Pulmonary cryptococcosis coexisting with lung adenocarcinoma: A case report and review of the literature

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Abstract. Pulmonary cryptococcosis (PC) is an invasive pulmonary fungal disease caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. It often presents as a single nodule or mass on radiology, which is easily misdiagnosed as lung cancer or metastases. However, cases of PC coexisting with lung cancer are rare and when this scenario is encountered in clinical practice, it is easy to be misdiagnosed as metastatic lung cancer. The present study reported the case of a 65-year-old immunocompetent patient with PC coexisting with lung adenocarcinoma. Percutaneous lung biopsy was performed on the nodule in the anterior segment of the left upper lobe and the nodule in the posterior basal segment of the left lower lobe, which were diagnosed as primary adenocarcinoma and cryptococcus, respectively. Lung cancer was treated by surgery and PC was treated successfully by antifungal treatment. During the 5-year follow-up, contrast-enhanced CT showed no recurrence of either disease. This case reminds us of the possibility of dualism in the diagnosis of multiple pulmonary nodules based on CT examination, such as the coexistence of lung carcinoma and PC. In addition, early diagnosis and treatment contribute to good prognosis.

Introduction

Pulmonary cryptococcosis (PC) is a common opportunistic fungal infection caused by *Cryptococcus neoformans* or *Cryptococcus gattii* (1), which mainly invades the respiratory system, followed by the central nervous system (CNS) (2). It usually occurs in immunocompromised patients, such as patients with human immunodeficiency virus (HIV) infection, solid organ transplantation or autoimmune diseases, as well as patients who use corticosteroids and other immunosuppressants (3,4). However, the incidence of PC has recently increased rapidly in hosts with normal immune function (5,6). Different immune statuses may affect the pulmonary CT manifestations of cryptococcosis (7,8). The diagnosis of PC is challenging due to its diverse and nonspecific CT findings, which may mimic those of lung cancer, bacterial pneumonia or tuberculosis (5). Previous studies have indicated that advanced cancer may lead to immunodeficiency and cause cryptococcosis (9,10). Previous studies have reported on PC coexisting with lung carcinoma (9,11-17). Most of the reported cases presented with respiratory symptoms and a small number of them were asymptomatic. Certain cases are accompanied with other underlying diseases, such as diabetes, tumor history or systemic lupus erythematosus (11,12,14,17). In general, this coexistence relationship may be broadly divided into two types; one is that cryptococcal infection occurs in lung cancer nodules or masses (9,18); the other is that cryptococcal infection and lung cancer nodules/masses belong to two different lesions (15). It is radiologically nonspecific and is usually found by surgical excision or percutaneous lung biopsy. As with other early lung cancer, the treatment for lung cancer nodules or masses is aggressive surgical resection, while PC usually requires postoperative antifungal therapy. The prognosis of lung cancer is related to the pathological and clinical stage of lung cancer, and cryptococcal infection usually has a better prognosis. The present study reported the case of a 65-year-old patient with pulmonary adenocarcinoma complicated with PC infection.

Case presentation

A 65-year-old Han Chinese woman who worked as a crop farmer presented to Taihe Hospital (Shiyan, China) for a routine physical examination in August 2018. The patient had no respiratory symptoms and denied any other discomfort. Chest CT showed a 2.4x2.0-cm nodule in the anterior segment of the

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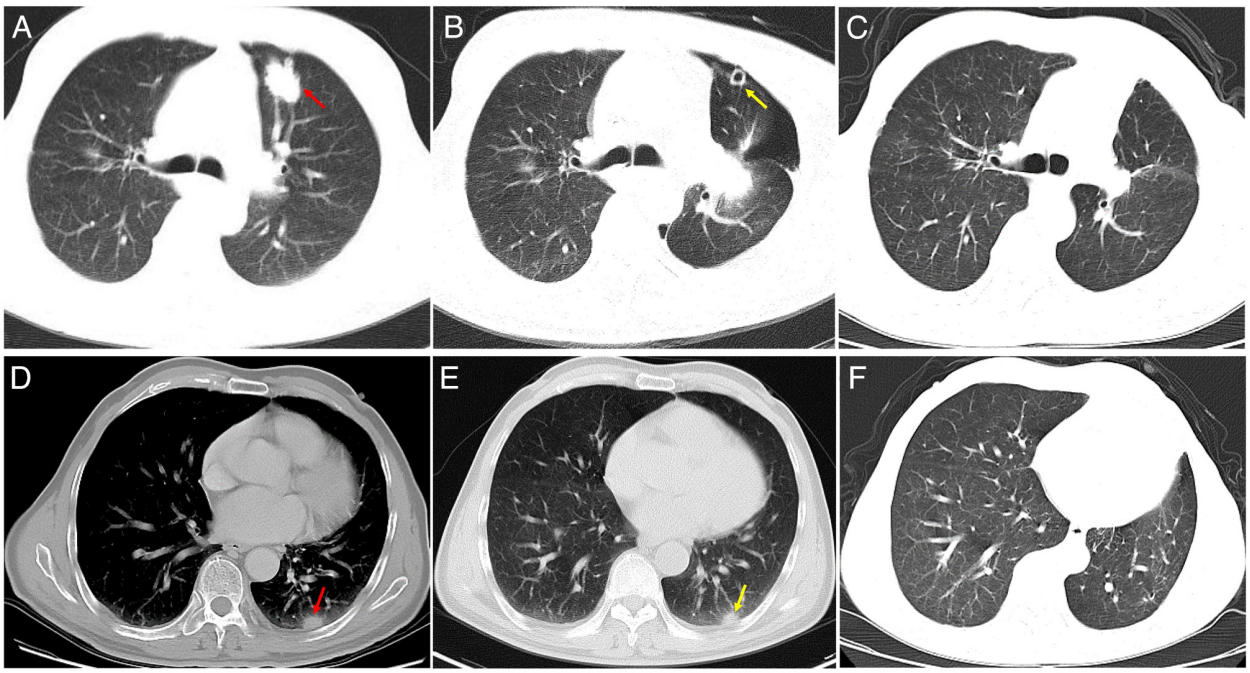

Figure 1. Chest images. (A) Chest CT scan showing a 2.4x2.0-cm nodule in the anterior segment of the left superior lobe (red arrow) and peripheral lung cancer was highly suspected. (B) Chest CT scan showing a thoracic tube (yellow arrow) after surgical resection of a nodule in the anterior segment of the left upper lobe, which was diagnosed as adenocarcinoma. (C) Chest CT scan indicating no recurrence of lung cancer during the 5 years after surgery. (D) Chest CT scan showing a 1.3x0.9-cm nodule in the posterior basal segment of the left lower lobe (red arrow) and intrapulmonary metastasis was suspected. (E) Chest CT scan indicating that the posterior basal segment nodule of the left lower lobe with the diagnosis of PC (yellow arrow) was reduced in size after one month of antifungal treatment. (F) Chest CT scan showing that the PC nodule in the posterior basal segment of the left inferior lobe had disappeared after 6 months of antifungal therapy during the 5-year follow-up. PC, pulmonary cryptococcus; CT, computed tomography.

left superior lobe (Fig. 1A), which was highly suspected to be peripheral lung cancer. A 1.3x0.9-cm nodule was detected in the posterior basal segment of the left lower lobe (Fig. 1), which was suspected to be intrapulmonary metastasis. Hospitalization was recommended for further examination and treatment.

The patient denied any respiratory symptoms, such as cough, sputum, fever, chest pain, wheezing or weight loss. Immune function was normal, the patient had no history of travel or exposure to pigeon feces or soil, no history of smoking or alcohol consumption within the last month, and had not been extensively treated with hormones and/or antibiotics before coming to the hospital. The patient's medical history included surgery for varicose veins in the left lower extremity 30 years earlier, cataract surgery of the left eye 10 years ago and hemorrhoid surgery 2 years previously. On admission, the vital signs etc. were normal On physical examination, there were no skin lesions, lymphadenopathy or splenomegaly.

Laboratory examination indicated the following: Whole blood leukocytes, $4.82x10^9$/l [neutrophils, 68.8% (normal range, 50-70%); lymphocytes, 24.3% (normal range, 20-50%); monocytes, 5.6% (normal range, 3-10%); eosinophils, 1.5% (normal range, 0.4-8%); basophils, 0% (normal range, 0-1%)]; red blood cells, $4.37x10^{12}$/l (normal range, 4.3 to $5.8x10^{12}$/l); hemoglobin, 127 g/l (normal range, 130-175 g/l); platelets, $175x10^9$/l (normal range, 125 to $350x10^9$/l); blood glucose, 4.45 mmol/l (normal range, 3.9-6.1 mmol/l); total bilirubin, 9.8 μmol/l (normal range, 3.42-20.5 μmol/l); aspartate aminotransferase, 17 U/l (normal range, 0-40 U/l); alanine aminotransferase, 12 U/l (normal range, 0-50 U/l); lactate dehydrogenase, 99 IU/l (normal range, 100-240 IU/l); and highly sensitive C-reactive protein, 0.15 mg/l (normal range, 0-5 mg/l). A urinalysis and microscopic examination were normal. Tumor markers were as follows: Neuron-specific enolase, 10.1 ng/ml (normal range, 0-16.3 ng/ml); carcinoembryonic antigen, 1.77 μg/l (normal range, 0-5 μg/l); and ferritin, 357 ng/ml (normal range, 30-400 ng/ml), all of which were at normal levels; however, Cyfra21-1 was 3.75 μg/l higher than the upper limit of the normal level (normal range, 0-3.3 μg/l). Sputum Gram staining (19) and bacterial culture showed no microorganisms. Acid-fast staining (20) and sputum culture showed no acid-fast bacteria. Bronchofiberscopy showed no lesions in the trachea and bronchus, and bacterial, cytological and pathological examinations from the bronchoscope provided negative results.

To obtain a definitive diagnosis, a CT-guided percutaneous lung biopsy was performed on a nodule of radiologically high suspicion of lung cancer in the anterior segment of the left upper lobe, which was pathologically confirmed to be adenocarcinoma. To evaluate the stage of lung cancer and select appropriate treatment, a CT-guided percutaneous lung biopsy was performed on the nodule in the posterior basal segment of the left inferior lobe 1 week later, which was confirmed by histopathology as PC infection. Histologically, hematoxylin & eosin staining (21) revealed granulomatous inflammation and yeast-form fungi in multinucleated cells, and cryptococcus was identified by periodic acid Schiff (PAS), Gomori methenamine silver (GMS) and mucicarmine (MC) staining (Fig. 2A-D, respectively). The above staining procedures were performed according to standard protocols. Two weeks later, the patient underwent thoracoscopic resection of the left lung

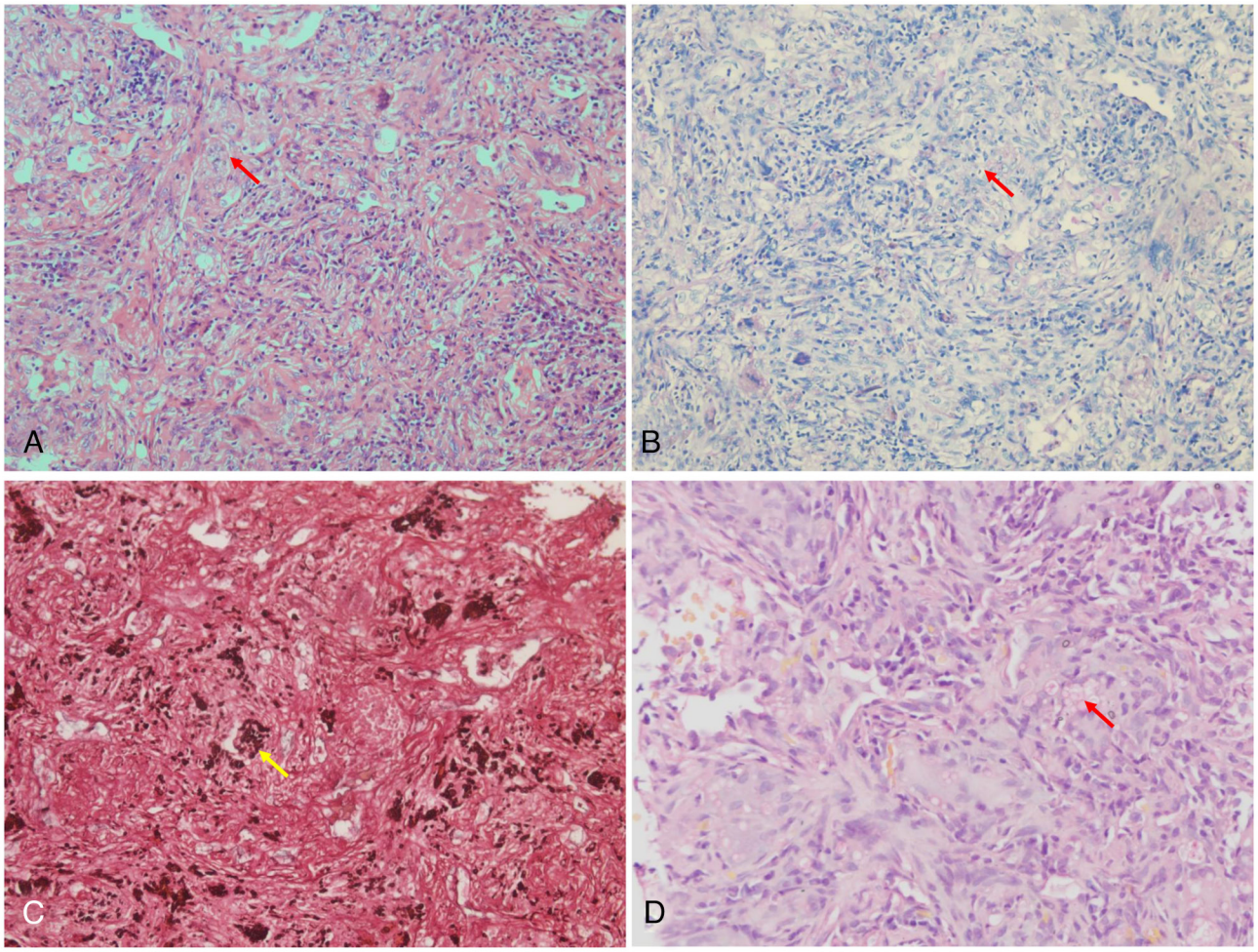

Figure 2. Histologic examination images of the nodule in the posterior basal segment of the left lower lobe. (A) Nodular granuloma lesion with multinucleated giant cells, which contain many *cryptococcal* yeasts (H&E stain); (B) periodic acid-Schiff-positive stain (red arrow); (C) Gomori methenamine silver-positive stain (red arrow); (D) mucicarmine-positive organisms (red arrow; original magnification, x200 for all).

cancer. Macroscopic examination revealed that the excised 14x9.5x3.5-cm upper left lobe included a 3.1x2.5x2-cm mass with gray and grayish black sections, solid, medium in texture, and indistinct from the surrounding boundary (Fig. 3). The mass was adjacent to the pleura and did not involve the bronchus. Histologically, the tumor cells were moderately to poorly differentiated adenocarcinoma of the acinar and micropapillary type (Fig. 4A-D), and no cryptococcal infection was observed. No metastatic cancer was found in the lymph nodes (0/11), the bronchial incisive margin was negative and the pathological TNM stage was T2aN0Mx. In addition, the patient received fluconazole (Pfizer Inc.) 200 mg/day antifungal therapy for 6 months. Within five years after the resection, the patient was admitted to the respiratory department of our hospital regularly for further follow-up (every 6 months for the first 2 years and once a year for the last 3 years), and the latest follow-up was in August 2023. The patient was in good condition and contrast-enhanced CT showed no recurrence of either disease (Fig. 1B, C, E and F).

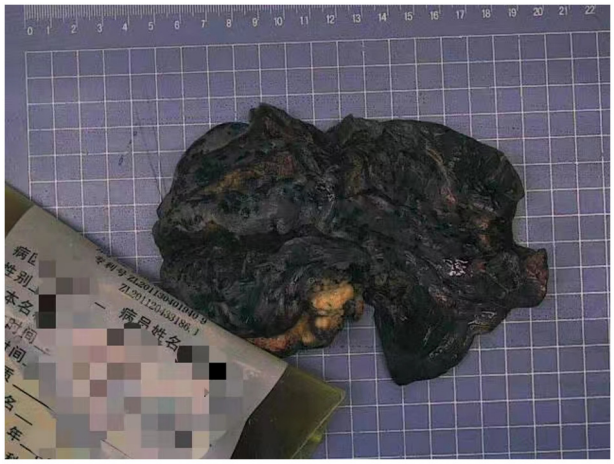

Figure 3. Macroscopic examination revealed that the excised 14x9.5x3.5-cm upper left lobe included a 3.1x2.5x2-cm mass with gray and grayish black sections, solid, medium in texture and indistinct from the surrounding boundary (the size/scale of the grid in the background is 1x1 cm).

Discussion

Cryptococcosis is a fatal fungal infection mainly caused by *Cryptococcus neoformans* or *Cryptococcus gattii* (1). Cryptococcosis caused by *Cryptococcus neoformans* is common in China (22). At present, PC is the third most common pulmonary fungal infection in China and previous studies

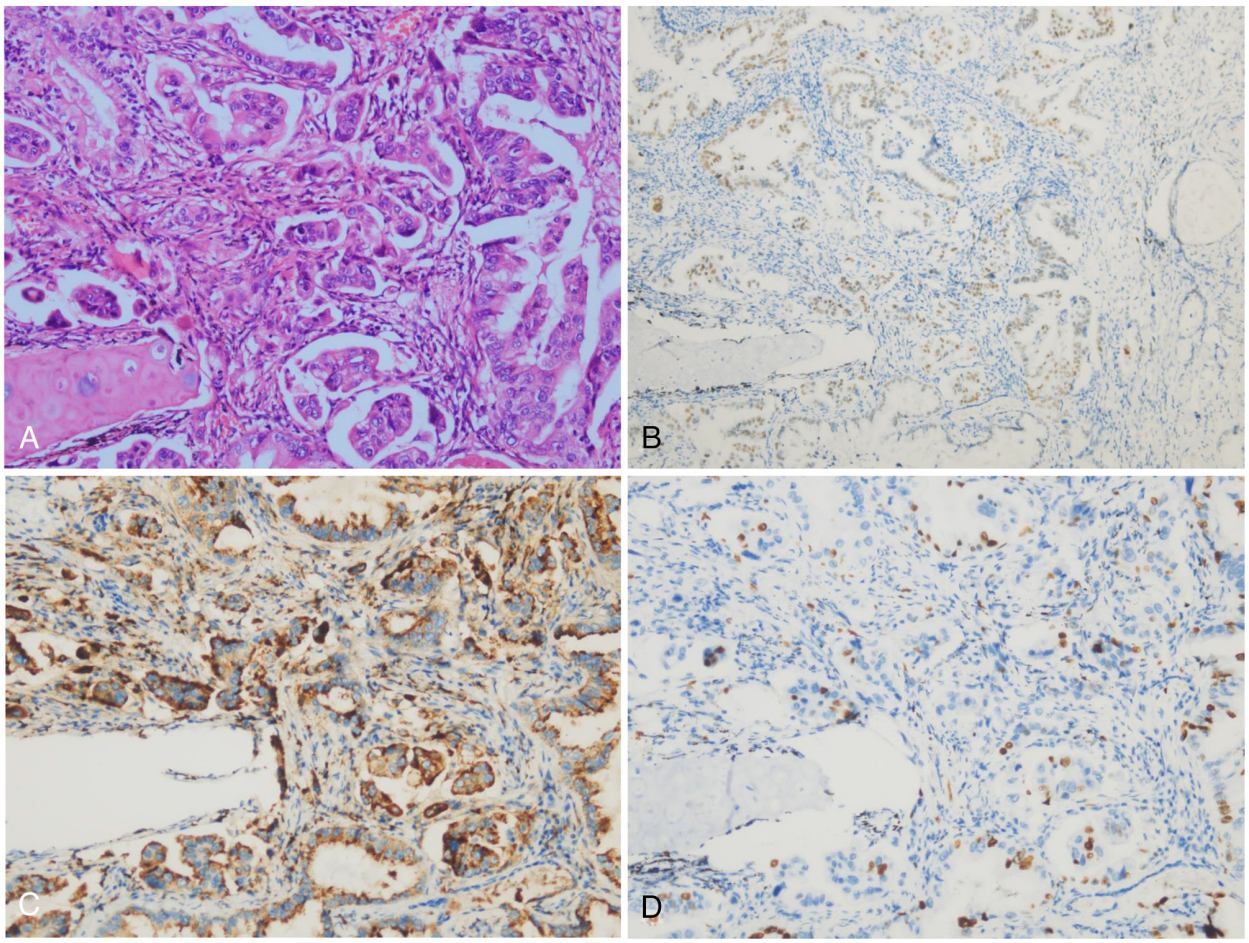

Figure 4. Histologic examination images of the nodule in the anterior segment of the left superior lobe. (A) The tumors were mostly micropapillary, and the acinar type was occasionally seen (H&E stain). Immunohistochemical stains showed strong positivity for (B) thyroid transcription factor-1, (C) Napsin A and (D) Ki-67 (40% positivity) (original magnification, x200 for all).

have shown that the majority of cryptococcosis cases in China were reported in HIV-uninfected patients (particularly immunocompetent hosts) (22,23). The case of the present study was a patient with normal immune function, without any history of illness of the immune system, underlying diseases such as diabetes or use of immunosuppressants or glucocorticoids. PC can be confirmed by histopathology or tissue culture (24). In the present case, the histopathologic diagnosis of PC was obtained through biopsy, surgery and special staining, such as PAS, GMS and MC. Of course, in addition to invasive diagnostic methods, there are noninvasive methods for PC, such as blood culture and Cryptococcus antigen (CrAg) (25). However, culture often yields negative results in immunocompetent hosts (26); occasionally, histopathologically confirmed cases are culture-negative (27). The CrAg test is a sensitive and specific test for the diagnosis of cryptococcosis in immunocompromised patients (28). However, the sensitivity is lower in patients with isolated PC. In the present case, the nodule in the anterior segment of the left upper lobe was highly suspected to be lung cancer on radiology, and the nodule in the posterior basal segment of the left lower lobe was suspected to be pulmonary metastasis. Therefore, initially, the possibility of cryptococcus was not considered in advance, and thus, no non-invasive tests, such as cryptococcal antigen testing, were performed before percutaneous lung biopsy. PC symptoms are nonspecific, presenting with cough, sputum, fever, dyspnea, pleuritic chest pain, hemoptysis and malaise (3,29), which are indistinguishable from other causes of pneumonia (30). However, a subset of patients are asymptomatic and the condition is usually detected incidentally during chest radiological examination (23,31). The patient of the present study had no clinical symptoms, even with lung cancer of the upper lobe of the left lung. Different immune statuses may affect the CT imaging features of patients with PC (32). Based on previous literature and clinical experience, pulmonary nodules/masses, either solitary or multiple, were the most common CT findings in PC, which usually occurs in the peripheral lung, adjacent to or involving the pleura (29,32,33). As reported in previous studies, when PC consists of solitary or multiple nodules, these nodules may be confused with lung cancer on chest CT and it is often difficult to distinguish PC from lung carcinoma (5,16). Igai *et al* (34) tried to distinguish PC from lung cancer by fluorodeoxyglucose positron emission tomography (FDG-PET); however, their results showed that FDG-PET has difficulty distinguishing PC from malignancies. In the patient of the present study, the confirmed posterior basal pleural nodule of the left lower lobe was consistent with this CT feature and the final diagnosis was cryptococcal infection. In the present case, multiple nodules were found in the left lung and based on chest CT, it was highly suspected that the nodules in the anterior

Table I. Features of previously reported cases of PC coinciding with lung cancer.

Case no./age, years/sex	Author, year	Country	Symptoms	Immuno-suppressive underlying disease	Chest CT of lung cancer/PC	Histologic subtypes of cancer	Lung cancer TNM staging	Therapy	Follow-up time after discharge	Prognosis	(Refs.)
1/73/M	Ahn, 2005	South Korea	Mild dyspnea on exertion and cough	Diabetes mellitus and hypertension	Anterior segment of the right upper lobe	Moderately differentiated squamous cell carcinoma	pT1aN0M0 (Stage IA)	Surgical excision + AFT	10 months	No recurrence	(11)
2/74/M	Robinson, 1999	Australia	Right-sided pleuritic chest pain and mild dyspnea	None	Left lower lobe opacity	Moderately differentiated adenocarcinoma	pT2N1 (Stage IIB)	Surgical excision + AFT	NA	NA	(9)
3/73/F	Kawasaki, 2004	Japan	Asymptomatic	None	GGO, the left anterior superior subsegment/two nodules, the left anterior basal segment	Adenocarcinoma	pT1N0M0 (Stage IA)	Surgical excision + AFT	3 years	No recurrence	(13)
4/52/F	Li, 2018	China	Cough	History of thyroid adenoma resection	Solitary nodule, the right posterior segment/multiple nodules, the right lateral basal segment	Adenocarcinoma	pT1bN2M0 (Stage IIIA)	Surgical excision + ANCT + AFT	3 years	No recurrence	(14)
5/72/M	Yao, 2020	China	Dry cough	None	Irregular mass, left hilum of the lung/ multiple nodules, dorsal segment of the right lower lobe	Moderately-poorly differentiated squamous cell carcinoma	NA	Surgical excision + AFT	5 years	Cancer recurrence	(15)
6/64/F	Huang., 2019	China	Cough and sputum production	Diabetes mellitus	Solitary nodule, L-S3/solitary nodule, L-S7,8	Invasive ADC	pT1aN0M0 (Stage IA)	Surgical excision + AFT	4 years	No recurrence	(12)
7/55/M	Huang, 2019	China	Asymptomatic	None	SNGGO, R-S6/ solitary nodule, R-S3	Invasive ADC	pT2aN0M0 (Stage IB)	Surgical excision + AFT	7 years	No recurrence	(12)
8/69/F	Huang. , 2019	China	Asymptomatic	None	Solitary nodule, R-S2/multiple nodules, R-S2[a]	Non-mucinous AIS	Tis	Surgical excision + AFT	4 years	No recurrence	(12)

Table I. Continued.

Case no./age, years/sex	Author, year	Country	Symptoms	Immuno-suppressive underlying disease	Chest CT of lung cancer/PC	Histologic subtypes of cancer	Lung cancer TNM staging	Therapy	Follow-up time after discharge	Prognosis	(Refs.)
9/57/F	Huang., 2019	China	Cough and sputum production	Gastric cancer after operation	Solitary nodule, L-S1/solitary nodule, R-S1[a]	Invasive ADC	pT1aN0M0 (Stage IA)	Surgical excision + AFT	4 years	No recurrence	(12)
10/43/F	Huang., 2019	China	Cough, chest distress and chest pain	None	Solitary nodule, R-S3/solitary nodule, R-S1[a]	Invasive mucinous ADC	pT2aN0M0 (Stage IB)	Surgical excision + AFT + ANCT	6 years	Cancer recurrence	(12)
11/38/F	Huang., 2019	China	Cough and phlegm with blood	None	Solitary nodule, R-S2/solitary nodule, R-S6	Invasive mucinous ADC	pT1bN2M0 (Stage IIIA)	Surgical excision + AFT + ANCT	8 years	Cancer recurrence	(12)
12/52/F	Huang., 2019	China	Chest pain, cough and sputum production	None	SNGGO, R-S2/ multiple nodules, R-S6	Invasive ADC	pT1aN0M0 (Stage IA)	Surgical excision + AFT	4 years	No recurrence	(12)
13/67/F	Huang., 2019	China	Fever? Cough and sputum production	None	Air-space consolidation, R-LL/air-space consolidation, R-LL	Invasive mucinous ADC	cT4N0Mib (Stage IV)	AFT+ ANCT	10 months	Deceased	(12)
14/69/M	Zheng, 2020	China	Cough and chest discomfort	None	Multiple nodules, the left upper lobe/ multiple nodules, the right lower lobe	Adenocarcinoma	NA	Surgical excision + AFT	2 years	No recurrence	(17)
15/54/M	Zheng, 2020	China	Asymptomatic	None	GGO, the posterior segment of the right upper lobe apex/ multiple nodules, the left upper lobe	Alveolar cell carcinoma	NA	Surgical excision + AFT	2 years	No recurrence	(17)
16/46/F	Zheng, 2020	China	Asymptomatic	Systemic lupus erythematosus, chronic viral hepatitis B and use of methyl-prednisolone sodium succinate	Multiple nodules, the dorsal segment of the lower lobe of the right lung/ solitary nodule, the outer basal segment of the lower lobe of right lung	Alveolar cell carcinoma	NA	Surgical excision + AFT	2 years	No recurrence	(17)

Table I. Continued.

Case no./age, years/sex	Author, year	Country	Symptoms	Immuno-suppressive underlying disease	Chest CT of lung cancer/PC	Histologic subtypes of cancer	Lung cancer TNM staging	Therapy	Follow-up time after discharge	Prognosis	(Refs.)
17/71/M	Harada, 2006	Japan	Asymptomatic	None	Solitary thin-walled cavitary nodule, the apical segment of the right lung	Well-differentiated papillary adenocarcinoma	T1N0M0 (Stage IA)	NA	1 year	No recurrence	(16)

[a]Coexisting cryptococcosis and carcinoma within the same lobe. ADC, adenocarcinoma; AFT, antifungal therapy; AIS, adenocarcinoma *in situ*; ANCT, antineoplastic chemotherapy; cTNM staging, clinical TNM staging; F, female; LL, lower lobe; M, male; NA, information not available; PC, pulmonary cryptococcosis; pTNM staging, pathological TNM staging; R, right; S, segment; SNGGO; solitary nodular ground-glass opacity.

segment of the left upper lobe were peripheral lung cancer, while the other subpleural nodules in the posterior basal segment of the left lower lobe were intrapulmonary metastases, which were later confirmed by biopsy and surgery as adenocarcinoma and PC infection, respectively. These imaging features of the present case were consistent with those reported in the literature above. Huang *et al* (12) suggested that cryptococcosis lesions coexisted with lung cancer and resembled primary or metastatic tumors. Harada *et al* (16) indicated that, since most patients were in an immunocompetent state, the coexistence of cryptococcosis and carcinoma was coincidental. However, Robinson *et al* (9) thought that lung malignancy may have resulted in a degree of immune suppression, predisposing the patient to infection with cryptococcus. This issue is currently controversial and further studies are needed to clarify the possible relationship between lung cancer and cryptococcal infection. It may be speculated that there is another possibility that pulmonary cryptococcal infection can lead to the occurrence of lung cancer. Similarly, The coexistence of pulmonary tuberculosis and lung cancer is not an uncommon clinical observation (35), it has been proposed that chronic inflammation in the lungs due to tuberculosis may cause clastogenic activity in the DNA of bronchial epithelium. Another possibility is lateral gene transfer; since *Mycobacterium tuberculosis* is an intracellular organism, bacterial DNA may integrate into bronchial epithelial cells to induce neoplastic transformation (36). In addition, for cases co-existing in the same nodule or mass, latent cryptococcus infection may have a long-term chronic inflammatory stimulation, and there is vast preclinical and clinical evidence suggesting that strong and chronic inflammatory responses promote cancer development and progression through different mechanisms (37,38). The option that PC may cause lung cancer has not been reported, but it is worthy of further research. Histopathology is still the most important diagnostic method for PC and it is often necessary to combine special staining to obtain a definitive diagnosis. It has been reported that the detection rates of *C. neoformans* by PAS, GMS, MC and Alcian blue staining were 100, 100, 87 and 67%, respectively (39).

A comprehensive search of the PubMed, Google Scholar and Web of Science databases was conducted and only 17 cases of PC coexisting with pulmonary carcinoma have been reported in the English language worldwide, which were from Japan, China, South Korea and Australia (9,11-17). The clinical characteristics of PC coexisting with pulmonary carcinoma in the previous literature are summarized in Table I. The patient of the present case study was asymptomatic; among the 17 patients reported in the literature, 6 were asymptomatic. Furthermore, 12 patients were immunocompetent and 5 patients had immunosuppressive and underlying diseases, including diabetes mellitus, a history of gastric cancer and thyroid adenoma resection, systemic lupus erythematosus, chronic viral hepatitis B and a history of hormone use. Compared with previous reports, the unique feature of the present case was the relatively small size of the lung cancer and PC nodule, which were 2.4x2.0 and 1.3x0.9 cm, respectively. The patient of the present study had no underlying diseases and was immunocompetent. Of the 17 patients reported in the literature, 7 were diagnosed with coexisting cryptococcosis and carcinoma within the same lobe; however, in the present

case, the carcinoma nodule and cryptococcal nodule were not in the same lobe. As reported in the literature, the histological types of cancer in most cases were adenocarcinoma (13 cases), 2 cases were squamous cell carcinoma and 2 cases were alveolar cell carcinoma. The histological type of cancer in the case of the present study was adenocarcinoma. In terms of treatment, almost the same treatment method was adopted in the present case and the previous literature, namely surgical excision plus antifungal therapy. According to previous results, most of the patients had a good prognosis and the patient of the present case study was followed for 5 years with no recurrence of either disease.

The present case study reminds us of the possibility of dualism in the diagnosis of multiple pulmonary nodules based on CT examination, such as the coexistence of lung carcinoma and PC. If medical conditions permit, lesion resection should be performed to treat suspected malignant lung nodules, including cryptococcal nodules that do not respond to antifungal therapy.

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Availability of data and materials

The datasets generated in the present study are not publicly available to protect the patient's privacy but are available from the corresponding author on reasonable request.

Authors' contributions

HW and MW were involved in the conception and design of the study. HW and XC drafted the manuscript and performed the acquisition, analysis and interpretation of data for the study. YT and YW made contributions to the interpretation of the data for the study and revised the manuscript critically for important intellectual content. DY and YW acquired pathological and surgical data of the patient/performed measurements. YZ and YL researched the clinical case, participated in the treatment of the patient and revised the manuscript. MW, HW and YT confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Taihe Hospital (Shiyan, China), and was performed in accordance with the principles of Good Clinical Practice following the Tri-Council guidelines.

Patient consent for publication

Written informed consent for anonymized information and images to be published in this article was obtained from the patient.

Competing interests

The authors declared that they have no competing interests.

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