



Disseminated histoplasmosis with lesions restricted to the larynx in a patient with AIDS. Report of a case and review of the literature

Rubén Solari¹, Marcelo Corti¹, Diana Cangelosi¹, Manuel Escudero¹, Ricardo Negroni², Christian Saccheri³ y Ricardo Schtirbu⁴

¹División de HIV/SIDA, ²Laboratorio de Micología, ³Servicio de Otorrinolaringología, ⁴Laboratorio de Histopatología, Hospital de Enfermedades Infecciosas F. J. Muñiz, Buenos Aires, Argentina

Summary

Histoplasmosis is an endemic and systemic mycosis, caused by the dimorphic fungus *Histoplasma capsulatum* var *capsulatum*. Disseminated disease in immunocompromised patients generally results from the reactivation of latent foci after a prolonged period of asymptomatic infection. We report a case of laryngeal histoplasmosis as the unique clinical manifestation of a progressive form of the disease in a patient with advanced HIV/AIDS disease. Histopathological analysis of laryngeal biopsy smears revealed granulomas containing *Histoplasma*-like organisms. Treatment with amphotericin B followed by itraconazole resulted in complete remission of laryngeal lesions. To our knowledge, this is the third case report of laryngeal histoplasmosis in a patient with AIDS.

Key words

Histoplasma capsulatum, Laryngeal histoplasmosis, AIDS, HIV

Histoplasmosis diseminada con lesiones limitadas a la laringe en un paciente con SIDA. Reporte de un caso y revisión de la literatura

Resumen

La histoplasmosis es una micosis sistémica, endémica en varios países de América, producida por un hongo dimorfo, denominado *Histoplasma capsulatum* var *capsulatum*. Las formas diseminadas de la enfermedad afectan a los pacientes inmunocomprometidos y son la consecuencia de la reactivación de una infección latente. Presentamos un paciente con sida que desarrolló una histoplasmosis laringea como única manifestación clínica de la enfermedad. El diagnóstico se confirmó por la histopatología de las lesiones con la presencia de levaduras compatibles con *Histoplasma capsulatum*. El tratamiento con anfotericina B seguida de itraconazol se asoció con una remisión completa de las lesiones laringeas. En nuestro conocimiento este sería el tercer caso de histoplasmosis de laringe en un paciente con sida.

Palabras clave

Histoplasma capsulatum, Histoplasmosis laringea, Sida, VIH

Histoplasmosis is an endemic mycosis with a higher prevalence in Africa and America. The areas of highest occurrence are located in the United States along the Mississippi Valley, the Missouri and the Ohio Rivers and in South America, Serra do Mar in Brazil and the Rio de

La Plata, in Argentina and Uruguay, also show a high prevalence of the infection due to *Histoplasma capsulatum*. In Argentina it is commonly found in rural and urban areas [8].

Histoplasmosis is the third potentially fatal opportunistic mycosis in patients with AIDS. Although disseminated cryptococosis with CNS involvement, pneumocystosis and oropharyngeal candidiasis are present in patients with AIDS, in endemic areas, disseminated histoplasmosis is the most frequent mycosis in this population [5].

Acute disseminated cases derive from the reactivation of latent foci of infection and are more severe in patients with AIDS than in those with other immunodeficiencies.

We report a patient who developed a localized laryngeal histoplasmosis after discontinuing antiretroviral therapy and secondary prophylaxis for this opportunistic AIDS-defining disease.

Corresponding author:

Dr. Marcelo Corti
División "B"
Hospital de Enfermedades Infecciosas F. J. Muñiz
Puán 381 2° C 1406 CQG
Buenos Aires, Argentina
E-mail: marcelocorti@fibertel.com.ar

Aceptado para publicación el 10 de enero de 2007

©2007 Revista Iberoamericana de Micología
Apdo. 699, E-48080 Bilbao (Spain)
1130-1406/01/10.00 €

Case report

A 48-year-old male, born in Santo Tome, Santa Fe, Argentina, where he lived until he was 10-year-old, moving then to Buenos Aires, his current place of residence. He was admitted at the F.J. Muñiz Infectious Disease Hospital with a four-month history of fever (38-38.5 °C), weight loss, dysphonia, dry cough and progressive dysphagia.

AIDS was diagnosed eight years before his current hospitalization, due to the developed an acute disseminated histoplasmosis. At this time, he started on highly active antiretroviral therapy (HAART) with poor compliance to treatment and to prophylaxis with itraconazole.

At admission, fever (38 °C), dry cough, weight loss (approximately 6 kg less than his previous weight) and a bad general state were established. The general clinical examination revealed laryngeal stridor, progressive dyspnoea and liver and spleen enlargement. No lymphadenopathy or mucocutaneous lesions were appreciated on physical examination. Relevant laboratory findings included pancytopenia, accelerated blood sedimentation rate (130 mm), and a discrete elevation of transaminases levels. The level of lactic acid dehydrogenase was normal.

Chest X ray was normal; abdominal ultrasound demonstrated a heterogeneous liver enlargement with multiple hyperechoic images, homogeneous splenomegaly and findings compatible with AIDS-associated cholangiopathy. Direct laryngoscopy revealed epiglottitis, enlargement and mobile vocal cords with granulomatous lesions deforming and infiltrating the glottis and subglottis.

A fibrobronchoscopy with bronchoalveolar lavage (BAL) was performed and it did not reveal lesions in the trachea and bronchi.

Gram, Ziehl Nielsen, Grocott and Giemsa stains as well as cultures of sputum and the material obtained by BAL were negative. Hemocultures were also negative for common bacteria, micobacterias and fungi. The CD4 T cell count was of 135 cells/ μ l (5%) and the HIV plasma viral load was of 14,000 copies/ml (log 10 4,2).

Histopathology of laryngeal biopsies with hematoxyline and eosin stain revealed and scamous epithelium with acanthosis; extensive ulcers, intense unespecific inflammatory infiltration and some poorly defined granulomas with macrophages and multinucleated giant cells were shown in the corium (Figure 1). PAS and Grocott stains revealed microorganisms compatible with *Histoplasma capsulatum* (Figure 2).

Due to the severity of his mycosis, the patient was initially treated with 0,8mg/kg/day of amphotericin B up to reach a total accumulated dose of 360 mg was started. Afterwards, he received 400 mg/day of oral itraconazole with clinical improvement and laboratory normalization. There were no fibrous obstructive sequel in the respiratory tract. Dysphagia was resolved and his voice turned back to normal. He improved rapidly and one month after he was discharged from the hospital in good clinical condition. It was his decision not to follow the clinical controls after the discharge from the hospital.

Discussion

Histoplasmosis is a systemic mycosis, endemic in Argentina. The clinical spectrum of the disease is variable, ranging from a severe multisystem illness involving bone marrow, the liver, the spleen and the lungs to an indolent infection localized to the gastrointestinal tract, the skin, the adrenal glands, the larynx or other extrapulmonary sites. It affects 4% to 5% of patients with AIDS in which it causes, generally, acute or subacute clinical disease with dissemi-

nated illness. These presentations of the infection take place in advanced stages of the HIV/AIDS disease with CD4 T cell lymphocytes lower than 200 cells/ μ l [1]. This severe complication of AIDS should be suspected in the presence of prolonged fever, weight loss and pulmonary disease. Mucocutaneous lesions are demonstrated in up to 70 to 80% of this kind of patients [4].

Laryngeal location is extremely rare and derives from haematogenous spread of *Histoplasma capsulatum*, generally from a primary pulmonary focus or an unknown infectious focus [7].

Laryngeal involvement, as the unique clinical manifestation of a progressive histoplasmosis, is a common finding in the chronic disseminated histoplasmosis, frequently observed in HIV-negative males, above sixty years of age [9].

The first description of laryngeal histoplasmosis was made by Parker et al. and published in 1949 [11]. After this case, numerous new cases have been published. Most of this affected immunocompetent patients and most of them were published as single cases. In 1993, Sataloff et al. published the first case of laryngeal histoplasmosis in an immunocompromised patient who showed an excellent response to treatment [13].

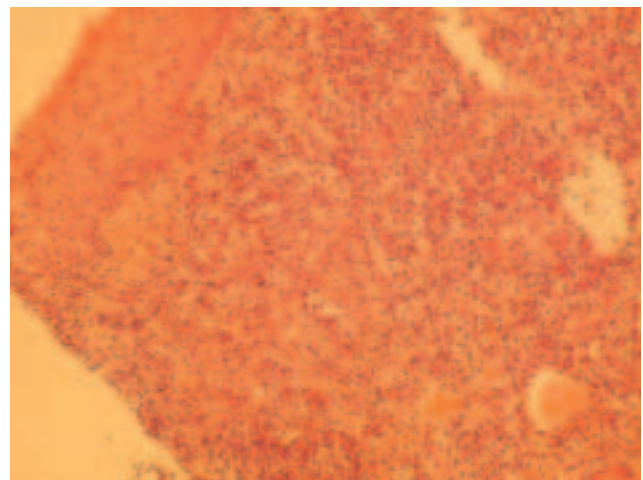


Figure 1. Hematoxylin-eosine stain showing an intense and unespecific inflammatory infiltrate with granulomas, macrophages and multinucleated giant cells.

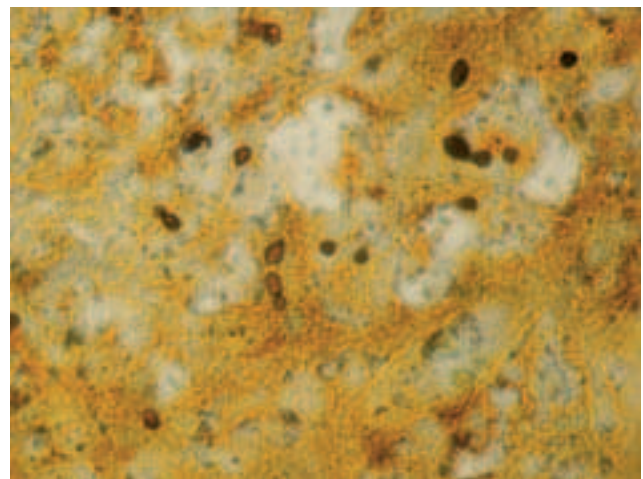


Figure 2. Grocott stain showing microorganisms compatible with *Histoplasma capsulatum*.

In patients with advanced HIV/AIDS disease the diagnosis of acute forms of disseminated histoplasmosis is made by biopsy of mucocutaneous lesions, hemocultures and microscopic direct observation and culture of bone marrow biopsy [4,12]. Blood culture is a simple and effective way to recover the organism. Culture of the blood by lysis-centrifugation are positive in over than 60% of patients with AIDS associated histoplasmosis and in about 20%, it is the sole diagnostic method [2,3]. Laryngeal location involves biopsy of lesions to reach the final diagnosis [2].

We think that our patient had laryngeal involvement as an extrapulmonary manifestation, and should be considered as a disseminated form of the disease in spite of the negative cultures from blood and sputum. Differential diagnosis includes other granulomatous diseases such as tuberculosis, paracoccidioidomycosis, laryngeal carcinoma and, in endemic areas, with the mucocutaneous clinical manifestations of American leishmaniasis.

In a data base search that included Medline, Embase, Lilacs and Cochrane only two cases of laryngeal histoplasmosis in patients with AIDS were found. The one of them was a patient with acute disseminated disease with long term fever, mucocutaneous lesions, liver and bone

marrow infiltration with pancytopenia and elevation of transaminases [6]. The other one had laryngeal involvement with airway obstruction and good response to medical treatment [14].

In conclusion, histoplasmosis should be considered in the differential diagnosis of the laryngeal compromise in AIDS patients, especially when it is associated with prolonged febrile illness, weight loss and pulmonary symptoms. Laryngeal involvement presented in these patients with fever, stridor, progressive dyspnoea, dysphonia and dry cough, as in our patient.

Early diagnosis followed by specific therapy based on amphotericin B or itraconazole and the immune reconstitution associated with the use of highly active antiretroviral therapy are necessary to improve the prognosis of these patients [10].

References

- Bava AJ. Histoplasmosis in the Muñiz Hospital of Buenos Aires. *Rev Inst Med trop S Paulo* 1995; 37: 531-535.
- Benetucci JA, Corti ME. Tratamiento de las infecciones endémicas de Latinoamérica en pacientes VIH positivos. En: Gatell JM, Clotet B, Podzamczar D, Miró JM, Mallotas J, eds. *Guía Práctica del SIDA. Clínica, Diagnóstico y Tratamiento*. Barcelona (España). Masson, S.A., 8ª edición 2005; 318-323.
- Bianchi M, Robles AM, Vitale R, Helou S, Arechavala A, Negroni R. The usefulness of blood culture systems in diagnosing HIV-related systemic mycoses: evaluation of a manual lysis centrifugation method. *Med Mycol* 2000; 38: 77-80.
- Corti M, Cendoya C, Soto I, Esquivel P, Trione N, Villafañe MF, Corbera KM, Helou S, Negroni R. Disseminated histoplasmosis and AIDS: Clinical aspects and diagnostic methods for early detection. *AIDS patient care and STDs* 2000; 14: 149-154.
- Corti M, Negroni R, Esquivel P, Villafañe MF. Histoplasmosis diseminada en pacientes con sida: análisis epidemiológico, clínico, microbiológico e inmunológico de 26 pacientes. *Enf Emerg* 2004; 6: 8-15.
- Kao TW, Hung CC, Hsueh PR, Lin TY, Chen MY, Luh KT, Chuang CY. Microbiologic and histologic diagnosis of histoplasmosis in Taiwan. *J Formos Med Assoc* 1997; 96: 374-378.
- Klein AM, Spiro J, Lafreniere D. Histoplasmosis of the larynx: a case report. *Ear Nose Throat J* 2002; 81: 309-310.
- Negroni R. Micosis del aparato respiratorio. In: Negroni R (Ed.). *Lecciones de Micología Médica*. Buenos Aires; La Agenda 1997; 43-72.
- Negroni R. Clinical spectrum and treatment of classic histoplasmosis. In: *Biology of Dermatophytes and other Keratinophilic Fungi*. Kushwaha RKS and Guarro J (Eds). *Rev Iberoam Micol* 2000; 159-167.
- Negroni R, Helou S, López Daneri G, Robles AM, Arechavala A, Bianchi M. Interrupción de la profilaxis secundaria antifúngica en la histoplasmosis asociada al sida. *Rev Iberoam Micol* 2004; 21: 75-78.
- Parker M, Burtoff S. Histoplasmosis of the larynx: report of a case. *Med Ann Dist Columbia* 1949; 18: 641-643.
- Sarosi G, Johnson PC. Disseminated histoplasmosis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1992; 14 (Suppl 1): S60-67.
- Sataloff RT, Wilborn A, Prestipino A, Hawkshaw M, Heuer RJ, Cohn J. Histoplasmosis of the larynx. *Am J Otolaryngol* 1993; 14: 199-205.
- Troncoso A, Gulotta H, Olenchuk A, Bava J. Histoplasmosis laríngea como manifestación de sida. *Enferm Infecc Microbiol Clin* 2003; 21: 273-278.