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Risk factors for oral hairy leukoplakia in HIV-infected adults of Brazil

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BACKGROUND: Oral hairy leukoplakia (OHL) may be an indicator of the progression of Human Immunodeficiency Virus (HIV)-induced immuno-depression, and the evaluation of risk factors leading to OHL is important in the management of these HIV-infected patients. However, there are few studies that analyze risk factors leading to OHL in the Brazilian population. The aim of this case–control study is to present data about prevalence rates and risk factors leading to OHL in a sample of HIV-infected adults in Brazil.

METHODS: This case–control study included 111 HIV-infected patients treated at a clinic for sexually transmitted diseases and HIV. In the initial examinations with dentists, variables were collected from all patients. Diagnosis of OHL was performed in accordance with the International Classification System and cytological features. The Fisher and the chi-squared tests were used for statistical analysis. The proportional prevalence and odds ratio were estimated.

RESULTS: Outcome presented a positive, statistically significant association among the presence of OHL and viral load of 3000 copies/μl or greater ($P = 0.0001$; odds ratio (OR) = 5.8), presence of oral candidiasis ($P = 0.0000$; OR = 11.1), previous use of fluconazole ($P = 0.0000$; OR = 24.6), and use of systemic acyclovir ($P = 0.032$; OR = 4.3). Antiretroviral medication presented a negative, statistically significant association with the presence of OHL ($P = 0.002$; OR = 8.4).

CONCLUSIONS: Prevalence of OHL was 28.8%. Viral load, oral candidiasis, previous use of fluconazole, and systemic acyclovir were determined to be risk factors for OHL. Antiretroviral medication proved to be protective against the development of OHL.

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Introduction

In the natural history of Human Immunodeficiency Virus (HIV)-infection, patients frequently present oral manifestations, including oral hairy leukoplakia (OHL). OHL may be an early warning of HIV-infection when the serological state of the patient is not recognized. The recognition of early signs of immune suppression may have a significant impact on the treatment decision of HIV-infection as well as on patient survival and quality of life (1, 2).

Since the mid-80s, research has been developed for clinical markers monitoring the progression of the initial HIV-infection to full-blown AIDS (1). OHL is considered a predictor of the HIV-infection to AIDS and a marker of the severity of the disease. Furthermore, it can also be related to laboratory variables (3–10). There are numerous studies about the prevalence of oral manifestations associated with HIV-infection; however, only a few assess risk factors for HIV-associated oral diseases (6–11).

In Brazil, Pinheiro *et al.* (12) showed no differences in the prevalence of oral manifestations of HIV infection among age, sex, mode of transmission and types of drug therapy. There are no studies in Brazil that correlate risk factors for OHL. In the present study, a sample of HIV-infected adult patients from Brazil was evaluated (1) to establish prevalence rates for OHL and (2) to establish independent risk factors for the development of OHL.

Materials and methods

Study data and variables

The present study was performed during the period of 2002–2004 and included 111 HIV-infected adults from the Orestes Diniz Treatment Center of Parasitic and Infectious Diseases (CTR-DIP; Belo Horizonte, Minas

Gerais, Brazil). Each subject volunteered to participate in the study and signed a detailed consent form. The protocol of this study was approved by the Committee on Bioethics in Research at UFMG (COEPE/UFMG: number 339/03). All patients were first diagnosed with HIV-infection by enzyme-linked immunosorbant assay (ELISA) as a primary detection test and then by Western blot as a confirmatory test. In all patients, the diagnosis for HIV-infection had already been established during the period of the initial exam.

Extra- and intra-oral exams were performed on all patients using a single calibrated oral medicine trained dental examiner (MDGM), in accordance with World Health Organization standards (13). The following variables were collected from medical records: age, gender, race, route of transmission, clusters of differentiation (CD) 4 T lymphocytes count, viral load, plaques, salivary flow, xerostomia, oral candidiasis, previous use of fluconazole, previous use of systemic acyclovir, use of highly active anti-retroviral therapy (HAART), use of zidovudine (AZT), drug use by injection, smoking and alcohol consumption. The division for CD4 T lymphocyte count was 200 cells/mm^3, 3000 copies/μl per viral load and 100 000/mm^3 (thrombocytopenia) for plaques (2, 10, 14–16). AZT was used in combination with others drugs. The measurement of the salivary flow was performed through the collection of stimulated saliva, for 5 min, according to the methods described by Tárzia (17). The salivary flow was considered normal (0.70 ml/min flow) and low (mild = 0.50 a 0.70-ml/min flow; moderate = 0.30 a 0.49-ml/min flow; severe = 0 a 0.29-ml/min flow). Xerostomia was considered to be present when the patient complained of dry mouth. The diagnosis of oral candidiasis was established according to clinical features and PAS (Periodic Acid Schift) stain. Oral candidiasis was treated with fluconazole (50 mg/day for 7 days). Smoking and alcohol consumption were considered when the patient smoked at least 20 cigarettes a day and consumed alcohol daily.

Case definition

Patients that presented a diagnosis of OHL were considered as *case* and those who did not develop the condition were *controls*. The diagnosis of OHL was in accordance with International Classification Systems (18). Clinical features of OHL included a white plaque, which was not removable when scraped, poorly demarcated and presented a flat, corrugated or hairy surface, located on the lateral border of tongue. The patients were submitted to antifungal treatment (fluconazole, 50 mg/day for 7 days) and considered OHL when there was a lack of response to the antifungal treatment. Also, features of the exfoliative cytology, in accordance with Kratochvil *et al.* (19), Fraga-Fernandes and Vicandi-Plaza (20), Migliorati *et al.* (21) and Epstein *et al.* (22), were considered in the diagnosis of OHL.

Statistical analysis

Univariate analyses were assessed for the variables in this study. Variables were assessed by the Fisher's and chi-squared tests, using two-sided tests. Statistical significance was at a 0.05 level. The results of this analysis were expressed as odds ratio (OR) with its 95% confidence interval (CI). All analyses were performed in SPSS (Statistical Package for Social Service, Chicago, IL, USA).

Results

Of the 111 HIV-positive adults evaluated, 32 (28.8%) presented OHL, while 79 (71.2%) did not. There were 81 (72.9%) men and 30 (27.1%) women. Fifty-seven patients (51.4%) were caucasians and 54 were black (48.6%). The age varied from 20 to 59 (average 39.5). Route of transmission included 4 (3.6%) drug users, 18 (16.2%) not informed, 53 (47.7%) heterosexual, 31 (27.9%) men who have sex with men (MSM) and 5 (4.5%) bisexual. Of the 32 patients with OHL, 19 (59.4%) were heterosexual, 9 (28.2%) MSM, 2 (6.2%) bisexual, 1 (3.1%) was drug user and 1 (3.1%) not informed.

Significantly, HIV-patients with a viral load of 3000 copies/μl or greater (Table 1; $P = 0.0001$; OR = 5.8), with oral candidiasis (Table 1; $P = 0.0000$; OR = 11.1), who previously used fluconazole (Table 1; $P = 0.0000$; OR = 24.6) and who previously used systemic acyclovir (Table 1; $P = 0.032$; OR = 4.3), developed OHL. In contrast, a large number HIV-patients that used HAART (Table 1; $P = 0.002$; OR = 8.4) did not develop OHL. Proportionally, OHL was more frequent in HIV-patients with a CD4 T lymphocyte count of < 200 cells/mm^3, with a reduction in salivary flow, xerostomia, without the use of AZT and in alcohol consumers (Table 1).

Discussion

This study verified the prevalence rates and risk factors leading to OHL in a sample of the Brazilian population. In the study of Pinheiro *et al.* (12), the prevalence of OHL was 9.3%. In the present study, the prevalence of OHL was 28.8%. Kerdpon *et al.* (15) reported a prevalence of 38.8% and 21.8% in northern and southern Thai patients. Chattopadhyay *et al.* (10) verified a prevalence of 18.0% in North Carolina. Logan *et al.* (23) in Australia, Eyeson *et al.* (24) in South London, Bemdick *et al.* (25) in Cambodia, Ramirez-Amador *et al.* (26) in Mexico and Bravo *et al.* (27) in Venezuela verified an OHL prevalence of 45.2%, 9.95%, 45.5%, 22.6% and 53.0% respectively. These differences may be related to methodological issues.

The relation between OHL and route of transmission is controversy. The present study found that OHL was more prevalent among heterosexuals. Patton *et al.* (28) and Chattopadhyay *et al.* (11) verified that OHL was significantly more prevalent among MSM and bisexuals respectively. This difference may be also related to the methodological issues or conduct feature of the sample (10, 11).

The majority of authors have used the division of 200 cells/mm^{3}for the CD4 T lymphocyte count, as did this study (2, 10, 11, 14, 15, 23, 27, 29, 30). The results of

Table 1 Proportional prevalence and univariate risk factors for oral hairy leukoplakia (CTR-DIP, Belo Horizonte, Minas Gerias, Brasil, 2002–2004; $n = 111$).

Variable	*Level*	*PP*	*Patients with OHL (n = 32)*	*Patients without OHL (n = 79)*	*OR(CI)*	*P-value*
CD4 T lymphocyte count (cells/mm^3)	< 200	34.7	8	15	–	0.479
	≥200	27.2	24	64		
Viral load (copies/μl)	< 3000	14.0	9	55	5.8 (2.4–14.5)	0.0001
	≥3000	48.9	23	24		
Plaques (mm^3)	< 100 000	25.0	1	3	–	1.00
	≥100 000	28.9	31	76		
HAART	Yes	24.0	24	76	8.4 (2.0–34.3)	0.002
	No	72.7	8	3		
Gender	Men	28.3	23	58	–	0.868
	Women	30.0	9	21		
Reduction of salivary flow	Yes	31.4	22	48	–	0.429
	No	24.0	10	31		
Xerostomia	Yes	31.4	11	24	–	0.682
	No	27.6	21	55		
Oral candidiasis	Yes	62.8	22	13	11.1 (4.3–29.0)	0.0000
	No	13.1	10	66		
Previous use of fluconazole	Yes	80.0	20	5	24.6 (7.8–78.2)	0.0000
	No	13.9	12	74		
Previous use of systemic acyclovir	Yes	60.0	6	4	4.3 (1.1–16.5)	0.032
	No	25.7	26	75		
Use of AZT	Yes	23.2	17	56	–	0.074
	No	39.4	15	23		
Drug use by injection	Yes	22.2	2	7	–	1.00
	No	29.4	30	72		
Smoking	Yes	28.5	14	35	–	0.958
	No	29.0	18	44		
Alcohol consumption	Yes	33.3	3	7	–	1.00
	No	28.7	29	72		

OR, odds ratio; CI, 95% confidence interval; PP, proportional prevalence; OHL, oral hairy leukoplakia; HAART, highly active anti-retroviral therapy.

the present study regarding the CD4 T lymphocyte count are in accordance with the studies of Logan *et al.* (23), Barr *et al.* (31), Kolokotronis *et al.* (32) and Greenspan *et al.* (33), which found no relation between the OHL and the CD4 lymphocyte count. However, we observed that, proportionally, the OHL was slightly higher in patients who showed a CD4 T lymphocyte count of < 200 cells/mm^3. Others studies have found a relation between the OHL and the CD4 T lymphocyte count of < 200 cells/mm^3 (4–6, 8–11, 14, 27, 29, 30). The HAART is of easy and free access in Brazil, especially in CTR-DIP. This contributes to having a large number of patients showing improvement in the immune state and an increase in the CD4 T lymphocyte count (above 200 cells/mm^3).

Patton *et al.* (8) and Chattopadhyay *et al.* (10) described the division as 20 000 copies/μl, Tappuni and Fleming (14) as 3000 copies/μl and Patel and Glick (2) between 4000 and 6000 copies/μl per viral load. As in the findings of Tappuni and Fleming (14), this study verified that OHL was more frequently found in patients with a viral load of 3000 copies/μl or greater. Bravo *et al.* (27) verified that patients with a viral load of 30 000 copies/μl exhibited oral lesions related to HIV-infection. Barr *et al.* (31), Greenspan *et al.* (32), Patton (34) and Chattopadhyay *et al.* (10) found that patients with high viral loads developed OHL. Thus, the OHL can be a clinical marker of a viral load of 3000 copies/μl or greater.

Patton (16) observed that thrombocytopenia may predispose HIV-positive patients to the development of oral manifestations, as verified in 15.5% of 516 HIV-infected patients. A statistically significant association between thrombocytopenia and the presence of OHL was not verified in our study. This finding may be justified by the fact that the number of individuals with thrombocytopenia was small (3.6%). Also, there are no other studies in previous literature assessing the relation between thrombocytopenia and the presence of OHL.

Oral hairy leukoplakia can be considered a measure of assessment of the need to begin antiretroviral medication (8, 15). In the present study, a negative, statistically significant association between the use of HAART and OHL was verified. Likewise, Tappuni and Fleming (14) and Chattopadhyay *et al.* (11) found no association between antiretroviral medication and the presence of OHL. Margiota *et al.* (7) reported a positive correlation between antiretroviral medication failure and OHL. Logan *et al.* (23) observed an association between a reduced prevalence of OHL in patients who were taking antiviral medication. Kerdpon *et al.* (15) also found an inverse relationship between antiretroviral medication and OHL. Thus, the use of antiretroviral medication (HAART) is protective against the development of OHL. The differences in the studies may be related to the types of antiretroviral medications, to which there may be no therapy, monotherapy, or combination therapy (HAART; 8, 10, 14, 15). In the

CTR-DIP, the antiretroviral medication is only HAART.

The lack of a statistically significant association between the presence of OHL and gender indicated that men and woman were similar regarding the development of OHL, as in studies of Margiotta *et al*. (7) and Pinheiro *et al*. (12). However, Shiboski *et al*. (35) showed a significantly higher prevalence of OHL in men. Patton *et al*. (30) affirmed that men had 4.45 times more chances of developing OHL. Chattopadhyay *et al*. (10, 11) found that the prevalence of OHL was associated with the male gender. In Brazil, there are many HIV-infected women, approximately 30% (36). This percentage is representative of women in the state of Minas Gerais and in its capital city, Belo Horizonte (37). Moreover, other authors found no explanations as to the higher frequency of OHL in men and there are controversies about the frequency of OHL in men (10, 24, 30).

Oral hairy leukoplakia was proportionally more frequent in patients with a reduction of salivary flow and xerostomia. Barr *et al*. (31) found no significant differences in the rate of salivary flow among those with OHL and those without this lesion. HIV patients frequently use drugs (anti-depressive, HAART) that interfere in the salivary flow (1, 31). Therefore, the salivary flow or xerostomia may be purely coincidental in the presence of OHL.

Although our study was directed towards OHL, the presence of oral candidiasis and OHL was also verified, simultaneously, as being the two most common oral lesions in HIV-infected adults. The association between the presence of OHL and oral candidiasis verified in this study has also been observed in many other studies in the US and Europe (2, 3, 5, 38, 39).

A statistically significant association between previous use of fluconazole and OHL was verified. A study with HIV-infected adults in North Carolina observed that those with antifungal medication were about three times as likely to develop OHL, but the authors found no explanations as to this association (10). Chattopadhyay *et al*. (11) verified that the prevalence of OHL was associated with antifungal medication use. Furthermore, other authors found different results. Schmidt-Westhausen *et al*. (9) concluded that the presence of oral lesions associated with HIV-infection did not have a correlation with the use of fluconazole. Therefore, this study seeks new arguments to explain these facts.

There was a statistically significant association between the previous use of systemic acyclovir and the presence of OHL. Boulter *et al*. (40) assessed the risk factors of EBV replication and affirmed that acyclovir therapy is not associated with changes in the risk of EBV replication. A clinical meaning of previous acyclovir therapy can be explained by the fact that patients who previously used acyclovir may present OHL, and this lesion may have disappeared during the use of this medication and recurred after its discontinuation.

Katz *et al*. (41) reported that AZT monotherapy was not associated with the decrease in the occurrence of OHL. This study also observed no relation between the use of AZT and the presence of OHL. Therefore, proportionally speaking, OHL was more frequent in patients who did not use AZT. This may in turn suggest that the use of AZT is in fact a protector against the development of OHL.

The association between the use of drugs by injection and the presence of OHL was not verified; this was in accordance with others studies (10, 30). This was related to the low frequency of injection drug users and carriers of OHL. Chattopadhyay *et al*. (11) found that OHL was associated with current recreational drug use. Also, there are controversies about smoking and OHL (10, 15, 33, 38, 42–45). OHL may be stimulated by the deposit of tobacco and other toxins related to tobacco on the tongue (42, 44). There was no statistically significant association between alcohol consumption and the presence of OHL; however, proportionally, OHL was more frequent in patients who were alcohol consumers. Similarly, study which assessed HIV-infected patients in Thailand found that the consumption of alcohol was not associated with the presence of OHL (42).

Our study demonstrated (1) an OHL prevalence of the 28.8% and that (2) viral loads of 3000 copies/μl or greater, oral candidiasis, previous use of fluconazole and previous use of systemic acyclovir are risk factors of OHL and HAART is protective against the development of OHL.

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