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Case Report

Metagenomic next-generation sequencing diagnoses *Talaromyces marneffei* infections: case report and review

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Abstract

Introduction: *Talaromyces marneffei* is a pathogenic dimorphic fungus known for causing severe opportunistic infections that can be life-threatening. The fungus is most commonly found in Southeast Asia and southern China.

Case report: This case report describes the case of a young male patient infected with *T. marneffei* who was neither human immunodeficiency virus (HIV)-positive nor possessed anti-IFN-γ antibodies, and who resided outside the typical endemic regions. The patient developed cough and sputum three months after the removal of the left arm fracture fixator, and was initially misdiagnosed with tuberculosis; however, the response to anti-tuberculosis treatment was not good. The diagnosis of subsequent recurrence was unknown. The condition recurred during the illness, and he was ultimately diagnosed with talaromycosis via metagenomic next-generation sequencing (mNGS). The patient's condition improved after appropriate treatment with liposomal amphotericin B.

Conclusions: Previous studies have found that *T. marneffei* infections are concentrated in patients with acquired immunodeficiency syndrome due to HIV infection, and in anti-IFN-γ antibody-positive patients. However, infections are increasing in individuals who are not immunosuppressed and are often misdiagnosed and underdiagnosed during the initial course of the disease. Therefore, clinicians should be aware that mNGS is an effective technique for detecting *T. marneffei* infection in non-endemic areas where they encounter non-HIV infected patients. This case report aims to raise the awareness of physicians regarding this rare disease in non-endemic areas and non-HIV patients.

Key words: talaromycosis; lung; metagenomic next-generation sequencing; anti-IFN-γ autoantibodies; skin involvement; case report.

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Introduction

Talaromyces marneffei, the only pathogenic thermodimorphic fungus among Talaromyces, is one of the three major opportunistic infections in human immunodeficiency virus (HIV)-positive hosts in Southeast Asia and southern China [1,2]. Human infection with *T. marneffei* may occur by inhalation of conidia in the environment into the lungs. Once a fungal pathogen enters the lungs, conidia are able to replicate in alveolar macrophages in the form of yeasts to cause infection and can be disseminated to other parts of the body via the hematogenous pathway, ranging from localized infections of the skin and lungs to severe systemic infections [3–5]. Individuals at risk include patients with acquired immunodeficiency syndrome (AIDS); anti-IFN-γ autoantibodies (AIGA) positive patients; those with autoimmune diseases, primary immunodeficiencies, and diabetes; patients who use steroids and immunosuppressants; and patients with other immunodeficiencies. In addition, the combination of other opportunistic pathogens, misdiagnosis, and underdiagnosis are main factors affecting their prognosis [6,7]. However, *T. marneffei* infection may also occur in HIV-negative individuals without significant immunosuppression, and granulomas may be seen in the lungs, liver, skin, and subcutaneous tissues of immunocompetent hosts, which may lead to misdiagnosis of tuberculosis [2]. Moreover, the clinical presentation of *T. marneffei* infection is nonspecific and diverse, making the culture of *T. marneffei* critical for diagnosis. However, *T. marneffei* is morphologically very similar to *Histoplasma capsulatum*, and this makes differentiation challenging [8,9]. Therefore, rapid and accurate pathogen identification is crucial for the early initiation of appropriate antimicrobial therapy [10].

A case of *T. marneffei* infection in a 27-year-old

Chinese male from a non-endemic region is described here. The patient was HIV-negative and AIGA-negative. The patient exhibited a persistent cough for 5 years and was initially misdiagnosed with tuberculosis. The correct diagnosis of talaromycosis was ultimately established in our hospital via metagenomic next-generation sequencing (mNGS).

Case presentation

A 27-year-old male presented with a 5-year history of recurrent cough and 2 months of hemoptysis accompanied by chest pain. Physical examination on admission revealed tachycardia (110 bpm), dullness to percussion over the right upper lung, and bilateral coarse crackles. The patient had a history of left arm and rib fractures in 2015 and was treated with open reduction and internal fixation (ORIF). In 2016, he developed cough and sputum production without hemoptysis three months after hardware removal. Notably, preoperative chest radiographs showed no abnormalities. The local hospital diagnosed "pulmonary tuberculosis" and prescribed 2HRE/7HR treatment, which was discontinued after the lesions were absorbed (Figure 1). The symptoms recurred in

Figure 1. First-onset chest CT in 2016.

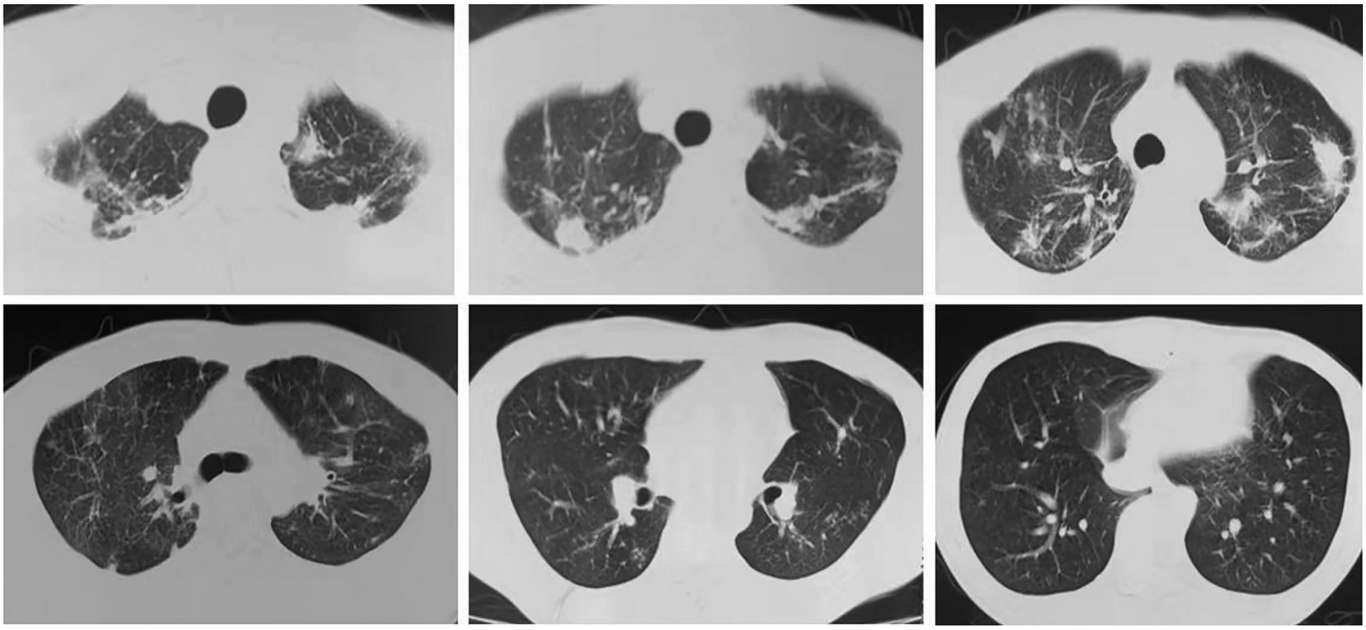
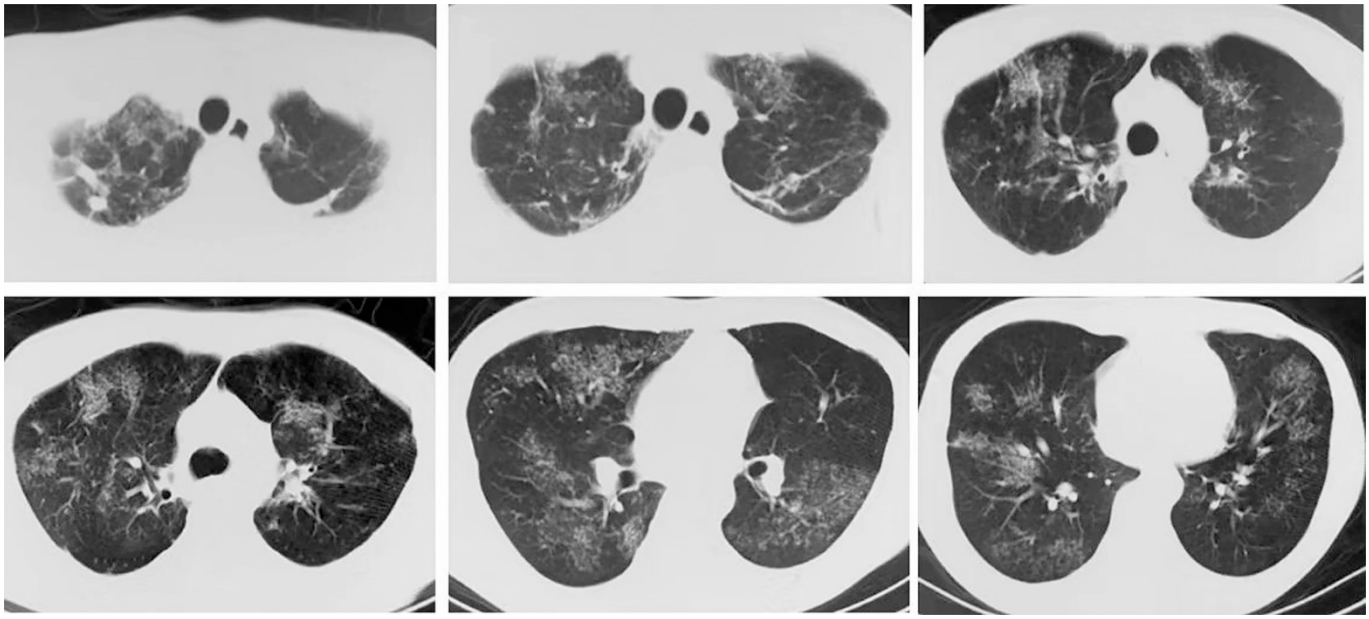


Figure 2. Chest CT for reoccurrence in 2019.



2019 with bilateral pulmonary lesions on computed tomography (CT) (Figure 2). Laryngeal biopsy demonstrated granulomatous inflammation without caseous necrosis. The symptoms improved but radiographic abnormalities persisted despite receiving another 1-year course of anti-tuberculosis treatment. On 15 January 2021 the patient had a recurrence of coughing symptoms with hemoptysis accompanied by mild chest pain, and progression of the lesion from 2019 on chest CT. Tracheoscopy did not show any significant luminal abnormalities, peripheral blood eosinophil ratio was highest at 44.1%, and alveolar lavage fluid was sent for routine pathogenetic cultures (including bacterial and fungal cultures). In addition, the tuberculosis X-pert was negative. Cefoperazone sulbactam was used as an anti-infective treatment for 2 weeks; however, the lesion was not absorbed. Next, methylprednisolone 40mg qd was given for 2 weeks, and the lesion was absorbed. Cough, hemoptysis and chest pain also improved (Figure 3).

However, the patient was admitted to the hospital on 19 February 2021 due to initial unclear diagnosis. The patient's social history included being single and childless with no sexual partner. The patient had worked in security, construction, logistics, and garment ironing over the previous 7 years; and denied any history of promiscuous behavior, chronic diseases, blood transfusions, drug or food allergies, family medical history, or exposure to organic dust and toxic substances. The admission examination parameters were: hypersensitive C-reactive protein (CRP) 70.20 mg/L, eosinophil count 1.54 × 10^9/L, sputum fungal fluorescence: -/+/+, hepatitis B serologic test, hepatitis C, HIV, syphilis antibody (-), and inhalation and food allergen combination (-). Blood fungal G test and GM test were (-), and these tests were performed using commercial kits (G test: Jinshanchuan Technology, Zhuhai, China; GM test: Bio-Rad Laboratories, Hercules, USA). Tuberculosis effect T cell was (-), and sputum smear indicated Gram-negative bacilli 2+/2+/2+. Immunoglobulin M (IgM) was 0.33 g/L, erythrocyte sedimentation rate (ESR) was 50 mm/h. Other parameters were: procalcitonin (PCT) 0.152 ng/mL, serum amyloid A (SAA) 91.7 mg/L, and interleukin-6 (IL-6) 15.0 pg/mL. The tumor markers tests indicated pro-gastrin-releasing peptide (ProGRP) 24.89 pg/mL, cytokeratin 19 fragment (Cyfra21-1) 3.38 ng/mL, neuron-specific enolase (NSE) 31.78 ng/mL, and cancer antigen 125 (CA-125) 212.40 U/mL; which were elevated levels of tumor markers. CD4 count was 308/μL, CD8 count was 200/μL, and CD3 count was 544/μL; these values were decreased. The predominant nuclear pattern of antinuclear antibodies (ANA) was cytoplasmic-fibrillary. The antinuclear antibody titer was weakly positive at 1:100. All other autoantibody screenings were negative. An initial treatment regimen was established, given the patient's history and clinical presentation with bilateral pulmonary infiltrates accompanied by peripheral eosinophilia, unresponsive to conventional anti-infective therapy, and with lesion resolution upon steroid treatment. This involved administering piperacillin-tazobactam (2.5 g every 12 hours) and discontinuing methylprednisolone. However, after the discontinuation of steroids, the chest CT on 25 February showed an increase in lesions as compared with that on February 20 (Figure 4). A bone marrow biopsy was performed to exclude hematologic malignancies. Lung biopsy pathology revealed pulmonary consolidation with extensive chronic inflammatory cell infiltration and formation of small

Figure 3. Comparison of chest CT before (**A**) and after (**B**) methylprednisolone administration on 31 January 2021 and 5 February 2021 respectively.

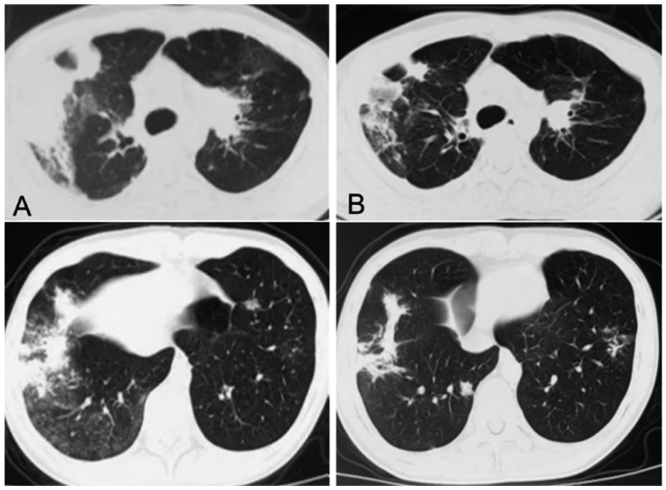


Figure 4. Comparison of chest CT after hormone withdrawal.

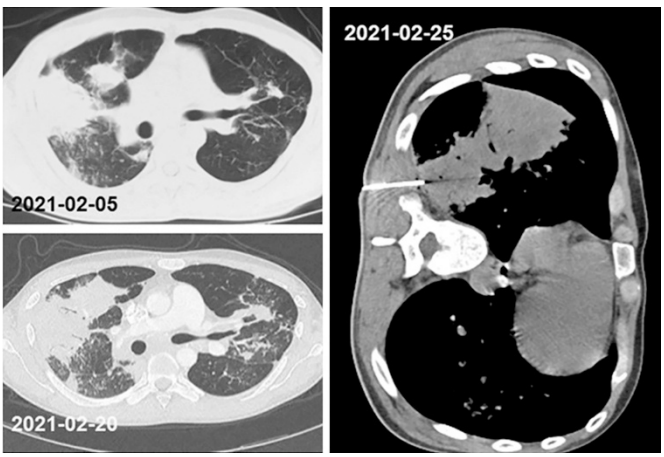
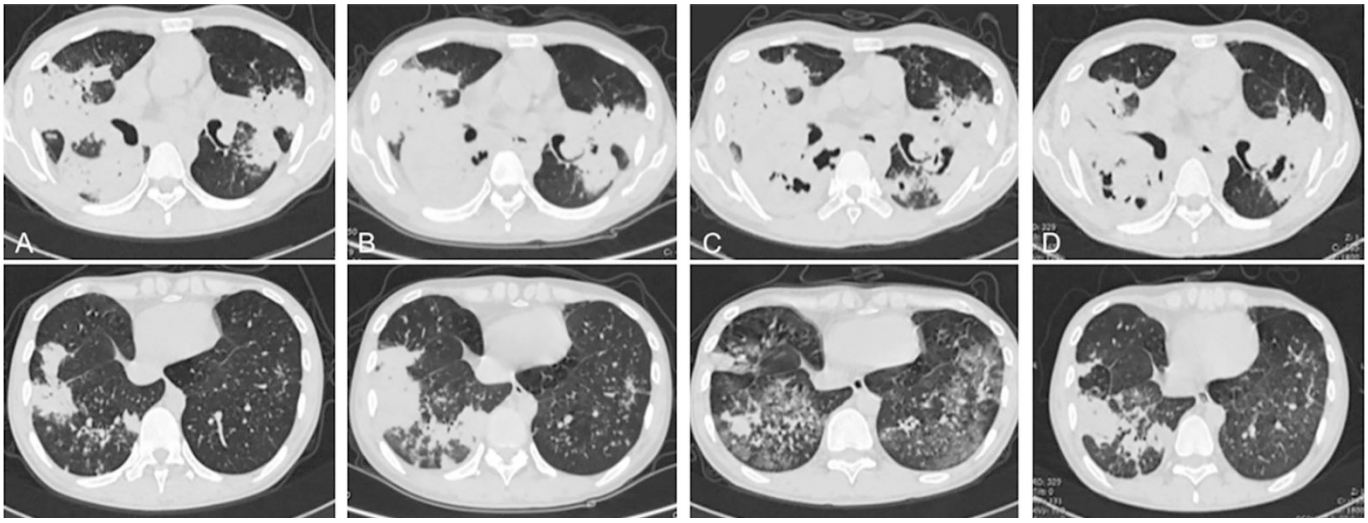


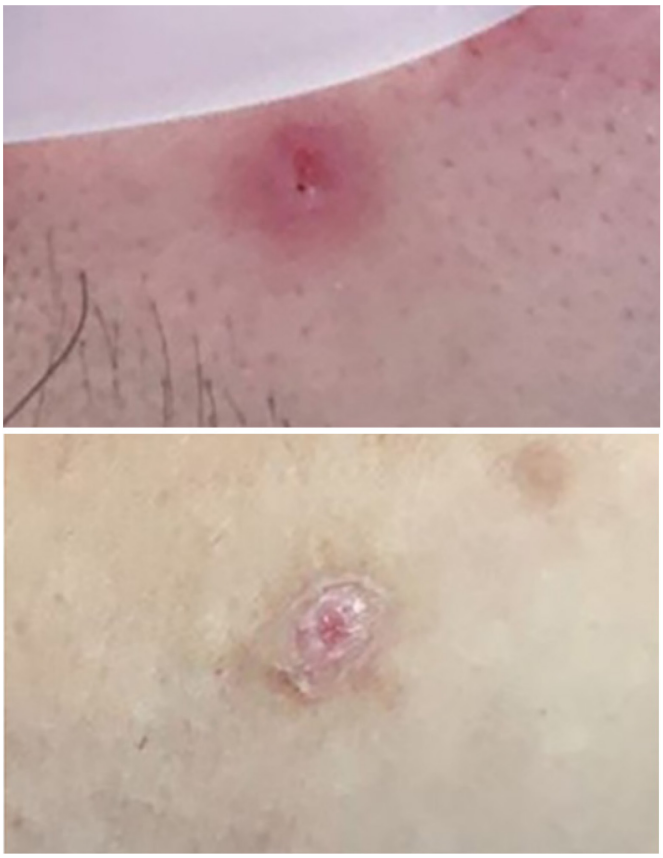
Figure 5. Comparison of chest CT tests on 15 March (**A**), 29 March 29 (**B**), 6 April (**C**), and 28 April (**D**), 2021.



epithelioid granulomas within the lung interstitium, with no definitive pathogens observed on special staining and no eosinophilic infiltration (Supplementary Figure 1). Periodic acid-Schiff (PAS) stain, acid-fast stain, and tuberculosis polymerase chain reaction (PCR) were all negative. The patient requested further steroid therapy and was given methylprednisolone 40 mg once daily for 7 days. A follow-up chest CT on March 15 showed no significant resolution of lesions, and the patient was advised to continue oral methylprednisolone 40 mg once daily and to follow up in 2 weeks (Figure 5A).

On the third day after discharge, the patient's cough worsened after the rain, with expectoration of approximately 40 mL/day of yellow purulent sputum and hemoptysis of approximately 15 mL/day with fresh blood or bloody sputum. The patient experienced increased chest pain and exacerbated dyspnea upon exertion. Facial edema and scattered erythematous papules and plaques were present on the face and trunk (Figure 6), and fever was noted after hormone cessation. He was re-admitted to the hospital on 29 March 2021, and a repeat chest CT showed disease progression (Figure 5B). A follow-up percutaneous lung biopsy on March 30 revealed necrosis and a few residual alveoli, with the presence of reactive histiocytes and intracytoplasmic spherical organisms, Gomori's methenamine silver (GMS) PAS staining was positive (Figure 7), and elastin staining showed alveolar wall destruction. The morphology tended to be capsulatum. Piperacillin and voriconazole were administered sequentially for empirical treatment with suboptimal response. The initial voriconazole dose was 6 mg/kg every 12 hours for the first 24 hours, followed by a maintenance dose of 4 mg/kg every 12 hours. The dyspnea symptoms did not improve, and the body temperature did not normalize. Re-examination of CT revealed ongoing disease progression (Figure 5C). Blood and tissue samples were collected for metagenomic next-generation sequencing (mNGS). DNA was extracted, libraries were prepared, and single-end sequencing was performed using the Illumina Next-seq platform (Illumina, San Diego, CA,

Figure 6. Scattered red maculopapular rash on the face and trunk.



USA). The sequence output was filtered from human sequences, and unmapped reads were aligned to a microbial database. As a result, *Talaromyces marneffei* was consistently identified, and the patient tested negative for anti-IFN-γ autoantibody.

The medication was adjusted after the identification of the pathogen. The new medications started on April 7; and included amphotericin B administered, with an initial dose of 1 mg on day 1, and the dose was increased by 5 mg daily or every other day depending on the patient's tolerance. Premedication with promethazine and hydrocortisone succinate 25 mg was given prior to the first dose of the drug to minimize adverse reactions. However, the patient exhibited intolerance when the drug dosage reached 0.6 mg/kg. The medication was switched to voriconazole on April 27 due to drug side effects. Chest CT on April 28 showed progression with cavity formation (Figure 5D). The patient developed recurrent fevers, worsening symptoms, and a recurrent rash. Subsequently, secondary mNGS of blood and sputum revealed *T. marneffei*. The drug was switched to liposomal amphotericin B on May 1, and the patient's pulmonary infection symptoms improved (Figure 8). Chest CT was repeated on 14 July 2022 and the patient's prognosis was good.

Figure 7A. Periodic acid-Schiff (PAS) staining; **B.** Gomori methenamine silver (GMS) staining (magnification: × 40).

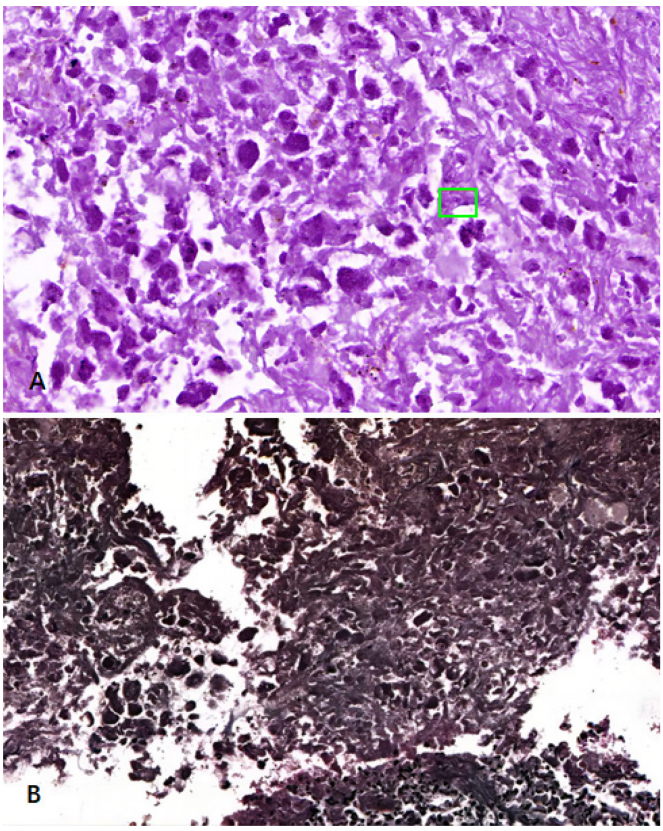
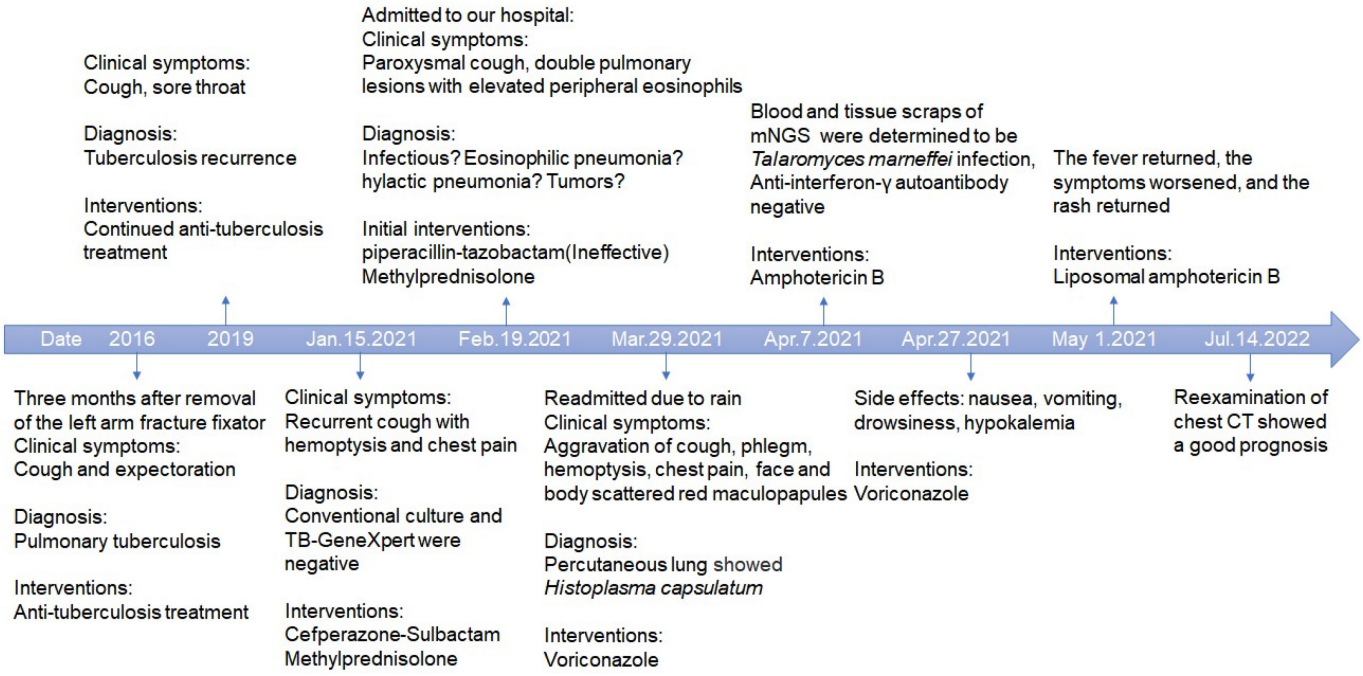


Figure 8. Timeline of patient onset, and related data on clinical diagnosis and interventions.



Discussion

T. marneffei is a dimorphic pathogenic fungus distributed in Southeast Asia and southern China [11,12]. It was initially isolated from bamboo rats; however, the route of human transmission remains unclear. While some studies suggest bamboo rats as potential hosts, others highlight environmental exposure, especially to soil, during rainy seasons as the key risk factor [13,14]. Current consensus posits that environmental conidia are inhaled and phagocytosed by alveolar macrophages, transforming into pathogenic yeast forms [15,16]. Most patients reside in or travel to endemic areas [17], but sporadic cases lack direct exposure history [18,19], and incubation periods vary [20]. The case presented here involved a patient with no endemic-area exposure, underscoring that *T. marneffei* infection should be considered even in non-endemic regions when pathological findings include pulmonary consolidation, chronic inflammatory infiltration, or interstitial epithelioid granulomas.

T. marneffei usually causes infections in HIV-infected individuals. However, the epidemiological landscape of *T. marneffei* infection has shifted since the economic boom of the 1990s which was accompanied by improvements in healthcare infrastructure. Since then, there has been a rise in infections among HIV-negative patients with immunodeficiency [1,7]. In the case of HIV-positive hosts, the primary mechanism of *T. marneffei* infection is cell-mediated immunodeficiency caused by a reduction in CD4+ T cells. Conversely, the pathogenesis in HIV-negative hosts is not simply attributable to cellular immune deficits, as most patients exhibit normal total T cell counts, CD4+ T cell counts, and CD4/CD8 ratios [21]. Of these, AIGA accounted for the highest proportion of risk factors for susceptibility to *T. marneffei* in HIV-negative hosts, and it has been documented that high titers of AIGA underlie disseminated *T. marneffei* infection [2], However, not all AIGA-positive patients are infected with *T. marneffei*, suggesting that this immunodeficiency is not necessarily the only factor and that the pathogenesis of *T. marneffei* and AIGA is not fully understood. In this case, the patient was HIV-negative and did not have AIGA; therefore, the mechanisms of *T. marneffei* infection in HIV-negative hosts are complex and varied [7]. Under these circumstances, rapid diagnosis of *T. marneffei* may be a crucial step in effectively controlling the associated mortality rate [21].

Traditional diagnostic methods for *T. marneffei* infections rely on culture or microscopic examination, which are time-consuming and have a low positivity rate, and may negatively affect the selection of appropriate treatments [21]. *T. marneffei* is typically characterized by the massive production of red pigment by fungal colonies at 25 °C [9]. Histologically, the septa within yeast cells are the most distinctive feature of *T. marneffei*. However, organisms can aggregate and overcrowd tissues; therefore, it is often difficult to identify yeast cells with characteristic septal structures, which makes it difficult to distinguish *T. marneffei* from capsulatum [22]. In this case, the microscopic examination of the patient's right lung puncture specimen was misdiagnosed morphologically as capsulatum. Therefore, it is crucial to diagnose these diseases promptly and accurately to improve the prognosis. The combination of quantitative polymerase chain reaction (qPCR) and serum galactomannan GM assay is usually a valuable tool for the diagnosis of *T. marneffe* infection [23,24]. In contrast, mNGS has been successfully applied to the diagnosis of *T. marneffei* infection in many previous reports and has been shown to be useful in the diagnosis of *T. marneffei* infection in skin lesion specimens [4,25,26]. Being a culture-independent method, mNGS provides a rapid etiologic diagnosis, especially in patients with uncommon manifestations of *T. marneffe* infection. However, mNGS has several limitations; including high costs, limited accessibility in resource-poor settings, and the requirement for specialized equipment and bioinformatics expertise; which may restrict its widespread adoption. Pathogens have been isolated from previous clinical specimens, including blood, skin lesions, lymph node biopsy specimens, bone marrow, sputum, bronchoalveolar lavage fluid, urine, and feces. Of these, bone marrow cultures, skin biopsy specimens, and blood have demonstrated high sensitivity in diagnosing *T. marneffei* infections [18]. As can be seen in the case of this patient, the tissue debris and blood specimen of the lesion may represent a suitable specimen for mNGS, which may be persuasive in obtaining a targeted diagnosis and treatment.

The PubMed database was searched using the keywords "Talaromyces marneffei" and "case report," resulting in the identification of a total of 19 cases (Supplementary Table 1) from different regions of China. The patients' ages ranged from 19 to 80 years, with a male predominance (only 3 female cases). Regarding HIV status, 5 out of 19 patients were HIV-positive, while the remaining were HIV-negative. AIGA testing was positive in 4 cases, with the status either unreported or negative in others. Clinically, fever was the most common symptom, often accompanied by cough, fatigue, and, in some cases, cutaneous lesions,

headache, or abdominal pain. Diagnosis was primarily confirmed by culture (12 cases), while mNGS played a significant role in detecting the pathogen in 7 cases by providing crucial diagnostic support. The main treatments included voriconazole and amphotericin B. In terms of outcomes, 11 patients improved, 6 died, and the prognosis was unspecified in the remaining cases. These cases demonstrate the diversity of *Talaromyces marneffei* infections in terms of patient demographics, clinical manifestations, diagnostic approaches, and treatment responses. The findings offer valuable insights for clinicians in recognizing and managing this infection, thereby improving diagnostic accuracy and therapeutic outcomes.

T. marneffei infection in HIV-infected patients is usually disseminated and involves multiple organs. The infection in HIV-negative patients may be focal or disseminated, depending on the underlying immunocompromised status and time of diagnosis [27]. However, the clinical manifestations of *T. marneffei* infection are nonspecific and varied, and may be characterized by fever, cough, sputum, weight loss, skin lesions, generalized lymph node enlargement, and hepatomegaly, which are atypical and easily confused with other conditions such as tuberculosis, pneumonia, lung cancer, esophagitis, hematologic disorders, and metastatic neoplasms. Imaging features of *T. marneffei* lung infections also lack specificity and are similar to those of tuberculosis [19]. *Mycobacterium tuberculosis* is the same intracellular bacillus as *T. marneffei*, and both manifest as lymphatic tract or interstitial lung infection. It is difficult to distinguish between talaromycosis and tuberculosis when the pathology shows chronic granulomatous inflammation [12]. In this case, the patient was initially misdiagnosed with tuberculosis and the symptoms continued to recur after two courses of antituberculosis treatment. Therefore, cutaneous involvement in disseminated talaromycosis is commonly used as an adjunctive diagnosis, with skin lesions usually appearing on the face and limbs [22]. In this case, the patient also presented with typical skin lesions.

Although guidelines for *T. marneffei* infection in HIV-positive patients have been published, standardized treatment for HIV-negative patients has not yet been established [28,29]. The recommended therapeutic approaches for *T. marneffei* in the literature include amphotericin B, voriconazole, and itraconazole [1,30]. The patient was treated with amphotericin B following the initial mNGS results. On the first day (7 April) of the treatment cycle, the patient received a 1 mg test dose; and premedication with promethazine plus hydrocortisone succinate at a dose of 25 mg was administered to reduce adverse reactions. The dosage of amphotericin B was subsequently increased daily or every other day by 5 mg depending on the patient's tolerance. However, intolerance occurred when the dosage reached 0.6 mg/kg. Treatment was switched to voriconazole the following day, and the patient developed a fever and worsening of symptoms on the second day after the change. A second treatment cycle was then initiated based on the results of the second mNGS test, and on May 1st, amphotericin B was discontinued and replaced with liposomal amphotericin B, which was used in combination with voriconazole. The pulmonary mass had significantly decreased and improved 1 month after the start of combination therapy. Notably, the diffuse exudative lesions were absorbed after the initial administration of corticosteroids upon the patient's admission. It has been hypothesized that these changes may be related to fungal death and the release of inflammatory mediators during treatment [31]. The binding of certain fungi or parasites to airway or alveolar epithelial cells may activate inflammatory signaling, recruiting eosinophils and T lymphocytes, and secreting typical Th cell cytokines [32]. Glucocorticoids have potent anti-inflammatory effects and a broad spectrum of therapeutic activity, reducing lung monocyte macrophage levels and decreasing the production of inflammatory mediators [33]. This led to the false impression of efficacy during the initial phase of corticosteroid treatment, and subsequent corticosteroid therapy failed to effectively treat the fungal infection, resulting in a lack of lesion absorption.

HIV-negative patients with *T. marneffei* infection often exhibit nonspecific clinical manifestations, leading to underdiagnosis, misdiagnosis, and high mortality. This case highlights the need for heightened clinical vigilance in the following scenarios: (i) unexplained fever accompanied by characteristic skin lesions (central facial umbilicated papulonodules); (ii) pulmonary consolidation with lymphadenopathy; and (iii) granulomatous inflammation refractory to anti-tuberculosis therapy. The diagnostic approach should prioritize microscopic examination (identifying yeast-like cells with transverse septa) and 25 °C culture (detecting diffusible red pigment). If conventional methods yield inconclusive results, mNGS or species-specific PCR can facilitate rapid pathogen identification.

This study has several limitations, including restricted generalizability due to its single-case design, incomplete immunological profiling inherent to

retrospective analysis, and the practical challenges of implementing mNGS in resource-limited settings. Multicenter prospective studies are warranted to validate diagnostic algorithms and establish evidence-based management guidelines for this emerging patient population.

Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s), and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

All authors contributed to the article and approved the submitted version.

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Conflict of interest

No conflict of interest is declared.

References

1. Vanittanakom N, Cooper CR Jr, Fisher MC, Sirisanthana T (2006) *Penicillium marneffei* infection and recent advances in the epidemiology and molecular biology aspects. Clin Microbiol Rev 19: 95–110. doi: 10.1128/CMR.19.1.95-110.2006.
2. Guo J, Ning XQ, Ding JY, Zheng YQ, Shi NN, Wu FY, Lin YK, Shih HP, Ting HT, Liang G, Lu XC, Kong JL, Wang K, Lu YB, Fu YJ, Hu R, Li TM, Pan KS, Li XY, Huang CY, Lo YF, Chang IY, Yeh CF, Tu KH, Tsai YH, Ku CL, Cao CW (2020) Anti-IFN-γ autoantibodies underlie disseminated *Talaromyces marneffei* infections. J Exp Med 217: e20190502. doi: 10.1084/jem.20190502.
3. Cao C, Xi L, Chaturvedi V (2019) Talaromycosis (penicilliosis) due to *Talaromyces* (*Penicillium*) *marneffei*: insights into the clinical trends of a major fungal disease 60 years after the discovery of the pathogen. Mycopathologia 184: 709–720. doi: 10.1007/s11046-019-00410-2.
4. Xu L, Chen X, Yang X, Jiang H, Wang J, Chen S, Xu J (2023) Disseminated *Talaromyces marneffei* infection after renal transplantation: a case report and literature review. Front Cell Infect Microbiol 13: 1115268. doi: 10.3389/fcimb.2023.1115268.
5. Bourassa L, Doppalapudi A, Butler-Wu SM (2019) Closing the brief case: pneumonia caused by *Talaromyces marneffei*. J Clin Microbiol 57: e01691–18. doi: 10.1128/JCM.01691-18.
6. Qiu Y, Feng X, Zeng W, Zhang H, Zhang J (2021) Immunodeficiency disease spectrum in HIV-negative individuals with talaromycosis. J Clin Immunol 41: 221–223. doi: 10.1007/s10875-020-00869-5.
7. Lin F, Yang Z, Qiu Y, Zeng W, Liu G, Zhang J (2021) *Talaromyces marneffei* infection in lung cancer patients with positive AIGAs: a rare case report. Infect Drug Resist 14: 5005–5013. doi: 10.2147/IDR.S340694.
8. Deng ZL, Connor DH (1985) Progressive disseminated penicilliosis caused by *Penicillium marneffei*. Report of eight cases and differentiation of the causative organism from *Histoplasma capsulatum*. Am J Clin Pathol 84: 323–327. doi: 10.1093/ajcp/84.3.323.
9. Mootsikapun P, Srikulbutr S (2006) Histoplasmosis and penicilliosis: comparison of clinical features, laboratory findings and outcome. Int J Infect Dis 10: 66–71. doi: 10.1016/j.ijid.2004.10.006.
10. Ning C, Lai J, Wei W, Zhou B, Huang J, Jiang J, Liang B, Liao Y, Zang N, Cao C, Chen H, Ye L, Liang H (2018) Accuracy of rapid diagnosis of *Talaromyces marneffei*: a systematic review and meta-analysis. PLoS One 13: e0195569. doi: 10.1371/journal.pone.0195569.
11. DiSalvo AF, Fickling AM, Ajello L (1973) Infection caused by *Penicillium marneffei*: description of first natural infection in man. Am J Clin Pathol 60: 259–263. doi: 10.1093/ajcp/60.2.259.
12. Du R, Feng Y, Mao H (2023) Case report: diagnosis of *Talaromyces marneffei* infection in an HIV-negative patient with septic shock and high-titer anti-interferon gamma autoantibodies by metagenomic next-generation sequencing. Front Cell Infect Microbiol 13: 1163846. doi: 10.3389/fcimb.2023.1163846.
13. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Praparattanapan J, Nelson KE (1997) Case-control study of risk factors for *Penicillium marneffei* infection in human immunodeficiency virus-infected patients in northern Thailand. Clin Infect Dis 24: 1080–1086. doi: 10.1086/513649.

14. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE (1996) Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? J Infect Dis 173: 1490–1493. doi: 10.1093/infdis/173.6.1490.
15. Andrianopoulos A (2020) Laboratory maintenance and growth of *Talaromyces marneffei*. Curr Protoc Microbiol 56: e97. doi: 10.1002/cpmc.97.
16. Boyce KJ, Andrianopoulos A (2013) Morphogenetic circuitry regulating growth and development in the dimorphic *pathogen Penicillium marneffei.* Eukaryot Cell 12: 154–160. doi: 10.1128/EC.00234-12.
17. Pruetpongpun N, Khawcharoenporn T, Damronglerd P, Suthiwartnarueput W, Apisarnthanarak A, Rujanavej S, Suwantarat N (2016) Disseminated *Talaromyces marneffei* and *Mycobacterium abscessus* in a patient with anti-interferon-γ autoantibodies. Open Forum Infect Dis 3: ofw093. doi: 10.1093/ofid/ofw093.
18. Wong SY, Wong KF (2011) *Penicillium marneffei* infection in AIDS. Patholog Res Int 2011: 764293. doi: 10.4061/2011/764293.
19. Chen L, Zhang M, Guo W, Ding W, Tan J, Du H, Zhao Z, Zhong W (2022) Case report: acute *Talaromyces marneffei* mediastinitis in an HIV-negative patient. Front Microbiol 13: 1045660. doi: 10.3389/fmicb.2022.1045660.
20. Zheng J, Gui X, Cao Q, Yang R, Yan Y, Deng L, Lio J (2015) A clinical study of acquired immunodeficiency syndrome associated *Penicillium marneffei* infection from a non-endemic area in China. PLoS One 10: e0130376. doi: 10.1371/journal.pone.0130376.
21. Jiang J, Meng S, Huang S, Ruan Y, Lu X, Li JZ, Wu N, Huang J, Xie Z, Liang B, Deng J, Zhou B, Chen X, Ning C, Liao Y, Wei W, Lai J, Ye L, Wu F, Liang H (2018) Effects of *Talaromyces marneffei* infection on mortality of HIV/AIDS patients in southern China: a retrospective cohort study. Clin Microbiol Infect 25: 233–241. doi: 10.1016/j.cmi.2018.04.018.
22. Widaty S, Santoso ID, Ricky D, Yunihastuti E, Rihatmadja R, Wahyuningsih R (2020) Talaromycosis clinically and histopathologically mimicking histoplasmosis in an immunocompromised patient. Dermatol Online J 26: 13030/qt9r49g227. doi: 10.5070/D3269050160.
23. Li X, Zheng Y, Wu F, Mo D, Liang G, Yan R, Khader JA, Wu N, Cao C (2020) Evaluation of quantitative real-time PCR and Platelia galactomannan assays for the diagnosis of disseminated *Talaromyces marneffei* infection. Med Mycol 58: 181–186. doi: 10.1093/mmy/myz052.
24. Wei HY, Liang WJ, Li B, Wei LY, Jiang AQ, Chen WD, Guo PH, Xu J (2021) Clinical characteristics and risk factors of *Talaromyces marneffei* infection in human immunodeficiency virus-negative patients: a retrospective observational study. World J Emerg Med 12: 281–286. doi: 10.5847/wjem.j.1920-8642.2021.04.005.
25. Liu L, Sun B, Ying W, Liu D, Wang Y, Sun J, Wang W, Yang M, Hui X, Zhou Q, Hou J, Wang X (2022) Rapid diagnosis of *Talaromyces marneffei* infection by metagenomic next-generation sequencing technology in a Chinese cohort of inborn errors of immunity. Front Cell Infect Microbiol 12: 987692. doi: 10.3389/fcimb.2022.987692.
26. Lang Q, Pasheed Chughtai A, Kong WF, Yan HY (2020) Case report: successful treatment of pulmonary *Talaromyces marneffei* infection with posaconazole in a renal transplant recipient. Am J Trop Med Hyg 104: 744–747. doi: 10.4269/ajtmh.20-0909.
27. Chan JF, Lau SK, Yuen KY, Woo PC (2016) *Talaromyces* (*Penicillium*) *marneffei* infection in non-HIV-infected patients. Emerg Microbes Infect 5: e19. doi: 10.1038/emi.2016.18.
28. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H, Centers for Disease Control and Prevention (CDC), National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America (2009) Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 58: 1–207. doi: 10.1037/e537722009-001.
29. Nelson M, Dockrell D, Edwards S, BHIVA Guidelines Subcommittee, Angus B, Barton S, Beeching N, Bergin C, Boffito M, Breen R, Cartledge J, Clarke S, Fisher M, Freedman A, Gazzard B, Grant A, Greig J, Jones R, Khoo S, Leen C, Lipman M, Manji H, Miller R, Mitchell S, Ong E, Pozniak A, Schmid M, Shiew M, Singer M, Wilkins E, Williams I, Wood C, Weston R (2011) British HIV Association and British Infection Association guidelines for the treatment of opportunistic infection in HIV-seropositive individuals 2011. HIV Med 2: 1–140. doi: 10.1111/j.1468-1293.2011.00944_1.x.
30. Limper AH, Adenis A, Le T, Harrison TS (2017) Fungal infections in HIV/AIDS. Lancet Infect Dis 17: e334–e343. doi: 10.1016/S1473-3099(17)30303-1.
31. Chen Y (2020) A *Talaromyces marneffei* infection with osteolytic lesions in an HIV-negative patient at non-endemic areas: a case report. SAGE Open Med Case Rep 8: 2050313X20938242. doi: 10.1177/2050313X20938242.
32. De Giacomi F, Vassallo R, Yi ES, Ryu JH (2018) Acute eosinophilic pneumonia. causes, diagnosis, and management. Am J Respir Crit Care Med 197: 728–736. doi: 10.1164/rccm.201710-1967CI.
33. Zhang J, Ge P, Liu J, Luo Y, Guo H, Zhang G, Xu C, Chen H (2023) Glucocorticoid treatment in acute respiratory distress syndrome: an overview on mechanistic insights and clinical benefit. Int J Mol Sci 24: 12138. doi: 10.3390/ijms241512138.
34. Ji Y, Zhuo B, Jiang T, Chen M, Xu W, Shen Y, Cheng D, Ge Y (2024) *Talaromyces marneffei* endocarditis initially detected by next generation sequencing: a case report. Int J Med Microbiol 314: 151615. doi: 10.1016/j.ijmm.2024.151615.
35. Yang S, Lou L, Ma S, Wang H, Rong L, Liu Y, Zhang K, Ai Q, Shi X (2024) Disseminated *Talaromyces marneffei* infection initially presenting as cutaneous and subcutaneous lesion in an HIV-negative renal transplant recipient: a case report and literature review. BMC Infect Dis 24: 473. doi: 10.1186/s12879-024-09351-8.
36. Liu X, Xing H, Lin J, Sun J, Wang Y, Liu Y, Cao W, Liu Z, Li T (2024) Coexisting of primary central nervous system lymphoma and *Talaromyces marneffei* brain abscess in an AIDS patient, a case report and review of the literature. Infect Drug Resist 17: 709–718. doi: 10.2147/IDR.S432697.
37. Liu Y, Guo H, Yuan W, Zou Y, Qian Z, Mei X, Ji L, Wang J, Zhang Y (2024) HIV-negative case of *Talaromyces marneffei* pulmonary infection with liver cirrhosis in China: a case report and literature review. Infect Drug Resist 17: 1333–1343. doi: 10.2147/IDR.S451880.
38. Wu Q, Yu Y, Feng S, Fang B, Zheng R, Sun W, Zhao J (2024) Secondary hemophagocytic syndrome in an acquired immunodeficiency syndrome and alpha-thalassemia patient infected with *Talaromyces marneffei*: a case report and

literature review. IDCases 36: e01954. doi: 10.1016/j.idcr.2024.e01954.
39. Li Q, Li M, Wang S, Geater AF, Dai J (2024) Clinical diagnostic challenge in a case of disseminated *Talaromyces marneffei* infection misdiagnosed initially as pulmonary tuberculosis: a case report and literature review. Infect Drug Resist 17: 3751–3757. doi: 10.2147/IDR.S471938.
40. Yao Z, Pan Z, Li G, Liao Z, Yu Z, Zhan L, Xia W (2024) Talaromycosis from Wuhan: two-case report and literature review. Front Cell Infect Microbiol 14: 1347677. doi: 10.3389/fcimb.2024.1347677.
41. Li K, Zhang Y, Zhang D, Chen Q, Fang X (2024) Case report: Systemic multi-organ involvement in an adult-onset immunodeficiency patient infected with *Talaromyces marneffei*. Front Immunol 15: 1430179. doi: 10.3389/fimmu.2024.1430179.
42. Li X, Wang J, He J, Zhang H, Luo M (2024) *Talaromyces marneffei* central nervous system infection unveiled by the novel Mp1p antigen detection assay in AIDS patient. BMC Infect Dis 24: 1456. doi: 10.1186/s12879-024-10336-w.
43. Yu X, Xu H, Zhou J, Zhu Z, Li B (2025) Case report: a 3-year follow-up on nodal marginal zone lymphoma coexisting with disseminated *Talaromyces marneffei* infection in a non-endemic area. Front Oncol 14: 1407893. doi: 10.3389/fonc.2024.1407893.
44. Luo S, Yan P, Wang X, Ren X, Sun K, Guo L, Lv J, Su X, Zhao K, Chen J, Wang R (2024) *Talaromyces marneffei*: a challenging diagnosis in a kidney transplant patient. Clin Case Rep 12: e9028. doi: 10.1002/ccr3.9028.
45. Xing F, Deng C, Zou S, Tsang CC, Lo SKF, Lau SKP, Woo PCY (2024) Emergence and rapid diagnosis of *Talaromyces marneffei* infections in renal transplant recipients by next-generation sequencing. Mycopathologia 189: 91. doi: 10.1007/s11046-024-00898-3.
46. Ye LY, Zhao XL, Qin JJ, Lin J (2024) Metagenomic next-generation sequencing assisted in the successful treatment of pneumonia caused by *Talaromyces marneffei* in an immunocompetent patient. J Infect Dev Ctries 18: 1296–1300. doi: 10.3855/jidc.19061.
47. Liang H, Duan X, Li T, Hu L, Guo J (2024) Disseminated combined *Talaromyces marneffei* and *Enterococcus faecium* bloodstream infection presenting as gastrointestinal perforation in a patient with *CARD9* gene mutation. Infect Drug Resist 17: 4783–4790. doi: 10.2147/IDR.S479629.
48. Li LF, Lin M, Chen YS, Yue WX (2024) *Mycobacterium tuberculosis* infection complicated by talaromycosis in a patient with positive anti-interferon-γ autoantibodies: a case report. Zhonghua Jie He He Hu Xi Za Zhi 47: 1154–1158. [Article in Chinese].
49. Hasbullah NE, Raja Sabudin RZA, Asri AS, Yusof N, Leong CF, Mohammed F, Ding CH, Tumian NR (2024) Marrow talaromycosis as the initial presentation in a case of Burkitt lymphoma. Malays J Pathol 46: 325–329.
50. Wu S, Liang S, Liang H, Ning Y, Li X, He Z (2024) Multiple pathogen infections accompanied with ocular pathologies in a patient with high-titer anti-IFN-γ autoantibodies: a case report. BMC Infect Dis 24: 1319. doi: 10.1186/s12879-024-10217-2.
51. Li B, Li T, Lu Q, Liang D, Cao C (2025) Severe disseminated *Talaromyces marneffei* infection in idiopathic CD4 lymphopenia. IDCases 39: e02148. doi: 10.1016/j.idcr.2025.e02148.

Annex – Supplementary items

Supplementary Table 1. Cases of *Talaromyces marneffei* infection reported in the literature.

Case	Region	Gender	Age (years)	HIV Status	AIGA Status	Clinical manifestations	Diagnostic methods	Treatment	Outcome	Reference
1	China	Female	80	Negative	–	Chest distress, fever	mNGS, culture	Voriconazole	No improvement	[34]
2	China	Male	54	Negative	–	Skin and subcutaneous lesions	Culture	Amphotericin B	Death	[35]
3	China: Beijing	Male	19	Positive	–	Fever, hand tremor	mNGS, culture	Voriconazole	Improvement	[36]
4	China: Anhui	Male	52	Negative	–	—	mNGS	Amphotericin B, Voriconazole	Improvement	[37]
5	China: Guangxi	Male	30	Positive	–	Fever	Culture	Amphotericin B, Itraconazole	Improvement	[38]
6	China	Male	43	Negative	Negative	Cough, fever	mNGS	Voriconazole	Improvement	[39]
7	China: Guangzhou	Male	48	Positive	–	Fever	Culture	Voriconazole	Death	[40]
8	China: Fuzhou	Male	49	Negative	–	Fever, anemia, fatigue, skin damage	Culture	Sulfonamides and caspofungin	Death	[40]
9	China: Hangzhou	Female	62	Negative	Positive	Headache with neck pain, numbness in both hands, fever	mNGS, culture	Amphotericin B, itraconazole	Improvement	[41]
10	China	Female	35	Positive	–	Dizziness, headache, fatigue, anorexia, dry cough, shortness of breath, and diarrhea	Culture	Amphotericin B	Improvement	[42]
11	Zhejiang	Male	76	Negative	–	Fever, cough	Culture	Voriconazole	Improvement	[43]
12	China	Male	68	Negative	–	Urgency and pain in urination	mNGS	Voriconazole	Death	[44]
13	China: Shenzhen	Male	37	Negative	–	Fever, cough, and dyspnea	mNGS, culture	Voriconazole	Improvement	[45]
14	China: Zhejiang	Male	63	Negative	Negative	Fever, cough, expectoration	mNGS, culture	Voriconazole	Improvement	[46]
15	China: Shanghai	Male	63	Negative	–	Severe and persistent mid-upper abdominal pain	mNGS, culture	Voriconazole, amphotericin B	Death	[47]
16	China: Fujian	Male	49	Negative	Positive	Recurrent cough, expectoration with persistent fever	Culture	Amphotericin B	Improvement	[48]
17	Malaysia	Male	23	Positive	–	Intermittent fever, cough	Culture	Amphotericin B	Death	[49]
18	China: Guangxi	Female	53	Negative	Positive	Cough	Culture	Voriconazole	Improvement	[50]
19	China	Male	40	Negative	Positive	Fever, headache, fatigue, vomiting, anorexia	Culture	Voriconazole, amphotericin B	Improvement	[51]

HIV: human immunodeficiency virus; AIGA: anti-IFN-γ autoantibodies; mNGS: metagenomic next-generation sequencing.

Supplementary Figure 1. Pathologic findings of lung puncture (Magnification: ×40).