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Oral Medicine

Tongue disease in advanced AIDS

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OBJECTIVE: This study describes the involvement and the histological alterations found in the tongues of 92 autopsied patients who died with AIDS.
MATERIALS AND METHODS: Sex, age, CD4 cell count and clinical history were obtained from the files of 92 patients who died with AIDS. All the tongues were examined for macroscopical alterations and stained using H&E, Gomori-Grocott, Ziehl-Neelsen, PAS, Brow-Hopps and Mucicarmine. Histological autopsy findings were grouped based on a protocol that was designed following the World Health Organization recommendations.
RESULTS: The mean age of the patients who died of AIDS and CD4 cell count were 36 years and 82 cells μL^{-1}, respectively. Histological alterations of the tongues were found in 75% of the cadavers. The most common lesions were hairy leukoplakia (HL) (42 cases), candidosis (31 cases) and non-specific chronic glossitis (29 cases), followed by concomitant lesions (28 cases), non-specific chronic ulceration (17 cases), melanotic pigmentation (13 cases), herpes simplex (10 cases), lymphoepithelial cysts (two cases), cryptococcosis (two cases), mycobacteriosis (one case), histoplasmosis (one case), cytomegalovirus infection (one case) and non-Hodgkin Lymphoma (one case). HL with oral candidosis ($n = 13$) were the most common concomitant lesions.
CONCLUSION: These findings indicate that the tongue is a favorite site to occurrence of reactive, infectious and concurrent lesions in the end-stage of AIDS patients.
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Keywords: autopsy, HIV, tongue, viral infections, fungal infections, bacterial infections

Introduction

The detection of oral candidosis (OC) and hairy leukoplakia (HL) in patients with human immunodeficiency virus (HIV) infection has been considered to be an important outcome measure in this disease, contributing to staging and prognosis systems (Greenspan and Greenspan, 2002). It is accepted in the literature that the diagnosis of these lesions and other oral pathologies is associated with decrease of CD4 cell numbers and high HIV viral load in the peripheral blood.

In developing countries the clinical importance of the recognition of oral diseases cannot be underestimated. In these countries, oral diseases may serve as a first indicator of HIV disease (Greenspan and Greenspan, 2002). In countries without access to CD4 counts, OC remains the available marker of immune deterioration. In a Thai study, the presence of oral diseases (OC and HL) was related to the presence of systemic diseases such as tuberculosis and *Pneumocystis carinii* pneumonia (Nittayananta *et al*, 2002).

In a recent International Workshop addressing the prevalence and classification of oral diseases in HIV/AIDS, the needs of having additional data of HIV-related lesions in patients with associated systemic diseases or social conditions, especially coming from developing countries, were emphasized (Patton *et al*, 2002). Indeed, the literature is very scarce in systematic observations concerning oral manifestations in advanced AIDS, when systemic infections or disseminated neoplastic conditions are common. We have previously published the frequency of parotid gland involvement in a cohort of 100 Brazilian patients who died of AIDS, and observed that tuberculosis was the more frequent encountered lesion (Vargas *et al*, 2003). Concerning tongue involvement, there is a single European study that has addressed tongue alterations in 20 autopsies of patients who died from AIDS (Leonard *et al*, 1997). In this series, abnormalities in 90% of the cases, non-specific ulceration (nine cases) and candidosis (eight cases) were the most common findings. We present histological alterations found in the tongues of 92 Brazilian patients who died of AIDS from 1997 to 2001.

Materials and methods

The Ethics Committee of the Medical Faculty of the University of São Paulo approved the use of autopsy samples for the present study.

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Patient population
We studied the tongue of 92 patients with AIDS who have died in the University Hospital of the São Paulo Medical School between 1997 and 2001. In 82 of 92 patients of this series parotid gland involvement has been previously reported (Vargas *et al*, 2003). A complete autopsy was performed in all patients. The time frame from patients' death until autopsy was 6–10 h and all autopsies were collected sequentially, for each sex and age were obtained. The last CD4 cell count recorded in the clinical chart was used in this study. Final autopsy reports were analyzed for main diseases.

Tissue processing
During autopsy, the tongues were removed and divided in four regions: anterior, medial, posterior and lateral (Figure 1). Any macroscopical abnormality was fully represented. After dissection, each region was fixed in buffered 10% formalin solution for 24 h and six fragments were randomly obtained from each region. The material was routinely processed and stained with H&E, periodic acid-Schiff (PAS), Gomori-Grocott, Brown-Hopps, Zielh-Neelsen and Mucicarmine. The specimens were not submitted to microbiological studies.

Histological analyses
The findings were grouped partially based on the protocol designed by the EC-Clearinghouse on Oral Problems Related to HIV Infections and World Health Organization Collaborating Centre on Oral Manifestation of the Immunodeficiency Virus (1993) and listed below:

1. *Lesions strongly associated with HIV infection:* OC, HL, non-Hodgkin lymphoma (NHL) and Kaposi's sarcoma (KS);
2. *Lesions less commonly seen in HIV infection:* tuberculosis, mycobacteriosis, melanotic pigmentation, non-specific ulceration, herpes simplex virus (HSV);
3. *Lesions seen in HIV infection:* cryptococcosis, histoplasmosis, cytomegalovirus (CMV);
4. *Non-specific conditions:* non-specific chronic glossitis, lymphoepithelial cyst;
5. *Concomitant lesions:* HL/OC, HL/melanotic pigmentation, OC/HSV, histoplasmosis/mycobacteriosis, OC/cryptococcosis, CMV/HSV, OC/melanotic pigmentation;
6. *No histological alterations.*

Two experienced oral pathologists evaluated all cases. HL was diagnosed following the histopathological criteria proposed by Fernandez *et al* (1990). Non-specific chronic glossitis was defined by the presence of variable degrees of lymphocytic inflammation, without identification of etiological agents. Further, these were semiquantitatively classified in three categories, as follows: mild (when lymphocytes occupied until 10% of the lamina propria of the connective tissue), moderate (when lymphocytes occupied 11–20% of the lamina propria of the connective tissue) and intense (when lymphocytes occupied more than 20% of the lamina propria of the connective tissue).

Immunohistochemistry and in situ hybridization
In some cases, immunohistochemistry was performed for confirmation of the histological diagnosis, using the antibodies and protocols as previously described (Vargas *et al*, 2003). *In situ* hybridization for Epstein–Barr virus (EBV) was performed in one case of NHL, as previously described (Vargas *et al*, 2003).

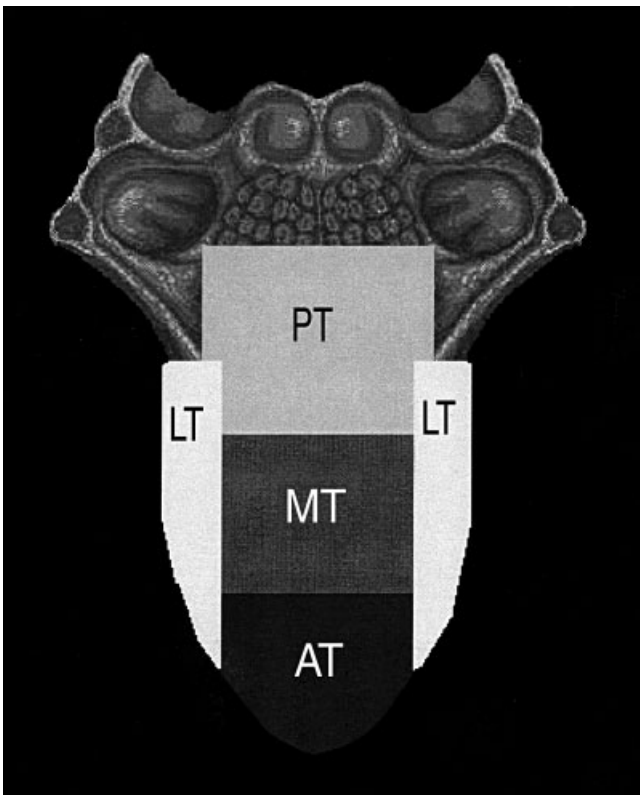

Figure 1 Schematic representation of the localization of the lesions in tongue

Results

Patient population
Sixty-two patients were male and 30 female. Their age ranged from 8 to 69 years with mean ± standard deviation (s.d.) of 36 ± 10. The last CD4 count performed before death was retrieved in 65 patients, with mean ± s.d. of 82 ± 115 cells μL^{-1}. Mycobacteriosis (29%) and septic shock (23%) were the main causes of death.

Histological findings
Sixty-nine patients (75%) displayed histological alterations in the tongue. The lateral region was more affected (42%), following by anterior (26%), medial (17%) and posterior (15%) regions. Table 1 shows age, sex, CD4 counts, autopsy and tongue histopathological findings of the infectious cases.

Table 1 Age, sex and CD4 counts of 43 AIDS patients that presented infectious lesions of the tongue at autopsy

Patients	*Age (years)*	*Gender*	*CD4 count (cells μL^{-1})*	*Autopsy findings*	*HIV tongue infections*
1	33	F	Na	Granulomatous disease, NOS	Candidosis
2	33	M	5	Pneumocystosis and chronic pancreatitis	Candidosis
3	47	–	Na	Mycobacteriosis	Candidosis
4	30	F	585	Congestive cardiac failure	Candidosis
5	30	F	34	Cerebral toxoplasmosis and ganglionar tuberculosis	Candidosis
6	27	M	Na	Disseminated cryptococcosis	Candidosis
7	31	F	3	Bronchopneumonia and septic shock	Candidosis
8	35	M	Na	Pneumocystosis	Candidosis
9	24	M	Na	Cerebral toxoplasmosis and bronchopneumonia	Candidosis
10	26	F	Na	Tuberculosis and cytomegalovirus disease	Candidosis
11	27	F	46	Strongyloidiasis and septic shock	Candidosis
12	33	M	8	Disseminated cryptococcosis	Candidosis/cryptococcosis
13	45	M	159	Cirrhosis and pancreatitis	Candidosis
14	29	F	162	Septic shock	Candidosis
15	68	M	95	Bronchopneumonia and septic shock	Candidosis
16	8	M	78	Bronchopneumonia	Candidosis
17	29	M	16	Pneumocystosis	Candidosis
18	50	M	18	Bronchopneumonia and cerebral cryptococcosis	Cryptococcosis
19	51	M	Na	Cytomegalovirus disease and cryptosporidiosis	Candidosis
20	44	M	Na	Gastric non-Hodgkin lymphoma	Candidosis
21	35	M	Na	Bronchopneumonia and Burkitt's lymphoma	Candidosis
22	29	M	36	Disseminated tuberculosis	Candidosis
23	34	M	Na	Disseminated histoplasmosis	Candidosis
24	44	M	66	Disseminated non-Hodgkin lymphoma	Candidosis
25	28	M	16	Cerebral toxoplasmosis	Candidosis
26	38	M	Na	Cerebral cryptococcosis and pneumocystosis	Candidosis
27	25	F	10	Cytomegalovirus disease and pneumocystosis	Candidosis
28	46	M	12	Disseminated mycobacteriosis and histoplasmosis	Histoplasmosis/mycobacteriosis
29	45	M	78	Cerebral toxoplasmosis and *Staphylococcus aureus* sepsis	Candidosis
30	51	F	Na	Disseminated tuberculosis	Candidosis
31	38	M	18	Disseminated tuberculosis	Candidosis
32	34	F	270	Hepatitis C	Candidosis
33	24	F	Na	Disseminated tuberculosis	Candidosis
34	44	M	45	Septic shock	Herpetic
35	28	F	21	Cachexia	Herpetic
36	31	M	Na	Cerebral toxoplasmosis and bronchopneumonia	Herpetic
37	29	F	Na	Disseminated tuberculosis	Herpetic
38	40	M	375	Bronchopneumonia	Herpetic
39	32	M	21	Pulmonary thromboembolism	Herpetic
40	26	M	15	Pneumocystosis and disseminated mycobacteriosis	Herpetic/cytomegalovirus infection
41	34	M	Na	Disseminated histoplasmosis	Herpetic
42	46	M	290	Cerebral cryptococcosis and bronchopneumonia	Herpetic
43	25	F	10	Cytomegalovirus disease and pneumocystosis	Herpetic

Na, not available; M, male; F, female.

Lesions strongly associated with HIV infection

Hairy leukoplakia was diagnosed in 42 patients (45.6%). The lateral region was the most commonly affected (62.3%). The frequency of HL among women and men was similar (50% female; 43.5% male). Histologically, the lesions were characterized by acanthosis and parakeratosis of variable thickness associated with little or absent chronic inflammation in the subepithelial layer. In the prickle layer varying numbers of swollen, ballooned cells with pyknotic nuclei and perinuclear halos suggestive of EBV inclusions bodies (Figure 2) were found. *Candida* pseudohyphae were observed on the superficial layer of epithelium in 32% of the HL cases (see Concomitant lesions).

Oral candidosis occurred in 31 patients (33.6%). The lateral and the anterior borders were more commonly involved (30.7 and 29.3%, respectively). The frequency

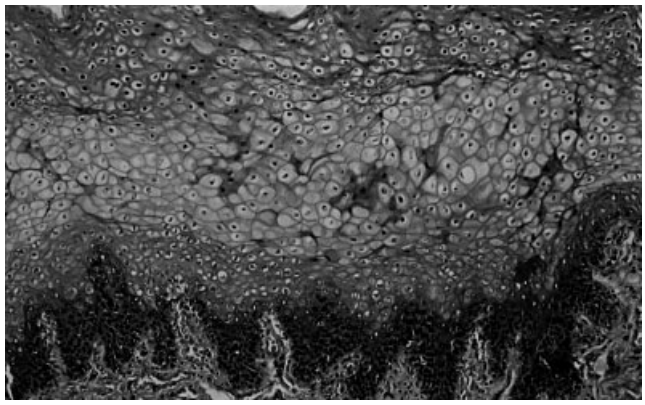

Figure 2 Case of hairy leukoplakia showing keratinocytes with ballooned cytoplasm and pyknotic nuclei with halo perinuclear and absence of chronic inflammatory cells (H&E, original magnification ×100)

of OC among women and men was very similar (36.6% female, 35.4% male). Histologically, massive numbers of microorganisms were seen in the epithelium with small or absent infiltration of polymorphonuclears (Figure 3).

In one patient of the present series a malignant tumor in the tongue, a large B-cell NHL, EBV positive, was detected. The lymphoma infiltrated diffusely the anterior and posterior regions of the tongue (Figure 4). Immunohistochemistry showed that the neoplastic cells were CD45/CD20 positive and positive for EBV by *in situ* hybridization. Although four patients presented KS in other organs, in none of them the neoplasia was detected in the tongue.

Lesions less commonly seen with HIV infection

Ten patients (10.8%) developed histological alterations compatible with HSV in the tongue (Figure 5). Anterior and posterior regions were more affected (31.6% each). The ulcerated lesions were characterized by large amounts of multinucleated keratinocytes, with marked ballooning degeneration and an intense mixed inflammatory cellular infiltrate. Typical intranuclear inclusions were found in all cases. In four of 10 cases herpes virus lesions were present in the ductal cells of minor salivary glands (Figures 6 and 7). In one patient HSV infection occurred simultaneously with CMV infection (see Concomitant lesions). Cytomegalic inclusions were

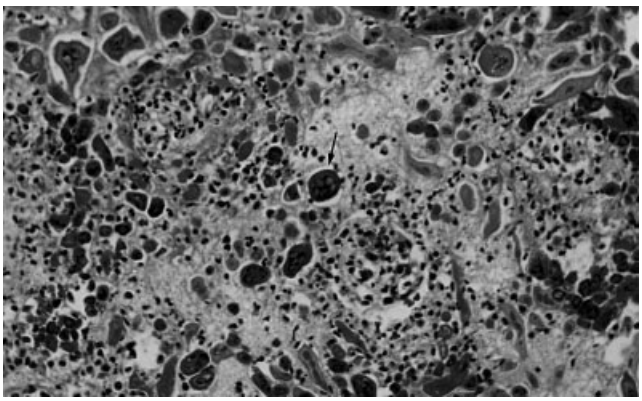

Figure 5 Keratinocytes displaying eosinophilic cytoplasm and nuclear inclusion consistent with herpetic infection (arrow) (H&E, original magnification ×200)

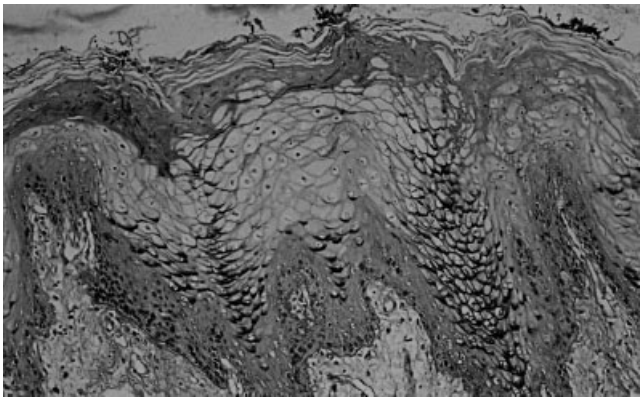

Figure 3 Candidal infections on superficial lingual of the HIV patients associated with HL showing numerous hyphae and absence of microabscesses (PAS, original magnification ×40)

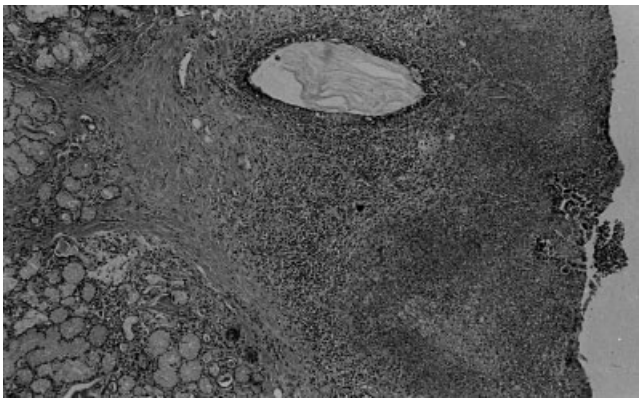

Figure 6 Ulcerated area showing ductal salivary gland epithelium infected by herpes simplex virus (H&E, original magnification ×50)

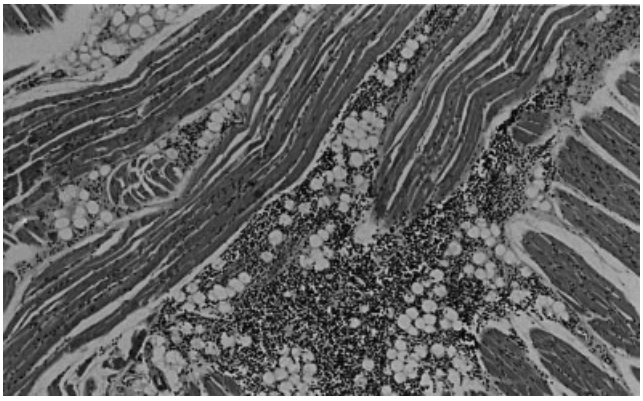

Figure 4 Histological features of anaplastic large non-Hodgkin lymphoma showing diffuse infiltrated inside of muscle and adipose tissue of the tongue (H&E, original magnification ×100)

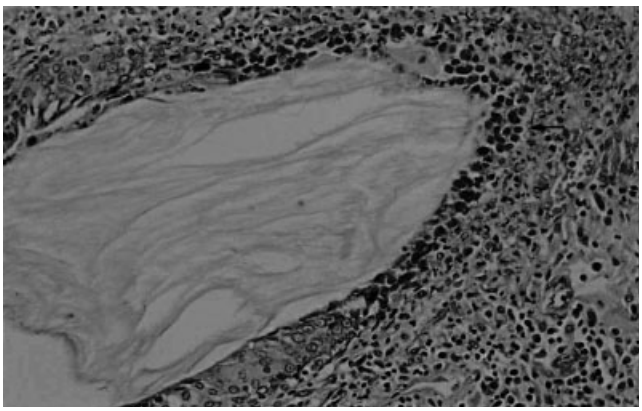

Figure 7 Case showing involvement by herpetic infection in ductal cells of salivary gland (arrow) (H&E, original magnification ×200)

detected in endothelial cells located in the ulcerated area (Figure 8).

Seventeen (18.4%) patients presented non-specific ulceration in the tongue, with lateral region the more affected (36.4%). Histologically, the lesions were characterized by a thick fibrinous layer interspersed with neutrophils covering the ulcerated area. The underlying subepithelium showed little amounts of chronic inflammation. No microorganisms or viral inclusions were identified.

Melanotic pigmentation occurred in 13 patients (14%), with lateral region the main affected site (61%). Microscopically, there was marked melanin deposition in the basal cell layer and in the upper portion of the lamina propria. Melanin appeared within melanophages or free in the connective tissue (Figure 9). There were no atypical melanocytes.

One patient presented mycobacteriosis in the tongue, concomitant to histoplasmosis (see Lesions seen in HIV infection and Concomitant lesions). Microscopically the case displayed an infiltrate of foamy macrophages, full of mycobacteria (Ziehl-Neelsen stain positive), scant areas of necrosis and no granuloma formation.

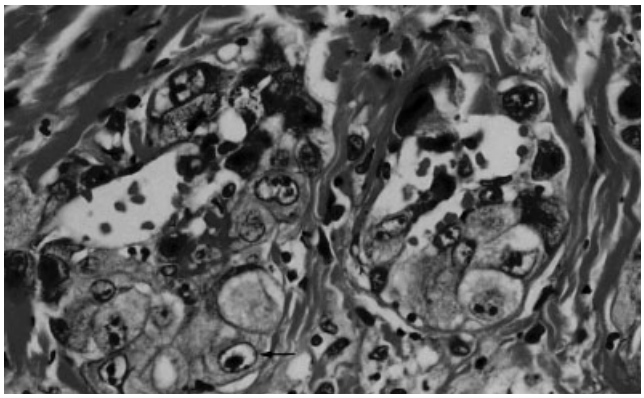

Figure 8 Endothelial cells demonstrated large intranuclear inclusion surrounded by clear halo (eye's owl) and basophilic granular intracytoplasmic inclusion (arrow) caused by CMV (H&E, original magnification ×400)

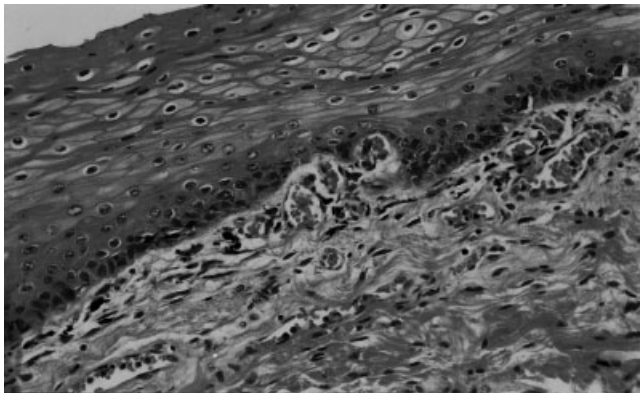

Figure 9 Presence of melanin within basal cell layer and the upper portion of the lamina propria (H&E, original magnification ×200)

Lesions seen in HIV infection

Two patients presented cryptococcosis and the lateral region was the main affected site (66.7%). Histologically, many fungal structures of different shapes and sizes, positive for mucicarmine, were found below the epithelial layer (Figure 10). There was scarce inflammatory response around the lesions.

Histoplasmosis was diagnosed in one patient with a concomitant mycobacteriosis lesion (see Concomitant lesions). Histologically, all regions of the tongue were involved and displayed vacuolated histiocytes containing numerous rounded tiny intracytoplasmic fungic structures permeated by dense mononuclear inflammatory infiltrate (Figures 11 and 12). Immunohistochemical analysis using anti-*Histoplasma* antibody was positive. We have previously reported this findings elsewhere (Vargas *et al*, 2003).

Non-specific conditions

Non-specific chronic glossitis was observed in 29 patients (31.5%). Non-specific chronic glossitis was scored as mild, moderate and intense in 58.7, 24 and 17.3 of cases, respectively. The posterior region was affected in 36% of cases. Two patients (2.2%) presented

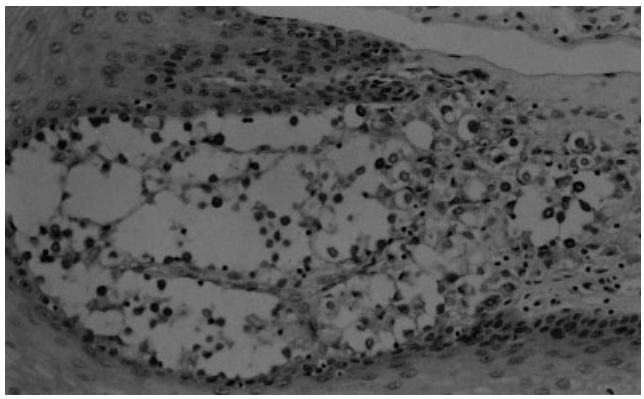

Figure 10 Numerous *Cryptococcus* sp. yeast in tongue in patients with disseminated disease. Note fungus cells of different shapes displaying appearance of 'soaps' blister' and mild inflammatory infiltrate around of lesion (Mucicarmine, original magnification ×200)

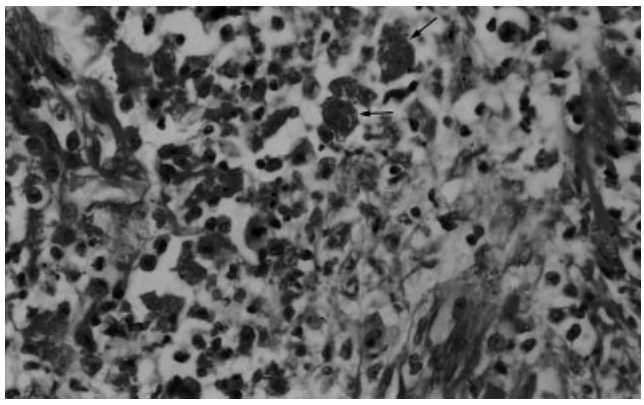

Figure 11 Large numerous or small, round to oval, yeast (arrows) within macrophages consistent with histoplasmosis (PAS, original magnification ×200)

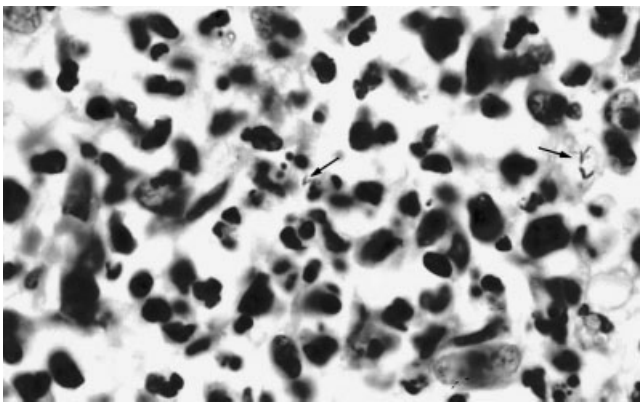

Figure 12 Mycobacteriosis in the tongue showing an infiltrate of foamy macrophages, full of mycobacteria (arrows), scant areas of necrosis and no granuloma formation (Ziehl-Neelsen, original magnification ×1000)

small lymphoepithelial cyst in the posterior region of the tongue (lingual tonsils). Microscopically, the cysts were located beneath the surface epithelium and both were lined by parakeratinized stratified squamous epithelium. Their lumen contained a proteinaceous, amorphous substance. Around the wall in both cysts, the inflammatory infiltrate was scarce and without germinative centers (Figure 13).

Concomitant lesions

Twenty-eight of 92 patients (30.4%) developed concomitant lesions in the tongue. The more common concurrent lesions were HL associated with OC (13 cases). Other concomitant lesions observed were: HL/melanotic pigmentation (five cases), HL/non-specific ulceration (three cases), OC/HSV (two cases), melanotic pigmentation/HSV (two cases), OC/non-specific ulceration (two cases), histoplasmosis/mycobacteriosis (one case), OC/cryptococcosis (one case), CMV/HSV (one case), and OC/melanotic pigmentation (one case). Sixty-three patients of this series presented AIDS-related disseminated infections or neoplastic diseases as a major finding at the autopsy. Table 2 shows the frequency (%) of tongue involvement in each disseminated condition at autopsy.

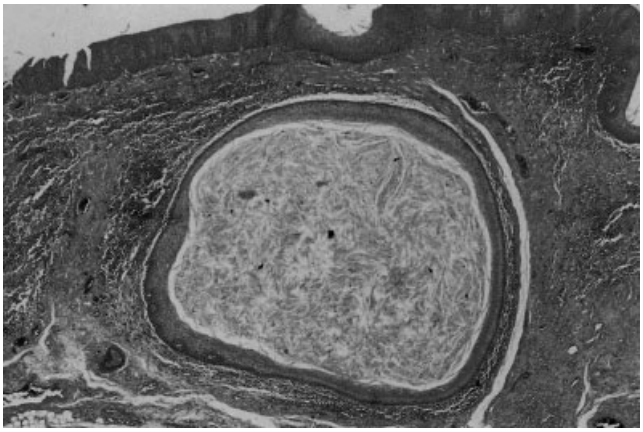

Figure 13 Lymphoepithelial cyst in tongue. Note the depletion of lymphoid tissue around of wall cyst (H&E, original magnification ×25)

Table 2 Tongue involvement (%) in 63 patients who presented systemic diseases related to AIDS

Diseases	*Main autopsy findings* (n)	*Tongue involvement* (n)	*Percentage of tongue involvement*
Tuberculosis	14	0	0
Cytomegalovirus infection	13	1	7.5
Pneumocystosis	10	0	0
Mycobacteriosis	7	1	14
Cryptococcosis	7	2	28.5
Histoplasmosis	4	1	25
Non-Hodgkin lymphoma	4	1	25
Kaposi's sarcoma	4	0	0

No histological alterations

Twenty-three patients (25%) did not exhibit histological alterations in the tongue.

Discussion

Our results demonstrate that involvement of tongue in advanced AIDS is very common. Seventy-five percent of the cadavers of this series displayed some histological alteration in the tongue. The most common lesions were HL (45.6%), OC (33.6%), non-specific chronic glossitis (31.5%) and concomitant lesions (30.4%).

Leonard *et al* (1997) studied a cohort of 20 patients and described a larger frequency of histological alterations than us, although in a smaller population. In our series the main lesion was HL (45.6%, $n = 92$) followed by OC (33.6%, $n = 92$). Leonard *et al* (1997) detected mainly non-specific ulceration (45%) and OC (40%). They reported an unexpectedly low prevalence of HL (5%), despite the fact that 70% of their patients presented CD4 cell counts below 200. These authors suggested that antiviral and antiretroviral therapy were major factors in contributing to the low prevalence of HL in their study. In fact, HL has been shown to regress in response to antiviral therapy with acyclovir and ganciclovir, and antiretroviral drug zidovudine (Patton *et al*, 2000; Eyeson *et al*, 2002). In our cohort, HL frequency in the tongue is similar to the pre-highly active antiretroviral therapy (HAART) era. Although we were not able to get data concerning the use of HAART in our study, the differences observed in the two cohorts could be attributed to the characteristics of populations, or more likely, to the use of different antiretroviral therapies. As reported by several authors, factors such as geographical location, ethnicity, endemic disease and mode of expression of EBV virus in the oral epithelium could also contribute to the differences in HL prevalence observed in different populations (Shiboski *et al*, 1996; Patton *et al*, 2002).

Two interesting findings of our study are: (a) the tongue is affected by local rather than systemic pathologies; and (b) a large number of concomitant lesions are

present in patients with advanced AIDS. This latter observation is in agreement with the one previously reported by Ranganathan *et al* (2000). These authors described in 300 South Indian patients, the presence of two or more lesions in the oral cavity of 33 and 49% of the non-AIDS HIV and AIDS patients, respectively.

We described the parotid gland alterations in patients with advanced AIDS and showed that the parotid gland is a common site of dissemination of AIDS (Vargas *et al*, 2003). For instance, 76% of the patients with disseminated mycobacteriosis and 69% with CMV infection presented with parotid gland involvement. In contrast, in the tongue 7.6% of the patients with disseminated mycobacteriosis (one patient) and 7.6% with CMV (one patient) showed tongue involvement (Table 2). This can be partially explained by the large number of intraparotid lymph nodes in the parotid gland when compared with the localized presence of the lingual tonsils. Moreover, the tongue is more affected than the salivary glands probably because of anatomical localization of the tongue, which facilitate the occurrence of local pathologies.

The prevalence of OC vary from 11 to 96% around the world, with various reports showing rates more than 50% in AIDS patients (Kolokotronis *et al*, 1994; Ranganathan *et al*, 2000; Holmes and Stephen, 2002). It appears with the progression disease and with the decrease of CD4 T lymphocytes count (Touyz *et al*, 1996; Leonard *et al*, 1997). The palate, dorsum and lateral surfaces of the tongue are the main affected sites by candidosis (Samaranayake, 1992). In the present study, candidosis were mainly seen on the lateral and anterior regions of the tongue with 30.6 and 29.4%, respectively. In addition, the absence of formation of microabscesses on the lingual epithelium and presence of mild subepithelial inflammation might be explained by the accentuated immunodepression of our patients. Candidosis associated with HL occurred in 34% out of 42 cases of the HL. Our results are in line with the literature, as it has been shown that candidal hyphae can be isolated from 30 to 80% of the HL lesions (Triantos *et al*, 1997; Dias *et al*, 2000). The explication for high number of cases of HL with associated hyphae of *Candida* on the superficial layer of the epithelium is not yet clear. However, in recent work from our laboratory, Rangel (2001) showed that the adherence of yeasts of *Candida* on superficial layer of the keratinized epithelium is significantly higher in the presence of a bacterial colony in a mechanism mediated by polysaccharides synthesized by it.

Some studies have associated male gender with HL and KS, but not with OC (Patton *et al*, 2002). Especially in developed countries, HL seems to be more frequent in men. Our data reproduce other studies in developing countries, as we could not find a difference between gender and the frequency of HL/OC. Ramirez-Amador *et al* (1998) in Mexico City analyzed 379 men and 57 women with HIV infection and reported that oral ulcers, KS and necrotizing periodontal disease were present only in men, whereas the other lesions studied, including HL and OC, had no significant gender predilection. Arendorf *et al* (1997) in South Africa did not find significative difference of gender in HL cases but in OC cases there was a slight prevalence in women than men (46 and 37%, respectively).

We have found unusual infections affecting the tongue in this study. Although extrapulmonary cryptococcosis is considered an indicator disease of AIDS, it is rarely reported in the tongue (Leonard *et al*, 1997; Monteil *et al*, 1997). In our series, two patients presented cryptococcosis of the tongue, among seven patients with systemic disease (Table 2). Tissue reaction to the *Cryptococcus* may vary from scant to a non-suppurative granulomatous reaction with variable degrees of necrosis (Monteil *et al*, 1997).

Histoplasmosis may affect any site of the oral cavity (Economopoulou *et al*, 1998). In some occasions the oral lesions may be the primary or even the only one manifestation of this disease (Heinic *et al*, 1992; Nittayananta *et al*, 1997; Warnakulasuriya *et al*, 1997). Histologically, tissue response to *Histoplasma* can vary from granuloma formation to macrophagic pattern (Vargas *et al*, 2003). A single patient in this series presented with disseminated histoplasmosis associated with mycobacteriosis, including the tongue.

Non-HL-like virotic lesions were the second type of infections more prevalent in our cohort (12%, $n = 92$). Most of the lesions were compatible with HSV-associated lesions, a frequent finding in AIDS patients (Itin and Lautenschlager, 1997). A sole patient of our series showed the concomitant occurrence of HSV and CMV infection, a not rare finding in the oral cavity of patients with HIV/AIDS (Jones *et al*, 1992; Heinic *et al*, 1993; Flaitz *et al*, 1996; Regezi *et al*, 1996). Another interesting finding, not previously reported in the English literature, was the presence of herpetic inclusions in the ductal cells of the minor salivary glands in four cases. We argue that it may have occurred as a consequence of extension of the epithelial lesions to the ductal cells of the salivary glands, probably as consequence of intense immunosuppression.

Non-Hodgkin lymphoma of the oral cavity accounts for 3% of all malignant lymphomas in HIV positive patients and most lymphomas harbor EBV (Dodd *et al*, 1992; Jordan *et al*, 1998). NHL in the tongue is unusual and the sites most commonly affected are the fauces and gingiva (Jordan *et al*, 1998). From four patients with AIDS-associated NHL the tongue was diffusely involved in one. KS rarely affects the tongue. A single description (Leonard *et al*, 1997), reported the simultaneous occurrence of NHL and KS in the tongue of one autopsied AIDS patient. Despite four patients presenting with KS in our cohort, none had tongue involvement.

Lymphoepithelial cyst affects mainly the parotid gland and may be found in 3–6% of HIV patients (Vargas *et al*, 2001). We found two patients presenting lymphoepithelial cyst in the posterior region of the tongue. These cases represent the first description of lymphoepithelial cysts in the tongue of patients with

advanced AIDS. Lymphoepithelial cyst usually occurs in the early stages of HIV infection and is rarely found in advanced AIDS (Vargas *et al*, 2001). An interesting histologic feature was the absence of lymphoid follicles around the wall of the cysts, a feature usually described in these lesions. A possible explanation to this finding is that it may reflect the generalized immunedepletion these patients had.

Non-specific ulceration was a frequent finding in our series as seen by Leonard *et al* (1997). Aphthous-like ulcers in AIDS are described with rates quoted as 1.9–4% (Laskaris *et al*, 1992; Leonard *et al*, 1997). Chronic non-specific ulceration can appear when the immunosuppression is very severe (Glick and Muzyka, 1992; Kademani and Glick, 1998). The etiopathology of non-specific ulceration remains unknown (Piluso *et al*, 1996). Regezi *et al* (1993) discussed the role of macrophages and adhesion molecules in the pathogenesis of apthous-like ulcers of HIV-infected patients. However, the occurrence of non-specific ulceration on the tongue can be due to medical proceedings such as nasotracheal intubation or the use of medications (Kademani and Glick, 1998). In our cohort melanotic pigmentation occurred in 13 patients (14.1%) being more frequent than of the reported in the general AIDS population (2–10% of the patients). Several endogenous and exogenous factors are associated with the appearance of melanotic pigmentation in HIV-infected patients such as cigarette smoking, race, zidovudine and ketoconazole therapy, and adrenocortical deficiency (Langford *et al*, 1989). Recently, Ceballos-Salobreña *et al* (2000) proposed that the frequency of melanotic pigmentation could be increasing in association with the use of HAART.

Non-specific chronic glossitis was observed in 29 patients (31.5%). The specialized literature does not associate the occurrence of non-specific glossitis with HIV/AIDS patients, as well as a possible relation with immunosuppression. However, Rocha *et al* (1999) found non-specific chronic glossitis in 2% of HIV negative patients and concluded that several factors can cause glossitis such as mechanical, physical and chemical agents. In our cohort these agents certainly have contributed to the non-specific chronic glossitis occurrence.

In summary, we present the largest series of the literature showing the involvement of the tongue in advanced AIDS patients. Our data show that the tongue is a favorite site for numerous local and systemic infections and reactive diseases in end-stage AIDS patients. We believe that better knowledge of tongue pathology in advanced AIDS is essential to better map the full spectrum of oral disease in HIV infection/AIDS.

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