Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/tfe83902

A STUDY OF MUCOCUTANEOUS MANIFESTATIONS IN HIV-INFECTED PATIENTS PRESENTING TO A TERTIARY CARE INSTITUTE IN PUNJAB.

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Introduction:
Human immunodeficiency virus (HIV) infection & Acquired immunodeficiency syndrome (AIDS) have been a significant public health concern worldwide with an estimated global prevalence of 40.8 million people.[1] According to latest NACO guidelines, Punjab has a high prevalence of HIV – 0.42% in 2023. Mucocutaneous diseases are common in HIV infection and they increase in frequency and severity with progression of infection and declining CD_4 counts. They can function as visual markers of disease progression especially in regions with insufficient resources to test CD_4 T cell counts & HIV viral load.[2–4] Being an easily assessable site for examination & biopsy, the skin can give a clue to underlying immune status, hence, evaluation of skin plays an important role in HIV infected patients. The present study was conducted to determine the pattern & prevalence of mucocutaneous manifestations in HIV positive patients and their correlation with CD_4 counts in a tertiary care institute.

Material & Methods:
This observational cross-sectional study was conducted over a period of 1.5 years in the Departments of Dermatology and General Medicine at Christian Medical College and Hospital, Ludhiana, Punjab. Ethical clearance was obtained from the Institutional Research and Ethics Committee prior to the commencement of the study.
A total of 110 serologically confirmed HIV-positive patients were enrolled. Inclusion criteria comprised individuals diagnosed using 4th generation ELISA (J. Mitra) who presented to the HIV clinic, dermatology outpatient department (OPD), or were admitted as inpatients during the study period. HIV-positive blood donors were excluded. To prevent duplication, an index was maintained for all enrolled patients.
Each participant underwent a comprehensive clinical evaluation, including detailed history taking and physical examination. Clinical diagnoses of mucocutaneous manifestations were supported by appropriate laboratory investigations, such as potassium hydroxide (KOH) mount, Tzanck smear,

Gram stain, Herpes serology, Venereal Disease Research Laboratory (VDRL) test, and histopathological examination, wherever indicated.
CD4 cell counts were recorded for all patients; if recent data (within the past six months) were unavailable, fresh counts were obtained. Clinical and immunological staging was performed in accordance with World Health Organization (WHO) guidelines. All findings were systematically documented in a predesigned proforma.
Statistical tests were applied as follows**:**

- Quantitative variables were compared using independent T test / Mann – Whitney test (when the data sets were not normally distributed) between infection & no infection.
- Qualitative variables were correlated using Chi square test.

A P value of < 0.05 was considered statistically significant. The data was entered in MS Excel spreadsheet and analysis was done using SPSS version 21.0.

Results:
Out of a total 110 HIV positive patients, 80 were males while 30 were females with a sex ratio of 2.7:1. Majority of patients were between 31 – 40 years of age. The most common route of transmission was heterosexual (90.69%) followed by intravenous drug abuse (7.27%). Maximum patients (50.91%) had severe immunosuppression and the mean CD_4 counts of patients were 268.74 $\pm$ 245.94 cells/mm^3. Mucocutaneous manifestations were seen in 109 patients. The average number of dermatoses per patient was 10.57.

Table 1: Most common mucocutaneous manifestations seen

Mucocutaneous Manifestations	Frequency	Percentage	Mean CD4 cell count	P value
Xerosis	75	68.18%	237 ± 244.93	0.02
Candidiasis	68	61.82%	199.81 ± 199.75	0.0002
Longitudinal ridging	67	60.91%	255.31 ± 249.3	0.394
Dermatophytosis	57	51.82%	231.44 ± 220.37	0.127
Diffuse hair loss/ dull hair	54	49.09%	212.44 ± 219.96	0.026
Hyperpigmented facies	40	36.36%	232.78 ± 255.36	0.075
Seborrhoeic dermatitis	38	34.55%	236.42 ± 190.35	0.758
Longitudinal melanonychia	37	33.64%	275.81 ± 261.24	0.934
Distal onycholysis	29	26.36%	252.97 ± 251.17	0.508
Leuconychia	28	25.45%	239.82 ± 197.67	0.816
Half and half nails	27	24.55%	221.07 ± 244.15	0.12
Furunculosis	16	14.55%	188.06 ± 166.59	0.199
Mucosal pigmentation	16	14.55%	239.19 ± 216.67	0.722
Ichthyosis	15	13.64%	214.53 ± 193.83	0.428
Herpes simplex virus infection	15	13.64%	135.92 ± 184.37	0.009
Condyloma acuminata	11	10%	242.63 ± 346.05	0.168

The number of dermatoses per patient statistically increased with immunological worsening (Fig.1). Infectious dermatoses were seen in 103 patients and non-infectious dermatoses were seen in 106 patients. 29 patients had sexually transmitted infection (STI). The number of infectious dermatoses was found to significantly increase with advancing clinical stage. Maximum number of non-infectious dermatoses was seen in WHO clinical stage 2 and 3 which was statistically significant.

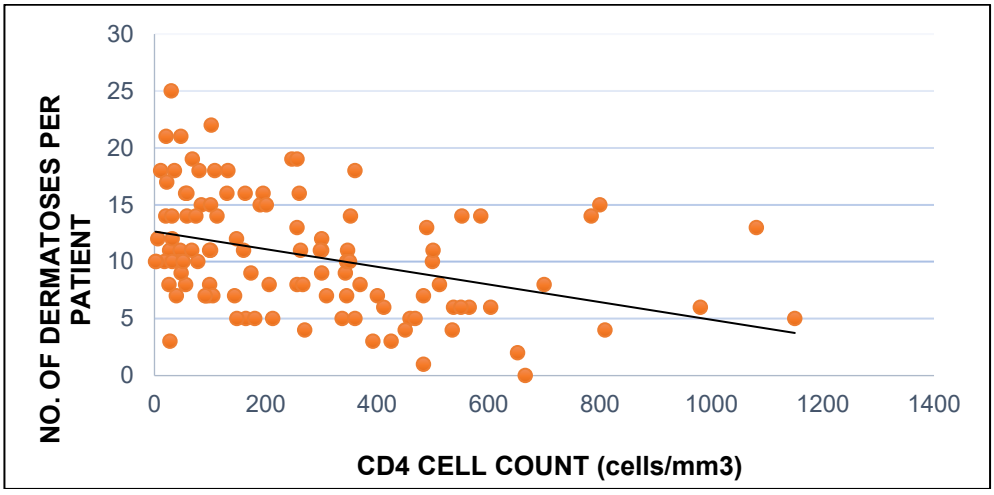

Figure 1 - **: Correlation between CD4 cell count and Number of dermatoses**

As shown in Figure 1, the number of dermatoses per patient statistically increased with immunological worsening ($r = -0.41$, $p < 0.0001$).

Among infections, fungal infections were most common (76.36%) followed by bacterial infections (28.18%), viral infections (27.27%) & parasitic infestations (0.91%). Infectious dermatoses were seen at an average CD_4 count of 254.39 $\pm$ 244.6 cells/mm^3. The most common fungal infection was candidiasis (61.82%) followed by dermatophytosis (51.82%). Majority of fungal infections were seen in patients with WHO clinical stage 3 and CD_4 counts < 200 cells/mm^3. The prevalence of oral candidiasis was found to be inversely related with CD_4 counts. Total dystrophic onychomycosis was the most common nail involvement. Only one patient had proximal subungual onychomycosis. Deep fungal infections were not observed. Furunculosis & folliculitis were the most common bacterial infections seen in patients having CD_4 counts between 200-349 cells/mm^3. There was one patient of leprosy (in reaction) and one of scrofuloderma, both in WHO clinical stage 4 having advanced immunosuppression. Viral infections were seen in 27.27% patients, majority of which were seen in WHO clinical stage 4 having severe immunosuppression. Warts were the most common (14.55%) followed by herpes simplex virus (HSV) infection (13.64%), molluscum contagiosum (MC) (5.45%) and herpes zoster (1.52%). Statistically significant association was found between HSV infection and WHO clinical staging. STI was seen in 26.36% patients, most common being condyloma acuminata (10%), followed by herpes genitals (8.18%), candidal balanitis (5.45%), MC (3,64%), vuluovaginal candidiasis (3.64%) and urethral discharge (3.64%). Table 2 and Table 3, depict correlation between dermatoses and WHO immunological and clinical staging.

Table 2: Correlation between dermatoses and WHO immunological staging (CD4 count)

	CD4 CELL COUNT (cells/mm^3)				**Total**	**P value**
	> 500	**350-499**	**200-349**	**< 200**		
Infectious dermatoses	15 (83.33%)	13 (86.67%)	19 (90.48%)	56 (100%)	103 (93.64%)	0.035
Noninfectious dermatoses	15 (83.33%)	15 (100%)	21 (100%)	55 (98.21%)	106 (96.36%)	0.014
STI	4 (22.22%)	3 (20.00%)	5 (23.81%)	17 (30.36%)	29 (26.36%)	0.801
Total	**18 (100%)**	**15 (100%)**	**21 (100%)**	**56 (100%)**	**110 (100%)**	

As depicted in Table 2, CD4 cell counts below 200 cells/mm3 were significantly associated with maximum infectious dermatoses, whereas CD4 cell counts between 200 - 499 cells/mm^3 were significantly associated with maximum noninfectious dermatoses. Although, not statistically significant, majority of STIs were seen with CD4 cell counts < 200 cells/mm^3.

Table 3: Correlation between dermatoses and WHO clinical staging

	WHO CLINICAL STAGING					**Total**	**P Value**
	Primary HIV	**Stage1**	**Stage 2**	**Stage 3**	**Stage 4**		
Infectious dermatoses	1 (50%)	15 (75%)	21 (95.45%)	33 (100%)	33 (100%)	103 (93.64%)	0.0001
Noninfectious dermatoses	2 (100%)	17 (85%)	22 (100%)	33 (100%)	32 (96.97%)	106 (96.36%)	0.049
STI	1 (50%)	5 (25%)	4 (18.18%)	8 (24.24%)	11 (33.33%)	29 (26.36%)	0.689
Total	**2 (100%)**	**20 (100%)**	**22 (100%)**	**33 (100%)**	**33 (100%)**	**110 (100%)**	

There was a statistically significant difference between prevalence of fungal infections ($p < 0.0001$), including, oral candidiasis ($p < 0.0001$) and tinea unguium ($p < 0.011$), and HSV infection ($p < 0.004$) according to WHO clinical staging.

According to immunological staging a statistically significant difference was observed between prevalence of fungal infections ($p = 0.021$) and bacterial infections ($p = 0.033$). When mean CD_4 counts of each infectious manifestation was compared with mean CD_4 counts of patients not having similar manifestation, significant difference was observed in the following dermatoses – fungal infections ($p=0.012$), including, oral candidiasis ($p < 0.0001$) and tinea unguium ($p = 0.013$), and HSV infection ($p = 0.009$). The most prevalent non-infectious dermatoses was xerosis (68.18%). Longitudinal ridging (60.19%) diffuse hair loss (49.09%), hyperpigmented facies (36.36%), sunken cheeks (34.55%) seborrhoeic dermatitis (34.55%) and pruritic papular eruption (PPE) (5.45%) were among others. Psoriasis was seen in 3.64% patients, being more prevalent in clinical stage 1 and in patients with CD_4 counts between 350 – 499 cells/mm3. All psoriatic patients had extensive lesions. Only 1 patient had oral hairy leucoplakia. One patient had kaposi's sarcoma and was in WHO clinical stage 4 with CD_4 counts of 102 cells/mm^3. No patient of bacillary angiomatosis or eosinophilic folliculitis were seen. There was a statistically significant difference between prevalence of seborrhoeic dermatitis ($p = 0.005$), xerosis ($p = 0.015$) and psoriasis ($p = 0.049$) according to WHO clinical staging. According to immunological staging of HIV infection, statistically significant difference was observed between prevalence of xerosis ($p = 0.005$), hyperpigmented facies ($p=0.040$) and diffuse hair loss/ dull hair ($p = 0.027$).

Discussion:

Mucocutaneous manifestations have been found to reflect a patient's underlying immune status. Singh et al[4] & Smith et al[5] have documented that certain dermatological diseases increase both in severity & frequency with progression of HIV infection and declining CD_4 counts. Various studies have reported varying frequencies of mucocutaneous manifestations ranging from 53.8%[6] – 95.2%.[7] The average dermatoses per patient in our study was 10.57, much higher compared to other studies.[2,4,8] This could be because majority of our patients were in WHO clinical stage 3 and 4 and had severe immunosuppression. Our institution, being a tertiary care institute, attracts patients already in advanced stages of disease. The number of dermatoses per patient statistically increased with immunological worsening ($p < 0.001$). Ali Azfar et al. could not show any association between skin manifestations and CD4 cell counts [9]. On the other hand, Fernandes and Bhat reported statistically significant association with CD4 T-cell count in pyodermas, dermatophytoses and papular pruritic eruptions.[10] The number of non-infectious and infectious dermatoses were at par. In contrast, Chawhan et al[11] & Vasudevan et al[12], found infectious dermatoses to be more prevalent than non-

infectious dermatoses. The number of infectious dermatoses was found to increase significantly with advancing clinical stages; non-infectious dermatoses were seen is WHO clinical stage 2 and 3. CD_4 counts </= 200 cells/mm^3 were associated with maximum infectious dermatoses while non-infectious dermatoses were associated with CD_4 counts of 200-499 cells/$mm^{3.}$ This finding is in concordance with studies which have shown that lower CD_4 counts were associated with more infectious diseases.[3,7,13,14] The most common individual manifestations are Xerosis (68.18%), candidiasis (61.82%) and longitudinal ridging (60.91%). Seborrhoeic dermatitis and candidiasis have been reported to be the most common dermatological disorders among HIV patients in various studies.[15,16] however, in our study only 34.5% had seborrhoeic dermatitis. Xerosis was found commonly in our patients. Mirnezami et al [7] too observed xerosis to be prevalent in high percentage of HIV patients. This may be due to malnutrition and cachexia associated with late stages of HIV infection. Few other studies have reported xerosis less frequently.[2,6]

Among the infectious dermatoses, fungal infections were the most prevalent. Candidiasis has been found to be the most common fungal infection in other studies too, similar to our study[2,8] In our study, the number of patients with candidiasis statistically increased with immunological worsening ($p = 0.001$), a finding similar to other studies.[7] Prevalence of dermatophytosis was higher in our study as compared to an earlier study[2]; being significantly more common in WHO clinical stage 3 and inversely correlated with CD_4 counts. The higher prevalence of dermatophytosis could be explained by the fact that in recent times, incidence of dermatophyte infection has increased great fold among general population becoming a matter of public health concern and individuals who are already immunocompromised get infected easily. Bacterial infections were observed in 28.18% patients, higher than few other studies[2,11] Viral infections were seen in 27.27% patients similar to other studies [11] Human papillomavirus (HPV) infection was the most common followed by HSV infection and MC. Kore et al found HSV infection to be the most common,[2] while Chawhan et al found MC to be the common viral infection.[11] Similar to other studies [11,19] no significant correlation was seen for warts with WHO clinical and immunological staging. Scabies was seen in only 1 patient. The data regarding the overall incidence of scabies and HIV infection is not well documented, however, in one study it was reported to be as high as 20% [20] The most common STI was condyloma acuminata followed by herpes genitalis. Kore et al found herpes genitals to be the most common STI.[2] Incidence of herpes genitals has risen above bacterial infections; this could be due to intake of multiple courses of antibiotics by the patient from various medical practitioners/ over the counter medications before they present to a tertiary care institute. We had only 2 patients of syphilis having maculopapular rash and scaly plaques on hands. In recent times, the number of patients having active syphilis in HIV infection is declining, although, serology may be positive. Among the non-infectious dermatoses, xerosis was most common, seen in 68.18% patients. Contrary to other studies [15,16], seborrhoeic dermatitis was seen only in 34.55% patients. Hyperpigmented facies was seen in 36.36% patients. Singh et al found generalized hyperpigmentation in 46.67% patients.[4] This could be due to Zidovudine therapy; but it has also been found that HIV positive patients have increased levels of melanocyte stimulating hormone which could also contribute to increased pigmentation[4] Only 6 patients had pruritic papular rashes(PPE) similar to studies conducted in Chhattisgarh[11] and Karnataka[22] indicating low prevalence among Indian patients. According to Noruka's research, pruritic papular rashes (PPE) were most commonly found in CD4 counts <200 and seborrheic dermatitis was observed in patients with CD4 counts between 201 and 500.[23] PPE is a sign of advanced degree of immunosuppression and severity of rash correlates inversely to CD_4 counts.[5] In our study also the patients with PPE had CD_4 counts < 200 cells/mm^3. Psoriasis was seen in 3.64% patients in clinical stage 1 and all of these patients had extensive lesions. Psoriasis in HIV tends to be a severe, extensive, destructive, recalcitrant with predilection for scalp, flexures and palmoplantar areas.[24] We had only one patient each of oral hairy leukoplakia similar to a study conducted by Vasudevan et al.[12] while Ashwani et al reported 6 cases of OHL.[6] In HIV patients, OHL serves as an indicator of disease severity and rapid progression. Proximal subungual onychomycosis and Kaposi's sarcoma were seen in one patient each. Specific markers like bacillary angiomatosis and eosinophilic folliculitis were absent in our study group. While skin manifestations are frequently

observed in individuals with HIV, their prevalence, presentation, and underlying factors differ significantly across populations. Understanding the regional variations in AIDS-related skin disorders is essential for improving patient care and tailoring effective treatment strategies.

Conclusion:

Mucocutaneous manifestations serve as important visual markers of HIV infection and may give a clue to underlying immune status. They can predict disease progression and immunological worsening. However, the prevalence of these manifestations may differ among different geographical locations. Hence, the specific markers of HIV infection may need to be modified according to the location.

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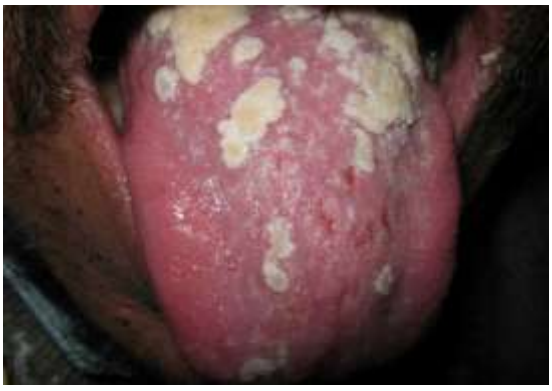
I - Secondary Syphilis

II - Condyloma Acuminata



III - Florid oral candidiasis