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Case Report

Successful voriconazole treatment of *Talaromyces marneffei* infection in an HIV-negative patient with osteolytic lesions☆

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ABSTRACT

Talaromyces marneffei (T. marneffei) is a dimorphic fungus that causes systemic infection in immunocompromised patients. Here, we present a case of *T. marneffei* infection in an immunocompetent patient with an osteolytic lesion. Diagnosis was established by fungal culture. The patient responded rapidly to intravenous voriconazole, followed by oral voriconazole. We reviewed 18 reported cases of *T. marneffei* infection with osteolytic lesions, which suggests a much higher rate of osteolytic lesions in immunocompetent patients than previously thought.

1. Introduction

Talaromyces marneffei (*T. marneffei,* previously *Penicillium marneffei*) is an opportunistic fungus that typically infects immunocompromised people in Southeast Asia [1]. In 1973, Disalvo et al. first reported *T. marneffei* infection in a patient with Hodgkin's disease [2]. Since then, scattered cases of *T. marneffei* infection have been reported [1,3]. *T. marneffei* infection has also been reported in patients with acquired immunodeficiency syndrome (AIDS), HIV-negative transplant recipients and patients with cancer, tuberculosis, or diabetes [4,5].

T. marneffei infection with osteolytic lesions often shows hematogenous spread, and patients typically have poor prognosis [5–8]. For patients with systemic infection, amphotericin B is usually the cornerstone treatment. Here, we present a case of *T. marneffei* infection with osteolytic lesions in an immunocompetent subject. The patient showed a rapid, sustained response to voriconazole treatment.

2. Case report

A 59-year-old man presented with recurrent episodes of productive coughing lasting 3 months. One month previously, the patient had noted a non-tender lump on the right of the forehead. The patient denied a history of headache, chest pain, or hemoptysis, but revealed having decade-long schistosomiasis and gout. The patient had received unknown antibiotics for "pulmonary shadows" on a chest CT at a local hospital but the symptoms persisted.

Body temperature was 38.4 °C and both lungs were clear. However, chest computed tomography (CT) revealed mass-like hyperdensities in the lower lobe of the left lung, with enlargement and necrosis of multiple mediastinal lymph nodes upon contrast enhancement (Fig. 1S A in Supplementary Material). Physical examination revealed a lump measuring 3 × 3 cm on the right temple (Fig. 1A). Cranial magnetic resonance imaging (MRI) revealed destruction to the skull at the site of the lump (Fig. 1B–C). Abdominal ultrasonography revealed a widened portal vein and splenomegaly, which are abnormalities indicative of schistosomiasis. An aspirate of the skull lesion was taken on day 12 of hospitalization and cultured.

Laboratory tests indicated the following: white blood cell count, 27.9 × 10^9/L; neutrophils, 87.3%; erythrocyte sedimentation rate, 78 mm/h; *C*-reactive protein concentration, 184.9 mg/L; procalcitonin concentration, 0.611 ng/mL; and the following proportions of lymphocyte types, $CD45^+$ lymphocytes, 4.05%; total $CD3^+CD45^+$ T cells, 67.05%; and ratio of CD4 to CD8 cells, 0.64. Results were negative for the Widal test, serum cryptococcal antigen latex agglutination test and *Candida* galactomannan antigen test. Hepatic and renal tests were unremarkable. Serum levels of chorionic embryonic antigen and alpha-fetoprotein were normal. Tests for

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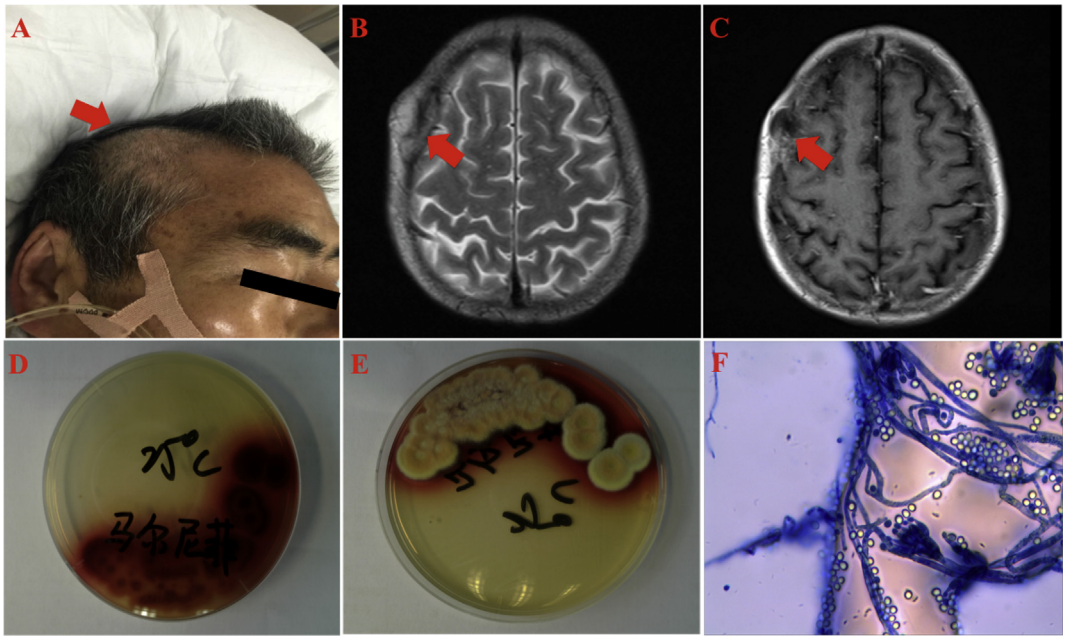

Fig. 1. (A) The patient presented with a lump measuring 3 × 3 cm in the right temple. (B–C) Cranial MRI revealed skull tissue destruction at the site of the lump. (D–F) Culture of bone marrow, blood, sputum, and skull lump puncture fluid revealed *Talaromyces marneffei*, which appeared as sausage-shaped yeast cells with septation. The yeast cells produced red pigment at 25 °C but not 37 °C.

hepatitis B virus, hepatitis C virus, human immunodeficiency virus (HIV), and syphilis were negative. Given these negative results, the patient's chronic schistosomiasis, the normal lymphocyte results and the lack of risk factors for immunosuppression (e.g. cancer, diabetes mellitus, autoimmune disease, steroids, or immunosuppressants), we concluded that the patient was immunocompetent.

On admission, sputum samples were subjected to microbiological examination for fungi, acid-fast bacilli, and bacteria, and the results were negative. Similarly, the Pastorex Aspergillus test was conducted on serum and blood culture on admission, and the results were negative. Lymph node biopsy, performed under bronchoscopy, revealed inflammatory necrosis and infiltration. CT-guided lung biopsy of an area in the left lower lobe showed chronic inflammation. Cultures of lymph node and lung biopsy were not performed. The patient was treated with the antibiotics piperacillin, tazobactam, meropenem, linezolid, imipenem and cilastatin, but his condition did not improve. Body temperature remained between 38 °C and 39.8 °C.

On day 19 of hospitalization, the patient suddenly developed hypoxemia. He was given high-flow oxygen through a mask, but oxygen saturation remained <80% based on analysis of arterial blood gases. He was transferred to the intensive care unit, where he was mechanically ventilated. CT pulmonary arteriography showed an obvious increase of inflammatory infiltration in both lungs, and allowed us to exclude pulmonary embolism (Fig. 1S B in Supplementary Material). These results, together with the inefficacy of long-term antibacterial therapy, led us to suspect a pulmonary fungal infection such as aspergillosis. The patient promptly received empirical antifungal treatment of voriconazole by infusion with a loading dose of 400 mg, followed by a dose of 200 mg (q12h).

On the same day 19, biphasic fungal culture of the skull lesion aspirate taken on day 12 of hospitalization gave a positive result for *T. marneffei* infection. The yeast cells appeared sausage-shaped with septation (Fig. 1F), and they produced red pigment at 25 °C (Fig. 1D) but not 37 °C (Fig. 1E). *T. marneffei* infection was confirmed on culture of sputum, blood and bone marrow (Fig. 1D–F). The skull damage at the site of the lump seen on cranial MRI was compatible with a lesion due to *T. marneffei* infection.

After one week of voriconazole infusion, the patient's fever subsided and chest radiography showed rapid improvement and a decrease in inflammatory infiltration (Fig. 2S in Supplementary Material). Upon discharge from the hospital, the patient was instructed to take oral voriconazole (200 mg bid) for 3 months. At 3-month follow-up, chest and cranial CT scans showed markedly improved infection (Fig. 3S in Supplementary Material).

3. Discussion

T. marneffei is the third most important opportunistic infection in HIV-positive patients in Southeast Asia, after extrapulmonary tuberculosis and cryptococcosis [1–4]. Upon disseminated infection, *T. marneffei* mainly invades the reticuloendothelial system, and osteolytic lesions are rare. We conducted a systematic search of PubMed, Web of Science and Google Scholar, and identified 18 reported cases of *T. marneffei* infection with osteolytic lesions [5–8] (Table 1). In a retrospective study of 100 patients with disseminated *Talaromycosis,* of whom 65 were HIV-positive, all 14 patients with osteolytic lesions were HIV-negative [5]. This suggests a high rate of osteolytic lesions in HIV-negative patients with *Talaromycosis.* We identified only one report of an HIV− and *Talaromycosis*-infected patient with osteolytic lesions in the extremities [9]. The higher rate of osteolytic lesions in HIV-negative patients possibly reflects their higher white blood cell count and function. Focal neutrophil aggregates, when abundant, can assemble at the osseous site and increase uptake at osteolytic sites, which can be detected using emission CT, as well as increase overall bone metabolic activity, which can be detected using positron emission tomography [10]. Neither imaging modality was applied to the present case, leaving open the possibility that he had osteolytic lesions at other sites.

Risk factors for osteolytic lesions in immunocompetent individuals may include comorbidities such as diabetes, tuberculosis, and cancer [5]. We are unaware of reports on the impact of schistosomiasis on *T. marneffei* infection. Further work is needed to understand background diseases in *T. marneffei*-infected patients, especially immunocompetent patients. Although we considered

Table 1
Reported cases of Talaromyces marneffei infection with osteolytic lesions in a literature review-1990 to 2018.

Case	Zone	Clinical presentation	Osteolytic lesions	Underlying disease	Treatment	Outcome	Reference
1	Hong Kong	multiple painful swollen joints and a chronic facial ulcer	knee, ankle, elbow, wrist, and finger joints	pulmonary tuberculosis	amphotericin B (2 months) and 5-fluorocystosine (7 months)	recovery	Chan et al. [6]
1	Hong Kong	fever, cervical lymphadenopathy, and soft-tissue mass on the forehead	cervical spine 2 vertebral body, the head of left humerus, and the right femur	mixed connective disease	amphotericin B and fluconazole	improved	Pun et al. [7]
1	Thailand	fever, multiple painful ulcerated oral lesions, generalized non-pruritic erythrematous skin papules and nodules, and multiple swollen, warm, and tender joints	metacarpophalangeal joints, wrist, right distal radius, and ulnar	immune reconstitution inflammatory syndrome and HIV infection	amphotericin B (2 weeks) and fluconazole (4 months)	recovery	Sudjaritruk et al. [9]
1	Southern China	intermittent fever, generalized lymphadenopathy, and a skin rash	left clavicle and sternum	tuberculosis	amphotericin B	improved	Liu et al. [8]
14	Southern China	fever (14), Malasise (14), weight loss (13), anemia (13), ostealgia (13), cutaneous lesions (12), lymphadenopathy (11), hepatosplenomegaly (10), cough and sputum production, stethalgia (9), dyspnea (5), hemoptysis (2)	skull (6), vertebrae (10), ribs (5), sternum (2), femur (6), Ilium (4), clavicle (3), scapula (3), humerus (3), shinbone (3), radial (2), sternum (2), innominatum (2), fibula (2), bones of hand (2), elbow-bone (1), ischium (1),pubesacetabulum (1), bones of foot (1), sacrum (1), cartilage (1), joint involvement (5), soft tissue swelling (7)	diabetes mellitus (4), previous glucocorticoid therapy (2), β-thalassemia (1), breast cancer (1), Langerhans cell histiocytosis (1), no comorbidities (5)	amphotericin B and itraconazole	death (6), recovery (4), replase (4)	Qiu et al. [5]
1	Southern China	coughing, expectoration, and fever	skull	schistosomiasis and gout	voriconazole (3 months)	recovery	this study

the possibility of a malignant tumor in our patient, this was discarded when *T. marneffei* infection was confirmed upon culture of the skull lesion aspirate.

Osteolytic lesions are often neglected in HIV-negative patients with *T. marneffei* infection, especially since most such patients present with swelling and tenderness in the joints and soft tissues around the bones [5]. Multiple well-delineated osteolytic lesions tend to occur in flat bones and long bones (Table 1). In our case, an osteolytic lesion occurred in the skull. Fungal culture is the gold standard for the diagnosis of *T. marneffei* infection. Histopathologic examination can identify yeast cells with a clear central septum. Interestingly, *T. marneffei* is thermally dimorphic. *Talaromyces marneffei* produces a red pigment at 25 °C, but not 37 °C. Microscopically, sausage-shaped cells are mixed with hyphae-like structures, and segments start to develop [4,11]. Samples collected from the skull lesions, bone marrow, and the sputum in our case showed features characteristic of *T. marneffei*.

Cultured *T. marneffei* is highly susceptible to a variety of antifungal agents *in vitro,* including amphotericin B, itraconazole, fluconazole, and voriconazole [12]. In a survey conducted in China, 569 patients who received antifungal therapy had a mortality rate of 24.3%, whereas 99 patients who did not receive antifungal therapy had a mortality rate of 50.6% [13]. Currently, the standard treatment for *T. marneffei* infection in patients with AIDS is intravenous amphotericin B (0.6–1.0 mg/kg/day for 2 weeks), followed by oral itraconazole (400 mg/day for 8–10 weeks) [13]. There is no standard antifungal regimen for *T. marneffei* infection in HIV-negative patients. While amphotericin B is often used, it is associated with nephrotoxicity, electrolyte imbalance, hepatotoxicity and other adverse events. The broad-spectrum triazole antifungal agent voriconazole has been reported to be effective and well-tolerated for prevention of *T. marneffei* infection [14]. In our case, we chose to administer voriconazole because we suspected pulmonary fungal infection. The patient responded well to the treatment, showing remarkable improvement of clinical manifestations and lung inflammation. This therapeutic efficacy led us to keep the patient on voriconazole even after culture tests indicated *T. marneffei* infection. In fact, voriconazole can be more effective *in vitro* against *T. marneffei* than amphotericin B, itraconazole, or fluconazole [14]. In addition, one retrospective study of 12 T. *marneffei*-infected patients without AIDS responded favorably to voriconazole during 16-week follow-up [15].

At 3-month follow-up, the patient had not relapsed and showed no adverse events. These results suggest that voriconazole can be an effective therapeutic option for *T. marneffei* infection in the presence or absence of HIV infection. Our patient responded favorably to intravenous voriconazole, followed by oral voriconazole for 3 months. This is consistent with a report that voriconazole treatment for longer than 12 weeks was effective against *T. marneffei* infection in HIV-infected individuals [14]. Furthermore, a study of 7 patients without HIV showed that voriconazole therapy lasting longer than 16 weeks was associated with no relapse in long-term follow-up [15].

In conclusion, we herein present a case of successful treatment of *T. marneffei* infection in an HIV-negative patient with osteolytic lesions with voriconazole. The finding encourages the use of voriconazole if amphotericin B is contraindicated. Moreover, our results and the relevant literature suggest that voriconazole treatment against *T. marneffei* should last longer than 12 weeks, and potentially longer than 16 weeks in certain clinical contexts, such as disseminated or refractory invasive fungal infections.

Ethical approval

No approval was required. All authors complied with the ethics policies of the journal.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2018.08.007.

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