

Case Report

Diagnosis and treatment of four cases of pulmonary cryptococcosis: case report and literature reviewShan Song^{1#}, Tai Guo^{1#}, Tiebin You¹, Ping Wang¹¹ Department of Respiratory Medicine, The Fourth Hospital of Hebei Medical University, Shijiazhuang, Hebei, China

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Abstract

Introduction: Cryptococcosis has attracted global attention due to its high mortality rate, unique geographical distribution, and tendency to cause severe and rapid disease progression. Metagenomic next-generation sequencing (mNGS) is a novel detection technology that provides diagnostic insights for identifying pathogens, particularly rare ones. The present article describes 4 individuals diagnosed with pulmonary cryptococcosis (PC) using mNGS of bronchoalveolar lavage fluid (BALF).

Case presentation: Among these patients, 3 had cancer, 1 had sarcoidosis and diabetes, and 2 were exposed to pigeons and/or pigeon droppings. These patients experienced symptoms, including fever, cough, and chest pain. They were diagnosed with PC after mNGS of BALF. The patient was diagnosed based on mNGS test results. Subsequently, the patient was treated with fluconazole, and the patient's chest computed tomography scan showed significant absorption of the lung lesions.

Conclusions: mNGS of BALF can quickly diagnose PC. This diagnostic method has minimal trauma to the body and is worthy of clinical promotion. Fluconazole remains the preferred and best therapeutic drug for PC treatment.

Key words: Cryptococcosis; metagenomic next-generation sequencing; immunocompromised patients.

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Introduction

Cryptococcosis is a general term for infections caused by members of the Basidiomycetes yeast genus *Cryptococcus*. These infections have attracted global attention due to their high mortality rate, unique geographical distribution, and tendency to cause severe and rapid disease progression in both healthy and immunosuppressed individuals [1]. It is closely associated with bird excrement, particularly from pigeons [2]. *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*) are the main etiological agents of cryptococcosis [3]. Fungal spores are inhaled into the human body through the respiratory tract; and, in non-immunodeficient organisms these spores enter the respiratory tract and reach the distal airway through the alveolar interstitium. The spores come into contact with macrophages and activate them, thereby stimulating T-helper 1 type CD4⁺ cell-mediated immune responses, ultimately forming granulomas or masses in the lungs [4]. Patients who are immunocompromised due to cancer, hereditary syndromes, or transplantation are extremely vulnerable to infections. In this setting, the causative agent can include a number of both common and uncommon pathogens, ranging from viruses to bacteria, fungi, and other parasites [5]. In immunocompromised organisms,

Cryptococcus infects the lung and enters the bloodstream through the alveolar capillary barrier. Some spread through the bloodstream to other organs throughout the body, whereas others enter the central nervous system (CNS) through the blood-brain barrier, causing cryptococcal meningitis [6].

Pulmonary cryptococcosis (PC), a rare lung infection, lacks specificity in clinical and imaging aspects, making it prone to misdiagnosis and missed diagnosis. If diagnosis and/or treatment are delayed, the condition may spread to the central nervous system [7]. Therefore, early diagnosis and treatment are clinically significant. Presently, the gold standard for diagnosis of PC is pathogen and pathological testing; however, there are problems with low positivity rates and the poor feasibility of invasive procedures. In recent years, metagenomic next-generation sequencing (mNGS) has provided new leads for the early and rapid diagnosis of difficult, complex, and special infectious diseases. To enhance the understanding of cryptococcosis, this article describes the clinical characteristics, diagnosis, and treatment course of 4 cases of PC confirmed using mNGS of bronchoalveolar lavage fluid (BALF) from January 2022 to December 2023.

Cases presentation

Case 1

Case 1 involved a 65-year-old female who was admitted to the hospital primarily due to persistent cough, expectoration, chest pain, and fever lasting for 2 weeks (day 0). She experienced a two-week history of fever up to 38.5 °C, which was relieved by ibuprofen. Physical examination revealed no discernible signs. She had a medical history of limited small cell lung cancer and had previously undergone 6 cycles of etoposide and cisplatin chemotherapy, along with 1 cycle of radiotherapy. She was on steroid treatment before admission due to radiation pneumonitis caused by radiation therapy. It is noteworthy that one of her neighbors maintains a flock of pigeons. Notably, chest computed tomography (CT) on day 0 revealed multiple inflammatory lesions in the right lung. The laboratory test results from day 0 are shown in Table 1. After bronchoscopy on day 7, mNGS testing of BALF confirmed the presence of *C. neoformans*, along with a positive detection of cryptococcal capsular polysaccharide antigen (CrAg). Consequently, the patient received fluconazole 0.4 g once daily starting on day 9 as anti-*Cryptococcus* therapy, leading to a significant improvement in symptoms after 10 days. Two months later, the lesion in the right lung was smaller than that on day 0. After nearly 1 year of anti-cryptococcal therapy, the lesion in the right lung had significantly decreased in size. The results are summarized in Table 1 and Figure 1A–C.

Case 2

Case 2 involved a 40-year-old male admitted to the hospital with a cough lasting over a month and right back pain for 8 days. Physical examination revealed thick breath sounds in both lungs. The patient had a documented history of papillary thyroid cancer for over 2 years and denied any exposure to pigeons or poultry. He presented to our hospital outpatient department on day-1 and underwent a chest CT, revealing consolidation in the lower lobe of the right lung. After admission, the patient underwent relevant examinations, and the results are shown in Table 1. Sputum microbial analysis, including bacterial detection, fungal culture, acid-fast staining, and Gram-staining, revealed no abnormalities. After BALF examination, mNGS analysis of BALF on day 4 revealed the presence of *Staphylococcus aureus* and *C. neoformans*. Blood CrAg tested positive on day 10. Accordingly, fluconazole was administered on day 5 at a daily dose of 400 mg. Two months later, the lesion in the lower lobe of the right lung had reduced compared with previous findings. After 7 months of anticyptococcal therapy, the right lung lesions had almost completely resolved. The results are summarized in Table 1 and Figure 1D–F.

Case 3

Case 3 involved a 58-year-old female who was admitted to the hospital on day 0 due to a persistent cough for 6 months and a two-week history of dull pain

Table 1. Clinical characteristics of the four patients.

	Case 1	Case 2	Case 3	Case 4
Gender	Female	Male	Female	Female
Age (year)	65	40	58	32
Medical history/treatment history	Small cell lung cancer	Papillary thyroid cancer	Sarcoidosis, diabetes.	Breast cancer
Exposure to pigeons and/or pigeon droppings	Yes	No	Yes	Yes
Clinical manifestations	Fever, cough, chest pain	Cough, back pain	Cough, chest pain	Fever
WBC (10 ⁹ /L)	6.65	6.86	14.85	13.23
NEUT (10 ⁹ /L)	5.62	5.13	12.86	12.36
NEUT (%)	84.4	74.8	86.5	93.4
CRP (mg/L)	74.25	17.18	7.55	60.94
PCT (ng/mL)	0.01	0.03	0.05	0.32
SAA (mg/L)	> 500	> 500	21.2	409.5
G test (pg/mL)	< 10	96.6	< 10	< 10
GM test (μg/L)	0.12	0.12	0.12	0.12
Microbiological detection of sputum	Negative	Negative	Negative	Negative
Microbiological detection of BALF	A large number of fungal spores	Negative	Negative	Negative
mNGS result of BALF (Sequence number, relative abundance)	<i>C. neoformans</i> (460, 47.29%)	<i>C. neoformans</i> (7, 70%); <i>Staphylococcus aureus</i> (14, 8.81%)	<i>C. neoformans</i> (187102, 94.25%)	<i>C. neoformans</i> (187102, 94.25%); human respiratory syncytial virus type B (36621, 74.92%)
CrAg test	Positive	Positive	Positive	Negative

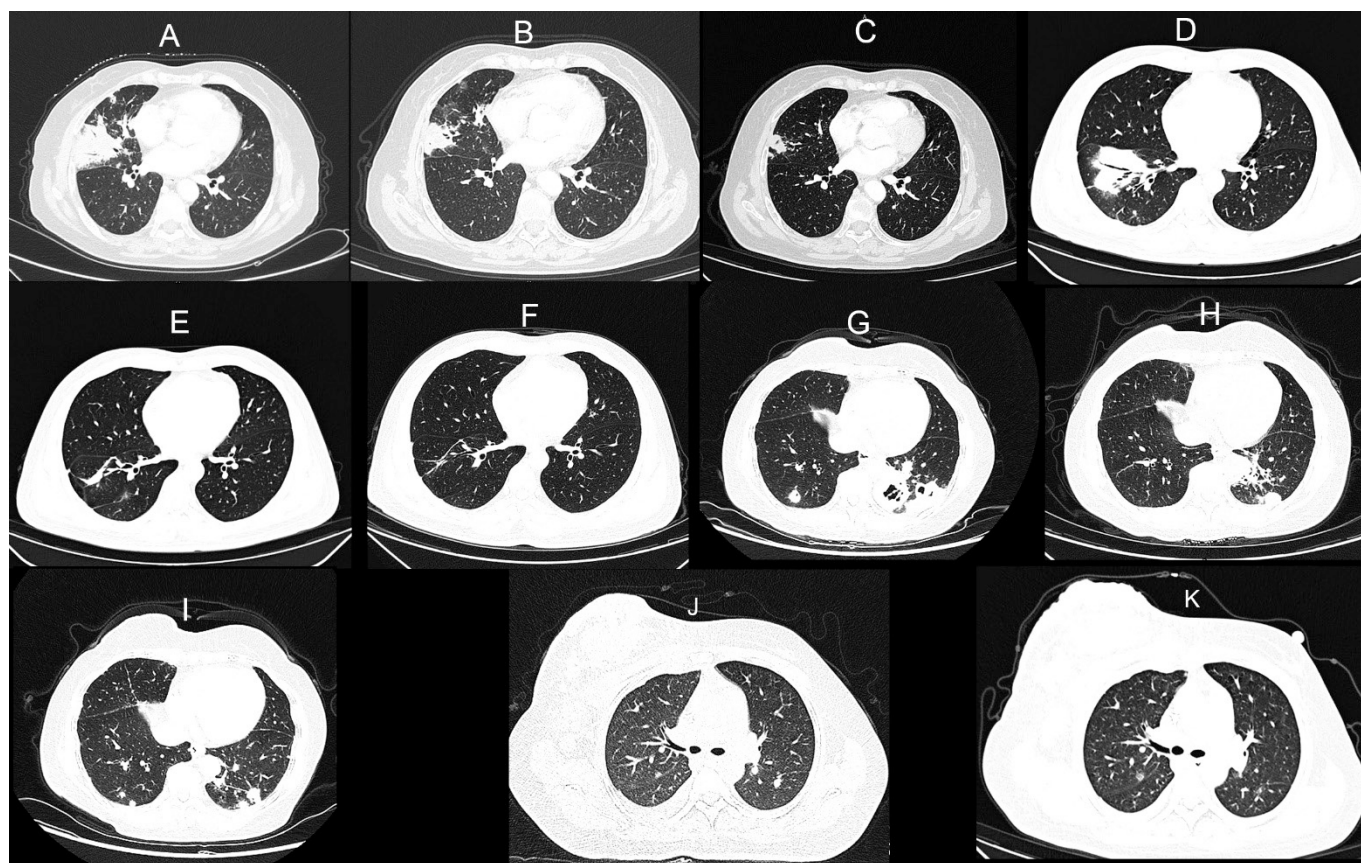
WBC: white blood cell count; NEUT: neutrophil count; CRP: C reactive protein (normal reference range: 0–10 mg/L); PCT: procalcitonin (normal < 0.05 ng/mL); SAA: serum amyloid A (normal reference range: 0–10 mg/L); G test: < 100.5: negative; 100.5–151.5: weakly positive; > 151.5: positive; GM test: < 0.5: negative; ≥ 0.5: positive; mNGS: metagenomic next-generation sequencing; BALF: bronchoalveolar lavage fluid; CrAg: cryptococcal capsular polysaccharide antigen.

in the left chest wall. No positive physical examination findings were observed, and a CT scan on day 1 revealed a shadow and cavitation in the left lower lobe. The patient had a documented history of diabetes that spanned 2 decades. Sarcoidosis was diagnosed in the patient over 5 months ago, after which oral methylprednisolone therapy was started at a dosage of 40 mg/day. Currently, the dosage has been reduced to 4 mg/day. There was no history of contact with pigeons or poultry, and the laboratory test results on day 0 are shown on Table 1. Sputum microbiological examination, bacterial and fungal cultures, acid-fast staining, and Gram-staining results were within normal limits. However, after examining the BALF on day 0, mNGS analysis on day 1 revealed *C. neoformans*. Furthermore, blood test results on day 2 confirmed the presence of CrAg, and a significant abundance of fungal spores in the BALF. The definitive diagnosis of PC was established based on the patient's detailed medical history, diagnostic and treatment records, and imaging findings. On day 2, fluconazole was

administered as antifungal treatment. On day 6, cranial magnetic resonance imaging revealed no abnormalities, and the patient declined cerebrospinal fluid examination. Two months later, the shadow in the left lower lobe decreased, and the cavity resolved. After 5 months of antifungal treatment, a CT scan revealed reduced scattered shadows, which were reduced as reported in Table 1, and the imaging changes are shown in Figure 1G–I.

Case 4 involved a 32-year-old woman who had been suffering from breast cancer for two years. Nodular lesions were found in both lungs during a CT re-examination on day 4. The patient had continuous fever for 5 days, reaching a peak temperature of 38.3 °C. The fever was not effectively relieved despite taking antipyretic drugs. The patient underwent chemotherapy and received immune checkpoint inhibitors, with the most recent treatment given within 2 weeks before presentation. Notably, she had raised pigeons a few months prior. The laboratory test results on day 0 are shown in Table 1. After BALF examination

Figure 1. Imaging changes in the four patients before and after treatment.



A. Chest computed tomography (CT) before treatment in case 1 on day 0. B. Chest CT in case 1 after treatment 2 months later. C. Chest CT in case 1 after treatment nearly 1 year later. D. Chest CT before treatment in case 2 on day 1. E. Chest CT after treatment in case 2, 2 months later. F. Chest CT after treatment in case 2, 7 months later. G. Chest CT before treatment in case 3 on day 1. H. Chest CT in case 3 after treatment 2 months later. I. Chest CT in case 3 after treatment 5 months later. J. Chest CT before treatment in case 4 on day 4. K. Chest CT after treatment of case 4 on day 27.

on day 3, the microbiological analysis of BALF on day 4 revealed no abnormalities in bacterial growth, fungal culture, acid-fast staining, or Gram-staining. Blood CrAg levels were negative. Interestingly, mNGS analysis of BALF on day 6 revealed a coinfection with *C. neoformans* (sequence number: 63; relative abundance: 21.26%) and human respiratory syncytial virus type B (sequence number: 36621; relative abundance: 74.92%). Fluconazole was administered on day 6. After a three-week treatment regimen of fluconazole at a daily dose of 400 mg, a CT scan on day 27 revealed a reduction in the size of the pulmonary nodules compared with the previous state. The results are summarized in Table 1, and Figure 1J and K.

Discussion

PC is a fungal infection caused by *Cryptococcus*, which can be categorized into two species: *C. neoformans* and *C. gattii*. *C. neoformans* is found worldwide and mainly impacts immunocompromised individuals. *C. gattii* is limited to specific regions like Australia and New Zealand, typically affecting people with healthy immune systems, and resulting in more severe clinical symptoms [3]. The species can be further classified based on the specificity or molecular system of *Cryptococcus* antigen binding, which has the potential to predict future treatment outcomes [8]. PC is highly prevalent in patients with cryptococcal infections. An international cohort study (MSG07) found that infections among 709 patients with cryptococcal infection were distributed as follows: CNS (59%), lung(s) (42.5%), and blood (24.5%) [9]. PC is commonly associated with immunocompromised populations, including individuals infected with human immunodeficiency virus (HIV), recipients of solid organ transplantation, patients with malignant tumors, those undergoing long-term glucocorticoid therapy, and individuals with chronic lung disease [10]. In addition, environmental factors, such as exposure to pigeons and pigeon droppings, may increase susceptibility to PC [11]. In this study, all 4 patients were immunocompromised individuals (3 patients had malignant tumors, 1 patient had sarcoidosis and diabetes), and 2 patients were exposed to pigeons or pigeon droppings, rendering them all susceptible to PC.

The clinical manifestations of PC depend on the immune status of the patient. In the absence of immunosuppression, most patients remain asymptomatic or experience only mild non-specific symptoms such as cough, expectoration, chest tightness, and fever. Conversely, immunosuppressed individuals exhibit more pronounced and severe

symptoms, including high fever, dyspnea, hypoxemia, and respiratory failure [6,12]. The imaging appearance of PC may be influenced by variations in immune status. Patients with intact immune function are more prone to developing granulomas, whereas those with compromised immune function are more susceptible to diffusion. Typical CT findings of PC include solitary or multiple pulmonary nodules or masses. Additional features, such as halo and bronchial inflation signs, may also be present. Additional imaging characteristics that can be observed include reticular infiltration, hilar and lymph node enlargement, cavity formation, pleural effusion, and ground-glass opacity [9,13]. The imaging features of the 4 patients in this study included cavitation, pleural thickening, ground-glass opacity, and bronchial ventilation signs, respectively. Given the similarities in symptoms and imaging features between PC and pulmonary tuberculosis or lung cancer, it is imperative to differentiate them based on clinical experience and other supporting evidence. Numerous studies have also found that the clinical characteristics of *Cryptococcus* infection are difficult to distinguish from other lung diseases [14,15].

Commonly used methods for the etiological diagnosis of PC include traditional microbiological, CrAg, and histopathological examinations. However, traditional microbiological examinations are affected by issues such as low positivity rates and a prolonged wait period. Histopathological examination involves invasive procedures like bronchoscopic biopsy, CT-guided lung puncture, and surgical resection; all carrying risks of bleeding, pneumothorax, and post-operative complications. CrAg is an important detection method for cryptococcosis. Some studies have reported that the sensitivity and specificity of serum CrAg detection in cryptococcal meningitis and disseminated cryptococcal infection are 93–100% and 93–98% [16]. However, it is reported that the sensitivity of serum CrAg detection in HIV-negative PC patients is only 25–56%, leading to false-negative serum CrAg results, which may be related to the immune status of the patient [17]. The false negative result of CrAg in case 4 may be related to the use of immune checkpoint inhibitors by the patient, and there are reports suggesting that false negatives are associated with immune complexes [18].

mNGS is an emerging detection method that offers several advantages over traditional microbial detection methods, including lack of bias, wide coverage, rapid detection, and independence from factors such as hospitalization duration or prolonged use of hormones and anti-infective drugs [5,19]. In addition, mNGS is

capable of detecting a wide range of potential pathogens, including viruses, bacteria, fungi, and other parasites; in a single test without speculating the specific pathogens. It not only identifies *C. neoformans*, but also aids in distinguishing between different subtypes of *Cryptococcus* based on their pathology and surface characteristics [7]. For most pathogens, mNGS yields higher detection rates than conventional microbiological tests. A study found that the diagnostic specificity and sensitivity of mNGS in 502 patients with pulmonary infections were 74.9% and 72.5% [20]. Another study found that the positive detection rate of mNGS for bacteria and fungi in cancer patients with severe pneumonia was significantly higher than the culture method, especially for polymicrobial infections.

In spite of these unique diagnostic advantages, some disadvantages are inherent to mNGS. First, there is currently no unified standard guidance the implementation of mNGS. Second, as a highly sensitive test method, mNGS is incapable of distinguishing contamination or colonization from disease causing pathogens. Third, the relatively high cost, particularly when not included in national health insurance, considerably limits the clinical application of mNGS [19,21,22]. Moreover, the presence of a thick capsule in the *C. neoformans* poses a challenge for mNGS detection, potentially leading to false negative results due to the difficulty in disrupting the thick capsule [7]. In conclusion, mNGS is a supplementary method, but not a substitute for traditional microbiology and other methods. In this study, lung biopsy was not performed in cases 1, 2, and 3, owing to the invasive nature of the procedure. Case 4 was a patient with advanced breast cancer and poor prognosis and had physical limitations that made lung biopsy non-feasible. Consequently, the etiology of PC was expeditiously identified within 3 days' post bronchoscopy using mNGS technology. Furthermore, 3 out of 4 patients tested positive for the CrAg test, supporting the accuracy of mNGS diagnosis, as evidenced by improved clinical manifestations and imaging after treatment.

Cryptococcus meningitis, an infectious disease of the CNS that is primarily caused by the invasion of *Cryptococcus*, is the most common type of cryptococcal infection [9]. Cryptococcal meningitis is clinically characterized by non-specific symptoms and signs such as fever, headache, nausea, vomiting, papilledema, and cranial nerve damage. A previous study reported that in the case of PC patients with normal immunity, up to 67% experienced CNS involvement and subsequent development of cryptococcal meningitis [23]. The American Society of Infectious Diseases recommends

lumbar puncture to rule out meningitis in immunocompromised patients, while lumbar puncture can be avoided for immunocompetent patients without CNS symptoms [24]. In this study, all patients refused to undergo lumbar puncture or cerebrospinal fluid examination due to the absence of neurological symptoms. Therefore, the patients' choices were respected and their symptoms were closely monitored during regular brain magnetic resonance imaging examinations. No signs of intracranial infection were found during follow-up.

The treatment of PC aims to control the infection and prevent its spread. Currently, the treatment options for PC are limited. The effectiveness of drugs like micafungin in combating this pathogen is reduced due to *Cryptococcus*' inherent resistance to echinocandins [25]. Despite the fact that *Cryptococcus* has the potential to develop resistance against fluconazole, it is recommended as the primary therapeutic option for mild-to-moderate cryptococcosis in both immunocompetent and immunocompromised patients [26]. In the case of patients with severe infection, it is recommended to adjust the dosage and course of antifungal therapy after induction therapy with amphotericin B or fluconazole combined with fluorouracil, which can reduce drug resistance and improve efficacy. Surgical resection can be considered in patients in whom conventional antifungal drug treatments are ineffective, and antifungal treatment should be continued for 2 months after surgery to prevent the dissemination of cryptococcal bacteria [24]. The symptoms of the 4 patients in this study were significantly alleviated, and the imaging lesions exhibited a significant reduction following fluconazole treatment, thereby corroborating the reliability of the previous diagnosis of PC.

Conclusions

The main pathogenic bacterium of PC is *Cryptococcus neoformans*, which causes atypical clinical features and requires further diagnosis through laboratory testing methods. mNGS of BALF can quickly diagnose PC and this diagnostic method has minimal trauma to the body; therefore, it is worthy of clinical promotion. Fluconazole remains the preferred and best therapeutic drug for PC treatment.

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Ethics approval

This study was approved by the Ethics Review Committee of the Fourth Hospital of Hebei Medical University with registration number 2023KS206.

Authors' contributions

SS, TG: manuscript original draft, review, and editing; TY: manuscript editing; PW: research and data analysis. All authors contributed to the article and approved the submitted version. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

No conflict of interest is declared.

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