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Co-infection of *Chlamydia psittaci* and *Tropheryma whippiei*: A case report

Zhu-Man Du, Pei Chen

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Abstract

BACKGROUND

The co-infection of *Chlamydia psittaci* (*C. psittaci*) and *Tropheryma whippiei* (*T. whippiei*) is unusual, and the detection of pathogenic microorganisms is particularly important for patients with severe diseases or poor experience in treatment. Early identification of pathogens can significantly improve the prognosis of the patients. Targeted next-generation sequencing (tNGS) is currently widely used in clinical practice for various infectious diseases, including respiratory infections, to achieve early, accurate, and rapid microbial diagnosis.

CASE SUMMARY

We report a case of a 40-year-old female patient with a history of contact with parrots who was diagnosed with *C. psittaci* and *T. whippiei* infection through bronchial lavage fluid targeted next generation sequencing. After moxifloxacin treatment, the patient's symptoms improved significantly, and the imaging changes were obviously resolved.

CONCLUSION

Coinfection with *C. psittaci* and *T. whippiei* is not common. In this case, timely and accurate identification of both pathogens was achieved using tNGS. Moreover, the efficacy of monotherapy with moxifloxacin was confirmed.

Key Words: Infectious diseases; *Chlamydia psittaci*; *Tropheryma whippiei*; Targeted next generation sequencing; Case report

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Core Tip: The co-infection of *Chlamydia psittaci* and *Tropheryma whippelii* is not common. Due to its ability to cause severe infections, timely and reliable diagnosis is crucial for improving prognosis. In recent years, the development of targeted next-generation sequencing has made the diagnosis of pathogenic microorganisms more economical and efficient.

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INTRODUCTION

Psittacosis is a zoonotic infectious disease caused by *Chlamydia psittaci* (*C. psittaci*), which is a gram-negative bacterium belonging to the *Chlamydia* spp. This pathogen mainly parasitizes parrots, pigeons, poultry, etc. Humans are mainly affected by direct contact with birds and poultry excrement and respiratory secretions. Handling the feathers, tissues, or corpses of infected birds also carries a risk of infection[1]. The first description of psittacosis in the medical literature was in 1879[2], and according to subsequent reports, psittacosis may be the cause of one percent of cases among community-acquired pneumonia[3]. Clinical manifestations of psittacosis vary from asymptomatic infection to severe systemic symptoms and may even lead to fatal systemic illness. Symptoms of infected individuals may include headache, chills, fever (even high fever), myalgia, and dry cough during the course of the disease, which may be accompanied by dyspnoea and chest tightness[4]. *Tropheryma whippelii* (*T. whippelii*) is a gram-positive bacterium first described by American pathologist George Hoyt Whipple in 1907 and belongs to the trophozoite genus[5]. The most obvious symptoms include arthralgia, diarrhoea, abdominal pain, and weight loss, and reports of endocarditis, nervous system infection, uveitis, arthritis and osteoarthritis infection can also be seen[6]. However, there are few reports about pneumonia caused by *T. whippelii*. A previous study found that the respiratory infection rate was only 13%-14%[7], of which only approximately 30% of patients had respiratory symptoms[8], but the symptoms were not typical and included dyspnoea, cough, chest pain, and vital capacity reduction[9]. Reports of coinfection of *C. psittaci* and *T. whippelii* are extremely rare, but due to their ability to cause severe infections, rapid progression, and life-threatening conditions, timely and reliable diagnosis is crucial for treatment.

In recent years, high-throughput sequencing methods have developed rapidly, mainly including whole genome sequencing (WGS), metagenomic next-generation sequencing (mNGS), and targeted next-generation sequencing (tNGS). Among them, WGS is less directly applied in clinical practice and is generally used in epidemiological investigations and research on the evolution of drug-resistant strains. MNGS can detect all pathogens in the sample without discrimination, while tNGS mainly focuses on common infectious pathogens in clinical practice. TNGS designs specific primers, uses a super multiplex polymerase chain reaction (PCR) library system to target and amplify the target sequence, and then uses high-throughput sequencing for synchronous detection of amplification products, achieving a new method of broad-spectrum accurate detection of pathogens. In this report, tNGS was used to confirm the clinical rarity of pneumonia caused by *C. psittaci* and *T. whippelii*.

CASE PRESENTATION

Chief complaints

A 40-year-old female patient was admitted to the hospital for fever on November 6, 2022.

History of present illness

The patient had a fever for 10 d and a maximum body temperature of 39.6 °C, accompanied by dizziness and headache, but she had no other symptoms, such as cough, abdominal pain, or diarrhea.

History of past illness

The patient had previously been physically fit, but she had bought three parrots one week before the onset of symptoms, one of which was sick.

Personal and family history

The patient had no special history of personal history or family history.

Physical examination

On examination, body temperature was 36.0 °C; heart rate was 94 beats/min; respiratory rate was 21 breaths/min; blood pressure was 100/72 mmHg; and pulse oxygen saturation was 96%. The patient was well built and cooperative, had no pharyngeal hyperaemia, and had no enlargement or purulent discharge of the tonsils. Breath sounds in both lungs were rough, and moist rales could be heard in the lower lobe of the right lung. Heart and abdominal examinations showed no

significant findings.

Laboratory examinations

A preliminary hematological examination (Table 1) showed that the hypersensitive C-reactive protein was significantly increased, transaminase and direct bilirubin were slightly increased, and electrolyte metabolism was deranged. The white blood cells and their respective classification ratios were normal, and procalcitonin was normal. In addition, during coronavirus disease 2019 (COVID-19), we tested the patient for COVID-19 nucleic acid, and the results were negative.

Imaging examinations

A computed tomography (CT) scan on November 6, 2022 (Figure 1A-C) revealed multiple large uneven ground glass shadows in the lower lobe of the right lung, with grid shadows visible inside, close to the pleura, and special pathogen infections could not be ruled out.

FINAL DIAGNOSIS

The patient received fiber bronchoscopy examination, and fiber bronchoscopy reached the lower lobe bronchus of the right lung. The lower lobe bronchus of the right lung was repeatedly irrigated. The collected samples were then sent to the laboratory for tNGS testing and analysis, which revealed *C. psittaci* and *T. whipplei* infection.

TREATMENT

The patient was treated with moxifloxacin 0.4 g once daily for 10 d.

OUTCOME AND FOLLOW-UP

During hospitalization, the patient experienced coughing, phlegm, and diarrhea. Following treatment, the body temperature returned to normal, and the above symptoms disappeared completely. Hypersensitive C-reactive protein, transaminase and direct bilirubin returned to normal values. After 10 d of anti-infection treatment with moxifloxacin, a CT scan on November 16, 2022 (Figure 1D-F) showed that patch shadows and ground glass shadows in the right lower lobe lesions were obviously resolved. After discharge, the patient insisted on taking moxifloxacin orally for one week, but she was unwilling to undergo a recheck chest CT again for a review as her physical condition was good.

DISCUSSION

This article reports a rare case of co-infection caused by *C. psittaci* and *T. whipplei*. There are no specific clinical manifestations of psittacosis, and routine detection methods lack sensitivity and specificity, making it difficult to determine the epidemiology of psittacosis. Before 2013, some literature mentioned the occurrence of psittacosis cases, but with the increasing number of poultry raised in households and farms, large-scale outbreaks of psittacosis have frequently occurred, especially since 2020. The majority of transmission modes of psittacosis are limited to human exposure to contaminated birds and their excreta. However, some literature has reported the possibility of human-to-human transmission, and there is no definitive conclusion on whether there is human-to-human transmission in the second and third generations[4]. The diagnosis and treatment of Whipple's disease in the digestive system is relatively mature, but reports of infection in the respiratory system are rare. In addition, strong evidence shows that *T. whipplei* is a pathogen of acute pneumonia. Previous studies have found that *T. whipplei* is detected in the alveolar lavage fluid of patients with immune deficiency and patients with pneumonia who were admitted to intensive care units[10,11]. This evidence strongly supports a link between *T. whipplei* and pulmonary infection. It is noteworthy that *T. whipplei* can also exist in the saliva of asymptomatic patients[12], who inhale pathogenic bacteria from the mouth, leading to pneumonia[13]. In this case, the patient had a clear history of contact with sick parrots, with fever symptoms initially appearing and headache and respiratory symptoms gradually developing during the course of the disease. Hematological examination showed that the hypersensitive C-reactive protein was significantly increased, and transaminase and direct bilirubin were slightly increased. These symptoms and examinations are consistent with psittacosis and *T. whipplei* pneumonia, and tNGS testing confirmed the presence of *C. psittaci* and *T. whipplei* in the alveolar lavage fluid.

In clinical practice, traditional microbial culture methods and empirical diagnosis are still the mainstream, and the efficiency of traditional pathogen diagnosis methods is not high. Bacterial cultivation takes a long time, and in clinical practice, it is usually not possible to wait until the pathogenic microorganisms have been reported before taking medication. In addition, the positive rate of microbial culture is relatively low, resulting in many pathogenic infections that cannot obtain microorganisms. The emergence of high-throughput sequencing technology has improved this situation to some extent. At present, a variety of high-throughput sequencing technology have been used for the identification of pathogenic microorganisms in clinical infectious diseases, especially when there is a lack of diagnostic clues, it

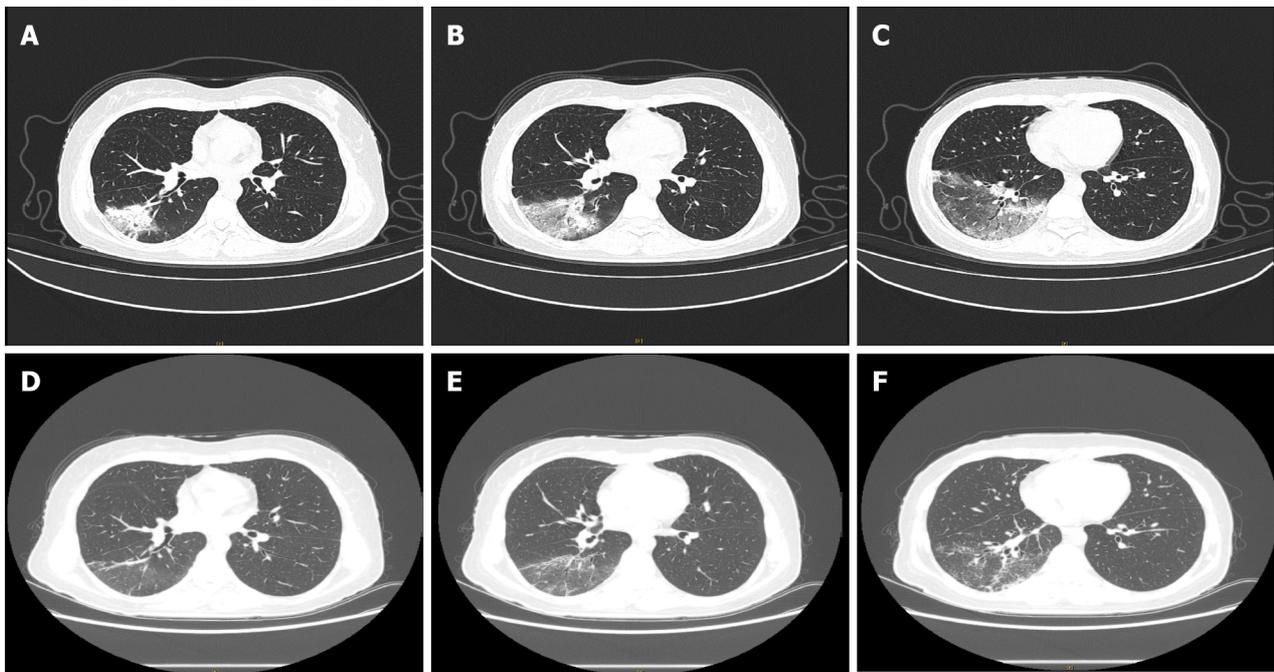
Table 1 Results of blood tests on admission

Blood tests	Results	Normal range
White blood cells (/L)	5.78×10^9	3.5×10^9 - 9.5×10^9
Neutrophils (%)	70.5	40.0-75.0
Lymphocytes (%)	22.2	20.0-50.0
Red blood cells (/L)	4.2×10^{12}	3.8×10^{12} - 5.1×10^{12}
Haemoglobin (g/L)	119	115-150
Platelets (/L)	186×10^9	125×10^9 - 350×10^9
Total protein (g/L)	68.9	65.0-85.0
Albumin (g/L)	42.0	40.0-55.0
Total bilirubin (umol/L)	16.3	< 23.0
Direct bilirubin (umol/L)	9.4	< 6.8
Aspartate aminotransferase (IU/L)	53	13.0-35.0
Alanine aminotransferase (IU/L)	61	7.0-40.0
Lactate dehydrogenase (IU/L)	431.2	120.0-250.0
Creatinine (umol/L)	48.1	41.0-73.0
Sodium (mmol/L)	128	137.0-147.0
Potassium (mmol/L)	3.08	3.5-5.5
Chloride (mmol/L)	92.4	99-110
Hypersensitive C-reactive (mg/L)	165.75	0.5-10
Procalcitonin (ng/mL)	< 0.05	< 0.5
Prothrombin time (s)	13.5	9-14
Activated partial thromboplastin time (s)	28.9	20-40

IU: International unit.

has significant advantages in identifying pathogenic microorganisms. According to different detection strategies, high-throughput sequencing methods are mainly divided into tNGS, mNGS and WGS. MNGS technology is to directly conduct unbiased detection and sequence analysis of all nucleic acids in the specimen, including but not limited to the detection of pathogenic bacteria nucleic acids, and also includes the nucleic acid detection of other pathogens and a large number of human host cells[14]. Due to the complex and time-consuming data processing of mNGS, it has the characteristics of high cost. In particular, mNGS is greatly influenced by human genes making the results easily misunderstood and interfered with. TNGS is a combination of multiplex PCR amplification and sequencing technology, which can detect dozens to hundreds of common pathogenic microorganisms and their virulence and drug resistance genes in samples. Through targeted amplification, it can improve the reliability of pathogen detection. At the same time, it can also provide personalized medication tips for suspected pathogenic microorganisms according to different infection sites. Because only specific target regions need to be sequenced, data processing and analysis are usually easier, making it faster and more economical. However, as mentioned earlier, due to the high cost and time-consuming nature of mNGS, the clinical application of pathogen metagenome sequencing is still limited to a small range, leaving a collaborative space for tNGS. But rather than replacing the application space of mNGS in clinical practice with tNGS, the two complement each other and jointly improve the efficiency of hospital pathogen diagnosis. An article published in 2022 pointed out that there is no significant difference in the detection efficiency of bacteria, fungi, and viruses between mNGS and tNGS, but the removal of human genetic background by tNGS may affect the detection rate of G-negative bacteria, viruses, and intracellular bacteria, leading to higher false-negatives[15].

The guidelines are consistent with the literature recommendations for psittacosis. The first-line medication is tetracyclines, with a duration of at least 7-14 d, and the second choice of antibiotics include azithromycin, clarithromycin, erythromycin, and chloramphenicol[1]. There is not much evidence for the clinical use of quinolones alone. However, there are also studies suggesting that moxifloxacin has an anti-chlamydia effect, and moxifloxacin in this case has shown a good therapeutic effect, so first-line treatment is not used. This case also provides new evidence for the use of quinolones for psittacosis. The drugs for the treatment of *T. whipplei* mainly include penicillin, streptomycin, tetracycline, ceftriaxone, meropenem, compound trimethoprim, doxycycline and hydroxychloroquine. In the past, tetracycline was once listed as a first-line treatment drug, but a high recurrence rate was observed after treatment[16]. However, most of the treatments target digestive disorders caused by *T. whipplei*, and there are few reports on the treatment experience of



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Figure 1 Chronological computed tomography of the chest demonstrating changes in the lungs. A-C: Multiple large uneven ground glass shadows in the lower lobe of the right lung, with grid shadows visible inside, close to the pleura, as shown on a computed tomography on November 6, 2022; D-F: The patchy and ground glass shadows in the lesion of the lower lobe of the right lung were clearly resolved on November 16, 2022.

pneumonia related to Whipple's disease. Therefore, there is still no broad consensus on the treatment of Whipple's disease-related pneumonia, and there is a lack of clinical treatment experience for a large number of cases. The anti-infection treatment plans are all empirical treatments, lacking sufficient evidence support.

CONCLUSION

Collectively, we believe that tNGS is promising in the diagnosis of unexplained pneumonia, and quinolones are effective in the treatment of psittacosis and Whipple's disease, which deserves more clinical attention.

FOOTNOTES

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