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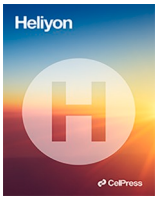

Case report

Acute pneumonia due to *Tropheryma whipplei* diagnosed by metagenomic next-generation sequencing and pathology: A case report

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ABSTRACT

Tropheryma whipplei (TW) is a rod-shaped, gram-positive bacterium that, when chronically infects humans, can lead to multi-system pathologies, including joint pain, abdominal pain with diarrhea and weight loss, myocarditis, pericarditis, and neurologic inflammation. Moreover, acute infections can lead to bronchopulmonary infections, bacteraemia, and acute diarrhea. However, fewer cases of acute pneumonia due to TW have been reported, and this diagnosis is not well founded. Herein, we report a case of acute pneumonia caused by a TW infection. The patient, a middle-aged man, underwent bronchoscopic alveolar lavage, and the metagenomic next-generation sequencing of the lavage fluid suggested TW infection. A lung puncture biopsy tissue specimen was also positive based on periodic acid-Schiff staining. After confirming the diagnosis, the patient was administered ceftriaxone for anti-infection treatment, improving clinical symptoms and lung imaging results. Therefore, in cases where conventional anti-infective treatment is ineffective for patients with acute pneumonia, we should consider the possibility of TW infection, conduct prompt pathogenetic examination, and provide timely treatment after diagnosis to improve overall patient prognosis.

1. Introduction

Whipple's disease is a clinically rare infectious disease, first described by George Hoyt Whipple in 1907 [1]. Subsequently, Wilson et al. determined that it is caused by a newly discovered bacterium, taxonomically belonging to the Actinobacteria order Fibrillomonadaceae, named *Tropheryma whipplei* (TW). This determination was based on the detection of 16S rRNA in specimens from patients with Whipple's disease at the site of duodenal injury via polymerase chain reaction (PCR) [2]. The clinical manifestations of Whipple's disease are highly polymorphic and can be categorised into at least four types, including classical Whipple's disease, limited chronic infection, acute infection, and asymptomatic carriage [3,4]. Acute infections often present as gastroenteritis, pneumonia, and bacteraemia [5]. TW infections in immunodeficient patients can lead to acute pneumonia [6,7]. However, there are difficulties in

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diagnosing this disease. This report presents the diagnosis and management of an immunocompetent patient with acute pneumonia, who was diagnosed with TW infection based on an alveolar lavage metagenomic next-generation sequencing (mNGS) test and tissue puncture staining of lung lesions. To our knowledge, this is the first case diagnosed by mNGS co-pathology.

2. Case presentation

A 62-year-old male patient presented with "cough and sputum with intermittent fever for 3 days", who had a history of tuberculosis 10 years ago, which had been cured after systematic anti-tuberculosis treatment. There was no history of diabetes mellitus, malignant tumors, organ transplantation, or long-term use of glucocorticoids or immunosuppressive drugs. Before admission, a chest X-ray suggested: multiple patchy high-density shadows in both lungs, the patient's highest temperature reached 41 °C, high fever with chills, cough, cough yellow sputum, no symptoms such as abdominal pain, diarrhea, joint pain, etc., after taking antipyretic medication the body temperature can be lowered to normal, and then rises again after 5–6 hours, and the anti-infective treatment plan of the outside hospital is not known.

The patient's temperature was 40.2 °C on admission, the rest of his vital signs were normal, and a few wet rales were audible on lung auscultation. After admission, the chest CT examination was perfected, suggesting that there were multiple nodular and patchy high-density shadows in both lungs, with some foci of solid lesions (Fig. 1a). A CT scan of the entire abdomen did not show any obvious abnormalities, and routine blood tests revealed a white blood cell count of 11.24×10^9/L, with 80.7% neutrophils and a lymphocyte count of 1.08×10^9/L. Blood biochemistry results revealed levels of serum albumin at 29.3 g/L, ferritin at 450.91 ng/mL, and C-reactive protein at 28.3 mg/L; haematocrit at 57 mm/hr; and blood sedimentation rate at 57 mm/hr. Additionally, routine urine and stool examination, along with tests for calcitonin gene, coagulation function, HIV antibody testing, (1,3)-β-D-glucan and galactomannan levels, respiratory pathogen nucleic acid, lung tumour marker, T lymphocyte subpopulation, T cell spot test for *Mycobacterium tuberculosis* infection in blood (T-spot), and other relevant tests yielded normal results.

The patient was admitted to the hospital with a diagnosis of pulmonary infection, with emphasis on identifying tuberculosis, fungal

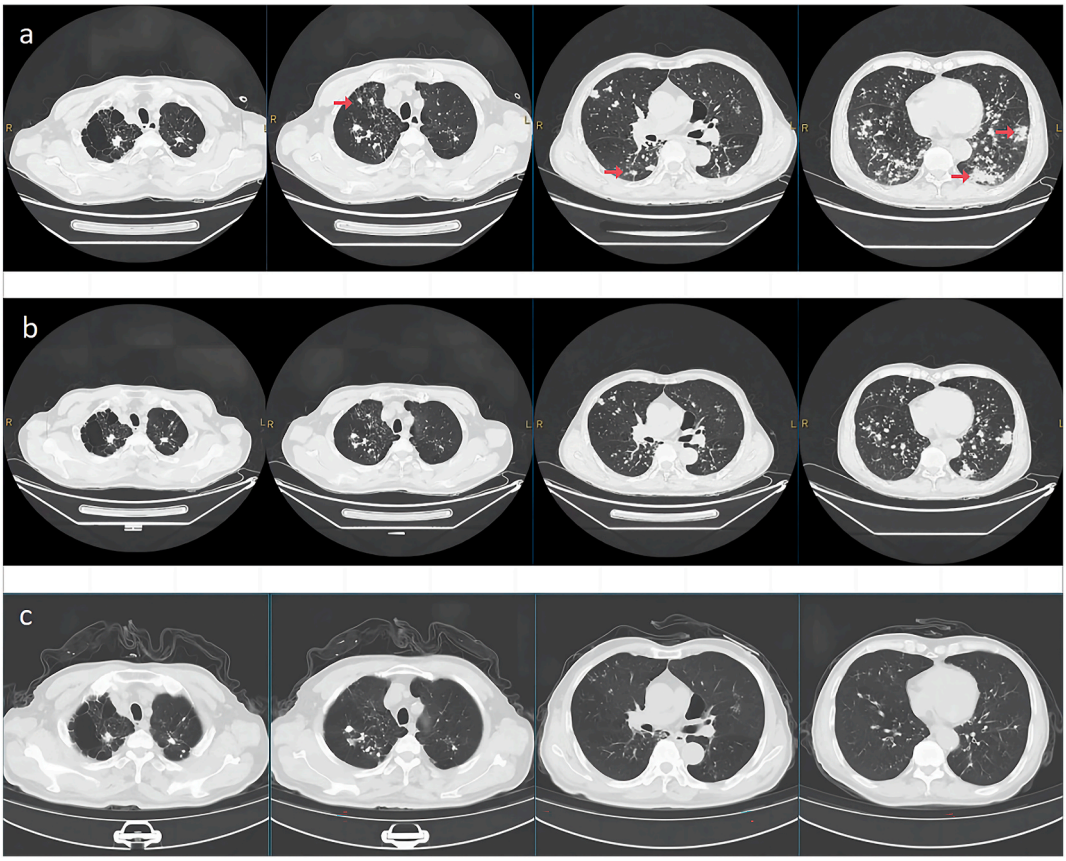

Fig. 1. Chest CT of the patient on the 1st and 10th day of admission and 2 months after discharge, (a) Chest CT of the patient on admission showed multiple nodular and patchy hyperdense shadows in both lungs, shown by red arrows, (b) Chest CT of the patient after 10 days of treatment showed partial resorption of the lesions compared with the previous ones, (c) Chest CT of the patient after 2 months of discharge suggested continued resorption of the lesions compared with the previous ones, especially the resorption of the lesions in the lower lungs was obvious. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and rare pathogen infections. Piperacillin-tazobactam (4.5g q8h) was empirically selected for anti-infective treatment after the diagnosis on admission to the hospital. However, the patient continued to experience recurrent fever without a significant decrease in peak temperatures, and the results of blood culture, sputum culture, sputum acid-fast bacilli tests yielded negative results. Additionally, we conducted electronic bronchoscopy for the patient, which revealed a small amount of mucous secretion in the bronchial tubes of each lobar segment, with clear lumens after aspiration. Because all previous pathogen test results were negative, we sent the alveolar lavage fluid to metagenomic next-generation sequencing (mNGS) for testing, which detected TW with a sequence number of 36543 and an abundance of 0.43%, and no other pathogens were detected.

Based on the patient's symptoms and imaging results, no other pathogens were identified through mNGS, and previous tests for tuberculosis and fungi were negative, we considered TW as the likely causative agent. To confirm TW infection, we performed a puncture biopsy of the lung lesion in the patient's left lower lobe, revealing positive results with PAS staining (Fig. 2). Combining the patient's clinical symptoms, imaging findings, and laboratory results, we diagnosed the patient with acute pneumonia caused by TW. Following recommendations from relevant studies [5], we adjusted the treatment from piperacillin-tazobactam to intravenous ceftriaxone (2g qd). The patient's temperature normalized after two days of treatment, and the symptoms of cough and sputum improved, the specific temperature trend graph and the anti-infective treatment are shown in Fig. 3. A follow-up chest CT after one week showed partial absorption of the lung lesion compared to the previous scan (Fig. 1b). To rule out the possibility of concurrent intestinal lesions, we performed a colonoscopy, which revealed no abnormalities. With symptom improvement, the patient was discharged after two weeks and advised to take oral cotrimoxazole (160/800mg bid) after discharge. A chest CT follow-up two months later showed continued absorption of the lung lesion (Fig. 1c). Meanwhile, the patient indicated at this follow-up visit that the treatment effect was obvious and he was free of discomfort at present.

3. Discussion

TW is a conditionally pathogenic commensal organism often found in contaminated environments, such as sewage and soil, and is known to be transmitted via the faecal–oral route. It is also present in the saliva of asymptomatic people and has been detected in 3% of bronchoalveolar lavage fluid samples and peripheral blood of patients with pneumonia, suggesting that the oral inhalation of TW by patients can lead to pneumonia [7,8]. The mechanism by which TW causes pneumonia may be related to its survival within macrophages, which are the main target cells for TW infection. The abundance of macrophages in the alveolar tissue possibly provides a suitable environment for TW to survive [5]. In the present case, the patient had no gastrointestinal symptoms, and the colonoscopy and CT of the whole abdomen did not reveal any notable abnormalities. Therefore, it was hypothesized that the patient inhaled TW from the saliva, causing lung infection. Subsequent mNGS of tracheoscopic lavage fluid and periodic acid-Schiff (PAS) staining of lung puncture tissue confirmed the diagnosis for the patient.

In recent years, few cases of acute pneumonia caused by TW have been reported. Andreas et al. reported a case of acute pneumonia after infection with TW in a 24-year-old male patient with a history of HIV infection who was treated with ceftriaxone and cotrimoxazole, administered sequentially after diagnosis, and discharged from the hospital 2 weeks later [6]. In a US study of pulmonary TW colonization in HIV-infected patients, 33 (13.4%) of 76 HIV-positive patients with alveolar lavage or induced sputum were TW-positive [9]. Lagier et al. performed PCR testing for T Whipple on 1,438 alveolar lavage samples, identifying 88 positive cases, including 58 cases of patients with pneumonia. A subsequent subgroup analysis based on the immunodeficiency status of the patients revealed that the immune status has no significant effect on TW infection [10]. Our patient had a history of tuberculosis, with no record

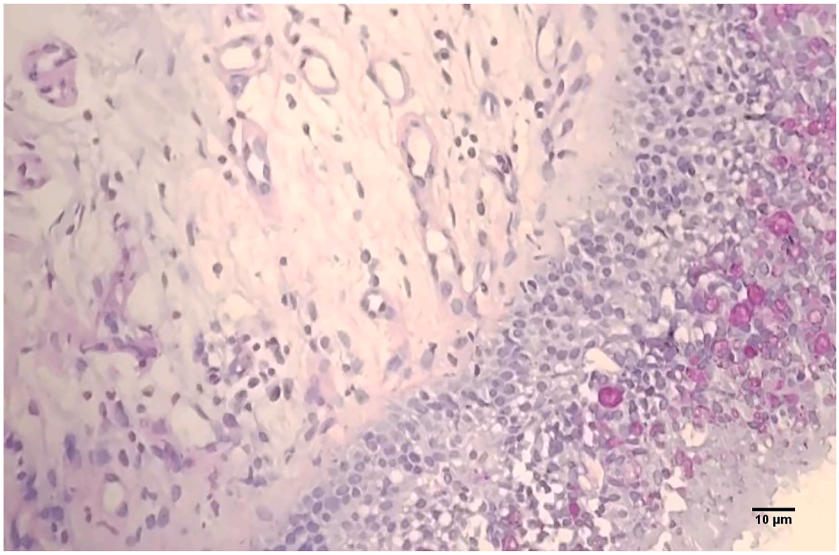

Fig. 2. Positive PAS-stained sections of the patient's lung puncture biopsy specimen (× 10).

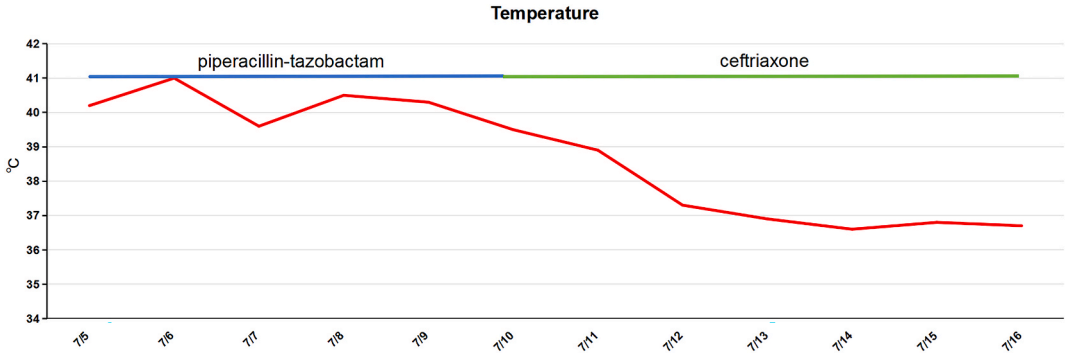

Fig. 3. Trend chart of the patient's temperature and course of anti-infective treatment.

of organ transplantation, chemotherapy, or prolonged use of glucocorticoids. The T-lymphocyte subpopulations were within normal range, and there was no evidence of immunodeficiency. However, through our detailed questioning of the patient's history, we found that this patient was a waste disposal worker with a history of rain showers before admission, and that the patient had recently had poor sleep, sleeping only 2–3 hours per day. Therefore, we considered that the patient's TW infection was related to recent immunocompromise and high exposure to TW-contaminated environment. In summary, further studies are necessary to ascertain any potential correlation between immune status and TW infection.

TW infection can lead to a variety of symptoms; gastrointestinal symptoms, such as chronic diarrhea, abdominal pain, and weight loss due to malabsorption, can be observed in typical Whipple's disease. Patients can also exhibit symptoms such as arthralgia [11]. In our case, the lungs were predominantly involved, and hence, the symptoms included cough, sputum, and fever without any other systemic symptoms. Hujoel et al. found that the most common abnormalities, based on laboratory investigations following TW infection, were anemia and elevated C-reactive protein levels [12]. Notably, 50% of the patients exhibited an elevated erythrocyte sedimentation rate and hypo-proteinemia. The presence of elevated C-reactive protein, increased sedimentation rate, and hypo-proteinemia in our patient is more in line with the findings of the study.

Zhang et al. retrospectively analyzed the case data of 20 patients with pulmonary infections due to TW and reported variable imaging presentations, with ten patients presented with pulmonary nodules, five with interstitial changes, five with patchy shadows, and a few with cavities, enlarged mediastinal lymph nodes, and pleural effusions [13]. Imaging examination in our patient revealed predominant pulmonary nodules; some of which were observed as patchy shadows with solid changes. Although the mechanism by which TW causes lung injury is unclear, previous findings suggest that it may result in impaired macrophage degradation, decreased cytokine secretion, and induction of apoptosis in host cells [4]. With more in-depth studies of the disease, a more definitive mechanism of lung injury will become available in the future.

Currently, the diagnosis of TW primarily relies on histopathological tests, including PAS staining and quantitative PCR [5]. In recent years, owing to the popularisation of mNGS technology, TW has also been detected in some body fluid specimens, especially in the alveolar lavage fluid of many patients with pneumonia. Lin et al. detected 70 TW-positive alveolar lavage specimens in 1725 cases, among the cases, 15 patients were diagnosed with pneumonia [14]. However, determining the specific causative pathogens posed a challenge because in most cases, multiple pathogens were simultaneously detected using mNGS. In the present case, TW was identified as the only pathogen, confirmed through PAS staining of the lung puncture biopsy specimen, and no abnormality was observed in the colonoscopy; thus, it can be assumed that TW was the causative pathogen of the lung infection in the patient.

The most common anti-infective regimen for the treatment of Whipple's disease includes intravenous ceftriaxone (2 g qd) or meropenem (1 g q8h, if ceftriaxone is not tolerated) for 2 weeks, followed by cotrimoxazole for 1 year, or doxycycline if cotrimoxazole is not tolerated. Another alternative regimen that has been used by some specialists is hydroxychloroquine (600 mg qd) and doxycycline (200 mg qd) for 12 months [15,16]. The general recommendation involves collecting duodenal biopsy specimens at 6-month intervals during the follow-up period, and treatment continuation is advised as long as these biopsy specimens remain positive. However, this follow-up strategy is currently controversial, mainly because frequent surgical biopsies increase the physical and financial burden on the patient; moreover, a positive biopsy specimen for PAS does not indicate uncontrolled disease. Furthermore, considering the high recurrence rate of Whipple's disease, certain experts propose lifelong maintenance treatment with doxycycline to prevent reinfection following alternative therapy with doxycycline (200 mg qd) and hydroxychloroquine (600 mg qd) for 12 months [17]. In our patient, after the sequential administration of ceftriaxone and cotrimoxazole, substantial improvements were noted in symptoms and imaging results.

4. Conclusion

In this report, we presented the case of acute pneumonia caused by a TW infection, where alveolar lavage mNGS combined with pathologic PAS staining of lung puncture biopsy facilitated the diagnosis of TW infection. Clinical consideration should be given to the possible presence of TW infections in patients with pneumonia who are unresponsive to empiric anti-infective therapy. Alveolar lavage mNGS testing combined with PAS staining of lung puncture biopsy tissue may complement each other for diagnosing TW-associated

lung infection. Furthermore, the sequential administration of ceftriaxone and cotrimoxazole may be the treatment of choice for Whipple's disease. In addition, late dynamic follow-up is also essential to assess changes in the patient's condition. However, there are some limitations in this case report, on the one hand, the cause and route of the patients' infection with TW are still unclear, and on the other hand, the mechanism of the patients' pathogenesis is still unknown.

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Ethics statement

The ethics Statement was not applicable for case reports according to the Fuyang Infectious Disease Clinical College of Anhui Medical University; however, informed consent was obtained from the patient. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Ya Shen: Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Formal analysis, Conceptualization. **Shun-shun Cui:** Writing – original draft. **Xiao-bao Teng:** Writing – original draft. **Ming-feng Han:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e26747.

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