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CASE REPORT

Case Report: Pneumonia Caused by *Chlamydia Psittaci* and *Cryptococcus* Co-Infection

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Abstract: This study presents a rare case of pneumonia caused by a co-infection of *Chlamydia psittaci* and *Cryptococcus*, confirmed by metagenomic next-generation sequencing (mNGS). The patient, who had underlying chronic hepatitis B, had adopted a stray pigeon before the onset of the disease. The primary symptoms were fever, and a productive cough. The patient recovered following treatment with moxifloxacin and itraconazole. *C. psittaci* and *Cryptococcus* infections may both have been transmitted from the stray pigeon. This report highlights the potential for infections caused by multiple zoonotic pathogens and the value of mNGS for making the diagnosis of these infections.

Keywords: pneumonia, *Chlamydia psittaci*, *Cryptococcus*, co-infection, metagenomic next-generation sequencing

Introduction

Previous studies have reported mixed infections of *Chlamydia psittaci* with viruses or bacteria in avian species,[1,2] as well as co-infections of *Cryptococcus* and *Pneumocystis carinii* in humans.[3] However, to our knowledge, co-infections of *C. psittaci* and *Cryptococcus* have not been reported previously. Bird exposure as a potential source of infection is frequently overlooked during medical history-taking. This, along with the challenges in culturing *C. psittaci* and *Cryptococcus*, can lead to delayed or missed diagnosis of such conditions. Here, we present a case of pulmonary infection caused by *C. psittaci* and *Cryptococcus* in a patient with a history of bird exposure to raise awareness of such diseases among clinicians.

Case Presentation

The patient, a 41-year-old male farmer, had a 20-year history of chronic hepatitis B infection, which was managed with traditional Chinese medicine. Additionally, he had a 10-year history of fatty liver disease. Five days prior to admission, he had developed a fever, with a peak body temperature of 39.9°C and symptoms of a respiratory infection, including a sore throat, cough, and yellow sputum. He self-medicated with ibuprofen for the fever; however, he experienced recurrent fever and therefore sought treatment at our hospital. Blood tests on admission showed a white blood cell count of 9.65×10^9/L, neutrophil count of 7.37×10^9/L, neutrophil percentage of 76.3%, lymphocyte count of 1.24×10^9/L, and lymphocyte percentage of 12.8%. The C-reactive protein (CRP) and procalcitonin levels were 189.28 mg/L and 0.09 ng/mL, respectively. Arterial blood gas analysis showed a pH of 7.458, partial pressure of oxygen (pO_2) of 70.5 mmHg, partial pressure of carbon dioxide (pCO_2) of 35.2 mmHg, and $HCO3^-$ of 24.9 mmol/L, which gave an oxygenation index of 214 mmHg. The hepatitis B surface antigen test was positive, with alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK) levels of 128 U/L, 57.8 U/L, and 336 U/L, respectively (see

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Table 1 for details). The cryptococcal antigen test was positive. The β-D-glucan test for fungal infections was at 45.54 pg/mL and the aspergillus antigen test 0.2 μg/L. Influenza A and B antigen tests, and the dengue NS1 antigen test, were negative. Chest computed tomography (CT) revealed bilateral pneumonia (Figure 1A–D). The patient was diagnosed with pulmonary infection and treated with intravenous moxifloxacin (0.4 g daily), carbocisteine for expectoration, compound methoxyphenamine capsules for cough relief, physiotherapy for sputum clearance, and sodium glucuronic acid injection and compound glycyrrhizin capsules as adjuvant treatments for hepatitis B. On the third day of hospitalization, fiberoptic bronchoscopy was performed due to persistent fever, and bronchoalveolar lavage was conducted in the right lower lobe bronchus. A total of 20 mL of lavage fluid was sent to Guangzhou Huayin Medical Laboratory Center for metagenomic next-generation sequencing (mNGS) analysis. The mNGS detected *C. psittaci* (read count: 3820) and *Cryptococcus neoformans* (read count: 51). A separate mNGS test of a throat swab also revealed *C. neoformans* (read count: 1). However, mNGS of a blood sample did not detect any pathogens. On further inquiry into the patient's history, he recalled having adopted a stray pigeon 2 weeks before the symptom onset. Based on these findings, he was diagnosed with pneumonia caused by *C. psittaci* and *C. neoformans* co-infection. He was treated with itraconazole for *Cryptococcus* (200 mg orally twice a day) because our hospital does not stock fluconazole, and the moxifloxacin administration was continued to treat the *C. psittaci* infection. The patient's temperature dropped down to normal on the third day after starting itraconazole treatment. After antimicrobial treatment, the patient's inflammatory indices and liver transaminase levels improved. Follow-up chest CT 2 weeks after completing treatment showed significant alleviation of lung inflammation (Figure 1E–H). His hematology parameters as well as CRP and liver transaminase levels also showed improvement.

The patient was treated with moxifloxacin for 2 weeks. Following discharge, the patient continued taking itraconazole (200 mg twice a day). At the 4-week follow-up, chest CT revealed that the lesions in both lungs had healed (Figure 1I–L). His hematology results and CRP levels returned to normal, and his liver transaminase levels showed further improvement. The patient was treated with itraconazole for 3 months.

Table 1 Laboratory Test Results of the Patient

Test Parameter	Reference Range	On the Day of Admission	After 2 Weeks of Treatment
WBC count ($\times 10^9$/L)	4–10	9.65	6.81
Neutrophil count ($\times 10^9$/L)	1.8–6.3	7.37	3.79
Neutrophil (%)	40–75	76.3	55.6
Lymphocyte count ($\times 10^9$/L)	1.1–3.2	1.24	2.14
Lymphocyte (%)	20–40	12.8	31.4
CRP (mg/L)	0–5	189.28	12.5
Procalcitonin (ng/mL)	0–0.05	0.09	0.07
ALT (U/L)	9–50	128	76.5
AST (U/L)	15–40	57.8	42.9
LDH (U/L)	109–245	238	254
Creatinine (μmol/L)	62–106	88.3	73.2
CK (U/L)	26–196	336	138
CK-MB (U/L)	0–25	10	10.3

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CK-MB, creatine kinase muscle isoenzyme; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell.

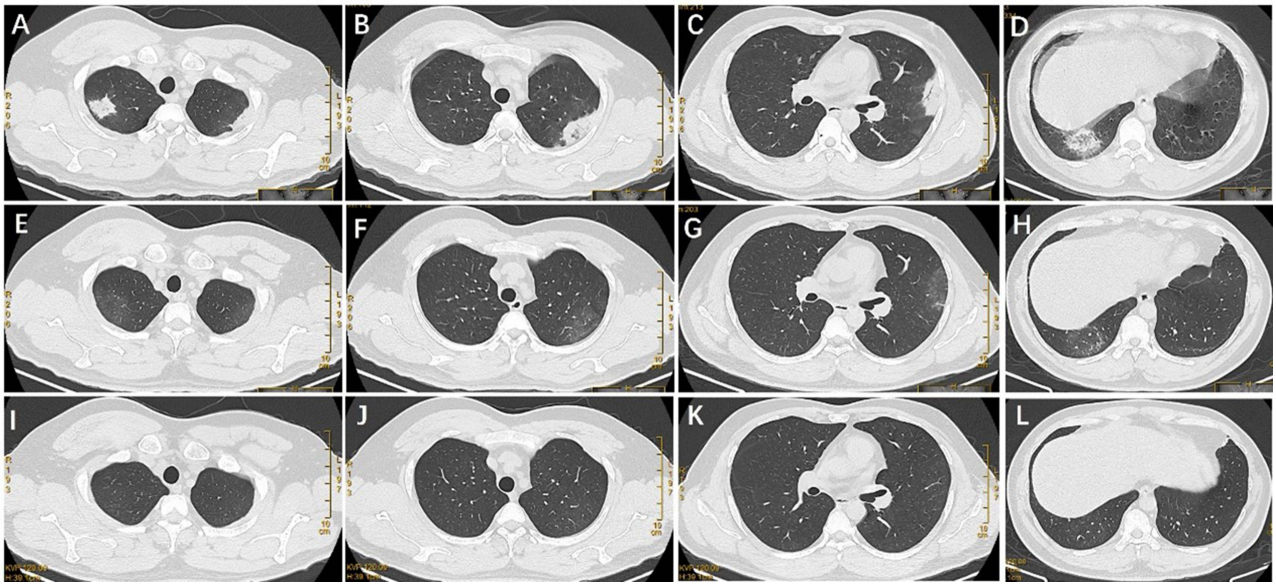

Figure 1 Chest computed tomography (CT) images of the patient. Chest CT on admission showing bilateral pneumonia (**A**–**D**). Chest CT after 2 weeks of treatment showing improvement in the bilateral pneumonia (**E**–**H**); Chest CT after 4 weeks of treatment showing complete resolution of the lung changes (**I**–**L**).

Discussion

Psittacosis is a zoonotic disease caused by *C. psittaci*. Humans can contract this disease either via direct contact or by inhaling particles of excreta and respiratory secretions of infected birds.[4] *C. neoformans* is an opportunistic fungal pathogen. Individuals with compromised immune systems, such as those with HIV infection, are at increased risk of infection.[5] As with *C. psittaci, Cryptococcus* can be isolated from bird feces.[6] Peralta et al[7] reported a case of cryptococcal meningitis in a patient who had contact with a parrot and was suspected to have contracted the infection by zoonotic transmission of *Cryptococcus* from the parrot. The patient suffered neurological sequelae due to delayed diagnosis and treatment.

It is unclear whether our patient was infected with *Cryptococcus* or *C. psittaci* first. The patient had a definitive history of exposure to pigeons, potentially the source of both the *C. psittaci* and *Cryptococcus* infection. Individuals with compromised immunity are more susceptible to *Cryptococcus* infection. Chronic hepatitis B virus infection can induce T-cell and natural killer cell dysfunction.[8,9] The patient's chronic hepatitis B virus infection may have caused immunodeficiency, thus increasing his risk of *Cryptococcus* infection.[10] We speculate that the patient might have initially been infected with *C. neoformans*, which has the capacity to induce apoptosis in macrophages via its capsular polysaccharides, predominantly galactoxylomannan and glucuronoxylomannan.[11,12] Macrophages play an important role in the immune response against chlamydial infection,[13] a reduction in macrophages could enhance susceptibility to *C. psittaci* infection. Another study suggested a synergistic interaction between adenovirus and *C. psittaci* in affected parrots, in which the adenovirus induced immune suppression in the host, resulting in an increase in the *C. psittaci* bacterial load.[1]

Awareness of psittacosis is limited owing to its nonspecific clinical manifestations such as fever and cough.[14] Additionally, routine diagnostic tests, including serological testing and culture, have limitations in diagnosing psittacosis.[15] These factors make diagnosing psittacosis challenging. Pet birds are frequently overlooked as a potential source of *Cryptococcus* infection[7] and clinicians often do not consider the possibility of this infection. Therefore, infection by rare pathogens should be considered during the differential diagnosis in patients exhibiting atypical symptoms of pulmonary infection, with negative results for routine pathogens and no improvement after empirical antibiotic treatment. In such cases, a timely bronchoalveolar lavage for mNGS should be considered.

A 2021 report showed that compared with culture and serological testing, mNGS offered a sensitivity of 81–86% and specificity of 91–95% for bacterial detection, and a sensitivity of 63–70% and specificity of 92–96% for fungal detection.[16] In addition, mNGS can identify *C. psittaci* more rapidly and exhibits distinct advantages for detecting

mixed pathogen infections.[14] Therefore, mNGS is a valuable for diagnosing co-infections with *C. psittaci* and other respiratory pathogens.

C. psittaci can compromise the functionality of chicken macrophages, thereby facilitating the invasion of the H9N2 avian influenza virus.[13] In birds co-infected with *C. psittaci* and H9N2, *C. psittaci* has been shown to suppress the host's immune response by inhibiting humoral immunity and altering the Th1/Th2 balance, leading to an elevated mortality rate in the host.[17] Based on these findings, we speculate that co-infections of *C. psittaci* and *Cryptococcus* could exacerbate the disease severity, resulting in enhanced damage and an increased mortality rate. In this case, the patient received prompt fiberoptic bronchoscopy after admission, and the collected bronchoalveolar lavage fluid was sent for mNGS analysis. With early diagnosis and treatment, the patient made a good recovery, and further progression of the disease was prevented.

Conclusion

Pneumonia caused by a co-infection of *C. psittaci* and *Cryptococcus* is rare and has no specific clinical manifestations. Metagenomic next-generation sequencing and detection of serum cryptococcal antigen are valuable tools for accurate diagnosis.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Approval and Informed Consent

The studies involving human participants were reviewed and approved by the Ethics Review Committee of Zhongshan People's Hospital. The patient provided his written informed consent to participate in this study.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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