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Pneumonia is the main manifestation combined with skin infection with Whipple's disease: report of two cases and literature review

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ABSTRACT

To explore the clinical characteristics and treatment strategies of pulmonary and cutaneous infections caused by Tropheryma whipplei. We report a case of T. whipplei infection presenting primarily as pneumonia and skin infection. Using the keywords "Whipple's disease" and "lung," we searched the Wanfang and CNKI databases, retrieving 12 Chinese articles. Additionally, we searched PubMed and Google Scholar with the keywords "Whipple's disease" and "lungs," reviewing 5 foreign articles. A patient with persistent symptoms of cough, sputum, and wheezing despite initial antibiotic treatment was diagnosed with T. whipplei infection through metagenomic next-generation sequencing (mNGS). After adjusting the antibiotic regimen, the patient's symptoms significantly improved. Combining this case with 19 previously reported cases, a total of 20 cases were analyzed, including 3 females and 17 males. Among them, 7 patients had compromised immune systems, 6 had chronic underlying diseases, 3 were on long-term immunosuppressive therapy, 2 had skin involvement, and 1 was on targeted therapy. Commonly used treatments included sulfamethoxazole, ceftriaxone, piperacillin-tazobactam, doxycycline, and imipenem. Following targeted antibiotic therapy, 19 patients recovered, and 1 died. T. whipplei is an opportunistic pathogen, and the clinical manifestations and imaging findings of Whipple's disease are nonspecific. When initial antibiotic therapy fails, mNGS should be promptly utilized to identify the pathogen. Targeted treatment for T. whipplei generally leads to a favorable prognosis in most patients.

KEYWORDS

Whipple's disease; lung with skin infection; immunodeficiency; prognosi

Whipple's Disease (WD) is caused by infection with *Tropheryma whipplei* (TW), a Gram-positive, facultative aerobic bacillus that is widely present in the environment and acts as a commensal bacterium in humans. WD is a rare, chronic systemic disease. In previous studies, TW was rarely considered pathogenic. However, current evidence suggests that TW has a broad spectrum of clinical infections, including chronic systemic infections, chronic localized infections, and acute infections [1]. Humans are the only known host of TW [2]. WD has been rarely reported in China, with even fewer cases involving the central nervous system and respiratory system [3]. The disease is more commonly observed in middle-aged white males, with an annual incidence of >1/1,000,000. This paper reports two cases of TW infection presenting initially with pulmonary infections and skin involvement. The diagnosis was confirmed by detecting TW in bronchoalveolar lavage fluid (BALF) using metagenomic next-generation sequencing (mNGS). Antibiotic treatment was adjusted according to guidelines, resulting in significant therapeutic outcomes. By reviewing both domestic and international literature, this study aims to enhance the diagnosis and treatment of this disease.

1 Clinical Data

A 58-year-old male farmer was admitted on June 9, 2022, due to "cough with wheezing for over one month, aggravated for 3 days." The patient experienced unexplained dry cough without sputum, accompanied by wheezing after physical activity. There was no fever, chest pain, hemoptysis, loss of appetite, abdominal pain, or diarrhea. A chest CT scan performed at a local hospital on June 7 revealed: (1) multiple round, speckled, and nodular shadows in the subpleural regions of both lungs, suggesting the need for enhanced imaging or biopsy to differentiate between infection, organizing pneumonia, neoplastic lesions, or other conditions; and (2) a linear shadow in the left upper lobe, possibly indicating localized atelectasis or fibrosis. The patient received intravenous treatment (details unknown) at the local hospital on June 7, with unsatisfactory results. He was admitted to our hospital for further evaluation of "lung shadows of unknown origin." The patient had a medical history of a cavernous hemangioma in the left cerebellar hemisphere, which was untreated, and a family history of ankylosing spondylitis. He reported elevated blood pressure over the past week, with diastolic pressure >90 mmHg, and was taking hydrochlorothiazide for blood pressure control, with suboptimal results. On admission, his vital signs were as follows: body temperature 36.6°C, pulse 79 beats/min, respiratory rate 18 breaths/min, blood pressure 133/94 mmHg, height 182 cm, and weight 86 kg. Physical examination revealed dullness on lung percussion, coarse breath sounds, and dry and wet rales in both lungs. Cardiac and abdominal examinations were

unremarkable. Symmetrical hyperkeratosis was observed on the palms and soles, as shown in Figure 1. Neurological examination revealed no abnormalities. Laboratory tests on June 9 showed: white blood cell count 5.64×10^{9}/L, hemoglobin 119 g/L, platelet count 267×10^{9}/L, neutrophil percentage 75.8%, erythrocyte sedimentation rate 50 mm/h, procalcitonin 0.1 ng/mL, and C-reactive protein 41.79 mg/L. The 1,3-β-D-glucan test (G-test) was negative. Tests for SARS-CoV-2 (oropharyngeal swab), influenza A, and influenza B (nasopharyngeal swab) were all negative. Viral serology, lung cancer markers, and coagulation profiles were normal. Abdominal ultrasound indicated mild fatty liver and prostatic hyperplasia with calcification, while the gallbladder, pancreas, spleen, kidneys, and bladder appeared normal. Sputum culture, fungal culture, purified protein derivative (PPD) test, and acid-fast staining of sputum smears on June 11 were all negative. The admission diagnoses were: (1) lung shadows (bilateral lung lesions of unknown etiology) and (2) hypertension. Initial treatment included intravenous ceftazidime 1.0 g three times daily and levofloxacin 0.5 g once daily for anti-infective therapy, supplemented with salbutamol 2.5 mg + acetylcysteine 0.3 g twice daily via nebulization for wheezing relief. Bronchoscopy was performed on June 10, and bronchoalveolar lavage fluid (BALF) was sent for metagenomic next-generation sequencing (mNGS). On June 11, mNGS results identified *Tropheryma whipplei* at 2×10^{3} copies/mL, with no other bacteria, fungi, viruses, parasites, or atypical pathogens detected. Given the patient's family history of spondyloarthropathy, a sacroiliac joint CT scan was performed on June 11, revealing blurred edges of the bilateral sacroiliac joints, localized sclerosis and erosion, and mild joint space narrowing. Human leukocyte antigen B27 (HLA-B27) was positive, indicating a potential immunodeficiency disorder and increased risk of opportunistic infections. Based on the clinical presentation and mNGS results, a diagnosis of *Tropheryma whipplei* infection was confirmed. The antibiotic regimen was adjusted to intravenous ceftriaxone 2 g + levofloxacin 0.5 g once daily. By June 15, the patient's cough and wheezing had significantly improved, and lung rales were reduced. A follow-up CT scan on June 15 showed marked reduction in lung infections (as shown in Figure 2, left). Anti-infective therapy was continued, and by June 22, the patient's symptoms had further improved, with stable condition. He was discharged with a prescription for oral doxycycline 200 mg once daily for at least 12 months. A follow-up CT scan on August 8 demonstrated significant resolution of pulmonary inflammation (as shown in Figure 2, right).

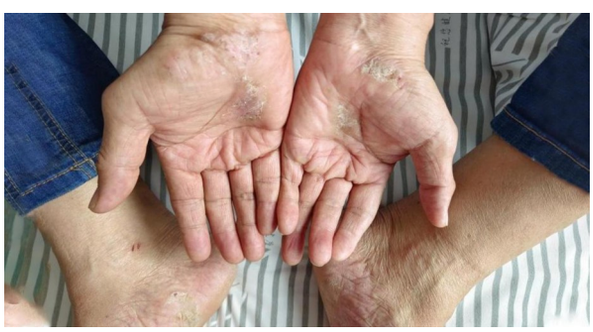

Figure 1 Cutaneous manifestations of the patient

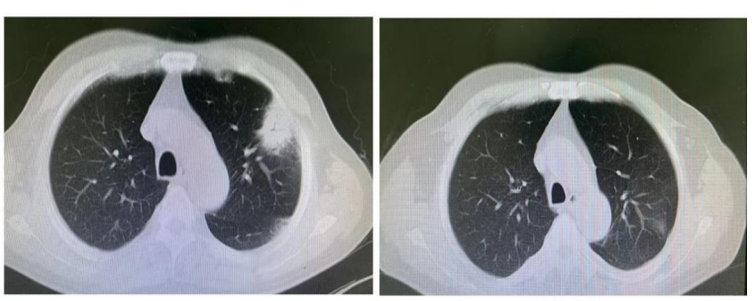

Figure 2 Chest CT scans from June 15 (left) and August 8 (right)

2 Literature Review

A comprehensive literature search was conducted using the keywords "Whipple's disease" and "lung" in the Wanfang and CNKI databases, and "Whipple's disease" and "lungs" in PubMed and Google Scholar. The search was limited to studies published up to September 2024. After excluding studies with incomplete clinical data or duplicate publications, a total of 17 articles were included, reporting 19 cases. Among these, 12 were Chinese articles , including 6 case reports, 1 literature review, and 5 original articles, reporting 14 cases. Additionally, 5 foreign articles were included, all of which were case reports, describing 5 cases.

A total of 20 cases were reported across 17 domestic and international studies. Zeng Haoyu et al. [4] reported a 28-year-

old male diagnosed with *Tropheryma whipplei* via mNGS, presenting with bilateral lung consolidation on imaging. The patient improved after treatment with ceftriaxone and sulfamethoxazole-trimethoprim. Zhou Ying described two male patients, aged 25 and 39, without underlying diseases, diagnosed with *T. whipplei* via mNGS. Imaging revealed multiple bilateral lung nodules with cavitation and small vacuoles within some lesions. Both patients improved after sulfamethoxazole treatment. Wang Lu et al. reported a 58-year-old male with underlying conditions including type 2 diabetes, uremia, renal hypertension, hyperlipidemia, and hyperuricemia, who was on immunosuppressive therapy with prednisone, mycophenolate sodium, and cyclosporine. Diagnosed via mNGS, imaging showed scattered inflammation, consolidation, and atelectasis in both lungs. The patient improved after treatment with meropenem and sulfamethoxazole-trimethoprim. Zhang Haiming et al. reported three cases, including a 29-year-old male with fatty liver and sleep apnea syndrome, diagnosed via mNGS, showing bilateral ground-glass opacities on imaging. He improved after treatment with meropenem and doxycycline. A 57-year-old male without underlying diseases, diagnosed via mNGS, exhibited cavitary and exudative lung lesions and improved after piperacillin-tazobactam and moxifloxacin treatment. A 42-year-old female with fatty liver and HIV infection, diagnosed via mNGS, showed diffuse ground-glass opacities, mediastinal lymphadenopathy, and pleural thickening. She improved after meropenem and doxycycline treatment. Lin Jiaping et al. reported a 67-year-old male with hypertension and advanced lung cancer, diagnosed via mNGS. Imaging revealed thickened lung markings, diffuse patchy opacities, ground-glass changes, and pleural effusion. Despite treatment with ceftriaxone and doxycycline, the patient died. He Qian et al. described a 51-year-old male diagnosed via mNGS, showing patchy and linear opacities in the right middle and lower lobes. He improved after ceftriaxone and sulfamethoxazole-trimethoprim treatment. Chen Ping et al. reported a 57-year-old female with rheumatic heart disease, mitral stenosis, and atrial fibrillation, diagnosed via mNGS. Imaging showed inflammatory lesions in the right middle and lower lobes and the left upper lingular segment. She improved after ceftriaxone and sulfamethoxazole-trimethoprim treatment. Wu Xinggui et al. reported a 56-year-old male with hypertension, type 2 diabetes, solitary pulmonary nodule, and coronary artery disease, diagnosed via mNGS. Imaging revealed multiple small nodules, ground-glass opacities, and a soft tissue mass in the left upper lobe. He improved after ceftriaxone and sulfamethoxazole-trimethoprim treatment. Han Yingjie et al. described a 60-year-old male diagnosed via mNGS, showing abnormal density in the left lower lobe, a nodule in the right upper lobe, and centrilobular emphysema. He improved after ceftriaxone and doxycycline treatment. Lu Xing et al. reported a 21-year-old male diagnosed via mNGS, with clustered high-density opacities in the right upper lobe and left lower lobe. He improved after ceftriaxone and doxycycline treatment. Zhou Xinyi et al. reported a 44-year-old male with uveitis on immunosuppressive therapy (methylprednisolone, cyclosporine, and thalidomide), diagnosed via mNGS. Imaging showed consolidation in the right upper lobe and mediastinal lymphadenopathy. He improved after ceftriaxone and sulfamethoxazole-trimethoprim treatment. Yue Xiaolei et al. described a 68-year-old male with diabetes, Alzheimer's disease, pulmonary mucinous adenocarcinoma, and squamous cell papilloma, on anlotinib. Diagnosed via mNGS, imaging revealed bilateral inflammatory changes, nodules, a right lung mass, and pleural effusion. He improved after piperacillin-tazobactam treatment. Jun Y et al. [5] reported a 28-year-old male with HIV, diagnosed via mNGS, showing bilateral ground-glass opacities. He improved after treatment with sulfamethoxazole-trimethoprim, meropenem, caspofungin, and methylprednisolone. Mei WZ et al. [6] described a 26-year-old male diagnosed via mNGS, with a thick-walled cavity in the left upper lung and vascular convergence. He improved after ceftriaxone and sulfamethoxazole-trimethoprim treatment. Yifan G et al. [7] reported a 23-year-old female diagnosed via mNGS, who improved after treatment with imipenem and polymyxin B. Binghua Z et al. [8] reported a 44-year-old male with type 2 diabetes and hepatitis C, diagnosed via mNGS, showing miliary nodules and ground-glass opacities. He improved after treatment with trimethoprim-sulfamethoxazole, isoniazid, rifapentine, amikacin, and ethambutol.

3 Discussion

Although Whipple's disease (WD) was first described in 1907, *Tropheryma whipplei* (TW) was successfully cultured only a century later, significantly advancing scientific understanding of infections caused by this bacterium [9]. TW is an intracellular bacterium recognized as the causative agent of intestinal WD. The colonization rate of TW in humans depends on geographic region, age, and exposure methods [21]. The disease may have two primary modes of transmission: fecal-oral transmission in impoverished regions and saliva-mediated transmission in affluent countries, suggesting a purely interpersonal spread [10]. In South Africa, TW is among the most common fecal microorganisms [11]. The classic clinical manifestations of WD include arthralgia (87%), diarrhea (81%), weight loss (93%), lymphadenopathy (52%), neurological symptoms (33%), fever (38%), and hyperpigmentation (41%). However, 15% of patients lack these typical symptoms [12]. Most individuals develop a protective immune response to TW infection, and asymptomatic infections are common. Disease progression in a minority of individuals may be due to subtle genetic predispositions or immunodeficiencies [25]. WD is a systemic infectious disease primarily affecting the gastrointestinal tract. Long-term antibiotic use may increase the risk of *Helicobacter pylori* infection [13]. Recent studies using culture-independent

techniques to examine the lung microbiome have shown that TW is present in the lungs of healthy individuals. TW in the lungs may originate from the aspiration of gastric contents or translocation from the gastrointestinal tract [14]. Nevertheless, it remains challenging to assess the pathogenic role of TW in pneumonia [15]. After diagnosing WD via metagenomic next-generation sequencing (mNGS), a review of relevant literature revealed that TW-induced skin infections can manifest as hyperkeratosis. Additionally, the cutaneous manifestations of classic WD can be divided into nonspecific and specific skin lesions. Nonspecific lesions are often associated with malnutrition-related dermatoses, while specific lesions exhibit histopathological features characteristic of WD. These may present as hyperpigmentation, ecchymosis, purpura, hyperkeratosis, peripheral edema, subcutaneous nodules, or erythema nodosum-like lesions. The lesions are typically multifocal, predominantly localized to the lower extremities, but may also appear on the upper extremities, trunk, face, and neck [16].

The case reports presented in this study, combined with a review of the literature, demonstrate that the clinical manifestations of Whipple's disease (WD) are nonspecific. Most patients present with symptoms such as cough, sputum production, and dyspnea upon exertion. Radiological findings of WD typically include consolidation, nodules, and cavities of varying sizes, which may be solitary or multiple. The clinical and radiological features of WD closely resemble those of pneumonia, tuberculosis, fungal infections, and bronchiectasis, making differential diagnosis challenging. When TW is co-infected with other bacteria or viruses, the clinical manifestations are often more severe, and the response to anti-infective therapy is poor. For patients with immunodeficiency, the risk of opportunistic infections is significantly higher. In cases of treatment failure or recurrent infections, it is crucial to promptly obtain etiological evidence and adjust the antibiotic regimen to target the specific pathogen. This approach ensures effective anti-infective therapy and improves patient outcomes.

The key to a definitive diagnosis lies in obtaining etiological evidence. The detection of *Tropheryma whipplei* (TW) traditionally relies on periodic acid-Schiff (PAS) staining of small intestinal biopsies, where granular "foamy" macrophages can be observed under light microscopy. However, this method has low specificity, as PAS-positive macrophages may persist for years even after successful eradication of TW [17]. Alternatively, metagenomic next-generation sequencing (mNGS) applied to bronchoalveolar lavage fluid (BALF) enables in situ sequencing of all nucleic acids, allowing for the detection of TW DNA. The clinical applications of mNGS are extensive, including infectious disease diagnosis, outbreak tracking, infection control monitoring, and the discovery of novel pathogens. It has been widely adopted to guide infectious disease management and inform treatment strategies [18]. In this study, one case and a total of 20 cases from the literature review were diagnosed with TW through mNGS. Therefore, when etiological diagnosis is unclear, mNGS can be utilized to obtain genomic information on rare microorganisms without the need for culturing [19]. This approach is particularly valuable for identifying pathogens that are difficult to detect using conventional methods.

Whipple's disease (WD) is a lifelong condition, with recurrence and reinfection caused by different strains of *Tropheryma whipplei* (TW) even in patients who have been apparently cured. Recurrence can occur up to 20 years after the initial diagnosis and may involve previously unaffected organs. Currently, there are no specific treatment guidelines or recommendations for acute infections or chronic carriers [20]. If not promptly identified and treated, central nervous system involvement may develop, which can be fatal [21]. The risk of TW remaining latent in the body for years after discontinuation of antibiotic therapy is estimated to be 9%-15% [22]. Therefore, long-term anti-infective therapy is essential. Based on the literature review, the commonly used treatment regimens include sulfamethoxazole, ceftriaxone, piperacillin-tazobactam, doxycycline, and imipenem. For patients intolerant to ceftriaxone, meropenem can be used as an alternative. Similarly, for those intolerant to sulfamethoxazole, doxycycline may serve as a substitute. Once the pathogen is identified, timely adjustment of antibiotics for targeted anti-infective therapy leads to significant improvement in most patients.

In summary, *Tropheryma whipplei* (TW) is an opportunistic pathogen that predominantly affects individuals with compromised immune systems or those on long-term immunosuppressive therapy. When empirical antibiotic therapy fails, the possibility of TW infection should be considered. Given that the clinical features and imaging findings of TW infection are nonspecific, and the sensitivity of sputum cultures and histopathological examinations is extremely low, timely diagnosis through metagenomic next-generation sequencing (mNGS) of bronchoalveolar lavage fluid (BALF) is crucial. Once the pathogen is identified, prompt initiation of targeted antibiotic therapy is key to improving clinical outcomes and prognosis.

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