

ORIGINAL ARTICLE

Dermatoses in Human Immunodeficiency Virus Infected Patients with A Focus on Infections: A 12-month Cross-sectional Study in Hospital Sungai Buloh

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Abstract

Background

Cutaneous disorders are common clinical manifestations of the Human Immunodeficiency Virus (HIV). In the era of antiretroviral therapy (ART), the spectrum of cutaneous disorders in HIV-infected patients has changed. We assessed the types of dermatoses, including cutaneous infections in HIV-positive patients and the association between the peripheral CD4 cell count and the severity of skin infection.

Methods

All HIV-positive patients referred to the Dermatology Department of Hospital Sungai Buloh from January 2021 – December 2021 were enrolled in a prospective cross-sectional study. Patients were subjected to a complete medical and physical examination and appropriate investigation to confirm the diagnosis.

Results

A total of 112 (92.6%) male and 9 (7.4%) female patients with a mean age of $38.76 \pm$ SD years participated. The majority of patients were Malay (56.2%), with MSM (54.5%) being the commonest mode of transmission. 65.2% of patients had $CD4 \geq 350$ cells/mm³ and 86.7% of patients were on ART. Infections (56.1%) were the most common group of mucocutaneous manifestations, with 45.6% of these due to viral infections. There was no statistically significant correlation between the CD4 count and the severity of skin involvement in bacterial ($p=0.302$), viral ($p=0.145$) and fungal ($p=0.533$) infections.

Conclusion

Viral infection were the commonest cutaneous manifestations in HIV- positive patients. The frequency and severity of the cutaneous infections were much more common in patients with more advanced immunosuppression.

Keywords: *HIV, mucocutaneous manifestations, CD4 count*

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Introduction

Cutaneous disorders are common clinical manifestations of the Human Immunodeficiency Virus (HIV). These skin manifestations are not only associated with terminal immunodeficiency but also occur throughout the course of HIV

infection.¹ More than 90% of patients will develop skin lesions at some time during their illness.²⁻³

Skin diseases have been proven to be a sensitive and useful measure by which HIV progression can be monitored. With diminished and dysregulated cell-mediated immunity, HIV-infected individuals are susceptible to myriad skin conditions⁴, which can be broadly classified into infectious and noninfectious dermatoses. Although these skin manifestations are also encountered in immunocompetent individuals, their occurrence in HIV-infected patients tend to present earlier, are often atypical, more severe, explosive, extensive or resistant to therapy.⁵

The clinical spectrum and prevalence of skin disorders in HIV- infected patients are well documented in western populations. However, there are fewer data available from Asia. Bender et al. found significant racial differences in the prevalence and risk of dermatological conditions in patients with HIV.⁶ Studies in Singapore and Thailand reported notable differences in the prevalence and types of skin conditions in their local population of HIV- infected patients compared to the Western cohorts.⁷

This study aimed to determine the type of dermatoses affecting HIV-infected patients, describe the types of cutaneous infections and determine the relationship between HIV-related immunodeficiency with type and severity of cutaneous infection in a Malaysian HIV-infected population.

Materials and Methods

A prospective cross-sectional study was performed. The study population was all HIV-positive patients referred to the Dermatology Department in Hospital Sungai Buloh for assessment who fulfilled the inclusion and exclusion criteria during the study period from January 2021 – December 2021. Hospital Sungai Buloh is the main referral center for Infectious diseases and HIV in Malaysia and serves a large number of Klang Valleys HIV-

positive population. Accessibility to a large cohort of HIV-positive individuals provides an opportunity to fully explore the prevalence of skin infections of HIV-infected patients in our local population. The inclusion criterion was Malaysian, HIV- positive patients aged 18 and above. HIV-infected patients with adverse drug reactions were excluded from the study.

All patients were subjected to a detailed face-to-face interview and physical examination. Information was collected on demography details, mode of transmission of HIV infection, Anti-retroviral therapy (ART) treatment, most recent CD4 count and viral load. When required to confirm a diagnosis, appropriate investigations were performed as per standard clinical management. This included, when necessary, skin biopsies, tissue cultures, tzank smears, skin scrapings and PCR analysis. The mucocutaneous manifestations were classified as skin infections (bacterial, fungal, viral and parasitic infections) or inflammatory dermatoses (eczematous, psoriasis, seborrheic dermatitis and Pruritic Papular Eruption in HIV). Cutaneous infections were subsequently subclassified into superficial or subcutaneous skin infections.

The sample size of this study was calculated based on a cross-sectional study by Uthayakumar et.al⁸ Sample size estimation was calculated using the population proportion formula. The prevalence of cutaneous manifestations in HIV-infected patients was 0.914. The population size of 1000 was based on Hospital Sungai Buloh's internal database. The Type I error probability in rejecting the null hypothesis was 0.05. With the additional 5% dropout rate, the sample size required was 114 patients.

Analysis of the data was done using the IBM-Statistical Package for the Social Sciences (IBM-SPSS®) version 25.0 for Windows. Descriptive statistics described the sample characteristics. Continuous variables were expressed as mean and standard deviation. For non-normally distributed data, median and interquartile ranges were used. For categorical

variables, frequency and percentage were used to present the data. Fischer exact test tested the hypothesis of whether there was an association between type of infection and CD4 count categories. The level of significance was set at 0.05 with two-tailed probabilities. A p value less than 0.05 concludes significant associations between two categorical variables.

This study was conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. Data collection was commenced after obtaining Medical Research and Ethics Committee approval. (Approval reference: KKM/NIHSEC/P20-2250(11)).

Results

A total of 121 HIV-positive patients were enrolled. Of these, 112 (92.6%) were male and 9 (7.4%) were female. The majority of the patients were Malay (56.2%), followed by Chinese (33.9%) and Indians (9.9%). Their average age was 38.7 years. The commonest mode of HIV transmission was men who have sex with men (MSM) (54.5%). Heterosexual and intravenous drug use (IVDU) accounted for 29.8% and 10.7% of transmission respectively. A total of 79 patients (65.2%) had CD4 \geq 350 cells/mm³ and 34.7% had CD4 < 200-349 cells/mm³. The majority of the patients were on antiretroviral therapy (ART) (86.7%). Characteristics of the study population are summarized in Table 1.

When screening for cutaneous infections, 43.8% of the patients had non-infective skin dermatoses commonly associated with HIV, including seborrheic dermatitis (11.5%), psoriasis (3.3%), eosinophilic folliculitis (6.6%), pruritic papular eruption in HIV (14.8%) and papular eczema (7.4%). This is summarized in Table 2.

The most common cutaneous manifestations seen were infectious in origin. Of the 121 patients enrolled in the study, 68 (56.1%) patients had infectious lesions. Table 3 summarizes the type of cutaneous infections in the study population. Sixteen out of the 68 patients (23.5%) in this

subgroup had cutaneous bacterial infections. This included botryomycosis (1.4%), folliculitis (11.8%), cutaneous tuberculosis (4.4%) and cutaneous manifestations of syphilis (5.9%).

The diagnosis of botryomycosis was suspected clinically. The patient presented with a fleshy, subcutaneous nodule which developed into a non-healing ulcer over the dorsum of the hand. Tissue culture grew *Staphylococcus aureus*. The patient was treated with amoxicillin/clavulanic acid and responded well with resolution of the lesion after 2 weeks of treatment.

Viral Infections accounted for the majority of infective cutaneous lesions (45.6%). Ten patients (14.7%) had cutaneous lesions due to *human papillomavirus* (condyloma acuminata), 7.4% of patients had lesions due to *poxvirus* (molluscum contagiosum), *herpes simplex virus* (oral and anogenital ulcers) and *human herpes virus* (Kaposi sarcoma). 8.8% of patients had lesions due to *Varicella zoster virus* infection (Varicella Zoster).

Cutaneous fungal infections accounted for 26.5% of infectious lesions. Talaromycosis (14.7%), histoplasmosis (1.4%), sporotrichosis (2.9%) and dermatophyte infection (7.4%) were the second most common infectious causes seen in the study population after viral infections. Three (4.4%) cases of parasitic infections (scabies) were encountered.

Sub analysis was done to determine the association between cutaneous infections with the CD4 count. The cutaneous infections encountered were grouped based on their invasiveness or severity. Superficial cutaneous infections were defined as infections of the epidermis, hair and nails. These included molluscum contagiosum, folliculitis, varicella zoster infection, scabies, tinea corporis, tinea cruris, genital warts and herpes simplex infection.

Infections that penetrated the epidermis and the dermis to infect the deeper tissues were classed as subcutaneous or systemic infections.

Table 1: Characteristics of the study population

| Characteristics | Mean±SD or n (%) |
|---|------------------|
| Age, in years | 38.76±10.96 |
| Minimum | 18 |
| Maximum | 74 |
| Gender | |
| Male | 112 (92.6) |
| Female | 9 (7.4) |
| Ethnicity | |
| Malay | 68 (56.2) |
| Chinese | 41 (33.9) |
| Indian | 12 (9.9) |
| Duration of HIV diagnosis (months) | 58.41±42.59 |
| Minimum | 12 |
| Maximum | 240 |
| Mode of transmission | |
| MSM | 66 (54.5) |
| Heterosexual | 36 (29.8) |
| IVDU | 13 (10.7) |
| Undisclosed | 6 (5.0) |
| CD4 count | |
| CD4 ≥ 350 cells/mm ³ | 79 (65.2) |
| CD4 < 200 -349 cells/mm ³ | 42 (34.7) |
| Viral load | |
| Suppressed (< 200 copies/ ml) | 67 (55.3) |
| Not suppressed (> 200 copies/ ml) | 54 (46.6) |
| Not Available | 5 (4.1) |
| ART | |
| No | 16 (13.2) |
| Yes | 105 (86.7) |
| Systemic co-morbidities | |
| Diabetes | 7 (5.7) |
| Hypertension | 7 (5.7) |
| Hepatitis/ Liver Cirrhosis | 11 (9.1) |
| Syphilis | 12 (9.9) |
| Tuberculosis | 10 (8.2) |

Table 2: Types of non-infective dermatoses affecting HIV-infected patients in Sungai Buloh Hospital

| Type of Dermatoses | n (%) |
|----------------------------------|-----------|
| Seborrheic Dermatitis | 14 (11.5) |
| Psoriasis | 4 (3.3) |
| Eosinophilic Folliculitis | 8 (6.6) |
| Eczematous Dermatoses | |
| Pruritic Papular Eruption in HIV | 18 (14.8) |
| Papular Eczema | 9 (7.4) |

These included kaposi sarcoma, cutaneous tuberculosis, sporotrichosis, secondary syphilis, histoplasmosis, botryomycosis and penicilliosis. Table 4 summarizes these findings.

Amongst patients with subcutaneous or systemic bacterial infections, 77.8 % had a CD4 < 200-349 cells/mm³ and 22.2% had a CD4 ≥ 350 cells/mm³. Majority of cutaneous viral infections were in patients with CD4 < 200-349 cells/mm³, for both superficial and subcutaneous infections. In patients with subcutaneous/ systemic fungal infections, 11 patients had a CD4 < 200-349, compared to 2 patients with CD4 > 350 cells/mm³. Subcutaneous or systemic viral infections were found in all patients with CD4 < 200-349 cells/mm³. There was no significant association between CD4 count with severity of infection

Overall, when comparing all types of superficial infections (bacterial, viral and fungal), 22 patients had a CD4 < 200-349 cells/mm³ and 17 patients had a CD4 ≥ 350 cells/mm³. The difference was more obvious when comparing subcutaneous/ systemic infections with 24 patients having CD4 < 200-349 cells/mm³ and only 6 patients with CD 4 ≥ 350 cells/mm³

Table 3: Types of cutaneous infection in the study population

| Type of Infection | n (%) |
|--|------------------|
| Bacteria | 16 (23.5) |
| Botryomycosis | 1 (1.4) |
| Folliculitis | 8 (11.8) |
| Cutaneous Tuberculosis | 3 (4.4) |
| Syphilis | 4 (5.9) |
| Viral | 31 (45.6) |
| Herpes simplex Virus | 5 (7.4) |
| Varicella Zoster Virus | 6 (8.8) |
| Human Papillomavirus (condyloma acuminata) | 10 (14.7) |
| Poxvirus (molluscum contagiosum) | 5 (7.4) |
| Human Herpes Virus (Kaposi Sarcoma) | 5 (7.4) |
| Fungal | 18(26.5) |
| Talaromycosis | 10 (14.7) |
| Histoplasmosis | 1 (1.4) |
| Sporotrichosis | 2 (2.9) |
| Dermatophytes | 5 (7.4) |
| Parasitic | 3 (4.4%) |
| Scabies | 3 (4.4) |

Table 4: Relationship between HIV-related immunodeficiency based on CD4 count with the type of cutaneous infection

| Type of infection, n (%) | CD4 count | | p-value |
|--------------------------|--|----------------------------------|---------|
| | < 200 -349 cells/mm ³ n (%) | ≥350 cells/mm ³ n (%) | |
| Bacteria (n=16) | | | 0.302 |
| Superficial | 3 (42.9) | 4 (57.1) | |
| ubcutaneous | 7 (77.8) | 2 (22.2) | |
| Virus (n=31) | | | 0.145 |
| Superficial | 16 (64.0) | 9 (36.0) | |
| ubcutaneous | 6 (100) | 0 (0) | |
| Fungus (n=18) | | | 0.533 |
| Superficial | 3 (60.0) | 2 (40.0) | |
| ubcutaneous | 11 (84.6) | 2 (15.4) | |

Discussion

It is estimated that 87,041 people live with HIV (PLHIV) in Malaysia at the end 2018.⁹ Skin disorders are extremely common in PLHIV and in many patients, they may be the earliest sign of HIV disease.¹⁰

The epidemiologic profile of dermatologic illnesses in relation to HIV varies between countries.¹⁰ Tan et al and Jing et al found that this is mainly affected by economic and political factors pertaining to the availability of HAART, as well as the risk-taking behavior of patients.¹⁰⁻¹¹ This study prompted us to revisit these conditions and examine the changing incidence and prevalence of these conditions in the local population of Malaysia.

Demographic and Clinical Characteristics

In this study, the majority of the patients were Malay males with a mean age of 38. This is consistent with our national data⁹ stating that > 70% of HIV- infected patients were males between the age of 20 and 39 years. Similar data were reported in 2 other studies in the region, reported by Huang et al in China and Goh et.al in Singapore.^{1,7} The trend of HIV epidemic in Malaysia has now shifted to sexual transmission since 2011. Men who have sex with men (MSM) were expected to become the main driver for the epidemic⁹ and this is reflected in the results of this study with the commonest mode of transmission being MSM (54.5%).

The main aim of the Global AIDS Monitoring indicators was to have at least 90% of people who know their HIV-positive status accessing ART by 2020.¹² In this study, 86.7% of the study population were on ART, with 55.3% having suppressed viral loads.

Types of dermatoses affecting HIV-infected patients

Skin disease may be uniquely associated with HIV infection or AIDS, but is more often due to common disorders that are more severe and recalcitrant to treatment in HIV patients.¹³ Seborrheic dermatitis, psoriasis and varicella zoster virus infection are examples of common clinical skin conditions that are both more frequent and more severe with advanced immunosuppression. Kaposi sarcoma and pruritic papular eruption (PPE) in HIV are examples of skin disorders that serve as a marker of disease progression.¹⁴ These cutaneous conditions can also present as new dermatological manifestations related to Immune reconstitution inflammatory syndrome (IRIS) or as worsened forms of previous disease.¹⁵

In this study, 43% and 56.1% of patients had non-infective and infective lesions respectively. Of the non-infective lesions, purpuric papular eruption (PPE) in HIV was the most common diagnosis (14.8%). These results were comparable with Goh et al and Chan et al who reported PPE as the most common non-infectious manifestations in their study cohort at 14.9% and 31% respectively.^{7,16} It is well recognized that PPE is a cutaneous marker of advanced HIV infection⁷ and this was confirmed in this study with all patients diagnosed with PPE having a CD4 < 200-349 cells/mm³.

Seborrheic dermatitis (SD) is an early skin manifestation that is mostly seen in patients who have CD4 > 200.¹⁷ In this study, SD was found to be the second most common noninfectious manifestation (11.5%), which was also reported by Edith et al.¹⁷ Four (3.3%) of patients in this study were diagnosed with psoriasis. These results are comparable to an audit done by

Davarpanah et al and Supanaranond et al which reported 2.9% and 4.7% of their study population who were diagnosed with psoriasis.¹⁸⁻¹⁹

Eosinophilic folliculitis (EF) is a common skin disorder in individuals with HIV who have CD4 count < 250cells/mm³ and is uncommon in persons without HIV.¹³ Eight (6.6%) patients in this study were diagnosed with EF. Similar results were reported by Goh et al reporting 4% of their cohort being diagnosed with EF.⁷

Cutaneous infections in HIV-infected patients

In HIV-infected individuals, typical skin lesions, with more inflamed, widespread, disfiguring and destructive presentations may be the result of diminished CD4-positive T cell- mediated immune response.⁴ In the era of ART, the spectrum of cutaneous infections has changed. However, common cutaneous infections from methicillin-resistant *Staphylococcus aureus* (MRSA) and human papillomavirus (HPV) are growing causes of morbidity and mortality despite overall seemingly improved immune function with antiretroviral therapy.¹⁵

We found that the most common dermatoses in our cohort of patients were infectious in origin (56.1%). Similar results were reported with slightly higher prevalence by, S. Uthayakumar et al. in the UK, Chan et al in Malaysia and Basida et al in India.^{8,16,20}

Cutaneous viral infections have been reported as the most common dermatological disorder among HIV patients in various studies in the past decade. Similar results were observed in this study and in China, Taiwan and India.^{1,2,3} In this study, condyloma acuminata contributed the majority of the total viral- related dermatoses (14%). Uthayakumar et al similarly observed condyloma acuminata (14%) to contribute to the majority of cutaneous viral infections.⁸ Human papillomavirus (HPV) infection is more common in the HIV/AIDS population, as HPV has been found to facilitate HIV gene expression.¹³ Diagnosis and treatment of these lesions are important because of the risk of HPV-associated anal and cervical carcinomas.

It is well recognized that Kaposi sarcoma (KS) develops almost exclusively in HIV positive homosexual men and that homosexual contact is a risk factor for *human herpes virus-8* (HHV-8) acquisition.⁷ In this study, Kaposi Sarcoma was diagnosed as frequently as the common cutaneous lesions due to *herpes simplex virus* and *pox virus* (7.4%), suggesting that KS still represents one of the more common HIV associated cutaneous conditions in this population. Interestingly, other studies in this region, i.e., Singapore and Thailand reported no cases of KS in their cohorts.^{7,21} The apparent absence of KS in their study to be due to the significantly lower proportion of homosexual individuals in their study population. This is another contrast to the demography this study, where the majority (54.5%) of the study population were homosexual individuals.

Fungal infections were the second most common cutaneous infection observed in this study (26.5%). Talaromycosis accounted for the majority (14%) of fungal dermatoses, a result which was similarly reported by Chan et al and Wiwanitkit.^{16,21} The high prevalence of Talaromycosis in this region relative to western studies is likely due to *Penicillium marneffeii* being endemic to tropical Asia and is now considered an AIDS-defining illness in endemic areas.⁴

Dermatophyte infections only accounted for 7.4% of total cutaneous fungal infections in our study cohort, which differs from findings in previous studies. Vasudevan et al reported dermatophytosis as the most common cutaneous fungal infection.²² The reason for this difference seen in this study may be referral bias. Patients with milder skin disorders, that are treatable by HIV physicians may have not been referred to us and therefore, may not represent the true prevalence in the HIV population.

Staphylococcus aureus is the most common cutaneous and systemic bacterial pathogen in HIV- infected individuals. Approximately 54% of AIDS patients experience symptoms due to *S. aureus*.¹³ The high frequency of *S. aureus* skin

infections in HIV-infected patients is attributed to high rates of recurrent or chronic nasal carriage in this population, including carriage of methicillin-resistant organisms.⁴ This is reflected in the results of this study with 9 out of 16 patients with cutaneous bacterial infections diagnosed with *S. aureus* skin manifestations; i.e., folliculitis and botryomycosis.

Relationship between immunodeficiency and severity of infection

HIV attacks the helper/Inducer T cells (CD4+ cells), resulting in syncytial formation and lysis with slow but progressive destruction of this cell population. In general, the CD4+ cells (%CD4+ or absolute count) progressively decreases as HIV disease advances.²⁰

Traditionally lower CD4 counts are reported to be associated with infective dermatoses.²³ Cutaneous infections encountered among those with CD4 <200-349 cells/mm³ in our cohort were 2 times more than those with CD4 >500 cells/mm³. These results are comparable to Chan et al who reported 2.7X more cutaneous infections in patients with a CD4 < 500 cells/mm.^{3,16}

Overall, when comparing the severity and invasiveness of these cutaneous infections, we observed that those with advanced HIV (CD4 <200-349 cells/mm³) had relatively higher percentages rates for both, superficial and subcutaneous manifestation for all types of cutaneous infections. S Uthayakumar et al similarly reported an increasing severity index in the skin lesions associated with a CD4 count of less than 200cells/mm³.⁸ Fleischer et al and Kaplan et al. demonstrated a significant association between the number and severity of cutaneous abnormalities and low CD4 count.^{24,25}

The difference was not statistically significant in this study. Supanaranond et al and Coopman et al reported no statistically significant association between the incidence of skin infections and the level of CD4 counts.^{19,26} The reason for these results may be the small sample size in this subgroup analysis.

Similar studies previously done in Malaysia were retrospective in nature. However, the data from this prospective study is limited by the relatively modest sample size. Further larger-scale prospective studies are needed to better describe the mucocutaneous manifestations of HIV-infected individuals, its changing spectrum in the era of ART and its evolution through the different stages of HIV.

Conclusion

The spectrum of cutaneous disorders in our study differs slightly from data around South East Asia, namely Singapore and Thailand with the preponderance of infective lesions observed in our study. MRSA infections, malignant transformations of HPV disease and Kaposi sarcoma due to HHV-8 infection are likely to continue to increase as HIV populations have longer life expectancies in the era of ART. Awareness of the varied types and patterns of these manifestations would help in the early diagnosis and management of HIV infection and ultimately decrease the morbidity and improve the quality of life of HIV-infected patients.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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