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ORIGINAL RESEARCH

Clinical Features and Diagnostic Challenges of *Talaromyces marneffei* Infection in Non-Endemic Regions: A 6-Case Study Highlighting NGS and Tailored Antifungal Therapy

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Background: *Talaromyces marneffei* is an opportunistic fungal infection with marked geographical endemicity. While traditionally associated with HIV infection, its incidence is increasing in non-endemic areas, driven by improved diagnostics and a growing population of immunocompromised hosts.

Methods: This retrospective study analyzed six cases (5 male, 1 female) of *Talaromyces marneffei* infection managed at Shaoxing People's Hospital between 2023 and 2024, focusing on clinical manifestations, diagnostic approaches, and therapeutic outcomes.

Results: Among the six patients (median age 44.5 years, range 24–69 years), four were HIV-negative and two were HIV-positive. Non-HIV patients (4/6) presented with fever (4/4), productive cough (3/4), and lymphadenopathy (3/4), with underlying conditions including diabetes, autoimmune disorders, and myelofibrosis. Laboratory findings included lymphocytopenia, elevated CRP/ESR, and hypoalbuminemia. Imaging showed pulmonary infiltrates (3/4), hilar/mediastinal lymphadenopathy (3/4), and abscess (1/4). HIV-positive patients exhibited anemia, abdominal pain, disseminated lymphadenopathy, and splenomegaly, with reduced $CD4^+$ T-cell percentages and elevated IgG. Due to atypical presentations, four cases were initially misdiagnosed. Diagnosis was confirmed via NGS (4/6), NGS plus culture (1/6), or histopathology (1/6). Treatment was individualized: severe cases received extended amphotericin B lipid complex (ABLC) (cumulative dose up to 31.8g in case1) induction followed by azole maintenance; milder cases received oral itraconazole alone. Two patients continue maintenance therapy; four discontinued after improvement with no relapse. All patients improved, and there were no deaths.

Conclusion: This series highlights the diagnostic challenges of *Talaromyces marneffei* infection in non-endemic areas, especially among non-HIV immunocompromised hosts. NGS was essential for early detection. Individualized antifungal therapy-tailored to immune status and disease severity achieved favorable outcomes, underscoring the importance of personalized treatment strategies.

Keywords: *Talaromyces marneffei*, diagnosis and treatment, NGS, amphotericin B lipid complex

Introduction

Talaromyces marneffei is a thermally dimorphic fungus, and the disease caused by its infection is known as Talaromycosis.[1] It is primarily endemic to Southeast Asia, and regions in South China, such as Guangxi, Guangdong, and Hong Kong, are also high-incidence areas, the epidemic range of this disease is still expanding.[2] In recent years, cases have been reported in Europe, North America, South Korea, and Japan.[3] In central-eastern and northern China, patients infected with this disease have also been identified.[4] Historically, Talaromycosis was primarily observed in HIV patients. However, with the increasing number of immunocompromised patients and advances in disease-related testing and diagnostic techniques such as next-generation sequencing (NGS), the incidence of this disease has also significantly risen in HIV-negative hosts.[1,5] Talaromycosis is prone to causing widespread systemic infections, and its clinical symptoms lack specificity. Infections are often overlooked or

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misdiagnosed, leading to poor prognosis. In the epidemic areas of China, the mortality rate ranges from 13.8% to 25.09%.[3,6] Therefore, this study aims to collect and analyze clinical data from talaromycosis patients with varying manifestations to explore the disease's characteristics, diagnosis, and treatment.

Materials and Methods

Study Population

We retrospectively analyzed six patients with *Talaromyces marneffei* infection treated at Shaoxing People's Hospital between January 2023 and December 2024. Comprehensive data extracted from medical records encompassed demographic characteristics (gender, age, occupation, residence, living area), underlying diseases, clinical manifestations, and laboratory parameters at initial symptom presentation, including complete blood count, biochemistry, inflammatory markers, cytokines, lymphocyte subsets, urinalysis, ferritin, plasma D-dimer, fungal G-test, GM-test, and NGS. Additionally, diagnostic evaluations incorporated chest CT, lymph node ultrasound, and histopathological findings, alongside documentation of therapeutic interventions and clinical outcomes.

Diagnostic Criteria

In this study, the diagnostic criteria for *Talaromyces marneffei* infection included the presents with clinical manifestations of infection and meets at least one of the following ancillary test results: (a) histopathological examination of biopsy specimens; (b) isolation of *Talaromyces marneffei* from sample culture; (c) detection of *Talaromyces marneffei* sequences by NGS; diagnostic criteria for severe cases: severe immunocompromised status (HIV patients with a $CD4^+$ T lymphocyte count <100 cells/μL), multiple organ dysfunction, or specific clinical symptoms.

Results

Clinical Characteristics

Among the six patients, four were born in Zhejiang Province and one in Anhui Province; all five were long-term residents of Zhejiang. One (Case 3) from Chongqing, sought medical treatment there. None had a history of living in or traveling to regions endemic for *Talaromyces marneffei*. The cohort included five males and one female, with a median age of 44.5 years (range 24–69 years). Their occupations were as follows: farmer (n=1), office worker (n=1), laborer (n=2), and self-employed (n=2). Two patients were HIV-positive, and the remaining four have an underlying condition of immunosuppression. The common clinical manifestations of these patients include fever, expectoration, anemia, and lymphadenopathy and so on. Initially, the diagnosis of *Talaromyces marneffei* infection was not established in 4 cases. Case 1 was initially misdiagnosed as bacterial soft tissue infection, Case 2 as lung abscess with pneumonia, Case 4 as cryptococcal pneumonia, and Case 6 as lymphoma (Table 1).

Laboratory Examination Results

Complete blood count (CBC) analysis revealed lymphocytopenia in all patients, ranging in severity. Additional CBC findings included neutrophilia (3 patients), leukocytosis (2 patients), and anemia (2 patients). Flow cytometry, performing on 4 patients, identified lymphocyte subset reductions in Cases 2 and 6. Biochemical analysis demonstrated elevated CRP and ESR universally, alongside hypoalbuminemia. Hyperferritinemia was present in 3 patients. Case 5 exhibited no significant laboratory abnormalities (Supplementary Table S1).

Imaging Examination Results

Chest computed tomography (CT) scans in five patients revealed a spectrum of pulmonary lesions, predominantly featuring inflammatory lesions (n=4), hilar enlargement (n=3), multiple enlarged mediastinal lymph nodes (n=3), and pulmonary nodules (n=3), with bullae also noted in two patients (Figure 1). Additional CT findings encompassed isolated instances of abscess formation and cavity formation. Superficial lymph node ultrasound in three of these patients demonstrated lymphadenopathy (Figure 1), while PET/CT imaging performed on a separate patient identified multiple enlarged lymph nodes widespread throughout the body (Figure 2).

Table 1 Characteristics of the 6 Patients with *Talaromyces marneffei* Infection

Patients	Hometown/ Current Residence	Underlying Diseases	Clinical Manifestations	Imaging Studies (Ultrasonography, CT, PET-CT)	Etiological Analyses (Histopathology, Culture, NGS)	Initial Treatment	Post-confirmation Treatment	Prognosis
Case1	Zhejiang Province/ Zhejiang Province	Diabetes; Ankylosing spondylitis; Uveitis; Hypertension; Hyperlipidemia	Fever, erythema, swelling, warmth, and pain in the left upper limb, enlarged and tender lymph nodes in the left axilla and elbow	CT: Enlarged right hilum, lesion in the outer segment of the right middle lobe; scattered tiny nodules in both lungs; bullae in the right lung; chronic inflammatory foci in both lower lobes; multiple enlarged lymph nodes in the mediastinum; thickening of both lower pleura. Small pericardial effusion (Figure 1C and D). Lymph Node Ultrasonography: enlarged left axillary lymph nodes (Figure 1E)	Histopathology: Granulomatous inflammation with necrosis in the left axillary lymph node biopsy. IHC: CD3 (-), CD68 (+), CD163 (+), CD38 (+), Ki-67 (+10%), CD3 (+), CD20 (+), EMA (-), PAS (-), AFS (-), PASM (+); Pus culture: Serratia marcescens (+++); *Raoultella ornithinolytica* (+); Blister fluid culture: *Talaromyces marneffei* (+); Lymph node NGS: *Talaromyces marneffei* sequence count 9806; Lung tissue NGS: *Talaromyces marneffei*	Piperacillin/ tazobactam and Teicoplanin	Amphotericin B lipid complex (escalating to 200 mg qd for 7 weeks, cumulative dose 31.8g). Voriconazole (200 mg PO q12h) for 1 week, then posaconazole (300 mg PO qd) for ongoing suppression	General condition satisfactory
Case2	Zhejiang Province/ Zhejiang Province	Myelofibrosis; Pneumocystis pneumonia	Cough, expectoration, nausea, and vomiting	CT: Infectious lesion in the right lower lobe with abscess formation. Slightly enlarged lymph nodes at the right hilum. Small pleural effusions in both pleural cavities. Multiple pulmonary bullae in both lungs (Figure 1A and B)	Sputum culture: Candida albicans; Lung tissue NGS: *Talaromyces marneffei* sequence count 3009	Piperacillin/ sulbactam combined with Moxifloxacin, and Vancomycin combined with Moxifloxacin	Amphotericin B lipid complex (escalating to 150 mg qd) for 2 weeks. Voriconazole (200 mg PO q12h) for 3 months	Discontinued treatment. Current general condition is satisfactory
Case3	Chongqing City/ Chongqing City	Diabetes; Pulmonary tuberculosis; Chronic viral hepatitis B	Fever, chills, cough, expectoration, nasal congestion and rhinorrhea, slight epistaxis, headache, sore throat, fatigue	CT: Scattered patchy lesions in the right lung with cavity formation, multiple slightly enlarged and calcified lymph nodes in the mediastinum. Multiple nodules in both lungs; emphysema in both lungs; bullae in both lungs; scattered fibroproliferative lesions in both lungs	BALF Culture: *Haemophilus influenzae* +; BALF NGS: *Haemophilus influenzae* 4789; *Talaromyces marneffei* 3743	Piperacillin/ tazobactam	Voriconazole (200 mg PO q12h) for 1 week, followed by Amphotericin B lipid complex (1 month intravenous) and then an oral triazole for 1 month) (details unknow)	Discontinued treatment. Generally well during phone follow-up.
Case4	Anhui Province/ Zhejiang Province	HIV	Chest tightness and pain, fever and chills, generalized myalgia, nasal congestion and rhinorrhea, cough, expectoration, headache	CT: Diffuse miliary and multiple small nodules in both lungs, with multiple enlarged lymph nodes in both hilar and mediastinal regions. Lymph Node Ultrasonography: Enlarged lymph nodes in the right supraclavicular area; enlarged left axillary lymph nodes	Blood tNGS: *Talaromyces marneffei* sequence count 20	Nemonoxacin Maleate	Amphotericin B lipid complex for 2 weeks (details unknow), followed by itraconazole (200 mg PO bid) for 50 days	Generally well during phone

(*Continued*)

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Table 1 (Continued).

Patients	Hometown/ Current Residence	Underlying Diseases	Clinical Manifestations	Imaging Studies (Ultrasonography, CT, PET-CT)	Etiological Analyses (Histopathology, Culture, NGS)	Initial Treatment	Post-confirmation Treatment	Prognosis
Case5	Zhejiang Province/ Zhejiang Province	Previous pneumonia; Crohn's disease; Immunosuppression	Sore throat, cough, expectoration	CT: Space-occupying lesion in the right lower lobe, possible mucoid impaction in the proximal bronchu Several patchy lesions in both lungs	Right lung biopsy: Chronic mucosal inflammation, interstitial plasma cell infiltration with necrosis; NGS of Right Lung Biopsy: *Talaromyces marneffei*; BALF NGS: Detected 55 sequences of *Pseudomonas aeruginosa* and 15 sequences of *Circovirus*	–	Itraconazole (200 mg PO qd for 1 month, then 100 mg PO qd for 2 weeks)	Discontinued treatment. Generally well during phone
Case6	Zhejiang Province/ Zhejiang Province	HIV; EB virus infection; Splenomegaly; Left renal calculus; Mild anemia	Fever, abdominal pain	Lymph Node Ultrasonography: Multiple lymph nodes in the left neck, approximately 0.5 cm × 1 cm; one lymph node palpated in the left inguinal region, 1 cm × 1 cm; Contrast-enhanced CT of the Whole Abdomen: Splenomegaly, multiple enlarged lymph nodes in the abdomen and retroperitoneum, lymphoma highly suspected. PET-CT: 1. Multiple enlarged lymph nodes in the left neck, left supraclavicular region, bilateral diaphragmatic crus, mesenteric root of the abdomen, retroperitoneum, and beside the abdominal aorta, with abnormally increased FDG metabolism. 2. Splenomegaly with heterogeneous FDG uptake. 3. Minor fibrotic foci in both lower lobes of the lungs. 4. Small renal calculus in the left kidney; minimal pelvic effusion; prostate hyperplasia. 5. Mixed-density nodule in the right iliac bone without abnormal FDG metabolism; mild degenerative changes in the spine. (Figure 2A–C)	Ultrasound-guided Fine-needle Aspiration Biopsy of the Left Cervical Lymph Node: Granulomatous inflammation with special pathogen infection (*Talaromyces marneffei* infection)(Figure 2D); Immunohistochemistry: CD20 (-), CD3 (+), CD21 (-), Bcl-2 (focal +), CKpan (-), Ki-67 (hotspot area, +50%), TIA (+), CD56 (-).	–	Amphotericin B lipid complex for 2 weeks (details unknow), followed by itraconazole (200 mg PO bid) for 3 months	Discontinued treatment. Generally well during phone

Notes: Imaging Studies: including Ultrasonography, CT, PET-CT; Etiological Analyses: including Histopathology, Culture, NGS; (+): positive; (+++): strongly positive; (-): negative.
Abbreviations: tNGS, targeted Next-Generation Sequencing; NGS, metagenomic Next-Generation Sequencing; BALF, Bronchoalveolar Lavage Fluid.

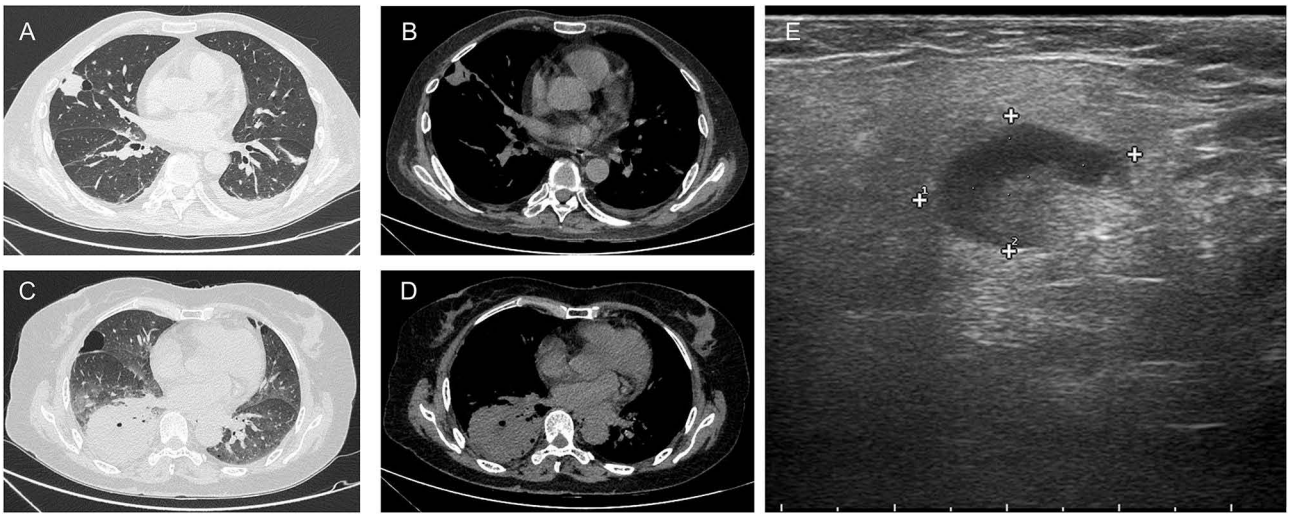

Figure 1 (**A**) Lung window and (**B**) mediastinal window settings from a computed tomography (CT) scan of Case 2: Infectious lesion in the right lower lung lobe with abscess formation, slightly enlarged right hilar lymph nodes, small bilateral pleural effusions, and multiple pulmonary pneumatoceles in both lungs. (**C**) Lung window and (**D**) mediastinal window settings from CT scan of Case 1: Infectious lesions at the right hilum and the lateral segment of the right middle lobe, with a right pulmonary bulla; chronic inflammatory foci in both lower lungs; multiple enlarged lymph nodes in the mediastinum; small bilateral pleural effusions. (**E**) Lymph node sonography of Case 1: A 20*12 mm hypoechoic lymph node with centrifugal homogeneous hypo-enhancement is observed in the left subaxillary region. The four cross marks ("+") on the image indicate the outermost boundaries of the lymph node (leftmost, rightmost, uppermost, and lowermost points).

Pathogen Detection

Fungal G tests were negative in four tested patients. Among three patients undergoing GM testing, two were serum-positive (Supplementary Table S1). *Talaromyces marneffei* infection was confirmed in six cases using different methods: histopathology (Case 6), vesicular fluid culture combined with NGS (Case 1), and NGS alone (four cases). Case 1 also yielded cultures of *Serratia marcescens* and *Raoultella ornithinolytica*. Additionally, two other bacterial species were identified by NGS in two cases: *Haemophilus influenzae* (Case 3) and *Pseudomonas aeruginosa* (Case 5) (Table 1).

Treatments and Outcomes

Among six patients, four initiated treatment with intravenous amphotericin B lipid complex, while one began oral itraconazole and another oral voriconazole. Two received induction therapy with ABLC followed by long-term oral itraconazole. Case 1 transitioned from ABLC to voriconazole (200 mg q12h, 1 week), was readmitted for 3 months of ABLC (cumulative ABLC: 31.8g), then maintained on posaconazole (300 mg qd) for ≥18 months total. Case 2 completed 3 weeks of ABLC followed by 3 months of voriconazole; CT showed lesion reduction, and medication was discontinued, with telephone follow-up indicating satisfactory status. Case 3 started with voriconazole (200 mg q12h, 1 week) then ABLC (1 month intravenous), followed by an unspecified oral triazole for 1 month, which was discontinued after symptom improvement. Case 5 received itraconazole (200 mg qd × 1 month, then 100 mg qd × 2 weeks) before discontinuing due to mild symptoms, maintaining satisfactory condition. All patients exhibited symptomatic improvement during the treatment period. To date, our follow-up has revealed no significant adverse events and no mortality.

Discussion

Talaromyces marneffei primarily invades through the respiratory tract and then disseminates to other tissues and organs. The warm and humid climate of Southeast Asia, northeastern India, and southern China provides favorable environmental conditions for the growth and transmission of *Talaromyces marneffei*.[7] However, in recent years, *Talaromyces marneffei* infections have been reported in non-endemic areas of 34 countries, including the United States, Australia, France, Japan, Germany, Singapore, and Canada, due to advances in cancer treatment, organ transplantation, rheumatologic/immune diseases, steroid therapy, and other fields, improvements in diagnostic techniques such as NGS, enhanced disease recognition, and global factors including immigration, travel, and climate change.[3,7] In mainland China, cases have been reported in 21 provinces and municipalities beyond the traditional endemic regions of Guangxi and Guangdong, including Qinghai, Gansu,

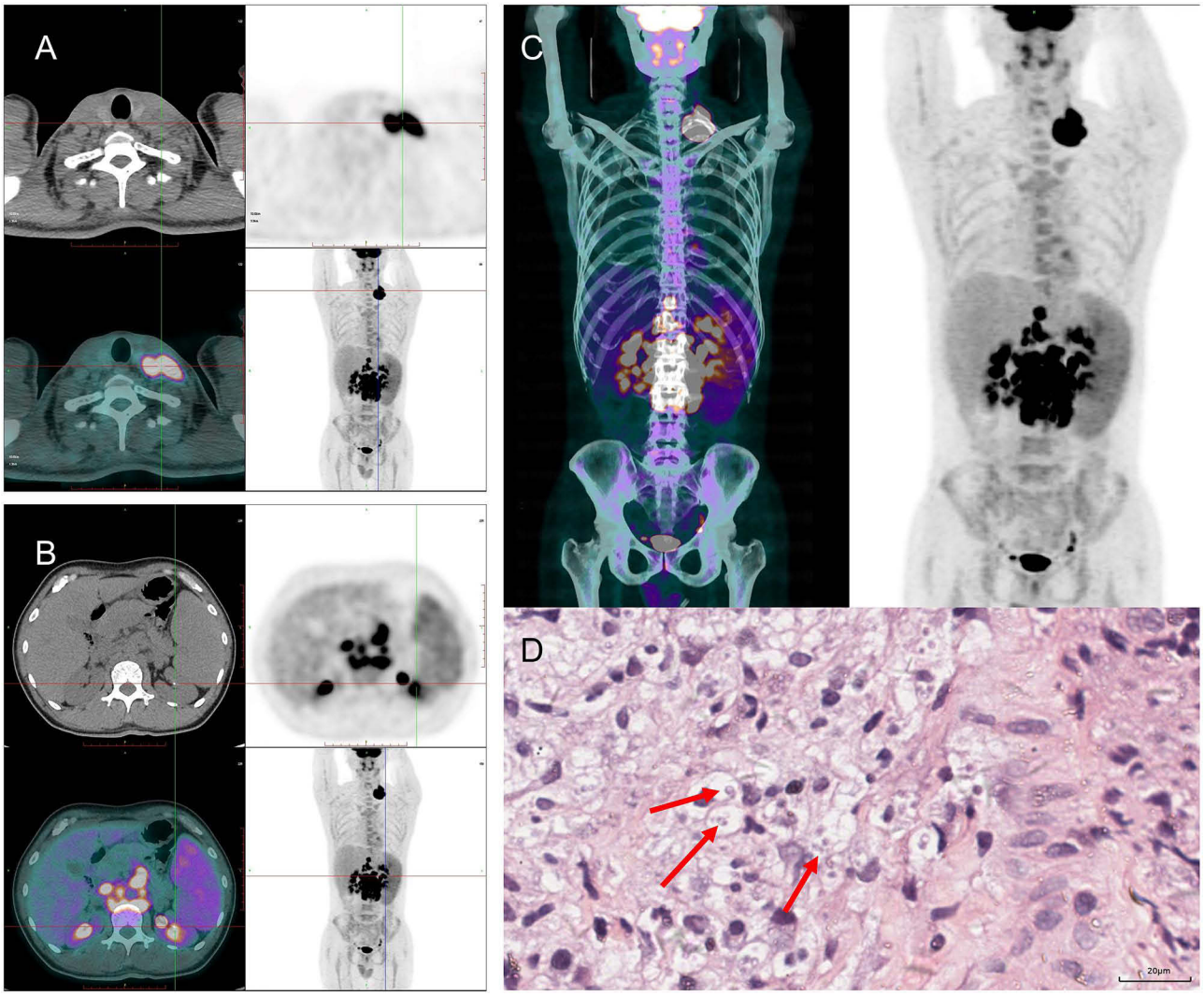

Figure 2 (**A**) In the PET/CT images of Case 6, multiple enlarged lymph nodes with abnormally increased FDG metabolism were observed in the left supraclavicular region. (**B**) In the PET/CT images of Case 6, multiple enlarged lymph nodes with abnormally increased FDG metabolism were observed in the retroperitoneal region. (**C**) In the whole-body PET/CT images of Case 6 (from the skull to the upper thighs), multiple enlarged lymph nodes with abnormally increased FDG metabolism were observed. (**D**) Fine-needle Aspiration Biopsy of the Left Cervical Lymph Node of case 6: The three red arrows indicate *Talaromyces marneffei.*

Shanxi, Beijing, and Jilin,[4] showing a trend of "south-to-north shift". In this study, five of the six patients had long-term residence in Zhejiang Province, and one in Chongqing, both non-endemic areas.

Common clinical manifestations of *Talaromyces marneffei* infection include fever, weight loss, anemia, weakness, skin lesions, lymphadenopathy, and hepatosplenomegaly.[4] In this study, all six patients exhibited varying degrees of fever, cough with sputum, anemia, and lymphadenopathy. These non-specific symptoms, combined with the relatively insidious and mild onset of the disease, often lead to delayed diagnosis or misdiagnosis by clinicians unfamiliar with the disease presentation.[8] For example, Case 6 initially presented with abdominal pain and an enhanced abdominal CT scan showing splenomegaly and multiple enlarged lymph nodes in the abdomen and retroperitoneum, mimicking lymphoma, leading to admission to the hematology ward for further workup, including bone marrow biopsy and whole-body PET/CT. Integrated FDG PET/CT, initially a widely used imaging technique for various oncologic indications, has expanded its clinical application beyond cancer imaging into the realm of suspected infections and inflammation.[9] Many previous studies have shown that both hematologic malignancies and *Talaromyces marneffei* infection can involve lymph nodes and bones, presenting similar clinical features such as fever, bone destruction, and lymphadenopathy, complicating differential diagnosis.[10] Early FDG PET/CT imaging has been shown to more accurately detect occult tumors or sources of fever and identify other disease sites, guiding appropriate therapy.[11] In our patient, although distinguishing between

infectious/inflammatory lesions and malignancy based solely on FDG uptake intensity in Case 6 was challenging, the combination of FDG uptake patterns and available clinical information made an infectious diagnosis much more likely than malignancy.[12] Early biopsy of hypermetabolic lymph nodes in Case 6 led to the histopathologic confirmation of *Talaromyces marneffei* infection. Additionally, infections in atypical locations can increase the likelihood of misdiagnosis. In this study, three patients had lymphadenopathy of varying degrees on superficial lymph node ultrasound. Case 1 presented with swelling of the left forearm and a 3 cm × 3 cm ulceration at the wrist, with palpable lymph nodes ≥2 cm in the left axilla and elbow, leading to a misdiagnosis of soft tissue infection for over 1 month, delaying appropriate treatment and affecting prognosis.

The diverse chest imaging findings in this study, including infectious lesions, hilar enlargement, multiple enlarged mediastinal lymph nodes, pulmonary nodules, bullae, abscess formation, and cavity formation, are similar to those reported by Zhu et al[13] However, these chest CT findings are not unique to *Talaromyces marneffei* infection and cannot provide a definitive diagnosis. For example, Case 2–4 were initially misdiagnosed as pneumonia caused by other pathogens. Moreover, these imaging features overlap with other pulmonary diseases such as bronchogenic carcinoma, tracheal tuberculosis, and bronchial aspergillosis, making differentiation difficult.

Recent advances in fungal laboratory detection techniques have enhanced possibilities for early diagnosis of fungal infections. Serum-based assays like the galactomannan test (GM test) and (1,3)-β-D glucan detection test (G test), valued for their short turnaround times and operational convenience, are widely used for early detection of invasive fungal infections.[14] The GM test also offers prognostic value in HIV-positive patients, where persistently elevated levels indicate a poor prognosis.[15] However, these tests have significant limitations: they lack species specificity, cannot identify the exact pathogen, are susceptible to interference, and exhibit limited sensitivity. GM test specificity is only approximately 80%, and normal levels cannot exclude *Talaromyces marneffei* infection.[16] Consequently, highly sensitive and specific rapid diagnostic methods beyond these are needed. Among molecular techniques, metagenomic next generation sequencing (mNGS) has emerged as a powerful tool for pathogen detection and identification.[17] mNGS significantly improves the diagnostic rate of *Talaromyces marneffei* infection and offers several advantages over conventional culture: a shorter diagnostic time that avoids delays associated with culture, which may lead to patient improvement or deterioration before empirical treatment; comprehensive pathogen coverage (including viruses, bacteria, fungi, and parasites) with enhanced resolution for distinguishing closely related strains, thereby overcoming the limitation of conventional culture; and the avoidance of false-negative results caused by issues such as antibiotic use, sample collection, sample transport, and being highly dependent on the skills of the specimen collector, resulting in higher positivity rates in bronchoalveolar lavage fluid (BALF) and skin tissue samples.[18–20] This study demonstrated mNGS's superior sensitivity. Testing five specimens from patients with negative conventional cultures identified *Talaromyces marneffei* sequences in lung tissue (three patients), lymph nodes, BALF, and blood. These findings confirm mNGS as a highly sensitive detection method capable of reducing early misdiagnosis.

However, this high sensitivity presents a key challenge: NGS can detect sequences from non-pathogenic or commensal organisms (eg, *Serratia marcescens, Raoultella ornithinolytica, Circovirus, Epstein-Barr virus*), complicating clinical interpretation. This necessitates careful physician correlation, especially since co-infections often present with non-specific symptoms (eg, fever, cough, elevated ESR/CRP/ferritin) easily mistaken for other infections. Immunocompromised patients often carry opportunistic Gram-negative pathogens with high antimicrobial resistance, which makes treatment more challenging. Due to underlying health conditions or prior antibiotic exposure, their treatment options may be limited, leading to chronic and recurrent infections. These can cause severe infections, including pneumonia, sepsis, and bloodstream infections, all of which may be life-threatening.[21] Therefore, in immunocompromised patients with persistent symptoms despite standard therapy, mNGS can be crucial for promptly identifying unusual pathogens requiring targeted treatment.[22]

For disseminated *Talaromyces marneffei* infection, antifungal therapy should be based on systemic treatment, divided into induction, consolidation, and maintenance phases. Multiple studies comparing amphotericin B and itraconazole for *Talaromyces marneffei* infection have shown that amphotericin B alone or in combination with azoles provides better prognosis than azoles alone.[23] For HIV-positive patients, the recommended regimen includes 2 weeks of intravenous amphotericin B (0.6 mg/kg/day) or amphotericin B lipid complex, followed by 10 weeks of oral itraconazole (400 mg/day) for consolidation and then maintenance therapy with itraconazole 200 mg/day. Two trials in Thailand demonstrated that maintenance therapy with itraconazole (200 mg/day) in patients with advanced HIV disease not only reduced the recurrence

rate from 57% to 0% but also decreased the incidence of invasive fungal infections (ie, *Talaromyces marneffei* infection, cryptococcosis, and esophageal candidiasis) in HIV-infected patients with $CD4^+$ lymphocyte counts below 200 cells/μL.[24]

Currently, there is no standardized treatment regimen for HIV-negative hosts, and treatment typically follows the guidelines for HIV-positive patients, using the same medications but with less defined durations. In this study, four HIV-negative patients all initially received induction therapy with amphotericin B lipid complex. Case 1 received treatment for up to 4 months, with a cumulative dose of 31800 mg, far exceeding the guide-line-recommended induction period. Cases 2 and 3 followed the guideline-recommended duration of 2 weeks. Case 2 was later switched to oral voriconazole. Voriconazole, a second-generation triazole antifungal agent with good bioavailability and high tissue penetration, has proven to be an effective and well-tolerated option for *Talaromyces marneffei* infection. It can be considered a first-line treatment.[25] One study demonstrated that voriconazole induction therapy was comparable to amphotericin B deoxycholate in terms of allcause mortality. However, the optimal duration of voriconazole induction therapy remains unclear.[26]

For mild *Talaromyces marneffei* infections, oral itraconazole (200mg twice daily) alone is effective. Studies indicate that amphotericin B offers no significant advantage over itraconazole in non-fungemic patients regarding clinical response or mortality. Given its higher cost, complex administration requirements, and need for intensive toxicity monitoring, itraconazole demonstrates superior long-term cost-effectiveness.[27] Thus, itraconazole is recommended as first-line therapy for mild-to-moderate infections when amphotericin B is unavailable. Vietnamese HIV guidelines report that only 20.5% of severe cases receive amphotericin B, while 77.2% are treated with itraconazole or ketoconazole.[28] Overall, most patients require long-term suppressive therapy to prevent relapse. However, the optimal long-term management strategy for HIV-negative patients, including choice of regimen and treatment duration, remains uncertain and warrants further investigation through large-scale clinical studies.

This study has several limitations. First, the study recruited patients from a single hospital, and the relatively small sample size may inevitably lead to some biases. Second, as this was a retrospective study, detailed follow-up information was unavailable for some patients, resulting in missing data.

Conclusion

In summary, for immunocompromised patients presenting with persistent fever, unexplained lymphadenopathy, pulmonary infiltrates, or poor response to broad-spectrum antibiotic therapy, clinicians in non-endemic regions should maintain a high index of suspicion for Talaromyces marneffei infection, even in the absence of travel history to traditionally endemic areas. Early diagnosis can be facilitated by metagenomic next-generation sequencing (mNGS), which offers superior sensitivity over conventional culture and histopathology, particularly when clinical presentations are atypical. Treatment should be individualized based on disease severity: patients with severe immunocompromised status, multiple organ dysfunction, or specific clinical symptoms warrant induction therapy with amphotericin B lipid complex (3–5 mg/kg/day for at least 2 weeks), followed by oral azole maintenance; milder cases may be effectively managed with oral itraconazole (200 mg twice daily). Given the lack of standardized regimens for HIV-negative patients, treatment duration should be guided by clinical response, radiological improvement, and immune reconstitution. Further multicenter studies are needed to establish optimal induction strategies and total treatment duration, particularly in non-HIV immunocompromised populations.

Data Sharing Statement

Data are contained within the article. Further inquiries can be directed to the corresponding author.

Informed Consent Statement

The research followed the principles of the Declaration of Helsinki. The Ethics Committee of Shaoxing People's Hospital approved this study (2025-Scientific research project 182-01) and waived the requirement for informed written consent, given its nature of retrospective study. All data were processed anonymously.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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