

Oral Manifestations in HIV-TB Co- infected Patients and Their Correlation with CD4 Count in Telangana State, India

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ABSTRACT

Aims and Objectives: Human immunodeficiency virus (HIV)-related oral lesions are often an early finding, and they reflect the underlying immunosuppression, and tuberculosis (TB) coinfection can have further deteriorating effect. Hence, a cross-sectional study was conducted to evaluate clinical and oral presentations of patients coinfecting with HIV–TB, correlating with various parameters such as the type of TB with CD4 cell count, the type of TB with oral manifestations, site of the lesion, oral manifestations with CD4 cell counts, age, and gender. **Materials and Methods:** A cross-sectional study was conducted among selected 200 patients coinfecting with HIV–TB, registered at Gandhi Medical College, Hyderabad, Telangana, India, and demographic data, CD4 count, diagnosis of TB, and clinical presentation of TB were correlated with site, age, gender, and the type of lesions in the oral cavity. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, (IBM SPSS), version 20 (Chicago, IL, USA), with the chi-square test, and the significant *P* value for all the parameters was considered as <0.05. **Results:** A total of 200 patients with HIV–TB coinfection, who presented with oral lesions of 258 coinfecting cases, were examined. Among which, 129 patients were with pulmonary tuberculosis (PTB), 61 patients with extrapulmonary TB, 2 patients with disseminated TB, and 8 patients with PTB and pneumonia. There were multiple oral manifestations involving different sites of oral cavity, oral candidiasis (28.5%), angular cheilitis (24.5%), linear gingival erythema (21.5%), oral hairy leukoplakia (1.5%), melanotic pigmentation (29.0%), ulcers (20.0%), depapillation of tongue (26.5%), lobulated tongue (12.0%), hairy tongue (11.5%), and papules (10.0%). The correlation of the type of TB with CD4 cell count, oral lesions with the type of TB in tongue, labial mucosa, and palate was significant. **Conclusion:** A total of 77.5% patients coinfecting with HIV–TB had shown oral manifestations emphasizing that the presence of oral lesions can be considered as a strong indicator of coinfection. The oral lesions might be used as a clinical indicator or screening mechanism in patients who were HIV seropositive for TB coinfection and should be necessarily evaluated for TB.

KEYWORDS: *Candidiasis, hairy tongue, human immunodeficiency virus, lobulated tongue, tuberculosis*

Received : 31-12-18.
Accepted : 29-10-19.
Published : 24-01-20.

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV) and is characterized by profound immunosuppression. India is one of

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How to cite this article: Gannepalli A, Krishna AB, Baghirath PV, Vinay BH, Khaled S, Anjum B. Oral Manifestations in HIV-TB Co- infected Patients and Their Correlation with CD4 Count in Telangana State, India. J Int Soc Prevent Communit Dent 2020;10:21-35.

Access this article online	
Quick Response Code: 	Website: www.jispcd.org
	DOI: 10.4103/jispcd.JISPCD_448_18

those countries where the HIV epidemic is growing rapidly.^[1] The National AIDS Control Organization estimated that 1.8–2.9 million HIV-positive individuals were living with HIV/AIDS in India in 2007.^[2,3] HIV infection is rising and is emerging as the most important risk for developing tuberculosis (TB), which itself is a major public health problem in most of the developing world. According to the recent estimates by the World Health Organization (WHO) and Joint United Nations Programme on HIV/AIDS (UNAIDS), nearly 39.4 million people were living with HIV/AIDS, worldwide, more than a half of them in sub-Saharan Africa and nearly a fifth in south and southeast Asia and India.^[4,5] In dually infected patients, the lifetime risk of developing TB is 50%–70% as compared to a 10% risk in HIV-negative individuals^[6] due to detrimental effects of TB coinfection on immune system, leading to progression and transmission.

In India, 56% patients with AIDS have been reported to be with TB. So it has become necessary to look for TB in HIV-infected individuals and vice versa.^[6,7] Unlike other opportunistic infections, which occur at CD4+ counts below 200/mm³, active TB occurs throughout the course of HIV disease. But clinical presentation of TB in HIV-infected individuals depends on the level of immunosuppression resulting from HIV infection.^[8]

The emergence of oral lesions correlates with the HIV progression and indicates the immunosuppression, accounting them to be readily detectable prognosticator, especially the relationship between oral candidiasis, hairy leukoplakia, immunological impairment, and viral load. Association of such oral lesions with other AIDS-defining diseases such as pneumocystosis and TB has been put forth by various studies.^[7,8] Oral involvement is rare in TB, which ranges from 0.005% to 1.5%, and occurrence of oral tubercular lesions has gained importance since the onset of HIV.^[9,10] Very few reports are present with oral manifestations in patients coinfecting with HIV–TB, and as oral lesions can be readily detected in a standardized, objective manner, this observational study was performed to identify the oral manifestations in them and to correlate with the immune status.

MATERIALS AND METHODS

This cross-sectional study was undertaken by the department of oral pathology and microbiology, Panineeya Mahavidyalaya Institute of Dental Sciences, and was conducted at the Antiretroviral Treatment (ART) ward of Gandhi Medical Hospital, Hyderabad, Telangana, India, for 3 months. The subjects who were recently diagnosed with HIV infection/AIDS

with TB coinfection (>18 years) and who were willing to participate in the study were selected. The study methodology was followed according to the guide for epidemiological studies of oral manifestations of HIV infection. Inclusion criteria consisted of the HIV-seropositive subjects along with TB who presented with oral manifestations and estimated CD4 counts. The exclusion criteria included the patients with antituberculosis treatment/ART/highly active antiretroviral therapy (HAART), patients with any other systemic immunosuppression conditions, and patients with missing information and without oral manifestations. Data collection included demographic information, mode of transmission of disease, and the results of the clinical examination; purified protein derivative, chest X-ray findings, sputum examination, and CD4 count were reviewed and evaluated for the diagnosis of TB and immune status. The patient's oral examination was carried out in natural light using disposable wooden spatula, gloves, masks, brightly illuminating torch, and sterile pieces of cotton and gauze.

The oral lesions associated with HIV–TB coinfection were classified into three groups based on the presumptive criteria provided by the EC Clearinghouse on oral problems related to HIV infection and the WHO collaborating centre on oral manifestations of the human immunodeficiency virus. Oral lesions observed other than the aforementioned criteria were grouped under miscellaneous category. The CD4 cell counts (per mm³) were divided into three groups <200, 201–500, >500/mm³.

Statistical analysis: The statistical analysis was carried out using the Statistical Package for the Social Sciences software (IBM SPSS), version 20 (Chicago IL, USA), and the significant *P* value for all the parameters was considered as <0.05. Descriptive analysis was carried out. Correlation between the type of TB, oral manifestations and CD4 count, site of oral manifestation, age, and gender was determined using Pearson's chi-square test. The study was approved by the institutional ethics committee with a reference number 00138, and the hospital authorities and the patients who willingly participated in the study were included after obtaining their consent.

RESULTS

A total of 200 (77.5%) of the 258 subjects coinfecting with HIV–TB with oral manifestations, who fulfilled the study criteria, were selected. The age of these patients ranged from 21 to 70 years, with a mean age of 40 years. There was a slight predominance of females

over males with 52.5% (105) females and 46% (92) males and 1.5%^[3] cases of transgender. The predominant mode of transmission of HIV infection was found to be heterosexual contact in 98.5% cases and others in 1.5%.

Regarding TB presentation, pulmonary TB (PTB) accounted for 64.5% (129/200), 30.5% (61/200) with extrapulmonary TB (EPTB), 1% (2/200) with disseminated TB (DTB), and 4% (8/200) with PTB with pneumonia. Of 200 coinfecting cases, 8.5% (17/200) had CD4 cell count (per mm³) \leq 200/mm³, 61% (122/200) had 201–500/mm³, and 30.5% (61/200) had $>$ 500/mm³ [Table 1]. There was a significant correlation ($P < 0.05$) between CD4 cell count and type of TB [Table 2].

In relation to the anatomic location, the most commonly affected site was periodontal tissues (100%) with periodontitis of varying severity, followed by gingivitis; hence, only specific characteristic lesions of these sites were noted and included in the study. The most common site observed was tongue (38.5%), followed by labial mucosa (21.5%), gingiva (21%), buccal mucosa (15%), and hard and soft palate (4%). Most of the patients presented with more than one lesion in the mouth and more than one affected site.

Analyzing the specific oral manifestations, candidiasis was more prevalent with a total number of 57 (28.5%) patients. It was evaluated in different clinical presentations with erythematous candidiasis (45, 22.5%) being predominant [Figure 1], followed by pseudomembranous candidiasis (11, 5.5%) [Figure 2]

and hyperplastic candidiasis (1, 0.5%) [Figure 3]. The next prevalent lesions were melanotic pigmentations (58, 29%) [Figure 4]; depapillation of tongue (53, 26.5%) [Figure 5]; angular cheilitis (49, 24.5%); linear gingival erythema (43, 21.5%); hairy tongue (23, 11.5%); oral ulcers (40, 20%) of which 7 were aphthous ulcers, 32 nonspecific ulcers, and 1 patient showed ulcer with rolled margins; oral hairy leukoplakia (OHL) (3, 1.5%); lobulated tongue (24, 12%) [Figure 6]; papules over the palate (20, 10%); and enlarged circumvallate papillae (10, 5%) [Table 1].

On comparison of the type of oral manifestation and site with the type of TB, it was found that majority of lesions were present on tongue with numerous combinations of lesions and had shown significant correlation, followed by labial mucosa and palate [Tables 3 and 4]. A total of 176/200 had lesions on tongue with significant correlation with the type of TB. On correlation of oral manifestations and CD4 counts, it was noted that OHL, hyperplastic candidiasis was significant [Table 5] and all three cases of OHL had CD4 count less than 500/mm³. The majority of the oral manifestations were observed in 201–500/mm³ range of CD4 count. On comparison of the type of oral manifestation in different sites with the gender [Table 6], it was observed that palatal papules had shown significant correlations, which were present in female patients [Table 7].

According to EC Clearinghouse classification, most of the lesions observed were under commonly associated lesions with HIV except melanotic hyperpigmentation and ulcers, which were less commonly associated with HIV but had more prevalence in our study. Miscellaneous lesions appreciated were depapillation/atrophy of tongue, lobulated tongue, hairy tongue, swollen circumvallate papillae, and papules over the palate.

DISCUSSION

HIV–TB coinfection has been described as “cursed duet” with approximately 25%–65% patients with HIV/AIDS having TB of any organ. The number of patients with AIDS who develop TB varies widely between countries and regions with a rising trend observed in African countries and southeast Asian countries.^[11,12] This increase may be due to lack of public health efforts to control TB, the epidemic of HIV infection, increase in poverty and the large number of people in crowded shelters, and development of multidrug-resistant species of bacteria.^[13]

CD4 T cell depletion is the main feature of AIDS and an important contributor to the increased risk of

Table 1: Association between types of TB with age-groups, gender, and levels of CD4 counts

Factors	Total	%
Age-groups		
<20 years	1	0.50
21–30 years	40	20.00
31–40 years	79	39.50
41–50 years	51	25.50
>50 years	29	14.50
Gender		
Male	93	46.50
Female	107	53.50
CD4 (per mm ³)		
\leq 200	17	8.50
201–500	121	60.50
$>$ 500	62	31.00
Types of TB		
Pulmonary	128	64.00
Extrapulmonary	61	30.50
Disseminated	2	1.00
TB meningitis	1	0.50
Pulmonary TB with pneumonia	8	4.00
Total	200	100.00

Table 2: Comparison of status of oral manifestations and the type of tuberculosis

Main	Sub	Pulmonary	%	Extrapulmonary	%	Disseminated	%	TB meningitis	%	Pulmonary TB with pneumonia	%	Chi-square test	P value
Tongue	Erythematous candidiasis	34	26.56	9	14.75	0	0.00	0	0.00	1	12.50	4.6860	0.3210
	Pseudomembranous candidiasis	10	7.81	3	4.92	0	0.00	0	0.00	0	0.00	1.3790	0.8480
	Depapillation	34	26.56	18	29.51	0	0.00	1	100.0	1	12.50	4.5040	0.3420
	OHL	23	17.97	2	3.28	0	0.00	1	100.0	0	0.00	16.0780	0.0030*
	Ulcer	9	7.03	5	8.20	2	100.0	0	0.00	0	0.00	23.9490	0.0001*
	Melanin pigmentation	22	17.19	14	22.95	0	0.00	1	100.0	3	37.50	6.9960	0.1360
	Lobulated tongue	10	7.81	13	21.31	1	50.00	0	0.00	2	25.00	10.3600	0.0350*
	Swollen papillae	2	1.56	11	18.03	0	0.00	0	0.00	1	12.50	17.8170	0.0010*
	Ulcer	10	7.81	4	6.56	0	0.00	0	0.00	0	0.00	0.9760	0.9130
	Melanin pigmentation	11	8.59	3	4.92	0	0.00	0	0.00	2	25.00	4.2510	0.3730
LM	Candidiasis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
	Ulcer	7	5.47	4	6.56	0	0.00	0	0.00	1	12.50	0.8880	0.9260
	Angular cheilitis	16	12.50	31	50.82	2	100.0	0	0.00	1	12.50	39.3550	0.0001*
Palate	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
	Papules and petechia	2	1.56	9	14.75	0	0.00	0	0.00	0	0.00	14.5090	0.0060*
Gingiva	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
	LGE	26	20.31	12	19.67	0	0.00	0	0.00	4	50.00	4.9540	0.2920
FOM	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-

*P < 0.05, comparison of status of oral manifestations and the type of TB, there is a significant relation between OHL with TB meningitis and oral ulcers and angular cheilitis with disseminated TB



Figure 1: Erythematous candidiasis with a central erythematous, smooth appearance over the dorsum of tongue



Figure 3: Hyperplastic candidiasis over the tongue



Figure 2: Pseudomembranous candidiasis characterized by curdy white plaque over the dorsum of tongue and hyperpigmentation



Figure 4: Erythematous candidiasis with erythematous, smooth surface and hyperpigmentation



Figure 5: Brownish black thick hairy plaque over dorsum of the tongue



Figure 6: Erythematous, nodular areas on anterolateral surface of tongue

TB. HIV manipulation of macrophage bactericidal pathways, deregulated chemotaxis, and a tipped Th1/Th2 balance are other contributing factors. TB and

Table 3: Comparison of age-groups with present status and site of the lesions

Main	Sub	<20 years	%	21-30 years	%	31-40 years	%	41-50 years	%	>50 years	%	Total	%	Chi-square test	P value
Tongue	Erythematous candidiasis	1	100.00	6	15.00	17	21.52	13	25.49	7	24.14	44	22.00	5.1380	0.2730
	Pseudomembranous candidiasis	0	0.00	2	5.00	7	8.86	2	3.92	2	6.90	13	6.50	1.5070	0.8250
	Depapillation	0	0.00	12	30.00	21	26.58	14	27.45	7	24.14	54	27.00	0.6850	0.9530
	OHL	0	0.00	16	40.00	7	8.86	2	3.92	1	3.45	26	13.00	33.1850	0.0001*
	Ulcer	0	0.00	6	15.00	4	5.06	4	7.84	2	6.90	16	8.00	3.7250	0.4440
	Melanin pigmentation	0	0.00	7	17.50	15	18.99	11	21.57	7	24.14	40	20.00	0.8460	0.9320
	Lobulated tongue	0	0.00	5	12.50	13	16.46	4	7.84	4	13.79	26	13.00	2.2080	0.6980
	Swollen papillae	0	0.00	0	0.00	2	2.53	7	13.73	5	17.24	14	7.00	13.7250	0.0080*
BM	Ulcer	0	0.00	4	10.00	5	6.33	2	3.92	3	10.34	14	7.00	1.9240	0.7500
	Melanin pigmentation	0	0.00	1	2.50	12	15.19	2	3.92	1	3.45	16	8.00	9.2490	0.0550
	Candidiasis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
LM	Ulcer	0	0.00	4	10.00	3	3.80	4	7.84	1	3.45	12	6.00	2.5200	0.6410
	Angular cheilitis	1	100.00	10	25.00	16	20.25	16	31.37	7	24.14	50	25.00	5.0650	0.2810
Palate	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
	Papules and petechia	0	0.00	0	0.00	2	2.53	5	9.80	4	13.79	11	5.50	9.3810	0.0500*
Gingiva	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-
	LGE	0	0.00	5	12.50	20	25.32	9	17.65	8	27.59	42	21.00	3.9990	0.4060
FOM	Ulcer	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-

*P < 0.05, comparison of age-groups with present status and site of the lesions, significant correlation is seen with OHL in 21-30 years group, papules and petechia in 41-50 years group

Table 4: Comparison of gender with present status of site of the lesions

Main	Sub	Male	%	Female	%	Total	%	Chi-square test	P value
Tongue	Erythematous candidiasis	28	30.11	16	14.95	44	22.00	6.6590	0.0100*
	Pseudomembranous candidiasis	5	5.38	8	7.48	13	6.50	0.3610	0.5480
	Depapillation	22	23.66	32	29.91	54	27.00	0.9860	0.3210
	OHL	5	5.38	21	19.63	26	13.00	8.9330	0.0030*
	Ulcer	6	6.45	10	9.35	16	8.00	0.5660	0.4520
	Melanin pigmentation	19	20.43	21	19.63	40	20.00	0.0200	0.8870
	Lobulated tongue	17	18.28	9	8.41	26	13.00	4.2840	0.0380*
	Swollen papillae	10	10.75	4	3.74	14	7.00	3.7600	0.0500*
	Ulcer	6	6.45	8	7.48	14	7.00	0.0800	0.7770
	Melanin pigmentation	6	6.45	10	9.35	16	8.00	0.5660	0.4520
BM	Candidiasis	0	0.00	0	0.00	0	0.00	-	-
	Ulcer	4	4.30	8	7.48	12	6.00	0.8900	0.3460
	Angular cheilitis	26	27.96	24	22.43	50	25.00	0.8110	0.3680
Palate	Ulcer	0	0.00	0	0.00	0	0.00	-	-
	Papules and petechia	1	1.08	10	9.35	11	5.50	6.5480	0.0110*
Gingiva	Ulcer	0	0.00	0	0.00	0	0.00	-	-
	LGE	19	20.43	23	21.50	42	21.00	0.0340	0.8540
FOM	Ulcer	0	0.00	0	0.00	0	0.00	-	-

*P < 0.05, comparison of gender with present status of site of the lesions; erythematous candidiasis, lobulated tongue, swollen papillae, and papules and petechia showed a male predilection, and OHL showed female predilection

HIV co-infection has profound effects on the immune system, as they are capable of disarming the host's immune responses; alveolar macrophages are the primary target and facilitate M. tuberculosis infection and disease in individuals with HIV by targeting the CD4 and CD8 cells which impairs the immune system and up-regulation of M. tuberculosis entry receptors on macrophages.^[14,15]

In our study, the peak age of occurrence was in the third decade of life with 39.5% patients, and the mean age was 40 years, which was similar to that observed in other Indian studies.^[1] There was female predilection with 52.5%, and 46% were males and 1.5% were transgender. Our findings corroborated with few Indian studies^[12] but were in contrast to other Indian studies on HIV-infected individuals who showed male predilection.^[1,16,17] The trend of feminization of HIV disease is being reported over the world,^[5,18] and gender differences also occur in relation to oral lesions in patients who were HIV positive. da Silva *et al.*^[19] observed female predilection of oral lesions, whereas Ranganathan *et al.*^[17] noted male predilection.

According to Pawlowski *et al.*,^[14] the most common type of TB in non-HIV-infected patients was pulmonary form, but in seropositive individuals, it was EPTB, which could be due to hematogenous mycobacterial dissemination.^[8] But our findings were consistent with various Indian studies and other studies from the developing countries, which have shown PTB as the most common presentation in coinfection.^[11] The majority of the patients were affected with PTB (64.5%) but increased numbers of EPTB cases (30.5%) were appreciated. Many reports^[20] showed that fall in CD4 counts is not related to the type of TB, and majority of the HIV cases with CD4 count less than 200 are associated with PTB followed by EPTB and only disseminated TB cases were in correlation with the CD4 count (below 200/mm³).^[9] In our sample, the type of TB and CD4 cell counts were statistically correlated but more number of EPTB (61%) and DTB (100%) cases showed low CD4 count <200/mm³.

An important observation made in our study was that 200 (77.5%) patients of 258 patients coinfecting with HIV-TB showed oral manifestations with varying presentations, severity, and sites. A significant association between the occurrence of the oral lesions and systemic TB has been observed.^[17,21] Oral manifestations in individuals with HIV are well-documented, but oral lesions of TB are nonspecific and are reported in less than 1% of the TB population. The paucity of oral TB lesions may be due to protective effect of saliva, presence of saprophytes, thickness of

Table 5: Relation of oral manifestation with CD4 count

Oral Manifestation			CD4 Count			Total	Chi- square	p-value
			<200 (N=17)	201- 500 (N=122)	>500 (N=61)			
Erythematous candidiasis	Present	N	4	27	14	45	0.027	0.987
		%	8.9%	60.0%	31.1%	100.0%		
	Absent	N	13	95	47	155		
		%	8.4%	61.3%	30.3%	100.0%		
Pseudomembranous candidiasis	Present	N	0	7	4	11	1.134	0.567
		%	0.0%	63.6%	36.4%	100.0%		
	Absent	N	17	115	57	189		
		%	9.0%	60.8%	30.2%	100.0%		
Hyperplastic candidiasis	Present	N	1	0	0	1	10.819	0.004*
		%	100.0%	0.0%	0.0%	100.0%		
	Absent	N	16	122	61	199		
		%	8.0%	61.3%	30.7%	100.0%		
Melanin pigmentation	Present	N	5	33	20	58	0.652	0.722
		%	8.6%	56.9%	34.5%	100.0%		
	Absent	N	12	89	41	142		
		%	8.5%	62.7%	28.9%	100.0%		
Hairy tongue	Present	N	1	13	9	23	1.247	0.536
		%	4.3%	56.5%	39.1%	100.0%		
	Absent	N	16	109	52	177		
		%	9.0%	61.6%	29.4%	100.0%		
Oral Hairy Leukoplakia	Present	N	2	1	0	3	13.434	0.001*
		%	66.7%	33.3%	0.0%	100.0%		
	Absent	N	15	121	61	197		
		%	7.6%	61.4%	31.0%	100.0%		
Ulcers	Present	N	2	25	13	40	0.805	0.669
		%	5.0%	62.5%	32.5%	100.0%		
	Absent	N	15	97	48	160		
		%	9.4%	60.6%	30.0%	100.0%		
Linear gingival erythema	Present	N	4	27	12	43	0.191	0.909
		%	9.3%	62.8%	27.9%	100.0%		
	Absent	N	13	95	49	157		
		%	8.3%	60.5%	31.2%	100.0%		
Depapillation	Present	N	6	30	17	53	0.962	0.618
		%	11.3%	56.6%	32.1%	100.0%		
	Absent	N	11	92	44	147		
		%	7.5%	62.6%	29.9%	100.0%		
Angular cheilitis	Present	N	6	31	12	49	1.894	0.388
		%	12.2%	63.3%	24.5%	100.0%		
	Absent	N	11	91	49	151		
		%	7.3%	60.3%	32.5%	100.0%		
Lobulated tongue	Present	N	3	14	7	24	0.561	0.755
		%	12.5%	58.3%	29.2%	100.0%		
	Absent	N	14	108	54	176		
		%	8.0%	61.4%	30.7%	100.0%		
Swollen papillae	Present	N	0	1	0	1	0.643	0.725
		%	0.0%	100.0%	0.0%	100.0%		
	Absent	N	17	121	61	199		
		%	8.5%	60.8%	30.7%	100.0%		
Papules	Present	N	1	14	5	20	0.836	0.658
		%	5.0%	70.0%	25.0%	100.0%		
	Absent	N	16	108	56	180		
		%	8.9%	60.0%	31.1%	100.0%		

*Statistical significance (p<0.05)

On comparison of Site and Oral manifestations with CD4 count significance is seen with Oral Hairy Leukoplakia and Hyperplastic Candidiasis.

Table 6: Relation of oral manifestations in tongue according to gender

Site	Oral Manifestation	Gender			Total	Chi-square	p-value
		Male	Female	Transgender			
Tongue	NAD	N	14	0	24	67.487	0.103
		%	58.3%	0.0%	100.0%		
	Erythematous candidiasis	N	13	1	34		
		%	38.2%	2.9%	100.0%		
	Pseudomembranous candidiasis	N	5	1	9		
		%	55.6%	11.1%	100.0%		
	Depapillation	N	21	0	31		
		%	67.7%	0.0%	100.0%		
	Hairy tongue	N	8	1	12		
		%	66.7%	8.3%	100.0%		
	Ulcers	N	3	0	4		
		%	75.0%	0.0%	100.0%		
	Melanin pigmentation	N	11	0	14		
		%	78.6%	0.0%	100.0%		
	Lobulated tongue	N	6	0	8		
		%	75.0%	0.0%	100.0%		
	Swollen papillae	N	0	0	10		
		%	0.0%	0.0%	100.0%		
	Oral hairy leukoplakia	N	1	0	1		
		%	100.0%	0.0%	100.0%		
	Melanin Pigmentation & Depapillation	N	4	0	9		
		%	44.4%	0.0%	100.0%		
	Hairy tongue & Ulcers	N	2	0	3		
		%	66.7%	0.0%	100.0%		
	Erythematous Candidiasis & Oral Hairy Leukoplakia	N	0	0	2		
		%	0.0%	0.0%	100.0%		
	Hairy tongue & Lobulated tongue	N	0	0	1		
		%	0.0%	0.0%	100.0%		
	Erythematous Candidiasis & Melanin Pigmentation	N	1	0	3		
		%	33.3%	0.0%	100.0%		
	Hairy tongue & Depapillation	N	6	0	6		
		%	100.0%	0.0%	100.0%		
	Pseudomembranous Candidiasis & Ulcers	N	2	0	2		
		%	100.0%	0.0%	100.0%		
	Melanin Pigmentation & Ulcers	N	1	0	2		
		%	50.0%	0.0%	100.0%		
	Lobulated tongue & Depapillation	N	0	0	4		
		%	100.0%	0.0%	100.0%		
	Melanin Pigmentation & Hyperplastic Candidiasis	N	0	0	1		
		%	0.0%	0.0%	100.0%		

Table 6: Continue

Site	Oral Manifestation	Gender			Total	Chi-square	p-value
		Male	Female	Transgender			
	Melanin Pigmentation & Swollen papillae	N 0 0.0%	3 100.0%	0 0.0%	3 100.0%		
	Pseudomembranous candidiasis & Lobulated tongue	N 1 100.0%	0 0.0%	0 0.0%	1 100.0%		
	Swollen papillae & Erythematous candidiasis	N 0 0.0%	1 100.0%	0 0.0%	1 100.0%		
	Ulcers & Lobulated tongue	N 2 66.7%	1 33.3%	0 0.0%	3 100.0%		
	Melanin Pigmentaion & Lobulated tongue	N 6 85.7%	1 14.3%	0 0.0%	7 100.0%		
	Depapillation & Erythematous Candidiasis	N 2 66.7%	1 33.3%	0 0.0%	3 100.0%		
	Ulcers & Depapillation	N 1 100.0%	0 0.0%	0 0.0%	1 100.0%		
	Erythematous Candidiasis, Melanin Pigmentation & Lobulated Tongue	N 1 100.0%	0 0.0%	0 0.0%	1 100.0%		
Total		N 92 46.0%	105 52.5%	3 1.5%	200 100.0%		

On comparison of Oral manifestations on tongue with the gender no significance was appreciated

Table 7: Relation of oral manifestations in different sites with gender

Site	Oral Manifestation	Gender		Total	Chi-square	p-value
		Male	Female			
Buccal mucosa	NAD	N 80 47.1%	N 87 51.2%	170 100.0%	2.819	0.831
	Ulcers	N 5 41.7%	N 7 58.3%	12 100.0%		
	Melanin Pigmentation	N 6 35.3%	N 11 64.7%	17 100.0%		
	Pseudomembranous Candidiasis	N 1 100.0%	N 0 0.0%	1 100.0%		
Labial mucosa	NAD	N 63 45.0%	N 74 52.9%	140 100.0%	6.043	0.812
	Ulcers	N 3 30.0%	N 7 70.0%	10 100.0%		
	Angular cheilitis	N 26 51.1%	N 24 48.9%	50 100.0%		
Palate	NAD	N 92 47.9%	N 97 50.5%	192 100.0%	7.540	0.023*
	Papules	N 0 0.0%	N 8 100.0%	8 100.0%		
Gingiva	NAD	N 73 46.2%	N 82 51.9%	158 100.0%	0.856	0.652
	Linear gingival erythema	N 19 45.2%	N 23 54.8%	42 100.0%		
	NAD	N 92 46.0%	N 105 52.5%	200 100.0%	----	----

*Statistical significance (p<0.05)

On comparison of Site and oral manifestations with the gender, the palatal papules were significant

protective epithelial covering. The occurrence of oral tubercular lesions and its prevalence have assumed significance since the onset of HIV infection. Oral TB lesions may be either due to primary or secondary infection, and primary lesions are extremely rare. Primary lesions remain painless in the majority of cases and are manifested in immunocompromised conditions (e.g., HIV infection).^[22] The mode of acquisition of oral TB lesions may be self-inoculation from infected sputum or by hematogenous or lymphatic dissemination.^[21]

In our study of HIV–TB coinfection cases, the gingival–periodontal lesions were most frequent, followed by oral candidiasis. Among oral candidiasis, the cases of erythematous candidiasis (22.5%) outnumbered those of pseudomembranous candidiasis (5.5%), and one case (0.5%) of hyperplastic candidiasis was also appreciated. Most of the erythematous cases presented as mild to severe atrophy of papillae on tongue. Majority of studies have reported pseudomembranous candidiasis as the predominant lesion rather than erythematous candidiasis.^[17,23]

The presence of *Candida* in oral cavity can be related to many conditions, opportunistic nature, immunosuppression, poor drug adherence, and comorbid conditions. Nittayananta *et al.*^[21] and Ahmad *et al.*^[11] showed that oral candidiasis in patients with TB provides a high suspicious index for HIV infection, and significant association of oral candidiasis and TB was observed in their cohort. HIV is associated with increased colonization rates, and absolute CD4 count has traditionally been cited as the greatest risk factor for development of overt disease, which was not significant in the present study.^[24] Erythematous candidiasis could be due to loss of pseudomembrane or may develop as a *de novo* lesion^[25,26] and further investigations should be carried out to identify the strain of *Candida* prevalent in co-infected patients.

Melanotic hyperpigmentation (29%) of the oral mucosa was found to be a common oral manifestation, which was distinct from racial pigmentation and was similar to studies reported by Bodhade *et al.*,^[1] Ranganathan *et al.*,^[17] and Krishna *et al.*^[27] in patients with HIV. The possible reasons proposed were increased release of α -melanocyte-stimulating hormone (α -MSH) due to deregulated release of cytokines in HIV disease, use of melanocyte-stimulating drugs such as certain antiviral or antifungal agents, and Addison's disease.^[1,17,25]

Depapillation of tongue (26.5%) and angular cheilitis (24.5%) were predominant lesions next to oral candidiasis and melanotic pigmentation. Angular cheilitis has been included as a type of candidal infection

by various authors but could be due to various other nonspecific factors such as systemic vitamin deficiency. Hence, we did not include it under candidiasis, as it was predominantly seen in female patients, and most of the Indian female population is afflicted by anemia and vitamin deficiencies.^[16] The majority of atrophic tongue cases from mild to severe were included in atrophic/erythematous candidiasis but others with nonspecific depapillations were considered a separate entity. Most of these cases were noted with low CD4 count and as mild atrophic change has a high probability of being a candida-induced lesions^[27] and India being a country with population afflicted with nutritional deficiencies, further studies should be conducted with matched controls. The high prevalence of gingivitis and periodontitis in Indian population limits the significance of occurrence in HIV population.^[17] Hence, only specific lesions with predominant occurrence noticed were linear gingival erythema (20.3%).

The groups of lesions occupying the next place were the ulcers (20%), which were consistent with other studies.^[1,17,22,28] Apart from HIV, most cases of oral TB present as chronic ulcerative mucosal lesions. Oral TB ulcers are single rather than multiple, and have an indurated, irregular, and undermined margin with a necrotic base.^[29–32] The ulcerations in the study were observed on the hard palate, buccal mucosa, and labial mucosa followed by the tongue.^[29,30] Seven patients showed aphthous ulcers and 32 nonspecific ulcers, one case showed a chronic large ulcer with indurated margins, which was diagnosed as oral TB.

An interesting observation was the presence of miscellaneous lesions such as lobulated tongue, papules, hairy tongue, and enlarged circumvallate papillae in our study. Ivan D Miziara encountered irregular ulcers and papillomatous lesions on palate and tongue in cohort of HIV-TB co-morbid patients similar to our findings.^[9] The oral lesions of TB can also appear as erythematous patches or papules, indurated soft tissue lesions, lobulated tongue, nodules, fissures, and osteomyelitis of the jaws.^[22] Papules were erythematous and raised from the mucosal surface, were seen from few to many with an incidence of 10%, and as palate being the most commonly involved site in oral TB, these papular lesions could be suspected as complication of TB but the exact reason, however, is not known. The lobulated tongue, erythematous nodules, and multiple nodules were included under this category, which were observed in 24 patients (12%) in our sample.

Hairy tongue was found in 23 cases (11.5%) in this study. And the plausible etiology for hairy tongue could

be due to poor oral hygiene, prolonged medication, or even immunocompromised state.^[33] Enlarged circumvallate papillae, which are tiny threadlike structures, are seen with minimal incidence in 10 cases (5%). These lesions cannot be corroborated with any specific etiology. In this study, only three cases of OHL were observed (1.5%). OHL is less frequently reported in Indian studies, and the overall prevalence of OHL in the Indian subcontinent was found to be low. This low prevalence could be the result of its strong association with homosexual men in the studies from the developed countries and differences in diagnostic capabilities among investigators.^[1,17]

The comparison of CD4 cell count and the oral manifestations was found correlative in our cohort with respect to hyperplastic candidiasis and OHL, which was also evident from other studies, which proposed a significant association between oral lesions and low CD4 levels, especially below 200 cells/mm³.^[1,9,19] When oral lesions were correlated with the type of TB, significant correlation was found between angular cheilitis and lobulated tongue with EPTB and hairy tongue with PTB. Similarly, current guidelines suggest that there is an increased risk of oropharyngeal candidiasis with CD4 count below 200/mm³^[24] but in this study, majority of cases were seen with CD4 count between 200 and 500/mm³. Even though there was a significant association of the type of TB with CD4 count, oral lesions were observed irrespective of CD4 count, indicating that TB may act as a cofactor to accelerate or modify the clinical course of HIV infection as proposed by Whalen *et al.*^[34-36] OHL was significantly observed in the younger age-groups, which heralds severity of the HIV infection.^[37] The gender differences for the oral presentation among patients coinfecting with HIV-TB were observed with males being the significantly affected gender with a predilection for manifestations such as erythematous candidiasis and lobulated tongue, and females with palatal papules. And, this difference could be due to the immunity pattern difference, that is, females have a tendency for effective cell-mediated immunity response, and the hormonal differences shown by both the genders.^[38]

Hence, we summarize that with the increasing number of TB cases in patients who were HIV positive, unusual forms of the disease in the oral cavity are more likely to occur as observed in the present cohort such as lobulated tongue, papules on palate, erythematous nodular lesions, nonspecific ulcers, and TB ulcers, which may be representative of oral TB. Oral candidiasis was the common oral presentation in comorbid patients

with HIV-TB though not significantly correlated with CD4 count, and few nonspecific lesions such as hairy tongue were not pathognomonic but significantly correlated. Oral manifestations, though not correlated with CD4 count, were major clinical indicators in the present cohort as 200/258 naive patients had TB coinfection. The potential limitation was that this was an observational study, and hence further clinical studies with culture analysis of oral tubercle bacilli could corroborate the clinical presentation of oral TB in HIV-TB comorbidity. The early interception of the disease will be helpful in decreasing the morbidity and mortality of the patients. To the best of our knowledge, no report was available that details the prevalence of oral lesions in a cohort of patients coinfecting with HIV-TB as this study.

CONCLUSION

In this study, 77.5% patients coinfecting with HIV-TB who fulfilled the criteria had shown oral manifestations emphasizing that the presence of oral lesions is a strong indicator of HIV-TB coinfection, and although rare, doctors and dentists should be aware of these oral lesions for effective screening of HIV and TB. CD4 count may not be a sufficient indicator of TB risk in patients with HIV, suggesting that laboratory parameters partially reflect disease stage and progression but addition of clinical markers more accurately reflects the overall disease status. It is very important to screen for TB in patients with HIV in general and more so with patients presenting oral manifestations irrespective of CD4 count. Oral lesions of patients with HIV can predispose to oral TB, and such patients being highly susceptible can be a potential source of infection with major implication in public health.

ACKNOWLEDGEMENT

We would like to express our gratitude to all the staff members of Antiretroviral Therapy (ART) Clinic, Gandhi Medical College, Hyderabad, Telangana, India.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil.

CONFLICTS OF INTEREST

There are no conflicts of interest.

AUTHORS CONTRIBUTIONS

Dr. Ashalata Gannepalli - Study conception, Data collection, acquisition and analysis, data interpretation, Drafting and revising manuscript critically. Dr. Ayinamoudi B Krishna - Data Analysis, Data

interpretation, Manuscript writing, revising manuscript critically. Dr. Pacha V Baghirath - Manuscript revising Dr. Balistty Hari Vinay - Manuscript writing. Dr. Sana Khaled - Data collection, aquisition and an alysis. Dr. Bushra Anjum-Study conception, Data collection, aquisition and analysis, data interpretation, manuscript writing. All the authors approved the final version of the manuscript for publication.

ETHICAL POLICY AND INSTITUTIONAL REVIEW BOARD STATEMENT

The present study was approved by the institutional ethics committee with a reference number-00138

PATIENT DECLARATION OF CONSENT

Consent was obtained from the patients who were included in the study. As we have not included minor patients so there is no consent from the parents.

DATA AVAILABILITY STATEMENT

The entire data has been submitted to the journal in the form of Tables and statistical evaluation in the article.

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