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Mucocutaneous manifestations of HIV/AIDS infection: literature review



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ABSTRACT

Mucocutaneous manifestations are the first recognized human immunodeficiency virus (HIV) infections. More than 90% of HIV-infected patients develop at least one or more types of typical or atypical skin lesions during the disease. Mucocutaneous manifestation can also indicate the progression of HIV infection and cluster of differentiation 4 (CD4) cell count as an indicator of the development of acquired immunodeficiency syndrome (AIDS). It is important to know mucocutaneous manifestations and their correlation with the patient's immune status to provide appropriate treatment to improve the patient's quality of life.

Keywords: Mucocutaneous manifestations, human immunodeficiency virus, acquired immunodeficiency syndrome.

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INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a life-threatening disease syndrome characterized by reduced self-defense ability due to Human immunodeficiency virus (HIV) infection.¹ Mucocutaneous manifestations can be the first indication of HIV infection, a marker of severity and immune status by counting CD4+ counts. Approximately 90% of HIV/AIDS patients generally experienced one or more mucocutaneous manifestations during the disease.² Lie et al. reported as many as 83 HIV/AIDS patients, and about 70 patients (85%) had mucocutaneous manifestations with CD4+ counts <200 cells/ μ L.³

The spectrum of mucocutaneous manifestations based on the cause were divided into infection, non-infection, malignancy, and adverse cutaneous drug reactions (ACDR) due to antiretroviral therapy (ART) or other drugs. Recently, it has been reported that mucocutaneous manifestations of HIV/AIDS patients are more often due to non-infection and drug allergic eruptions.⁴ Mucocutaneous manifestations of HIV/AIDS patients are highly variable and can be found at all stages but are most often advanced.⁵ Mucocutaneous manifestations of HIV/

AIDS patients will appear atypical, more severe, more widespread, recalcitrant, and great imitators are causing delays in diagnosis and treatment.⁶ It is important for clinicians who treat patients with atypical mucocutaneous manifestations and who have two or more pathological conditions to suspect an HIV infection.² Additionally, mucocutaneous manifestations can be used as an indicator of severity, especially in countries with limited CD4+ counts.⁷

MUCOCUTANEOUS MANIFESTATIONS OF HIV/AIDS PATIENTS

HIV infection progresses in several stages and shows different mucocutaneous manifestations.⁴ A retrospective study by Shehu et al. reported that of 355 HIV-infected patients during the period 2008-2015 showed that the prevalence of mucocutaneous manifestations in HIV/AIDS patients increased with the stage of the disease and was more frequent at CD4+ counts <200 cells/ μ L. Mucocutaneous manifestations at stage 1 (15.5%), stage 2 (37.2%) and stage 3 (47.4%).⁸ Based on the cause, mucocutaneous manifestations were reported more often due to non-infection. A cross-sectional study by Claasens reported that of 123

HIV/AIDS patients, the most common mucocutaneous manifestations associated with non-infectious (71%) were pruritic papular eruption (PPE) (20%) and seborrheic dermatitis (DS) (6%), followed by infection, includes tinea corporis (8%) and oral candidiasis (6%), but there was no significant association with CD4+ count, viral load and history of taking ART.⁷

Mucocutaneous Manifestations of HIV/AIDS Due to Non-Infectious

The most-reported mucocutaneous manifestations associated with inflammation were papular pruritic (PPE) in the range of 20%, and papulosquamous with DS in the range of 6%.⁷

Papulosquamous Mucocutaneous Manifestations

Papulosquamous mucocutaneous manifestations in HIV/AIDS patients may include seborrheic dermatitis, psoriasis, and others (xerosis and acquired ichthyosis). Seborrheic dermatitis (DS) can be found at all stages of HIV infection, and its severity is associated with advanced immunodeficiency conditions.⁶ The incidence of DS in HIV patients is around 40%, and AIDS is around 80%.⁷ Mucocutaneous manifestations of DS are

more severe and resistant to treatment in HIV patients. with a CD4+ count of 200-500 cells/ μ L.⁹ Disseminated seborrheic dermatitis (DS) can be found on the sternum, back, axilla, and buttocks, with the severity of the lesions depending on the progression of HIV infection.¹⁰ Psoriasis reported in HIV patients may represent a new diagnosis or an exacerbation.⁶ The incidence of psoriasis in HIV/AIDS patients ranges from 1-4% more than the general population, clinical manifestations are more severe,¹¹ and resistant to usual therapy.⁴ Plaque-type psoriasis is the most common, which is 78%, followed by the inverse (37%), guttate (29%), erythroderma (14%), palmoplantar (8%), and pustular (8%).¹⁰ Other papulosquamous mucocutaneous manifestations have been reported in about 30% of HIV patients.¹²

Non-Infectious Pruritic Papular Mucocutaneous Manifestations

Pruritic papular eruption (PPE) is a non-infectious pruritic papular cutaneous manifestation with a prevalence of 11-64%. Predisposing factors for PPE were CD4+ count < 200 cells/ μ L, insect bites,⁷ latent phases of HIV infection, and high viral load. Persistent or recurrent PPE is associated with a high viral load and failure of antiretroviral therapy.² Clinical manifestations include papules, excoriations, and multiple, discrete pruritus with itching. The most common predilection for PPE is on the trunk, extensor extremities, and face and then spreads throughout the body^{6,7} and heals as a hyperpigmented superficial scar which is an important sign of HIV infection.² The most common differential diagnosis of PPE is eosinophilic folliculitis (EF) in the form of a known follicular hypersensitivity reaction of unknown cause. Cutaneous manifestations are small red papulopustular with a predilection for the trunk, arms, neck, and forehead.⁶ PPE and EF manifestations can be seen in Figures 1 (a) and (b).

Mucocutaneous Manifestations of HIV/AIDS Due to Infection

Mucocutaneous manifestations of HIV/AIDS due to infection can be divided of viruses, bacteria, fungi, parasites,

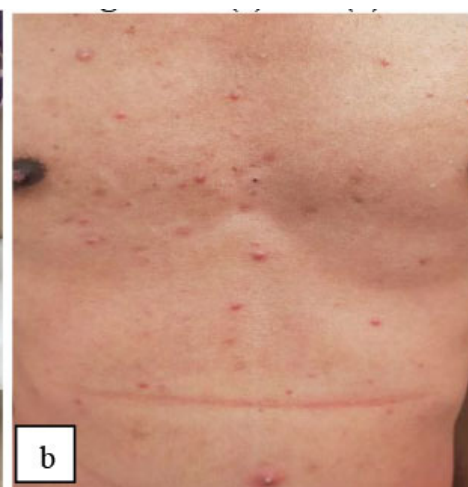


Figure 1. PPE (a) and EF in HIV/AIDS patients (personal documentation) (b).

ectoparasite infestations, and parasitic.⁴ An observational study by Basida et al. (2021) reported that opportunistic mucocutaneous infections in HIV seropositive patients were the most common due to fungal infections (33.03%), namely oral candidiasis and dermatophytes with a CD4+ count of 353-467 cells/ μ L, followed by bacterial (28.18%) and viral infections (14.55%).¹³

Fungal Infection

Candida albicans is the most common cause of candidiasis or opportunistic fungal infections and the first manifestation of HIV infection. HIV patients with candidiasis have a CD4+ count of <300 cells/ μ L, but the risk of oropharyngeal candidiasis increases when the CD4+ count is <200 cells/ μ L.¹² Mucocutaneous manifestations of *Candida albicans* are pseudomembrane (thrush), cheilitis, chronic paronychia, onychodystrophy,⁴ and candidiasis vaginalis. Pseudomembranous manifestation (thrush) is the most common form characterized by a white plaque on the oral mucosa such as the tongue, uvula, palate, or buccal, which can be removed by scraping a spatula two as shown in Figure 2. Dermatophytes, namely *Trichophyton rubrum* can cause other fungal infections.¹² Epidemiological study by Bragine-Ferreira T et al. reported of 306 HIV/AIDS patients, 153 patients had cutaneous lesions, hair or nails due to dermatophytes, and more often men. Based on the culture results, *Trichophyton rubrum* was found more often followed by *Trichophyton interdigitale*. This, in



Figure 2. Oral candidiasis in HIV/AIDS patients (personal documentation).



Figure 3. *Condyloma acuminata* in HIV/AIDS patients (personal documentation).

contrast to previous studies by Costa et al. reported that of 20 HIV/AIDS patients, tinea corporis (70%) was found more frequently.¹⁴ Other clinical manifestations such as tinea pedis appear hyperkeratotic plaques and nodular perifolliculitis (Majocchi granuloma) in the form of deep follicular papulopustules or granulomatous nodules.^{4,7}

Invasive fungal infections in HIV patients are cryptococcosis and histoplasmosis. Cryptococcosis is caused by encapsulated spores of *Cryptococcus neoformans* with non-specific clinical manifestations in the form of papules, plaques, pustules, nodules, and ulcers⁶ on the palate and tongue.¹ Histoplasmosis infection is caused by *Histoplasma capsulatum*.¹⁵ Nonspecific mucocutaneous histoplasmosis manifestations such as diffuse erythema, papulopustular covered with crusts, ulcers to lesions are psoriasiform, thus often underdiagnosed.⁶ Histoplasmosis infection should be suspected in patients with clinical manifestations of immunodeficiency and a history of travel to endemic countries.¹⁵

Viral Infection

Primary HIV exanthema (Acute Retroviral Syndrome) is one of the manifestations that are quite often found in HIV patients. Around 80% of patients occur after 2-6 weeks of HIV infection. Primary HIV exanthema occurs in the early phase of HIV-1 replication, causing the CD4+ count to drop drastically and become an opportunistic infection. Clinical manifestations include fever, headache, arthralgia, pharyngitis, lymphadenopathy, and night sweats. Mucocutaneous manifestations of an acute retroviral syndrome in the form of morbilliform exanthema lesions (40-80% of cases) are found on the face and trunk for 4-5 days and then generalized. In addition, genital and oral ulcers may be found. Clinical manifestations may be self-limiting and recurrent within days to weeks. The disease progresses rapidly in severe and prolonged acute retroviral syndrome accompanied by a high viral load.⁴

Other manifestations of viral infection can include herpes simplex with a predilection for ulcers due to herpes simplex that can be found on the perianal, genitalia, and tongue.⁴ Disseminated herpes simplex was reported by Brown et al. showed that in a 22-year-old man with a small ulcerated initial lesion on the left arm, then spread rapidly in 5 days.¹⁶ Herpes zoster was reported as the first indication of AIDS.^{6,12} Mucocutaneous manifestations include chronic ulcers, hyperkeratotic verrucous plaques, and multidermatomal

to disseminated.⁴ In disseminated herpes zoster, lesions >10 outside the primary dermatome or morphology are atypical.¹⁷ Lai et al. in a cohort study in Taiwan showed of examined patients with herpes zoster as an early sign of HIV infection. As a result, patients with herpes zoster were 4.37 times more likely to be diagnosed with HIV, were more frequent in men, and aged 21-30 years. Herpes zoster patients with comorbidities, namely a history of sexually transmitted infections, had a greater risk than IDUs, although they were not statistically significant. Routine HIV screening should be recommended, especially in male patients with a history of herpes zoster in the past year and having risky behavior.¹⁸ Another report states that *condyloma acuminata* (CA) is often found in HIV/AIDS patients because it facilitates the expression of the HIV gene.¹² Puspawati and Gotama in a retrospective study, reported that 260 patients diagnosed with CA were predominantly male (67.31%), and 59 patients (22.3%) had HIV/AIDS infection, often severe and requires more aggressive therapy, with a CD4+ count <500 cells/L.¹⁹ Clinical manifestations of CA in HIV patients can be seen in Figure 3.

Oral hairy leukoplakia (OHL) has also been reported frequently in HIV patients due to Epstein-Barr Virus (EBV) infection, characterized by hyperkeratotic plaques that can be removed by scraping a spatula,² white, accompanied by a hair-like appearance with a lateral predilection of the tongue. The prevalence of OHL is around 25% of HIV patients, can occur at all stages of HIV, and appears more severe when the CD4+ count is <200 cells/L.^{4,12} OHL manifestations can indicate the possible progression of HIV infection to AIDS at 16 months in 48% and after 31 months in 83%.¹² Disseminated cytomegalovirus (CMV) is associated with CD4+ count <100 cells/ μ L and is cause mortality and morbidity in AIDS patients.⁴

Bacterial Infection

The most common cutaneous bacterial infection in AIDS patients is caused by *S. aureus* in 54%.¹² The risk factor is increased in HIV/AIDS patients with low CD4+ counts with injecting drug transmission factors.⁴ In HIV/AIDS patients, *S. aureus*

infection is recalcitrant with no clinical manifestations. The clinical picture is atypical and includes botryomycosis, chronic suppurative infection with purulent material,¹² and typical such as impetigo, folliculitis, furunculosis, cellulitis, and botryomycosis.⁴ Another reported bacterial infection may include *scrofuloderma*. A cohort study by Mann et al. reported 15 cutaneous TB patients with HIV status positive.² As a result, the most common manifestations found were *scrofuloderma* (80%) and *guma* (20%), with a mean CD4+ cell count of 262 cells/ μ L.²⁰

Syphilis and HIV can overlap and are most common in MSM.²¹ Syphilis patients with HIV coinfection account for about 25% of cases and can indicate HIV infection. Clinical manifestations of primary syphilis in the form of multiple ulcers can be found together with secondary syphilis, and the disease progresses to secondary and tertiary syphilis more quickly.¹² Fernandes and Ervianti reported one case, a 24-year-old man with HIV/AIDS and secondary syphilis. Cutaneous manifestations found multiple erythematous macules on the chest, back, buttocks, palms, and feet and complaints of "moth-eaten" alopecia. Laboratory results found a CD4+ count of 88 cells/ μ L (previously 168 cells/ μ L), VDRL 1:32, and Treponema pallidum haemagglutination assay (TPHA) 1:20480. This shows that the higher the stage of clinical manifestation of syphilis with HIV, the lower the CD4+ count increases the risk of developing neurosyphilis complications and treatment failure.²¹

Ectoparasite Infestation

Crusted scabies is an infestation of the mite *Sarcoptes scabiei* var. *hominis*, often found in HIV/AIDS patients. In patients with progressive immunodeficiency, i.e., CD4 cell count <200 cells/ μ L, clinical manifestations may be localized or almost all over the body. Clinical manifestations are generalized papules covered with crusts⁴ and not itching⁶, developing into grayish-white hyperkeratotic plaques with sand-like scales. Another parasitic infection, Demodicosis, is caused by infection with *Demodex folliculorum* and *D. brevis*. Clinical manifestations such as

itching or burning on the face accompany erythema, papules, pustules, and scales. Predilection is found on the neck, perioral, and chin. Investigations that can be done with skin scrapings added with KOH can be found in multiple *Demodex lice*.⁴

Nail and Hair Disorders

Some manifestations of HIV patients can be seen in the nails and hair. Telogen effluvium phase hair loss is triggered by systemic infection or localized alopecia such as secondary syphilis or tinea capitis to the side effects of ARVs. Trichomegaly can occur in the eyelashes, characterized by a prolonged anagen phase in patients receiving ARV therapy (zidovudine and interferon- α). A prospective study of nails in HIV/AIDS patients has shown that total and lateral/distal subungual dystrophic onychomycosis is more common.⁴ A cross-sectional study by Claasens et al. demonstrated that patients with proximal subungual onychomycosis should be suspected of having HIV infection.⁷ da Silva et al. also reported similar results that severe, dystrophic and chronic nail involvement and unresponsive to antifungal therapy were more common in HIV/AIDS patients.¹⁴

Mucocutaneous Manifestations of HIV/AIDS Patients Due to Malignancy

HIV/AIDS patients have a greater risk of developing cancer, earlier onset, and more aggressiveness. Several factors influence malignancy in HIV/AIDS patients, such as immunodeficiency, coinfection with oncogene viruses, and environmental factors (e.g., ultraviolet radiation). In addition, HIV has a direct active role in proto-oncogene processes, impaired cell cycle regulation, and inhibition of tumor suppressor genes. Several malignancies are associated with HIV infection, such as Kaposi sarcoma (KS), basal cell carcinoma (BCC), squamous cell carcinoma (SSC), and lymphoma.⁴

HIV infection increases the risk of KS 800-fold, especially in patients with CD4+ counts >350 cells/ μ L. The most common predilection for KS is in the lower extremities and may be accompanied by lymphedema in the genitals and/or legs.¹⁰ Classic KS manifestations include macules, plaques patches, and red nodules

or violaceous. The lesions are asymptomatic but can develop into ulcers with secondary infection.⁶

In general, the risk of developing squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) increases 2-3 times in HIV/AIDS patients. Squamous cell carcinoma (SSC) and BCC in HIV/AIDS patients were found younger than the general population, the most common location being the body or extremities. In HIV/AIDS patients, SCC has a higher risk of recurrence and metastasis, while KSB does not show a more aggressive nature than non-HIV/AIDS patients. Melanoma in HIV/AIDS patients is found to be multiple, metastatic more often, and has a poor prognosis. Another malignancy reported in HIV/AIDS patients is lymphoma. Clinical manifestations of lymphoma in the form of papules or violet-pink nodules can progress from ulcers to panniculitis. B-cell non-Hodgkin lymphoma is the most common type of lymphoma compared to T-cell lymphoma.⁴

Adverse Cutaneous Drug Reactions (ACDR) of HIV/AIDS Patients

Adverse cutaneous drug reactions (ACDR) significantly cause morbidity and mortality worldwide. HIV/AIDS patients have a 100-fold risk of allergic drug eruptions. Risk factors associated with an allergic drug eruption were the large number of drugs taken, a history of drug allergy,⁶ slow acetylator status, relative glutathione deficiency, CD4 count <200 cells/ μ L, latent infection with EBV and CMV, and CD8+ count >460 cells/ μ L.^{6,22} Morbilliform eruptions and SJS are the most common mucocutaneous manifestations of drug allergy. This is supported by previous studies, which stated that morbilliform eruptions and SJS were found in more than half of HIV/AIDS patients with CD4+ counts <200 cells/ μ L.²³ Several drugs were associated with morbilliform eruptions, such as ARTs, trimethoprim-sulfamethoxazole (TMP/SMX), and anti-tuberculosis drugs. The prevalence of morbilliform eruptions due to ART is approximately 10-17%,⁷ TMX/SMP approximately 2.6-8%, and anti-tuberculosis drugs approximately 73%.²² A retrospective study by Maharani

et al. reported that non-nucleoside reverse transcriptase inhibitors (NNRTI) ARTs, namely efavirenz (26.7%) and nevirapine (14.5%) were the most common causes of ACDR.²³ The most common reported incidence of ACDR due to anti-tuberculosis drugs was pyrazinamide, followed by streptomycin, ethambutol, rifampin, and isoniazid.²²

CONCLUSION

Mucocutaneous manifestations can be the first marker of immunodeficiency conditions in HIV/AIDS patients. The severity, extent of mucocutaneous manifestations, and resistance to standard therapy can be the basis for suspicion of an HIV infection.

CONFLICT OF INTEREST STATEMENT

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

AUTHORS CONTRIBUTIONS

Author MD, MIHP, and SAN were contributing from the idea to construct the main topic to manuscript preparation and publication. Author YFY and IAA were supervised the research and theoretical perspective. Author KS also contributed in manuscript submission.

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