**Talaromyces marneffei** infection in an HIV infected patient with hematological malignancy - first report from Turkey

Ahmet Furkan Kurt¹, Ebru Cicek², Tamer A.M. Alhelou³, Bilgul Mete¹, Ridvan Karaali¹, Mert Ahmet Kuskucu⁴, Zeynep Yazgan⁴, Hatice Yasar Arsu¹, Sibel Yildiz Kaya¹, Gokhan Aygun¹, Fehmi Tabak¹

¹Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey; ²Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Department of Internal Medicine, Istanbul, Turkey; ³Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Department of Chest Diseases, Istanbul, Turkey; ⁴Istanbul University-Cerrahpasa, Cerrahpasa School of Medicine, Department of Medical Microbiology, Istanbul, Turkey

**SUMMARY**

*T.marneffei*, encountered mostly in Southeast Asia, leads to a systemic infection, especially in immunocompromised individuals such as HIV-infected patients with low CD4 level. A 32-year-old male patient, residing in Hong Kong for the last two years, admitted with fever, cough, weakness, and weight loss. Physical examination revealed bilateral cervical and axillary multiple lymph nodes and hepatosplenomegaly. Screening of the pancytopenic patient revealed HIV infection. Histopathological examination of the cervical lymph node revealed plasmoblastic lymphoma. Blood and urine cultures remained sterile. Antiretroviral therapy was started. Fungal hyphae were detected in Gram staining of hemocultures taken in the third week due to ongoing fever, and antifungal therapy was started empirically. Red pigment around colonies on Sabouraud dextrose agar and microscopic appearance arose suspicion of *Talaromyces* spp. *T.marneffei* was identified by ITS 1-4 sequence analysis. Chemotherapy was started when fungemia was controlled. On the fifth day of chemotherapy, the patient’s general condition deteriorated, broad-spectrum antibiotics were started and the patient was transferred to ICU. The cultures remained sterile and he expired five days later. In conclusion, although talaromycosis is not endemic in Turkey, it should be considered in patients with travel history to endemic regions and/or an underlying immunosuppressive disease such as HIV infection.

**INTRODUCTION**

*Talaromyces marneffei*, formerly known as *Penicillium marneffei*, leads to a systemic fungal infection termed talaromycosis, especially in immunocompromised individuals. Less frequently, infections have been reported in patients with a travel history (Supparatpinyo et al., 2022). The organism, which was first isolated from a bamboo rat (Rhizomys sinensis) in Vietnam in 1956, was first reported in 1989 in an individual with HIV from Bangkok (Capponi et al., 1956; Sathapatayavongs et al., 1989). *T.marneffei* is a thermal dimorphic fungus and is mostly encountered in Southeast Asia, notably Thailand, Vietnam, Hong Kong, Southern China, Taiwan, India, Indonesia, Cambodia and Laos (https://life-worldwide.org/talaromyces-marneffei-infection). Although the route of transmission is not clearly defined, clinical manifestations of talaromycosis are considered to develop secondary to hematogenous spread. Signs and symptoms can vary from isolated skin lesions to respiratory failure and circulatory collapse (Sirisanthana, Sirisanthana, 1995). *T.marneffei* is an important cause of morbidity and mortality, especially in immunocompromised individuals such as HIV-infected patients with low CD4 cell counts (Supparatpinyo et al., 2022). In endemic areas of Asia, disseminated infections have also been reported in non-HIV-infected persons with underlying diseases such as autoimmune or immunosuppressive diseases and malignancies (Kawila et al., 2013; Browne et al., 2012).

In this manuscript, a case of talaromycosis caused by *T.marneffei* in a patient who admitted after residing in Hong Kong for a while and found to have hematological malignancy and HIV infection as a result of tests performed, is reported for the first time from Turkey.
CASE REPORT

A 32-year-old male Turkish citizen who had been living in Hong Kong for the last two years admitted to our outpatient clinic with fever, night sweats, cough, weakness and 15 kg loss in the last four months. Bilateral cervical and axillary multiple lymph nodes (with the largest diameter of 2 cm in size) and hepatosplenomegaly were present on physical examination. Laboratory examination revealed leukocyte: 3300/mm³, lymphocyte: 900/mm³, hemoglobin: 7.7 g/dl, platelets: 61,000/mm³, C-reactive protein: 170 mg/L (N:<5), procalcitonin: 0.75 ng/mL (N:<0.5), erythrocyte sedimentation rate: 112 mm/h. The pancytopenic patient was evaluated in terms of HIV. Anti-HIV test resulted positive and confirmed with Western Blot. The patient was internalized with preliminary diagnosis of lymphoproliferative disease and opportunistic infections. The patient was febrile (39°C). CD4 count was 139/mm³ and HIV RNA 15,848,931 IU/ml. Blood and urine cultures remained sterile. Positron emission tomography-computed tomography (PET-CT) revealed bilateral pleural-pericardial effusion, hepatosplenomegaly, multiple supra and infradiaphragmatic (most prominently left cervical) lymph nodes with increased hypermetabolism at the level of malignancy. Histopathological examination of the excisional biopsy of the left cervical lymph node resulted in plasmablastic lymphoma. After exclusion of tuberculosis, antiretroviral therapy (tenofovir/emtricitabine+dolutegravir) was started on the 18th day of hospitalization. Meanwhile, blood cultures obtained on the 24th day due to continuing fever revealed fungal hyphae on Gram staining (Figure A). With the preliminary diagnosis of Fusarium spp. infection, liposomal amphotericin-B (3 mg/kg/day, IV) + voriconazole (2x6 mg/kg first day; 2x4 mg/kg maintenance, IV) was initiated empirically. The suspicion of T.marneffei arose when the red pigment spreading around the colonies on Sabouraud dextrose agar (SDA) and microscopic mycelia, conidiophore and conidial structures (Figure B, C, D) were observed and the patient's travel history was taken into account. When the colonies were left to incubate at 37°C, yeast colonies developed on SDA and microscopically oval elongated yeasts were observed (Figure E, F). The fungal strain was identified by ITS 1-4 sequence analysis. After the microorganism that grew in the blood culture was identified as T.marneffei, voriconazole was discontinued and amphotericin-B treatment was continued. Trimethoprim-sulfamethoxazole was added to the treatment, considering the preliminary diagnosis of pneumocystis pneumonia/talaromycosis as a result of bilateral diffuse ground glass appearance in the thorax CT of the patient, whose cough relapsed in the same period. The patient, whose blood culture became negative with antifungal therapy and whose

Figure 1 - Macroscopic and microscopic images of T.marneffei.
fever was partially controlled, was started on chemotherapy (Vel/Dex protocol: bortezomib 1.3 mg/m² ve dexamethasone 40 mg/day) for plasmoblastic lymphoma on the 7th week of hospitalization. On the 5th day of chemotherapy, the patient’s general condition deteriorated and he became febrile, tachypneic and hypoxic; broad-spectrum antibiotic therapy was started and he was transferred to the intensive care unit. The cultures remained sterile. The patient expired five days later.

**DISCUSSION**

Talaromycosis in HIV-infected patients has been reported from many countries outside of endemic regions, such as the United States, Europe, Japan, and Australia, after travel to endemic areas (Vanittanakom, Sirisanthana, 1997). To the best of our knowledge, this is the first case of talaromycosis due to *T.marneffei* in our country, which developed in an HIV-infected patient who had resided in Hong Kong for a while.

The mode of transmission of *T.marneffei* is not clearly known. Humans and bamboo rats are the only known hosts (Gugnani *et al.*, 2004). Although it has been considered that *T.marneffei* infection is more common in rainy seasons and that there may be a relationship between exposure to soil, this association has not been clearly demonstrated (Chariyalertsak *et al.*, 1996; Chariyalertsak *et al.*, 1997; Chariyalertsk *et al.*, 1996). The patient stated that he worked as a peddler in Hong Kong and was frequently exposed to soil. We think that there was a latent infection in our patient, probably due to inhaling *T.marneffei* conidia, and a clinical infection emerged with the development of immunosuppression. This issue is also supported by a case report from Australia with a 10-year period between possible exposure and development of infection (Jones, See, 1992).

Disseminated infections have also been reported in non-HIV-infected persons in endemic areas or after travel to endemic regions. Underlying diseases such as autoimmune/rheumatological diseases, malignancies, organ transplantation and diabetes were reported in some of these patients (Hart *et al.*, 2012; Kawila *et al.*, 2013; Zhou *et al.*, 2014). Our patient was diagnosed with HIV and lymphoma almost simultaneously.

In three large case series, the most common findings were fever, weight loss, cough, abdominal pain, diarrhea, skin lesions, anemia, hepatosplenomegaly and diffuse lymphadenopathy (Supparatpinyo *et al.*, 1994; Le *et al.*, 2011; Ranjana *et al.*, 2002; Zhou *et al.*, 2014). In our case, common findings were all present apart from skin lesions, diarrhea and abdominal pain. In some situations it may be difficult to distinguish lymphoma and disseminated talaromycosis, since signs, symptoms, and radiological findings may be similar, or even talaromycosis may develop in a patient with lymphoma. Histopathological and microbiological examination is required for definitive diagnosis. In case of co-existence of both diseases the clinical picture is more complex and difficult to treat (Yang *et al.*, 2021). Similarly, our patient, who developed talaromycosis, had been diagnosed with lymphoma as well as HIV infection. Although culture of the lymph node biopsy revealing lymphoma remained sterile, *T.marneffei* was isolated from blood culture.

Laboratory abnormalities frequently seen in the course of the disease are anemia, leukocytosis/leukopenia, mild elevations in aminotransferase and bilirubin levels, and increase in serum alkaline phosphatase (Supparatpinyo *et al.*, 2022). In our case, anemia, leukopenia, five-fold increase in aminotransferase levels, and two-fold increase in bilirubin and serum alkaline phosphatase levels were determined. Definitive diagnosis is possible by fungal culture of blood, samples of skin, bone marrow; or lymph node biopsies. *T.marneffei* has also been isolated in cultures of cerebrospinal fluid, feces, pericardial fluid, urine and synovial fluid (Jayanetra *et al.*, 1984; So *et al.*, 1985; Louthrenoo *et al.*, 1994). In our patient, *T.marneffei* was isolated in blood culture but could not be isolated from bone marrow aspiration.

Since mortality is quite high without treatment, antifungal therapy should be started as soon as possible in all patients with talaromycosis (Supparatpinyo *et al.*, 1994). Although antifungal treatment varies according to the severity of the disease, liposomal amphotericin-B is recommended as the first line in disseminated infections with or without other antifungals (Hoenigl *et al.*, 2021). Evaluation of in vitro antifungal susceptibilities of 39 yeast isolates of *T.marneffei* from patients and bamboo rats in Southern China revealed that voriconazole and itraconazole were most active (Liu *et al.*, 2013). In this context, voriconazole is among other recommended drugs considered mostly for salvage therapy (Hoenigl *et al.*, 2021). Moreover, for prevention, travel to endemic areas by immunocompromised individuals should be restricted if possible and the immunodeficiency status of HIV-infected individuals should be improved with antiretroviral therapy. If travel to endemic areas is mandatory, it is recommended to start antifungal prophylaxis before travel and close follow-up after return (http://aidsinfo.nih.gov/content-files/lvguidelines/adult_oi.pdf). In the relevant case, antiretroviral treatment was started and fungemia improved with liposomal amphotericin-B treatment. However, the patient died due to respiratory failure that developed after chemotherapy.

In conclusion, we think that this case is very important in terms of stressing the importance of anamnesis in clinical practice and the approach to an immunosuppressive patient with talaromycosis. Although talaromycosis is not endemic in Turkey, it should
definitely be considered in patients with a travel history and/or an underlying immunosuppressive disease such as HIV infection, and it should not be forgotten that clinical signs may vary from skin lesions to respiratory failure and circulatory collapse.

References


Supparatpinyo K., Kauffman C.A., Borogodskaya M. Epidemiology and clinical manifestations of Talaromyces (Penicillium) marneffei infection. UpToDate: Versin 23.0.


