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CASE REPORT

Metagenomic Next-Generation Sequencing Unravels Talaromyces Marneffei-Induced Bone Destruction in an HIV-Negative Woman: A Case Report with Fatal Outcome

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Introduction: *Talaromycosis* is an opportunistic fungal disease caused by *Talaromyces marneffei (TM)*, a significant pathogen predominantly affecting immunocompromised individuals, especially those with HIV infection. Although traditionally regarded as an HIV-associated infection, increasing cases have been reported among HIV-negative patients.

Case Presentation: This report details a case of a 36-year-old HIV-negative woman infected with *Talaromyces marneffei*. The patient presented with bone destruction and was diagnosed through metagenomic next-generation sequencing (mNGS). Despite receiving antifungal, anti-inflammatory, and symptomatic treatment, the infection remained uncontrolled, ultimately progressing to multi-organ failure and resulting in death.

Conclusion: Bone damage due to *Talaromyces marneffei* infection is very uncommon in HIV-negative patients. Thus, healthcare providers should be alert for possible skeletal lesions linked to this infection. Early diagnosis and appropriate antimicrobial treatment are vital for the patient's prognosis.

Keywords: *Talaromyces marneffei*, HIV-negative, bone destruction, metagenomic next-generation sequencing, antifungal treatment

Background

Talaromyces marneffei is a dimorphic fungus predominantly found in Southeast Asia, including countries like Thailand, Vietnam, and China,[1–3] and it can cause severe infections.[4] While infections typically occur in HIV-positive individuals, there have been increasing reports of cases in non-HIV patients.[5–7] Culturing *T. marneffei* is critical for diagnosis; however, the urgency of infections, along with the lengthy culture time and low yield, presents challenges for clinical diagnosis.[8] Accurate identification of the pathogen is essential for timely initiation of appropriate antimicrobial treatment.[9,10] Therefore, developing rapid and accurate identification methods is crucial.[11] We describe a case of a 36-year-old woman from China, HIV-negative, who exhibited symptoms including cough and bone pain. During her hospital stay, she experienced septic shock, and *T. marneffei* infection, which had caused bone destruction, was eventually diagnosed through metagenomic next-generation sequencing (mNGS). We review the clinical presentation of this case to enhance awareness and understanding of this infection.

Case Presentation

A 36-year-old Chinese woman was admitted to the hospital on June 22, 2023, due to a persistent cough lasting four months, bone pain for one month, and a recently discovered pulmonary mass four days prior. The patient reported that her cough began in February 2023, without sputum production, hemoptysis, chills, fever, chest tightness, or dyspnea, and the results of

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the nucleic acid test for the novel coronavirus are negative. After self-medicating, her cough somewhat improved. In May 2023, she developed pain in the right side of her back, which did not significantly improve with acupuncture and physiotherapy at a local clinic, and the pain spread to both sides of her back. On June 18, 2023, a chest CT scan at a local hospital revealed a mass lesion in the upper lobe of the right lung, with a suspicion of malignancy and possible invasion into adjacent ribs. There was also evidence of bone destruction in the T1 vertebra with a pathological compression fracture, and slight inflammation in both lungs was noted. The patient subsequently came to our hospital for further diagnosis and treatment. She reported no history of unprotected sexual intercourse or blood transfusions and had no personal or hereditary disease history. She also denied traveling outside her hometown in the past 10 years. Two years ago, she experienced cervical lymphadenopathy and was diagnosed with tuberculous lymphadenitis via lymph node fine-needle aspiration biopsy at a local hospital, for which she completed a six-month course of anti-tuberculosis therapy. Upon initial examination, her vital signs were: body temperature 36.5°C, blood pressure 92/65 mmHg, heart rate 84 beats per minute, and respiratory rate 20 breaths per minute. The physical examination was largely normal, except for small palpable lymph nodes on both sides of the neck, approximately 0.5 cm in diameter, clearly defined, slightly firm, moderately mobile, non-tender, and with no abnormal skin changes. After admission, routine tests were conducted, including blood biochemistry, urine and stool analysis, liver and kidney function tests, electrolytes, tumor markers, ECG, bone ECT, and percutaneous lung biopsy. The dynamic laboratory test results at key clinical time points are summarized in Table 1, with detailed immunological data provided in Supplementary Table 1. The blood HIV test was negative, and levels of squamous cell carcinoma antigen, non-small cell lung cancer antigen, neuron-specific enolase, as well as serum and urine immunofixation electrophoresis, were all normal. Abdominal and pelvic CT scans showed destruction of the L1 vertebral body and left pedicle, along with both sacral alae, and

Table 1 Laboratory Test Results

Check Item	Admission	Diagnosis Confirmed	Condition Worsened
WBC ($\times 10^9$/L)	14.99 ↑	19.91 ↑	22.9 ↑
PLT ($\times 10^9$/L)	389.00 ↑	396.00 ↑	45 ↓
LYM%	0.198 ↓	0.049 ↓	0.075 ↓
NEU ($\times 10^9$/L)	10.17 ↑	17.51 ↑	16.89 ↑
PCT (ng/mL)	0.330 ↑	0.35 ↑	0.047
PT (s)	14.20 ↑	17.00 ↑	17.20 ↑
hsCRP (mg/L)	136.95 ↑	172.50 ↑	—
GLU (mmol/L)	3.87 ↓	—	16.30 ↑
ALB (g/L)	28.7 ↓	23.0 ↓	23.4 ↓
GLO (g/L)	62.4 ↑	53.4 ↑	49.4 ↑
GGT (U/L)	83 ↑	299 ↑	272 ↑
HBsAb (mIU/mL)	≫640 ↑	—	—
HBeAb (PEIU/mL)	0.479 ↑	—	—
HBcAb (PEIU/mL)	6.922 ↑	—	—
IgG (g/L)	45.51 ↑	—	—

Notes:↑: elevation; ↓: reduction. —; Not available or not tested at this time point,
Abbreviations: WBC, White Blood Cell Count; PLT, Platelet Count; LYM%, Lymphocyte Percentage; NEU, Neutrophil Count; PCT, Platelet Crit (Platelet Volume); PT, Prothrombin Time; hsCRP, High Sensitivity C-Reactive Protein; GLU, Glucose (Fasting); ALB, Albumin; GLO, Globulin; GGT, Gamma-Glutamyl Transferase; HBsAb, Hepatitis B Surface Antibody; HBeAb, Hepatitis B e-Antibody; HBcAb, Hepatitis B Core Antibody; IgG, Immunoglobulin G.

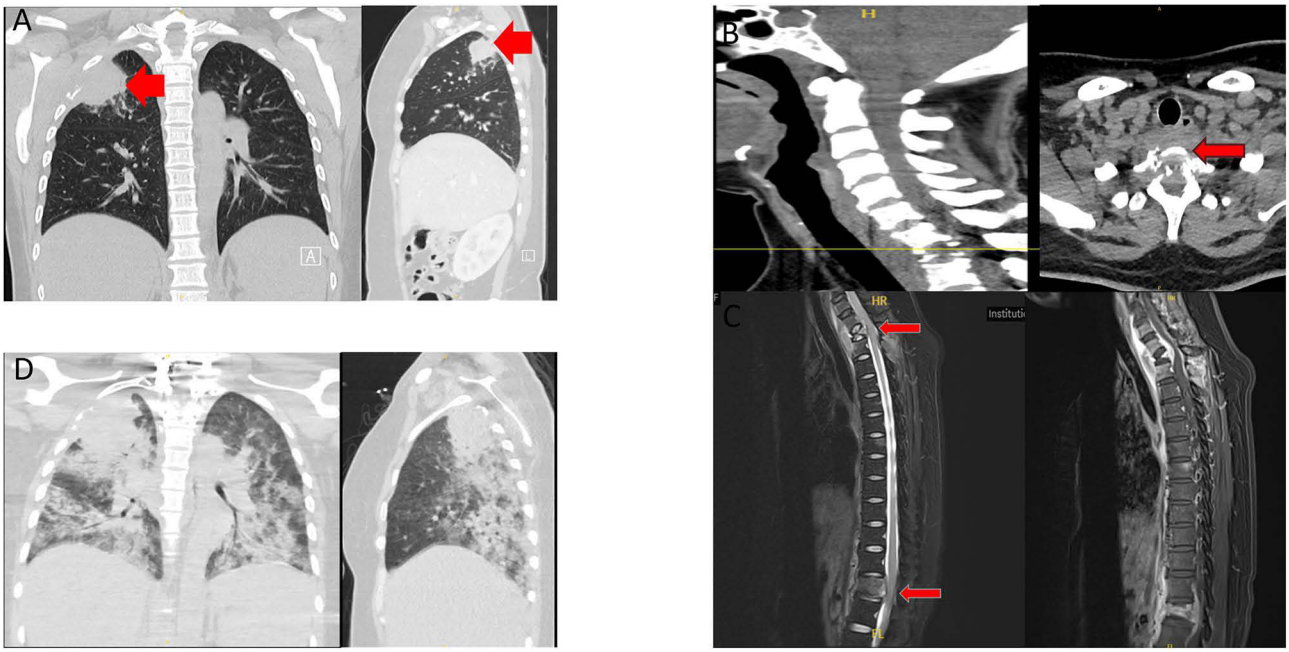

Figure 1 Imaging. (**A**) Preoperative chest CT: A poorly demarcated, irregular soft tissue mass (indicated by the red arrow) measuring approximately 4.9 cm × 3.8 cm × 3.7 cm was observed adjacent to the posterior segment of the right third rib in the thoracic cavity. The lesion exhibited indistinct boundaries with the adjacent right pleura, chest wall, and intercostal muscles, and protruded toward the apical segment of the right upper lobe. (2023-6-23). (**B**) Preoperative cervical spine CT: Osteolytic bone destruction was observed involving the vertebral bodies from C6 to Th2, predominantly affecting the Th1 vertebral body. These findings are suggestive of a pathological fracture of the Th1 vertebra (red arrow), with secondary spinal canal stenosis at the Th1 segment. (2023-7-3). (**C**) Preoperative whole spine MRI: Flattening of the Th1 and L1 vertebral bodies was observed (red arrows), suggestive of pathological fractures. Abnormal fluid-like signal intensities were noted in the Th1 and L1 vertebral bodies, their appendages, and surrounding soft tissues, protruding into the spinal canal and resulting in spinal cord compression at the levels of Th1 and L1. (2023-7-3). (**D**) Postoperative lung CT: An irregular, patchy soft tissue density mass located at the posterior segment of the right third rib in the right thoracic cavity increased in size compared to the previous examination. Patchy and linear high-density shadows appeared in both lungs, indicating progression of pulmonary inflammation relative to the preoperative state. (2023-7-6).

the formation of a soft tissue mass, suggesting a possible metastatic tumor. The chest CT revealed bone destruction of the right 3rd rib, C7-Th2 vertebrae, and the left 4th posterior rib, with associated pathological fractures, as well as multiple enlarged lymph nodes in the mediastinum and right hilum, possibly indicating malignancy (Figure 1A–C). To clarify the diagnosis, an ultrasound-guided lung lesion biopsy was performed on June 26, 2023. Pathology indicated inflammatory fibrous tissue hyperplasia, considered an inflammatory pseudotumor, and immunohistochemistry did not support IgG4-related inflammation, recommending further examination. Due to progressive weakness in both lower limbs caused by multiple bone destructions and pathological fractures, the likelihood of a malignant tumor was considered high, with a significant risk of paraplegia. Therefore, posterior thoracic lesion resection was performed on July 3, 2023. Postoperatively, the patient developed a high fever, with a maximum temperature of 40°C. Considering intraoperative findings, the possibility of tuberculosis infection could not be excluded, so empirical anti-tuberculosis treatment was initiated. Postoperative investigations showed persistent infection or inflammatory response, accompanied by significant anemia, liver dysfunction, hypoxemia, and electrolyte imbalances. Pathological examination and mNGS of the bone tissue obtained from the posterior thoracic lesion resection revealed *T. marneffei* (See Supplementary Material 1 for detailed MNGS methodology, with relevant pathological images shown in Supplementary Figure 1A–C), which was further confirmed by special culture, leading to the cessation of tuberculosis medication. After a confirmed diagnosis of *T. marneffei* infection, treatment with amphotericin B was initiated on July 5, 2023. The initial dose was 5 mg/day and was gradually escalated to a maintenance dose of 35 mg/day, administered via intravenous infusion over more than 6 hours each time to minimize drug-related toxicities. During the early phase of treatment, the patient experienced persistent fever with a peak temperature of 39.5°C, and oxygen saturation remained between 86% and 92% under nasal cannula oxygen, accompanied by dyspnea. Due to suboptimal infection control, intravenous meropenem at 1 g every 8 hours was added starting July 6. On July 11, follow-up chest CT indicated worsening inflammation in both lungs (Figure 1D), and the patient's condition deteriorated, developing

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severe pneumonia and acute respiratory distress syndrome (ARDS), necessitating endotracheal intubation and mechanical ventilation. Linezolid at 0.6 g every 12 hours was concurrently initiated. Despite aggressive antimicrobial therapy, inflammatory markers continued to rise, circulatory status remained unstable, and the patient ultimately succumbed to multiple organ failure on July 12.

Discussion

In the 1990s, increasing numbers of HIV-negative patients were diagnosed with *T. marneffei* infection, often exhibiting weakened cell-mediated immunity.[12] TM is a dimorphic fungus that appears as a mycelium at 25°C and as a yeast form at 37°C.[13–15] In southern China, *T. marneffei* infections are more common in individuals with immunodeficiency or those who are HIV positive. *T. marneffei* primarily affects the lungs and the mononuclear phagocyte system, and its clinical manifestations can be classified as either localized or disseminated.[16,17] Localized infections typically enter through the respiratory tract, with symptoms mainly concentrated in the lungs. These symptoms resemble those of pulmonary tuberculosis, leading to frequent misdiagnosis, which can result in prolonged illness and adversely affect the patient's quality of life.[18,19] *T. marneffei* can proliferate extensively within human tissues, but the exact route of infection remains unclear. Some studies suggest that human infection may not result from direct contact with bamboo rats but rather from inhaling conidia spores present in rain-soaked soil.[20] In this case, the HIV-negative patient without obvious immunodeficiency risk factors developed disseminated *T. marneffei* infection with unusual bone involvement, consistent with prior reports. A 10-year retrospective analysis showed that HIV-negative patients with *T. marneffei* infection had higher neutrophil counts, more severe organ damage, and increased mortality compared to those who were HIV-positive.[21] Therefore, early diagnosis and treatment are crucial for reducing mortality rates.

Early and accurate diagnosis of *T. marneffei* infection is essential, yet difficult to achieve. Traditionally, identifying *T. marneffei* relied on isolating the fungus from clinical samples, which is not conducive to rapid diagnosis due to its long incubation period.[22,23] However, with the advent of next-generation sequencing (NGS) technology, *T. marneffei* can be detected within 48 hours, even when pathologists cannot identify the pathogen through microscopic morphology alone.[24–26] This is particularly important for early diagnosis in cases with atypical lesions and clinical presentations. In this patient, initial misdiagnosis as inflammatory pseudotumor and tuberculosis led to delayed initiation of targeted antifungal therapy, which likely contributed to disease progression and poor outcome. This case underscores the importance of early use of molecular diagnostic tools like NGS, especially in atypical lesions. The combination of NGS genetic testing with clinical presentation, imaging studies, and laboratory results ultimately confirmed the *T. marneffei* infection. Clinically, it is advisable to first conduct tissue pathology, staining, and culture. If no specific microorganism is identified, mNGS should be considered as a further diagnostic tool.

Several factors may have contributed to the fatal outcome. First, the delay in initiating antifungal therapy due to initial misdiagnosis possibly allowed extensive fungal proliferation and dissemination. Second, the persistent high fever and progressive respiratory failure despite broad-spectrum antibiotics suggest possible co-infections or overwhelming inflammatory response, which are known to worsen prognosis in *T. marneffei* infection. Third, although amphotericin B was administered and dose-escalated appropriately,[27] the patient's advanced disease stage, extensive bone destruction, and compromised respiratory status may have limited the efficacy of treatment.

In HIV-negative patients, bone involvement due to *T. marneffei* infection is relatively rare. Therefore, for patients presenting with recurrent fever, pulmonary masses, and bone lesions, it is important to consider not only tuberculosis and tumors but also the possibility of *T. marneffei* and other rare pathogenic infections. This case highlights the need for further research into *T. marneffei*, particularly regarding its manifestations and prognosis in atypical hosts. Additionally, developing more sophisticated methods for assessing immune function is crucial to identify individuals who may be more susceptible to such infections. A deeper understanding of this infection in HIV-negative patients could enhance timely diagnosis and treatment, ultimately improving health outcomes. This calls for heightened clinical awareness and consideration of a broader range of potential diagnoses in similar clinical scenarios.

Conclusions

This case report reminds clinicians that *T. marneffei* infection is not limited to HIV-positive patients and should also be vigilant for its possibility in non-HIV patients. Due to the difficulty in diagnosis, overlooking *T. marneffei* infection can lead to serious consequences if it spreads. Utilizing next-generation sequencing (NGS) technology allows for rapid and accurate diagnosis of *T. marneffei* infection, thereby improving patient outcomes.

Data Sharing Statement

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

Ethical Approval and Consent to Participate

We confirm that written informed consent for publication from the patient's legal guardian was obtained. The research was approved by the Ethics Committee of the Second Affiliated Hospital of Guangxi Medical University (2024-KY-0394) in accordance with the Helsinki Declaration of the World Medical Association and the ethical principles formulated by the Chinese GPC. This report was approved for publication by the Second Affiliated Hospital of Guangxi Medical University.

Consent for Publication

Informed consent was obtained from all individual participants included in this study.

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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. Jiayi Chen and Zixiang Pang contributed equally to this work and should be considered co-first authors.

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Disclosure

The authors declare that they have no competing interests in this work.

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