

Fungal Infection Mimicking Pulmonary Malignancy: Clinical and Radiological Characteristics

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Received: 3 June 2013 / Accepted: 19 August 2013
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Abstract

Objective The purpose of this study was to evaluate the clinical and radiological features of patients with fungal infection mimicking thoracic malignancy and to establish a diagnostic approach for both clinicians and radiologists to avoid misdiagnosis.

Methods In this retrospective study, we reviewed clinical and computed tomography (CT) findings from 27 patients who presented with suspicion of thoracic malignancy who were ultimately diagnosed with fungal disease.

Results Patients' median age was 55.7 (range 31–78) years. The most common clinical findings were cough (48.1 %), expectoration (33.3 %), chest pain (25.9 %), weakness (25.9 %), weight loss (18.5 %), and hemoptysis, dyspnea, and fever (7.4 % each). The median lesion size was 35.5 (range 10–85) mm. CT findings included a solid nodule (51.9 %), solid mass (37 %), or both (11.1 %).

Nodule and mass margins were lobulated in 9 (33.3 %) patients, ill-defined in 5 (18.5 %), spiculated in 4 (14.8 %), and smooth in 4 (14.8 %) patients. Additional findings included consolidation in 4 (14.8 %) patients, cavitation in 3 (11.1 %), pleural effusion in 2 (7.4 %), and lymphadenopathy in 11 (40.7 %) patients. In all patients, specific diagnoses were made and confirmed by histopathology; final diagnoses were histoplasmosis (25.9 %), coccidiomycosis (22.2 %), cryptococcosis (22.2 %), aspergillosis (14.8 %), North American blastomycosis (7.4 %), mucormycosis (3.75 %), and paracoccidioidomycosis (3.75 %). **Conclusions** Fungal infection can present with clinical and radiological features that are indistinguishable from thoracic malignancy, such as lung nodules or masses. Because the management and outcomes of fungal infection and malignancy are entirely distinct, the establishment of a specific diagnosis is critical to provide appropriate therapy.

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Keywords Fungal infection · Lung neoplasm · Metastasis diagnosis · Computed tomography

Introduction

Pulmonary infections occasionally present with clinical and radiological features that are indistinguishable from thoracic malignancy [1]. This situation presents a diagnostic challenge and may delay treatment significantly. The infectious processes of several agents, such as bacteria (*Fusobacterium*, *Pseudomonas*, *Streptococcus*), mycobacteria (*Mycobacterium tuberculosis*, *M. kansasii*), parasites (*Dirofilaria*), fungi, and, rarely, viruses (*Cytomegalovirus*), can mimic cancer [2]. Fungal infections that can mimic malignancy include coccidioidomycosis, histoplasmosis, aspergillosis, North American blastomycosis, and cryptococcosis [3]. The clinical symptoms of these infections are nonspecific and can include dyspnea, fatigue, cough, and even hemoptysis. Radiological features suggestive of lung cancer include parenchymal nodule or masses with spiculated margins, lobulations, subsolid nodules, thick-walled cavities, cavities with nodular margins, and chest wall and mediastinal invasion [4–6]. However, these findings are nonspecific, and many other nonmalignant conditions, such as pulmonary infections, infarctions, and abscesses, may have similar appearances [7, 8].

Pulmonary fungal infection mimicking lung cancer is a rare entity with few series described in the literature [1–3]. The misdiagnosis can cause detrimental effects to the patient by delaying proper treatment. This scenario is especially important in endemic areas, in the presence of negative findings for malignancy, and/or when treatment for common lung infections yields a poor response. The purpose of this study was to evaluate the clinical and radiological features of patients with fungal infection mimicking thoracic malignancy and to establish a diagnostic approach for both clinicians and radiologists to avoid misdiagnosis.

Materials and Methods

We retrospectively reviewed medical records and the computed tomography (CT) scans of 27 patients treated at two different oncological hospitals: 12 patients from a cancer institution located in Houston, TX, and 15 patients from a cancer institution located in São Paulo/SP, Brazil, during a 5-year period between August 2007 and July 2012. Two inclusion criteria were considered: (1) presence of pulmonary lesion with CT characteristics suggestive of malignancy, (2) histological confirmation of pulmonary fungal infection. Because this is a retrospective study and

the patients came from different institutions being studied according to each Radiology Department's routine, no standardization of chest CT scan was performed. The Institutional Review Boards of both hospitals approved this study, and the requirement for informed patient consent was waived.

Two chest radiologists with more than 10 years of experience independently reviewed imaging and clinical data from all patients, and decisions concerning the findings were reached by consensus. Clinical data were collected from electronic records. Medical records created at the time of admission were reviewed for complaints of chest pain, cough, sputum, fever, weakness, and weight loss. Chest CT images acquired for all patients at admission were examined in the Picture Archiving and Communication System to determine the presence of nodules, masses, areas of consolidation, atelectasis, ground-glass opacities, and the tree-in-bud pattern. For all nodules and masses (based on 3.0 cm size criteria), the location, size, margins, presence of cavitation, necrosis (determined by low attenuation), and number of lesions (solitary or multiple, based on two or more lesions criteria) were recorded. Associated findings, including pleural effusion and lymphadenopathy, also were recorded. If available, positron emission tomography (PET)/CT images were reviewed and standardized uptake values (SUVs) were recorded.

Descriptive analyses of demographic, clinical, radiological, and pathological characteristics were performed. Microsoft Excel 2000 software was used for data collection and to calculate correlations. All statistical analyses were performed using SPSS software (version 17.0, SPSS) for Microsoft Windows; $p < 0.05$ was considered to indicate a significant difference.

Results

Patients' demographic and clinical characteristics, diagnostic methods, and final diagnoses are summarized in Tables 1 and 2. The median age was 55.7 (range 31–78) years. Fourteen of 27 (51.8 %) patients underwent extra-thoracic primary tumor treatment before the detection of pulmonary lesions suspicious for malignancy. Fifteen (55.6 %) patients were symptomatic at the time of lung lesion detection; lesions were detected during follow-up in 9 (33.3 %) patients and detected incidentally on radiographs taken for other reasons in the remaining 3 (11.1 %) patients. The most common clinical finding was cough ($n = 13$; 48.1 %) followed by expectoration ($n = 8$; 29.6 %), chest pain ($n = 7$; 25.9 %), weakness ($n = 6$; 22.2 %), weight loss ($n = 5$; 18.5 %), and hemoptysis, dyspnea, and fever ($n = 2$ each; 7.4 %). The main diagnostic hypothesis was primary lung cancer in 13 (48.2 %)

Table 1 Demographic data, primary tumor (if present), chest CT indication, diagnostic hypothesis, biopsy method, and final diagnosis in patients with lung fungal infection mimicking malignancy

Patients/ countries	Age (years)/ gender	Primary tumor ^a	Chest CT indication	Diagnostic hypothesis	Biopsy method	Final diagnosis
1/BR	54, female	Breast	Follow-up	MT	SB	Histoplasmosis
2/BR	48, male	Melanoma	Follow-up	MT	CT	Histoplasmosis
3/BR	67, male	Liver	Symptoms	MT	CT	Histoplasmosis
4/BR	40, male	–	Symptoms	MT	TBB	Histoplasmosis
5/USA	49, male	–	Incidental	LC	CT	Histoplasmosis
6/BR	69, female	Lung	Symptoms	LC/MT	CT	Histoplasmosis
7/BR	37, female	–	Symptoms	LC	TBB	Histoplasmosis
8/USA	63, male	Esophagus	Symptoms	MT/LC	TBB	Coccidioidomycosis
9/USA	50, female	–	Incidental	LC	CT	Coccidioidomycosis
10/USA	56, female	–	Symptoms	LC	CT	Coccidioidomycosis
11/USA	64, female	–	Symptoms	LC	CT	Coccidioidomycosis
12/USA	49, male	–	Incidental	LC	CT	Coccidioidomycosis
13/USA	62, female	–	Symptoms	LC	CT	Coccidioidomycosis
14/BR	59, male	–	Symptoms	MT	CT	Cryptococcosis
15/BR	53, male	–	Symptoms	LC	CT	Cryptococcosis
16/BR	75, female	Lymphoma	Follow-up	MT	CT	Cryptococcosis
17/USA	59, male	–	Symptoms	LC	CT	Cryptococcosis
18/USA	66, male	Esophagus	Follow-up	MT	CT	Cryptococcosis
19/BR	46, male	Pancreas	Follow-up	LC/MT	CT	Cryptococcosis
20/BR	52, female	Breast	Follow-up	LC	CT	Aspergillosis
21/BR	50, male	–	Symptoms	LC	TBB	Aspergillosis
22/USA	63, female	Colorectal	Follow-up	MT	TBB	Aspergillosis
23/BR	78, male	Leukemia	Symptoms	LR/MT	CT	Aspergillosis
24/USA	68, male	Esophagus	Follow-up	LC/MT	CT	Blastomycosis
25/USA	39, male	Thyroid	Symptoms	LC/MT	TBB	Blastomycosis
26/BR	31, female	Melanoma	Follow-up	LC	SB	Paracoccidioidomycosis
27/BR	58, male	–	Symptoms	LC	TBB	Mucormycosis

BR Brazil, USA United States of America, LC lung cancer, MT metastasis, LR locoregional recurrence, CT CT-guided biopsy, TBB transbronchial biopsy, SB surgical biopsy

^a If patient has extrapulmonary tumor before lung lesion detection

Table 2 Major clinical findings among the patients

Diagnosis/clinical findings	<i>n</i> (%)
Cough	13 (48.2)
Sputum	9 (33.3)
Weakness	7 (25.9)
Chest pain	7 (25.9)
Weight loss	5 (18.5)

patients, metastasis in 8 (29.6 %), either of these conditions in 5 (18.5 %), and local recurrence of a primary thoracic tumor in 1 (3.7 %) patient.

Table 3 summarizes the patients' radiological characteristics. The median lesion size was 35.5 (range 10–85) mm. On CT, a solid nodule was found in 14 (51.9 %) patients, a solid mass in 10 (37 %) patients, and both of

these features in 3 (22.2 %) patients. Lobulated margins were encountered most frequently ($n = 9$; 33.3 %), followed by ill-defined and smooth margins ($n = 5$ each; 18.5 %), and spiculated margins and a combination of two margin types ($n = 4$ each; 14.8 %). Upper lobe involvement was found in 12 (44.4 %) cases, lower lobe involvement in 8 (29.6 %), and involvement of both lobes in 7 (26.0 %) cases. Additional findings included lymphadenopathy ($n = 11$; 40.7 %), consolidation ($n = 4$; 14.8 %), cavitation ($n = 3$; 11.1 %), and ground-glass opacities associated with the tree-in-bud pattern ($n = 1$; 3.7 %). Pleural effusion was seen in only 2 (7.4 %) patients. Eight (29.6 %) patients underwent PET/CT examination, and all showed fluorodeoxyglucose (FDG) activity in the lung lesions (false-positive result for lung cancer) with SUV greater than 3.0 (range 3.2–8.6).

Table 3 Major CT findings according to the fungal infection diagnosis

Diagnosis/CT findings	Histo (n = 7)	Cocci (n = 6)	Crypto (n = 6)	Asperg (n = 4)	Blasto (n = 2)	PSM	Mucor	Total
Type								
Nodule	6	3	3	1	1	–	–	14 (51.9 %)
Mass	–	2	3	2	1	1	–	9 (33.3 %)
Both	1	1	–	1	–	–	1	4 (14.8 %)
Margins								
Smooth	4	–	1	–	–	–	–	5 (18.2 %)
Ill-defined	1	1	–	2	–	1	–	5 (18.2 %)
Spiculated	1	2	–	–	1	–	–	4 (14.8 %)
Lobulated	1	1	4	2	1	–	1	10 (37.0 %)
Mixed	–	2	1	–	–	–	–	3 (11.1 %)
Number^a								
Solitary	4	5	3	2	2	1	–	17 (63.0 %)
Multiple	3	1	3	2	–	–	1	10 (37 %)
Lymphadenopathy								
H	–	2	1	–	1	–	–	4 (14.8 %)
M	2	–	–	1	–	–	–	3 (11.1 %)
HM	1	3	–	–	–	–	–	4 (14.8 %)

Histo histoplasmosis, *Cocci* coccidioidomycosis, *Crypto* cryptococcosis, *Asperg* aspergillosis, *Blasto* blastomycosis, *PSM* paracoccidioidomycosis, *Mucor* mucormycosis, *LN* lymphadenopathy, *H* hilar, *M* mediastinal, *HM* both hilar and mediastinal

^a Solitary, if the patient has only one lesion, or multiple lesions, if the patient has more than two lesions

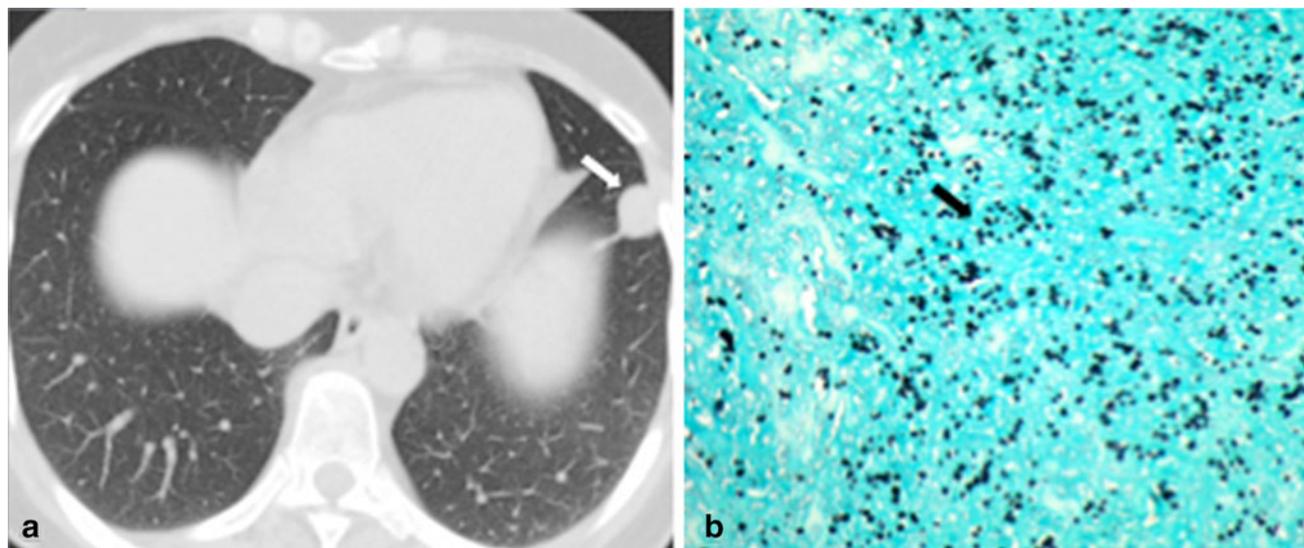


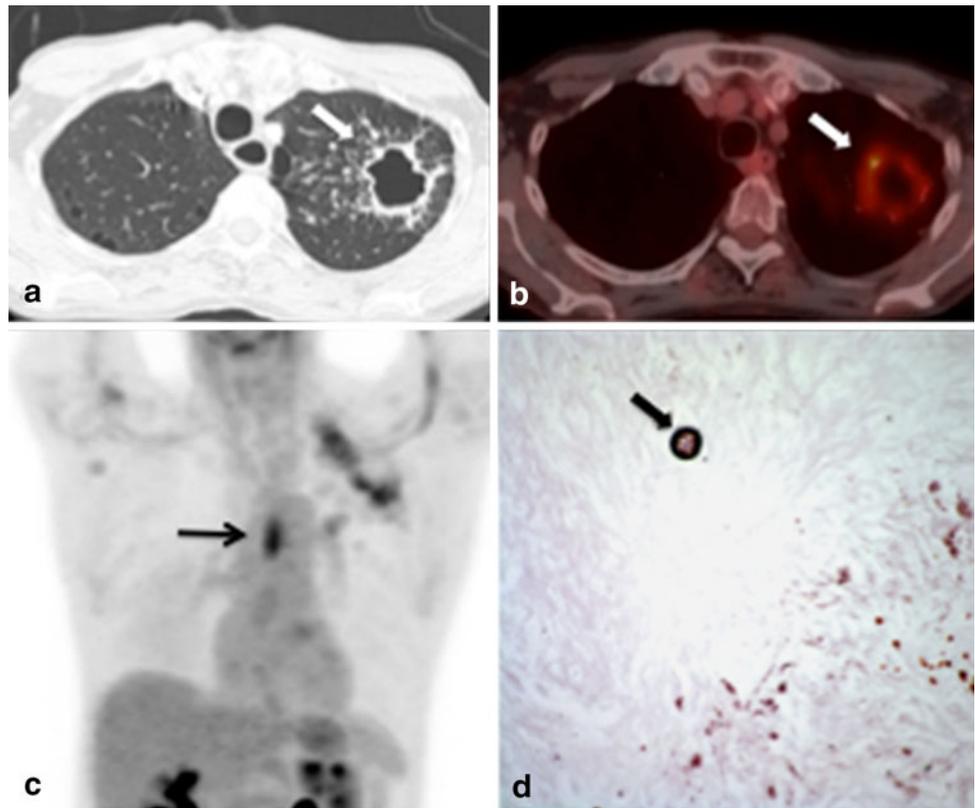
Fig. 1 54-year-old female patient with history of breast cancer treated 3 years previously. **a** Follow-up CT showed a solid nodule (arrow) in the left lower lobe. **b** CT-guided biopsy with Grocott's

staining demonstrated the presence of round black yeast (arrow) compatible with histoplasmosis

Fungal infections were diagnosed by CT-guided biopsy in 18 (66.7 %) cases, transbronchial biopsy in 7 (25.9 %), and surgical biopsy in 2 (7.4 %) cases. None of these procedures was associated with major complications. All patients received specific diagnoses that were confirmed by histopathological examination. Final

diagnoses were histoplasmosis ($n = 7$; 25.9 %; Fig. 1), coccidiomycosis ($n = 6$; 22.2 %; Fig. 2), cryptococcosis ($n = 6$; 22.2 %; Fig. 3), aspergillosis ($n = 4$; 14.8 %), blastomycosis ($n = 2$; 7.4 %), mucormycosis ($n = 1$; 3.75 %), and paracoccidioidomycosis ($n = 1$; 3.75 %).

Fig. 2 63-year-old male patient who was a heavy smoker with an insidiously productive cough during follow-up after treatment for esophageal squamous cell carcinoma. **a** CT showed signs of emphysema and a cavitated mass (*arrow*) with ill-defined margins in the *left upper lobe*. **b** Axial PET/CT showed high fluorodeoxyglucose (FDG) uptake on the lesion wall (*arrow*). **c** Coronal PET also showed abnormal FDG uptake in a mediastinal lymph node (*arrow*). **d** Histological examination with Gomori's methenamine silver staining showed a large fungal organism and shadows of endospores (*arrow*), typical of coccidioidomycosis



All seven patients with histoplasmosis had solid nodules, 1 (14.3 %) of which was associated with a solid mass. Lesion margins were smooth in 4 (57.1 %) patients and ill-defined, spiculated, and lobulated in 1 (14.3 %) patient each. Four (57.1 %) patients had solitary lesions and 3 (42.9 %) had multiple lesions.

Among the six patients with coccidioidomycosis, a solid nodule was present in 3 (50 %) cases, a solid mass in 2 (33.3 %), and both in 1 (16.7 %) case. A solitary lung lesion was identified in 5 (83.3 %) patients. Lesion margins were spiculated in 2 (33.3 %) cases, lobulated in 1 (16.7 %) case, both spiculated and lobulated in 2 (33.3 %) cases, and ill-defined in 1 (16.7 %) case.

Of the six patients diagnosed with cryptococcosis, solid nodules and masses were present in 3 (50 %) patients each. Three (50 %) patients each had solitary and multiple lung lesions. Lobulated margins were encountered in 4 (66.7 %) cases, lobulated and ill-defined margins in 1 (16.65 %) case, and smooth margins in 1 (16.65 %) case.

Among the four patients with aspergillosis, a solid nodule was present in 1 (25 %), a solid mass in 2 (50 %), and both in 1 (25 %) patient. Solitary and multiple lesions were identified in 2 (50 %) patients each. Lung lesion margins were lobulated and ill-defined in 2 (50 %) cases each.

One patient with blastomycosis had a solitary, spiculated, solid nodule and the other patient had a solitary,

lobulated, solid mass in the lower lobe. The patient with paracoccidioidomycosis had a solitary, ill-defined solid mass. The patient with mucormycosis had multiple lesions with lobulated and ill-defined margins. The clinical suspicion of primary lung tumor was present in both patients.

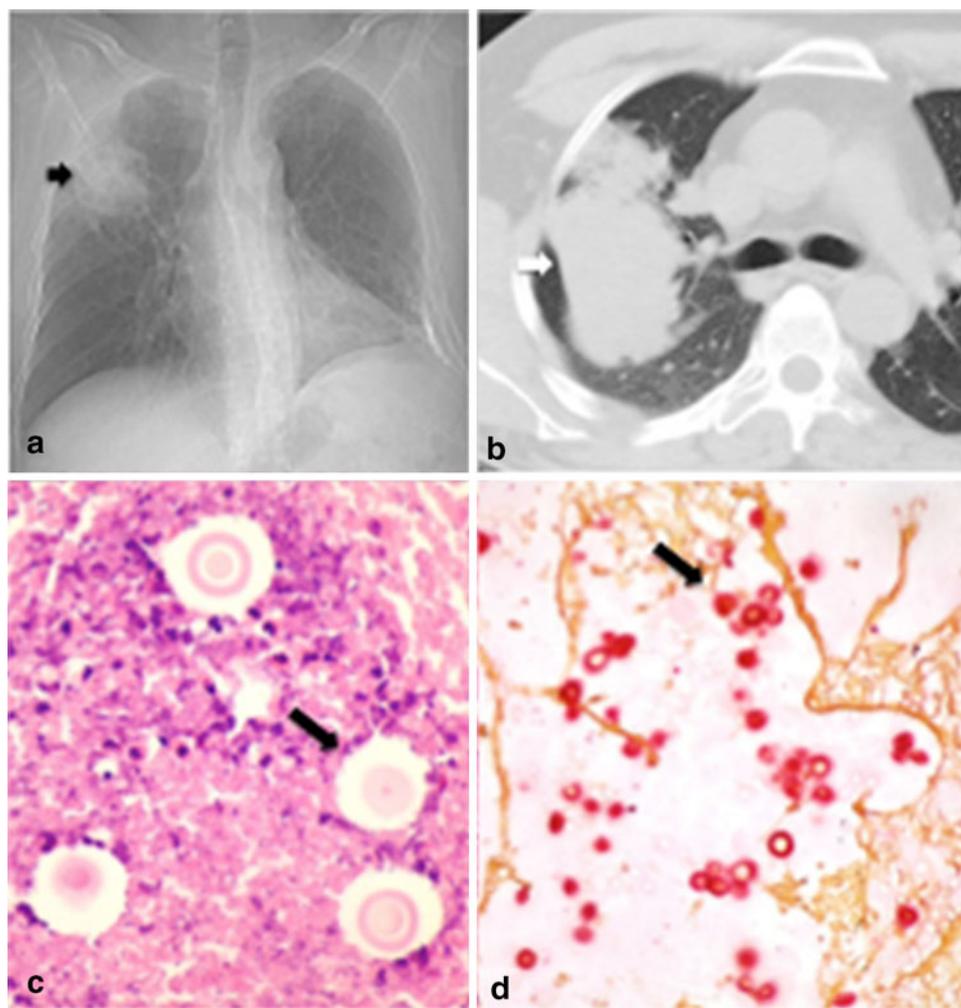
All patients underwent antifungal treatment according to the institutions' individual protocols and showed satisfactory therapeutic responses, with the normalization of clinical and laboratory parameters. All lesions showed improvement or resolution on follow-up posttreatment CT examinations.

Discussion

The present study was conducted in hospitals from two different countries. Each country with a peculiar endemic fungal distribution. The American Hospital located in Houston, TX, receives frequently patients from the Mississippi Valley and Arizona Desert, endemic areas for histoplasmosis and coccidioidomycosis, respectively. The Brazilian Hospital located in São Paulo/SP receives frequently patients from the countryside and rural areas endemic for paracoccidioidomycosis, histoplasmosis, and cryptococcosis [7–10].

Radiological features suggestive of lung malignancy are occasionally seen in other nonmalignant conditions, such

Fig. 3 53-year-old male patient with complaints of chest pain, cough, and expectoration for 1 month without significant improvement after antibiotic therapy. **a** Chest X-ray showed an opacity in the *right upper lobe* (*arrow*). **b** CT scan was suggestive of primary lung mass (*arrow*). **c** Histological examination with hematoxylin and eosin showed the presence of spore (*arrow*). **d** Mucicarmine staining (*arrow*) confirmed the diagnosis of *Cryptococcus*



as pulmonary infection, infarction, and abscess [11, 12]. The PET/CT finding of FDG activity is indeterminate because infectious, inflammatory, and malignant lesions are usually hypermetabolic; false-positive results thus occur more frequently in endemic areas of infection [13, 14].

In the present study, radiological findings suspicious for malignancy were solid nodules and masses with lobulated, irregular, and spiculated margins, cavitation, consolidation, and lymphadenopathy. All patients who underwent PET/CT examinations showed high FDG uptake, consistent with a false-positive result for neoplastic disease. Radiologists should bear in mind that the usefulness of PET/CT lies in its high negative predictive value. A positive result is usually not helpful, because it may neoplastic, infectious, or inflammatory disease [15–17].

Opportunistic and nonopportunistic fungal infections can compromise unusual sites in the body and present with various forms [18–20]. Their clinical and radiological features can mimic benign and malignant diseases, causing misdiagnosis [21–24]. Although we found few case series

in literature, many pulmonary fungal infections mimicking malignancies have been described as case reports [25–30].

Rolston et al. [3] found that 37 of 2,908 (1.3 %) patients who underwent biopsy with a presumed diagnosis of lung cancer were ultimately diagnosed with infection, most commonly fungal ($n = 17$; 46 %). Although the incidence of pulmonary infections simulating cancer was low in their study, fungi were the most common pathogens.

Fungal infection should be considered in suspicious lesions negative for malignancy or when treatment for typical lung infections yields a poor response [1, 2]. The microorganisms detected in the present study were similar to those reported in others studies [31–35]. In patients with histoplasmosis, the most common infection in the present study, the suspicion of metastasis was predominant due to presumed factors, such as the increased occurrence of extrathoracic primary tumors, lung lesions with smooth margins in most cases, and the predominance of lower lobe involvement. Goodwin and Snell [36] demonstrated that histoplasmosis, a delayed form of histoplasmosis that

mimics pulmonary malignancy occurred more often in the posterior lower lobes; this finding is similar to our results.

In patients with coccidioidomycosis included in the present study, presumed diagnoses of primary lung cancer were based on the presence of solitary pulmonary lesions with irregular margins, predominance in the upper lobes, and association with lymphadenopathy in most cases. Primary pulmonary coccidioidomycosis is the most common presentation of this fungal infection and usually resolves spontaneously. However, approximately 5 % of patients develop chronic disease presenting with a solitary lung nodule. Invasive procedures are commonly performed in these patients due to the suspicion of lung cancer [32].

Due to the heterogeneity of clinical and radiological characteristics, presumptive diagnoses were primary lung cancer and metastasis in 50 % each of the patients with cryptococcosis in the present study. Lindell et al. [33] observed multiple lesions in 70 % and solitary nodules in 20 % of patients. They described one case of cavitation, whereas cavitation occurred in two patients with coccidioidomycosis and one patient with mucormycosis in our study.

Pulmonary infections and malignancies can occasionally co-exist successively or simultaneously in the same patient [37, 38]. This situation presents considerable diagnostic and therapeutic challenges, rendering a multidisciplinary approach important for therapeutic success. In the present study, 14 (51.8 %) patients had been diagnosed with extrathoracic primary tumors, leading to presumed diagnoses of metastasis in most ($n = 12$; 85.7 %) cases. The remaining two cases of this group had an initial diagnosis of infection according to the clinical spectrum.

Two patients had a confirmed diagnosis of invasive fungal infection. One was diagnosed with leukemia and developed a pulmonary aspergillosis and the other, although without a previous history of neoplasia, was in late follow-up of renal transplant and developed mucormycosis. In case of cancer patients such infections delay or interrupt chemotherapy impairing appropriate treatment usually with impact on survival rate [30].

It might seem redundant but based on experience acquired during these 5 years we can state that to establish a proper diagnostic approach is essential that clinicians and radiologists be aware of all clinical and radiological findings. A comprehensive assessment is important to consider the fungal infection in the differential diagnosis, especially in endemic areas, in the presence of negative findings for malignancy, and/or when treatment for common lung infections yields a poor response [39–42]. Recent advances in radiology by multidetector CT and functional imaging, such as magnetic resonance with diffusion sequence and PET/CT, have contributed to a better characterization of thoracic lesions suspicious for malignancy. These tools are

very useful, especially when it is necessary to differentiate malignant from benign lesions, including fungal infections [16, 17, 42].

Some limitations of the present study should be emphasized. First, the retrospective selection of patients, examined at cancer hospitals under strong presumption of malignancy, clearly introduced selection bias into our series. Second, our analytical methodology prevented the identification of predictive clinical or radiological factors that could aid in the diagnosis of fungal infection, especially in the presence of clinical and radiological characteristics suggestive of malignancy. However, to our knowledge, this study describes the largest series of patients with pulmonary fungal infection simulating neoplastic diseases to date.

In conclusion, because the management and outcomes of fungal infection and malignancy are entirely distinct, the establishment of a specific diagnosis is critical to provide appropriate therapy. When evaluating clinical and radiological findings suspicious for malignancy, clinicians and radiologists should be aware that other conditions, including fungal infections, should be included in differential diagnoses.

Acknowledgments None.

Conflict of interest The authors have no conflicts of interest or financial ties to disclose.

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