

Mucocutaneous Manifestations of Human Immunodeficiency Virus (HIV) Infection in Relation to the Degree of Immunosuppression

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Abstract: ***Background:** Human immunodeficiency virus (HIV) infection is becoming a common occurrence. Worldwide, limited studies have been done on the mucocutaneous manifestations in HIV-positive patients. The aim of our study was to analyze the spectrum of mucocutaneous manifestations of HIV infection and correlate to degree of immunosuppression. Material and methods, 72 patients with HIV, who presented to the departments of dermatology were examined for mucocutaneous manifestations. Patients were classified into four groups of immunodeficiency such as normal (CD4 count >500 cells/mm³), mild (CD4 350-499), advanced (CD4 200-349) and severe (CD4 <200), based on NACO guidelines of immunosuppression. The most recent CD4 count (within 6 months of study period) was considered. **Results:** 72 patients with skin manifestations were examined. The highest incidence of mucocutaneous manifestations was in 40-50 age group. Males were 30, females were 42 cases. Tinea infection 15 (21%) was the most common condition, with highest prevalence in severe CD4 category (30%). Verruca vulgaris 5 (7%) was the most common infectious condition, with highest prevalence in advance CD4 category (14%). Syphilis 7 cases (9%) was the most common STD infection followed by Donovanosis (1 case). Adverse drug reactions (ADR) caused by various drugs were seen in 7 (10%) patients. The percentage of skin manifestations was highest in the severe category 22 cases (30%) and advanced 20 cases (27%) CD4 category. There was no significant difference in manifestations between those who were on antiretroviral therapy (ART) and those not. **Conclusion:** The percentage of skin manifestations increased with degree of CD4 depletion. However, opportunistic infections did not correlate with severity of immunodeficiency. Human immunodeficiency virus (HIV) infection is perhaps the single greatest pandemic that mankind is facing in recent times. Skin manifestations constitute one of the most common clinical features in children, and the clinical pattern and severity is more or less in accordance with the degree of immunosuppression.*

Keywords: Mucocutaneous manifestation, human immunodeficiency virus, HIV, immunosuppression

1. Introduction

Worldwide about 37 million people are living with HIV infection according to the most recent data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2017.¹ The Centers for Disease Control and Prevention estimates the prevalence of HIV infection to be 2.1 million people in the INDIA with an incidence of about 88,000 new infections per year.²

HIV-associated dermatoses are very common. Skin disease can be uniquely associated with HIV disease, but more often represents common disorders, which may be more severe and recalcitrant to treatment. The spectrum of skin conditions includes skin findings associated with primary HIV infection and a broad range of skin problems related to the immune deficiency of advanced AIDS [5]. Recognition of characteristic eruptions can facilitate early diagnosis of HIV. A broad variety of neoplastic, infectious and non-infectious diseases can manifest in the skin and may alert the clinician to decline of the immune system.

Aims

The primary aim was to study the spectrum of mucocutaneous manifestations of HIV infection, and the secondary aim was to correlate mucocutaneous manifestations of HIV infection with the degree of immunosuppression.

2. Materials and Methods

An approval by the institutional review board and informed consent from the parents of the subjects were obtained who were diagnosed to have HIV infection were included in the study and were classified based on the NACO Guidelines of immunosuppression into normal, mild, advanced, and severe categories.

The latest CD4 cell count and measurement of the CD4 percentage, done within 6 months of inclusion in the study was recorded. A complete one-time dermatological examination of the skin, mucosae, hair, and nail was performed. The diagnosis of cutaneous disorders was made clinically, and relevant investigations were done wherever indicated to confirm diagnosis such as KOH examination, Tzanck smear, cultures, biopsies, serology etc. The spectrum of dermatological diseases in these cases was analyzed and sample data expressed in percentages. Statistical methods of chi-squared test for comparing manifestations with different categories of immunosuppression ($P > 0.05$) and z-test to compare sample proportions of type of manifestation were used.

3. Results

The total number of patients examined during the course of this study was 72. Out of this, 72 patients had mucocutaneous manifestations. There were 30 males (42%) and 42 females (58%). In both males and females, the

highest number of patients was in the severe category of immunosuppression.

This association was statistically significant ($P > 0.05$) using the z-test for sample proportions.

The percentage of skin manifestations was more in the severe category, 22 cases (30%) and advanced (27%) CD4 category.

Tinea 15 cases (21%) was the most common infectious condition with highest prevalence in the severe CD4 category (fig-2).

7 patients had adverse drug reactions, two of whom were presented with maculopapular reaction (both having advanced category), 2 cases were in severe and mild category. Drug induced pigmentation was seen in 2 cases.

Herpes Zoster infection was seen in one patient in normal category and one in advanced category. All lesions on the face were ulcerated and crusted.(fig-1)

Xerosis was seen in 5 patients, two in the severe CD4, one in the advanced CD4 and remaining 2 cases in two category. Generalized fine bran-like scaling was seen.

Syphilis 7 cases (9%) was the most common STDs infection followed by Donovanosis(1 cases)(fig-5) and molluscum contagiosum (1 case).

There was no significant difference in the percentage of manifestations between those who were on ART and those who were not ($P < 0.05$) (Fig. 6). Hence, the presence of skin disease did not predict immunodeficiency.

4. Discussion

HIV is a disease with high morbidity. Often, it is the dermatologist from whom a patient first seeks help. Diagnosis of cutaneous disease can be challenging. While some conditions reliably present with stereotyped lesions, other diseases may have highly variable manifestations, leading to diagnostic uncertainty that may necessitate specialist consultation and skin biopsy. The approach to diagnosis of skin lesions includes the assessment of location, extent, primary lesions, and secondary changes.

The atypical features and severity of the skin disease is what commonly leads to the diagnosis of HIV infection. Cutaneous manifestations of HIV in India may be different from that in other countries, as racial and geographic predisposition to disease may differ.

In a country like India, it is important to identify cutaneous markers which will predict the degree of immunosuppression, as it may not be possible to do CD4 counts in all patients on a regular basis.

The incidence of skin manifestations was more in the advanced and severe category of immunosuppression. However, incidence of infectious manifestations was more or less equal in the normal, mild, and advanced category and

least in the severe category of immunosuppression. The incidence of noninfectious manifestations was highest in the severe category of immunosuppression.

Papules, plaques, and nodules can be caused by infectious, inflammatory, as well as neoplastic disease. Infectious etiologies include diseases like warts, molluscum contagiosum, staphylococcal and streptococcal as well as bacillary angiomatosis, and atypical mycobacterial as well as deep fungal infections. Frequent external rubbing and scratching can lead to lichenification as well as the development of prurigo nodularis. Neoplasms, especially skin cancer, can also present as papules with various secondary changes, often noted in sun-exposed skin. Kaposi sarcoma, an AIDS-defining cancer, presents with red to brown papules and nodules.³

Plaques can be associated with infectious diseases like cellulitis or intertrigo, as well as non-infectious causes. Inflammatory diseases like papular eczema can present with localized as well as widespread papules coalescing to plaques which are often associated with scaling and pruritus. Other common rashes associated with HIV include seborrheic dermatitis, which presents as erythematous papules and plaques with greasy scale, usually in a seborrheic distribution (oily and hair-bearing skin). There can be an overlap with psoriasis which typically shows well-demarcated plaques with silvery scale on the extensor surfaces; nail findings, including pitting and oil spots, can be helpful in distinguishing the two entities.

Vesicles and bullae and their presentation should raise concern for underlying infectious disease. Grouped vesicles on an erythematous base are a common presentation for herpes simplex, while herpes zoster often presents similarly in a dermatomal distribution. Both diseases can be widespread or generalized in case of severe immunosuppression. A honey-colored crust is a common finding in bullous impetigo, while bullous tinea or candida will present with very superficial erosions. Of course other causes including contact dermatitis, edema, or pressure bullae need to be ruled out. Follicular inflammatory papules and pustules are suggestive of folliculitis.⁴

Macular and morbilliform erythematous eruptions are often associated with drug reactions, but can also represent a viral infection. If widespread erythema is associated with bullous lesions, desquamation, and mucosal involvement, then severe drug reactions like Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) need to be excluded.

In the era of antiretroviral therapy (ART), the spectrum of cutaneous manifestations in HIV-infected patients has changed, and clinicians are faced with different skin complaints today.

4.1 Pruritus

Lichen planus 3 cases (2 in normal and 1 in severe cases), 6 cases of Photo allergic dermatoses found.

Xerosis was seen in 5 patients, two in the severe CD4, one in the advanced CD4 and remaining 2 cases in two category. Generalized fine bran-like scaling was seen.

In the post-antiretroviral era, pruritus has become the most common skin-related symptom reported by patients with HIV. The majority of the participants were receiving antiretroviral therapy. Majority of the surveyed patients reported pruritus with negative effects on their quality of life. Overall, no significant association between the reported pruritus and CD4.^{3,4,5}

The most common dermatoses found were xerosis, fungal infection, seborrheic dermatitis, and eczema. Pruritic papular dermatitis was reported in three cases.

Since most patients with skin lesions presented with stage 3 and 4 HIV infection, specific cutaneous manifestations were considered a good clinical indicator for the patient's immune status.

4.2 Bacterial Infections

Bacterial infections were seen in a total of 2 patients (3%). Folliculitis was seen in one patient and cellulitis in one. These were seen predominantly in the severe category.

Despite improved disease control, infections continue to be a relevant morbidity in the HIV infected population. They include fungal, bacterial, viral, as well as parasitic infections and can be an indicator of the degree of immunosuppression. Many infections common in the general population appear to be more recalcitrant in HIV.

The presence of chronic skin conditions or wounds was also associated with a higher colonization burden. Compared with HIV-negative patients, the HIV population had a higher proportion of chronic skin disease. CD4 count and viral load was not found to influence the colonization burden.⁶

4.3 Viral Infections

There were 5 patients who had human papillomavirus (HPV) infection. There was two patient each in the mild and advanced category, and the remaining one in the normal category. It is important to note that the warts resolved with conventional therapy (such a electrocautery and cryotherapy).

There was two patients with Herpes Zoster (HZ). This patient was in the normal category and one was in advanced. The lesions involved the left eyelid and face with discrete lesions over the forehead, nose, cheeks, and angle of the mouth. They were hemorrhagic crusts. Molluscum contagiosum was found in 1 case (fig-4).

Viral infections are also more prevalent in immunosuppressed patients and can be associated with malignancies. In the era of ART, the focus of attention has shifted from long-known viral infections like herpes, molluscum, and virus associated with AIDS-defining cancers to the discovery of new viral disease. Also, the presence of multiple viruses was more common in HIV-

positive persons. Viral loads, CD4 count, and ART did not seem to have an impact on the HPV status.

Further studies and long-term follow-up will be necessary to determine the significance of the infections.

HIV-associated immunosuppression was proposed to play an important but reduced role compared to transplant patients. Infectious causes in patients with a decreased CD4 count. The lesions are HPV-associated and rare cases have been reported. Similar to previous reports, immunologic recovery and viral load suppression upon ART did not lead to improvement of the cutaneous lesions. Long-term follow-up is necessary since the risk of cutaneous malignancy is unknown.⁶

4.4 Other infections

The 15 fungal infections cases seen in our study, six of the patients were in the severe CD4 category, three cases were in the advanced category, four cases were in mild category and 2 cases were in normal category.

Other conditions seen included classical scabies 6 cases (4 in severe category and 2 in advanced category).

4.5 Medication Toxicity

Seven patients presented with drug reactions. Two patients who belonged to the advanced category had maculopapular drug rash, and two patients from the severe and two patients from mild category had drug induced pigmentation.

Skin reactions to drugs complicate in 2–3 % of all hospital-based treatments. These reactions can range from morbilliform eruptions to life-threatening forms like TEN. HIV infection has been associated with an increased risk for SJS and TEN. Increased exposures to medications or decreased immunity have been proposed as possible etiologies.

Skin and nail pigmentation secondary to drugs are seen.⁷ Antiretroviral drugs appear to pose an additional risk of disease-related toxicity, and a high frequency of antiretroviral drugs as the cause of SJS has been reported. There was also a trend to more severe reactions in the HIV-infected population.⁸

T cells have been proposed a role in mediating keratinocyte cytotoxicity . Especially, regulatory T cells might play a protective role in the skin . An inverse correlation of the serum CD4 count and the incidence of cutaneous drug reactions have been reported.⁸

18% of the study participants who were receiving ART at the time of recruitment into the study were diagnosed to have skin diseases within a median time of 5 months, which was attributed to immune reconstitution inflammatory syndrome (IRIS).

5. Conclusion

Human immunodeficiency virus (HIV) infection is perhaps the single greatest pandemic that mankind is facing in recent times. In conclusion, the commonest condition may vary in different parts of the world. The percentage of skin manifestations increased with degree of CD4 depletion. However, opportunistic infections did not correlate with severity of immunodeficiency.

Our study was conspicuous for the absence of infectious conditions such as candidiasis and seborrheic dermatitis. The presence of skin disease may not predict immunodeficiency; however, the severity may. Nevirapine was one of the common causes of drug rash. PPE is the most predictive

cutaneous indicator of immunosuppression as shown in past studies.

Limitation: Small sample size

Financial support and sponsorship: Nil

Table 1: Relationship between number of patients and CD4 count

CD4 counts (cells/mm3)	No of patients
<200	22
200-349	20
350-499	14
>500	16

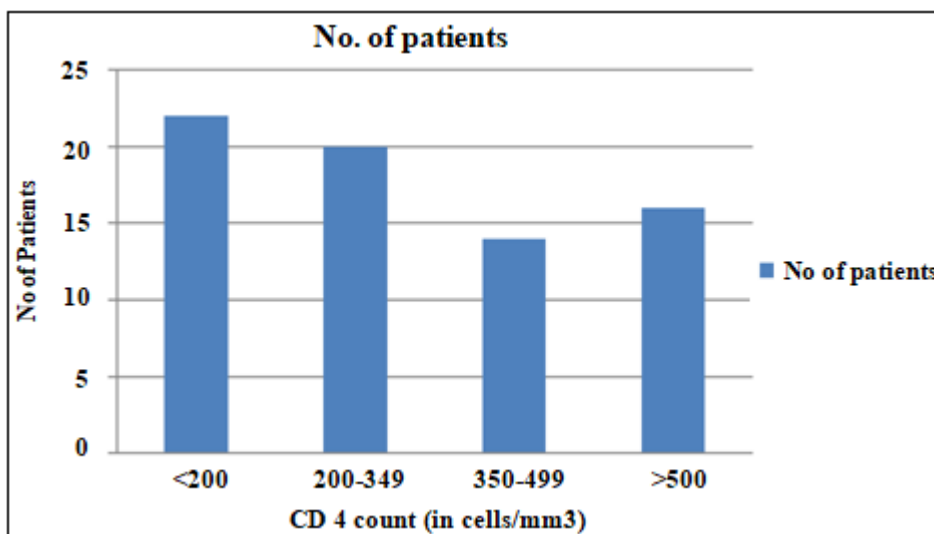


Table 2: Distribution of cases according to age

Age of patients(in years)	No of patients
0-10	0
20-30	2
30-40	9
30-40	21
40-50	24
50-60	13
>60	3

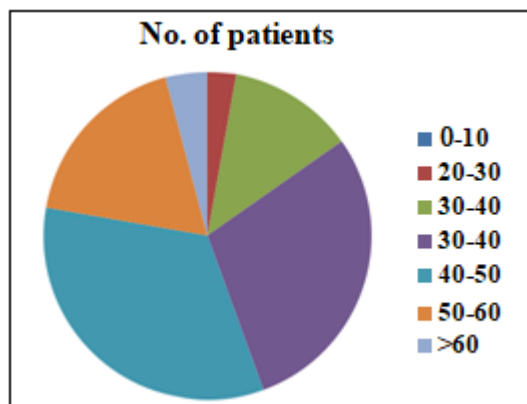


Table 3: Relationship between skin disorders and CD4 counts (cells/mm3)

Types of cases	Normal (CD4 >500)	Mild (CD4 350-499)	Moderate (CD4 200-349)	Severe (CD4 count <200)
Tinea	2	4	3	6
Aphthous ulcer		1		
Pityriasis versicolor	2	2		
Scabies			2	4
Molluscum			1	
Seborrheic dermatitis		1		
Balanoposthitis			2	
Herpes Zoster	1		1	
Syphilis	1		2	4
Donovanosis			1	
Prurigo Nodularis	2		1	
Lichen planus	2			1
DLE	1			
Adverse Drug reactions	1	2	2	2
Bacterial Infections				2
Verruca Vulgaris	1	2	2	
Photo allergic Dermatitis	1	2	2	1
Xerosis	2		1	2
Total	16	14	20	22

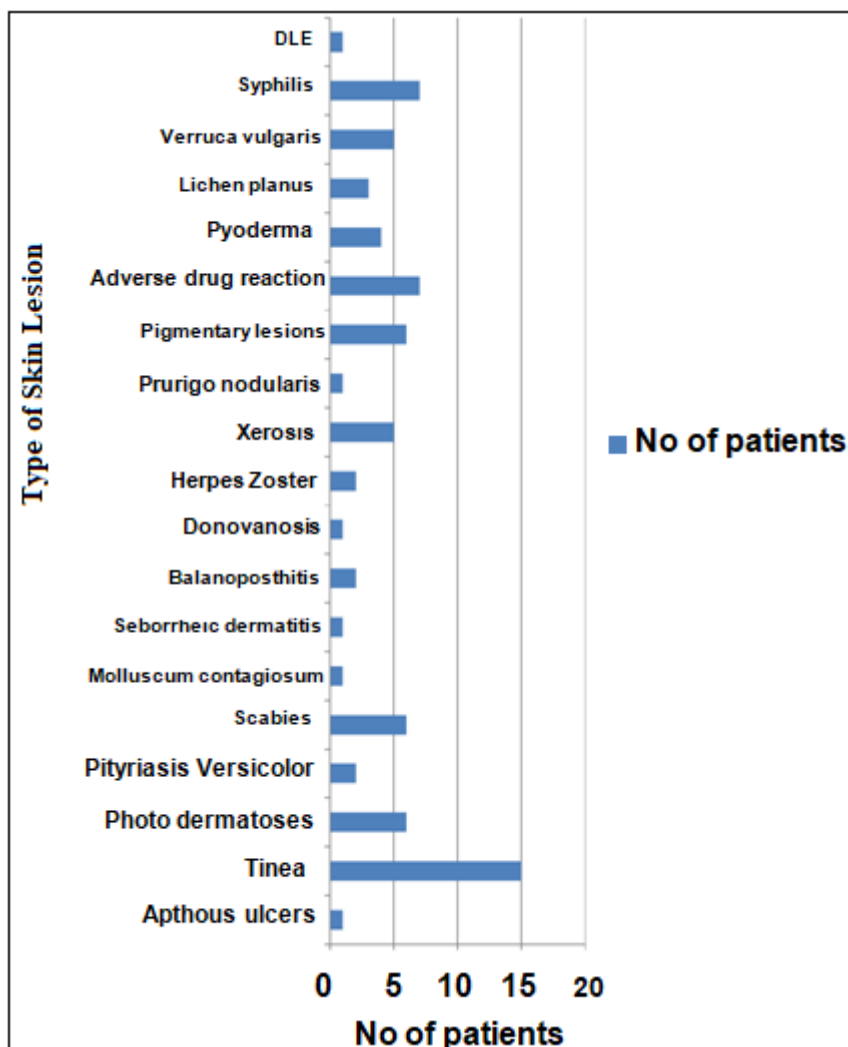




Figure 1: Herpes Zoster



Figure 2: Tinea corporis



Figure 3: Aphthous ulcer



Figure 4: Molluscum contagiosum



Figure 5: Donovanosis



Figure 6: Photo allergic Dermatitis



Figure 7: Lichen planus pigmentosus

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