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ORIGINAL RESEARCH

Clinical Features of Patients with *Tropheryma Whipplei* Detected in Lower Respiratory Tract Samples in China

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Introduction: *Tropheryma whipplei* (TW) can cause various infections that are relatively rare worldwide. With the development of molecular biology, the ability to detect TW has increased in recent years. However, its significance in lower respiratory tract samples remains unclear.

Patients and Methods: We collected the clinical data of 5 patients admitted to a tertiary care hospital in Beijing with TW detected by bronchoalveolar lavage fluid (BALF) mNGS and reviewed all case reports of TW-related pneumonia in China (up to November 2024) to analyse the features of this disease among Chinese patients.

Results: A total of 41 articles reporting 55 cases were identified. Fifty-two (94.5%) patients had respiratory symptoms. Fifteen (27.3%) patients developed severe pneumonia. Confirmation of TW infection was achieved through methods including the assessment of TW reads and relative abundance (63.6%), empirical treatment (18.2%), lung biopsy histopathology (14.5%), and qPCR confirmation (3.6%). Fifty (90.9%) patients received antibiotic therapy. Fifty-one (92.7%) patients had a good prognosis.

Conclusion: TW can enter the lower respiratory tract through multiple routes. When TW sequences are detected in lower respiratory tract samples, it is important to consider not only the read and relative abundance but also histopathological findings such as interstitial pneumonia and the presence of PAS- or PASM-positive bacilli within foamy macrophages as they can aid in diagnosing TW infection. MDT discussions and empirical antibiotic therapy targeting TW are viable options when a patient's condition deteriorates. Microbiological testing of saliva, gastric fluid, blood, and faeces may help clarify the source of TW.

Keywords: *Tropheryma whipplei*, lower respiratory tract, metagenomic next-generation sequencing, bronchoalveolar lavage fluid, pneumonia

Introduction

Tropheryma whipplei (TW) is a gram-positive, periodic acid-Schiff (PAS)-positive, nonacid-fast bacillus that is relatively common and ubiquitous.[1] TW can cause a broad spectrum of infections, ranging from asymptomatic carriage, symptomatic primary infections, and chronic localized infections to systemic chronic infection, the latter of which is known as classical Whipple's disease (WD).[1] WD is a rare disease with an estimated prevalence ranging from 3 per million in Italy to 9.8 per million in the United States.[2,3] This disease is commonly characterized by a classic triad of symptoms: weight loss, diarrhoea, and arthralgia. The definitive diagnosis typically relies on duodenal biopsy, with histological examination revealing pathognomonic findings such as foamy macrophages laden with diastase-resistant, PAS-positive granules in the lamina propria. While these findings are most frequently observed in the duodenum, they may also extend to the gastric antrum, jejunum, or ileum.[4]

Although culture media is considered the gold standard for microbiological identification, it is currently unsuitable for the clinical detection of TW infection. This is primarily because TW does not grow in conventional culture media and

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requires specialized media,[1] such as rational axenic culture media,[5] which is not routinely available in general hospitals in China. Histopathological diagnosis is invasive and highly dependent on the operator's skill and experience. Immunoassays and polymerase chain reaction (PCR)-based nucleic acid tests rely on prior assumptions about the suspected pathogen.[6] In contrast, metagenomic next-generation sequencing (mNGS) is a powerful, unbiased technique capable of rapidly identifying a broad spectrum of microbial pathogens, including rare and novel organisms,[6] without the need for predefined targets.[7] Furthermore, mNGS results are less likely to be affected by prior antibiotic exposure than culture-based methods are.[8] Thus, mNGS is a clinically valuable tool for identifying rare pathogens such as TW. In recent years, the implementation of mNGS in general hospitals across China has become increasingly widespread, contributing to a notable increase in reported cases of TW infection. A better understanding of the clinical characteristics of TW-associated pneumonia in China may facilitate earlier diagnosis, enable targeted therapy, reduce the unnecessary use of broad-spectrum antibiotics, and ultimately improve patient outcomes. In this article, we present the clinical data of 5 patients admitted to a tertiary care hospital in Beijing with TW detected by bronchoalveolar lavage fluid (BALF) mNGS, and we review all case reports of TW-related pneumonia in China (up to November 2024) to characterize this disease's national profile.

Case Reports

Patient 1 was admitted to the hospital after his chest high-resolution computed tomography (HRCT) scan revealed a shadow during a routine checkup (Figure 1A). The patient was asymptomatic. He was treated with levofloxacin as an anti-infection agent. Transbronchial lung biopsy (TBLB) revealed a broken alveolar septum, atrophied alveoli, scattered lymphocytes in the interstitium, and a small number of PAS-positive bacilli. BALF mNGS was performed, which identified TW as the only pathogen. The patient refused treatment and was discharged. He was followed up two years later, and no respiratory symptoms were noted.

Patient 2 was admitted to the hospital with a two-week history of cough and shortness of breath. He had been immunosuppressed due to treatment for rheumatoid arthritis and was taking 10 mg of oral prednisone daily, 12.5 mg of

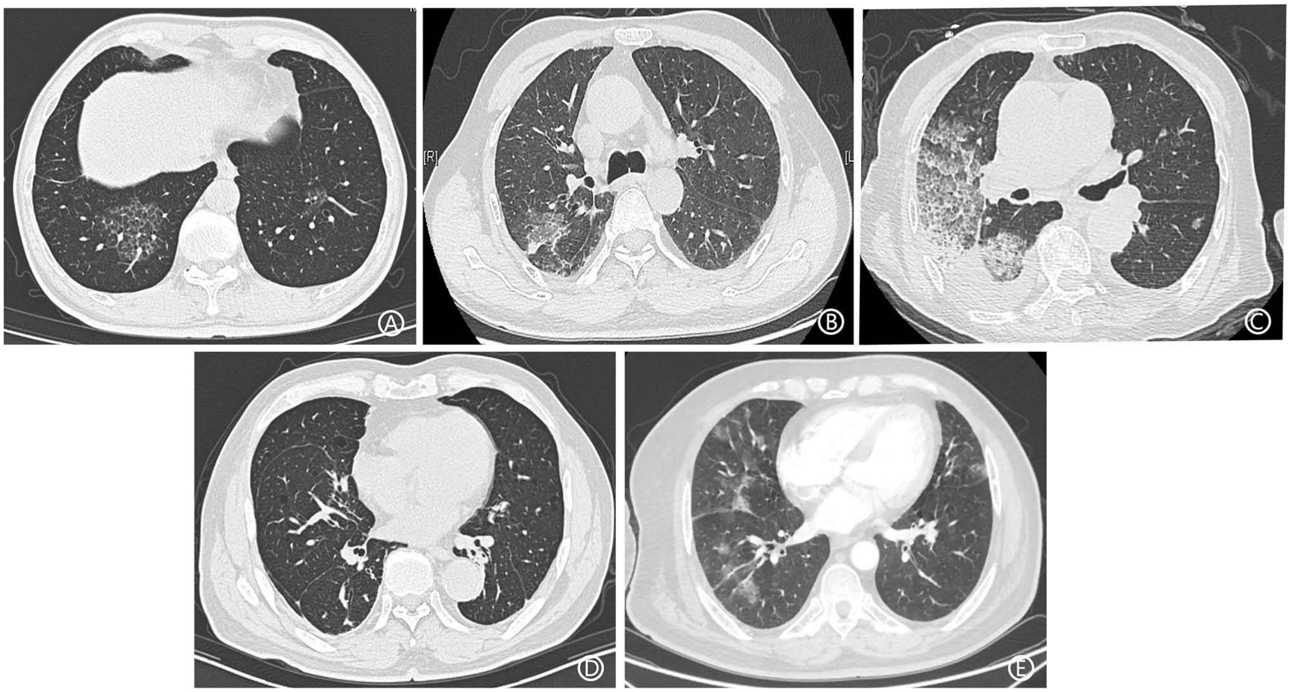

Figure 1 Chest CT images of the five patients.

Note: (**A**) Patient 1 - Bilateral ground-glass opacities, with bronchial dilatation in the right lower lobe. (**B**) Patient 2 - Patchy and linear high-density lesions in the right upper lobe, with localized bronchiectasis. (**C**) Patient 3 - Multiple nodular, patchy, and lobar ground-glass opacities, high-density lesions in both lungs, and a right-sided pleural effusion. (**D**) Patient 4 - Patchy consolidation in the right middle lobe. (**E**) Patient 5 - Multiple ground–glass opacities, patchy blurred areas, and linear opacities in both lungs.

methotrexate weekly, and 20 mg of tripterygium glycosides three times a day. His chest CT image is shown in Figure 1B. Upon admission, the patient was treated with moxifloxacin and later with the compound sulfamethoxazole on the basis of the BALF mNGS results. The patient experienced significant improvement in symptoms and inflammatory markers and was discharged from the hospital.

Patient 3 was admitted because of cough, sputum and chest pain for 2 weeks and haemoptysis for 1 week. She had a medical history of thyroid nodules, hypertension, coronary artery disease, and hip replacement. Her chest CT image is shown in Figure 1C. Her BALF was haemorrhagic and lung biopsy pathology revealed metastatic thyroid cancer. The patient developed severe fever and haemoptysis during treatment. She received ceftriaxone, moxifloxacin, and imipenem for anti-infection, invasive mechanical ventilation and blood transfusion. Her condition rapidly deteriorated due to acute coronary syndrome and atrial fibrillation with a rapid ventricular rate. The patient ultimately passed away.

Patient 4 was admitted with intermittent cough and sputum for 5 years and pulmonary atelectasis for 2 days. His medical history included hypertension, insomnia, prostatic hyperplasia, anxiety, kidney stones, gallbladder stones and tuberculous pleurisy (cured). His chest CT image is shown in Figure 1D. He received oral levofloxacin as an anti-infection agent and was discharged after his symptoms resolved. Six months later, the patient was followed up in the outpatient clinic, and there was no deterioration.

Patient 5 was admitted due to chest tightness for one month and intermittent fever for five days. His medical history included hypertension, diabetes mellitus, gastroesophageal reflux disease (GERD), osteoporosis, hepatitis, and diffuse large B-cell lymphoma (after 8 cycles of chemotherapy). His chest CT image is shown in Figure 1E. Sputum culture revealed small amounts of *Pseudomonas aeruginosa* and *Candida tropicalis*. BALF mNGS initially detected TW (read 9, relative abundance 56.25%, genomic coverage 0.06%). Despite the initiation of an anti-infective regimen consisting of vancomycin, imipenem, cotrimoxazole, fluconazole, and levofloxacin, the patient's fever persisted. A follow-up BALF mNGS revealed the presence of *Enterococcus faecalis* (read 2,246,494, relative abundance 89.85%, genomic coverage 88.16%) along with TW (as shown in Table 1). The patient also tested positive for novel coronavirus nucleic acid. He was subsequently treated with oral nirmatrelvir/ritonavir, intravenous vancomycin, and inhaled amikacin. This treatment led to a significant reduction in symptoms, and his fever resolved. The patient was eventually discharged. Six months later, a follow-up chest CT revealed that the inflammation had largely resolved.

Materials and Methods

We collected data from 5 patients admitted to a tertiary care hospital in Beijing from November 2014 to July 2023 with TW detected by BALF mNGS. The collected data included demographic information, smoking history, history of suspected exposure, immunosuppression status, clinical symptoms, laboratory tests, chest imaging manifestations, and pathological results.

A systematic review of the PubMed and CNKI (China National Knowledge Infrastructure) databases (1907–November 2024) was conducted using the MeSH terms "*Tropheryma whipplei*" AND "pneumonia". The exclusion criteria were as follows: duplicate records, cases lacking diagnostic confirmation or complete clinical documentation, postmortem studies, and paediatric populations (<18 years).

TW was detected in all patients using one of the following methods: (1) mNGS, nanopore sequencing or fluorescence quantitative polymerase chain reaction (qPCR) of BALF; (2) pathology (PAS staining or electron microscopy), mNGS, or qPCR of lung tissues.

Immunocompromised status was defined as the presence of any of the following conditions: (1) congenital or acquired immunodeficiency disorders; (2) malignant tumours; or (3) long-term use of glucocorticoids or other immunosuppressive medications.

Results

The clinical data of the 5 patients are detailed in Table 1, and their chest CT data are presented in Figure 1.

Our systematic review identified 41 articles reporting 55 cases of TW-associated pneumonia in China. The cohort comprised 38 males (69.1%) and 17 females (30.9%), aged 21–85 years old. All the cases were domestically acquired,

Table 1 Clinical Data of the Five Patients

Clinical Item	Case 1	Case 2	Case 3	Case 4	Case 5
Admission time	2021	2021	2021	2022	2023
Gender	Male	Male	Female	Male	Male
Age group (Years)	60-70	70-80	80-90	60-70	60-70
Exposure history	None	None	None	None	None
Smoking history	Yes	None	None	None	None
Immunosuppressive factors	None	Immunosuppressive drugs	Cancer	None	Cancer
Symptoms	None	Cough, shortness of breath, joint pains	Cough, expectoration, haemoptysis	Cough, expectoration, haemoptysis	Fever, chest tightness
Blood laboratory tests					
WBC (10^9/L)	5.74	9.23	9.24	4.94	5.05
HGB (g/L)	141	137	85	133	101
PLT (10^9/L)	218	254	172	131	172
NEUT% (%)	54.5	78.9	77.1	65.8	67
LY% (%)	36.7	13.1	14.1	26.8	25
CRP (mg/L)	<0.5	21.87	30.88	5.1	90.03
ESR (mm/h)	2	14	38	10	124
PCT (ng/mL)	<0.020	0.025	0.16	0.0332	0.0926
ALT (U/L)	7.8	17.7	17.2	18.2	49.8
AST (U/L)	13.3	24.5	17.1	20.9	27.3
LDH (U/L)	142	256	248	134	241
Scr (umol/L)	73.6	72.5	70	99	90
Arterial blood gas					
PaO_2 (mmHG)	Not found	64.2	69.4	82	84.7
$PaCO_2$ (mmHG)	Not found	37.2	35.2	36	32.4
Lac (mmol/L)	Not found	1.9	2.3	1	2.5
IGRA	Negative	Negative	Negative	Negative	Positive
GM test	Not found	Negative	Negative	Not found	Negative
G test	Positive	Negative	Negative	Negative	Negative
BALF test					
Percentages of macrophages	85%	80%	90%	81%	90%
Percentages of neutrophils	0	5%	8%	19%	10%
Bacterial culture	Negative	Negative	Negative	*Pseudomonas aeruginosa*	Negative
Fungal culture	Negative	Negative	Negative	Negative	Negative
Acid-fast staining	Negative	Negative	Negative	Negative	Negative
TB-DNA	Negative	Negative	Negative	Negative	Negative
mNGS					
TW reads	470	4	13118	5163	9
TW relative abundance	100%	Not found	66.24%	94.80%	56.25%
TW genomic coverage	5.47%	0.02%	74.80%	27.78%	0.06%
Other pathogens	None	*Staphylococcus aureus,* *Pseudomonas aeruginosa,* *Pneumocystis jirovecii*	Human herpesvirus-4	*Pseudomonas aeruginosa*	None

Abbreviations: WBC, white blood cell; HGB, haemoglobin; PLT, platelet; Neut, neutrophil; LY, lymphocyte; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; Scr, serum creatinine; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; Lac, lactate; IGRA, interferon–gamma release assay; GM test, Galactomannan test; G test, 1,3-beta-D-glucan measurement; BALF, bronchoalveolar lavage fluid; TB-DNA, tuberculosis deoxyribonucleic acid; mNGS, metagenomics next generation sequencing; TW, *Tropheryma whipplei.*

with the geographic distribution illustrated in Figure 2. Three patients (5.5%) reported alcohol abuse prior to symptom onset. Sixteen (29.1%) patients were immunocompromised. Thirty-two patients (58.2%) had comorbidities (Table 2).

Among the 55 patients analysed, only one patient (1.8%) was asymptomatic, with pulmonary nodules incidentally identified during a postoperative follow-up for thyroid cancer. The remaining 54 patients (98.2%) presented with various symptoms:

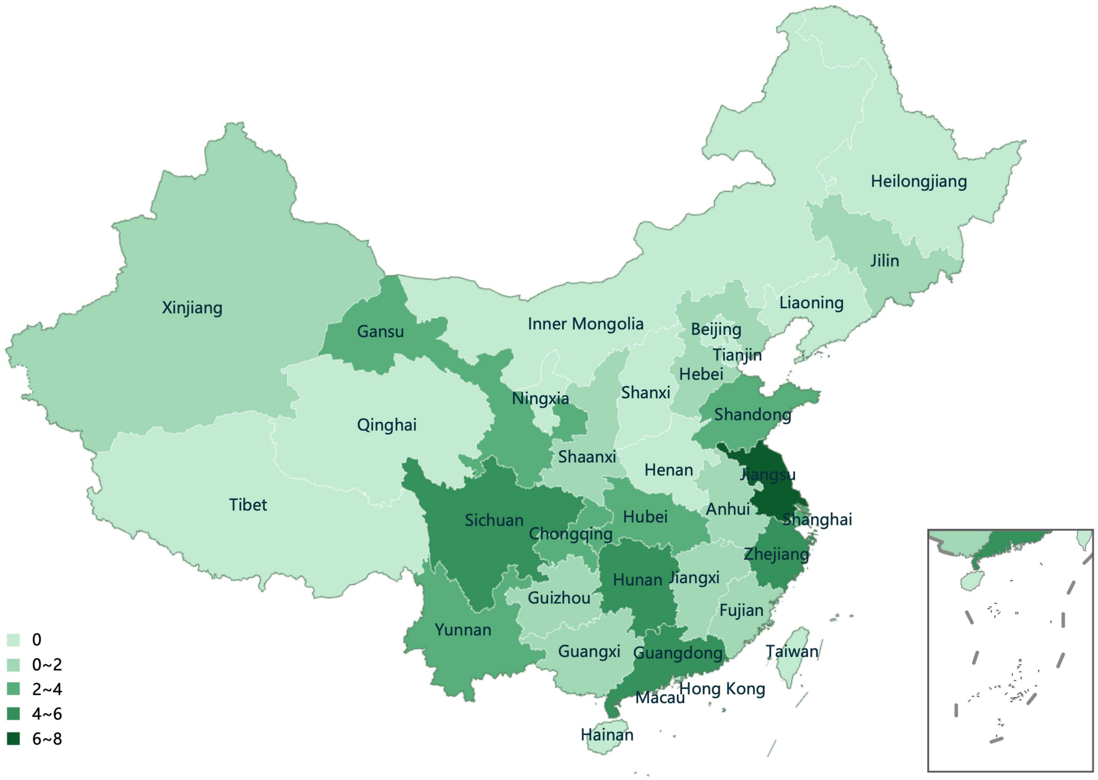

Figure 2 Geographical distribution of *Tropheryma whipplei* pneumonia cases in China.
Note: The figure displays the number of cases per region. *Tropheryma whipplei* pneumonia cases were clustered mainly in southern provinces.

respiratory symptoms (94.5%, n=52), gastrointestinal involvement (27.3%, n=15), arthralgia (10.9%, n=6), systemic symptoms (49.1%, n=27), and other manifestations (16.4%, n=9). The complete clinical characteristics are detailed in Table 2.

Fifteen (27.3%) patients developed severe pneumonia, 8 (14.5%) of whom were coinfected with other pathogens, including *Legionella pneumophila, Mycobacterium tuberculosis, Acinetobacter baumannii, Candida tropicalis, Candida glabrata, Streptococcus pneumoniae, Pneumocystis carinii, Chlamydophila psittaci*, human metapneumovirus, and influenza A virus. Thirteen (23.6%) patients underwent intubation and mechanical ventilation.

Table 2 Features of 55 Patients with *Tropheryma Whipplei* Detected in Lower Respiratory Tract Samples in the Previous Literature in China

Feature (N = 55)	**N (%)**
Underlying disease	
Hypertension	8(14.5)
Diabetes mellitus	8(14.5)
Operation history	7(12.7)
Cancer	6(10.9)
Heart disease	5(9.1)
Chronic liver disease	4(7.3)
Chronic kidney disease	3(5.5)
Connective tissue disease	3(5.5)
AIDS	2(3.6)
Organ transplants	2(3.6)

(*Continued*)

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Table 2 (Continued).

Feature (N = 55)	**N (%)**
Clinical manifestations	
Respiratory symptoms	
Cough	41(74.5)
Shortness of breath	34(61.8)
Expectoration	25(45.5)
Chest/Back pain	12(21.8)
Haemoptysis	4(7.3)
Digestive symptoms	
Diarrhoea	9(16.4)
Vomiting	4(7.3)
Anorexia	4(7.3)
Stomach ache	2(3.6)
Haematochezia	1(1.8)
Joint symptoms	
Joint swelling and pain	6(10.9)
Systemic symptoms	
Fever	22(40.0)
Weight loss	5(9.1)
Fatigue	5(9.1)
Sweating	1(1.8)
Other symptoms	
Headache, dizziness, etc.	9(16.4)
Asymptomatic	1(1.8)
Radiographic findings of lungs	
Patchy infiltrates/Consolidation	36(65.5)
Ground glass opacity/Grid shadow	24(43.6)
Nodule/Mass	19(34.5)
Pleural effusion	9(16.4)
Cavitation	9(16.4)
Enlarged hilar or mediastinal lymph nodes	4(7.3)
Bronchiectasis	3(5.5)
Diagnostic basis	
TW read and relative abundance	35(63.6)
Empirical treatment effect	10(18.2)
Lung biopsy histopathology	8(14.5)
qPCR confirmation of BALF	1(1.8)
qPCR confirmation of lung tissue	1(1.8)

Abbreviations: AIDS, acquired immune deficiency syndrome; TW, *Tropheryma whipplei*; qPCR, quantitative polymerase chain reaction; BALF, bronchoalveolar lavage fluid.

In our study, patchy infiltrates or consolidations (65.5%) represented the most frequent intrapulmonary lesions, followed by ground-glass opacities or reticular shadows (43.6%) and nodules or masses (34.5%). Chest CT revealed lung abscesses in 3 patients (5.4%). Additional radiographic findings are detailed in Table 2.

TW was detected directly by NGS of lung tissue in one patient and by NGS of BALF in the other 54 (98.2%) patients. Fifty-two (94.5%) patients had BALF samples tested using NGS, and the other 2 patient samples were tested using third-generation sequencing technology. After TW was detected, further confirmation of TW infection was performed through many different methods, including the assessment of TW reads and relative abundance, the assessment of the effects of empirical treatment, lung biopsy histopathology, and qPCR confirmation (shown in Table 2). TW was the only pathogen detected in the BALF of 12 (21.8%) patients, and it was the pathogen with the highest read or relative abundance in the

BALF of 16 (29.1%) patients, with relatively high reads in the BALF of 7 (12.7%) patients. Among all the patients, 4 (7.3%) were diagnosed through multidisciplinary team (MDT) discussion.

In our study, 50 (90.9%) patients accepted medical therapy. Among these patients, 49 patients survived and were discharged in good condition, and 1 patient died of gastric cancer. Five (9.1%) patients refused antibiotic treatment. Among these patients, 2 patients experienced partial improvement of respiratory symptoms, 1 patient experienced no change, 1 patient's condition deteriorated, and 1 patient died of acute myocardial infarction.

Discussion

TW naturally inhabits the environment, including soil and aquatic sediments (both freshwater and marine). This ecological distribution explains its detection in 37–66% of influxes to sewage plants.[4] TW-induced chronic infections include neurological infections, endocarditis, arthritis, osteoarticular infections, uveitis, and isolated adenopathies.[9] Acute TW infections include bacteraemia, acute gastroenteritis and pneumonia.[9] Morris et al conducted a comparative analysis of the upper and lower respiratory tract microbiomes in healthy, HIV-uninfected adults. Their study revealed the presence of TW in BALF from 26% of participants, whereas it was absent in oral wash samples.[10] These findings suggest that TW can inhabit the lower respiratory tract and that TW may represent a component of the indigenous lung microecological community. To date, the exact function of the lung microbiome in establishing and maintaining respiratory health is unclear, although it likely contributes substantially to mucosal immune homeostasis.[11] While the detection of TW DNA in respiratory samples may reflect commensal colonization, its pathogenic potential is likely to emerge in immunocompromised individuals or in the presence of mucosal barrier disruption—as illustrated by Cases 1 and 2 in this report. Therefore, the identification of TW in lower respiratory tract samples warrants cautious clinical interpretation.

According to our study, 94.5% of patients with TW infection developed respiratory symptoms, particularly cough, sputum production, chest tightness and even dyspnoea. In some cases, rapid disease progression led to respiratory failure, requiring endotracheal intubation and ventilatory support. Common chest CT findings in patients with TW pneumonia included patchy infiltrates, consolidation, ground-glass opacity, grid shadows, and nodules. Acute TW infection or coinfection with other pathogens can also lead to the development of lung abscesses.[12,13] When TW sequences are detected in lower respiratory tract samples, in addition to evaluating the reads, relative abundance, and genomic coverage of TW, TW infection can also be confirmed through MDT discussion or lung histopathology. Empirical antibiotic therapy targeting TW may be considered when the patient's condition deteriorates. TW infection can be confirmed on the basis of the clinical course and treatment response.

The presence of TW in the lower respiratory tract of these patients may be attributed to exposure to contaminated environments or the possibility of misinhalation. There are reports of healthy individuals carrying TW in their saliva. In a random sample of 40 healthy individuals, 35% showed evidence of TW DNA in their saliva.[14] In France, the prevalence of TW in saliva was 2.2% (5/231 samples included) among sewer workers[15] and 3.7% among the homeless (8/238 samples included).[16] These TWs can enter the lower respiratory tract in the event of misinhalation, potentially contributing to aspiration pneumonia, either alone or in conjunction with pathogens from the oral flora. In one study, PCR results of BALF were positive for TW DNA, collected from 6 patients in intensive care unit.[17] Four patients presented with typical oral microbiota. Among these patients, two had aspiration pneumonia, whereas the remaining two had ventilator-associated pneumonia.[17] In one of the reported cases, TW was the unique pathogen identified.[17] A case–control study, which included patients with TW detected in BALF and control subjects, revealed a significant association between TW and aspiration pneumonia (20.5% [18/88] vs 6.8% [6/88] in controls; $*p*<0.05$), and TW was identified as the sole pathogen in 9 patients.[18] Second, gastric juice reflux and aspiration may also contribute to the presence of TW in the lower respiratory tract. Ehrbar's study revealed a high rate (11.4%) of positive TW–PCR results in gastric juice samples from patients who did not show clinical signs or other evidence of WD.[19] In addition, TW can reach the lower respiratory tract when the patient is experiencing bacteraemia. A Senegalese study identified TW DNA in blood samples from 36 febrile patients presenting with pulmonary symptoms in a rural area.[9] Another study conducted in Gabon (2014–2015) reported the presence of TW DNA in 0.2% of blood samples from 410 febrile patients.[20] A related case was reported in China by Wu Yu. One patient was admitted to the hospital with abdominal pain and diarrhoea. This patient developed septic shock during treatment, and mNGS of his BALF suggested TW. The researchers suggested that the patient had gastrointestinal infection, the barrier function of his intestinal mucosa was reduced, and TW had invaded the blood via the intestinal mucosa, which caused lung infection.[21] In this study, patient 3 had a high level of oral bacteria in the BALF, and the TW might have originated from the oral cavity. Patient 5 had a history of GERD, and the TW might have originated from the gastrointestinal tract. These hypotheses require further investigation. For the remaining three patients, the source of the TW infection could not be determined.

Classic WD is characterized by extensive intestinal mucosal infiltration with TW-infected macrophages.[22] However, these macrophages appear unable to kill TW successfully. This partly stems from pathogen-mediated CD11b down-regulation in macrophages, causing suboptimal antigen processing by both macrophages and dendritic cells. Consequently, a distinct immunological environment emerges, characterized by the increased expression of interleukin-10 (IL-10), CC chemokine ligand 18 (CCL-18), and transforming growth factor-β (TGF-β), coupled with diminished IL-12 and interferon-γ (IFN-γ).[22] Within this environment, TW-infected macrophages display impaired phagolysosomal maturation and reduced thioredoxin expression, collectively preventing bacterial elimination and effective antigen presentation.[23] These immune evasion strategies facilitate TW replication within macrophages and subsequent systemic dissemination.[22] Histopathological examination of the lung tissue of these patients revealed interstitial pneumonia with lymphocyte and plasmacyte infiltration in the alveolar septum and focal proliferation of fibrous tissue.[24] Numerous foamy macrophages have been identified within alveolar air spaces, and these macrophages have been shown to be positive for CD68 by immunohistochemistry.[24] A substantial number of PAS-positive bacilli were found inside and outside the foamy macrophages. Periodic acid silver methenamine (PASM) of lung tissue sections revealed similar findings.[25] The thoracoscopic biopsy of a patient from abroad revealed acute parenchymal damage with endoalveolar fibrin "balls", some nonspecific foamy macrophages and type 2 pneumocyte hyperplasia; no hyaline membranes were present. The pleural biopsy revealed nonspecific pleuritis. The histological features are consistent with acute fibrinous and organizing pneumonia (AFOP) and nonspecific pleuritis.[26] Importantly, enteroscopy in patients with TW-related pneumonia might yield negative results.[27,28] The specific pathological and molecular mechanisms by which TW induces pneumonia require further study.

There are several limitations in this study. First, coinfection with other pathogens may play a significant role in the progression of pneumonia, potentially confounding chest CT manifestations. Second, some patients were diagnosed on the basis of treatment outcomes or MDT discussions, which means that relevant pathological data were lacking. Many patients with gastrointestinal symptoms did not undergo gastroenteroscopy or salivary testing to further define the source of TW in the lower respiratory tract, primarily due to a lack of awareness of WD among physicians. Additionally, these patients need further follow-up so that we can understand the long-term development and prognosis of WD.

Conclusion

In conclusion, TW can enter the lower respiratory tract through multiple routes and colonize it. When TW sequences are detected in lower respiratory tract samples, it is important to consider not only the read and relative abundance but also histopathological findings such as interstitial pneumonia and the presence of PAS- or PASM-positive bacilli within foamy macrophages, as they can aid in diagnosing TW infection. MDT discussions and empirical antibiotic therapy targeting TW are viable options when a patient's condition deteriorates. Microbiological testing of saliva, gastric fluid, blood, and faeces may help clarify the source of TW if necessary.

Ethical Statement and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of Beijing Tsinghua Changgung Hospital. The requirement for written informed consent was waived by the committee for the following reasons: the study involved the retrospective analysis of anonymized clinical data with no impact on patient care, and the research posed minimal risk to these patients' privacy and welfare.

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Author Contributions

All authors made a significant contribution to the work reported, whether 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; 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 report no conflicts of interest in this work.

References

1. Boumaza A, Ben Azzouz E, Arrindell J, Lepidi H, Mezouar S, Desnues B. Whipple's disease and Tropheryma whipplei infections: from bench to bedside. *Lancet Infect Dis*. 2022;22(10):e280–e291. doi:10.1016/S1473-3099(22)00128-1
2. Biagi F, Balduzzi D, Delvino P, Schiepatti A, Klersy C, Corazza GR. Prevalence of Whipple's disease in north-western Italy. *Eur J Clin Microbiol Infect Dis*. 2015;34(7):1347–1348. doi:10.1007/s10096-015-2357-2
3. Elchert JA, Mansoor E, Abou-Saleh M, Cooper GS. Epidemiology of Whipple's disease in the USA Between 2012 and 2017: a Population-Based National Study. *Dig Dis Sci*. 2019;64(5):1305–1311. doi:10.1007/s10620-018-5393-9
4. Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. *Lancet Infect Dis*. 2016;16(3):e13–e22. doi:10.1016/S1473-3099(15)00537-X
5. Renesto P, Crapoulet N, Ogata H, et al. Genome-based design of a cell-free culture medium for Tropheryma whipplei. *Lancet*. 2003;362(9382):447–449. doi:10.1016/S0140-6736(03)14071-8
6. Diao Z, Han D, Zhang R, Li J. Metagenomics next-generation sequencing tests take the stage in the diagnosis of lower respiratory tract infections. *J Adv Res*. 2021;38:201–212. doi:10.1016/j.jare.2021.09.012
7. Wang J, Han Y, Feng J. Metagenomic next-generation sequencing for mixed pulmonary infection diagnosis. *BMC Pulm Med*. 2019;19:252. doi:10.1186/s12890-019-1022-4
8. Li H, Durbin R. Fast and accurate short read alignment with Burrows–Wheeler transform. *Bioinformatics*. 2009;25(14):1754–1760. doi:10.1093/bioinformatics/btp324
9. Lagier JC, Fenollar F, Raoult D. Acute infections caused by *Tropheryma whipplei*. *Future Microbiol*. 2017;12(3):247–254. doi:10.2217/fmb-2017-0178
10. Morris A, Beck JM, Schloss PD, et al. Comparison of the Respiratory Microbiome in Healthy Nonsmokers and Smokers. *Am J Respir Crit Care Med*. 2013;187(10):1067–1075. doi:10.1164/rccm.201210-1913OC
11. Man WH, de Steenhuijsen Piters WAA, Bogaert D. The microbiota of the respiratory tract: gatekeeper to respiratory health. *Nat Rev Microbiol*. 2017;15(5):259–270. doi:10.1038/nrmicro.2017.14
12. Zhou H, Zhang J. Short-term Amoxicillin Clavulanate in the treatment of pulmonary abscess caused by Tropheryma whipplei infection diagnosed by targeted next-generation sequencing: a case report and literature review. *Infect Drug Resist*. 2024;17:4607–4616. doi:10.2147/IDR.S488740
13. Yue X, Xi X, Zhang M, Bian J, Chen Y. Pulmonary Mucinous Adenocarcinoma combined with bronchial squamous cell papilloma and infection with Tropheryma Whipplei: a Case Report. *Chin J Lung Cancer*. 2023;26(7):553–558. doi:10.3779/j.issn.1009-3419.2023.106.13
14. Street S, Donoghue HD, Neild GH. Tropheryma whippelii DNA in saliva of healthy people. *Lancet*. 1999;354(9185):1178–1179. doi:10.1016/S0140-6736(99)03065-2
15. Fenollar F, Trani M, Davoust B, et al. Prevalence of asymptomatic Tropheryma whipplei carriage among humans and nonhuman primates. *J Infect Dis*. 2008;197(6):880–887. doi:10.1086/528693
16. Keita AK, Brouqui P, Badiaga S, et al. Tropheryma whipplei prevalence strongly suggests human transmission in homeless shelters. *Int J Infect Dis*. 2013;17(1):e67–e68. doi:10.1016/j.ijid.2012.05.1033
17. Bousbia S, Papazian L, Auffray JP, et al. Tropheryma whipplei in patients with pneumonia. *Emerg Infect Dis*. 2010;16(2):258. doi:10.3201/eid1602.090610
18. Lagier JC, Papazian L, Fenollar F, et al. Tropheryma whipplei DNA in bronchoalveolar lavage samples: a case control study. *Clin Microbiol Infect off Publ Eur Soc Clin Microbiol Infect Dis*. 2016;22(10):875–879. doi:10.1016/j.cmi.2016.07.010
19. Ehrbar HU, Bauerfeind P, Dutly F, Koelz HR, Altwegg M. PCR-positive tests for Tropheryma whippelii in patients without Whipple's disease. *Lancet Lond Engl*. 1999;353(9171):2214. doi:10.1016/S0140-6736(99)01776-6
20. Mourembou G, Nzondo SM, Ndjoyi-Mbiguino A, et al. Co-circulation of plasmodium and bacterial DNAs in blood of febrile and afebrile children from urban and rural areas in Gabon. *Am J Trop Med Hyg*. 2016;95(1):123–132. doi:10.4269/ajtmh.15-0751
21. Yu W, Qiang W, Hong W, et al. Successful treatment of a patient with septic shock and cardiac and respiratory arrest caused by Tropheryma whipplei. *Chin J Emerg Med*. 2021;30(09):1138–1141. doi:10.3760/cma.j.issn.1671-0282.2021.09.018
22. Dolmans RAV, Boel CHE, Lacle MM, Kusters JG. Clinical Manifestations, Treatment, and Diagnosis of Tropheryma whipplei Infections. *Clin Microbiol Rev*. 2017;30(2):529–555. doi:10.1128/CMR.00033-16
23. Moos V, Schmidt C, Geelhaar A, et al. Impaired immune functions of monocytes and macrophages in whipple's disease. *Gastroenterology*. 2010;138(1):210–220. doi:10.1053/j.gastro.2009.07.066
24. Ruan W, Xu J, Yang F, Wu X, Ying K. Tropheryma whipplei infection in the lung of a patient with long COVID: a case report. *BMC Infect Dis*. 2024;24:292. doi:10.1186/s12879-024-09183-6
25. Zhou Y, Yang N, Ruan S, Wu S, Yu D, Jin J. Lung cancer patient with Tropheryma whipplei and Nocardia co-infection. *Ultrastruct Pathol*. 2023;47(5):451–459.
26. Canessa PA, Pratticò L, Sivori M, et al. Acute fibrinous and organising pneumonia in Whipple's disease. *Monaldi Arch Chest Dis Arch Monaldi Mal Torace*. 2008;69(4):186–188. doi:10.4081/monaldi.2008.382

27. Li H, Wu J, Mai X, et al. Novel patterns in high-resolution computed tomography in Whipple Pneumonia. *Emerg Infect Dis*. 2024;30(5):1042. doi:10.3201/eid3005.231130
28. Shen Y, Cui SS, Teng XB, Han MF. Acute pneumonia due to Tropheryma whipplei diagnosed by metagenomic next-generation sequencing and pathology: a case report. *Heliyon*. 2024;10(4):e26747. doi:10.1016/j.heliyon.2024.e26747