Mucocutaneous manifestations in children with human immunodeficiency virus infection

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ABSTRACT

Skin is one of the most frequently involved organs in human immunodeficiency virus (HIV) infection, and mucocutaneous manifestations may be one of the earliest markers of AIDS. The prevalence of cutaneous abnormalities in HIV approaches nearly 90%. Mucocutaneous manifestations may also act as a prognostic marker of HIV infection. Children are increasingly being affected by HIV infection and it is important to realize the presence of the infection early in the disease process as their immune status is not mature enough to handle the stress of various infections. Skin manifestations can serve as early markers and prognostic indicators of HIV infection. This review highlights the epidemiology, transmission, pathogenesis, and the mucocutaneous manifestations of HIV infection in children.

Key words: Children, human immunodeficiency virus, mucocutaneous

INTRODUCTION

Human immunodeficiency virus (HIV) infection in children is becoming a common occurrence. In children, it is largely a preventable disease. Skin manifestations constitute one of the most common clinical features in such children and their clinical pattern and severity is more or less in accordance with their CD4 counts. Thus an early recognition of such features is important for an early diagnosis and also to assess the prognosis of HIV infection. Children with HIV infection are more prone to adverse cutaneous drug reactions, both to anti-retroviral therapy (ART) and to other drugs that are given concomitantly for co-morbid illnesses.

The first pediatric case of AIDS was reported to the Centre for Disease Control and Prevention (CDC) in November 1982. Globally, there were a total of 33.2 million people living with HIV, in 2007, of which 2.5 million (7.5%) were children under the age of 15 years.[1] Total number of deaths was 2.1 million, of which 330,000 were children. It is estimated that more than 90% of children living with HIV acquired the virus during pregnancy, birth, or breastfeeding, forms of HIV transmission that can be prevented.[2]

In 2007, it is estimated that there are 2.31 million (1.8-2.9 million) people living with HIV/AIDS in India (making it the third largest country with regard to the number of people with HIV) with an estimated adult HIV prevalence of 0.34% (0.25-0.43%). Out of the estimated number of PLHA (people living with HIV/AIDS), 39% are females and 3.5% are children.[3]

Transmission of HIV can occur in following three ways:

1. Sexual route
2. Contaminated blood and body fluids
3. Vertical transmission

HIV infection in children occurs mainly through vertical transmission, i.e. from mother to child. The risk of transmission by an infected mother occurring before or during birth (without interventions to reduce transmission) is 15-25%. Breastfeeding by an infected mother increases the risk by 5-20% to a total of 20-45%.[4] In a study done in Brazil, vertical transmission
was seen in 97.5% of children. Various studies done in India have reported vertical transmission as a cause of pediatric HIV in 51-83% of cases.

**PATHOGENESIS**

HIV infection is characterized by an insidious deterioration of the cellular immune system. The degree of immunodeficiency associated with HIV infection, as defined by the onset of opportunistic diseases, correlates closely with plasma CD4 T-cell counts.

HIV enters into the CD4 T-cells by the process of binding and fusion. It synthesizes DNA from its RNA with the help of reverse transcriptase, which then integrates into the host DNA and undergoes transcription. The new protein thus formed assembles into a new virion which is released by budding and goes on to infect the other CD4 T cells.

Approximately 100 billion new viral particles are produced every day, and 1 to 2 billion CD4 T cells die each day. This depleted pool of CD4 T cells is not completely replaced and the host thus remains deficient in CD4 T cells. Although marked reduction in CD4 T cells can account for most of the immunodeficiency, there is evidence that qualitative defects in T cells can be detected even in asymptomatic individuals.

**CLINICAL FEATURES**

HIV is a multi-system infection affecting virtually every organ of the body. HIV infection produces a spectrum of illness from totally asymptomatic infection to AIDS.

Patterns of disease expression and progression differ among HIV infected children. Most children with HIV infection acquired from the mother will display features of the infection within 6 months of life, whereas some remain asymptomatic till the age of 8-10 years. The onset of HIV infection in children has a wide spectrum of clinical manifestations. Some infants present with features of severe immunodeficiency, whereas others have non-specific findings such as hepatosplenomegaly, failure to thrive, unexplained persistent fever, parotitis, and recurrent gastroenteritis. During the first year, lymphadenopathy, splenomegaly, and hepatomegaly, singularly or combined, have been observed in more than 50% of children; other signs including failure to thrive, fever, diarrhea, and AIDS defining secondary infections, are frequently observed, but can also present at a later age.

**CUTANEOUS MANIFESTATIONS**

Skin is commonly involved in HIV infection and nearly 90% of patients with HIV infection have dermatological manifestations at some stage during the course of their disease.

The data currently with regard to the mucocutaneous manifestations of HIV infection in pediatric population come mainly from the western literature. The prevalence of mucocutaneous manifestations in children with HIV infection, from various parts of the world, is highly variable, ranging from as low as 42% to almost 93%.

In India, skin manifestations among HIV-infected children show a prevalence rate varying from 30 to 80%. HIV-infected children often present with common childhood infections. These, however, tend to be more severe, may manifest atypically, are often resistant to treatment, and tend to have a high rate of recurrence. The various clinical manifestations seen in children are tabulated in Table 1.

**INFECTIONS**

**Fungal infections**

**Candidiasis:** Candidiasis is one of the most common mucocutaneous manifestations of HIV infection in children, and its incidence has been estimated to range between 20% to 72%. Oral involvement is the most common presentation of which can be as: (1) pseudomembranous (thrush), (2) erythematous (atrophic), (3) papillary hyperplasia, (4) chronic hyperplastic, (5) angular cheilitis, and (6) median rhomboid glossitis. It has been suggested in several studies that thrush is a marker of rapid HIV disease progression and death. Although it can occur without severe cell depletion, it is more commonly seen with low CD4 counts or symptomatic HIV disease. The manifestations in an HIV positive differ from those in an immuno-competent child by persistence beyond the age of 6 months, the presence of severe or recurrent episodes, and the coexistence of lymphadenopathy, splenomegaly, or wasting syndrome. *Candida albicans* is the usual pathogen causing oral candidiasis, but other strains can occasionally be isolated.
**Dermatophytosis**: Infection by dermatophytes occurs with an increased frequency and aggressiveness in HIV-infected patients. Tinea corporis, tinea capitis, tinea faciale, and onychomycosis [Figure 1b] are particularly common. Cases of severe (such as kerion) and recurrent tinea capitis have been observed. Proximal white subungual onychomycosis of fingernails, periungual involvement, and rapid spreading of the infection to involve all 10 finger and toenails are common findings in HIV-infected individuals with low CD₄ cell counts. Dermatophytic infections are particularly resistant to topical agents, and recurrences after topical and systemic therapy are common.

**Deep fungal infections**: *Histoplasma capsulatum, Coccidioides immitis, Aspergillus fumigatus, Malassezia furfur, Sporothrix schenckii*, and others can cause opportunistic infections in HIV-infected adults, but are rarely observed in HIV-infected children. Disseminated sporotrichosis with painful ulcers has been described in children. Sirisanthana et al. reported a series of 21 HIV-infected children with disseminated *Penicillium marneffei* infection. Papular skin lesions with central umbilication on the face and extremities appeared in 67% of patients and provided the most significant clue to the diagnosis. The disease occurs late in the course of HIV infection.

**Bacterial infections**

**Pyoderma**: Generally, children manifest recurrent bacterial infections rather than primary opportunistic ones as seen in adults. The most common isolates are *Streptococcus pneumoniae, Haemophilus influenzae* type B, and *Salmonella* species. Staphylococcal infections are the most common skin infections, usually presenting as cellulitis, ecthyma, erysipelas, furunculosis (occasionally of disseminated nature), persistent and recurrent folliculitis, and impetigo.
**Bacillary angiomatosis:** Although the disease has been described in immunocompetent children, it is rarely seen in HIV-infected children. The etiologic agent is *Bartonella henselae* and *B. quintana*. Lesions begin as small, erythematous, vascular papules that may enlarge to form exophytic, friable nodules surrounded by a collarette of scale with or without erythema.

**Mycobacterial infections:** HIV-infected children are at an increased risk of tuberculosis but cutaneous involvement is not a common occurrence. *Mycobacterium avium* intracellular complex (MAC) is one of the most frequent atypical mycobacterial infections in HIV-infected patients. Skin is rarely infected, and children with late stage disease (CD4 <100 cells/mm³) are more prone. Cutaneous abscesses, macular lesions, and perianal ulcerations have been reported in HIV-infected adults but may also occur in pediatric cases. A large prospective done over a population of 1,52,000 adult patients revealed no differences in the incidence, presentation, or severity of cutaneous tuberculosis in HIV-positive patients.

**Viral infections**

**Chicken pox:** Varicella may run a prolonged course (>10 days) in HIV-infected children, and persistent and recurrent infections are particularly problematic. Von Seidlein et al. documented an association between increasing numbers of episodes of VZV infection and a low CD4 count at the time of primary infection.

**Herpes zoster:** Herpes zoster (HZ) is rare in immunocompetent children but occurs with increased frequency in HIV-infected children. In addition to classic papulovesicular HZ, persistent ulcerative and disseminated forms [Figure 2] may be observed. Von Seidlein et al. documented that the presentation of zoster as the first recurrence of VZV infection is associated with low CD4 counts.

**Herpes simplex virus:** HSV infection correlates primarily with CD4 cell counts. The most common feature of HSV in pediatric HIV infection is herpetic gingivostomatitis, with painful, recurrent, or chronic ulcerations of the lips, tongue, palate, and buccal mucosa. The frequency of herpetic gingivostomatitis is especially high in those with CD4 counts <50 cells/mm³.

**Human papilloma virus:** HPV may cause verruca vulgaris, widespread flat warts, and condylomata acuminata. Warts can be single but usually are multiple. Extensive anogenital warts, very resistant to treatment, have also been observed. Epidermodysplasia verruciformis, an HPV infection caused by HPV types 5 and 8, is an autosomal recessive disorder and has been known to occur in association with many immunodeficinet states including HIV.

**Molluscum contagiosum:** In children with HIV infection, it often involves atypical areas, such as the face and neck and occasionally extremely numerous. In addition, giant lesions (>1 cm) may occur. Lim et al. noted that unusual features may occur without severe CD4 cell depletion. In contrast to the usual course in healthy children, molluscum lesions in HIV-infected patients tend to persist.

**Measles:** In developing countries, measles has been reported to run a more severe course in HIV-infected children, with estimated fatality rates of 40-70%. The increased mortality has been attributed to a higher rate of measles giant cell pneumonia. Some of the children do not manifest the typical measles exanthem.

**Cytomegalovirus infection:** In AIDS patients, the most common lesions reported to contain CMV have been ulcerations of the orofacial or perineal area.

**Epstein-Barr virus:** Oral hairy leukoplakia, characterized by discrete, whitish patches with parallel vertical ridges on the lateral border of the tongue, has been reported to occur rarely in HIV-infected children.

**Infestations**

**Scabies:** Independently of CD4 counts, most patients have scabetic burrows at characteristic sites, such as the wrists and finger web spaces. Patients with CD4 counts <150 cells/mm³ may present with crusted Norwegian scabies. The infestation might be particularly resistant to treatment.

**Pediculosis and demodicosis:** Pediculosis is particularly common, especially in children with low socio-economic status. Papular lesions on the face of two HIV-infected children in relation to *Demodex* mites have been described. The main defense against *Demodex* mites are the CD4 cells, which are defective in HIV infection.
**Inflammatory dermatoses**

**Pruritic papular eruption (PPE):** PPE is often one of the earliest manifestations of HIV infection and is a useful cutaneous marker for immune status in such patients. The concentration of the lesions is highest on the extremities [Figure 3], but the trunk and face are also involved in half of the patients. It is a sign of waning immunity in these patients, and usually occurs at counts <50 cells/mm³.

**Seborrheic dermatitis (SD):** It is possibly one of the most common cutaneous manifestations of HIV disease, its incidence ranging from 32 to 83%. In children with HIV infection, SD seems to occur with increased frequency. Its severity has been correlated with the degree of HIV-related immunodeficiency and the CD₄ cell count. In infants, the disorder may take the form of severe erythema and scaling of the face, scalp, and diaper area, sometimes progressing to erythroderma.

**Atopic dermatitis:** Parkin et al. documented the association of atopic manifestations with established AIDS. Atopic dermatitis appears to be triggered by HIV seroconversion in genetically predisposed individuals. In certain series, atopic dermatitis does not seem to be more frequent in seropositive children than in the healthy population.

**Psoriasis:** In adults with HIV infection, psoriasis may appear suddenly and with extreme severity, while it is subject to precipitous flares and resistance to treatment. Both plaque and guttate psoriasis in children and adolescents with HIV infection have been observed.

**Drug eruptions:** Patients with HIV disease are particularly prone to hypersensitivity drug eruptions. Hachem et al. reported an incidence of 12% of drug-related rashes among 85 HIV-infected children. It is seen as morbilliform skin appearing 8-10 days after initiation of therapy [Figure 4] and resolving quickly after discontinuation of the drug. Dusky erythematous macules, Stevens-Johnson syndrome, and toxic epidermal necrolysis may also occur. Co-trimoxazole, ampicillin and antituberculous medication are other agents frequently implicated in drug eruptions.

**Vasculitis:** Leukocytoclastic vasculitis may develop as a result of drug reaction, concomitant infection, or HIV infection itself. Chren et al. reported a 9-year-old girl with persistent, palpable purpura of the lower extremities as the sole manifestation of HIV infection. Three children with vasculitic lesions resembling cutis marmorata have also been reported. Other vascular phenomena known to occur in children with HIV infection are splinter hemorrhages, telangiectasias, and immune thrombocytopenia.

**Neoplastic conditions**

**Kaposi’s sarcoma (KS):** KS is rare in children. KS in children points to a nonsexual mode of transmission. HHV-8 can be acquired as a common childhood infection and may possibly be horizontally transmitted from mother to child during birth or breastfeeding. There is a male preponderance for childhood HIV-related KS, and the median age of presentation is 4 years. Clinically, it may look like a red, bluish, or brownish macule, papule, small plaque, or a smooth raised tumor. Lesions may appear anywhere on the skin including palms, soles, body folds, ears, scalp, and mucosal surfaces, particularly the hard palate.

**Non-Hodgkin lymphoma (NHL):** NHL is more common in children and adolescents with AIDS. An important role for Epstein-Barr virus has been suggested, and all children have low CD₄ counts at the time of diagnosis. In a British study, seven cases of NHL were identified among 302 HIV-infected children.

**Hair and Nail changes**

**Hair abnormalities:** Hair changes such as hypertrichosis of the eyelashes, thinning of hair, premature graying, telogen effluvium, and alopecia due to severe SD, malnutrition or unknown causes have been reported to occur in HIV infection.

**Nail abnormalities:** Nail changes such as yellow discoloration, transverse or longitudinal ridging, paronychia, onychomycosis, etc. have been described in association with HIV infection. These can occur either primarily or secondary to infections or anti-retroviral drugs given.

**Miscellaneous**

**Alopecia** due to severe seborrheic dermatitis, nutritional deficiency, or unknown causes may be observed in the HIV-infected pediatric population. An exanthematous eruption associated with the
HIV-infected children are more vulnerable to abuse. A peculiar annular eruption in a 7-year-old girl finally proved to be the result of the abusive behavior of her adoptive parent.\

Manifestations due to anti-retroviral therapy
Two regimens of ART are currently followed: the first regimen utilizes two nucleoside analogs (one of which is usually lamivudine) and a non-nucleoside reverse transcriptase inhibitor. The second regimen utilizes two nucleoside analogs and a protease inhibitor. Initiation of ART in children is guided by child’s WHO clinical stage as well as the CD4 count, taken together [Table 2].

The advent of HAART (highly active anti-retroviral therapy) or combined ART has changed the spectrum of skin disorders by improving host immunity. HIV-infected patients are more likely, than the general
Another event seen in children on ART is immune reconstitution inflammatory syndrome (IRIS). It is defined as “a collection of signs and symptoms resulting from the ability to mount an immune response to antigens or organisms associated with immune recovery on ART.” It is seen more commonly in those with severe immunodeficiency and presents most commonly within 2-12 weeks of initiating ART. It presents as an unexpected deterioration of clinical status soon after commencing ART. Subclinical infections, such as TB, are unmasked, which present as new active disease and there may even be development of abscess at the BCG vaccination site. Most common IRIS events seen are *M. tuberculosis*, herpes zoster and cryptococcal disease.

**CONCLUSIONS**

Skin manifestations are a common occurrence in HIV-infected children and their pattern can help predict the severity of the disease. The type and the characteristics of various mucocutaneous disorders seen in HIV co-relate well with the CD4 counts and can help predict the degree of immunodeficiency with fair precision. Such knowledge is especially helpful in resource poor countries like ours where availability of CD4 counts is limited.

**REFERENCES**

Mucocutaneous manifestations in children with HIV infection


Multiple Choice Questions

1. Prevalence of HIV infection in India is:
   a. 1.8 million  b. 2.3 million  
   c. 4.5 million  d. 6.7 million

2. All of the following are TRUE except:
   a. Global prevalence of pediatric HIV infection is 2.5 million
   b. Vertical transmission is the most common mode of HIV infection in children
   c. Highest risk of HIV infection in children is during the perinatal period
   d. Breast feeding decreases the risk of acquiring HIV infection

3. All of the following are TRUE regarding HIV infection in children except:
   a. Most of the children present with clinical symptoms during the neonatal period
   b. They usually present with non-specific symptoms of immunodeficiency
   c. Skin is one of the most commonly involved organs with HIV infection
   d. Children may remain asymptomatic upto the age of 8-10 years

4. Prevalence of skin infections in HIV infection is approximately:
   a. 50-60%  b. 70-80%
   c. 90-100%  d. Extremely rare

5. Which of the following is TRUE regarding the skin manifestations in HIV infection:
   a. Malignancies are the most common cutaneous manifestation
   b. Infectious manifestations usually present atypical morphologies
   c. Candida is the most common cutaneous infection in most series
   d. Skin manifestations have no correlation with the CD4 counts of the patient

6. Fungal infection not seen with increased frequency in HIV-infected children is:
   a. Pityriasis versicolor  b. Oral thrush
   c. Dermatophytosis  d. Histoplasmosis

7. Epidermodysplasia verruciformis is caused by which of the following HPV serotypes:
   a. 1  b. 3
   c. 5  d. 11

8. Which of the following is not TRUE about papular pruritic eruption in HIV infection:
   a. It is one of the earliest manifestations of HIV infection
   b. It is an HIV-specific cutaneous manifestation
   c. Arthropod bites have been postulated to be one of the causative factors
   d. It does not serve as a cutaneous marker of underlying immune status

9. IRIS commonly occurs after how many weeks of ART initiation:
   a. 1-4 weeks  b. 2-12 weeks
   c. 12-24 weeks  d. After 6 months

10. Lipodystrophy is most characteristically seen with
    a. Zidovudine  b. Nevirapine
    c. Indinavir  d. Tenofovir

ANSWERS

1. b 2. d 3. a 4. c 5. c 6. a 7. c 8. d 9. b 10. c