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Cutaneous manifestation in children with HIV/AIDS

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ABSTRACT

The most recent studies have explained almost 2.3 million children are affected with HIV up to the end of 2009. Sub-Saharan Africa is the main region affected by AIDS compare to other parts of the world. Despite providing competent healthcare services to prevent mother-to-child transmission as a main way of infection to a newborn, an estimated 370,000 children were newly infected to HIV in 2009. Skin disorders are common and may even be the first manifestation of HIV in children. The most common skin illnesses are classified in four categories; infectious, inflammatory, neoplastic, and drug related (Highly Active Antiretroviral Therapy). In addition, unusual anatomical sites, disseminated skin lesions, increased frequency and severity, unexplained clinical presentation, rapid onset, and finally treatment failure may be the other specified skin conditions in HIV/AIDS children. CD4 count and viral load are two basic factors playing an important role in terms of type and severity of skin illness. The aim of this review was to show the common and crucial cutaneous findings among HIV/AIDS children via published articles with the same subject.

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Introduction

A variety of studies have found that mucocutaneous disorders are more common and frequent in adults and children infected by HIV or AIDS than in the non-infected adults and children. Disorders of the skin and mucous membranes occur frequently during the course of human immunodeficiency virus (HIV) disease and may affect more than 90% of patients at some stage of the illness. Mucocutaneous lesions may be the initial or the only problem for much of the course of HIV/acquired immune deficiency syndrome (AIDS) or may be the most debilitating element of the patient's condition. Serious opportunistic infections may occur for the first time on the skin. Skin disorders in patients with HIV may appear unusually and may be inaccurately diagnosed. This may lead to poor response to therapy.[1-4] The incidence, severity, and number of skin lesions increase as immune function deteriorates. Furthermore, there is a correlation between the increasing number and severity of mucocutaneous lesions and declining immunity as mirrored by CD4+ count.[5,6] The most common skin manifestations of HIV/AIDS in children are fungal infections.[7, 8] Inflammatory lesions, fungal, viral, and bacterial skin conditions are more common in children who have HIV/AIDS compared with their healthy counterparts. When found, these conditions are also more difficult to treat than in immunocompetent children.[1,2,7] Examples of mucocutaneous lesions in HIV/AIDS include oral candidiasis, dermatophytosis, pruritic papular dermatitis, and lesions associated with nutritional deficiencies, among others.[6, 7] The common triggers of drug eruptions among children who suffer from HIV/AIDS include cotrimoxazole, ampicillin, and nevirapine. This study described the mucocutaneous manifestations in a group of seropositive children and their main skin presentation.

Epidemiology of HIV/AIDS

Millions of people in the world are infected with HIV, especially in sub-Saharan Africa. Number of people infected with HIV in 2010 were 2.7 million.[9] However, the rate of HIV infection, except in some central Asia and Eastern Europe, has stabilized in recent years, [10] but there were approximately 390000, 2200, 6800 new HIV infected children in 2010 in sub-Saharan, East Asia, Middle East with North Africa, respectively.[9]

Mortality of AIDS is still high, especially in low income regions, although in the last few years access to antiretroviral drug has improved in these countries.[11] In 2010, an estimated 250 000 [220,000–290,000] children less than 15 died from AIDS-related causes.[9]

Pathogenesis

Two types of HIV (1 and 2) from retroviridae family have incubation period from 3 to 6 weeks. After infection, the virion binds to CD4+ T lymphocytes, dendritic and monocyte-macrophage cells, then the virus RNA is injected into cytoplasm. After the DNA expression and new RNA synthesis, the host cell was destroyed and as a result the host's immune system was impaired, especially the cellular system.[12] AIDS is diagnosed when CD4+ cell falls under 200 cells/mm3, its percentage under 14 and/ or the presence of AIDS-defining criteria.

Immunodeficiency, neoplasm and opportunistic infection caused by AIDS could have mucocutaneous manifestations.[13]

Skin manifestations: Infectious and non-infectious

Viral infections:

Primary HIV

Usually early cutaneous manifestation occurs after 2-4 weeks of HIV contamination called "Acute retroviral syndrome" that presented with

generalized morbilliform exanthem. The other manifestations include genital or oral ulcer. Differential diagnoses of this phase are: viral infections (e.g. EBV, enteroviruses, HBV, CMV), secondary syphilis and drug reactions. Opportunisic infection is uncommon unless severe decline in CD4 T cells happened.[14, 15]

Herpes simplex virus (HSV)

When the CD4 T cells fall to immune suppression level, chronic, deep and non-healing ulcer of HSV presents that favour the anogenital and tongue.[16, 17] In some cases, smear or biopsy of lesions is needed for the definite diagnosis or evaluation of antiviral resistance.[18]

Varicella zoster virus (VZV)

Primary and reactivation of herpes zoster accrue more frequently in HIV-infected individuals and can be presented as typical or lethal course.[19]

The zoster development could be a sign of worsening of immune suppression in HIV-infection.[20]

Manifestation of VZV varied from typical eruption to disseminated, recurrent, ulcerative, chronic and verrucous lesion with or without systemic involvement, drug resistant and bacterial super infection.[20]

Poxvirus

Immune deficient HIV infected patients commonly affected by Molluscum contagiosum that could have larger, resistant or disfigured than classic lesions.[21]

Human papilloma virus (HPV)

HPV lesions are more common in HIV infected persons and could be more extensive with large joined plaques or verruca.[22]

Acquired Epidermodysplasia Verruciform (AEDV), cervical intraepithelial neoplasia, anal intraepithelial neoplasia, and squamous cell carcinomas (SCC) may develop in HIV infected individuals.[23, 24]

Recently, the use of quadrivalent HPV vaccine in HIV infected children has created more hope to prevent warts, dysplasia and cancer.[25]

Epstein-Barr virus (EBV)

An early sign of HIV infection is hairy cell leukoplakia that is present up to 25% of such patients. This condition is an EBV-associated non-premalignant mucosal lesion that could occur in other immunosuppressive diseases.[26]

Cytomegalovirus (CMV)

Cutaneous lesion of CMV in HIV is uncommon and includes anogenital ulcers, verrucous or hyper pigmented plaques, purpuric vesicles, papules and morbilliform rash.[27]

Bacterial infections:

Staphylococcal infections

The most common bacterial infection in HIV infected patients caused by staphylococcus aureus and infection with methicillin-resistant species is much higher in these patients. The usual manifestations include folliculitis, impetigo, furunculosis and cellulitis.[25]

Gram negatives

The lesions of skin or any other site in the body called “Bacillary angiomatosis” is caused by Bartonella spp. and manifest as single or multiple vascular-appearing papules, nodules or ulcers with or without visceral or osseous lesions.[28]

Mycobactrial infections

A febrile immune deficient HIV-infected patient with erythematous non-pruritus papules, nodules, ulcer, verrucous plaques or deep nodules must be observed for cutaneous micobactrial infection.[25]

Syphilis

All patients with HIV infection must be tested for syphilis. Treponema pallidumin HIV-infected patients could be presented as classic papulosquamous lesions or uncommon manifestations such as noduloulcerative form, molluscum like, palmoplantar cratoderma and septicemic disease or norosyphilis.[27, 29]

Fungal infection:

Candidiasis

Manifestation of candidiasis in HIV patients varied from localized cutaneous lesions to disseminated multiple-organ involvement and its incidence correlates with CD4+ cell counts.[27, 30]

Dermatophytoses

In addition to the common manifestation of dermatophytosis such as foot or interdigitaltinea, onychomycosis and so on, these infections could provide entry for bacterial pathogens.[26, 31]

Systemic fungal infection

Any dimorphic fungi could lead to systemic disease in HIV-infected individual including cryptococcosis, histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, penicilliosis and sporotrichosis.[32]

Systemic involvement with these fungi usually occur when the CD4+ counts fall below 250 cells/mm3.

Pneumocystis carinii (recently p. jiroveci) is one of fungal like organism that could lead to systemic infection and must be treated with prophylactic agents in immunocompromised patients.[33]

Parasitic infections:

Leishmaniasis

Skin, mucocutaneous and multiple organ or visceral presentation of leishmaniasis in HIV infected patients could have classical or atypical presentation. Typical skin involvement present as ulcerated nodules or plaques but could presented atypically by diffused erythemous, ulcerative, necrotic or disseminated lesions.[34]

Strongyloidiasis

Larval penetration of the skin and serpiginous urticarial eruption are common superficial strongyloidiasis manifestation.

In immune suppressed patients dissemination may occur and could be fatal, its cutaneous presentation may like as urticaria or livedo reticularis.[22, 35, 36]

Acanthamebiasis

A canthamoeba could be apart of normal oral flora but in HIV immunosuppressed individual, it might disseminate to the skin and manifested with necrotic nodules and painful ulcers.[37]

Infestations:

Scabies

In HIV infected patients the most common ectoparasitic skin infestation is Scabies. Presentations may vary from classic crusted papules to sever keratotic, crustedand pruritic dermatitis[38] and could involve sites not usually affected like as ears, face and scalp.

Other HIV-related skin disorders:

Seborrheic dermatitis

Up to 85% of HIV infected patients affected with seborreic dermatitis[22] could be present similarly to classic disease or exaggerated.[25]

Psoriasis

Classic, severe, eruptive or inverse distribution of psoriasis may occur in any stage of HIV infection, although the overall incidence of psoriasis is not increased.[39]

New onset of reactive arthritis may be associated with HIV infection then these patients should undergo HIV evaluation.[40]

General xerosos, itchyosis, atopic dermatitis (more frequent in children), pityriasis rubra pilaris (with or without follicular spines, acne conglobata or hidradenitis suppurativa) are some of other dermatosis in HIV-infected patients.[26, 41]

Other skin disorders in HIV infected patients that caused by direct or indirect effect of infection or its treatment are listed below:

Eosinophilic folliculitis, popular pruritic eruption of AIDS, alopecia, sudden hair graying, vitiligo, trichomegaly of the eyelash, proximal subungual onychomycosis, paronychia, nail ridging, hyper pigmentation of the nail, cutaneous vasculitis with or without systemic involvement, hyperpigmentation, ultraviolet light hypersensitivity, acquired porphyria cutaneatarda, chronic actinic dermatitis, HIV/ART associated lipodystrophy, linear telangiectasias, cutaneous manifestations of malnutrition, primary cutaneous mucinoses, lichen myxedematosus, granuloma annulare, major aphthosis[22, 39, 42-47] and some of cutaneous neoplasm like: squamous cell carcinomas, basal cell carcinomas, lymphomas, Kaposi sarcomas, melanoma and cutaneous smooth muscle tumors.[48-53]

Articles review:

An epidemiologic and clinical study of HIV in Ugandan children younger than 18 months explained skin abnormality was probably an important factor in the selection of suspected HIV-infected children because fifty percent of HIV-infected children had dermatologic disorder including Non-Specific Generalized Dermatits (NSGD), sub-cutaneous abscesses, eczema, impetigo, herpes zoster, and Kaposi Sarcoma (KS).[54]

Another prospective study among 127 children with HIV under 13 years old on 2007 showed; Dermatosis occurred in 81% of the evaluations, and the most commonly observed conditions were xerosis (23.0%), popular urticaria (20.0%), seborrheic dermatitis, (6.7%), residual discromia (6.2%), candidiasis (5.7%), atopic dermatitis (4.8%), pityriasis alba (4.6%), piodermitis (3.6%), molluscum contagiosum (3.6%) (Fig 1), and pediculosis (3.3%).[55]

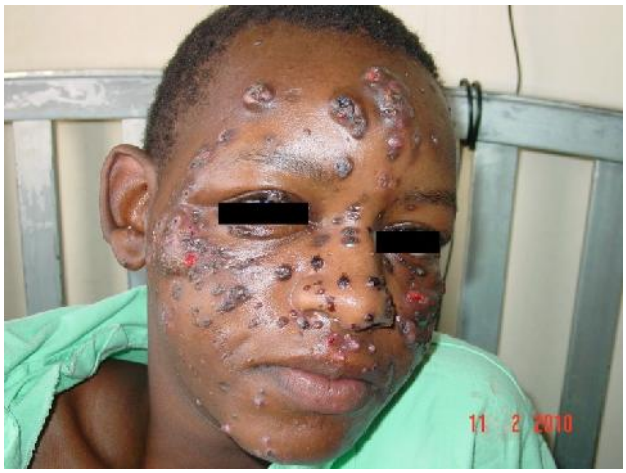

Figure 1: A rare case of giant and multiple Molluscum contagiosum on the face of an HIV infected case at Kenyata Hospital Nairobi, Kenya. By Dr Emadi.

A cross-sectional study at the pediatric outpatient clinic in Nigeria in 2008 revealed a high prevalence on 64 (64.0%) skin condition among the 100 HIV children between 18 months to 16 years (subject) compared with 12 (12.0%) of HIV-negative (control). The prevalence of mucocutaneous lesions among 3 groups (severe, moderate, and non-immune suppressed) was 93.8%, 55.2%, and 46.1%. This means, skin illness among those who had severe immunosuppression (CD4-positive, less than 14%) was (32%), moderate immunosuppression (CD4, 15-24%) was (29%), and no evidence of immunosuppression (CD4 more than 25%) was (39%), respectively. They

were significantly more common in those who had moderate and severe immunosuppression than in those without evidence of immunosuppression. Multiple lesions were found in 86.7%, 37.5%, and 16.7% of those who had severe, moderate, and no immunosuppression, respectively. This study also revealed that mucocutaneous findings were more frequent and more severe as the immune status worsened.

Nineteen different types of lesions were noticed among the subjects, whereas, only four different lesion types were noticed among the controls. Among the subjects, oral thrush (OT), pruritic papular eruption (PPE), plantar warts (PW), Seborrheic dermatitis, Xerosis and dermatophytosis were the most frequent lesions. Impetigo, acne, molluscum contagiosum (MC) and pityriasis versicolor were noticed as well. OT, PPE, herpes simplex (HS), and herpes zoster (HZ), were noticed only among the subjects. A 4-year-old subject who had severe immunosuppression had herpes ulcer, which required four weeks of treatment with acyclovir before resolution. Again, a subject with severe immunosuppression had tinea unguium and tinea capitis involving the whole scalp, and another child with severe immunosuppression had atypical tinea corporis involving the upper limb with several newer crops of tinea lesions occurring within a larger pre-existing tinea corporis.[56]

In 1995, the analysis of the frequency of dermatologic disorder among 166 HIV/AIDS children in Italy showed that 89% (76/85) of the HlV/AIDS-infected patients had one or more cutaneous manifestations as compared to 42% (34/81) of those not infected.

In this study, the cutaneous manifestations in HIV infected patients were divided into two major groups. The most important (73%) were infections or infestations due to fungal, bacterial, and viral agents or Scabies and pediculosis that tended to be more severe, recurrent, and less responsive to conventional therapy than in healthy children. The second group was composed of inflammatory disorders, which included vasculitis, drug reactions, seborrheic and atopic dermatitis, and alopecia. Almost all children with AIDS developed oral candidiasis during their illness (93%). The other valuable result of this study was the comparison of the frequency of skin manifestation in both children and adult. In fact, Candida, Herpes simplex, CMV, Molluscum contagiosum, Scabies (Fig 2), Atopic dermatitis, Vasculitis, Alopcia and Nutritional deficiency in Children were more common than adult, while Tinea, wart, Seborrheic dermatitis, drug reaction, Kaposi sarcoma, and Oral hairy leukoplakia were more common in adult.[57]

The survey of 91 HIV children under the age of 13 years in 1994 in Thailand, in addition to finding the most frequent skin presentation which was oral candidiasis (36.3%), drug rash, pruritic papular eruption, herpes zoster, cutaneous candidiasis also explained the four clinical categories:

a. Category N (not symptomatic)
b. Category A (mildly symptomatic)
c. Category B (moderately symptomatic)
d. Category C (severely symptomatic)

Mucocutaneous manifestations were found in 47 (51.6%) of those children. The prevalence of mucocutaneous manifestations in categories A, B, and C were 4%, 62%, and 75%, respectively. The mucocutaneous manifestations in patients in categories B and C were significantly more common than in those category A ($p < 0.001$). [58]

A study of oral manifestation in 45 HIV children under 10 years old in Thailand revealed: Erythematous candidiasis was the most common lesion (17.8%). Oral hairy leukoplakia was seen in 6.7% (n=3).

Geographic tongue, not usually considered to be associated with HIV infection, was seen in 6.7% (n=3). Severe herpes simplex virus (HSV)

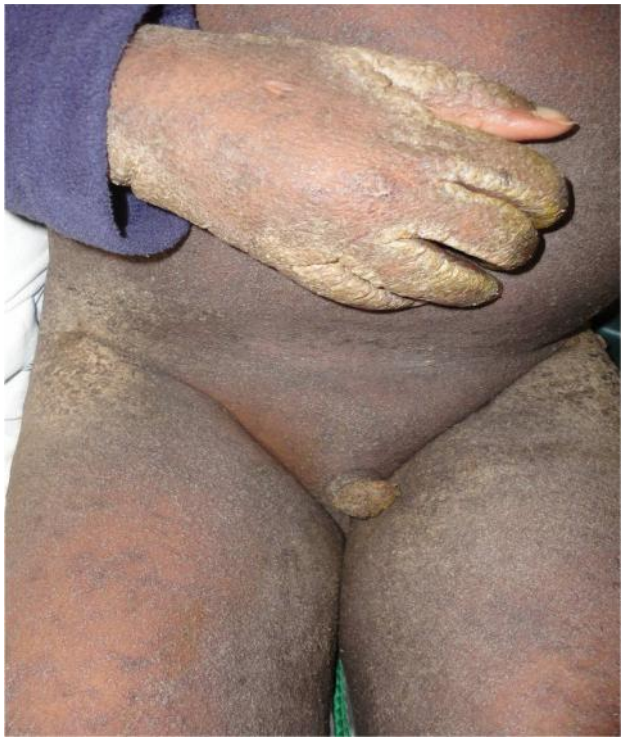

Figure 2: Crusted scabies in a HIV/AIDS child with CD4= 5 at Iran clinic under the Iranian Red Crescent Society, Nairobi Kenya. By Dr Emadi.

infection of the oral cavity and face was seen in one case.[59]

Children with HIV disease have a potential of developing hypersensitivity drug eruptions.

In two studies, drug-related rashes among HIV-infected children were 12% and 16%, respectively. Dusky erythematous macules, Erythema multiform, hypersensitivity-like eruption, Fixed Drug Eruption, Stevens-Johnson syndrome, and toxic epidermal necrolysis may occur to Trimethoprim-sulfamethoxazole, Nevirapin, Abacavir, Efaviorence, and Ampicillin (Fig-3). Drug reaction in HIV-infected children could be more dangerous and fetal than non-infected person. Rapid-onset and the developed form of drug hypersensitivity (steven johnson syndrome and toxic epidermal necrolysis) may happen very short time after primarily macula and papules.[60-61] Therefore, the special care and close

Figure 3: A 4-year old Ghanaian boy with both mucocutaneous presentations (Stevens-Johnson syndrome) just two weeks after giving ARV's drugs including Nevirapin. Accra, Ghana. By Dr Emadi.

monitoring for the kids who is going to be treated with Antiretrovirals (ARV's) for the first time is absolutely necessary. Discontinuation or changing of the offending medication is mandatory.

Kaposi sarcoma (KS) and Non-Hodgkin Lymphoma (NHL) were two frequent neoplasms in HIV/AIDS children. Among the 17 children who acquired HIV infection prenatally, only two developed Kaposi sarcoma (KS) lesions, whereas nine of 13 children who acquired the infection postnatally had cutaneous KS.[62]

Discussion

The main limitation in this study was rare case-control studies as well as not giving information about histopathological finding in cases with skin disorder. Therefore, next studies need combination of clinical and histological investigation to reveal better clinical approach in association with histological study**.**

This review demonstrated a close association of oral trash and malnutrition in the majority of children with HIV/AIDS. Hence, it can present

this clime that the hidden and extended candida to esophagus particularly when it does not have clear sign and symptoms on the mouth might be the main reason to nutritional deficiency due to in-appropriate feeding (loss of appetite, dysphasia and swallowing) apart from the potential and interfering of the nature of HIV disease on nutrition and weight loss. This means, a malnutrated HIV kids without visible oral trash needs a correct and exact investigation to determinate the possibility of the involvement of esophagus and GI tract by candida or other opportunistic infection. So that, it can be valuable in para-clinical approach of HIV.

On the other hand, according to reviewed studies, fungal, bacterial and viral infections as a communicable disease are the more frequent presented illness in HIV/AIDS children. As a result of this matter, educating the parents would be the crucial and essential manner to keep the HIV positive children away from the both sources (place and individual) of communicable (infections and infestations) diseases. So that, educating the parents is a valuable prophylactic tool in HIV/AIDS children.

Other findings about localized and systemic infections revealed, Staphylococcus was the most common isolate bacterial pathogen from the infected skin such as cellulitis, ecthyma, erysipelas, furunculosis and impetigo which were persistent and recurrent. While in systemic infections (respiratory and urinary), the most common isolates were Streptococcus pneumoniae, Haemophilus influenza type B, and Salmonella species.[63, 64] These statements explained, the different locations of infection could be presented with different types of bacterial pathogen especially on the skin which might be persistent and recurrent. Therefore, considering an effective regimen of treatment for isolated pathogen and recurrent cutaneous infections would be the main step in management. Therefore, these findings are valuable to select the appropriate therapeutic regimen.

About the frequency and severity of some dermatoses and genodermatoses such as psoriasis, vitiligo, lichenplanus, Darier Disease, xeroderma pigmentosumin Individuals who are infected with Human Immunodeficiency are different reports and outcomes. There are a few case reports that showed lichen planuse (hypertrophic form) and Darier Disease may have severe, atypical and late onset occurring as an associated feature of HIV infection. This means, unexpected, atypical and widespread presentation of some dermatoses in children particularly in high risk kids may be a warning to check the status of HIV.[25, 65, 66]

The observation of malignancy has led to the hypothesis that different routes of HIV infection may be associated with different KS clinical manifestations. To follow this point, a study concentrating on the seroprevalence of HHV-8 among Zambian women of childbearing age without KS and mother-child pairs with KS concluded that all children with KS had mothers who were HHV- 8–seropositive, while not all children whose mothers had KS were infected with HHV-8.[67] Vertical transmission of KS from an HIV-seropositive mother to her child has been reported.[68]

Other valuable comment from different manuscripts on KS showed: There is a male preponderance for childhood HIV related KS, and the median age of presentation is 4 years. The distribution of childhood HIV-related KS is mainly lymphadenopathic and mucocutaneous with two major patterns: orofacial-dominant (79%) and inguinal-genital dominant (13%). KS lesions occasionally exhibit the Koebner phenomenon and appear at sites of previous trauma or infection.[69]

The frequency of Non-Hodgkin Lymphoma (NHL) tends to increase significantly with age and is more common in boys than in girls. An

important role for Epstein-Barr virus has been suggested, and all children have low CD4 counts at the time of diagnosis.[70]

In order to above mention finding, careful lymphatic, orofacial and inguinal-genital examination especially in the sex of male is mandatory which may be the important key to find out any possible presentation of KS and NHL in predisposed kids with HIV.

Conclusions

Skin diseases may be the first presenting sign of HIV infection or may serve as a prognostic marker and an ominous sign of the deterioration of the child's immunodeficiency. More likely it has an important role in recognizing and treating them effectively and earlier, as they can worsen the quality of life of these children and lead to devastating sequelae.

Therefore, not only the nature of HIV disease but also the super imposed infection and infestations, related neoplasm's to HIV and drug reaction due to ARV's may have separate and clear skin presentation which could be a very effective direction or guidance to medical groups in their approach to increase the quality of life of HIV/AIDS children. For example, it will be very important to know the skin illness in an infected HIV kids is related to his/her viral infection or ARV's medication such as nevirapine or abocavir. Because saving the life of children in a short time after skin presentation might be very crucial.

Conflict of Interest

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