IDCases 33 (2023) e01831

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcases

Case report

Rare cases of *Talaromyces* pneumonia in individuals with underlying cancer and no travel to endemic areas

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ARTICLE INFO

Keywords:
Talaromyces marneffei
AIDS
Southeast Asia
Southern California
Malignancy
Immunosuppression

ABSTRACT

Introduction: *Talaromyces marneffei* causes a systemic fungal infection, referred to as talaromycosis, in immunocompromised individuals. Talaromycosis is an AIDS (acquired immunodeficiency syndrome) defining illness for patients living in the Southeast Asian region. Here we present two rarely reported cases of pulmonary talaromycosis in Southern California in patients with active cancer, negative HIV status, and no prior travel history to endemic regions.

Case description: Case 1: A 76-year-old male with a past medical history of emphysema and latent tuberculosis status post rifampin treatment, presented with a necrotic lung mass. He was diagnosed with squamous cell lung carcinoma and bronchoalveolar lavage cultures grew *Talaromyces marneffei.* He had no animal exposure or prior travel history to Asia. Due to a transfusion reaction to liposomal amphotericin (the mainstay of treatment), he required a transition to posaconazole. He was HIV-negative and expired due to underlying cancer and infection complications.

Case2: A 63-year-old male with a past medical history of tuberculosis, diabetes, and cavitary pneumonia with bronchoscopy positive for *Talaromyces* presented with worsening back pain and was found to have multiple sites of poorly differentiated adenocarcinoma likely originating from gastric adenocarcinoma. He was HIV-negative and expired due to complications from underlying cancer and infection.

Conclusion: We demonstrate that patients with pulmonary *Talaromyces* are becoming more prominent outside of endemic areas even in the setting of no prior travel. In addition, since patients with this infection are severely immunosuppressed, they require extensive workup for other comorbidities such as possible underlying cancer or tuberculosis.

Introduction

Penicillium, also known as *Talaromyces marneffei*, is a dimorphic fungus that has historically systemically infected individuals who are immunocompromised in Southeast Asia, India, and China [1]. *Talaromyces marneffei* is considered to be an acquired immunodeficiency syndrome (AIDS) defining illness for patients with human immunodeficiency virus (HIV) living in the Southeast Asia region. The transmission of *T. marneffei* has not been fully elucidated yet, however, studies suspect possible soil inhalation, especially during rainy season, or rodent-to-human transmission as possible avenues of infection [2]. T. *marneffei* has not been proven to transfer from person to person [2]. Those with HIV who successfully complete primary treatment with amphotericin benefit from secondary prophylaxis with oral itraconazole to prevent relapse [2].

In individuals who are HIV positive originating from endemic geographical regions presenting with pulmonary or systemic infection, *T. marneffei* should be considered as one of the differentials. However, without endemic risk factors, the diagnosis of *T. marneffei* can be overlooked. Here we present two rarely reported cases of pulmonary *talaromyces* in the Inland Empire of Southern California in patients originating from Mexico: one with squamous cell lung carcinoma and one later found to have metastasis from presumed gastric origin.

Case 1. A 76-year-old male with a past medical history of chronic obstructive pulmonary disease and atrial fibrillation presented for necrotic left lower lung mass (Fig. 1). The patient was originally from

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https://doi.org/10.1016/j.idcr.2023.e01831
Received 18 May 2023; Received in revised form 26 June 2023; Accepted 26 June 2023
Available online 28 June 2023
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Mexico and moved to California over 20 years ago and has never returned since. There was no active animal exposure nor prior travel history to Asia. He was diagnosed with stage IIIa squamous cell lung carcinoma via bronchoscopy. Initial infectious workup was negative except for a positive QuantiFERON test. He was diagnosed with latent tuberculosis and was started on a 4-month course of rifampin while pending initiation of paclitaxel and carboplatin. He then presented for hospitalization approximately 2 months later for worsening dyspnea and cough prior to the initiation of chemotherapy. It was noted that prior fungal bronchoalveolar lavage cultures resulted in T. marneffei and were started on liposomal amphotericin B (L-amB) given severe lung involvement in the setting of malignancy. His course was complicated by an infusion reaction with L-amB leading to acute respiratory failure needing transfer to the medical intensive care unit (MICU). The patient was switched to posaconazole due to significant contraindications with concurrent use of itraconazole, or voriconazole with rifampin. Plan was to continue Pposaconazole until completion of rifampin, then switch to itraconazole. The patient was stabilized and transferred out of the MICU prior to discharge home. He later expired outside of the hospital due to the progression of pulmonary malignancy.

Case 2. A 63-year-old male with a past medical history of hypertension and diabetes initially presented to our southern California pulmonary clinic for evaluation of a right lung cavitary pneumonia presumed secondary to extended-spectrum beta-lactamase (ESBL) Escherichia *coli* susceptible to trimethoprim/sulfamethoxazole (Fig. 2). A bronchoscopy demonstrated negative Aspergillus cultures, but positive for *Penicillium* species fungal cultures. The patient shown initially some clinical improvement with trimethoprim/sulfamethoxazole, but over the following six months, he developed a worsening productive cough with brown sputum, hemoptysis, night sweats, fevers, and chills. He was admitted to the hospital for worsening hemoptysis and initially started on meropenem given a history of ESBL *E. coli* on prior sputum culture. He was also given itraconazole 200 mg twice daily for the treatment of penicillium pneumonia with subsequent improvement of symptoms. One month later the patient presented with worsening back pain and was found to have multiple sites of poorly differentiated adenocarcinoma in the liver, bone, adrenal gland, and pancreas, likely originating from gastric adenocarcinoma. He was HIV-negative and expired due to complications from underlying cancer and infection.

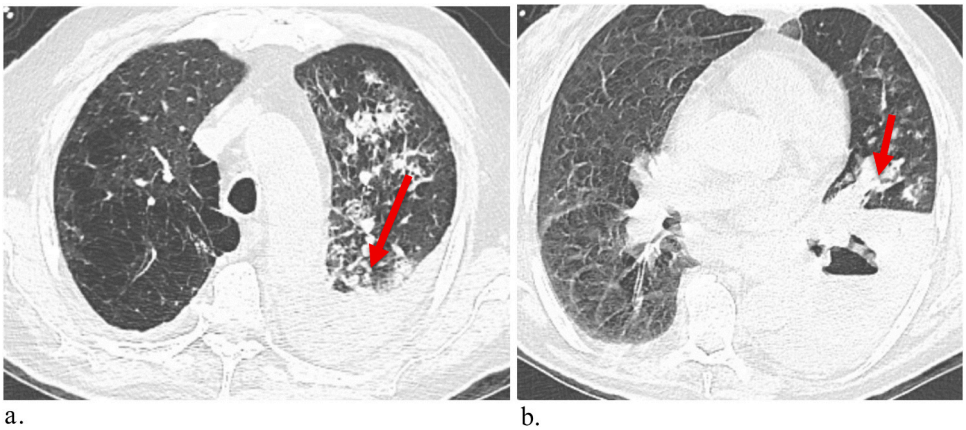
Discussion

Talaromyces marneffei is a dimorphic fungus that affects mammals, including humans. This fungus mainly targets the link and uses lymphatics and hematogenous spreads to affect other internal organs [3]. *Talaromyces marneffei* is prevalent in patients with HIV/AIDS due to reduced/defective CD4 cell function [3]. *Talaromyces marneffei* also is prominent in Southeast Asia. *T. marneffei* was first found in bamboo rats (*Rhizomys sinensis*) and was found to be affected in 75% of bamboo rats that resided in Thailand [4]. Although prevalent in HIV/AIDS patients, other conditions such as cancer, primary adult-onset immunodeficiency due to anti-interferon-gamma autoantibodies, and secondary immunosuppressive conditions including other autoimmune diseases, solid organ, and hematopoietic stem cell transplantations, T-lymphocyte-depleting immunosuppressive drugs can lead to increased susceptibility to *T. marneffei* [1].

Both cases exemplify patients without travel to endemic regions and at the time of presentation had no known risk factors for *T. marneffei.* It was not until the fungal cultures collected during bronchoscopy that T. *marneffei* was known to be contributing to pulmonary compromise in both patients. Appropriate initial treatment would include an antifungal and treatment for underlying immunosuppressive conditions. Amphotericin B and itraconazole have been shown to effectively treat *T. marneffei* and prevent recurrence [5]. Case 1 demonstrates initiation of 4th line treatments of pulmonary *Talaromyes* due to contraindications of liposomal Amphotericin with infusion reaction and drug interactions between rifampin and Itraconazole/voriconazole. It is unknown that earlier intervention of pulmonary *Talaromyces* would have played a significant role in the effectiveness of chemotherapy for squamous cell lung carcinoma.

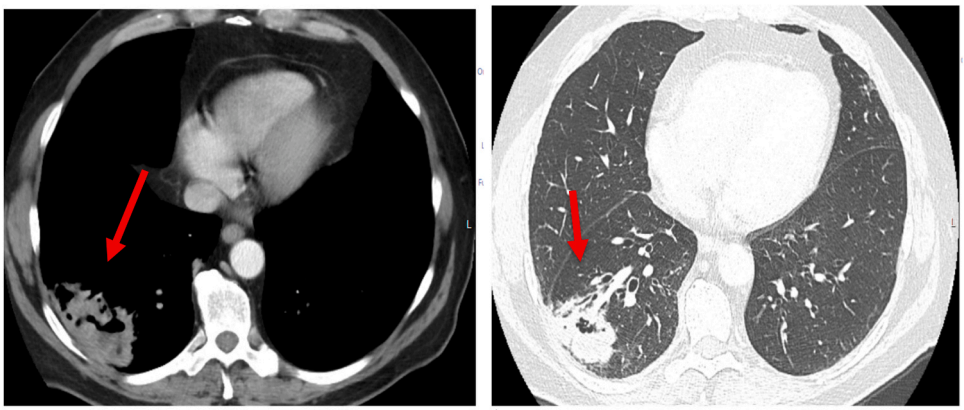
In Case 2, the initial clinical improvement with trimethoprim/sulfamethoxazole did not warrant the initiation of antifungals. However, once the patient returned with worsening symptoms, he was started on itraconazole 200 mg twice daily. If this patient was started on itraconazole once fungal cultures confirmed growth, the patient may not have had recurrence and exacerbation of symptoms related to his left cavitary lesion. More interestingly, the patient returned a month later due to back pain that imaging revealed was caused by metastatic disease. Although the patient died due to complications of his cancer, the unexplained *Talaromyces* could have provided the healthcare team a clue that the patient may be immunosuppressed. Multiple sites of poorly differentiated adenocarcinoma were discovered in the liver, bone, adrenal gland, and pancreas, thus indicating that further workup may have brought the originating adenocarcinoma to light sooner.

While the number of cases of talaromycosis in HIV/AIDS patients has been decreasing due to antiretroviral therapy, the number of cases in non-HIV/AIDS individuals has since increased [1,2]. Non- HIV-infected patients were found to have higher case fatality rates with this fungal infection, which may be related to the delayed diagnosis given lower suspicion [1]. There might be a high correlation between *Talaromyces marneffei* and indolent diseases such as cancer or tuberculosis given the findings in the studies above, which we believe should prompt future investigations to determine the actual prevalence and possible need to test for *Talaromyces* in these patient populations empirically. Given the



a. b.

Fig. 1. a and 1b: Axial CT scan of patient 1 showing necrotic lung mass.



a. b.

Fig. 2. a and 2b: Axial CT scan of patient 2 showing cavitary pneumonia.

high mortality rates of this fungal infection, these cases demonstrate the significance of the prompt diagnosis of this fungal disease in all immunocompromised individuals to prevent any delay in treatment.

Conclusion

Talaromyces marneffei is historically known to be prominent in Southeast Asia as an AIDS-defining illness, however, these cases reveal that patients do not always fit into the classic presentation of this rare fungal infection. We demonstrate that patients with pulmonary *Talaromyces* 1) are becoming more prominent outside of endemic areas even in the setting of no prior travel, 2) *Talaromyces* does not always indicate HIV-positive infection, and 3) since patients with this infection are severely immunosuppressed, they require extensive workup for other comorbidities such as possible underlying cancer or tuberculosis. The minimal risk factors of each of these patients infected with pulmonary *Talaromyces* call into question whether classically endemic diseases are spread more frequently due to the growing nature of travel and trade on an international level.

Consent

Written informed consent was obtainedfrom the patient for publication of this case report and accompanying images. Acopy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Ethical approval

Obtained from the patients.

Funding

No fundings.

CRediT authorship contribution statement

Manpreet K. Singh: Writing – original draft, Writing – review & editing. **Sheldon Borson**: Writing – original draft, Writing – review & editing. **Victor Lei**: Writing – review & editing. **Rhett Molloy:** Writing – review & editing. **Bruce Weng:** Supervision, collection, Writing – review and editing. **Made Sutjita:** Supervision, Writing – review & editing.

Declaration of Competing Interest

There are no conflicts of interest to disclose.

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