BMC Pulmonary Medicine

CASE REPORT

Open Access

A case of pneumonia caused by infection with Tropheryma whipplei complicated by cryptococcus during treatment with a Janus kinase inhibitor: a case report

Xiaoxi Shan[1†], Zhishu Li[2†] and Lixia Dong[1*]

Abstract

This report describes the case of a 41-year-old male patient complaining of a hacking cough. The patient was treated with a Janus kinase (JAK) inhibitor for psoriasis. Blood tests revealed mild lymphopenia and high levels of serum *cryptococcal* antigen. Chest computed tomography revealed infection in the lower lobe of the left lung. Metagenomic next-generation sequencing of bronchoalveolar lavage fluid revealed *Tropheryma whipplei*. *Tropheryma whipplei* and *Cryptococcus* antimicrobial therapies were sequentially administered. During follow-up, the patient showed clinical and radiographic improvement. *Tropheryma whipplei* is an opportunistic Gram-positive rod-shaped bacterium belonging to the family Actinomycetes. Lung involvement is an unusual but classic manifestation of Whipple's disease. This is the first report of pneumonia caused by infection with *Tropheryma whipplei* complicated by *Cryptococcus*. To our knowledge, this is the first case report of *Tropheryma whipplei* infection following the use of JAK inhibitors. Clinicians should be aware of opportunistic infections that can occur during treatment with JAK inhibitors.

Keywords Pneumonia, Opportunistic infection, Actinomycetes, Metagenomics next-generation sequencing

Background

Tropheryma whipplei pneumonia is an uncommon opportunistic infection that is often overlooked. Lung involvement is an unusual but classic manifestation of Whipple's disease.The clinical manifestations can be heterogeneous, making diagnosis challenging. In this study, we report a case of *Tropheryma whipplei* with *Cryptococcus* co-infection in a patient with psoriasis who was treated with a Janus kinase (JAK) inhibitor.

Case report

A 41-year-old Chinese man sought care at the outpatient clinic of Tianjin Medical University for a hacking cough (no fever, hemoptysis, chest pain, or headache) that appeared 7 days earlier. The patient's past medical history was significant because of a history of psoriasis and atopic dermatitis. Tofacitinib (5 mg/day) had been used for the treatment of his psoriasis for a year; however, one year prior, it was switched to upadacitinib (30 mg/day). The patient was an office worker, employed by the government, with a clean working and living environment.

†Xiaoxi Shan and Zhishu Li contributed equally to this work.

*Correspondence:
Lixia Dong
luckydonglixia@163.com; donglixia2023@126.com
[1]Department of Respiratory and Critical Care Medicine, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin, China
[2]Department of Respiratory and Critical Care Medicine, Guangyuan Central Hospital, Guangyuan, China

He had no history of tourism or contact with *Tropheryma whipplei*. Aside from a generalized rash, no other abnormalities were observed during clinical examination. His body mass index was 25 kg/m^2. A chest computed tomography (CT) scan was performed, and it demonstrated a region of patchy consolidation in the subpleural area of the left lower lobe. Small cavities were observed within the pulmonary consolidation (Fig. 1). Serum was positive for *cryptococcal* antigen lateral flow assay (CrAg-LFA, colloidal gold method, 10.25.<0.04 negative). The T-cell spot test for tuberculosis was negative. However, the chest radiographic findings were consistent with the typical imaging findings of *Cryptococcus*. The patient was then admitted for further diagnosis and treatment. The examination results were as follows: A blood test revealed mild lymphopenia (total 1274 cells/ul, CD3+CD4+/CD45+:37.1%, CD3+CD8+/CD45+:29.1%, CD4/CD8:1.27) and a 2.2 mg/dl increase in C-reactive protein. Immunoglobulin (IgA, IgG, and IgM) and complement protein levels were within normal ranges. Serum IgM tests for *C-pneumoniae*, *M- pneumoniae*, *respiratory syncytial virus*, *adenovirus*, *influenza A virus*, *influenza B virus*, *coxsackieviruses B virus*, *human parainfluenza virus*, and *echovirus* were negative. Serum 1-3-β-D glucan and Aspergillus galactomannan tests were both negative. However, the radiological manifestations of pulmonary cryptococcosis lack specificity, making it prone to misdiagnosis or missed diagnosis when compared with conditions such as tuberculosis or tumors; therefore, we admitted the patient for further bronchoscopic examination. Bronchoscopy revealed hyperemia of the bronchial mucosa. The sample collection process was in line with clinical operation standards and followed the principles of sterility. A transbronchial biopsy of the basal segment of the left lower lobe showed negative periodic acid-Schiff (PAS) staining, examiner silver staining, and acid-fast staining. No signs of malignancy were observed. Detection of 1-3-β-D glucans and culture of the bronchoalveolar lavage fluid (BALF) were negative. The BALF was analyzed using metagenomic next-generation sequencing (mNGS). *Tropheryma whipplei* was detected at a sequence number of 925,422 (relative abundance: 99.9311%); it was the only known pathogen. Since *Tropheryma whipplei* infections are rarely detected in this area, after reviewing the literature, we carefully collected the patient's medical history. He also stated that he had been suffering from arthralgia for nearly a year. He did not initially mention these symptoms because he believed that they were associated with psoriasis. Unfortunately, we lack the resources to improve the related PCR examination. We proposed a colonoscopy for this patient, but he refused.

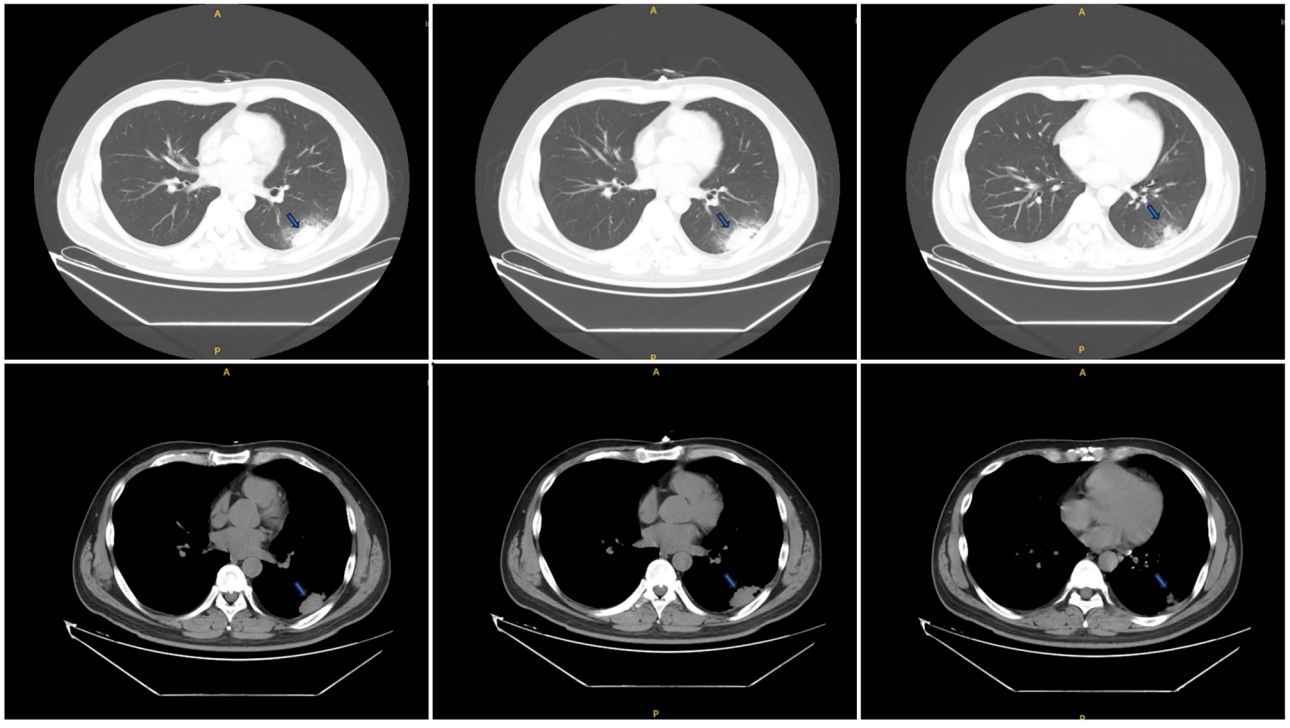

Fig. 1 Chest CT showing consolidation in the lower lobe of the left lung, with a cavitary lesion in the consolidated lung tissue and some ground-glass opacity surrounding the consolidated lung tissue before treatment

The pathogens were most likely *Tropheryma whipplei* and *Cryptococcus*, based on the mNGS results from the BALF, the higher serum concentration of *cryptococcal* antigen, and the features of the chest CT. We devised a treatment method that was effective against both *Tropheryma whipplei* and *Cryptococcus*. To ensure safety, JAK inhibitors and biologics were discontinued. Intravenous therapy was initiated with ceftriaxone 2 g and fluconazole 400 mg both administered four times daily.

After receiving care for five days, the patient was released from the hospital. After being discharged from the hospital, he continued to receive intravenous ceftriaxone for 9 days before being switched to oral trimethoprim-sulfamethoxazole (0.96 g every two days). The patient continued oral fluconazole therapy (300 mg/day) after discharge. Seven days after beginning medication, his cough symptoms started to improve. In the fourth week of treatment, a follow-up chest CT scan showed improvement in the consolidation and ground-glass opacity. However, the size of the cavitary lesion increased significantly after treatment (Fig. 2). The patient's cough and arthralgia resolved. We believe that the enlargement of the cavities on the patient's chest CT was due to the absorption of exudative lesions, which made the preexisting cavitary lesions more easily observable. Combined with a significant improvement in the patient's clinical symptoms, we decided to continue with the current treatment plan. In the fifteenth week of treatment, the size of the cavitary lesion had visibly reduced (Fig. 3). In the twentieth week of treatment, the detection of the *Cryptococcus* antigen in the serum was negative. In the sixth month of treatment, a CT scan of the patient's chest demonstrated near-complete resolution of the cavitary lesions, with only minimal residual consolidation and fibrotic bands observed (Fig. 4). The patient is still undergoing treatment and follow-up.

Discussion and conclusions

Tropheryma whipplei is an opportunistic pathogen and a gram-positive rod-shaped (1–2×0.2 μm) bacterium belonging to the Actinomycetes family. Common signs of typical Whipple's disease include heart, gastric, joint, and neurological dysfunction. Weight loss, diarrhea, and arthralgia were prevalent in 93%, 81%, and 73% of reported cases, respectively. Lung involvement is an unusual but classic manifestation of Whipple's disease, and has been reported in only 13–14% of cases [1]. Sometimes, an isolated cough is the first symptom revealing the disease [2]. Our patient presented with a cough as the primary symptom and no gastrointestinal symptoms,

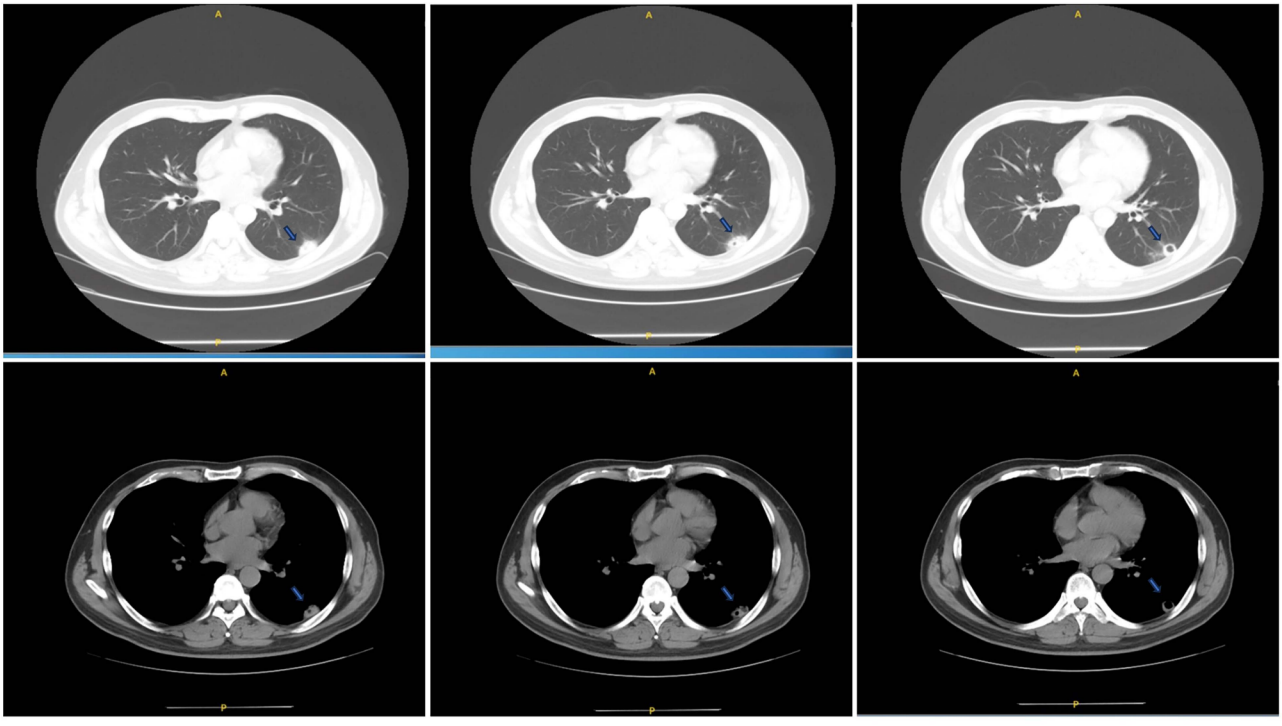

Fig. 2 Chest CT showing resolution of the consolidation and ground-glass opacity in the fourth week of treatment. The cavitary lesion was larger than before, and the inner wall was smooth

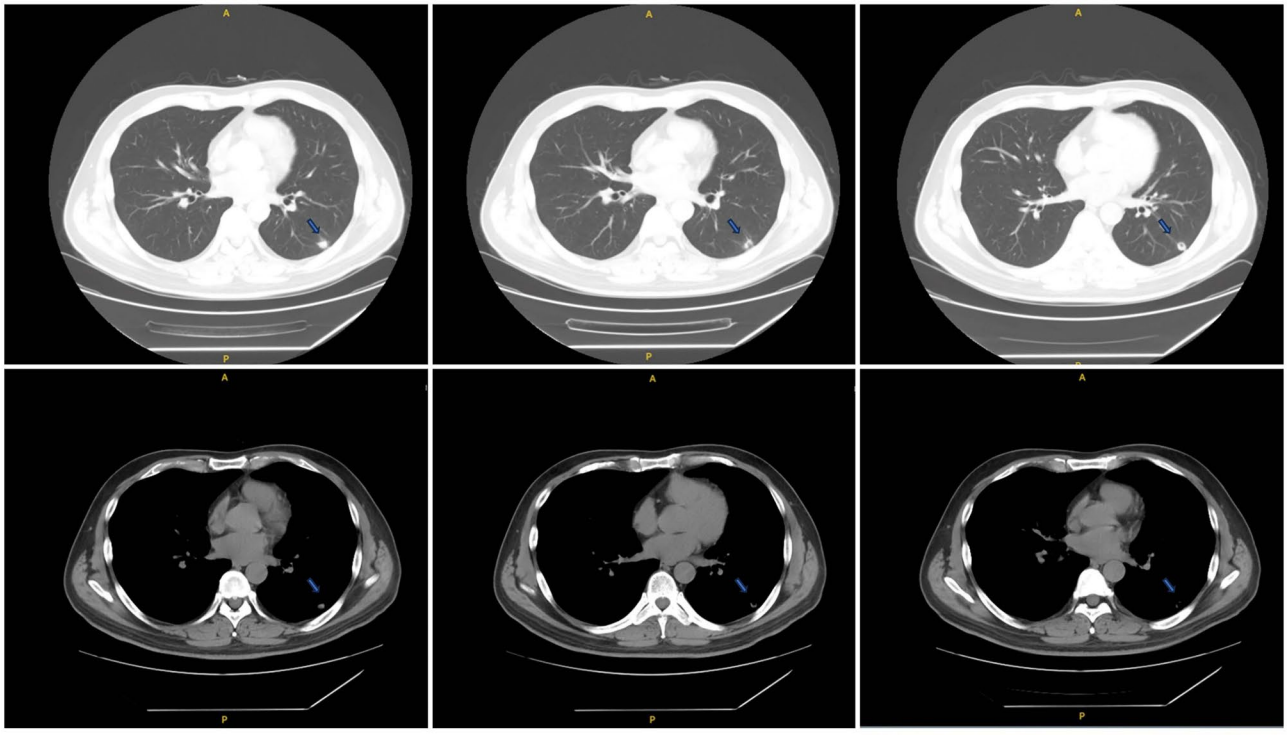

Fig. 3 Chest CT showing the cavitary lesion with a visibly reduced size in the fifteenth week of treatment

which is unusual. The most common chest radiological findings are nodules that can be small or large, solitary or distributed, ground-glass or solid, or many centimeters in diameter. Other CT findings include interstitial alterations, patchy infiltration, and a cavity [3].

As reported in previous cases, patients infected with *Tropheryma whipplei* can be co-infected with *Pneumocystis jirovecii* and *Candida albicans* [4, 5]. However, no case of co-infection with *Cryptococcus* has been reported. Sulis et al. proposed a relationship between Whipple's disease and cellular immune dysfunction [6]. *Tropheryma whipplei* can cause macrophages in the duodenum to polarize into alternately activated M2 macrophages during the pathogenesis of classic Whipple's disease. T-cell responses are further weakened by the impaired antigen-presenting function of macrophages and dendritic cells [7]. *Tropheryma whipplei* cannot invade tissues according to a mouse model, but it can linger in cells such as macrophages by inhibiting the xenogenic phagocytosis process, a type of selective autophagy that targets pathogens [8]. Some macrophages, in particular, appear to play a role in limiting *Cryptococcus* invasion [9]. Patients with Whipple's disease have markedly altered Th1 reactivity and low interferon levels. These changes may be responsible for the increased susceptibility to opportunistic infections. However, owing to a lack of research on the pathogenesis of *Tropheryma whipplei* in lung infections, it is unclear whether *Tropheryma whipplei* and *Cryptococcus* are closely related to pneumonia.

Some studies have shown that Whipple's disease can occur in immunodeficient or immunosuppressed patients. *Tropheryma whipplei* is more likely to emerge in acquired immunodeficiency syndrome (AIDS) patients with a low CD4 level as well as in patients receiving TNF-α inhibitor treatment [10]. The use of some JAK inhibitors may result in an early, dose-dependent decrease in the number of T- and B-lymphocytes [11]. This class of drugs also blocks the signaling of several cytokines, thus exerting anti-inflammatory and antimicrobial actions. Some adverse effects occur as a result of these actions. The most serious adverse events included opportunistic infections, tuberculosis, and cancers [12]. In this case, long-term use of JAK inhibitors may have been a potential cause of infection with *Tropheryma whipplei* and *Cryptococcus*. Additional studies are required to confirm the relationship between *Tropheryma whipplei* infection and the use of JAK inhibitors. Nevertheless, it is certain that patients with *Tropheryma whipplei* infection should not use immunosuppressants, to avoid aggravating the condition [10].

Tropheryma whipplei is an intracellular pathogen that requires cell culture medium, harsh culture conditions, and extended culture time; therefore, culture is crucial for epidemiological reasons and for monitoring antibiotic sensitivity but is of little value in making a diagnosis.

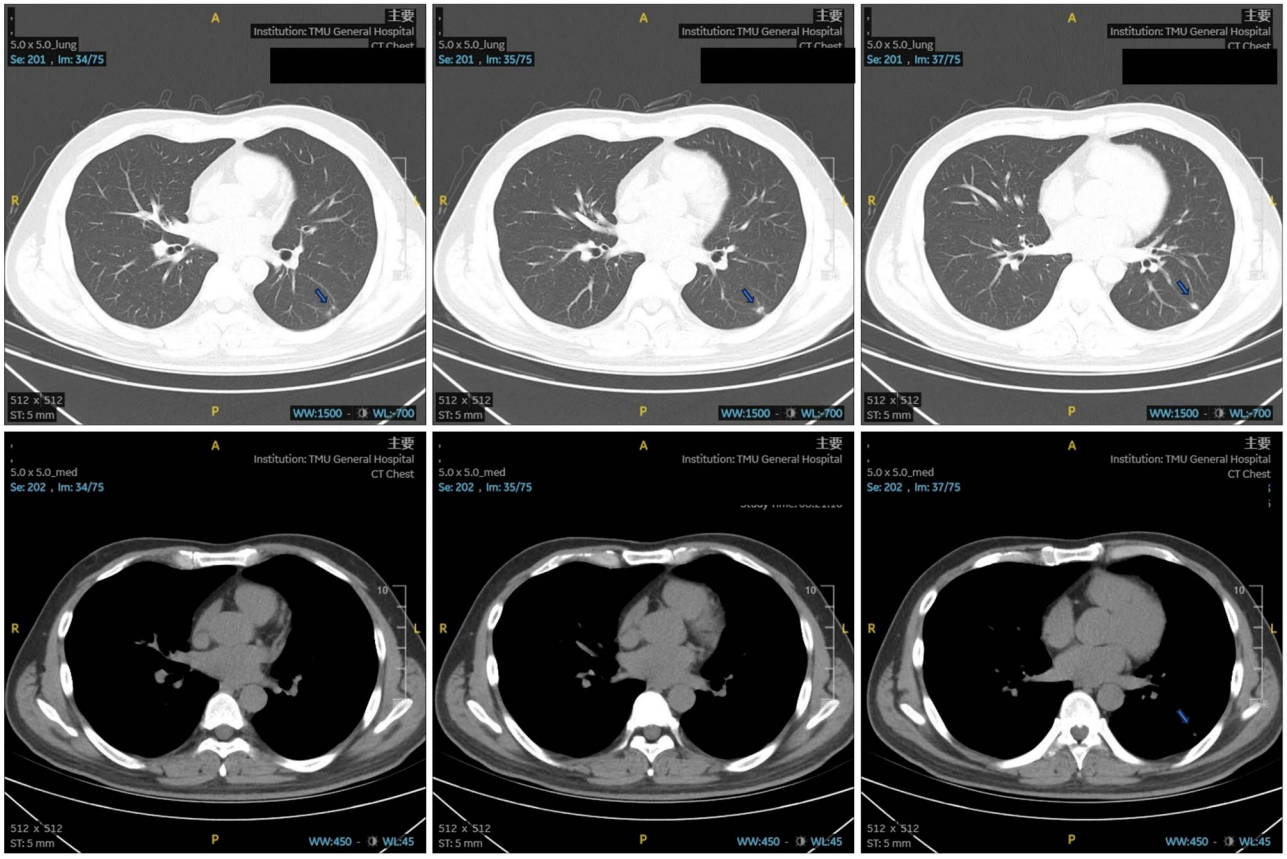

Fig. 4 Chest CT showing near-complete resolution of cavitary lesions, with only minimal residual consolidation and fibrotic bands observed, in the sixth month of treatment

Before 1991, the diagnosis of Whipple's disease was based on histopathological examination and was characterized by positive PAS-stained inclusions within intestinal macrophages. After 1991, a program control register was introduced in clinical practice. NGS is a recently developed technique. Currently, nearly all infectious agents contain DNA or RNA genomes, making sequencing an attractive approach for pathogen detection. For patients with immune deficiency, NGS can help to identify rare pathogens and some difficult-to-culture pathogens. In comparison with routine bacterial cultures, our method using mNGS may be more clinically advantageous for providing a broader perspective on airway bacterial infections, especially for hospitals that lack adequate pathogen detection conditions. Notably, the best method for diagnosing Whipple's disease is the histopathological examination of duodenal mucosal biopsies. Therefore, we believe that duodenal mucosal biopsy can be considered for patients suspected of *Tropheryma whipplei* infection to further improve diagnosis.

Owing to the high recurrence and mortality rates associated with Whipple's disease, long-term treatment is needed. Currently, there is no unified international treatment consensus or guideline. One such regimen is ceftriaxone (2 g intravenously once a day) for 14 days followed by oral co-trimoxazole (960 mg orally twice a day) for 12 months. In 2010, a prospective randomized controlled trial analyzed the outcomes of 40 previously untreated patients with Whipple's disease [13]. Patients received induction therapy with either ceftriaxone or meropenem for 14 days, followed by oral co-trimoxazole for 12 months. This study showed a high rate of prolonged clinical remission (37 [93%] of 40 patients). If a patient cannot tolerate these drugs, an alternative treatment approach is required. Meropenem (1 g intravenously three times per day) was used instead of ceftriaxone. The co-trimoxazole treatment was changed to doxycycline (100 mg orally twice daily) and hydroxychloroquine (200 mg orally three times daily). Rapid improvements and clinical remission have been reported following antibiotic treatment. During treatment, vigilance for immune reconstitution inflammatory syndrome (IRIS) must be maintained. IRIS is strongly associated with the use of immunosuppressive therapy before the diagnosis of Whipple's disease and can be observed even after longer intervals. Fever and arthritis are the common symptoms of IRIS. A range of other symptoms have been described (e.g., cutaneous signs, such as erythema

nodosum; and central nervous system symptoms, such as meningitis or brain abscess, pleuritis, endocarditis, and orbitopathy). The prompt use of oral corticosteroids has been shown to be effective against major symptoms and thus might be lifesaving.

In this case, the patient had been using JAK inhibitors for a long time, and their immune function was suppressed. According to the Consensus of Zhejiang Experts on Pulmonary Cryptococcosis [14], if a patient has typical clinical characteristics and imaging findings, along with a positive serum cryptococcal antigen, pulmonary cryptococcosis can be clinically considered. The patient's serum was positive for CrAg-LFA and was accompanied by cough and chest imaging manifestations, which met the diagnostic criteria for pulmonary cryptococcosis. However, the mNGS results of the BALF showed that *Tropheryma whipplei* was the only pathogen identified, with extremely high sequence numbers and relative abundances. Based on the current information, we can still conclude that the pneumonia was caused by *Tropheryma whipplei* and *Cryptococcus*. The successful treatment in this case also supports the clinical diagnosis.

This study had some limitations. First, PAS staining or histological examination of small-bowel biopsy specimens, which is the gold standard for Whipple's disease, was not performed because of the patient's unwillingness. Second, we were unable to obtain lung tissue samples for quantitative PCR analysis through percutaneous lung biopsy.

In summary, this is the first report of pneumonia caused by infection with *Tropheryma whipplei* complicated by *Cryptococcus*. Whipple's disease is a multisystem disease and untreated disease is fatal. We hope that our report can serve as a reference for the diagnosis and treatment of this disease, and that more clinical data will be published to provide more support. Moreover, BALF mNGS can improve the diagnosis of infectious diseases caused by pathogens that are difficult to culture.

Acknowledgements
The authors thank Dr. Rui Wang from the Department of Respiratory and Critical Care Medicine, Tianjin Medical University General Hospital, for his assistance during the writing of this manuscript.

Author contributions
All authors made significant contributions to the study conception, design, and execution, as well as data acquisition, analysis, and interpretation. All authors were involved 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 agreed to be accountable for all aspects of the work.

Funding
No specific grant for this research was provided by any funding organization in the public, private, or non-profit sectors.

Data availability
Biosample (SAMN44460009,SAMN44460010) and Bioproject (PRJNA1177974) information has been submitted to the NCBI (https://www.ncbi.nlm.nih.gov/bioproject/PRJNA1177974).

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article. Clinical trial number: not applicable.

Consent for publication
All authors of this manuscript and the patients involved in the article have given their consent for the publication of the paper.

Competing interests
The authors declare no competing interests.

Received: 22 April 2024 / Accepted: 18 November 2024
Published online: 20 December 2024

References

1. Marth T. Whipple's disease. Acta Clin Belg. 2016;71(6):373–8. https://doi.org/10.1080/17843286.2016.1256586.
2. Damaraju D, Steiner T, Wade J, Gin K, FitzGerald JM. Clinical problem-solving. A surprising cause of chronic cough. N Engl J Med. 2015;373(6):561–6. https://doi.org/10.1056/NEJMcps1303787.
3. Zhang WM, Xu L. Pulmonary parenchymal involvement caused by Tropheryma whipplei. Open Med (Wars). 2021;16(1):843–6. https://doi.org/10.1515/med-2021-0297.
4. Li W, Zhang Q, Xu Y, Zhang X, Huang Q, Su Z. Severe pneumonia in adults caused by Tropheryma whipplei and Candida Sp infection: a 2019 case series. BMC Pulm Med. 2021;21(1):29. https://doi.org/10.1186/s12890-020-01384-4.
5. Yan J, Zhang B, Zhang Z, et al. Case report: Tropheryma whipplei hide in an AIDS patient with pneumocystis pneumonia. Front Public Health. 2021;9:663093. https://doi.org/10.3389/fpubh.2021.663093.
6. Sulis G, Villanacci V, Missale G, Salemme M, Castelli F, Caligaris S. Whipple's disease concomitant with candida esophagitis and subsequent Giardia lamblia coinfection. Eur J Gastroenterol Hepatol. 2014;26(10):1181–5. https://doi.org/10.1097/MEG.0000000000000154.
7. Schinnerling K, Moos V, Geelhaar A, et al. Regulatory T cells in patients with Whipple's disease. J Immunol. 2011;187(8):4061–7. https://doi.org/10.4049/jimmunol.1101349.
8. Al Moussawi K, Malou N, Mege JL, Raoult D, Desnues B. An experimental mouse model to establish Tropheryma whipplei as a diarrheal agent. J Infect Dis. 2011;204(1):44–50. https://doi.org/10.1093/infdis/jir219.
9. Johnston SA, May RC. Cryptococcus interactions with macrophages: evasion and manipulation of the phagosome by a fungal pathogen. Cell Microbiol. 2013;15(3):403–11. https://doi.org/10.1111/cmi.12067.
10. Lagier JC, Fenollar F, Raoult D. Acute infections caused by Tropheryma whipplei. Future Microbiol. 2017;12:247–54. https://doi.org/10.2217/fmb-2017-0178.
11. Cutolo M, Meroni M. Clinical utility of the oral JAK inhibitor tofacitinib in the treatment of rheumatoid arthritis. J Inflam Res. 2013;6(default):129–37. https://doi.org/10.2147/JIR.S35901.
12. Wang F, Sun L, Wang S et al. Efficacy and safety of tofacitinib, baricitinib, and upadacitinib for rheumatoid arthritis: A systematic review and meta-analysis. *Mayo Clin Proc.* 2020;95(7):1404–1419. https://doi.org/10.1016/j.mayocp.2020.01.039
13. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. Gastroenterology. 2010;138(2):478–86. quiz 11, 11–12. https://doi.org/10.1053/j.gastro.2009.10.041.

14. Zhejiang Medical Association Society of Respiratory Diseases. Expert consensus on diagnosis and treatment of pulmonary cryptococcosis. Chin J Clin Infect Dis. 2017;10(5):321–6. https://doi.org/10.1093/mmy/myy086.

Publisher's note