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Case Report

Pulmonary histoplasmosis on the Chinese mainland: two case reports and literature review

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Abstract

Introduction: Pulmonary histoplasmosis is a fungal disease that is endemic in North and Central America. It is relatively rare in China and commonly misdiagnosed as tuberculosis or cancer due to nonspecific clinical and radiographic manifestations. Rapid and accurate pathogen tests are critical for the diagnosis of pulmonary histoplasmosis.

Methodology: We report two cases of pulmonary histoplasmosis. We collected all the relevant case reports on the Chinese mainland (from 1990 to 2022) to analyze features of this disease among Chinese patients.

Results: A total of 42 articles reporting 101 cases were identified, and the two cases reported in this article were also included for analysis. Sixty-three (61.2%) patients had respiratory symptoms and 35 (34.0%) patients were asymptomatic. The most common radiographic findings were pulmonary nodules or masses (81.6%). Twenty-two (21.4%) patients were misdiagnosed as tuberculosis, and 37 (35.9%) were misdiagnosed as lung tumors before pathological findings. Metagenomic next-generation sequencing (mNGS) testing provided a rapid diagnostic and therapeutic basis for three patients.

Conclusions: Clinical features and imaging findings of pulmonary histoplasmosis are not specific. Relevant epidemiological history and timely pathogen detection are important for diagnosis. mNGS can shorten the time required for diagnosis and allow earlier initiation of targeted antibiotic therapy.

Key words: pulmonary histoplasmosis; *Histoplasma capsulatum*; Chinese mainland; mNGS.

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Introduction

Histoplasmosis and its causative agent, *Histoplasma capsulatum*, are found worldwide but particularly in North and Central America. The severity of illness and disease manifestations after primary inhalation exposure to *H. capsulatum* vary depending on the intensity of exposure and the immunity of the host [1]. Histoplasmosis induces disseminated infection in immunocompromised hosts and is symptomatic in 10% of immunocompetent patients [2]. Common types of histoplasmosis include disseminated histoplasmosis, acute, subacute and chronic pulmonary histoplasmosis. This disease was first reported in China in 1958 [3]. Epidemiological and clinical data of this disease in China remain scarce and fragmented, especially those of pulmonary histoplasmosis. In this article, we report two cases of pulmonary histoplasmosis and collect all the relevant case reports in China (from 1990 to 2022) aiming to analyze features of this disease in China.

Case report

Case 1

A 33-year-old female who had previously received a kidney transplant was admitted to the hospital with fever on 4 October 2020. The patient had a fever 10 days before admission, with peak body temperature of 38.8 °C, along with chills and chest pain. She visited the fever clinic. At the fever clinic, her routine blood tests showed a white blood cell (WBC) count of 7.19 × 10^9/L, and the neutrophil percentage was 68.4%. Chest computed tomography (CT) demonstrated patchy infiltrates in the left upper lobe and an 8.5 mm × 11.5 mm nodule in the right middle lobe (Figure 1). The patient was diagnosed with pneumonia, after which she was given levofloxacin, moxifloxacin, and ertapenem. There was no improvement after 10 days therapy. The patient still had a fever and began to cough. She was admitted to the inpatient department for further treatment. Her body temperature was 36.1 °C, pulse

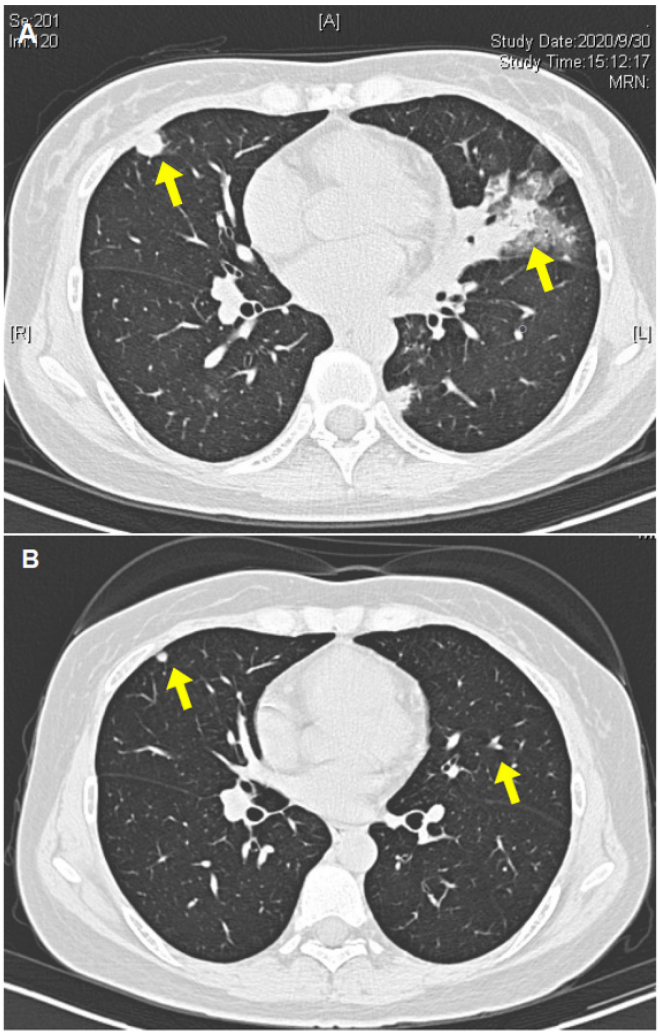
was 93 bpm, blood pressure was 114/72 mmHg, and respiratory rate was 16 breaths per minute at the time of admission. Wet rales could be heard in both lungs, especially in the left upper lung. The cardiovascular system, abdomen, and nervous system were normal on examination.

Her medical history noted a kidney transplant 10 months prior, which was secondary to stage VI chronic kidney disease due to IgA nephropathy. Her immunosuppressive therapy at admission was 10 mg of prednisone once daily, 2 mg of tacrolimus twice daily, and 250 mg of mycophenolate mofetil twice daily. The patient also had hypertension, bronchial asthma, and thyroid nodules.

We actively searched for likely pathogens. No pathogens were found in bacterial and fungal cultures. Tuberculosis-related tests, including sputum acid-fast bacilli (AFB) smears and serologic antibody assays, were negative. IgM detection for common pathogens including influenza virus, para-influenza, adenovirus, respiratory syncytial virus, echovirus, Coxsackie virus, *Mycoplasma pneumoniae*, *Chlamydophila pneumonia*, and *Legionella*, was negative. Cytomegalovirus (CMV) DNA was less than 4.00×10^2 copies. Other laboratory test results can be found in Table 1.

After admission, the patient's prednisone was tapered down to 5 mg once daily, while mycophenolate mofetil was held. The dose of tacrolimus was adjusted based on the patient's blood concentration. At the same time, combination therapy with cefoperazone sodium and sulbactam sodium (1.5 g twice daily, intravenously) plus fluconazole (50 mg once daily, intravenously) was given for the first 14 days. Her body temperature returned to normal, and laboratory tests showed a significant decrease in C-reactive protein (CRP). Chest CT scans conducted 8 days after admission showed that the pulmonary infection was alleviated. However, the

Figure 1. Chest computed tomography (CT) of case 1.



A. Pre-treatment chest CT (30 September 2020); **B.** Post-treatment chest CT (20 May 2022). The yellow arrows in the pictures show the location of lung lesions.

Table 1. Laboratory test results of the two cases.

Laboratory test	Case 1	Case 2
Blood routine		
WBC ($\times 10^9$/L)	7.48	5.81
HGB (g/L)	117	110
PLT ($\times 10^9$/L)	245	203
Neut % (%)	67.1	54.5
PCT (ng/mL)	0.058	Not found
CRP (mg/L)	38	Not found
Biochemical indices		
ALT (U/L)	16.8	10.8
Scr (μmol/L)	109.3	85
BUN (mmol/L)	6.05	7
IgG (g/L)	9.91	Not found
Arterial blood gas		
pH	7.44	7.393
PCO_2 (mmHg)	33	38
PO_2 (mmHg)	86	69.8
Tumor marker		
SCCAg (ng/mL)	0.7	0.8
CEA (ng/mL)	1.83	2.37
CYFRA21-1 (ng/mL)	2.65	1.38
NSE (μg/L)	Not found	11.9
pro-GRP (pg/mL)	Not found	33.51
HIV test	Not found	-
GM test (μg/L)	2.49	Not found
G test (pg/mL)	-	Not found
pneumocystis test	-	Not found
CD4/CD8	1.66	Not found

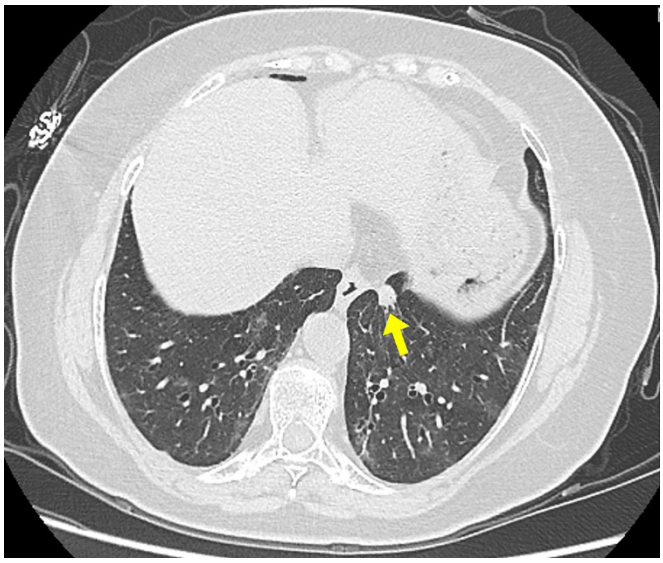
WBC: white blood cell; HGB: hemoglobin; PLT: platelet; Neut: neutrophil; PCT: procalcitonin; CRP: C-reactive protein; ALT: Alanine aminotransferase; Scr: serum creatinine; BUN: urea nitrogen; IgG: immunoglobulin G; SCCAg: squamous cell carcinoma related antigen; CEA: carcinoembryonic antigen; CYFRA21-1: cytokeratin fragment 19; NSE: neuron-specific enolase; pro-GRP: pro-gastrin-releasing peptide; HIV: human immunodeficiency virus; GM test: Galactomannan test; G test: 1:3-Beta-D-glucan measurement; PCP test: CD4+/CD8+: CD4/CD8 T-cell ratio.

patient's cough became more continuous throughout the day and produced yellow and occasionally blood-streaked sputum. To identify the pathogen, flexible bronchoscopies were performed on the 13th day, and bronchoalveolar lavage fluid (BALF) was sent for next-generation sequencing (NGS) testing. Two days later, NGS results indicated *Histoplasma capsulatum*. Taken together, these findings were consistent with the diagnosis of pulmonary histoplasmosis. Antifungal therapy with itraconazole was the first choice according to the guideline recommended [1]. Considering that itraconazole may affect the blood concentration of tacrolimus, we chose posaconazole (200 mg three times daily, orally) as the final treatment. One month later, the patient's cough resolved, and chest CT showed smaller lesions in both lungs. The patient accepted 19 months of posaconazole treatment, and changes in her chest CT are shown in Figure 1.

Case 2

A 64-year-old female was admitted to the hospital on April 24, 2022, after chest CT showed a nodule in the left lower lung (Figure 2). Five days before admission, the patient underwent positron emission tomography (PET)-CT, which showed that the maximum standardized uptake value (SUVmax) of the nodule was 7.4 and that the metabolism of multiple lymph nodes in the mediastinum was increased. The patient was suspected of having metastatic lung cancer and admitted for surgery.

Figure 2. Preoperative chest computed tomography (CT) of case 2.

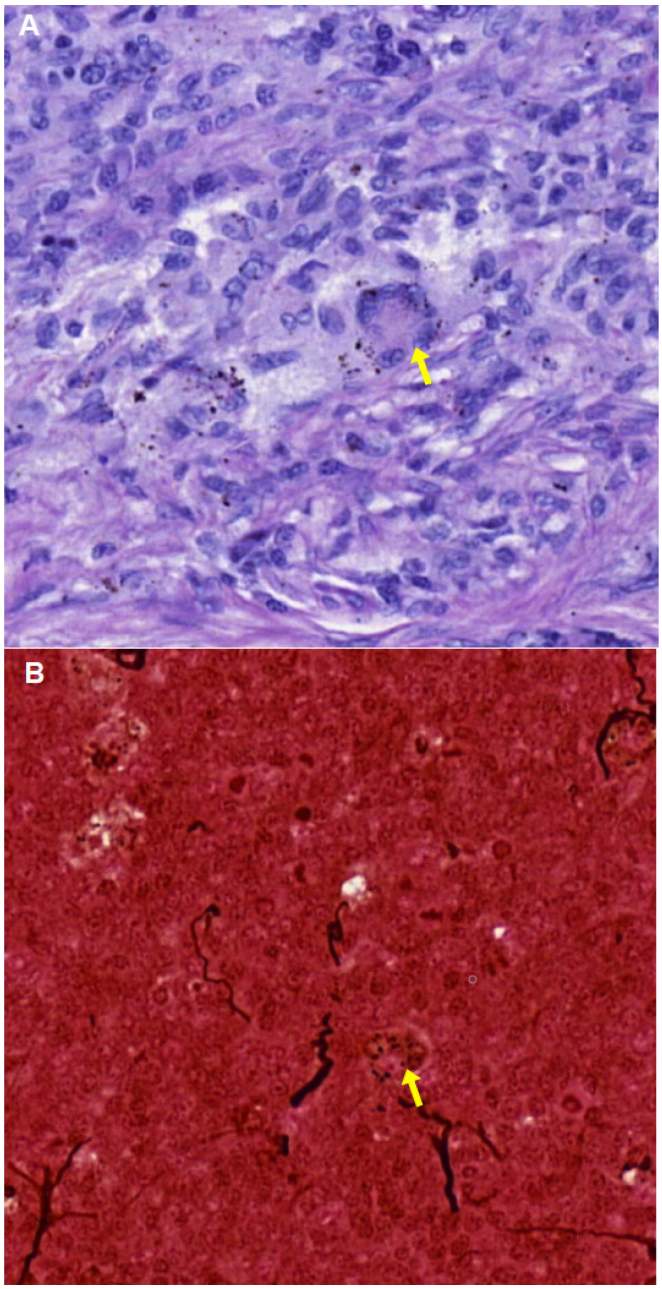


The yellow arrow in the picture shows the location of the lung nodule.

Her medical history was notable for left mammary carcinoma 3 years prior. The patient underwent breast-conserving surgery (BCS) and postoperative chemotherapy. The patient also had hypertension.

The patient's laboratory test results are presented in Table 1. She underwent a diagnostic wedge resection by video-assisted thoracic surgery (VATS) on the 3rd day after admission. Intraoperative frozen section analysis and postoperative pathology showed signs of

Figure 3. Histopathology of case 2.



A. Periodic acid-Schiff (PAS) staining (×60). The yellow arrow shows the cell with PAS-stained positive ovoid granules. **B.** Grocott hexamine silver staining (×60). The yellow arrow shows a cell with brownish-black ovoid granules.

granulomatous inflammation. Immunohistochemistry of the lung biopsy showed positive staining for CD68. Both periodic acid-Schiff (PAS) staining and hexamine silver staining were positive, while acid-fast staining was negative (Figure 3). Histopathology ultimately suggested histoplasmosis. The patient was finally diagnosed with pulmonary histoplasmosis, which was confirmed by the aforementioned imaging and pathological findings. She had a good postoperative recovery and was successfully discharged.

Methodology

We retrospectively analyzed the features of pulmonary histoplasmosis cases reported in China, and included both English-language journals and local Chinese case reports. We conducted a comprehensive search of English and Chinese medical literature via the PubMed and CNKI (China National Knowledge Infrastructure) databases. We used 'histoplasmosis' and 'pulmonary histoplasmosis' as key words to search the entire CNKI database to collect Chinese articles within a specific date range (January 1990 to August 2022). The search terms in the PubMed database were combined with 'Chinese mainland'. Duplicate literature and case reports with incomplete information or insufficient diagnostic basis were excluded.

Results

A total of 42 articles reporting 101 cases were identified, and the two cases in this article were also included for analysis. There were 67 (65.0%) males and 36 (35.0%) females aged 19-69 years diagnosed with pulmonary histoplasmosis. Twelve male patients had worked abroad as miners before the onset of the disease. Three patients were considered to have definitely acquired the pathogen in Mexico and 9 in Guyana. Other sporadic cases were acquired within China, as these patients had no related overseas travel history. We

Figure 4. Geographical distribution of locally acquired patients with pulmonary histoplasmosis on the Chinese mainland.

The figures in this picture represent the numbers of cases. The heterogeneous geographical distribution of the cumulative number of histoplasmosis cases was mainly clustered in southern China.

show the geographical distribution of locally acquired pulmonary histoplasmosis on the Chinese mainland in Figure 4. These cases spanned from Hainan (in southern China) to Inner Mongolia (in northern China). Unlike the study by Pan *et al*. [4], we took the Qinling-Huaihe line as our boundary. According to our analysis, 89 (86.4%) cases of pulmonary histoplasmosis were distributed in southern China.

The environmental reservoir of *Histoplasma* is primarily soil contaminated with bird or bat droppings, and infection can occur after exposure to aerosolized soil or guano (i.e., accumulated excrement of seabirds and bats), typically associated with construction or caving [5]. In our study, a description of risk behaviors was provided in the case of 31 (30.1%) patients. They had known exposure to chicken houses, bird roosts, old buildings, mines, or caves with bats. Twenty-four (23.3%) patients had impaired immunity due to cancer, acquired immune deficiency syndrome (AIDS), long-term glucocorticoids or other immunosuppressive therapy. Forty-three (41.7%) patients were reported to have one or more underlying diseases (Table 2).

The clinical spectrum of pulmonary histoplasmosis varies according to the extent of exposure, presence of underlying lung disease, general immune status, and specific immunity to *H. capsulatum* [6,7]. Among the 103 cases in our study, 35 (34.0%) patients were asymptomatic. Their pulmonary nodules were found incidentally when they received check-ups or postoperative follow-up of cancer. Among the 68 (66.0%) symptomatic patients, 63 (61.2%) patients had respiratory symptoms, 41 (39.8%) patients had systemic symptoms, and 14 (13.6%) patients had other symptoms. The clinical features are provided in Table 2.

In our study, 27 (26.2%) patients presented with bilateral lung lesions, and the rest were unilateral. The most common type of intrapulmonary lesions were pulmonary nodules or masses (81.6%). Among those 84 patients, 59 cases had single nodules or masses, 14 cases had multiple nodules, and the remaining 11 cases had diffuse nodules in both lungs. Other radiographic findings are listed in Table 2. There was a lack of specificity in the imaging of pulmonary histoplasmosis, so the disease was easily misdiagnosed. Twenty-two (21.4%) patients were diagnosed with tuberculosis, and 37 (35.9%) were diagnosed with lung tumors.

Of all the cases, 79 (76.7%) patients were diagnosed based on the histologic appearance of lung or lymph node biopsy specimens. Six patients were diagnosed by fungal culture and identification. mNGS provided diagnostic evidence for 3 patients. The detailed diagnostic basis is presented in Table 2.

In our study, surgical resection alone was used to treat 47 patients. Among those patients, 45 patients survived, 1 patient died of cancer and 1 patient was lost to follow-up. Another 8 patients were treated with

Table 2. Features of patients with pulmonary histoplasmosis on the Chinese mainland.

Feature (N = 103)	n (%)
Underlying disease	
Cancer	18 (17.5)
Hypertension	13 (12.6)
Diabetes mellitus	12 (11.7)
Tuberculosis	3 (2.9)
AIDS	2 (1.9)
Liver disease	2 (1.9)
Organ transplants	2 (1.9)
Syphilis	1 (1.0)
Hyperlipidemia	1 (1.0)
MsPGN	1 (1.0)
ITP	1 (1.0)
Clinical manifestation	
Respiratory symptoms	
Cough	54 (52.4)
Expectoration	28 (27.2)
Hemoptysis	14 (13.6)
Shortness of breath	14 (13.6)
Chest pain	13 (12.6)
Systemic symptoms	
Fever	36 (35.0)
Sweats	7 (6.8)
Fatigue	7 (6.8)
Chills	3 (2.9)
Weight loss	3 (2.9)
Other symptoms	
Headache: myalgias: anorexia: nausea: vomiting: sweats: diarrhea: etc.	14 (13.6)
Asymptomatic	35 (34.0)
Radiographic findings of lungs	
Nodule/Mass	84 (81.6)
Patchy infiltrates	36 (35.0)
Enlarged hilar or mediastinal lymph nodes	24 (23.3)
Calcification	13 (12.6)
Cavitation	11 (10.7)
Pleural effusion	7 (6.8)
Diagnostic method	
Histopathology	
Lung biopsy	79 (76.7)
Lymph node biopsy	6 (5.8)
Antigen detection and serologic testing	9 (8.7)
Fungal culture and identification	
Sputum	4 (3.9)
Lung biopsy	2 (1.9)
mNGS	
Lung biopsy	2 (1.9)
BALF	1 (1.0)

Data are presented as number and proportion of total cases in each feature category. AIDS: acquired immune deficiency syndrome; MsPGN: mesangial proliferative glomerulonephritis; ITP: idiopathic thrombocytopenic purpura; mNGS: metagenomic next-generation sequencing; BALF: bronchoalveolar lavage fluid.

antifungal therapy after surgical resection. Of the remaining cases, 38 patients were treated with antifungal agents, 8 patients had no relevant description of their treatment, 1 patient died on referral, and 1 patient was discharged from the hospital after giving up treatment. Two patients died even after antifungal treatment.

Discussion

Histoplasmosis is a fungal infection caused by the dimorphic fungus *H. capsulatum*. This fungus was originally discovered in Panama in 1906 by Darling [8]. Histoplasmosis most commonly presents as pulmonary disease, which can be difficult for clinicians to distinguish from other causes of acute and chronic pneumonia and can also become disseminated, usually in individuals who are immunocompromised, such as people with HIV or those who take immunosuppressant medications [5].

Both the cases in our hospital were immunocompromised and they were susceptible to mycoses. Their clinical manifestations and chest imaging were nonspecific, so it was difficult to make a quick diagnosis. Common pathogen tests in case 1 were all negative, and *H. capsulatum* infection was eventually confirmed by BALF mNGS. Case 2 was misdiagnosed with metastatic lung cancer. This affirms the clinical value of mNGS for the rapid diagnosis of unexpected pathogens.

Histopathology using stains for fungi, cultures, antibody detection, antigen detection, and mNGS can all help make the diagnosis of pulmonary histoplasmosis. The sensitivity of the different detection methods is shown in Table 3. Histopathologic or direct microscopic identification of *H. capsulatum* or its recovery in culture from clinical specimens are considered a definitive diagnosis of histoplasmosis [16]. The sensitivity and specificity of the microscopic examination are limited and depend on the operator's expertise as well as on the clinical form of the disease [17]. Patients with chronic pulmonary or disseminated histoplasmosis have a higher rate of positive results than patients with acute or subacute pulmonary disease [15]. Fungal cultures are time-consuming. *H. capsulatum* commonly grows within 2 to 3 weeks, and it may even take up to 8 weeks. The overall sensitivity of a culture-based diagnosis of disseminated histoplasmosis in patients with HIV/AIDS was 77% [18]. The lowest sensitivity values are observed in the acute and subacute forms of pulmonary histoplasmosis, whereas higher values can be found in chronic pulmonary and disseminated histoplasmosis due to the patients' higher fungal burden [19]. Detection of specific antibodies to *H. capsulatum* has played an important role in the diagnosis of subacute and chronic pulmonary histoplasmosis. One concern with antibody detection is differentiation of current and past infection. Antibody levels may persist for several years after clinical recovery [15]. Separate detections of IgG and IgM antibodies can help identify current infections, and their sensitivity and specificity were 88.8% and 91.9%, respectively [20]. Antigen detection assays have high sensitivity in disseminated histoplasmosis cases and the concentration of antigenuria correlates with the severity of disease, so they are of great value for the follow-up of patients with disseminated histoplasmosis [15]. Specificity was 99.0% for patients with nonfungal infections and in healthy subjects, but cross-reactivity occurred in patients with paracoccidioidomycosis, *Penicilliosis marneffei*, coccidioidomycosis or aspergillosis [9,15]. Antibody and antigen detection assays are only performed in few laboratories and is not available on Chinese mainland. More importantly, they can only detect known or predicted pathogens and therefore require a reasonable primary judgment. Pulmonary histoplasmosis is rare in China and has atypical clinical presentations, which makes it difficult for Chinese clinicians to presume the presence of the disease. mNGS can identify multiple unexpected microorganisms from a single sample. This technology is increasingly being used in comprehensive hospitals on Chinese mainland, especially when routine

Table 3. Sensitivity of diagnostic tests for the different forms of histoplasmosis.

Assay	Acute pulmonary	Subacute pulmonary	Chronic pulmonary	Disseminated	Reference
Microscopy	0–47%	0–67%	10–75%	12–85%	[9,10]
Culture	0–34%	9–82%	65–85%	74–92%	[9,10]
Sputum	23%	10%	56%-61%	71%	[10-12]
Bronchial washing/BALF	39%	0%	60%	70%-86%	[10,11,13]
Lung	25%	21%	66%	25%-85%	[11,14]
Mediastinal node	-	11%	-	-	[11]
Blood	50%	0%	-	40%-91%	[10,11]
Antibody detection	40–80%	78–95%	65–100%	58–73%	[15]
Antigen detection	43–65%	39%	25–87%	90–98%	[15]

BALF: bronchoalveolar lavage fluid.

pathogenetic tests are negative. In addition to case 1 reported in our hospital, there were 2 other patients in our country who were diagnosed with pulmonary histoplasmosis by mNGS. In one case, PAS staining and Grocott hexamine silver staining of the lung tissue were positive. The pathologists could not determine the specific type of fungus, so they sent the lung tissue culture for NGS [21]. In the other case, the patient's BALF culture was negative, and the patient refused to have a biopsy, so the physician subjected the BALF to NGS [22]. All three patients were accurately diagnosed by mNGS and received targeted antibiotic therapy with a good prognosis. Reliable data on the sensitivity and specificity of mNGS for the detection of *H. capsulatum* are lacking due to the very limited number of studies and the small number of cases. Further studies are need to be carried out in order to evaluate its utility in histoplasmosis diagnosis.

Conclusions

The clinical features and imaging findings of pulmonary histoplasmosis are not specific, so the disease is easily misdiagnosed as tuberculosis and lung tumors, which may delay treatment. A relevant epidemiological history and timely pathogen detection are important for diagnosis. mNGS can shorten the time required for diagnosis and allow earlier initiation of targeted antibiotic therapy.

Authors' contributions

Jun Guo made substantial contributions to the conception and the design of the study and to the analysis and interpretation of the data. Qi Chen and Wei Guo wrote the main manuscript text. Qi Chen and Wei Guo contributed equally to this article. Wenjia Guo and Xiangdong Mu prepared Figure 1-4 and Table 1-3. All authors reviewed the manuscript and agreed to its submission to the journal.

Ethics statement

This study is in line with the Declaration of Helsinki and was approved by the Beijing Tsinghua Changgung Hospital Ethics Committee. After Beijing Tsinghua Changgung Hospital Ethics Committee approval, the study was exempted from informed consent.

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Conflict of interests: No conflict of interests is declared.