# Use of metagenomic next-generation sequencing to diagnose *Tropheryma whipplei* infection-related pneumonia: A case report

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**Abstract.** Whipple's disease is caused by *Tropheryma whipplei* (*T. whipplei*), an uncommon pathogen that is often related to gastrointestinal symptoms. Extraintestinal involvement, particularly pulmonary manifestations, is rare and poses notable diagnostic challenges. An objective technique for identifying undiscovered infections is the application of metagenomic next-generation sequencing (mNGS). The present case report described a 55-year-old female presenting with community-acquired pneumonia (CAP), who received empirical treatment with moxifloxacin, ultimately diagnosed through mNGS performed on bronchoalveolar lavage fluid. The results indicated that the patient was infected with *T. whipplei* and that the patient exhibited notable clinical improvement within 2 weeks following intravenous moxifloxacin during hospitalization and continuation of oral moxifloxacin following discharge.The present case report highlighted the utility of mNGS in diagnosing atypical infections and identified *T. whipplei* as a potential etiological agent of CAP in immunocompetent hosts.

## Introduction

Chronic diarrhea, arthralgia and weight loss are the hallmarks of Whipple's disease (WD), which is conventionally associated with the fastidious Gram-positive actinobacterium *Tropheryma whipplei* (*T. whipplei*) (1). WD is a chronic systemic infectious disease, with an incidence of ~0.1 per 100,000 annually, that mainly affects the gastrointestinal tract (1), whereas pulmonary parenchymal involvement is particularly rare (2). Before the advent of antibiotics WD was often fatal if untreated. With modern treatment, prognosis has improved significantly, though untreated cases can still be potentially fatal. WD mainly affects individuals with immunocompromised states (for example, individuals with HIV or recipients of organ transplants) and is transmitted via a fecal-oral route (1). Environmental exposure to *T. whipplei* is also a key risk factor. Conventional microbiological techniques, such as bacterial culture and serum analysis, frequently yield false-negative results due to the slow growth, intracellular tropism and low antibody titers of the organism (2). Metagenomic next-generation sequencing (mNGS) is a culture-independent diagnostic technique that can directly utilize the patient specimen for pan-nucleic acid detection (3). In mNGS, all nucleic acids in the specimen are extracted and sequenced in parallel, so as to obtain the sequence of the host and microorganisms. Therefore, mNGS has emerged as a notable tool for detecting unculturable or unexpected pathogens (3). The present study outlines a case of *T. whipplei*-associated pneumonia diagnosed using mNGS, emphasizing its diagnostic utility in atypical respiratory infections.

## Case report

Following 4 days of wheezing, coughing and fever (38.5˚C), with random blood glucose levels ranging from 8.0-18.8 mmol/l, a Chinese woman, aged 55, was admitted to Taizhou Second People's hospital (Taizhou, China) in October 2023. The medical history of this patient included well-controlled hypertension and elevated blood glucose levels. The patient had a history of elevated blood glucose levels, but did not undergo regular glycemic monitoring or adhere to prescribed glucose-lowering medications. In addition, the patient did not have any immunodeficiency disease and had not been taking any immunosuppressive drugs. The patient was a farmer without a history of travel and had never interacted with any individual or animal known to be infected with *T. whipplei*. The patient involved in the present study was subjected to standard clinical practice and provided written informed consent for the publication of medical data and images.

A thorough physical examination was performed, including assessment of vital signs (temperature, blood pressure, heart rate and respiratory rate). Lung auscultation revealed clear

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breath sounds in the left lung, while a few fine crackles were audible in the right lung fields. No wheezes or rhonchi were noted. No chest tenderness was noted on palpation. Cardiac examination indicated normal heart sounds without murmurs, gallops or rubs and no jugular vein distention was observed. Abdominal examination was unremarkable, with a soft abdomen, lack of tenderness or rebound tenderness, normal bowel sounds (4-5 times/min) and lack of peripheral edema. Lymph node examination revealed no palpable lymphadenopathy in the cervical, axillary or inguinal regions. Neurological and musculoskeletal evaluations showed no focal deficits such as limb weakness and sensory disturbance or joint abnormalities such as swelling and tenderness. A chest CT scan obtained in October 2023 (Fig. 1) indicated patchy and nodular opacities with slightly increased density and ill-defined borders. Test results for 1,3-β-D-glucan, erythrocyte sedimentation rate, C-reactive protein, endotoxin and procalcitonin were within normal ranges (Table I). *Legionella pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, respiratory viruses, coronavirus disease of 2019 and HIV were negative in serological testing. The results for autoantibodies were still negative. Diagnostic tests, including sputum smear and bacterial culture yielded negative results. The patient was diagnosed with community-acquired pneumonia (CAP) and empirical treatment with moxifloxacin was initiated. During hospitalization, moxifloxacin was administered intravenously at a daily dose of 0.4 g. To identify the etiology of the illness, the patient underwent bronchoscopy, which revealed edematous bronchial mucosa (Fig. 2). In addition, the bronchoalveolar lavage fluid (BALF) was analyzed using mNGS. The sequencing of mNGS was performed by Adicon Clinical Laboratories, Inc. (Hangzhou, China). The service report indicated qualified internal and negative controls, host read removal, nucleic acid extraction concentration of 0.11 ng/μl, and library concentration of 29.60 ng/μl. Sequencing QC metrics included 17,699,043 total reads, 1,252,093 non-human reads, and 96.37% Q30. Microbial identification was conducted by comparing sequencing reads to reference microbial nucleic-acid databases, with *T. whipplei* detected at a total of 19,731 base pairs (bp), a coverage of 2.26%, and an average depth of 1.01X. The report also described a machine learning-based pipeline for error correction, denoising, and exact sequence inference. Antibiotic resistance gene interpretation referenced the CARD database. The results identified *T. whipplei* (sequence number: 399; relative abundance: 0.08%) as the only pathogen (Fig. 3). After treatment for 8 days, the patient's symptoms improved, with cough resolution and normalization of body temperature. Following discharge, the patient continued oral moxifloxacin at a daily dose of 0.4 g for 1 week and remained in good health. A follow-up chest CT scan in November 2023 (Fig. 4) indicated complete resolution of the bilateral patchy/nodular opacities. A telephone follow-up was conducted after discharge. The patient reported that she was in good health and had not experienced any further complications. The patient declined to visit the hospital for follow-up examinations, including a chest CT scan.

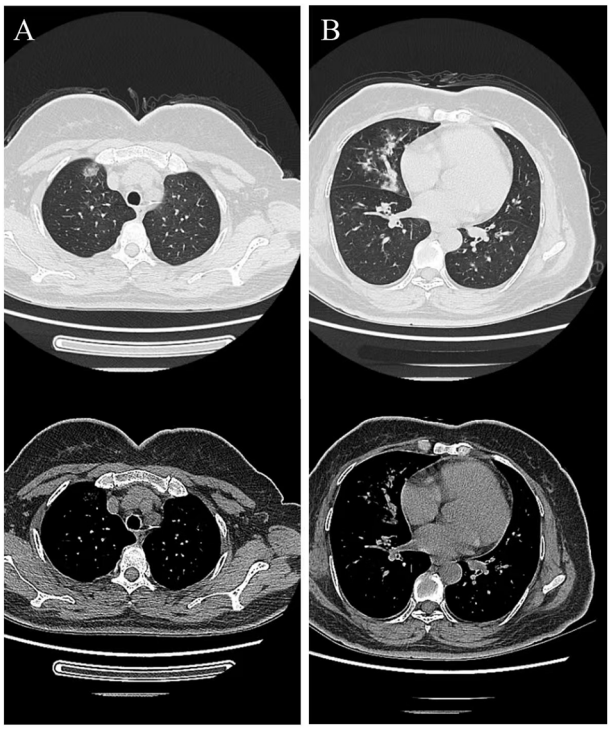


Figure 1. Chest CT imaging of lung lesions upon admission in October 2023. (A) Lung and mediastinal windows of the upper lung lobes. (B) Lung and mediastinal windows of the lower lung lobes. Patchy and nodular opacities with slightly increased attenuation and ill-defined margins are visible.

## Discussion

*T. whipplei* is a potentially harmful commensal organism that is naturally found in 1.5-7% of the general population, without exhibiting any symptoms (4). Some cases reported WD had immunocompromised conditions or immunopathologic abnormalities, suggesting impaired host immunity may be a predisposing factor (5). These individuals typically acquire the infection through exposure to contaminated water or soil. Notably, it is the fecal-oral pathway that leads to the spread of *T. whipplei* (1,6) and pneumonia can result from the subject inhaling *T. whipplei* orally (7). In addition, saliva from asymptomatic patients contains *T. whipplei* (8). The digestive tract, nervous system, skin and heart are the primary organs affected by this condition, with the lungs being less commonly affected (9). To the best of our knowledge, only a limited number of case reports have described respiratory infections, despite the advanced detection and treatment of Whipple's disease in the digestive tract (1,10). The present case report indicated that, despite a history of raised blood glucose levels, the patient did not undergo regular checkups or adhere to prescribed medications, which may have contributed to *T. whipplei* infection.

The established method for diagnosing *T. whipplei* infection is histopathology combined with PCR (8). However, for *T. whipplei*-related pneumonia, lung biopsies are invasive and not routinely performed. With this, the use of BALF exhibits lower sensitivity due to the presence of a low bacterial load. Conventional bacterial cultures are impractical due to the slow proliferation of *T. whipplei* (9). In the present case report, mNGS analysis of BALF identified *T. whipplei* as the only pathogen present. mNGS, while not well established as a technique in this context, detected the pathogen without prior suspicion and exhibited results that aligned with the clinical response of the patient to moxifloxacin. Other pathogens were

Table I. Admission laboratory test results of the patient.

A, Blood glucose markers

| Specific test item | Result | Normal range |
|---|---|---|
| Random blood glucose, mmol/l | 8.0-18.8 | 3.9-6.1 (fasting); 7.8 (2 h postprandial) |
| Fasting blood glucose, mmol/l | 9.1 | 3.9-6.1 |
| Glycated hemoglobin, % | 7.8 | 4.0-6.0 |

B, Inflammatory markers

| Specific test item | Result | Normal range |
|---|---|---|
| 1,3-β-D-glucan, pg/ml | <30 | <60 |
| Erythrocyte sedimentation rate, mm/h | 15 | 0-20 (females) |
| C-reactive protein, mg/l | 8.2 | 0-10 |
| Endotoxin, EU/ml | <0.05 | <0.1 |
| Procalcitonin, ng/ml | 0.12 | <0.5 |

C, Routine blood test

| Specific test item | Result | Normal range |
|---|---|---|
| White blood cell count, $x10^9$/l | 6.8 | 4.0-10.0 |
| Neutrophil % | 62 | 50-70 |
| Lymphocyte % | 30 | 20-40 |
| Hemoglobin, g/l | 125 | 115-150 (females) |
| Platelet count, $x10^9$/l | 148 | 100-300 |

D, Biochemical indicators

| Specific test item | Result | Normal range |
|---|---|---|
| Serum alanine aminotransferase, U/l | 22 | 7-40 |
| Serum aspartate aminotransferase, U/l | 23 | 13-35 |
| Serum creatinine, $\mu$mol/l | 51 | 44-97 $\mu$mol/l |
| Blood urea nitrogen, mmol/l | 5.17 | 2.9-8.2 |
| Serum sodium, mmol/l | 138 | 137-147 |
| Serum potassium, mmol/l | 4.1 | 3.5-5.3 |

E, Autoantibodies

| Specific test item | Result | Normal range |
|---|---|---|
| Antinuclear antibody | Negative | Titer <1:40 |
| Anti-double-stranded DNA antibody | Negative | Negative |
| Anti-neutrophil cytoplasmic antibody | Negative | Negative |
| Anti-cyclic citrullinated peptide antibody | Negative | Negative |
| Rheumatoid factor, IU/ml | 10 | 0-20 |

Serological tests for pathogens (antibodies against *Legionella pneumoniae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae* and HIV, as well as COVID-19 nucleic acid) and diagnostic microbiological tests (sputum smear and bacterial culture) are not included to avoid redundancy. All data in the table were obtained on the patient's admission day and complement the 'treatment monitoring data' (blood glucose during hospitalization and post-discharge review indicators) in the 'Case report' section, collectively completing the patient's clinical information chain.

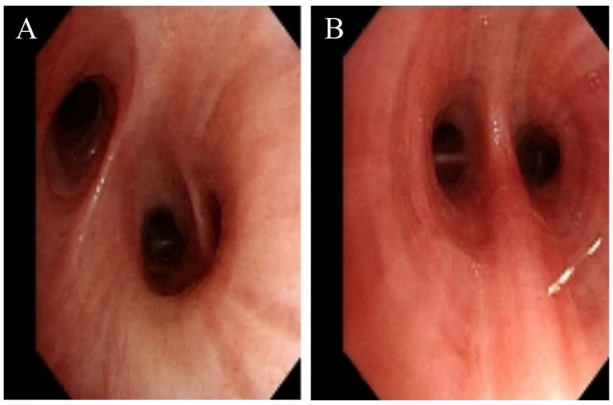


Figure 2. Bronchoscopic images indicating mild mucosal edema in the (A) right intermediate bronchus and (B) left lower bronchus.

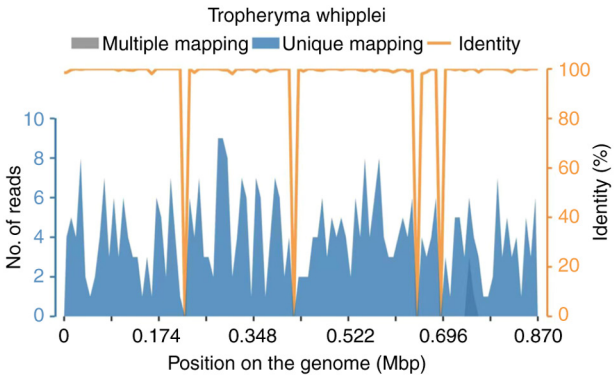


Figure 3. Metagenomic next-generation sequencing analysis indicating *Tropheryma whipplei* -specific reads and their nucleotide positions along the reference genome, with the sequence no. 399 and relative abundance of 0.08%.

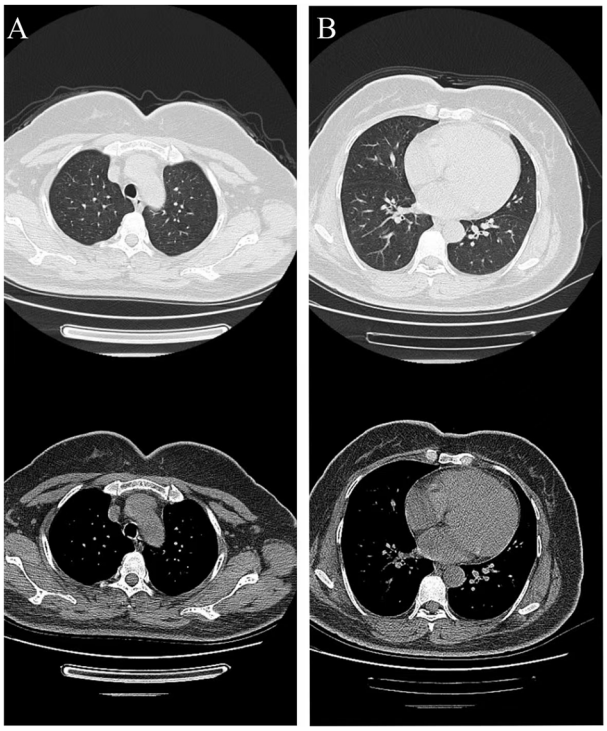


Figure 4. Follow-up chest CT images from November 2023, 1 month following admission. (A) Lung and mediastinal windows of the upper lung lobes. (B) Lung and mediastinal windows of the lower lung lobes. The patchy/nodular opacities observed in Fig. 1 were completely resolved.

excluded through negative sputum culture and serological tests. Histopathology was not performed due to the stable condition of the patient and the invasiveness of conducting a lung biopsy. BALF PCR for *T. whipplei* was not available at the time of diagnosis; therefore, mNGS served as an alternative to detect pathogen nucleic acid, which aligns with guidelines suggesting mNGS as a valuable tool for rare or unculturable pathogens (3,9). In conclusion, mNGS was shown to be a practical and effective method, particularly for rare manifestations, such as pneumonia, where standard tests are inaccessible.

Since the initial effective treatment of *T. whipplei* infection in 1952, a number of antibiotic combinations have been utilized (11). This includes penicillin, tetracycline, streptomycin, meropenem and doxycycline, trimoxazole, hydroxychloroquine and ceftriaxone. Treatment procedures for typical Whipple's disease, including a combination of oral doxycycline with trimethoprim-sulfamethoxazole or hydroxychloroquine for 1 year, have been described in previous case reports (12,13).

However, large-scale clinical trials have not been conducted and previous studies have contained small sample sizes (10,14). To the best of our knowledge, currently there are no guidelines for the management of *T. whipplei* infection (12). Zhou *et al* reported (13) optimal short-term clinical results using amoxicillin/clavulanic acid for the management of *T. whipplei*-induced lung abscesses. Furthermore, the efficacy of moxifloxacin monotherapy in treating co-infection of *Chlamydia psittaci* and flagellates has been reported (15). Although these findings suggest that both amoxicillin/clavulanic acid and moxifloxacin may be effective short-term treatment options for *T. whipplei* infection, further research is needed to confirm their efficacy.

In the present case report, insulin was administered to maintain optimal blood glucose control. While awaiting diagnostic results, empirical moxifloxacin therapy was initiated for CAP. Once mNGS identified *T. whipplei* as the causative pathogen, the patient indicated notable clinical improvement within 1 week and moxifloxacin was continued as a short-term treatment. Following discharge, the patient completed a 1-week course of oral moxifloxacin and remained stable. A follow-up chest CT scan 1 month later indicated complete resolution of the bilateral opacities. The patient's condition continued to improve and the patient declined further chest CT scans. Although moxifloxacin is not a guideline-recommended treatment for *T. whipplei* infection, its short-term use in the present case was reasonable given the acute presentation of the patient, the absence of other pathogens and the requirement for prompt therapy. Despite the favorable response, evidence supporting fluoroquinolone monotherapy for *T. whipplei* infection remains limited (16,17). Further studies are needed to evaluate the efficacy and durability of such regimens and to establish optimal treatment strategies for *T. whipplei* infections.

In conclusion, the present case report underscores the utility of mNGS in diagnosing atypical infections and highlights

*T. whipplei* as a potential cause of CAP in immunocompetent hosts. While moxifloxacin was used empirically and indicated efficacy, additional research is required to clarify its role in the management of *T. whipplei* infection.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author. mNGS data were deposited in the National Center for Biotechnology Information under the BioProject number PRJNA1390448 (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1390448).

**Authors' contributions**

GX and JP conceived and designed the present study. YL and HD analyzed and summarized the data and wrote the manuscript. YL, HD and GX collected the laboratory examination data and CT images of the case. GX critically revised the manuscript. YL and HD confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

**Patient consent for publication**

The patient involved in the present study provided written informed consent for the publication of medical data and images.

**Competing interests**

The authors declare that they have no competing interests.

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