Case report

*Talaromyces marneffei* infection in a non-HIV non-endemic population

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**ABSTRACT**

Introduction: *Talaromyces marneffei* infection is a systemic mycosis, caused by a dimorphic fungus, an opportunistic pathogen formerly known as *Penicillium marneffei*. This disease is endemic to Southeast Asia and common in human immunodeficiency virus (HIV) infected patients with low CD4 counts. Here we present a very rarely reported case of *Talaromyces marneffei* infection in an apparent non-immunosuppressed patient presenting decades later in a non-endemic setting (United States).

Presentation of case: Our patient was a 75-year-old Caucasian Navy veteran, who served in Vietnam as a part of the Swift Boat service in 1966. He presented to his primary care provider with uncontrolled nonproductive cough and abnormal chest computerized tomography. Bronchoscopy specimens showed *Talaromyces*. He was empirically treated with itraconazole and then switched to voriconazole after confirmation of diagnosis but he later deteriorated was changed to liposomal amphotericin B and isavuconazole. Patient did well for the next 90 days on isavuconazole until the therapy was stopped. Soon after stopping the medication (isavuconazole) his symptoms recurred and ultimately patient expired.

Discussion: Talaromycosis generally presents as pulmonary infection with manifestations similar with other endemic fungi. It is often seen HIV patients with travel to South east Asia. Very rarely this infection is seen and reported in non-immunosuppressed and in non-endemic areas. To date there are 4 well-documented cases among non-HIV, non-endemic population.

Conclusion: Talaromyces can cause infection in non-HIV and non-endemic population and could be an under-recognized cause of pulmonary infections among veterans with even a remote history of exposure to the organism during deployment.

**Introduction**

*Talaromyces* (*Penicillium*) *marneffei* is a dimorphic fungus and the only member in its genus known to be pathogenic to humans. It can cause both localized as well as overwhelming disseminated infection. *T. marneffei* is endemic to Southeast Asia [1,2]. It is an important opportunistic infection in HIV-infected patients who live in or have traveled to endemic regions and is considered an acquired immunodeficiency syndrome (AIDS) defining illness. Recently, there have been several case reports of *T. marneffei* infection in HIV-negative patients who are otherwise not immunosuppressed [2]. We report a case of a HIV negative Vietnam war veteran with advanced chronic obstructive pulmonary diseases (COPD) who presented with pulmonary *T. marneffei* lung infection which reactivated 40 years after a one year tour in Vietnam.

**Case**

Our patient was a 75-year-old Caucasian man, a Navy veteran, who served in Vietnam in the Swift Boat service in 1966. He had a history of
bulous emphysema and presented to his primary care provider with uncontrollable nonproductive cough, for which he was prescribed oral levofloxacin and steroids with no improvement. He was then referred to pulmonary medicine because of an abnormal chest computerized tomography (CT), which showed a cavitary left lower lobe (LLL) infiltrate and several lung nodules (Fig. 1).

Bronchoscopy with bronchoalveolar lavage (BAL) yielded no specific etiology and he was treated symptomatically. After transient improvement, there was recurrence of productive cough, night sweats, malaise, and new hemoptysis. A second chest CT showed increase in the size of the LLL cavitary infiltrate, a new small necrotizing lesion in the left lung, and a new small left pleural effusion. Repeat bronchoscopy with transbronchial biopsy and BAL as well as thoracentesis was performed, revealing a sterile exudate and nondiagnostic findings on transbronchial biopsy and BAL. The patient was empirically started on itraconazole suspension on suspicion of an indolent fungal infection even though serologies for Histoplasma, Cryptococcus, and Coccidiomycosis were negative. Therapy had to be stopped due to gastrointestinal (GI) side effects. The patient was then changed to voriconazole but his symptoms continued unabated.

At this point, the patient was referred to Infectious Disease. Initial evaluation revealed a man with a severe cough, hemoptysis, and purulent sputum. Sputum samples were obtained for culture. Voriconazole was continued but only for short time because of side effects. The initial BAL grew a mold. Because he remained ill, the patient was started on liposomal amphotericin B (LAMB) and isavuconazole. The other bronchoscopy samples grew the same mold, which was identified as *Talaromyces* (*Penicillium*) *marneffei*. He was given 28 days of LAMB and isavuconazole with an excellent response and was discharged home on daily isavuconazole. On follow-up, he did very well and the antifungal was stopped at day 90. However, soon thereafter productive cough and malaise recurred. He was then readmitted and both isavuconazole and LAMB were resumed. His symptoms slowly worsened and isavuconazole was changed to voriconazole, but he continued to worsen. New lesions developed in his left lung as did a right lung cavitary opacity. Micafungin was added empirically and despite triple therapy, the patient progressed clinically and radiographically, and eventually succumbed to his infection. An extensive workup for an immunosuppressive state was nondiagnostic; HIV testing was repeatedly negative, including HIV viral load.

**Discussion**

*T. marneffei* infection is an important systemic mycosis in HIV-infected individuals who reside in or have traveled to Southeast Asia. It was described in many regions of Thailand, Vietnam, northeastern India, Southern China, Hong Kong, Taiwan, Laos, Malaysia, Myanmar, and Cambodia [2]. The prevalence of *T. marneffei* infection in non-HIV, non-endemic population is very low, only 4 cases were identified in the literature [3–6].

The first reported case of *T. marneffei* infection was laboratory acquired in France in 1959 and the first case due to natural exposure was reported in 1973, in a patient who had Hodgkin’s disease and lived in North America and who had traveled to Southeast Asia [1]. However, it was not until the late 1980s, with the arrival of the HIV epidemic in Asia, that the incidence of *T. marneffei* infection increased in the endemic population and among visitors traveling to Southeast Asia [7]. Hence, *T. marneffei* infection is considered an AIDS defining opportunistic infection.

With the use of potent antiretroviral therapy, the incidence of HIV-associated *T. marneffei* infection decreased considerably [2]. At the same time, the incidence increased in HIV-negative patients with other immunocompromising conditions who traveled to Southeast Asia. This change in epidemiology poses a diagnostic challenge. As a result, there may be delays initiating therapy which may result in disease progression and poor outcomes [7,8]. Often, the only clue a physician may have to make the appropriate diagnosis is a history of travel to an endemic area.

The pathogenesis of *T. marneffei* infection is unclear. The main mode of acquisition is inhalation of conidia from the environment. Phagocytic cells are the primary host defense against the fungus, resulting in granulomatous and suppurrative reactions in immunocompetent patients and necrotizing reactions in those who are immunocompromised [1]. Disseminated disease via the reticuloendothelial system is common in immunosuppressed individuals, in whom the severity of disease depends on the degree of immunosuppression. Five cases have been reported to date among non-HIV non-endemic patients, including the case described here [3,5,6,9], (Tables 1 & 2). Many of the HIV-negative non-endemic patients had immunocompromising conditions as well as disseminated disease at the time of diagnosis. Yet, only one of the patients reported died of *T. marneffei* infection. The fatality rate among patients with *T. marneffei* infection is low but this is based upon knowledge derived from only 5 cases. Since the prognosis of *T. marneffei* infection is less favorable if diagnosed late, clinician education about this
| Case | Sex/Age | Residence | Travel to Asia | Comorbidities | Symptoms | Chest X-ray/Computerized Tomography (CT)/other Diagnostic Procedure of T. marneffei | Treatment Outcome | Reference |
|------|---------|------------|----------------|---------------|----------|----------------------------------------------------------------------------------|----------------|----------|
| 1    | Male/45 | Australia  | Laos, Vietnam   | None          | Fever, lymphadenopathy, right-sided cough, left-sided pleuritic chest pain (4-month history) | CT: pulmonary infiltrates and mediastinal lymphadenopathy | Before definite diagnosis, he was treated empirically with TMP-sulfamethoxazole. | Resolution   | Joosten SA [9] |
| 2    | Male/79 | France     | Thailand, China | Chronic obstructive pulmonary disease (has received inhaled corticosteroid for several years) | Hemoptysis (2009) | 2009: BAL: negative; 2012: Thickening of the walls of the left cavity, BAL culture on Sabouraud dextrose agar with chloramphenicol | 2009: October-December, voriconazole 2012: amphotericin B for 10 days, followed by itraconazole for 3 months | Resolution   | A. De Monte [5] |
| 3    | Male/67 | Australia  | Vietnam: 10-day vacation | Received a cadaveric renal transplant for ESRF secondary to systemic vasculitis in 2004 | Ten months after trip to Vietnam: several weeks’ history of wheezing, reduced exercise tolerance, headache, fever, weight loss, anemia, leukopenia | Chest x-ray: no evidence of fungal disease; before definite diagnosis, he was started on IV piperacillin and tazobactam. | Treated empirically with IV piperacillin and tazobactam followed by 12 days of voriconazole and discharge on oral voriconazole for 12 months | Resolution   | A. Sebekha [3] |
| 4    | Female/41| Australia | Vietnam: 2-weeks post lung transplantation: Malaysia, Singapore | Ten months post-lung transplantation: fever, cough, weight loss, headache, rash, leukopenia | Six months after trip to Vietnam: several weeks’ history of wheezing, reduced exercise tolerance, headache, fever, weight loss, anemia, leukopenia | Chest CT: bilateral lung nodules and cavitary lesions, necrotizing lesion on left lung and pleural effusion | Histopathological analysis of resected colon revealed cryptitis, mycobacterial and non-typical granuloma. | Resolution   | A. Stathakis [3] |
| 5    | Male/75 | USA        | Vietnam War: 1966 | Vietnam War: 1966 | Bullous Emphysema | Worsening of his left upper lobe pain, fever, cough, night sweats, malaise, leukopenia | Reinitiated LAMB and isavuconazole, later exchange isavuconazole to voriconazole and added micafungin | Resolution   | Death Case report |
condition should be encouraged to improve early diagnosis and treatment.

It is very important to remember that T. marneffei is a primary pulmonary pathogen which may well use macrophages to proliferate and later cause acute pulmonary, disseminated and/or reactivation disease. The laboratory diagnosis is performed by identifying the fungus by microscopy and culture from a variety of specimens including blood, skin, bone marrow, lymph nodes, respiratory sources, liver biopsies, cerebrospinal fluid, urine, stool, kidney, pericardium, intestine or gastric specimens. A definitive diagnosis of T. marneffei infection by fungal culture has been reported with 100%, 90% and 76% sensitivity from bone marrow, skin biopsy and blood, respectively [1]. T. marneffei can be found on direct examination of a peripheral blood smear in patients with disseminated disease. Histopathological sections stained with hematoxylin and eosin, Grocott methenamine silver or periodic acid Schiff stain will demonstrate T. marneffei in biopsy specimens. In tissue, the yeast forms can be found with clearly defined central septae, characteristic of T. marneffei.

T. marneffei is generally susceptible to miconazole, itraconazole, ketoconazole and fluconazole, whereas amphotericin B has only intermediate fungicidal activity for this pathogen [1]. Current infectious disease guidelines recommend liposomal amphotericin B for 2 weeks, followed by oral itraconazole for ten weeks, followed by secondary prophylaxis [4]. This regimen has resulted in a 97.3% cure rate in a non-randomized study [10]. In our review, 3 patients who were treated initially with IV amphotericin B and later discharged on itraconazole had complete resolution. Our patient succumbed to this invasive fungal infection despite 6 months of intensive antifungal therapy. Initial therapy consisting of 30 days of amphotericin B plus itraconazole achieved an excellent response. Unfortunately, the infection recurred 3 months later. Voriconazole plus amphotericin B trial was started then, and ultimately, triple therapy with voriconazole, itraconazole and amphotericin B was administered with no positive outcome. Although we believe itraconazole in combination with LAMB had clinical success, time proved that we did not accomplish microbiological eradication since in his recurrence 4 months later this combination was not able to contain the invasive and progressive fungal respiratory infection, nor did any combination that we implemented thereafter. We believe the patient may have had an underlying immunosuppressive disorder that was neither HIV, hypogammaglobulinemia or any other obvious hematological disorder which remained undefined even after a reasonable extensive investigation.

Although there are only a handful of T. marneffei cases described in the literature among non-HIV, non-endemic patients, this should not keep health care providers from considering the diagnosis in the appropriate clinical context. Early diagnosis and appropriate treatment should result in clinical success and microbiological eradication, but delays in a timely diagnosis may result in a fatal outcome. *Penicillium* spp often grow from bronchoscopic samples and are typically disregarded as contaminants, but sub-speciation should be pursued in the appropriate clinical setting so as not to miss this potentially lethal pathogen.

We speculate that our patient is not the first Vietnam veteran who has developed late reactivation of this fungus, which we suspect remains all too frequently undiagnosed. We hope this case report will raise awareness of the potential for late reactivation of this dimorphic fungus in our Vietnam veteran population and promote its inclusion in the differential diagnosis of atypical lung infections in these patients.

**Conflict of interest**

All authors have no conflicts of interests to declare.

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**Contributors**

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**Competing interests**

None.

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| Table 2 | Non-HIV Patients with T. marneffei infection clinical symptoms*. |
|---------|----------------------------------|
| Symptom                  | P (%)               |
| Hemoptysis               | 4                  |
| Neutropenia              | 12                 |
| Abdominal pain           | 15                 |
| Diarrhea                 | 15                 |
| Arthritis                | 16                 |
| Splenomegaly             | 19                 |
| Hepatomegaly             | 23                 |
| Dyspnea                  | 33                 |
| Weight loss              | 34                 |
| Pneumonia                | 43                 |
| Anemia                   | 47                 |
| Malaise                  | 48                 |
| Cough                    | 50                 |
| Lymphadenopathy          | 50                 |
| Cutaneous or subcutaneous lesions | 53 |
| Thrombocytosis           | 55                 |
| Fever                    | 89                 |