Mycopathologia
https://doi.org/10.1007/s11046-022-00630-z

CORRECTION

Correction to: Chronic Pulmonary Histoplasmosis in the State of Rio de Janeiro, Brazil

Domenico Capone · Bodo Wanke · Paulo Cezar Fialho Monteiro · Márcia dos Santos Lazéra · Geraldo de Noronha Andrade · Antonio Carlos Francesconi do Valle · Alejandro Marcel Hasslocher-Moreno · Alberto Thomaz Londero

Correction to: Mycopathologia (1999) 145: 75–79
https://doi.org/10.1023/A:1007016414833

In the original publication, the 7th author name was incorrectly published as "Alejandro Marcel H. Moreno". The correct name is "Alejandro Marcel Hasslocher-Moreno".

The original article has been corrected.

The original article can be found online at https://doi.org/10.1023/A:1007016414833.

D. Capone (✉)
Institute of Thoracic Diseases, IDT-UFRJ), Federal University of Rio de Janeiro, University of the State of Rio de Janeiro (UERJ), Rio Grande do Sul, Brazil
e-mail: wanke@dcc001.cict.fiocruz.br

B. Wanke · P. C. F. Monteiro · M. dos Santos Lazéra
Laboratory of Medical Mycology, Evandro Chagas Hospital, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil

G. de Noronha Andrade
Institute of Thoracic Diseases, Federal University of Rio de Janeiro (IDT-UFRJ), Rio Grande do Sul, Brazil

A. C. F. do Valle · A. M. Hasslocher-Moreno
Laboratory of Clinical Research, Evandro Chagas Hospital, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil

A. T. Londero
Federal University of Santa Maria, Rio Grande do Sul, Brazil

Mycopathologia **145:** 75–79, 1999.

Chronic pulmonary histoplasmosis in the State of Rio de Janeiro, Brazil

Domenico Capone[1], Bodo Wanke[2], Paulo Cezar Fialho Monteiro[2], Márcia dos Santos Lazéra[2], Geraldo de Noronha Andrade[3], Antonio Carlos Francesconi do Valle[4], Alejandro Marcel H. Moreno[4] & Alberto Thomaz Londero[5]

[1]*Institute of Thoracic Diseases of the Federal University of Rio de Janeiro (IDT-UFRJ) and University of the State of Rio de Janeiro (UERJ), Brazil;* [2]*Laboratory of Medical Mycology, Evandro Chagas Hospital, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil;* [3]*Institute of Thoracic Diseases of the Federal University of Rio de Janeiro (IDT-UFRJ), Brazil;* [4]*Laboratory of Clinical Research, Evandro Chagas Hospital, Oswaldo Cruz Institute, FIOCRUZ, Rio de Janeiro, Brazil;* [5]*Federal University of Santa Maria, Rio Grande do Sul, Brazil*

Received 10 February 1999; accepted in revised form in 14 July 1999

Abstract

Three cases of chronic pulmonary histoplasmosis affecting aged patients with chronic obstructive pulmonary disease are reported. They had a history of recurrent episodes of respiratory infection and presented radiological lung lesions inducing a misdiagnosis of chronic pulmonary tuberculosis of the adults. The diagnosis of histoplasmosis, suggested by the immunodiffusion test and the detection of yeastlike cells in smeared and stained sputum, was confirmed by the isolation and identification of *Histoplasma capsulatum* var. *capsulatum* in selective media. The treatment was carried out with amphothericin B and ketoconazole or itraconazole. Clinical, radiologic, mycologic and serologic improvement was obtained in all the patients. However, relapses occurred within a period of 1 to 18 months after the interruption of the treatment. Mycological diagnosis and the difficulties observed in the tretament were discussed. In addition data on the epidemiology of histoplasmosis in the state of Rio de Janeiro, Brazil, were presented.

Keywords: chronic pulmonary histoplasmosis, *Histoplasma capsulatum* var. *capsulatum*, histoplasmosis capsulati, mycological diagnosis

Abbreviations: CPH = chronic pulmonary histoplasmosis; COPD = chronic obstructive pulmonary disease; ID = double imumnodiffusion test

Introduction

Classical histoplasmosis or histoplasmosis capsulati is a systemic mycosis caused by the dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*. Chronic pulmonary histoplasmosis (CPH) affects adults, usually heavy smokers, with a lung structural defect. A centrilobular or bullous emphysema is usually the anatomic substratum for the establishment of the infection. CPH is an organ specific manifestation of histoplasmosis, commonly associated with a subjacent chronic obstructive bronchopulmonar disease (COPD) [1, 2]. Early lesion usually is an apical or subapical infiltration which progress to a persistent cavitation [3]. Early and later, clinical and radiological manifestations of CPH are very similar to those of chronic pulmonary tuberculosis, with which CPH is frequently misdiagnosed [1, 3].

Three cases of CPH affecting residents in the city of Rio de Janeiro will be herein reported. Formerly these cases were part of a thesis [4]. In addition, we will comment on the epidemiology of histoplasmosis in the state of Rio de Janeiro, Brazil.

Case reports

Case 1

This patient was a 64 year-old man, born and resident in the city of Rio de Janeiro. Heavy smoker since the age of 14, he presented COPD.

In 1986, the patient sought medical attention for recurrent episodes of respiratory infection, during which he had slight fever and cough with yellowish expectoration. On the basis of a positive immunodiffusion test (ID) and the isolation of *H. capsulatum* var. *capsulatum* from the sputum a diagnosis of histoplasmosis was established. He was treated with ketoconazole (400 mg/day) with improvement. Nevertheless, in the sixth month of treatment he presented an acute episode of respiratory infection. For that reason he was referred to the Hospital Evandro Chagas (FIOCRUZ).

At admission the patient complained of fever, cough and expectoration. On physical examination crackles were heard in both lungs. A chest X-ray revealed gross reticulo nodular lesions in both lungs, with a predominance in the middle and lower right lung, and a small cavity in the right upper lobe (Figure 1a). Laboratory findings were as follows: tuberculin skin test negative; no acid fast bacilli were detected in 13 sequential Ziehl-Neelsen stained smeared sputum; no growth of *Mycobacterium* spp were obtained in 6 attempts for culturing them; serology anti-HIV was negative; no reactor to histoplasmin skin test; precipitin bands **M** and **H** against *H. capsulatum* var. *capsulatum* antigen were obtained in ID test (titer 1:32). With these results sputum samples were smeared and stained by Gomori-Grocott technique, plated on Mycobiotic agar (Difco) incubated at room temperature, and inoculated intraperitoneally into mice. Small oval yeast-like cells compatible with *H. capsulatum* var. *capsulatum* were detected in microscopic examination of sputum smears (Figure 1b). Isolates obtained on Mycobiotic agar were subcultured into BHI agar and incubated at 37 °C, in order to identify *H. capsulatum* var. *capsulatum* by its dimorphic forms. The patient was treated with itraconazole (100 mg/day). For six months the disease evolved alternating periods of improvement and worsening in spite of the patient having been hospitalized several times due to cardio-respiratory problems. However, in the meantime a progressive decrease in the titers of ID test was observed and the fungus could not be disclosed in sputum.

At the 7th month a new episode of respiratory infection occurred, with exacerbation of the symptoms of COPD, in spite of the continuous treatment with itraconazole. A chest X-ray revealed an enlargement of the cavitation, expansion of fibrotic lesions and the appearence of a round consolidation in the left upper lobe. Specimens collected by bronchoscopy did not reveal malignant cells, but *H. capsulatum* var. *capsulatum* was again detected in sputum examination. For this reason amphothericin B was introduced. Four months after receiving 1 gr of the drug the sputum became negative and ID titers decrease to 1:4. After six months the patient was again readmitted complaining of epigastric pain, intestinal bleeding, soon followed by shock and death. Necropsy revealed a perforated peptic ulcer involving the pancreas, an epidermoid carcinoma in the left upper lobe and chronic granulomatous lesions of the lung. In cut sections of this lesion acid fast bacilli were detected but no fungal elements could be disclosed.

Case 2

The patient was a 58 year-old Hungarian man living in the city of Rio de Janeiro for the last 20 years. In 1988 he was referred to Evandro Chagas Hospital (FIOCRUZ) for the diagnosis of recurrent respiratory infection.

The first episode of fever and cough with yellowish expectoration occurred in 1985. A chest X-ray showed emphysema, an ill defined condensation in the right upper lobe and an infiltration in the middle third of the right lung (Figure 2a). The patient improved under therapy with antibiotics. In 1987, he presented again with fever and cough with abundant dun colored expectoration. He received cephalosporin and erythromycin with no improvement.

In 1988, at admission, the patient, a heavy smoker since the age of 15, presented symptoms and signs of COPD. Tuberculin and histoplasmin skin tests were negative. HIV serologic tests were negative. No acid fast bacilli were detected in 6 sequential sputum smears. No growth was obtained in 3 attempts of culturing *Mycobacterium* spp. ID test with histoplasmin showed **M** and **H** precipitin bands (titer 1:256). *H. capsulatum* var. *capsulatum* was disclosed in Gomori–Grocott stained sputum smears and the fungus was isolated from sputum culture. The patient was treated with ketoconazole (400 mg/day) for 6 months.

Under therapy, clinical and radiologic improvement was observed and titer of ID decreased to 1:4.

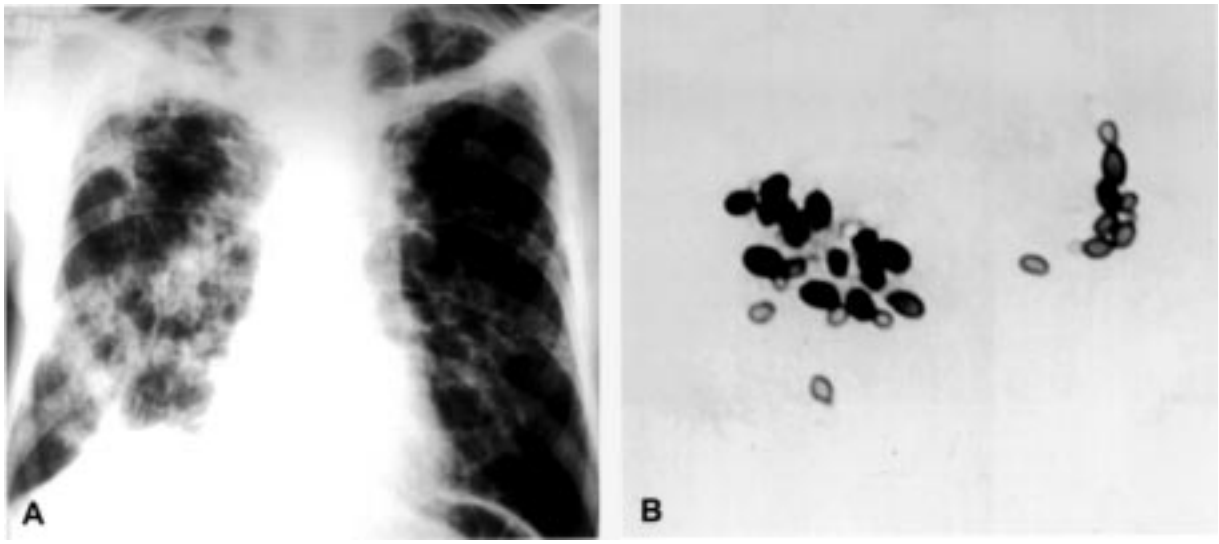

Figure 1. Case 1. (a) X-ray of the chest in PA showing reticulonodular images of both lungs, predominant in the medium and inferior fields of the right lung. (b) *H. capsulatum* var. *capsulatum* in sputum smear, Grocott's stain. ×1000.

However, in the fifth month of treatment the patient presented an exacerbation of the symptoms and chest X-ray revealed cavities and extensive fibrotic lesions in both upper lobes (Figure 2b). ID serologic titer increased, the fungus was again disclosed in sputum examination and also isolated in culture. For that reason itraconazole (100 mg/day) was introduced. At the second month of treatment a good improvement of the clinical picture and a decrease in ID titer to 1:8 were obtained, and the fungus could not be identified nor isolated from sputum. At the end of 22 months, as an outpatient in use of itraconazole, the patient died suddenly at home. No necropsy was permitted.

Case 3

A 74 year-old black man, born and resident in the city of Rio de Janeiro, sought medical attention complaining with frequent episodes of colds, cough with expectoration, chest pain and loss of weight. In 1989, with a presumed diagnosis of tuberculosis he was treated with rifampicin, isoniazid and pyrazinamide. In 1990, a chest X-ray showed emphysema, fibrotic lesions in the upper right lobe and a cavitation in the left upper lobe. Requested serological tests for pulmonary mycosis revealed **M** and **H** precipitin bands in ID with histoplasmin (titer 1:16). For this reason he was referred to the Evandro Chagas Hospital (FIOCRUZ).

On physical examination of the patient, a heavy smoker since 11 years of age, complained of symptoms and presented signs of a COPD. Laboratory findings: nonreactive to tuberculin and histoplasmin skin tests; HIV serologic test negative; no acid fast bacilli were seen in stained sputum smears (9 attempts); no *Mycobacterium* spp growth was obtained in 5 attempts to culture them; in Gomori–Grocott stained sputum smears yeast-like cells suggestive of *H. capsulatum* var. *capsulatum* were seen. The fungus was isolated and identified in culture obtained from mice inoculated intraperitoneally. With these findings amphotericin B was given for 3 months (1 g).

The patient improved clinically and serologically. Mycological investigation for *H. capsulatum* var. *capsulatum* in sputum resulted negative. However, 18 months after to stop the drug, the disease relapsed. Itraconazole (400 mg/day) was then given for 8 months, and again after stopping the drug, 9 months later, the disease relapsed. Presently as an outpatient he is under continuous itraconazole therapy since January 1995, without relapse.

Commentaries

In 1997, Severo et al. [5] reported two cases of CPH and gathered eleven cases from the Brazilian literature. Six out of these 11 cases dealt with patients residents in the state of Rio de Janeiro [4, 6, 7].

The first Brazilian case of chronic disseminated histoplasmosis and the first one of CPH were reported, respectively, in 1945 [8] and 1959 [6]. Both these patients were residents in Rio de Janeiro. The first

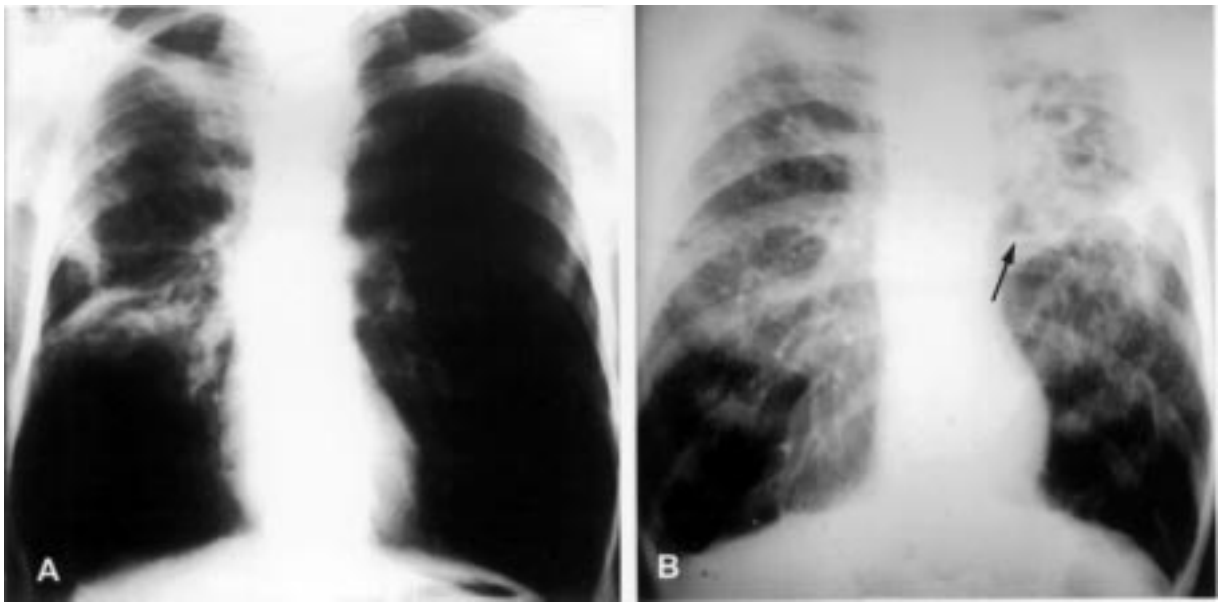

Figure 2. Case 2 – (a) Condensation of ill defined limits and non-homogenous density localized in the upper and medium third of the right lung and areas of hypertransparency in the bases. (b) Bilateral pulmonary cavities, some of them with hydroaerial levels (arrow) and extensive fibrotic barriers in the upper lobes of the lungs.

report of a microepidemy of histoplasmosis occurred in Brazil, in 1959, dealt also with native children of Rio de Janeiro [9]. Surveys with histoplasmin skin test [7,10] and the isolation of *H. capsulatum* var. *capsulatum* from the soil [7, 11] from mongrel dogs [10] and from wild animals [7, 12] point to the existence of areas of high endemicity of the mycosis in Rio de Janeiro. The fungus was also isolated from a hollow of a living tree in an avenue of the city of Rio de Janeiro [13]. In a two years period (1981–1982), Wanke [7] collected and studied 43 cases of histoplasmosis in this state. These 43 cases may be grouped in the following clinical forms: (1) 40 cases of acute pulmonary histoplasmosis (four outbreaks involving 35 individuals and 5 isolated cases), (2) two patients presenting the CPH form, and, (3) one patient with the chronic disseminated form. These data clearly demonstrate that the occurrence of CPH, as well as other clinical forms of histoplasmosis, have been underestimated.

The rarity of the diagnosis of CPH in Rio de Janeiro is mainly because histoplasmosis is not considered in the differential diagnosis of chronic pulmonary infections. Usually it has been confused as chronic pulmonary tuberculosis, due to the similarity of the clinical and radiological features of both diseases. On the other hand, laboratory diagnosis is usually requested specifically for the search of acid fast bacilli in the clinical specimens. Furthermore, useful techniques for detection, isolation and identification of small yeast-like cells of pathogenic fungi in sputum are rarely available.

With regard to the therapy, we observed that all the drugs used, ketoconazole, itraconazole, and amphothericin B, produced clinical, radiologic, mycological and serological improvement, but suspension of each of them led to a relapse of the mycosis within a period varying between I and 18 months. For this reason, the antifungal therapy in these cases probably had merely a suppressive effect. Consequently, a prolonged post-therapeutical follow-up is indispensable in order to discover a cure for CPH.

In advanced cases of CPH, like those described, the diagnosis may be accomplished by sputum examination. In all our patients COPD was a subjacent condition, and in one of them tuberculosis was associated.

In conclusion, it may be emphasized that the CPH presents clinical and radiological features as that of reinfection-type pulmonary tuberculosis of the adult. Patients with COPD and with a picture compatible with tuberculosis but with sputum negative for mycobacteria should be submitted as a routine to serological investigation for mycoses, besides mycological examination of bronchopulmonary specimens.

References

1. Goodwin RA, Owens FT, Snell JD, Hubbard WW, Buchanan RD, Terry RT, Des Prez RM. Chronic pulmonary histoplasmosis. Medicine 1976; 55: 413–452.
2. Wheat LJ, Wass J, Norton J, Kohler RB, French MLV. Cavitary histoplasmosis occurring during two large urban outbreaks. Analysis of clinical, epidemiologic, roentgenographic and laboratory features. Medicine 1984; 63: 201–209.
3. Goodwin RA, Snell JD, Hubbard WW, Terry RT. Early chronic pulmonary histoplasmosis. Am Rev Resp Dis 1966; 93: 47–61.
4. Capone D. Histoplasmose pulmonar crônica [Thesis]. Rio de Janeiro, Brazil: Federal University of Rio de Janeiro, 1992, 84 pp.
5. Severo LC, Rizzon CFC, Roesch EW, Oliveira FM, Porto NS. Chronic pulmonary histoplasmosis in Brazil: Report of two cases with cavitation diagnosed by transthoracic needle biopsy. Rev Inst Med Trop S Paulo 1997; 39: 293–297.
6. Paula A, Blundi E, McClure E, Pernambuco P. Histoplasmose pulmonar. Tratamento pela anfotericina B. Rev Serv Nac Tuberc 1959; 3: 5–10.
7. Wanke B. Histoplasmose. Estudo epidemiológico, clinico e experimental [Thesis]. Rio de Janeiro, Brazil: Federal University of Rio de Janeiro, 1985, 167 pp.
8. Duarte E. Histoplasmose. Mem Inst Oswaldo Cruz 1945; 43: 457–494.
9. Paula A. Microepidemia de histoplasmose. Rev Ser Nac Tuberc 1959, 3: 11–20.
10. Silva-Ribeiro VL, Ferreira da Cruz MF, Wanke B, Galvão Castro B. Canine histoplasmosis in Rio de Janeiro: natural and experimental infections. J Med Vet Mycol 1987; 25: 319–322.
11. Zancopé-Oliveira RM, Wanke B. Distribuição das fontes de infecção do *Histoplasma capsulatum* var. *capsulatum* em Rio da Prata – Município do Rio de Janeiro (RJ), Rev Inst Med Trop S Paulo 1987; 29: 243–250.
12. Zancopé-Oliveira RM, Wanke B. Isolamento do *Histoplasma capsulatum* de animais silvestres no município do Rio de Janeiro. Cadernos Saude Publica (Rio de Janeiro) 1986; 2: 42–52.
13. Lazéra MS. Fontes saprofíticas de *Cryptococcus neoformans* na cidade do Rio de Janeiro [Thesis]. Rio de Janeiro, Brazil: Federal University of Rio de Janeiro, 1989, 127 pp.

Address for correspondence: Domenico Capone, Rua Dois de Dezembro, 23/402, 22220-040 Rio de Janeiro, RJ Brazil
E-mail: wanke@dcc001.cict.fiocruz.br