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Case Report

Disseminated *Talaromyces marneffei* and *Mycobacterium intracellulare* coinfection in an HIV-infected patient

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ABSTRACT

A 25-year-old man with human immunodeficiency virus (HIV) infection presented with fever that had lasted 1 month. The CD4+ T lymphocyte count was 7 cells/μL and computed tomography showed several small lung nodules, splenomegaly, and multiple lymphadenopathy. *Talaromyces marneffei* was isolated in the initial blood cultures. As the fever persisted despite clearance of fungemia and 10 days of liposomal amphotericin B treatment, cervical lymph node fine-needle aspiration was performed. *Mycobacterium intracellulare* was isolated from sputum and neck node aspiration cultures. The patient was successfully treated with liposomal amphotericin B, clarithromycin, and ethambutol in addition to antiretroviral therapy. This case suggests that we should consider coinfection of opportunistic pathogens in febrile immunosuppressed patients if the patient does not respond properly to the initial treatment.

1. Introduction

Talaromyces marneffei, previously known as *Penicillium marneffei*, is a facultative intracellular dimorphic fungus that causes disseminated and progressive infection in immunocompromised hosts, especially patients with human immunodeficiency virus (HIV) infection.[1,2] *T. marneffei* is characterized by its geographic endemism in Southeast Asia and southern China, although several imported cases have been reported in non-endemic countries.[1,3] Although coinfection of *T. marneffei* with another opportunistic infection is theoretically possible as most *T. marneffei* infection occurs in patients with an immunocompromised status, reports of coinfected cases are scarce. Here we report the first case of disseminated *T. marneffei* and *Mycobacterium intracellulare* infection in an HIV-infected patient.

2. Case

A 25-year-old man visited our emergency room with fever and cough that had persisted for a month. He was found to be infected with HIV 5 years previously, and was diagnosed with AIDS 1 year ago when he was admitted to another hospital with *Pneumocystis jirovecii* pneumonia. Although anti-retroviral therapy (ART) with emtricitabine-tenofovir and ritonavir-boosted atazanavir had been started during admission, he voluntarily stopped taking the ART. After his discharge he initially stayed in Guangzhou, China, but returned to Korea when the fever persisted despite oral antipyretic medications. On examination, he had multiple erythematous papules with central umbilication on his face, and 1- to 2-cm sized palpable lymphadenopathies on his cervical, supraclavicular, axillar, and inguinal area. He had blood pressure of 119/66 mmHg, pulse rate of 133 beats/min, respiratory rate of 24 breaths/min, body temperature of 39.9 °C, and oxygen saturation of 99%. Laboratory tests showed a white blood cell count of 6,620/μL with neutrophils 96.3%, hemoglobin 10.3 g/dL, platelet count 162,000/μL, erythrocyte sedimentation rate 84 mm/hr, and C-reactive protein level 6.15 mg/dL. Peripheral CD4+ T lymphocyte count was 3 cells/μL and HIV-RNA viral load was 719 copies/mL. Chest and abdomen computed tomography revealed several small lung

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nodules, splenomegaly, and multiple lymphadenopathies of cervical, supraclavicular, axillary, mediastinal, mesenteric, and inguinal lymph nodes. On hospital day 2, two separate pairs of blood cultures reported growth of microorganisms. As mold type fungi were seen on Gram stain, treatment with amphotericin B deoxycholate was started empirically, but was changed to liposomal amphotericin B because of severe shivering after infusion. On hospital day 6, we observed colonies producing a red-wine colored pigment that diffused into Sabouraud dextrose agar plate (Figure 1A), and septated hyphae with phialides branching from the conidiophores and chain-shaped microconidia with Lactophenol cotton blue stain (Figure 1C). After sequencing of the internal transcribed spacer (ITS) rRNA gene regions, sequence similarity searches using basic local alignment search tool (BLAST) revealed a complete (100%) match with *T. marneffei*. ART with emtricitabine-tenofovir and ritonavir-boosted darunavir were started on the same day. On hospital day 11, fine needle aspiration of the left supraclavicular lymph node was performed because the fever persisted despite proper antifungal treatment and negative conversion of fungemia. Acid-fast bacilli (AFB) stain revealed 1-9 AFB/10 high power fields, and *Mycobacterium tuberculosis* complex polymerase chain reaction (PCR) was negative for both the sputum culture and lymph node aspiration. Ethambutol and clarithromycin were added to the treatment on suspicion of disseminated *Mycobacterium avium* complex infection and the fever subsided 3 days later. The final report of supraclavicular lymph node culture showed both *T. marneffei* and nontuberculous mycobacteria, which was later identified as *Mycobacterium intracellulare* by a PCR-hybridization method. The patient was discharged with oral itraconazole, ethambutol, clarithromycin, and ART after 2 weeks of liposomal amphotericin therapy.

3. Discussion

T. marneffei, a temperature-dependent dimorphic fungus previously known as *Penicillium marneffei*, is an important pathogen of HIV-associated opportunistic infection in endemic areas.[2] It was first isolated from liver of the bamboo rat (*Rhizomys sinensis*) in 1956, and subsequently from an HIV-infected human in 1988. In endemic areas, which include Southeast Asia, Southern China, Hong Kong, northeastern India, and Taiwan, *T. marneffei* can cause fatal disseminated infection in immunocompromised hosts by inhalation of fungal conidia into the lungs.[1,3] Korea is not an endemic area, and only three cases of *T. marneffei* infection in this country have been reported.

To our knowledge, this is the first report of disseminated *T. marneffei* and *M. intracellulare* coinfection in an HIV-infected person. Although coinfection of *T. marneffi* with other opportunistic pathogens is plausible as *T. marneffei* infection mostly occurs in immunocompromised hosts,[1] reports of coninfection are scarce. In a case series that reviewed 24 patients with *T. marneffei* infection, two HIV-negative patients were coinfected with disseminated *M. intacellulare* and *M. fortuitum*, respectively.[4] Considering that these infections are rare in healthy people, those two individuals might have other immunocompromising conditions that were not described in the report. Clinical presentation of these disseminated infections may mimic each other, and a proper diagnostic approach is necessary to avoid insufficient treatment. From this point of view, we think that the present case is clinically informative.

The most common presentation of *T. marneffei* infection is fever and weight loss, occurring in more than 75% of patients. Other manifestations are anaemia, skin lesions, lymphadenopathy, hepatomegaly, and pulmonary disease, in decreasing order of

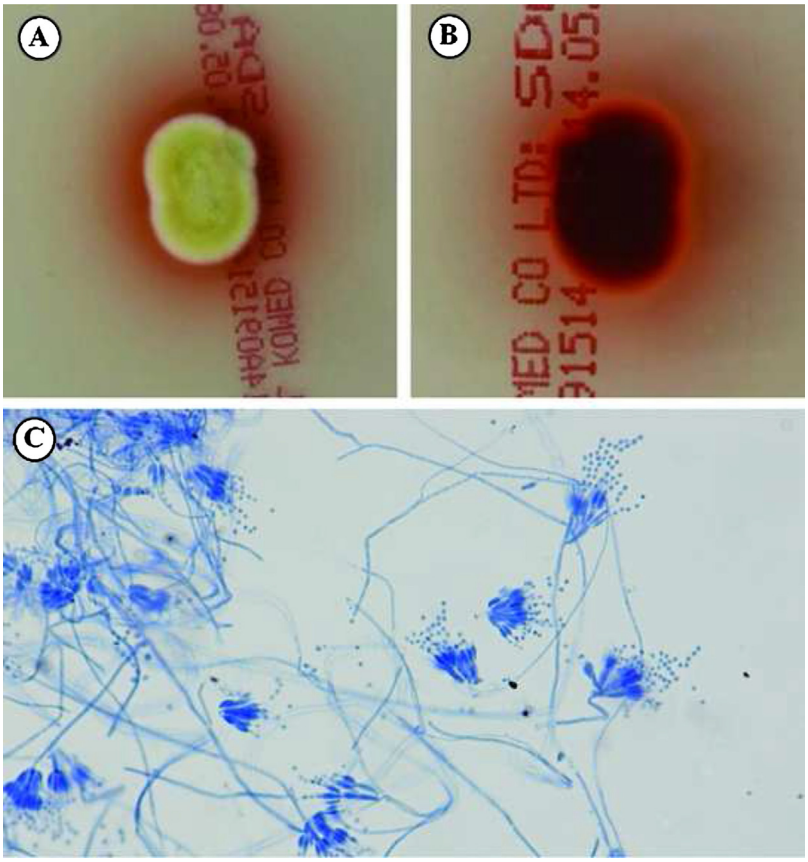

Figure 1. (A) A colony producing a red-wine colored pigment that diffused into Sabouraud dextrose agar plate, (B) Reverse side of the colony, (C) Septated hyphae with phialides branching from the conidiophores and chain-shaped microconidia (Lactophenol cotton stain, ×400).

frequency. Skin lesions are seen in 71% of patients, and include generalized papules, central umbilicated papules, and acne-like lesions.[1,5] Clinical manifestations of disseminated *Mycobacterium avium* complex (MAC) disease, including *M. intracellulare* infection, are fever, night sweats, weight loss, abdominal pain, and diarrhea. Hepatosplenomegaly, lymphadenopathy, pulmonary nodules, and anemia can also be observed. In the case presented here, the initial presentations of fever, skin lesions, lymphadenopathy, low CD4+ lymphocyte count, and hyphae on Gram stain were highly suggestive of disseminated fungal infection, and empirical antifungal treatment was started without delay. Although fever, several small lung nodules, splenomegaly, and multiple lymphadenopathies also suggest the possibility of disseminated MAC disease, a further diagnostic plan was not considered after the report of fungemia because *T. marneffei* can also cause these manifestations. However, the fever persisted after 10 days of antifungal treatment and eradication of fungemia, and lymph node aspiration was performed on hospital day 11. Culture of aspirated lymph node revealed growth of both *T. marneffei* and *M. intracellulare*. *M. intracellulare* was also reported in the sputum culture. The fever subsided 4 days after administration of ethambutol and clarithromycin. Without the findings of lymph node aspiration, prophylactic use of low-dose azithromycin might have eventually resulted in induction of macrolide resistance.

We report the first case of disseminated *T. marneffei* and *M. intracellulare* infection in an HIV-infected patient. Features of the present case suggest that we should consider coinfection of opportunistic pathogens in febrile immunosuppressed patients if the patient does not respond properly to the initial treatment and emphasize the importance of appropriate diagnostic approaches.

Conflict of Interest/Funding: None

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