CASE REPORT OF *TALAROMYCES MARNEFFEI* FUNGEMIA IN AN HIV-NEGATIVE PEDIATRIC PATIENT TREATED AT THE NATIONAL HOSPITAL FOR TROPICAL DISEASES

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Talaromyces marneffei is a dimorphic fungus frequently encountered in immunocompromised individuals. Particularly, in those with HIV/AIDS or other predisposing factors. Talaromyces marneffei commonly induces invasive and disseminated infections, including fungemia. In this report, we present a case of a 44-month-old male child admitted with a protracted febrile illness. The patient had a history of pulmonary tuberculosis under stable management, presenting with sustained fever, persistent cough, cachexia, anemia, bilateral fine crackles and wheezing upon auscultation, hepatosplenomegaly, and no signs of respiratory distress. Immunological assays assessing both humoral and cellular immunity were unremarkable, and the patient tested negative for HIV. Chest computed tomography revealed bilateral strip-like and nodular pulmonary infiltrates, along with bilateral hilar lymphadenopathy. Blood cultures confirmed the presence of Talaromyces marneffei. The patient exhibited a favorable clinical and laboratory response to Amphotericin B treatment and was subsequently maintained on Itraconazole therapy post-discharge.

Keywords: Talaromyces marneffei, Prolonged Fever of Unknown Etiology, HIV-negative.

OVERVIEW

Talaromyces marneffei (previously classified as Penicillium marneffei) is a dimorphic fungus with the potential to cause systemic mycoses, particularly in tropical and subtropical regions such as Southeast Asia, including Vietnam[1]. This pathogen poses significant clinical challenges due to its ability to present with non-specific, atypical symptoms and a wide spectrum of clinical manifestations, often leading to a high incidence of misdiagnosis as other diseases, such as pulmonary tuberculosis or pneumonia. Such diagnostic errors hinder the prompt initiation of effective antifungal treatment, thereby exacerbating the risk of complications and increasing mortality rates. Although *T. marneffei* is predominantly recognized as a pathogen in immunocompromised individuals, particularly those infected with HIV, it is essential to identify and understand this fungal infection in HIV-negative populations as well. Certain HIV-negative patients may develop *T. marneffei* infections due to congenital immunodeficiencies arising from genetic mutations that impair immune function. Early and accurate diagnosis of *T. marneffei* in HIV-negative individuals is critical not only for effective and timely therapeutic intervention but also for mitigating the public health impact through prevention of disease transmission within the broader community[2].

CLINICAL CASE REPORT

A 44-month-old male patient, with a history of pulmonary tuberculosis, exhibited clinical stability after completing the first month of treatment and defervescence. The patient was in the sixth month of anti-tuberculosis therapy at the time of presentation, with no known family history of chronic diseases,

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and residing in Ngo Quyen Ward, Hai Phong City. The symptoms began 1.5 months prior to admission, including prolonged high-grade fever, persistent cough, marked fatigue, and weight loss of 2.5 kg over the preceding month. No cutaneous lesions were observed. The patient had been previously admitted and treated at two central hospitals with a presumptive diagnosis of prolonged fever of unknown origin, with considerations for possible tuberculosis relapse or sepsis. The treatment regimen included anti-tuberculosis therapy with a resistant-strain protocol, alongside empirical antibiotic therapies: Imipenem for 10 days, meropenem for 20 days, linezolid for 15 days, amikacin for 10 days, trimethoprim-sulfamethoxazole (biseptol) for 14 days, and oral voriconazole for 14 days. Despite extensive treatment, the patient's clinical status did not improve; he continued to experience intermittent high-grade fevers (38 - 40°C), persistent cough without dyspnea, hepatosplenomegaly (grade 2), pronounced fatigue, and pallor of the skin and mucosae, with no evidence of rash or papular skin lesions. The patient was subsequently transferred to the National Hospital for Tropical Diseases for further diagnostic evaluation. Diagnostic investigations were conducted, as summarized in Table 1, including blood cultures for bacterial and fungal pathogens. While bacterial cultures were negative, blood cultures confirmed the presence of *Talaromyces marneffei*.

Table 1. Patient's laboratory evaluation results

Test	Results	Test	Results
Red blood cells (T/L)	3.16	CD4+ T cells (cells/mm³)	4524
Hemoglobin (g/L)	85	CD3+ T cells (cells/mm³)	5447
White blood cells (G/L)	18.7	CD8+ T cells (cells/mm³)	2396
Neutrophils (%)	59.1	IgA (g/l)	1.7
Lymphocytes (%)	33.9	IgM (g/l)	2.05
Platelets (G/L)	89	IgE (IU/ml)	398
Prothrombin (%)	82	HIV confirmatory test	Negative
Procalcitonin (ng/L)	2.47	HBsAg	Negative
C-Reactive protein (CRP) (mg/L)	168.4	HCV	Negative
Urea/creatinine (mmol/L)	4.1/23	Cerebrospinal fluid culture	Negative
AST (U/L)	57	Cerebrospinal fluid protein (g/L)	0.12
ALT (U/L)	63	Cells in cerebrospinal fluid	8

Furthermore, comprehensive investigations for tuberculosis were conducted. Bronchoscopy revealed bronchial mucosal inflammation, and analysis of bronchial lavage fluid was negative for acid-fast bacilli (AFB), GeneXpert, and *Mycobacterium tuberculosis* PCR. Blood PCR for *Mycobacterium tuberculosis* also returned negative results. Chest X-ray demonstrated a heterogeneous opacity in the upper lobe of the left lung, while computed tomography (CT) of the chest revealed subpleural linear opacities. In the left upper lobe, both linear and nodular opacities were observed. The mediastinum displayed bilateral hilar lymphadenopathy, with the largest lymph node measuring 21 x 17 mm (Figure 1). Abdominal ultrasound indicated increased hepatic echogenicity and hepatomegaly, with the right liver lobe measuring 139 mm and the left liver lobe 103 mm in length. Doppler echocardiography and thyroid ultrasound findings were unremarkable.

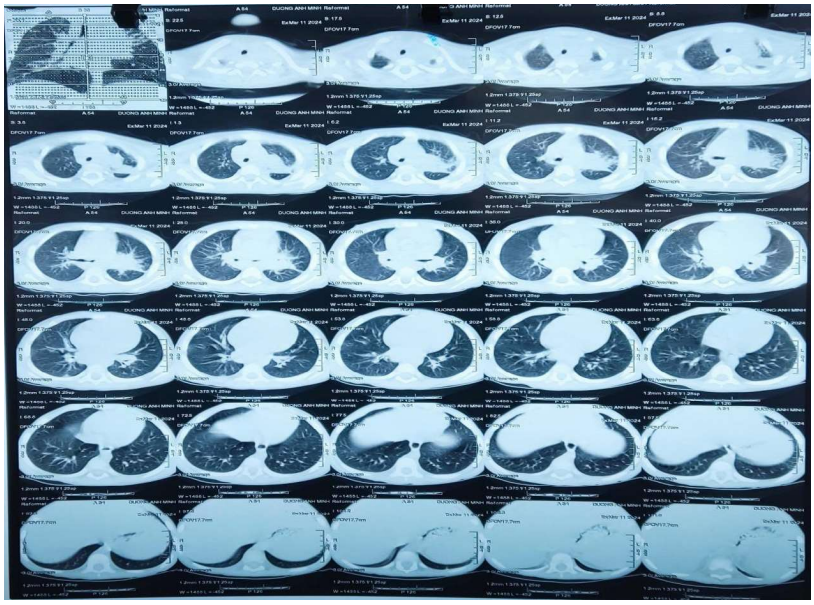

Figure 1. Thoracic CT imaging showing pulmonary infiltrates

The patient was diagnosed with Talaromyces marneffei fungemia and initiated on antifungal therapy with intravenous amphotericin B at a dosage of 1 mg/kg/day for a 14-day course, followed by oral itraconazole at a dose of 200 mg (2 tablets) twice daily for 10 weeks. During the treatment, the patient's hepatic and renal function, as well as serum electrolytes, were closely monitored. Upon completing the 14-day course of intravenous amphotericin B and 7 days of oral itraconazole, the patient demonstrated significant clinical improvement, characterized by complete defevescence, improved oral intake, restored mucosal coloration, and weight gain. The patient was subsequently discharged in stable condition, with instructions to continue maintenance antifungal therapy as an outpatient.

DISCUSSIONS

Talaromyces marneffei is a common fungal pathogen in Southeast Asia, including regions such as Thailand, Vietnam, Northeastern India, Southern China, Hong Kong, Taiwan, Laos, and Malaysia3. The distribution of this infection is closely associated with the hot and humid climate of these areas, which provides ideal conditions for fungal growth. The spread of *T. marneffei* to non-endemic regions, including Australia, Europe, Japan, and the United States, is increasingly recognized, often linked to travel from endemic areas[4]. The primary mode of infection with *T. marneffei* is through the inhalation of airborne conidia, which enter the alveolar spaces of the lungs. Once inside the host, the fungus undergoes a morphological shift from a mold in the environment to a yeast form at body temperature, a key factor in its pathogenicity. In the lungs, *T. marneffei* can evade the immune response by surviving within alveolar macrophages, allowing the fungus not only to persist but also to disseminate to other organs. Infections with *T. marneffei* can present with a wide array of clinical manifestations, depending on the immune status of the host[3]. While the literature suggests that in immunocompetent individuals, infections tend to be localized or present with mild symptoms, patients with delayed or missed diagnoses remain at risk of fatal outcomes. However, in Vietnam, we have not encountered nor reported cases of *T. marneffei* infection in HIV-negative individuals before this case[5]. Our case represents the first report of *T. marneffei* fungemia in an HIV-negative pediatric patient with normal humoral and cellular immune function.

The radiological presentation of *Talaromyces marneffei* infection is notably diverse, reflecting its capacity to involve various pulmonary and extrapulmonary sites. Typical imaging findings

range from interstitial infiltrates to nodular lesions and areas of consolidation. However, these features are non-specific and can easily be mistaken for other infections, thus complicating the diagnostic process[1]. Misdiagnosis of *T. marneffei* infections is common, with pulmonary tuberculosis being the most frequent due to overlapping clinical and radiographic characteristics. In a retrospective analysis by Qiu et al., 38.1% (24/63) of patients with confirmed *T. marneffei* respiratory infections were initially misdiagnosed as having pulmonary tuberculosis, while 7.9% (5/63) were misdiagnosed with bacterial pneumonia6. When empirical antibiotic therapies fail to elicit the expected clinical response, clinicians should consider the possibility of infection by less common pathogens[1,7]. Studies suggest that bone marrow smears represent a relatively simple and expedient method for identifying disseminated *T. marneffei* infection. However, in pediatric populations, the decision to pursue bone marrow biopsy or advanced histopathological and immunohistochemical examinations is often delayed unless hematological evidence strongly indicates such a need. This delay may result in missed diagnoses and postponement of appropriate antifungal treatment. Galactomannan (GM), a heteropolysaccharide found in the cell walls of most Aspergillus and Penicillium species, has been reported to be significantly elevated in the serum of patients with *T. marneffei* infection. Elevated GM levels may serve as a valuable diagnostic marker in patients with persistent, unexplained febrile illnesses and atypical clinical presentations, prompting further investigation[8].

In recent years, the prevalence of *Talaromyces marneffei* infection among HIV-negative patients has increased, with many of these individuals presenting with various forms of immunodeficiency, such as neutropenia, lymphopenia, or aberrations in serum immunoglobulin profiles and lymphocyte subsets. You CY et al. conducted a systematic review of studies available on PubMed as of December 1, 2020, aimed at further elucidating the clinical characteristics of *T. marneffei* infections in patients diagnosed with immunodeficiency linked to known genetic mutations. The search employed the keywords "Talaromyces marneffei," "Penicillium marneffei," "Penicilliosis," and "Talaromycosis." Articles reporting cases of *T. marneffei* infection in patients with genetic immune deficiencies were included, with all HIV-positive cases excluded. A total of 21 confirmed cases of primary immunodeficiency (PID) across 12 articles were analyzed, four of which resulted in mortality. The ages of the patients ranged from 5 months to 34 years, with 95% (20/21) being pediatric patients (under 16 years of age). Notably, 86% of the cases (18/21) were from China, with the remaining cases originating from Thailand. The predominant clinical manifestations involved disseminated pathology affecting the lungs, gastrointestinal tract, skin, lymph nodes, liver, and spleen[9].

In the case report by You CY et al., genetic testing is emphasized as a critical tool for diagnosing primary immunodeficiencies. The authors provide compelling evidence that mutations in STAT1, STAT3, CD40L, and IFNGR1 have been documented in patients with *Talaromyces marneffei* infections who exhibit compromised immune function. Among these, STAT1 and CD40L mutations accounted for 33.3% (7/21) and 38.1% (8/21), respectively, of the known immune-related genetic mutations identified in *T. marneffei*-infected individuals[9]. However, additional genetic mutations may also confer increased susceptibility to *T. marneffei* infection. This presents a significant challenge in Vietnam, where advanced genetic testing remains underdeveloped, highlighting the urgent need for future research and investment in genetic diagnostics.

CONCLUSIONS

Talaromyces marneffei remains a significant fungal pathogen in Southeast Asia, with growing global relevance due to increased international travel and migration. Clinical vigilance is crucial, particularly for patients with nonspecific symptoms and a history of exposure to endemic regions. Accurate diagnosis requires the integration of clinical evaluation, imaging, and microbiological confirmation to ensure timely identification. Early detection is vital, especially in immunocompromised patients who face a higher risk of severe disseminated infection, long time antibiotic using and poor outcomes.

Raising awareness of *T. marneffei* among clinicians, even in non-endemic regions, is essential to reduce diagnostic delays and improve survival rates. In resource-limited settings, advancing diagnostic tools, including genetic testing for immunodeficiency, will play a key role in early detection and management. Enhanced surveillance and global collaboration are necessary to better understand the epidemiology and control the spread of this life-threatening infection. This case underscores the importance of recognizing *T. marneffei* as a serious pathogen and improving diagnostic and therapeutic strategies to address this critical health threat.

REFERENCES

1. Castro-Lainez, M. T.; Sierra-Hoffman, M.; J, L. L.-Z.; Adams, R.; Howell, A.; Hoffman-Roberts, H.; Fader, R.; Arroliga, A. C.; Jinadatha, C., Talaromyces marneffei infection in a non-HIV non-endemic population. IDCases 2018, 12, 21-24.

2. Guo, J.; Li, B. K.; Li, T. M.; Wei, F. L.; Fu, Y. J.; Zheng, Y. Q.; Pan, K. S.; Huang, C. Y.; Cao, C. W., Characteristics and Prognosis of Talaromyces marneffei Infection in Non-HIV-Infected Children in Southern China. Mycopathologia 2019, 184 (6), 735-745.

3. Vanittanakom, N.; Cooper, C. R., Jr.; Fisher, M. C.; Sirisanthana, T., Penicillium marneffei infection and recent advances in the epidemiology and molecular biology aspects. Clinical microbiology reviews 2006, 19 (1), 95-110.

4. Hu, Y.; Zhang, J.; Li, X.; Yang, Y.; Zhang, Y.; Ma, J.; Xi, L., Penicillium marneffei infection: an emerging disease in mainland China. Mycopathologia 2013, 175 (1-2), 57-67.

5. Hamilton, A., Penicillium marneffei: penicilliosis and the red peril in the east. The mycologist 2003, 17 (2), 84-85.

6. Qiu, Y.; Zhang, J. Q.; Pan, M. L.; Zeng, W.; Tang, S. D.; Tan, C. M., Determinants of prognosis in Talaromyces marneffei infections with respiratory system lesions. Chinese medical journal 2019, 132 (16), 1909-1918.

7. Stathakis, A.; Lim, K. P.; Boan, P.; Lavender, M.; Wrobel, J.; Musk, M.; Heath, C. H., Penicillium marneffei infection in a lung transplant recipient. Transplant infectious disease : an official journal of the Transplantation Society 2015, 17 (3), 429-34.

8. Qin, L.; Zhao, L.; Tan, C.; Chen, X. U.; Yang, Z.; Mo, W., A novel method of combining Periodic Acid Schiff staining with Wright-Giemsa staining to identify the pathogens Penicillium marneffei, Histoplasma capsulatum, Mucor and Leishmania donovani in bone marrow smears. Experimental and therapeutic medicine 2015, 9 (5), 1950-1954.

9. You, C. Y.; Hu, F.; Lu, S. W.; Pi, D. D.; Xu, F.; Liu, C. J.; Fu, Y. Q., Talaromyces Marneffei Infection in an HIV-Negative Child with a CARD9 Mutation in China: A Case Report and Review of the Literature. Mycopathologia 2021, 186 (4), 553-561.