ELSEVIER

Skin Manifestations of HIV-1 Infection in Children

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The first pediatric case of AIDS was reported to the Centers for Disease Control and Prevention (CDC) in November 1982, 18 months after the first description of AIDS in adults. It is estimated that 3.5 million women of childbearing age have been infected with HIV-1, and 3000 additional women become infected every day. According to the World Health Organization (WHO), by December 1998, 1.2 million children under the age of 15 years were infected with HIV.[1] One million of them live in Africa and in general have been infected through vertical mother-to-child transmission of HIV.[1] HIV-1 infection has a significant impact on childhood mortality and morbidity and is one of the leading causes of death, especially among African children.

The established modes of transmission of HIV-1 infection are through (1) sexual contact, (2) from mother to infant, and (3) through exposure to infected blood (such as transfusion, needle sharing). Transmission of HIV-1 from mother to child (vertical) is the predominant source of acquisition of HIV-1 in children. Data support the transmission during the antepartum and intrapartum periods as well as postpartum by breastfeeding. Zidovudine given antepartum and intrapartum to the mother and the newborn for 6 weeks reduces the risk of maternal-infant HIV transmission by approximately two thirds[2] and is safe.[3] Many children, especially hemophiliacs, have been infected through infected blood products, but transfusion-related transmission is now rare in the Western world but still applies for the developing countries. Routes of transmission of HIV in adolescents are similar to those for adults.

Several studies revealed that perinatal infection had a more varied clinical picture and a worse outcome than infection acquired later in childhood.[4–6] About one third of infants born to HIV-seropositive mothers will have evidence of infection or AIDS by the age of 18 months, and about one fifth of them will die.[3,7] Subsequently, the disease progresses more slowly, and most children remain stable or even improve during the second year.[8]

The diagnosis of HIV-1 infection is a special diagnostic challenge. In 1994 the CDC revised the classification system published in 1987, aiming not only to establish disease surveillance but also to define its progression. In the current classification system, children are grouped into mutually exclusive categories based on three parameters: (1) infection status (exposed, infected, seroconverter; (2) clinical status (asymptomatic, mild, moderate, or severe symptoms); and (3) immunological status (age-related categories of no, moderate, or severe suppression). Reclassification to a less severe category does not occur even if the child' s clinical or immune status improves. Recent data suggest that determination of the plasma viral concentration (viral load) in conjunction with CD4+ cell count are more accurate predictors of prognosis and survival than each marker alone. The viral load $>5\log_{10}$ per ml within the first 30 months of life and $>4.3\log_{10}$ after 30 months are associated with an increased risk of disease progression.[9]

Immunology

Although HIV-1 is particularly tropic for CD4+ (helper) T lymphocytes, monocytes, macrophages, and central nervous system cells that express CD4+ receptors, abnormalities in humoral immunity may precede the development of the more characteristic ones of cell-mediated immunity. B cells from HIV-infected children demonstrate polyclonal activation and hyperproliferation with hypersecretion of polyclonal immunoglobulins. Despite B-cell activation, HIV-infected children functionally appear hypogammaglobulinemic, with B cells unable to respond efficiently to specific antigens, and consequently, they become extremely prone to devastating bacterial infections. Impaired T-cell immunity is manifested as decreased in vivo and in vitro function of T cells as well as quantitative abnormalities of T cells. The suppressor CD8+ lymphocytes usually increase in number initially, resulting in a decrease of the normal

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CD4+ to CD8+ ratio, and are not depleted until late in the disease. The most severely affected cells are the CD4+ lymphocytes, whose function and numbers steadily decline as the disease progresses.

The skin and mucous membranes are the first barriers to be disrupted, so mucocutaneous signs are very important markers of disease progression. In a Nigerian study it has been estimated that skin manifestations can be the presenting feature in as many as 37% of HIV-infected children. The occurrence of certain skin manifestations has been noted to correlate with the CD4+ cell count.[10,11] As the CD4+ cell count declines, more severe and multiple cutaneous manifestations appear that are less responsive to conventional treatment.[10] Mucocutaneous manifestations can be divided into infectious and noninfectious ones and are listed in Table 1.

Table 1. Cutaneous Manifestations of HIV-1 Infection in Children

- Infections and infestations
  - Fungal infections
    - Candidosis
    - Dermatophytosis
    - Deep fungal infections
  - Bacterial infections
    - Bacillary angiomatosis
    - Mycobacterial infections
  - Viral infections
    - Varicella zoster infection
    - Herpes simplex infections
    - Human papilloma virus infection
    - Molluscum contagiosum infection
    - Other viral infections
      - Measles
      - Cytomegalovirus infection
      - Epstein-Barr virus infection
  - Infestations
    - Scabies
    - Pediculosis
    - Demodicosis
  - Protozoal infections
    - Acanthamoeba infection
- Neoplastic disorders
  - Kaposi sarcoma
  - Non-Hodgkin lymphoma
- Inflammatory Disorders
  - Seborrheic dermatitis
  - Atopic dermatitis
  - Psoriasis
  - Urticaria
  - Drug eruptions
  - Vasculitis
  - Aphthous ulcers
- Nutritional deficiencies
- Miscellaneous
  - Alopecia
  - Hypertrichosis of the eyelashes
  - Hypertrichosis of lanugo type
  - HIV infection primary rash
  - Sweet syndrome
  - Pyoderma gangrenosum
  - Gianotti Crosti syndrome
  - Erythema dischromicum perstans
  - Vitiligo
  - Eruptive dysplastic nevi
  - Trauma from child abuse

Fungal Infections

Candidosis

Candidosis is the most common mucocutaneous manifestation of HIV infection in children, and its incidence has been estimated to range between 20% and 72%.[8,10–12] Although thrush can occur without severe CD4+ cell depletion,[10,17] it is more common in children with low CD4+ cell counts or symptomatic HIV disease.[12,17,18] It has been suggested in several studies that thrush is a marker of rapid HIV disease progression and death.[8,12,18] Esophageal candidosis, which manifests as loss of appetite or dysphagia, may coexist with oropharyngeal candidosis or occur independently, with an estimated incidence of 15.4%.[19] Disseminated candidosis is uncommon in AIDS patients but may occur particularly in neutropenic patients and patients with central venous catheters.[20]

Thrush is a common and benign disorder in children under the age of 6 months and in infants receiving antibiotic therapy or who were born to drug-abusing mothers.[21] The difference in the HIV positive child is the persistence beyond the age of 6 months, the presence of severe or recurrent episodes, and the coexistence of lymphadenopathy, splenomegaly, or wasting syndrome.[21,22] There are six typical modes of presentation of oral candidosis: (1) pseudomembranous, (2) erythematous (atrophic), (3) papillary hyperplasia, (4) chronic hyperplastic, (5) angular cheilitis, and (6) median rhomboid glossitis.[18] Pseudomembranous candidosis is characterized by removable white plaques that may occur at any mucosal surface. Erythematous candidosis appears as a red thumbprint-like patch on the palate and/or the dorsum of the tongue, often causing a metallic taste or a local burning sensation. The buccal mucosa is involved less frequently. Papillary hyperplasia, which represents a chronic infection, is noted more commonly on the anterior hard palate and gives the impression of a clustering of small, ovoid nodules on an erythematous mucosa. The chronic hyperplastic form may be seen as a thickened hyperkeratotic mucosa on the tongue or the retrocommissural region, resembling an area of leukoplakia. Angular cheilitis presents as cracking or fissuring at the corners of the mouth, alone or in combination with the other forms. Median rhomboid glossitis has a nodular or fissured appearance on the tongue and is asymptomatic. The manifestations of oral candidosis may fluctuate over time (from pseudomembranous to erythematous and back to pseudomembranous).[17,23] In a recent study, erythematous candidosis was found to occur more commonly

than pseudomembranous, particularly in children with advanced disease,[17] but this has not been confirmed by others.[16] *Candida albicans* is the usual pathogen causing oral candidosis, but other strains can occasionally be isolated (*C. parapsilosis, C. pseudotropicalis, C. guillermondii, C. krausei, C. tuloropsis, C. tropicalis, C. rugosa*).[16,24,25]

Children with HIV infection may also develop severe or persistent candidal diaper dermatitis, with widespread papules and pustules, and may also have involvement of the intertriginous areas such as the neck folds and the axillae.[22,26] Occasionally, granulomatous lesions may occur.[26] Chronic candidal paronychia seems to present more commonly between the ages of 2 and 6 years and is sometimes associated with severe nail dystrophy.[26]

Oral candidosis is often difficult to eradicate, as recurrences are high once treatment is discontinued.[25,27] The goal of therapy is not only the cure but also the prevention of the dissemination of disease to the esophagus. Maintenance of good oral hygiene and prevention of xerostomia are important. Nystatin oral pastilles and clotrimazole oral troches clear the infection effectively.[12,18,23,25,28,29] The usual duration of treatment is 14 days. For refractory cases or those with severe involvement, treatment with ketoconazole or fluconazole in a single daily dose of 3–6 mg/kg is effective.[25,27] A higher dosage is significantly more effective in eradicating the organism.[24] The cure rate of fluconazole is reported to be about 90%,[24,25,27] but the rate of eradication of the organism ranges between 76% and 82%.[24,25] Itraconazole offers an alternative option.[18] Another concern is the emergence of resistant organisms, which largely involves non-*albicans* species.[12,17,23,24] Spreading of the disease to the esophagus requires systemic treatment with fluconazole, ketoconazole, or amphotericin B. Prophylactic or maintenance therapy may be indicated in children who have had esophageal candidosis and two or more episodes of oral candidosis. Nystatin oral suspension given twice daily[18] and fluconazole given daily or weekly seem effective.[12,18,23] Hepatotoxicity can be a concern with the azole group, especially with ketoconazole.

Dermatophytoses

Infection by dermatophytes occurs with an increased frequency and aggressiveness in HIV-infected patients, and many children with HIV infection may develop atypical forms of dermatophytoses. Don et al[30] studied the mucocutaneous fungal colonization in HIV-infected children and concluded that the rates of yeast and mold colonization were the same for 13 HIV and 12 control children. Interestingly a case of widespread mucocutaneous colonization of *T. beigelii*, the cause of white piedra, was observed in an HIV-infected child in their series of patients.

Tinea corporis, tinea capitis, tinea faciale, and onychomycosis are particularly common.[11,31,32] Tinea corporis lesions usually are erythematous, scaly, and pruritic plaques, but atypical presentations like flat-topped, discrete papules may also occur.[33] *T. rubrum* is a particularly common isolate,[10] and *T. tonsurans* can give rise to unusual clinical features. Cases of severe and recurrent tinea capitis have been observed.[22] Onychomycosis in HIV-infected patients has some unusual features, which are rare in immunocompetent individuals. 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.[34]

Dermatophytic infections are particularly resistant to topical agents, and recurrences after topical and systemic therapy are common.[32] Oral griseofulvin may prove to be effective,[11,28] and other antifungals such as fluconazole, itraconazole, or terbinafine may be useful. Onychomycosis responds poorly to treatment. Fluconazole and itraconazole are reasonable therapeutic options, but for severely ill patients, keeping the nails short and using topical broad-spectrum antifungal solutions may be more appropriate.[34]

Deep Fungal Infections

In patients with profound immunodeficiency, a myriad possible opportunistic fungal infections are possible. *Histoplasma capsulatum, Coccidiodes immitis, Aspergillus fumigatus, Malassezia furfur, Sporothrix schenckii*, and others can cause opportunistic infections in HIV-infected adults[19] but are rarely observed in HIV-infected children.[31] Cryptococcosis, sporotrichosis, and histoplasmosis may occur in either localized or disseminated forms. Papules, nodules, plaques, ulcers, or abscesses may occur.[35] Disseminated sporotrichosis with painful ulcers has been described in children.[36]

Cutaneous lesions indicate systemic involvement, so administration of a single agent or multidrug systemic chemotherapy with amphotericin B, flucytosine, fluconazole, or itraconazole is the appropriate treatment.[37]

Penicillium marneffei is a dimorphic fungus that is endemic in southeast Asian countries and China. It has been suggested that *P. marneffei* infection should be regarded as another AIDS-defining illness. Sirisanthana et al[38] reported a series of 21 HIV-infected children with disseminated *P. 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, which is made by isolation of the organism from blood and skin specimens. Other findings included generalized lymphadenopathy, fever, hepatosplenomegaly, severe anemia, and thrombocytopenia. The disease occurs late in the course of HIV infection and is fatal unless treated with

antifungals (amphotericin B, fluconazole, or ketoconazole).

Bacterial Infections

An increased susceptibility to bacterial infections has been documented in children suffering from HIV. The bacterial infections encountered are similar to those seen in immunologically normal pediatric patients.[19] Generally, children manifest recurrent bacterial infections rather than primary opportunistic ones as seen in adults.[21] Clinical syndromes include bacteremia, urinary tract infection, pneumonia, and skin or soft tissue infections, by frequency of their occurrence.[19] The most common isolates are *Streptococcus pneumoniae*, *Haemophilus influenza* type B, and *Salmonella* species,[21,31] although different bacterial pathogens are being recognized lately. 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.[10,19,31,33,39] A case of staphylococcal scalded skin syndrome in a child with AIDS has also been reported.[26] Pyomyositis has been described in a child with AIDS.[40] The initial sites of colonization with *S. aureus* before infection are the nares.[37] Several studies have demonstrated a nasal carriage at approximately 50% of HIV-positive homosexual men at all stages of HIV disease, twice the rate of controls.[37,41,42]

Gram-negative infections can be quite troublesome. Prose[22] observed severe periorbital infection in a child with AIDS. This form of infection requires rapid intervention with intravenous antimicrobiols to prevent meningitis or sepsis.

Pseudomonas bacteremia can produce cutaneous manifestations, including ecthyma gangrenosum and a papular rash that appear uncommonly in non-HIV–infected patients.[43] Otitis externa due to *Pseudomonas* has also been reported.[10]

For the initial presentation of common superficial infections, a Gram stain of purulent material is adequate, and empirical therapy against both streptococci and staphylococci is usually effective.[28,37] For deeper and recurrent infections, culture and susceptibility testing of material obtained from the skin lesions is recommended.[37] Culture of material from the nares is also useful to assess the possibility of chronic carriage.

The treatment will depend on the clinical presentation. Any toxic-appearing child should be admitted for intravenous antibiotic therapy.[21] For those who appear well, oral antibiotics and close follow-up are acceptable. The duration of therapy may exceed that required for HIV-seronegative patients. For recurrent infections, long-term application of mupirocin ointment in the nares may prevent recurrent nasal colonization.[37] The use of antiseptic soaps must be cautious because they can cause skin dryness and irritation.

To prevent serious and recurrent bacterial infections, the use of immune intravenous globulin has been recommended.[44] In their survey, Hachem et al[11] attributed the low prevalence of bacterial infections to the preventive therapy with intravenous immune globulin and cotrimoxazole prophylaxis for *Pneumocystis carinii* pneumonia.

Bacillary Angiomatosis

Bacillary angiomatosis (BA), a cutaneous infection caused by *Bartonella henselae* and *B. quintana*, was originally described in adults with HIV infection. The lesions of BA begin as small, erythematous, vascular papules that may enlarge to form exophytic, friable nodules surrounded by a collarette of scale with or without erythema.[37] Subcutaneous and eruptive lesions of BA may also occur.[37] The disease can affect virtually every organ system, including the liver and spleen, and may be accompanied by fever and weight loss. Although the disease has been described in immunocompetent children,[45,46] it is rarely seen in HIV-infected children. BA presenting with abdominal visceral granulomas in a child with HIV infection has been reported.[47] The case of an HIV-infected child has been reported, with a vascular nodule on the scalp and red papules on the right arm and back, who eventually proved to suffer from BA and was successfully treated with erythromycin.[48] The reason for the rarity of BA in children is not known. Previous exposure to the bacillus might be necessary to initiate the reaction. Pediatric HIV-positive patients are unlikely to have past exposure to the bacillus and may also have a different susceptibility profile.[46]

The disease needs to be differentiated from Kaposi sarcoma, and the diagnosis is made histologically. Electron microscopy, culture, polymerase chain reaction, and serological testing may prove helpful to the diagnosis.[37] In general, patients with cutaneous disease without visceral involvement or bacteremia respond well to 8–12 days of therapy with erythromycin or doxycycline.[37] BA is resistant to penicillin and cephalosporins.

Mycobacterial Infections

HIV-infected children are at increased risk of tuberculosis (TB), not only because of their failing immunity but also because many of them are living with HIV-infected adults, who are infected with *Mycobacterium tuberculosis*.[49] A study of the impact of HIV infection on the development of tuberculosis revealed that children with TB were significantly more likely to be HIV-seropositive, but none of the children in the study had cutaneous involvement.[50]

Nontuberculous mycobacterial infection, particu-

larly with *M. avium* intracellulare complex (MAC), is less common in children than in adults, occurs in 6–14% of infected children overall, and more commonly affects transfusion-associated AIDS cases.[5] Children with late-stage disease and CD4+ counts <100 mm^3 are particularly affected. MAC can involve any organ system; however, the skin is rarely the site of extrapulmonary mycobacterial infection.[5,31] Cutaneous abscesses, macular lesions, and perianal ulcerations have been reported in HIV-infected adults[35] but may also occur in pediatric cases.[36] Chemoprophylaxis may be warranted for MAC.[5]

In the United States and in areas with a low prevalence of TB, BCG is not recommended. In developing countries, however, where the prevalence is high, the WHO recommends that BCG should be given to all asymptomatic infants at birth, regardless of maternal HIV infection.[44] Severe complications appear to be rare, justifying continued vaccine use.

Viral Infections

Varicella Zoster Virus (VZV) Infection

VZV infection, which is usually self-limited in immunocompetent children, can be very problematic for HIV-infected children. Typical varicella may occur at any stage of HIV disease. The typical vesicular eruption may be observed, but more profuse or atypical ulcerative forms, hemorrhagic, poxlike, or disseminated ecthymatous are also possible.[51,52] Varicella runs a milder course in HIV-infected children with relatively normal CD4+ counts than that observed in leukemic children.[53] and does not seem to precede any clinical deterioration. Nevertheless, complications may occur, like hepatitis, pulmonary involvement, disseminated intravascular coagulation,[51] superinfection of the skin, or thrombocytopenia.[54] Kelley et al[55] did not observe any complicated VZV infections among 13 HIV-infected children, but this can be attributed to their almost-normal CD4+ counts and the early administration of VZV immune globulin and acyclovir. Varicella may run a prolonged course (>10 days) in HIV-infected children,[54] and persistent and recurrent infections are particularly problematic. In a retrospective study of 421 HIV-infected patients (including adults and children), 15 had varicella and one patient experienced three relapses of atypical varicella.[51] Von Seidlein et al[56] documented an association between increasing numbers of episodes of VZV infection and a low CD4+ count at the time of primary infection. It is of note that 53% of 73 HIV-infected children enrolled in the study had one or more recurrences of VZV infection (either zoster or recurrent varicella), 45% had a recurrence in 24 months, and 10 of 73 children had a persistent infection for 2–24 months.

Chronic VZV infection is a well-documented condition seen almost exclusively in HIV-infected individuals. Patients develop disseminated ulcerative and hyperkeratotic nodular lesions that persist.[5,26,57–60] Deaths from central nervous system involvement have been reported with this form of infection.[36,59] Except for chronic infection, inadequate acyclovir therapy or coinfection may result in hyperkeratotic VZV lesions.[61] The failure of the lesions to heal may signal the development of a strain of VZV that is resistant to acyclovir.[57]

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 may be observed.[61] The skin lesions tend to be deeper, more extensive, and more painful than in the immunocompetent child.[26] There is a significant incidence of scarring, and there may be a very brief interval between an episode of chickenpox and reactivation in the form of HZ.[62] Von Seidlein et al[56] documented that the presentation of zoster as the first recurrence of VZV infection is associated with low CD4+ counts. In the study of Gershon et al,[53] HZ developed in 70% of HIV-infected children with low levels of CD4+ counts at the time of the development of varicella.

The diagnosis of VZV infection can be confirmed by examination of a Tzanck smear and a viral culture of vesicular fluid.

In an effort to prevent severe varicella, the administration of VZ immune globulin has been recommended for use after chicken pox exposure.[55] In view of the potentially higher risk for severe chicken pox in HIV-infected children, intravenous acyclovir is given (1500 mg/m^2/d divided in three doses), although oral acyclovir at a dose of 900 mg/m^2/dose every 6 hours may be used in less severe cases.[28,63] For acyclovir-resistant strains which lack thymidine kinase, foscarnet may be effective, even temporarily.[57]

Immunization against VZV with live attenuated vaccine is unlikely to be deleterious. If immunization is offered when CD4+ levels are still normal, there may be a lower rate of reactivation of VZV.[53]

Herpes Simplex Virus Infection

Herpes simplex virus (HSV) infection is common in immunologically normal children, with rapid and usually uneventful recovery. HIV-infected children, however, can develop severe, chronic, and recurrent HSV disease.[19,29] In one study, as many as 21% of 85 HIV-infected children suffered from HSV infection,[11] and in another study, 120 episodes of HSV stomatitis lasting >2 months were observed in a group of 158 HIV-infected children.[12] Recurrent HSV stomatitis in children is indicative of moderately symptomatic disease in the revised classification system of the CDC for HIV infection. HSV infection correlates primarily with CD4+ cell counts. When CD4+ cell counts exceed 400 cells/mm^3, only 13% of ulcerative lesions are HSV as-

sociated, whereas when CD4+ counts are <50 cells/mm^3, then 58% of all ulcerations contain HSV.[7,64]

The most common feature of HSV in pediatric HIV infection is herpetic gingivostomatitis,[65] with painful, recurrent, or chronic ulcerations of the lips, tongue, palate, and buccal mucosa,[26] that interfere with oral intake and cause significant morbidity requiring hospitalization.[33] Recurrences are common and disfiguring and may result in persistent erosions that involve both the vermilion border and the intraoral mucosa and resemble primary infection.[10,29] Autoinoculation of HSV from the chin to the fingers resulting in herpetic whitlow has also been reported.[33] Prose[26] has observed several cases of herpetic whitlow in children with AIDS. Herpetic whitlow may be progressive, recalcitrant to treatment, and ulcerative and may scar the nail apparatus.[34] Lesions of HSV may appear at other locations such as the soles and the perianal area.[31] HSV can also spread from the oral mucosa to the esophagus, but cutaneous and visceral disseminations usually are rare.[19] In cutaneous dissemination, widespread hemorrhagic vesicles and bullae may develop.

After Tzanck smears and viral cultures have been obtained for the confirmation of the diagnosis, therapy must be instituted. Acyclovir either orally for mild mucocutaneous disease or intravenously for moderate or severe involvement is usually effective.[12,21,22,28,29,31,33] Patients with frequent or severe recurrences can be given acyclovir daily for prophylaxis.[12,19] Acyclovir resistance has been observed in children[33] and in adults.[12] It is attributed to viral deficiency of thymidine kinase and usually presents if acyclovir has not been instituted until the ulcer is large.[65] Foscarnet is used for the treatment of acyclovir-resistant infections.[12,29] Once lesions due to acyclovir-resistant HSV have healed with foscarnet, then acyclovir suppression may be reinstituted, since thymidine kinase–resistant strains have limited capacity for ganglionic latency.[65] Unfortunately, clinically significant foscarnet-resistant HSV infections may occur.[66] Such infections can be treated with the addition of acyclovir to foscarnet or with a 6-week continuous infusion of parenteral acyclovir.[66]

Human Papilloma Virus Infection

Infection with human papilloma virus may cause a number of cutaneous manifestations in a child with HIV-related illness, like verruca vulgaris, widespread flat warts, and condylomata acuminata. Warts can be single but usually are multiple.[11,22,31]

Multiple hemorrhagic verrucae involving the torso and the extremities with resistance to cryotherapy have been described in a child with HIV infection.[10] The case of a 10-year-old HIV-infected boy has been reported with widespread flat warts and tinea versicolor-like lesions.[67] Human papilloma virus-3 was identified within his cutaneous lesions.

Extensive anogenital warts, very resistant to treatment, have also been observed.[68,69] Sexual abuse might be suspected in children with condylomata acuminata, but this is not always the case. An 18-month-old girl with AIDS who presented with condylomata acuminata had no history of sexual abuse. Topical therapy did not offer any help, but there was spontaneous regression when she reached 22 months of age.[33]

Ordinary warts can be treated with the daily application of a salicylic acid preparation.[28] Hachem et al[11] successfully tried curettage under general anesthesia for widespread flat warts covering almost the entire skin surface. For condylomata acuminata, 20% podophyllin resin can be tried first, but for large lesions, surgical excision might be considered.[28] Another option is intralesional interferon-alfa.[68]

Molluscum Contagiosum

Molluscum contagiosum (MC) is caused by a DNA poxvirus and has been reported with increased frequency in HIV-infected individuals, its incidence ranging between 5% and 18%.[70] An Australian survey revealed positive antibody responses for MC virus in 91% of those with coexistent MCV and HIV infection.[71]

MC in healthy hosts presents with multiple, pearly white, dome-shaped, umbilicated papules, 1–4 mm each, sparing the mouth, palms, and soles. Spontaneous resolution can be expected in 3–12 months. In children with HIV infection, these lesions often involve atypical areas, such as the face and neck[11,33] and tend to be more confluent and occasionally extremely numerous[11,26,36] In addition, giant lesions may occur.[11,26,36] Lim et al[10] noted that unusual features may occur without severe CD4+ cell depletion, but others documented a negative correlation between CD4+ counts and the number of MC lesions.[37,71] Molluscum dermatitis, a localized eczematous reaction around MC lesions, represents a delayed hypersensitivity reaction to viral antigens but has not been reported yet in HIV-infected patients.[73]

It is important to document the viral inclusions in the central core of MC lesions because cryptococcosis and histoplasmosis may mimic closely those lesions.[74]

In contrast to the usual course in healthy children, molluscum lesions in HIV-infected patients tend to persist and are extremely recalcitrant to conventional therapies. Local destruction (with cryotherapy, curettage, or 50% trichloroacetic acid (TCA) may be attempted.[37,73] A combination of cryotherapy or 50% TCA and 0.025% tretinoin cream can give good results.[73] Lesions have been noted to clear after the initiation of zidovudine treatment.[22] Resolution of MC lesions with intravenous and topical cidofovir (as a 3% cream in a combination vehicle) has been reported.[70] Generally, MC lesions tend to recur, regardless of the treatment used.

Other Viral Infections

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% in Africa.[1] 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.[75]

Cytomegalovirus (CMV) Infection

CMV infection in HIV-infected children may manifest as interstitial pneumonia, encephalitis, myelitis, hepatitis, gastritis, colitis, and/or chorioretinitis.[19] In AIDS patients, the most common lesions reported to contain CMV have been ulcerations of the orofacial or perineal area.[65] In these reports, HSV has frequently been present as well.[65] Cutaneous CMV infection has been reported in an infant with HIV infection. The infant suffered from a pustular and vesicular diaper dermatitis. CMV infection was documented by biopsy and culture of skin lesions.[76] Hachem et al[11] observed ulcerative lesions on an HIV-infected child's arms and legs. CMV infection was confirmed by biopsy. Ganciclovir and foscarnet have in vivo and in vitro activity against CMV.[19]

Epstein-Barr Virus Infection

Oral hairy leukoplakia, which is related to the Epstein-Barr virus and is 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.[11,17,29,76–79] Oral hairy leukoplakia may resolve with acyclovir treatment.[17,29]

Infestations

Scabies

The manifestations of scabies infestation depend on the host's ability to perceive the infestation and scratch the affected sites. Independently of CD4+ counts, most patients have scabetic burrows at characteristic sites, such as the wrists and finger web spaces.[37] Patients with CD4+ counts <150 cells/mm^3 may present with crusted Norwegian scabies.[10,26,37] Scaly, fissured, crusted, erythematous, hyperkeratotic plaques, mainly on the neck, scalp, buttocks, flexures, palms, soles, and web spaces, are present.[31] Atopic dermatitis or psoriasis may be misdiagnosed. A 6-month-old HIV-infected infant developed an eczematous dermatitis later diagnosed as crusted scabies.[80] Prose[26] observed two infants with hundreds of vesicular and crusted papules on the entire skin surface in response to infestation by the scabies mite. Similar cases with extensive vesicular lesions have been reported by others.[11] In Norwegian scabies, the nail bed and plate may be hypertrophic and loaded with mites.[34] Scabies can be diagnosed with the identification of mites, ova, or feces from the skin lesions.

The infestation might be particularly resistant to treatment. Permethrin 5% lotion should be tried first. For resistant cases, gamma benzene hexachloride and ivermectin orally at a single dose are options to be considered.

Pediculosis and Demodicosis

Pediculosis is particularly common, especially in children with low socioeconomic status.[11]

Papular lesions on the face of two HIV-infected children in relation to *Demodex* mites have been described.[81,82] The main defense against *Demodex* mites are the CD4+ cells, which are defective in HIV infection.

Protozoal Infections

Acanthamoeba infection in HIV status has been described in adults.[83] In children it is rare. The case of an 8-year-old child with advanced AIDS has been reported, who developed tender, firm, pink subcutaneous nodules rapidly progressing to deep ulcers.[83] The child had also sinus involvement, and the infection was confirmed by histology. Empirical therapy with ketoconazole and sulfadiazine only temporarily stabilized the progression of the child's amebic infection, which eventually became generalized.

Neoplastic Disorders

Kaposi Sarcoma (KS)

KS is the most common HIV-related cancer in adults and is more prevalent in homosexual men. The disease is rare in children in the Western world. Overall, 33 children from Europe and the United States and 49 adolescents (18 from Europe and 31 from the United States) had KS at the time of AIDS diagnosis.[84,85] The proportion of cases with KS significantly increases with age, 1.7 years being the average.[84,85] The disease has been described in a 6-day-old HIV-infected infant.[86] Among 17 children who acquired HIV infection perinatally, only two developed KS lesions, whereas nine of 13 children who acquired the infection postnatally had cutaneous KS.[84] This observation has led to the hypothesis that different routes of HIV infection may be associated with different KS clinical manifestations.

Recently, human herpesvirus-8 (HHV-8) has been identified as the cause of KS. A study conducted in Uganda revealed a higher socioeconomic status among KS-infected individuals, which suggests an enhanced exposure to a possibly sexually transmitted agent or a delayed exposure to a childhood infection.[87] Water as a possible source of HHV-8 transmission is implicated.[87] Prior infection with Epstein-Barr virus may cross-protect against de novo HHV-8 infection or reactivation.

KS in children points to a nonsexual mode of transmission. HHV-8 can be acquired as a common childhood infection[88] and may possibly be horizontally transmitted from mother to child[89] during birth or breastfeeding.[14] 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.[89] Vertical transmission of KS from an HIV-seropositive mother to her child has been reported.[90]

Before the HIV epidemic, KS was already endemic in Uganda, Zimbabwe, and Zambia, most commonly in older men. Childhood KS was rare. With the advent of the HIV epidemic in these countries, KS has become more common in children.[14,89,91] In Zambia, a 10-fold increase in the incidence has been noted,[89] and in Uganda, a 40-fold increase has been observed. In other countries, however, no obvious increase has been observed.[92]

There is a male preponderance for childhood HIV-related KS, and the median age of presentation is 4 years.[14] 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.[14] Cutaneous lesions range from solitary nodules to widely disseminated plaques or nodules.[14]

Single or combination chemotherapy is the usual therapeutic approach, although it may worsen the underlying immunodeficiency. Systemic interferon-alpha has been used with variable success rates.[93]

Non-Hodgkin Lymphoma (NHL)

NHL turns out to be more common in children and adolescents with AIDS. The proportion of children with NHL at the time of AIDS diagnosis was higher in the United States (0.5%) than in Europe (0.9%). The frequency of this neoplasm tends to increase significantly with age and is more common in boys than in girls.[85] An important role for Epstein-Barr virus has been suggested, and all children have low CD4+ counts at the time of diagnosis.[94] In a British study, seven cases of NHL were identified among 302 HIV-infected children, and two of them had NHL involving the tonsil and soft palate.[94] Chemotherapy is the treatment of choice.

Inflammatory Dermatoses

Seborrheic Dermatitis (SD)

Seborrheic dermatitis (SD) is possibly one of the most common cutaneous manifestations of HIV disease, its incidence ranging from 32–83%.[95] An association if not a causative role for *Pityrosporum* has been suggested.[96] In children with HIV infection, SD seems to occur with increased frequency,[10] although in some series the usual incidence is observed.[11] Its severity has been correlated with the degree of HIV-related immunodeficiency and the CD4+ cell count.[10,21] In infants, the disorder may take the form of severe erythema and scaling of the face, scalp, and diaper area, sometimes progressing to erythroderma.[22,36] Nonscarring alopecia may be one of the sequelae. Older children (between the ages of 2 and 5) may develop the adult form of SB, with a thick, scaly eruption on the nasolabial folds, retroauricular areas, axillae, and scalp, which is unique for HIV infection.[26]

Hydrocortisone cream and 1% or 2% ketoconazole shampoo are the best available treatments.

Atopic Dermatitis

Parkin et al[97] documented the association of atopic manifestations with established AIDS. Atopic dermatitis appears to be triggered by HIV seroconversion in genetically predisposed individuals. A shift to the Th2 profile of cytokine production after HIV infection would theoretically support the increased IgE levels and allergic symptoms commonly seen in HIV-infected patients.[98] In a recent survey, increased serum immunoglobulin E levels were observed in HIV-infected children, just as in adults; however, the elevated serum immunoglobulin E level did not correlate with allergic disease nor with the degree of immune dysfunction.[98] In certain series, atopic dermatitis does not seem to be more frequent in seropositive children than in the healthy population.[11] In other studies, acquired ichthyosis and xerosis, occasionally resulting in prurigo nodularis, have been noted in this particular pediatric setting.[10]

A British national survey revealed an increased incidence of atopic dermatitis in seropositive hemophiliac children.[99] Atopic dermatitis in those children either occurred for the first time after seroconversion or recurred with increased severity.

Several HIV-infected children, without any history of atopy, develop a severe and generalized eczematous eruption combined with growth retardation and diarrhea.[26] This syndrome, previously termed Leiner' s disease, may be caused by several immunological defects, and HIV infection may be an additional cause.[26]

Children with HIV infection and atopic dermatitis are at particular risk for secondary bacterial infections and Kaposi's varicelliform eruption. Topical steroids, lubrication, and antibiotics against *S. aureus* are the mainstays of treatment.[31] Adult patients with HIV-related atopic dermatitis have responded to therapy with interferon-gamma.[97]

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.[100] Both plaque and guttate psoriasis in children and adolescents with HIV infection have been observed[11,22] AIDS-related psoriasis may respond to oral zidovudine and antiretroviral treatment.[101]

Urticaria

Both cold and idiopathic urticaria have been observed in pediatric HIV-infected patients,[33] but its relation to HIV infection remains unknown.

Drug Eruptions

Patients with HIV disease are particularly prone to hypersensitivity drug eruptions. Hachem et al[11] reported an incidence of 12% of drug-related rashes among 85 HIV-infected children, whereas Straka et al[33] noted that 16% of 50 children with AIDS developed a hypersensitivity-like eruption to trimethoprim-sulfamethoxazole. Trimethoprim-sulfamethoxazole prophylaxis for *Pneumocystis carinii* pneumonia is frequently complicated by morbilliform skin eruptions appearing 8–10 days after initiation of therapy and resolving quickly after discontinuation of the drug. Dusky erythematous macules,[102] Stevens-Johnson syndrome,[22] and toxic epidermal necrolysis[26] may also occur. Ampicillin and antituberculous medication are other agents frequently implicated in drug eruptions.[31]

Discontinuation of the offending medication is mandatory. Substitution of trimethoprim-sulfamethoxazole with aerosolized or intravenous pentamidine for *Pneumocystis carinii* pneumonia prophylaxis is possible.[33]

Vasculitis

Leukocytoclastic vasculitis may develop as a result of drug reaction, concomitant infection, or HIV infection itself. Chren et al[103] reported a 9-year-old girl with persistent, palpable purpura of the lower extremities as the sole manifestation of HIV infection. A 3-year-old HIV-infected girl developed palpable purpura complicated with nephropathy.[26] Three children with vasculitic lesions resembling cutis marmorata have also been reported.[104]

Thrombocytopenia of immunological origin with high levels of circulating immune complexes and antiplatelet antibodies can manifest as petechiae or easy bruising and may lead to life-threatening bleeding.[10,105] Parenteral gamma globulin or oral prednisone may be of benefit.[105]

Aphthous Ulcers

Several forms of recurrent aphthous ulcers are observed in HIV-infected patients. Minor, major, and herpetiform aphthae may occur. At Baylor College of Medicine, 22 episodes of aphthous stomatitis were observed in symptomatic children with HIV infection and only one episode in asymptomatic ones from 1990–1994.[12] This indicates that aphthous ulcerations are a manifestation of moderate to severe disease.

Before making the diagnosis of aphthous ulceration, one has to consider other infectious or iatrogenic causes. Prolonged granulocytopenia induced by myelosuppressive medication, as well as dideoxycytidine and foscarnet therapy, can all be the causes of oral ulcers.

One suggested regimen for severe, painful aphthous ulcers is the administration of a topical glycocorticoid solution, but it is imperative to exclude viral causes first.[19]

Nutritional Deficiencies

Oral pathology, anorexia, malabsorption, and diarrhea commonly seen in HIV-infected children can lead to severe nutritional deficiencies. Dry, cracked, and flaky skin and thinning of the hair similar to kwashiorkor can be observed.[11,26] Pellagralike eruptions have been reported.[106] A follicular petechial rash on the legs of an HIV-infected child and bleeding of the gums were suggestive of scurvy.[33]

Straka et al[33] observed zinc levels at least 1 standard deviation below normal in two thirds of pediatric HIV patients. Acrodermatitis enteropathica has been reported in a 14-month-old seropositive child as a presenting sign of HIV infection.[107]

Multiple nutritional deficiencies may occur, so prompt nutritional supplementation is mandatory. It is interesting that vitamin A supplementation has been shown to decrease by 30% the overall mortality of HIV-infected infants in developing countries.[1]

Miscellaneous Conditions

Alopecia due to severe SD,[10] nutritional deficiency, or unknown causes may be observed in the HIV-infected pediatric population.[10,11] Hypertrichosis of the eyelashes necessitating frequent trimming has been reported in both adults and children with HIV infection.[108,109] Hypertrichosis of the lanugo type in an infant with HIV-related KS has also been noted.[86]

An exanthematous eruption associated with the flulike syndrome of primary HIV infection has been documented in adults.[26] A similar rash has been reported in a 14-month-old girl from Switzerland[33] and in a 10-year-old girl.[110] In a series of 82 HIV-infected children from Uganda, 33% developed a primary HIV rash.[14]

Sweet syndrome has been reported as the presenting manifestation of HIV infection in a 3-month-old infant.[111] Pyoderma gangrenosum on the left preauricular area and right eyelid has been noted in a child with HIV infection.[112] Gianotti-Crosti syndrome has been ob-

served in two children with concomitant HIV and CMV infection.[110]

Other skin disorders like vitiligo,[36] erythema dyschromicum perstans,[113] and eruptive dysplastic nevi[114] have also occurred, but their relationship to HIV infection is unknown.

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.[115]

Conclusions

Skin diseases may be the presenting sign of HIV infection or may serve as a prognostic marker and an ominous sign of the deterioration of the child's immunodeficiency. It is important to be able to recognize them and treat them effectively, as they can worsen the quality of life of these children and lead to devastating sequelae.

More and more HIV-infected children benefit from the new antiviral treatments and survive longer, but unfortunately, these medications are not available worldwide. AIDS is a complex epidemic. The response to the epidemic is not only best practice but also new practice.

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The current Canadian nickel is made of 100% nickel metal, while the United States nickel is 75% copper and 25% nickel. Using a magnet one can show the difference in metal content. Magnets are weakly attracted to nickel, the Canadian coin being 100% nickel is attracted to a strong magnet while the United States nickel being only 25% nickel does not attract a magnet.

From the collection of Raymond T. Kuwahara, MD, Memphis, TN

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