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Case report

# Pulmonary cryptococcosis mimicking lung cancer: 3 case report

Zhifei Xin [a,1], Bowen Li [a,b,1], Wenfei Xue [a], Wei Lin [a], Qingtao Zhao [a], Xiaopeng Zhang [a,*]

[a] Hebei General Hospital, Shijiazhuang, Hebei, China
[b] North China University of Science and Technology, Tangshan, Hebei, China

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ABSTRACT

*Introduction and importance:* Pulmonary cryptococcosis is an opportunistic pathogen. However, it is difficult to differentiate it from other diseases by imaging. Therefore, the clinical presentation and imaging features of patients with pulmonary cryptococcosis are analyzed and summarized to improve clinicians' early recognition of the disease.

*Case presentation:* We present a case where preoperative imaging was difficult to differentiate between pulmonary cryptococcosis and non-small cell lung cancer. A pathological biopsy was taken by surgical treatment to clarify the diagnosis.

*Clinical discussion:* Three cases of *Cryptococcus* pulmonary patients diagnosed by pathology in our department were analyzed. We believe that the diagnosis should be confirmed as soon as possible through surgery, relevant laboratory tests, and pathological examinations, and antifungal treatment should be carried out in time.

*Conclusion:* We believe that an earlier and clearer diagnosis of pulmonary cryptococcosis requires an earlier interplay of imaging, pathology, testing, and individual patient differences.

## 1. Introduction

Pulmonary cryptococcosis is a relatively rare fungal disease caused by a novel cryptococcal infection, an opportunistic pathogen that often occurs in immunocompromised patients, but is now increasingly common in immunocompetent patients [1]. The poor specificity of the imaging presentation of pulmonary cryptococcosis and the limited means of pathogenic detection has led to a high rate of clinical misdiagnosis and underdiagnosis [2]. The imaging presentation of pulmonary cryptococcosis has many similarities with lung cancer, tuberculosis, bacterial pneumonia, and other pulmonary fungal diseases, making it difficult to differentiate it from other diseases. Therefore, we summarized and analyzed the clinical data, imaging manifestations, and pathological findings of three patients with pathologically confirmed pulmonary cryptococcosis in our department, expecting to provide reference significance for the diagnosis of this disease and to reduce the rate of misdiagnosis and leakage.

## 2. Clinical information

### 2.1. Case 1

The patient, male, 53 years old, had a history of hypertension for more than 20 years, with stable blood pressure control after oral antihypertensive medication, a history of bilateral inguinal lymph node enlargement for 5 years, and intermittent hemoptysis for more than 5 years, but none of them had been treated. He was admitted to the hospital on 2019-08-07 for "right lung nodule found on examination for 1 day" without any history of pigeon droppings exposure. One day before admission, the patient again had coughing sputum with blood in the sputum, and a chest CT was performed at the hospital and revealed a solid nodule in the posterior basal segment of the lower lobe of the right lung (Fig. 1A, D). After admission, the patient had mildly elevated gastrin-releasing peptide precursors; immunofluorescence staining for total T lymphocytes (CD3+) was mildly elevated; blood sedimentation and four pulmonary tumor items were not significantly abnormal. MRI of the head showed no significant abnormalities and negative findings. The patient was treated with cefamandole sodium anti-inflammatory therapy, and no significant absorption of the lesion was observed. On

* Corresponding author at: Department of Thoracic Surgery, Hebei General Hospital, Shijiazhuang, Hebei 050051, China.
*E-mail address:* zxp8756@163.com (X. Zhang).
[1] Zhifei Xin and Bowen Li contributed equally to this article.

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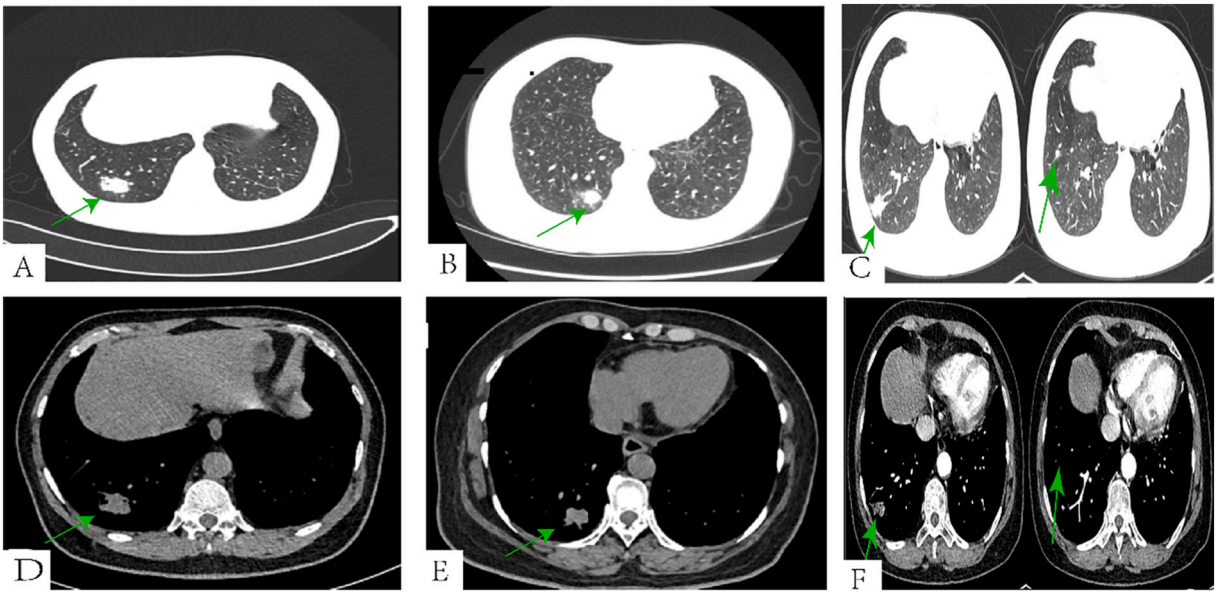
2019-08-12, a single-port thoracoscopic wedge resection of the lower lobe of the right lung was performed, and the postoperative pathological findings were: regional pulmonary solid lesions in the right lung nodules with multiple lymphocytes and plasma cell infiltrates, multinucleated giant cell reaction, fibroblast hyperplasia, and focal suppuration. Immunohistochemical results suggested: CD38 (plasma cell+), CD138 (plasma cell+), IgG (plasma cell+), IgG4 (scattered+), IgG4/IgG positive ratio <40%, kappa and lambda showed polyclonal phenotype, ALK (D5F3) (−), ALK(Neg) (−), Ki-67 positive rate about 10%. Special staining: PAS(+) (Fig. 2A), PASM(+) (Fig. 2B). Antacid staining: no antacid bacilli were detected. Combined with immunohistochemical staining and special staining, it was consistent with cryptococcal infection. The patient recovered well after surgery. After discharge from the hospital, he was treated with oral fluconazole antifungal medication, and a repeat lung CT on 2019-11-13 suggested good postoperative pulmonary recovery.

### 2.2. Case 2

The patient, female, 59 years old, had a hysterectomy for "uterine fibroid", had a history of diabetes mellitus for 2 years, had stable glycemic control after regular oral hypoglycemic medication, had hypothyroidism for 1 year, and was regularly treated with oral eugenol. 40 days ago, she was admitted to a local hospital with right-sided chest pain, and was diagnosed with pneumonia, which improved after conservative treatment. He was admitted to the hospital on 2021-05-25 due to "pulmonary nodules found on physical examination for 1 month". After admission, a chest CT showed an irregular nodule-like soft tissue density shadow in the posterior basal segment of the lower lobe of the right lung (Fig. 1B, E). MRI of the head showed no significant abnormalities and negative findings. The lymphocyte immunoassay (regulatory T cells) and lymphocyte immunoassay five: auxiliary/induced T cells (CD3+CD4+) and CD4/CD8 were mildly elevated; suppressor/cytotoxic T cells (CD3+CD8+) and NK cells (CD3-CD16+CD56) were decreased; blood sedimentation, gastrin-releasing peptide precursor, and lung tumor four were not significantly abnormalities. The patient was given amoxicillin clavulanate potassium for anti-inflammatory treatment, and no significant absorption of the lesion was observed. On 2021-05-28, a single-port thoracoscopic wedge resection of the lower lobe of the right lung + pleural adhesion branding was performed, and the pathological results were reported: granulomatous inflammation (right pulmonary nodule), combined with special staining: PAS(+) (Fig. 2C), PASM(+) (Fig. 2D), and antacid staining did not detect antacid bacilli, consistent with cryptococcal infection. The patient recovered well after surgery and was discharged from the hospital on oral fluconazole antifungal medication, and the lung CT was reexamined on 2021-07-04 indicating good postoperative pulmonary recovery.

### 2.3. Case 3

The patient, a 65-year-old female, had a history of "bronchiectasis" for more than 20 years and "viral hepatitis B", and no significant abnormality in the infectious indexes on review, both without special consultation. The patient complained of a history of feeding poultry and pigeons. He was admitted to the hospital on 2022-1-9 because of "pulmonary nodules found on physical examination for more than 2 months". On admission, chest CT showed nodules or lamellar hyperdensity in the lower lobes of both lungs, and anti-inflammatory therapy was recommended for review to exclude occupying lesions (Fig. 1C, F). The patient was admitted to the hospital for five lymphocyte immunoassays and lymphocyte immunoassay (regulatory T cells): total T lymphocytes (CD3+), suppressor/cytotoxic T cells (CD3+CD8+), and B cells (CD3-CD19+) were seen to be mildly elevated; NK cells (CD3-CD16+CD56) were seen to be mildly decreased; immunofluorescence staining for diagnosis (cytokine seven), blood sedimentation, gastrin-releasing peptide precursors, and lung tumor four did not show any significant abnormalities. The patient was given preoperative anti-inflammatory treatment with piperacillin sodium tazobactam, and no significant resorption of the lesion was observed. On 2022-01-13, a single-port thoracoscopic wedge resection of the lower lobe of the right lung + thoracic adhesion release was performed. Postoperative pathological findings were reported: inflammatory granulomatous lesion, combined with special staining: -3 slices PAS (+) (Fig. 2E), PASM (+) (Fig. 2F), antacid staining (antacid bacilli were not detected), consistent




Note: Panels A and D show the lung window, mediastinal window of a lobar solitary nodule; Panels B and E show the lung window, mediastinal window of a lobar solitary nodule;Panel C and E shows the lung window and mediastinal window with multiple nodules in both lobes.

**Figure 1.** CT image of the case.
Note: Panels A and D show the lung window, mediastinal window of a lobar solitary nodule; Panels B and E show the lung window, mediastinal window of a lobar solitary nodule; Panel C and E shows the lung window and mediastinal window with multiple nodules in both lobes.

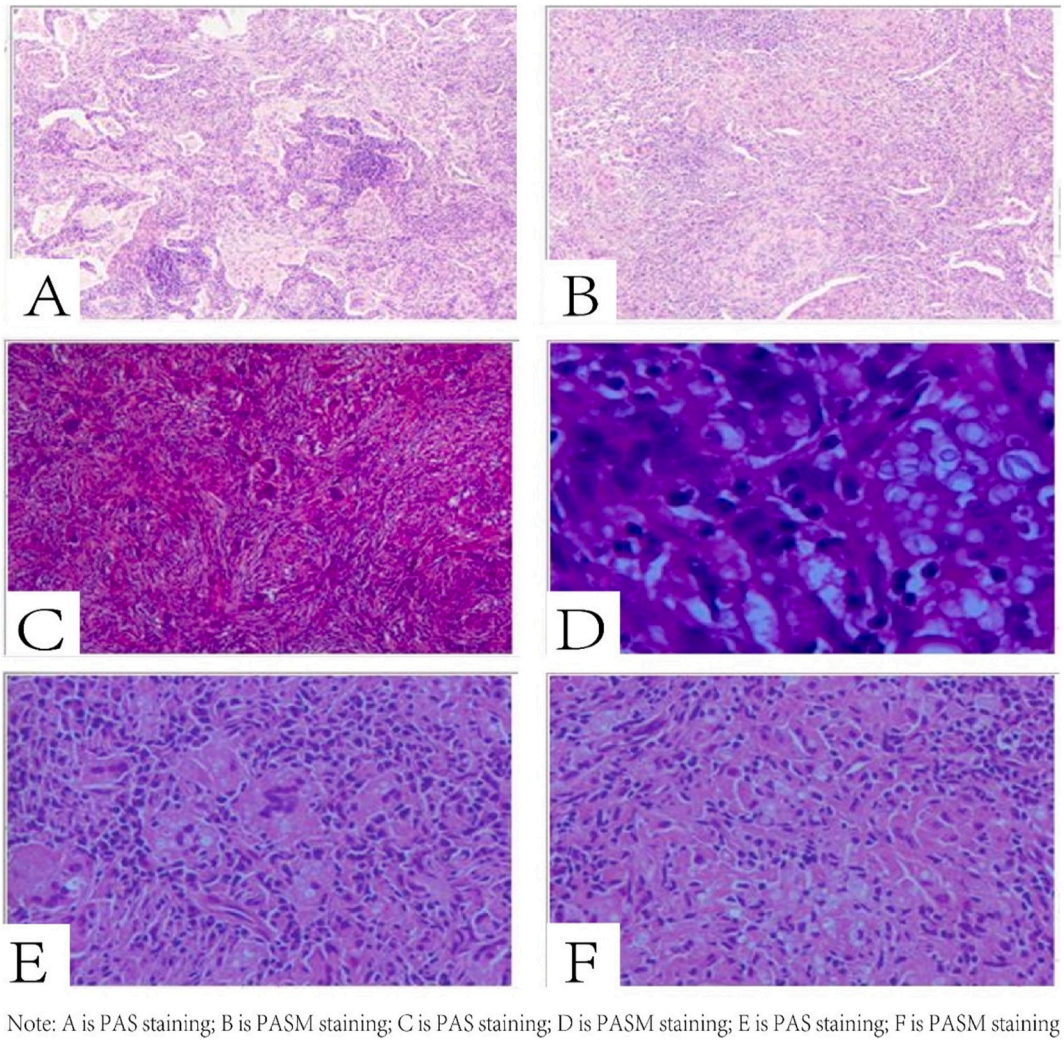



**Fig. 2.** Related histological pictures of 3 patients.
Note: A is PAS staining; B is PASM staining; C is PAS staining; D is PASM staining; E is PAS staining; F is PASM staining.

with cryptococcal pneumonia. The patient recovered well after surgery and was discharged from the hospital on oral fluconazole antifungal medication. On 2022-02-16, the lung CT was repeated and showed significant absorption of both lung lesions.

## 3. Discussion

*Cryptococcus* is a unicellular gonococcal yeast. Of the more than 30 known species of *Cryptococcus*, two of the major ones that affect humans are *Cryptococcus neoformans* and *Cryptococcus gattii* [3]. It is worth noting that *Cryptococcus* does not produce toxins and thus its infection does not cause tissue destruction, hemorrhage, necrosis, and infarction, nor does it lead to fibrosis and calcification; the direct effect is due to an increase in yeast cells that occupy space and compress the surrounding tissue. Pathological examination often reveals a large number of cryptococcal organisms aggregated in mounds within the lesion at the initial stage and cryptococcal spores phagocytosed by multinucleated giant cells and monocytes at the later stage. Cryptococcosis mainly invades the central nervous system, lungs, and skin, and cerebral cryptococcosis accounts for 80% of cases with a high mortality rate because of its high affinity for meninges and brain tissue. Thus, pulmonary cryptococci are relatively uncommon [4]. Notably, animal feces are an important source of cryptococcal infection, with pigeon feces being the most common [3]. However, among the three patients with pulmonary cryptococcosis we counted, only one had a history of pigeon droppings exposure, but we cannot exclude the possibility of unconscious environmental exposure and other factors in the remaining two patients.

Imaging of pulmonary cryptococcosis showed nodular mass type in about 55.6%, pleural depression sign in about 33.3%, and inflammatory solid type in about 40.0%. Nodules are commonly found in the subpleural area and appear as single or multiple. Careful differentiation from non-small cell lung cancer is required when signs such as lobar, burr, bronchial inflation, vacuolation, and satellite signs are manifested [5]. Studies suggest that the incidence of solid lesions of isolated nodular pulmonary cryptococcosis misdiagnosed as lung cancer is higher than that of lung cancer, while the incidence of mixed solid lesions is lower than that of lung cancer. The presentation of lesions as solid oval or lobulated solid nodules on CT images may be related to the formation of inflammatory granulomas and fibrous tissue after phagocytosis of novel cryptococci by macrophages, and fibrous tissue has contractile force due to uneven contraction, thus presenting this sign on images [6]. This study suggests that most pulmonary nodules due to pulmonary cryptococcosis manifest in a more regular morphology and provide a strong reference for us to reduce the misdiagnosis rate of lung cancer. Among the three patients mentioned above, case 4 and case 2 showed single nodules on imaging, and case 3 showed multiple nodules in both lungs, all of which are consistent with the feature that pulmonary cryptococcal infections in immunocompetent patients tend to present in the nodular

form [7]. Most of the features exhibited by imaging CT of nodules in the three patients in this study were lobar signs, burr signs, and pleural traction. In cases 1 and 3, the vacuolation sign and burr sign was more often seen; in cases 2 and 3, significant pleural traction was seen. This presents a challenge in identifying pulmonary malignancy on imaging. Case 3 patient is of particular concern, being the only one of the three patients in this case report with multiple pulmonary nodules in both lungs. The pulmonary nodule signs showed typical signs of malignancy such as lobar signs, burr signs, pleural traction, in addition to specific signs such as mixed solid lesions and halo signs. This also obviously increases the difficulty of differential diagnosis. However, the special signs such as smooth margins of pulmonary nodules and vascular collection signs demonstrated by imaging CT in the above three patients also provided evidence to clarify the diagnosis of pulmonary cryptococcosis. It is worth noting that pulmonary cryptococcosis mostly appears as solid nodules on CT images before a definite pathological diagnosis is made, so it is necessary to perform a lung puncture biopsy before surgery to clarify the pathological findings. Thus, in the process of definitive diagnosis, it is important to pay attention not only to the interplay of clinical, imaging, pathology, and individual patient differences, but also to pay more attention to laboratory diagnostic experiments, including fungal culture, histopathology, serology, and molecular testing, which have some reference significance for differential diagnosis [8,9].

Treatment of pulmonary cryptococcosis: Fluconazole is the drug of choice for the treatment of pulmonary cryptococcosis. Asymptomatic or symptomatic patients with normal immune function are treated with 400 mg/day oral fluconazole for 6–12 months. If fluconazole is not available or drug allergy occurs, alternative therapy with voriconazole or itraconazole (200 mg) twice daily is available [10]. In patients with combined immune deficiency, fluconazole therapy is recommended in mild cases at the same dose as in immunocompetent patients. Patients with severe or combined central nervous system infections need to be given 200–400 mg/day according to symptoms and fluconazole maintained for life in addition to the treatment measures for severe immunocompetent patients [11]. The above three patients showed good imaging uptake on review of bilateral lung CT after postoperative administration of fluconazole antifungal therapy.

In summary, pulmonary cryptococcosis, as the third major fungal infectious disease of the lung, is not easily diagnosed early and is difficult to differentiate from non-small cell lung cancer because of the absence of significant individual differences in incidence such as gender, age, and immune function, and the variable imaging presentation and lack of specificity. By comparing pulmonary nodules caused by *Cryptococcus* lung and lung cancer, it was concluded that isolated nodular pulmonary cryptococcosis is easily misdiagnosed as lung cancer or tuberculosis based only on what is seen on chest CT examination, but imaging features such as smooth lesion margins, solid lesions, mixed solid lesions, vascular bundle set to sign, and halo sign have some reference significance for the differential diagnosis. Therefore, pathologic histological examination should be performed as early as possible to clarify the diagnosis when the diagnosis is unclear. In patients with pulmonary cryptococcosis, the most dangerous thing is not the pulmonary lesion itself, but the possibility of systemic dissemination. Because of the high affinity of cryptococci for meningeal tissue, the possibility of central nervous system infection should not be overlooked. If necessary, lumbar puncture cerebrospinal fluid examination, bone marrow culture, and biopsy of suspected skin lesions should be completed as early as possible to clarify the presence or absence of dissemination and determine the treatment plan as early as possible, which will help improve the prognosis of patients.

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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## Ethical approval

The ethical committee approval was not required given the article type (case report).

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## CRediT authorship contribution statement

All authors contributed to writing the paper.

## Declaration of competing interest

The authors state that they have no conflicts of interest for this report.

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