Original Article

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Risk factors for oral candidiasis in Brazilian HIV-infected adult patients

Mariela Dutra Gontijo Moura[1], Soraya de Mattos Camargo Grossman[1], Linaena Méricy da Silva Fonseca[2], Maria Letícia Ramos-Jorge[3], Ricardo Alves Mesquita[4]

[1]MSc, Graduate students, Department of Oral Pathology, Dental School, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
[2]PhD, Assistant Professor, School of Health, Faculdades Pitágoras, Belo Horizonte, MG, Brazil
[3]PhD, Professor. Department of Dentistry, Federal University of Vales Jequitinhonha and Mucuri, Diamantina, MG, Brazil
[4]PhD, Associate Professor, Department of Oral Pathology, Dental School, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

Abstract

Aim: The goals of this study were: 1) to estimate the prevalence of oral candidiasis (OC) in a sample of Brazilian HIV-infected adult patients, and 2) to investigate the risk factors for HIV-associated OC in this sample. **Methods:** This case-control study included 112 HIV-infected patients treated between 2002 and 2004 at a clinic for sexually transmitted diseases. Data were collected from medical records and clinical examinations. Diagnosis of OC was performed in accordance with the International Classification System and cytological features. Seventeen clinical and laboratorial variables were registered. Univariate analyses were performed on all variables. Multiple logistic regression techniques were used to develop a model and identify the set of variables that may predict risk factors in HIV-infected adult patients with OC. **Results:** Prevalence of OC was 31.3%. OC was associated with oral hairy leukoplakia (OHL) [p<0.001; odds ratio (OR) = 10.2 (95%CI: 4.0-26.0)], previous use of fluconazole [p<0.001; OR=27.4 (95%CI: 8.1-92.0)] and viral load [p=0.042; OR=2.3 (95%CI: 1.0-5.3)]. **Conclusions:** These results are important for the development of strategies to eliminate these risk factors and significantly reduce OC in HIV-infected patients.

Keywords: AIDS, candidiasis, HAART, HIV infection, prevalence ratio, risk factors.

Introduction

Oral candidiasis (OC) is the most frequent HIV infection-associated oral disease, and can also act as a marker for immunosuppression[1-6]. The prevalence and incidence of HIV infection in Brazil are 7.5% and 1.39%, respectively[5]. The literature supports the position that systemically applied antifungal drugs have the greatest efficacy for the treatment of OC. However, these therapies must be prescribed following a thorough assessment of the risk for developing drug-induced toxicities[6]. OC responds to antifungal therapy, but eradication is rarely achieved unless the underlying immune-compromised state is resolved[2,7].

Data about risk factors for HIV infection-associated oral lesions in the South American population are insufficient[1,3,8]. Some studies have identified potential risk factors for development of HIV-associated oral diseases[3-4,7,9-11]. Moura et al.[4] demonstrated statistically significant associations between oral hairy leukoplakia (OHL) and HIV-1 viral load, OC, previous use of fluconazole and systemic acyclovir in Brazilian HIV-infected adult patients. Therefore, the goals of this study were: 1)

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Correspondence to:
Ricardo Alves Mesquita
Faculdade de Odontologia da UFMG
Disciplina de Patologia Bucal, sala 3202-D
Av. Antônio Carlos, 6627
Pampulha - 31270-901
Belo Horizonte - MG, Brasil
Phone: +55-31-3409-2499
E-mail: ramesquita@ufmg.br

to estimate the prevalence of OC in a sample of Brazilian HIV-infected adult patients, and 2) to investigate the risk factors for HIV-associated OC in this sample.

Material and Methods

Between 2002 and 2004, 112 HIV-infected adult volunteers were recruited from the Orestes Diniz Treatment Center of Parasitic and Infectious Diseases (CTR-DIP) (Belo Horizonte, MG, Brazil) to participate in this case-control study, approved by the UFMG's Bioethics Research Committee (protocol number 339/03). All patients were first diagnosed with HIV-infection by enzyme-linked immunosorbant assay (ELISA) as the primary detection test, and the diagnoses were subsequently confirmed by the Western blot test. The diagnosis for HIV-infection had already been established during the period of the first exam for all patients. A single, validated examiner, trained in oral medicine, conducted the oral clinical exam in accordance with the World Health Organization standards[12]. OC diagnosis was based on the published standard presumptive clinical criteria of International Classification Systems[13]. Also, cytological features were considered in the diagnosis of OC: morphologic microscopic observation of fungal mycelial filaments from a non-cultured specimen scraped from the oral mucosa by Periodic Acid Schiff (PAS) staining. Patients with a confirmed diagnosis of OC were included in the case group; those without clinical features of OC were included in the control group.

The following variables were obtained from the case and control groups: age, gender, race, route of transmission, CD4 T lymphocytes count, viral load, platelets count, salivary flow, xerostomia, OHL, previous use of fluconazole, previous use of systemic acyclovir, use of highly active anti-retroviral therapy (HAART), use of zidovudine (AZT), intravenous drug use, smoking, and alcohol consumption. The CD4 T lymphocyte count was divided into <200 cells/mm^3 and ≥ 200 cells/mm^3. The viral load was divided into $<3{,}000$ copies/μL and $\geq 3{,}000$ copies/μL. Platelet count was divided into $<150{,}000$/mm^3 and $\geq 150{,}000$/mm^3[3,4,14-16]. The measurement of the salivary flow was performed through the collection of stimulated saliva, over the course of five minutes, in accordance to Tárzia[17]. The salivary flow was identified as normal ($>$ 0.70mL/min), moderately low (0.50 to 0.70 mL/min), low (0.30 to 0.49 mL/min), or severely low (0 to 0.29 mL/min)[17]. Xerostomia was identified when the patient complained of dry mouth. The diagnosis of OHL was established according to clinical features and exfoliative cytology[18-19]. OHL was treated with topical applications of either podophyllin resin (25%) (prepared at UFMG's pharmacy), or podophyllin resin (25%) together with acyclovir cream (5%) (EMS-Genéricos®, São Bernardo do Campo, SP, Brazil)[20]. Smoking individuals were identified as those who had smoked ≥ 100 cigarettes over their lifetime and smoked at the time of the study. Non-smoking individuals were identified as those who had not smoked ≥ 100 cigarettes in their lifetime[16]. Alcohol consumption was considered when the patient consumed alcohol on a daily basis.

Statistical analysis of data was performed using the Statistical Package for Social Service (SPSS) software program (version 16.0, SPSS Inc., Chicago, IL, USA). Univariate analyses were performed on all variables of this study using the Fisher's and Chi-squared tests (2-sided tests). Statistical significance was at a level of 0.05. The results of this analysis were expressed as an odds ratio (OR) with a 95% confidence interval (CI). Variables with $p<0.25$ were identified and included in the multivariate analyses. Multiple logistic regression techniques were then used to develop a model and identify the set of variables that may predict risk indicators in HIV-infected adult patients with OC.

Results

The sample included 35 (31.3%) HIV-infected adult patients with OC and 77 (68.7%) patients who did not have OC. The majority of patients, 82 (73.2%), were men. Sixty-five patients (58.0%) were Caucasian and 47 (42.0%) were Black. Age varied from 20 to 59 years (mean age of 39.5 years). Regarding the route of transmissions, the sample included 4 (3.6%) intravenous drug users, 13 (11.6%) not informed, 51 (45.5%) heterosexuals, 40 (35.7%) men who have sex with men (MSM) and 4 (3.6%) bisexuals. Of the 35 patients with OC, 20 (57.1%) were heterosexual, 8 (22.8%) were MSM, 2 (5.7%) were bisexual, 1 (2.8%) was intravenous drug user, and 4 (11.4%) did not inform.

OC was erythematous in 19 cases (54.3%), pseudo-membranous in 10 cases (28.6%), and both in 06 cases (17.1%). Angular cheilitis (9 cases) was also identified in our study, but all cases were in association with erythematous OC. Table 1 summarizes the proportional prevalence and univariate analyses. Statistically significant association was identified between the viral load of 3,000 copies/μL or greater ($p=0.042$; $OR=2.3$), the OHL ($p<0.001$; $OR=10.2$) and the previous use of fluconazole ($p<0.001$; $OR=27.4$) with OC. Platelets count ($<150{,}000$/mm^3), HAART (patients that did not take), gender (men), reduction of salivary flow, previous use of systemic acyclovir, use of AZT (patients that did not take) and intravenous drug use (patients that did not use) were more frequently present in association with OC, though without a significant relationship (table 1).

Table 2 demonstrates the logistic regression models. Multiple logistic regression tests confirmed the statistically significant association between the previous use of fluconazole and OHL with OC, regardless of the use of HAART. Adjusted results showed that HIV-infected patients with OHL, and those who had previously used fluconazole, were 3.6 times (95% CI = 1.1-12.3) and 14.3 times (95% CI = 3.8-53.6) more likely to present OC, respectively, regardless of the use of HAART.

Discussion

It has been suggested that OC represents a relevant marker of immune system status in HIV-infected patients,

Table 1. Proportional prevalence and univariate analyze for oral candidiasis among 112 HIV/AIDS patients attended to at the CTR-DIP, Belo Horizonte, MG, Brazil, during 2002 to 2004

Variable	Level	PP	Patients with OC (n=35)	Patients without OC (n=77)	P
CD4 T lymphocyte count (cells/mm^3)	<200	33.3	8	16	0.804^F
	≥200	30.7	27	61	
Viral load (copies/µL)	<3,000	23.4	15	49	**0.042***
	≥3,000	41.7	20	28	
Platelets count (mm^3)	<150,000	50.0	2	2	0.370^F
	≥150,000	30.6	33	75	
HAART	Yes	28.9	28	69	0.140^F
	No	46.6	7	8	
Gender	Men	32.9	27	55	0.527*
	Women	26.7	8	22	
Reduction of salivary flow	Yes	34.1	14	27	0.615*
	No	29.6	21	50	
Xerostomia	Yes	33.3	12	24	0.743*
	No	30.3	23	53	
Oral hairy leukoplakia	Yes	66.7	22	11	**<.001**
	No	16.5	13	66	
Previous use of fluconazole	Yes	84.0	21	4	**<.001**
	No	16.1	14	73	
Previous use of systemic acyclovir	Yes	50.0	5	5	0.160^F
	No	29.4	30	72	
Use of AZT	Yes	28.7	21	52	0.438*
	No	35.9	14	25	
Intravenous drug use	Yes	22.2	2	7	0.424^F
	No	32.0	33	70	
Smoking	Yes	32.0	16	34	0.878*
	No	30.6	19	43	
Alcohol consumption	Yes	30.0	3	7	0.619^F
	No	31.4	32	70	

*Chi-square test; ^{F}Fisher's Exact Test; PP: proportional prevalence; OC: oral candidiasis; HAART: highly active anti-retroviral therapy

Table 2. Unconditional simple and multiple logistic regression analysis between independent variables and oral candidiasis (final model) among 112 HIV/AIDS patients attended at the CTR-DIP, Belo Horizonte, MG, Brazil, during 2002 to 2004

Variable	Level	OR unadjusted (95% CI)	P	OR adjusted (95% CI)	P
HAART	Yes	1	0.173	1	0.823
	No	2.2 (0.7-6.5)		0.84 (0.2-4.0)	
Oral hairy leukoplakia	No	1	<.001	1	0.041
	Yes	10.2 (4.0-26.0)		3.6 (1.1-12.3)	
Previous use of fluconazole	Yes	1	<.001	1	<.001
	No	27.4 (8.1-92.0)		14.3 (3.8-53.6)	
Viral load (copies/µL)	<3,000	1	0.042		
	≥3,000	2.3 (1.0-5.3)		nam	

HAART: highly active anti-retroviral therapy; OR: odds ratio; CI: 95% confidence interval; nam: non adjusted to the model

and is also a clinical predictor of AIDS progression[3-4,7,11,14]. In the present study, the prevalence of OC was 31.3%. Most studies have reported prevalence rates of OC between 17.2% and 58.6%[3,7,11,21].

It is intuitive to expect an increase of OC in patients with low CD4 T lymphocyte count (<200 cells/mm^3)[3,7,9-10,14,22-23]. Campisi et al.[24], Ghate et al.[9] and Shiboski et al.[25] did not find any relation between OC and low CD4 T lymphocyte count in HIV-infected adults, as is reflected in the current study. In our study, this may be attributed to the fact that HAART is easily accessible in Brazil, especially in CTR-DIP, which contributes to the improvement of patient immunity, favoring an increase in the CD4 T lymphocyte count (>200 cells/mm^3)[4].

Previous studies have reported a heterogeneous division of viral load, ranging from 3,000 to 30,000 copies/µL[3,14,22-23,25]. The high viral load presented a significant association with OC, as reported in the findings of other studies[3,14,23,25].

Mercante et al.[10] and Coogan et al.[26] suggested that viral load may be a more important predictor for oropharyngeal candidiasis than CD4 T lymphocyte count.

OC was more frequent in patients with platelet count $<150,000$, though without a significant association. Patton et al.[27] observed that platelet count $<150,000$ may predispose HIV-infected patients to the development of oral manifestations, as verified in 15.5% of 516 patients. One possible explanation for our results is the fact that the number of individuals with platelet count $<150,000$ was small (1.7%).

OC can be considered a measure of assessment of the need to begin antiretroviral medication1[1,7-8,11,14,25,28]. In contrast, we did not find statistically significant association between HAART and OC. Tappuni and Fleming[28] found no association between antiretroviral medication and the presence of OC. Thompson et al.[1] confirmed that OC remains a significant infection in advanced AIDS, even with HAART.

Gender, salivary flow, xerostomia, previous use of systemic acyclovir, use of AZT, intravenous drug use, smoking, and alcohol consumption do not represent risk indicators for OC[7,14,24-26,29]. Although it was not statistically significant, in the present study, OC was proportionally more frequent in men, in patients with a reduced salivary flow, with previous use of systemic acyclovir, who were not taking AZT and who did not use intravenously drug.

Although our study was directed towards OC, the presence of OHL and OC was also verified, simultaneously, as being the two most common oral lesions in HIV-infected adults. The association between the presence of OC and OHL verified in this study has also been observed in many other studies in the US and Europe[3,7,11,27,29].

The previous use of fluconazole was a strong indicator of risk for OC. Schmidt-Westhausen et al.[30] found different results, and they concluded that the presence of oral lesions associated with HIV-infection did not have a correlation with the use of fluconazole. It is possible that *Candida* resistance to fluconazole is responsible for our finding. The high incidence of mucosal and deep seated forms of candidiasis in HIV-infected patients has resulted in the use of fluconazole. Their widespread use has been followed by an increase in antifungal resistance and *Candida* resistance. Various factors may contribute to fluconazole resistance, such as the degree of immunosuppression of the patients, the chemotherapeutic use of drugs and the intrinsic resistance of *Candida* species[2]. Fluconazole used for prolonged periods can select for less susceptible species *Candida*[2]. The resistance of *Candida*, isolated to currently available antifungal drugs, is a highly relevant factor because it presents important implications for morbidity and mortality[1,6]. Systemically applied antifungal drugs have the greatest efficacy for the treatment of oral candidiasis. However, these therapies must be prescribed following a thorough assessment of the risk for developing drug-induced toxicities, the likelihood of *Candida* species resistance, and the cost-effectiveness of medications. Fluconazole prophylaxis should be reserved for patients at high risk for recurrence of fungal infections, and not for routine prophylaxis[6]. Additionally, another explanation for the association of OC with previous use of fluconazole could be the fact that patients with HIV infection can have recurrent OC and that are treated with fluconazole[1].

These results are important for the development of strategies to eliminate these indicators of risk and significantly reduce OC in Brazilian HIV-infected adult patients.

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