeks followed by oral itraconazole, 200mg every 12 hours for a subsequent duration of 10 weeks	Liposomal amphotericin B (3.0mg/kg daily) for 1–2 weeks, followed by oral itraconazole (200mg 3-times daily for 3 days and then 200mg twice daily for a total of at least 12 months)

that GMS staining visualizes the septae better than the routine hemotoxylin and eosin staining [19]. Other staining that can also be used to identify the intracytoplasmic fungal structure is periodic acid-Schiff. This staining should be used on all mucocutaneous biopsies whenever disseminated histoplasmosis is being considered [20]. In this report, microbiological culture was essential to confirm the diagnosis of talaromycosis and to exclude the possibility of histoplasmosis. *T. marneffei* colonies are colored red whereas the *H. capsulatum* colonies are white [3,9]. Differentiating these two diseases is important for the management and prognosis. *Penicillium spp* organisms are normal flora and easily found in environment. Therefore, prolonged medication is needed to avoid relapse. *Histoplasma* is a true pathogenic fungus causing high mortality and distinctive disseminated infections in AIDS patients and needs aggressive treatment. Source contact avoidance to prevent reinfection is suggested [18,21].

Conclusion

This report highlights the importance of microbiological culture together with histological special staining as diagnostic tools in immunocompromised patients. In this case, microbiological culture proved to be essential to confirm the diagnosis of talaromycosis and to exclude the possibility of histoplasmosis.

Potential conflicts of interest

The authors declare no conflicts of interests.

References

1. Kawila R, Chaiwarith R, Supparatpinyo K. Clinical and laboratory characteristics of penicilliosis marneffei among patients with and without HIV infection in Northern Thailand: A retrospective study. *BMC Infect Dis*. 2013;13:464. [PMID: 24094273].
2. 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;96:1350-4. [PMID: 28719279].
3. Mootsikapun P, Srikulbutr S. Histoplasmosis and penicilliosis: Comparison of clinical features, laboratory findings and outcome. *IJID*. 2006;10:66-71. [PMID: 16242368].
4. Lupi O, Tyring SK, McGinnis MR. Tropical dermatology: fungal tropical diseases. *J Am Acad Dermatol*. 2005;53:931-51. [PMID: 16310053].
5. Liu G-n, Huang J-s, Zhong X-n, et al. Penicillium marneffei infection within an osteolytic lesion in an HIV-negative patient. *Int J Infect Dis*. 2014;23:1-3. [PMID: 24657269].
6. Liyan X, Changming L, Xianyi Z, Luxia W, Suisheng X. Fifteen cases of penicilliosis in Guangdong, China. *Mycopathologia*. 2004;158:151-5. [PMID: 15518342].
7. Wong SYN, Wong KF. Penicillium marneffei Infection in AIDS. *Patholog Res Int*. 2011;2011:763293. [PMID: 21331327].
8. Cohen PR. Oral histoplasmosis in HIV-infected patients. *Oral Surg Oral Med Oral Pathol*. 1994;78:277-8. [PMID: 7970584].
9. Chang P, Rodas C. Skin lesions in histoplasmosis. *Clin Dermatol*. 2012;30:592-8. [PMID: 23068146].
10. Dwiyana RF, Rowawi R, Lestari M, et al. Skin disorders in HIV-infected patients from West Java. *Acta medica Indonesiana*. 2009;41 Suppl 1:18-22. [PMID: 19920293]**.**
11. Karo FA, Kembaren T, Saragih R, et al. Cutaneous penicilliosis due to penicillium marneffei infection in human immunodeficiency virus infected patients. *IOP Conf Ser Earth Environ Sci*. 2018;125:012060. [PMID: 28719279].
12. Samaranayake L. Penicillium species—the good and the ugly. *Comment in Oral Dis*. 1999;5:269. [PMID: 10561712].
13. Cohen PR, Bank DE, Silvers DN, Grosmann ME. Cutaneous lesions of disseminated histoplasmosis in human immunodeficiency virus-infected patients. *J Am Acad Dermatol*. 1990;23:422-8. [PMID: 2212140].
14. Guimaraes AJ, Nosanchuk JD, Zancope-Oliveira R. Diagnosis of histoplasmosis. *Braz J Microbiol*. 2006;37:1-13. [PMID: 20445761].
15. 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;184:709-20. [PMID: 31811603].
16. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *CID*. 2007;45:807-25. [PMID: 17806045].
17. US Department of Health and Human Services. Talaromycosis (formerly penicilliosis). Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV.. 2019. https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/349/talaromycosis--penicilliosis-. Accessed on May 18, 2020.
18. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev*. 2010;20:115-32. [PMID: 17223625].
19. Guamer J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev*. 2011;24: 247–80. [PMID: 21482725].
20. Cohen PR, Grossman ME, Silvers DN. Disseminated histoplasmosis and human immunodeficiency virus infection. *Int J Dermatol*. 1991;30:614-22. [PMID: 1938071].
21. Cano MV, Hajjeh RA. The epidemiology of histoplasmosis: A review. *Semin Respir Infect*. 2001;16:109-18. [PMID: 11521243].