Clinical Correlation of Oral Manifestations In HIV Seropositive Patients With CD4+ Cell, CD8+Cell Counts And CD4+/CD8+ Ratio.

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Abstract: *The Aim of this study was to investigate the correlation of oral lesions in HIV positive patients with their CD4, CD8 cell count and CD4/CD8 ratio. 150 HIV seropositive patients of any age and sex were evaluated. Then analyses of data obtained were revealed Pseudo membranous candidiasis (P-0.0043) was the most common variant, mostly seen when CD8 count was increased (>500 cells/mm^3, P-0.05) and CD4/CD8 ratio was > 0.31(P-0.0034). Periodontal diseases (29%) mostly were seen in patients with CD4 count >400 cell/ mm^3 (P-0.045), CD8 count >500 CD8 cell/mm^3 (P-0.55) and CD4/CD8 ratio < 0.3(P-0.28). Oral lesions were seen when CD8 count is increased >500 cells/mm^3 and CD4/CD8 ratio is in between 0.31 - 0.6. Oral lesions especially oral candidiasis can be useful as a diagnostic marker for immunosuppression in HIV positive patients, particularly where laboratory assessment cannot be done routinely.*
Keywords: *AIDS, CD4+ cell, CD8+cell counts, CD4+/CD8+ ratio, HIV positive Indians*

I. Introduction

The oral and perioral manifestations are common in HIV infected patients, and often influence the debilitating general health status and they can serve as a strong predictor for HIV infection. To date, CD4 cell count, viral load are recognized and widely used as a marker of HIV related disease progression[1].

The stage of infection can be determined by measuring the patient's CD4$^+$ T cell count, and the level of HIV in the blood. Acute viremia is associated in virtually all patients with the activation of CD8$^+$ T cells, which kill HIV-infected cells, and subsequently with antibody production, or seroconversion. The CD8$^+$ T cell response is thought to be important in controlling virus levels, which peak and then decline. A good CD8$^+$ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus. The CD4:CD8 ratio helps determine the risk of disease progression in HIV-infected patients on HAART [2].

Being aware of individual significance of CD4, CD8 cell count and oral lesions in assessing the disease status, it was thought worthwhile to correlate whether the presence of specific oral manifestations and the number of different concurrent intraoral lesions among HIV-seropositive patients are associated with the levels of CD4+ cell count, CD8+ cell count and the CD4+/CD8+ ratio and to evaluate whether oral examinations would be an essential component for early recognition of disease progression and comprehensive evaluation of HIV-infected patients.

II. Materials And Methods

This study involved clinical and laboratory assessment of 150 HIV seropositives patients of any age and sex irrespective of anti retroviral therapy. The study was carried out in a year 2010 in the Regional AIDS Teaching, Training & Research Department, at Prayas–Amruta Clinic, Pune Maharashtra, India. Voluntary Counselling and Testing Centre for HIV and also a centre for estimating CD4, CD8 cell and CD4/CD8 counts under National AIDS Control Organization exist in this Department. Since informed consent was obtained from each of the study subjects, the ethical clearance was not required in the circumstances.

Each patient selected for this study was subjected to thorough clinical oral examination. A special effort was made to observe and record oral manifestation which was according to the diagnostic criteria given by WHO (Clearinghouse diagnostic criteria). Recent laboratory investigations records for CD4+ cell, CD8+ cell counts and CD4/CD8 ratio for each and every patient were obtained. Then analysis of data obtained was done by chi-square test and T-test to see the correlation between oral manifestation and immune suppression in HIV infected patients.

III. Tables

Table- 1- Distribution of oral lesions in relation to CD4 counts, CD8 Cell count and CD4/CD8 ratio

Oral lesions	No. of Oral Lesions-Present or Absent	CD4 cells /mm^3 count by categories				CD8+ cells/mm^3 count by categories				CD4/CD8 ratio categories		
		<200	201-400	>400	p-value (Chi-square test)	<300	301–500	>500	p-value (Chi Square Test)	<0.30	0.31-0.60	>0.60
Linear Gingivitis	Absent	20	27	69	0.456	5	3	108	0.001	30	54	32
	Present	9	8	17		2	7	25		9	18	7
Necrotizing Gingivitis	Absent	26	32	84	0.156	7	8	127	0.089	34	71	37
	Present	3	3	2		0	2	6		5	1	2
Necrotizing Periodontitis	Absent	26	33	85	0.078	7	10	127	0.671	35	71	38
	Present	3	2	1		0	0	6		4	1	1
Pseudo-membranous candidiasis	Absent	18	29	74	0.017	6	5	110	0.039	30	54	37
	Present	11	6	12		1	5	23		9	18	2
Erythematous candidiasis	Absent	29	34	81	0.356	7	9	128	0.535	39	70	35
	Present	0	1	5		0	1	5		0	2	4
Angular Chelitis	Absent	18	34	84	0.785	7	10	130	0.822	38	71	38
	Present	1	1	2		0	0	3		1	1	1
Hyperplasic candidiasis	Absent	27	35	82	0.335	7	10	126	0.625	37	69	37
	Present	2	0	4		0	0	7		2	3	2
Apthous ulceration	Absent	29	34	78	0.186	7	10	123	0.504	38	65	37
	Present	0	1	8		0	0	10		1	7	2
Herpetic lesions	Absent	29	33	85	0.693	6	10	132	0.009	39	72	37
	Present	0	2	1		1	0	1		0	0	2
Hairy Leukoplakia	Absent	28	34	85	0.688	7	10	130	0.822	38	71	38
	Present	1	1	1		0	0	3		1	1	1
Xerostomia	Absent	26	34	81	0.005	7	9	125	0.694	36	68	37
	Present	3	1	5		0	1	8		3	4	2
Melanin pigmentation	Absent	21	34	60	0.005	6	5	95	0.239	29	49	28
	Present	8	1	26		1	5	38		10	23	11
Kaposi's sarcoma	Absent	29	25	86	0.105	7	10	133	--	39	72	39
	Present	0	10	0		0	0	0		0	0	0
Non Hodgkin's Lymphoma	Absent	29	35	86	-----	7	10	133	--	39	72	39
	Present	0	0	0		0	0	0		0	0	0
Oral Wart	Absent	28	35	85	0.478	7	9	132	0.046	38	72	38
	Present	1	0	1		0	1	1		1	0	1
Focal Epithelial Hyperplasia	Absent	28	35	82	0.434	7	8	130	0.009	38	71	36
	Present	1	0	4		0	2	3		1	1	3
Squamous Cell carcinoma	Absent	28	35	86	0.122	7	10	133	0.002	39	72	39
	Present	1	0	0		0	1	0		0	0	0
Other Lesions	Absent	23	35	77	0.022	5	7	110	0.412	31	65	34
	Present	6 (Bald Tongue -1, Burning mouth – 1, Leukoplakia – 2,Pigmentations on Skin	0	9 (Bald Tongue -0, Burning mouth – 2, Leukoplakia - 2,Pigmentations on Skin – 1, Eczema – 1,		2 (Bell's palsy - 1, Herpes lesions on skin - 1	3 (Pigmented Skin – 2, Bald Tongue – 1)	15 (Bald Tongue -0, Burning mouth – 3, Leukoplakia – 5, Pigmentations on Skin – 1, Eczema – 2,		8	7	5

		– 2)	Geograp-hic Tongue – 1, OSMF – 1, Urticaria – 1)		Geograp-hic Tongue – 1, OSMF – 1, Urticaria – 1, Lichen Planus – 1		

Table 2:-Correlation between Oral Candidiasis with CD4 Cell Count, CD8 Cell Count, CD4/CD8 Ratio
*- Statistically Significant by T-Test,   Sd - Standard deviation

	Oral lesion present				Oral lesion absent				P value For CD4 count	P value For CD8 count	P value For CD4/CD8 levels
	No. of Cases	CD4 cells/mm³ Count (Mean ± Sd)	CD8 cells/mm³ Count (Mean ± Sd)	CD4/CD8 ratio (Mean ± Sd)	No. of Cases	CD4 cells/mm³ Count (Mean ± Sd)	CD8 cells/mm³ Count (Mean ± Sd)	CD4/CD8 ratio (Mean ± Sd)			
Candidiasis	35	395 ± 251	959 ± 434	0.423 ± 0.231	115	518 ± 333	1154 ± 678	0.497 ± 0.279	*0.022	*0.047	0.12
Pseudo Candidiasis	29	356 ± 251	958 ± 454	0.374 ± 0.190	121	521 ± 326	1145 ± 666	0.507 ± 0.281	*0.0043	*0.05	*0.0034
Erythematous Candidiasis	6	526 ± 180	805 ± 369	0.722 ± 0.281	144	488 ± 324	1121 ± 640	0.471 ± 0.266	0.64	0.096	0.085
Angular Chelitis	3	380 ± 314	905 ± 384	0.807 ± 0.313	147	492 ± 320	1113 ± 637	0.43 ± 0.270	0.60	0.46	0.72
Hyper plastic candidiasis	7	421 ± 335	421 ± 335	0431 ± 0.328	143	493 ± 319	493 ± 319	0.484 ± 0.628	0.60	0.60	0.69

Table 3:-Correlation Periodontal Diseases Between With CD4 Cell Count, CD8 Cell Count, CD4/CD8 Rat

	Oral lesion present				Oral lesion absent				P value For CD4 count	P value For CD8 count	P value for CD4/CD8 levels
	No of Cases	CD4 cells/mm³ Count (Mean ± Sd)	CD8 cells/mm³ Count (Mean ± Sd)	CD4/CD8 ratio (Mean ± Sd)	No. of Cases	CD4 cells/mm³ Count (Mean ± Sd)	CD8 cells/mm³ Count (Mean ± Sd)	CD4/CD8 ratio (Mean ± Sd)			
Periodontal diseases	44	412 ± 293	1057 ± 687	0.442 ± 0.279	106	522 ± 325	1130 ± 612	0.496 ± 0.266	*0.045	0.55	0.28
Linear gingivitis	34	426 ± 273	426 ± 273	0.477 ± 0.274	116	508 ± 330	508 ± 330	0.483 ± 0.270	0.15	0.15	0.91
Necrotizing gingivitis	8	303 ± 179	1132 ± 780	0.393 ± 0.380	142	500 ± 322	1170 ± 627	0.486 ± 0.265	*0.019	0.93	0.55
Necrotizing Periodontitis	6	388 ± 444	1078 ± 334	0.322 ± 0.295	144	494 ± 314	1110 ± 643	0.488 ± 0.268	0.59	0.83	0.23

* - Statistically Significant by T-Test, Sd - Standard deviation

IV.   Results

In our study total 150 patients were evaluated. The mean age of the participants in the study was 38.21 years. The maximum number of patients was in the age group of 31 – 40 yrs. Out of total 150 participants, 65% were male and 35% were female; whereas 17% were illiterate and 83% were literate. Marital status of the participants was distributed as 89% as married and remaining 11% were unmarried. Most of the general symptoms such as weight loss (16%), fatigue (10%) and neurological symptoms (7%) were observed among the participants.

IV.I Distribution of oral lesions: (Table-1)

Oral candidiasis lesions were observed in 24% cases. Pseudo membranous candidiasis was the most common variant (19%), and other variants such as erythematous candidiasis (4%), angular cheilitis (2%), and hyperplastic candidiasis (5%) were also observed. Periodontal diseases were noted in 44 patients (i.e. 29%).

Linear gingival erythema cases were recorded in 23% patients. Necrotizing ulcerative gingivitis was seen in 5% cases and necrotizing ulcerative periodontitis was seen in 4% cases. Other oral lesions such as oral hairy leukoplakia, Xerostomia, atypical ulcerations, Melanotic pigmentation and herpetic lesions were observed in 2%, 6%, 7%, 29 % and 1% cases respectively. Lesions such as oral wart, fibro epithelial hyperplasia, skin pigmentations etc were found very less.

IV.II Oral lesions in relation with CD4 count- (Table-1 & 2)

Out of 35 cases of oral candidiasis, 14 cases had CD4 count <200 cells/mm^3, 8 cases had CD4 count 200-400 cells/mm^3 and 23 cases had CD4 cell count >400 cells/mm^3. Pseudo membranous candidiasis was most common variant i.e. 27 cases. Out of which 11 cases had CD4 count <200 cells/mm^3, 6 cases CD4 count 200-400 cells/mm^3 and 12 cases had CD4 cell count >400 cells/mm^3. The occurrence of erythematous candidiasis and angular cheilitis were commonly seen when CD4 count was <200 cells/mm^3.The periodontal diseases were more commonly seen when CD4 count was >400 CD4 cell/ mm^3. 17 subjects had linear gingival erythema with CD4 count >400 cells/mm^3. Most cases of necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis had CD4 count upto 400 cells/mm^3. Oral hairy leukoplakias were observed in equal proportion irrespective of CD4 count. Most cases of melanin pigmentation had CD4 count > 400 cells/mm^3. 8 cases of Atypical ulceration had CD4 count > 400 cells/mm^3, Herpetic lesions were observed in 3 patients who had CD4 count more than 200 cells/mm^3. There was statistical significant correlation between necrotizing ulcerative gingivitis, oral candidiasis and CD4 count in this study. Other lesions being very few in numbers it is not possible to draw any valid conclusion. However it can be stated P value was not significant for other lesions.

IV.III Oral lesions in relation with CD8count and CD4/CD8 ratio- (Table-1 & 2)

Most commonly (23cases) pseudo membranous candidiasis cases were seen when CD8 count increased >500 cells/mm^3 and CD4/CD8 ratio was > 0.3. Erythematous candidiasis, angular cheilitis and hyperplastic candidiasis cases had CD8 count >500 cells/mm^3 and CD4/CD8 ratio was in between 0.31 - 0.6. 25 cases of linear gingival erythema had CD8 count < 300 cells/mm^3 and 18 cases of linear gingival erythema had CD4/CD8 ratio 0.31 to 0.6. Necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis were commonly seen when CD8 count was 301 – 500 cells/mm^3 and CD4/CD8 ratio was > 0.3 In this study, other lesions such as apthous ulcerations, herpetic lesions, hairy leukoplakia, melanin pigmentations and xerostomia were commonly seen when CD8 count increased >500 cells/mm^3 and CD4/CD8 ratio was in between 0.31 - 0.6. There was statistical significant correlation between oral candidiasis and CD8 count and CD4/CD8 ratio in this study. Other lesions being very few in numbers & hence it was not possible to draw any valid conclusion.

V.   Discussion

In our study, we found there were no significant differences about socio-demographic data as compared to other research projects all over the world [3,4,5]. Literature review of impact of education level on HIV/AIDS prevalence rate by world food programme (2005)[6] revealed that better educated populations are reacting more strongly than less educated and non educated populations in their responses towards protection through changes in risky sexual behavior. A Zambian study[7] found that AIDS spreads twice as fast among uneducated patients. All the same, some studies[8] have found no significant correlation in between prevalence of oral manifestations and age, sex, marital status in HIV seropositive cases. So we can conclude that not only literacy but through social awareness is necessary.

The data obtained in the present study about general symptoms is similar to previous several studies[9,10].

Oral lesions are common in individuals with HIV infection. Early recognition and treatment of these oral lesions may reduce morbidity. Oral lesions may be the first clinical features of HIV infection and lead to its diagnosis. Their presence is an indication of immunodeficiency and predicts the progression of HIV disease[11]. Oral lesions such as oral candidiasis and periodontal diseases were more common in individuals with HIV infection. This is consistent with findings from previous studies investigating HIV associated oral lesion[12]. Increased no of oral candidiasis cases can be observed when subjects not under HAART only, are included for the study[13].

Pseudo membranous variety of candidiasis is most commonly found in individuals with HIV infection[3,8,13], however erythematous candidiasis variant can be more common variety[4]. Very few cases of hyperplastic candidiasis were common finding while angular cheilitis cases were high in some studies[15]. This may be because difference in sample size.

Periodontal disease manifestations in HIV infected individuals include linear gingival erythema, necrotizing ulcerative gingivitis and necrotizing ulcerative periodontitis and diagnosticians have convinced about common occurrences of periodontal diseases especially linear gingival erythema in HIV seropositive patients.[3,8]

Presence of oral hairy leukoplakia is a fairly reliable indicator of HIV seropositive and is a predictor of declining immunocompetence. As most of the our patients were on HAART, immunocompetence was good, hence less no of oral hairy leukoplakia cases were seen as compared to other findings from previous studies investigating HIV associated oral lesion.[3,8,13, 15,16]

Less no of cases of xerostomia, atypical ulceration, herpetic lesions in our HIV infected subjects is suggestive of good immunocompetence. Occurrence rate of melanin pigmentation was quite high as it could be due to chronic use of anti retroviral drugs by most of our subjects.

The presence of oral lesion in HIV infected person as well as the presence of wide range of other opportunistic infections is generally accepted as the result of severe immunosuppression caused primarily by destruction of T helper cells after infection by HIV virus. Indeed it has been shown that the low circulating CD4 cell count is associated with the progression of HIV infection to AIDS and used as a marker for the commencement of the patient therapy. We found a close association between the patient's immune state and the presence of oral candidiasis, with an increase in frequency of oral candidiasis as CD4 count decreased.

Most of the cases of oral candidiasis were found in low CD4 count (<200 cells/mm^3). & pseudo membranous candidiasis was the most common variant. The periodontal disease occurred in less severe immunosuppression with its mean CD4 count being 491. The most common variant linear gingival erythema cases were observed in high CD4 count (>400 CD4 cell/ mm^3). We found that hairy leukoplakia was not associated with increasing level of immunosuppression because the presence of this oral lesion did not significantly increase as CD4 cell count decreased. These findings were consistent with the findings of other studies. [12,17,18]

Several medications used in the treatment of HIV related disease may cause xerostomia. Xerostomia is also associated with increased frequency of candidiasis in patient with HIV infection and it is found in low CD4 count (126 cells/mm^3).[19,20]

Majority of the oral lesions were seen when CD4 count was less than 500 cells/mm^3, thereby suggesting close relationship between immunodeficient state of patients and the occurrence of oral lesions. The studies[14] investigating the relationship between immunodeficiency and HIV associated oral lesions have found that the prevalence of oral manifestations was higher with low CD4 count <200 cell/mm^3.

Thus, our study revealed the specific common oral lesions are strongly associated with immune suppression, as measured by CD4 cell counts. Several studies [16] also support to our findings with their report as oral lesion especially oral candidiasis could be useful as a marker for immunosuppression, particularly where CD4 count cannot be determined routinely.

The CD8$^+$ T cell response is thought to be important in controlling virus levels. But now days, it is the most reliable indicator of prognosis. The CD4:CD8 ratio helps to determine the risk of disease progression in HIV-infected patients. Its strong immune response correlates directly with a healthy clinical status and reduced response is concomitant with progression to disease.[21]

We found a close association between the patient's immune status and the presence of oral candidiasis and periodontal diseases; as increased incidence of oral candidiasis and periodontal diseases were associated with increased CD8 Cell count and decreased CD4/CD8 ratio. There is close association of elevated CD8 Count and immunosuppression in HIV symptomatic patients[22] and as CD4+ T-cell numbers decline in the final stages of infection, the residual lymphocyte population is almost entirely composed of CD8+ T-cells[23].

For immune failure in HIV patients, oral candidiasis can be considered as clinical marker.[24] CD8+ cell count was significantly increased and the CD4+/CD8+ ratio was significantly decreased in the gingival connective tissue of the HIV+ patients which shows correlation with periodontal diseases in HIV patients. Several studies also support to our correlation between periodontal diseases and immune suppression in HIV individuals.[25,26,27]

This study had all other oral lesions which are seen when CD8 count is increased >500 cells/mm.^{3} and CD4/CD8 ratio is in between 0.31 - 0.6. Close correlations between increased CD8 cell count and salivary gland diseases including xerostomia have been established previously[28].

We acknowledge here the presence of oral lesions and wide range of other opportunistic infections in HIV infected person is generally accepted as the result of severe immunosuppression caused primarily by destruction of T helper cells (CD4) after infection by HIV virus and increase killer T cells (CD8) which recognize antigens on the surface of HIV virus infected cells, binds to the infected cell and kill it. It is found that CD8 cell count increases as immune reconstitution of HIV infected patients undergoing antiretroviral therapy is developed which is an indicator of favorable response of antiretroviral therapy.

CD4/CD8 ratio is an important diagnostic measure of immune system functioning. In particular, CD4/CD8 ratio predicts the time taken for progression of HIV infection to acquired immune deficiency syndrome (AIDS) and the long-term survival of AIDS patients. [29]

VI. Conclusion

As there was statistical significant correlation found between oral pseudo membranous candidiasis and CD4, CD8 count, CD4/CD8 ratio in this study, these Oral lesions especially oral candidiasis can be useful as a diagnostic marker for immunosuppression in HIV positive patients, particularly where laboratory assessment cannot be done routinely.

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