Clinical Case Report

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Coinfection of disseminated *Talaromyces marneffei* and *Mycobacteria kansasii* in a patient with papillary thyroid cancer

A case report

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Abstract

Rationale: Recently, *Talaromyces marneffei* (*T. marneffei*) has been reported in human immunodeficiency virus (HIV)-negative patient with underlying diseases, such as oral cancer, colon cancer, haematological malignancies, connective tissue disease, diabetes mellitus, and corticosteroids or immunosuppressive agents. Similar to HIV-positive ones, such patients were observed with CD4 lymphocytopenia.

Patient concerns: We reported a case of a 45-year-old woman who was diagnosed with disseminated *T. marneffei* and *Mycobacteria kansasii* (*M. kansasii*) with papillary thyroid cancer as the underlying disease. T-cell subsets counts, CD4 T-cell%, CD8 T-cell%, CD4/CD8 ratio, and NK cell% were all turned out to be normal.

Diagnoses: Based on bronchoalveolar lavage fluid and skin lesions secretion cultures, blood culture, the patient was diagnosed with disseminated *T. marneffei* and *M. kansasii*. Pathological examination reported papillary thyroid cancer with cervical lymph node metastasis.

Interventions: The patient received the combined and longer antifungal therapy and drug regimens for *M. kansasii*. She had total thyroidectomy with radical neck dissection to treat the papillary thyroid cancer.

Outcomes: The patient had a favorable outcome for 19 months without recurrence.

Lessons: *T. marneffei* could infect non-HIV individuals with underlying disease under the condition of normal T-cell counts. The symptoms were lack of specificity and were more likely to be misdiagnosed. Such patients with unidentified T-cell dysfunction or other unidentified primary immunodeficiency disorders may prone to coinfect with other opportunistic pathogens, such as *M. kansasii*. Compared with HIV-positive ones, they need combined and much longer antifungal therapy.

Abbreviations: *T. marneffei* = *Talaromyces marneffei*, *M. kansasii* = *Mycobacteria kansasii*, HIV = human immunodeficiency virus.

Keywords: mycobacteria kansasii, talaromyces marneffei, T-cell

1. Introduction

Recently *Talaromyces marneffei* (*T. marneffei*) (formerly named *Penicillium marneffei*)[1] has been reported to cause systemic mycosis in patients without HIV infection. Previous study observed that HIV-negative patient with underlying diseases (oral cancer, colon cancer, haematological malignancies, connective tissue disease, diabetes mellitus, and corticosteroids or immunosuppressive agents) had a remarkable lower lymphocyte cell counts than those without underlying diseases, especially the CD4 cell counts.[2] *Mycobacteria kansasii* (*M. kansasii*), which belongs to the group of nontuberculous mycobacteria (NTM), is another HIV-associated opportunistic pathogen. Here, we present a non-HIV patient with underlying disease who was diagnosed with disseminated *T. marneffei* and *M. kansasii* under the condition of normal T-cell counts.

2. Case report

A 45-year-old Chinese woman presented with arthralgia, productive cough, and fever for 10 months. Her past medical

Editor: Emmanuel Roilides.

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This work was supported by the National Natural Science Foundation of China (NO.81600065).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:52(e9072)

Received: 24 June 2017 / Received in final form: 11 November 2017 / Accepted: 13 November 2017

http://dx.doi.org/10.1097/MD.0000000000009072

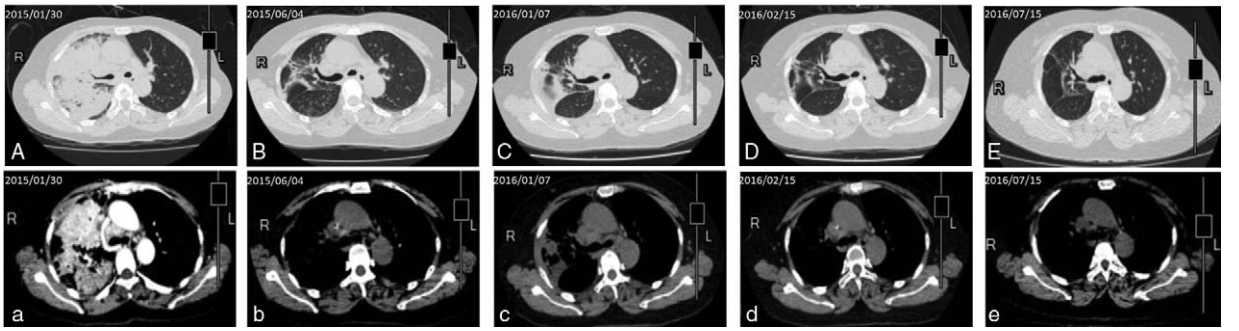

Figure 1. Chest CT images from Jan 30, 2015 to July 15, 2016. (A and a) The chest CT scan on admission displayed extensive consolidation in the right upper lung, with enlarged mediastinal lymph nodes. The extensive consolidation in the right upper lung presented uneven enhancement on the enhanced CT scan, whereas the densities of the enlarged mediastinal lymph nodes were enhanced evenly. (B and b) The chest CT scan after the first time treatment for *T. marneffei* showed that pulmonary consolidation was absorbed partly. (C and c) The chest CT scan after ultrasound-guided thoracentesis demonstrated the progressed consolidation of right lung at the second admission. (D and d) The chest CT scan revealed that the consolidation of right lung was absorbed obviously after anti-fungal therapy and treatment for *M. kansasii*. (E and e) The chest CT scan performed during the follow-up period in our Respiratory Clinic showed that the consolidation was almost absorbed.

history and family history were unremarkable except for a pituitary tumor removement 3 years ago. Her husband and 2 adult sons were in good health. There was no history of recurrent unusual infections including human T-lymphotropic virus-1 (HTLV-1) or blood transfusion, nor history of the usage of corticosteroids, immunosuppressive agent, NSAIDS, antimalarial drugs, antiepileptic drugs, or herbal medicine. In the past 10 months, she has been treated in 3 hospitals sequentially. Notable laboratory findings included positive T-SPOT.TB test and positive acid-fast staining in sputum for twice. Chest CT revealed consolidation in the right upper lung, enlargement of right hilar lymph nodes, and mediastinal lymph nodes. Three times of CT-guided right upper lung needle biopsies all reported chronic suppurative granulomatous inflammation with negative for acid-fast and fungal stainings (Grocott's methenamine silver staining and periodic acid-Schiff staining). As the etiology remained unclear, she received broad-spectrum antibiotics, antivirus therapy, treatment for *Pneumocystis jiroveci*, and 3 months of anti-Mycobacterium tuberculosis chemotherapy successively, but her symptoms did not alleviate. Therefore, she asked to be referred to our hospital in January 2015.

The patient's vital signs were as follows: temperature, 37.5°C; BP, 134/91 mm Hg; heart rate, 100 beats/min; respiratory rate, 21 breaths/min. Physical examination revealed ulcerating lesion in the skin of shoulder and multiple skin masses in the left anterior cervical, retroauricular, and retroauricular occipital. The biggest one was approximately 3cm × 2.5 cm. A nodule was also found on the right lobe of thyroid with the size of 1 cm × 1 cm.

HIV-antibody, HTLV 1/2 antibody, 3 sputum acid-fast bacillus smears and culture tests, autoimmune screen, bone marrow biopsy, and brain MRI scans were all negative, whereas Mantoux skin test was positive. There was no evidence of immunodeficiency after quantitative examinations for immunoglobulins (IgG: 42.9 g/L) and T-cell subsets (CD4%: 48%, CD8%: 28%, CD4/CD8 ratio: 1.7, NK%: 13.7%). The thyroid ultrasound showed thyroid carcinoma with cervical lymph node metastasis. Chest CT displayed extensive consolidation in the right upper lung, infiltrates in the lower lobe of the left lung and the middle and lower lobes of right lung (Fig. 1A, a). Furthermore, osseous destruction at the right first rib and enlarged hilar and mediastinal lymph nodes were also noted. Bronchoscope found a polypoid neoplasm at the opening of right principal bronchus (Fig. 2A), and congestion and edema of the mucous membrane in the superior lobar bronchus of the right lung (Fig. 2B). Biopsies demonstrated granulation tissue formation below the epithelial cells and chronic inflammation of bronchial mucosal, respectively. Bronchoalveolar lavage fluid (BALF) from the right upper lobe and skin lesions secretion cultures all yielded *T. marneffei* (Fig. 2C–D), but were negative for acid-fast staining and cultures for tuberculosis. Thus the patient was prescribed with Amphotericin B (AmB) for almost 5 months (Fig. 3A). After the initial intravenous infusion of 2 mg/d, the dosage of AmB was gradually increased to 45 mg Qd (0.75 mg/kg/d) in 10 days. Under these medications, not only her fever and cough resolved, but also the skin and osteolytic lesions got improved gradually. However, the maintenance dose of AmB needs to be gradually cut down because of acute renal injury. Itraconazole (400 mg/d) was initiated immediately when the development of a new pulmonary infiltrate was detected by chest CT on April 9, 2015. Chest CT was reexamined (Fig. 1B, b) before discharge, and then she continued Itraconazole at a dosage of 200 mg/d for another 10 weeks as secondary prophylaxis.

6 months later, the patient complained of low fever again, dyspnea with pain in the chest, and then she was admitted to our hospital for the second time in December 2015. Chest X-ray revealed a large amount of right pleural effusion. Ultrasound-guided thoracentesis was performed immediately, and pleural effusion analysis showed exudates effusion with culture negative for bacteria, fungi, and tuberculosis. Chest CT (Fig. 1C, c) displayed the progressed consolidation in the right lung. *M. kansasii* was identified in single hand blood culture for the first time on January 20, 2016. EBUS-TBNA biopsies of mediastinal lymph node reported lymphoid hyperplasia, whereas no pathogen was isolated by Gram's staining, acid-fast, and fungal stainings. As we still suspected recurrent *T. marneffei* infection, AmB was given again since January 20 (Fig. 3B). However, the dose of AmB was maintained at 35 mg Qd (0.58 mg/kg/d) due to drug-induced renal toxicity. Under these treatments, her fever was relieved. Itraconazole (400 mg/d) was also added to improve antifungal efficacy as previously. On February 5, a subsequent single hand blood culture confirmed *M. kansasii*, and then drug regimens for *M. kansasii* including Isoniazid, Rifampicin, Ethambutol, and Clarithromycin were initiated. After reexamination of chest CT (Fig. 1D, d), she underwent total

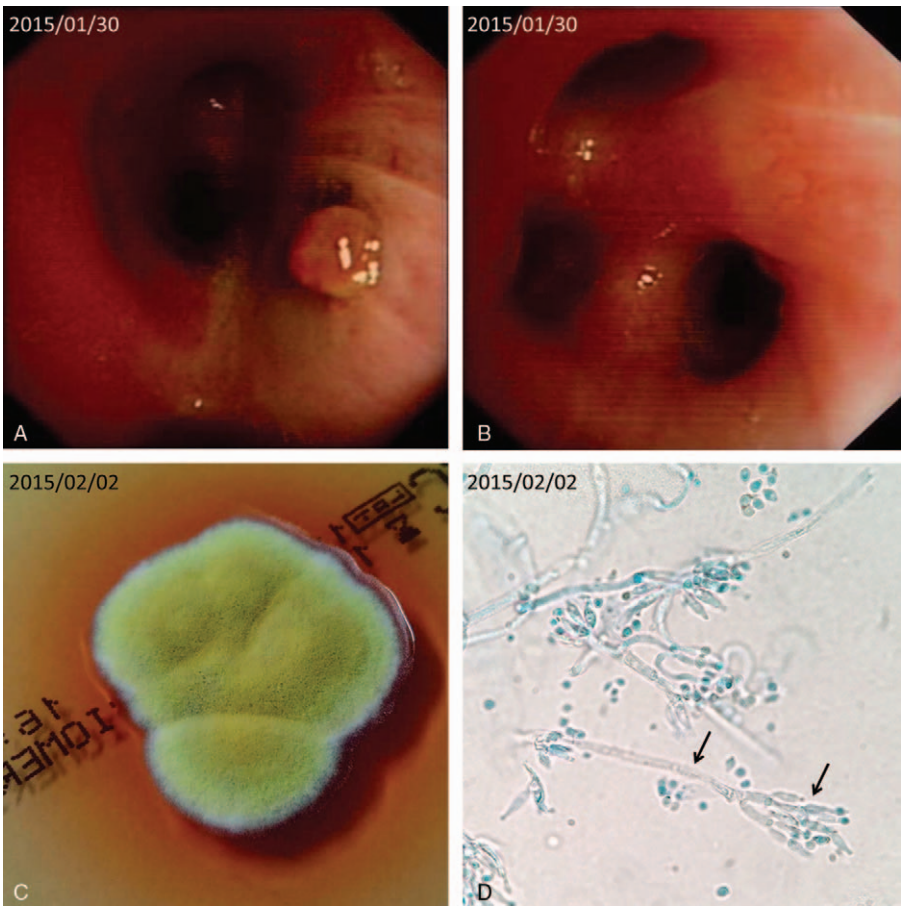

Figure 2. (A) A polypoid neoplasm at the opening of right principal bronchus could be observed under bronchoscopy. (B) Bronchoscopy image displayed the congested and edematous mucous membrane of the right superior lobar bronchus. (C) Culture of *T. marneffei* from our patient with bright red diffusing pigmentation (after 5 days incubation at 28°C, Sabouraud agar). (D) Typical phialides and penicillus (arrows) of *T. marneffei* at the microscopy observation (lactophenol cotton blue stain).

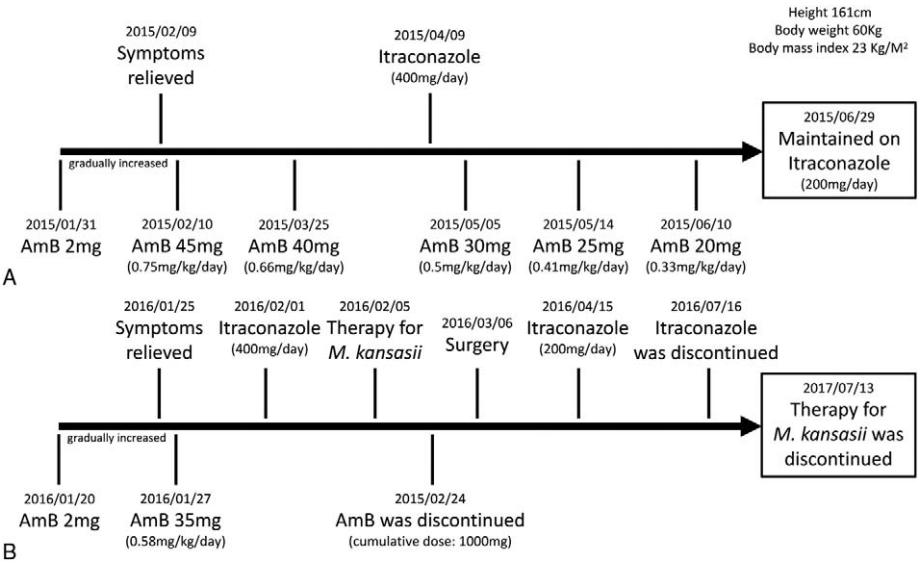

Figure 3. (A) Treatment timeline during her first hospitalization. (B) Treatment timeline during her second hospitalization.

thyroidectomy with radical neck dissection on March 6. Pathological examination reported papillary thyroid cancer with cervical lymph node metastasis. The patient recovered well after the operation and ultimately maintained on Itraconazole and regimens for *M. kansasii*. During the 19-month follow-up period, 3 times of chest CT, which were performed on July 15, 2016, November 4, 2016, and July 10, 2017, showed that the lesions in the right lung were almost absorbed, leaving few fibrous stripes (Fig. 1E, e), and therefore Itraconazole and regimens for *M. kansasii* were discontinued successively (Fig. 3B).

3. Discussion

Clinically, disseminated *T. marneffei* infection is characterized by fungal invasion of multiple body organ systems, including blood, skin, lungs, and so on. Based on the BALF and skin lesions secretion cultures, disseminated *T. marneffei* infection was diagnosed definitely in our patient. When she was admitted to our hospital for the second time, effective anti-fungal treatment and the detection of *M. kansasii* occurred simultaneously. However, were the mixed infections took place concurrently or successively? In our patient, although disseminated *M. kansasii* was confirmed later in the second admission, it should be pointed out that positive T-SPOT.TB test and acid-fast staining in sputum were detected before she was transferred to our hospital. Unfortunately, our patient did not undergo strain identification at local hospitals, even though studies provided evidence that infections with several strains of NTM including *M. kansasii* also could result in a positive T-SPOT.TB result.[3] In addition, the lung lesions were not absorbed completely after antifungal therapy during her first hospitalization, indicating the potential infections with 2 or more pathogens. Thus, in our opinion, the mixed infections of disseminated *T. marneffei* and *M. kansasii* were to occur concurrently instead of sequentially.

Although the current guideline for treatment of *T. marneffei* in HIV-positive patients was intravenous AmB for 2 weeks, followed by oral itraconazole,[4] there were no recommendations about the appropriate duration of treatment in HIV-negative ones. Our patient received intravenous AmB for almost 5 months during the first hospitalization, which was much more longer than the guildlines for HIV-positive patients. What is more, considering the development of new pulmonary infiltrate during this period, we even added oral Itraconazole to AmB instead of the sequential treatment which was recommended in HIV-positive ones.

Both *T. marneffei* and *M. kansasii* were opportunistic pathogens, which indicated the presence of impaired cell-mediated immunity. Previous studies from China and Thailand demonstrated that cancer, including solid tumors and hematological malignancies, was one of the major underlying diseases in *T. marneffei* -infected individuals without HIV.[2,5–6] Recently, Qiu et al reported that HIV-negative patients with underlying disease had much lower CD4 T-cell counts and CD4 T-cell% than those without underlying disease.[2] In contrast, CD4 T-cell counts, CD4 T-cell%, CD8 T-cell%, CD4/CD8 ratio, and NK cell% were all turned out to be normal in our patient with papillary thyroid cancer as the underlying disease. The mechanisms involved in the cancer-induced immunosuppression were complicated and not yet fully clarified. Therefore, we strongly speculated that the impaired cell-mediated immunity in HIV-negative individuals at least partly because of T-cell dysfunction instead of T-cells lymophocytopenia.

Immunodeficiency due to IFN-γ autoantibodies was an emerging adult-onset immunodeficiency syndrome first described in 2004.[7–8] The affected patients have a high-titer of neutralizing anti-IFN-γ autoantibodies that inhibit STAT1 phosphorylation and IL-12 production, leading to a higher susceptibility to infections associated with intracellular pathogens, including *T. marneffei*, NTM, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and so on.[9] Our patient experienced mixed infection with *T. marneffei* and *M. kansasii*, suggesting the possibility of the deficiency in the IFN-γ-IL-12 pathways. Unfortunately, she did not undergo the test of anti-IFN-γ autoantibodies because of the lack of laboratory resources in our hospital. Recently, Pruetpongpun et al noticed that such patients who did not receive specific treatment for anti-IFN-γ autoantibody were reportedly on relapse or developed new NTM infection during the 1- or 2-year follow-up.[10] Now our patient agrees that if she needs to be rehospitalized in the future, she will give her consent to the examinations of IFN-γ-IL-12 pathways.

From the clinical point of view, *T. marneffei* could infect non-HIV individuals with normal T-cell counts, and could cause fatal systemic mycosis. The clinical manifestations of disseminated *T. marneffei* were lack of specificity. Disseminated *T. marneffei* infection should also be considered when patients presented with multiple organ lesions which could not be explained by common pyogenic infection. In addition, those patients with unidentified T-cell dysfunction or other unidentified primary immunodeficiency disorders such as anti-IFN-γ autoantibodies might prone to coinfect with other opportunistic pathogens, such as *M. kansasii*, which could make diagnosis even more difficult. Lastly, besides treating the underlying disease or condition, there was a great need for combined and much longer antifungal therapy than HIV-positive individuals.

This case also has 2 limitations. First, clinical picture of cutaneous lesions and skin biopsy were refused by our patient. Second, the comparison of the molecular pathways involved in T-cell dysfunction between *T. marneffei* with underlying disease and without underlying disease was not investigated due to the small number of cases.

4. Conclusions

We presented a patient had coinfection of disseminated *T. marneffei* and *M. kansasii* with normal T-cell subsets counts, which was not reported yet in non-HIV individuals with underlying disease. Such patients may have unidentified T-cell dysfunction or other unidentified primary immunodeficiency disorders such as anti-IFN-γ autoantibodies, and the combined and much longer antifungal therapy was strongly recommended in these patients. However, the efficacy and duration of treatment need further evaluation.

Acknowledgments

We thank Penghao Guo for technical assistance with this study.

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