

Itraconazole plus 640 nm high-power red-light combination therapy for recalcitrant ulcers associated with *Talaromyces marneffe* infection

Dear Editor,

Talaromyces marneffe (*T. marneffe*) is a fatal pathogenic fungus that invades the skin of immunocompromised patients, especially those with AIDS. Although early, appropriate antifungal treatment may result in a better prognosis in general, the ulcers in *T. marneffe* infected patients are difficult to heal. Here, we report three cases of refractory ulcers successfully treated by combining anti-fungal drugs and high-power red-light.

Case 1

A 40-year-old HIV-positive male patient was admitted to our hospital with a two-year history of generalised necrotic skin rash, itching and ulcers on the buttocks [Figure 1a]. The patient visited a local hospital due to intermittent cough and fever that lasted for two months and received antibiotics. Upon further evaluation, he was diagnosed with systemic *T. marneffe* infection, AIDS, anaemia and bacterial pneumonia. He was treated with fluconazole 400 mg daily together with antibiotics for four weeks and was also simultaneously started on highly active antiretroviral therapy, which was continued. The fever and lung infection were brought under control, but the gluteal ulcers had worsened. The patient was then transferred to our hospital. Ulcer biopsy slides showed granulomas in the dermis consisting of a large number of eosinophils, some neutrophils, lymphocytes, histiocytes and multinucleate giant cells [Figure 1b]. PAS positive fungal spores were identified in the dermis and subcutaneous tissue [Figure 1c]. The smear from the ulcer didn't reveal any positive acid-fast bacilli on staining.

Case 2

A 29-year-old HIV positive male patient had multiple large ulcers on the perianal, glans penis and sacral regions [Figure 2a] and had an intermittent fever since three months. Laboratory investigations showed that he CD4+ T-cell count

was 29/ μ l. *T. marneffe* was identified in blood cultures. Histology from the ulcer showed granulomas and PAS positive fungal spores [Figures 2b and 2c]. Diagnosed with *T. marneffe* infection and AIDS, he was then given highly active antiretroviral therapy including cotrimoxazole and fluconazole 400 mg daily for 10 weeks. New ulcers still continued to appear gradually.

Case 3

A 76-year-old male patient presented with a nontender, slowly growing, ulcerative plaque and nodule on his right foot [Figure 3a]. A physical examination found ipsilateral inguinal lymphadenopathy. He had lost five kilograms of body weight over nine months. Erythromycin, gentamycin and fluconazole were administered with little effect. The routine examination of blood, urine, stool, liver and renal functions was normal. *T. marneffe* was identified in fungal cultures from both blood and skin biopsy tissues. The pus swab culture reported enterococcus faecalis. The ulcer skin biopsy showed granulomas and PAS positive fungal spores [Figures 3b and 3c]. He was then diagnosed with a *T. marneffe* infection.

The recalcitrant ulcers in patients with severe cutaneous *T. marneffe* infections are difficult to treat. Two of the three patients were treated with fluconazole 400 mg daily, but the ulcers showed no noticeable improvement. Therefore, we devised a therapy combining antifungal medication with high-power red-light radiation. Itraconazole was given 200 mg orally twice daily for at least 4 weeks, followed by 200 mg orally daily for at least 24 weeks. While taking itraconazole, the case two patient was treated with high-power 640 nm visible LED red light (Lifotronic Technology Co. Ltd) with 120 mw/cm² density and 216 J/cm² energy density (30 minutes) daily. Case 1 and 3 patients received the same red-light treatment twice daily. Within 7 days, the combination therapy elicited good response in all three patients, with

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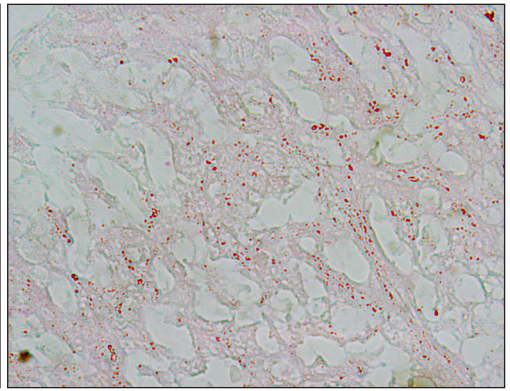
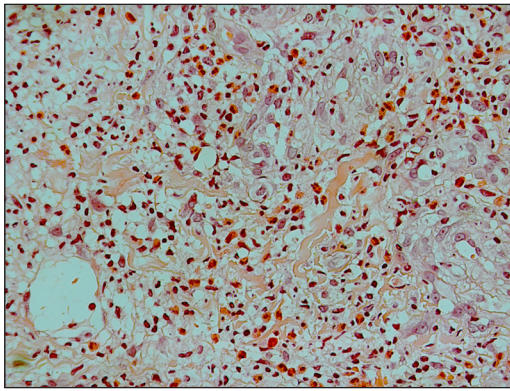


Figure 1a: Case 1- Multiple ulcers over the buttocks, before therapy.

Figure 1b: Histopathology showed infiltration of multiple inflammatory cells, large number of eosinophils and small round or oval fungal spores (H&E, 400×).

Figure 1c: PAS positive spores (PAS, 400×).

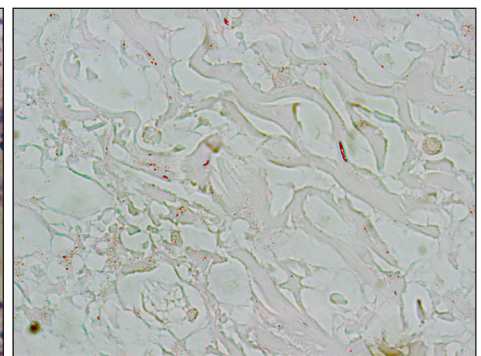
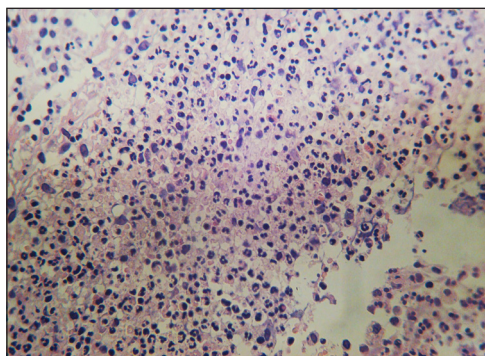


Figure 2a: Case 2- Before therapy.

Figure 2b: Histopathology showed infiltration of the inflammatory cells. Most of the cells were lymphoid cells with small number of eosinophils (H&E, 200×).

Figure 2c: A few PAS positive spores: allanto-like with abjunctions (PAS, 400×).

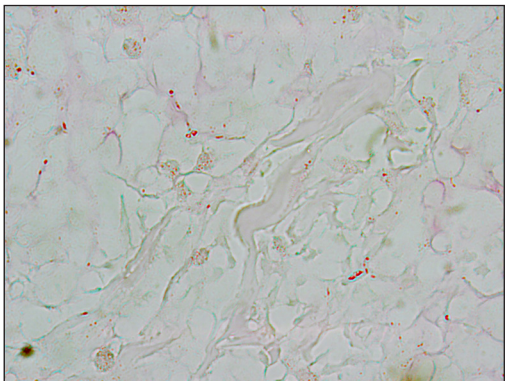
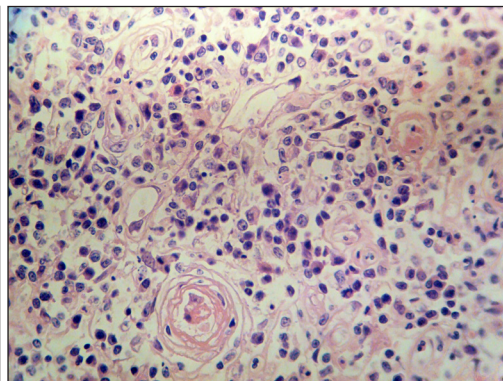


Figure 3a: Before the treatment: large ulcer and multiple nodules on the foot.

Figure 3b: Histopathology showed inflammatory cells infiltration (H&E, 400×).

Figure 3c: PAS positive spores: small round or oval red particles 2–3 μm in size (PAS, 400×).

lesional healing, reduced oedema and exudation. The ulcers showed improvement in 1–2 weeks and healed in 4–8 weeks [Figures 4a, 4b and 4c]. No adverse effects were observed in any of the three patients during the combined therapy.

T. marneffei usually causes opportunistic infections and is endemic in South-East Asia.¹ Early diagnosis and prompt, effective management are important to avoid life-threatening systemic mycosis. The typical clinical manifestations include fever, anaemia, weight loss, lung infection, hepatic

involvement and lymphadenopathy.² The characteristic skin lesions such as umbilicated papules or nodules with a necrotic centre, resembling those seen in molluscum contagiosum, are the most common symptoms of cutaneous *T. marneffei* infection.³ In line with other reports, ulcers are the earliest manifestation associated with *T. marneffei*.⁴ In addition, patients with cutaneous *T. marneffei* infection are more likely to have combined bacterial infections, resulting in refractory large ulcers. In this scenario, antifungal monotherapy has limited efficacy.



Figure 4a: Case 1- After 8 weeks of combination therapy; the ulcer has healed. **Figure 4b:** Four weeks after therapy: the ulcer healed.

Figure 4c: Ten weeks after therapy: the ulcer and nodules resolved.

A high-dose antifungal agent is usually effective for *T. marneffeii* infections. The minimum inhibitory concentrations of the commonly used medicines, ranking from lowest to highest, are voriconazole, itraconazole, terbinafine, amphotericin-B and fluconazole.⁵ For our patients, itraconazole 400 mg per day was more efficient than the previous treatments. For AIDS patients with *T. marneffeii*, highly active antiretroviral therapy together with antifungal therapy should be initiated early.¹ After initiating antiretroviral therapy, immunosuppression may improve. Under this condition, the antifungal therapy becomes more effective and the antifungal prophylactic regimen aiming to reduced risk of *T. marneffeii* relapse might be discontinued sooner.

Previous reports showed that skin ulcers and infections benefit from low-level light/laser therapy.⁶ The benefits may be explained by the improved blood flow and neovascularization, decreased inflammatory cell levels, induction of anti-inflammatory cytokines, chemokines and other mediators. It may also restore the collagenesis/collagenase balance, which accelerates wound healing.⁶ In our experience, in all these three cases, the new therapy, which combined an antifungal drug and a high-power red-light, drastically improved the ulcers. However, the exact mechanism underlying the accelerated wound healing and fungicidal effect of the combination therapy remains to be determined.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflict of interest

There are no conflict of interest.

**MingHua Chen, Juan Xu, Shengmei Xu¹,
Pengfei Song, Jing Wang**

Departments of Dermatology, ¹Pathology,
The Eighth Affiliated Hospital Sun Yat-sen University,
Shenzhen, Guangdong, China

Corresponding author:

Dr. Jing Wang

Department of Dermatology, The Eighth Affiliated Hospital Sun Yat-sen University, Shenzhen, Guangdong, China.
wangj567@mail.sysu.edu.cn

References

1. Wong SY, Wong KF. *Penicillium marneffeii* infection in AIDS. *Patholog Res Int* 2011;2011:764293.
2. Hu Y, Zhang J, Li X, Yang Y, Zhang Y, Ma J, et al. *Penicillium marneffeii* infection: an emerging disease in mainland China. *Mycopathologia* 2013;175:57–67.
3. Nor-Hayati S, Sahlawati M, Suresh-Kumar C, Lee KC. A retrospective review on successful management of *Penicillium marneffeii* infections in patients with advanced HIV in Hospital Sungai Buloh. *Med J Malaysia* 2012;67:66–70.
4. Cui Y, Jin C, Li X, Wu N. *Penicillium marneffeii* infection presenting as vulv-ulcer in an HIV-infected woman. *Eur J Med Res* 2011;16:425–6.
5. Liu D, Liang L, Chen J. In vitro antifungal drug susceptibilities of *Penicillium marneffeii* from China. *J Infect Chemother* 2013;19:776–8.
6. Wu X, Alberico S, Saidu E, Rahman Khan S, Zheng S, Romero R, et al. Organic light emitting diode improves diabetic cutaneous wound healing in rats. *Wound Repair Regen* 2015;23:104–14.