Clinical Characteristics and Prognosis of Penicilliosis among Human Immunodeficiency Virus–Infected Patients in Eastern China

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Abstract. *Talaromyces marneffe* infection is increasingly observed in people living with human immunodeficiency virus (HIV) in eastern China, a nonendemic area. This study aimed to draw the clinician's attention to this disease by presenting the clinical characteristics and prognosis of penicilliosis among HIV-infected patients from this region. We retrospectively analyzed HIV-infected patients with culture-proven *T. marneffe* infection admitted during January 1, 2014–December 31, 2015, at the Shanghai Public Health Clinical Center. A total of 48 patients with confirmed HIV infection and penicilliosis were enrolled, which accounted for a mean of 3.2% (95% confidence interval: 2.4–4.2%) of yearly HIV infection admissions among patients from eastern China. Symptoms included fever, cough, and gastrointestinal complaints, whereas the most common sign was skin lesions. Anemia occurred in 87.5% (42/48) of the patients. The overall mortality rate was 16.7%. Low CD4 T-cell count and hemoglobin level were correlated with mortality. Based on these results, we concluded that penicilliosis should be considered in HIV-infected patients from eastern China who present with fever, cutaneous lesions, and anemia. The clinical characters and the prognosis of patients with penicilliosis are similar to those in endemic areas. More attention should be paid to penicilliosis patients with low CD4 T-cell count and/or low hemoglobin level.

INTRODUCTION

Talaromyces marneffe (formerly *Penicillium marneffe*) is a pathogenic thermally dimorphic fungus causing systemic mycosis named penicilliosis in immunocompromised patients. People living with human immunodeficiency virus (HIV) are the most affected population.

Although unproven, humans are assumed to become infected by inhaling aerosolized infectious conidia originating from thus far unidentified environmental sources.¹ Bamboo rat is also deemed as the reservoir for *T. marneffe* infection in humans as *T. marneffe* is consistently and reproducibly isolated from several species of bamboo rat across its known range including China.^{2–5} Similar to the distribution of bamboo rat, penicilliosis is currently endemic in southeast Asia including southern China, Vietnam, Thailand, etc.^{1,6–8} In these areas, *T. marneffe* causes about 50,000 new infections in HIV-infected patients and up to 5,000 deaths every year.^{9,10} However, it is increasingly diagnosed in immunocompromised individuals from nonendemic regions who have traveled to the endemic areas.^{11–14}

In mainland China, since the first Chinese case reported in 1984, there had been an accumulation of 668 cases until 2009.^{15–17} Guangxi and Guangdong provinces accounted for > 80% of the reported cases.^{7,18} Other provinces including Yunnan, Fujian, Hunan, and Hong Kong are also deemed to be endemic areas of penicilliosis. Immunocompromised patients in China from the nonendemic areas who traveled to the above provinces and became infected with *T. marneffe* were also reported.¹⁹

Most of the provinces in eastern China, except Fujian Province, are not the traditional endemic areas of penicilliosis. However, the number of patients from eastern

China infected with *T. marneffe* is increasing. Herein, we present the clinical characteristics and outcome of penicilliosis in HIV-infected patients in eastern China.

METHODS

Study populations. Electronic and hard copy medical records from the Shanghai Public Health Clinical Center (SPHCC), Shanghai, China, were searched for HIV-infected patients diagnosed with *T. marneffe* infection from January 1, 2014 to December 1, 2015. SPHCC is the only hospital that treats HIV infection in Shanghai, and also a tertiary referral hospital for difficult and complicated HIV-infected cases in eastern China. Penicilliosis was defined by a culture positive for *T. marneffe* from patients' specimens including sputum, blood, bone marrow, lymph nodes, etc. Cultures of clinical specimens were established on Sabouraud's dextrose agar at 25°C and 37°C.

Information including epidemiological history (place of birth, place of residence, travel history to the epidemic areas, and duration of stay), presenting complaint, physical examinations, and laboratory tests (blood routine test, liver function tests, CD4 T-cell count, specimen culture, and biopsy), as well as therapy for each cases was recorded. Patients were followed up at the outpatient clinic after discharge or received follow-up phone call at least 12 weeks since antifungal therapy. Information including any symptoms (e.g., fever, skin lesion, and abdominal pain) occurring after discharge, adherence to therapy, and the latest CD4 T-cell counts, if available, was collected during follow-up. Ethical approval was granted by the Ethics Committee of SPHCC (Ethics approval number: 2016-S-044-01). Due to the retrospective nature of the study, informed consent was waived.

Data analysis. Anemia was classified as mild (11.9–10.0 g/dL), moderate (9.9–8.0 g/dL), severe (7.9–6.5 g/dL), and life threatening (< 6.5 g/dL) based on the hemoglobin level in the blood. Thrombocytopenia was defined as platelet count below 100×10^9 cells/L. Elevated transaminase levels were considered as the blood concentration of either

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alanine transaminase or aspartate transaminase higher than 40 U/L.

Depending on the distribution, continuous variables were described as mean $\pm$ standard deviation or as median and range, respectively. Student's *t* test was performed to assess differences between two groups. Wilcoxon rank-sum tests were used for nonnormally distributed data. All analyses were performed using STATA v12.0 (StataCorp, College Station, TX).

RESULTS

Demographic data and epidemiological characters. A total of 48 patients with confirmed HIV infection and penicilliosis were enrolled in this study. The demographic characters of this population were shown in Table 1. The majorities of the patients were male with median age of 30 years. Except one case who was born in Heilongjiang Province but raised in Shanghai, all the other patients were born and raised in eastern China. Two patients had a short stay (less than 2 weeks) in Hainan and Guangxi provinces, respectively. One patient had worked in Guangdong Province for 1 year and another patient had traveled to Thailand before one set of symptoms. Other patients, except patients from Fujian Province, had never been to the endemic regions of penicilliosis.

Nearly half of the patients (23 cases) were from Jiangxi and Fujian provinces (12 and 11 cases, respectively). Other patients were from Zhejiang, Jiangsu, Anhui provinces, and Shanghai. (Figure 1) During this period, the accumulated number of HIV-infected inpatients from these provinces was 1,999. Thus, penicilliosis accounted for a mean of 3.2% (95% confidence interval: 2.4–4.2%) of yearly admissions among HIV-infected patients from eastern China. The prevalence of *T. marneffei* infection among HIV-infected patients from Jiangxi Province was highest (9.4% [5.0–15.9%]), followed by Fujian Province (8.0% [4.1–13.9%]). As SPHCC is the pointed hospital to treat HIV infection in Shanghai, its prevalence was lowest in Shanghai (0.6% [0.1–1.6%]) when compared with other provinces.

Clinical and laboratory features. The clinical and laboratory characteristics of the patients are summarized in Table 1. The most common symptoms were fever, fatigue, and skin lesions. The most consistent laboratory abnormal-

ity was anemia, which occurred in 87.5% (42/48) of the patients. Most of the anemia recorded was of the mild-moderate type with 7.1% severely anemic. Seven (14.6%) patients had initiated combination antiretroviral therapy (cART) before symptoms appeared. Two of these patients took ART drugs discontinuously for 1 and 3 years, respectively. The other five subjects had received cART with good compliance for a median of 10 months.

Talaromyces marneffei was mostly isolated from blood (39/48, 81.3%). Other clinical specimens including lymph node (four cases), sputum (three cases), and bone marrow (two cases) were also of important diagnostic value. The interval between one set of the symptoms and diagnosis was 37 (5–250) days. Seven patients (14.6%) were misdiagnosed as tuberculosis (TB) or pulmonary bacterial infection and received anti-TB or antibacterial therapy before the diagnosis of penicilliosis was reached.

Concurrent opportunistic infections (OIs) were diagnosed in 22 patients (45.8%), including microscopically confirmed TB or nontuberculous mycobacterial infection (six cases and one case, respectively), *Pneumocystis pneumonia* (PCP, four cases), cytomegalovirus (CMV) infection (two CMV retinitis cases and one CMV gastritis case), and other bacterial pneumonia (eight cases). Kaposi sarcoma was diagnosed in three of the other patients.

Treatment and outcome. Antifungal therapy was initiated in all the patients immediately after the diagnosis of penicilliosis was made. Treatment of *T. marneffei* infection used amphotericin B (0.4 mg/kg qd) intravenously for 2 weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks. Patients intolerant of amphotericin B were treated with intravenous voriconazole (400 mg every 12 hours on day 1 and then 200 mg every 12 hours for at least 3 days, followed by oral voriconazole, 200 mg twice daily for 12 weeks). Patients with mild disease were treated with oral itraconazole 400 mg/day for 8 weeks. Seven (14.6%) of the 48 patients received itraconazole, 39 (81.3%) of 48 received amphotericin B, and the remaining two (4.2%) of 48 received voriconazole. Itraconazole was continued at 200 mg once daily to prevent relapse until the patients regained a CD4 T-cell count > 100 cells/mm³ for over 6 months.²⁰

Regimens for cART were chosen based on the available drugs in China. Most of the regimens comprised of tenofovir + lamivudine + efavirenz. Lopinavir/ritonavir and raltegravir were also used as an alternative to efavirenz. The doses of cART drugs and antifungal drugs were adjusted according to the drug-drug interactions.

The outcome of the most majority of patients (40/48, 83.3%) was an improvement or cure at discharge. All these patients received itraconazole for prevention of recurrence. Eight patients (16.7%) died at a median of 15 days (range: 7–65 days) after admission. Two of them died of Kaposi sarcoma although antifungal therapy and chemotherapy were given. When comparing with patients with an improvement outcome, patients with documented death had lower CD4 T-cell count (2.5 [2–96] cells/mm³ versus 15 [1–163] cells/mm³, *P* < 0.05) and lower hemoglobin level (74.0 $\pm$ 19.2 g/L versus 98.5 $\pm$ 20.6 g/L, *P* < 0.01). The median interval between one set of the symptoms and diagnosis among patients was comparable in these two populations (57 [20–187] days versus 36.5 [5–250] days,

TABLE 1
Clinical and laboratory characters of the study population

Characters	All patients (N = 48)
No. (%) of men	47 (97.9%)
Age (years)	30 (21–67)
One set of symptoms/signs	
Fever, N (%)	40 (83.3%)
Fatigue, N (%)	22 (45.8%)
Skin lesions, N (%)	21 (43.8%)
Respiratory symptoms, N (%)	16 (33.3%)
Digestive symptoms, N (%)	8 (16.7%)
Hepatomegaly and/or splenomegaly, N (%)	16 (33.3%)
Lymphadenopathy, N (%)	10 (20.8%)
Laboratory test	
CD4 T-cell count (cells/mm ³)	14 (1–163)
Hemoglobin level (g/dL)	9.4 $\pm$ 2.2
Thrombocytopenia, N (%)	20 (41.7%)
Elevated transaminase levels, N (%)	29 (60.4%)

FIGURE 1. The geographic distribution of penicilliosis cases among human immunodeficiency virus–infected patients in eastern China.

$P = 0.36$). The mortality rate was higher in patients initiated with cART before admission than that in patients naïve to therapy, although the difference did not reach statistical significance (42.9% versus 12.2%, $P = 0.08$).

At the end of the follow-up, the CD4 cell count increased to 74.5 (2–292) cells/mm³. Penicilliosis relapsed in one patient who discontinued itraconazole and ART drugs. Three patients were rehospitalized because of fever, all of who were diagnosed with TB and relieved after anti-TB therapy.

DISCUSSION

Eastern China is not the traditional endemic area of penicilliosis. To our knowledge, this is the first study that reports the epidemiology of penicilliosis in this area. In the current study, penicilliosis accounted for a mean of 3.2% of yearly admissions among HIV-infected patients from eastern China. It is much lower than the 9.36–12.5% reported from Guangdong Province, China, and 11.0% reported from the National Hospital for Tropical Diseases in Hanoi City, northern Vietnam. But it is comparable to the 4.4% reported from the major referral hospital for infectious diseases in Ho Chi Minh City, southern Vietnam.^{21–24} Most importantly, most of the patients in this study had not traveled to the endemic area, suggesting the endemic area of penicilliosis may be extended. Thus, more researches, especially the epidemiological studies on penicilliosis, in eastern China are needed.

The median interval from the onset of symptoms to the diagnosis was 37 days, and even as long as 250 days in one case in our study. Although it did not affect the prognosis of patients in this study, a previous research did find that delay of the diagnosis for penicilliosis independently

predicted the early mortality of the patients.¹⁹ Meanwhile, seven patients (14.9%) were misdiagnosed as TB or pulmonary bacterial infection and received anti-TB or antibacterial therapy before the diagnosis of penicilliosis was reached. These indicate the unawareness of clinicians in these areas to penicilliosis. Thus, penicilliosis should be added as a differential diagnosis in HIV-infected patients from eastern China presenting with fever, cutaneous lesions, cough, sputum production, anemia, as well as low CD4 T-cell count.

In the current study, most of the patients were diagnosed based on the isolation of *T. marneffe* from blood culture. Previous study showed that skin biopsy/scrapings are of highest sensitivity for the isolation of *T. marneffe*, followed by blood and lymphoid node.²³ More than half of the patients in our study did not have any skin lesion, whereas most of them had fever. Thus, blood culture but not skin biopsy was routinely performed. Nevertheless, the presence of skin lesions may sometimes be suggestive of the diagnosis and results in more rapid initiation of empirical anti-fungal treatment in endemic areas.²³ Thus, skin biopsy/scrapings should be routinely prepared in patients suspected of penicilliosis.

Microbiological culture remains the gold standard for the diagnosis of penicilliosis. However, to initiate early treatment, a presumptive diagnosis can be made when the characteristic morphologic findings of this fungus are found in cytology or biopsy specimens. *Talaromyces marneffe* appear as oval or elongated yeast-like organisms with a clearly defined central septum which is characteristic of *T. marneffe* as it reproduces by binary fission. The distinguishing features of microorganisms which may be confused with *T. marneffe* in tissue examination has been reviewed elsewhere.²⁵ Epidemiologic link to area of endemicity of the fungi can also aid in the diagnosis.

However, besides patients who were misdiagnosed of TB, there were 12.5% cases that were coinfectd with *Mycobacterium tuberculosis* or nontuberculous mycobacteria. The prevalence of TB in HIV-infected patients is as high as 22.8% in China which complicated the diagnosis of penicilliosis.²⁶ Skin lesions could help to differentiate penicilliosis from TB. However, epidemiological data and specimen examination are essential to make a diagnosis for patients without skin lesions, whereas interferon gamma release assays also play a role.

The mortality of the patients is 16.7%, which is similar to that in the previous studies.^{19,23,27–30} Besides low CD4 T-cell count, the well-known predictor of bad outcome, low hemoglobin level is also associated with increased mortality risk in this study. This is different from the previous studies.^{19,23} In the current study, anemia occurred among 87.5% of patients, which significantly complicated the treatment of penicilliosis. Amphotericin B is the preferred drug to treat *T. marneffei* infection, especially in severe cases.²⁰ However, amphotericin B may further worsen anemia. Meanwhile, 45.8% of the patients had concurrent OIs, including TB, PCP, and CMV infection. Another 6.3% of the patients had Kaposi sarcoma. Several of the first-line medicines for the treatment of these diseases also have the side effect of myelosuppression. This may partially explain the result that low hemoglobin level predicts mortality of the patients in this study. Itraconazole and voriconazole are the alternative choices for penicilliosis treatment. However, potential drug–drug interaction between itraconazole/voriconazole and other agents including the ART drugs and anti-TB drugs need to be considered. Itraconazole is not recommended to be used together with efavirenz.³¹ Coadministration of lopinavir/ritonavir and itraconazole would increase the blood level of itraconazole.³² Thus, high doses of itraconazole should also be avoided. Integrase inhibitors such as raltegravir and dolutegravir which has few drug–drug interaction with antifungal drugs are preferred. Besides anti-retroviral drugs, there are also drug–drug interactions between antifungal drugs and anti-TB drugs, especially the rifamycins. Thus, it's better not to use the rifamycins when treating penicilliosis and TB simultaneously.

A small proportion of patients were already on cART on admission, indicating that they might have had an ongoing *T. marneffei* infection that was not revealed, but was unmasked after the initiation of cART.^{22,33,34} Interestingly, although the difference is not of statistical significance, the mortality of these patients is higher than that in patients naïve to cART. The relatively high mortality of immune reconstitution inflammatory syndrome in HIV-infected patients may partially explain this phenomenon. Meanwhile, in patients infected with *T. marneffei*, although immune systems are partially recovered after cART, the count of spore they exposed may be much higher than that in cART-naïve patients. In addition, the diagnosis of penicilliosis is more likely to be ignored in patients under cART. Thus, the effect of prior cART before antifungal therapy may need further investigation.

CONCLUSIONS

Penicilliosis should be considered in HIV-infected patients from eastern China who present with fever, cutaneous lesions,

and anemia. The clinical characters and the prognosis of patients with penicilliosis are similar to those in endemic areas. More attention should be paid to penicilliosis patients with low CD4 T-cell count and/or low hemoglobin level.

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