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CASE REPORT

Challenges in Diagnosis and Treatment of HIV-Negative Host Pulmonary *Talaromyces marneffei* in Non-Endemic Areas: A Case Report with a History of Pulmonary Tuberculosis

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Abstract: *Talaromyces marneffei* is an important opportunistic fungal pathogen closely related to acquired immunodeficiency syndrome (AIDS), and its infection is relatively rare in human immunodeficiency virus (HIV)-negative populations. Although HIV-related immunosuppression remains the main risk factor, the history of treated tuberculosis and subsequent structural lung damage may constitute an underrecognized predisposing condition in non-epidemic areas, especially in elderly patients. This report described a 69-year-old HIV-negative male pulmonary infection case from a non-endemic area of *T. marneffei*, with a history of treated pulmonary tuberculosis and residual fibrotic lesions on imaging. The patient complained of chest tightness and cough for one month and fever (temperature 38.0–38.5°C) for a week upon admission. The chest computed tomography (CT) scan observed patchy consolidation and multiple cavities in the upper lobes of both lungs, accompanied by pulmonary texture disorder and pleural adhesions and thickening. The imaging findings were difficult to distinguish from active pulmonary tuberculosis. The diagnosis of *T. marneffei* infection was confirmed through sputum culture, bronchoscopy sampling culture, matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS), and metagenomics next-generation sequencing (mNGS). After diagnosis, the patient was given oral voriconazole 200 mg every 12 hours, resulting in gastrointestinal intolerance. Subsequently, the dosage was adjusted to 100 mg every 12 hours, and the gastrointestinal symptoms improved significantly. The patient was eventually discharged but subsequently lost to follow-up. The case emphasizes that among HIV-negative individuals in non-epidemic areas of *T. marneffei*, for patients with unexplained pneumonia, especially those who have a history of tuberculosis and other potential immunological impairments, the differential diagnosis approach should be broadened and modern diagnostic techniques should be actively applied. It also highlights the importance of addressing drug tolerance issues and implementing long-term follow-up management in clinical treatment.

Keywords: *Talaromyces marneffe*i, HIV-negative, pulmonary tuberculosis, pulmonary infection

Introduction

Talaromyces marneffei (*T. marneffei*) is a temperature-dependent biphasic fungus that is both opportunistic and pathogenic, mainly prevalent in Southeast Asian countries and southern China (such as Guangdong, Guangxi, and other provinces).[1–3] In these regions, the disease has clear endemic characteristics, especially among HIV-infected populations, where it was once the third most common opportunistic infection.[1,4] In addition to the core epidemic areas, although other provinces in mainland China and other regions in the world also reported cases, most of them were sporadic, and the number of cases was significantly lower than that in the core epidemic areas.[5] In recent years, with the increase of population mobility and the improvement of clinical diagnostic awareness, sporadic case reports in non-traditional epidemic areas (such as East China, North China, etc.) have gradually increased, indicating the heterogeneity of the

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disease in geographical distribution.[6,7] However, the vast majority of cases worldwide are still highly concentrated in the known epidemic areas mentioned above.[8]

Recently, with the intensification of population aging, the extensive use of immunosuppressants, and deeper understanding of autoimmune diseases, primary immunodeficiency, and immune regulation-related gene mutations, the population at risk of immunosuppression or in a state of immune dysfunction has significantly expanded.[9] This trend directly leads to a continuous increase in cases of *T. marneffei* infection among HIV-negative individuals.[9] It is worth noting that the respiratory system is the most commonly affected area of this infection and also the earliest system to show symptoms.[9] The clinical symptoms of *T. marneffei* infection lack specificity, mainly manifesting as recurrent fever, cough, weight loss, hepatosplenomegaly, lymphadenopathy, dyspnea, and gastrointestinal abnormalities.[10,11] Because the clinical manifestations and imaging characteristics are highly similar to tuberculosis, the infection of *T. marneffei* is often misdiagnosed as tuberculosis or delayed in diagnosis.[10,12] However, the rapid progression of *T. marneffei* infection often leads to fatal consequences once diagnosis or antifungal treatment is delayed.[10] At present, there are still few reports on the cases of *T. marneffei* infection among HIV-negative patients with a history of tuberculosis, particularly those from non-traditional epidemic areas in China. This research gap underscores the importance of reporting rare cases and enhancing clinical diagnosis and treatment awareness. Therefore, in clinical practice, it is crucial to improve the understanding of *T. marneffei* infection in HIV-negative populations, which has important clinical significance for reducing the misdiagnosis rate and improving the prognosis of non-HIV-infected individuals with potential immunodeficiency bases (such as previous tuberculosis, autoimmune diseases, immunosuppressive therapy, specific gene mutations, etc). It further emphasizes that even without a typical epidemiological exposure history, clinical doctors in non-traditional epidemic areas should maintain a high level of suspicion towards this infection when managing elderly patients with lung lesions and immunocompromised backgrounds.

Case Presentation

Clinical Features

On August 2, 2025, a 69-year-old male patient was admitted to the Affiliated Hospital of Jiaxing University due to chest tightness, a cough (with grayish-white sputum) for one month, and fever (temperature fluctuating between 38.0 and 38.5°C) for a week. The patient had tuberculosis seven years ago and was clinically cured after 1 year of anti-tuberculosis treatment. There was a history of old cerebral infarction in the past, denying the history of diabetes, autoimmune disease, and tumors. Long-term residence in Anhui Province, China (not a traditional endemic area of *T. marneffei*), with no recent travel history to epidemic areas.

On the first day of admission, the patient's vital signs were as follows: temperature 38.3°C, heart rate 103 beats/minute, respiratory rate of 20 beats/minute, blood pressure 163/96 mmHg, and peripheral blood oxygen saturation (SpO_2) 98%. Physical examination showed no rash, subcutaneous nodules, or ulcers throughout the body, and no palpable swelling of superficial lymph nodes. The coarse breath sounds of both lungs were rough, with no obvious dry or wet rales heard. The abdomen was soft, without tenderness, and the liver, spleen, and ribs were not palpable.

Laboratory Tests

Laboratory tests on admission showed that the patient's white blood cell (WBC) count was 7.11 × 10^9/L (reference range: 3.5–9.5 × 10^9/L), which was within the normal range. The percentage of neutrophils was significantly elevated to 83.9% (reference range: 40–75%), indicating a marked acute inflammatory response. Hemoglobin (Hb) level was 126 g/L (reference range: 130–175 g/L), representing mild anemia, and the platelet (PLT) count was 352 × 10^9/L (reference range: 125–350 × 10^9/L), at the upper limit of normal. Infection-related markers were notably elevated, including c-reactive protein (CRP) of 105.4 mg/L (reference range: <10 mg/L), serum amyloid A (SAA) of > 200 mg/L (reference range: ≤10 mg/L), and interleukin-6 (IL-6) of 11.01 pg/mL (reference range: <7 pg/mL). Procalcitonin (PCT) was slightly elevated to 0.11 ng/mL (reference range: <0.05 ng/mL) (Table 1). The HIV antibody test result was negative. To assess immune function, phenotypic analysis of peripheral blood lymphocyte subsets was performed using flow cytometry. The results demonstrated significantly reduced percentages of $CD3^+$ T lymphocytes (47.10%; reference range: 53.33–81.22%), $CD4^+$ T lymphocytes (18.81%; reference range: 24.04–49.05%), and $CD19^+$ B lymphocytes (5.21%; reference range: 5.39–18.23%), along with a notably increased percentage of $CD16^+CD56^+$ NK cells (45.58%; reference range: 6.37–34.83%) (Table 2). Other serum tumor

Table 1 Laboratory Examination Results of the Patient

Laboratory Indicators	Reference Interval	Measurements
White blood cell count (10^9/L)	3.50–9.50	7.11
Neutrophil count (10^9/L)	1.8–6.3	6.0
Neutrophilic proportion (%)	40.0–75.0	83.9 ↑
Lymphocyte count (10^9/L)	1.1–3.2	1.0 ↓
Red blood cell count (10^{12}/L)	4.30–5.80	4.36
Hemoglobin (g/L)	130–175	126 ↓
Platelet count (10^9/L)	125–350	352 ↑
D-Dimer (ng/mL)	0–500	1090 ↑
C-reactive protein (mg/L)	<10.0	105.4 ↑
Procalcitonin (ng/mL)	<0.05	0.11
Interleukin-6 (pg/mL)	<7	11.01 ↑
Serum amyloid A (mg/L)	≤10.0	> 200
Albumin (g/L)	40.0–55.0	32.5 ↓
Globulin (g/L)	20.0–40.0	42.8 ↑
Alanine Aminotransferase (IU/L)	9–50	12
Aspartate Aminotransferase (IU/L)	15–40	19
Creatine kinase (U/L)	50–310	128
Lactate dehydrogenase (U/L)	120–250	193
Anti-HIV (COI)	< 1.00	0.08

Notes: ↓: decreased; ↑: increased.

Table 2 Analysis Results of Lymphocyte Subsets in the Patient

	Measurements	Reference Interval
CD3+ T lymphocytes (%)	47.10 ↓	53.33–81.22
CD4+ T lymphocytes (%)	18.81 ↓	24.04–49.05
CD8+ T lymphocytes (%)	27.14	15.71–38.24
CD4+ (%)/CD8+ (%)	0.69	0.60–2.88
CD16+CD56+NK cell (%)	45.58 ↑	6.37–34.83
CD19+B lymphocyte (%)	5.21 ↓	5.39–18.23

Notes: ↓: decreased, ↑: increased.

markers, tuberculosis-related tests, 1,3-β-D-glucan tests, and the Aspergillus galactomannan tests were all negative. The above results indicated that the patient had a significant acute inflammatory response (elevated CRP, SAA, IL-6, and neutrophil percentage) and an immune disorder characterized by the decrease of T lymphocytes and B lymphocytes and the increase of NK cells.

Imaging Examination and Painless Bronchoscopy Examination

On August 2, 2025, the chest CT showed increased and disordered lung texture; patchy consolidations in the upper lobes of both lungs with multiple cavitations, accompanied by surrounding cord-like high-density opacities, pleural adhesion, and thickening; and scattered patchy high-density opacities in both lungs, with the right lung being more prominent (Figure 1A). Preliminary diagnosis: bilateral emphysema, bilateral upper lobe lesions (tuberculosis suspected), and scattered infectious lesions in both lungs. The painless bronchoscopy examination showed that there were many purulent viscous secretions blocking the tube opening inside the lumen and carbon deposits existed (Figure 1B). Bronchoalveolar lavage fluid (BALF) was collected for mNGS, bacterial culture, fungal culture, tuberculosis culture, and acid-fast staining detection.

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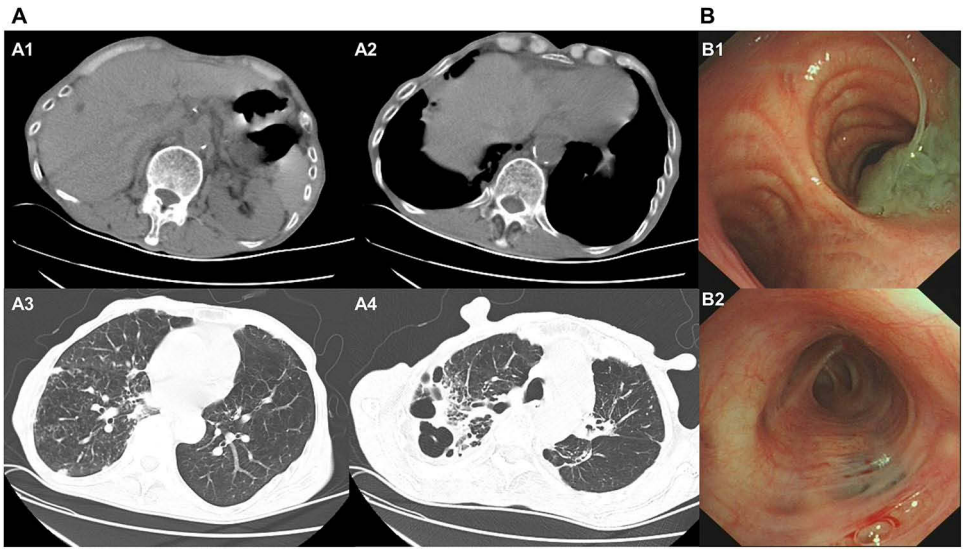

Figure 1 (**A**) Chest CT examination. (A1) No obvious abnormalities were observed. (A2) Subpleural nodular shadows. (A3) Emphysema was found in both lower lungs, with a small amount of patchy increased density in the right lower lung, accompanied by subpleural small nodular shadows. (A4) Increased and disordered pulmonary markings; patchy consolidations in the upper lobes of both lungs with multiple cavitations, accompanied by surrounding cord-like high-density opacities, pleural adhesion, and thickening. (**B**) Bronchoscopy examination. (B1) A large amount of purulent and viscous secretions blocked the tube orifice. (B2) Carbon deposition was present.

Etiological Examination

On the first day of admission (August 2, 2025), sputum samples were collected and subjected to sputum smear microscopy and plate inoculation culture according to laboratory standard operating procedures. After Wright-Giemsa staining, the sputum smear showed "one river, two banks" fungal spores under the microscope, which were suspected to be *T. marneffei* (Figure 2A). At the same time, the sputum specimens were inoculated onto Sabouraud dextrose agar (SDA) and cultured at 28°C and 37°C, respectively. Under 37°C cultivation conditions, non-pigmented yeast-like colonies were formed (Figure 2B). At 28°C, the fungi appeared as moldy colonies with red wine pigments (Figure 2C). After staining with lactophenol cotton blue, the mycelium had a smooth and transparent branching structure with typical broom-like branching characteristics, with 2–10 bottle-shaped stems scattered on non-parallel stem bases, gradually narrowing at the top and scattered single-stranded conidia (Figure 2D). On August 5, 2025 (the 3rd day after admission), the colony was identified using matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF MS, Bruker, Germany), and the result was *T. marneffei*, with a reliability score of 2.30 (≥ 2.0 as a reliable identification standard, Figure 3). The strain was also cultured from the subsequent bronchoalveolar lavage fluid samples. And the samples of BALF were also analyzed by mNGS (Dian Diagnostics Group Co., Ltd., Hangzhou, China). The detection used ultra-multiplex PCR targeted amplification technology to enrich pathogen nucleic acids in the sample, and the sequencing was completed on the MGI DNBSEQ-G400 sequencing platform, generating double-ended sequencing data with an average read length of PE100 bp. During the experiment, molecular internal standards were added to monitor the efficiency of nucleic acid extraction and amplification, and semi-quantitative analysis of pathogen load was performed using the tNGS quantitative algorithm developed by the detection institution. The sequencing results further confirmed that *T. marnefei* was the dominant pathogen (sequence number: 38725). Based on these findings and clinical characteristics, the diagnosis was made on August 8, 2025 (the 6th day after admission), as a pulmonary infection caused by *T. marneffei*.

Treatment and Outcome

After obtaining definitive microbiological evidence, targeted antifungal therapy was initiated on the day of diagnosis (the 6th day after admission) with oral voriconazole (200 mg every 12 hours). Following the start of treatment, the patient developed gastric discomfort on August 10th (the 8th day after admission). After communication between doctors and patients and weighing the efficacy and tolerability, the dose was adjusted to voriconazole 100 mg every 12 hours. After

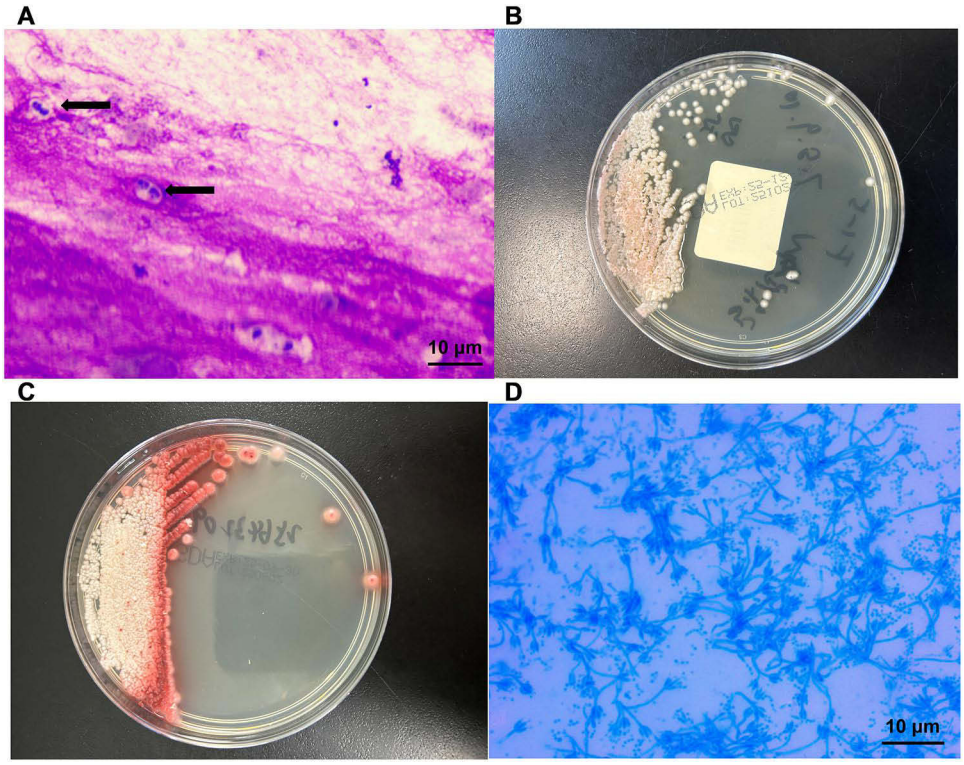

Figure 2 Cultivation and microscopic observation of *T. marneffei* in sputum samples. (**A**) Wright-Giemsa staining showed the characteristic fission yeast form of *T. marneffei* (black arrow indicates oval yeast cells undergoing binary fission) (×1000 magnification, scale bar = 10 μm). (**B**) The morphological characteristics of the colony of *T. marneffei* after 3 days of cultivation in SDA at 37°C. (**C**) After 3 days of cultivation in SDA at 28°C, the morphological characteristics and wine-red pigment of the colony of *T. marneffei* were observed. (**D**) After staining with lactophenol cotton blue, the typical broom-like branching septate hyphae morphology was observed (×400 magnification, scale bar = 10 μm).

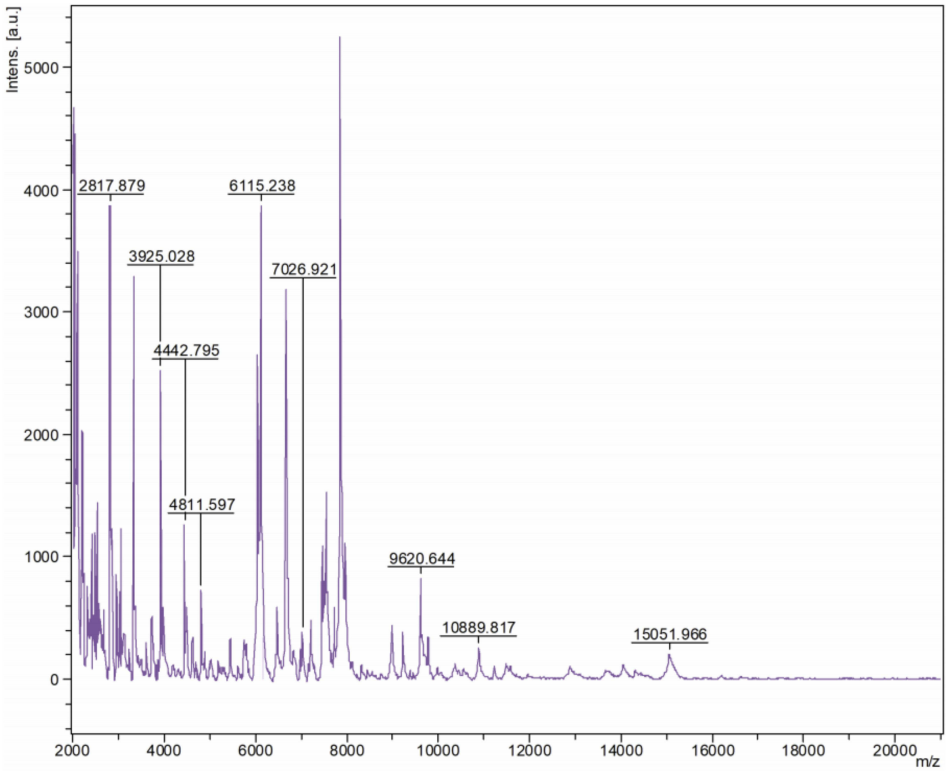

Figure 3 The Bruker MALDI-TOF MS analysis identified the strain as *T. marneffei*, with a score of 2.30.

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adjusting the dosage and continuing treatment for 5 days, the patient's gastrointestinal reactions disappeared, body temperature returned to normal, and cough and chest tightness symptoms improved significantly. Vital signs were stable, the lung examination was the same as before, and the patient was discharged. The patient was instructed to strictly follow the doctor's advice and continue taking voriconazole (100 mg every 12 hours) orally. It was emphasized that the patient must return to the hospital or undergo a reexamination of liver and kidney function, blood routine, inflammatory indicators, and chest CT at a local authoritative hospital after 2 weeks. Unfortunately, the patient was ultimately lost to follow-up and did not receive information on subsequent treatment reactions and outcomes.

Discussion

T. marneffei is an opportunistic pathogen mainly prevalent in Southeast Asian countries and southern China, with cases in Guangdong and Guangxi provinces alone accounting for 83.4%.[13,14] This pathogen exists in soil rich in organic matter, and humans are mainly infected by inhaling airborne spores dispersed in the environment.[15] Although traditionally considered as non-endemic or low-risk areas, sporadic case reports in atypical regions are no longer uncommon with increasing population mobility and deepening clinical awareness. In HIV-negative individuals, *T. marneffei* infection can manifest as focal or disseminated, depending on the host immune status and diagnosis time.[16] Compared to typical lung involvement in HIV-infected individuals, *T. marneffei*-related lung infections in HIV-negative populations are more likely to be misdiagnosed as tuberculosis or lung tumors, and the difficulty of clinical identification is significantly increased.[9,17] The common risk factors for *T. marneffei* infection include advanced age, anti-IFN-γ autoantibodies (AIGA), autoimmune diseases, use of immunosuppressants, and malignant tumors.[16,18]

This case involves an elderly HIV-negative male patient from the East China region. Despite residing in a traditionally non-endemic region, his infection resulted from the synergistic effect of multiple risk factors. The potential for regional environmental exposure laid the etiological foundation for the infection. The physiological cellular immune aging caused by advanced age and the significant decrease in $CD3^+$ and $CD4^+$ T lymphocytes suggested by lymphocyte subpopulation analysis collectively induced severe cellular immune deficiency.[19] Meanwhile, the decrease in $CD19^+$ B lymphocytes suggested that early humoral immune responses may be affected.[20] Especially when $CD4^+$ T lymphocyte dysfunction occurs, the early antifungal defense mediated by natural immunoglobulin M (IgM) produced by B lymphocytes becomes exceptionally critical.[20,21] Recent studies have confirmed that IgM can recognize antigens such as β-glucan on the fungal cell walls and eliminate pathogens in the early stages of infection by activating the complement system and regulating phagocytosis.[21] Therefore, the immune dysfunction in this patient not only involves cellular immunodeficiency but may also have an insufficient early IgM response. In addition, the elevated percentage of $CD16^+$ $CD56^+$ NK cells may be a compensatory natural immune activation, but its effect on controlling intracellular fungal infections is limited.[22] Although the patient's prior pulmonary tuberculosis has been clinically cured, the remaining lung structure destruction and local immune microenvironment imbalance provide favorable conditions for the colonization and invasion of inhaled spores.[23,24] Therefore, among non-HIV-infected hosts in non-epidemic areas, the past history of tuberculosis in the elderly can become an important potential risk factor for *T. marneffei* infection through the synergistic effect of systemic immune decline and local lung tissue microenvironment abnormalities.

The clinical manifestations of *T. marneffei* infection have nonspecific characteristics and diverse symptoms, making it difficult to diagnose *T. marneffei* infection solely based on clinical manifestations.[25] Previous studies have indicated that the main symptoms of *T. marneffei* pulmonary infection are cough, fever, difficulty breathing, and lymphadenopathy.[26] Chest CT scans of patients often show nodules, masses, pleural effusion, and may also reveal pulmonary cavities, pleural thickening, and enlarged hilar and mediastinal lymph nodes.[1] This indicates that the clinical manifestations and chest imaging features of *T. marneffei* are highly similar to those of lung cancer and tuberculosis, making differentiation difficult.[26,27] Bronchoscopy examination can not only detect respiratory tract involvement early but also timely obtain respiratory specimens for pathogen assessment, thereby guiding the development of targeted treatment plans.[26,28] Therefore, for patients with respiratory infections as the initial symptom and unknown pathogens, it is necessary to combine multiple sample types (such as sputum, blood, BALF, and tissue biopsy) and different detection methods (such as smear, culture, and mNGS) to compensate for the limitations of a single sample or technique.[28]

Multiple studies have shown that cases of *T. marneffei* infection continue to rise among HIV-negative individuals.[13] Due to delayed initiation of antifungal treatment, the mortality rate of *T. marneffei* has increased from 24% to 50%.[10] If the patient receives an accurate diagnosis of *T. marneffei* infection and timely antifungal treatment, ultimately achieving a good prognosis. Currently, microbial culture remains the gold standard for diagnosing *T. marneffei* infection.[29] Although it has high accuracy, it has drawbacks such as long cultivation time (3–14 days) and limited positivity rate, which often delay the optimal diagnosis and treatment timing.[18] In addition, traditional laboratory fungal diagnosis relies on pathogen isolation and/or direct microscopic examination, which have insufficient sensitivity and specificity and are prone to missed detections.[30] As a novel nucleic acid detection technology, mNGS combines rapidity and accuracy, effectively compensating for the inherent delays in traditional culture detection.[31] This study combined mNGS and MALDI-TOF MS detection and found that *T. marneffei* infection was detected in both sputum and BALF samples of patients, and the diagnostic results of the two tests were highly consistent.

Currently, amphotericin B is the first-line antifungal drug for people living with HIV with concurrent *T. marneffei* infection.[18] However, the standard recommendations for treatment and prevention of HIV-negative patients with *T. marneffei* infections are not yet clear.[28] Oral voriconazole is one of the preferred regimens recommended by domestic and international guidelines, with the advantage of avoiding dose-dependent toxicity (such as nephrotoxicity, electrolyte imbalance, etc.) and venous pathway-related complications that may arise from long-term intravenous use of amphotericin B.[10,32] However, voriconazole also has common gastrointestinal adverse reactions (such as nausea and vomiting), which often affect patients' long-term tolerance and may lead to treatment interruption or non-compliance.[33] In clinical practice, halving the dose is a practical decision made by doctors after weighing factors in order to reduce adverse reactions and improve patient compliance while ensuring efficacy.[34] However, this may raise concerns about whether the drug concentration is sufficient to clear pathogens and whether it may induce drug resistance. Therefore, when using a low-dose voriconazole regimen, therapeutic drug concentration monitoring (TDM) is particularly important.[35,36] Through TDM, it is possible to ensure that the drug trough concentration reaches the effective therapeutic range (usually recommended >1 mg/L), thereby maximizing efficacy while reducing dosage and helping to assess the risk of drug resistance.[35] However, the routine implementation of TDM in China faces significant challenges, as many hospitals lack corresponding detection equipment and technology platforms, resulting in high detection costs and long cycles.[35] At the same time, the clinical pharmaceutical services and interpretation standards for voriconazole TDM have not been fully popularized.[11,35] These factors collectively limit the widespread application of TDM in most medical institutions, making it difficult to optimize individualized dosing regimens.A major limitation of this case report is the loss to long-term follow-up, which precludes assessment of final treatment outcomes and potential relapse. *T. marneffei* requires sufficient and full-course antifungal treatment (usually consolidated and maintained for several months to more than six months after induction therapy). Premature discontinuation or insufficient dosage increases the risk of recurrence. This serves as a profound warning that for patients with chronic deep fungal infections in outpatient management, a strong patient education system and follow-up tracking mechanism must be established. Overall, our case emphasizes the urgent need for structured follow-up plans and enhanced patient education in the clinical management of chronic fungal infections, which may involve multidisciplinary outpatient care to optimize treatment compliance and disease monitoring. For clinicians in non-endemic regions, this further highlights the importance of strict post-discharge management alongside timely etiological diagnosis and individualized treatment, as comprehensive follow-up is an essential component for improving long-term prognosis and reducing recurrence rates in patients with *T. marneffei* infection.

Conclusion

This case successfully diagnosed a case of pulmonary *T. marneffei* disease with atypical epidemiological characteristics and complex basic diseases, highlighting the value of modern microbiological diagnostic techniques. At the same time, it also reflects the challenges faced by patients in terms of drug tolerance and long-term treatment compliance in clinical practice. Improving awareness of this disease, developing individualized treatment plans, and ensuring complete follow-up are key to improving the prognosis of such patients. For clinical practice in non-epidemic areas, we propose the following suggestions. For example, for patients with weakened immune function and persistent pneumonia, regardless of their HIV infection status or travel history, the possibility of *T. marneffei* disease should be considered. Actively

utilizing advanced diagnostic technologies such as mNGS and MALDI-TOF MS to achieve early identification. Conduct immunological examinations (such as lymphocyte subset analysis) to assess potential immune dysfunction. When conditions permit, it is recommended to use voriconazole under the guidance of therapeutic drug monitoring for treatment. At the same time, a systematic chronic infection management and follow-up plan should be developed.

Ethics Approval and Consent to Participate

This study was a retrospective case report, and its publication has been approved by the Ethics Committee of the Affiliated Hospital of Jiaxing University (No. 2025-KY-695), and the patient has signed a written informed consent form, agreeing to publish the case details and all accompanying imaging materials.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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