



Oropharyngeal histoplasmosis: report of eleven cases and review of the literature

Histoplasmose orofaríngea: relato de onze casos e revisão da literatura

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ABSTRACT

Introduction: Histoplasmosis is a systemic mycosis endemic in Brazil, especially in the State of Rio Grande do Sul, where *Histoplasma capsulatum* was isolated from the soil. *H. capsulatum* may compromise unusual areas, including the oropharynx, particularly in patients presenting disseminated histoplasmosis; which is associated with a state of immunosuppression, such as AIDS. **Methods:** During database analysis of a total of 265 cases of histoplasmosis, the medical records of 11 patients with histological or microbiological diagnoses of oral histoplasmosis (OH) between 1987 and 2008 were retrospectively reviewed. **Results:** This work reports 11 cases of OH, the majority presenting histopathological or microbiological evidence of disseminated histoplasmosis (DH). In the patients with DH, OH was the first manifestation of histoplasmosis. Five of the 11 patients discussed were HIV-seropositive with clinical and laboratory findings of AIDS. Four patients presented active pulmonary tuberculosis concomitant with histoplasmosis. Treatment was based on the use of itraconazole and amphotericin B deoxycholate. Eight patients responded successfully to therapy after one year, two did not come back for reevaluation and one died despite adequate therapy. **Conclusions:** Oral histoplasmosis is closely associated with immunosuppression status, especially in patients presenting AIDS; moreover, in many cases, OH is the first sign of disseminated histoplasmosis.

Keywords: Histoplasmosis. *Histoplasma capsulatum*. HIV infection. AIDS.

RESUMO

Introdução: Histoplasmose é uma micose sistêmica, endêmica no Brasil, especialmente no Estado do Rio Grande do Sul, onde *Histoplasma capsulatum* foi isolado do solo. *H. capsulatum* pode acometer áreas não-usuais, como cavidade orofaríngea, particularmente em pacientes com histoplasmose disseminada, por sua vez, associada com estado de imunossupressão, como na AIDS. **Métodos:** A partir de 265 casos de histoplasmose em um banco de dados de um laboratório de micologia, foram analisados retrospectivamente 11 prontuários de pacientes com diagnóstico histológico ou microbiológico de histoplasmose oral (HO) entre 1987 e 2008. **Resultados:** Reportamos neste trabalho onze casos de HO, a grande maioria com evidências histopatológicas e microbiológicas de histoplasmose disseminada (HD). Nos pacientes com HD, HO foi a primeira manifestação de histoplasmose. Cinco dos onze casos relatados eram portadores do vírus do HIV, todos com diagnóstico clínico e laboratorial de AIDS. Quatro pacientes do total tinham concomitantemente tuberculose pulmonar e histoplasmose. Tratamento foi baseado no uso de itraconazol e anfotericina B principalmente. Oito pacientes tiveram sucesso terapêutico após um ano, dois não retornaram para reavaliação e um faleceu apesar da adequada terapia antifúngica. **Conclusões:** Histoplasmose oral está associada muitas vezes com estado de imunossupressão, especialmente em pacientes com AIDS. Em muitos casos pode representar o primeiro sinal indicativo de histoplasmose disseminada.

Palavras-chaves: Histoplasmose. *Histoplasma capsulatum*. Infecção pelo HIV. AIDS.

INTRODUCTION

Histoplasmosis is a worldwide systemic mycosis caused by *Histoplasma capsulatum*, a dimorphic fungus that has been isolated from soil contaminated with bird or bat droppings in endemic areas, as reported in Brazil and central United States¹⁻⁴. Infection occurs almost exclusively by inhalation of airborne conidia or mycelial fragments¹⁻⁴.

The course of histoplasmosis can be influenced by the immune status of the host and by the quantity of infective propagules the host is exposed to^{1,5,6}. Disease manifestations range from asymptomatic infection in the normal host with low-inoculum exposure, to rapidly fatal, disseminated infection in the severely immunocompromised host, emphasizing the importance of cellular immunity in defense against *H. capsulatum*¹.

Disseminated histoplasmosis (DH) refers to the relentless growth of the fungus in multiple organ systems. It can develop by re-exposure to a large inoculum of the fungus or by reactivation of dormant endogenous foci^{1,6}. The most important risk factors are immunosuppression, including transplantation, chronic renal disease, prolonged use of corticosteroids, acquired immune deficiency syndrome (AIDS) and age over 54 years-old^{1,7}. In the last few years, AIDS has contributed to the increased incidence of DH, described in some series as up to 25%^{1,6,8}.

Occasionally, as a consequence of DH, though less prevalent as a unique manifestation, *H. capsulatum* may involve unusual areas, such as the oropharynx. The most common sites of oral cavity affected are the tongue, palate and buccal mucosa⁸. The clinical significance of oropharyngeal lesions is primarily diagnostic. Goodwin et al showed that up to two-thirds of chronic patients with DH presented oropharyngeal involvement, which was almost invariably part of the clinical status leading to a diagnosis⁶. Oropharyngeal involvement is more frequently observed in immunocompromised patients, who often develop DH^{1,5}.

This report is based on a series of 11 cases of oropharyngeal histoplasmosis (OH) observed

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over from 1987 to 2008 selected from the medical records of the Laboratory of Mycology, Santa Casa Hospital Complex (*Complexo Hospitalar Santa Casa*), Porto Alegre, Brazil.

METHODS

During database analysis of a total of 265 cases of histoplasmosis, the medical records of 11 patients with histological or microbiological diagnoses of OH between 1987 and 2008 were retrospectively reviewed. The patients were referred from five public hospitals in Porto Alegre, Brazil, for definitive diagnosis. Diagnoses were determined in all cases by a combination of the following criteria: direct visualization of oropharyngeal lesion; biopsy of the lesion; and presence of characteristic yeast structures of *H. capsulatum*. Serology for *H. capsulatum* was performed on almost all patients. Patients with DH were defined as those with evidence of any other focus of infection other than the oropharynx, as analyzed by clinical examination, laboratory results and radiological data present in their records.

RESULTS

Baseline characteristics

Between March 1987 and October 2008, 11 patients (seven men and four women; age range, 24-66 years-old; mean 42 years-old) with *H. capsulatum* oral lesions positive by histological or microbiological methods, were identified in the files of the laboratory of mycology of our institution. The baseline characteristics of these patients are shown in **Table 1**. Five (45.5%) patients had clinical and laboratory diagnosis of AIDS before confirmation of DH and none of them were taking highly active antiretroviral therapy (HAART) regularly. CD4 counts were not available in all patients presenting with AIDS. In three cases, patients presented CD4 < 100/ μ L. Of the 11 patients, only two presented no evidence other than histoplasmosis in the oropharynx. In seven cases, clinical or microbiological pulmonary involvement was observed concomitant with oral histoplasmosis. Regarding patients with AIDS, four of the five described presented microbiological or histopathological evidence of DH, proving the strong association between DH and immunocompromised patients, as reported in literature^{1,3,7}. Four (36.4%) patients had a history of active pulmonary tuberculosis when the diagnosis of DH was made.

Signs and symptoms

The most common presenting symptoms were weight loss (72.7%), asthenia (63.6%), dysphagia (45.5%), chronic cough (36.4%) and fever (36.4%). All patients presented oral lesions. The most commonly involved sites of oropharyngeal histoplasmosis were buccal mucosa (54.5%), tongue (45.5%) and palate (18.2%). One case presented with gingival histoplasmosis, two cases presented concomitant tongue and buccal mucosa involvement and one case with gingival and buccal mucosa involvement by histoplasmosis.

Microscopy, culture, histopathology and immunodiffusion for *Histoplasma capsulatum*

Regarding microbiology and pathology, the organisms were morphologically consistent with the diagnosis of *H. capsulatum* in the biopsies performed from all cases reported, as shown in **Table 2**.

Treatment

Patients were treated with amphotericin B deoxycholate, itraconazole or ketoconazole. All patients were administered therapy for at least 6 months despite different treatment, except for two cases, treated exclusively with amphotericin B deoxycholate for 3 weeks. Four patients used amphotericin B deoxycholate for induction, with duration ranging from 2 to 4 weeks. Of these patients, one received ketoconazole for a further 6 months, one continued with amphotericin B deoxycholate twice weekly for a further 6 months and one patient stopped therapy after 3 weeks of initial induction. These three cases responded well to treatment. One patient, presenting with AIDS, died from systemic sepsis during therapy, despite initial induction with amphotericin B deoxycholate for 3 weeks. Seven patients received itraconazole during treatment. Duration ranged from 6 to 12 months. Five of them responded to therapy. Two patients did not return for reevaluation. In only one case, initial induction was performed with ketoconazole for two weeks, with posterior introduction of itraconazole.

Outcome

Two (18.1%) of the 11 cases never returned for reevaluation following the initial treatment. One (9.1%) patient responded initially to amphotericin, but developed sepsis and died despite treatment. The remaining cases (8 patients, 72.7%) responded well to therapy, as shown in **Table 1**. Patients who improved after therapy were followed for at least one year, with no sign of relapse. Three patients from the group that showed clinical improvement with therapy were HIV-seropositive.

TABLE 1 - Clinical features of 11 patients with oropharyngeal histoplasmosis.

Case	Age	Sex	Underlying condition	Symptoms, course prior	Therapy	Outcome
1	24	F	AIDS, active TB	WL, AS, D, OL, 2 months	amphotericin B	improved
2	30	M	AIDS	OL, unknown	Itraconazole	unknown
3	33	M	AIDS	WL, AS, D, 6 months	amphotericin B	improved
4	34	F	AIDS	WL, AS, CS, Fv, D, OL, unknown	amphotericin B	died
5	38	F	Hodgkin lymphoma	CS, OL, 1 year	Itraconazole	improved
6	38	M	active TB	WL, AS, OL, 1 month	Itraconazole	improved
7	38	M	none	WL, AS, CS, Fv, OL, 2 months	ketoconazole/ itraconazole	improved
8	40	F	AIDS, active TB	WL, AS, Fv, OL, 2 months	Itraconazole	improved
9	58	M	lung cancer	WL, AS, D, OL, 1 month	Itraconazole	unknown
10	63	M	active TB	WL, AS, Fv, D, OL, 1 year	amphotericin B/ ketoconazole	improved
11	66	M	COPD	WL, CS, 1 year	Itraconazole	improved

M: male, F: female, TB: tuberculosis, AIDS: acquired immunodeficiency syndrome, COPD: chronic obstructive pulmonary disease, WL: weight loss, AS: asthenia, Fv: fever, CS: cough with sputum, D: dysphagia, OL: oral lesion.

TABLE 2 - Sites where *Histoplasma capsulatum* was isolated.

Case	Age	Sex	Material	Mycology			IDh
				microscopy	culture	histopathology	
1	24	F	palate	+	-	+	-
2	30	M	tongue	+	+	ND	ND
3	33	M	oral mucosaskin	--	--	+ND	ND
4	34	F	tongue	ND	ND	+	-
			lung	+	+	ND	
5	38	F	lip	+	-	+	ND
			tongue	+	-	+	
6	38	M	oral mucosa	+	-	ND	+, M Band*
			tongue	+	-	ND	
			sputum	+	-		
7	38	M	oral mucosa	+	-	ND	-
			lung	ND	ND	+	
8	40	F	tongue	-	-	+	+, M Band*
9	58	M	oral mucosa	ND	ND	+	ND
			palate	+	+	ND	
10	63	M	gingival mucosa	ND	ND	+	+, M Band*
			oral mucosa	-+	—	+	
			sputum				
11	66		palate	-	-	+	+, M Band*

M: male, F: female, IDh: immunodiffusion for histoplasmosis, ND: not done, +: positive, -: negative.
*M Band indicates recent contact with the fungus.

DISCUSSION

Histoplasmosis is a systemic mycosis endemic in Brazil, particularly in the State of Rio Grande do Sul, where *H. capsulatum* was isolated from the soil^{8,9}. While most infections are asymptomatic or self-limiting, some individuals develop acute pulmonary infections or severe and progressive disseminated infection. Although hematogenous dissemination probably occurs in most patients during acute infection, progressive illness is unusual, except in immunocompromised hosts and those at the extremes of age¹.

The clinical manifestations of DH and the timing of presentation differ based on host immunodeficiency and degree of exposure to the fungus⁵. Thus, diagnosis is made based on a combination of clinical findings, serology, light microscopy and microbiological culture of the organism¹⁰.

Up to 12% of DH involves the gastrointestinal tract. Lesions more often involve the colon and ileum, though can occur from the anus to the mouth⁷. Oral compromise is fairly unusual, with most of cases presented in patients with DH, as a consequence of the spread of respiratory mycosis acquired through aspiration of airborne spores found in the excreta of birds¹⁰⁻¹¹.

Clinical presentation in the oropharyngeal area includes ulceration, nodular-ulcerative lesions, granulomas, verrucous and plaque-like lesions. Even following the outbreak of AIDS, reports of oral involvement by histoplasmosis have been rare in America and Europe^{2,10-12}.

This study reports 11 cases of oropharyngeal histoplasmosis, mostly with histopathological or microbiological evidence of DH. In nine cases, oral histoplasmosis was the first manifestation of DH. Five of the 11 patients presented were HIV-seropositive with clinical and laboratory findings of AIDS. Oral lesions of histoplasmosis were

also the first manifestations of DH in four of the five cases presenting AIDS.

Six patients of a total of 11 were HIV-seronegative. Four patients presented active pulmonary tuberculosis concomitant with histoplasmosis (two were HIV-seropositive), one presented with lung cancer, one with Hodgkin lymphoma and one patient with chronic obstructive pulmonary disease. Only one patient had no history of concomitant illness at the time of diagnosis of histoplasmosis.

Diagnosis of histoplasmosis was achieved in all cases by fungal identification from the oral lesion. In seven cases, cultures were performed, with positive results in three cases. Immunodiffusion for *Histoplasma capsulatum* was performed in 10 cases, four of which were positive.

The most common symptoms presented in the cases were weight loss, asthenia, dysphagia, chronic cough and fever. The sites involved in order of frequency of oral histoplasmosis were buccal mucosa, tongue and palate.

Treatment was based on the use of itraconazole (seven patients) and amphotericin B deoxycholate (four patients). Eight patients responded well to therapy after one year, two did not return for reevaluation and one died despite adequate therapy.

In conclusion, oral histoplasmosis is closely associated with immunosuppression status, especially in patients presenting AIDS^{1,2,6,10-13}. In some cases, it is the initial indication of AIDS, as reported in literature^{11,12}. Moreover, in the majority of cases, oral histoplasmosis is the first sign of DH, as observed in nine of the 11 cases presented in this article.

Awareness of the different manifestations of histoplasmosis may enable earlier diagnosis and the administration of correct therapy when a new unexplained lesion is present, especially in immunocompromised patients, leading to a clearer understanding of histoplasmosis, including the disseminated form, and improved evaluation of the disease.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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