Whipple's disease of the respiratory system: A case report

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Abstract. Whipple's disease (WD) is a multiple-system chronic disease caused by *Tropheryma whipplei* (*T. whipplei*) infection. The present study describes 3 cases of WD with clinical manifestations of cough, chest pain, headache, dyspnea, sputum, joint pain, abdominal pain, diarrhea and weight loss. Chest computed tomography (CT) showed signs of plaques, nodules and pleural thickening; and bronchoscopic alveolar lavage fluid metagenomic-sequencing indicated that it was *T. whipplei*. One patient was treated with meropenem as the starting regimen and two patients were treated with ceftriaxone as the starting regimen. Furthermore, two patients were provided with a maintenance regimen of cotrimoxazole and one was given a maintenance regimen of minocycline, which was combined with meropenem and ceftriaxone in order to improve their cough, chest pain, headache and dyspnea symptoms. To the best of our knowledge, there are few reports on WD of the respiratory system caused by *T. whipplei*, and differential diagnosis is the key to clinical diagnosis. When WD of the respiratory system is difficult to diagnose, metagenomic second-generation sequencing (mNGS) may be a better choice, which can achieve early diagnosis and early treatment. However, its clinical value is still limited; therefore, more research needs to be conducted in the future.

Introduction

Whipple's disease (WD) is a complicated and rarely chronic multi-system disease caused by *Tropheryma whipplei* (*T. whipplei*); while the disease has been observed and investigated for >100 years, it remains a difficult diagnostic and therapeutic challenge in clinical practice (1,2). The majority of cases of WD disease have been reported in North America and Europe, with only a minority of cases reported in native Asian and African individuals (3). The annual incidence rate is an approximate of <1,000,000, with a mean age of onset of symptoms of 55 years (3,4). The disease is more frequent in the male population, with a male/female ratio of 4:1 (5).

The imaging manifestations of WD lung involvement are also diverse, with the most common chest imaging manifestations being nodules, interstitial changes and patchy infiltrates, of which nodules are the most commonly observed, with cavitation-like changes, pleural thickening and pleural effusion being less common (6). WD is mainly a chronic infection with multi-organ involvement, with occasional acute onset (7). Due to the heterogeneity of the clinical manifestations of the disease and the variety of imaging manifestations, there is a possibility that the disease may not be diagnosed and treated in a timely manner, leading to serious consequences or even mortalities (7).

The present article presents an analysis of three patients with WD admitted to the Department of Respiratory Medicine, The Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) from January 2022 to August 2023, as well as a review of the relevant literature, with the goal of raising awareness of WD for clinical physicians.

The Clinical characteristics of three patients with WD are presented in Table I. All patients had signed the informed consent form and consented to publication appropriately.

Case report

Case 1. A 53-year-old male presented to the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) outpatient clinic with persistent chest pain on the right side that was aggravated by inspiration, accompanied by dizziness, headache, cough, and white mucous sputum, with progressive aggravation of the symptoms. The patient was admitted to our outpatient clinic with the condition of 'Chest pain to be investigated' (July 2023). Since the onset of the disease, the mental health and appetite of the patient were fine, his bowel and urine were normal and there was no significant change in his weight. Past history was physically healthy. A physical examination of the heart, lungs and abdomen revealed no abnormalities. On the same day as presentation, a computed tomography (CT)-enhanced examination of the chest revealed

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Table I. Clinical characteristics of patients with Whipple's disease.

Patient no.	Sex	Age, years	Past medical history	Fever	Cough, sputum, joint pain, abdominal pain, diarrhea and weight loss?	Chest pain	Other	BMI, kg/m^2
1	Male	53	Pulmonary nodule	No	Yes	Yes	Headaches	28.1
2	Male	37	Bronchial asthma	Yes	Yes	No	Dyspnea	26.0
3	Female	34	Thyroid cysts, adenomyosis, post-chocolate cyst debridement	No	Yes	Yes	Headaches	28.8

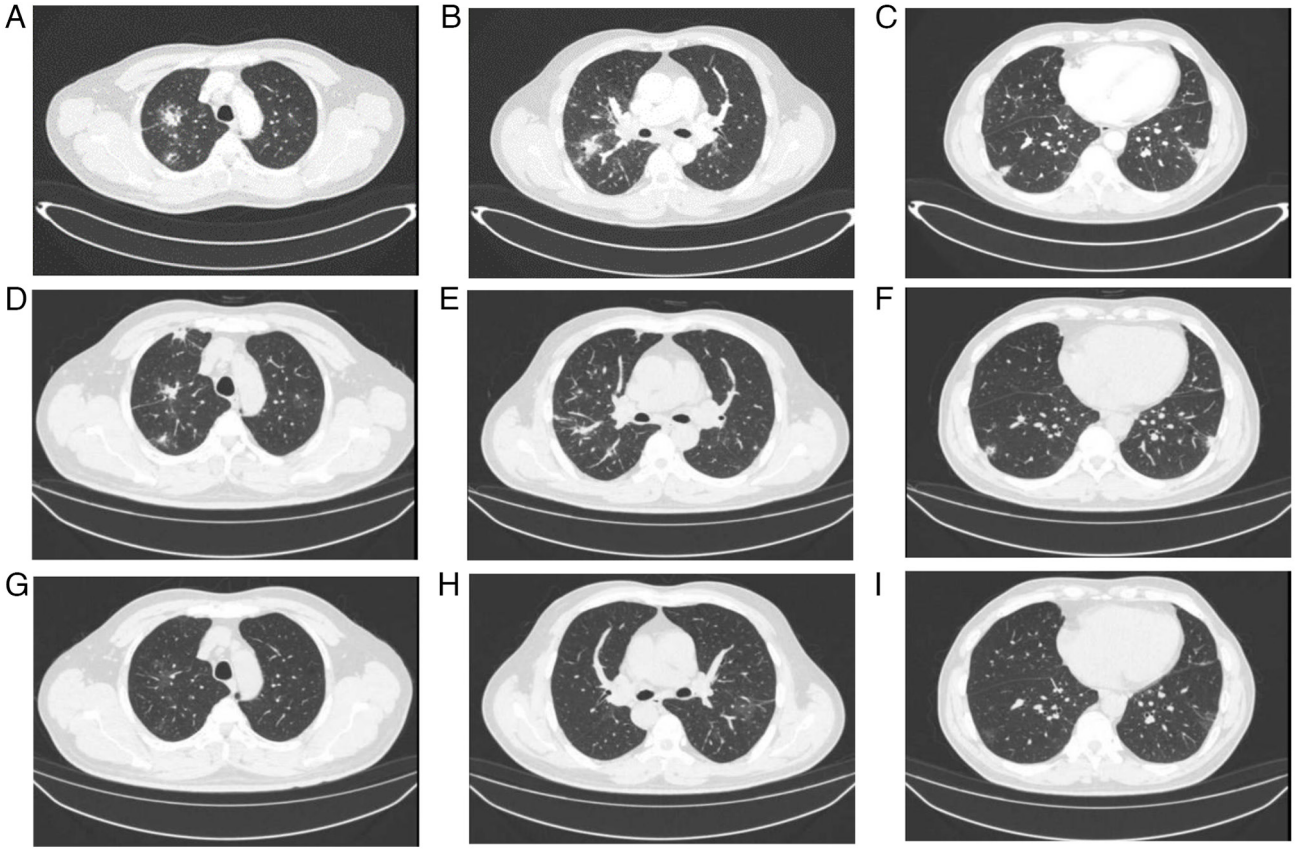

Figure 1. Comparison of chest CT in patient 1. (A-C) Chest CT in July 2023. (D-F) Chest CT 2 weeks later. (G-I) Chest CT in August 2023. The lesions were more clearly absorbed in August compared with at the first CT scan in July.

(Fig. 1A-C): i) Possible infectious lesions in both lungs; ii) multiple enlarged lymph nodes in the hilar and mediastinum of both lungs; iii) multiple air-containing cystic cavities in both lungs; iv) minor effusions in the pleural cavities bilaterally; and v) sclerosis of the aorta and coronary arteries.

At 2-days post admission, brain MRI revealed: i) High signal in the cerebral white matter (Fazekas grade I) considered to be associated with small vessel hemorrhage; and ii) no other structural or organizational abnormalities. Electron bronchoscopy revealed that the left and right main bronchi and their mucous membranes of the lobes and segments were congested, carbon deposition was observed in the middle lobe of the right lung and a white, thin sputum was observed. The results of other relevant laboratory tests are presented in Table II.

Therefore, the patient was initially diagnosed with pneumonia and WD. Meropenem 1 g* q8h anti-infective treatment was given, and the patient was discharged after 8 days of symptom improvement, followed by cotrimoxazole 0.96 g *bis in die* (BID; twice a day) maintenance treatment for 1 year.

After treatment, the chest CT was reviewed in July 2023 (Fig. 1D-F) and August 2023 (Fig. 1G-I), respectively, and significant improvement of the lesion was observed.

Case 2. A 37-year-old male was admitted to the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) in March 2023, with recurrent wheezing for 4 months, aggravated by fever for 3 days. The patient was intubated, sedated, and administered an analgesic, so the examinations were limited, and the findings of the relevant

Table II. Laboratory Results in patients with Whipple's Disease.

Inspection and examination	Case 1	Case 2	Case 3
Hemoglobin (115-150 g/l)	130	137	140
WBC (3.5-9.5 g/l)	5.16	14.24	5.53
N, % (45-75%)	68	93.8	59.5
L, % (20-50%)	15.3	2.2	31.1
Ultra-sensitive CRP <1 mg/l	>5	>5	1.82
CRP (<10 mg/l)	75.31	52.44	<5
PCT (0.02-0.05 ng/ml)	0.15	0.3	0.03
Fecal occult blood	(-)	(-)	(±)
Creatine kinase (38-174 U/l)	119.5	581	187
ESR (0-15 mm/first h)	79	-	-
GGT (10-60 U/l)	103	79	19
ALT (9-50 U/l)	39	52	16
AST (15-40 U/l)	37	29	20
Serum albumin	41.8	41.4	39.3
Respiratory failure	No	Yes	No
Chest CT	(July 2023) Multiple patches, nodules and striated high-density shadows in both lungs with uneven density and unclear borders, with thickening of the surrounding interlobular septa, and some foci located in the bilateral subpleura in the adjacent pleura with slightly thickened adhesions	(March 2023) Scattered inflammation and nodules in the upper lobes of both lungs and the lower lobe of the right lung	(January 2022) Patchy solid metaplasia and perifocal small speckled exudates in the extra-basal segment of the lower lobe of the right lung, considering the possibility of an infectious lesion
Alveolar lavage fluid mNGS results	219 for *T. whipplei*, 1 for Pneumocystis japonicus	21,793 for *T . whipplei*, and 20,889 for the influenza A virus	*T. whipplei*

N, neutrophil; L, lymphocyte; GGT, γ-glutamyl transpeptidase; WBC, white blood cells; CRP, C reactive protein; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

physical examinations were as follows: Respiratory sounds were low bilaterally, and no obvious rales or wet rhonchi were heard. A physical examination of the heart and abdomen revealed no abnormalities. Electronic bronchoscopy was performed and bronchial congestion and edema were observed in all lobe segments of the left lung and the upper and lower lobes of the right lung; a small amount of yellowish-white mucous sputum was aspirated.

At 6 days post-admission, a chest CT (Fig. 2A-C) suggested scattered inflammation and nodules in the upper lobes of both lungs and the lower lobe of the right lung. The results of metagenomic second-generation sequencing (mNGS) and other relevant laboratory tests are presented in Table II. The initial diagnosis was critical bronchial asthma, type II respiratory failure, WD and influenza A.

Invasive ventilation, anti-inflammatory [methylprednisolone 40 mg quaque die (qd) for 5 days], and bronchodilator (budesonide 2 mg BID for 7 days) treatments were given, followed by oseltamivir antiviral and ceftriaxone 2 g qd anti-infective treatments for 7 days. According to the mNGS results, symptoms of wheezing, exhaustion and dyspnea improved. influenza A nucleic acid was negative, and the patient was discharged, with postminocycline 200 mg *quaque 12 hora* (every 12 h), and 100 mg BID for maintenance treatment for 1 year.

Subsequent review of the chest CT in April 2023 (Fig. 2D-F) and August 2023 (Fig. 2G-I) showed significant improvement of the lesion.

Case 3. A 34-year-old female patient was admitted to the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China) in January 2022, with a cough that had been worsening for >1 month and had been present for half a month. Chest CT in January 2022 (Fig. 3A-C) revealed: i) Patchy solid shadow and small perifocal speckled exudative foci in the extra-basal segment of the lower lobe of the

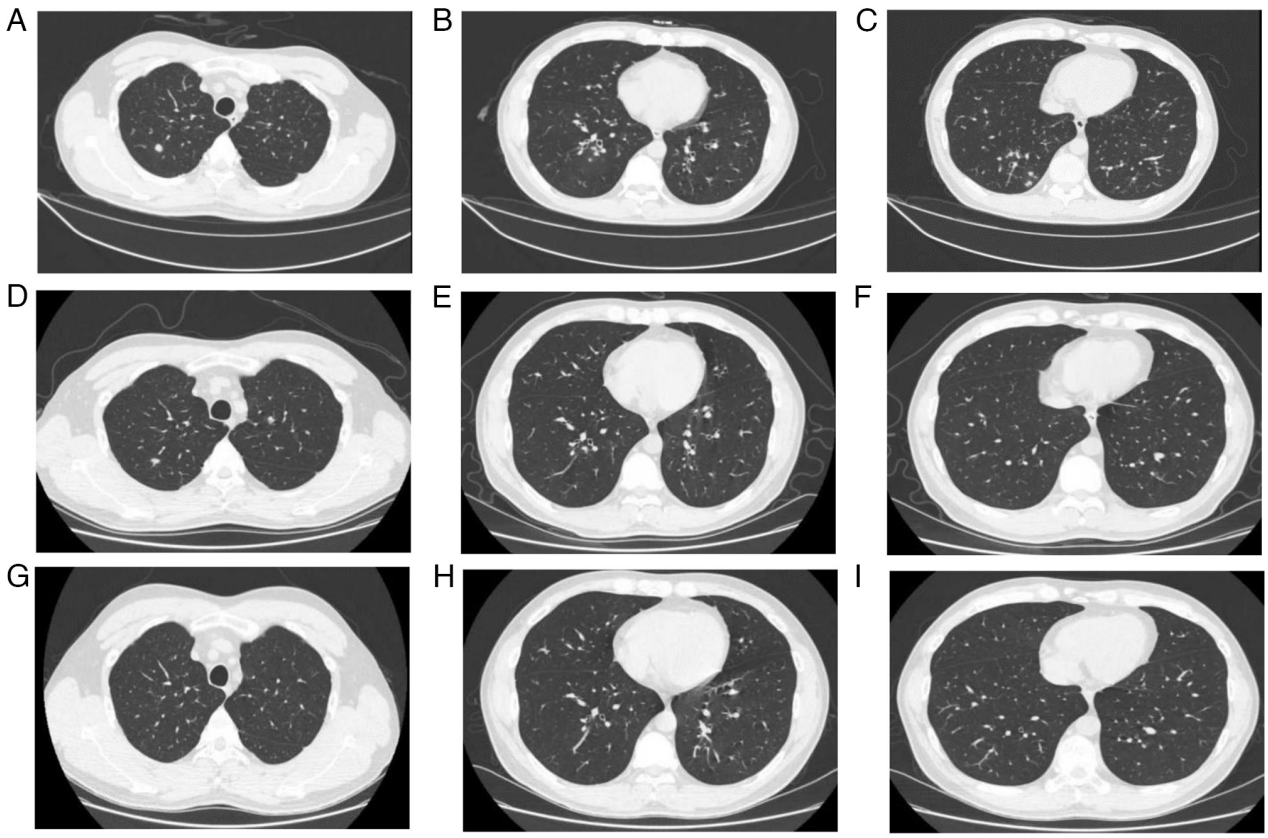

Figure 2. Comparison of chest CT in patient 2. (A-C) Chest CT in March 2023. (D-F) Chest CT in April 2023. (G-I) Chest CT in August 2023. The lesions were more clearly absorbed in August compared with in March.

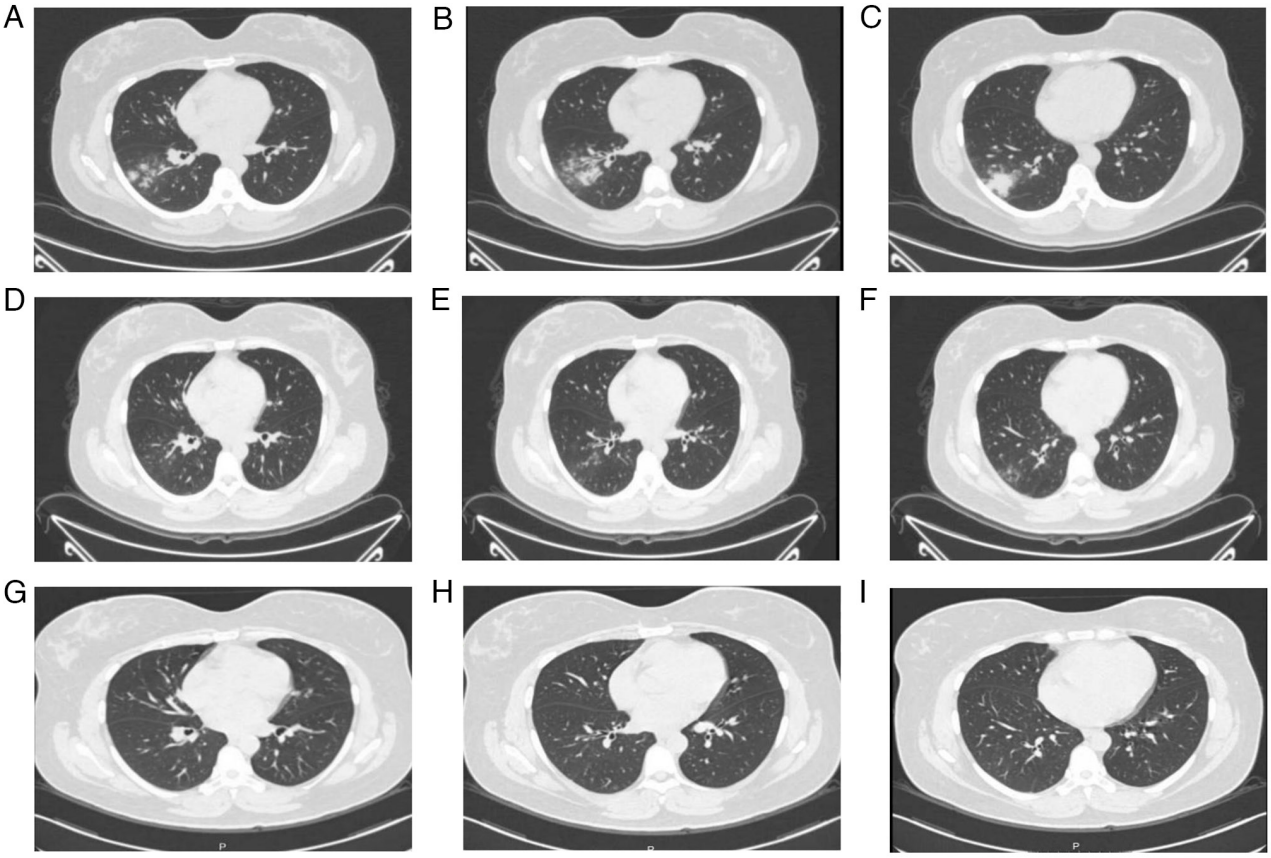

Figure 3. Comparison of chest CT in patient 3. (A-C) Chest CT in January 2022. (D-F) Chest CT 2 weeks later. (G-I) Chest CT in March 2022. The lesions were more clearly absorbed in March compared with at the first CT scan in January.

Table III. Treatment and cost of patients with Whipple's Disease.

Clinical data	Case 1	Case 2	Cases 3
Therapeutic regimen	Meropenem 1 g q8h*8 days	Ceftriaxone 2 g qd*7 days	Ceftriaxone 2 g qd*7 days
Maintenance regimen	Cotrimoxazole 0.92 g BID	Minocycline 100 mg BID	Cotrimoxazole 0.92 g BID
Average hospitalization days	16	12	10
Hospitalization costs ($)	3,080	5,460	1,820

BID, *bis in die*/twice a day; qd, *quaque die*/every day; q8h, *quaque 8 hora*/every 8 h.

right lung, indicating the possibility of an infectious lesion; and ii) several small nodular foci in both lungs. An electronic bronchoscopy was performed, which revealed congested and swollen bronchial tubes in all lobar segments bilaterally. The results of mNGS and other relevant laboratory tests are presented in Table II.

Therefore, the initial diagnosis was pneumonia with WD. The patient was discharged from the hospital after 7 days of anti-infective treatment with ceftriaxone (2 g qd), followed by maintenance treatment with cotrimoxazole (0.96 g BID). Subsequently, a follow-up chest CT in January 2023 (Fig. 3D-F) and March 2023 (Fig. 3G-I) showed significant improvement of the lesion.

Discussion

The present study diagnosed two male and one female patients; all three were middle-aged patients with an average age of 41.3 years. In terms of clinical symptoms, all three patients had cough and sputum; two had chest pain; two had mixed headache manifestations; and one had fever and dyspnea that were thought to be associated with influenza A and bronchial asthma. One of the three patients had elevated leukocyte and neutrophil percentages, two had decreased lymphocyte percentages, all three patients had ultrasensitive C-reaction protein (CRP) and significantly elevated CRP, two patients had increased calcitoninogen, two patients had raised creatine kinase and γ-glutamyl transpeptadase, and one patient with influenza A and bronchial asthma had combined respiratory failure and was critically ill. The chest CT manifestations of the three patients showed exudative changes in the form of patches of shadows; two patients showed lung nodules, and one patient had pleural thickenings and adhesion manifestations.

In terms of treatment protocols, one patient was given meropenem as the starting regimen and two were given ceftriaxone as the starting regimen; furthermore, two were provided with a maintenance regimen of cotrimoxazole and one was given a maintenance regimen of minocycline; the mean hospitalization day of the three patients was 12.3 days, and the mean hospitalization cost was $3,900 (Table III). After the treatment, all three patients improved, and the lesions were significantly improved.

T. whipplei is a gram-positive bacterium found mainly in water and soil. WD is most commonly seen in immunodeficient patients, such as HIV-infected patients with low CD4 levels, use of corticosteroid hormone therapy, diabetes mellitus, tumors, organ transplants and the use of TNF-α inhibitors, who are usually infected after contact with contaminated soil or water (8,9). WD is genetically susceptible to the human leukocyte antigen alleles DRB1*13 and DQB1*06 (10). WD mainly affects the digestive tract, nervous system, heart and skin, and less frequently the lungs. It has been reported that the respiratory infection rate of WD is only 13-14%, that the digestive system mainly manifests symptoms such as weight loss due to malabsorption, abdominal pain and diarrhea, and that some patients suffer from insidious gastrointestinal hemorrhage; some patients also have hidden gastrointestinal bleeding (10,11). The common clinical manifestations of the respiratory system are chest pain, dyspnea, chronic cough and phlegm (8). Other systems are characterized by migratory arthritis, uveitis, endocarditis, pericarditis and a variety of neurological symptoms (12).

Laboratory results of WD showed that 90% of patients have combined anemia as well as iron, folate or vitamin B12 deficiencies, and ~1/3 had neutrophilia with decreased lymphocyte counts, hypoalbuminemia and elevated C-reactive protein being more common; if *T. whipplei* nucleic acid is not detected before treatment, some patients may test negative for *T. whipplei* nucleic acid after broad-spectrum antibiotic therapy, but this may be a false negative (4,13). It has been suggested that: i) Positive macrophage peroxynitrite-staining in pathologic tissues; ii) anomalies in pathological specimens and a positive *T. whipplei* polymerase chain reaction (PCR); and iii) a positive *T. whipplei* PCR in sterile tissues can validate the diagnosis of WD. When one of the three aforementioned criteria are met, the diagnosis is verified (14).

mNGS has performed well in identifying rare, novel, difficult-to-detect and co-infectious pathogens directly from clinical samples and has shown great potential in resistance prediction by sequencing antibiotic resistance genes, providing new diagnostic evidence that can be used to guide the treatment of infectious diseases (15). Owing to the rapid development of mNGS, the number of confirmed cases of WD has increased significantly, and the number of related case reports has also increased in recent years compared with the previous ones (16-18). The three patients with WD reported in the present study had their pathogens identified by mNGS.

The treatment of WD is mainly antibiotic anti-infection treatment; commonly used drugs include penicillin, tetracycline, streptomycin, ceftriaxone, meropenem, hydroxychloroquine, doxycycline and cotrimoxazole (4). Initial treatment with ceftriaxone and meropenem for 2 weeks followed by maintenance treatment with cotrimoxazole

for ~1 year is the typical treatment protocol, but in recent years, some studies have shown that *T. whipplei* is resistant to cotrimoxazole, which may increase the chances of recurrence of WD (19-21). In this situation, doxycycline combined with hydroxychloroquine as an alternative treatment can also achieve improved efficacy (19-21).

In the present case reports, one patient improved after treatment with ceftriaxone combined with cotrimoxazole; one patient improved after treatment with meropenem combined with cotrimoxazole; and one patient benefited after treatment with ceftriaxone combined with minocycline. There are fewer reports related to the treatment of WD with minocycline, which provides some value to the study of minocycline for WD. Clinical symptoms of WD improve significantly within a few days to weeks after treatment with antibiotics, but WD requires a certain period of maintenance therapy to prevent recurrence (22). Nevertheless, WD has a lifelong potential for relapse, and Lin *et al* (6) suggested that the disease requires lifelong monitoring.

WD is a rare multi-system disease with no obvious specificity in clinical manifestations, laboratory tests, or imaging tests. Currently, WD can be diagnosed by mNGS detection of *T. whipplei*, which can achieve early diagnosis and early treatment. Previous studies only indicated that WD disease damages the respiratory system, but there were no concrete case reports. In the present case report, the three patients, all with the respiratory system as the main manifestation, achieved good efficacy after treatment, and there was no recurrence or death in the follow-up, which provides a valuable reference for the diagnosis and treatment of WD in the future. Since they did not have obvious symptoms of other systems, they did not have other system-related examinations, which demonstrates that clinical physicians need to fully communicate with the patients and screen for multisystemic diseases in WD. Furthermore, to the best of our knowledge, there have been no reports of differences in symptoms or prognosis due to differences of ethnicity. It is necessary to merge Asian and Caucasian data on Whipple's disease for analysis to clarify whether ethnic differences lead to different symptoms or prognosis; however, due to regional discrepancies, the present study was unable to do this.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YD conceived and designed the work. YD and XC analyzed and summarized the data and wrote the manuscript. HZ, ZZ, JL and TZ collected the laboratory examination and CT images of the case. XC critically revised the manuscript. YD and XC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Research Medical Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University.

Patient consent for publication

The patients involved in the present study were subjected to standard clinical practice and provided written, informed consent for publication.

Competing interests

The authors declare that they have no competing interests.

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