

# Original Article

## Chronic pulmonary histoplasmosis mimicking tuberculosis\*

GISELA UNIS<sup>1</sup>, LUIZ CARLOS SEVERO<sup>2</sup>

### ABSTRACT

**Objective:** To evaluate cases of chronic pulmonary histoplasmosis diagnosed in recent years at the Complexo Hospitalar Santa Casa in Porto Alegre, in the state of Rio Grande do Sul, Brazil. **Methods:** Cases diagnosed at the Santa Casa Hospital Complex within the last 25 years were reviewed. Four cases in which the diagnosis was made through histopathological analysis or culture and confirmed by with serologic testing are described. Cases from the Brazilian literature are also discussed. **Results:** The principal clinical manifestations were cough, dyspnea, fever, anorexia and weight loss. Among the radiological findings were emphysema, cystic cavities, bronchiectasis and pleural thickening. All patients had an epidemiological history of contact with chicken feces. One of the patients presented *Aspergillus fumigatus* colonization of cavities. **Conclusion:** Chronic pulmonary histoplasmosis must be considered in patients with chronic obstructive pulmonary disease presenting cavitary lesions of the lung, sputum smear microscopy negative for acid-fast bacilli and negative tuberculin skin test. Hemoptysis occurring in the presence of cured or fading pulmonary lesions is suggestive of *Aspergillus* colonization.

**Keywords:** Histoplasmosis/diagnosis; Histoplasmosis/drug therapy; Histoplasma/isolation & purification; Tuberculosis, pulmonary/diagnosis; Itraconazole/drug therapy; Sputum/microbiology; Diagnosis, Differential

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\* Study conducted in the Mycology Laboratory of the Santa Casa Hospital Complex, Porto Alegre (RS) Brazil.

1. Doctoral student in the Postgraduate Pulmonary Medicine Program of the Universidade Federal do Rio Grande do Sul (UFRS, Rio Grande do Sul Federal University), Porto Alegre (RS) Brasil.

2. Researcher for CNPq.

Correspondence to: Dr. Luiz Carlos Severo. Laboratório de Micologia, Hospital Santa Rita, Santa Casa-Complexo Hospitalar. Annes Dias 285. CEP 90020-090. Fax: 55 51 3214-8435. E-mail: severo@santacasa.tche.br

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## INTRODUCTION

The thermal dimorphic fungus *Histoplasma capsulatum* var. *capsulatum* causes various clinical manifestations depending on the anatomical and immunologic state of the host and on the quantity of fungal inoculum.<sup>(1-3)</sup> Chronic pulmonary histoplasmosis (CPH) is an opportunistic manifestation of the mycosis in pre-existing emphysematous air spaces of the lung parenchyma and caused by prolonged exposure to fungi. There are small amounts of fungi and limited tissue invasion. Parenchyma inflammation and the resulting necrosis and fibrosis represent an immune response of the host against the fungal antigens.<sup>(4)</sup>

In the present study, we report four new cases of CPH in the state of Rio Grande do Sul, and we review diagnostic aspects of other CPH cases published in the Brazilian literature.<sup>(5)</sup>

## METHODS

Patient charts from the archives of the Laboratório de Micologia do Complexo Hospitalar Santa Casa de Porto Alegre (Mycology Laboratory of the Santa Casa Hospital Complex in Porto Alegre) were retrospectively reviewed regarding age, gender, race, epidemiological history, origin of referral, signs and symptoms, concomitant or predisposing conditions, treatment, evolution and complications.

The criteria for the diagnosis of chronic pulmonary histoplasmosis and for the inclusion of cases in the study were: compatible clinical disease in individuals residing in the state of Rio Grande do Sul; laboratory evidence of histoplasmosis, that is, positive culture for *H. capsulatum*, histopathological findings showing fungal elements consistent with *H. capsulatum* or immunodiffusion test results revealing H or M bands; culture or histopathological evidence of *H. capsulatum* located exclusively in the lungs of patients presenting structural defects in lung anatomy.

Materials used for diagnosis were sputum, bronchoalveolar lavage fluid or lung biopsy sample. The smears on the slides were stained with silver methenamine according to the Grocott Gomori technique. Cultures were grown on Sabouraud agar (DIFCO, Detroit, MI, USA), 1% chloramphenicol (União Química Farmacêutica Nacional S.A., São Paulo, Brazil), and Mycosel® (BBL) media, processed in a model FVL, series 636 Class II biosafety laminar

flow hood (Trox do Brasil Ltda., São Paulo, Brazil), and incubated at 25°C. Cultures testing positive for *H. capsulatum* var. *capsulatum* were confirmed by the micromorphological aspect (tuberculate macroconidia), and thermal dimorphism was characterized through conversion to the yeast phase on brain heart infusion (BHI) agar at 37°C.

## RESULTS

In the present study, the clinical charts of 212 patients diagnosed with histoplasmosis over a 25-year period (1997–2002) were obtained from the archives of the Mycology Laboratory of the Santa Casa Hospital Complex. Of these, ten files were eligible for evaluation. However, four of these had to be excluded because, although there were compatible clinical and radiological criteria, laboratory confirmation revealed positive results only for the immunodiffusion test. Of the six cases found, two have previously been reported in the literature,<sup>(2)</sup> and four are reported in the present study:

CASE 1- A 69-year-old male Caucasian, resident of the city of São Leopoldo, in the state of Rio Grande do Sul (RS) and a shoemaker, was admitted to the hospital with dyspnea, productive cough, fever and weight loss. The patient had been smoking 20 cigarettes a day for 47 years and had been diagnosed with chronic obstructive pulmonary disease a long time prior. He had also recently been diagnosed with diabetes mellitus due to the chronic use of corticoids. The patient had been submitted to empirical treatment for tuberculosis for six months, even including repeated negative sputum smear microscopy for acid-fast bacilli and tuberculin tests using the Mantoux technique. The progression of symptoms led to his hospitalization.

Epidemiological history: There was a chicken coop on his property.

Imaging: Radiographic and tomographic findings indicating a mass with dense soft parts within the cavity in the upper right lobe and the post-treatment control thereof (Figure 1).

Mycological evaluation: Immunodiffusion serology was positive for *H. capsulatum*, and the M band was present; immunodiffusion was negative for *Aspergillus fumigatus*; ELISA test for antigen detection (galactomannan) was positive for *A. fumigatus*; Grocott-Gomori silver methenamine staining of the bronchoalveolar lavage fluid revealed

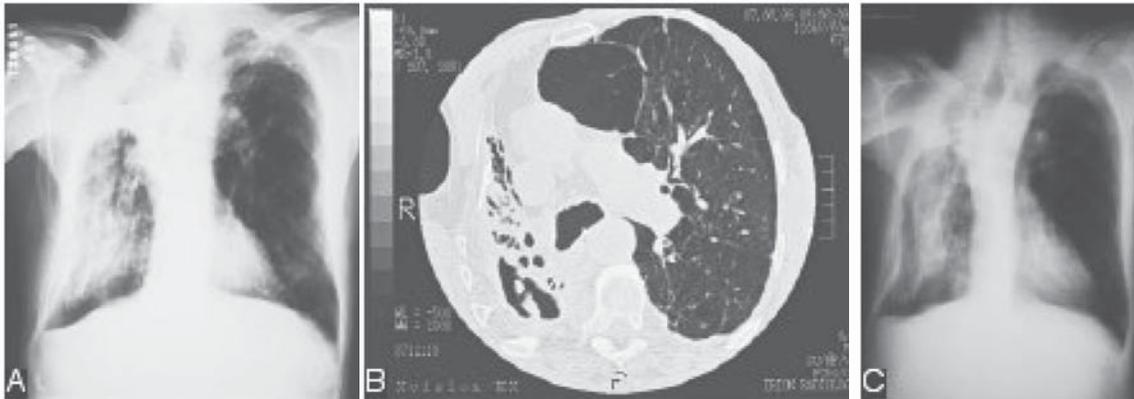


Figure 1 - A) Chest X-ray of a mass within the cavity in the upper lobe of the right lung; C) Control examination carried out two years after treatment with itraconazole, revealing the elimination of the mass within the cavity; B) Computed tomography (CT) scan showing a mass within a cystoid cavity at the lung apex, with density in the soft parts and adjacent pleural thickening, together with architectural distortion of the right upper lobe (with bronchiectasis and subtotal atelectasis), pleural thickening (with bilateral calcifications), nodules and striations (with calcifications at the left lung apex), and emphysematous areas, some of which are bilateral and clearly related to scarring.

small, budding yeast-like organisms suggestive of *H. capsulatum*; culture was negative.

Treatment and evolution: Itraconazole (100 mg/day) was given for four months. Five years later, there was exacerbation of the disease, and the patient received the same medication for an additional three years.

CASE 2 - A 63-year-old male Caucasian, resident of Novo Hamburgo, RS, a mason and a pack-a-day smoker since the age of 11 was hospitalized with progressive weight loss for nine months (14/62 kg), productive cough with hyaline sputum, progressive dyspnea, anorexia, asthenia and fever. The patient reported no hemoptysis, night sweats or chest pain. Symptoms began nine months prior to hospitalization. Physical examination revealed the patient was emaciated, dehydrated and pale. Three months later, the patient was discharged without a conclusive diagnosis and was treated for symptoms of chronic obstructive pulmonary disease. Due to worsening of clinical symptoms, the patient was rehospitalized eight months later for a second diagnostic investigation. Several sputum smear tests were carried out, and all were negative for acid-fast bacilli.

Epidemiological history: Some years prior, the patient had participated in the demolition of an old chicken coop, where bats resided.

Imaging: Areas of consolidation of the axillary subsegments of the right lung, shown in Figure 2, as well as control of the evolution and the tomographic imaging.

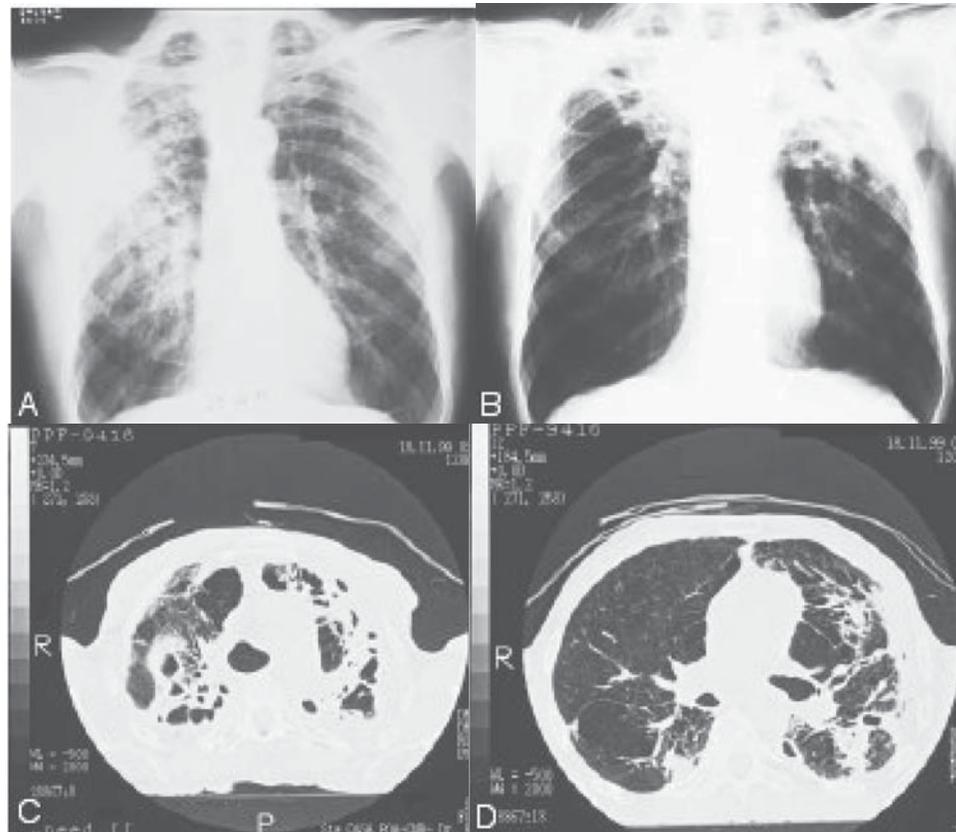
Mycological evaluation: Immunodiffusion serology was positive for *H. capsulatum*, and the M band was present; immunodiffusion was negative for *A. fumigatus*; sputum staining was negative, and Grocott-Gomori silver methenamine staining of the biopsy sample was positive for *H. capsulatum*; the punch-biopsy sample of the lung revealed chronic inflammation in the lung parenchyma with accentuated fibrosis and a small focus of epithelioid granuloma with caseous necrosis; culture was positive for *H. capsulatum*.

Treatment and evolution: the patient was treated with itraconazole (200 mg/day); the patient regained his initial weight and was submitted to 18 months of treatment; the patient presented significant clinical improvement, and the antifungal treatment was suspended.

CASE 3 - A 53-year-old Caucasian male, resident of Sapucaia do Sul (RS), a security guard and pack-a-day smoker was hospitalized due to persistent fever, night sweats and weight loss (19 kg/3 months). Despite the fact that multiple sputum and bronchoalveolar lavage fluid smear tests were negative for acid-fast bacilli, the patient was submitted to empirical treatment for tuberculosis, to no effect.

Epidemiological history: The patient had been in contact with chicken droppings while working in an herb garden.

Imaging: Radiographic and tomographic aspects are shown in Figure 3.



**Figure 2** - A) Chest X-ray showing areas of consolidation in the axillary subsegments of the right lung. B) Evolution assessment seven months later revealed complete atelectasis in the upper right lobe (including elevation of the corresponding pulmonary hilum), which caused apparent regression of the areas of consolidation of axillary subsegments, which might be located in the upper lobe, presently showing atelectasis. Areas of consolidation with necrosis were revealed in the upper left hilum, combined with pleural thickening, atelectatic retraction (with elevation of the corresponding hilum) and areas of scarring-related emphysema. C) Computed tomography (CT) scan showing fibroatelectatic retractions of the upper lobes with cystoid cavities and bronchiectasis and areas of atelectasis with consolidation of the parenchyma adjacent to dilated bronchial airways, with evident cranial predominance; D) Computed tomography (CT) scan showing that all cavities presented anfractuous walls (some with minor septations), together with bilateral pleural thickening (mainly apical), elevation of pulmonary hila, areas of scarring-related emphysema and no ostensive evidence of enlarged lymph nodes in the mediastinum.

**Mycological evaluation:** Immunodiffusion serology was positive for *H. capsulatum*, and the M band was present; mycological examination of fresh sputum was negative; Grocott-Gomori silver methenamine staining of the sputum smear revealed small oval budding yeast-like organisms suggestive of *H. capsulatum*; sputum culture was negative for *H. capsulatum* on Sabouraud agar and positive for *H. capsulatum* on Mycosel®.

**Treatment and evolution:** The patient was given ketoconazole (400 mg/day) for a month, followed by itraconazole (100 mg/day) for nine months.

**CASE 4** - A 38-year-old Caucasian male, a resident of Viamão, RS and a 10-cigarette-a-day smoker,

presented with a cough (including expectoration) and asthenia for three months.

**Epidemiological history:** Contact with a chicken coop. **Imaging:** Chest X-ray revealed fibronodular lesions, atelectasis and right-sided apical pleural thickening.

**Mycological evaluation:** Immunodiffusion serology was positive for *H. capsulatum*, and the M band was present; mycological test of fresh sputum was negative; Grocott-Gomori silver methenamine staining of the sputum smear revealed small oval budding yeast-like organisms suggestive of *H. capsulatum*; sputum culture was negative for *H. capsulatum*.

**Treatment and evolution:** Ketoconazole (200

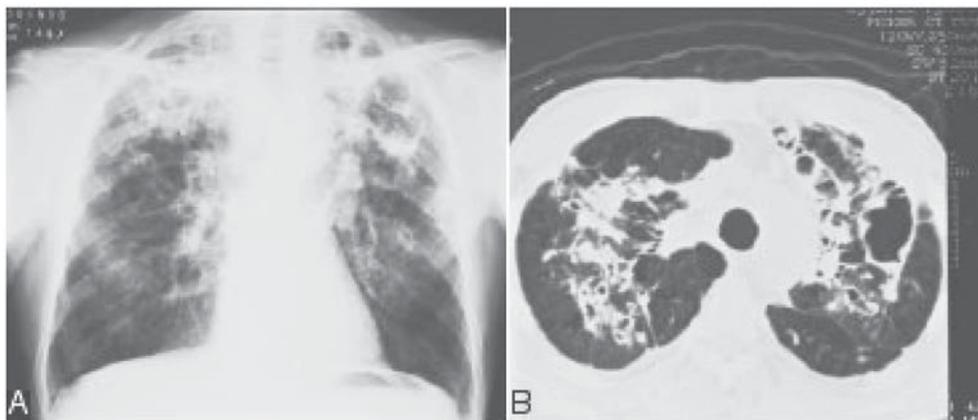


Figure 3 - A) Chest X-ray showing poorly-defined opacities and possible cavities, predominantly in the upper lobes; B) Computed tomography (CT) scan showing structural remodeling of both lungs, especially in the upper lobes, with areas of consolidation and atelectasis (mainly distributed along the axial interstices), as evidenced by bronchiectasis, cystoid cavities, parenchyma opacity and scarring-related emphysematous bullae. On the left side, cavities were larger and some contained septations or intracavitary vegetation. No ostensive lymph node enlargement was seen, although some lymph nodes were slightly more enlarged than usual.

mg/day) was prescribed, and the patient was discharged. He did not return to the hospital.

Table 1 shows the diagnostic findings of the patients in this study, comparing them with the cases previously described in the literature. Table 2 shows demographic data, clinical profiles, treatment and evolution of the cases evaluated in the present

study, as well as of those previously described.

## DISCUSSION

The first extensive study of CPH was conducted in tuberculosis sanatoriums involving patients suspected of being infected with tuberculosis.<sup>(6)</sup> Most of the patients were initially submitted to treatment with tuberculostatic drugs prior to being diagnosed with mycosis, as was shown in 12 (92%) of the 13 cases of CPH with cavitation reported in another study.<sup>(7)</sup> We discovered that, in Brazil, the proportion of patients submitted to empirical treatment for tuberculosis (50%) remains high, indicating that we tend to direct the diagnosis towards tuberculosis, which delays recognition of the clinical manifestation of mycosis, consequently allowing its progression.

The initial injury consists of interstitial pneumonitis, with frequent emphysematous air spaces, especially of the centrilobular or bullous type.<sup>(4)</sup> The colonization of these air spaces produces fluids rich in fungal antigens that cause segmental pneumonitis due to bronchial dissemination. Later-stage injury is essentially characterized by a preexisting area of cavitation. Infected cavities tend to foster disease progression, with pulmonary fibrosis and exacerbation of respiratory insufficiency.<sup>(4)</sup> The rapid change in the pattern of the lung parenchyma injury seen on the Case-2 chest X-ray is attributable

TABLE 1

Case	Sample	Mycological diagnosis		
		GMS	Culture	IDh
LITERATURE				
1(13)	Sputum	+	+	H, M
2(13)	Sputum	+	+	H, M
3(13)	Sputum	+	+	H, M
4(5)	Sputum	+	+	NF
	BAL		+	+
5(5)	Biopsy	+	+	
	Sputum	+	+	M
	Biopsy	+	+	
PRESENT SERIES				
6	Sputum	-	-	M
(case 1)	BAL	+	-	
7				
(case 2)	Sputum	-	-	M
	Biopsy	+	+	
8				
(case 3)	Sputum	+	+	M
9				
(case 4)	Sputum	+	-	M

TABLE 2

Chronic pulmonary histoplasmosis with cavitation in Brazil: clinical manifestations, comorbidities, treatment and evolution

Case	Age, Gender	ET	Symptoms	Treatment	Evolution; co-morbidities
<b>LITERATURE</b>					
1(13)	64, M	No	fever, productive cough	Ketoconazole - 6m Itraconazole - 7m	Epidermoid lung carcinoma; Death
2(13)	58, M	No	fever, productive cough	Amphotericin B - 1g Ketoconazole - 6m Itraconazole - 22m	Death
3(13)	74, M	Yes	productive cough, chest pain, weight loss	Amphotericin B - 1g Itraconazole	No evolution
4(5)	62, M	No	productive cough, hemoptysis, fever, anorexia, dyspnea, weight loss	Ketoconazole - 7m Amphotericin B - 1g	fungus ball caused by <i>A. fumigatus</i> ;
5(5)	64, M	Yes	productive cough, fever, dyspnea, weight loss, night sweats	Ketoconazole - 30m Itraconazole - 18m Itraconazole - 13m	postoperative death Cure; fungus ball caused by <i>A. fumigatus</i>
<b>PRESENT SERIES</b>					
6 (case 1)	69, M	Yes	dyspnea, productive cough, fever, weight loss	Itraconazole - 4m Itraconazole - 36m	Cure; fungus ball caused by <i>A. fumigatus</i>
7 (case 2)	63, M	No	dyspnea, productive cough, fever, anorexia, asthenia, weight loss	Itraconazole - 18m	Cure
8 (case 3)	53, M	Yes	fever, night sweats, weight loss	Ketoconazole - 1m Itraconazole - 9m	Cure

ET: empirical treatment (for tuberculosis); M: male; m: months

to fibrotic retraction around the emphysematous bulla, which is a pattern characteristic of pulmonary histoplasmosis.<sup>(4)</sup>

Due to its high sensitivity, the immunodiffusion test is a good trial method for CPH, presenting positive results in virtually 100% of cases in which the diagnosis is later confirmed.<sup>(8)</sup> Diagnostic confirmation is achieved through isolation of *H. capsulatum* in sputum or bronchoscopy samples in 60% to 85% of the cases if multiple samples are tested.<sup>(9)</sup> For definitive confirmation of the diagnosis, clinical samples should be submitted to Grocott-Gomori silver methenamine staining and seeded on selective culture media.<sup>(8)</sup>

In Case 2, a four-month long investigation in a tertiary-care hospital did not result in an etiologic diagnosis, despite the fact that an invasive approach, fiberoptic bronchoscopy with transbronchial biopsy, was employed. Some explanations for that are that the biopsy sample was not submitted to special staining (with silver methenamine according to the Grocott-Gomori technique), which is crucial for the visualization of minor fungal elements, nor was the bronchoalveolar lavage material submitted to culture

on selective media during the first diagnostic investigation. Mycosel® and the similar product, Mycobiotic®, are selective media recommended for the isolation of dermatophytes. The inclusion of an antibiotic (chloramphenicol) and of an antifungal (cycloheximide) prevents the contamination of bacteria and fungi, allowing *H. capsulatum*, which has a slower growth rate, to be isolated.<sup>(10)</sup>

The recommended treatment for CPH is the administration of amphotericin B for severe cases (those requiring hospitalization), and itraconazole for mild and moderate cases.<sup>(11)</sup> Regardless of the antifungal used, relapse may occur. In patients treated with itraconazole, especially if the drug is used for periods shorter than the currently recommended 12 to 24 months, relapse rates can range up to 15%.<sup>(11)</sup> Patients in whom fungus ball is suspected and who present negative results on immunodiffusion tests may be submitted to serologic triage using the ELISA method for antigen detection.<sup>(12)</sup>

Only thirteen cases of CPH have been reported in Brazil.<sup>(5)</sup> Of these, five were CPH with cavitation: three occurring in the state of Rio de Janeiro,<sup>(13)</sup> and two in the state of Rio Grande do Sul.<sup>(5)</sup> These two states

are recognizably endemic for histoplasmosis, presenting high rates of histoplasmin skin test positivity (93% and 89%, respectively),<sup>(14-15)</sup> and the fungus can be easily isolated from the soil.<sup>(16-17)</sup> A hypothetical diagnosis of CPH should be considered for patients with chronic obstructive pulmonary disease and exacerbation of symptoms whose epidemiologic history indicates the handling of soil contaminated with chicken droppings or bat guano. Serologic evaluation is extremely useful for diagnostic triage, as was observed in the present case study.

Cases of histoplasmosis preceding or concomitant to fungus ball have been reported, typically require immediate surgical treatment.<sup>(18)</sup> In most cases of CPH with cavitation, pulmonary function has already been affected and, due to the presence of emphysematous bullae and fibrosis, and there are no cleavage plans for surgical excision. In such cases, surgery may accelerate the incidence of evident pulmonary insufficiency and mortality.<sup>(4)</sup> Itraconazole is a treatment alternative.<sup>(19)</sup> Of the Brazilian patients, three were diagnosed with fungus ball (Table 2), and two of these presented fungal colonization resulting from active histoplasmosis. Only one patient underwent surgery, which led to the death of that patient.<sup>(5)</sup>

We would like to highlight the fact that the presence of cavitory lesions in the upper lobes of patients with chronic obstructive pulmonary disease, especially those who present negative for acid-fast bacilli sputum smear microscopy and tuberculin skin test results and reside in endemic areas, should lead to a hypothetical diagnosis of CPH. In this group of patients, only 5% of the cases are likely to be infected with tuberculosis.<sup>(20)</sup> Hemoptysis in the presence of late lesions or after the disease has been cured is indicative of *Aspergillus* colonization.

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