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Oral histoplasmosis associated with HIV infection: a comparative study

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OBJECTIVE: Histoplasmosis is a granulomatous fungal disease caused by *Histoplasma capsulatum*. The objective of the present paper was to describe the prevalence of oral histoplasmosis (OH) in two services from an endemic area in Argentina between 1991 and 2002 and to compare the clinicopathological profile of OH between HIV-positive and HIV-negative patients.

METHODS: About 733 HIV+ (group A) and 14 260 patients (group B) were examined. Clinical diagnosis was confirmed by cytology, biopsy or culture.

RESULTS: About 21 (3%) and 10 (0.07%) cases of OH were diagnosed in group A and B respectively. Most patients were male. A total of 90% of patients in group A were <45 years old whereas 70% of group B were more than 45 years old. Palate, gingiva and oropharynx were the most frequent locations. The importance of including histoplasmosis in the differential diagnosis of ulcerated oral lesions in immunocompromised patients was discussed.

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Introduction

Histoplasmosis is a granulomatous fungal disease of worldwide distribution caused by *Histoplasma capsulatum*. The infecting agents are airborne spores from the mycelial form. It is usually found in warm, humid environments that contain bird and bat excreta (1–7). The most endemic areas for *H. capsulatum* are certain river valleys of the world between latitudes 45° north and 30° south of the equator (1, 4, 6–15). In Argentina, the endemic region is around the central, east and northeast area (5, 16–18).

Clinically, histoplasmosis has been classified as: (i) a primary acute pulmonary form, (ii) a chronic pulmonary and (iii) a disseminated form (DH) occurring in infants, elderly or in immunocompromised patients (6, 19–23). In 1985, the Centre for Disease Control added DH to the spectrum of infections that characterize the acquired immunodeficiency syndrome (AIDS). The main reason for the delay in recognizing histoplasmosis as an opportunistic infection in those patients was that early AIDS cases appeared first in non-endemic areas. With spread of the disease to endemic areas, it has emerged as an important opportunistic infection in patients with AIDS (8, 9, 24, 25). About 30–66% of patients with DH have oral lesions, frequently presenting as the initial sign. Generally lesions of histoplasmosis in the oral cavity, are the local manifestation of pulmonary or disseminated disease (16, 26) but rarely they may be the primary or even the only manifestation of the disease (3, 4, 8, 10, 16, 17, 27–29). The diagnosis is usually based on clinical signs and symptoms, organ function tests and fungal demonstration or culture from a lesion or secretion. Serological testing may help together with other suggestive but non-diagnostic clinical criteria (4–6, 11, 17). Recently, molecular typing of *H. capsulatum* has been shown to be useful in distinguishing relapse from reinfection, and in defining the likely source of the infection (21, 30, 31). Furthermore, molecular typing of *H. capsulatum* by the random amplified polymorphic DNA polymerase chain reaction (RAPD–PCR) method, is able to discriminate among clinical isolates, making it a useful tool for epidemiological investigation (21).

Treatment

Historically, amphotericin B has been the drug of choice for systemic histoplasmosis (1–3, 8, 12, 16, 17, 32–37).

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The options have broadened considerably since the introduction of the azole compounds, ketoconazole and itraconazole (2, 6, 8, 38).

The aim of the present paper is to describe the prevalence of OH in two services from an endemic area in Argentina and to compare the clinicopathological profile of histoplasmosis oral lesions of HIV-infected (HIV+) and HIV-negative (HIV−) patients.

Material and methods

In this retrospective study, the clinical records made by us in HIV+ patients of Rawson Hospital: group A, and in those attended in Clinical Stomatology B (a referral clinic for oral soft-tissue lesions): group B, between December 1991 and December 2002 were revised in order to analyse and compare the prevalence of OH in both groups. Group A included 733 patients and group B 14 260. Written consent was obtained from each patient before the study; oral examinations and the diagnosis at both centres were made by the same trained professionals and supervised by the head professor. All the patients with OH were tested for HIV infection and the HIV-positive excluded of group B. When an ulcerated granulomatous lesion suggesting OH was found, the diagnosis was based on the demonstration of the microorganism in biopsies, cytological smears or culture (4–7, 11, 16). Biopsies were stained with haematoxylin and eosin and with periodic acid-Schiff (PAS) stain reaction; in some cases the Grocott silver methenamine (GSM) procedure was used. Cytological smears were stained with May Gründwald Giemsa (MGG) and with Papanicolaou stain (EA36-Hematoxylin). Additional confirmation was obtained by isolation and identification of the organism from tissue or secretion cultures. The tissue was added to the following media: Sabouraud dextrose agar + chloramphenicol, ampicillin and gentamicin. The tubes were incubated at 28°C to observe the mycelial and at 35°C to observe the levaduriform or infecting form. Positive colonies were then transferred to blood agar plates and incubated at 35°C, eventually resulting in conversion to the yeast form. The diagnosis was confirmed by the dimorphism of both cultures.

Results

In group A (HIV+ patients), 21 (3%) had OH, while in group B (HIV−) only 10 (0.07%) did. The analysed data on age, gender, general condition, other involvement and diagnosis of these patients are shown in Table 1. The age ranged from 23 to 77 years. Nineteen patients (90%) in group A, were <45 years old whereas seven (70%) in group B were more than 45 years old, indicating a positive correlation between age and HIV infection in patients with OH ($P = 0.001$, Fisher's exact test). Most of the patients were male, 81% in group A and 90% in group B. Weight loss followed by persistent cough and dysphagia, were the most frequent symptoms in both groups; in addition, 67% of the HIV+ patients had fever. The average of CD4 count in HIV+ patients was 60/mm^3 and ranged from 3 to 162/mm^3.

Oral lesions had similar clinical presentation in both groups, described as painful granulomatous ulceration. The lesions began as erythematous, painful red patches (see Fig. 1) that latter became elevated, granulomatous and ulcerated as shown in Fig. 2. The ulcerations were covered by yellowish pseudomembranes difficult to remove and tender to palpation. Most of the patients in both groups, had more than two lesions. The most frequent locations were hard and soft palate, gingiva and oropharynx, followed by tongue. Gingival lesions were associated with bone loss. Presence of histoplasmosis was diagnosed by cytology, culture, biopsy or direct examination.

Microscopic findings

Yeast forms were quite easily visualized in cytological smears or biopsies. The smears revealed in addition to squamous cells of the oral mucosa, several erythrocytes, neutrophils and macrophages-containing intracellular spherical to ovoid bodies each surrounded by a small light halo (Fig. 3). Biopsy specimens showed a normal maturing, thinly stretched and ulcerated stratified squamous epithelium. The lamina propia showed focal accumulations of mononuclear macrophages stuffed with 2–5 micron fungal yeasts and some isolated organisms that stained highly positive with PAS and GSM. Yeast forms were seen intracellularly within the histiocytes, and as described in the literature, they had a thin wall instead of a true capsule (39). The ulcerated surface was coated with fibrin and the area beneath the ulcer showed a moderate acute inflammatory infiltrate. Several small microorganisms, with frequent transepithelial migration were found in group A, whereas in group B they were scarce but more voluminous. On the contrary, conspicuous granulomas with giant cells were observed in HIV− patients (Fig. 4), whereas in group A they were exceptional. Vasculitis phenomena were occasionally observed. Cultures were positive in seven cases of group A.

The OH was marker disease in 10 HIV+ patients (48%). The treatment was dependant on the immunological condition of the patient, and on the availability of drugs in our public hospital. In 14 cases of the group A the treatment begun with amphotericin B, and when the infection was controlled, an azole antifungal was used; in six cases it was controlled only with itraconazole. This was the drug of choice in group B. The evolution was good in all patients but three of group A relapsed some months later, only two died after therapy but histoplasmosis was not the cause of death.

Discussion

Most investigators believe that human infection occurs via inhalation of aleuriospores in dust (5, 6, 15). Ritter (40) and Gordon et al. (41), however, suggest that at least in some instances the spores gain entry to the gastrointestinal tract from contaminated drinking water. On the contrary, some investigators claim that primary

Table 1 Clinical features of oral histoplasmosis in 21 HIV-infected patients and 11 no HIV patients

Case number	*Age*	*Sex*	*Risk factor*	*General condition*	*Other involvement*	*Diagnosis*
1	31	M	HIV+	Leucocytes 4500/mm^3, lymphocytes (L) 11%, CD4 78/mm^3	Skin	Culture+, direct examination+
2	65	M	HIV+	Leucocytes 6500/mm^3, L 39%	Larynx	Culture+, direct examination+, immunodiffusion 2 band+
3	30	M	HIV+	Leucocytes 4200/mm^3, L 16%, CD4 36/mm^3, viral copies 179 000	Skin	Culture+, direct examination+, cytology+
4	31	M	HIV+	Leucocytes 7100/mm^3, L 4%	Skin, lung	Culture+, direct examination+, haemoculture+, cytology+
5	28	M	HIV+	Leucocytes 2805/mm^3, L 44%, CD4 131/mm^3	Skin, lung	Biopsy+
6	40	M	HIV+	Leucocytes 2300/mm^3, L 39%, CD4 90/mm^3	Skin, lung	Direct examination −, biopsy+, bone marrow culture+
7	42	M	HIV+	Leucocytes 4100/mm^3, L 24%, CD4 117/mm^3, viral copies 27 890	–	Cytology+
8	63	M	HIV+	Leucocytes 4200/mm^3, L 31%, viral copies 64 000, CD4 162/mm^3	–	Cytology+
9	24	M	HIV+	–	–	Direct examination+, biopsy+, culture−
10	23	F	HIV+	Leucocytes 2700 mm^3, CD4 69/mm^3, viral copies 270 000	Skin	Biopsy+, cytology+, bone punction+
11	32	F	HIV+	Leucocytes 4700/mm^3, L 10%, CD4 64/mm^3	Skin, joint	Direct examination+, cytology+, culture−
12	32	F	HIV+	Leucocytes 3100/mm^3, L 48%, CD4 36/mm^3, viral copies 168 700	Skin	Biopsy+
13	36	F	HIV+	–	–	Direct examination+, culture+
14	30	M	HIV+	Hepatomegaly, leucocytes 4500/mm^3, CD4 3/mm^3	Lung	Biopsy+, cytology+
15	43	M	HIV+	Anaemia −, leucocytes 3600/mm^3, CD4 54/mm^3	Skin, nasal mucosa	Biopsy+, cytology+
16	38	M	HIV+	Leucocytes 3300/mm^3, L 30%	Skin	Biopsy+
17	40	M	HIV+	Pneumonia	Lung	Cytology+
18	33	M	HIV+	Oral and cutaneous Kaposi's sarcoma	–	Cytology+, biopsy+
19	39	M	HIV+	–	Skin, lung	Cytology+
20	45	M	HIV+	–	–	Cytology+, culture+
21	30	M	HIV+	Leucocytes 3310, CD4 6/mm^3	Skin, lung, bone marrow	Cytology+
22	68	M	Farmer HIV−	Leucocytes 5000, L 18%	Lung	Biopsy+, culture+
23	48	M	Rural area HIV−	Patient on dialysis	–	Biopsy+, culture+
24	62	M	Rural area HIV−	Good	–	Biopsy+, culture+
25	27	M	Rural area HIV−	Lepra lepromatous	Skin, lung	Biopsy+, cytology+
26	46	M	Farmer HIV−	Diabetes mellitus	Lung, skin	Biopsy+, culture+
27	72	M	Rural area HIV−	Diabetes mellitus HTA	–	Biopsy+, cytology−
28	56	M	Rural area HIV−	–	lung	Biopsy+
29	44	M	Rural area HIV−	Kidney transplant	–	Biopsy+, cytology−
30	44	M	HIV−	Leucocytes 17 000, L 11%, asthmatic	–	Cytology+
31	77	F	Rural area HIV−	Leucocytes 6300, N 52%, L 40%, Hb 12, SGV 25 mm	–	Biopsy+

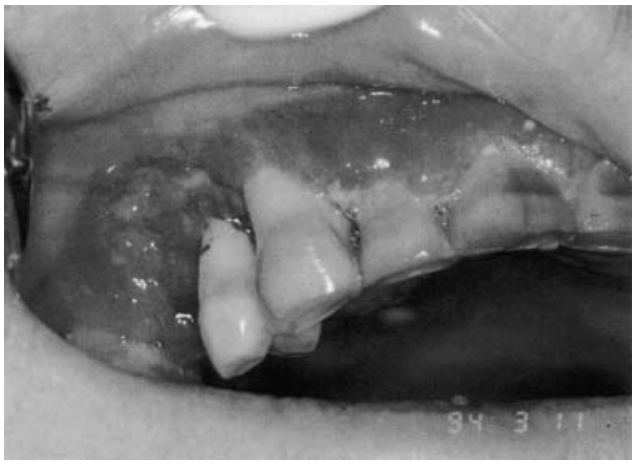

Figure 1 Clinical features of an HIV+ patient. Red patch involved the marginal and attached gingiva of the anterior area; ulcerated lesions of the premolar area are also present.

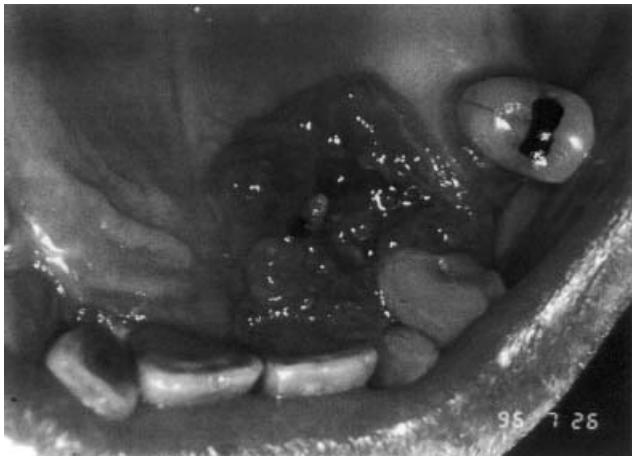

Figure 2 Clinical features of an HIV patient showing an elevated granulomatous lesion in hard palate and right maxillary gingiva.

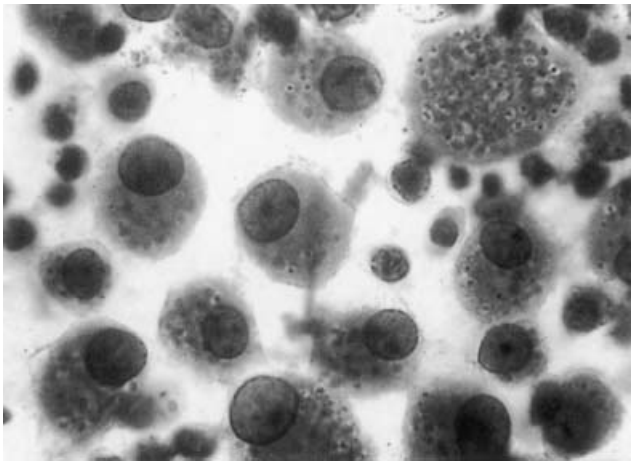

Figure 3 Cytological smear from an HIV+ patient, showing several macrophages containing intracellular spherical to ovoid bodies, each surrounded by a small light halo (papanicolaou stain, original magnification ×100).

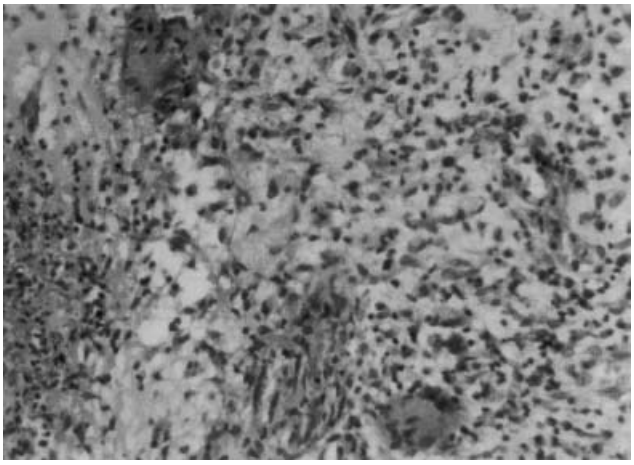

Figure 4 Biopsy specimen showing a granulomatous suppurated lesion from an HIV patient and the *Histoplasma capsulatum* within a giant cell (haematoxylin and eosin stain, original magnification ×60).

OH is possible and may occur from direct inoculation of the fungus into the mucosa (4, 5, 24). The possibility of human-to-human transmission between sexual partners is still an intriguing question (42). In the cases analysed in this paper OH lesions were found 43 times more frequently in HIV+ vs. HIV− patients; in addition all the HIV− patients lived on a farm or worked in contact with bird and bat excreta, whereas it was very difficult to establish the source of contamination in HIV+ patients. Clinical presentation and location of the oral lesions as well as the average of CD4 count ($60/mm^3$) were similar to those reported by other authors (11, 32). Although histoplasmosis is a disease that traditionally affects old people (12, 16), since the appearance of AIDS its prevalence has increased in younger people as in the present study (32, 43, 44). From these results it can be inferred that if histoplasmosis is diagnosed in a young patient, then a search for current HIV infection is justified. A higher prevalence among males was observed, as previously reported (4, 32, 44–47); nevertheless in this paper an increase in the prevalence among females was found in HIV+ patients, a tendency also observed by Casariego et al. (45). Most patients had a favourable response to the therapy; only two died after therapy but histoplasmosis was not the cause of death.

This report shows the importance of including OH in the differential diagnosis of ulcerated lesions in immunocompromised patients. Early recognition and prompt management of these infections are of paramount importance in maintaining the health and prolonging lifetime of patients with AIDS.

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