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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 immunosuppresssed [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

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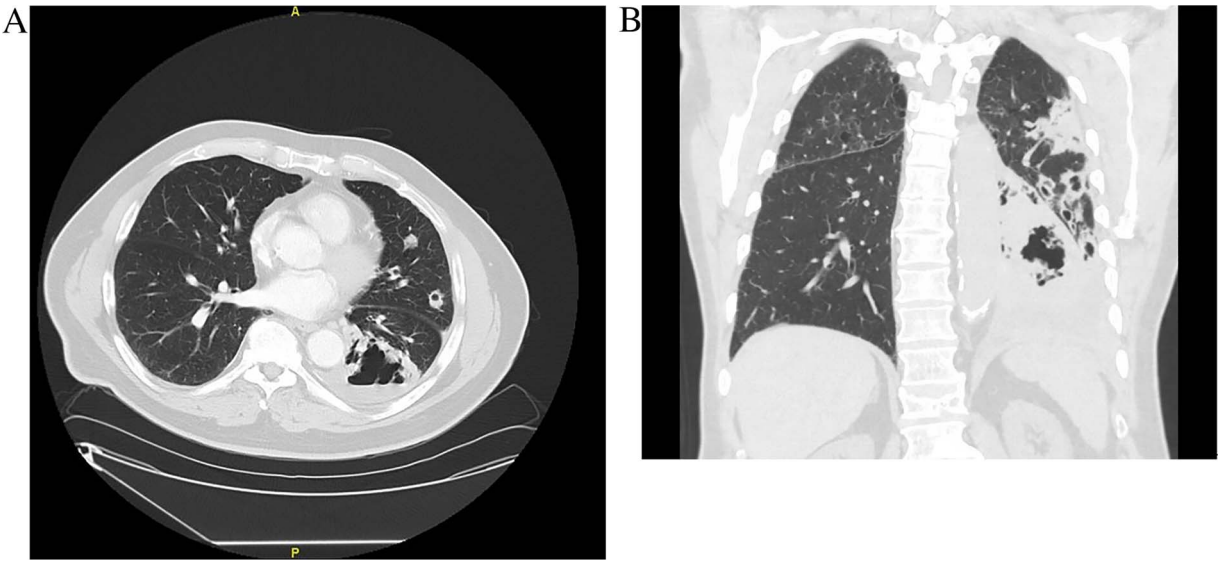

Fig. 1. a & b: Computerized tomography of the patient's lung showing the pulmonary lesion.

bullous 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 suppurative 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

Table 1
Talaromyces marneffei Infection in non-HIV, non-Endemic Infected Adult Patients.

	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 (recent travel; not specified how long ago before initial symptoms	None	Fever, lymphadenopathy, night sweats, cough, left sided pleuritic chest pain (4-month history)	CT: pulmonary infiltrates and mediastinal lymphadenopathy	Fiberoptic bronchoscopy; histopathological analysis and culture	First, he was treated empirically with TMP sulfamethoxazole. After diagnosis: inpatient with iv amphotericin B, discharge with Itraconazole	Resolution	Joosten SA [9]
2	Male/79	France	Thailand 1979 and China in 2002 for 15 days	Chronic obstructive pulmonary disease (has received inhaled corticosteroid for several years)	Hemoptysis (2009)	2009: CT: left apical opacity, BAL: negative 2012: Thickening of the walls of the left cavity, BAL	2012: BAL: culture on Sabouraud dextrose agar with chloramphenicol	2009: for suspected Aspergilloma: voriconazole October 2009-October 2010. 2012: amphotericin B for 10 days followed by itraconazole for 3 months	Resolution	De Monte A [5]
3	Male/67	Australia	Vietnam: 10-day vacation in December 2008	Received a cadaveric renal transplant for ESRF secondary to systemic vasculitis in 2004 (maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisolone.)	Two weeks after his return from vacation, his serum creatinine increased (124 to 190) and renal biopsy showed recurrent vasculitis. Six weeks later: he presented with a 3-week history of abdominal pain and diarrhea, with 2 days acute severe lower abdominal pain which progressed to septic shock	Chest x-ray: no evidence of fungal disease Laparotomy: perforated sigmoid colon diverticulum and intraperitoneal pus.	Blood and peritoneal fluid cultures after 3 days of incubation grew TM. Histopathological analysis of resected colon revealed CMV colitis but no fungal elements were seen on periodic acid-Schiff or Grocott's methenamine staining	Before definite diagnosis, the patient was started on IV piperacillin and tazobactam. After a diagnosis of TM: IV liposomal amphotericin B for two weeks followed by itraconazole as induction therapy for 3 months. After induction, prophylaxis of itra 300 mg daily was continued.	Resolution	J. Hart [6]
4	Female/41	Australia	2010: prior lung transplantation: Malaysia, Singapore, Thailand 18 months post-transplant: Vietnam for 2 weeks	2011: Underwent uncomplicated bilateral sequential lung transplantation for cystic fibrosis (maintenance immunosuppression consisted of tacrolimus, mycophenolate mofetil, and prednisolone.)	Ten months after trip to Vietnam: several weeks' history of wheezing, reduce exercise tolerance, headache, fever, weight loss, anemia, leukopenia	• Chest x-ray: mild peri-bronchial thickening in the retrocardiac area • Chest CT: bulky mediastinal and left hilar lymphadenopathy with narrowing of her left lingular and left lower lobe airways, peri bronchial infiltrate, lingual consolidation, atelectasis and a focal cavitating nodule in the posterior segment of her left upper lobe	BAL, blood cultures, and lymph node samples	Treated empirically with IV piperacillin-tazobactam and IV voriconazole for 12 days, discharge on oral voriconazole for 12 months	Resolution	A. Stathakis [3]
5	Male/75	USA	Vietnam War: 1966	Bullous Emphysema	Productive cough, night sweats, malaise, hemoptysis	• Chest CT: bilateral lung nodules and cavitary lesions, necrotizing lesion on left lung and pleural effusion • Bronchoscopy and Thoracentesis: negative • Biopsy: negative	BAL, sputum cultures	Treated with Liposomal amphotericin B plus isavuconazole for 28 days; discharged on oral isavuconazole for 90 day. At relapse: LAMB and Isavuconazole were reinitiated, later exchange isavuconazole to voriconazole and added micafungin	Death	Case report

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
Fungemia	43
Anemia	47
Malaise	48
Cough	50
Lymphadenopathy	50
Cutaneous or subcutaneous lesions	53
Thrombocytosis	55
Fever	89

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 flucytosine, 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 isavuconazole achieved an excellent response. Unfortunately, the infection recurred 3 months later. Voriconazole plus amphotericin B trial was started then, and ultimately, triple therapy with micafungin, voriconazole and amphotericin B was administered with no positive outcome. Although we believe isavuconazole 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, hypogammaglobinemia 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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Competing interests

None.

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