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CASE REPORT

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

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Summary

A lung transplant recipient was diagnosed with penicilliosis due to *Talaromyces marneffei*, a fungus endemic in South-East Asia, which was acquired by donor transmission. This first case of *Talaromyces marneffei*-transmission by transplantation underscores that current globalisation of travelling necessitates increased vigilance for transmission of unusual pathogens in organ recipients.

KEYWORDS
emerging disease, fungal infection, infection by mode of transmission, lung transplantation, penicilliosis, zoonotic infection

1 | INTRODUCTION

A 61-year-old, Belgian Caucasian male underwent a bilateral lung transplantation in May 2015 (ABO blood type A positive, *cytomegalovirus* (CMV) seronegative) for smoking-related emphysema. The donor was a 71-year-old, Belgian Caucasian male, without medical antecedents, except arterial hypertension, who had suffered from a haemorrhagic cerebrovascular accident and became a multi-organ donor after brain death (A positive, CMV seropositive, ventilated for 17 h prior to lung removal). Transplant surgery (ischaemic times 250 min for left lung and 429 min for right lung; procedure without extracorporeal

Take home message:
Current globalisation of travelling necessitates increased vigilance for transmission of unusual pathogens in organ recipients.

support) and initial posttransplant course were uneventful. Recipient extubation occurred after 24 h, discharge from intensive care unit on postoperative day 2 and discharge from hospital on day 19. Standard immunosuppressive regimen consisted of tacrolimus, mycophenolate and methylprednisolone. Infection prophylaxis consisted of lifelong sulfamethoxazole-trimethoprim for *Pneumocystis jirovecii*, 3 months of valganciclovir for CMV and 3 months of inhaled amphotericin-B lipid complex for *Aspergillus* species according to local standard protocol. No episodes of acute allograft rejection occurred during the first three postoperative months (negative screening lung biopsies after 1 and 3 months).

Four months after transplantation, 26 days after cessation of valganciclovir and amphotericin prophylaxis, the recipient presented with fatigue, fever, oral ulcers, anorexia, diarrhoea and diffuse abdominal pain since one week. Clinical investigation revealed a haemodynamic stable patient without signs of peritonitis; and otherwise normal cardiopulmonary, abdominal and dermal examination. Laboratory tests disclosed acute renal impairment with creatinine 2.09 mg/dL (normal: 0.67-1.17 mg/dL), normal white blood cell count (9490 × 10^6/L; 4000-10 000), but severe B-cell and $CD4^+$-T-cell lymphopenia [absolute lymphocyte count 673 × 10^6/L (1208-3586), $CD19^+$ lymphocytes 8 × 10^6/L (82-476) or 1.2% (5-20), $CD3^+$ lymphocytes 628 × 10^6/L (798-2823) or 93.3% (58-84), $CD3^+/CD4^+$ lymphocytes 215 × 10^6/L (455-1885) or 31.9% (33-62), $CD3^+/CD8^+$ lymphocytes 355 × 10^6/L (219-1124) or 52.8% (13.5-42.4), $CD4^+/CD8^+$ ratio 0.6 (0.8-3.5)] and elevated C-reactive protein of 131 mg/L (<5 mg/L). Imaging by chest X-ray, abdominal ultrasound and abdominal computed tomography (CT) scan was normal.

Empirical treatment with intravenous fluid, meropenem and ganciclovir was started. The subsequent day, blood polymerase chain reaction for CMV, which was negative before, proved to be positive (5.86 log copies/mL), confirming suspected CMV disease due to primary CMV infection. Surprisingly, repeated blood cultures, taken on admission and during the following days because of ongoing fever, demonstrated fungal hyphae after a median of 42.3 (30.3-83.0) hours of incubation. Yeast-like colonies grew upon subculture of the positive blood culture bottles on blood agar at 36.5°, while velvety, grey-green growth with a diffusing red pigment was noticed on Sabouraud agar incubated at room temperature, suggestive for *Talaromyces* species (Figure 1). Microscopy revealed hyaline filamentous forms with sporulating structures having a brush-like appearance and smooth conidia, typical for *Penicillium* species. Based on these characteristics, the isolated fungus was presumptively identified as *Talaromyces* (formerly *Penicillium*) *marneffei*. Subsequent sequence analysis of the internal transcribed spacer (ITS) region of the ribosomal DNA (length of ITS sequence: 530 bp, databases: BLAST and CBS) confirmed *T. marneffei* infection.

Further diagnostic work-up demonstrated negative HIV serology, but chest CT scan revealed bulky mediastinal and right hilar lymphadenopathies, with compression of bronchus intermedius (Figure 2A). Whole-body positron emission tomography and CT (18F-FDG PET–CT) scan showed intensely increased 18^F-fluorodeoxyglucose uptake in mediastinal, infracarinal and right hilar lymphadenopathies, as well as in a subcentrimetric hypermetabolic nodule in the dorsal segment of the right lower lobe, considered the primary focus of infection, but no increased extra-thoracic metabolic activity (Figure 2B, upper panel). Bronchoscopy with endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), with sampling of lymph nodes in position seven, 11 right and four left, was performed. This revealed no malignancy on histological examination, but fungal cultures also demonstrated *T. marneffei*.

FIGURE 1 Culture of *Talaromyces marneffei* on Sabouraud medium in the described case. Inoculation on Sabouraud medium at room temperature of the patient's blood cultures demonstrates velvety, grey-green growth with a diffusing red pigment, suggestive for *Talaromyces* species. Subsequent sequence analysis of the internal transcribed spacer (ITS) region of the ribosomal DNA (length of ITS sequence: 530 bp, databases: BLAST and CBS) indeed confirmed *Talaromyces* (formerly *Penicillium*) *marneffei* infection

Upon diagnosis of penicilliosis, intravenous liposomal amphotericin-B was initiated (5 mg/kg/day, reduced to 3 mg/kg/day because of renal insufficiency), after which there was gradual improvement in the patient's condition. Meropenem was stopped after 7 days and ganciclovir converted to oral valganciclovir upon discharge. After 15 days, blood cultures became negative for *T. marneffei*, after which intravenous liposomal amphotericin-B was changed to maintenance therapy with oral voriconazole (4 mg/kg bid). Voriconazole was continued for 6 months, at which moment, 18F-FDG PET–CT no longer

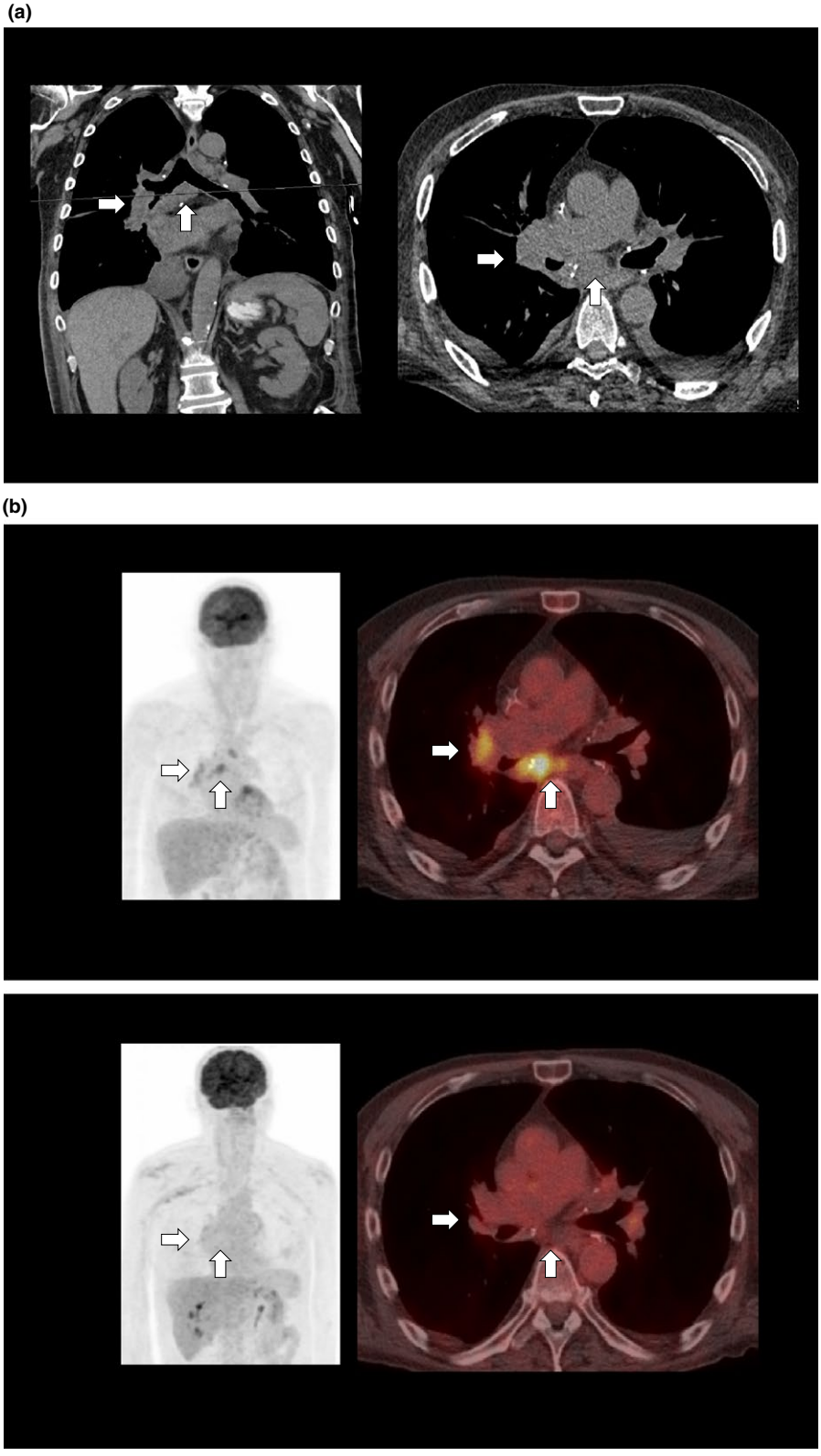

FIGURE 2 Radiologic evaluation by chest computed tomography scan and 18^{F}-fluorodeoxyglucose positron emission tomography and computed tomography scan upon diagnosis of penicilliosis due to *Talaromyces marneffei* infection; and after six months of voriconazole treatment. A, Coronal and axial chest computed tomography (CT) scan image of our lung transplant recipient upon diagnosis of penicilliosis due to *Talaromyces* (formerly *Penicillium*) *marneffei* infection showing bulky mediastinal and right hilar lymphadenopathies (white arrows) with compression of bronchus intermedius. B, Coronal attenuation-corrected image and axial positron emission tomography and computed tomography (PET–CT) fusion image demonstrating increased metabolic activity (18^{F}-fluorodeoxyglucose uptake) of mediastinal and right hilar lymphadenopathies (upper panel, white arrows) in our lung transplant recipient upon diagnosis of penicilliosis due to *Talaromyces* (formerly *Penicillium*) *marneffei* infection, which had disappeared after six months of antifungal treatment (lower panel, white arrows)

demonstrated local hypermetabolic activity (Figure 2B, lower panel) and blood cultures had repeatedly been negative. During the subsequent year after cessation of voriconazole, blood cultures remained negative for *T. marneffei*, and the patient's general condition further improved to normalise.

Talaromyces marneffei is a thermally dimorphic fungus, normally appearing as a mould at temperatures of 25-30°C and as a yeast at a temperature of 37°C. It is an opportunistic pathogen, mainly related to HIV infection, but acquired infection in endemic regions has been described in solid organ transplant recipients.[1–6] However, to date, no

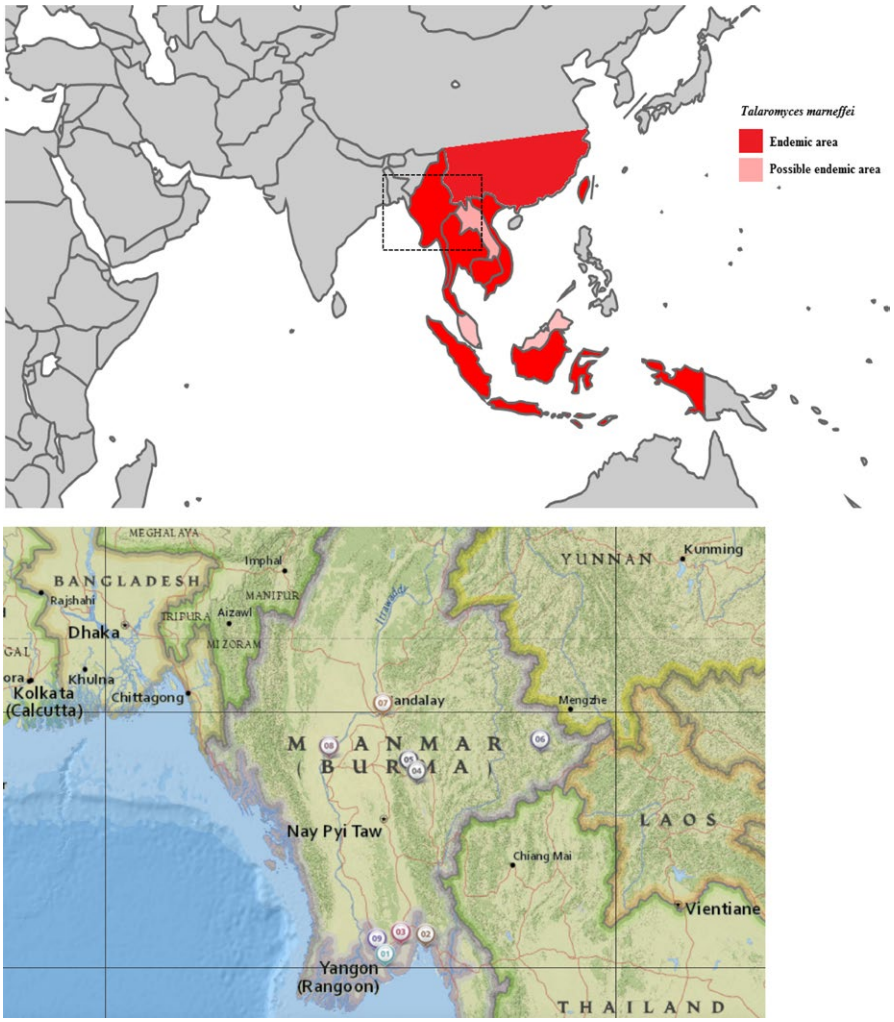

FIGURE 3 Map depicting occurrence of *Talaromyces marneffei* (upper panel) and visited sites during the donor's visit of Myanmar (lower panel). Upper panel: Geographical map depicting occurrence of *T. marneffei* in South-East Asia (red: endemic areas, pink: possible endemic areas); map created with http://english.freemap.jp/ using available data of fungal occurrence from Leading International Fungal Education (LIFE); http://www.life-worldwide.org/ and from US Centers for Disease Control and Prevention (CDC); www.cdc.gov). Dotted square represents the location of a more detailed map depicted in the lower panel. Lower panel: Travelling route of the donor during his visit of Myanmar, visiting several caves, pagodas and meeting local inhabitants in rural areas during a 20-day trip three months before expiring (numbers indicate the different cities or villages travelled to: 1 Yangon, 2 Kyaiktio, 3 Bago, 4 Heho, 5 Pindaya, 6 Kyaingetong, 7 Mandalay, 8 Bagan, 9 Yangon); map created with http://mapmaker.education.nationalgeographic.org/

cases of *T. marneffei* infection transmitted from donor to recipient have been reported. *T. marneffei* is endemic in South-East Asia, but is not prevalent elsewhere (Figure 3). Indeed, most of the published cases from other regions had previously travelled to South-East Asia, notably Thailand, Vietnam, Hong Kong, Southern China, Taiwan, India, Indonesia, Cambodia or Laos. Some 10% of AIDS patients in Hong Kong and 30% of patients in Thailand will present with *T. marneffei* infections. Patients with AIDS and penicilliosis, however, may present all over the world following global travelling. Only one confirmed case with infection in a non-endemic country has been described in a HIV-positive patient in Togo, who had not travelled to an endemic region.[7] Thus far, the only known hosts for *T. marneffei* are humans and bamboo rats (*Rhizomyinae*; widespread in Asia and with a wide variety of habitats: from bamboo forest to cultivated land up to 4000 m altitude), although many aspects of the ecology and potential reservoirs of *T. marneffei* and its relationship with human infection remain unknown.[8,9] Airborne inhalation of conidia and direct inoculation are known modes of transmission.[10]

Most patients with penicilliosis present with symptoms related to infection of the reticuloendothelial system, including generalised lymphadenopathy, hepatomegaly and splenomegaly. Initial presenting features of the disease are usually non-specific, like fever, anaemia and weight loss. Molluscum contagiosum-like skin lesions are seen in most patients, and may be the best clue to diagnosis. Patients may also present with various respiratory, gastrointestinal and neurological symptoms. Mortality of untreated *T. marneffei* infection is reported to be 100%. Treatment of choice is intravenous amphotericin-B (liposomal formulation 3 to 5 mg/kg/day or lipid complex formulation 5 mg/kg/day) for 2 weeks, followed by oral itraconazole (400 mg/day) for 10 weeks or alternatively voriconazole can be used (6 mg/kg bid on day 1, followed by 4 mg/kg bid for at least 12 weeks).[11,12]

Thorough travel history of our lung transplant recipient revealed neither travelling to an endemic region since transplantation nor any contact with people returning from South-East Asia, making *T. marneffei* infection in Belgium unlikely. Thus, donor-related transmission was suspected. Contact with the donor's relatives confirmed that he had travelled to Myanmar three months before expiring, visiting several caves, pagodas and meeting local inhabitants in rural areas during a 20-day round-trip (Figure 3). Therefore, donor infection likely occurred during this trip, after which latent pulmonary *T. marneffei* infection was present, resulting in penicilliosis in our lung transplant recipient due to concurrent use of immunosuppressive therapy, cessation of antifungal prophylaxis with inhaled amphotericin-B lipid complex and primary

CMV infection causing severe lymphopenia, such as is seen in HIV patients. Interestingly, contact tracing and screening revealed no evidence for *T. marneffei* infection in any of the other recipients receiving organs from the same multi-organ donor (i.e. both lungs, kidneys, liver and pancreas for islets had been transplanted), as one would expect in case of latent, asymptomatic donor pulmonary infection.

Donor-to-host transmission of fungal infections (mostly *Aspergillus* species) is a relatively frequent finding after lung transplantation;[13] and other dimorphic fungal infections transmitted via solid organ (lung) transplantation, such as *Coccidioides immitis* or *Histoplasma capsulatum*, has previously also been described.[14–17] However, this first known transmission of the dimorphic fungus *T. marneffei* via lung transplantation highlights the need for increased vigilance regarding thorough donor travel history given the current globalisation of travelling. It also underscores the importance of adequate microbiological typing of unusual pathogens in immunocompromised patients, and the challenges of preventing and detecting transmission of these pathogens through transplantation.

AUTHORS CONTRIBUTIONS

HF: performed data collection, wrote the paper and assisted in its critical appraisal. OS: performed fungal isolation and helped with critical appraisal of the manuscript. DK: coordinated organ allocation, helped in identifying donor travel history and with critical appraisal of the manuscript. TD: performed endoscopic procedure and critical appraisal of the manuscript. VDE: performed the lung transplant procedure and critical appraisal of the manuscript. VGM: responsible physician during the preoperative period and helped with critical appraisal of the manuscript. VEK: performed histopathological analysis and critical appraisal of the manuscript. VBP: assisting treating physician during the postoperative period and helped with critical appraisal of the manuscript. LK: helped in performing fungal isolation and identification; and critical appraisal of the manuscript. VR: responsible physician during the postoperative period, performed design of the case report, data collection and helped with critical appraisal of the manuscript.

CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose. The authors confirm that: the work described has not been published previously, it is not under consideration for publication elsewhere, its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out and that if accepted, it will not be published elsewhere in the same form in English or in any other language, without the written consent of the copyright holder. The patient in the current paper provided consent for publication of his case.

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