Dermatologic Manifestations of Human Immunodeficiency Virus Infection

MARK J. ZALLA, M.D., W. P. DANIEL SU, M.D., ANTHONY F. FRANSWAY, M.D.,
Department of Dermatology

Human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS) have become major health problems in the United States, and patients with manifestations of these diseases are seen by physicians in all areas of medicine. Cutaneous manifestations develop in as many as 92% of HIV-positive persons. Familiarity with these manifestations facilitates early diagnosis and enhances the care of HIV-infected patients. The spectrum of mucocutaneous disorders in these patients include an acute exanthem, multiple infections, neoplastic processes, and miscellaneous disorders. Herein we review the most common and the most specific dermatologic manifestations associated with HIV infection, which often are atypical, more severe, or less responsive to treatment than the corresponding diseases encountered in non-HIV-infected persons.

In one study, cutaneous manifestations were noted in 92% of HIV-positive persons, and such manifestations may affect almost all patients at some point in the course of their illness. Awareness and recognition of these manifestations may facilitate early diagnosis of HIV infection and enhance patient care. The initial manifestation of mucocutaneous diseases in HIV-infected persons may be typical, but often it will be atypical, more severe, and less responsive to usual treatment regimens than that in non-HIV-infected persons. Herein we review the major dermatologic manifestations of HIV infection and provide representative clinical examples of the most common or specific entities; complete atlas compilations are available for interested readers.

The spectrum of mucocutaneous disorders in HIV-infected persons includes exanthems indicative of acute HIV infection as well as benign and malignant processes encountered in advanced disease. This spectrum can be divided into several major categories: (1) acute exanthems, (2) neoplastic processes, (3) infections, and (4) other (Table 1). Most mucocutaneous disorders manifest in infected persons after the helper T-cell count decreases to less than 100 cells/μl; however, a recent investigation found no significant differences in prevalence or severity of skin disease between asymptomatic patients and those with AIDS-related...
Table 1.—Cutaneous Manifestations Associated With Human Immunodeficiency Virus (HIV) Infection

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*See text for discussion of this manifestation.

Modified from Fisher and Warner. By permission of the International Society of Dermatology: Tropical, Geographic and Ecologic, Inc.
complex (no longer a part of the classification scheme of the Centers for Disease Control) or AIDS.

**ACUTE HIV EXANTHEM**

Primary infection with HIV may lead to sudden onset of an acute retroviral syndrome, which is estimated to occur in a half to two-thirds of infected persons, but symptoms may be minimal and easily misdiagnosed as a nonspecific influenza-like syndrome or infectious mononucleosis. This syndrome can occur 1 to 8 weeks after infection and is self-limited; symptoms and laboratory abnormalities usually subside after 1 to 3 weeks. Symptoms may include fever, sweats, malaise, pharyngitis, myalgia, arthralgia, lymphadenopathy, diarrhea, abnormalities of the central nervous system (headache, photophobia, meningitis, and encephalitis), and an exanthem. Transient leukopenia, thrombocytopenia, and an inverted helper-suppressor ratio of T cells may be found. In 30 to 50% of patients with primary HIV infection, an associated exanthem and enanthema are present—usually a macular or maculopapular eruption on the trunk, face, and upper extremities. Lesions may be maculopapular or roseola-like, scaling and pityriasis rosea-like, or occasionally hemorrhagic or necrotic. Palms and soles may be involved, and the findings resemble secondary syphilis. An enanthema, which varies from erythema to frank ulceration and severe dysphagia, is also usually present.

Most patients with an acute retroviral syndrome have had the presence of HIV antigen (p24 core antigen) confirmed in the serum during the acute phase, and seroconversion to HIV antibody positivity usually occurs within 1 to 2 months after the onset of symptoms.

Although nonspecific exanthems occur in most HIV-infected children, an acute exanthem is infrequently diagnosed in such children, presumably because seroconversion frequently occurs in utero in these patients.

**NEOPLASMS**

In approximately 30 to 40% of patients with AIDS, neoplastic disease develops, and Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma constitute 95% of such disease states. Neoplasms rarely occur in children with AIDS. Kaposi's Sarcoma.—KS, the most common neoplasm that occurs in HIV-infected persons, develops in 11 to 15% of patients diagnosed with AIDS in the United States. Of all cases of AIDS-associated KS (AIDS-KS), 95% have occurred in homosexual men; however, for unclear reasons, the incidence of AIDS-KS has decreased since 1981—from 44% of men with AIDS to less than 20% in 1989. KS is a tumor of endothelial origin. Hypotheses exist about potential roles of coinfection with cytomegalovirus, endothelial growth factors, genetic predisposition of persons with HLA-DR5, some unidentified infectious agent transmitted by sexual contact, and environmental cofactors. Lesions of KS can develop at any time during the course of HIV infection, may be widely distributed, and may have varied morphologic features, from the earliest asymptomatic macular stage to indurated papules, plaques, and nodules (Fig. 1). Lesions vary from several millimeters to several centimeters; are round, oval, or irregular; and are pinkish red to violaceous. They tend to be symmetrically distributed along skin tension lines and often enlarge or coalesce. Common sites include the lower extremities, upper trunk, head and neck, hard palate and oropharyngeal mucosa, and occlusal and periauricular regions. Lesions occur in patients of all ages.

AIDS-KS frequently involves lymph nodes and the gastrointestinal tract, lungs, liver, kidney, and spleen. Although more aggressive than the classic type of KS, AIDS-KS rarely causes death. Indeed, patients with KS as an initial manifestation of HIV infection have a better prognosis than those who have opportunistic infections. Although AIDS-KS is most often asymptomatic, treatment may be warranted for symptomatic or cosmetically troublesome lesions. Local radiotherapy is effective, although such treatment for oral lesions may result in severe mucositis. Liquid nitrogen cryotherapy, electrocautery, excision, and intralesional administration of vincristine sulfate, vinblastine sulfate, bleomycin, or interferon-α are effective alternatives for selected lesions. Systemic chemotherapy may be considered for disseminated or resistant disease, although it provides palliation only and does not influence overall survival. Interferon-α may be the treatment of choice when systemic management is necessary. Chemotherapy may actually further compromise the patient's already impaired immune function. Spontaneous resolution has also occurred.

In children with AIDS, KS rarely develops (5.6%), and those in whom KS develops often do not have skin lesions but, rather, aggressive systemic lesions with a fulminant course. The reason for the rarity of KS in children is uncertain; perhaps it is related to the infrequent coinfection of children with cytomegalovirus in comparison with the 90 to 95% frequency of cytomegalovirus infection in adult patients with AIDS. Similarly, other potentially sexually transmitted cofactors would be less likely in the pediatric than in the adult subpopulation.

Lymphomas.—HIV infection increases the risk for the development of several neoplasms that may affect the skin—in particular, non-Hodgkin’s lymphomas. The incidence is commensurate to that seen in other immunodeficiency states. In general, any HIV-infected patient with indeterminate or suspicious skin lesions or any patient with risk factors for HIV infection should undergo biopsy for histologic study.
Fig. 1. Kaposi’s sarcoma of nasal tip in patient with human immunodeficiency virus infection. Note similar lesion on left lower aspect of cheek and seborrheic dermatitis on malar areas.

Lymphoma in HIV-infected patients is most often the B-cell type and is associated with an aggressive disease state; it frequently is diagnosed at an advanced stage, extranodal involvement is common, and response to chemotherapy is poor.24 A third of the patients with HIV-associated lymphoma have persistent generalized lymphadenopathy.22.26.29 Non-Hodgkin’s lymphomas, the second most frequent neoplasm in patients with AIDS (4 to 10%),30 tend to be intermediate or high grade, B-cell type.20.24 Frequently diagnosed as advanced disease (stage III or IV), these lymphoproliferative states follow the development of KS or opportunistic infections in two-thirds of the patients. The most frequently affected organs include the central nervous system (40%), bone marrow (33%), gastrointestinal tract (17%), and mucous membranes and skin (15%).22.20 Cutaneous lesions are usually papules and nodules. Many B-cell lymphomas in HIV-infected patients contain the Epstein-Barr virus genome, which is thought to be an important pathogenic factor.22.24.30 The median survival of patients with AIDS and non-Hodgkin’s lymphoma is as brief as 5 months; death is often attributed to infection.22.29 Thus, less intensive chemotherapy, immunomodulators, or antiretroviral agents may result in a superior outcome in comparison with aggressive intervention.20

Hodgkin’s disease in HIV-infected persons has a similarly aggressive course; the median survival is 14 months. Death is frequently due to intercurrent opportunistic infection. Skin involvement and noncontiguous spread of the disease are more common in HIV-infected than in noninfected patients.31 Other B-cell malignant processes, including chronic lymphocytic leukemia and multiple myeloma, have been reported in HIV-infected patients,29 as have systemic B-cell lymphoma, primary B-cell lymphoma of the brain, and Burkitt-like lymphoma.26.27 Mycosis fungoides, a cutaneous T-cell lymphoma, has occurred in several patients with HIV infection;27 however, it is encountered more frequently in association with infection by the related retrovirus human T-cell lymphotropic virus type I (implicated as the agent that causes the adult T-cell lymphoma-leukemia syndrome).10.26 Lymphomas in HIV-infected children are extremely rare.28

Carcinomas.—Epithelial malignant and premalignant neoplasms, including actinic keratosis, squamous cell carcinoma, Bowenoid papulosis, keratoacanthoma, basal cell carcinoma, and cloacogenic carcinoma, have been observed in a wide variety of immunosuppressed patients. Lesions are often multiple, and premalignant lesions may progress rapidly to cancers.26,30 Although HIV infection has not been shown to increase the incidence of such neoplasms, they may exhibit aggressive growth behavior and occasionally manifest atypically.30 The appropriate management of any epithelial carcinoma in an HIV-infected patient is complete excision.30 Squamous cell carcinoma usually manifests as a shallow, nonhealing ulcer or erosion that is surrounded by a wide, elevated, indurated border. In HIV-infected patients, the incidence of squamous cell carcinoma is disproportionately high in comparison with basal cell carcinoma. An increased incidence of squamous cell carcinoma of the anus and oral mucosa is found in immunodeficient homosexuals, although the relationship to the immunodeficient state is uncertain.10.22.26.32 Human papillomavirus genotypes 16, 18, and 33 are strongly associated with the development of anogenital carcinomas.

Bowenoid papulosis, a papular eruption that resembles genital warts clinically but has histologic features of squamous cell carcinoma in situ, has been associated with multiple human papillomavirus genotypes, especially genotype 16. Lesions may regress spontaneously, but they have developed into frank squamous cell carcinoma in several HIV-infected patients.27.33.34 Cloacogenic carcinomas of the anorectum have been identified in homosexual men, whether HIV positive or not, who engage in receptive rectal intercourse and have been associated with an increased incidence of condyloma acuminatum in comparison with that in patients who have other colorectal malignant lesions (Fig. 2). This neoplasm arises from transitional zone mucosa of the anal canal. Patients usually experience rectal bleeding, pain, constipation, or, occasionally, perianal erythema or induration. The neoplasm is highly associated with human papillomavirus genotypes 16, 18, and 33.29 Cervical intraepithelial neoplasms have also been found in HIV-infected patients in association with condylomas.29 Basal cell carcinomas are usually small, pearly bordered papules or nodules with telangiectatic vessels and a tendency toward slow enlargement with central ulceration. These
common skin cancers have been detected in patients with AIDS and have even metastasized on rare occasions.10,27,29

Malignant Melanoma.—Whether the incidence of malignant melanoma is increased in HIV-infected patients is unclear, but melanomas, including multiple primary tumors, have been reported in such patients.27,35,36 At the time of diagnosis, these tumors tend to be thicker (mean, 2.61-mm depth of invasion)37 and to have less inflammatory cell response than do malignant melanomas in non-HIV-infected patients; both features suggest a poor prognosis. Metastatic involvement is common.27,30,37,38 Investigators have also described a syndrome of eruptive dysplastic nevi, in which multiple new moles with dysplastic features, clinically and histologically, erupt in patients with no prior history of dysplastic nevi and no family history of melanoma.39 These progressive nevi tend to develop with the onset of HIV-related symptoms; thus, obtaining biopsy specimens in HIV-infected persons is important.

INFECTIONS
Infections are the largest category of dermatologic manifestations of HIV infection, especially in affected children. They are nondiagnostic but, in some cases, highly suggestive of HIV infection and may be premonitory signs for the development of AIDS. The manifestation of even common infections in immunosuppressed patients may be atypical; responsible microorganisms are more resistant to therapy than in normal control subjects.

Viral Infections.—The most common viruses that cause skin lesions in HIV-infected patients are herpes simplex virus, varicella-zoster virus, Epstein-Barr virus, molluscum contagiosum virus, human papillomavirus, and cytomegalovirus.

Herpes Simplex Virus.—The incidence of herpes simplex virus infection in HIV-positive patients is increased throughout the course of the disease, particularly after helper T-cell counts decrease to less than 100 cells/μl; the prevalence has been estimated to be as high as 27%.40 In most studies, the incidence is 3 to 6%, and herpes simplex virus is the most common viral infection that produces skin lesions in these patients.1,6,41

The initial manifestation varies from grouped vesicles on the lip or elsewhere that resolve without incident to chronic nonhealing ulcers, particularly in labial or perianal regions (Fig. 3).40 Glossal lesions may manifest as vacciniform white or yellow papules with depressed centers;10 primary, recurrent, or nonhealing herpetic gingivostomatitis and dehydration may occur, especially among HIV-infected children, in whom the condition tends to be severe.21 Chronic recalcitrant perianal ulceration in homosexual men represents herpes simplex virus-induced disease until proved otherwise. Herpetic proctitis may occur; it exhibits mild redness and edema but is associated with severe anorectal pain, tenesmus, hematochezia, paresthesias, and urinary retention. Chronic ulceration in other regions, Kaposi’s varicelliform eruption, esophageal and tracheobronchial involvement, and systemic dissemination may all occur. After diagnosis by

Fig. 2. Cloacogenic carcinoma with erythema and erosion around anus in patient with human immunodeficiency virus infection.

Fig. 3. Typical lesions of herpes simplex virus infection, beginning as grouped vesicles on a red base, which then rupture and form crusts as depicted here in patient with human immunodeficiency virus infection.
the Tzanck test (demonstration of multinucleate giant cells), biopsy, or culture, acyclovir therapy should be administered. Prolonged or indefinite treatment may be necessary.\textsuperscript{40} After discontinuation of therapy, recurrences are common, and intravenous administration of acyclovir may be necessary for severe or resistant cases.\textsuperscript{28} Occasionally, patients with recurrent or chronic nonhealing herpes simplex virus-induced lesions have been infected with acyclovir-resistant strains of herpes simplex virus. Foscarnet (phosphonoformate) is reported to be effective in such patients; the efficacy of this drug is superior and the toxicity is less frequent in comparison with vidarabine. The relapse rate after treatment, however, remains high.\textsuperscript{42} Other potential agents for acyclovir-resistant herpes simplex virus include vidarabine, ganciclovir, and interferon-\(\alpha\).\textsuperscript{43,44}

Molecular studies have shown that herpesviruses (and perhaps other chronic B-cell stimulants) may activate HIV gene expression through the production of cytokines such as tumor necrosis factor alpha and interleukin 6 by B cells; this process causes active virus expression by infected latent T cells. Thus, B-cell stimulants, such as herpesviruses, may act as cofactors in promoting the development of AIDS.\textsuperscript{3}

**Varicella-Zoster Virus.**—Varicella-zoster virus infection affects 3 to 4\% of HIV-positive patients and may cause severe primary chickenpox (Fig. 4) as well as dermatomal or generalized herpes zoster, occasionally with systemic involvement. In one study, eruptions of varicella occurred in 3.5\% of HIV-positive patients, and 3 of 15 patients had atypical poxlike lesions of varicella (not zoster), which were due to a reactivation of varicella-zoster virus infection.\textsuperscript{45}

Herpes zoster is often the initial manifestation of immune dysfunction, and it can precede other symptoms by a mean of 1.5 years.\textsuperscript{46} In children, herpes zoster is prone to dissemination.\textsuperscript{21} The usual manifestation is a vesicular, erosive eruption that in HIV-positive patients is characterized by chronicity, multidermatomal distribution, severe pain, and scarring (Fig. 5). Recently, investigators have also described patients with chronic localized or disseminated disease, hyperkeratotic plaques, and confirmed acyclovir resistance, perhaps because of inadequate initial treatment.\textsuperscript{47,48} The frequency of postherpetic neuralgia may be high, and herpes zoster in any young patient with appropriate risk factors may indicate HIV infection (which suggests the need for an enzyme-linked immunosorbent assay and a western blot serologic determination).

In a study of homosexual men with herpes zoster, investigators estimated that, over time, AIDS would develop in approximately 1\% per month\textsuperscript{49} and that the cumulative incidence of AIDS in such men would be 23\% within 2 years after the development of herpes zoster and 46\% within 4 years.\textsuperscript{11,13} Patients with active disease require high-dose orally administered acyclovir, and intravenous treatment is necessary for severe disease.\textsuperscript{13,27} Persistent disease should prompt viral isolation and assessment of viral thymidine kinase activity.\textsuperscript{46-48} HIV-infected patients with primary varicella may also require intravenously administered acyclovir.\textsuperscript{10} In addition, immunoglobulin has been administered intravenously in some cases.\textsuperscript{10,28}

**Epstein-Barr Virus and Oral Hairy Leukoplakia.**—Epstein-Barr virus, another virus in the herpes family, may act as an HIV cofactor by enhancing the growth capabilities of the virus in lymphocytes, and it is associated with the development of lymphoma in HIV-infected persons.\textsuperscript{11} Epstein-Barr virus is also the cause of oral hairy leukoplakia, one of the most specific cutaneous manifestations of HIV infection;\textsuperscript{11} hairy leukoplakia has been noted only rarely in immunosuppressed persons who are not HIV infected.\textsuperscript{50} The exact incidence is uncertain because of frequent confusion with oral candidiasis, but hairy leukoplakia has been identified in all HIV-associated risk groups except infants; it is rare in HIV-infected children.\textsuperscript{21} One study showed a 48\% probability of the development of AIDS within 16 months
and 83% within 31 months of the diagnosis of oral hairy leukoplakia. Leukoplakia usually manifests as asymptomatic, adherent, whitish gray plaques that are localized to the lateral aspects of the tongue and that occasionally involve the buccal mucosa (Fig. 6). Actively replicating Epstein-Barr viruses have been found within these lesions and are believed causative, although papillomaviruses and *Candida* species may be cofactors. The lesion is not premalignant and therefore treatment is not imperative; however, acyclovir, ganciclovir sodium, azidothymidine (AZT, zidovudine), desiccovir, and topically applied tretinoin solution have been associated with temporary regression. Clotrimazole troches, 100 mg daily for several days, may also help. Confirmation of the presence of Epstein-Barr virus should be a criterion for the diagnosis of leukoplakia.

*Molluscum Contagiosum.*—The characteristic lesions of molluscum contagiosum are waxy, flesh-colored, umbilicated papules that are caused by a poxvirus and generally occur in children or in anogenital areas of adults. In HIV-infected patients and those with AIDS, in whom the incidence is 0.4 to 2% and 8 to 15%, respectively, lesions are usually localized to the anogenital area or the face but may be disseminated and may rapidly enlarge or coalesce into large plaques that can ulcerate (Fig. 7). Local destruction and excision have been used, but recurrence is common. Molluscum bodies should be demonstrated in the lesions because disseminated histoplasmosis or *Cryptococcus* in immunosuppressed patients may mimic molluscum contagiosum, in which case fungal stains, fungal serologies, and culture of biopsy specimens are confirmatory.

*Common Warts and Condyloma Acuminatum.*—Multiple common, filiform, and flat warts occur with increased frequency in HIV-infected patients, particularly on the face, neck, hands, and feet; treatment is often ineffective. Anogenital warts occur in up to 40% of HIV-positive homosexual men and in 3 to 6% of all HIV-positive patients, and they may develop into large vegetating lesions that are highly resistant to treatment. These condylomas are also common within the anal canal in this population. Human papillomavirus types 6 and 11 have frequently been associated with anal condylomas and are present in 72 to 94% of lesions; human papillomavirus types 16, 18, 31, and 33 have also been noted. One study found anal intraepithelial neoplasms in conjunction with anal condylomas in about 30% of all patients. Anal intraepithelial neoplasms were found in both HIV-positive and HIV-negative patients in association with human papillomavirus types 6 and 11, in addition to the traditional "high-risk" types 16, 18, 31, and 33. Topical caustic agents or destructive procedures often fail, as may surgical or laser removal.

*Cutaneous Cytomegalovirus.*—Cutaneous cytomegalovirus infection in HIV-positive patients is uncommon but is associated with a poor prognosis, and patients usually have nonhealing perianal ulceration, which does not diminish after acyclovir therapy. Disseminated cutaneous cytomegalovirus infection may manifest as small, elevated, purpuric, reddish papules and macules that often ulcerate; the Tzanck test may be helpful in the diagnosis, and serologic studies and culture should be done to distinguish cytomegalovirus from herpes simplex and varicella-zoster infection. Chronic, latent, systemic cytomegalovirus infection, present in almost all patients with AIDS, has been successfully treated with ganciclovir.

*Bacterial Infections.*—Recurrent or severe chronic bacterial folliculitis, impetigo, and ecthyma may be clues to...
immunosuppression and are common in HIV-positive patients, especially intravenous drug abusers; 50% of symptomatic HIV-infected persons may also be affected. An early pattern is bullous impetigo of the axilla or groin; subsequently, facial or truncal acneiform folliculitis, furunculosis, or ecthyma develops. An uncommon manifestation is a staphylococcal folliculitis that consists of violaceous plaques (up to 10 cm), superficial pustules, and crusts that occur in the groin, axilla, or scalp. *Staphylococcus aureus* groups A, C, and G and *Streptococcus* are the most common causes of folliculitis and furunculosis, but relatively uncommon pathogenic organisms such as *S. epidermidis* or diphtheroids may be involved. These infections may be resistant to treatment; often, prolonged systemic administration of antibiotics is necessary.

Bacterial cellulitis, abscesses, and ulcers are also common, especially in the perianal areas, frequently attributable to *S. aureus*; surgical débridement is necessary in some cases. Pyomyositis or staphylococcal scalded skin syndrome caused by *S. aureus* may also occur.

B-cell immunologic defects have a more prominent role in HIV infection in pediatric patients than in adults; consequently, morbidity and mortality as a result of bacterial infections are higher in this age-group. Investigators have hypothesized that HIV stimulates continuous B-cell activation; subsequently, responsiveness of lymphocytes to specific antigenic stimulation is decreased and therefore antibody response is poor. *S. aureus* is the most common organism that infects the skin of children with AIDS, in the forms of impetigo, cellulitis, or persistent folliculitis; *S. pneumoniae, Haemophilus influenzae* type B, and *Salmonella* cause most outpatient episodes of bacteremia. Several investigators recommended monthly therapy with parenterally administered immunoglobulin, which decreased the incidence of serious bacterial and viral infections in one study group of pediatric patients with AIDS.

**Mycobacteria.**—Mycobacterial infections in HIV-positive patients may manifest as acneiform papules that mimic folliculitis, indurated crusted plaques, abscesses, or swollen matted lymph nodes with overlying erythema. Rarely, ill-defined macules or ecthymatous lesions are noted. Frequent causative organisms include *Mycobacterium avium-intracellulare* and *M. tuberculosis*; rarely, *M. kansasii* and *M. marinum* are incriminated. Disseminated *M. avium-intracellulare* infection is common in patients with advanced HIV infection; however, cutaneous involvement is rare, although patients who have been taking zidovudine have occasionally had only a localized cutaneous disease that responded well to incision and drainage. Active tuberculosis reportedly affects approximately 10% of all patients with AIDS, particularly intravenous drug users, and at least one extrapulmonary site is involved in more than half of these cases. Treatment of mycobacterial infections generally involves combinations of antimycobacterial agents.

**Syphilis.**—Syphilis is common in HIV-infected patients, especially homosexuals, and any stage of syphilis may occur. Syphilitic chancre and other genitoulcerative diseases are risk factors that predispose to HIV infection because of decreased barrier function; syphilis may be the initial manifestation in patients with concurrent HIV positivity. Progression from primary to tertiary syphilis within a few months has been reported, as have recrudescent cutaneous secondary syphilis, neurosyphilis without previously confirmed syphilitic infection, possible syphilitic relapse after bacille Calmette-Guérin vaccination, and recurrent neurosyphilis after administration of standard antibiotic regimens. Secondary syphilis may manifest as a generalized maculopapular eruption with or without scaling; palmoplantar vesicles, papules, or macules; hypopigmented axial macules; and oral erosions. Coexistent lesions of secondary syphilis and tertiary gummas have been described. Precocious tertiary syphilis may also manifest with noduloulcerative lesions and lymphadenopathy. Reservoirs for treponemes have been found in the central nervous system, lymph nodes, aqueous humor, aorta, spinal cord, and liver; all allow possible relapse. Serologic studies may be unreliable because of artifact or true absence of antibody,
although Treponema pallidum may be identifiable in tissue biopsy specimens, which therefore become an important aspect of diagnosis. A patient with HIV infection who is receiving treatment and is persistently seropositive for syphilis represents a management challenge, particularly if intermittent titer increases are verified. In these patients, standard doses of penicillin G benzathine for early syphilis may fail; overtreatment could be advocated as a maxim of management.

Bacillary Angiomatosis.—The recently described, potentially fatal disease of bacillary angiomatosis has primarily been noted in HIV-infected patients. It is caused by a previously uncharacterized, weakly reactive, gram-negative rickettsia-like organism most closely related to Rochalimaea quintana, the causative agent of trench fever, and to Bartonella bacilliformis, the agent of bartonellosis. The agent of bacillary angiomatosis seems distinct from the incompletely characterized agent of cat-scratch disease, although some patients with bacillary angiomatosis have recently been scratched by a cat.

Patients with bacillary angiomatosis usually have few to many reddish rubbery to firm papules and nodules that resemble pyogenic granulomas. Initially, these are pinpoint, but occasionally they become several centimeters in diameter (Fig. 8). They may be found anywhere on the skin—often on the upper trunk and face and occasionally on the oral, anal, or gastrointestinal mucosa or in visceral organs; several cases of peliosis hepatitis have been attributed to the organism that causes bacillary angiomatosis. Deep-seated nodules or tumors that involve the subcutaneous tissue may also be noted. Lesions often bleed profusely when traumatized. Organisms are usually seen in biopsy specimens with use of Warthin-Starry stain and electron microscopy. Usually the condition responds to erythromycin therapy (minimum, 4-week treatment period). Locally destructive measures may be sufficient for one to several lesions.

Bacillary angiomatosis may be clinically and histologically similar to KS. Thus, biopsy specimens and special stain confirmation of suspected KS in HIV-infected patients are necessary.

Chancroid.—Chancroid, a sexually transmitted disease caused by H. ducreyi, manifests as one to several tender, soft genital ulcers, often with an undermined border and associated inguinal lymphadenitis, which can give rise to inguinal abscesses termed “buboes.” Chancroid has become endemic in southern Florida and New York City, and studies in East Africa have shown chancroid to be the major risk factor for heterosexual transmission of HIV-1 in East Africa (presumably due to egress or entry of virions through ulcerated skin). Chancroidlike ulcers may occur in herpes simplex infections or syphilis, and cultures for herpes simplex virus as well as dark-field examination should be performed in suspected cases of chancroid. The diagnosis of chancroid is confirmed by culture of ulcer exudate, and it is treated with trimethoprim-sulfamethoxazole, amoxicillin-clavulanic acid, ceftriaxone sodium, or ciprofloxacin.

Fungal and Yeast Infections. Candidiasis.—Candidiasis and Pneumocystis carinii pneumonia are the most frequent opportunistic infections in HIV-positive patients, in whom the prevalence of mucocutaneous candidiasis has been estimated to be 37 to 47%. In one study, 50% of patients with both unexplained oral candidiasis and risk factors for AIDS experienced multiple subsequent opportunistic infections. In 42% of one group of patients with oral candidiasis, full-blown AIDS developed within a 42-week follow-up period in comparison with only 6% who did not have oral candidiasis. Infection seems to correlate with the immune status of the patient; it often occurs when helper T-cell counts are less than 400 cells/µl, increases when they are less than 100 cells/µl, and becomes intractable when they are less than 10 cells/µl.

The initial manifestation of candidiasis varies from small and large, pseudomembranous, white plaques on the oral mucosa to deep erosions on the tongue and thick plaques in the posterior aspect of the pharynx. Severe dysphagia may accompany esophageal candidiasis. Diffuse candidiasis of the gastrointestinal tract, anus, and vagina may occur and is difficult to treat. Candidal onychodystrophy may be refractory to therapy and generally correlates with an absolute helper T-cell count of less than 100 cells/µl. An extensive diffuse diaper-type dermatitis may be seen in children and involves both the trunk and the extremi-
Fig. 9. Oral candidiasis with white plaques on tongue and buccal mucosa in patient with human immunodeficiency virus infection. A potassium hydroxide smear revealed pseudohyphae.

cutaneous candidiasis may also be generalized in adults (Fig. 10). Systemic candidiasis may involve any organ, including the brain and liver. Potassium hydroxide smear reveals typical pseudohyphae and yeast forms from cutaneous plaques.

Initial treatment involves topically applied antifungal agents such as nystatin (mouthwash or tablets), clotrimazole troches, or miconazole nitrate, although continuous use is often necessary. In these cases or those resistant to topically administered therapy, systemically administered ketoconazole is useful and may also be needed continuously; careful monitoring of liver enzymes is necessary. Ketoconazole may interfere with the metabolism of rifampin and other drugs that the HIV-infected patient may be required to take. Orally administered fluconazole has been effective for oral candidiasis in several studies and was more effective than ketoconazole in one, in which the incidence of side effects was similar. Clotrimazole may also be effective. With any agent, the recurrence rate is high after discontinuation of treatment.

In one study, a conspicuous absence of candidiasis was noted in patients with AIDS who were receiving 200 mg of zidovudine every 4 hours. Improvement of immunologic surveillance and increasing helper T-cell counts probably explain this response.

Dermatophytosis.—Dermatophytosis has been found in approximately 20% of HIV-infected patients and may manifest as tinea corporis, cruris, faciei, pedis, manuum, or unguium. A severe widespread dermatophytosis may also be seen, particularly in children. Involved areas are usually erythematous, scaly, and pruritic (Fig. 11). Dermatophytosis may resemble palmar plantar keratoderma with diffuse thickening of the skin of the palms or soles; infection of the nail or paronychia, usually spared by dermatophytes, occurs more commonly in HIV-infected than in noninfected patients. Usually, these infections are caused by *Trichophyton rubrum*, and potassium hydroxide smears for hyphae and culture are recommended for diagnosis. Lesions are often resistant to topically applied imidazole antifungal agents, and systemically administered griseofulvin or ketoconazole is often the drug of choice (if treatment is warranted). Recurrences are common.

*Tinea versicolor* infection, caused by the yeastlike fungus *Pityrosporum orbiculare*, is common and may be seen early in the course of HIV infection when helper T-cell counts are more than 300 cells/μl. Patchy or extensive areas of fine scale and hypopigmentation are present, and irregular acanthosis may be noted when helper T-cell counts decrease to less than 100 cells/μl. Infection is usually resistant to topically applied agents, such as selenium sulfide, miconazole, or clotrimazole; systemically administered ketoconazole may be efficacious, but recurrent infection is common.

Cryptococcosis.—Cryptococcosis has been reported to occur in 2 to 9% of patients with AIDS. Incidence estimates for cutaneous spread vary from none to 10 to 15%, and involvement is almost always associated with disseminated disease, although cutaneous manifestations have occasionally preceded systemic signs of infection. Skin lesions may be polymorphic, including nodules, abscesses, papules, pustules, herpetiform papulovesicles, vegetating plaques, and deep ulcers (Fig. 12). Multiple flesh-colored to reddish, dome-shaped, translucent 1- to 4-mm papules that resemble molluscum contagiosum are common manifestations; exclusion of cryptococcosis necessitates biopsy of molluscoid growths.
Fig. 11. Discrete and confluent annular plaques of tinea corporis, with characteristic peripheral erythema and scale, in patient with human immunodeficiency virus infection.

Methenamine silver and mucicarmine stains of histologic specimens are helpful in identifying the Cryptococcus organisms. Once the diagnosis has been made, investigation for systemic involvement, including analysis of cerebrospinal fluid, serum, urine, sputum, and prostatic secretions, should be undertaken. Early use of systemically administered antifungal agents may be lifesaving in these patients, although relapses occur in more than 50%. The combination of amphotericin B and flucytosine is often used. Maintenance treatment has been suggested for prevention of relapse.

Histoplasmosis.—Cutaneous histoplasmosis may occur in HIV-infected patients in association with symptomatic primary pulmonary or disseminated histoplasmosis—especially in endemic areas of the United States, such as the Ohio River valley where up to 90% of the population has evidence of prior pulmonary infection. Histoplasmosis has also been associated with cave exploration and with residence in the Caribbean, Central or South America, and Cuba. In a recent review, Cohen and associates identified 239 HIV-infected patients with disseminated histoplasmosis in reports through December 1989, of whom 11% had cutaneous lesions. The actual incidence of skin lesions in patients with disseminated histoplasmosis may be higher because of the nonspecific nature of the lesions. Initial manifestations vary, including shallow crusted ulcers, pustules, psoriasiform papules, papulonecrotic plaques, a cellulitis-like eruption, perianal ulceration, mild diffuse dermatitis, a disseminated maculopapular eruption, and widespread 2- to 6-mm pink to red papules with mild folliculitis. Crushed-tissue preparation, special stains for fungi, and culture of skin and bone marrow specimens will usually provide the diagnosis. Histoplasma capsulatum complement-fixation titers may or may not be positive in these patients.

Amphotericin B does not permanently cure histoplasmosis in patients with AIDS, and relapses necessitate long-term antifungal therapy. Long-term treatment with ketoconazole has been reported to decrease the rate of relapse.

Sporotrichosis.—Systemic sporotrichosis, caused by Sporothrix schenckii, is uncommon in HIV-infected patients but has been seen with no history of exposure to soil or plants. Unifocal or multifocal systemic sporotrichosis, asymptomatic pulmonary sporotrichosis, or primary cutaneous inoculation sporotrichosis may occur. In HIV-positive patients, the portal of entry is usually the lungs; hematogenous dissemination occurs subsequently. Skin lesions are uncommon but may consist of widespread, enlarging, erythematous and violaceous nodules that ulcerate and leave crusted necrotic centers. Involvement of the synovium, periosteum, and bone, which is seen in up to 80% of patients with disseminated sporotrichosis, leads to chronic erosive arthritis and osteomyelitis. The use of appropriate fungal stains and cultures for skin biopsy specimens facilitates diagnosis.

Amphotericin B is the treatment of choice for disseminated sporotrichosis, and maintenance doses may be neces-

Fig. 12. Cutaneous cryptococcosis, shown as a large, dry, noninflammatory crusted ulcer. Culture is necessary for diagnosis.
sary. Orally administered flucytosine may help, although renal toxicity is often a limiting factor. In some cases of cutaneous disease, ketoconazole may be effective. In one report, supersaturated potassium iodide was beneficial but not curative. Despite all drug therapy, patients may die of disseminated sporotrichosis.

Protozoal Infections.—Cutaneous P. carinii infection is rare but may be associated with P. carinii pneumonia or disseminated disease. Nonspecific nodular lesions that involve the external auditory canal, presumably resulting from middle ear infections, have been described. In a recent study, two patients had nonspecific macules or molluscum contagiosum-like papules on the trunk or head and neck. Intravenously administered trimethoprim-sulfamethoxazole or pentamidine has been efficacious.

Arthropod Infections.—Infection with Sarcoptes scabiei in HIV-infected patients usually results in a more severe and generalized eruption than in uninfected hosts. The typical extremely itchy red papules may be found in the intertriginous areas (Fig. 13), wrists, and finger web spaces, but they may also develop on the face and scalp, areas usually spared in non-HIV-infected adults. Lesions usually heal with use of gamma benzene hexachloride (1% lindane) topically applied to the entire body for 8 to 12 hours; shampoo may also be used.

Norwegian scabies, a rare variant, has been described in adult and pediatric patients with AIDS, usually as their clinical status deteriorates. Patients with this variant have hyperkeratotic and scaly crusted plaques on an erythematous base, primarily on the neck, scalp, and trunk. These patients harbor thousands of mites. This variant is highly contagious, and in one report, an infant infected 21 health-care workers despite routine scabies isolation precautions. Gamma benzene hexachloride is usually effective for this variant, but repeated applications may be necessary. Postscabietic dermatitis, after successful therapy, may be a problem in patients with AIDS; sometimes it persists for several months (until all residual foreign antigens of the organisms and ova are eliminated). Scabies infestation should be a consideration in any patient with an unexplained pruritic eruption or dermatitis. It can be diagnosed by finding the mite, ova, or fecal material in scrapings from a lesion.

MISCELLANEOUS DERMATOSES

Vascular Lesions.—Vasculitis in HIV-infected patients may be classified in two broad categories: (1) systemic vasculitis, including periarteritis nodosa-like disease and granulomatous angiitis, and (2) cutaneous leukocytoclastic or necrotizing vasculitis. Purpura attributed to leukocytoclastic vasculitis has been reported in patients with P. carinii pneumonia and cytomegalovirus pneumonitis. Bright fluorescence was noted with use of high-titer anti-HIV serum in the vessels of one of these patients.

Telangiectasia has been associated with the complete spectrum of HIV disease. A characteristic manifestation involves telangiectases in a crescent-shaped distribution over the upper chest, shoulder, and clavicular areas, often in conjunction with a mild diffuse erythema. Telangiectases of the hands and ankles, angiomomas on the ears, and splinter hemorrhages of the nail beds also have been reported. Diffuse petechiae attributed to thrombocytopenia may be seen in advanced disease; thrombocytopenic purpura in patients with AIDS may be idiopathic or attributable to cytomegalovirus infection.

Febrile patients with swelling, erythema, and tenderness of the lower extremities and indurated cords along the course of superficial veins have been described; however, these conditions are not due to deep venous thromboses but rather to KS that involves lymph nodes, with resultant edema. This has been termed the "hyperalgesic pseudothrombophlebitis syndrome." Anticoagulation is unnecessary in these cases, but the KS must be treated.
**Papulosquamous Disease.**—The papulosquamous dermatoses associated with AIDS represent the complete spectrum of disease from mild disorders such as xerosis generalisata to severe psoriasis, Reiter's syndrome, and ichthyosis.

**Xerotic (Asteatotic) Eczema.**—A "generalized dry skin syndrome," xerotic eczema is one of the most common scaling dermatoses among HIV-positive patients; it occurs in 5 to 20% of such patients. This condition is often severely pruritic and resistant to antihistamines. The pruritus may be disproportionate to the clinically obvious xerosis, which often manifests as fine branlike scaling with occasional discrete thickened patches. The eruption has occurred when helper T-cell counts are less than 400 cells/µl and often may precede other papulosquamous disorders. Other itchy, scaling dermatoses such as scabies and fungal infections must be excluded, and treatment of the underlying xerosis includes use of emollients that contain urea and lactic acid, H1 antihistamines, and supersaturated fatty acid soaks.

A frequent association of xerosis, seborrheic dermatitis, and erythroderma (generalized red skin) with the development of dementia and spinal cord disease has been noted in patients with AIDS. This finding has led to speculation that the neurologic disease and these proliferative disorders could result from the same mechanism.

**Seborrheic Dermatitis.**—Seborrheic dermatitis is one of the most common noninfectious skin manifestations of HIV-infected patients; the reported prevalence is 20 to 80% in comparison with 5 to 12% in non-HIV-infected patients. Seborrheic dermatitis is characterized by pinkish-to-red, scaly, occasionally greasy patches and plaques over the malar areas, eyebrows, scalp, and chest; occasionally, the axillary, groin, and genital areas may be involved. Inflammation may be intense, and areas of hypopigmentation or hyperpigmentation may occur within the inflammatory patches and plaques. The eruption may generalize with occasional progression to erythroderma, and plaques may resemble psoriasis clinically. The severity and extent of disease and resistance to topically applied corticosteroids separate this entity from the common type of seborrheic dermatitis; histologic differences have also been noted. The severity often correlates with the degree of immunosuppression. Seborrheic dermatitis may be the initial manifestation of HIV infection and may predate the diagnosis of AIDS by up to 2 years.

The yeastlike fungus *P. orbiculare* has been associated with seborrheic dermatitis in both HIV-positive and uninfected patients, and topically or orally applied ketoconazole has been helpful for many patients. Additional therapy may include topically applied coal tar, selenium sulfide and salicylic acid shampoos, and low- and medium-potency corticosteroid creams and solutions. Control generally deteriorates in conjunction with progressive depletion of helper T cells.

**Psoriasis.**—Psoriasis affects approximately 1 to 2% of the general population and has been noted in 1.3 to 5% of the HIV-infected population; one study found psoriasiform lesions in 20% of HIV-infected persons. Usually, the severity of psoriasis is greatest in HIV-infected persons. Psoriasis may be the initial sign of HIV infection and has been considered a poor prognostic indicator. The sudden onset of previously undiagnosed psoriasis or the acute worsening of preexistent disease may indicate HIV infection in patients with appropriate risk factors. Mild to severe disease has been reported among HIV-positive patients, and two clinical patterns have been described. One pattern shows discrete guttate (droplet) or large plaques, and the other is a more diffuse psoriasiform dermatitis, often associated with palmoplantar keratoderma or thickening, which culminates in generalized disease. The distribution may be atypical; primary involvement of the groin, axillae, and scalp is termed "inverse psoriasis." Cultures for staphylococcal, streptococcal, and yeast infection should be considered in these patients because coexisting infection may worsen the psoriasis.

Investigators have hypothesized that papulosquamous disease occurs in HIV-infected patients as a spectrum from seborrheic dermatitis to psoriasis vulgaris to pustular psoriasis and Reiter's syndrome. At least for psoriasis, the underlying cause may be in the activity of CD8 cytotoxic suppressor T cells, perhaps in response to dysfunctional or infected Langerhans cells. Management of HIV-related psoriasis may be difficult because of additional treatment-related immunosuppression, and lesions may be refractory because of underlying immunoincompetence. Methotrexate therapy should generally be avoided in these patients. Corticosteroids, ultraviolet-B phototherapy, ultraviolet-A phototherapy with psoralen, and cyclosporine all create some degree of immunosuppression and must be used with caution, if at all. Ultraviolet light therapy has been associated with the new onset of KS in some of these patients. Etretinate may be effective, but it can complicate the situation because presumed side effects, such as headache and increased hepatic enzyme values, could instead be the result of occult infection. Therefore, use of etretinate necessitates close monitoring. Orally administered zidovudine helps heal psoriatic lesions in some patients, and some investigators think that zidovudine is the treatment of choice for severe psoriasis in patients with HIV infection.

**Palmoplantar Keratoderma and Reiter's Syndrome.**—Keratoderma or thickening of the skin on the palms and soles may be an isolated finding in HIV-positive
patients or a feature of psoriasis or dermatophyte infection. It may also occur as areas of pustulation within hyperkeratotic plaques, a condition referred to as keratoderma blennorrhagicum. This condition has been described in association with Reiter's syndrome, including the classic triad of arthritis, conjunctivitis, and urethritis; it resembles pustular psoriasis\(^9\) (Fig. 14). Estimates of the prevalence of Reiter's syndrome in HIV-infected patients vary from 0.5 to 10%, and approximately 75% of patients are HLA-B27 positive.\(^9\) The clinical and histopathologic resemblance of Reiter's syndrome to psoriasis is strong, but pathogenetic or precipitating factors may differ.\(^9\) Infectious agents such as Yersinia, Salmonella, Shigella, Campylobacter, Chlamydia, Giardia, and M. avium may trigger Reiter's syndrome; this situation accounted for 30% of cases in one study.\(^89\) In another study, Chlamydia antibodies were found in 60% of patients.\(^90\)

Therapeutic regimens for palmoplantar keratoderma are similar to those for psoriasis; however, keratolytic agents are added. Treatment-induced immunosuppression remains an issue in HIV-infected patients.\(^89\) The keratoderma in these patients is resistant to therapy. Nonsteroidal anti-inflammatory agents, zidovudine, and phenylbutazone have been efficacious, and a trial of sulfasalazine may also be warranted.\(^90,93,94\)

**Ichthyosis.**—Acquired ichthyosis has been described in HIV-infected patients and other patients with immunodeficiencies, such as Hodgkin's disease, lymphoma, and sarcoidosis.\(^9\) The cause is uncertain. Ichthyosis in patients with AIDS usually begins on the legs and often progresses to a more generalized eruption. It may be associated with palmoplantar keratoderma. In one study of patients with AIDS, the group with generalized ichthyosis and helper T-cell counts of less than 50 cells/µl experienced rapid deterioration and had the poorest prognosis.\(^89\) The keratoderma in these patients is resistant to therapy. Nonsteroidal anti-inflammatory agents, zidovudine, and phenylbutazone have been efficacious, and a trial of sulfasalazine may also be warranted.\(^90,93,94\)

**Oral Diseases.**—Angular cheilitis or perlèche is common in HIV-infected patients and is usually associated with oral candidiasis. It responds well to topically applied antifungal-hydrocortisone combination creams.\(^1^0\)

Recurrent aphthous ulceration was noted in 3% of HIV-positive patients in one study and occasionally may be severe; the cause is unclear.\(^7,10,41\) Ulcerative tonsillitis or pharyngitis, the cause of which is unknown, has also been reported, and tetracycline or penicillin has been found to be efficacious.\(^7\)

Gingivitis is common in HIV-positive persons and occasionally responds to penicillin or metronidazole. An acute necrotizing gingivitis, associated with red edematous gums, bleeding, and necrosis of gingival margins and interdental papillae, has also been described. Rapid loss of periodontal bone attachments and subsequent tooth loss may occur. No cause is known.\(^9,10\)

Zidovudine therapy commonly produces brownish hyperpigmentation of the oral mucosa, especially of the tongue and gums, that is seen most often in black patients after 4 to 8 weeks of therapy. Usually this condition is reversible after the dose has been decreased or use of the drug has been discontinued. The hyperpigmentation is due to melanin.\(^97,98\)

**Hair Disease.**—A fine diffuse "downy" alopecia has been reported in HIV-positive patients; the hair shafts are thinner than normal, but no inflammation is noted clinically. Diffuse thinning, beginning over the crown and progressing toward the frontal region, results. Premature frontal recession of the hairline may also be seen, the cause of which is uncertain.\(^10,13,27\) Alopecia areata that leads to patchy hair loss without severe inflammation or scarring has been described. This condition is probably related to some abnormality in the T lymphocytes.\(^10\) Telogen effluvium, a reversible condition of rapid loss of large amounts of hair, has also been described.\(^10\) Premature graying of the hair (canities) may occur in HIV-infected patients; complete graying can occur in 6 to 8 months.\(^27\)

Frequently, the eyelashes of HIV-infected patients are unusually elongated; apparently, this condition is caused by a prolongation of the anagen or growth phase of this hair.\(^27\)
Both alopecia and eyelash hypertrichosis have also been described in pediatric patients with AIDS.28

**Nail Disease.**—In addition to onychomycosis associated with fungal infections and onychodystrophy or nail pitting attributed to psoriasis, several other nail changes may occur in HIV-infected patients. Leukonychia or white nails, a yellow discoloration of the distal part of the nail, transverse or longitudinal ridging, loss of the lunula, and opaqueness and yellow nail syndrome have all been reported.7,10,98 Additionally, longitudinal pigmented nail bands have been noted in almost 50% of patients taking zidovudine; this condition, similar to the previously mentioned mucosal hyperpigmentation, is more common in dark-skinned than in light-skinned persons and usually occurs within 4 to 8 weeks after initiation of therapy. The pigment is melanin, and the process usually reverses after the dose is decreased or use of the drug is discontinued.95-99 Azure lunulae and transverse bands may also be associated with zidovudine therapy. This hyperpigmentation also may generalize. The mechanism is unknown.97,98

**Miscellaneous Manifestations**

**Reactions to Drugs.**—Morbilliform drug eruptions occur in 30 to 85% of HIV-infected patients who receive trimethoprim-sulfamethoxazole or other sulfonamides for treatment of *P. carinii* pneumonia and other infections.13,104,101 The eruption commonly occurs during the second week of therapy and may be associated with fever, malaise, and peripheral cytopenias.101 Morbilliform exanthems, the most common manifestation of drug reactions in HIV-infected patients, rapidly resolve after discontinuation of the offending agent.101 Lesions consist of itchy or asymptomatic, fine, erythematous macules and papules that coalesce into plaques and subsequently progress to generalized involvement. The eruption may also be urticarial or hivelike. Typically, patients with AIDS receive numerous medications during the course of their illness, all of which are possible causes of dermatitis medicamentosa. In two small studies, reactions to amoxicillin-clavulanate and dideoxycytidine occurred in 44% and 70% of cases, respectively.101 Investigators have hypothesized that Epstein-Barr virus or cytomegalovirus infection may predispose HIV-positive patients to a skin rash analogous to that associated with ampicillin in patients with mononucleosis.101

Rarely, erythema multiforme with classic targetoid lesions may develop and progress to Stevens-Johnson syndrome or toxic epidermal necrolysis, which is associated with sloughing of sheets of skin and severe systemic symptoms.102,103 Sulfonamides have been most commonly implicated, and a history of multiple cutaneous drug reactions seems to be a risk factor for the development of either Stevens-Johnson syndrome or toxic epidermal necrolysis.101 Systemically administered antihistamines may allow continuation of therapy in patients with mild reactions; the use of systemically administered corticosteroids for severe reactions is controversial in HIV-infected patients.

Cutaneous eruptions from pentamidine or zidovudine therapy have been noted less commonly than those associated with the previously mentioned drugs.10 Intramuscularly injected pentamidine may cause sterile abscesses and even ulceration at injection sites because of its local irritating effects.10 Clofazimine, which is used for *M. avium-intracellulare* infections, may cause a characteristic purplish discoloration of the skin and eyes.10

**Eosinophilic Folliculitis.**—A pruritic follicular eruption with histologic features similar to eosinophilic pustular folliculitis (Ofuji’s disease), a rare condition previously seen primarily in Japanese patients, has been described in HIV-infected patients.13,104-106 The common finding is a predomiance of eosinophils within and around follicles. Whether this eruption in HIV-infected patients occurs in a spectrum with classic Ofuji’s disease or represents a specific entity is unclear. A recent study distinguished HIV-associated eosinophilic folliculitis on the basis of its chronic persistent course; invariable presence of pruritus; normal or decreased peripheral leukocyte count; and discrete, erythematous, urticarial, follicular papules, present primarily on the trunk, head, neck, and proximal area of the extremities (Fig. 15).105 A relative or absolute eosinophilia is present in most affected patients, as are increased serum IgE levels.104,105 Rosenthal and colleagues105 found CD4 counts of less than 250 cells/μl in 10 of 13 patients and interpreted eosinophilic folliculitis as a marker for patients at risk for the development of opportunistic infections.

Patients with classic Ofuji’s disease have occasionally been found to harbor *Demodex* mites or dermatophytes,10 although this condition has not been regularly noted in HIV-infected patients with eosinophilic folliculitis. Treatment is difficult in these patients; topically applied clobetasol propionate has been helpful, as have astemizole and ultraviolet-B light therapy in some cases.103,106 Dapsone, nonsteroidal antiinflammatory agents, sulfapyridine, colchicine, and systemically administered antibiotics have occasionally been beneficial for patients with classic Ofuji’s disease;10,13,27,106 their effect in patients with HIV-associated eosinophilic folliculitis remains to be seen.

**Pruritus.**—Some HIV-infected patients have a generalized intractable pruritus with no identifiable cause10,107 and, occasionally, with no other skin findings but an onset coincident with the initial manifestations of the HIV infection. An associated exanthem may or may not be noted, but scratching may cause excoriations or prurigo-like lesions, which are red, firm, thickened papules and nodules. Scabies and
lymphoma must be excluded from the differential diagnosis by appropriate studies.

A spectrum of eruptions composed of pruritic papules exists and has been variously termed—papular urticaria, malignant prurigo associated with AIDS, and, most recently, pruritic papular eruption associated with AIDS.\textsuperscript{10,13,27,108-110} Eosinophilic folliculitis may also be within this spectrum. Pruritic papular eruption occurs more commonly in HIV-infected patients from Haiti and Africa than in those from the United States and Europe; this condition was noted in 46\% of Haitian patients with AIDS and was the initial manifestation of AIDS in 79\% of them.\textsuperscript{21,108,109} In a study in Florida,\textsuperscript{110} patients with HIV had generalized pruritic, skin-colored to red, usually 2- to 4-mm papules, primarily over the trunk and extremities and on the face in 50\%. Initially, lesions may resemble insect bites, and vesicles may overlay the papules. Secondary lesions may be excoriations, prurigo-like nodules, or postinflammatory hyperpigmented macules. The pruritus usually waxes and wanes and is resistant to most topically applied or orally administered therapy; ultraviolet-B and ultraviolet-A phototherapy with psoralen have been helpful in some cases.\textsuperscript{13,27,110} IgE levels may be increased, and peripheral eosinophilia may or may not occur.\textsuperscript{108,110}

Histologically, pruritic papular eruption shows primarily an eosinophilic, perivascular, and perifollicular infiltrate, occasionally sparing the follicles. Although it does not resemble classic Ofuji’s disease clinically, histologic evidence of eosinophilic folliculitis was present in a fourth of the patients described by Hevia and co-workers.\textsuperscript{110} The cause is unknown; however, environmental factors such as insects, allergies, or an unknown hypersensitivity reaction have been postulated.\textsuperscript{108}

**Dermatitis.**—A spectrum of dermatitis exists, particularly in pediatric patients with AIDS, including nonspecific exanthems in most cases of childhood AIDS, frequent and recalcitrant seborrheiform dermatitis, generalized pruritic papular eruption commonly seen in children with AIDS in Africa, and an atopic-like dermatitis.\textsuperscript{10,21} The relationship between these eruptions and AIDS is unclear, if one exists.

Atopic dermatitis has been described in 50\% of cases of AIDS in pediatric patients, and it has a tendency to wax and wane.\textsuperscript{10} Lesions are itchy, red, scaly, and lichenified and may be crusted or oozing; they are located primarily on the extensor portions of the extremities in infants and the flexor areas in children and adults. Atopic dermatitis is commonly associated with other immunodeficient diseases of childhood.\textsuperscript{10} In adults, the disease may develop de novo in temporal relationship to the development of AIDS, or it may severely exacerbate preexisting atopic dermatitis. Atopic dermatitis in non-HIV-infected patients is frequently associated with increased IgE levels, and new onset atopic disease in HIV-infected patients may be related to abnormal production of IgE associated with the hypergamma globulinemia seen in HIV infection.\textsuperscript{100} Topically applied corticosteroids, lubrication, and avoidance of aggravating factors remain the mainstay of treatment.

**Nutritional Deficiencies.**—Nutritional deficiencies are common in patients with AIDS, especially in children. Episodic or chronic diarrhea certainly has a role. Pellagra attributed to deficiency of niacin or tryptophan has been described; usually, exposed areas show erythema or vesicles and bullae and, later, hyperpigmented scaly thickened plaques.\textsuperscript{28} Scurvy associated with bleeding gums and perifollicular petechiae on the legs has been noted. A deficiency of zinc may lead to acquired acrodermatitis enteropathica, which is characterized by periorificial and acral dermatitis, moist erythema, occasional vesicles, and scaling (Fig. 16). In a study done in Newark, New Jersey, a third of the pediatric patients with AIDS had zinc levels one standard deviation below normal.\textsuperscript{28} This condition may also be seen in patients receiving long-term peripheral hyperalimentation with formulas low in zinc.\textsuperscript{52} Orally administered zinc replacement is helpful.

**Porphyria Cutanea Tarda.**—Porphyria cutanea tarda in conjunction with characteristic cutaneous symptoms and
biochemical signs before the development of AIDS has been described in several patients. Both familial and acquired types have been observed. Patients had vesicles, bullae, ulcers, papules, and plaques over sunlight-exposed regions, particularly the dorsal surface of the hands and the face. Hyperpigmentation and milia are usually present; results of urinary porphyrin studies are abnormal. Avoidance of excess sunlight, alcohol, and certain medicaments and the use of sunscreens are necessary. The response is usually good. The basis for the association between porphyria cutanea tarda and HIV infection is poorly understood; however, several other HIV-positive patients with photosensitive disorders have also been described.111-113

CONCLUSION

The spectrum of mucocutaneous manifestations of HIV infection is broad, and frequently the eruptions are atypical or more severe and refractory to treatment than similar eruptions in noninfected patients. Often, the cutaneous findings may not correspond precisely to a well-defined entity or may mimic other dermatoses. Papulosquamous disorders, infections, and neoplastic diseases, including seborrheic dermatitis, xerosis, candidiasis, dermatophytosis, herpes virus infections, and KS, are most commonly seen in HIV-infected patients. Some dermatoses, including oral hairy leukoplakia, bacillary angiomatosis, and eosinophilic pustular folliculitis, are unique to HIV-infected patients or are rare outside this population. An unusual eruption or a common eruption in an unusual setting may be a clue to HIV infection in patients with appropriate risk factors. Biopsy specimens and cultures are necessary for establishing the correct diagnosis in these patients, even when lesions seem clinically characteristic. Primary-care physicians and dermatologists may be able to diagnose HIV infections on the basis of individual initial cutaneous signs, and knowledge of the varied manifestations facilitates rapid institution of appropriate therapy.

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