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Laryngeal Histoplasmosis–Description of Two Cases Autochthonous In Brazil and Review of Literature

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Abstract

Histoplasmosis is primarily an inhalation-acquired mycosis with rare cases of cutaneous inoculation histoplasmosis being described. Although it is the third potentially fatal opportunistic mycosis in patients with AIDS, histoplasmosis infection involving the larynx is a rare manifestation. Mucosal lesions may mimic tuberculosis and malignancy and a high index of suspicion is needed to establish the diagnosis correctly, and must be considered in the differential diagnosis of a patient with hoarseness, diagnosed with histoplasmosis and, moreover, in the differential diagnosis of tumors in the vocal folds, causing hoarseness. Disseminated histoplasmosis may occur in immunocompromised hosts and in those exposed to large inoculums of fungal organisms. We report two cases: one who developed a localized laryngeal histoplasmosis after discontinuing antiretroviral therapy and secondary prophylaxis for this opportunistic disease, and the other with disseminated histoplasmosis who presented in an endemic region (Brazil) with an eroded epiglottic mass.

Keywords: Histoplasmosis; Laryngeal Histoplasmosis; AIDS; Mycosis

Introduction:

Histoplasma capsulatum is a dimorphic fungus endemic to the Americas and Africa. The areas of highest occurrence are located along the Mississippi Valley and the Missouri and the Ohio Rivers in the United States and along the Rio de La Plata in Argentina and Uruguay in South America [1,2]. Rare cases of histoplasmosis have been described in nonendemic regions and are difficult to recognize [3].

Histoplasmosis is primarily an inhalation-acquired mycosis, with rare cases of cutaneous inoculation histoplasmosis being described [3]. Although it is the third most common potentially fatal opportunistic mycosis in patients with AIDS [1], histoplasmosis infection involving the larynx is a rare manifestation [2]. Mucosal lesions may mimic tuberculosis [4] and malignancy, and a high index of suspicion is needed to establish the diagnosis correctly [4], and must be considered in the differential diagnosis of a patient with hoarseness.

Disseminated histoplasmosis may occur in immunocompromised hosts and in those exposed to large inoculums of fungal organisms. Oropharyngeal and laryngeal ulcers are common clinical manifestations of disseminated histoplasmosis [3].

We report the cases of two patients: one who developed localised laryngeal histoplasmosis after discontinuing antiretroviral therapy and secondary prophylaxis for this opportunistic infection, and another with disseminated histoplasmosis whose chief complaint was epiglottic mass.

Case One:

A 25-year-old woman, homeless, born in Maracanau, Ceará, Brazil, presented to our institution complaining of a 1-month history of fever (38-39°C), nausea and weight loss and a 3-year history of hoarseness.

This patient was diagnosed with AIDS during pregnancy nine years before. After five years, she was started on Highly Active Antiretroviral Therapy (HAART) but exhibited poor compliance to the treatment. She reported seven previous hospitalisations, three for treatment of larynx tuberculosis. She was taking medication for multidrug-resistant tuberculosis empirically.

At the time of admission at our centre, the patient had a temperature of 37°C, a blood pressure of 90/60 mmHg, a pulse rate of 74 beats/min, and a respiratory rate of 20 breaths/min. She appeared acutely ill and was cachectic. Her oropharynx showed signs of oral candidiasis. Cervical lymphadenopathy was also present. She had sibilant rhonchi bilaterally in the lung fields. Her relevant lab data included a white blood cell count of 1,380/mm3, hematocrit of 20.5%, and platelet count of 94,000/mm^3, and an Lactate Dehydrogenase (LDH) level of 1435 UI/l (range is 105 - 333 IU/l). A chest radiograph revealed bilateral alveolar patchy infiltrates, The CD4 T cell count was of 52 cells/µl.

Flexible bronchoscopy revealed the presence of an ulcerated mass in the glottis space, and biopsy were obtained. Histopathological analysis of the laryngeal biopsy samples with hematoxylin and eosin staining revealed squamous epithelium with acanthosis, intense nonspecific inflammatory infiltration, some defined granulomas with macrophages and multinucleated giant cells. Grocott stains revealed microorganisms compatible with *Histoplasma capsulatum*. Hemocultures were negative for common bacteria, mycobacteria and fungi, with *culture durations of 21 days*.

Treatment with amphotericin B was initiated (Abelcet, 5 mg/ml at 40 ml/day), but the patient developed nosocomial pneumonia (fever, diffuse rhonchi and leukocytosis with neutrophilia) during hospitalization. Therefore, treatment with piperacillin and tazobactam was associated. After 4 days, the patient developed hypotension and septic shock. Piperacillin and tazobactam were discontinued, and imipenem was associated. The patient died of cardiovascular complications.

Case Two:

The second patient was a 34-year-old male, worker in a shoe factory, born in Itapipoca, Ceará, Brazil, where he lived until he was 10-years-old, after which time he moved to Fortaleza, Ceará, his current place of residence.

The patient was diagnosed with AIDS after he developed acute pulmonary tuberculosis seven years before the current hospitalisation. At this time, he was started on Highly Active Antiretroviral Therapy (HAART), with poor compliance to the treatment.

He was admitted our centre with a six-month history of fever, weight loss, dysphonia and progressive dysphagia. His CD4 T cell count was 72 cells/µl, and the HIV plasma viral load was 23,302 copies/ml a year before. His past medical history was significant for two episodes of pulmonary tuberculosis (2004 and recurrence in 2007) and pulmonary histoplasmosis 3 years before, which he said were completely resolved. Secondary prophylaxis for histoplasmosis was not initiated. He was a smoker (20 cigarettes per day for 7 years).

Upon admission to our centre, the patient had a pulse rate of 78 beats/min and a respiratory rate 22 breaths/min. He appeared acutely ill and exhibited weight loss (currently 56 kg, weighing approximately 10 kg less than one year before). He had purulent discharge in the pharynx. No neck lymphadenopathy was identified. The results of a cardiopulmonary examination were unremarkable. The liver and spleen were enlarged. Mucocutaneous lesions were observed during the physical examination. His relevant lab data included a white blood cell count of 1,200/mm^3, a hematocrit of 26.6%, a platelet count of 128,000/mm^3, an LDH level of 3960 UI/l, an Aspartate transaminase (AST) level of 646 UI/l (8 to 48 U/L), and an Alanine Transaminase (ALP) level of 135 UI/l (45 to 115 U/L). A chest radiograph was normal. Abdominal ultrasound demonstrated a homogeneous liver, splenomegaly and ascites.

Laryngoscopy revealed epiglottitis with granulomatous lesions on the epiglottis, vestibular folds and vocal cords suggestive of tuberculosis. Histopathological analysis of laryngeal biopsy samples with hematoxylin and eosin staining revealed squamous epithelium with acanthosis. In addition, extensive ulcers, intense nonspecific inflammatory infiltration, poorly defined granulomas with macrophages and multinucleated giant cells were observed in the corium. Grocott stains revealed microorganisms compatible with *Histoplasma capsulatum*. Hemocultures were negative for common bacteria, mycobacteria and fungi, with *culture durations of 21 days*.

Due to the severity of his mycosis, the patient was initially treated with 0.8 mg/kg/day of amphotericin B three times per week. Subsequently, he received 400 mg/day of oral itraconazole and exhibited clinical improvement and laboratory normalisation. There were no fibrous obstructive sequelae in the respiratory tract. Dysphagia was resolved, and his voice returned to normal. He improved rapidly, and one month later, he was discharged from the hospital in good clinical condition. It was the patient's decision not to follow the clinical recommendations after discharge from the hospital.

Discussion

Histoplasmosis is a granulomatous disease of universal distribution that is caused by a dimorphic intracellular fungus, *Histoplasma capsulatum [4]*. Histoplasmosis is considered a non-endemic infection in Brazil [2]. The clinical spectrum of the disease is variable, ranging from a severe multisystem illness involving the bone marrow, liver, spleen and lungs to an indolent infection localised to the gastrointestinal tract, skin, adrenal glands, larynx or other extrapulmonary sites [1]. The first description of laryngeal histoplasmosis was published by Parker et al. [5].

Histoplasmosis affects 4% to 5% of patients with AIDS, in whom it generally causes acute or subacute clinical disease with disseminated illness. These presentations of the infection take place in patients with CD4 T cell counts lower than 200 cells/µl [1]. This severe complication of AIDS should be suspected when patients present with prolonged fever, weight loss and pulmonary disease. Mucocutaneous lesions are found in up to 70 to 80% of this type of patient [6].

Laryngeal infection is extremely rare and is the result of the haematogenous spread of *Histoplasma capsulatum*, generally from a primary pulmonary focus or an unknown infectious focus [7]. Clinical presentations in the oropharyngeal area include ulceration, nodular-ulcerative lesions, granulomas and verrucous and plaque-like lesions. Even following the spread of AIDS, reports of oral involvement in cases of histoplasmosis have been rare in the Americas and Europe [8].

Macroscopically, histoplasmosis must be differentiated from carcinoma, mid-line granuloma, mucormycosis, lymphoma, syphilis, tuberculosis and other granulomatous diseases of the head and neck. Microscopically, histoplasmosis may be mistaken for paracoccidioidomycosis, which has a similar appearance. Granulomatous histoplasmosis can be mistaken for tuberculosis, and there are reports of central caseous necrosis - similar to tuberculosis - and of squamous cell carcinoma - similar to the atypical epithelial response [1].

In patients with HIV/AIDS disease, the diagnosis of acute forms of disseminated histoplasmosis is made based on biopsies of mucocutaneous lesions, hemocultures and microscopic direct observation and culture of bone marrow biopsy samples [6]. Blood culturing is a simple and effective way to recover the causative organism. Cultures of blood by lysis-centrifugation are positive in more than 60% of patients with AIDS-associated histoplasmosis and in approximately 20% of cases, blood culturing is the sole diagnostic method used [9]. Laryngeal examination involves the biopsying of the lesions to reach the final diagnosis [10].

Laryngeal histoplasmosis must be treated similarly to the other forms of the disease. Although typically benign, histoplasmosis can be disseminate and cause severe or even fatal disease. Treatment is carried out with endovenous amphotericin B, 0.3-0.6 mg/kg of body weight per day, with a total dose of 2-4 mg. Mucosal lesions respond quickly (6-8 weeks), although there may be recurrences. Goodwin Jr et al. reported that a serum level of amphotericin B of 1.56 mg/mL for 10 weeks, equivalent to a total of 1 g of intravenous medication, was usually enough to achieve a cure, or, when the serum dosage cannot be monitored, one can use 50 mg per day or three times per week, equivalent to a total dose of 2.0 g [10]. Of their 84 cases treated with

amphotericin B, 11 were not completely cured and required further treatment. Goodwin et al. reported a case of histoplasmosis affecting only the larynx, which was treated with 200 mg of ketoconazole three times a day for 3 months. The patient underwent objective testing 14 months after treatment, with good results [10]. Fernandez et al. reported successful treatment with itraconazole [11]. Negroni et al. treated 17 histoplasmosis patients with itraconazole, 100 mg daily, until a clinical cure was achieved and then changed the treatment regimen to 50 mg/day for six more months. All of the infections were clinically cured or improved greatly. Twelve cases reached a clinical cure, 4 exhibited extreme relief, and 1 patient, who interrupted the treatment after 2 months of itraconazole, died [12].

In conclusion, histoplasmosis should be considered in the differential diagnosis of laryngeal disease in AIDS patients, especially when associated with prolonged febrile illness, weight loss and pulmonary symptoms. Laryngeal involvement presented in these patients along with fever, stridor, progressive dyspnea, dysphonia and dry cough. Early diagnosis followed by specific therapy based on amphotericin B or itraconazole and immune reconstitution associated with the use of highly active antiretroviral therapy are necessary to improve the prognosis of these patients.

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