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CASE REPORT

Severe Pneumonia Due to *Tropheryma Whipplei* Infection Complicated by Tuberculosis and COVID-19

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ABSTRACT

Background: ***Tropheryma whipplei*** **is a rare cause of pneumonia, but its detection has increased in clinical practice.**
Methods: **We report a severe case of** ***T. whipplei*** **pneumonia complicated by** ***Mycobacterium tuberculosis*** **and SARS-CoV-2 co-infections in a 21-year-old man presenting with acute respiratory failure, ARDS, and septic shock.**
Results: **mNGS of bronchoalveolar lavage fluid rapidly identified** ***T. whipplei*** **and** ***M. tuberculosis*****, enabling timely targeted therapy with ceftriaxone, anti-tuberculosis treatment, and antivirals for COVID-19. The patient recovered after prolonged hospitalization.**
Conclusions: **This case underscores the diagnostic value of mNGS in complex mixed infections and highlights the need for optimized treatment strategies for** ***T. whipplei*** **pneumonia.**
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KEYWORDS

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INTRODUCTION

Tropheryma whipplei (TW) is a Gram-positive bacterium widely present in the environment and residing intracellularly within macrophages and monocytes. Cultured successfully only in 2000, it is among the slowest-growing human pathogens, with a generation time of approximately 18 days [1]. TW is considered a conditional pathogen responsible for *Whipple*'s disease, an extremely rare and debilitating condition with an incidence of fewer than 1 per 1,000,000 individuals [2], occurring predominantly in Caucasians and infrequently in Asian or African populations [3]. Classically, the disease affects the gastrointestinal tract, manifesting as chronic diarrhea and weight loss, although chronic localized and acute infections, including endocarditis, pulmonary involvement, and ocular uveitis, have increasingly been reported. TW may cause active infection or

exist as a colonizer, and its multisystem involvement frequently leads to delayed diagnosis and suboptimal outcomes [4].

The widespread adoption of metagenomic next-generation sequencing (mNGS) has markedly enhanced the detection of rare and mixed infections, providing substantial advantages over conventional diagnostic methods. In this report, we describe a rare case of severe TW pneumonia complicated by co-infections with *Mycobacterium tuberculosis* and SARS-CoV-2. mNGS enabled rapid pathogen identification, and targeted antimicrobial therapy resulted in significant clinical improvement. Given the exceptional rarity of such mixed infections, this case contributes to the growing understanding of TW-associated pulmonary disease and underscores the diagnostic value of mNGS in complex clinical scenarios.

CASE PRESENTATION

On June 14, 2023, a 21-year-old male farmer was transferred by ambulance to the emergency department due to shortness of breath, brief fainting, loss of consciousness for several minutes, urinary and fecal incontinence, and excessive sweating. He reported a history of recurrent cough and respiratory distress lasting for 15 days, along with a fever for one day. Initially, he experienced breathing difficulties, intermittent dry cough, and white, sticky sputum. He denied having had chest pain, hemoptysis, nausea, or diarrhea. However, his respiratory distress progressively worsened, accompanied by lethargy, fatigue, and decreased appetite. Additionally, significant weight loss was noted during this period.

Upon admission, the patient exhibited a temperature of 39.5°C, a pulse of 120 beats per minute, a respiratory rate of 28 breaths per minute, blood pressure of 127/77 mmHg, and an oxygen saturation (SpO2) of 70%. He appeared emaciated and mentally confused. Lung auscultation revealed bilateral dry and wet rales. Heart sounds were faint without pathological murmurs, and the abdomen was soft and non-tender. The patient had no significant medical history, including hypertension, diabetes, coronary heart disease, hepatitis B, or tuberculosis, nor a history of major trauma, surgery, or blood transfusions.

Auxiliary examinations yielded the following results: a white blood cell count of 3.7 x 10^9/L, neutrophils at 3.2 x 10^9/L, lymphocytes at 0.4 x 10^9/L, red blood cells at 3.96 x 10^{12}/L, hemoglobin at 97 g/L, and platelets at 106 x 10^9/L. The C-reactive protein level was 65.51 mg/L. Biochemical analysis showed creatinine at 115.0 µmol/L, total protein at 53.2 g/L, albumin at 24.8 g/L, alanine aminotransferase at 66 U/L, aminotransferase at 177 U/L, lactate dehydrogenase at 1,050 U/L, creatine kinase at 488 U/L, and CK-MB at 30 U/L. Sodium was measured at 130.2 mmol/L, potassium at 3.58 mmol/L, and lactate at 9.4 mmol/L. Troponin I (TNI) was 0.04 ng/mL, and procalcitonin (PCT) was 2.34 ng/mL. Arterial blood gas analysis revealed a pH of 7.461, pCO2 of 24.0 mmHg, a pO2 of 43.0 mmHg, and an oxygen saturation of 80.9%. Echocardiography showed normal cardiac chamber sizes with reduced left ventricular function (EF approximately 30%). Chest and abdominal CT scans revealed diffuse bilateral lung infections, pleural effusions, enlarged mediastinal lymph nodes, a thickened colonic wall, mild abdominal fluid, and multiple low-density liver lesions (Figure 1a - b).

The patient was diagnosed with severe pneumonia and acute respiratory failure. Intubation and mechanical ventilation were promptly initiated. He was transferred to the intensive care unit (ICU) and started on empiric antimicrobial therapy, including ceftriaxone, moxifloxacin, and doxycycline, supplemented with ulinastatin and corticosteroids. mNGS of the bronchoalveolar lavage fluid identified *T. whipplei* (78.75%) and *M. tuberculosis* (0.12%). *The* Xpert MTB/RIF assay confirmed rifampicin-sensitive *M. tuberculosis*, with positive RNA detection and culture after 12 days. RT-PCR confirmed COVID-19 (CT value 34.19).

On June 17, 2023, the patient was transferred to a tuberculosis ICU for further treatment. Individualized anti-tuberculosis therapy (HRZ combined with moxifloxacin) was initiated alongside the administration of corticosteroids. The patient was also given ceftriaxone for *whipple*'s disease infection and ritonavir/saquinavir for COVID-19.

In the ICU, the patient's white blood cell count dropped to as low as 18.3 g/L, and a further decline in hemoglobin was noted, with blood pressure instability. The patient received blood transfusions, proton pump inhibitors, and other supportive treatments. His hemodynamic status gradually stabilized, and lung auscultation revealed significant improvement in rales. By June 20, 2023, the patient could pass the spontaneous breathing trial and was successfully extubated on June 21, 2023. Follow-up chest CT showed improved lung consolidation (Figure 2), and inflammatory markers decreased.

The patient's condition gradually improved, and by June 23, 2023, he was transferred to a tuberculosis ward for continued anti-tuberculosis therapy (HREZLfx regimen). By July 8, 2023, tests, including blood counts, liver and renal function, electrolytes, and C-reactive protein, returned to normal, and no significant symptoms were reported. The patient was discharged on July 10, 2023, with oral medications. Four months later, a follow-up chest CT showed significant resolution of the pulmonary lesions (Supplementary Figure 1), and an abdominal ultrasound revealed no significant abnormalities.

DISCUSSION

Severe pneumonia poses a persistent clinical challenge, particularly when caused by rare or unidentified pathogens. Pneumonia due to TW is seldom reported, and its pathogenic mechanisms within the lung remain poorly

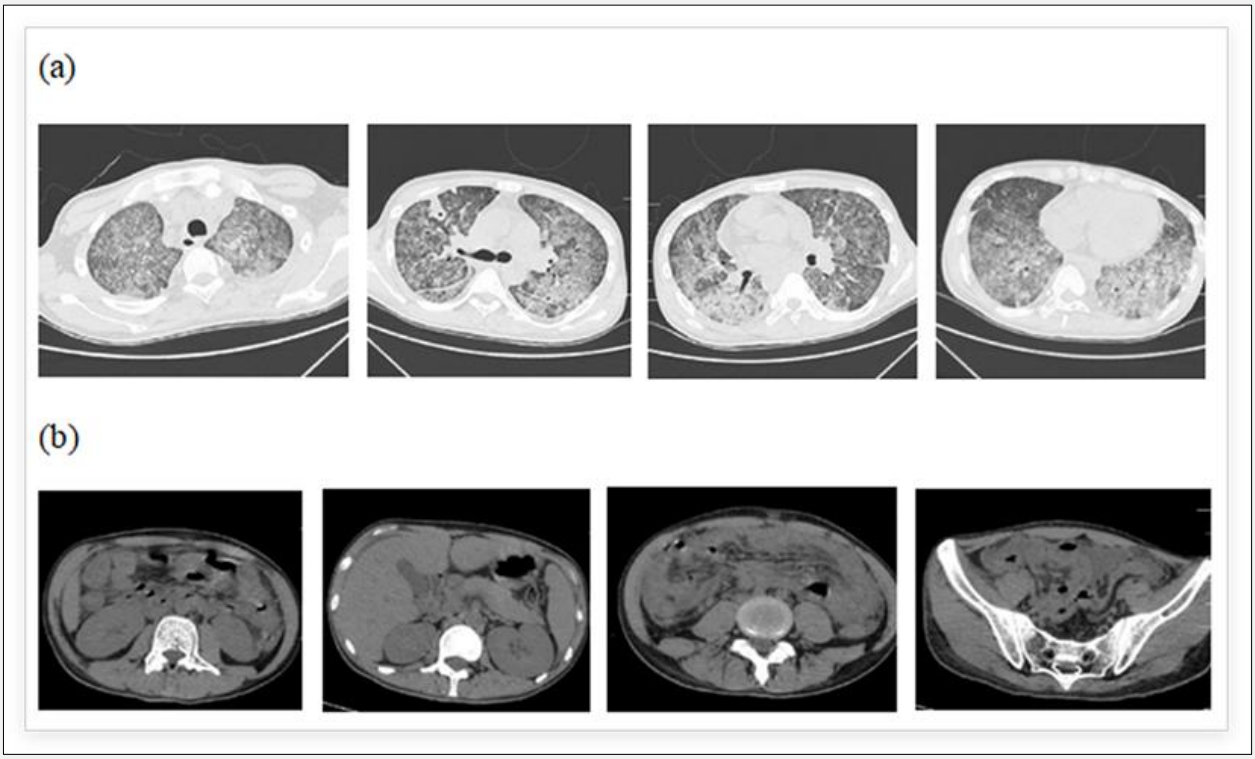

Figure 1. Chest CT (June 14, 2023).

a: revealed diffuse ground-glass opacities and patchy consolidations bilaterally, predominantly in the lower lobes, with focal crazy-paving patterns. Right upper lobe consolidation with air bronchograms was noted. Mediastinal and hilar lymphadenopathy, bilateral pleural effusions, and patent bronchial lumens were present. Abdominal imaging (June 14, 2023, b: showed a smooth-contoured liver with multiple small hypodense lesions, no biliary dilation, and normal pancreas, kidneys, and gallbladder. Colonic wall thickening at the hepatic flexure, mesenteric stranding, and ascites were also observed.

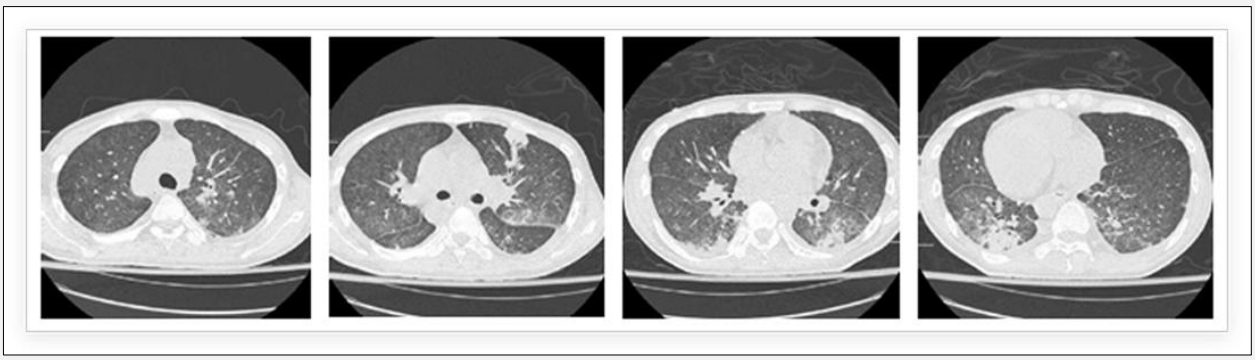

Figure 2. Chest CT (June 21, 2023) revealed reduced pulmonary translucency bilaterally, with scattered nodular and patchy high-attenuation opacities, predominantly in the right upper and left lower lobes.

Multiple enlarged mediastinal lymph nodes and mildly prominent hilar structures were observed. Bilateral pleural effusions were also present.

understood. One proposed explanation is the organism's tropism for macrophages, cells abundant in alveolar tissue, providing a favorable niche for replication [5]. Severe *T. whipplei* pneumonia is exceptionally uncommon, especially in the presence of co-infections. The present report describes a case of *T. whipplei* pneumonia complicated by *M. tuberculosis* and SARS-CoV-2, in which the patient developed severe pneumonia, acute respiratory failure, acute respiratory distress syndrome (ARDS), and septic shock, with a Sequential Organ Failure Assessment score of 6.

Whipple's disease primarily affects immunocompromised individuals, including those with HIV infection and low CD4 counts, prolonged corticosteroid exposure, diabetes mellitus, malignancy, transplantation, or treatment with TNF-α inhibitors. Infection is often associated with environmental exposure to contaminated soil or water [6,7], which is particularly relevant to agricultural workers; in this case, the patient's occupation likely increased exposure risk. Genetic susceptibility has been linked to specific HLA alleles, notably DRB1*13 and DQB1*06 [8]. Although gastrointestinal, neurologic, cardiac, and dermatologic involvement is characteristic, pulmonary disease is less common, with respiratory manifestations reported in only 13 - 14% of cases. Symptoms of *Whipple*'s disease include malabsorption-related weight loss, abdominal pain, diarrhea, and occasionally occult bleeding, while respiratory involvement may manifest as chest pain, dyspnea, chronic cough, and sputum production [6]. Systemic features can include migratory arthritis, uveitis, endocarditis, pericarditis, and neurologic disturbances such as cognitive impairment or seizures [9]. In this patient, ARDS, hypoxemia, severe cough, dyspnea, profound fatigue, and significant weight loss were accompanied by neurological symptoms including confusion, syncope, and transient loss of consciousness.

Diagnosis is challenging due to nonspecific clinical manifestations. Traditional diagnostic criteria include PAS-positive foamy macrophages in small-bowel biopsies, PCR detection of *T. whipplei*, and immunohistochemical staining. Laboratory abnormalities often include anemia, leukocytosis, and neutrophilia. Given the lengthy culture process, bronchoalveolar lavage fluid (BALF) was subjected to next-generation sequencing (NGS). BALF sampling reduces misdiagnosis linked to asymptomatic colonization, which may occur in up to 26% of healthy individuals [10]. NGS offers major advantages over culture, enabling rapid and sensitive detection of DNA- or RNA-containing pathogens. It is particularly valuable in severe infections of unclear etiology, improving diagnostic accuracy and guiding early targeted therapy. NGS excels in detecting viral and mixed infections and has become pivotal in identifying rare bacterial pathogens. In this case, NGS rapidly identified *T. whipplei* and *M. tuberculosis*, the latter subsequently confirmed by Xpert MTB/RIF.

The expanding use of NGS has substantially increased the recognition of *Whipple*'s disease, contributing to a rise in reported cases in recent years. However, treatment strategies for *T. whipplei* pneumonia remain non-standardized. In this patient, ceftriaxone administration, guided by mNGS findings, resulted in clinical improvement. Current therapies for *Whipple*'s disease rely on antibiotics such as penicillin, tetracycline, streptomycin, ceftriaxone, meropenem, hydroxychloroquine, doxycycline, and cotrimoxazole [5]. Standard regimens include an initial 2-week course of ceftriaxone or meropenem followed by ~1 year of cotrimoxazole. However, treatment failures with trimethoprim-sulfamethoxazole have been documented [11], and *T. whipplei* demonstrates intrinsic resistance to trimethoprim and often to sulfadiazine. Increasing reports of cotrimoxazole resistance raise concern regarding relapse risk. Alternative therapy combining doxycycline with hydroxychloroquine has shown promising outcomes [12-14]. Tigecycline has been proposed as an additional option in refractory cases, supported by isolated case evidence [15], though broader validation is lacking. Long-term follow-up remains essential given the potential for recurrence and post-infectious sequelae.

In conclusion, this case illustrates the diagnostic and therapeutic complexity of *T. whipplei* pneumonia, particularly when compounded by *M. tuberculosis* and SARS-CoV-2 co-infection. mNGS played a critical role in the rapid identification of implicated pathogens, enabling timely and targeted therapy. Although optimal treatment regimens remain undefined, ceftriaxone demonstrated clinical benefit in this instance. Continued research is required to refine antimicrobial approaches and treatment duration. Given the potential for relapse and multisystem involvement, extended clinical follow-up is warranted.

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Informed Consent:
Written informed consent was obtained from individual participants.

Declaration of Interest:
The authors declare no competing interests.

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