Original Article

Clinical characteristics and risk factors of *Talaromyces marneffei* infection in human immunodeficiency virus-negative patients: A retrospective observational study

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BACKGROUND: To investigate the clinical characteristics and risk factors of human immunodeficiency virus (HIV)-negative patients with *Talaromyces marneffei* (*T. marneffei*) infection.

METHODS: We retrospectively collected the clinical information of HIV-negative patients with *T. marneffei* infection from January 1, 2010 to June 30, 2019, and analyzed the related risk factors of poor prognosis.

RESULTS: Twenty-five cases aging 22 to 79 years were included. Manifestations of *T. marneffei* infection included fever, cough, dyspnea, chest pain or distress, lymphadenopathy, ear, nose, and throat (ENT) and/or skin lesions, bone or joint pain, edema and pain in the lower extremities, digestive symptoms, icterus, malaise, and hoarseness. Two cases had no comorbidity, while 23 cases suffered from autoimmune disease, pulmonary disease, cancer, and other chronic diseases. Sixteen cases had a medication history of glucocorticoids, chemotherapy or immunosuppressors. Pulmonary lesions included interstitial infiltration, nodules, atelectasis, cavitary lesions, pleural effusion or hydropneumothorax, bronchiectasis, pulmonary fibrosis, pulmonary edema, and consolidation. The incidence of osteolytic lesions was 20%. Eight patients received antifungal monotherapy, and 11 patients received combined antifungal agents. Fifteen patients survived and ten patients were dead. The Cox regression analysis showed that reduced eosinophil counts, higher levels of blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), myoglobin (Mb), procalcitonin (PCT), and galactomannan were related to poor prognosis (hazard ratio [*HR*]>1, *P*<0.05).

CONCLUSIONS: Bone destruction is common in HIV-negative patients with *T. marneffei* infection. Defective cell-mediated immunity, active infection, multiple system, and organ damage can be the risk factors of poor prognosis.

KEYWORDS: *Talaromyces marneffei*; Human immunodeficiency virus; Bone destruction; Risk factors

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INTRODUCTION

Talaromyces marneffei (*T. marneffei*), formerly known as *Penicillium marneffei*, is an opportunistic pathogen prevalent in Southeast Asia, especially in Thailand, Vietnam, Laos, Myanmar, Cambodia, Malaysia, China, and India.[1-4] *T. marneffei* infection has been previously considered as a life-threatening disseminated fungal infection exclusively in HIV-positive patients.[5,6] However, the use of antiretroviral therapy and other control measures for the HIV infection have changed the epidemiology of *T. marneffei* infection, with an increasing number of infected cases reported in HIV-negative patients who were in other congenital or acquired immunocompromising conditions.[7] Higher

mortality in HIV-negative patients with *T. marneffei* infection than in HIV-positive patients has been reported, which is possibly caused by delayed diagnosis.[5,8] In this study, we aim to analyze the characteristics and clinical outcomes of HIV-negative patients with *T. marneffei* infection in our hospital from Southern China to discover some risk factors for this opportunistic and lethal infection.

METHODS

Study population

HIV-negative patients with culture-documented *T. marneffei* infection in our hospital from January 1, 2010 to June 30, 2019 were reviewed. Only patients with adequate clinical information and specimens available for analysis were included.

Diagnostic criteria for *T. marneffei*

Patients with positive cultures of *T. marneffei* from blood, marrow, stool, urine, lymph node, bronchoalveolar lavage fluid (BALF), sputum, or secretions from skin lesions were diagnozed to have *T. marneffei* infection. Blood cultures were performed with the BacT/ALERT 3D system (BioMérieux®, Marcy l'Etoile, France). The specimens were incubated for seven days before being reported as negative. Positive fungal cultures were confirmed by Gram staining of a smear of the blood culture broth, followed by subculture onto Sabouraud dextrose agar (SDA) without cycloheximide with incubation at 25 ℃ and 37 ℃ in room air. *T. marneffei* was identified by the following criteria: (1) demonstration of thermal dimorphism by showing conversion from the yeast-like form at 37 ℃ to the mold-like form at 25 ℃;[9] (2) production of diffusible red pigment from the mold form when it is cultured at 25 ℃ on SDA; (3) the microscopic morphology of the mycelia including the presence of conidiophore-bearing biverticillate penicilli, with each penicillus being composed of four to five metulae with smooth-walled conidia.[7] Clinical specimens other than blood were examined microscopically both by Gram staining and after digestion with 20% KOH, for the presence of fungal elements. The specimens were then cultured on SDA at 25 ℃ and 37 ℃.

Data collection

Clinical information on age, gender, comorbidities, medication history, symptoms, mean diagnosis time from admission, laboratory results, imaging manifestations, antibiotic therapies, and clinical outcomes was collected and analyzed. If the death occurred within two weeks after diagnosis or if persistent positive fungal cultures were found at the time of death, then a causal relation between *T. marneffei* infection and the death was considered.

Statistical analysis

All patients were divided into the survival group and the death group according to their clinical outcome. Data were presented in numbers (%), mean±standard deviation (SD) for normally distributed values, median and interquartile range (IQR) for non-normally distributed values. We used the Mann-Whitney *U*-test, Student's *t*-test or Kruskal-Wallis test as appropriate to compare the demographic data and clinical characteristics between the survival group and the death group. Univariable analysis and multivariable analysis of risk factors for all-cause mortality were used for logistic regression analysis. Variables with a *P*-value <0.10 from the univariable analysis were then tested in multivariable models using forward stepwise procedures. Analysis was performed through IBM SPSS Statistics for Windows, version 16 (SPSS, Inc., Chicago, USA). A *P*-value of <0.05 was used to indicate statistical significance.

RESULTS

Demographic data and clinical characteristics

Twenty-five HIV-negative patients with *T. marneffei* infection, aging 22.0–79.0 years, were included in our study. The median age was 51.3 years. The ratio of male and female was 15:10. Demographic data and clinical characteristics of *T. marneffei*-infected patients are listed in Table 1.

Laboratory findings

The culture-positive specimens (*n*=32) were obtained from sputum (53%), blood (19%), urine (9%), lymph node (6%), BALF (6%), skin (3%), and central venous catheter tip (3%). Ten (40%) patients had no concurrent infection, while 15 (60%) patients were co-infected with fungi such as *Candida Glabrata* (*n*=1), *Candida albicans* (*n*=2), *Aspergillus* (*n*=3), *Trichosporon asahii* (*n*=1), and bacteria such as *Pseudomonas aeruginosa* (*n*=1), *Burkholderia cepacia* (*n*=4), *Haemophilus influenzae* (*n*=2), *Streptococcus pneumoniae* (*n*=1), *Acinetobacter bauman* (*n*=1), *Stenotrophomonas maltophilia* (*n*=2), *Staphylococcus* (*n*=1), *Staphylococcus aureus* (*n*=1), *Staphylococcus haemolyticus* (*n*=1), *Klebsiella pneumonia* (*n*=2), *Enterobacter cloacae* (*n*=1), *Enterococcus faecium* (*n*=1), *Escherichia coli* (*n*=1), *Mycobacterium tuberculosis* (*n*=1), and *Mycobacterium kansasii* (*n*=1).

Table 1. Clinical characteristics of *T. marneffei*-infected patients, *n* (%)

Variables	Total (*n*=25)	Survival (*n*=15)	Death (*n*=10)	*P*-values
Male	15 (60.0)	10 (66.7)	5 (50.0)	0.405
Female	10 (40.0)	5 (33.3)	5 (50.0)	0.405
Median age, years, median (interquartile range)	51.3 (22.0–79.0)	50.6 (24.0–76.0)	52.4 (22.0–79.0)	0.801
Mean diagnostic days from admission, days, median (interquartile range)	9.2 (1.0–24.0)	7.5 (1.0–24.0)	11.9 (2.0–24.0)	0.147
Symptoms				
Fever	13 (52.0)	8 (53.3)	5 (50.0)	
Cough	13 (52.0)	8 (53.3)	5 (33.3)	
Dyspnea	9 (36.0)	5 (33.3)	4 (20.0)	
Chest pain or distress	4 (16.0)	3 (20.0)	1 (10.0)	
ENT/skin lesions	2 (8.0)	2 (13.3)	0 (0)	
Lymphadenopathy	2 (8.0)	1 (6.7)	1 (10.0)	
Bone or joint pain	2 (8.0)	2 (13.3)	0 (0)	
Edema and pain in lower extremities	2 (8.0)	0 (0)	2 (20.0)	
Digestive symptoms	2 (8.0)	1 (6.7)	1 (10.0)	
Urinary frequency & urgency	2 (8.0)	2 (13.3)	0 (0)	
Icterus	1 (4.0)	1 (6.7)	0 (0)	
Malaise	1 (4.0)	1 (6.7)	0 (0)	
Comorbidities				
SLE	2 (8.0)	0 (0)	2 (20.0)	
COPD	6 (24.0)	3 (20.0)	3 (30.0)	
Renal transplantation	6 (24.0)	4 (26.7)	2 (20.0)	
Diabetes	6 (24.0)	3 (20.0)	3 (30.0)	
Pulmonary tuberculosis	3 (12.0)	3 (20.0)	0 (0)	
Cancer	4 (16.0)	3 (20.0)	1 (10.0)	
Nephrotic syndrome	1 (4.0)	0 (0)	1 (10.0)	
Pemphigus	1 (4.0)	0 (0)	1 (10.0)	
Ulcerative colitis	1 (4.0)	0 (0)	1 (10.0)	
Asthma	1 (4.0)	1 (6.7)	0 (0)	
Silicosis	1 (4.0)	0 (0)	1 (10.0)	
Rheumatoid arthritis	1 (4.0)	0 (0)	1 (10.0)	
Epilepsy	1 (4.0)	1 (6.7)	0 (0)	
Congenital heart disease	1 (4.0)	0 (0)	1 (10.0)	
Hypertension	2 (8.0)	1 (6.7)	1 (10.0)	
None	2 (8.0)	2 (13.3)	0 (0)	
Contact history of poultry	1 (4.0)	1 (6.7)	0 (0)	
Antifungal therapies	19 (76.0)	11 (73.3)	8 (80.0)	
Monotherapy	8 (32.0)	3 (20.0)	5 (50.0)	
Combined therapy	11 (44.0)	8 (53.3)	3 (30.0)	
Azoles	14 (52.0)	8 (53.3)	6 (60.0)	
Echinocandins	12 (44.0)	5 (33.3)	7 (70.0)	
Amphotericin B	6 (24.0)	4 (26.7)	2 (20.0)	
5-Flucytosine	1 (4.0)	1 (6.7)	0 (0)	
Chemotherapy	1 (4.0)	1 (6.7)	0 (0)	
Immunosuppressor	10 (40.0)	5 (33.3)	5 (50.0)	0.405
Glucorticoids	16 (64.0)	8 (53.3)	8 (80.0)	0.174
Co-infection	15 (60.0)	6 (40.0)	9 (90.0)	0.012*
WBC ≥10×10^9/L	12 (48.0)	7 (46.7)	5 (50.0)	0.870
Neutrophil ≥6.3×10^9/L	14 (56.0)	8 (53.3)	6 (60.0)	0.742
Eosinophil ≥0.005×10^9/L	13 (52.0)	12 (80.0)	1 (10.0)	0.001*
Monocyte counts ≥0.03×10^9/L	17 (68.0)	13 (86.7)	4 (40.0)	0.014*
Lymphocyte ≥0.19×10^9/L	5 (20.0)	4 (26.7)	1 (10.0)	0.307
Hb ≥100 g/dL	15 (60.0)	9 (60.0)	6 (60.0)	1.000
PLT ≥10×10^9/L	19 (76.0)	12 (80.0)	7 (70.0)	0.566
BUN ≥8.6 mg/L	13 (52.0)	4 (26.7)	9 (90.0)	0.002*
Cr ≥120 μmol/L	8 (32.0)	4 (26.7)	4 (40.0)	0.484
ALT ≥40 U/L	8 (32.0)	2 (13.3)	6 (60.0)	0.014*
AST ≥40 U/L	7 (28.0)	1 (6.7)	6 (60.0)	0.004*
TBIL ≥24 mmol/L	3 (12.0)	1 (6.7)	2 (20.0)	0.119
DBIL ≥6 mmol/L	3 (12.0)	1 (6.7)	2 (20.0)	0.315
IBIL ≥10.2 mmol/L	2 (8.0)	0 (0)	2 (20.0)	0.071
ALP ≥125 U/L	4 (16.0)	2 (13.3)	2 (20.0)	0.656
LDH ≥240 U/L	12 (48.0)	3 (20.0)	9 (90.0)	0.001*
ALB ≥35 g/L	16 (64.0)	11 (73.3)	5 (50.0)	0.234
APTT ≥40 seconds	16 (64.0)	9 (60.0)	7 (70.0)	0.610
PT ≥14 seconds	18 (72.0)	10 (66.7)	8 (80.0)	0.467
TnT ≥0.014 ng/L	10 (40.0)	2 (13.3)	8 (80.0)	0.001*
Mb ≥75 ng/mL	8 (32.0)	2 (13.3)	8 (80.0)	0.014*
CK-MB ≥1.0 ng/mL	12 (48.0)	5 (33.3)	7 (70.0)	0.072
BNP ≥900 pg/mL	10 (40.0)	2 (13.3)	8 (80.0)	0.001*
PCT ≥0.5 ng/mL	14 (56.0)	5 (33.3)	9 (90.0)	0.005*
G test ≥50	9 (36.0)	0 (0)	9 (90.0)	0.000*
GM test ≥1	5 (20.0)	1 (6.7)	4 (40.0)	0.041*

ENT: ear, nose, and throat; SLE: systemic lupus erythematosus; COPD: chronic obstructive pulmonary disease; WBC: white blood count; Hb: hemoglobin; PLT: platelet; BUN: blood urea nitrogen; Cr: creatinine; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; DBIL: direct bilirubin; IBIL: indirect bilirubin; ALP: alkaline phosphatase; LDH: lactic dehydrogenase; ALB: albumin; APTT: activated partial thromboplastin time; PT: partial thromboplastin time; TnT: troponin T; Mb: myoglobin; CK-MB: creatine kinase-MB; BNP: brain natriuretic peptide; PCT: procalcitonin; G test: β-1,3-glucanase test; GM test: galactomannan test; *: *P*-value <0.05.

Imaging results

The chest computed tomography (CT) manifestations in 19 patients with pulmonary lesions were as follows: interstitial infiltration (63.1%), nodules (26.3%), atelectasis (21.0%), cavitary lesions (21.0%), pleural effusion or hydropneumothorax (15.7%), bronchiectasis (15.7%), pulmonary fibrosis (15.7%), pulmonary edema (10.5%), consolidation (5.2%). Though some patients in our study were co-infected with *Aspergillus*, no patient showed any typical signs of aspergillosis. Six patients had no lung involvement.

Osteolytic lesions were found in 5 (20%) patients whose lumbar vertebrae, thoracic vertebrae, humerus, ribs, axial bone and pelvis were involved. Positron emission tomography-computed tomography (PET-CT) showed generalized lymphadenopathy, active bone metabolism, and bone destruction.

Therapy of *T. marneffei* infection

Nineteen (76%) patients received antifungal therapy. Eight patients were treated with monotherapy, while 11 patients were treated with combined antifungal agents. Used antifungal agents included amphotericin B, voriconazole, itraconazole, caspofungin, micafungin, and 5-flucytosine. In consideration of contamination, 6 (24%) *T. marneffei*-positive patients were not given antifungal treatment. They were treated with antibiotics for bacterial infection.

Clinical outcomes

In our study, 15 (60%) patients survived at discharge, and 10 (40%) patients were dead. The mean diagnostic time from admission in surviving patients was 7.5 days, while it was 11.9 days in dead patients. Comparing these two groups, we found statistically significant differences ($P<0.05$) in the percentage of co-infection, eosinophil counts, monocyte counts, the levels of blood urea nitrogen (BUN), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), troponin T (TnT), myoglobin (Mb), brain natriuretic peptide (BNP), procalcitonin (PCT), β-1,3-glucanase, and galactomannan. The univariate Cox regression showed that the diagnostic time, reduced eosinophil and monocyte counts, higher levels of BUN, ALT, AST, LDH, TnT, Mb, BNP, PCT, β-1,3-glucanase, and galactomannan were related to poor prognosis (95% confidence interval [*CI*], $P<0.05$). The multivariate Cox regression showed that reduced eosinophil counts, higher levels of BUN, ALT, AST, LDH, Mb, PCT, and galactomannan were related to poor prognosis (hazard ratio [*HR*]>1, $P<0.05$).

DISCUSSION

The current study found that the HIV-negative patients with disseminated *T. marneffei* infection manifested similar symptoms to those reported in the literature.[8] As one of the intracellular pathogens, *T. marneffei* proliferates in macrophages and disseminates via the reticuloendothelial system.[10] The infection is characterized by fungal invasion of multiple systems, especially blood, bone marrow, skin, lungs, and reticuloendothelial tissues, which was also found in our study.

About 20% of included patients had bone damage in the spine, pelvis, humerus, and ribs. Here we should mention that *T. marneffei* infection combined with osteolytic bone destruction is not rare.[8,11-13] A previous study reported that the osteolytic lesions often occurred in long bones and flat bones, such as femur, humerus, tibia, clavicle, ribs, skull, scapula, vertebrae, and ilium.[14] They can be multiple lesions, accompanied by obvious bone pain, and prone to pathological fractures.[15] HIV-positive patients often have leukopenia, positive blood cultures, fever, splenomegaly, and umbilical skin lesions, but HIV-negative individuals are more likely to have increased leukocytes (higher $CD4^+$ cell counts), negative blood cultures, dyspnea, and bone destruction.[2,4,7] Kudeken et al[16,17] reported that the osteolysis could be caused by the effect of leukocyte hydrolase in the lesion, and was closely related to strong autoimmune response induced by leukocyte and high antibody titers. The rare occurrence of osteolysis in HIV-positive patients may be due to insufficient quantity and deficient function of leukocyte. Bone imaging often manifests multifocal radioactive concentration, which can be easily misdiagnosed as metastases, suppurative osteomyelitis, multiple myeloma, and bone tuberculosis. Talaromycosis involving bone destruction often indicates more severe levels of the disease and a higher recurrence rate. Thus, patients should be treated with prolonged antifungal therapy along with regular monitoring of blood routine tests and bone imaging, avoiding the possibility of relapse.[18]

The host defense against *T. marneffei* infection depends on effective cell-mediated immunity with the activation of macrophages by T-lymphocyte-derived cytokines, especially those from the T helper type 1 (Th1) response, such as interleukin-12 (IL-12), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). A polarized Th1 response prevents immune evasion by *T. marneffei* in invaded mononuclear phagocytes and induces macrophage killing of intracellular *T. marneffei* via the L-arginine-dependent nitric oxide pathway.[1,8] These reports suggest that patients with deficient cell-mediated immune status can be susceptible to *T. marneffei*. In our study, most HIV-negative patients with talaromycosis

had comorbidities like diabetes that damaged the immune function, and chronic pulmonary diseases (tuberculosis, chronic obstructive pulmonary disease, asthma, and silicosis) that impaired the integrity of original tissue structure. Besides, those who suffered from autoimmune diseases, organ transplantation and cancer needed to be treated with glucocorticoids, immunosuppressors or chemotherapies, which weakened their immune function. With the increased incidence of autoimmune diseases and the use of immunotherapy (anti-CD20 or anti-IFN-γ monoclonal antibodies) in endemic regions of *T. marneffei*,[19] it would be important for clinicians to remain on high alert and perform continuous surveillance for the cell-mediated immune status and the opportunistic infections in those susceptible patients.

Through the primary analysis, we found statistically significant differences between the surviving group and the death group in co-infection and the levels of some biochemical biomarkers. These results showed that HIV-negative patients with *T. marneffei* infection could have higher mortality when combined with other infections, lower counts of eosinophils and monocytes, and higher levels of BUN, ALT, AST, LDH, TnT, Mb, BNP, PCT, β-1,3-glucanase and galactomannan, indicating defective immunity, active infection, multiple system and organ damage. In comparison, one study found that underlying disease, lower $CD4^+$ cell percentage, and T lymphocyte cell percentage were associated with overall survival.[20] Wang et al[21] mentioned that multiple system and organ damage was one main cause of poor prognosis for HIV-negative patients. We subsequently performed the Cox regression analysis to discover the risk factors of patients' poor prognosis. Both the univariate and multivariate analysis showed reduced eosinophil counts, higher levels of BUN, ALT, AST, LDH, Mb, PCT and galactomannan significantly associated with poor prognosis. Combining our previous findings, we suggested that defective cell-mediated immunity, active infection, multiple system, and organ damage could be the risk factors of poor prognosis.

In terms of antifungal therapy, the mortality of patients under monotherapy was 62.5% (5/8). Monotherapy included voriconazole or echinocandins. Meanwhile, the mortality of patients under combined therapy was 27.3% (3/11). One of the dead patients was treated with micafungin and caspofungin. An *in vitro* study found that the azoles had high activity against *T. marneffei* (except for fluconazole), amphotericin B showed intermediate antifungal activity, while echinocandins were intermediate to resistance.[22] International guidelines recommend amphotericin B as the first-line initial antifungal treatment for talaromycosis in HIV-infected patients, along with the itraconazole as maintenance treatment and prophylaxis.[23,24] However, the standard recommendation regarding the appropriate duration of treatment and prophylaxis of *T. marneffei* in HIV-negative patients is still unavailable. So the therapeutic protocol can vary significantly in different hospitals.

This study has several limitations. Firstly, we had limited results due to the small population. Secondly, the duration and dose of antifungal treatment were not mentioned clearly so that we could not observe and compare the effects of different antifungal agents on hospitality mortality. And we did not detect the $CD4^+$ cell counts of studied patients for immune status evaluation. We expect that further large-scale multicenter clinical studies will compare relevant effects of antifungal agents, discover further risk factors of *T. marneffei* infection or develop a reliable diagnostic tool for early identification.

CONCLUSIONS

Bone destruction is a common manifestation of HIV-negative patients with *T. marneffei* infection. Defective cell-mediated immunity, active infection, multiple system, and organ damage can be the risk factors of poor prognosis.

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Ethical approval: This study was approved by the Institutional Research Ethics Committee of our hospital. Informed consent was waived because of the retrospective nature of this study.

Conflicts of interests: All authors declared no conflicts of interest.

Contributors: HYW and WJL contributed equally to this work. JX and PHG conceived the project and designed the study. HYW, WJL and BL analyzed and interpreted the data. HYW and WJL drafted the primary draft of the manuscript. LYW, AQJ, WDC, PHG, and JX revised the manuscript critically for important intellectual content. All authors have revised and approved the final version of the manuscript. All authors confirm that the manuscript has not been published before and it represents honest work.

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