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ORIGINAL ARTICLE

Oral manifestations in HIV/AIDS infected patients from India

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OBJECTIVES: To assess types and prevalence of HIV-related oral lesions among HIV-infected individuals in south India and to correlate common oral findings with co-morbidities, gender, age and medication.

SUBJECTS AND METHODS: One hundred and one patients with HIV infection or AIDS at infectious diseases units of Attavar Hospital, Mangalore, and medical wards of Kasturba Medical College, Manipal, were selected. Sociodemographic information was obtained using a structured questionnaire. Oral lesions were diagnosed according to the presumptive criteria of EEC-Clearinghouse Classification. Clinical history was retrieved from patient's medical records.

RESULTS: Erythematous candidiasis (44.5%), melanotic hyperpigmentaion (34.6%) and xerostomia (29.7%) were among the most common oral manifestations. A significant association was found between oral candidiasis and advanced immunosuppression ($P < 0.05$). Oral hairy leukoplakia (OHL) was predominant in individuals <35 years ($P < 0.05$). Melanotic hyperpigmentation was significantly associated with highly active antiretroviral therapy ($P < 0.05$). OHL was more frequent in patients with HIV-associated tuberculosis. Linear gingival erythema was more predominant in females.

CONCLUSIONS: Oral hairy leukoplakia showed a positive relationship with patients younger than 35 years. Oral candidiasis can act as a marker for immunosuppression. Angular cheilitis was predominant in the symptomatic stage.

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Keywords AIDS; HIV; India; oral manifestations

Introduction

AIDS has emerged as a global crisis since its discovery in the summer of 1981 in the United States. The epicentre of the epidemic has now slowly, but surely shifted to Africa and Asia. At the end of 2004, around 42 million people in the world were infected with HIV/AIDS (Peterson, 2004). Of these, 5.1 million people were from India making it the second largest country in the world with HIV/AIDS population after South Africa. However, most of the studies pertaining to oral manifestations of HIV have been performed mainly in western countries (Palmer *et al*, 1996; Hilton *et al*, 1997; Patton *et al*, 1998; Margiotta *et al*, 1999) with Asian studies restricted mainly to Thailand (Nittayananta *et al*, 1997: Khongkunthian *et al*, 2001: Kerdpon *et al*, 2004). Surprisingly, in India, only three studies have been reported so far (Anil and Challacombe, 1997; Ranganathan *et al*, 2000, 2004). Hence, a cross-sectional study was undertaken to evaluate oral manifestations in HIV/AIDS patients with the objectives of assessing the types and prevalence of HIV-related oral lesions among HIV-infected individuals and evaluating the association of common oral findings with co-morbidities, gender, age and medication in two infectious diseases centres in south India.

Subjects and methods

The cross-sectional study protocol was approved by the Institutional Research Ethics Committee and written informed consent was obtained from participants (patients). The study cohort included 101 patients with HIV infection including AIDS. The patients were either attending an outpatient clinic in the Infectious Diseases Unit at Attavar Hospital, Mangalore, or hospitalized in medical wards of Kasturba Hospital, Manipal. The study was conducted during a period of 6 months from July 2004 to December 2004. The HIV status was evaluated by enzyme-linked immunosorbent assays (ELISA-HIV). Three separate positive ELISA-HIV tests were considered confirmatory. The stage of HIV

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infection was categorized as asymptomatic, symptomatic and AIDS according to CDC clinical staging (Centers for Disease Control and Prevention, 1992). Clinical history was obtained from patient's medical records. Sociodemographic information was obtained by using a structured questionnaire. Medications used by the patients at the time of the oral examination were assessed after examining the patient's medical records. Commonly prescribed medications were clustered into five different groups; antiretroviral therapy, antitubercular therapy, anti-fungal drugs, other anti-bacterials (i.e. trimethoprim-sulphamethoxazole, ciprofloxacin) and others (i.e. antidepressants, antihypertensives, vitamins and corticosteroids). Oral lesions were diagnosed according to the presumptive criteria of EEC-Clearinghouse Classification (1993). A single examiner trained in oral medicine examined all the patients and recorded oromucosal lesions.

Means and percentages of various variables were calculated. The chi-square test was used to find out the association between variables. The Mann–Whitney *U*-test was applied to assess the statistical differences between groups of patients. Logistic regression analysis was performed for association of oral opportunistic diseases with systemic manifestations, advanced immunosuppression and age (i.e. younger than 35 years). All statistical analyses were performed using the SPSS version 9 software. Statistical significance was set at ≤0.05 level.

Results

Our study predominantly included men (73 men and 28 women). The combined mean age for men and women was 35.3 years. Age, habits, suspected mode of transmission, medications used and systemic manifestations of HIV-seropositive patients are summarized in Table 1. Oral manifestations were seen in 80 (79.2%) patients, which included 58 men and 22 women. Twenty-nine (28.71%) patients revealed one manifestation; 17 (16.83%) patients two manifestations; 15 (14.85%) patients three manifestations; 12 (11.88%) patients four manifestations; five (4.95%) patients five manifestations; two (1.98%) patients six manifestations; and 21(20.8%) patients revealed no oral manifestation (Figure 1).

The most common diagnosis was erythematous candidiasis (EC) (44.5%) followed by melanotic hyperpigmentation (34.6%), oral hairy leukoplakia (OHL) (15.8%), linear gingival erythema (LGE) (15.8%), pseudomembranous candidiasis (PC) (11.8%), angular cheilitis (11.8%) and others. Individual analysis of both genders showed a similar ordinal distribution except for LGE, which was higher when compared with OHL in females. Table 2 shows the oral manifestations pertaining to gender. Apart from these oral manifestations, xerostomia (29.7%) and depapillation of the tongue (8.9%) were also observed which were included in the overall prevalence of oral manifestations.

Eighty-five patients (84.1%) had not received any antiretroviral therapy. Of the 16 patients receiving highly active antiretroviral therapy (HAART), 13 (81.2%) patients had oral manifestations. The three most common oral manifestations in patients receiving HAART were melanotic hyperpigmentation, EC and xerostomia. Comparison of oral manifestations of those patients on HAART with patients not receiving HAART is documented in Table 3. OHL was not found in patients on HAART.

The prevalence of oromucosal manifestations according to CDC clinical staging was 68.1% in stage A (asymptomatic), 77.7% in stage B (symptomatic) and 82.8% in stage C or AIDS (Table 4). An interesting finding observed was that all 12 cases of PC were seen in AIDS. This was found to be statistically significant ($P < 0.05$).

Logistic regression analysis of association between occurrence of oral opportunistic diseases with systemic manifestations, age (younger than 35 years)

Table 1 Distributionof demographic and clinical data of HIV-infected patients

	n
Gender	
Male	73
Female	28
Age (in years)	
16–24	7
25–34	36
35–44	43
45–54	11
> 54 years	4
Mode of transmission	
Heterosexual contact	97
Homosexual contact	3
Unknown	1
Tobacco habits	
Tobacco user	46
Non-tobacco user	55
Alcohol habits	
Alcoholic	32
Non-alcoholic	69
Smoking	
Smoker	28
Non-smoker	73
Medication used[a]	
Antiretroviral therapy	16
Antitubercular therapy	27
Antifungal drugs	0
Other antibacterial drugs	27
Others	37
Co-morbidities (systemic diseases)[b]	
Tuberculosis (TB meningitis, pulmonary TB, abdominal TB, disseminated TB)	36
Herpes zoster	8
Wasting syndrome	8
PCP	7
Anogenital herpes	7
Bacterial pneumonia	4
HIV encephalopathy	3
Others	
Toxoplasmosis, cryptococcosis histoplasmosis, CMV retinitis, CMV[b] esophageal ulcer, vaginal candidiasis, multi focal leucoencephalopathy, etc.	13

PCP, *Pneumocystis carinii* pneumonia; CMV, cytomegalovirus.
[a]Some cases were on more than one drug.
[b]Some cases had more than one systemic disease.

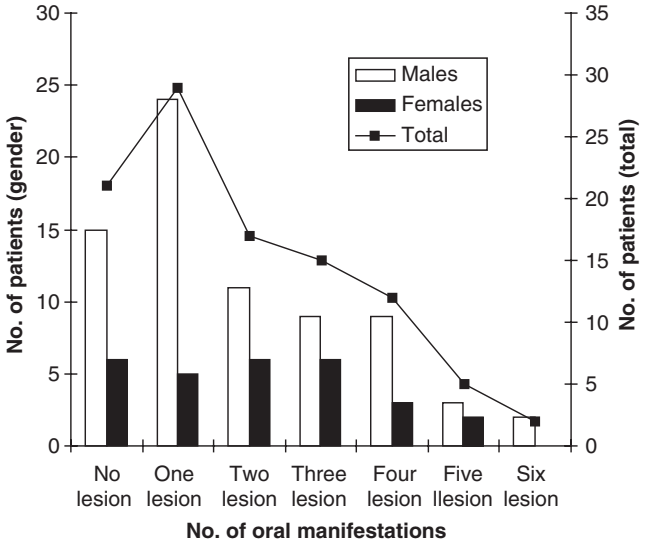

Figure 1 Number of oral lesion manifestations per patient

Table 2 Orallesion manifestations in relation to gender

Lesions	*Male*	*Female*	*Total*
Erythematous candidiasis	31 (42.4)	14 (50)	45 (44.5)
Hyper pigmentation	26 (35.6)	9 (32.1)	35 (34.6)
Oral hairy leukoplakia	12 (16.4)	4 (14.2)	16 (15.8)
Linear gingival erythema[a]	9 (12.3)	7 (25)	16 (15.8)
Pseudomembranous candidiasis	9 (12.3)	3 (10.7)	12 (11.8)
Angular cheilitis	9 (12.3)	3 (10.7)	12 (11.8)
Apthous ulceration			
Minor	3 (4.1)	1 (3.5)	4 (3.8)
Herpetiform	–	1 (3.5)	1 (0.9)
Hyperplastic candidiasis	1 (1.3)	1 (3.5)	2 (1.9)
Non-Hodgkin's lymphoma	2 (2.7)	–	2 (1.9)
Exfoliative cheilitis	1 (1.3)	–	1 (0.9)
Herpes zoster	1 (1.3)	1 (3.5)	2 (1.9)
Erythema multiforme	–	1 (3.5)	1 (0.9)
Stevens Johnson syndrome	1 (1.3)	1 (3.5)	2 (1.9)
Burning mouth syndrome	–	1 (3.5)	1 (0.9)
Necrotizing ulcerative gingivitis	1 (1.3)	–	1 (0.9)

Figures in bracket represent percentage of particular gender.
[a]Statistically significant.

Table 3 Comparisonof oral manifestations of patients on HAART ($n = 85$) and patients not on HAART ($n = 16$)

Oral manifestations	*Patients not on HAART*	*Patients on HAART*	*P-value*
Erythematous candidasis	38 (44.7)	7 (43.7)	0.944*
Melanotic hyperpigmentation	26 (30.5)	9 (56.3)	0.048**
Xerostomia	24 (28.2)	6 (37.25)	0.457*
Linear gingival erythema	14 (16.4)	2 (12.5)	0.690*
Angular cheilitis	9 (10.5)	3 (18.7)	0.355*
Necrotizing ulcerative gingivitis	–	1 (6.2)	–
Oral hairy leukoplakia	16 (185.8)	–	–

Values are expressed as *n* (%). HAART, highly active antiretroviral therapy.
*$P > 0.05$ (not significant); **$P < 0.05$ (statistically significant).

and advanced immunosuppression was carried out (Table 5). Advanced immunosuppression was significantly associated with oral candidiasis [odds ratio (OR) 2.58; confidence interval (CI) 1.04–6.40; $P < 0.05$]. An association between OHL and younger (<35 years) patients was found (OR 3.643; CI 1.160–11.442; $P < 0.05$).

Among the AIDS-defining diseases, tuberculosis (TB) was the most common finding present in 36 (35.6%) patients. Oral manifestations of this particular cohort are shown in Table 6. Erythematous candidasis was the most common diagnosis seen in 15 patients, followed by OHL in nine, hyperpigmentation in eight and PC in six patients.

Discussion

In this study, the majority of patients were men (72.2%). A similar finding was observed in most of the studies from south Asian countries (72.5%: Nittayananta *et al*, 1997; 77.4%: Ranganathan *et al*, 2004). The mean age (35.3 years) was slightly higher when compared with studies from Thailand (Nittayananta and Chungpanich, 1997; 28 years) and Cambodia (Bendick *et al*, 2002; 32 years).

Heterosexual contact, as in most other Asian studies (Nittayananta *et al*, 1997; Khongkunthian *et al*, 2001), was still the major route of transmission irrespective of age, sex and educational level.

The peak distribution in age (25–44 years) as shown in Table 1 reflects the status of HIV epidemic in India. A high prevalence of HIV infection in this age group could lead to a decrease in working force and have an adverse effect on the socioeconomic status of country.

In this study, 80 (79.2%) patients had at least one type of oral manifestation. Previous studies from Thailand (Nittayananta and Chungpanich, 1997), India (Ranganathan *et al*, 2000) and Cambodia (Bendick *et al*, 2002) have shown slightly higher prevalence rates of 82%, 86% and 90% respectively.

As in most studies of patients with HIV and AIDS from different geographical areas, oral candidiasis (50.4%) was the most common finding. EC was seen in 44.5% (45 patients), PC and angular cheilitis were each seen in 11.8% (12 patients). These figures were slightly higher than other studies performed at Thailand (Nittayananta *et al*, 1997; 24.8%), Singapore (Lim *et al*, 2001; 35%) and Cambodia (Bendick *et al*, 2002; 22.8%).

Oral hairy leukoplakia was seen in 15.8% of patients compared with 38% of patients in a study in northern Thailand (Kerdpon *et al*, 2004), 11% of HIV-infected patients in Hong Kong (Tsang and Samranayake, 1999) and 2.1% HIV-infected individuals in India (Ranganathan *et al*, 2004). The cause for the variation in the prevalence of hairy leukoplakia is not clear. The reasons could be attributed to diagnosis alone on the basis of presumptive criteria (EEC-clearinghouse criteria), difficulty in differentiation between candidal lesions and hairy leukoplakia, all of which could lead to misdiagnosis.

An interesting finding was that hairy leukoplakia was common in patients with TB (Tables 5 and 6). Although

Table 4 Clinical staging of HIV and oral manifestations in spectrum of HIV

Staging of HIV (no. patients)	*Oral manifestations present [n (%)]*	*No oral manifestations, n (%)*
Stage A (22)	EC, AC, xerostomia, hyperplastic candidasis, hyperpigmentation, OHL, LGE [15 (68.3)]	7 (31.7)
Stage B (9)	EC, AC, xerostomia, hyperpigmentation, OHL, herpes zoster, apthous ulcers [7 (77.7)]	2 (22.3)
Stage C (70) AIDS	EC, AC, PC, xerostomia, hyperplastic candidasis, hyperpigmentation, OHL, LGE, apthous ulcers, exfoliative cheilitis, EM, herpes zoster, NUG, NHL, BMS [58 (82.8)]	12 (17.2)

EC, erythematous candidiasis; AC, angular cheilitis; OHL, oral hairy leukoplakia; LGE, linear gingival erythema; PC, pseudomembranous candidiasis; NUG, necrotizing ulcerative gingivitis; NHL, non-Hodgkin's lymphoma; BMS, burning mouth syndrome; EM, erythema multiforme.

Table 5 Variables (advanced immunosuppression, age and TB) associated with common oral lesions in HIV-infected patients

Lesions	*Variable*	*OR*	*95% CI*	*P-value*
Oral candidasis	AIDS	2.58	1.04–6.40	0.040[a]
EC	AIDS	2.42	1.011–5.185	0.047[a]
LGE	AIDS	1.39	0.412–4.732	0.592[b]
OHL	AIDS	2.12	0.561–8.083	0.267[b]
Oral candidasis	TB	1.22	0.542–2.770	0.625[b]
EC	TB	0.83	0.366–1.897	0.664[b]
OHL	TB	2.76	0.930–8.20	0.062[b]
LGE	TB	0.79	0.252–2.490	0.690[b]
PC	TB	2.89	0.584–6.621	0.269[b]
OHL	Age <35 years	3.64	1.160–11.442	0.027[a]
Oral candidasis	Age <35 years	0.75	0.343–1.670	0.491[b]

OR, odds ratio; CI, confidence interval; EC, erythematous candidiasis; LGE, linear gingival erythema; OHL, oral hairy leukoplakia; PC, pseudomembranous candidiasis.
[a]Statistically significant.
[b]Not statistically significant.

association of OHL in patients with HIV-associated TB was not statistically significant ($P = 0.062$), the possibility of considering this as a clinical marker for HIV-associated TB cannot be underestimated. In regions where TB is prevalent, like in Asian countries, this finding can assume a clinical significance, as, this can also be used in conjunction with other clinical features in monitoring HIV disease in those areas where there is a lack of adequate resources for laboratory investigations. Therefore, indirectly helping in therapeutic management. More studies are needed to confirm this finding.

Linear gingival erythema was seen in 15.8% of patients. In accordance with EEC-clearinghouse presumptive criteria, diagnosis was made only if a fiery red band along the margin of the gingiva was seen. All these patients had absence of local factors in the immediate vicinity of erythema and no evidence of attachment loss was present. However, it was more common in females (25%) when compared with males (12.3%) (Table 2). So far, this finding has not been found in any study. It may however be an incidental finding and a study on a larger sample needs to be carried out to corroborate this finding.

An association between age and presence of oral lesions has been reported (McCarthy *et al*, 1991; Hilton *et al*, 1997; Nittayananta *et al*, 2001). In our study, higher odds of OHL before the age of 35 years ($P < 0.05$) was observed but no association between oral candidiasis and age was found (Table 5). This finding was exactly similar to that of Hilton *et al* (1997). In contrast, McCarthy *et al* (1991) reported that oral candidiasis was twice as likely to occur in patients over 35 years of age compared with younger patients. These contradictory findings suggest a need for further studies on this subject.

In the present study, no statistically significant differences were found in the oral manifestations in either sex, which is in contrast to some studies where men were

Table 6 Oral manifestations in the TB cohort

Oral manifestations	*Patients (n)*[c]	*Oral manifestations (%)*	*Overall oral manifestations (%)*	*P-value*
Erythematous candidasis	15	41.6	44.5	0.664[a]
Oral hairy leukoplakia	9	25	15.8	0.062[a]
Melanotic hyperpigmentation	8	22.2	34.5	0.129[a]
Xerostomia	8	22.2	29.8	0.221[a]
Pseudomembranous candidiasis	6	16.3	11.8	0.269[a]
Linear gingival erythema	5	13.8	15.8	0.690[a]
Angular cheilitis	3	8.3	11.8	–
Depapillation of tongue	2	5.5	8.9	–
NUG	1	5.5	0.9	–
Hyperplastic candidiasis	1	2.7	1.9	–
Exfoliative cheilitis	1	2.7	0.9	–

[a]Not statistically significant.
[b]Statistically significant.
[c]Some cases had more than one oral manifestation.

found to be more affected than women (Khongkunthian *et al*, 2001; Nittayananta *et al*, 2001) (Table 2).

Melanotic hyperpigmentation was predominant in patients on HAART ($P < 0.05$) which is a known side effect of HAART. The prevalence of overall oral manifestations (on exclusion of xerostomia in both groups) in patients on HAART was 68.3%, which was lesser than in patients not on HAART (74.2%). This finding was found to be consistent with other studies (Ranganathan *et al*, 2000; Nicolatou–galitis *et al*, 2004). This difference, however, was not statistically significant. On inclusion of xerostomia as oral manifestation in the HAART group, the prevalence of overall oral manifestations increased to 81.2%, which was higher than in patients not on HAART (79.2%) (Table 3).

In our study, the prevalence of xerostomia (30 patients; 22 men and 8 women) in patients on HAART was higher (six patients; 37.5%) than in patients not on HAART [24 patients (28.2%); $P = 0.457$ (not significant); Table 3]. Xerostomia has been reported to occur in patients with HAART by Navazesh *et al* (2003), who also suggested that the mechanism by which HAART causes xerostomia is probably by an antisecretory activity upon acinar cells. Salivary flow has also been found to be reduced in the early stages of HIV infection (Lin *et al*, 2003).In our study, a combination of various factors such as HAART, other medications and subclinical salivary gland disease due to HIV may have been contributory factors to xerostomia (though none were significantly associated). Direct attribution to HIV infection is difficult to justify, though the association of xerostomia with HIV has been documented previously (Schiodt, 1997).Thus, the presence of xerostomia warrants further research, as it may diminish the quality of life in these patients.

According to CDC clinical staging, an increased prevalence of oral manifestations was seen (Table 4). The number of oral lesions increased as the stage advanced ($P < 0.05$). This seems logical as with increase in immunosuppression more will be the number of lesions in an individual. The presence of 68.1% of patients having oral lesions in asymptomatic staging suggests that oral manifestations are seen in the initial stages of HIV infection, thus substantiating that the role of dentists in identifying patients with HIV is important and significant.

It was clear that oral candidiasis acts as a marker for progression of disease (Palmer *et al*, 1996; Robinson *et al*, 1997; MacPhail *et al*, 2002). Those who presented with oral candidasis had 2.5 times greater risk of progression to AIDS than those without oral candidasis (Table 5). However, no direct comparison could be made between EC and PC due to the non-existence of PC in stages A and B. A reappraisal of prognostic significance of the two forms of candidiasis will be required in longitudinal studies. Angular cheilitis was seen predominantly in the symptomatic stage. This was statistically significant ($P = 0.05$) and was mainly found in conjunction with EC ($P < 0.05$).

The results of the present study are consistent with the finding that oral Kaposi's sarcoma has not been reported from Asian studies where heterosexual mode of transmission is most common (Nittayananta *et al*, 1997; Tsang and Samranayake, 1999; Lim *et al*, 2001; Khongkunthian *et al*, 2001).

These differences in the prevalence of oral manifestations may be the result of variations in study population such as race, socioeconomic status, sex, drug therapy, genetics, oral habits, degree of immunosuppression and variations in diagnostic criteria. These reasons make comparisons difficult even within a single country.

The common oral manifestations in men were EC, hyperpigmentation, xerostomia, OHL, LGE and PC. In women, the common manifestations were EC, hyperpigmentation, xerostomia, LGE, OHL and PC.

The other common oral manifestation seen in our study was depapillation of the tongue (nine patients; five men and four women). This finding did not have any significant association with any of the variables included in this study and may be secondary to candidal infection/anaemia.

Nittayananta *et al* (2001) found no relationship between smoking and presence of oral manifestation. Our study showed a similar result. In addition, no association could be found between alcohol, tobacco and presence of any oral manifestation.

Our study showed that most of the HIV-infected patients were illiterate, poor and from rural areas. Thus, in a developing country like India, if it has to aim for a reduction in HIV outbreak, then a greater awareness about AIDS should be created and education should begin at grassroots level.

Our study revealed an increased incidence of OHL in the presence of TB, LGE being more common in females and advanced immunosuppression common to all cases of PC. All these results need to be further proved. More studies need to be carried out in Asia, especially in south Asian countries where data are scarce or not available.

To control a lethal and devastating pandemic such as AIDS, all developing and developed countries should work collectively for an AIDS-free world, which unfortunately now looks like a distant dream. Dentists can contribute through early identification of HIV, thus ensuring early treatment and a better quality of life.

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