Observational Study

Medicine®

OPEN

Concomitant lung adenocarcinoma and pulmonary cryptococcosis confirmed by pathologic examinations

Jinbao Huang, MS[a], Changqing Lan, MS[b], Hongyan Li, BS[a], Shuxing Chen, BS[c], Qinghua Lin, BS[d], Heng Weng, BS[a,*]

Abstract

To describe the characteristics of concomitant lung cancer and pulmonary cryptococcosis (PC) cases.

A total of 8 patients with lung cancer and coexisting PC, who were admitted to Fuzhou Pulmonary Hospital of Fujian from 1st January 2009 to 31st December 2015 and whose diagnoses were confirmed by pathological examinations, were studied.

One patient had a history of diabetes mellitus and 1 had a history of treated with surgery. The lesions in 7 cases manifested as nodular shadows; only 1 case showed the lesion of the 2 diseases mergedmixed together, and it manifested as a large flake-like infiltrated shadow in the same lobe. The histological type in all of the patients was lung adenocarcinoma. Lung cancer stage was advanced (III–IV) in 25.0% of the cases. The 5 patients who received surgery and drug treatment are presently healthy following resection. Recurrence and metastasis of lung cancer following surgery occurred in 2 patients in whom the tumor was controlled again after anti-tumor treatment. One patient with advanced lung cancer and PC was treated with antifungal therapy in combination with antineoplastic chemotherapy, but she failed to improve and died 10 months after symptom onset during the follow-up period.

PC coexisting with pulmonary carcinoma is rare. PC can manifest as pulmonary nodules and mimic malignant lesions, so it must be considered during a differential diagnosis of pulmonary nodules, especially in immunosuppressed patients.

Abbreviations: AB = alcian blue, BALF = bronchoalveolar lavage fluid, CT = computed tomography, GMS = methamine silver stain, HE = haematoxylin and eosin, HIV = human immunodeficiency virus, IC = immunocompromised, IRB = Institutional Review Board, LA = latex agglutination, MC = mucicarmine, PAS = periodic acid-Schiff, PC = pulmonary cryptococcosis, PNLB = percutaneous needle lung biopsy, SNGGO = solitary nodular ground-glass opacity, TBLB = transbronchial lung biopsy, VATS = video-assisted thoracoscopic surgery.

Keywords: adenocarcinoma, coexistence, lung cancer, pulmonary cryptococcosis, tomography, x-ray computed

1. Introduction

Pulmonary cryptococcosis (PC) is an invasive fungal infection, caused predominantly by *Cryptococcus neoformans* or *Cryptococcus gattii*, that affects both immunocompromised (IC) and non-IC patients.[1] Pulmonary cryptococcosis usually consists of pulmonary nodules or masses and focal areas of consolidation.[2–4] PC often misdiagnosed as primary lung cancer, lung metastasis, pneumonia, pulmonary tuberculosis, etc. In particular, the tuberous mass type of PC is more likely to be misdiagnosed as a neoplasm because the imaging findings closely mimic a pulmonary malignant lesion. In recent years, there have been many reports of PC, but PC coexisting with primary pulmonary carcinoma is rarely seen, and there have been only occasional case reports.

We report herein 8 cases of coexistence of lung adenocarcinoma and PC that were confirmed by pathologic examinations at Fuzhou Pulmonary Hospital of Fujian from 1st January 2011 to 31st December 2015. The clinical, radiological and pathological characteristics of the 8 patients were retrospectively analyzed to improve the diagnosis and management of this disease.

2. Patients and methods

2.1. Patients

We studied 8 patients with coexisting lung cancer and PC who were diagnosed by the histological presence of the organism in lung biopsy specimens. The patients were diagnosed from 1st January 2009 to 31st December 2015 at the Educational Hospital of Fujian Medical University, Fuzhou Pulmonary Hospital of Fu Jian, Fuzhou, China.

Editor: N/A.

JH, CL, and HL contributed equally to this work.

The work was sponsored by the fund of the Key Clinical Specialty Discipline Construction Program of Fujian, P.R.C. (2018–145) and the Clinical Medicine Center Construction Program of Fuzhou, Fujian, P.R.C. (2018080305).

The authors declare that they have no conflicts of interest.

[a] Department of Respiratory and Critical Care Medicine, [b] Department of Radiology, [c] Department of Thoracic Surgery, [d] Department of Pathology, Fuzhou Pulmonary Hospital of Fujian, Educational Hospital of Fujian Medical University, Fuzhou, China.

[*] Correspondence: Heng Weng, Department of Respiratory and Critical Care Medicine, Fuzhou Pulmonary Hospital of Fujian, Educational Hospital of Fujian Medical University, Fuzhou 350008, China (e-mail: 1552856821@qq.com).

How to cite this article: Huang J, Lan C, Li H, Shuxing C, Lin Q, Weng H. Concomitant lung adenocarcinoma and pulmonary cryptococcosis confirmed by pathologic examinations. Medicine 2019;98:50(e18316).

Received: 15 May 2019 / Received in final form: 18 October 2019 / Accepted: 7 November 2019

http://dx.doi.org/10.1097/MD.0000000000018316

2.2. Study design

The medical records of all patients, including demographics, underlying diseases, respiratory symptoms, laboratory tests, imaging data, treatments, and outcomes, were collected. The relevant follow-up patient information was obtained at regular clinic visits and by telephone follow-up. The last follow-up was on December 31, 2018. This study was approved by the Fuzhou Pulmonary Hospital of Fu Jian Medical Institutional Review Board (IRB). The IRB waived the need for informed consent for this study, and all of the data were analyzed anonymously.

2.3. Statistical analysis

Data are presented as median [range] or number (%) unless otherwise stated. All data were analyzed with SPSS 19.0 statistical analysis software (IBM, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Clinical characteristics of the 8 patients with lung cancer and PC are summarized in Table 1. Seven patients (87.5%) were women and only 1 (12.5%) was a man, with a median age of 56 [range: 38–69] years. Two of the 8 patients had underlying diseases, of whom 1 patient had diabetes mellitus and 1 had a history of gastric cancer treated with surgery.

The most common symptoms were cough, sputum production, chest pain, fever, and chest distress, but 2 (25.0%) patients were asymptomatic. Hematologic and biochemical analyses were unremarkable. Serum tumor markers were also unremarkable, and they were all negative for human immunodeficiency virus (HIV) antibodies. The diagnosis of PC and lung cancer for all of the patients was made by direct tissue examination. PC was confirmed by computed tomography-guided percutaneous needle lung biopsy (PNLB) in 1 patient and by video-assisted thoracoscopic surgery (VATS) in 7 patients, and lung cancer was confirmed by transbronchial lung biopsy (TBLB) in 1 patient, PNLB in 2 patients and VATS in 5 patients.

One patient (patient 8) was confirmed as having *Cryptococcus* infection by pathological findings of PNLB in a local hospital. Then, PNLB was performed again in our hospital 6 months after the failure of antifungal therapy, and this pathological examination revealed the presence of coexisting lung adenocarcinoma in the right lobe.

The yeast form of *Cryptococcus neoformans* was identified by staining of the granulation tissue obtained from the lung with haematoxylin and eosin (HE) (Fig. 1A) in 5 patients (62.5%) and with periodic acid-Schiff (PAS) (Fig. 1B) in all of the patients. Lung adenocarcinoma (Fig. 1C) was found in all of the patients, including 6 patients with stage Tis-II and 2 patients with stage III-IV.[5]

Treatment included antifungal drugs plus antineoplastic chemotherapy in 1 (12.5%) patient, surgery plus antifungal therapy in 5 (75.0%) patients, and surgery in combination with antifungal therapy and antineoplastic chemotherapy in 2 (25.0%) patients. All of the patients received follow-up with a median time of 48 [range: 10–96] months. The 5 patients who underwent surgery are all presently healthy following resection. However, recurrence and metastasis of lung cancer occurred in 2 patients (patients 4 and 5) 2.5 years and 8 years after surgery, respectively, but the tumor was controlled again after effective anti-tumor treatment. Only 1 patient (patient 8) with end-stage lung cancer who could not undergo surgery died of tumor progression 10 months after symptom onset during the follow-up period. There were no *Cryptococcal* infection recurrences observed in any of the patients.

3.2. Computed tomography (CT) findings of PC

The main chest CT manifestations of PC are summarized in Table 1. In 7 (87.5%) patients, the CT finding of PC was the presence of one or more pulmonary nodules (Fig. 2A-C), with a median diameter of 0.8 [range: 0.3–2.0] cm. A solitary nodule was seen in 71.4%, and multiple nodules were seen in 28.6% of the 7 patients. Lobulation sign was seen in 2 (28.6%) of the above 7 patients. In the remaining patient (patient 8), the lesions of PC and lung cancer were mixed together and manifested as a large flake-like infiltrated shadow in the right lower lobe (Fig. 2D).

Table 1

The clinical data of 8 cases of lung cancer coexisting with PC.

Case No. Age, yr/Sex	Symptoms	Immunosuppressive underlying disease	Chest CT of lung cancer / PC	Histologic subtypes of ADC	lung cancer TNM staging	Therapy	The follow-up time after discharge	Prognosis
1/64/F	cough and and sputum production	diabetes mellitus	Solitary nodule, L-S^{3}/ Solitary nodule, L-S^{7,8}	invasive ADC	pT1aNoMo (Stage I A)	Surgery excision +AFT	4 years	No recurrence
2/55/M	Asymptomatic	None	SNGGO, R-S^{6}/ Solitary nodule, R-S^{3}	invasive ADC	pT2aNoMo (Stage IB)	Surgery excision +AFT	7 years	No recurrence
3/69/F	Asymptomatic	None	Solitary nodule, R-S^{2}/ Multiple nodules, R-S^{2*}	non-mucinous AIS	Tis	Surgery excision +AFT	4 years	No recurrence
4/57/F	cough and and sputum production	gastric cancer after operation	Solitary nodule, L-S^{1}/ Solitary nodule, R-S^{1*}	invasive ADC	pT1aNoMo (Stage I A)	Surgery excision +AFT	4 years	No recurrence
5/43/F	Cough, chest distress and chest pain	None	Solitary nodule, R-S^{3}/ Solitary nodule, R-S^{1*}	invasive mucinous ADC	pT2aNoMo (Stage IB)	Surgery excision +AFT+ANCT	6 years	Cancer recurrence
6/38/F	Cough and phlegm with blood	None	Solitary nodule, R-S^{2}/ Solitary nodule, R-S^{6}	invasive mucinous ADC	pT1bN2Mo (Stage IIIA)	Surgery excision +AFT+ ANCT	8 years	Cancer recurrence
7/52/F	chest pain, cough and sputum production	None	SNGGO, R-S^{2}/Multiple nodules, R-S^{6}	invasive ADC	pT1aNoMo (Stage I A)	Surgery excision +AFT	4 years	No recurrence
8/67/F	fever? cough and sputum production	None	air-space consolidation, R-LL/ air-space consolidation, R-LL*	invasive mucinous ADC	cT4NoMib (Stage IV)	AFT +ANCT	10 months	Died

* Coexisting cryptoccossis and carcinoma within a 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, PC = pulmonary cryptococcosis, pTNM staging = pathological TNM staging, R = right, S = segment, SNGGO = solitarynodular ground-glass opacity.

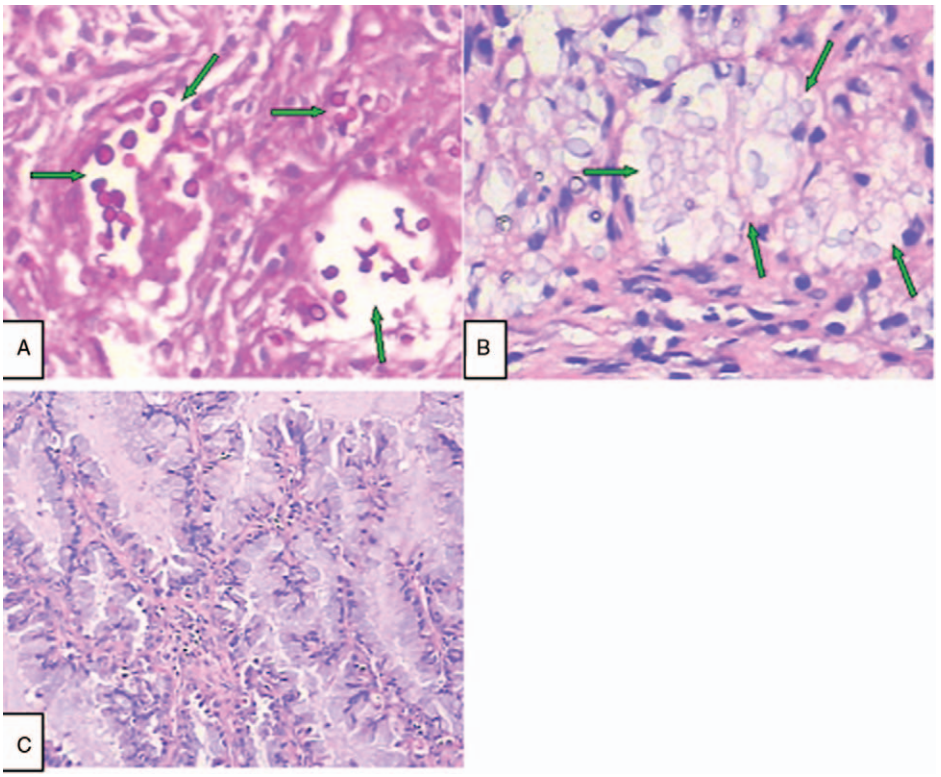

Figure 1. Histological findings in patient 5. A (haematoxylin and eosin stain, ×400), B (periodic acid-Schiff stain, ×400): There were a great number of cryptococcus spores throughout the granulation tissue in the resected pulmonary nodule in R-S^3 (green arrows). C (haematoxylin and eosin stain, ×100): The resected pulmonary nodule in R-S^1 was confirmed as invasive mucinous adenocarcinoma.

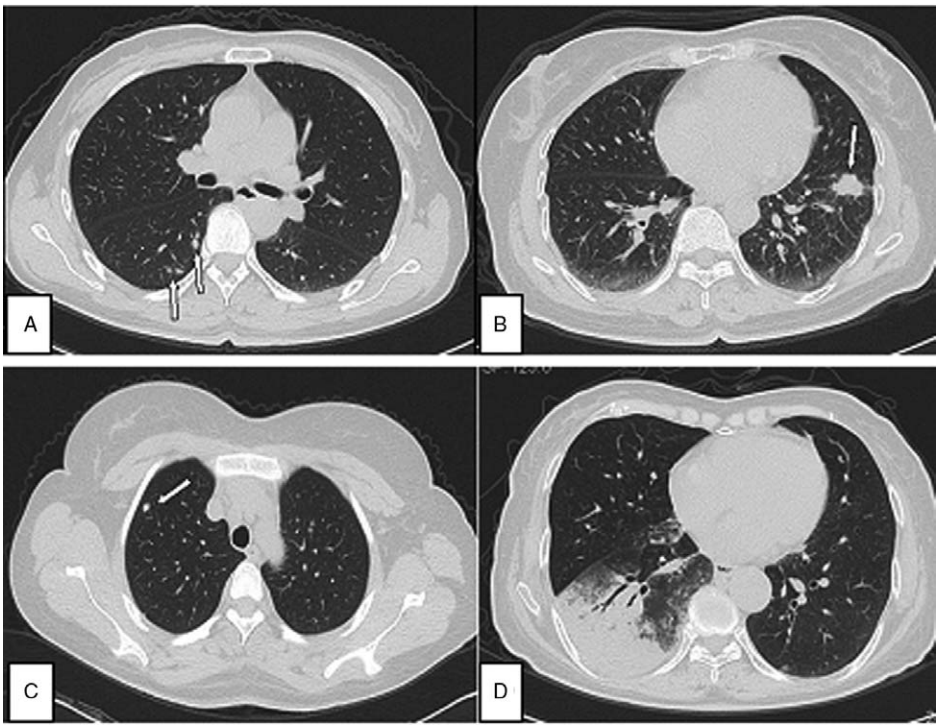

Figure 2. A: Chest CT showing a small nodular shadow in the right S^1 (green arrow, patient 5). B: Chest CT showing a nodule with lobulation sign in the left $S^{7,8}$ (green arrows, patient 2). C: Chest CT showing a large flake-like infiltrated shadow in the right lower lobe (green arrow, patient 8). D: Chest CT showing multiple small nodules in the right S^5 (patient 7).

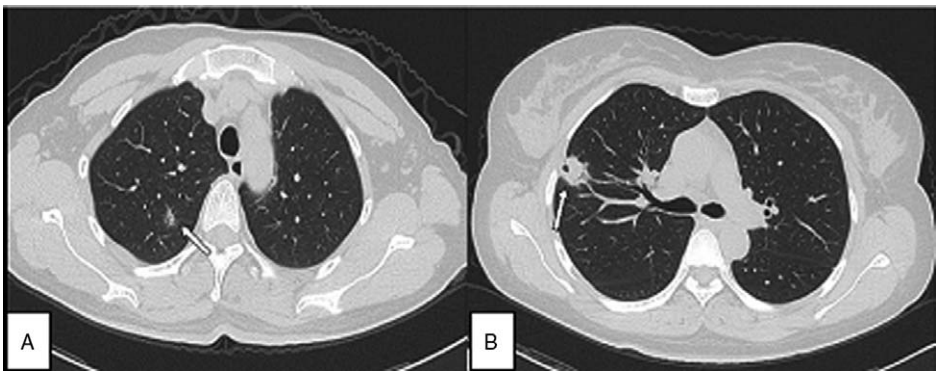

Figure 3. A: Chest CT showing a solitary nodular ground-glass opacity (SNGGO) in the right S^6 (green arrow, patient 7). B: Chest CT showing a tumour with lobulation sign, burr sign, pleural sag and vascular convergence in the right S^3 (green arrow, patient 5).

Lesions in the right lung were present in 7 (87.5%) patients, and lesions in the left lung were present in 1 (12.5%) patient, indicating the lesions were more frequently present in the right lung. Four (50.0%) patients had lesion involvement in the upper lobe, and 4 (50.0%) patients had lower lobe involvement. All of the lesions were located in 1 lobe and were adjacent to or involving the pleura.

3.3. CT findings of lung cancer

The main chest CT manifestations of lung cancer are summarized in Table 1. The most common CT finding of lung cancer was the presence of a solitary nodule (7 cases, 87.5%) (Fig. 3A, B), with a median diameter of 1.5 [range: 0.5–3.5] cm. Of the 7 patients, a variety of CT signs of tumor were present as follows: lobulation sign (4 cases, 57.1%), burr sign (3 cases, 42.9%), pleural sag (1 cases, 14.3%), vascular convergence (1 cases, 14.3%), bronchus encapsulated air sign (1 case, 14.35%), and irregular wall thick wall hollow (1 cases, 14.3%). Two (28.6%) patients were exhibited by solitary nodular ground-glass opacity (SNGGO). One (12.5%) patient (patient 8) initially exhibited air-space consolidation (Fig. 2D), and then, repeat chest CT scans showed an increase in lung lesions in the right lower lobe and multiple additional nodules in both lungs due to the tumor progression.

Lesions in the right lung were present in 6 (75.0%) patients, and lesions in the left lung were present in 2 (25.0%) patient, indicating the lesions were more frequently present in the right lung. Six (75.0%) patients had lesion involvement in the upper lobe, and only 2 (25.0%) patients had lower lobe involvement, indicating that lesions were more frequent in the upper lobe. All of the malignant nodules were in the peripheral lungs, and there was the coexistence of lung cancer and PC in the same lobe in 4 (50.0%) of the 8 patients.

4. Discussion

Infections due to *Cryptococcus* sp. occur globally and in a wide variety of hosts, ranging from those who are severely immunosuppressed to those who have phenotypically "normal" immune systems.[6] However, infections most commonly occur in immunocompromised hosts, such as HIV-infected or cancer patients, and rarely involve immunocompetent hosts.[7,8] We report herein 8 cases of primary lung adenocarcinoma accompanied by primary pulmonary cryptococcosis, which were confirmed by pathologic examinations. Two patients had underlying diseases (including diabetes mellitus and gastric cancer) with immunosuppression that caused them to be more prone to infection with *Cryptococcus*.[9] However, there were no other immunosuppressive diseases found, except coexisting lung cancer, in the other 6 patients. Harada et al[10] considered coexisting cryptococcosis and carcinoma to be coincidental. However, Robinson et al[11] thought that the lung malignancy may have resulted in a degree of immune suppression, predisposing the patient to infection with *Cryptococcus*. This issue is still currently controversial, and further studies are required to clarify the possible relationship between lung cancer and *Cryptococcal* infection.

PC usually occurs in the peripheral lungs and is adjacent to or involving the pleura.[3,12,13] When PC consists of solitary or multiple nodules, these nodular shadows can be confused with lung cancers on chest CT, and it is often difficult to distinguish PC from pulmonary neoplasia.[10] In patients 1 to 7, the lesions of the PC consisted of solitary or multiple nodules that were located close to the pleura on chest CT. In patients 1 and 2, lobulation signs were seen in the *Cryptococcus* nodules, but no other signs of lung cancer could be found. In the other 5 patients (patients 3–7), there were no signs of primary lung cancer, such as a lobulation sign, spicule sign, or vascular cluster, found in the *Cryptococcus* nodular shadows.

In contrast, except for patients 1 and 3 who lacked signs of a tumor, the lesions of lung cancer in the other 5 patients (patients 2 and 4–7) all had typical tumor characteristics as follows:

1. An irregular nodular surface was found in 5 patients, and 2 (patients 2 and 7) were characterized by SNGGO, which was considered to be closely associated with lung adenocarcinoma.[14]
2. These malignant nodules exhibited a variety of signs of lung cancer on chest CT, including lobulation sign, burr sign, pleural sag, vascular convergence, bronchus encapsulated air sign, irregular wall thick wall hollow, etc.

Compared with the primary pulmonary cryptococcosis, the peripheral lung cancer was also often characterized by a solitary pulmonary nodule and/or a mass, but the occurrence rate of the typical signs of lung cancer mentioned above was higher than the former.[13] Additionally, all of the *Cryptococcus* nodules including solitary and multiple nodules in our group were located in the subpleural lungs, which was in accordance with the

distribution characteristics of PC,[15] and these multiple nodules of PC showed a diversity of forms and sizes and were confined to a single lobe, which are different that the characteristics of pulmonary metastatic tumors that usually present with roundish uniform sizes and shapes with smooth edges and tend to occur in the lower lungs. Therefore, in general, such different characteristics might assist in the differential diagnosis of PC and lung cancer.

However, although cryptococcosis nodules in the above 7 patients lacked the typical characteristics of lung cancer except for 2 with lobulation sign, these nodular shadows were still preoperatively suspected to be malignant lesions. That was because all of the cryptococcosis nodules lacked the typical signs of fungal infection, such as a halo sign and air-bronchogram,[9] and the cryptococcosis lesions coexisted with lung cancer and mimicked primary or metastatic tumors; the *Cryptococcosis* nodules were very small (only 0.8 cm in median diameter) and were all located in the peripheral lungs, so it was difficult to reach the correct preoperative diagnosis by conventional biopsy methods, such as TBLB and PNLB.

These small nodules were resected directly by VATS and confirmed to be benign lesions (*Cryptococcus* infection) by pathologic examination. Therefore, it is rather difficult to definitely determine the nature of other forms of pulmonary nodules coexisting with lung cancer that is detected for the first time.[5] Furthermore, as seen in our patients 3, 5, and 6, when benign nodules and primary tumors are located in the same lobe, the former is more likely to be misdiagnosed as a malignant nodule (a metastatic tumor or a primary lung cancer). Therefore, PC must be considered during the differential diagnosis of pulmonary nodules not only when the lesions have the typical signs of a fungal infection but also when the nodules lack the typical signs of lung cancer, even if the lesions lack the signs of fungal infection at the same time.

In patient 8, chest CT initially showed a large flake-like infiltrated shadow in the right lower lobe, and the lesion was initially confirmed to be *Cryptococcus* infection by the pathological findings of PNLB. The patient was given fluconazole, then itraconazole, for 6 months, but she failed to improve on chest CT with an irregular follow-up in the outpatient clinic. Then, her coughing increased, and a repeat chest CT scan showed an increase in size of the lung lesions. PNLB was performed again in the right lower lung in our hospital, and the pathological examination revealed the presence of lung adenocarcinoma. That is, in this case, lung cancer and PC coexisted and were mixed together in the right lower lobe. In our opinion, the PC might have occurred after the cancer because lung malignancy may be a susceptibility factor for Cryptococcal infection.[11] The patient's clinical situation deteriorated due to progression of the tumor, which could not be initially found. This case illustrates the importance of early and frequent follow-up of PC and alerted the clinician to the possibility of a secondary Cryptococcal infection occurring within a pulmonary malignancy.[11]

Currently, the diagnosis of PC depends mainly on histopathological examination and pathogenic tests of puncture fluid.[16] Notably, since *C. neoformans* is a ubiquitous organism that has a pulmonary portal of entry[17] and can persist in the human oropharynx as bacteriopexia,[18] the detection of *C. neoformans* in respiratory specimens including sputum, pharyngeal swab, and bronchoalveolar lavage fluid (BALF) only has suspected diagnostic value. Additionally, due to the low detection rate of *Cryptococcus* by pathogenic smear and culture, pathology is still the most important diagnostic method for PC .[4,16,19] Since *Cryptococcus* HE staining does not result in an easily distinguishable color, it is usually necessary to apply a special stain in order to obtain a definite diagnosis. Although the morphology of the fungal elements (yeasts) can be similar to other species, it has been reported that the detection rates of *C. neoformans* by PAS, gomori methamine silver stain (GMS), mucicarmine (MC) and alcian blue (AB) were 100%, 100%, 87% and 67%, respectively,[20] and a combination of various histochemistry staining procedures is available and can be helpful in providing better microscopic clarity and detection of dead or degenerating cells, which might be refractory to only 1 staining procedure, so they can assist in visualizing the capsule in order to

Table 2

Literature review.

References	Nation	Age, yr/Sex	Immunosuppressive underlying disease	Histology of neoplasm	Histologic subtypes of ADC	Location of PC	Location of lung cancer
[10]	Japan	74/F	None	ADC	Unknown	R-S^{6}	R-S^{6*}
[10]	Japan	77/F	None	ADC	Unknown	L-S^{8,9}	L-S^{8,9*}
[10]	Japan	71/M	None	ADC	invasive ADC (papillary pattern)	R-S^{2}	R-S^{2*}
[10]	Japan	47/M	None	ADC	Unknown	R-S^{6}	R-S^{2}
[10]	Japan	74/F	None	ADC	Unknown	R-S^{10}	R-S^{10}
[10]	Japan	43/M	None	ADC	Unknown	R-S^{6,8}	R-S^{6}
[10]	Japan	76/M	None	ADC + SQCC	Unknown	R-LL	L-S^{4}
[10]	Japan	46/F	None	ADC	Unknown	R-LL	L-S^{8}
[10]	Japan	46/F	None	ADC	Unknown	L-S^{6}	R-S^{8}
[10]	Japan	60/M	None	ADC	Unknown	L-LL	R-ML
[10]	Japan	73/F	None	ADC	Unknown	L-LL	L-UL
[11]	Australia	74/M	None	ADC	invasive ADC (papillary pattern)	L-LL	L-LL*
[24]	Japan	73/F	None	ADC	invasive ADC (papillary pattern)	L-S^{8}	L-S^{3}
[25]	Korea	73/M	ICL	SQCC	Unknown	BL	R-UL
[26]	Japan	84/F	autoimmune hepatitis treated with long-term corticosteroid therapy	SQCC	Unknown	R-LL	R-LL*
[27]	Japan	63/F	None	ADC	invasive ADC (papillary pattern)	R-S^{10}	R-S^{6}

* Coexisting cryptoccossis and carcinoma within same nodule.

Ad = adenocarcinoma, BL = bilateral lung, F = female, ICL = Idiopathic CD4+ T-Lymphocytopenia, L = left, LL = lower lobe, M = male, ML = middle lobe, PC = pulmonary cryptococcosis, R = right, S = segment, Sq = squamous cell carcinoma, UL = upper lobe.

make a correct diagnosis of PC. In our patients, the detection rate of C. *neoformans* was 100% by PAS but only 62.5% by HE which was similar to the literature.[20,21] In addition, the use of serum Cryptococcal antigen detection tests by latex agglutination (LA) have become common in recent years, and the test has been reported to be worthwhile in assisting in the diagnosis of PC because of its high diagnostic value for PC.[22,23] Due to the laboratory limitations of our hospital, it is regrettable that this test could not be performed.

PC coexisting with pulmonary carcinoma is rare, and a review of the English medical literature revealed that only a few cases have been previously reported (Table 2).[10,11,24–27] In most cases, the pathological type of lung cancer was a pulmonary adenocarcinoma, which was similar to our patients (100%), probably because the *Cryptococcus* may prefer residing in the peripheral lung, where adenocarcinomas frequently occur.[26] The most common radiologic types of *Cryptococcus* and cancer were both characterized by pulmonary nodules, which is generally consistent with our patients (87.5%). In most cases, *Cryptococcus* and cancer co-existed as different nodules in different lobes. Notably, the Cryptococcal nodules all presented as single lesions in previous reports. However, in our study, 2 cases (patients 3 and 7) of Cryptococcal lesions presented with multiple nodules in the same lung lobes, and both cancer and multiple Cryptococcal nodules coexisted in the same lung lobe in 1 of them (patient 7), which further increased the difficulty of clinical differentiation. Additionally, coexistence of *Cryptococcus* and cancer in a solitary nodule is extremely rare,[10,11,26] and the coexistence of both lesions in a flake-like infiltrated shadow, as was seen in present patient 8, has never been reported previously and deserves clinical attention.

In summary, when PC coexists with lung cancer and manifests as isolated or multiple pulmonary nodules on chest CT, it can easily be misdiagnosed as malignant lesions. If routine examination cannot obtain a definitive diagnosis for indeterminate pulmonary nodules or pulmonary nodules suspected to be malignant, resection of the lesion should be performed to obtain a diagnosis under medically permissive conditions.[10] However, there are also some patients who have been definitively diagnosed with PC, but their response is poor to reasonable antifungal treatments. Under this condition, we should not only pay attention to the possibility of drug resistance but also consider the possibility of PC coexisting with lung cancer. The clinician should be alert to this situation and try to avoid the misdiagnosis and overlooked diagnosis.

Author contributions

Conceptualization: Heng Weng.
Data curation: Changqing Lan, Hongyan Li, Chen Shuxing, Qinghua Lin.
Formal analysis: Jinbao Huang, Hongyan Li.
Methodology: Jinbao Huang, Heng Weng.
Writing – original draft: Jinbao Huang, Changqing Lan, Hongyan Li.
Writing – review & editing: Heng Weng.

References

[1] Brizendine KD, Baddley JW, Pappas PG. Pulmonary cryptococcosis. Semin Respir Crit Care Med 2011;32:727–34.
[2] Fox DL, Müller NL. Pulmonary cryptococcosis in immunocompetent patients: CT findings in 12 patients. AJR Am J Roentgenol 2005;185:622–6.
[3] Ye F, Xie JX, Zeng QS, et al. Retrospective analysis of 76 immunocompetent patients with primary pulmonary cryptococcosis. Lung 2012;190:339–46.
[4] Wang BQ, Zhang HZ, Fan BJ, et al. Meta-analysis of clinical manifestations of pulmonary cryptococcosis in China Mainland. Chin J Clin Med 2013;20:351–4.
[5] Yang GF, Zhu H. The 7th edition of TNM staging of lung cancer and the value of imaging in the evaluation of TNM staging. Radi Pract 2012;27:803–6.
[6] Pappas PG. Cryptococcal infections in non-HIV-infected patients. Trans Am Clin Climatol Assoc 2013;124:61–79.
[7] Patz EFJr, Goodman PC. Pulmonary cryptococcosis. J Thorac Imaging 1992;7:51–5.
[8] Rozenbaum R, Gonçalves AJ. Clinical epidemiological study of 171 cases of cryptococcosis. Clin Infect Dis 1994;18:369–80.
[9] Kohno S, Kakeya H, Izumikawa K, et al. Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother 2015;21:23–30.
[10] Harada T, Hakuma N, Kamimura A, et al. Pulmonary cryptococcosis within a pulmonary carcinoma-review of reported cases. Intern Med 2006;45:369–72.
[11] Robinson TD, Barnes DJ, Watson GF. Coexisting cryptococcosis and carcinoma within a solitary pulmonary nodule. Aust NZ J Med 1999;29:561–2.
[12] Lacomis JM, Costello P, Vilchez R, et al. The radiology of pulmonary cryptococcosis in a tertiary medical center. J Thorac Imaging 2001;16:139–48.
[13] Xie LX, Chen YS, Liu SY, et al. CT features of pulmonary cryptococcosis in solitary nodular or mass-like pattern. J Med Imaging 2013;23:1703–6.
[14] Kim HY, Shim YM, Lee KS, et al. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. Radiology 2007;245:267–75.
[15] Lan CQ, Huang JB, Huang MP, et al. Analysis of CT features of nodular or mass-like type of pulmonary cryptococcosis. Chin J Radiol 2015; 49:741–4.
[16] Infectious diseases group of Chinese Society of Respiratory Medicine, Editorial Board of Chinese Journal of Tuberculosis and Respiratory Diseases. Chin J Tuberc Respir Dis 2007;30:821–34.
[17] Severo CB, Bruno RM, Oliveira FM, et al. A case of miliary pulmonary cryptococcosis and review of literature. Mycopathologia 2015;179:313–5.
[18] Salkowski CA, Bartizal KF, Balish MJ, et al. Colonization and pathogenesis of Cryptococcus neoformans in gnotobiotic mice. Infect Immun 1987;55:2000–5.
[19] Wang L, Shi Y, Ding Y, et al. Pulmonary cryptococcosis: a retrospective analysis of 65 cases. Chin J Tuberc Respir Dis 2014;37:764–8.
[20] Yi XH, Kong J, Zhu MF, et al. Pathological diagnosis and ultrastructure features of primary pulmonary cryptococcosis: a study of 27 cases. Zhonghua Bing Li Xue Za Zhi 2004;33:424–8.
[21] Xu LY, Liu DL, Yu YH, et al. Pulmonary cryptococcosis: analysis of 38 cases. Chin J Tuberc Respir Dis 2011;34:653–6.
[22] Mu XD, Li RY, Wan Z, et al. The diagnostic value of serum latex agglutination for pulmonary cryptococcosis. Chin J Tuberc Respir Dis 2008;31:360.
[23] Tanner DC, Weinstein MP, Fedorciw B, et al. Comparison of commercial kits for detection of cryptococcal antigen. J Clin Microbiol 1994;32:1680–4.
[24] Kawasaki H, Ishikawa K, Kuniyoshi M, et al. Lung adenocarcinoma with coexisting pulmonary cryptococcoma. Jpn J Thorac Cardiovasc Surg 2004;52:21–5.
[25] Ahn IS, Kim HG, Ryu JS, et al. A case of pulmonary cryptococcosis with non-small cell lung cancer in Idiopathic CD4+ T-Lymphocytopenia. Yonsei Med J 2005;46:173–6.
[26] Yuri T, Kimura A, Yoshizawa K, et al. Pulmonary and meningeal cryptococcosis after corticosteroid therapy for autoimmune hepatitis: Coexistence of cryptococci within pulmonary cancer nodule. Case Rep Pathol 2013;807197.
[27] Yamamoto Y, Ohi H, Narasaki F, et al. A case of pulmonary cryptococcosis with lung cancer in a pulmonary lobe. Kansenshogaku Zasshi (J Infect Chemotherapy) 1999;73:187–90.