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SHORT COMMUNICATION

Fatal *Talaromyces marneffei* Infection in a Patient with Autoimmune Hepatitis

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Abstract *Talaromyces marneffei*, previously known as *Penicillium marneffei*, is the most important pathogenic thermally dimorphic fungus causing systemic mycosis in Southeast Asia. Traditionally, *T. marneffei* infection in human was mainly associated with acquired immunodeficiency syndrome caused by HIV infection. In recent years, there has been an increasing number of *T. marneffei* infections reported in non-HIV-infected patients with other immunocompromised conditions, including autoantibodies against interferon-gamma, systemic lupus erythematosis, solid organ transplantation, Job's syndrome, hematological malignancies, and use of novel targeted therapies. In this article, we describe the first case of fatal *T. marneffei* infection in a patient with underlying autoimmune hepatitis, presented as fever without localizing features. The diagnosis of talaromycosis was confirmed with the identification of the fungi isolated from the blood culture specimen by conventional methods and using matrix-assisted laser desorption–ionization time-of-flight mass spectrometer. This case shows the importance of a high index of suspicion, particularly for such a highly fatal but potentially treatable fungal infection.

Keywords *Talaromyces marneffei* · Fatal infection · Autoimmune hepatitis · Matrix-assisted laser desorption–ionization time-of-flight mass spectrometer

Introduction

Talaromyces (*Penicillium*) *marneffei* is the most important pathogenic thermally dimorphic fungus causing systemic mycosis in Southeast Asia [1–3]. *T. marneffei* infection is endemic in tropical regions, especially Thailand, Vietnam, northeastern India, Southern China, Hong Kong, Taiwan, Laos, Malaysia, Myanmar, Cambodia, and Laos [1]. Bamboo rats (*Rhizomys* spp. and *Cannomys* spp.) and soil from their burrows are considered to be important enzootic and environmental reservoirs of *T. marneffei*, respectively [4–7]. Historically, *T. marneffei* infection in human has been considered to be exclusively associated with

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acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) infection [1, 8]. In some regions such as Hong Kong and southern China, *T. marneffei* infection has long been considered as one of the top three AIDS-defining opportunistic infections, alongside tuberculosis and cryptococcosis [2, 9].

In recent years, improved treatment of HIV infection with highly active antiretroviral therapy and control of the HIV/AIDS epidemic with other measures have led to a change in the epidemiology of *T. marneffei* infection, with an increasing number and proportion of cases being reported in non-HIV-infected patients who had other immunocompromising conditions [10–13]. In this article, we describe the first case of fatal *T. marneffei* infection in a patient with underlying autoimmune hepatitis. This case shows the importance of a high index of suspicion particularly for such a highly fatal but potentially treatable fungal infection.

Case Description

A 65-year-old Chinese woman with autoimmune hepatitis was admitted to our unit for liver transplantation assessment. She has been receiving mycophenolate mofetil (MMF) 1 g twice daily since 2009 and had just completed a tapering regimen of prednisolone for acute hepatitis flare. On the second day after admission, she developed a fever of 38.2 °C and reported mild dysuria. Examination showed a jaundiced patient who was hemodynamically stable. Abdominal examination reviewed mild suprapubic tenderness and splenomegaly. There were no skin lesions; cervical lymph nodes were not palpable. The patient's hemoglobin level was 7.7 g/L (reference range 11.5–14.8 g/L). Her neutrophil count was 5.46×10^3/μL (reference range 2.01–7.42 $\times 10^3$/μL), and lymphocyte count was 0.37×10^3/μL (reference range 1.06–3.61 $\times 10^3$/μL). Platelet count was 66×10^3/μL (reference range 154–371 $\times 10^3$/μL), and prothrombin time was prolonged to 20.1 s (reference range 25.1–33.9 s). The chest radiograph was clear.

The initial working diagnosis was urinary tract infection, and she was empirically started on intravenous amoxicillin–clavulanate after sepsis workup. However, her fever persisted with worsening coagulopathy and thrombocytopenia. Antibiotics were stepped up to intravenous ertapenem and vancomycin. Urine culture obtained by fresh catheterization grew ampicillin-resistant *Enterococcus faecium* ($> 10^5$ colony forming units/mL). On day 5 of admission, the patient developed acute deterioration of mental state with a Glasgow coma scale of 4/15. Computer tomography of the brain revealed an extensive intracranial bleed involving right temporal and parietal lobes with mass effect, which was likely due to hemorrhagic stroke. The patient passed away 6 h later.

The blood culture taken on the second day of admission became positive after 3 days of incubation. Gram stain of the positive blood culture broth revealed fungal elements (Fig. 1). Culture demonstrated typical features of *Talaromyces marneffei* (Fig. 2) and matrix-assisted laser desorption–ionization time-of-flight mass spectrometer (MALDI-TOF MS, Bruker Daltonics, Germany) with in-house expanded database identified the isolate as *T. marneffei* with a score of 2.6. Retrospective testing of serum galactomannan (Platelia *Aspergillus* ELISA for GM, Bio-Rad, California) and an in-house enzymatic immunoassay [9] for antibodies against *T. marneffei* were negative, while 1,3-β-D-glucan (fungus (1-3)-β-D-glucan assay, Dynamiker Biotechnology, Tianjin) was 142 pg/mL ($<$ 70 pg/mL = negative, 70–95 pg/mL = inconclusive, $>$ 95 pg/mL = positive).

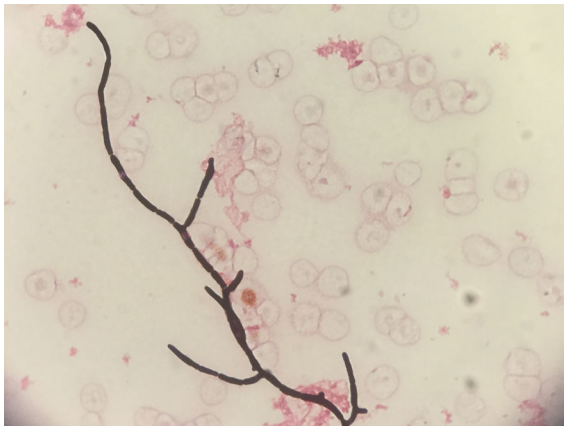

Fig. 1 Gram stain appearance of the positive blood culture demonstrated septated hyphae-like structures (magnification ×1000)

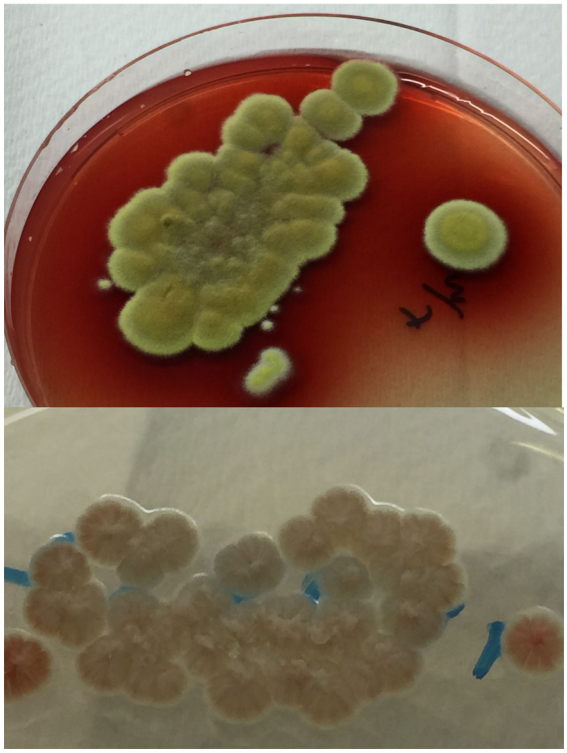

Fig. 2 Colony morphology of *T. marneffei.* Above: mycelial phase at 25 °C with yellow pigmented colonies and diffusible red pigment on agar; below: yeast phase at 37 °C with yeast-like colonies

Discussion

The above vignette highlights the importance of *T. marneffei* as a cause of severe infection in febrile immunocompromised patients resident in or returning from endemic areas. Infections due to *T. marneffei* are most often described in patients with advanced HIV, but it is also of emerging importance in patients with various non-HIV immunosuppressive conditions. Some of the most common non-HIV conditions associated with *T. marneffei* infection include autoantibody against interferon-gamma, systemic lupus erythematosis, post-transplant immunosuppressive states, Job's syndrome, hematological malignancies, and use of novel targeted therapies [1, 10, 11]. Patients with autoimmune disorders on high-dose immunosuppressants, like our patient in the present study, have been reported to be at risk of penicilliosis [10, 11]. In our patient, the diagnosis was difficult due to the absence of typical features such as skin papules with central necrotic umbilication or lymphadenopathy. In non-endemic areas, a lack of familiarity with the condition is also likely to contribute to the diagnostic difficulty [10, 14]. To the best of our knowledge, this is the first reported case of *T. marneffei* infection in a patient with autoimmune hepatitis. The recent course of prednisolone for acute hepatitis flare and chronic use of MMF have most likely predisposed this patient to disseminated *T. marneffei* infection. More reports of *T. marneffei* infections in non-HIV patients are likely in view of the growing population of immunocompromised patients, including transplant recipients, cancer patients on targeted therapy, and patients with autoimmune disease requiring immunosuppressants and biologic therapy [10].

A high index of suspicion is mandatory for recognizing the possibility of *T. marneffei* infection and hence ordering the correct microbiological test and/or prescribing empirical antifungal agents, as talaromycosis is a highly fatal but potentially treatable fungal infection. Laboratory diagnosis is most often confirmed by visualization of *T. marneffei* yeast-form cells with typical transverse septum directly in bone marrow aspirate, touch smears of skin biopsies or lymph node biopsy specimens [12, 15, 16], or from positive fungal cultures of blood, bone marrow, skin, lymph node, and other affected sites [1, 12, 15]. MALDI-TOF MS have been showed to be useful in rapid identification of both yeast and mold cultures of *T. marneffei* [17]. Serological tests have shown to be helpful in making the diagnosis [1, 9, 14]. Fatality of *T. marneffei* infections in HIV-infected patients ranged from 10 to 28%, where low platelet count, delayed initiation of antifungal treatment, absence of fever or skin lesions, and elevated respiratory rates predicted poor outcome [12, 15, 16, 18]. For penicilliosis in non-HIV patients, an estimated fatality rate of approximately 33% was inferred from a review of all published reports [10]. Presence of underlying disease, low CD4 cell count, and low T-lymphocyte cell percentage were associated with lower long-term survival [13]. In the present study, the patient died 5 days after admission to hospital, which was also the day that the blood culture became positive and subsequently identified to be *T. marneffei.* We should remain vigilant against the possibility of *T. marneffei* infection in immunocompromised patients with fever of unknown origin, who lived in, or had traveled to endemic areas.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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