Short Report: Co-Infection with Paracoccidioidomycosis and Human Immunodeficiency Virus: Report of a Case with Esophageal Involvement

Mariângela O. Brunaldi,* Rosamar E. F. Rezende, Sérgio Zucoloto, Sérgio B. Garcia,
José L. P. Módena, and Alcyone A. Machado

Departments of Medicine, Pathology, and Surgery, Faculty of Medicine of Ribeirão Preto,
University of São Paulo, Ribeirão Preto, Brazil

Abstract. Paracoccidioidomycosis (PCM) is a systemic and deep mycosis endemic in Latin America, especially in Brazil. In patients infected with human immunodeficiency virus (HIV), PCM can manifest with prominent involvement of the reticuloendothelial system. There are no reports in the literature of esophageal involvement by PCM in that population. We report a case of PCM with pulmonary and esophageal involvement without radiologic evidence of an esophageal-bronchial fistula in an HIV-infected patient.

Paracoccidioidomycosis (PCM) is a systemic mycosis endemic in Latin American countries, with higher prevalence in Brazil, especially in the southeastern, southern, and central-western regions.^{1,2} Patients are infected by inhaling the conidia of *Paracoccidioides brasiliensis*, a thermotolerant fungus, with the occurrence of a primary pulmonary infection.^{3,4} Infection is usually controlled by the cell-mediated immune response and is asymptomatic. However, viable forms may persist inside the healed primary lesion.⁵

In persons infected with human immunodeficiency virus (HIV), PCM occurs primarily in the juvenile form with prominent involvement of the reticuloendothelial system, although pulmonary and oral mucosa involvement, more typical of the chronic form, frequently coexist. The disease occurs mainly in patients with T CD4⁺ lymphocyte counts less than 200 cells/mm³.^{3,6,7}

There are no reports in the literature of esophageal involvement for PCM in HIV-infected patients. We report a case of pulmonary and esophageal PCM affecting an HIV-infected patient with no evidence of an esophageal-bronchial fistula or of associated skin or oral lesions and/or lymphadenopathy.

A 55-year-old, heterosexual, white man who was born and lived in the southeastern region of the state of São Paulo, Brazil, had a serologic diagnosis of HIV infection 10 years earlier. The patient reported postprandial epigastric and retrosternal pain and odynophagia of 20 days duration, daily evening fever of one-month duration, dry cough, and a weight loss of 15 kg over three 3 months. He also reported a history of treatment for pulmonary tuberculosis identified at the time of serologic diagnosis of HIV by culture of three sputum samples from which *Mycobacterium tuberculosis* was isolated.

Physical examination showed a patient in good general condition, without adenomegalies, who had hepatosplenomegaly and an inguinal hernia on the right side. A chest radiograph showed diffuse reticulonodular opacification in the upper thirds of both lungs. A rounded calcified nodule 0.8 cm in diameter was detected in the lower third of the left lung. He also showed obliteration of the left costophrenic sinus caused by a pleural reaction.

After admission to the hospital, the presence of acid-fast bacilli was tested in sputum; results were negative in three samples. The T CD4⁺ lymphocyte count was 269 cells/μL and serum HIV viral load was 219,829 copies/mL (log 5.3404). Upper digestive endoscopy showed a deep ulcer, without fibrin, in the distal third of the esophagus (Figure 1). Histologic examination of a biopsy specimen of this esophageal lesion by staining with hematoxylin and eosin showed an area of ulceration covered with a fibrin-leukocyte exudate. Mixed inflammatory infiltrate consisting of numerous neutrophils, lymphocytes, and macrophages was observed at the level of the lamina propria. There was no evidence of granulomas, but many small, rounded structures with a birefringent halo were detected throughout connective tissue (Figure 2). Staining with Gomori methenamine and silver identified the morphology of these structures and showed numerous rounded, double-walled fungal cells of various sizes, with single or multiple budding and focal rudder-shaped structures morphologically consistent with *Paracoccidioides brasiliensis* (Figure 3). Results of a test for acid-fast bacilli by using the Ziehl-Neelsen method were negative. Serum counterimmunoelectrophoresis was reactive for PCM, with titers ranging from 1:16 to 1:32, but not reactive for histoplasmosis, cryptococcosis or aspergillosis.

The patient received specific treatment for PCM, and showed remission of signs and symptoms and healing of the esophageal ulcer. Ten months later, he returned for surgical correction of the right inguinal hernia. The patient then had suture dehiscence, Fournier syndrome, bilateral pneumonia, septic shock, and died. An autopsy showed an esophagus, stomach, and small and large intestines without abnormalities. The lungs had a confluent bronchopneumonic process with a dense intra-alveolar neutrophil exudate, rare rudiments of granulomas, and occasional multinucleated giant cells. Staining with Gomori methenamine and silver showed numerous rounded fungi of various sizes amid areas of necrosis, with single or predominantly multiple budding, compatible with pulmonary PCM.

The estimated prevalence of PCM among HIV-infected persons seen at the Division of Infectious and Tropical Diseases of the University Hospital, Faculty of Medicine of Ribeirão Preto, University of São Paulo, is 1.4%, which is comparable to the prevalence of 1.5% reported for the state of Mato Grosso do Sul in the central-western region of Brazil.⁸ This prevalence is relatively low among patients with acquired immunodeficiency syndrome (AIDS) in Brazil and in other countries in South America when compared with other mycoses such as histoplasmosis and cryptococcosis. This finding may be caused

* Address correspondence to Mariângela O. Brunaldi, Departments of Medicine, Pathology, and Surgery, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil. Av. Bandeirantes, 3900, Monte Alegre, CEP 14048-900, Ribeirão Preto, São Paulo, Brazil. E-mail: m.brunaldi@usp.br

FIGURE 1. Endoscopic view of a deep ulcer in the distal third of the esophagus of the patient. This figure appears in color at www.ajtmh.org.

by other factors such as epidemiologic differences between HIV infections, which is a phenomenon in large urban centers (although the AIDS epidemic has spread to smaller cities and rural areas in Brazil), and infection by *P. brasiliensis*, which affects mainly small agricultural communities.^{4,5} Another factor is the prophylactic use of trimethoprim-sulfamethoxazole for infection with *Pneumocystis jirovecii*, which is also effective against *P. brasiliensis*.⁴ In experimental studies, Chiarella and others⁸ demonstrated an important role of CD8⁺ T cells in immunoprotection against pulmonary PCM in mice. Because patients infected with HIV have a relative increase in CD 8⁺ T cells and a decrease in CD4⁺ T cells, this factor may explain the low prevalence of PCM among patients with AIDS.

Our patient was from a town in the state of São Paulo that had mainly rural activity. Thus, PCM may have been the result

FIGURE 2. Esophageal biopsy of the patient, showing rounded fungal structure with double-refrinct walls (arrows) (hematoxylin and eosin stained, magnification $\times 1,000$) and detail of fungal structure. This figure appears in color at www.ajtmh.org.

FIGURE 3. Esophageal biopsy of the patient, showing numerous rounded fungal structures with single and multiple budding (arrows) (Gomori methenamine and silver staining, magnification $\times 400$) and detail of multiple budding. This figure appears in color at www.ajtmh.org.

of reactivation of a latent fungal infection acquired in the past and triggered by acquisition of HIV infection.⁹

Esophageal involvement by PCM is extremely rare. Reports by Oliveira and others¹⁰ and Ziliotto and others¹¹ of esophageal *P. brasiliensis* infection refer to patients not infected with HIV. Endoscopic findings reported by these investigators were stenosing and vegetating lesions suggestive of neoplasia located in the upper and middle third of the esophagus. In contrast to reports of esophageal PCM affecting immunocompetent persons, our patient had an ulcerated lesion in the distal third of the esophagus. Esophageal ulcers are important causes of morbidity among patients with AIDS. The agents most frequently observed in these lesions are cytomegalovirus, *Candida* sp., and herpes simplex virus. Infections with other fungi such as *Cryptococcus neoformans* and *Histoplasma capsulatum* are less common.¹² There are no reports in the literature of esophageal involvement by *P. brasiliensis* in HIV-infected persons.

The etiologic diagnosis of an esophageal ulcer in our patient was based on the combined results of complementary methods. Histologic examination of biopsy specimens from the esophageal ulcer after staining with hematoxylin and eosin showed rounded structures throughout connective tissue in the lamina propria. It was possible to obtain a good definition of the typical characteristics of PCM only by staining with Gomori methenamine and silver, which showed many rounded fungi of various sizes with single and multiple budding and focal rudder-shaped structures.

The differential diagnosis included *Histoplasma capsulatum* var *capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, and *Coccidioides immitis*.¹³ The multiple budding characteristic of PCM was important for the histopathologic diagnosis reached in agreement with these features. Serum counterimmunoelectrophoresis was reactive for PCM although at low titers (1:16–1:32), a feature similar to that reported by Paniago and others and probably caused by B cell dysfunction observed in HIV-infected patients.⁴ A chest radiograph showed a diffuse reticulonodular infiltrate, a change usually observed in pulmonary lesions caused by PCM, and a calcified nodular image of a residual aspect in the left lung (probably caused by previously treated pulmonary tuberculosis).

The autopsy findings showed, in addition to injuries caused by septic shock, pulmonary involvement caused by an abscessed bronchopneumonic process, which when examined histologically by staining with Gomori methenamine and silver, showed many fungal forms with morphologic characteristics identical to those observed in the esophageal biopsy specimens, and rare rudimentary granulomas intermingled with areas of necrosis, and parenchymatous hemorrhage. In our patient, the cause of death could be attributed to a combination of factors mainly caused by specific immunodeficiency associated with HIV infection, which favored the persistence of pulmonary PCM, and by the septic condition of the patient. These aspects coincide with those reported by Paniago and others, who demonstrated a high mortality caused by PCM in HIV-infected persons.⁴

Mortality data from the State Foundation of Analysis of Data of São Paulo, Brazil, during 1985–2005 showed 1,950 deaths; PCM was the cause of death in 59.7% of the cases and was an associated cause of death in 40.3%. Malignant neoplasias and AIDS were the main causes of death in which PCM was reported as an associated cause.¹⁴ Thus, similar to Morejón and others,⁵ we also believe that PCM should be classified as an opportunistic disease and included among the diseases that define AIDS in HIV-infected persons living in Latin America,⁵ although new studies are needed to corroborate these data. We conclude that PCM is a disease of great relevance in patients with HIV/AIDS in Latin America, especially in Brazil. It also shows peculiar clinical characteristics that should be considered in the possible etiology of esophageal ulcers in HIV-infected persons.

Received December 11, 2009. Accepted for publication February 11, 2010.

Authors' addresses: Mariângela O. Brunaldi, Rosamar E. F. Rezende, Sérgio Zucoloto, Sérgio B. Garcia, José L. P. Módena, and Alcyone A. Machado, Departments of Medicine, Pathology, and Surgery, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, Monte Alegre, Ribeirão Preto, São Paulo, Brazil, E-mails: m.brunaldi@usp.br, rosamarrezende@uol.com.br, szucolot@fmrp.usp.br, sbgarcia@fmrp.usp.br, jlpmoden@fmrp.usp.br, and aamachad@fmrp.usp.br.

REFERENCES

1. Shinakai-Yasuda MA, Telles Filho FQ, Mendes RP, Colombo AL, Moretti ML, 2006. Guidelines in paracoccidioidomycosis. *Rev Soc Bras Med Trop* 39: 297–310.
2. Fornajeiro N, Maluf ML, Takahachi G, Svidzinski TI, 2005. Paracoccidioidomycosis epidemiological survey using gp43, in two cities of northwestern region of Paraná, Brazil. *Rev Soc Bras Med Trop* 38: 191–193.
3. Marques SA, Robles AM, Tortorano AM, Tuculet MA, Negroni R, Mendes RP, 2000. Mycoses associated with AIDS in the Third World. *Med Mycol* 38 (Suppl 1): 269–279.
4. Paniago AM, Freitas AC, Aguiar ES, Aguiar JI, Cunha RV, Castro AR, Wanke B, 2005. Paracoccidioidomycosis in patients with human immunodeficiency virus: review of 12 cases observed in an endemic region in Brazil. *J Infect* 51: 248–252.
5. Morejón KM, Machado AA, Martinez R, 2009. Paracoccidioidomycosis in patients infected with and not infected with human immunodeficiency virus: a case-control study. *Am J Trop Med Hyg* 80: 359–366.
6. Karp CL, Auwaerter PG, 2007. Coinfection with HIV and tropical infectious diseases. II. Helminthic, fungal, bacterial and viral pathogens. *Clin Infect Dis* 45: 1214–1220.
7. Karp CL, Neva FA, 1999. Tropical infectious diseases in human immunodeficiency virus-infected patients. *Clin Infect Dis* 28: 947–963.
8. Chiarella AP, Arruda C, Pina A, Costa TA, Ferreira RCV, Calich VLG, 2007. The relative importance of CD4⁺ and CD8⁺ T cells in immunity to pulmonary paracoccidioidomycosis. *Microbes Infect* 9: 1078–1088.
9. Benard G, Duarte AJ, 2000. Paracoccidioidomycosis: a model for evaluation of the effects of human immunodeficiency virus infection on the natural history of endemic tropical diseases. *Clin Infect Dis* 31: 1032–1039.
10. Oliveira E, Goldenberg S, Rotondi AV, 1962. Blastomicose Sul-Americana do esôfago. *An Paul Med Cir* 83: 113–121.
11. Ziliotto A Jr, Kunzle JE, Takeda FA, 1980. South American blastomycosis of the esophagus. Report of a case. *Rev Inst Med Trop Sao Paulo* 22: 261–264.
12. Calore EE, Cavaliere JM, Perez NM, Campos Sales OS, Warnke KO, 1997. Esophageal ulcers in AIDS. *Pathologica* 89: 155–158.
13. Londero AT, Chandler FW, 1997. Paracoccidioidomycosis. Connor DH, Chandler FW, Schwartz DA, Manz HJ, Lack EE, eds. *Pathology of Infectious Diseases*. Stamford, CT: Appleton and Lange, 1045–1053.
14. Santo AH, 2008. Paracoccidioidomycosis-related mortality trend, state of São Paulo, Brazil: a study using multiple causes of death. *Rev Panam Salud Publica* 23: 313–324.