Review article

Fungal diseases mimicking primary lung cancer: radiologic–pathologic correlation

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Summary

A variety of fungal pulmonary infections can produce radiologic findings that mimic lung cancers. Distinguishing these infectious lesions from lung cancer remains challenging for radiologists and clinicians. In such cases, radiographic findings and clinical manifestations can be highly suggestive of lung cancer, and misdiagnosis can significantly delay the initiation of appropriate treatment. Likewise, the findings of imaging studies cannot replace the detection of a species as the aetiological agent. A biopsy is usually required to diagnose the infectious nature of the lesions. In this article, we review the clinical, histologic and radiologic features of the most common fungal infections that can mimic primary lung cancers, including paracoccidioidomycosis, histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis, mucormycosis and blastomycosis.

Key words: Fungal, fungal infections, fungal diseases, lung cancer, computed tomography.

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, with a 5-year survival rate of less than 15%. In 2010, approximately 28% of all cancer deaths were related to lung cancer.[1] Radiology is the main tool used for the diagnosis and staging of lung cancer. Recent studies have demonstrated that low-dose computed tomography (CT) screening can reduce mortality related to lung cancer by at least 20%.[1] In this context, knowledge of the main radiologic mimickers of this cancer is critical.

The main radiologic features suggestive of lung cancer include a parenchymal nodule or mass with irregular margins, lobulations, a thick-walled cavity and chest wall invasion.[2–4] However, several pulmonary infectious diseases occasionally cause inflammatory lung lesions resembling pulmonary carcinoma.[2–4] Despite improvements in imaging studies, serologic/microbiologic testing and interventional bronchoscopic/radiologic procedures, accurate diagnosis remains challenging.[3] The diversity of infectious agents involved, including bacteria,[2] mycobacteria,[2,3] fungi[4,5] and viruses,[6] adds further difficulty. In a series of 2908 patients with a presumed diagnosis of lung cancer who underwent biopsy, fungal infection was the most common pulmonary infection that mimicked cancer, accounting for 46% of diagnosed infections.[3] The clinical manifestations and radiographic findings of such infections are indistinguishable from those produced by pulmonary neoplasms.[2,3,7]

In this article, we review the clinical, histologic and radiologic features of the most common fungal

infections that mimic primary lung cancers, including paracoccidioidomycosis (PCM), histoplasmosis, cryptococcosis, coccidioidomycosis, aspergillosis, mucormycosis and blastomycosis.

Discussion

Paracoccidioidomycosis

Paracoccidioidomycosis is the most common systemic mycosis in Latin America. Although most cases occur in developing countries, recent immigration patterns have increased the numbers of cases appearing in the United States and Europe.[8] PCM is caused by dimorphic fungi *Paracoccidioides brasiliensis* and *P. lutzii*, which are transmitted by an airborne route.[8–10] Depending on the immune status of the host, the primary infection can resolve or develop into a progressive disease with an acute, subacute or chronic course.[8,9] Lung involvement usually presents non-specifically with cough, progressive dyspnoea and diffuse inspiratory crackles on physical examination.

Computed tomography is the method of choice for the evaluation of pulmonary PCM. CT findings are pleomorphic and include ground-glass attenuation, consolidation, small or large nodules, the 'reversed halo' sign, masses, cavitations, interlobular septal thickening, emphysema and fibrotic lesions.[8,11–13] In rare cases, the presence of a mass or spiculated nodule suggesting lung cancer is the main feature of PCM (Fig. 1).[9]

Biopsy should be performed to establish the correct diagnosis as soon as possible.[9] Typical histologic findings include granulomatous inflammation with extensive interstitial and conglomerate fibrosis, necrosis, arterial intimal fibrosis and directly identifiable fungi.
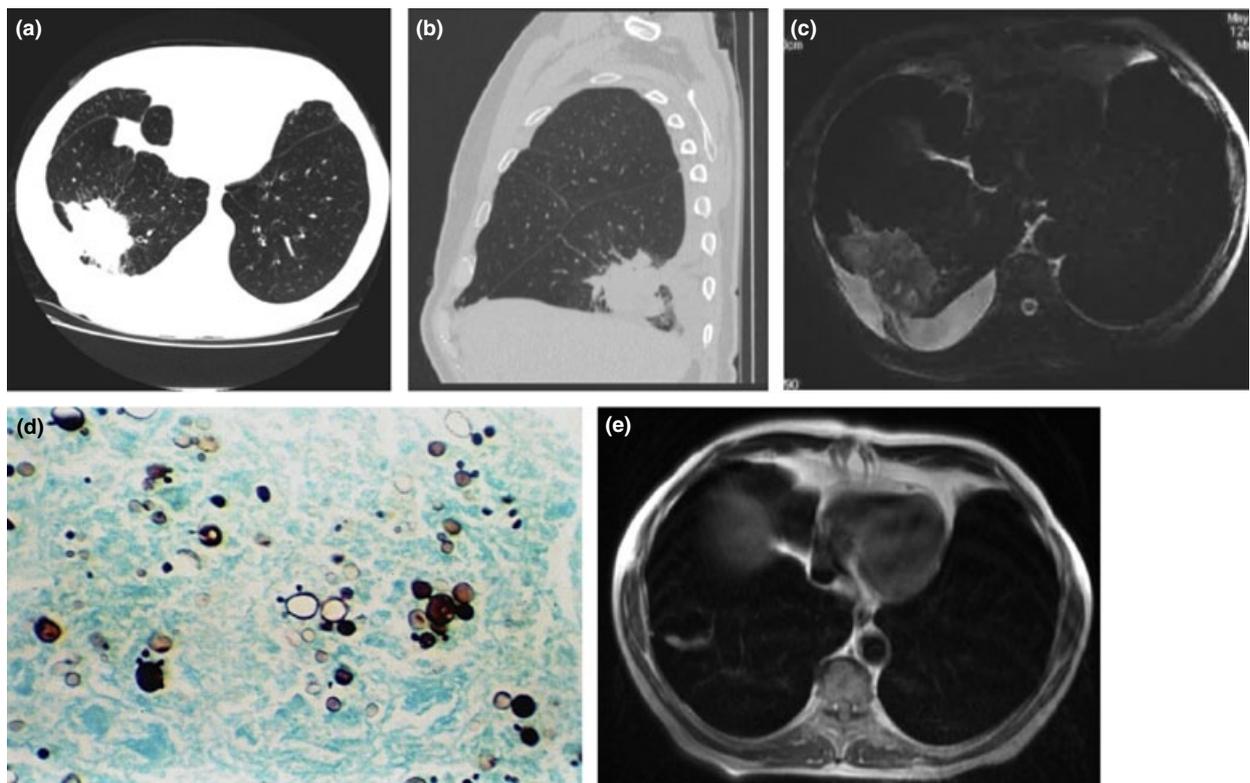

Figure 1 A 75-year-old man from Latin America who presented with a 3-month history of anorexia and weight loss. He also complained of haemoptysis associated with a non-productive cough. He denied any history of fever or night sweats. His medical history included a 60-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a spiculated pulmonary mass associated with pleural effusion in the right lower lobe, suggesting lung cancer. (b) CT image with sagittal reconstruction demonstrates the same findings. (c) Axial T2-weighted magnetic resonance image shows the pulmonary mass and septated pleural effusion. (d) Biopsy specimens contained predominantly non-caseating granulomas; intracellular and extracellular fungal elements compatible with budding forms of *Paracoccidioides brasiliensis* (Grocott, ×400). (e) Axial T1-weighted magnetic resonance image shows regression of the pulmonary mass and pleural effusion 6 months after treatment (amphotericin B and itraconazole).

In the absence of the characteristic budding forms of *Paracoccidioides* on histologic specimens, infection by this organism can be difficult to distinguish from other fungal infections. In addition to microbiologic and histologic methods, immunodiffusion (ID) is an important tool for the diagnosis of PCM, with a sensitivity of 84.3% and specificity of 98.9%.[9] PCM can also affect and mimic cancer in almost all other sites, such as the larynx, central nervous system (CNS) and colon.[14,15]

Histoplasmosis

Histoplasmosis is a fungal infection caused by the dimorphic fungus *Histoplasma capsulatum*, classically considered to be endemic mycosis. Currently, it is highly prevalent in certain areas of the United States (central and southern US, Mississippi and Ohio river valleys), Mexico, Panama and several Caribbean islands and South American countries.[16,17] The clinical features of histoplasmosis vary, including asymptomatic infection, chronic disease mimicking tuberculosis in patients with underlying emphysema and disseminated severe forms affecting patients with acquired immunodeficiency syndrome or haematologic malignancies and allograft recipients.[16–18] The majority of infections caused by *H. capsulatum* are asymptomatic or subclinical, self-limiting illnesses.[19,20]

The histopathologic findings of histoplasmosis are epithelioid granulomas that caseate, then fibrose (resembling lesions caused by *Mycobacteria tuberculosis*). In silver staining, the fungal walls are black and organisms are small (2–4 μm in diameter), uninucleate and spherical to ovoid; they have single buds and are often clustered.

In a retrospective 3-year series, histoplasmosis was the most common fungal infection that mimicked lung cancer.[3] In endemic regions, this fungal infection should thus be included in the differential diagnosis of neoplasia.[16] The most common radiologic finding of acute pulmonary histoplasmosis is the presence of bilateral and mediastinal hilar lymph node enlargement associated with bilateral perihilar reticulonodular infiltrate.[16–20] The radiologic findings of chronic pulmonary histoplasmosis are similar to those of adult or reinfection tuberculosis: progressive infiltrate in the upper lobe, cavitation and signs of fibrosis. Mediastinal enlargement can be seen principally on chest CT images of patients with mediastinal fibrosis secondary to histoplasmosis.[19,20] The presence of a solitary nodule or multiple nodules with central calcification is characteristic of the nodular form, histoplasmoma.[19–21] Typically, histoplasmomas have laminated calcific rings.[16,20] The presence of this feature on a chest radiograph can lead to a misdiagnosis of lung cancer (Fig. 2)[18]; thus, recognition of the benign pattern of calcification is important to distinguish this infection from bronchogenic carcinoma.[22–25]

Currently, F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is widely used and considered to be accurate for the evaluation of lung cancer. However, the PET finding of intense F-18 FDG uptake in a lesion is a common finding in both histoplasmosis and lung cancer, significantly reducing the accuracy of PET as a diagnostic modality for lung cancer in endemic regions of histoplasmosis (Fig. 3).[24] In an endemic region of granulomatous diseases, the specificity of FDG-PET for the diagnosis of lung cancer was 40%.[24]
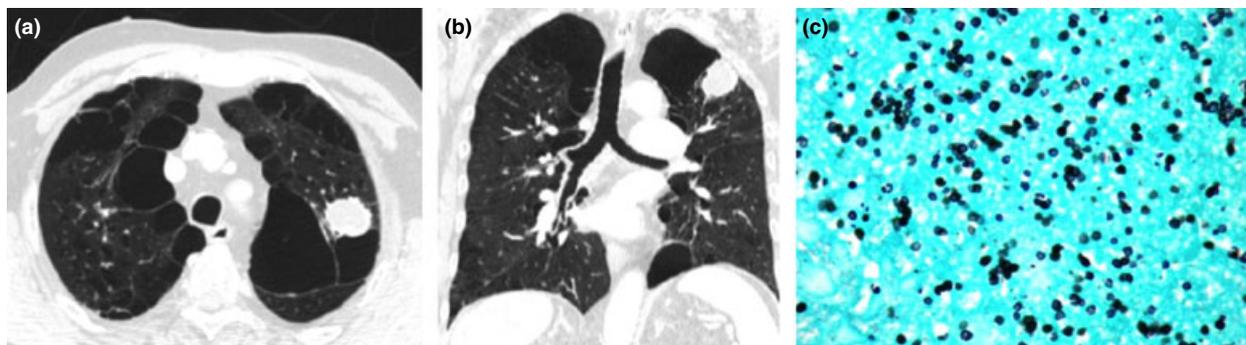

Figure 2 An asymptomatic 65-year-old man who underwent evaluation of a pulmonary nodule newly detected on a chest X-ray. He denied any history of fever or night sweats. His medical history included a 45-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a spiculated pulmonary nodule associated with adjacent bullous emphysema in the left upper lobe, suggesting lung cancer. (b) CT image with coronal reconstruction demonstrates the same findings. (c) Microscopic examination of transthoracic needle biopsy specimens showed yeast cells of *Histoplasma capsulatum* in smear. The fungal walls are black and organisms are small, uninucleate and spherical to ovoid; they have single buds and are often clustered. (Grocott, ×250).

Figure 3 An asymptomatic 44-year-old man who underwent evaluation of a pulmonary nodule. He denied any history of fever or night sweats. His medical history included a 75-pack-year smoking habit. (a) A positron emission tomography (PET)/computed tomography (CT) image with coronal reconstruction demonstrates a spiculated pulmonary nodule with high uptake [standardised uptake value (SUV) = 5.5]. (b) PET/CT image with coronal reconstruction demonstrates hilar and subcarinal lymph nodes with high uptake (SUV = 8.5). (c) Microscopic examination of mediastinoscopic biopsy specimens showed yeast cells of *Histoplasma capsulatum* in smear. (Grocott, ×250).

Serological tests available for the diagnosis of histoplasmosis include the complement fixation (CF) using histoplasmin, and the ID assay. Diagnosis is based on a fourfold rise in CF antibody titre. A single titre equal to or greater than 1 : 32 is suggestive, but not diagnostic. The CF test is less specific than the ID assay because cross-reactions occur with other fungal and granulomatous infections.[26,27] The ID assay is approximately 80% sensitive, but is more specific than the CF assay. Tests for antibody are most useful in patients who have chronic forms of histoplasmosis that have allowed enough time for antibody to develop. In patients who have acute pulmonary histoplasmosis, the documentation of a fourfold rise in antibody titre to *H. capsulatum* can be diagnostic. However, it may require 2–6 weeks for the appearance of antibodies. The utility is also lower in immunosuppressed patients, who mount a poor immune response.[28] The antigen detection method is more useful for the serological diagnosis of disseminated histoplasmosis in AIDS patients. In this population, *Histoplasma* antigen was detected in urine in 95% and in serum in 86% of patients, respectively.[29]

Cryptococcosis

Cryptococcosis is an infection caused by an encapsulated fungus of the genus *Cryptococcus* (*C. neoformans* or *C. gattii)*. The infection caused by the species *C. neoformans* has become the most relevant opportunistic infection in the HIV era. *Cryptococcus gattii* is considered to be a primary fungal pathogen because it virtually always affects immunocompetent patients.[30] *Cryptococcus neoformans* is a ubiquitous fungus, found particularly in soil contaminated by pigeon droppings and in tree hollows.[25,30–32] *Cryptococcus gattii* occurs mainly in tropical and subtropical climates and is associated with certain species of the Eucalyptus tree. However, a recent outbreak of *C. gattii* in Vancouver Island shows that the distribution of *C. gattii* is changing, with its ability to associate itself with a wide variety of trees, such as firs and oaks.[30]

Pulmonary cryptococcosis (PC) is caused by the inhalation of spores from *Cryptococcus* spp., with effects ranging from a self-limiting, asymptomatic pulmonary infection to severe pneumonia in cases of immunosuppression or massive inoculation of the yeast.[25,33,34] Patients with acute PC can present fever, productive cough, chest pain and weight loss. The CNS could be affected, with cerebral and meningeal involvement, as a result of dissemination from the lungs.[33,34] In immunocompromised patients, symptoms related to the systemic dissemination of the organism, typically to the CNS, usually predominate.[31–34]

Radiographically, PC may manifest as a solitary lung nodule or mass, multiple nodules, segmental or lobar consolidation, or, rarely, interstitial pneumonia (more common in immunosuppressed patients). Associated features include cavitation, lymphadenopathy and pleural effusion.[25,31–34] When presenting as a solitary nodule or mass, cryptococcosis can mimic lung cancer (Fig. 4).[3,25,32]

The manifestations of infection by *C. neoformans* and *C. gattii* can be different.[30,35] *Cryptococcus neoformans*

Figure 4 A 53-year-old man who presented with a 3-month history of right chest pain. He denied any history of fever or night sweats. His medical history included a 33-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a spiculated pulmonary mass in the right upper lobe with pleural contact, suggesting lung cancer. (b) CT image with sagittal reconstruction demonstrates the same findings. (c) Microscopic examination of transthoracic needle biopsy specimens showed yeast cells of *Cryptococcus neoformans* in smear; fungal cell wall is stained in black (Grocott, ×250). (d) A CT image shows regression of the pulmonary mass 7 months after treatment (fluconazole).
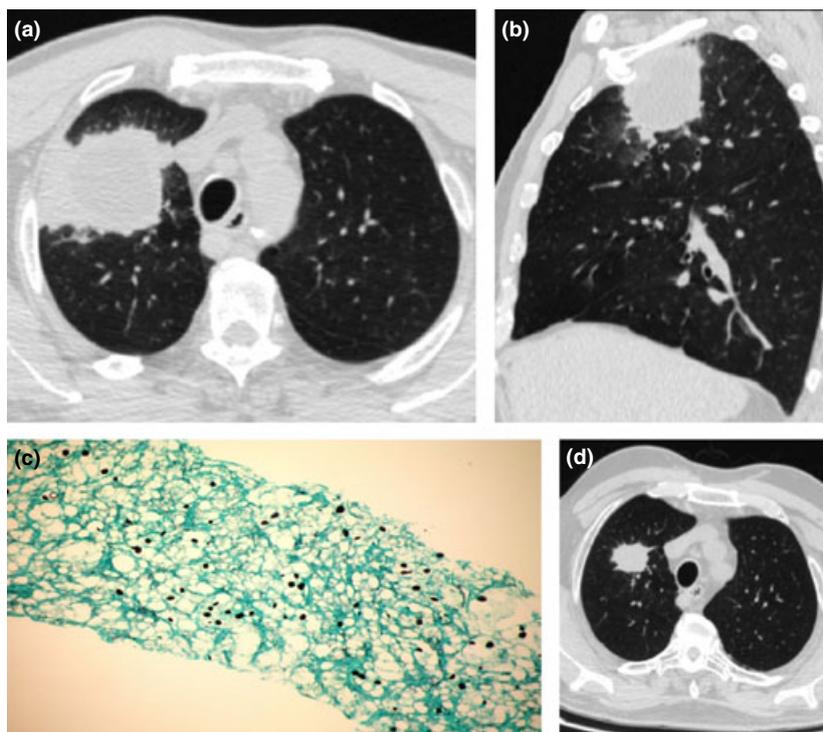
affects immunocompromised patients, with a tendency to cause diffuse pulmonary involvement associated with meningitis. *Cryptococcus gatti*, however, are more likely to cause focal pulmonary disease in immunocompetent hosts with large inflammatory masses, called cryptococcomas.[30,35] *Cryptococcus gattii* is less likely to cause CNS disease than *C neoformans*, but more likely to form cryptococcomas in brain.[30,35]

Cryptococcus antigen detection using latex agglutination assays on cerebrospinal fluid (CSF) or serum specimens is useful in the initial diagnosis. The reported sensitivity for latex agglutination assays ranges from 54% to 100%, with higher sensitivity in patients with CNS infection or pneumonia.[35] False-negative results may occur in cases with encapsulated nodules, or when patients have an overwhelming disease such that the amount of serum antigen in the sample is in excess of the amount of antibody in the assay, the prozone effect.[35,36] False-positive results may occur with *Trichosporon beigelii* infection.[35]

Therefore, the diagnosis of pulmonary disease requires direct evidence of *Cryptococcus* in sputum, bronchial washing, bronchoalveolar lavage fluid or lung tissue. Histopathological identification of the cryptococcosis is based on the micromorphological and staining features of the cryptococcal cells, and include histochemical techniques of haematoxylin and eosin

(HE) and Grocott′s silver stain (GMS), as well as Mayer′s mucicarmine method (MM), which stains the capsule magenta.[25,37] The Fontana–Masson procedure is a special technique, which stains fungal melanin reddish-brown, useful in the uncommon cases of capsule-deficient form.[37] However, these direct and histological stains do not differentiate between the species; only culture leads to *Cryptococcus* species and variety identification.[35]

Coccidioidomycosis

Coccidioidomycosis is a systemic mycosis caused by dimorphic fungi, endemic to arid and semiarid regions in the south-western United States and northern Mexico, and in certain areas of Central and South America.[38–41] Initially, it was thought that coccidioidomycosis was only caused by the fungus *Coccidioides immitis*. Based on molecular phylogeny studies, the existence of another species has been recently demonstrated. It is currently established that *C. immitis* is a fungus that is endemic in California, particularly in the San Joaquim Valley. The other species was 'hidden' with *C. immitis* and was designated as *C. posadasii*, after Alexandre Posadas, the man who discovered it. *C. posadasii* is prevalent in all the remaining endemic areas of the American continent, from the southern

United States to Argentina. The semiarid north-eastern region of Brazil has recently been identified as an area endemic for coccidioidomycosis.[41]

Approximately 60% of human primary infections are asymptomatic; the majority of symptomatic cases are characterised by mild-to-severe acute pulmonary infection that generally resolves spontaneously. Progressive pulmonary coccidioidomycosis is generally chronic and develops after the first infection, with symptoms failing to resolve after 2 months.[38–40]

Progressive pulmonary coccidioidomycosis may have the following presentations: 1) nodular or cavitary lesions, sometimes as an incidental radiologic finding; 2) cavitary lung disease with fibrosis and 3) miliary pulmonary dissemination with non-specific clinical and radiologic manifestations. The most common finding on chest X-rays is multiple, peripherally distributed lung nodules associated with parenchymal consolidation. Chest CT images reveal peripheral lung nodules that are predominantly cavitated.[5,41,42] This pathology usually simulates metastatic cancer. However, due to its chronic progression, the inclusion of progressive pulmonary coccidioidomycosis in the differential diagnosis of lung cancer and other granulomatous lung diseases is important (Fig. 5).[5,43]

Coccidioides sp. inhaled into the lung develop into thin-walled spherules that rupture and release numerous endospores, causing a granulocytic response that is histologically non-specific unless spherules and endospores can be recognised. As the inflammatory response progresses, an epithelioid granuloma containing large histiocytes and giant cells is formed.[38–41] Central necrosis and a variable degree of fibrosis may

be observed as healing occurs. The diagnosis of coccidioidomycosis is made by the isolation of *Coccidioides* sp. in culture or by positive results from smear microscopy (10% potassium hydroxide test), periodic acid-Schiff (PAS) staining or silver staining of any suspect material (e.g. sputum, CSF, skin exudate, lymph node aspirate); the characteristic parasitic form is the spherule.[41] Agar gel ID is the most widely used diagnostic test.[5,41,42]

Aspergillosis

Pulmonary aspergillosis refers to a clinical spectrum of lung diseases caused by species of the *Aspergillus* genus (usually *A. fumigatus*), a ubiquitous genus of soil fungi. The manifestations of pulmonary aspergillosis are determined by the number and virulence of organisms and the patient's immune response. The spectrum can be subdivided into five categories: saprophytic aspergillosis (aspergilloma), hypersensitivity reaction (allergic bronchopulmonary aspergillosis), semiinvasive (chronic necrotising) aspergillosis, airway-invasive aspergillosis and angioinvasive aspergillosis.[43,44] Angioinvasive disease and aspergilloma have been reported to mimic malignancy.[3,7,45] In a 3-year review, only one case of aspergillosis was recorded among fungal infections accounting for 46% of lesions simulating neoplasms.[3] In another series, 3/13 cases of inflammatory lesions imitating pulmonary carcinoma were subsequently identified as aspergilloma.[7]

Aspergilloma is the most common pulmonary manifestation of aspergillosis that mimics neoplasia. It is characterised by *Aspergillus* colonisation without tissue
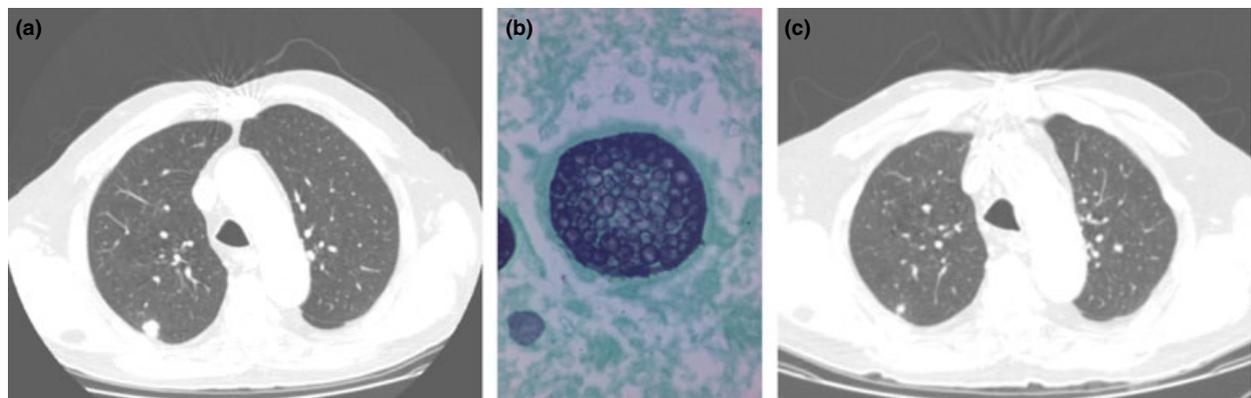
Figure 5 An asymptomatic 49-year-old woman underwent evaluation of a pulmonary nodule discovered on a chest X-ray. She denied any history of fever or night sweats. Her medical history included a 25-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a lobulated pulmonary nodule in the right upper lobe, suggesting lung cancer. (b) Microscopic examination of transthoracic needle biopsy specimens showed yeast cells of *Coccidioides immitis* (spherules in black) in smear (Grocott, ×250). (c) CT image shows regression of the pulmonary nodule 3 months after treatment (itraconazole).

invasion. The fungus colonises an existing pulmonary cavity, bulla or ectatic bronchus, forming a mass of intertwined fungal hyphae admixed with mucus and cellular debris. The most common underlying causes of the infection are tuberculosis and sarcoidosis. Although patients remain asymptomatic, the most common clinical manifestation is haemoptysis.[25,43,46] On CT, aspergilloma is characterised by the presence of a solid, round mass with soft-tissue density within a lung cavity.[46] These characteristics can simulate neoplasia (Fig. 6). However, the aspergilloma usually moves when the patient changes position.[43] Therefore, the acquisition of CT images with the patient in the dorsal and ventral decubitus positions is important for differential diagnosis. Another finding of aspergilloma is thickening of the cavity wall and adjacent pleura, which may be the earliest radiographic sign.[43]

The angioinvasive form of aspergillosis has also been described as simulating neoplasia. It is characterised by hyphal invasion and occlusion of small-to-medium sizes arteries and destruction of normal lung tissue.[43–46] Angioinvasive aspergillosis occurs almost exclusively in immunocompromised patients with severe neutropenia due to haematologic malignancies, and those who have undergone haematopoietic stem cell transplantation.[44–47] Among the recipients of solid-organ transplants the incidence of angioinvasive disease is lower because neutropenia is not the principal immunologic defect affecting these patients.[48,49] Angioinvasive aspergillosis is manifested clinically as a rapid progressive respiratory illness with cough, chest pain and haemoptysis. These clinical features are distinct from lung cancer, and suggest an infectious, rather than neoplastic disease. Characteristic CT findings consist of nodules surrounded by a halo of ground-glass attenuation (halo sign), or pleura-based, wedge-shaped areas of consolidation. The reversed halo sign (ground-glass opacity surrounded by a halo of consolidation) may also suggest this infection.[44–47]

In tissue sections, *Aspergillus* hyphae characteristically appear as uniform, narrow (3–6 μm in width), tubular and regularly septate (usually 45°) elements. Branching is regular, progressive and dichotomous. Hyphal branches tend to arise at acute angles from parent hyphae. Special stains for fungi, like PAS and GMS are superior to HE for the characterisation of hyphal morphology.[44,46]

Mucormycosis

Mucormycoses are a group of invasive, often fatal, opportunistic infections caused by fungi belonging to the class Zygomycetes, order Mucorales. Most clinically significant infections are caused by fungi of the genera Lichtheimia, *Rhizopus*, *Mucor* and *Cunninghamella*.[50–55] Risk factors for infection include haematologic malignancy, diabetes, organ transplantation, immunosuppression, graft-vs.-host disease and desferoxamine therapy. The majority of these risk factors act by impairing neutrophil function.[55] Six distinct clinical
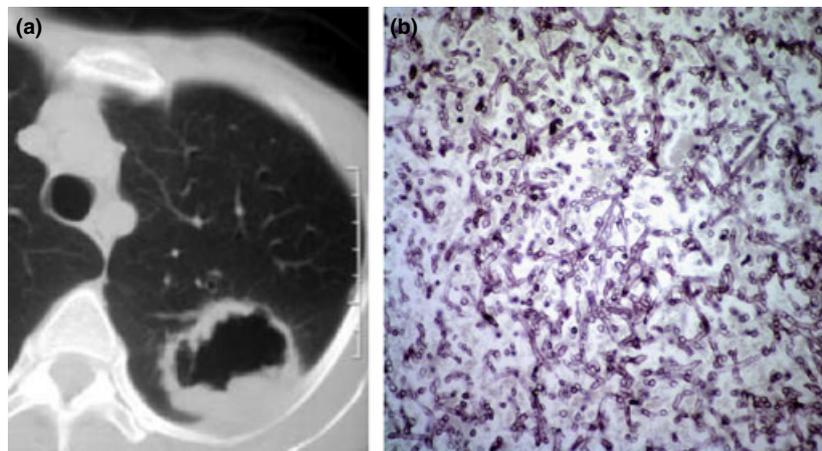

Figure 6 A 77-year-old man who presented with a 3-month history of bloody sputum. He denied any history of fever or night sweats. His medical history included a 60-pack-year smoking habit and previous treatment of pulmonary tuberculosis. (a) Axial computed tomography (CT) image shows a cavitated pulmonary mass with irregular thick walls, suggesting lung cancer. The patient underwent surgery, which confirmed the diagnosis of cavitary colonisation by *Aspergillus fumigates*. (b) Tissue sections contained narrow, tubular and regularly septate hyphae compatible with *Aspergillus fumigatus* (Grocott, ×100). Branching is regular, progressive and dichotomous; hyphal branches tend to arise at acute angles from parent hyphae.

syndromes are recognised: rhinocerebral, pulmonary, abdominopelvic, cutaneous, widely disseminated and miscellaneous mucormycosis.

The clinical presentation is associated with the predisposing conditions of the host. The principal presentation is the rhinocerebral form, which typically affects diabetic patients in ketoacidosis. Pulmonary infection is the second-most common form, accounting for more than 30% of infections.[51] The clinical hallmark of pulmonary mucormycosis is rapidly progressive pneumonia with angioinvasion and tissue necrosis, which is far more common in patients with haematologic malignant neoplasms. Symptoms include fever, cough, chest pain and dyspnoea. An indolent clinical course with a better outcome is commonly seen in diabetic patients.[25,50] Due to the rapidly progressive clinical picture, mucormycosis infection is not often confused with lung cancer. However, such misdiagnoses have been reported in the literature.[53] Thus, the radiological findings must be correlated with the clinical scenario.

The radiologic manifestations of pulmonary mucormycosis are non-specific and include progressive lobar or multilobar consolidation, pulmonary masses and nodules and the reversed halo sign.[25,47,51] Cavitation is seen in up to 40% of cases, but the air crescent sign is uncommon. The upper lobes are most commonly involved.[51] This infection may be associated with mediastinal or hilar adenopathy, vascular invasion and extrapulmonary involvement.[51] Horner's syndrome is rarely seen.[54] Rarely, radiologic aspects of mucormycosis have been described to simulate lung neoplasm (Fig. 7).[2,54]

On histopathologic examination, *Zygomycetes* hyphae are broad and irregular with right-angled branching, as opposed to *Aspergillus* hyphae, which are thinner with more acute-angled branching.[50–55] Pulmonary angioinvasion, vascular thrombosis or necrosis may be observed.[55] The mortality rate associated with mucormycosis is high; massive haemoptysis, secondary bacterial infection and acute respiratory failure are the most common causes of death.[24,50–55] Early diagnosis is of utmost importance because the early initiation of high-dose antifungal therapy is associated with improved outcomes.

It is very important to note that other invasive mycoses, like scedosporiosis and fusariosis, may affect lungs. Likewise, the clinical and radiological aspects of these infections are similar to those observed in other invasive filamentous fungi infections, such as invasive aspergillosis and mucormycosis.[56–59]

Blastomycosis

Blastomycosis is an uncommon fungal pathologic condition. It is caused by *Blastomyces dermatitidis*, a thermally dimorphic fungus endemic to Canada and the upper Midwest of the United States. Outside of North America, blastomycosis has been found in Africa.[60] Human exposure occurs when fungi in soil with organic content are disturbed, especially during outdoor activities. Inhaled airborne spores cause primary lung infection, which may become disseminated.[60] Affected patients may be asymptomatic or present with chronic clinical manifestations or even acute fulminant illness. Blastomycosis is not considered an
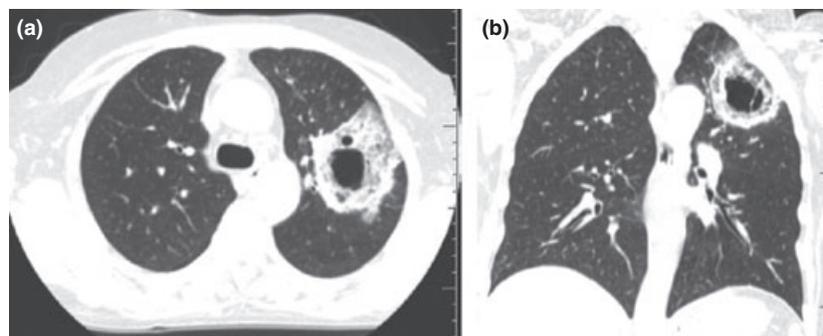

Figure 7 A 45-year-old male kidney transplant recipient presented with a 15-day history of bloody sputum and night sweats. His medical history included a 30-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a cavitated pulmonary mass with irregular thick walls. No centrilobular lesion suggesting the bronchogenic spread of a possible granulomatous infection is present. (b) CT image with coronal reconstruction demonstrates similar findings. Microscopic examination of a bronchoalveolar lavage specimen yielded findings compatible with mucormycosis. The lesion progressed despite appropriate treatment with antimycotic drugs, and the patient died 15 days after initiation of treatment. Within this context of immunosuppression, the possibility of invasive fungal infection should be favoured over lung cancer. Early diagnosis is of utmost importance in such cases.

opportunistic infection, but immunocompromised patients with AIDS or a history of transplantation more often have diffuse disease. Chronic pulmonary symptoms occur more frequently than acute symptoms.[60–62] Patients present with chest pain, low-grade fever, mild productive cough and haemoptysis. General symptoms of malaise, fatigue and weight loss are also often present.

Blastomycosis is sometimes found in patients referred for the evaluation of a nodule or mass suspicious for lung cancer.[60,61] Nodules or masses are the second-most common radiologic finding in blastomycosis, occurring in up to 31% of cases.[61] The lesions are usually well circumscribed and 3–10 cm in diameter; they tend to be paramediastinal or perihilar.[62] These manifestations can be difficult to differentiate from lung cancer (Fig. 8). In a series of 35 patients with North American blastomycosis, lung masses were resected in 55% of patients due to high suspicion for bronchogenic carcinoma.[63] Pleural effusions are uncommon.[64] The diagnosis of blastomycosis is often delayed because it can mimic many other diseases, including bacterial pneumonia, malignancy and tuberculosis.

Pathologic findings are suppurative or granulomatous lesions with numerous organisms in epithelioid and giant cells or located freely in microabscesses. The organism is spherical and single budding, with a broad base containing multiple basophilic nuclei in a double-walled central body.[61–64]

Conclusion

A variety of fungal pulmonary infections can present with radiologic findings that mimic lung cancer. Distinguishing between these infectious lesions and lung cancer remains challenging. Physicians should be aware of the clinical and radiologic features of these fungal diseases (summarised in Table 1). The geographic distribution of endemic areas must be considered when evaluating a patient for suspected fungal disease. A detailed anamnesis is essential, including the acquisition of information about the patient's travelling habits, migration, recreational activities and residence in endemic areas, as well as the history of any type of immunosuppression. Radiologists and clinicians need to work in collaboration, as the clinical context is essential for the appropriate interpretation of images. When a lung infection is considered to be likely (or possible), serologic tests, sputum smear, bronchoscopy with bronchoalveolar lavage and image-guided biopsy can be performed to assist in the diagnosis. The tissue material should be sent not only for histopathology but also for direct exam and culture. Precise diagnosis is crucial for the administration of appropriate treatment and to avoid unnecessary high-risk surgical procedures in these patients.

Figure 8 An asymptomatic 59-year-old man who had undergone surgery for oesophageal cancer. He denied any history of fever or night sweats. His medical history included a 35-pack-year smoking habit. (a) Axial computed tomography (CT) image shows a new spiculated pulmonary nodule in the left upper lobe, suspicious for lung cancer or metastasis. (b) Axial positron emission tomography (PET)/CT image demonstrates high fluorodeoxyglucose uptake (standardised uptake value = 6.5) by the spiculated pulmonary nodule. (c) Microscopic examination of transthoracic needle biopsy specimens showed that the pulmonary parenchyma had been replaced by necrotising granulomatous inflammation (haematoxylin and eosin, ×20). (d) Gomori methenamine silver histochemical staining showed yeast with broad-based budding typical of North American blastomycosis (×60).
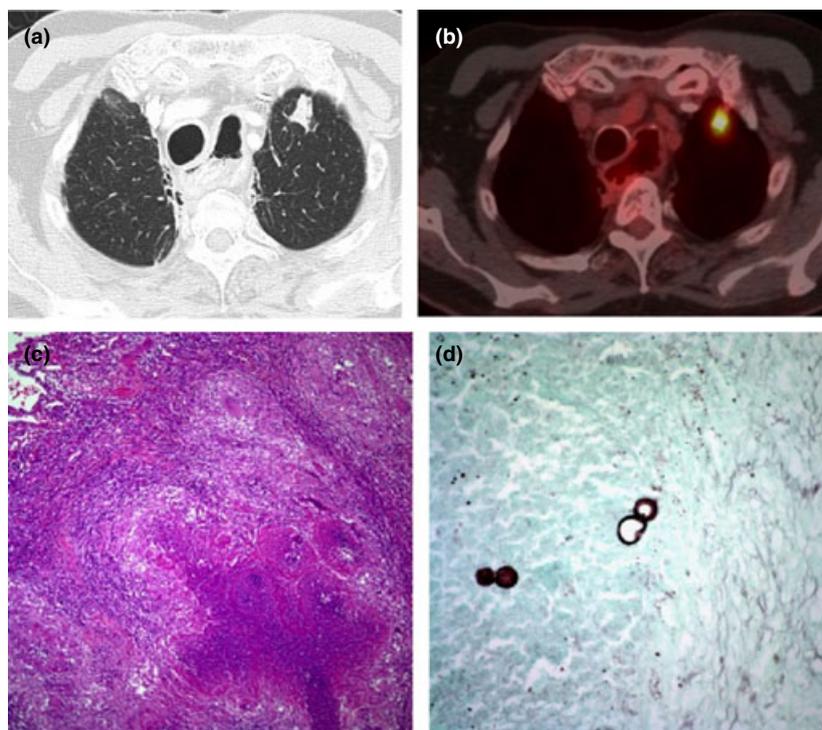
Table 1 Classical features in fungal diseases that assist in differential diagnosis with lung cancer.

Fungal disease	Pathogenesis	Areas of endemicity	Radiology	Diagnosis	Other
Paracoccidioidomycosis[8,9]	Primary pathogen/ Abnormal T-lymphocyte function	Latin America	Pleomorphic	Culture, biopsy, ID	Oral mucosal lesions
Histoplasmosis[3,17,19,27,29]	Primary pathogen/ Abnormal T-lymphocyte function	North America river valleys, several Caribbean islands, Central and South Americas	Solitary or multiple nodules with central calcification.	Culture, biopsy, ID, CF, Ag detection in serum/urine	Most common cancer mimicker
Cryptococcosis (*Cryptococcus gattii*) [30,31,32,35]	Primary pathogen/ Abnormal T-lymphocyte function	Ubiquitous	Solitary lung nodule or mass (cryptococcoma); multiple nodules	Culture, biopsy, direct examination of CSF, serum/CSF cryptococcal Ag	Immunocompetent; more likely to form cryptococcomas
Cryptococcosis (*C. neoformans*)[30,31,32,35]	Opportunistic pathogen/ Abnormal T-lymphocyte function	Ubiquitous	Multiple nodules, segmental or lobar consolidation, interstitial pneumonia	Culture, biopsy, direct examination of CSF, serum/CSF cryptococcal Ag	Immunocompromised; symptoms related to systemic dissemination, typically to the CNS predominate
Coccidioidomycosis[38,40,41]	Primary pathogen/ Abnormal T-lymphocyte function	*Coccidioides immitis*: California *C.posadasii*: all the remaining endemic areas of the American continent, from the southern United States to Argentina	Peripheral lung nodules that are predominantly cavitated	Culture, biopsy, ID	Simulates metastatic cancer and other granulomatous diseases
Aspergilloma[25,43,46]	Saprophytic/ Cavitary lung disease	Ubiquitous	Round mass with soft-tissue density within a cavity that moves when the patient changes position	Biopsy, direct microscopic exam and culture	Colonises a pulmonary cavity, forming a mass of intertwined fungal hyphae admixed with cellular debris
Angioinvasive Aspergillosis[25,43,44,46]	Opportunistic/ neutropenia	Ubiquitous	Halo sign, reversed halo sign, wedge-shaped consolidation	Biopsy, direct microscopic exam and culture	Neutropenia due to haematologic malignancies and HSCT
Mucormycosis[25,50,51]	Opportunistic/ neutropenia	Ubiquitous	Progressive lobar or multilobar consolidation, pulmonary masses and nodules	Biopsy, direct microscopic exam and culture	Rapidly progressive pneumonia in patients with haematologic malignancies
Blastomycosis[60,61,64]	Primary pathogen/ Abnormal T-lymphocyte function	Canada and the upper Midwest of the United States; Africa	Nodules or masses that tend to be paramediastinal or perihilar	Biopsy, direct microscopic exam and culture	Diagnosis is often delayed because it can mimic other diseases (bacterial pneumonia, malignancy and tuberculosis)

ID, immunodiffusion; CF, complement fixation; Ag, antigen; CSF, cerebrospinal fluid; CNS, central nervous system; HSCT, haematopoietic stem cell transplantation.

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