

Short-Term Amoxicillin Clavulanate in the Treatment of Pulmonary Abscess Caused by *Tropheryma whippelii* Infection Diagnosed by Targeted Next-Generation Sequencing: A Case Report and Literature Review

Hongyuan Zhou^{*}, Jian Zhang^{*}

Department of Respiratory and Critical Care Medicine, Yuyao People's Hospital, Ningbo City, Zhejiang Province, People's Republic of China

^{*}These authors contributed equally to this work

Correspondence: Jian Zhang, Department of Respiratory and Critical Care Medicine, Yuyao People's Hospital, No. 800 Chengdong Road, Fengshan District, Ningbo City, Zhejiang Province, People's Republic of China, Tel +8615068756296, Email 514041632@qq.com

Background: *Tropheryma whippelii* (*T. whippelii*) is a rod-shaped, Gram-positive, acid-fast bacterium. Classical Whipple's disease, a rare chronic infectious condition affecting multiple systems, is traditionally attributed to *T. whippelii* infection. The conventional treatment regimen consists of a one-year course of oral doxycycline (100 mg twice daily) and hydroxychloroquine (600 mg daily), followed by lifelong doxycycline maintenance therapy. However, the literature lacks discussion on short-term antimicrobial treatment for acute *T. whippelii* infections, such as pulmonary abscesses caused by this pathogen.

Presentation: This case report describes a 57-year-old male presenting with a pulmonary abscess. The patient underwent bronchoscopic alveolar lavage and pus cavity irrigation. The collected sample was subjected to pathogen targeted next-generation sequencing (tNGS) analysis. The tNGS results indicated that *T. whippelii* was the primary etiological agent responsible for the pulmonary abscess. Treatment with 6 weeks amoxicillin clavulanate led to a favorable clinical outcomes.

Conclusion: Existing case reports typically employ treatment protocols for classic Whipple's disease, such as oral doxycycline combined with hydroxychloroquine or trimethoprim/sulfamethoxazole for a one-year duration. The use of amoxicillin/clavulanic acid for short-term antimicrobial treatment of *T. whippelii*-induced pulmonary abscesses achieved favorable clinical outcomes. This case study explores the feasibility of short-term antimicrobial therapy for an acute *T. whippelii* infection.

Keywords: *Tropheryma whippelii*, pulmonary abscess, tNGS, bronchoscopic lavage

Background

T. whippelii is bacillus belonging to the Actinobacteria phylum, Actinomycetes class, Micrococcales order, and Habitataceae family.¹⁻³ Classical Whipple's disease, a rare chronic infectious condition affecting multiple systems, is caused by *T. whippelii*. The disease exhibits a higher incidence rate among Caucasian males, while being uncommon in individuals of Asian or African descent.⁴ The widespread application of next-generation sequencing technology has led to an increased detection of *T. whippelii* in respiratory specimens. However, these cases frequently do not present the classic symptoms of Whipple's disease, such as arthralgia, weight loss, diarrhea, and abdominal pain.⁵⁻⁸ Typically, case reports employ the standard treatment regimen for Whipple's disease, which involves initial intravenous administration of antibiotics effective against *T. whippelii* (such as ceftriaxone, amoxicillin, penicillin, and meropenem), followed by a year-long oral therapy with trimethoprim/sulfamethoxazole or doxycycline combined with hydroxychloroquine. However, the literature currently lacks documentation on the use of short-term anti-infective treatment of pulmonary abscesses primarily caused by *T. whippelii*. This article presents a case where *T. whippelii* was identified as the primary pathogen in a pulmonary abscess following glucocorticoid pulse

therapy. The subsequent literature review discusses the characteristics of this pathogen, its clinical manifestations, and treatment *strategies*.

Case Report

Medical History

A three-day history of coughing and blood-tinged sputum led to the hospitalization of a 57-year-old male with untreated type 2 diabetes. Two months prior to symptom onset, the patient was diagnosed with optic neuritis, presenting as blurred vision. The patient received short-term glucocorticoid pulse therapy, followed by oral prednisone maintenance therapy. At the onset of symptoms, the patient was taking 20 mg of prednisone daily. The patient had no other underlying medical conditions. He reported a 25-year history of alcohol consumption, consuming 50 milliliters of spirits daily, but had never smoked.

The patient's cough and hemoptysis began two months after initiating glucocorticoid maintenance therapy. The patient denied experiencing dyspnea, fever, rhinorrhea, or chest pain. The patient reported no history of night sweats. The patient did not experience abdominal pain, joint pain, or diarrhea, and no weight loss was observed. Upon seeking medical attention at our hospital, a chest CT scan revealed a cystic lesion in the left lung with a fluid level and minimal consolidation surrounding the abscess cavity, suggestive of abscess formation. Consequently, a diagnosis of pulmonary abscess was established.

Physical Examination

Upon examination, the patient's condition was largely unremarkable. Several decayed teeth were observed without accompanying signs of inflammation such as redness, swelling, or purulent discharge. No palpable enlargement of superficial lymph nodes was detected. The skin and mucous membranes exhibited no signs of jaundice. Auscultation revealed decreased breath sounds on the left side, while normal breath sounds were noted on the right side. The cardiac borders were within normal limits, without enlargement. The abdomen was soft and flat, with no palpable liver or spleen below the rib cage. A neurological examination yielded no significant findings.

Investigations

Complete blood count and high-sensitivity C-reactive protein (hs-CRP): The complete blood count revealed a white blood cell count of $14.6 \times 10^9/L$, with neutrophils at $10.2 \times 10^9/L$ and lymphocytes at $3.1 \times 10^9/L$. hs-CRP was elevated at 79.4 mg/L. Procalcitonin levels were below 0.04 ng/mL. Glycosylated hemoglobin (HbA1c) was measured at 8.1%. Interleukin-6 levels were elevated at 20.95 pg/mL, and ferroprotein levels were significantly increased at 1115.81 ng/mL. Sputum cultures, both aerobic and anaerobic, conducted over a 5-day period, yielded no bacterial growth. A chest computed tomography (CT) scan (Figure 1) revealed a cystic lesion with fluid levels and localized lung involvement in the left lung.

Treatment and Prognosis

Prior to the initiation of empiric antibiotic therapy, the patient underwent electronic bronchoscopy. The procedure revealed the presence of blood and purulent sputum throughout the left bronchi. The endoscopic aspiration cleared the intratracheal blood and purulent sputum, revealing a distorted and swollen basal trunk of the left lower lobe bronchus. Alveolar lavage was performed in the lateral basal region of the left lower lobe (Figure 2). The lavage procedure involved rinsing the affected bronchus twice with 120 mL of sterile physiological saline. The recollected turbid alveolar lavage fluid, containing purulent secretions, was submitted for tNGS. Following the diagnostic bronchoscopic alveolar lavage, multiple infusions of sterile normal saline were administered through the bronchoscope. After each infusion, thorough aspiration was performed until the aspirated liquid became clear. A total of 360 mL of normal saline was utilized. Subsequently, empirical antibiotic therapy with amoxicillin/clavulanate (5:1) was initiated (1200 mg intravenous drip at 8-hour intervals). An enhanced chest CT examination was conducted on the second day post-bronchoalveolar lavage treatment, as depicted in Figure 3. The Pus tNGS results (Table 1) predominantly identify *T. whipplei* (sequence count: 2362; reference content: 53079 copies/mL). Given that pulmonary abscess is typically considered a mixed infection, the

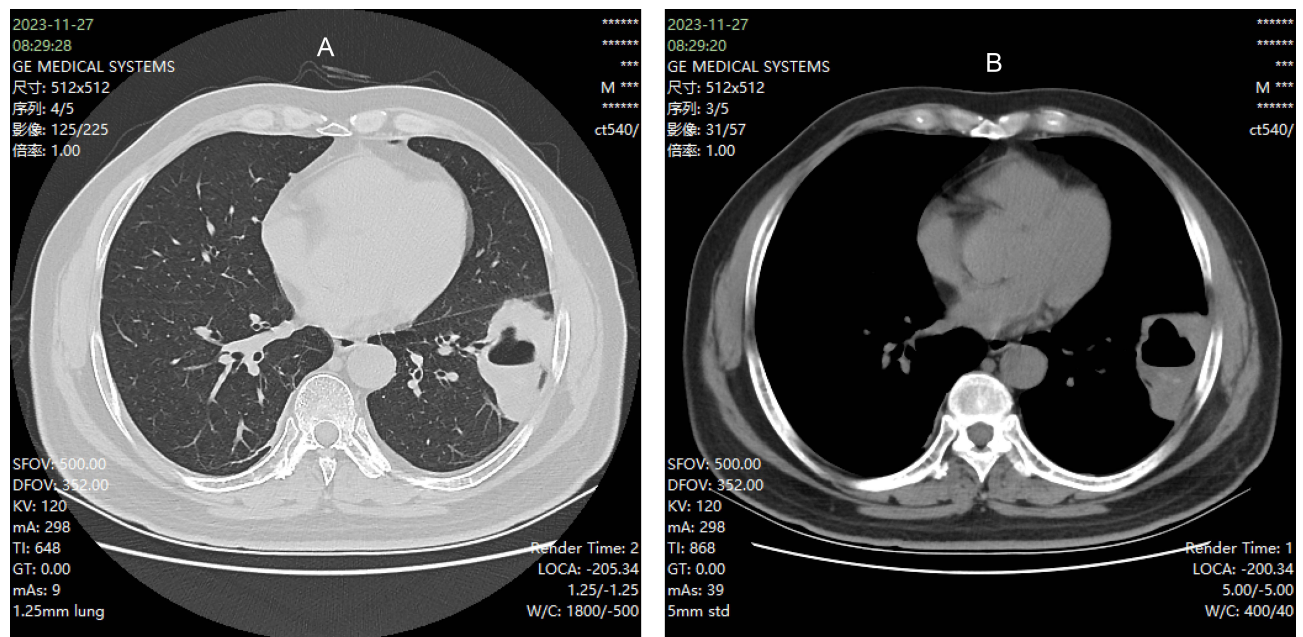


Figure 1 (A and B) Chest CT before treatment.

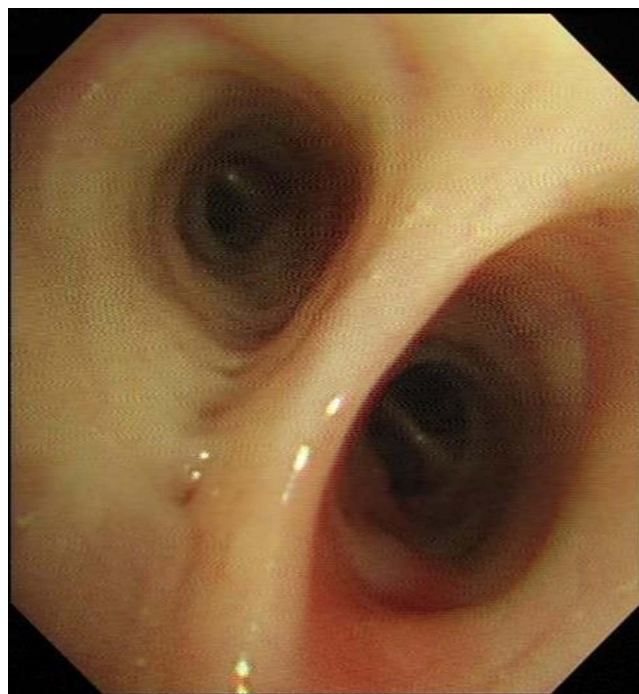


Figure 2 Anterior medial basal segment of left lower lobe.

pathogens listed in [Table 1](#) are primarily regarded as potential causative agents of pulmonary abscess, excluding viruses such as *Human gammaherpesvirus 4*, *Human betaherpesvirus 5*, and *Pneumocystis jirovecii*, which are known to colonize the lower respiratory tract. Despite the patient's prior high-dose glucocorticoid treatment (prednisone > 20 mg/d for over 1 month), the clinical presentation and CT images did not support a diagnosis of pneumocystis

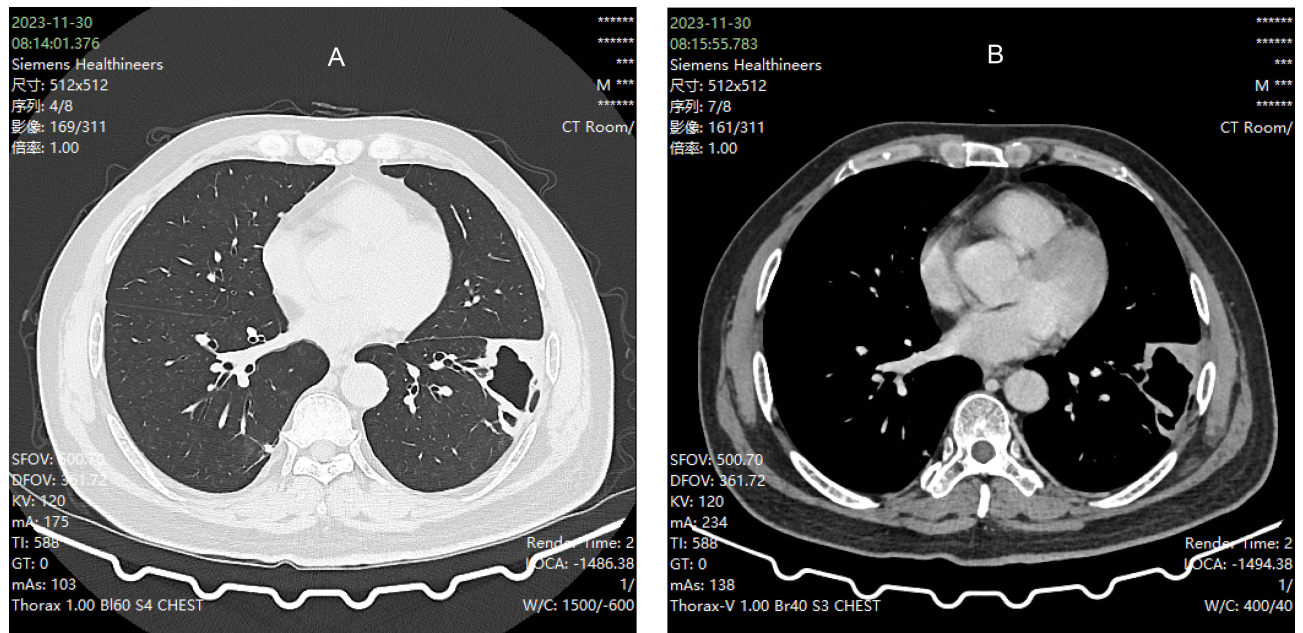


Figure 3 (A and B) Enhanced Chest CT after Electronic Bronchoscopy Treatment.

pneumonia. Consequently, trimethoprim/sulfamethoxazole or echinocandins were not added to the treatment regimen. Following 13 days of intravenous amoxicillin/clavulanic acid treatment, the patient’s infection-related biological markers normalized, and symptoms of cough and hemoptysis resolved. A follow-up chest CT (Figure 4) demonstrated shrinkage of the cavity lesions. Upon discharge, the patient was prescribed oral amoxicillin/clavulanate (914mg 7:1) for 4 weeks. Subsequent outpatient follow-up chest CT (Figure 5) indicated continued improvement of the lesion, leading to the discontinuation of amoxicillin/clavulanate. At approximately 8 weeks post-treatment cessation, a further follow-up chest CT (Figure 6) revealed complete closure of the abscess cavity. The patient’s clinical symptoms, including cough and hemoptysis, have not recurred in the 8 weeks following medication discontinuation.

Table I The Result of tNGS

Genus Name	Name of Pathogen	Reads Accum	Reference content (Copies/mL)
<i>Tropheryma</i>	<i>Tropheryma whipplei</i>	2362	53079
<i>Streptococcus</i>	<i>Streptococcus cristatus</i>	975	21910
<i>Streptococcus</i>	<i>Streptococcus mitis</i>	710	15955
<i>Neisseria</i>	<i>Neisseria subflava</i>	614	13798
<i>Eikenella</i>	<i>Eikenella corrodens</i>	107	2404
<i>Haemophilus</i>	<i>Haemophilus parainfluenzae</i>	101	2270
<i>Actinomyces</i>	<i>Actinomyces graevenitzi</i>	94	2112
<i>Lymphocryptovirus</i>	<i>Human gammaherpesvirus 4</i>	91	2045
<i>Pneumocystis</i>	<i>Pneumocystis jirovecii</i>	13	292
<i>Cytomegalovirus</i>	<i>Human betaherpesvirus 5</i>	9	202

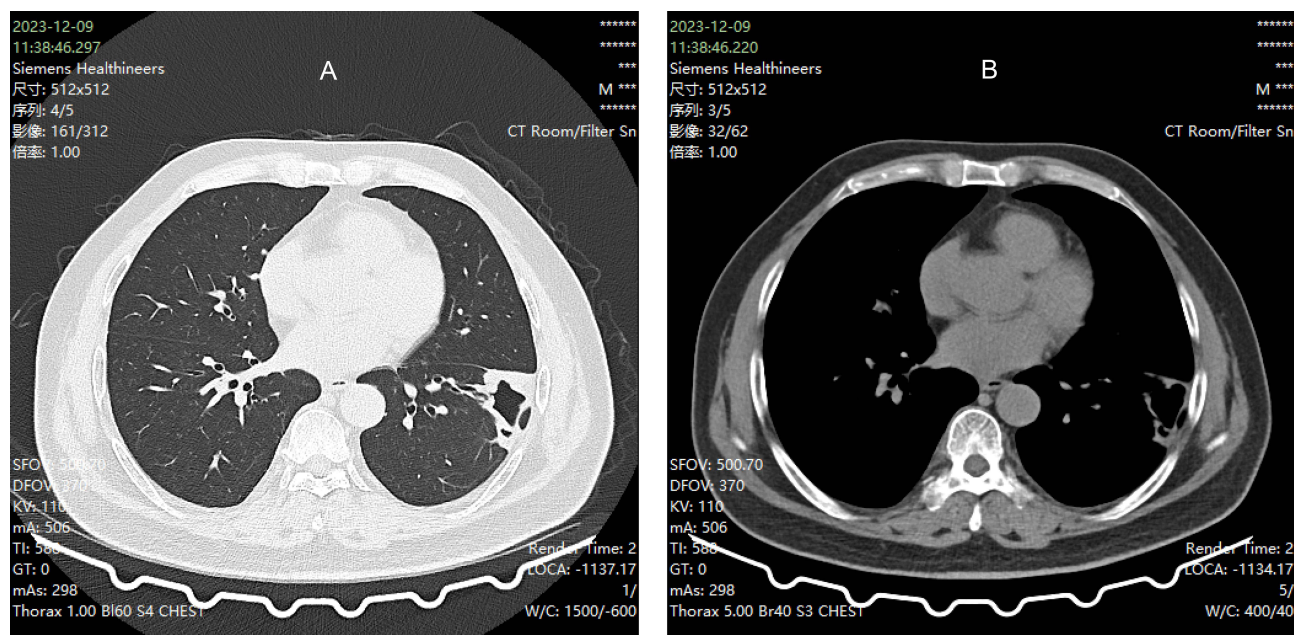


Figure 4 (A and B) Chest CT on discharge.

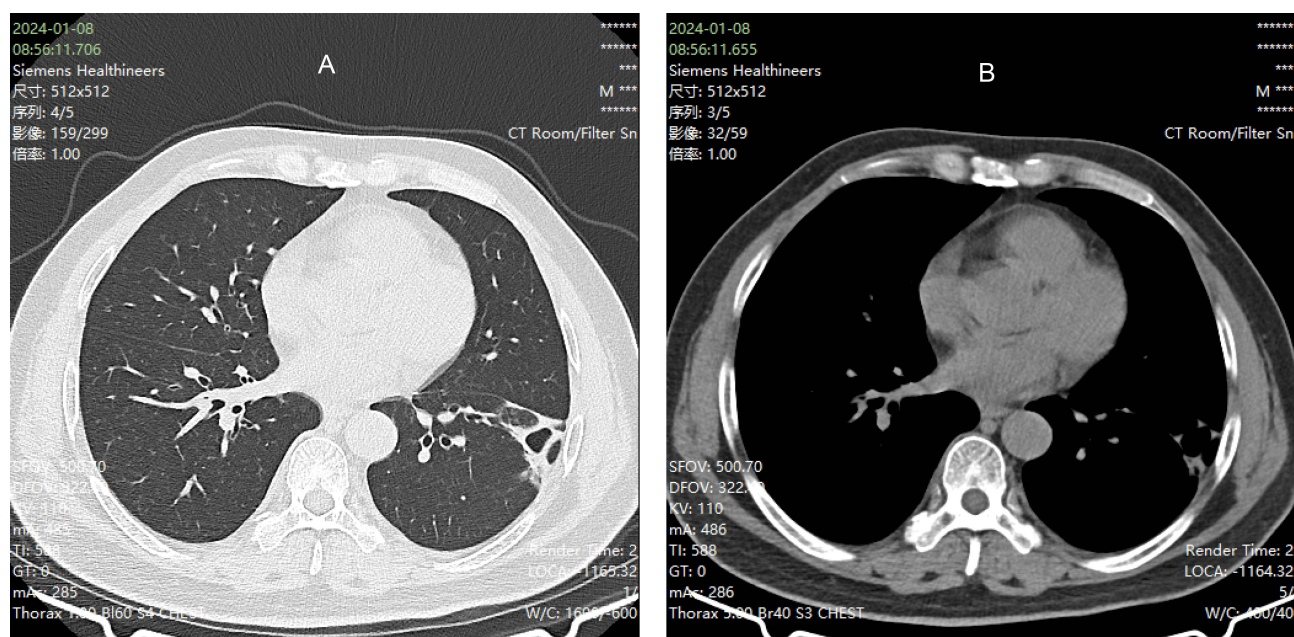


Figure 5 (A and B) Chest CT Scanning at discontinuation of medication.

Discussion

Tropheryma whippelii is characterized as a rod-shaped, Gram-positive, acid-fast bacterium.^{1–3} This microorganism is ubiquitously present in the environment^{9,10} and can colonize human oral cavities and intestines, often being detected in saliva and feces.^{11–13} Classical Whipple's disease, a rare chronic infectious condition, is traditionally associated with *T. whippelii*, despite only a small percentage of carriers becoming symptomatic.¹⁴ The disease exhibits a higher incidence rate among Caucasian males, while being uncommon in individuals of African or Asian descent.⁴ *T. whippelii* infection can manifest systemically, potentially leading to central nervous system involvement, endocarditis, and pneumonia.^{15,16} The bacterium presents significant challenges for in vitro cultivation, requiring the presence of living eukaryotic host

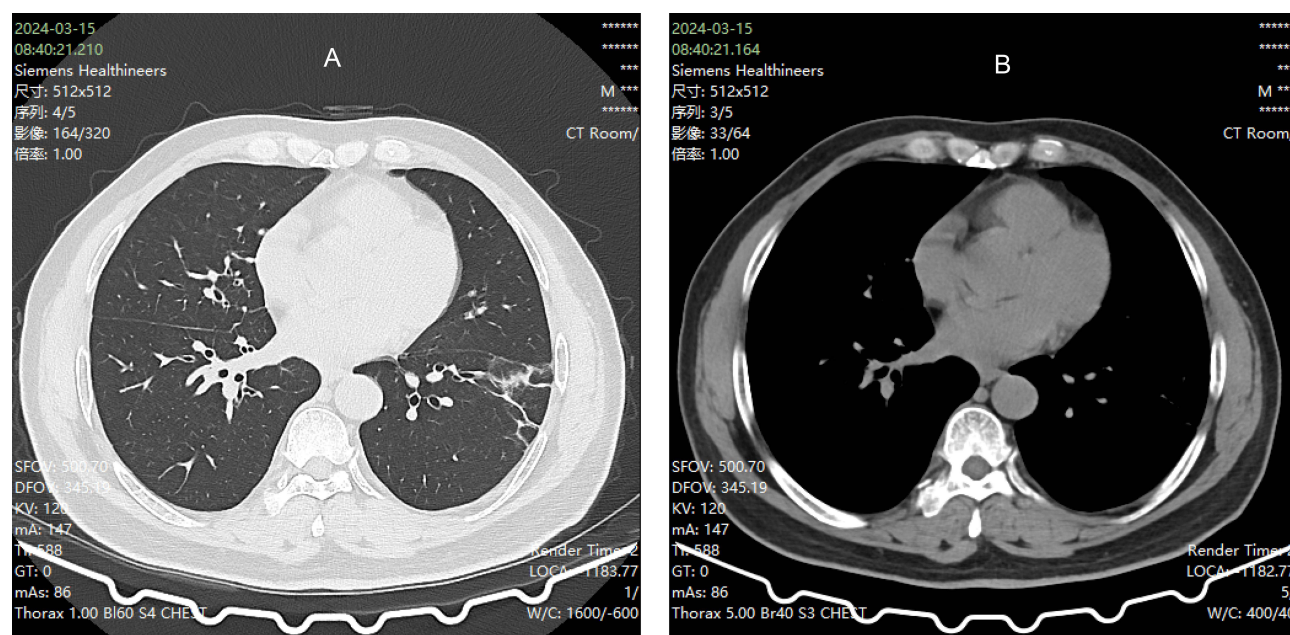


Figure 6 (A and B) Chest CT after discontinuing medication for 8 weeks.

cells.¹⁷ The cultivation process is characterized by prolonged duration, susceptibility to contamination, and low sensitivity.^{18,19} Consequently, diagnosis primarily relies on nucleic acid testing methodologies.^{12,13,20} The advent of next-generation sequencing (NGS) technology has facilitated increased detection of *T. whipplei* in respiratory specimens. A notable study revealed that 70 out of 1725 bronchoalveolar lavage fluid (BALF) samples (4.0%) tested positive for *T. whipplei*, indicating a significant pulmonary prevalence. This finding underscores the importance of considering *T. whipplei* as a potential contributing factor in certain lung diseases, even in immunocompetent patients.^{21,22} Interestingly, these cases often do not present with the classic symptoms of Whipple's disease, such as arthralgia, weight loss, diarrhea, and abdominal pain.^{5–8} *T. whipplei* infection has a variety of clinical manifestations, but studies tend to focus on specific clinical phenotypes, potentially limiting the full understanding of the infection's clinical spectrum. The absence of recognized diagnostic criteria has led to the adoption of treatment plans typically used for classical Whipple's disease in related case reports. Antimicrobial treatment regimens vary across studies, reflecting a lack of standardized treatment guidelines. A comprehensive review indicates that commonly employed antibiotics include penicillin, streptomycin, tetracycline, ceftriaxone, meropenem, trimethoprim-sulfamethoxazole, doxycycline, and hydroxychloroquine. The currently recommended treatment protocol involves initiating therapy with intravenous ceftriaxone or meropenem for 14 days, followed by oral trimethoprim-sulfamethoxazole for 12 months. For patients intolerant of ceftriaxone, meropenem serves as an alternative; similarly, doxycycline is suggested for those unable to tolerate trimethoprim-sulfamethoxazole. In some cases, lifelong treatment with doxycycline may be necessary. Patients presenting with late-stage symptoms involving the eyes, heart, or central nervous system pose significant treatment challenges and are associated with high relapse and mortality rates.²³ This case report presents a patient who developed a pulmonary abscess following oral prednisone maintenance therapy after short-term glucocorticoid pulse treatment for optic neuritis. The abscess was acutely infected by *T. whipplei*. Bronchoscopic lavage of the purulent cavity was performed, and subsequent high-throughput gene testing of the lavage fluid identified *T. whipplei* as the predominant pathogen. The use of bronchoscopy for thorough purulent irrigation was assessed to significantly reduce the pathogen load in the infected lesion. Considering the low virulence characteristics of the pathogen, the mixed infection status, and the absence of *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus*, a treatment regimen of amoxicillin/clavulanic acid for 6 weeks was implemented, aligning with the standard anti-infection course for pulmonary abscesses. Mid-term follow-up chest CT scans demonstrated continuous improvement of the lesion. At 8 weeks post-treatment cessation, complete closure and absorption of the lung abscess cavity were observed. Existing research suggests that when *T. whipplei*

manifests as classical Whipple's disease through chronic infection, long-term treatment with established regimens is necessary. However, this case report indicates that an acute infection leading to a pulmonary abscess may not require prolonged treatment. The patient's infection episode occurred against an immunosuppressive background of glucocorticoid use. Effective anti-infection therapy and reduced glucocorticoid dosages facilitated immune reconstitution and pathogen clearance. Nonetheless, further research is warranted to corroborate these observations.

Previous case reports primarily relied on metagenomic next-generation sequencing (mNGS) for pathogen diagnosis.^{5,6,8,21,22} However, this report also employed tNGS for diagnosis, as demonstrated in a case report of *T. whipplei* pneumonia.²⁴ Unlike mNGS, which directly extracts DNA/RNA from samples for high-throughput sequencing, tNGS uses pre-designed specific primers that exclusively target and amplify the pathogen's gene. Essentially, tNGS is a form of ultra-multiplex polymerase chain reaction (PCR), capable of detecting low concentrations of pathogenic nucleic acids more rapidly and sensitively, at a lower cost, and with reduced interference from human-derived nucleic acids.²⁵ A large-scale study on the diagnostic performance of tNGS in infectious diseases concluded that tNGS outperformed traditional culture methods, particularly in cases involving *Mycobacterium tuberculosis*, non-tuberculosis *Mycobacteria*, and anaerobic bacteria. The study demonstrated that tNGS can cover approximately 96.7% of the pathogenic targets associated with community-acquired pneumonia.²⁶ As a relatively cost-effective and efficient means of pathogen diagnosis, tNGS is an emerging molecular diagnostic technology with promising applications in multiple fields. This technology is anticipated to become a crucial tool for clinical microbiology diagnosis in the future.²⁷

Whipple may exhibit an increased infection rate in immunocompromised individuals, including those using glucocorticoids, immunosuppressants, those with AIDS, or long COVID-19 infection.^{5,8,16,28,29} In this case, the patient had type 2 diabetes and received pulse therapy with glucocorticoids, followed by low-dose maintenance treatment two months prior to the onset of a pulmonary abscess. This pathophysiological status is consistent with the disease's predisposing population. Patients with pneumonia who have compromised immune function are prone to deteriorate into severe pneumonia, often accompanied by mixed infections of multiple pathogens. A recent study have shown that the most commonly detected pathogens in pneumonia patients with compromised immune function include *Klebsiella pneumoniae*, *Pneumocystis carinii*, *Pseudomonas aeruginosa*, *Staphylococcus*, *Aspergillus*, *Candida*, as well as *cytomegalovirus*, Epstein-Barr virus, respiratory syncytial virus.³⁰ This study indicates that in pneumonia patients with compromised immune function, the use of bronchoalveolar lavage can significantly enhance the pathogen diagnosis rate, thereby improving treatment outcomes. In other aspects, another study has shown that bronchoscopy lavage to have a high yield in immunocompromised patients, even when performed only to rule-out tuberculosis.³¹ In the treatment of pyogenic infections, draining pus is a commonly used therapeutic method. We discovered that the pulmonary abscess cavity in this patient was connected to the bronchus. Therefore, we used sterile saline to thoroughly flush the abscess cavity. One day later, enhanced chest CT scan showed that the pus in the lesion cavity had been cleared, achieved the desired drainage effect and avoid the bronchopleural fistula issue that can easily occur with percutaneous puncture drainage. It is crucial to fully suppress the patient's cough reflex, minimize bronchial mucosal damage and bleeding when performing bronchoalveolar lavage, so as ensure the recovery volume of bronchoalveolar lavage fluid, and use 37°C sterile saline to reduce the tracheal spasm and asthma attacks. Most intraoperative decreases in partial pressure of oxygen are temporary, which can be resolved by oxygen inhalation, encouraging coughing, and prone positioning ventilation. Postoperative fever is also common, it is an absorption heat in most cases that does not require special intervention. However, we must also be vigilant for potential dissemination of infection foci. Additionally, based on personal experience, it is strongly recommended to perform preoperative enhanced CT evaluation for patients highly suspected of having tuberculous cavities or aspergillus cavities before bronchoalveolar lavage. This is because these patients' abscess lesions may undergo massive hemorrhage during operation, the bronchoscopy intervention team and vascular intervention team still need to be backup. Following the successful control of the patient's optic neuritis, glucocorticoid treatment was gradually discontinued, and insulin was administered to maintain the patient's blood sugar within the ideal range. Consequently, the patient's immunosuppression status improved. Subsequent follow-up chest CT scans revealed continuous improvement of pulmonary lesions after treatment discontinuation. This case suggests that in acute *T. whipplei* infections where the host's immune status can be reconstructed, timely discontinuation of immunosuppressive drugs and glucocorticoids, along with improvement of cellular and humoral immune levels, may obviate the need for long-term treatment with drugs such as doxycycline or trimethoprim/sulfamethoxazole. However, this report has limitations. Due to the absence of gastrointestinal symptoms, gastroscopy was not performed, precluding the acquisition of duodenal tissue pathology. Moreover, the patient's

reluctance to undergo repeat bronchoscopy, given the continuous improvement in chest CT imaging and absence of recurrent respiratory symptoms, prevents the determination of complete *T. whipplei* clearance from the patient's body. Consequently, an extended follow-up period is necessary.

Pulmonary abscess is a severe respiratory infection associated with substantial morbidity and mortality. The paucity of clinical evidence and international guidelines supporting pulmonary abscess management underscores the urgent need for larger prospective studies to enhance the detection and evaluation of this neglected disease.³² To the best of our knowledge, most pulmonary abscesses involve co-infection with multiple pathogens and correlate with the patient's underlying condition. Common pathogens include periodontal pathogens, *Klebsiella pneumoniae*, and *Staphylococcus aureus*, while common triggering factors encompass poor oral hygiene and long-term alcohol abuse.³³ This case demonstrates that *T. whipplei* can serve as the primary pathogen in pulmonary abscesses among immunocompromised populations. Given the diversity of infectious pathogens, the use of next-generation sequencing is recommended for pathogen identification. This approach has the potential to guide treatment, improve success rates, and reduce misdiagnosis and treatment failure.

Conclusion

Acute *T. whipplei* infection in pulmonary tissue can manifest as a lung abscess. Because polymicrobial infections are frequently present in pulmonary abscesses, the use of second-generation pathogen sequencing can facilitate diagnosis and provide valuable guidance for antibiotic selection. By reducing the pathogen burden at the infection site and promoting immune status recovery, bronchoscopy lavage enables short-term antibiotic monotherapy to achieve favorable therapeutic outcomes. This approach holds significant potential for minimizing antibiotic exposure duration. For *T. whipplei*-infected patients with reversible immunosuppression, discontinuation of immunosuppressants and glucocorticoids is recommended when feasible. Upon successful immune reconstitution, an acute *T. whipplei* infection may not necessitate prolonged antibiotic treatment. This case establishes a precedent for short-term antibiotic therapy in acute *T. whipplei* infection. Although the patient currently exhibits clinical cure, the risk of relapse persists even after symptom improvement. Relapses typically occur several years later, necessitating long-term monitoring. Further research on short-term antimicrobial treatment for acute *T. whipplei* infection is warranted to validate this approach.

Ethics Approval and Informed Consent

This study received approval from the Ethics Committee of Yuyao People's Hospital.

Consent for Publication

Informed consent for publication of the medical histories and photographs was obtained from the patient. Additionally, institutional consent for case publication was granted by Yuyao People's Hospital.

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Disclosure

The authors declare no conflicts of interest in relation to this work.

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