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Cutaneous Manifestations of Opportunistic Infections in Patients Infected with Human Immunodeficiency Virus

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INTRODUCTION

Cutaneous infections are extremely common among patients infected with the human immunodeficiency virus (HIV), and their incidence increases with deteriorating immune function (15). In addition, several cutaneous infectious diseases, such as bacillary angiomatosis (BA) and a variety of mucocutaneous viral infections, may represent the first clinical sign of HIV infection (11). Although numerous pathogens can affect the skin in the HIV-positive patient, this review will focus on the appearance and diagnosis of several common cutaneous infections that are either frequently misdiagnosed, associated with systemic disease, or persistent or resistant to treatment in the setting of advanced HIV infection.

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CUTANEOUS BACTERIAL INFECTIONS

BA

BA was first described in 1983 among HIV-infected patients with cutaneous and subcutaneous vascular lesions mimicking Kaposi's sarcoma (5, 60). Although five immunocompetent patients with BA have been described (65), the disease is predominantly seen among immunocompromised patients in the late stages of HIV infection and with CD4 lymphocyte counts of less than 100 cells per mm^3 (41). Over the past decade, the clinical spectrum of disease has been expanded to

include patients with single or multiple vascular lesions affecting virtually every organ system, including the liver (peliosis hepatis) and spleen (parenchymal bacillary peliosis) (37). However, skin lesions remain the most easily recognized and frequently reported clinical manifestation of BA.

The causative agents of cutaneous BA, established by culture of bacilli directly from skin lesions, include both *Rochalimaea henselae* and *Rochalimaea quintana* (36), confirming earlier molecular biologic studies suggesting that the BA bacillus was closely related to members of the genus *Rochalimaea* (51). These earlier studies used PCR to detect *Rochalimaea* DNA in BA tissue specimens. Although the histopathologic features of BA (characteristic vascular pattern with bacilli) establish the diagnosis in the vast majority of patients with cutaneous disease, confirmation of the diagnosis for patients whose lesions contain a paucity of organisms may require electron microscopy, the isolation of a *Rochalimaea* species, or the amplification of *Rochalimaea* DNA from tissue. Of special interest, *R. henselae* was subsequently isolated from the affected lymph nodes of two immunocompetent patients with apparent cat scratch disease (CSD) (17). PCR was then used to study multiple sources of CSD skin test antigen prepared from purulent material aspirated from CSD-affected lymph nodes. This material has been used historically by many clinicians for establishing a diagnosis of CSD. DNA sequences characteristic of *R. henselae* were amplified from each of the different skin test antigen preparations, suggesting that *R. henselae* is the predominant causative agent of CSD (1, 44).

In 1993, Brenner et al. proposed the unification of the genera *Bartonella* and *Rochalimaea* within the family *Bartonellaceae* on the basis of their genetic relatedness (8). These investigators recommend the removal of the family *Bartonellaceae* from the order *Rickettsiales*, because recent molecular evidence has demonstrated that neither *Bartonella* nor *Rochalimaea* species are closely related to other organisms currently classified in the order *Rickettsiales* (8). This classification has come into general use, and the causative agents of BA, CSD, and Carrion's disease are now named *Bartonella* (formerly *Rochalimaea*) *henselae*, *Bartonella* (formerly *Rochalimaea*) *quintana*, and *Bartonella bacilliformis*, respectively.

Before the causative agents of BA and CSD were isolated, Tappero et al. (66) conducted a case control study of BA patients to identify a variety of exposures that might be risk factors for infection. Traumatic contact with a cat (bite or scratch) was the only environmental exposure significantly associated with disease. Patients with BA were also more likely than controls to have a household kitten (a cat of $\leq$1 year of age). Subsequent investigations in the San Francisco Bay area by Koehler et al. (35) established the pet cat, *Felis domesticus*, as a reservoir for *B. henselae* infection and the cat flea, *Ctenocephalides felis*, as a possible vector for transmission of infection to humans. *B. henselae* was established as the cause of cutaneous BA in three of the four patients with BA in this study. *B. henselae* was subsequently isolated from the blood of all seven asymptomatic pet cats with which the BA patients had prolonged contact. This bacterium was also detected by both direct culture and PCR from several of the cat fleas combed from these bacteremic cats. In addition, the prevalence of infection among cats in the greater San Francisco Bay area was studied; 41% (25 of 61) of sampled pet or impounded cats had asymptomatic *R. henselae* bacteremia (35). Although the reservoir(s) for the second causative agent of BA (*B. quintana*) remains unknown, the human body louse (*Pediculus humanus*) was established as a vector for *B. quintana* infections causing trench fever during the First World War (61).

Clinical features. Cutaneous lesions of BA begin as small, erythematous vascular papules which may enlarge to form exophytic, friable nodules surrounded by a collarette of scale with or without erythema (Fig. 1). Subcutaneous lesions of BA may arise below the skin surface and have the appearance of flesh-colored cystic nodules or epidermal inclusion cysts, or they can develop more deeply, presenting as soft tissue masses. Enlarging soft tissue masses may give rise to the eruptive cutaneous vascular lesions of cutaneous BA (36).

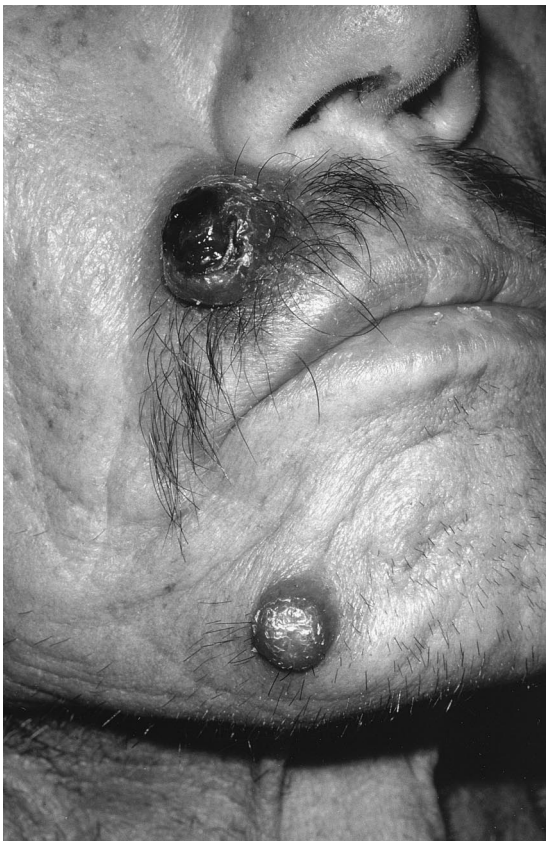

FIG. 1. Characteristic exophytic angiomatous nodules of BA with and without surrounding cellulitic erythema.

Diagnosis. A confirmatory diagnosis of cutaneous BA is made histologically. Skin specimens are easily obtained by either punch biopsy of small papular lesions and subcutaneous nodules or shave excision of large pedunculated lesions. Bleeding may be profuse immediately following cutaneous biopsy, but it is easily controlled with local pressure. Because fine-needle aspiration of deep subcutaneous masses of BA have been unsuccessful in confirming a tissue diagnosis, incisional biopsy is generally required.

(i) Histopathology. Routine hematoxylin and eosin staining of tissue specimens reveals a characteristic lobular proliferation of small, capillary-sized blood vessels with large (epithelioid) endothelial cells containing abundant cytoplasm (with or without cytologic atypia) surrounded by an inflammatory infiltrate containing many polymorphonuclear leukocytes, with scattered areas of focal necrosis (39). Purple granular material on hematoxylin and eosin stain, revealing clumps of tangled bacteria upon Warthin-Starry silver staining or electron microscopy, is scattered throughout a myxoid stroma, usually in close proximity to vessel lumina and neutrophilic debris (39). These organisms are not demonstrable with tissue strains for

fungi, acid-fast stains for mycobacteria, or Brown and Brenn tissue Gram stains.

The presence of bacillary organisms clearly distinguishes BA from other cutaneous vascular lesions in the histopathologic differential diagnosis, which includes lobular capillary hemangiomas (pyogenic granulomas), Kaposi's sarcoma, angiosarcoma, epithelioid (histiocytoid) hemangioma, and epithelioid hemangioendothelioma (37, 39). Immunocytochemical staining with polyclonal rabbit antiserum to *B. henselae* may also demonstrate the presence of bacillary organisms in tissue (48).

(ii) Culture, PCR, and serologic testing. The isolation of *Bartonella* species from infected tissue can be accomplished by direct plating of homogenized tissue onto chocolate agar or heart infusion agar without antibiotics and containing 5% rabbit blood (37). Plates are incubated at 35°C with 5% CO_2 at high humidity for at least 4 weeks. When this method fails to recover organisms, a more laborious technique requiring cocultivation with an endothelial cell monolayer may be successful (36). However, this technique is not widely available. Although patients with cutaneous BA are not always bacteremic, culturing of blood by using either Isostat lysis centrifugation tubes (Wampole, Cranbury, N.J.) (57) or blood collection tubes containing EDTA (49) followed by direct plating may be an easier method for isolating *Bartonella* species from BA patients than culture from tissue.

Following extraction of DNA from a BA tissue specimen, the oligonucleotide primers first described by Relman et al. may be used to amplify an approximately 300-bp 16S rDNA gene fragment from the *Bartonella* DNA present in the lesion (36, 51, 65, 66). However, this technique is labor-intensive and is not commercially available. Therefore, its use has been restricted primarily to research studies for the detection of *Bartonella* DNA in archived paraffin-embedded tissue specimens and in human tissue specimens likely to be superinfected with other bacterial species.

Recent advances have also been made in the serologic diagnosis of *Bartonella* infections. An indirect immunofluorescent-antibody test for the detection of antibodies to *Bartonella* species has been developed by the Centers for Disease Control and Prevention (50). Testing of sera obtained from California patients with either BA or CSD revealed high titers of antibody to *Bartonella* species, findings subsequently borne out by the Centers for Disease Control and Prevention in two large studies using this test on sera obtained from otherwise healthy patients with classical CSD (50, 68). Preliminary results from seven HIV-infected patients with cutaneous BA suggest that the indirect immunofluorescent-antibody test may be useful for the detection of *Bartonella* antibodies in immunocompromised patients (63). In one patient who had completed 4 months of antibiotic therapy for osseous BA, a rising titer preceded clinical relapse, suggesting that this test may be of use for both screening for *Bartonella* infections and monitoring patients following the completion of antibiotic therapy for BA.

Management. Although antibiotic therapy for persons with BA and bacillary peliosis has not been systematically evaluated, clinical experience and in vitro antimicrobial susceptibility testing for both *B. henselae* and *B. quintana* suggest that erythromycin and doxycycline are the agents of first choice (37, 64). In general, patients with cutaneous BA in the absence of osseous and parenchymal disease or bacteremia have responded well to 8 to 12 weeks of oral antimicrobial therapy with one of these two agents. The effectiveness of gentamicin, rifampin, trimethoprim-sulfamethoxazole, ceftriaxone, ceftizoxime, and ciprofloxacin has not been demonstrated; penicillin, penicillinase-resistant penicillins and aminopenicillins, and the cephalosporins have not been clinically efficacious.

Staphylococcal Skin Disease

Staphylococcus aureus is the most common cutaneous and systemic bacterial pathogen in HIV-infected adults (33, 52). The initial site of colonization with *S. aureus* prior to infection is the nares. Several studies have demonstrated a nasal carriage rate of approximately 50% in HIV-infected homosexual men at all stages of HIV disease, roughly twice the rate demonstrated among non-HIV-infected persons (6, 25). The combination of frequent nasal carriage, an impaired cutaneous barrier, and decreased numbers of and ineffective neutrophils leads to a high rate of cutaneous and systemic *S. aureus* infections (19). Indwelling venous catheters are associated with systemic infections (33), and pruritus and scratching may contribute to the development of cutaneous disease (18).

Clinical features. In general, the clinical lesions produced by *S. aureus* in HIV-infected persons are similar to those seen among HIV-seronegative persons and include bullous impetigo, ecthyma, folliculitis, and abscesses (Fig. 2). However, in the setting of HIV disease, *S. aureus* may cause unusual clinical patterns of infection. Botryomycosis, a chronic suppurative infection with grains in the purulent material (67), and atypical plaquelike lesions of the scalp, axilla, or groin have been reported (3). These lesions may be quite refractory to therapy. Pyomyositis, rarely seen among immunocompetent patients in temperate climates, has been described in several HIV-infected patients (26, 47).

Diagnosis. The diagnosis of staphylococcal pyoderma is established by Gram stain and culture. For the initial presentation of common superficial infections, a Gram stain of purulent material is adequate, and empiric therapy is usually effective. For deeper infections and for recurrent disease, culture and susceptibility testing of *S. aureus* isolates obtained from both skin lesions and the nares to assess chronic carriage are recommended. Because antibiotic resistance is common, and because adverse cutaneous drug reactions occur more often in HIV-infected patients than in HIV-seronegative populations (15), susceptibility tests help to guide initial and subsequent therapy.

Management. The treatment of *S. aureus* infections in HIV-infected persons is identical to that for HIV-seronegative persons. For all forms of staphylococcal pyoderma, loculated areas of purulence should be surgically drained. Oral antistaphylococcal antibiotics, such as a semisynthetic penicillin or a cephalosporin, are generally effective as empiric therapy. If these agents are contraindicated, alternative empiric agents include erythromycin, clindamycin, trimethoprim-sulfamethoxazole, and ciprofloxacin or ofloxacin. One or more of these alternative agents should be selected on the basis of results of culture and susceptibility testing. Close follow-up is encouraged because adverse drug reactions to clindamycin and trimethoprim-sulfamethoxazole occur frequently, resistance to erythromycin is common, and ciprofloxacin (and ofloxacin) may not provide adequate coverage against streptococci, which may also be present in staphylococcal pyodermas. Therapy should be continued until the infection is cleared; the duration of therapy may exceed that required for HIV-seronegative patients.

For recurrent infections, rifampin, 600 mg once daily for 5 to 10 days, may be added as a second oral antimicrobial agent to clear nasal carriage and enhance therapeutic response. Long-term application of topical mupirocin ointment in the nares may prevent recurrent nasal colonization. Rarely, patients with repeated infections require continuous low-dose oral antibiotic prophylaxis. Patients are also instructed to use antibacterial soap (e.g., benzoyl peroxide wash or chlorhexidine) regularly in areas of frequent infection such as the axilla and groin. How-

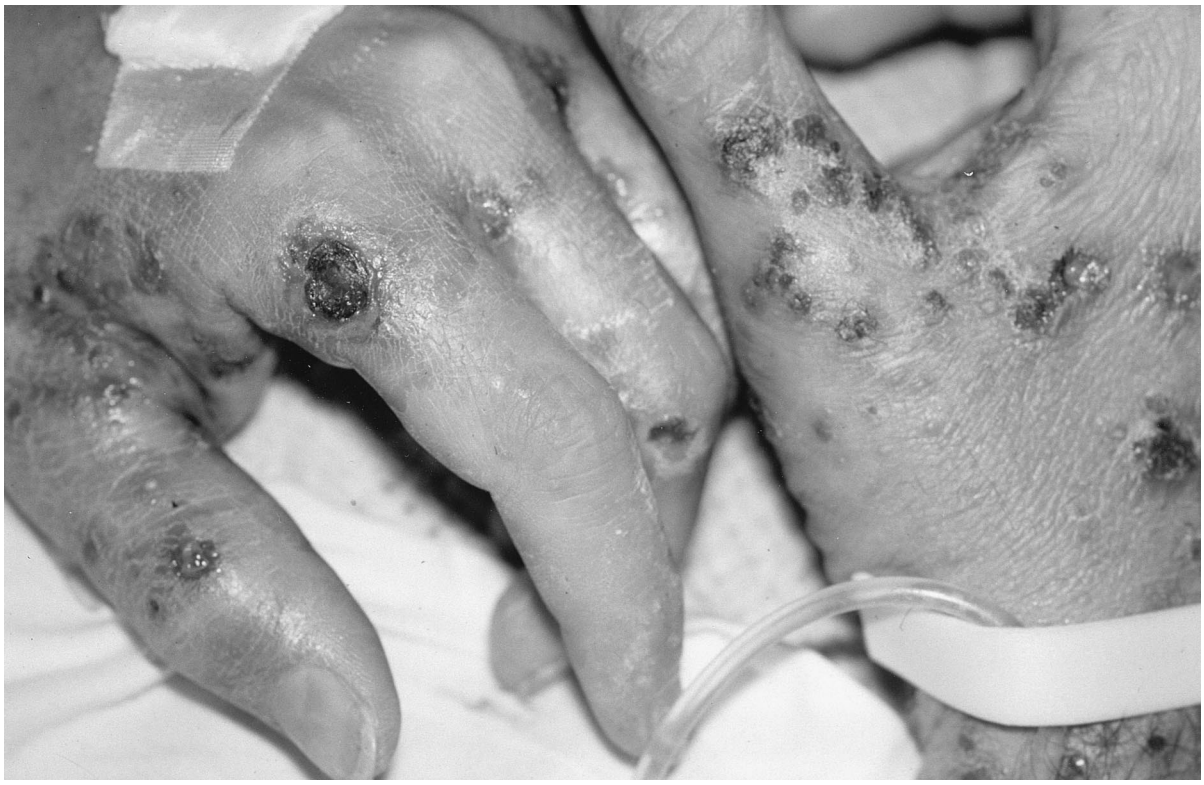

FIG. 2. Numerous ecthymatous lesions due to *S. aureus.*

ever, these strong soaps must be used with caution to avoid the induction of eczematous and xerotic dry skin. Patients with severely dry skin at these sites may benefit from the daily application of topical clindamycin lotion to affected areas. Oral antihistamines may help control pruritus associated with disease.

CUTANEOUS VIRAL INFECTIONS

Herpesviruses

Herpes simplex virus (HSV) and varicella-zoster virus (VZV) characteristically cause latent or recurrent infections of the skin and nerves. In the setting of HIV-associated immune suppression, previously latent asymptomatic or mild infections may become severe. Fortunately, antiviral chemotherapy with acyclovir (ACV) is generally effective in controlling severe disease. When accompanied by risk factors for HIV disease, both HSV and VZV infections are markers for unsuspected HIV infection, and these lesions should prompt appropriate counseling for HIV serologic testing (10, 14).

HSV

Clinical features. Early in the course of HIV disease, HSV infections are usually self-limited (16). Grouped lesions appear, ulcerate, and heal, usually in less than 2 weeks. However, once significant immune suppression occurs, lesions may persist, and the presence of mucocutaneous HSV infection for longer than 1 month is suggestive of advanced HIV infection (10). Tender, often painful, ulcerative lesions of the penis, perianal area, and lip are the hallmark of HSV in HIV-infected patients. Without treatment, these lesions may continue to enlarge peripherally, sometimes reaching over 100 cm^2 (Fig. 3). Periungual lesions (herpetic whitlow) and follicular facial lesions (herpetic folliculitis) are frequently misdiagnosed as bacterial infections (Fig. 4 and 5). Multiple scattered lesions in one area are not uncommon, but widespread dissemination of HSV is rare, even in patients with advanced HIV disease. Among HIV-infected patients, the likelihood of correctly attributing an ulcerated cutaneous lesion to HSV is highly correlated with CD4 lymphocyte counts; only 13% of ulcerative lesions are HSV associated when CD4 lymphocyte counts exceed 400 cells per mm^3, whereas 58% of all ulcerations and 67% of all perianal ulcerations contain HSV when CD4 lymphocyte counts are less than 50 cells per mm^3 (2).

Diagnosis. The diagnosis of HSV infection can almost always be made with a Tzanck smear, viral swab culture, or direct fluorescent-antibody (DFA) staining of scrapings from lesions. However, DFA staining is often not available as a rapid diagnostic test in the outpatient clinical setting. To enhance the sensitivity of these tests, specimens should be taken from the base of an intact blister or the advancing border of a lesion. If these test results are negative, a skin biopsy from the ulcer margin will usually demonstrate the characteristic histologic effects in epithelial cells of the skin, mucosa, or adnexal structures (38). A portion of the biopsy specimen should also be submitted for viral culture. Staining of tissue specimens with antibodies directed against HSV, or the amplification of HSV DNA by PCR, may establish the correct diagnosis in culture-negative, histologically atypical lesions of HSV (38). As with all biopsies from HIV-infected persons, special stains for acid-fast bacilli and fungi should be performed to rule out combined infections. Serologic tests are of no value in the diagnosis of cutaneous HSV infections.

Because ACV resistance occurs naturally, the likelihood of selection of a resistant HSV mutant is greatest for very large,

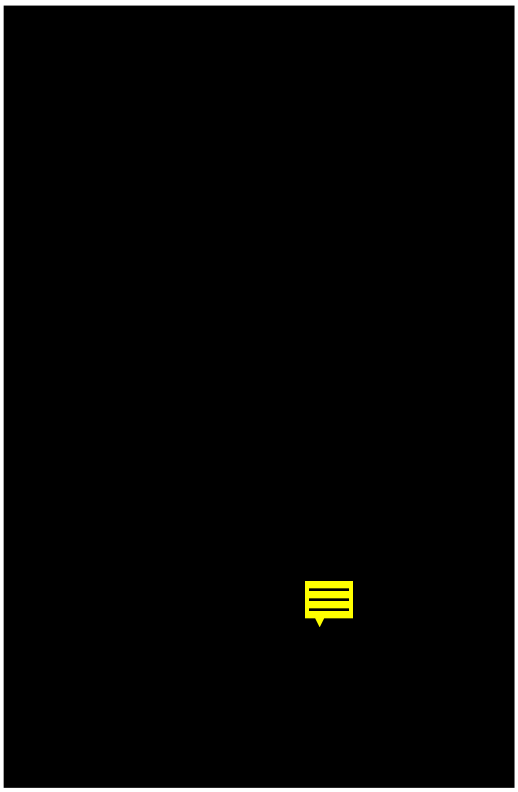

FIG. 3. Large, untreated perianal HSV ulceration at initial presentation. ACV-resistant HSV was isolated following a poor response to oral therapy.

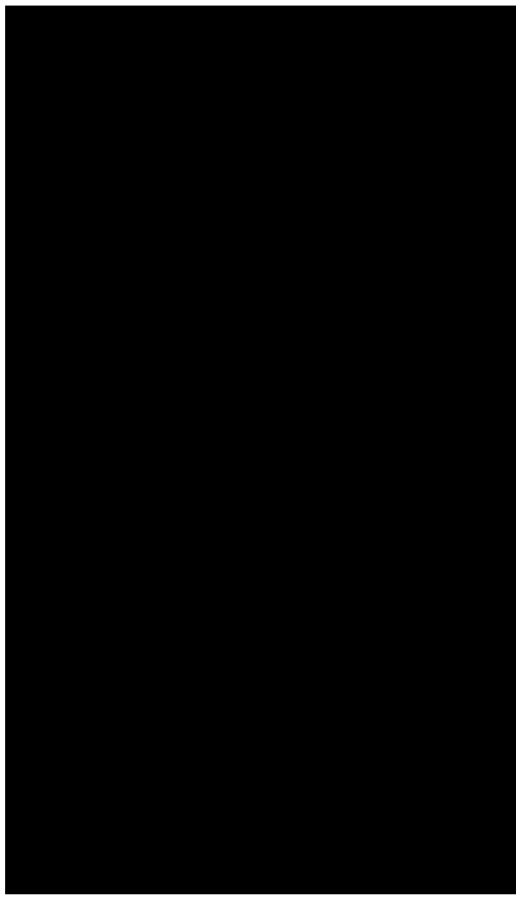

FIG. 4. Herpetic whitlow of the thumb. This patient's lesion was initially misdiagnosed as a bacterial infection and was surgically treated by removal of the nail.

untreated lesions (Fig. 3). A viral isolate should be obtained from poorly healing HSV lesions suspected of ACV resistance for susceptibility testing.

It is not uncommon to find evidence of cytomegalovirus expression within chronic, perianal ulcerative (and occasionally oral) lesions of patients with advanced HIV disease with or without coexistent HSV (29, 31, 38). Because cytomegalovirus cytopathic changes can be seen in normal skin, and because cytomegalovirus is expressed preferentially in areas of active inflammation, it is unclear whether cytomegalovirus is a cause of cutaneous ulceration or is simply expressed in lesions induced by HSV.

Management. In the majority of HIV-infected patients, mucocutaneous lesions of HSV respond completely to oral ACV, 200 mg five times daily. For the unusual patient for whom oral ACV at standard doses is ineffective, increased doses of oral ACV, up to 800 mg five times daily, or intravenous ACV (5 mg/kg three times daily) may be used. For Tzanck smear and DFA-negative perianal ulcerative lesions suspicious for HSV in HIV-infected patients with CD4 lymphocyte counts of less than 200 cells per mm^3, ACV therapy should be instituted pending laboratory confirmation (4). Following complete healing in this subset of patients, long-term suppressive prophylaxis with oral ACV, 400 mg twice daily, should be instituted indefinitely (4).

ACV-resistant HSV. While virtually all ACV-resistant mutants lack thymidine kinase, alterations of the viral DNA polymerase can also lead to drug resistance (22, 30). Any documented herpetic lesion failing to heal following the institution of appropriate ACV dosages should be biopsied and cultured to exclude an additional infectious pathogen; recovered HSV isolates should be evaluated by a reference laboratory for ACV resistance.

Intravenous trisodium phosphonoformate (foscarnet) has proved effective for the treatment of persons with ACV-resistant HSV (12, 21). Once lesions are healed with foscarnet, prophylactic ACV may be reinstituted, although suppressive foscarnet therapy may be required (28, 54). Unfortunately, clinically significant foscarnet-resistant HSV infections may occur in immunosuppressed patients with prior foscarnet exposure (55). In patients with foscarnet-resistant HSV infections, the addition of ACV to foscarnet therapy or the substitution of ACV may result in healing (55). Alternative therapy when oral ACV has failed because of ACV-resistant HSV type 2 mutants includes a 6-week continuous intravenous infusion of parenteral ACV (1.5 to 2.0 mg/kg per h) (20) and, for solitary lesions or limited-size lesions, topical treatment with (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine or trifluorothymidine with or without topical alpha interferon (7, 58).

VZV and HZ

Clinical features. HIV-infected persons may develop primary varicella (chicken pox) when exposed to VZV for the first time (45). In addition, serum antibodies to VZV do not appear to prevent varicella in HIV-infected persons, and varicella can recur. Varicella infections typically follow a benign course, with resolution of scattered vesicular lesions in the absence of

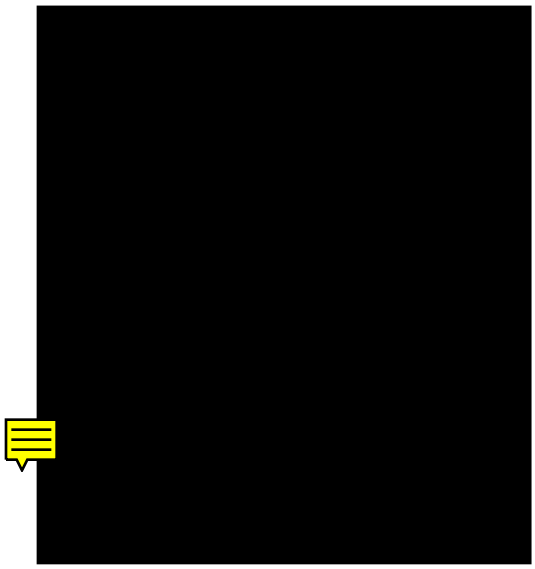

FIG. 5. HSV folliculitis resembling bacterial folliculitis.

therapy. However, pulmonary and hepatic involvement may eventuate in fatal disease, even in patients with asymptomatic HIV infection. Complications are more common among HIV-positive children than in adults (34, 45).

Herpes zoster (HZ) lesions are common among HIV-infected patients (15); roughly 30% of HIV-infected gay men develop HZ within 12 years of HIV seroconversion (9). HIV-infected children and adults with hemophilia have cumulative 10-year risks of developing HZ of 14 and 12%, respectively, with onset of disease occurring with average CD4 lymphocyte counts of 315 cells per mm^3 (23). Among HIV-infected children, HZ may develop rapidly following primary VZV infection (43).

HZ in asymptomatic HIV-infected patients typically pursues a benign course, with resolution of vesiculobullous lesions over 2 to 3 weeks, often without specific antiviral chemotherapy (16). However, severe painful ulcerations followed by postherpetic neuralgia upon healing are not uncommon (40). In addition, recurrent HZ occurs in up to 22% of HIV-infected patients (53).

Disseminated VZV is usually seen among HIV-infected persons with advanced disease. Disseminated disease may arise concurrently with dermatomal HZ, having the appearance of a primary varicella eruption, or may follow the development of a typical zosteriform vesicular eruption (13). Although infrequent, disseminated VZV is more common than disseminated HSV. All HIV-infected patients with disseminated lesions of herpes should be treated for disseminated VZV pending laboratory identification of the virus.

In addition to the vesiculobullous lesions commonly seen with disseminated VZV, patients with advanced HIV infection may develop unusual lesional patterns associated with ACV resistance: ecthymatous, crusted, punched out ulcerations or true verrucous lesions, which may be seen alone (Fig. 6) or in association with the vesicular, ecthymatous lesions (32, 42).

Diagnosis. The diagnosis of varicella and HZ is suspected by the clinical morphology of cutaneous lesions. A confirming

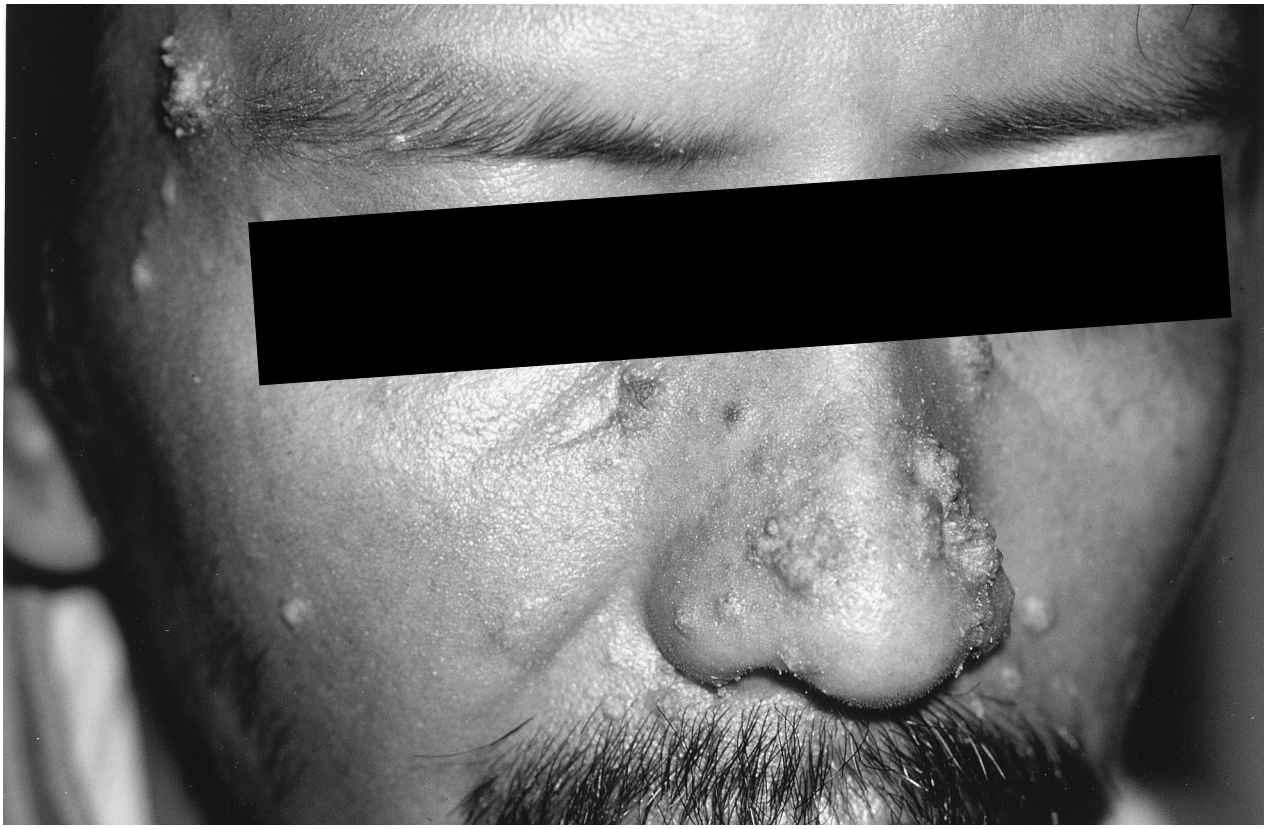

FIG. 6. Scattered facial verrucous lesions of ACV-resistant VZV.

Tzanck smear is usually all that is required. For atypical lesions and disseminated lesions, definitive tests including viral swab culture, DFA staining, or both should be performed. Because DFA testing is rapid and distinguishes between HSV and VZV, it is preferred to viral culture in this setting. As with HSV infections, when results of rapid diagnostic tests are negative, a skin biopsy for histologic examination may be required to exclude another pathogen or to obtain a viral isolate from tissue for susceptibility testing if ACV resistance is suspected. Multiple cultures may be required to obtain an isolate from chronic VZV lesions. Patients with cutaneous HZ in the distribution of the nasociliary branch of the ophthalmic nerve (lesions extending from the forehead to the side and tip of the nose with or without conjunctivitis) require ophthalmologic consultation to exclude ocular involvement with uveitis and keratitis.

Management. HIV-infected patients with varicella, as either a primary infection or reactivation, should be carefully evaluated for evidence of systemic involvement. If evidence of pulmonary, hepatic, or other systemic disease is found, intravenous ACV at a dosage of 10 mg/kg every 8 h, adjusted for renal function, should be given. Oral ACV, 800 mg every 4 h, may be used for persons without evidence of visceral disease, but these persons should be carefully monitored, and if evidence of visceral disease occurs, intravenous ACV therapy should be instituted.

The management of HZ is determined by two factors: the overall immune status of the patient and the location of the VZV infection. In patients with HZ early in the course of HIV disease (CD4 lymphocyte counts above 200 cells per mm^3), oral ACV therapy, 800 mg five times daily for 7 to 10 days, may shorten the duration of vesicular lesions (4). Patients with more advanced HIV disease should receive either oral ACV therapy to prevent the development of chronic lesions or intravenous ACV to shorten the duration and to control severe pain sometimes seen with these lesions. Because complications of HZ ophthalmicus are common even early in HIV infection, all HIV-infected persons with ophthalmic zoster should be given intravenous ACV, 10 mg/kg every 8 h, adjusted for renal function (4). Ocular involvement may require corticosteroid therapy. Patients with disseminated VZV or visceral disease should be treated with intravenous ACV, 10 to 15 mg/kg three times daily, corrected for renal function (4).

ACV-resistant VZV. The chronic forms of cutaneous VZV infection may require prolonged therapy. Ecthymatous lesions may respond to oral or intravenous ACV therapy (13) but frequently relapse following discontinuation of therapy (27). Verrucous lesions failing to respond to intravenous ACV suggest the presence of an ACV-resistant, VZV mutant strain deficient in thymidine kinase (32, 42). ACV-resistant VZV responds to intravenous trisodium phosphonoformate (foscarnet), 40 to 60 mg/kg every 8 h (21). However, healing of ACV-resistant lesions of VZV occurs more slowly (sometimes exceeding 3 weeks) than that of ACV-resistant HSV lesions.

Molluscum Contagiosum

Clinical features. Lesions of molluscum contagiosum are caused by a large (200 by 300 nm) double-stranded DNA poxvirus of the family *Poxviridae* which selectively infects human epidermal cells. These lesions are cutaneous markers for advanced HIV infection, occurring most commonly in the head and neck area in patients with CD4 lymphocyte counts of less than 200 cells per mm^3 (56). Patients with numerous lesions and with lesions involving multiple sites have CD4 counts of less than 50 cells per cm^3, almost without exception. These lesions cause significant morbidity because of their physical disfigurement (Fig. 7) and their potential to induce pruritus and eczematous reactions; molluscum contagiosum is the most common cutaneous manifestation for which AIDS patients seek outpatient dermatologic care (15).

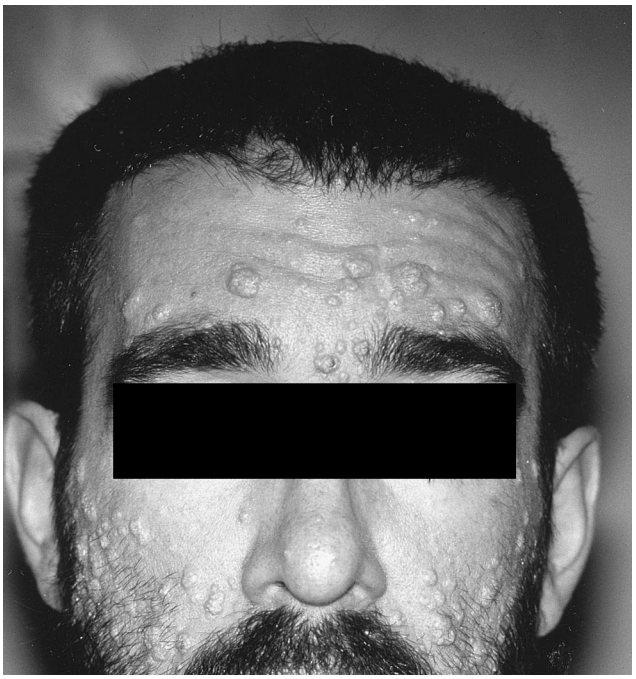

FIG. 7. Numerous scattered facial lesions of molluscum contagiosum in a patient with a CD4 lymphocyte count of 12 cells per cm^3.

Molluscum contagiosum lesions begin as discrete, pearly to flesh-colored, dome-shaped papules of 3 to 10 mm in diameter, often with central umbilication. These lesions are usually grouped but may disseminate widely. Giant lesions with cutaneous horns (up to 1 cm in diameter) have also been described in patients with advanced HIV disease.

Diagnosis. The diagnosis is easily suspected by the distinctive clinical morphology and may be confirmed by the expression of a white, curdlike core from just beneath the surface of an umbilicated lesion which reveals characteristic viral inclusions (molluscum bodies) upon staining (toluidine blue or Giemsa stain). Routine staining of biopsied lesions is also diagnostic, showing a downgrowth of epidermal cells bearing large, eosinophilic molluscum bodies.

Management. Patients with limited numbers of lesions respond well to destructive modalities such as cryotherapy with liquid nitrogen or curettage and electrodesiccation. However, destructive therapies have been disappointing for patients with hundreds of lesions, and no systemic therapy, including systemic alpha interferon, has proved effective (62).

SYSTEMIC FUNGAL INFECTIONS WITH CUTANEOUS MANIFESTATIONS

Clinical Features

The three most common systemic fungal infections with cutaneous manifestations in HIV-infected patients are crypto-

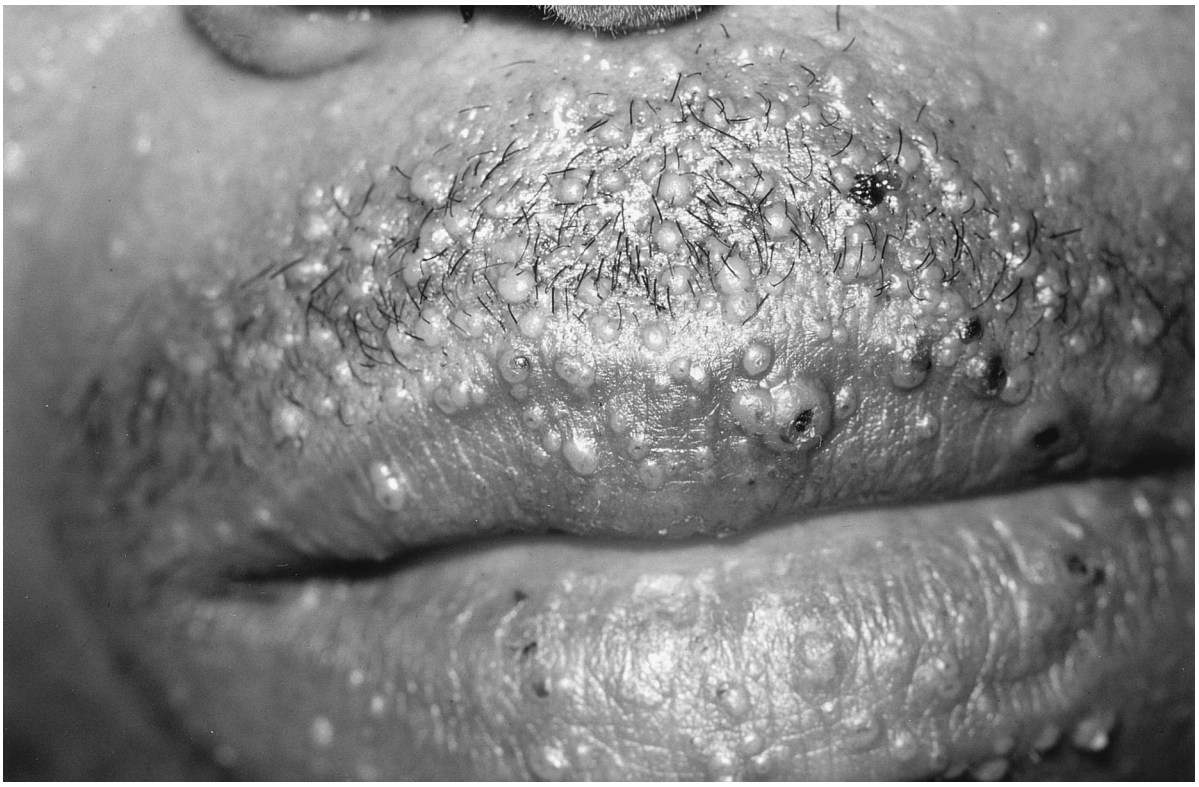

FIG. 8. Numerous flesh-colored, waxy papules with central umbilication due to *Cryptococcus neoformans*. These lesions mimic early lesions of molluscum contagiosum.

coccosis, coccidioidomycosis, and histoplasmosis. Cutaneous cryptococcal lesions may arise in relatively asymptomatic patients; however, all patients have systemic disease. These lesions characteristically resemble lesions of molluscum contagiosum (Fig. 8) (46). Cutaneous lesions of coccidioidomycosis have been reported almost exclusively in severely ill HIV-infected patients. Lesions of coccidioidomycosis in this setting are usually hemorrhagic but otherwise nonspecific in appearance. Cutaneous lesions of histoplasmosis in HIV-infected patients may take on a wide variety of patterns, including hemorrhagic, papular, and ulceronecrotic patterns (Fig. 9).

Diagnosis

To initiate appropriate systemic antifungal therapy without delay, cutaneous lesions suspicious for systemic fungal infection should be promptly biopsied for histopathologic examination of tissue and diagnostic confirmation by culture. Chemiluminescent DNA species-specific probes with greater than 97% sensitivity and 100% specificity for rapid (under 1 h) culture identification of *Cryptococcus neoformans*, *Coccidioides immitis*, and *Histoplasma capsulatum* are now commercially available (59).

The diagnosis of the three most common systemic fungal infections with cutaneous manifestations in the setting of HIV infection can be virtually established by the histologic demonstration within tissue of 4- to 7-μm, encapsulated budding yeast forms of *Cryptococcus neoformans*, 30- to 60-μm spherules containing 2- to 5-μm endospores of *Coccidioides immitis*, or 2- to 4-μm yeast forms of *H. capsulatum* packed within macrophages. These three organisms are well visualized with special tissue stains, including Gomori's methenamine silver and periodic acid-Schiff. *Cryptococcus neoformans* can also be demonstrated in tissue with Mayer's mucicarmine stain. The diagnosis of systemic cryptococcosis may also be rapidly established by cryptococcal antigen testing or by the demonstration of encapsulated *Cryptococcus neoformans* organisms on India ink-stained, wet-mount specimens of cerebrospinal fluid.

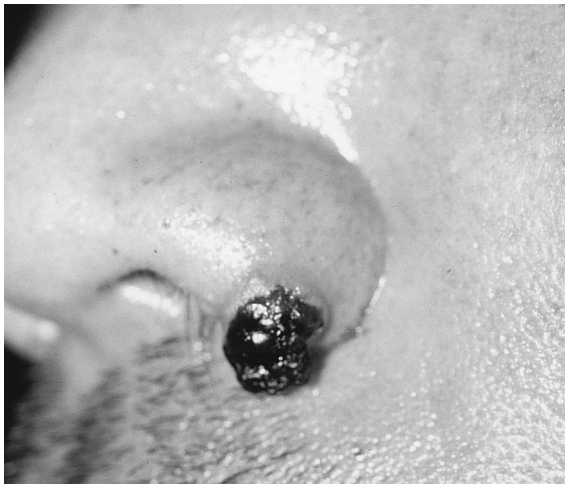

FIG. 9. Nodular lesion with overlying serosanguinous crusting caused by *H. capsulatum.*

FIG. 10. Large plaque of crusted scabies teeming with mites in an HIV-infected patient with altered mental status and CD4 lymphocyte counts of less than 50 cells per cm^3.

Management

Because cutaneous lesions of *Cryptococcus neoformans*, *Coccidioides immitis*, and *H. capsulatum* are indicative of systemic disease, these infections require either single-agent or multidrug systemic chemotherapy with amphotericin B, flucytosine, fluconazole, or itraconazole.

PRURITUS AND SCABIES INFESTATIONS

Pruritus in the HIV-infected patient may have several causes. However, before referring patients with this frustrating symptom to the dermatologist, the generalist and infectious disease specialist should not miss the etiologies of xerosis due to excessive bathing and use of harsh soaps, *S. aureus* infection with or without frank lesions (18), and scabies.

Clinical Features

Scabies infestations manifest with one of two clinical patterns that are dependent on the host's ability to both perceive the infestation and scratch affected sites. Independent of CD4 cell counts, most patients have scabetic burrows at characteristic sites such as the wrist and finger web spaces. A small subset of patients with CD4 counts of less than 150 cells per mm^3 and an altered peripheral or central nervous system interfering with the ability to either perceive the infestation or to scratch affected sites may present with crusted "Norwegian" scabies (24) (Fig. 10).

Diagnosis

The diagnosis is established by the identification of scabetic mites or mite ova or feces in scrapings removed from suspicious lesions with a sterile scalpel blade. Linear or serpiginous scabetic burrows measuring 0.3 to 1.0 cm in length and papulovesicular lesions located most commonly on the volar aspect of the wrists or in finger web spaces offer the best opportunity for a positive scraping. In addition, pruritic, crusted penile or scrotal papules are highly suggestive of scabies.

Management

For adult HIV-infected patients, lindane and permethrin are the antiscabetic agents of first choice. Scabicides should be applied to the entire body, including the head and neck and under the fingernails, for a minimum of 8 h (24). Repeated applications may be required, particularly for patients with crusted scabies. Asymptomatic, close household contacts should also be treated simultaneously. For children under 6 years of age, permethrin is preferred.

CONCLUSION

In this review, we summarize the clinical features, diagnoses, and management of several common opportunistic infections with cutaneous manifestations that either are frequently misdiagnosed, are associated with systemic disease, or are persistent or resistant to treatment in the setting of advanced HIV infection. In addition, BA, a new disease first described in HIV-infected patients presenting with cutaneous lesions, is

highlighted. Because cutaneous infections are extremely common among severely immunocompromised patients, a keen eye and a good understanding of the principles outlined here should help the clinician in caring for HIV-infected patients.

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