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Research Article

Candida Carriage and Risk Factors for Oral Candidiasis in Patients Attended Tertiary Hospital in Dehradun, India

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Abstract: The aim of this study was to evaluate prevalence and risk factors of oral candidiasis (OC) in patients attended tertiary hospital in Dehradun, India. A total of 130 patients with oral lesions attended tertiary hospital in Dehradun, India between January 2011 and July 2011 were evaluated. Patients were subgrouped as Group 1: HIV seronegative (n=111) and Group 2: HIV-infected (n=19). Ten clinical and laboratorial variables were registered. Univariate analyses were performed on all variables. Out of 130 patients, 70.0% were candida culture positive. Among group 1, 65.8% patients were culture positive while 94.7% of group 2 were positive. *C. albicans* was dominant isolate among group 1 while non-*albicans Candida* (NAC) were dominant in group 2. Statistically significant association was identified between the gender (male) ($p = 0.0240$; Odd ratio (OR) = 2.5), the reduced saliva flow rate ($p < 0.0001$; OR = 106.1), CD4 count < 200 cell/mm^3 ($p = 0.0041$; OR = 10.7), previous antibiotics users ($p < 0.0001$; OR = 30.1), AIDS ($p = 0.0029$; OR = 17.3), those did not received HAART ($p < 0.0001$; OR = 0.05), bronchitic ($p = 0.0013$; OR = 0.2), and gutka (smokeless tobacco) chewers ($p < 0.0001$; OR = 9.5) with OC. Our results are important for the development of strategies to eliminate these indicators of risk and significantly reduce OC in HIV-infected and non-infected adult patients of Dehradun, India..
Keywords: Oral lesions, *Candida* carriage, risk factors, *Candida albicans*, non-*albicans Candida*

INTRODUCTION

Oral candidiasis (OC) is the most frequent HIV infection-associated oral disease, and can also act as a marker for immunosuppression [1-6]. Oral lesions have been reported to be early clinical features of HIV infection and are associated with disease progression. These lesions are often indicators of immune suppression and can be used for early testing, diagnosis and management of patients with HIV/AIDS. Oral lesions contribute to patients' morbidity, affecting the psychological and economic functioning of the individual and community [7]. These lesions can cause pain, discomfort and other symptoms and in the most cases warrant treatment [8-9].

The infection is caused by *Candida albicans*, a dimorphic fungal organism that is typically present in the oral cavity in a non-pathogenic state in about one-half of healthy individuals but under favourable conditions, has the ability to transform into a pathogenic (disease causing) hyphal form. Conditions that favour this transformation include broad-spectrum antibiotic therapy, corticosteroids, xerostomia, immune dysfunction, diabetes mellitus, nutritional deficiencies, or the presence of removable prostheses [10]. There are several clinical manifestations of oral candidiasis, the most common being the pseudomembranous, erythematous, angular cheilitis, hyperplastic and mucocutaneous forms [11]. Diagnosis is made by clinical examination and exfoliative cytology. Treatment involves the use of antifungal therapy, but failures in treatment are observed as a result of the debility of the immune system of AIDS patients and drug resistance of the yeast species [11]. Oral candidiasis is heralded by a sustained reduction in the CD4 blood cell count and a sharp increase in HIV viral load [12]. In India, incidence of OC has been reported from 50 to 100%. Type of lesions may vary and some of the patients may lack classical picture of oral thrush especially when CD4 count is quite high [13].

We planned the present study to determine the prevalence of *Candida* carriage in both HIV-infected and non-infected patients together with our major impact was on risk factors associated with oral candidiasis in HIV-infected and non infected patients attending tertiary hospital in Dehradun, India.

EXPERIMENTAL SECTION

Patients

A total of 130 patients with oral lesions were included in this study. The individuals were recruited from outpatients of department of Doon Memorial Medical College and Hospital, Dehradun, India during the period from January 2011 to July 2011. All the patients were further subgroup as Group 1 (HIV seronegative patients with oral lesions, n=111) and Group 2 (HIV-infected patients with oral lesions, n=19). Informed consent was obtained from participants and procedures were performed according to

institutional board of ethical committee. The individuals were examined by physician for the clinical signs and symptoms of OC. Detailed case history was taken from each patient on a case history proforma. The data obtained from clinical history of each patient were the following: demographic information, systemic co-infection, previous antibiotic and antifungal treatment, CD4 T lymphocyte counts and treatment with highly active antiretroviral therapy (HAART).

HIV sero status of the individuals was tested according to NACO guidelines using three rapid tests based on different principles (Tridot Biomed Industries, COMB Elisa Span Diagnostic Ltd, HIV Capillus, Trinity Biotech Plc.).

Sample collection and processing

The samples were collected aseptically by oral rinse method. The patients were asked to rinse the mouth with 10 ml of sterile Phosphate Buffered Saline (PBS, pH 7.2) for 60 seconds and thereafter oral rinse was collected in sterile container. The oral rinse specimen was immediately centrifuged (Sigma 2K 15) at 3000xg for 10 minute at 4°C. The supernatant was discarded and sediment was resuspended in 1 ml of sterile PBS and vortexed for 1 minute. This solution was used for direct microscopic examinations, performed with lactophenol cotton blue and 100 µl of this preparation was inoculated onto Sabouraud's Dextrose Agar (SDA) plate with and without chloroamphenicol (Hi-Media, Mumbai, India). The plates were incubated at 37°C for 48 h. The colonies of *Candida* were counted to assess CFU/ml of rinse sample [14].

Identification of isolates

Yeast samples were first subjected to germ tube production test. To determine yeast morphology, Cornmeal-Tween 80 agar plates were streaked and stabbed with a 48-h-old yeast colony, covered with a sterile coverslip, incubated at room temperature for 3 to 5 days in dark to promote the production of chlamydospores, hyphae, pseudohyphae, and arthroconidia. Biochemical tests were performed, using HiCandida KB006 Kit (Hi-Media, Mumbai, India) containing sterile media for urease production and different carbohydrate utilization test. Each well on plate containing reference carbohydrate was inoculated with 50 µl of the inoculum ($2.5x10^3$ CFU/ml), and incubated at 25°C for 24-48 h. Change in colour indicates assimilation of the respective carbohydrates. Fermentation of sugars was performed by inoculating 100µl ($2.5x10^3$ CFU/ml) of 48-h culture suspensions of test isolates into tubes of fermentation broth containing 2% solutions of the respective sugars. A positive result was indicated by production of acid and gas [14].

Statistical analysis

The statistical analysis was performed using Graph Pad Prism 5. Univariate analyses were performed on all variables of this study using the Fisher's and Chi-squared tests (2-sided tests). The results of this analysis were expressed as an odds ratio (OR) with a 95% confidence interval (CI). A p value of < 0.05 was considered statistically significant.

RESULTS

A total of 130 patients with oral lesions were included in this study. Out of 130 patients, 19 were HIV-infected and 111 were HIV seronegative. Among all patients, 89 were male and 41 were female. Age varied from 25 to 62 years (with mean age of 38.4 years). Regarding the risk factors, 88 (67.7%) patients had reduced saliva flow rate, 86 (66.2%) had previously used antibiotics, 52 (40.0%) had previously used azoles, 16 (12.3%) were AIDS diagnosed, 31 (23.8%) had bronchitis asthma, 95 (73.1%) were gutka chewers and 75 (57.7%) were alcohol consumer (Table 1).

Table 1: Demographics of patients and underlying medical conditions in all groups

Demographics	Group 1*	Group 2†	Total Patients
No. of patients	111	19	130
Gender			
Male	70 (63.1)	19 (100)	89 (68.5)
Female	41 (36.9)	-	41 (31.5)
Mean Age (range years)	37.8 (25-61)	39.2 (32-62)	38.7 (25-62)
Saliva flow rate			
Reduced	69 (62.2)	19 /11(100)	88 (67.7)
Normal	42 (37.8)	-	42 (32.3)
CD4 count, cells/mm^3			
0-200	2 (1.8)	19 (100)	21 (16.1)
201-500	17 (15.3)	-	17 (13.1)
> 500	92 (82.9)	-	92 (70.8)
Antibiotic received	67 (60.4)	19 (100)	86 (66.2)
Azole received	37 (33.3)	15 (78.9)	52 (40.0)
AIDS diagnosed	-	16 (84.2)	16 (12.3)
HAART received	-	4 (21.1)	4 (3.1)
Bronchitis Asthma	31 (27.9)	-	31 (23.8)
Gutaka chewer	83 (74.8)	12 (63.2)	95 (73.1)
Alcohol	65 (58.6)	10 (52.6)	75 (57.7)

Data are shown in number (%) of patients, unless otherwise indicated. *, HIV seronegative patients with oral lesions; †, HIV-infected patients with oral lesions.

Out of 130 patients, 70.0% (91) were candida culture positive. Among Group 1 patients, 65.8% (73) of 111 patients were candida culture positive while 94.7% (18/19) Group 2 patients were culture positive (Table 2). *C. albicans* was the dominant isolate among Group 1 patients while non-*albicans Candida* (NAC) isolates were dominated in Group 2. NAC isolates were 33.8% (26/77) and 61.9% (13/21) in Group 1 and Group 2 population respectively. The frequency of isolation of *Candida* in Group 1 was: *C. albicans* (66.2%). *C. tropicalis* (12.9%), *C. glabrata* (14.3%), *C. parapsilosis* (3.9%), *C. krusei* (1.3%) and *C. guilliermondii* (1.3%) while in Group 2 was: *C. albicans* (38.1%), *C. tropicalis* (23.8%) and *C. glabrata* (38.1%) (Table 3).

Table 2: *Candida* isolation rate in all groups of study population

Study groups (n)	*Candida* carriage n (%)	*Candida* isolates (n)
Group 1[*] (111)	73 (65.8)	77
Group 2[†] (19)	18 (94.7)	21
Total (130)	91 (70.0)	98

Data are shown in number (%) of *Candida* spp. isolates; [*], HIV seronegative patients with oral lesions; [†], HIV-infected patients with oral lesions.

Table 3: Yeast distribution in different groups of study population

Species	Group 1[a] (n=77)	Group 2[†] (n=21)	Total (n=98)
C. albicans	47 (61.1)	5 (23.8)	52 (53.1)
C. tropicalis	7 (9.1)	5 (23.8)	12 (12.2)
C. glabrata	11 (14.3)	5 (23.8)	16 (16.3)
C. parapsilosis	3 (3.9)	-	3 (3.1)
C. albicans+ *C. tropicalis*	3 (3.9)	-	3 (3.1)
C. albicans+ *C. glabrata*	-	3 (14.3)	3 (3.1)
C. albicans + *C. krusei*	1 (1.3)	-	1 (1.1)
C. guilliermondii	1 (1.3)	-	1 (1.1)
non-*albicans Candida*	26 (33.8)	13 (61.9)	39 (39.8)

Data are shown in no. (%) of *Candida* isolates; [*], HIV seronegative patients with oral lesions; [†], HIV-infected patients with oral lesions.

Table 4 summarizes the proportional prevalence and univariate analyses. Statistically significant association was identified between the gender (male) ($p = 0.0240$; OR = 2.5), the reduced saliva flow rate ($p < 0.0001$; OR = 106.1), CD4 count < 200 cell/mm^3 ($p = 0.0041$; OR = 10.7), previous antibiotics users ($p < 0.0001$; OR = 30.1), AIDS patients ($p = 0.0029$; OR = 17.3), HAART (patients those did not take) ($p < 0.0001$; OR = 0.05), patients with bronchitis ($p = 0.0013$; OR = 0.2), and gutka (smokeless tobacco) chewers ($p < 0.0001$; OR = 9.5) with OC. Patients who previously received azoles and alcohol consumer were more frequently present in association with OC, though without a significant relationship.

Table 4: Proportional Prevalence and univariate analysis for oral candidiasis among 130 patients attended tertiary hospital of Dehradun, Uttarakhand, India.

Variable	Level	PP	Patients with OC (n=91)	Patients without OC (n=39)	P value	OR (95% CI)
Gender	Male	76.4	68	21	0.0240 [F]	2.5
	Female	56.1	23	18		
Saliva flow rate	< 1ml/min	98.5	67	1	0.0001 [F]	106.1
	> 2ml/min	38.7	24	38		
CD4 count	< 200	95.2	20	1	0.0041 [F]	10.7
	> 201	65.1	71	38		
Antibiotics	Yes	91.9	79	7	0.0001 [F]	30.1
	No	27.3	12	32		
Azole	Yes	78.8	41	11	0.0816 [F]	2.08
	No	64.1	50	28		
AIDS	Yes	100	16	0	0.0029 [F]	17.3
	No	65.8	75	39		
HAART	Yes	14.3	2	12	0.0001 [F]	0.05
	No	76.7	89	27		
Bronchitis	Yes	45.2	14	17	0.0013 [F]	0.2
	No	76.8	77	22		
Gutaka chewers (ST)	Yes	83.2	79	16	0.0001 [F]	9.5
	No	34.3	12	23		
Alcohol	Yes	68.0	51	24	0.6988 [F]	0.8
	No	72.7	40	15		

PP, proportional prevalence; OC, oral candidiasis; HAART, highly active anti-retroviral therapy; ST, smokeless tobacco; F, Fisher's Exact Test; OR, odd ratio; CI, 95% confidence interval; *p* value of < 0.05 was considered statistically significant

DISCUSSION

Two different populations of individuals were studied, HIV-infected patients with oral lesions and HIV-seronegative individual with oral lesions. In past few decades, there have been numerous reports of *Candida* infections in India [14-19]. In the present study, the overall prevalence of oral candidiasis was 70.0%. In a recent study, Jindwani *et al*. [20] from S.S. Medical College, Madhya Pradesh, India reported 59.94% prevalence of oral candidiasis. The overall prevalence of *C. albicans* and non-*albicans Candida* isolates was 60.2% and 39.8% respectively that is in agreement with previous reports in India [14, 17] and abroad [21-22]. Oral candidiasis (OC) is the most frequent opportunistic fungal infection among HIV-infected patients, and it has been estimated that more than 90% of HIV-infected patients develop OC often debilitating infection at some time during progression of disease [23]. *In the present study*, prevalence of 94.7% candida culture positive among HIV-infected patients and 64.9% in HIV negative individuals is in agreement with previous reports [18-19, 24]. In a recent study, Gautam and Garg [14] from Meerut, India reported 83.3% candida culture positive among 180 HIV-infected patients. Although we have small number of HIV-infected patients but epidemiological importance of data cannot be neglected. Mucocutaneous candidiasis is probably one of the commonest manifestations of HIV-infected status worldwide with OC being most widely reported. In India, its incidence has been reported from 50 to 100% [13]. In this study, two different yeast species were recovered from 7 of 91 patients who were candida culture positive. The presence of more than one species of *Candida* in oral mucosa may predispose to recurrent candidiasis, mainly with species resistant to azole drugs, such a *C. glabrata* and *C. krusei* [24]. In this study, good numbers of non-*albicans Candida* were isolated. *C. glabrata* was being predominant in both HIV-infected and HIV seronegative groups while *C. tropicalis* was the second most common isolates.

It is intuitive to expect an increase of OC in patients with low CD4 T lymphocyte count (< 200 cells/mm^3) [2, 25] as is reflected in the present study. Proportionally, 95.2% OC have been classified with CD4 count < 200 cell/mm^3. A continuous flow of saliva is important in preventing oral colonisation by *Candida* because it removes the unattached or loosely attached *Candida* from the oral cavity. Saliva flow rate as well as the quantity and the quality of the saliva affect microbial clearance [26]. An inverse correlation between salivary flow rate and OC has been reported [27] as is reflected in present study. In this study, significant relation was found between reduced saliva flow rate and OC. Proportionally, 98.5% OC was found with reduced saliva rate (< 1 ml/min). Broad-spectrum antibiotics used in the treatment of a wide range of disease conditions have also been attributed as a predisposing factor of OC, possibly because of changes in oral environment (fine balance of fungal and bacterial flora) and/or in the immune response reducing neutrophils candidacidal activity [28]. In this study, proportional prevalence of 91.9% OC was higher in patients who had previously received antibiotics. Fluconazole is the drug routinely and widely prescribed for the treatment and prophylaxis of OC in HIV/AIDS patients [29]. Fluconazole and itraconazole appear to be more effective in managing OC in HIV-infected patients in comparison to nystatin or clotrimazole [30]. There is another concern that prolonged use of fluconazole increases the risk of developing azole-resistant *C. albicans* and selection of non-*albicans Candida* species such as *C. glabrata* [31], which further complicates patient management. In this study, 40.0% of 130 patients had been previously treated with some of the following antifungal agents: fluconazole, itraconazole and ketoconazole. Proportional prevalence of 78.8% OC was found in patients who had previously received azoles.

All sixteen patients with AIDS in the present study were candida culture positive. The introduction of HAART in 1996 dramatically changed the course of HIV infection [32]. Concurrently, a marked decrease in the overall incidence of oral lesions, especially OC, was reported in patients receiving HAART [33-34]. The marked decrease of oral lesions following HAART is attributed to immune reconstruction after the reduction of the viral burden. Nicolatou-Galitis, *et al*. [34] reported that the introduction of HAART was associated with a significant decrease in the prevalence of OC coupled with an improved CD4 count. In this study, we have found statistically significant association between HAART (patients those did not taken) and OC. Proportional prevalence of OC was found higher in patients who did not received HAART. In Dehradun (Uttarakhand, India) smokeless tobacco (Gutka) chewing is common in adult peoples. In the present study, 79 of 130 patients were in habit chewing gutka since 4.1 years and consuming 5 to 8 gutka sachets daily. Proportional prevalence of OC was found higher in habitual gutka chewers (83.2%) in comparison with non chewers (34.3%). Although no statistically significant relationship of OC was found with patients who previously received azoles and alcohol consumer but these patients were more frequently present in association with OC.

CONCLUSION

In the present study, the higher oral candida carriage rate in HIV-infected patients buttresses the importance of oral *Candida* carriage for identification of patients with the propensity for rapid progression of HIV infection. Data from our study suggested that OC was significantly associated with gender (male), the reduced saliva flow rate, CD4 count < 200 cell/mm^3, previous antibiotics users, AIDS patients, HAART

(patients those did not taken) and gutka (smokeless tobacco) chewers. Our results are important for the development of strategies to eliminate these indicators of risk and significantly reduce OC in Indian HIV-infected adult patients.

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