

Identification of *Talaromyces marneffei* Infection in an HIV-Negative Patient by ITS Sequencing

Aihua Sun^{1,2,*}, Xiaoyu Gou^{1,2,*}, Yongze Zhu¹, Huoyang Lv¹, Yumei Ge¹⁻³

¹Laboratory Medicine Center, Department of Clinical Laboratory, Zhejiang Provincial People's Hospital (Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, 310014, People's Republic of China; ²School of Basic Medical Sciences and Forensic Medicine, Hangzhou Medical College, Hangzhou, Zhejiang, 310059, People's Republic of China; ³Key Laboratory of Biomarkers and in vitro Diagnosis Translation of Zhejiang Province, Hangzhou, Zhejiang, 310053, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yumei Ge, Laboratory Medicine Center, Department of Clinical Laboratory, Zhejiang Provincial People's Hospital (Affiliated People's Hospital, Hangzhou Medical College), Hangzhou, Zhejiang, 310014, People's Republic of China, Email 11218070@zju.edu.cn

Abstract: Disseminated ankle mycosis is a life-threatening systemic infection caused by the emerging opportunistic and lethal fungal pathogen *Talaromyces marneffei* which is more common in HIV-positive patients. However, an increasing number of infections are occurring in HIV-negative patients. Here, we report a case of *Talaromyces marneffei* infection in HIV-negative patient. A 50s HIV-negative male patient with fever, cough, bloody sputum expectoration, pulmonary sarcoidosis and body rashes was hospitalized at Zhejiang Provincial People's Hospital. CT scanning showed pulmonary multiple nodules with apical bronchial occlusion, patchy infiltration and pathological biopsy demonstrated bronchiolitis obliterans with organized pneumonia and chronic active inflammation of lung tissue with infiltration of numerous lymphocytes, plasma cells, phagocytes and neutrophils. Laboratory tests revealed significantly increased white blood cells count $18.3 \times 10^9/L$, neutrophil count $15.34 \times 10^9/L$, monocyte count $0.66 \times 10^9/L$, platelet count $517 \times 10^9/L$, C-reactive protein 116 mg/L, erythrocyte sedimentation rate 112mm/h. The β -D-glucan test was negative (33.06 pg/mL) while fungal culture of broncho alveolar lavage fluid revealed colonies with temperature-dependent dimorphic growth character and *Talaromyces marneffei* was confirmed by ITS sequencing of the colonies. The patient exhibited radiological improvement and clinical recuperation after intravenously guttae of voriconazole. Talaromycosis in immunocompetent and HIV-negative individuals is relatively rare and is characterized by an insidious onset, various clinical manifestations, and is clinically challenging. Fungal culture and ITS sequencing are warranted for diagnosis *Talaromyces marneffei* infection. This is the first report on identification of *Talaromyces marneffei* infection in an HIV-negative patient with skin involvement by ITS sequencing in Zhejiang.

Keywords: *Talaromyces marneffei*, pulmonary sarcoidosis, HIV-negative, voriconazole, ITS sequencing

Introduction

Disseminated talaromycosis is a life-threatening systemic infection caused by emerging opportunistic and fatal fungal pathogen *Talaromyces marneffei* (formerly *Penicillium marneffei*) (*T. marneffei*), which is frequently consistent with immunosuppressive and immunodeficient hosts including human immunodeficiency virus (HIV)-infected patients, autoimmune diseases, malignant tumors, and organ transplant patients and is prevalent in epidemic regions involving south and southeast Asia.¹⁻⁴ *T. marneffei* was first isolated from the liver of bamboo rat in 1956.⁵ At present, bamboo rats and other rodents have been widely reported to be the reservoirs of *T. marneffei* infection.⁶⁻⁸ In addition, dogs have also been considered as a possible reservoir of talaromycosis.⁹ Talaromycosis is generally considered to be an acquired immune deficiency syndrome (AIDS) defining disease.¹⁰ However, the increase in the number of *T. marneffei* infection in HIV-negative individuals suggests that we should not underestimate talaromycosis during clinical visits.^{11,12} Therefore, we report the clinical manifestation and prognosis of a 50s patient in Geyang, Jiangxi province, where bamboo rats are widely bred and popularized. This patient is HIV-negative and does not have the situation of impaired cell-mediated immunity or received immunosuppressive therapy, but the pulmonary nodules caused by *T. marneffei* infection.

Case Presentation

Clinical Features

A 50s male patient with cough, bloody sputum expectoration, slight fever and slightly visible body rashes at the thoracoabdominal junction (**Figure 1A**) presented to Zhejiang Provincial People's Hospital on July 6, 2021 because of pulmonary shadow found in physical examination of local hospital for more than half a year. The patient had been healthy and had not been infected with HIV in the past but had a 30-year history of smoking. After admission, the physical examination was completed. The body temperature was 37.6°C, pulse rate was 105 times/min, respiration was 20 times/min, blood pressure was 101/68 mmHg, and the breath sound was coarse through auscultation of both lungs. The results of the initial laboratory examination are shown in **Table 1**. In addition, we also monitored the laboratory test indicators of patients during hospitalization (**Figure 2A–D**). Chest computed

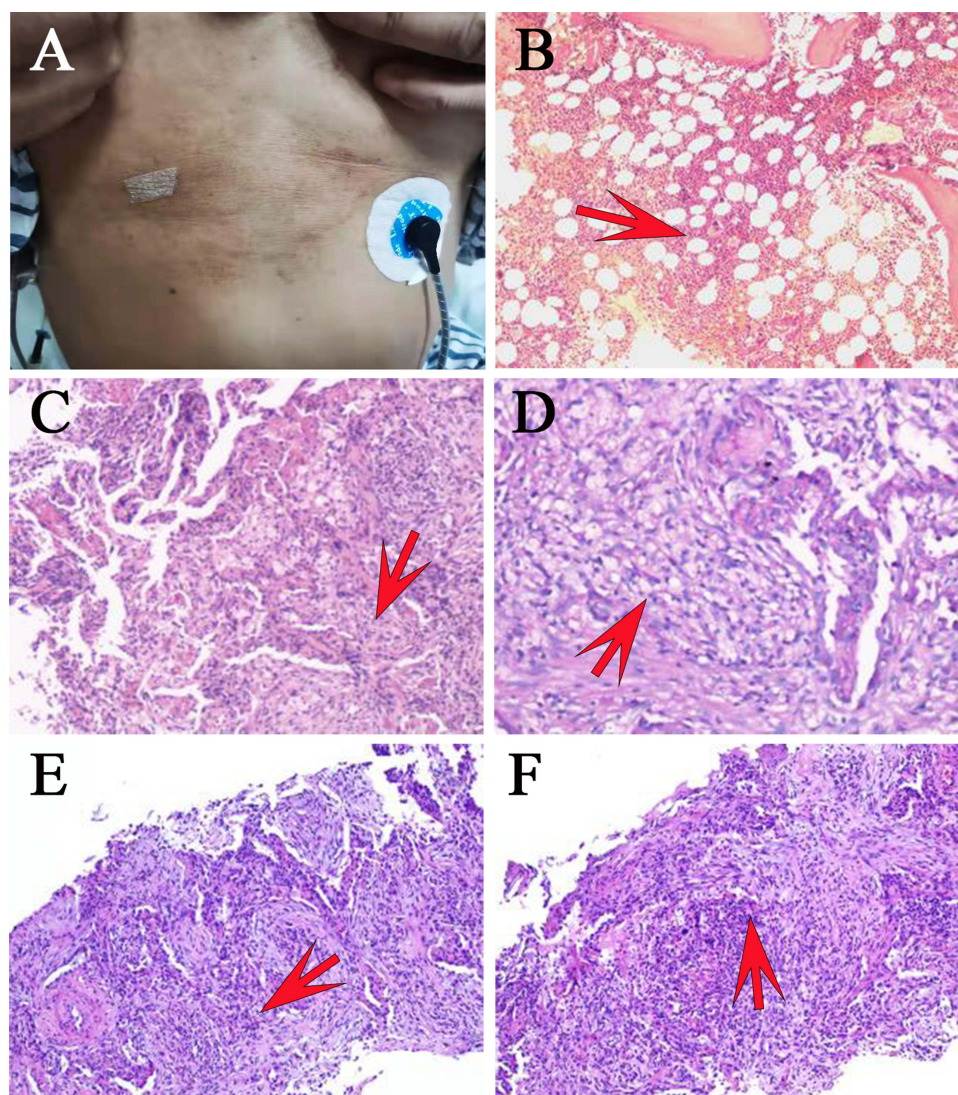


Figure 1 Exclusion of the proliferative neoplasms and indication the existence of infection by biopsy. **(A)** Body rashes were observed during physical examination on admission. Multiple rufous body rashes with central umbilication were scattered in the thoracoabdominal skin of the patient. **(B)** Nucleated cells in bone marrow smears showed normal blood picture of the patients with marked hyperplasia of active proliferation of erythroid, myeloid and megakaryocytes. **(C and D)** Histologic section of the mucosae from the pulmonary solid mass in the right upper lobe showed chronic active inflammation with organic consolidation. **(E and F)** Histologic section of the pulmonary solid mass in the right upper lobe showed multifocal areas of consolidation with fibrous polypoid tissue, alveolar epithelium and vascular hyperplasia in the alveolar cavity. A large number of lymphocytes, plasma cells, phagocytes and neutrophils were infiltrated in the lung tissue, and the pulmonary septum was widened, which suggested that chronic active inflammation of lung tissue with parenchymal lesions and bronchiolitis obliterans with organized pneumonia (BOOP). **(B–F)** The red arrow indicates the inflammatory infiltration area.

Table I Patient Laboratory Test Results

Laboratory Indicators	Result	Reference Range
White blood cells count	$18.3 \times 10^9 /L$	$3.5-9.5 \times 10^9 /L$
Neutrophil count	$15.34 \times 10^9 /L$	$1.8-6.3 \times 10^9 /L$
Monocyte count	$0.66 \times 10^9 /L$	$0.1-0.6 \times 10^9 /L$
Red blood cell count	$3.82 \times 10^{12} /L$	$4.3-5.8 \times 10^{12} /L$
Hemoglobin	100 g/L	130-175 g/L
Platelet count	$517 \times 10^9 /L$	$125-350 \times 10^9 /L$
C-reactive protein	116 mg/L	0-10 mg/L
Erythrocyte sedimentation rate	112 mm/h	0-21 mm/h
Fibrinogen	9.19 g/L	2-4 g/L
D-dimer	2260 μ g/L	0-550 μ g/L
Fibrin degradation product	7190 μ g/L	0-5000 μ g/L
Immunoglobulin G	22 g/L	7.51-15.60 g/L
Albumin	28.1 g/L	40-55 g/L
Globulin	45.3 g/L	20-40 g/L
HIV-1/2 antibody	Negative	Negative
HIV-P24 antigen	Negative	Negative

tomography (CT) showed pulmonary solid mass in the right upper lobe with apical bronchial occlusion, patchy infiltration and irregular thickening of local interlobular septum. There were multiple nodules, patchy and cord infiltration in the right lower lobe with fuzzy boundary, irregular thickening of interlobular septum and adjacent pleural thickening. Fibrous foci and tiny nodules were seen in the left lower lobe, presenting with a right pleural effusion (Figure 3A; July 8th).

Pathological Examination

No cancer cells were found in fibrobronchoscopic fluid, pleural effusion or pulmonary masses and no abnormal cells were seen by bone marrow biopsy. The histopathological results of the right pulmonary masses showed multifocal areas of consolidation with fibrous polypoid tissue, alveolar epithelium and vascular hyperplasia in the alveolar cavity. A large number of lymphocytes, plasma cells, phagocytes and neutrophils were infiltrated in the lung tissue, and the pulmonary septum was widened, which suggested that chronic active inflammation of lung tissue with parenchymal lesions and bronchiolitis obliterans with organized pneumonia (BOOP) (Figure 1B-F).

Etiological Examination

Tuberculosis screening laboratory demonstrated negative acid-fast staining in a suppurative inflammatory background with plentiful neutrophils and macrophages, which preliminarily ruled out the infection of *Mycobacterium* (Figure 4B). Blue fluorescent fungal spores were observed in the dark field indicating fungal infection by fungal fluorescence staining of sputum (Figure 4C). Gram staining of alveolar lavage fluid showed that deeply stained fungal spores were detected (Figure 4D). Scattered, slightly asymmetric and typical double-helical broom-like fungal hyphae with short, smooth walled, ellipsoidal, mono-verticillate penicillium conidiophores were observed under oil lens after gently touching scotch tape to the colonies and staining with lactophenol cotton blue (Figure 4E). Fungal culture of BALF revealed colonies with temperature-dependent dimorphic growth character, which showed yeast-like fungi producing soluble red pigment at 28°C and mycelia at 37°C in CANA, PDA and SDA (Figure 4F). Single band PCR amplification for internal transcribed spacer (ITS) region in genomic DNA of the clinical isolate was observed after electrophoresis (Figure 4A).¹³ The nucleotide sequences of the 563-bp ITS including the 5.8S rRNA and 26S rRNA gene were verified and utilized to perform phylogenetic analysis by the Molecular Evolutionary Genetics Analysis (MEGA) software version 11 through the minimum-evolution method as reported in the previous literature.¹⁴ A phylogenetic tree was constructed utilizing the sequence of *Talaromyces marneffeii* ZJPPH1 (GenBank number: ON287261.1) from the isolate

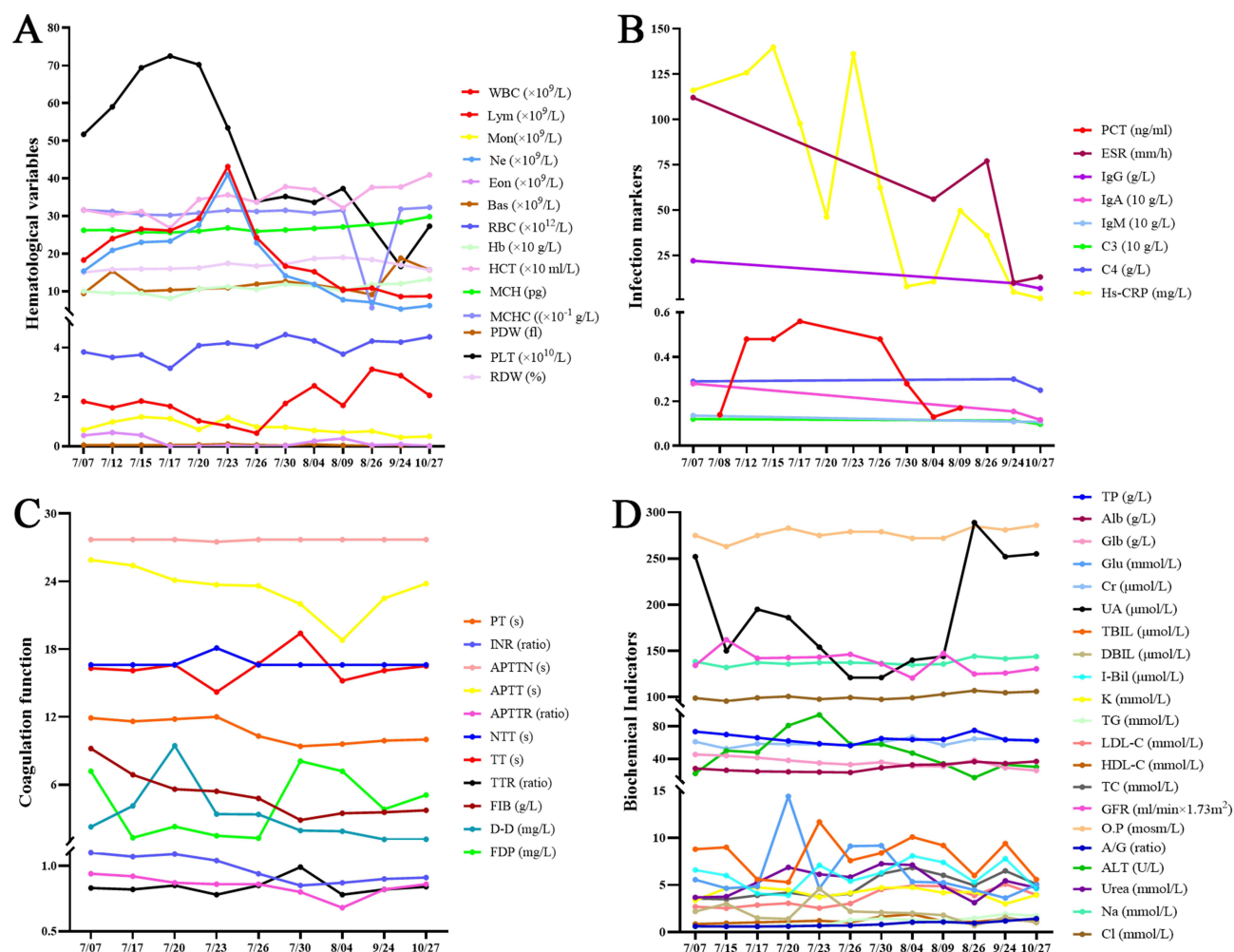


Figure 2 Monitoring of laboratory testing indicators during patient hospitalization. **(A)** Monitoring of hematological variables during the patient's hospitalization. **(B)** Monitoring of infection markers during the patient's hospitalization. **(C)** Monitoring of coagulation function indicators during the patient's hospitalization. **(D)** Monitoring of biochemical indicators during the patient's hospitalization.

of this study along with 53 available sequences with the highest homology retrieved from GenBank. The nucleic acid sequence of the present isolate revealed 99.62% similarity with *Talaromyces marneffei* strain AMC PM002 (Figure 5).

Treatment and Outcome

In the early stage of hospitalization, the cause of infection was unknown, and empirical anti-infection treatment was given. When a clear etiological evidence of *T. marneffei* infection was obtained, the patient was given voriconazole combined with piperacillin sodium and tazobactam sodium targeted anti-infection therapy and methylprednisolone anti-inflammatory therapy (Figure 3B). The patient still had recurrent fever during treatment (Figure 3C). CT images showed prominent improvement of pulmonary lesion with depauperation of patchy infiltration in original bilateral lung fields (Figure 3A; Aug 26th 2021) after antifungal therapy by voriconazole. In addition, the serum levels of 1-3- β -D glucan and galactomannan were kept at normal levels during hospitalization, and no pathogen were detected in blood culture. This suggested that the patient had not developed further disseminated infection. After 3 months, the patient had no cough and expectoration, recovered and returned to normal life.

Discussion

Talaromycosis is common in HIV-positive patients with cellular immune deficiency caused by CD4^+ T cells deficiency.^{15,16} However, cases analogue to this patient who is HIV-negative and has no obvious underlying

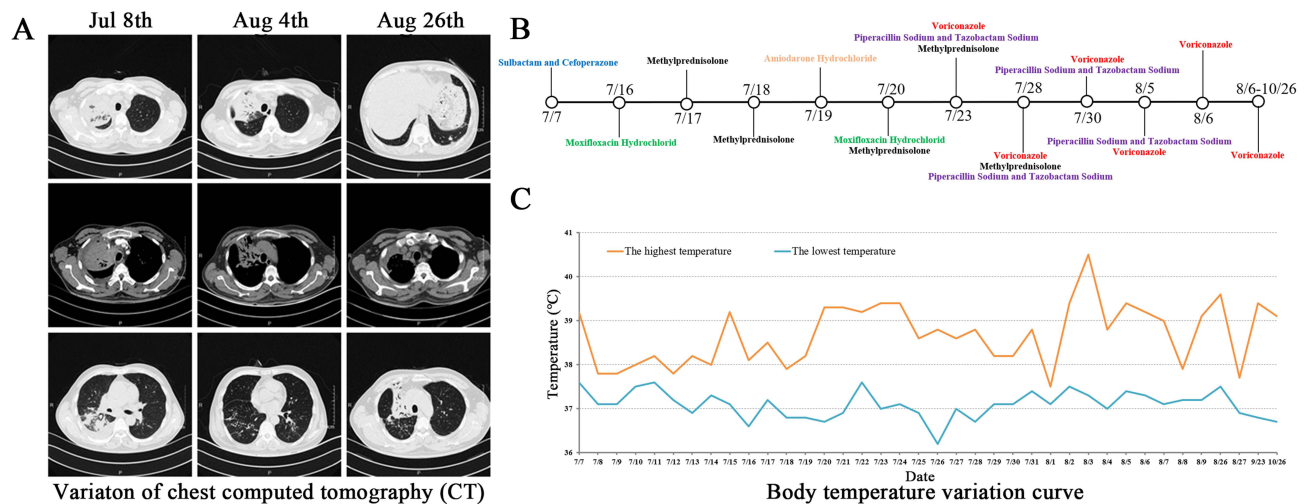


Figure 3 Patient medication status and outcomes. **(A)** Chest computed tomography (CT) showed an irregular solid nodule in the right upper lobe with apical bronchial occlusion, patchy infiltration and irregular thickening of local interlobular septum, fibrous foci and tiny nodules are seen in the left lower lobe, presenting with a right pleural effusion on July 8th 2021. CT images showed prominent improvement of pulmonary lesion with depauperation of patchy infiltration in original bilateral lung fields after effective antifungal therapy by voriconazole on Aug 4th 2021. CT reexamination showed that patchy high-density shadows of the two lungs were further absorbed on Aug 26th 2021. **(B)** Antibiotic anti-infective therapy timeline of the patient. **(C)** Body thermogram during treatment.

immune dysfunction in the past long life are not common. We will continue to pay attention to the mechanism of this type of talaromycosis in our clinical follow-up and research. β -D-Glucan as a biomarker for the fungal infection was often positive in the serum of patients with talaromyces in the past literature reports.¹⁷ While in this case, although the patient's lung was involved in infection of *T. marneffei*, serum β -D-glucan is negative, which indicated the patient was in the early stage of infection. We should pay attention to the clinical manifestations of this rare case. Recent studies have reported that *T. marneffei* could escape the recognition and clearance of macrophages, resulting in lung disoperation.¹⁸ It suggests that clinicians should pay special attention to the possibility of pulmonary *T. marneffei* infection.

T. marneffei is a biphasic endemic fungus, which is mainly prevalent in Southeast Asia, India, South China and may be related to the local climate and living habits.¹⁹ Bamboo rats are the natural hosts of *T. marneffei*, and exposure to bamboo rats has been proven to be a risk factor of talaromyces.²⁰ A recent study investigating bloodstream fungal infections in southern China found that *T. marneffei* was the most commonly isolated mycoemia pathogen (31.4%) in the region, with 70.5% of *T. marneffei* isolated from HIV-infected individuals. However, HIV-negative patients had a higher mortality rate (40.9%) than HIV-infected patients (17.1%).²¹ In addition, another survey showed the infection situation of *T. marneffei* in Jiangxi Province, a total of 241 infected patients were admitted in 10 years, 40.7% of the patients were infected with HIV, and 35.3% of the patients eventually died.²² The patient in this case comes from Jiangxi province in where some local farmers have the habit of eating bamboo rats. Because the patient could not be clearly diagnosed in the local hospital, he came to Zhejiang People's Hospital for further treatment, suggesting that the local government and CDC should focus on monitoring these epidemic areas with widespread *T. marneffei* and train the doctor and clinical technicians in these areas.

Although *T. marneffei* is a highly lethal invasive fungus that can lead to systemic complications, early treatment with antifungal drugs is usually effective. In this case, the accurate diagnosis of *T. marneffei* infection and timely antifungal treatment have made the patient obtain a satisfactory prognosis. At present, the observation method of colonial growth morphology and microscopy after fungal culture are mainly used in the identification of fungi in clinical laboratories. However, the identification of rare biphasic fungi such as *T. marneffei* based solely on phenotype is often challenging and difficult and requires experienced technicians in microbiological identification. 5.8S rDNA and 28S rDNA gene spacer (ITS region) is accepted as the primary fungal barcode.²³ The length and nucleotide sequence of this region is diversity and polymorphic. Sequencing and analysis of their amplicons can be used for the classification and identification of the fungal strains. The ITS in the nucleotide

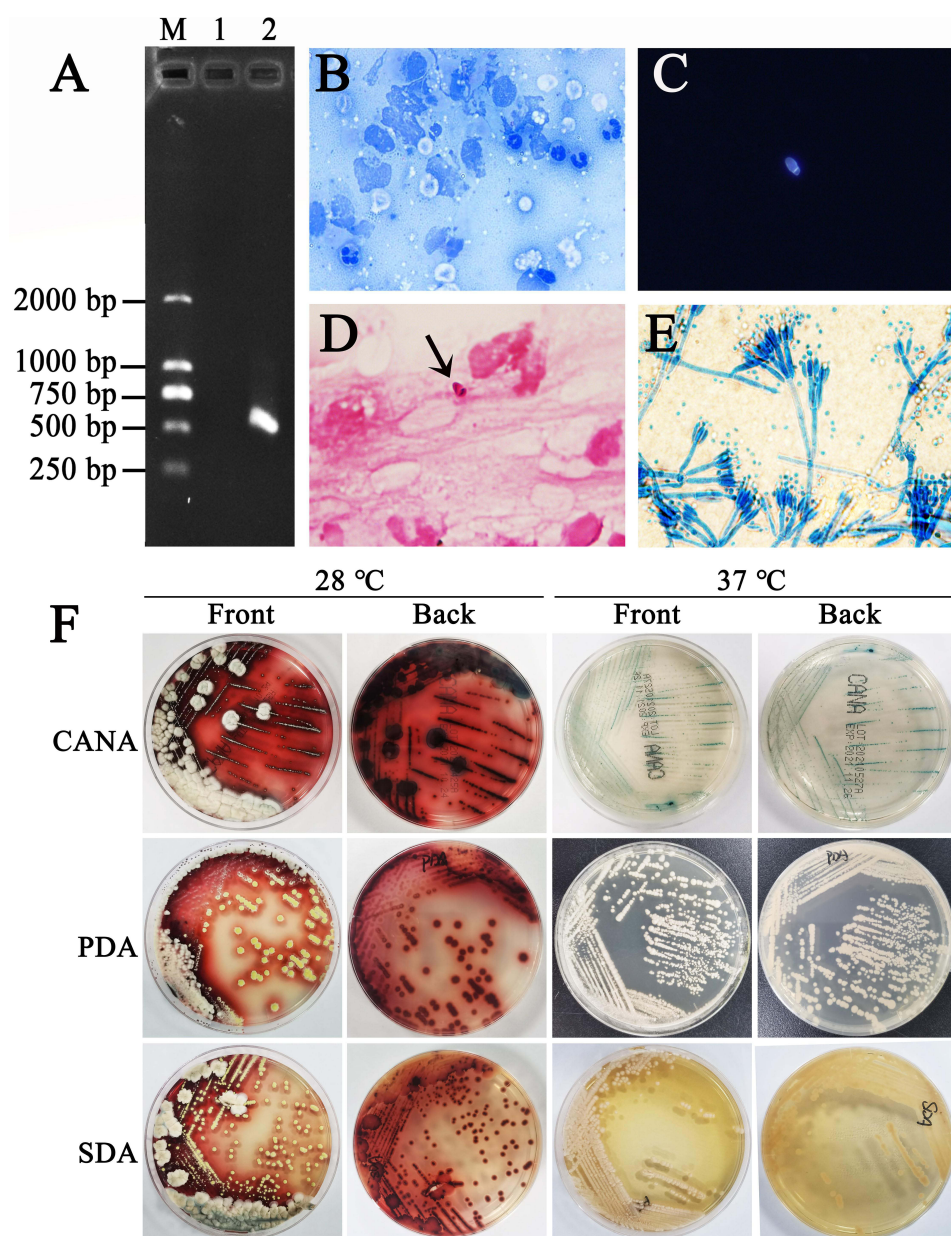


Figure 4 Etiological inspection and PCR amplification of the ITS region demonstrated talaromycosis and validated the variant. **(A)** PCR amplification for internal transcribed spacer (ITS) region in genomic DNA of the clinical isolate. Lane M: DNA ladder (Tsingke, China). Lane 1: negative control. Lane 2: amplicon (563 bp) of the strain with the ITS primers. **(B)** Acid-fast staining of sputum was negative in a suppurative inflammatory background with plentiful macrophages and neutrophils, which preliminarily excluded the Mycobacterial infection. **(C)** Blue fluorescent fungal spores were observed in the dark field indicating fungal infection by fungal fluorescence staining of sputum. **(D)** Gram staining of alveolar lavage fluid showed that deeply stained fungal spores were detected. The black arrow indicates a suspected discovery of fungal spores. **(E)** Microscopy analysis of the colonies grown on PDA at 28°C by lactophenol cotton blue staining. Scattered, slightly asymmetric and typical double-helical broom-like fungal hyphae with short, smooth walled, ellipsoidal, monoverticillate *Penicillium* conidiophores were observed (magnification $\times 1000$). **(F)** Fungal culture of BALF revealed colonies with thermally dimorphic growth character, which showed yeast-like fungi producing soluble red pigment at 28 °C and mycelia at 37 °C in *Candida* nutrient agar (CANA), potato dextrose agar (PDA) and Sabouraud dextrose agar (SDA).

sequence of fungal ribose is relatively conservative which can be used for fungal species identification, phylogenetic research and epidemiological investigation. Through evolutionary tree analysis, we found that this patient had the highest homology with the sequence uploaded by Assam Medical College & Hospital, barbari, Dibrugarh, Assam 786,002 and India.

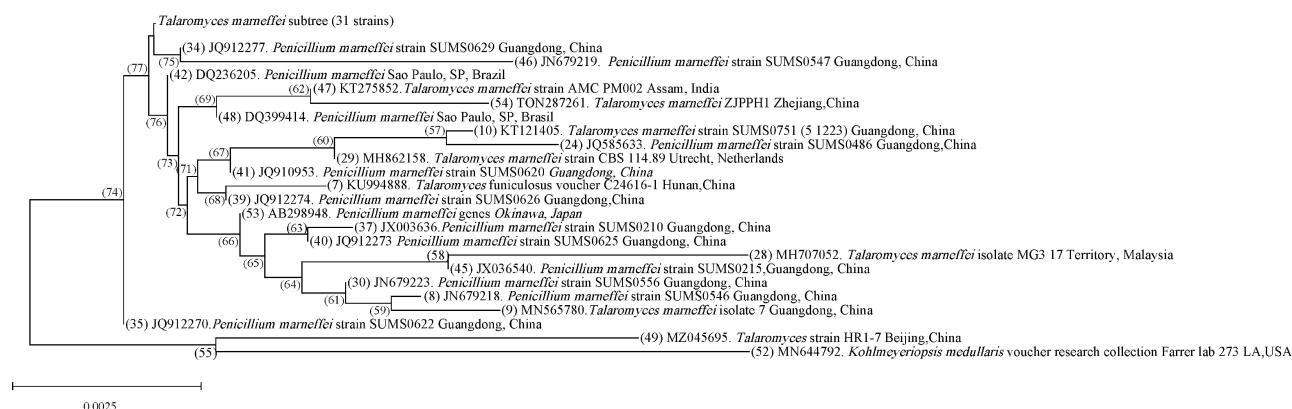


Figure 5 Phylogram of the clinical *T. marneffei* strain. It was based on ITS sequences and constructed utilizing the sequence of *Talaromyces marneffei* ZJPPH1 from the isolate of this study along with 53 available sequences with the highest homology retrieved from GenBank by MEGA11.

Conclusion

Cases of HIV-negative and immunocompetent patients with talaromycosis are relatively rare in clinical practice, especially when the patient's serum β -D-glucan is negative. It deserves clinicians' attention because timely antifungal treatment can obtain a satisfactory prognosis. Fungal culture and ITS sequencing are helpful to diagnose *T. marneffei* infection. Through the evolutionary tree analysis of its ITS, this study provides traceability data for the regional epidemic changes of the clinical strain. Villages of the farmers raising bamboo rats in Jiangxi province are an epidemic area of *T. marneffei*.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Yumei Ge on reasonable request.

Ethics Approval and Consent to Participate

This study was supported by the Ethics Committee of Zhejiang People's Hospital (Ethics Committee Approval of Biomedical Research Involving Humans, Approval No.: 2022JS008) and was carried out in accordance with the ethical standards of the Declaration of Helsinki.

Consent for Publication

Written and informed consent was obtained from the patient for publication of this research and any accompanying images.

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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 that they have no competing interests in this work.

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