

Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population

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ABSTRACT

Aim: To determine the prevalence of oral lesions in a HIV + group of patients, related to CD4 cell count and viral load in a Venezuelan population.

Materials and methods: In the present study, we evaluated 75 HIV+adult patients, attended at the Center of Infectious Diseases, at the Faculty of Dentistry, Central University of Venezuela. Each patient was clinically examined for detection of oral mucosal lesions. In addition, CD4 cell count was determined by flow cytometry, as well as viral load by RT-PCR (Amplicor HIV-RNA, TM test 1.5, Roche)

Results: 85% (64/75) of HIV/AIDS patients showed associated HIV lesions. Oral Candidiasis constituted the most common lesion representing a 61% (39/64), followed by Oral Hairy Leukoplakia 53% (34/64); Oral Leukoplakia 34% (22/64), Melanic Hiperpigmentation 38% (18/64); Papilloma 13 (6/64), Lineal Gingival Eritema 8% (5/64); Aphthous Recurrent Stomatitis 5% (4/64) and Kaposi's Sarcoma 5% (3/64). Only one case of the following lesions were represented by Non Hodgkin Lymphoma, Multifocal Epithelial Hyperplasia, Recurrent Herpes, Histoplasmosis and Molluscum Contagiosum. The patients with a viral load of 30.000 copies/mm³ exhibited oral lesions related with HIV, independent of CD4 cell count, although patients with CD4+ levels of 200 cel/mm³ were more susceptible to develop these lesions.

Conclusions: The most common oral lesion was Oral Candidiasis followed by Oral Hairy Leukoplakia, Oral Leukoplakia and Melanic Hyperpigmentation. A high viral load was strongly associated to the oral lesions occurrence independently of CD4+ cell count.

Key words: HIV+, CD4+, Viral load, oral lesions.

RESUMEN

Objetivo: Determinar la prevalencia de las lesiones bucales en un grupo de pacientes VIH+, su relación con el conteo de linfocitos CD4 y la carga viral, en una muestra de la población venezolana

Materiales y métodos: En el presente estudio se evaluaron 75 pacientes adultos VIH+, provenientes del Centro para la Atención de Pacientes con Enfermedades Infectocontagiosas de la Facultad de Odontología de la Universidad Central de Venezuela. Cada uno de ellos fue examinado clínicamente para la detección de las lesiones presentes en la mucosa bucal. Igualmente se les determinó el conteo de células CD4+ mediante citometría de flujo, así como la carga viral mediante la técnica TR-RCP (Transcriptasa Reversa-Reacción en Cadena de la Polimerasa) (Amplicor HIV-1-RNA, TM test 1.5, Roche).

Resultados: 85% (64/75) de los pacientes VIH/SIDA presentaron lesiones asociadas a la infección por VIH. Entre ellas, la Candidiasis constituyó la forma más frecuente representando un 61% (39/64), seguida por la Leucoplasia Velloso con 53% (34/64), Leucoplasia Bucal 34% (22/64), Hiperpigmentación Melánica 38% (18/64). Papiloma 13% (6/64), Eritema Gingival Lineal 8% (5/64), Estomatitis Aftosa Recidivante 5% (4/64), Sarcoma de Kaposi 5% (3/64). Se presentó un solo caso (2%) de cada una de las lesiones que se enumeran a continuación: Linfoma No Hodgkin, Hiperplasia Epitelial Multifocal, Herpes Labial, Histoplasmosis y Molusco Contagioso. Los pacientes con una carga viral de 30.000 copias/mm³, presentaron lesiones bucales relacionadas con VIH independientemente del conteo de células CD4+, aunque los pacientes con niveles de CD4+ menores a 200 cel//mm³, fueron mas susceptibles a desarrollar estas lesiones.

Conclusiones: La lesión oral mas frecuente fue la Candidiasis bucal, seguida por la Leucoplasia vellosa, Leucoplasia bucal, e Hiperpigmentación melánica. Una alta carga viral estuvo fuertemente asociada a la presencia de lesiones, independientemente del conteo de células CD4+.

Palabras clave: VIH+, CD4+, carga viral, lesiones bucales.

INTRODUCTION

HIV infection constitutes a main health problem worldwide. The oral and perioral manifestations are common in HIV infected patients, and often influence the debilitating general health status, a worse prognosis of the disease, as well as a diagnostic factor in the monitoring of the immune status of the patient (1,2,3).

The vast majority of the HIV infected subjects have presented at least one manifestation in the head and neck area in any state of the disease (4), representing these oral lesions the oral signs of the disease (5,6). In addition, the occurrence of these lesions indicate a great susceptibility for opportunistic infections and a great possibility of rapid progression to AIDS (7,8). The CD4 cell count and viral load have been used lately as the most important laboratory parameter to evaluate the evolution of the disease (9). Several studies have been focused in the correlation between oral lesions prevalence and the laboratory parameters, such as CD4 cell count and viral load in HIV/AIDS patient serum, evidencing a strong correlation between the oral lesions, lower CD4 cell count and high viral load, concluding that these are involved with monitoring and progression of the disease, as well as the antiretroviral therapy, (10,11,12,13). Recently, others investigations have reported the a CD4 cell count less than 200 cel/mm³ and a viral load higher than 10.000 copies/ml associated to other factors including tobacco consumption, poor oral hygiene, and xerostomia could facilitate the occurrence of oral lesions in these individuals (10,14). With the antiretroviral therapy (ART) implementation for the treatment of HIV/AIDS, some

investigations have emphasized the decreased in the oral lesions occurrence in seropositive patients (15,16).

The aim of this study was to determine the oral lesions prevalence in a group of HIV+ patients related to CD4 cell count and viral load in a Venezuelan population.

MATERIALS AND METHODS

In the present study, 75 HIV+ adult female/male patients were attended at the Infectious Diseases Center, Faculty of Dentistry, Central University of Venezuela with a positive HIV test, from January 2001 to June 2002.

Each one was clinically assessed by one calibrated examiner, following the Clearinghouse diagnostic criteria (17). Each patient signed the written informed consent before being enroll in the study. Each patient presenting oral leukoplakia was selected according to Axell et al (1996) criteria (18). Once clinically evaluated, the patients exhibiting oral lesions were biopsied to establish the definite diagnosis. The incisional biopsies were performed using scalpel, fixed in 10% formalin, paraffin embedded, sectioned in a microtome, Hematoxylin and Eosin stained to be observed under a light microscope for definite diagnosis.

In those cases with the provisional diagnoses of Oral Candidiasis, the lesions were scrapped and subsequently culture on Agar-Sabouraud Media.

Blood samples were obtained (5 ml), 78 hours after the clinical examination to determine cell subpopulations by flow cytometry as well as viral load by RT PCR (Amplicor HIV-1 Test, TM Kit Roche). The criteria used to evaluate the viral load was: low between 401-5000

copies/mm³, Intermediate between 5001-30.000 copies /mm³ The statistical analysis was done using SPSS Software Version 10.1. To correlate the viral load, the CD4+ cell count, and the oral lesions frequency. Chi square test was used to a significance level of $p < 0.05$. The Fisher Test and Kruskal –Wallis was also used to validate the variance analysis.

RESULTS

In the present study, 75 patients were evaluated, 61 male (81%) and 14 female (19%). The mean age was 37 years, with a mean rank of 20-55 years. The most affected age group was in the 4th decade of life (30-39 years), 51% (38/75), observing a male predominance 44% (33/75). According to ethnic group, our results showed that the most common affected group was caucasian (55%), 41/75, followed by blacks 29%, amerindians 13% 10/75 and indigenous 3% 1/75. ($p < 0.90$).

From a total of 75 evaluated individuals, 63% were under ART, although 37% were not under any therapy. Additionally, 83% were under highly active antiretroviral effectivity therapy (HAART). Of these, 19 subjects had between 7-12 months under this modality. 17% of the individuals were under bithrapy of these, 3 subjects had between 4-6 months and others had 7-12 months under this therapy. There were no patients reported under monotherapy. According to the mode of transmiación, the most common was the sexual transmission in 88%. Of the cases, 66/75 were represented by 44% who have sex with men (MSM), 40% were homosexuals and 16% were in the group of men who have sex with men and women (MSMW). The parenteral mode of transmission represented 3% of the evaluated cases, one case had blood transfusion and other had intrahospitalary accident. There were not intravenous drug users. (IDU).

Prevalence of oral lesions in HIV/AIDS patients:

The distribution of oral lesions in the evaluated subjects was 85%, 64/75 of the HIV/AIDS patients exhibited lesions associated to HIV infection and 15% 11/75 not exhibited any pathology. According to the oral lesions identified in the present study, Oral Candidiasis constituted the most common form representing a 61% 39/64, followed by Oral Leukoplakia (34%) 22/64, Melanic Hyperpigmentation (38) 18/64, Papilloma (13%) 6/64, Lineal Gingival Erythema (8%) (5/64), Recurrent Aphtous Stomatitis 5% (4/64), Kaposi’s Sarcoma 5% (3/64). Only one case of the following lesions was observed: Non Hodgkin Lymphoma, Multifocal Epithelial Hyperplasia, Recurrent Herpes, Histoplasmosis and Molluscum Contagiosum (Table 1). It is noteworthy, that these differences observed between the first two lesions and the next two were statistically

Table 1. Prevalence of oral lesions in HIV/AIDS individuals EC-Clearing-house (1993).

HIV/AIDS patients (N=64)			
	ORAL LESIONS	N	%
GROUP I Strongly oral hairy associated to HIV/AIDS infection	Oral Candidiasis	39	61
	Leukoplakia	34	53
	Kaposi’s sarcoma	3	5
	Lymphoma	1	2
	Lineal Erythema	5	8
GROUP II Less frequently associated to HIV/AIDS infection	Papillota	6	9
	Multifocal Epithelial Hyperplasia	1	2
	Melanic Hyperpigmentation	18	28
	Labial Herpes	1	2
GROUP III HIV/AIDS Infection	Histoplasmosis	1	2
	Recurrent Aphtous Estomatitis	4	6
	Molluscum Contagiosum	1	2

Table 2. Relation between patients HIV/AIDS with/without oral lesions and the immune condition

Patients with HIV/AIDS associated lesions	n	%	CD4+ Cell count/mm ³	
			Mean	Range
Strongly associated to HIV/AIDS infection	53/64	82	306	313
Less common associated to HIV/AIDS	26/64	41	295	311
In HIV/AIDS infection	6/64	9	163	180
HIV/AIDS patients without oral lesions	11/75	15	142	225

Table 3. Relation between HIV/AIDS patients with/without oral lesions and viral load

Patients with oral lesions asociare to HIV/AIDS	n	%	Viral load copies/mm ³	
			Mean	range
Strongly associated to HIV/AIDS infection	53/64	83	15102,00	169438,40
Less common associated to HIV/AIDS	26/64	41	1755,50	88700,16
In HIV/AIDS infection	6/64	9	38551,00	160423,70
HIV/AIDS patients without oral lesions	11/75	15	141,50	9010,90

Table 4. Relation between the immune condition and viral load in HIV/AIDS patients with and without oral lesions under ART and without ART

Patients HIV/AIDS (n=75)		Patients with oral lesions		Patients without oral lesions	
		With treatment n = 43	Without treatment n = 21	With treatment n= 8	Without treatment n = 3
Viral load	UNDETECTABLE	51,1% (22/43)	9,5% (2/21)	87,5% (7/8)	33,3% (1/3)
	LOW	0	19% (4/21)	0	33,3% (1/3)
	INTERMEDIATE	9,3% (4/43)	23,8% (5/21)	12,5% (1/8)	0
	HIGH	30,2% (13/43)	66,6 % (14/21)	0	33,3% (1/3)
CD4	Less of 200	23,2% (10/43)	57,1% (12/21)	50% (4/8)	0
	200 - 500	23,2% (10/43)	42,8% (9/21)	25% (2/8)	33,3% (1/3)
	More of 501	44,1% (19/43)	19% (4/21)	25% (2/8)	66,6% (2/3)
Duration of treatment	0-3	7		0	
	4-6	6		6	
	7-12	19		2	
	More of 12	7		0	

Table 5. Relation between the antiretroviral therapy and the duration of treatment in HIV/AIDS patients.

Patients with treatment (n=47)	Bitherypy	HAART
N	8/47	39/47
%	17,03	82,97
<i>Duration (months)</i>		
0-3	1	5
4-6	3	7
7-12	3	19
More of 12	1	9

significant ($p < 0.001$). Of the Oral Leukoplakia diagnostic cases, a 36% showed tobacco consumption and 32% alcohol use. According to the association between Oral Leukoplakia and ART, 59% (13/22) of the oral leukoplakia patients were under ART compared with 41% 9/22 of the Oral Leukoplakia diagnosed patients that were not under therapy, observing statistical significant differences ($p < 0.09$). Of these patients, 41% (9/22), were under Highly active Antiretroviral Therapy (HAART) and 18% (4/22) were under bitherypy. Furthermore, in the present investigation, the prevalence of one or more lesions in HIV/AIDS patients, showed a 31% 20/64 patients that simultaneously exhibited two types of oral lesions associated to this infection. A 25% exhibited only one lesion and finally 19% showed concomitantly three oral lesions

related to HIV infection. Relation between HIV/AIDS patients with and without oral lesions and the immune status. Table 2 represents that the group I. The mean CD4 count was 313 cel/mm³, although group II was 180 cel/mm³. Among those patients without oral lesions, the mean was 225 cel/mm³. These results evidenced statistical significant differences between the mean of the patients showing strongly associated lesions and those without lesions ($p < 0.05$). Relation between patients HIV/AIDS with and without oral lesions and viral load. In the group I. the mean of viral load was estimated in 169.438 copies/mm³, while in group II the mean was estimated in 88.700 copies/mm³ (Table 3).

The means of CD4 and viral load were represented in Tables 2, and 3 respectively.

Relation between the immune condition and viral load in patients with and without oral lesions associated to HIV/AIDS infection with and without ART

The frequency of oral lesions and ART related to CD4 cell count and viral load are represented in Table 4, observing 43 patients under ART with oral lesions occurrence. It is also noted that 22/43 (51%) had undetectable viral load, 4/43 (9%) intermediate viral load and 13/43 (30%) high viral load. In relation, to CD4 cell count, 10/43 (23%), showed <200 cel/mm³; 10/43 (23%) between 200-500 cel/mm³ and 19/43 (44%) more than 500 cel/mm³. The patient values on oral lesions without treatment, as well as the patients with oral lesions with and without treatment are represented in Table 4. Relation of ART type, duration of treatment and prevalence of oral lesions in HIV/AIDS.

The Table 5 shows that 47 of 75 (63%) individuals HIV/AIDS were under ART, while 28/75 (37%) were not under therapy. It is observed that 83% (39/47) of the patients were treated under HAART. Of these, 19 subjects had 7 to 12 months under this therapy. A 17% (19/47) of these individuals were under bithrapy, of these 3 subjects had 4 to 6 months of treatment and other 3 subjects had 7 to 12 months under this therapy.

DISCUSSION

Epidemiological data on AIDS in Venezuela have been reported by non government and government organizations, revealing an increase of AIDS cases in a 4.32% in 1986 to 50.89% to 1994. The estimation of seropositivity for 1988 was between 50.000/100.000 individuals and for 2003 were 110.000 cases (47.000 to 170.000) of infected subjects (19).

In the present investigation, we evaluate the relation between oral lesions observed in HIV/AIDS patients, viral load and CD4 cell count.

The distribution of the studied population by gender demonstrated that 81% of the individuals HIV/AIDS corresponded to male and 18.7% to female, with a male/female ratio of 4:1. The most affected age group was in the fourth decade of life (30-29 years), observing a great prevalence in males. The marked prevalence of HIV infection in male maybe due to the high index of MSM transmission. The data obtained in the present study is similar to previous reports (20).

The age range of the evaluated individuals was between 20-55 years, with a mean of 35 years, These results are in agreement with previous studies from Ceballos et al (14). The most affected ethnic group was the caucasoid

representing a 54.6%. This data was statistically significant when compared with the black population (29.3%), amerindians (12%) and indigenous (1.3%). The sexual transmission was the most common mode (88%) being the most affected group the MSM (44%), heterosexuals (40%) and MSMH (16%).

Although, the results of the present investigation are in accordance with previous investigations (12,21,22). According to risk group, the more prevalent was the MSM. It is remarkable the absence of IDU cases. This fact could be due to the free purchase of needles in our country, avoiding the sharing of contaminated needles. In relation to the oral manifestations occurrence in HIV/AIDS, these could be observed in a 85% of the evaluated subjects, statistical significant when compared with a 15% of individuals without any oral lesion. Similar results were reported by others (13,23,24). According to the oral lesions prevalence, the most frequent was Oral Candidiasis followed by Oral Hairy leukoplakia, Oral Leukoplakia and Melanic Hyperpigmentation, observing statistical significant differences

Other studies have agreed that Oral Candidiasis is the most frequent lesion in HIV/AIDS individuals (24,25) followed by Oral Hairy Leukoplakia. Additionally, several reports have point out the scarce occurrence of Melanic Hyperpigmentation in HIV/AIDS patients when compared with the present study results. (11,26). These differences could be related to the antiretroviral effect or to the antifungal therapy effect.

Although, Oral leukoplakia have been not reported previously in association to HIV/AIDS (17), Ranganathan et al (27) evaluated 300 indian patients reporting only one case of Oral Leukoplakia. These results are in contrast with the present investigation where Oral Leukoplakia represented 34% of the evaluated cases.

Furthermore, Patton et al (16) have suggested the urgent need to add worldwide data to modify the current classification and to establish a study group that may use the updated diagnostic criteria of oral lesions observed in HIV/AIDS adult patients.

Accordingly to the high prevalence of Oral leukoplakia observed in the present study, this could be due to the possible coinfection with other viruses such as HPV and HIV, although 63% of the patients were under antiretroviral therapy. These results will need further investigation.

In relation to the prevalence of one or more lesions, 31% of the evaluated subjects presented simultaneously two types of oral lesion associated to HIV/AIDS. Twenty five percent of the cases demonstrated only one lesion and finally 19% showed concomitant three oral lesions. These results differed from previous reports (28,29).

In relation to the immunological status it was estimated that the range of CD4 lymphocytes in the strongly associated group was 313 cel/mm³, while in group III thus range was 180 cel/mm³. In the HIV/AIDS group that not exhibited oral lesions the level was 225 cel/mm³. Analysing these values, in the present investigation, a significant statistical difference between the CD4 mean of the strongly associated subjects and the individuals without oral lesions was not observed.

Our results are contrary to those described by Margiotta (11), and those differences could be attributed to the amount of individuals with oral lesions in the present study (85%), to the ART and duration of the therapy.

Regarding, the antiretroviral therapy the results demonstrated that the subjects with oral lesions and ART, the majority (51%) showed undetectable values of viral load and referred between 7-12 months of treatment. These results are in accordance with Schmidt Westhausen (28) observing that a 63% of the subjects under ART showed low levels of viral replication; while in those individuals without treatment, the viral load was between 10.000-49.000 copies/mm³, showing similarities in both studies.

For those individuals under treatment that did not exhibited oral lesions, 88% had undetectable viral load, while 50% of these subjects showed CD4 cell count less <200 cel/mm³, The CD4 cell count increased in those patients under ART is low, in agreement with Schmidt-Westhausen et al observations (25) where the differences between CD4 values after 6 months of treatment were not statistical significant. However, Casariego et al (30), described the presentation of eruptive cheilitis in six cases as an adverse effect in HIV+ patients under HAART. In the present investigation, we could not note this entity, that is not included on Clearinghouse classification (17), Those patients with CD4 cell count <200 cel/mm³ were more exposed to present oral lesions in any of the three groups indicated by Clearinghouse (17).

The range of viral load in the strongly associated group was 169.436 copies/mm³ when compared these values with the patients without oral lesions the range was 9.000 copies/mm³, evidencing statistical significant differences in both groups.

According to the habits, a high prevalence of oral leukoplakia has been related to tobacco consumption, alcohol and frictional lesions (24). The Oral Leukoplakia patients included in the present study showed 41% of cheilophagia, 37% tobacco habits and 32% were alcohol users.

It is noteworthy that 55% of the HIV/AIDS individuals and Oral Leukoplakia of the present study reported high viral load (more than 30.0000 copies/mm³) when com-

pared to 27% of those with undetectable viral load. According to the immune status, 55% exhibited CD4 cell count in the 200-500 cel/mm³ range, in contrast to 23% of the individuals with values under 200 cel/mm³, 23% showed >500 cel/mm³. These results could suggest an association between high viral load, due the occurrence of these lesions independently from the immune condition.

CONCLUSIONS

The most common oral lesion was Oral Candidiasis, followed by Oral Hairy leukoplakia, Oral Leukoplakia and Melanic Hyperpigmentation. A high viral load was strongly associated to the occurrence of those lesions independent from the CD4 cell count.

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