Case Report: Esophageal Histoplasmosis Associated with Disseminated Tuberculosis in Acquired Immunodeficiency Syndrome

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Abstract. Bacterial and fungal infections are common in acquired immunodeficiency syndrome (AIDS). Histoplasmosis is a common fungal disease in severely immunocompromised patients infected with human immunodeficiency virus (HIV) in endemic areas. In this population the most frequent form of presentation of histoplasmosis is disseminated, with the clinical manifestations being similar to those of disseminated tuberculosis. Esophageal histoplasmosis and the association of histoplasmosis with tuberculosis are infrequent. We report here a rare case of esophageal histoplasmosis associated with disseminated tuberculosis in AIDS.

INTRODUCTION

Histoplasmosis is a systemic fungal disease acquired by the inhalation of microconidia of the filamentous phase of the fungus *Histoplasma capsulatum*. The infection is universally distributed and predominates in the Americas (United States and Latin America, including Brazil), being recognized as an important infection among patients with acquired immunodeficiency syndrome (AIDS) in these regions. In Brazil the exact incidence of histoplasmosis among patients with AIDS is unknown, but is estimated to be between 5% and 20%.

In immunocompetent individuals, histoplasmosis usually is self-limited or localized, whereas among AIDS patients it occurs in the disseminated form in 95% of cases. Primary esophageal infection is rare both in immunocompetent and immunodepressed individuals.

Histoplasmosis may be associated with other infections, but few cases of concomitant histoplasmosis in the disseminated form and tuberculosis have been reported. We report here a case of histoplasmosis of rare presentation localized in the esophagus and associated with disseminated tuberculosis in a patient with AIDS.

CASE REPORT

A 36-year-old homosexual black man, a prison inmate and ex-user of inhalatory and intravenous drugs with a serologic diagnosis of human immunodeficiency virus (HIV) made 4 months before the present study was referred for admission to the University Hospital, Ribeirão Preto Medical School, and the University of São Paulo. The patient complained of productive cough, yellowish secretion, daily afternoon fever, impaired general status, anorexia, and a 15 kg weight loss. Physical examination revealed a pale, tachypneic patient with a reduced vesicular murmur in the right apex and moderate pleural effusion on the right. An abdominal ultrasound revealed abdominal adenomegaly and discrete hepatosplenomegaly. Adenomegaly and skin lesions were absent. Laboratory tests revealed normocytic, normochromic anemia, leukopenia, a CD4 lymphocyte count of 86 cells/mm³. Treatment of tuberculosis and antiretroviral therapy was maintained and the patient was discharged. The patient returned to the service 2 months later reporting continuing fever, dry cough, intense epigastric pain, and odynophagia. He again reported irregular use of tuberculostatic and antiretroviral drugs, having discontinued tuberculostatic treatment 2 weeks before his return. The patient was hospitalized again and submitted to UDE, which revealed the presence of a shallow ulcer measuring approximately 0.7 cm and covered with thick fibrin in the distal third of the esophagus (Figure 1). Histologic examination of material stained with hematoxylin-eosin (HE) revealed an area of esophageal ulceration covered with a fibrin-leukocyte exudate. A mixed inflammatory infiltrate was observed at the level of the lamina propria, consisting of lymphocytes, numerous neutrophils, and macrophages. Countless clusters of rounded uninucleate structures of uniform size and surrounded by a light halo were identified inside the cervical lymph node demonstrated distortion of the general architecture by extensive necrosis of the caseous type with a polymorphonuclear and histiocytic infiltrate. Ziehl–Neelsen staining revealed alcohol-acid-fast bacilli (AAFB). The CD4 lymphocyte count was 86 cells/mm³. Treatment with tuberculostatic medications was started using a rifampicin, isoniazid, and pyrazinamide (RIP) scheme in combination with antiretroviral therapy. However, the patient was lost to follow-up, only returning 5 years later with complaints of dry cough, afternoon fever, nocturnal sudoresis, and intense epigastric pain of 3 months duration. He reported irregular treatment of tuberculosis for 9 months, 5 years before his return to the hospital. A RIP scheme had been prescribed again 3 months before his return and he had restarted antiretroviral treatment 1 year before. However, he was taking the tuberculostatic and antiretroviral medications on an irregular basis. Physical examination revealed a pale patient with a reduced vesicular murmur in the lower right third and hepatosplenomegaly. Adenomegaly and skin lesions were absent. Laboratory tests revealed normocytic, normochromic anemia, leukopenia, a CD4 lymphocyte count of 140 cells/mm³, and normal liver enzymes and function. A chest x-ray revealed opacification with soft part density in the right apex and moderate pleural effusion on the right. An abdominal ultrasound revealed abdominal adenomegaly and discrete hepatosplenomegaly. Pleural fluid, bone marrow, and blood cultures were negative for fungus and mycobacteria. Upper digestive endoscopy (UDE) was normal. A direct search for AAFB in a gastric aspirate was positive and culture revealed the presence of *Mycobacterium tuberculosis*. Treatment of tuberculosis and antiretroviral therapy were maintained and the patient was discharged. The patient returned to the service 2 months later reporting continuing fever, dry cough, intense epigastric pain, and odynophagia. He again reported irregular use of tuberculostatic and antiretroviral drugs, having discontinued tuberculostatic treatment 2 weeks before his return. The patient was hospitalized again and submitted to UDE, which revealed the presence of a shallow ulcer measuring approximately 0.7 cm and covered with thick fibrin in the distal third of the esophagus (Figure 1). Histologic examination of material stained with hematoxylin-eosin (HE) revealed an area of esophageal ulceration covered with a fibrin-leukocyte exudate. A mixed inflammatory infiltrate was observed at the level of the lamina propria, consisting of lymphocytes, numerous neutrophils, and macrophages. Countless clusters of rounded uninucleate structures of uniform size and surrounded by a light halo were identified inside...
the macrophage cytoplasm (Figure 2). Gomori methenamine silver (GMS) (Figure 3) staining revealed multiple rounded yeast-like fungal structures, 2–4 µm in diameter, compatible with *H. capsulatum*. Staining for mucin was negative in the small yeast-like fungal forms and no AAFB were detected by the Ziehl–Neelsen method. Immunohistochemistry was positive for *H. capsulatum* antigens when the technique of enzyme-conjugated polymers and secondary antibodies was used (Novolink Novocastra, United Kingdom) (Figure 4). Serum counterimmunoelectrophoresis for histoplasmosis was reactive, with a 1:8 titer. New serial blood cultures were started and revealed positivity for *M. tuberculosis* in three samples collected on consecutive days. After one week of hospitalization, the patient developed hospital pneumonia, respiratory insufficiency, and sepsis and died before antifungal therapy could be started and tuberculostatic therapy could be reinitiated.

**DISCUSSION**

The association of histoplasmosis with AIDS is more frequent in endemic areas, with a prevalence of 2% to 30%, and can be the first manifestation of AIDS.2,3 Histoplasmosis is characterized by a wide spectrum of clinical manifestations ranging from asymptomatic illness to severe disseminated disease. In AIDS, the most common form of presentation is the disseminated one, usually a result of hematogenic dissemination of the fungus through reactivation of a primary pulmonary focus, although it may also be a result of primary infection with dissemination. Fever, weight loss, and respiratory symptoms (cough, shortness of breath) may occur in the disseminated form. A chest radiograph may be normal or may show diffuse nodular infiltrates. Lymphadenopathy, hepatosplenomegaly, colonic lesions, and skin and painful oral ulcers (particularly on the tongue and oral mucosa) also occur. Laboratory findings may include anemia, neutropenia or thrombocytopenia (because of bone marrow involvement), and elevated hepatic enzymes. Between 5% and 10% of patients suffer an acute septic shock-like
syndrome that includes hypotension and evidence of disseminated coagulopathy.

In disseminated histoplasmosis, the gastrointestinal tract is involved in 70–90% of cases, with the colon (especially the right colon and the cecum), the oropharynx, and the small bowel being the sites most frequently involved. In disseminated histoplasmosis, the gastrointestinal tract is involved in 70–90% of cases, with the colon (especially the right colon and the cecum), the oropharynx, and the small bowel being the sites most frequently involved. Esophageal involvement is rare and is usually a result of complicated pulmonary histoplasmosis with mediastinal involvement or to dissemination of the disease. Dysphagia and odynophagia are the most frequently observed clinical manifestations, which may last for weeks or months. Endoscopy permits the visualization of erosions and ulcerations, as well as stenosis affecting the distal third of the esophagus. Cases of upper digestive hemorrhage have also been reported at a lower frequency, and cases of traction esophageal diverticula and bronchoesophageal fistulae resulting from mediastinal histoplasmosis.

In the present case, the relevant clinical gastrointestinal symptoms were intense epigastric pain and odynophagia, as also reported in previous studies, and UDE revealed an ulcerated lesion in the distal esophageal third.

Esophageal ulcers are important causes of morbidity among patients with AIDS. The agents most frequently observed in these lesions are cytomegalovirus, Candida sp., and simple herpes virus. Other less common infectious agents are fungi and mycobacteria. Human immunodeficiency virus itself is believed to be a possible etiologic agent of esophageal ulcers. In about 40% of cases the etiology is not identified, these being considered to be idiopathic ulcers. There are few reports about the separate involvement of the esophagus by H. capsulatum. Fucci and others described a case of primary esophageal histoplasmosis in a patient with immunologic involvement resulting from the chronic use of corticoids.

In the present study, the special staining methods applied to samples collected from the margins and the fundus of the esophageal ulcer permitted a consistent morphologic characteristic of H. capsulatum, and the differential diagnosis with other pathogens. Initial histologic examination using HE revealed ulceration covered with a fibrin-leukocyte exudate. A mixed inflammatory infiltrate was observed in the lamina propria, with countless macrophages containing in their cytoplasm rounded structures of uniform size and surrounded with a light halo which, when examined using complementary special staining methods (GMS, PAS, and Mayer’s mucicarmine) revealed a morphology consistent with H. capsulatum. A search for AAFB by the Ziehl–Neelsen method was negative in all samples examined.

Histoplasma capsulatum is a small, uninucleate fungus measuring 2–4 µm in diameter, with a single bud attached by a relatively narrow base, usually present in clusters inside the cytoplasm of macrophages, with a light area surrounding the organism (pseudocapsule).

The differential histopathologic diagnosis of H. capsulatum includes Torulopsis glabrata, Penicillium marneffei, Cryptococcus neoformans, and Blastomyces dermatitidis. Torulopsis glabrata usually occurs intracellularly and is of slightly larger size. It is amphophilic and stains entirely with HE, without the pseudocapsular or halo effect that is often seen with H. capsulatum. The spherical to oval yeast-like cells of Penicilliosis marneffei measure 2.5 to 5.0 µm or more, are often sequestered within mononuclear phagocytes, but do not bud. Instead, this fungus reproduces by schizogony (fission) with the formation of a prominent transverse septum. Most capsule-deficient cryptococci, however, are at least weakly carminophilic when stained with Mayer’s or other mucicarmine procedures. Cryptococci are more pleomorphic, ranging in size from 2 to 20 µm. Blastomyces dermatitidis is a more pleomorphic fungus with thick double-contour walls and multinucleated. Serum counterimmunoelectrophoresis for histoplasmosis was reactive, with a low 1:8 titer, confirming the anatomicopathologic findings. It is important to point out that immunologic methods may present low titers or may be negative in immunodepressed individuals.

A definitive diagnosis of histoplasmosis is based on culture of the fungus from clinical material, or by immunohistochemistry. In the present case, the morphologic data suggestive of H. capsulatum in the esophageal ulcer sample were confirmed by immunohistochemistry.

Tuberculosis is another infection occurring at high frequency in AIDS patients. About 50% of HIV-seropositive individuals infected with M. tuberculosis present extrapulmonary involvement frequently affecting lymph nodes and pleura, with the infection often becoming disseminated and affecting other organs. Disseminated tuberculosis is defined as infection involving the blood stream, bone marrow, liver or two or more noncontiguous sites, or miliary tuberculosis. The symptoms are nonspecific and their duration before diagnosis is variable. In the present report, the patient initially presented only involvement of lymph nodes and pleura by M. tuberculosis and, because of the degree of immunosuppression demonstrated by the low CD4 cell count and the poor treatment compliance, he developed dissemination of this infection, which was diagnosed by blood culture. Blood culture is positive in 40–60% of cases of disseminated tuberculosis and therefore should always be requested when there is a suspicion of disseminated tuberculosis. Some cases of AIDS associated with tuberculosis and disseminated histoplasmosis have been reported, with the latter condition being often diagnosed late because of the fact that the clinical manifestations of disseminated histoplasmosis are similar to those of disseminated tuberculosis.

The present report illustrates a case of tuberculosis of difficult management resulting from poor compliance with tuberculostatic medications and antiretroviral therapy, and present in the disseminated form in association with esophageal histoplasmosis.

We conclude that tuberculosis is a severe infection in AIDS and may be associated with other infections, such as fungal and bacterial ones, with high mortality mainly in the presence of poor treatment compliance. Histoplasma capsulatum should be considered as a possible etiology of esophageal ulcers in HIV-infected patients, especially in regions where this infection is endemic.

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ESOPHAGEAL HISTOPLASMOSIS ASSOCIATED WITH AIDS 349
REFERENCES


