

Pulmonary cryptococcoma: a rare and challenging diagnosis in immunocompetent patients

Nicole Haddad^a, Marina Costa Cavallaro^b, Mariana Pezzute Lopes^b, Johana Marlen Jerias Fernandez^b, Lorena Silva Laborda^c, José Pinhata Otoch^d, Cristiane Rubia Ferreira^e

Haddad N, Cavallaro MC, Lopes MP, et al. Pulmonary cryptococcoma: a rare and challenging diagnosis in immunocompetent patients. *Autopsy Case Rep* [Internet]. 2015; 5(2):35-40. <http://dx.doi.org/10.4322/acr.2015.004>

ABSTRACT

Cryptococcal infection is commonly seen in immunocompromised patients, although immunocompetent patients may also be infected. The pathogen's portal of entry is the respiratory tract; however, the central nervous system is predominantly involved. Pulmonary involvement varies from interstitial and alveolar infiltrations to large masses, which are frequently first interpreted as lung neoplasm. The diagnosis of pulmonary cryptococcosis, in these cases, is frequently challenging, which, in most cases, requires histopathological examination. The authors report the case of a young female patient who presented a 20-day history of chest pleuritic pain and fever at the onset of symptoms. HIV serology was negative and CD4 count was normal. The imaging work-up was characterized by a huge opacity in the left inferior pulmonary lobe with a wide pleural base. Computed tomography showed a heterogeneous mass involving the bronchial tree. Mediastinal involvement was poor, and there was a splenomegaly. The patient underwent an exploratory thoracotomy and inferior lobectomy. The histopathological examination revealed a cryptococcoma. As the serum antigenemia was positive, the patient was scheduled for long-term treatment with fluconazole. The authors call attention to including the cryptococcal infection in the differential diagnosis of lung mass, mainly when localized in the lung bases in immunocompetent patients.

Keywords

Cryptococcus; Lung diseases; Pulmonary Surgical Procedures; Therapeutics

CASE REPORT

A 17-year-old previously healthy Caucasian female patient sought the emergency unit complaining of left chest pleuritic pain during the last 20 days. She referred fever (axillary temperature of 38°C) at the onset of the symptoms but denied weight loss, sudoresis, cough, or any other systemic symptom. She had been initially

treated with clarithromycin and levofloxacin because previous chest x-ray and computed tomography (CT) images interpreted the condition as pneumonia. After taking antibiotics, the fever ceased but pain did not improve. She underwent another course of antibiotics, this time with amoxicillin and clavulanate

^a Internal Medicine Department - Hospital das Clínicas - Faculdade de Medicina - Universidade de São Paulo, São Paulo/SP - Brazil.

^b Infectious Disease Department - Instituto Emilio Ribas, São Paulo/SP - Brazil.

^c Internal Medicine Department - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.

^d Surgical Clinic Division - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.

^e Anatomy Pathology Service - Hospital Universitário - Universidade de São Paulo, São Paulo/SP - Brazil.



for 10 days, which were similarly worthless. Therefore, she was hospitalized referring unchanged thoracic pain. Physical examination revealed a well-looking patient, afebrile, with normal hemodynamic parameters. Edema and lymphadenopathy were not present. Cardiac

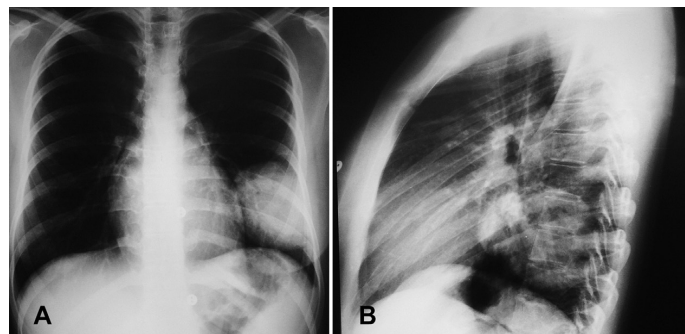


Figure 1. Chest x-ray showing a homogeneous wide pleural base opacity in the inferior left pulmonary lobe.

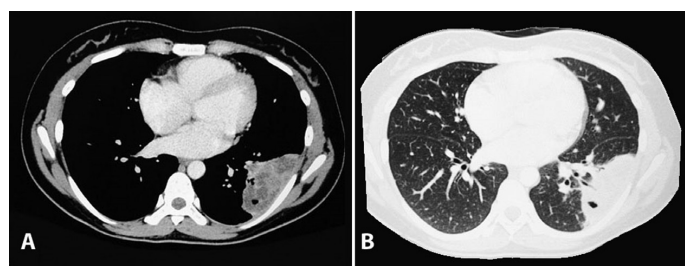


Figure 2. Thoracic axial computed tomography showing a pulmonary mass with heterogeneous attenuation coefficient in the left lower lobe. **A** - Mediastinal window; **B** - Parenchymal window.

examination was normal, and pulmonary sounds were reduced in the left pulmonary base. Traube's space was dull on percussion, but no organomegaly was palpable. Laboratory work-up was normal, and serologies for HIV, and hepatitis B and C were negative. The plain chest x-ray showed a well-circumscribed homogeneous round opacity, with a wide pleural base in the left inferior pulmonary lobe (Figure 1) that on the CT appeared as a nodular lesion with heterogeneous attenuation coefficient involving the bronchial tree in the left inferior lobe (Figure 2).

Splenomegaly was an additional finding on CT. Thoracic ultrasonography showed hypoechoic mass most probably of a solid nature. The bronchoscopy was normal and bronchoalveolar lavage (BAL) did not evidence acid-fast bacilli, fungus, or bacteria. The patient was submitted to an exploratory thoracotomy, which depicted a solid mass firmly adhered to the parietal pleura involving the left inferior lobe. The frozen biopsy, sampled from the non-necrotic tissue, revealed a dense histiocytic infiltration, but neither neoplastic nor inflammatory origins could be ruled out (Figure 3). An inferior lobectomy was undertaken (Figure 4), and the post-operative outcome was uneventful. The pathological examination revealed a firm heterogeneous mass, measuring 4.5 × 3.0 × 5.5 cm, intermingled with extensive necrotic areas (Figure 5).

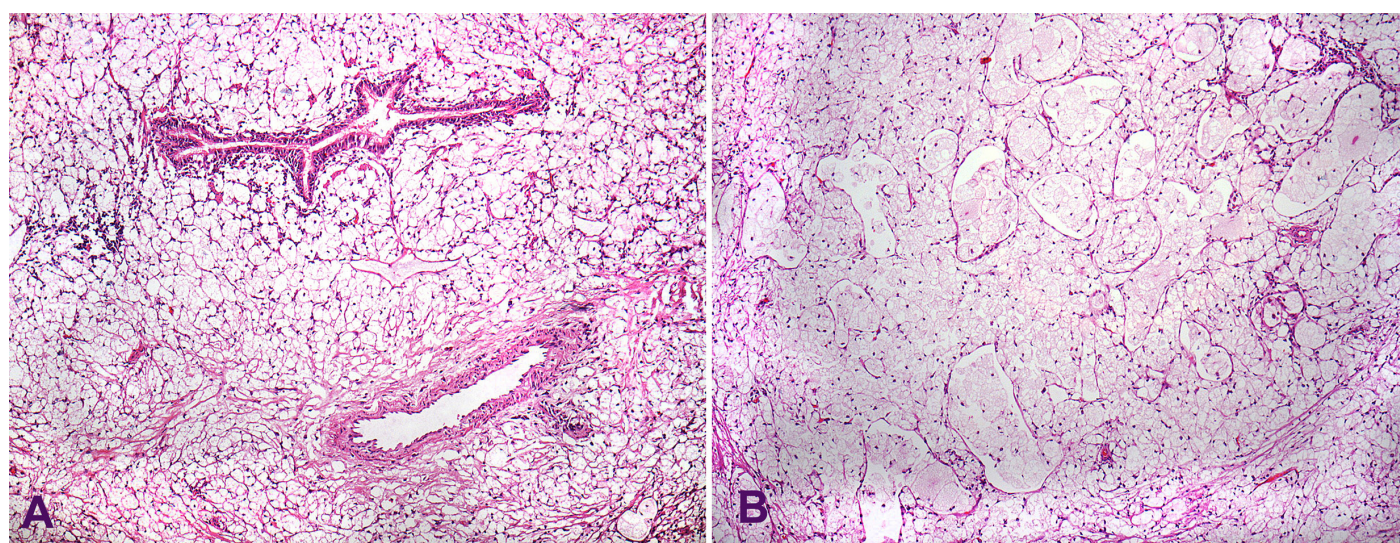


Figure 3. Photomicrography of the frozen biopsy. **A** - Pulmonary parenchyma showing a terminal bronchiole and vessel with altered architecture represented by total replacement of the alveolar tissue by a dense histiocytic infiltration (H&E, 100X); **B** - Detail of the foamy histiocytic infiltration replacing the alveolar parenchyma (H&E, 200X).

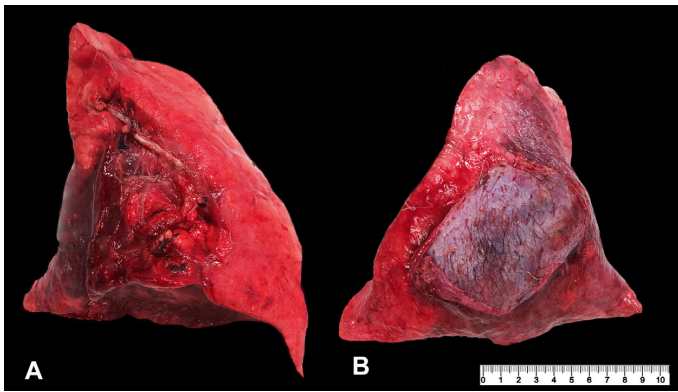


Figure 4. Gross view of the left inferior pulmonary lobe. **A** - Hilar view; **B** - Pleural surface view, showing the pleural thickening adhered to the pulmonary parenchyma.



Figure 5. Gross view of the tumoral cross section showing yellowish necrotic areas.

The histology showed extensive foamy histiocyte infiltration, necrotic areas surrounded by granulomas with epithelioid histiocytes and multinucleated giant cells besides the presence of numerous round birefringent structures with a peripheral halo resembling fungus. The grocott and mucicarmin stains were positive and diagnosed the structure as *Cryptococcus sp* (Figure 6). Thus, the final diagnosis was pulmonary cryptococcoma in an immunocompetent host. Brain computed tomography was normal, CD4 count was 1200 cells/mm³ and the cryptococcal antigenemia was positive (quantitative determination was not performed), which pointed towards treatment with fluconazole.

DISCUSSION

Cryptococcus sp is an encapsulated fungus that may cause disease either in immunosuppressed or immunocompetent patients. The most pathogenic species are represented by *C. neoformans* and *C. gattii*; the former has a worldwide distribution infecting both immunocompetent and immunosuppressed hosts, while the latter is more prevalent in tropical and subtropical regions of the globe infecting mostly the immunocompetent hosts.¹⁻³ In Brazil, *Cryptococcus neoformans* infections predominate the south and southeast regions, mostly associated with HIV infected patients, while *Cryptococcus gattii* predominates the north and northeast Brazilian states without evident association with immunosuppression.⁴

Cryptococcosis is more commonly seen in immunocompromised individuals, such as those with impaired cellular immunity like the HIV-infected patients, post-transplanted, chronic users of corticosteroids and/or immunosuppressant drugs or those patients with hematologic malignancies, sarcoidosis, or tuberculosis.^{3,5,6} Among the patients with cryptococcosis without a known cause of immunosuppression, some impairment in the lymphocyte response to *Cryptococcus sp* as well as low CD4 count has been observed.¹

The fungus, usually found in domestic dust, decaying wood, or bird droppings (notably pigeons), enters the host by the inhalation of yeast spores. The yeast's thick capsule inhibits the phagocytosis, thereby facilitating the pulmonary and blood stream invasion, and therefore spreads to different organs.^{4,7} The clinical features vary from asymptomatic infection to life-threatening disease.³ Although the respiratory tract is the portal of entry, the central nervous system (CNS) is the site that is mostly involved⁵ possibly presenting as cerebral cryptococcoma, meningitis, or meningoencephalitis. The lungs, eyes, prostate, osteomuscular system, skin, and mucosa represent other sites that could possibly be involved.^{1,4} The vast majority of immunocompetent patients present isolated pulmonary cryptococcosis.⁸ Among them, one-third are symptomless and are diagnosed incidentally when a chest x-ray is undertaken for any other purpose. However, when symptoms occur, they are represented by fever, weight loss, dyspnea, cough, mucoid sputum, hemoptysis, and chest pain.^{3,4,8} The differential diagnosis between the presentation form of the pulmonary nodules or masses involve primary or metastatic pulmonary neoplasia, granulomatous diseases

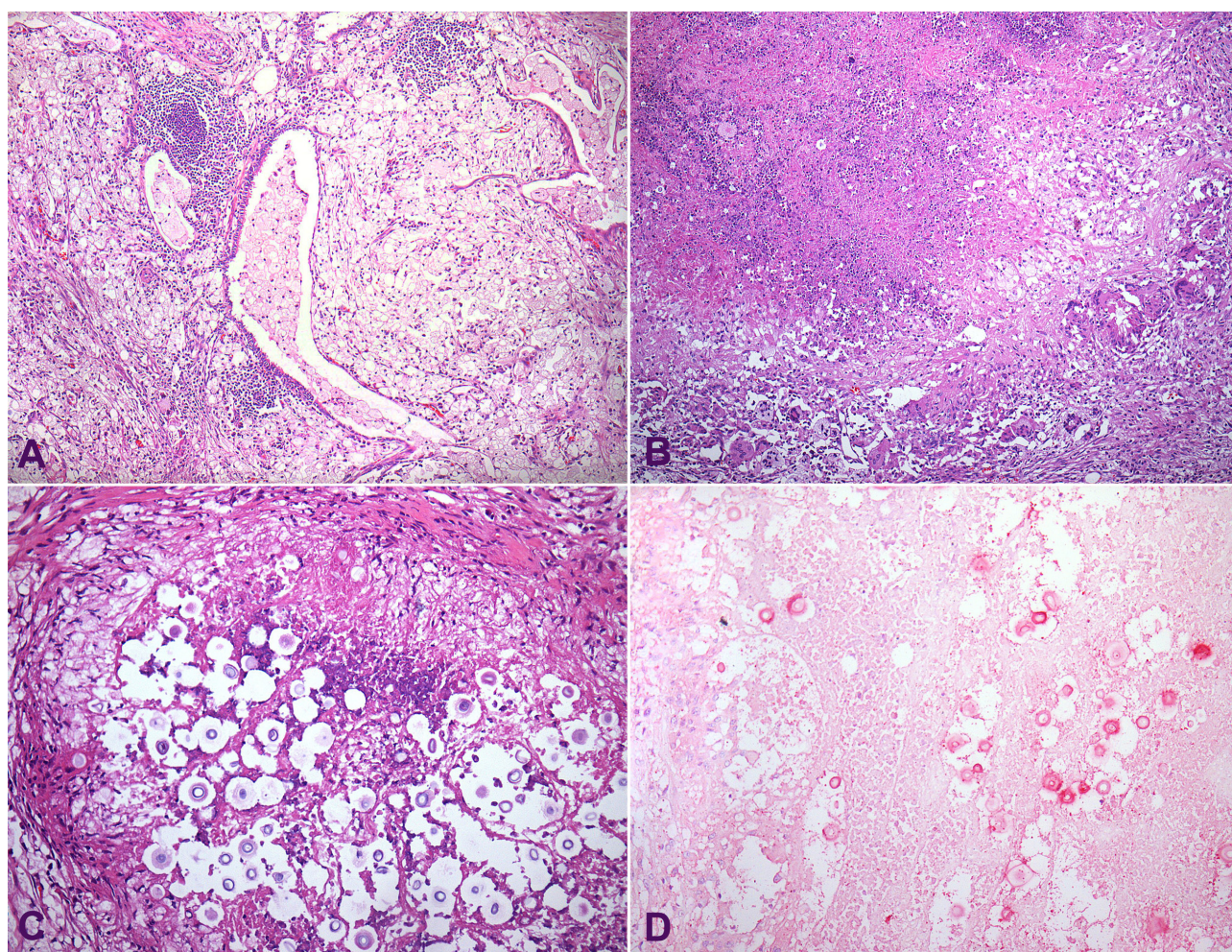


Figure 6. **A** - Pulmonary parenchyma showing a terminal bronchiole with chronic inflammatory infiltrate and dense histiocytic infiltration replacing the alveoli (H&E, 100X); **B** - Necrotic area surrounded by granulomas with epithelioid histiocytes and multinucleated giant cells (H&E, 100X); **C** - Detail of a necrotic area with presence of numerous round birefringent structures with a peripheral halo characteristic of *Cryptococcus sp.* (H&E, 400X); **D** - Mucicarmine staining positive decorating the capsule of the *Cryptococcus sp.* yeasts (400X).

of the lung, such as fungal or mycobacterial infections and septic embolization.^{7,9}

Imaging findings vary according to the length of the disease and the host immune response.⁹ Well-circumscribed, non-calcified, non-cavitated, multiple or single nodules, unilateral or bilateral, usually subpleural within the inferior lobes are the most common radiologic finding among the immunocompetent patients,¹⁰ unlike the imaging findings of the immunocompromised patients that seem to present predominantly interstitial and alveolar opacities.^{10,11} These nodules usually measure between 0.5 cm and 4 cm. Although already described, the lung masses are less common.¹² However, a Brazilian study showed that pulmonary masses were the most frequent finding (64.2%), followed by nodules (35.7%).¹³ Pulmonary consolidation, pleural effusions, lymphadenopathy, or cavitation were rarely detected on radiography of immunocompetent patients.^{10,11,14}

Diagnosis can be made by direct research of the fungus or the cryptococci antigen in the sputum and/or bronchoalveolar lavage. The demonstration of the fungus may be done in the histopathological examination of biopsy specimens or in BAL by India ink, Grocott-Gomori, mucicarmine, PAS, and alcian blue stainings. In our patient, the BAL research was negative for both the direct examination and cultures of the specific pathogens, but the histopathological examination yielded the diagnosis with the aid of Grocott and mucicarmine stainings.^{1,3} Definite diagnosis was made with the isolation of the pathogen in culture media. Although a negative result does not rule out the diagnosis (sensitivity of 50% in pulmonary forms)⁴ the serum antigenemia determination is still used with diagnostic purposes. In our case, the serum antigenemia was used to reinforce the necessity of the systemic treatment with fluconazole.

A thorough investigation of the CNS involvement with neuroimaging and cerebrospinal fluid examination is advisable whenever the diagnosis of pulmonary cryptococcosis is done in the presence of serum antigenemia greater than 1:512 (sensitivity of 95%),⁴ risk factors for disseminated disease, or if the patient presents any immunodeficiency.^{3,15} In the case reported herein, the patient did not present any neurologic sign or symptom and the neurological examination was normal. She did not present any known immunodeficiency, neurological examination was normal as well as the brain CT and the CD4 count was normal; reason why we did not go on investigating the CNS involvement.

The treatment schedule and its duration depend on the clinical manifestation as well as on the patient's immune system integrity.³ Even among the asymptomatic cases, the treatment reduces the dissemination risk,⁷ mainly among the immunosuppressed patients.

The infection confined to the respiratory tract should be treated with fluconazole 200 mg/daily¹⁵ for 6–12 months, either for immunocompetent or for immunocompromised patients.³ The pulmonary forms should always be treated in the presence of symptomatic and/or disseminated disease, and if the *Cryptococcus sp* antigenemia results are positive and/or if the patient presents any sort of immunosuppression.¹⁶

Asymptomatic, or patients with disease restricted to the lungs, as well as those patients whose lesions have been resected, can be thoroughly followed up (with clinical and laboratory examinations) without antifungal treatment. However, this approach is controversial, since some authors advocate specific therapy for pulmonary forms in all patients, regardless of the presence of symptoms.¹⁷

Currently, surgical treatment is not routinely recommended for pulmonary infection, except in the case of failure of clinical treatment or for the pseudotumoral lesions and exudative pleural effusion.¹⁶ The diagnosis of some cases of cryptococcosis is only made after histopathological examination of the surgical specimen (pulmonary mass), undertaken in the pursuit of neoplasia. In these patients, the total resection can be considered therapeutic,¹⁸ as aforementioned.

Mild-to-moderate infection confined to the respiratory tract may be treated with fluconazole from 200 to 400 mg/day for 6 to 12 months for both immunocompetent and immunocompromised patients. The severe cases, with CNS involvement or disseminated

disease, should be treated with amphotericin and flucytosine, followed by a consolidation treatment phase with fluconazole for 12 months in immunocompetent patients and for an undetermined period, or until immune reconstitution in immunosuppressed patients. The persistent positive antigenemia should not be considered as criteria for treatment extension.

We emphasize the importance to consider the cryptococcoma among the differential diagnosis of pulmonary masses, mainly in immunocompetent patients. Although cryptococcosis is highly associated with immunosuppression, the incidence among the immunocompetent patients is not negligible, and therefore should never be missed.

REFERENCES

1. Singh R, Joshi D, Gupta A, Gangane N. Large pulmonary cryptococcoma and cryptococcal meningitis in an immunocompetent patient: a case report. *Diagn Cytopathol*. 2010;38(12):929-31. <http://dx.doi.org/10.1002/dc.21345>. PMID:20301210.
2. Pisarevsky AA, Larriera A, Cean P, Petrucci EA. Pulmonary cryptococcoma with involvement of the chest wall in an immunocompetent patient. *Medicina (B Aires)*. 2010;70(2):166-8.
3. Goldman JD, Vollmer ME, Luks AM. Cryptococcosis in the immunocompetent patient. *Respir Care*. 2010;55(11):1499-503. PMID:20979679.
4. Coura JR. *Dinâmica das doenças infecciosas e parasitárias*. 2nd ed. São José: Guanabara Koogan; 2013. p.1250-60.
5. Ho CL, Chang BC, Hsu GC, Wu CP. Pulmonary cryptococcoma with CD4 lymphocytopenia and meningitis in an HIV-negative patient. *Respir Med*. 1998;92(1):120-2. [http://dx.doi.org/10.1016/S0954-6111\(98\)90043-9](http://dx.doi.org/10.1016/S0954-6111(98)90043-9). PMID:9519236.
6. Kebede T, Reda N. Pulmonary cryptococcoma mimicking pulmonary malignancy in an immunocompetent adult: a case report. *Ethiop Med J*. 2012;50(3):275-8. PMID:23409412.
7. Ahsanuddin AN, Williams HJ. Pathologic quiz case: solitary lung nodule in a 77-year-old male smoker. Pulmonary cryptococcoma. *Arch Pathol Lab Med*. 2003;127(12):1631-2. PMID:14632561.
8. Nadrous HF, Antonios VS, Terrell CL, Ryu JH. Pulmonary cryptococcosis in nonimmunocompromised patients. *Chest*. 2003;124(6):2143-7. PMID:14665493.
9. Huang CJ, Yang MC, Ueng SH. Large cryptococcoma mimicking lung cancer in an HIV-negative, type 2 diabetic patient. *J Thorac Imaging*. 2005;20(2):115-7.

- <http://dx.doi.org/10.1097/01.rti.0000154073.21571.77>. PMID:15818212.
10. Khoury MB, Godwin JD, Ravin CE, Gallis HA, Halvorsen RA, Putman CE. Thoracic cryptococcosis: immunologic competence and radiologic appearance. *AJR Am J Roentgenol*. 1984;142(5):893-6. <http://dx.doi.org/10.2214/ajr.142.5.893>. PMID:6609567.
 11. Rozenbaum R, Gonçalves AJR. Clinical epidemiological study of 171 cases of cryptococcosis. *Clin Infect Dis*. 1994;18(3):369-80. <http://dx.doi.org/10.1093/clinids/18.3.369>. PMID:8011818.
 12. Barbosa AT, Colares FA, Gusmão ES, Barros AA, Cordeiro CG, Andrade MC. Criptococose pulmonar isolada em paciente imunocompetente. *J Bras Pneumol*. 2006;32(5):476-80. <http://dx.doi.org/10.1590/S1806-37132006000500016>. PMID:17268753.
 13. Silva ACG, Marchiori E, Souza AS Jr, Irion KL. Pulmonary cryptococcosis: computed tomography findings. *Radiol Bras*. 2003;36(5):277-82. <http://dx.doi.org/10.1590/S0100-39842003000500005>.
 14. Lindell RM, Hartman TE, Nadrous HF, Ryu JH. Pulmonary cryptococcosis: CT findings in immunocompetent patients. *Radiology*. 2005;236(1):326-31. <http://dx.doi.org/10.1148/radiol.2361040460>. PMID:15987984.
 15. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2010;50(3):291-322. <http://dx.doi.org/10.1086/649858>. PMID:20047480.
 16. Moretti ML, Resende MR, Lazéra MS, Colombo AL, Shikanai-Yasuda MA. Guidelines in cryptococcosis--2008. *Rev Soc Bras Med Trop*. 2008;41(5):524-44. PMID:19009203.
 17. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. *Clin Infect Dis*. 2000;30(4):710-8. <http://dx.doi.org/10.1086/313757>. PMID:10770733.
 18. Mitchell DH, Sorrell TC. Pancoast's syndrome due to pulmonary infection with *Cryptococcus neoformans* variety *gattii*. *Clin Infect Dis*. 1992;14(5):1142-4. <http://dx.doi.org/10.1093/clinids/14.5.1142>.

Conflict of interest: None

Submitted on: March 11, 2015

Accepted on: April 21, 2015

Correspondence

Lorena Silva Laborda

Hospital Universitário - Divisão de Clínica Médica, Universidade de São Paulo

Av. Professor Lineu Prestes, 2565 - Cidade Universitária - São Paulo/SP – Brazil

CEP: 05508-000

Phone: +55 (11) 3091 9275

E-mail: lorilaborda@uol.com.br