

Skin in HIV

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Cutaneous Infections in HIV Disease

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INTRODUCTION

Diagnosing and managing cutaneous infections in a HIV positive patient is a formidable and challenging task. Cutaneous infections are usually atypical and recalcitrant to treatment which will lead to the clue of immunocompromised condition. The two central characteristics of infection in patients with HIV are: the array of potential pathogens is all inclusive, ranging from rare fungal or protozoan infections to common bacterial and viral infections; and the clinical presentation and course of even the most common infectious process may be greatly atypical or obscured by the impaired inflammatory response associated with HIV disease or its treatment. The skin and subcutaneous tissue are the primary barriers against infections and assume even greater importance in patients whose secondary host defenses are impaired. Second, the rich vascular supply of the skin provides, an opportunity for metastatic spread of infection, both from the skin as the initial portal of entry and to the skin from other sources. The factors predisposing to infection are: (a) neutropenia, (b) cellular immune dysfunction, (c) humoral immunodeficiency, and (d) damage to the anatomic barriers (skin or mucous membranes).

With the advent of effective Anti retroviral therapy, the incidence of opportunistic infections have decreased. Clinician must have a sound knowledge of all possible manifestations of opportunistic infections to manage efficiently. The nature of opportunistic infections gives a clue

to the degree of Immunosuppression in HIV patients. Just as the clinical manifestations, even histologic appearances are bizarre. An inflammatory response may be absent on a skin biopsy specimen. Certain cutaneous infections are classified as AIDS defining illnesses.

In addition to the classification of skin infections in the immunocompromised host on the basis of microbial etiology, these cases can also be categorized on the basis of the patho physiologic events that have occurred:

1. Cutaneous infections that commonly occur in immunocompetent patients also occur in HIV infected patients but with the potential for more serious consequences. Conventional forms of infections originating in the skin such as cellulitis appear to be increased in incidence and severity in immunocompromised patients. These infections are commonly caused by Gram-positive organisms such as Group A *Streptococcus* and *Staphylococcus aureus*.

2. Widespread or extensive cutaneous involvement with organisms that usually produce localized or trivial infection in immunocompetent individuals. Usually minor skin infections in normal individuals such as human papillomavirus and superficial fungal infections are more common, more extensive, and may be associated with serious systemic consequences in immunosuppressed patients. Warts (condyloma acuminata) may be so florid with HIV infection as to cause anal blockage. Atypical presentations like oral condyloma acuminatum may occur in these patients. More extensive skin involvement with organisms usually causing limited local infection may occur with herpes simplex, herpes zoster, molluscum contagiosum, human papilloma virus, *Malassezia* species, and scabies. These diseases do not respond to the usual therapies at all or may require higher doses of medication for prolonged periods. In many cases, treatment must be continued indefinitely because, when therapy ceases, prompt recurrence may be seen.

3. Infection originating in the skin caused by opportunistic organisms that rarely produce disease in immunocompetent patients but which may produce localized or disseminated infection in immunocompromised individuals. Infections occur subsequent to injury of the skin that provides the opportunity for these non-virulent microbes to enter and become pathogenic. Important causes of localized disease include the fungi *Paecilomyces*, *Penicillium*, *Alternaria*, *Fusarium*, and *Trichosporon*; atypical mycobacterium; alga- *Prototheca wickerhamii*. These are the most common emerging infections.

4. Disseminated systemic infection metastatic to the skin from a non cutaneous portal of entry. Hematogenous dissemination to the skin and subcutaneous tissues from a distant primary site may be the first clinical sign of a widespread life-threatening infection. Organisms responsible for this category of cutaneous infection are *Pseudomonas aeruginosa*, *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*, *Strongyloides stercoralis*, *Nocardia* species, *Aspergillus* species, *Cryptococcus neoformans*, *Candida* species, etc.

Immune reconstitution disease (IRD) defines a spectrum of conditions characterized by symptomatic and paradoxical inflammatory response to a pre-existing infection that is temporally

related to the recovery of the immune system [1]. More specifically, HAART-induced immune recovery is coincident with an increased CD4 cell count and/or reduced viral load [1]. IRD has been linked to a wide variety of infectious agents, such as *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, *Cryptococcus neoformans*, *Pneumocystis carinii*, CMV, VZV and HSV [2,3]. The disease manifestations have been attributed to paradoxical worsening or reactivation of previously quiescent disorders following HAART-induced immune reconstitution.

This chapter elaborates on the variant clinical manifestations of cutaneous infections in HIV disease.

HISTORY

Unusual infections were being reported in the continent of Africa before AIDS was formally described. In 1981 in the United States, case reports of Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia in cohorts of gay men were reported following which AIDS became clinically defined by a cellular immunodeficiency and by the numerous opportunistic infections that started becoming its inevitable consequence. In 1983, the etiologic virus, later termed the human immunodeficiency virus (HIV), was isolated.

KS and other cutaneous manifestations such as bacillary angiomatosis and disseminated fungal infections were the predominant visible markers of HIV infection during this time period.

Introduction of Highly active anti retroviral therapy HAART has markedly decreased the incidence of opportunistic infections in these patients. While certain cutaneous manifestations of HIV such as bacillary angiomatosis have decreased, others, including zoster, dermatophyte infections, and recalcitrant folliculitis have actually become more frequent. With slowed disease progression and prolonged survival, recognizing the cutaneous manifestation of HIV will take on additional importance with regard to quality of life concerns and as a marker of disease progression and Immunosuppression.

VIRAL INFECTIONS

Acute Exanthema of Human Immunodeficiency Virus Disease

Acute HIV infection, also known as acute retroviral syndrome (ARS) is the period from the initial infection with HIV to complete seroconversion. It is often subclinical and asymptomatic. In 25% to 75% cases ARS is symptomatic and is associated with HIV replication followed by an expansive immunologic response to the virus [4]. It has been shown that early identification and treatment of patients with ARS may preserve immune function.

Pathogenesis

Following transmission, HIV disseminates systemically and massive viral replication occurs. As this occurs, CD4 cells are depleted and the immune system becomes hyper activated. Enhanced immune activation in acute HIV is one of the strongest predictors of progression to AIDS [5]. It

has been suggested that the exanthema could be secondary to infection of Langerhans cells in the epidermis.

Clinical features

When primary HIV infection is symptomatic, the clinical manifestation resembles an acute nonspecific viral infection with fever, lethargy, malaise, arthralgias, myalgias, headache, sore throat, night sweats, anorexia, and lymphadenopathy. Cutaneous manifestations are seen in up to 75% of symptomatic patients and usually appear several days after the onset of symptoms. The most common is a morbilliform eruption with pink macules and papules [6]. The trunk is most commonly involved, followed by the face, lower limbs, and upper limbs [7]. Vesicles, pustules, urticaria, alopecia, desquamation of the palms and soles, and Stevens–Johnson syndrome (SJS) have also been reported [8]. In approximately 25% of ARS, the exanthem is accompanied by painful erosions and ulcerations of the mucous membranes. Ulcers range in size from 5 mm to 10 mm in diameter, are round to oval, shallow with white bases surrounded by a red halo, and can involve the sites of sexual contact like tonsils, palate, buccal, and/or esophageal mucosa. Although the oral cavity is most commonly involved, genital lesions have been reported rarely [9].

Table 2.1: Clinical Manifestations of the Acute Exanthem of HIV Disease

Time after exposure	Clinical manifestations	Laboratory analyses	Other notes
3 to 6 weeks	Malaise, followed by fever as high as 102°F, night sweats, pharyngitis, fatigue, lymphadenopathy, and fine morbilliform rash may develop	Demonstration of HIV p24antigen HIV seroconversion typically occurs within 6 weeks of the acute illness. ELISA or Western blot can be used to detect antibodies	The rash generally involves the trunk, chest, back and upper arms Associated mucosal involvement (oropharyngeal, esophageal, or genital) has also been reported
4–8 weeks	Entire syndrome usually resolves, with complete recovery		

Differential diagnosis

Primary cytomegalovirus (CMV) infection, primary Epstein–Barr virus (EBV) infection, influenza, streptococcal infection, secondary syphilis, toxoplasmosis, rubella, brucellosis, and malaria [10]. Drug reactions, early toxic shock syndrome, Rocky Mountain spotted fever, Lyme disease, herpesvirus infection, and viral hepatitis

Diagnosis

Because ARS may simulate many other conditions, awareness is requisite for diagnosis.

It has been observed that the severity of the seroconversion illness may predict the subsequent course of HIV infection. Symptomatic primary HIV infection may be a period in which initiation of treatment allows immune reconstitution which may improve the subsequent clinical course and CD4+count [11] as treatment with antiretroviral agents results in rapid remission of ARS

in the majority of patients. Patients are highly infectious during primary HIV infection due to pronounced viremia. Thus, it is of prime importance to identify newly infected patients to prevent further spread of the disease.

The diagnosis of primary HIV infection is usually made by documentation of HIV seroconversion, the development of anti-HIV antibodies, with the enzyme linked immunosorbent assay (ELISA) technique confirmed by Western blot assays. In early disease, HIV infection can be documented by isolation of HIV from blood or cerebrospinal fluid (CSF), or demonstration of p24 antigen. Detailed history of sexual and substance abuse must be elicited.

Histopathology

There is lymphohistiocytic infiltrates with occasional plasma cells in the superficial dermis with scattered necrotic keratinocytes in the epidermis.

Management

Treatment protocols for ARS are similar to those used in patients with advanced AIDS. Early treatment often leads to immune preservation and reconstitution. Treatment during primary infection also appears to restore the balance between naive and memory CD4+ T cells and improves lymphoproliferative responses to candidiasis and tetanus [12]. Furthermore; neutralizing antibodies appear more rapidly in treated patients than in untreated patients. In some patients, however, by the time acute symptoms arise, treatment may already be too late to prevent the accumulation of a large pool of infectious virus in CD4+ T-lymphocytes [13]. In addition, it has been suggested that removal of HIV antigen before the evolution of a complete immune response may impair future immune control. Because of the complexities of treating ARS, it is recommended that expert consultation be obtained as soon as the diagnosis of primary HIV infection is made.

Herpes Virus Infections

Herpesvirus infection refers to infection by any of the eight different viruses of the herpesvirus family. Double-stranded DNA herpesviruses include: herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpes virus type 8 (HHV-8). It was hypothesized that herpesviruses may play an important role in the etiology or pathogenesis of HIV. Chronic mucocutaneous herpes simplex virus (HSV) infections were one of the first opportunistic infections described in patients with AIDS, and both cytomegalovirus (CMV) and HSV infections were extremely common in individuals identified to be at highest risk for acquiring HIV, such as homosexual men, intravenous drug users and hemophiliacs. Subsequent clinical studies have indeed demonstrated that infections with HSV, CMV, EBV, and even varicella zoster virus (VZV) are frequent opportunistic infections which occur among AIDS patients [14].

Pathogenesis

HSV-1 is the most common cause of oral herpetic infection, while HSV-2 is the most common etiological agent for anogenital herpes infections. However, crossover infection occurs, likely due to orogenital sexual exposure [15]. Mucosal membrane contact facilitates transmission. It is well documented that genital ulcerations are risk factors for the acquisition of HIV infection. Given that HSV-2 is the most common cause of genital ulcerations HSV and HIV have important interactions that may have serious implications for patients with HIV infection.

HSV infection has been shown to activate latent HIV [16]. In vitro, HSV can potentiate HIV replication independent of HSV replication. This is a result of intracellular transactivation of HIV [17].

Opportunistic diseases associated with the herpesviruses in AIDS patients

Table 2.2: Types of herpes viruses

<i>Herpesvirus</i>	<i>Opportunistic disease</i>
CMV	Retinitis
	Gastrointestinal ulceration
	Hepatitis
HSV-I, HSV-2	Oral-genital/rectal ulceration
	Encephalitis
EBV	B-cell lymphomas
	Oral hairy leukoplakia
	Lymphoid interstitial pneumonitis
VZV	Shingles
HHV-6	Not known
HHV8	Kaposi sarcoma

Inter-Relationship Between HSV and HIV Infection

First, there is strong evidence that HSV infection may increase significantly both HIV transmission and acquisition. The importance of HSV-1 and HSV-2 as cofactors for HIV transmission is corroborated by a number of epidemiological studies and by the results of a recent meta-analysis [18]. In addition, the risk of acquiring HIV was substantially higher during the first 6 months of HSV seroconversion [19]. In line with these observations, studies of discordant couples have documented a decreased risk of HIV transmission when the HIV-seropositive patient was receiving HSV suppressive therapy [20]. These observations are plausible from a biological point of view. On the one hand, HIV shedding is increased through ulcerative herpetic lesions, thus facilitating transmission—HIV being consistently detected in genital ulcers caused by HSV-2 with no association with plasma HIV RNA levels [21]. In addition, HSV ulcerative lesions harbor a high concentration of activated CD4 lymphocytes, which are the target of HIV itself [22].

Another connection between HIV and HSV relates to the response of HIV infection to aciclovir. In early studies, aciclovir in association with zidovudine, a nucleoside analog anti-HIV drug, was associated with increased survival compared to zidovudine alone [23]. Several mechanisms

activation of CD4 cells induced by HSV, as well as the suppressive effect of aciclovir on HSV replication and reactivation, leading to a reduction of morbidity and mortality from herpesvirus infections.

Finally, there is evidence that HIV and HSV mutually interact both in vitro and in vivo. In vitro, it has been shown that some HSV proteins can upregulate the replication of HIV by interaction at a molecular level [24]. In addition, HSV infections seem to affect HIV replication in vivo.

High plasma HIV-1 load has been found to correlate with high rate of HSV shedding and, conversely, patients receiving aciclovir show lower HIV-1 RNA levels than those found in untreated patients [25].

Clinical Features

Herpes simplex

Infections caused by herpes simplex virus (HSV) are divided into primary and secondary (recurrent) forms, which are self-limited processes in normal hosts. Atypical infections in the immunocompromised patients include lesions of larger size, deeper, more invasive and painful, disabling ulcerations, satellite lesions, longer healing time, unusual locations, and atypical morphology. Untreated lesions may become deeply erosive and chronic (Figure 2.1) with the development of extensive areas of necrosis and bacterial superinfection that may distort the initial appearance, resulting in misdiagnosis. Patients with human immunodeficiency virus (HIV) infection have more frequent, persistent, and severe recurrences of HSV, and are more likely to be resistant to standard antiviral medications. Lesions may remain culture positive for HSV for extended periods of time with extensive tissue destruction.



Figure 2.1: Herpes simplex- Persistent ulcer

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)

Any periorificial ulceration in the immunocompromised host should be considered herpes simplex until proven otherwise. Chronic periorificial HSV characteristically has annular or polycyclic (scalloped border) erosions or ulcers. Upon close examination there may be a well

defined, raised, friable, or minute vesicular border surrounding the polycyclic ulcerations.

Recurrent herpes labialis is the most common manifestation of HSV infection in immunosuppressed patients, similar to the clinical pattern seen in normal hosts. However, intraoral involvement, a distinctly unusual finding in immunocompetent patients, is frequently seen in the immunocompromised population. When intraoral lesions occur without herpes labialis, the correct diagnosis may be overlooked. Intraoral HSV appears as single or multiple ulcers or erosions on the gingiva, palate, tongue, or buccal mucosa and display the characteristic polycyclic border. In majority of HIV positive hosts, the HSV infection is not primary but rather reactivation of latent HSV. When the tongue is involved with HSV, lesions are usually present on the lateral surface of the tongue. Linear fissures on the dorsum of the tongue due to HSV1, known as, herpetic geometric glossitis, is another atypical manifestation of HSV in the compromised host [26]. The extremely tender fissures may be longitudinal, cross hatched, or branched in a striking geometric pattern [27]. The central well papillated portion of the tongue is usually involved without accompanying HSV lesions on the lips or palate (Figure 2.2). The tongue lesions of HSV are painful and may impair nutrition. The break of mucosal integrity provides a portal of invasion by both pathogenic and normal microbial flora inhabiting the mouth.

Oral HSV infections may present a myriad of morphologies:

- diffuse erythema mimicking bacterial mucositis;
- coalesced yellow papules resembling *Candida* infection;
- an isolated tongue ulcer appearing traumatic in origin;
- crateriform ulcers with white raised borders containing small vesicles;
- a dark red or violaceous exophytic nodule with or without ulceration on the dorsum of the tongue;
- a yellow white rapidly growing nodule on the lateral tongue mimicking a squamous cell carcinoma [28].

Patients with oral and periorificial HSV (Figure 2.3a, 2.3b, 2.3c) may develop extension of the infection to the esophageal or respiratory tract. These usually occur in patients with HSV infection and nasogastric or endotracheal tubes, which traumatize the mucous membrane.



Figure 2.2: Herpes simplex on the tongue

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)



Figure 2.3a,2.3b,2.3c: Periorificial HSV

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)

Differential diagnosis

Ulcers from trauma (dental or other), radiation- or chemotherapy-induced mucositis, neutropenia, fungal or bacterial infections, and other oral lesions, such as erythema multiforme or recurrent aphthous stomatitis.

Anogenital herpes

Chronic perianal and buttock HSV occurs as single or multiple coalescent ulcers [29]. Because of the location in the perianal area, confusion may occur with superficial ulcers secondary to pressure, maceration, heat, and irritation from urine and or feces. Frank secondary infection with bacteria and/or *Candida* may be present, which may further add to the confusion.

Chronic herpetic lesions can develop into deep ulcerations requiring narcotic analgesics. The location of the ulcers may suggest a diagnosis of decubitus ulcers as well, especially in chronically ill, cachectic, debilitated, or bedridden patients. In contrast to pressure ulcers, HSV lesions are more superficial (Figure 2.4a, 2.4b), often painful, usually multiple with scalloped borders, not confined to pressure areas, and are more often extensive with involvement in the anterior perineal region as well. Anal and perianal HSV may present as chronic ulcers, hyperkeratotic and verrucous lesions, or exophytic plaques and nodules mimicking warts (human papillomavirus) or squamous cell carcinoma. The anal HSV may be accompanied by anal or perianal pain, tenesmus, altered bowel habit, and/or mucoid or bloody anal discharge. A rare manifestation seen as chronic polypoid vegetative plaque with erosions and ulcers on the perianal skin is termed herpes simplex vegetans [30], and it demonstrates pseudoepitheliomatous hyperplasia, plasma cell infiltration, and is positive for herpes simplex virus 1 (HSV1) and/or herpes simplex virus 2 (HSV2). Chronic herpetic ulcers in the inguinal or gluteal crease can result in “kissing,” or opposing, lesions. One variant of atypical herpes simplex virus infection is the presentation of deep linear fissures in the skin folds (inframammary, infra-abdominal, inguinal, or vulvar) termed the “knife-cut sign.” Rare presentations of HSV infection as the knife-cut sign are very likely to be overlooked, as a nonspecific intertrigo and therefore the infection may be undiagnosed and untreated [31].



Figure 2.4 a: Genital Herpes- vesicles

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)



Figure 2.4 b: Herpes genitalis showing multiple superficial ulcers over glans

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)

Digital herpes

In immunocompromised patients, herpetic whitlow may progress to a chronic digital ulceration frequently lasting more than a month, causing erosive crusted lesions with progressive destruction of nail structures and rarely leading to gangrene necessitating amputation [32-34].

Herpetic whitlow (Figure 2.5) may mimic a bacterial infection or paronychia and may undergo unwarranted and unnecessary treatments. The lesion may be unsuccessfully incised and drained or debrided until the atypical manifestations of infection with typical HSV is recognized. Herpetic whitlow is a recognized occupational hazard of medical, paramedical, and dental workers, but may also occur by autoinfection in the compromised host.

Herpetic folliculitis is a herpes simplex-inflicted inflammation of hair follicles that most commonly occurs on the face.



Figure 2.5: Herpetic whitlow

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)

Disseminated herpes infection

Disseminated HSV types 1 or 2 infections are more common in HIV disease. The HSV may result from primary infection or reactivation. HSV in the immunocompromised patient may disseminate hematogenously to visceral organs causing pneumonitis, hepatitis, pancreatitis,

esophagitis, retinal necrosis, or adrenal necrosis [35]. HSV hepatitis should be suspected in any immunocompromised patient presenting with skin lesions, high fever, leukopenia, and anicteric transaminitis [36].

Disseminated cutaneous HSV Types 1 or 2 (Kaposi's varicelliform eruption or eczema herpeticum) may occur in immunosuppressed patients. The eruption starts with small, closely grouped, monomorphic vesicles, usually but not always in areas of preexisting skin disease, and is often initially misdiagnosed as a worsening of the original disorder. The vesicles enlarge, umbilicate, and become pustular and crusted, or ulcerate, accompanied by high fever, malaise, and regional lymphadenopathy. In intertriginous areas, the lesions become confluent. New lesions continue to appear for up to two weeks. The eruption is most frequently located on the head, neck, and the upper part of the body with caudal spread.

Diagnosis

Prompt diagnosis using Tzanck smear, electron microscopy of fresh lesional fluid, DNA hybridization, rapid immunofluorescence using fluorescein-labeled monoclonal antibodies specific for HSV antigens, viral culture, and skin biopsy should be made.

Histopathology

Herpes simplex and VZV infections may manifest as an intraepidermal acantholytic vesicular dermatitis associated with characteristic cytopathic effects in epithelial cells. In severe cases, there is extensive cytonecrosis of the epidermis associated with abundant viral infection of keratinocytes [37]. Often, a complete syncytium of infected keratinocytes can be associated with involvement of follicles and adnexal structures. In some lesions, there may be extensive ulceration so that the herpetically infected cells cannot be visualized. In these cases, special immunoperoxidase stains and DNA probes may be useful in detecting viral antigens that may not be visible on routine microscopic examination.

Treatment

The treatment of HSV infection in HIV requires the systemic administration of specific antiviral drugs (of which aciclovir is the prototype). Higher doses and longer duration of treatment is required for treating HIV infected patients. Several antiviral drugs are currently available for treatment of these infections, including aciclovir, valaciclovir, famciclovir, foscarnet, ganciclovir, and cidofovir. Topical and systemic treatments for secondary bacterial infection are often necessary.

Long-term suppressive prophylaxis with aciclovir, valaciclovir or famciclovir, or foscarnet in case of aciclovir-resistant strains, is recommended. Before HAART introduction, suppressive treatment was to be continued lifelong. In patients presenting with extensive mucocutaneous lesions but who subsequently respond to HAART, interruption of suppressive therapy can be considered when the CD4 cell count increases above 200CD4/mL.

Aciclovir, valaciclovir, and famciclovir are all well tolerated. Rarely, patients receiving aciclovir might experience renal dysfunction and monitoring of renal function is recommended. Thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome resulting in death was reported in initial trials in HIV-infected patients receiving high-dose valaciclovir, but is extremely rare at recommended doses [38].

Drug resistance

Drug resistance occurs most often in HIV-infected patients. Recent case series reported a prevalence of aciclovir resistance among HIV-infected patients with genital herpes of

between 4% and 6% [39]. The degree of immunosuppression and the prolonged use of acyclovir are considered two important factors for the development of drug resistance. HSV mutants (i.e. those with mutant or absent viral thymidine kinase) are responsible for HSV resistance. Increasing the dosage of aciclovir is not useful because most of the resistant strains are characterized by the lack of thymidine kinase (TK-deficient mutants or TK-), thus preventing drug phosphorylation into the active form. In addition, these strains will be cross-resistant to famciclovir and ganciclovir, which also require this phosphorylation step for activation. On the other hand, susceptibility will be conserved towards cidofovir, because this nucleoside drug is not activated by viral, but by host-specific enzymes, and to foscarnet, which does not require phosphorylation to exert its antiviral effect Other causes of acyclovir resistance include erratic or suboptimal dosing or noncompliance with treatment regimens. Acyclovir resistant HSV should be considered whenever lesions persist for greater than one week, when they have atypical manifestations, or when new satellite lesions develop after three to four days of therapy [40]. Ideally, a viral isolate should be obtained for susceptibility testing; however, these tests are not performed routinely in all laboratories. On occasion, patients with seemingly resistant herpes zoster or simplex may be suffering from atrophic gastritis that prevents absorption of acyclovir. A change to intravenous administration of acyclovir or to oral valaciclovir or famciclovir may be effective. Current recommendations for treatment are shown in Table 2.3.

Table 2.3: Recommended Antiviral Treatment and Suppressive Regimens for HSV Infections in HIV-Infected Patients.

Mucocutaneous infection (initial or recurrent, mild)	Aciclovir: oral, 200–400mg 3–5 hr times/day 5–7 days Valaciclovir: oral, 1000 mg bid for 5–7 days Famciclovir: oral, 500 mg bid for 5–7 days
Mucocutaneous infection (moderate to severe)	Aciclovir: oral, 800mg 5 times/day Aciclovir: intravenous, 5–10 mg/kg tid until lesions begin to regress, then oral regimen Valaciclovir: oral, 1000 mg tid
Aciclovir-resistant HSV infection	Foscarnet: intravenous, 120–200 mg/kg/day divided into 2–3 doses Cidofovir: 5 mg/kg once weekly for 2 weeks, then every second weekb Topical trifluridine or cidofovir (1% cream OD)
Suppression of recurrences	Aciclovir: oral, 200mg tid or 400–800 mg bid or tid Valaciclovir: oral, 500–1000 mg bid Famciclovir: oral, 250–500 mg bid Foscarnet (aciclovir resistance): intravenous, 90 mg/kg once daily

Immune reconstitution HSV disease

HSV infections have been observed in the context of HAART-related immune reconstitution. IRD associated to HSV infections has included skin and mucosal lesions, as well as CNS disease. Perianal, genital, or perioral herpes have all been observed [41,42]. Cases have been reported of chronic erosive HSV genital infection presenting weeks to months after starting HAART and characterized by florid erosions and copious exudate and, histologically, by plasma cell and eosinophilic infiltrates [43]. In general, the clinical features of immune reconstitution HSV manifestations do not differ from those observed in typical HSV infections and the diagnostic approach is not different. Treatment is based on antiviral drugs. Corticosteroids may be considered in individual cases.

Herpes Zoster Infections

After primary chickenpox infection and varicella-zoster virus (VZV) viraemia, which usually occurs during childhood, VZV persists as a residual latent infection in the dorsal root ganglia. Although the pathomechanisms are not yet understood in detail, exogenic reinfection and/or immunological dysbalance, due to the decrease of T-cell related cellular immune functions and the loss of neutralising antibodies, may lead to a dermatomal reactivation in patients carrying the latent VZV infection.

Epidemiology

In 1986, Friedman-Kien et al. [44] pointed out, that herpes zoster is an early clinical sign of the development of AIDS. In 1986, the Centres for Disease Control (CDC, Atlanta) included shingles involving more than one dermatome in the symptomatic phase of the HIV disease and AIDS classification (B symptoms). Herpes Zoster is one of the clinical marker for HIV infection.

In many patients with HIV disease herpes zoster occurs prior to any other opportunistic infections. The median CD4-cell count at the time of zoster manifestation was relatively high (271 CD4cells/l) compared to other opportunistic infections. In 1986, Friedman-Kien et al. [44] presumed that the manifestation of shingles seems to facilitate the occurrence of Kaposi's sarcoma. A possible explanation for this comorbidity could be the fact that both diseases are due to viruses from the herpes virus family (VZV and HHV-8). Within this family of eight pathogen viruses, co-infections with two or more viruses, affecting the same type of human cells, have been observed.

Clinical Features

The skin lesions of VZ in the immunocompromised host occur in three forms: (1) dermatomal HZ (which may be one or multiple dermatomes), (2) disseminated HZ, and (3) chronic HZ or recurrent HZ.

Dermatomal Herpes Zoster

Dermatomal HZ is the most common presentation of HZ. The thoracic, cervical, and lumbar dorsal root ganglions are most commonly involved so that most eruptions involve the trunk or neck. A single dermatome (Figure 2.6) with a few scattered erythematous patches with vesicles may be present or multiple contiguous dermatomes (usually less than three)(Figure 2.7) may be involved. Large vesicles or bullae (1–2 cm) and pustules, some of which are certainly umbilicated, may coalesce. Hemorrhagic bulla (Figure 2.8) and marked epidermal necrosis with extensive ulcerations and black eschars may occur. These can slough, producing extensive scarring of the entire dermatome necessitating skin grafting.



Figure 2.6: Dermatomal Herpes Zoster

(Photocourtesy: Bowring and Lady Curzon Hospital, Bowring)



Figure 2.7: Herpes zoster of maxillary and mandibular division

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)



Figure 2.8 : Herpes zoster – hemorrhagic bullae

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)

Recurrent dermatomal HZ (Figure 2.9), usually at a different site, is a problem most often seen in HIV-positive patients. Non-contiguous multidermatomal HZ can occur, though rare. Most cases have been limited to two non-contiguous dermatomes. This unusual presentation has been referred to as zoster duplex unilateralis or bilateralis depending on whether one or both halves of the body are involved. When more than two noncontiguous dermatomes are involved it has been termed zoster multiplex.



Figure 2.9: Recurrent Herpes with scars of the previous episode

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)

Disseminated Herpes Zoster

Dissemination of HZ (Figure 2.10) is defined as cutaneous disease in more than three contiguous dermatomes, more than 20 lesions scattered outside of the initial dermatomal lesions, or systemic involvement. Systemic involvement usually follows the rash with pneumonitis, meningoencephalitis, and rarely hepatitis with acute liver failure which may be fatal.

Disseminated VZV can present with an acute abdomen, small bowel pseudo-obstruction, or pneumatosis intestinalis that precedes or occurs in the absence of skin involvement (zoster sine herpete). Early detection of blood VZV DNA can be done by polymerase chain reaction (PCR) which will facilitate early, empiric treatment with acyclovir. The vaccine strain of varicella (attenuated Oka strain of VZV) has produced disseminated life threatening infection when inadvertently administered to immunocompromised patients [45].

Another form of disseminated HZ seen exclusively in HIV-positive patients, is “recurrent primary varicella” or atypical recurrent varicella. These patients develop one or more episodes (relapsing chicken pox) of disseminated VZ in the absence of an initial dermatomal distribution which is usually painful and characteristic of HZ (shingles). This presentation is clinically indistinguishable from varicella except for

- (a) The occasional paucity of lesions,
- (b) The larger diameter of lesions (1–4 cm),
- (c) The same stage of development of all lesions, and

(d) The prolonged healing time

The alternative explanation to recurrent endogenous outbreaks is exogenous reinfection with VZ virus in an immunocompromised adult.



Figure 2.10: Herpes Zoster- Disseminated form

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)

Chronic Herpes Zoster

HZ persisting for more than 1 month is seen almost exclusively in HIV infected patients with low CD4 counts [46].

Chronic or persistent HZ occurs in three forms:

1. Hyperkeratotic HZ with persistent thickly crusted verrucous lesions which may be seen alone or in association with vesicular or ulcerated lesions [46]. They are usually very chronic (months or years) and are often resistant to acyclovir. The unusual appearance of the hyperkeratotic lesions may be due to coinfection with other organisms such as *Candida albicans*, *Mycobacterium-avium* complex (MAC) or *Pityrosporum* species.

2. Ecthymatous crusted punched out ulcerations with thick overlying eschar or central black eschar characteristically not surrounded by erythema. They may be surrounded by a rim of vesicles. Chronic ulcerative HZ up to 10 cm has been reported [47].

3. Disseminated cutaneous lesions described as vesicular, nodular, hyperkeratotic, necrotic, pox-like or pinpoint-sized papules [48].

In all of these forms of chronic HZ, there is continued prolonged active infection by VZ virus. These atypical chronic skin lesions can occur in HIV-positive patients who have received reduced or so-called maintenance doses (which are subtherapeutic) of acyclovir for prolonged courses.

In these immunosuppressed patients, chronic VZV can:

- (1) Follow varicella (in this situation the lesions show no tendency toward healing and progressively become verrucous or hyperkeratotic in appearance) [49],

(2) Develop directly from HZ, with slow progression from a zosteriform eruption to hyperkeratotic papulonodules, or

(3) Occur with no evidence of classic dermatomal HZ.

Herpes Zoster Ophthalmicus

The presence of erythema and vesicles on the tip and sides of the nose indicate likelihood of eye infection as a result of involvement of the nasociliary nerve (Figure 2.11). Severe eye involvement with corneal perforation, necrotising retinitis, chronic infectious pseudodendritic keratitis and iritis can occur in HIV patients. Sight-threatening eye involvement is rare in HIV infected with herpes zoster ophthalmicus who are started with early acyclovir treatment.



Figure 2.11: Herpes zoster ophthalmic and maxillary division

(Photo courtesy: Dr.Hanumanthayya K, Vydehi Institute of Medical sciences, Bangalore)

Neurological Complications

A higher rate of neurological complications including aseptic meningitis, myelitis, encephalitis, facial nerve palsy and radiculitis has been also reported in HIV-infected. This seems to be an age related complication. Post herpetic neuralgia is a common problem. Involvement of the geniculate ganglion is associated with peripheral facial nerve weakness and deafness (Ramsay Hunt syndrome).

Herpes Zoster, HIV and the Immune Reconstitution Syndrome

Severe immunodeficiency ($CD4^+$ T-lymphocytes $< 200/l$), as observed in untreated AIDS patients, seems to hinder the clinical manifestation of herpes zoster. However, in cases where HAART had been introduced successfully ($CD4^+$ -T-lymphocytes, HIV viral load) and had led to a relevant immune reconstitution, herpes zoster was reported to occur more frequently [50]. In these patients herpes zoster occurred on an average 16.6 weeks after HAART had been started.

Herpes Zoster and the progression of HIV disease towards AIDS

VZV infection in HIV-infected patients that is complicated by fever may signify faster progression of HIV disease.

Histopathology

The histopathologic features of varicella or herpes zoster cannot be distinguished from those of HSV infection: intraepithelial vesicles with ballooning degeneration and multinucleated keratinocytes containing nuclear inclusions are characteristic. Dermal inflammation and vascular damage are more severe with frequent swelling of endothelial cells, microthrombi, hemorrhage, and fibrinopurulent exudates. Diagnostic eosinophilic nuclear inclusions can be seen in endothelial cells, fibroblasts, and neurilemmal cells of peripheral nerves in addition to epithelial cells.

Microscopically, the chronic verrucous VZV lesions seen in AIDS patients show marked orthokeratotic hyperkeratosis, verruciform acanthosis with prominent papillomatosis, and only mild dermal inflammatory infiltrate. It is not uncommon to see involvement of hair follicles by viral cytopathic effects [51]. However, cases with evidence of VZV infection limited to hair follicles are rare: only one case of VZV folliculitis has been reported to date in which the clinical manifestations are described as painful erythematous plaques without appearance of vesicles [52].

Diagnosis

Tzanck smear, serologic testing, immunohistochemical studies, viral culture, or nucleic acid detection are often utilized to achieve the purpose of viral identification. VZV grows much slower in cell culture than HSV and it generally takes 5–7 days before cytopathic effects are detectable in cultured cells. Rapid culture methods (such as shell vial assay) can improve the sensitivity and shorten the test time. Immunofluorescent studies performed on tissue scrapings or immunoperoxidase studies on biopsy specimens are now utilized by many as the test of choice to diagnose VZV. They are fast and have higher sensitivity than viral culture. DNA hybridization or PCR techniques are currently used to detect VZV DNA in CSF or ocular fluids in cases suspicious of central nervous system (CNS) or ocular infections.

Management

Like HSV, the drug of choice for VZV infection is acyclovir, albeit at higher dosages [53]. Mild Varicella/herpes zoster in the early stage of HIV infection, when the immune function is only mildly compromised, can be treated with oral acyclovir (or famciclovir or valacyclovir) [54,55]. The oral acyclovir dosage is 800 mg five times a day for 7–10 days. Intravenous acyclovir is recommended as standard therapy for patients with varicella/zoster who are significantly immunocompromised, patients with severe clinical presentations of varicella or zoster, and patients with ocular or visceral complications. The intravenous dosage of acyclovir is 10 mg/kg three times a day for 7 days or longer.

Acyclovir-resistant VZV infections are rare. They are defined clinically by persistence of lesions for more than 10 days after initiation of acyclovir therapy. Acyclovir resistance may result from low-dosage suppressive therapy for prolonged periods of time. The clinical manifestations

of acyclovir-resistant cases are usually verrucous or crusted lesions that are few in number and localized [56]. Acyclovir resistance correlates with poor prognosis. Duration of acyclovir therapy be extended to 3 weeks before ordering sensitivity tests [56]. Acyclovir-resistant VZV infection is treated with intravenous foscarnet (40 mg/kg three times a day until the lesions heal) [57].

VZV vaccine should not be administered to HIV infected persons except for HIV-seropositive children with no or mild clinical disease [58]. Children with HIV should be followed up closely after VZV vaccination because they have an increased risk of breakthrough infection.

In instances where immunocompromised persons have been exposed to varicella or zoster, varicella-zoster immune globulin (VZIG) can be given to either prevent clinical disease or alleviate its severity. VZIG should be administered as soon as possible after the presumed exposure in order to achieve maximum benefit [59]. Passive immunity established by VZIG administration may last for approximately 3 weeks.

Postherpetic neuralgia, is treated with topical lidocaine patch or capsaicin, intralesional corticosteroids, nerve blocks, and oral analgesics, opioids, tricyclic antidepressants, carbamazepine or gabapentin.

Molluscum Contagiosum

Poxviruses are the large, complex DNA viruses and, of these, molluscum contagiosum and vaccinia have been reported to infect HIV-seropositive patients. They replicate in the cytoplasm and are especially adapted to epidermal cells. In adults whose HIV status is unknown, molluscum contagiosum may be the first sign of HIV infection. The prevalence of MC in HIV infections ranges from 5% to 18%. The severity of MC infection has been shown to be inversely related to the patient's CD4 count. Extensive MC may serve as a marker of poor prognosis or advanced stage of HIV disease.

Pathogenesis

The usual incubation period ranges from two to seven weeks but data from HIV infected cases strongly suggest that the virus may remain latent in the skin for years. The virus is usually transmitted from skin to skin contact with a person with active lesions, as well as through contaminated inanimate objects, such as towels and gymnasium equipment. Self-inoculation by picking, rubbing and shaving spreads the infection. The virus replicates in the cytoplasm and produces molluscum or Henderson Patterson bodies that fill the cytoplasm. The pathogenesis of molluscum contagiosum infection is thought to be related to an epidermal growth factor-polypeptide induced by infection with the virus [60]. Vaccinia causes a similar infection, but rather than the nucleus being filled with molluscum bodies, prominent vacuolar or ballooning degeneration develops within cells. There is prominent inflammation and scarring.

Clinical Features

Typical lesions of MC are centrally umbilicated shiny papules 3–5 mm in diameter. In

otherwise healthy hosts, MC is usually a self-limited cutaneous infection often with fewer than 20 lesions which may resolve spontaneously within 3–12 months. In HIV patients, MC has been clinically characterized by a large number of lesions, unusual distribution, atypical appearance, large size, resistance to treatment, and rapid recurrence. The infection is not self-limited and may spread widely. Severe cases of MC may rapidly develop with hundreds of lesions. The lesions are frequently localized to the face (Figure 2.12) and scalp rather than the genital area. Numerous MC may be so confluent as to give the face a cobblestone appearance or coalesce to form a large plaque. Individual lesions have a tendency to affect follicles and are therefore umbilicated with a central keratinous plug. In some cases, molluscum dermatitis occurs [61]. Extensive MC in the beard area is common and suggests that the infection can be spread by shaving. Giant (Figure 2.13) nodular lesions of MC, with a diameter greater than 10–15 mm, are frequently seen. The MC may become erythematous, lobulated, or verrucous nodules with central necrosis measuring 15–20 mm on the face or scalp. Facial MC may be disfiguring and recalcitrant to treatment [62]. The presence of molluscum lesions on the eyelids is not uncommon in AIDS patients and has been suggested to be pathognomonic of HIV infection. In addition to the well-known extensive periorbital and eyelid involvement in HIVinfected patients, MC can rarely involve the conjunctival cornea. Other unusual manifestations of MC include: a cold facial abscess in an HIV-positive patient with a history of disseminated MC and intraoral MC occurring as a gingival mass [63,64].



Figure 2.12: Molluscum contagiosum on face

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)



Figure 2.13: Giant Molluscum contagiosum

(Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore)

Vaccinia lesions are characterized by tense umbilicated vesicles and pustules that are similar to those described in other patients with widespread disseminated vaccinia infection. Patients are usually clinically ill with fever and acute toxic symptoms associated with viremia.

Differential Diagnosis

Cutaneous horn, basal cell carcinoma, keratoacanthoma, disseminated cryptococcosis, histoplasmosis.

Diagnosis

Application of a small amount of liquid nitrogen or ethyl chloride will highlight the central umbilication of individual lesions, a finding that strongly suggests the diagnosis. In most cases, the diagnosis is readily established on the basis of clinical appearance and/or by histological evaluation of a skin biopsy specimen or a smear of contents of a papule. Virus which replicates in the cytoplasm of infected keratinocytes are seen as basophilic intracytoplasmic inclusion bodies in cytological preparations treated with Giemsa stain. In contrast to the rare occurrence of two infective organisms in the same cutaneous lesion, coexistent histopathological features of both cutaneous cryptococcosis and histoplasmosis with molluscum contagiosum can be found in AIDS patients with severe immunosuppression [65].

Treatment

MC in the HIV population is usually resistant to conventional therapy. They run a chronic relapsing course. Treatment of molluscum contagiosum generally employs destructive measures. Destructive treatments include curettage, electrodesiccation, cryotherapy with liquid nitrogen, applications of trichloroacetic acid (50-90%), podophyllin (25-50%), podophyllotoxin, or cantharidin, excision, carbon dioxide laser ablation and pulse dye laser treatments [108]. Tretinoin (0.025-1%) cream or gel and 5-Fluorouracil, 5% or 1%, are less successful at eradicating lesions than retarding their growth and preventing formation of new ones. Imiquimod used three times a week and even daily has been effective in several cases. Cidofovir 3% successfully cleared some cases which had been recalcitrant to other treatments [66]. Cryotherapy may induce dyspigmentation in dark-skinned individuals. Several small reports have documented resolution of molluscum contagiosum five to six months after initiation of highly active antiretroviral therapy. Vaccinia infection may respond to treatment with cidofovir. Unfortunately, the condition is associated with a high morbidity rate.

Human Papillomavirus

Definition

Human papillomavirus (HPV) infection refers to infections with viruses of the family of Papovaviridae.

Incidence

In HIV-infected individuals, coinfection with HPV is very prevalent. Cutaneous warts account for 2.9-27% of all skin diseases in HIV-infected persons. In one study, anogenital warts were demonstrated in 20% of HIV-infected homosexual men and 27% of homosexual men with AIDS. There are over 120 recognized subtypes of HPV, many with predilection for certain anatomic sites (HPV-6 and 11 cause 90% of genital warts) and some with oncogenic potential (particularly HPV 16, 18, 34, and 39 in genital lesions, HPV16 in digital and periungual skin, and HPV 5 and 8 in *epidermodysplasia verruciformis*).

Pathogenesis

HPV has a tropism for squamous epithelium and enters the cells of the basal cell layer probably through microscopic abrasions. Furthermore, HIV tat protein transactivates HPV, leading to increased HPV expression. Infection with human papillomavirus (HPV) is among the most common viral infections of skin and is responsible for simple warts on glabrous skin, genital warts (condyloma accuminata), and bowenoid papulosis (which is histologically indistinguishable from Bowen's disease or squamous cell carcinoma in situ). Although both immunocompetent and immunosuppressed patients may be infected with HPV, lesions may be recalcitrant and difficult to control, morphologically more numerous, extensive and exuberant, painful, deeply affecting the patients' quality of life, and more numerous in the absence of a normal functioning immune system. Viral warts increase in prevalence with the duration of immunosuppression. Warts in immunocompromised patients may be associated with novel HPV subtypes. Patients with HIV infection, may have multiple verrucae vulgares (Figure 2.14), especially in periungual locations. Multiple plantar warts, including mosaic warts, may cause pain on walking. Palmoplantar warts (Figure 2.15) may be so numerous as to become confluent into keratodermatous plaques. The most common clinical presentation is multiple flat warts with stippled surfaces on the lips, labial commissures, buccal mucosa, and tongue. Extensive flat and filiform warts on the bearded area of the face manifest by small verrucous papules are also seen in HIV-infected individuals and may be the first sign of HIV infection.



Figure 2.14: Multiple warts

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)



Figure 2.15: Plantar Warts

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore)

Epidermodysplasia verruciformis

Epidermodysplasia verruciformis (Figure 2.16) has been reported in patients with HIV infection and consists of a widespread papular eruption of reddish to skin-colored, flat, wart-like lesions mostly involving the sun-exposed areas of the skin [67]. HPV has the appearance of gray, brown, or flesh-colored, sessile or pedunculated, exophytic papules, plaques, or tumors on the penis, vulva, cervix, anus, perineal or perianal areas (Figure 2.17), glabrous skin, or anal cavity. They may present as one lesion or multifocal lesions ranging in size from millimeters to centimeters. Increased proliferation of lesions is associated with progressive immunosuppression, or during immune reconstitution after initiation of HAART in HIV disease.

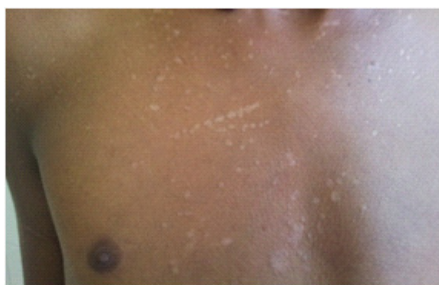


Figure 2.16: Epidermodysplasia verruciformis

(Photo courtesy: Dr. Leelavathy B, Bowring and Lady Curzon Hospital, Bangalore)

Genital warts (condyloma accuminata, CA)

In the immunocompromised host [68], CA may be recurrent (Figure 2.18), recalcitrant to therapy, become widespread, and form large confluent disfiguring cauliflower-like masses becoming several centimeters in size. While common CA are benign, HPV associated giant CA also known as Buschke-Lowenstein tumor (BLT) on the penis or perianal area may manifest

clinically as malignant disease (verrucous carcinoma). BLTs do not metastasize and have a benign histology. However, BLTs have the potential for expansive and destructive growth with malignant transformation occurring in up to 50% of cases [69]. The destruction of local tissues by BLT can cause pain, bleeding, pruritus, fistulae, mechanical obstruction interfering with defecation, and bacterial colonization of the fistulae with abscess formation and sepsis. Paradoxical worsening of BLT as a consequence of immune reconstitution syndrome after the start of HAART has been reported.

Reports of unusual morphologies and HPV subtypes associated with immunosuppression have included:

- HPV type 7, the cause of “butcher’s wart” and normally not associated with persons who are not meat handlers, being commonly found in the oral mucosa and facial skin of HIV seropositive Patients [70].
- Tinea versicolor–like lesions of acquired epidermodysplasia verruciformis(Figure), which are positive mainly for HPV types 5 and 8 in HIV-positive patients [71].
- Urethral and bladder condylomata caused by HPV 6 presenting as hematuria in an HIV-seropositive man [72].



Figure 2.17: Perianal condyloma acuminata

(Photo courtesy: Bowring and Lady Curzon Hospital)



Figure 2.18: Genital warts

(Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore.)

Laboratory Findings

HIV patients with extensive disease are often found to have CD4₊ cell numbers lower than 500 cells/mm³. Some investigators have recommended screening all HIV-infected patients with anal cytologic smears regularly, evaluating abnormal cytology with colposcopic guided biopsies, and obliterating high grade dysplastic lesions [73].

Diagnosis

The diagnosis of clinical HPV-induced lesions is based on clinical features in the context of histopathological findings. It is important to perform biopsies because any case could conceivably represent manifestations of a malignant HPV-induced condition.

Treatment

Unfortunately, no treatment has been shown to eradicate HPV entirely. Common treatments include cryotherapy, electrocautery, CO₂ laser ablation, pulse dye laser treatments, excision, intralesional bleomycin, cantharidin, and imiquimod [74]. Anogenital lesions can also be treated with podophyllotoxin, trichloroacetic acid, intralesional or intramuscular injections of alpha interferon, and cidofovir [74,75]. The use of acitretin at a dose of 25 mg twice daily has been found to be beneficial in promoting the resolution of even large HPV-related warts, although the lesions return upon discontinuation of this treatment [76].

Oral Hairy Leukoplakia (Epstein-Barr virus)

The prevalence of oral hairy leukoplakia (OHL) may be as high as 25% in HIV-infected individuals. The cause is believed to be reactivation of Epstein-Barr virus infection (EBV) (110). EBV selectively infects cells of the B-lymphocyte lineage and certain types of squamous epithelia. The majority of adults harbor a latent phase of EBV. Primary EBV infection is manifested as infectious mononucleosis. With advanced immunodeficiency in HIV-infected patients, EBV leads to OHL, Burkitt's lymphoma, or EBV-associated large-cell lymphoma. Multiple EBV strains can be detected in the lesions. CD4⁺ T lymphocyte counts are below 200 cells/mm³ in most cases, but may be as high as 500 cells/mm³. The lesions usually involute during treatment with effective antiretroviral therapy [77].

Clinical features

Grayish-white, corrugated, shaggy rug-like, verrucous plaques are located continuously or discontinuously along the lateral margins of the tongue (Figure 2.19). These glossal lesions may extend to the ventral and dorsal surfaces of the tongue. When present in the oral mucosa, gingiva or palate, the lesions are flat without hairy projections, strongly resembling oral candidiasis. However, the surface cannot be removed by scraping. The lesions may disappear spontaneously, presumably when cytotoxic T lymphocyte responses to Epstein-Barr virus are mounted, but may recur.

Although oral hairy leukoplakia is usually asymptomatic, some patients may seek treatment due to mild pain, uncomfortable sensation, taste alteration or unacceptable appearance.



Figure 2.19: Oral Hairy Leukoplakia

(Photo courtesy: Dr.Leelavathy B, Bowring and Lady Curzon Hospital, Bangalore)

Treatment

Oral acyclovir at high doses has been reported to achieve resolution within two weeks. Alternatively, daily application of tretinoin gel, cryotherapy or weekly application of trichloroacetic acid or podophyllin resin have also improved or resolved the lesions. Surgical excision is reserved for painful lesions, which are resistant to other therapeutic modalities [78].

Cytomegalovirus

Cytomegalovirus (CMV) belongs to the Herpesviridae family. Between 75-100% of HIV-infected patients are infected with CMV and active CMV infection occurs in 20% of those with CD4 counts below 100 cells/mm³. Acute infections are often asymptomatic, but once the infection is acquired, there is a lifelong latency along with the risk of intermittent reactivation. CMV disease in the immunocompromised host can be the result of either a primary CMV infection in a previously uninfected (seronegative) host, reactivation of latent virus, or reinfection with a new virus subtype. Infection is usually polymicrobial with HSV, Varicella zoster virus, Staphylococcus aureus being the common associated organisms. The patterns of organ involvement and clinical disease vary, with some manifestations characteristic, such as retinitis, gastrointestinal ulceration, hepatitis, interstitial pneumonitis and myelosuppression [79].

Clinical features

Cutaneous manifestations of CMV infection are not sufficiently distinctive. Skin lesions are predominantly those with ulcers and those with maculopapular exanthems. The most common manifestation of CMV infection in the skin is a chronic ulcer of the anal, perianal, or anogenital area. The ulcers may be single or multiple, some with satellite lesions, painful (occasionally non-painful), and vary in size (as large as 15 cm). The borders are sharply margined, round, oval, or irregular, and raised or verrucous. Perianal CMV ulcers may occur because of (1) fecal shedding

of the reactivated virus present anywhere latent along the gastrointestinal tract, particularly the colon which has a special tropism for the virus and is frequently colonized, (2) spread from contiguous CMV procto-colitis, (3) the affinity of CMV for granulation tissue in ulcers, (4) reinfection through anal intercourse reaching the anogenital area hematogenously [79].

Husain et al. described ulcers on the thigh and hand of an HIV-infected woman with pulmonary infiltrates, hepatitis, and retinitis which resolved with ganciclovir [80]. Although uncommon, oral manifestations of CMV infection have included painful erosions or ulcers of the tongue, buccal mucosa, and pharynx. Similar to the chronic perianal ulcers, CMV and HSV have been documented simultaneously in the same skin ulcer of the lower lip in a patient with AIDS [81]. Widespread exanthematous, maculopapular, or morbilliform eruptions often with petechiae or purpura may be a specific cutaneous lesion of CMV infection. Other morphologies of CMV in the immunocompromised host which may be the first clue to systemic CMV infection have included: hyperpigmented and indurated areas of the thighs [82]; a 4-cm verrucous plaque with central ulceration of the heel in a patient with AIDS [83]; crusted papules of the face and arms due to simultaneous CMV, *Staphylococcus aureus*, and an acid-fast bacillus in a patient with AIDS [84]; scattered verrucous cone-shaped plaques with central ulceration or necrosis associated with CMV viremia in a patient with AIDS [83].

Diagnosis

Deep cutaneous biopsies of ulcerated lesions with profuse exudate are needed to diagnose CMV co-infection. Conventional viral culture remains the gold standard method to detect CMV infection. PCR is a rapid and sensitive method to detect CMV DNA [85]. Serologic tests are often complicated by false positive and false-negative results in HIV-infected Patients [85].

Histopathology

Characteristic large intranuclear inclusions with a surrounding halo, or “owl’s eye” of CMV, can be demonstrated in endothelial cells of dermal or subcutaneous vessels in the morbilliform eruptions directly due to CMV and confirmed with immunoperoxidase stain. The swollen endothelial cells may evolve into an obstructive endothelitis, capillaritis, and small vessel vasculitis with accompanying evolution of skin lesions from morbilliform eruption to petechiae, palpable purpura, or infarction and ulceration [86]. On electron microscopy, many viral particles are found in the areas with inclusion bodies.

Treatment

Intravenous ganciclovir, valganciclovir, cidofovir or foscarnet.

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FUNGAL INFECTIONS

As the AIDS pandemic increased, it became the main predisposing factor for both superficial and deep mycoses. Atypical forms of cutaneous fungal infections are common in patients with AIDS. Dermatophyte infection and mucosal candidiasis make up the vast majority of superficial fungal infections in this population. In fact, 90% of HIV-positive patients have oral or vulvovaginal candidiasis. The various other cutaneous mycoses seen in HIV patients are mentioned in the Table 2.4. Cutaneous infection can occur via primary cutaneous inoculation due to trauma, or can manifest in the skin secondary to disseminated infection.

Table 2.4: Classification of Mycoses found in HIV infected patients.

Superficial Mycoses	Deep Mycoses
Candidiasis	Cryptococcosis
Dermatophytosis	Histoplasmosis
Phaeohyphomycosis	Coccidioidomycosis
Hyalohyphomycosis	Aspergillosis
Diseases caused by <i>Malassezia</i> species	Sporotrichosis
Black Piedra	Penicillium marneffeii
White Piedra	

Candidoses

Candidosis is the most frequent opportunistic fungal infection in AIDS and is related to defective cellular immunity [1]. It is caused mainly by *C. albicans*, but other species such as *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis* can also cause infection. Candidosis is considered an early marker of HIV infection but may be present in any phase of the disease. Neutropenia, CD4+ lymphocyte counts below 300 cells/mm³, and the great variety of antibiotics used in HIV patients are risk factors for *Candida* infection [2].

Clinical manifestations

They vary according to the patient's immunologic status, ranging from superficial to systemic infections. There are reports of intertrigo, chronic paronychia, onychodystrophy, and recurrent vaginal infection by *Candida* as signs that are suggestive of immunodepression [3]. Recurrent vaginal candidosis can be an alert for HIV and can manifest itself even with normal CD4 counts in contrast to oropharyngeal candidosis [4]. An estimated 90% of the patients infected with HIV will present oropharyngeal involvement [5]. Oropharyngeal candidiasis (thrush) caused by *Candida albicans*, is the most common opportunistic mucosal infection seen in HIV-infected persons. *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata* tend to cause infection in patients with advanced HIV infection. The clinical variants of mucocutaneous candidosis are:

1. Pseudomembranous form (Figure 2.20) is the acute and most common form which is characterized by whitish plaques in the oral mucosa, palate, tongue, and oropharynx resembling "curdled milk," that can be easily scraped off with a tongue depressor, leaving erythematous, eroded, or ulcerated bases, which may be tender and bleed easily.

2. chronic atrophic (erythematous) candidiasis appears as an occasionally symptomatic, red patch or velvet textured plaque, usually on the hard palate but also on the dorsal tongue and other mucosal surfaces.

3. angular cheilitis or perlèche, which presents as painful, unilateral or bilateral cracking, fissuring, and redness at the oral commissures.

4. chronic hyperplastic candidiasis, asymptomatic white plaques or papules that are adherent and unscrapable are most commonly present along the laterodorsal surfaces of the tongue

5. Intertriginous infections can involve the groin, axilla, (Figure 2.21a, 2.21b) or inframammary areas. Erythematous, moist, scaly patches and papules become confluent into plaques which are surrounded by tiny satellite reddish papulopustules which is the hallmark of candidal intertrigo.

Esophageal candidosis is described as a complication of oral candidosis rarely leading to gastrointestinal hemorrhage and perforation of the wall favoring fungal dissemination. In the anal area, pruritus ani is the chief symptom. Vulvovaginal candidiasis is a poorly tolerated complication that develops in 30 to 40% of HIV-infected women. In some women, the infection is chronic and intractable. HIV-infection should be suspected in non-diabetic men with recurrent candidal balanitis. Other manifestations that may develop include chronic paronychia and onychodystrophy. In infants with congenital HIV infection, candidal diaper rashes are more recurrent and severe [6].

Disseminated candidiasis is rare in HIV-infected individuals. Skin lesions of disseminated candidiasis are single, multiple, localized, or diffuse. They involve the trunk and proximal extremities with less involvement of the head and neck. There are erythematous papules and 0.5–1 cm papulonodules, most with pale centers. Less often the papules are purpuric with necrotic

centers. Other morphologic forms of disseminated candidiasis include necrotic eschars; necrotic pustules and ulcerative plaques mimicking ecthyma gangrenosum; nodular subcutaneous abscesses; nodular folliculitis in hair-bearing areas. Other clues to the diagnosis of disseminated candidiasis include ocular, musculoskeletal, and visceral involvement.



Figure 2.20: Oral Candidiasis

[Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore]

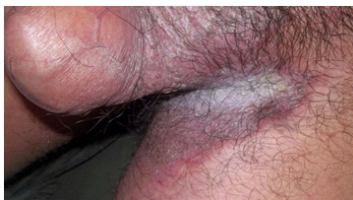


Figure 2.21a,2.21b : Intertrigo in axilla and groin

[Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore]

Diagnosis

Direct examination of lesion scrapings with 10% Potassium hydroxide (KOH), reveals yeasts with or without pseudohyphae. Culture is indicated in cases of resistance to treatment. Blood culture can confirm systemic cases [1]. Skin biopsy for culture will be positive in 50% of patients. Potassium hydroxide examination or Gram stain of a touch preparation of a punch biopsy specimen may allow for rapid diagnosis [7].

The histopathologic findings of candidiasis may be variable, ranging from a leukocytoclastic vasculitis to a sparse perivascular mononuclear cell infiltrate. Organisms are found mainly in and around dermal blood vessels. Identification of *Candida* is difficult on routine hematoxylin and

eosin (H&E) stained sections. Either periodic acid-Schiff (PAS) or Gomori methenamine-silver staining along with examination of step sections of the specimen may facilitate arriving at the diagnosis.

Treatment

Studies suggest that HAART reduces the prevalence of oral candidosis [8]. Treatment should be based on the patient's symptoms. Topical therapy with clotrimazole and nystatin is considered efficient, although recurrence in HIV is common. Topical therapy (for localized and less severe cases) requires contact for a sufficient time (20-30 minutes) between the drug and the oral mucosa and the presence of enough saliva to dissolve the medication. Treatment with only topical antifungal agents is effective in patients with early-stage HIV infection and becomes less effective as the disease progresses.

Systemic antifungals, such as fluconazole, itraconazole, and voriconazole, can be prescribed in cases refractory to topical treatment [1]. Among the orally active azole derivatives, triazoles (fluconazole and itraconazole) are preferred because they produce less toxicity, have less interaction with cytochrome P450, and have less inhibition of steroid synthesis than ketoconazole [9]. Another advantage is its excellent absorption in the alkaline gastric pH environment that is common in AIDS patients with esophageal candidosis. There is in vitro evidence that cross resistance sometimes occurs between fluconazole and itraconazole [10]. Intravenous amphotericin B or caspofungin [11] can be used when azole derivatives show a lack of efficacy, when they are contraindicated, and in cases of systemic candidosis. Secondary prophylaxis with fluconazole is indicated for extensive and severe cases of candidosis [12]. There is evidence, in cases of CD4 counts below 50 cells/mm³, that the excessive use of antifungals could reduce efficacy and induce resistance to treatment [5]. There are reports of primary resistance to fluconazole in the treatment of HIV-positive patients with oral candidosis. In these cases, other oral antifungals are indicated. Resistance is defined as the persistence of lesions of the oropharynx after 7 days of treatment with fluconazole at a minimum dose of 100 mg/d as well as the isolation of a large number of *C albicans* from the lesions [13]. It is considered that antifungal resistance generally occurs in the terminal state of the patient [2].

Dermatophytoses

Dermatophytoses are infections of skin, hair, or nails caused by dermatophytes, fungi with great affinity to keratin [14]. The depletion of CD4+ T lymphocytes (cell count below 200/mm³) in AIDS patients is a risk factor for fungal infections.

Etiology

Trichophyton, Microsporum and Epidermophyton are fungi causing dermatophytoses. The most common dermatophytic pathogens in HIV disease, ie, *T rubrum* and *T mentagrophytes*, are also the most common dermatophytes in individuals not infected with HIV. *T rubrum* causes

infection of the epidermis and nails, but is not a cause of tinea capitis. *T rubrum* commonly causes distal and lateral subungual onychomycosis (DLSO) in anyone, but causes PSO nearly exclusively in those infected with HIV. Superficial white onychomycosis (SWO), which is usually caused by *T mentagrophytes*, can be caused by *T rubrum* in HIV disease. Zoophilic dermatophytes such as *Microsporum gallinae* and *M canis* have also been reported to cause widespread epidermal dermatophytosis [15,16]. In some patients with dystrophic nails, a dermatophyte plus either *Candida* species or a non dermatophytic mold are isolated, constituting a so called “mixed infection.” In the majority of cases, the dermatophyte is the main pathogen and the other organisms colonizes the abnormal nail. In other instances with typical DLSO, *Candida* or nondermatophytic mold is isolated on culture without a dermatophyte, but a dermatophyte might still be the main causative pathogen.

Clinical manifestations

In the majority of cases, *T rubrum* colonizes the webspace of the feet. In time and with increasing immunocompromise, the infection may spread to involve the entire plantar aspect of the feet, ie, moccasin-pattern or chronic hyperkeratotic tinea. This is usually seen in individuals with an atopic diathesis. The toenails subsequently become infected. Epidermal infection may then spread to the hands (tinea manuum), to the groin (tinea cruris), to trunk and extremities (tinea corporis) (Figure 2.22), and to the face (tinea facialis).



Figure 2.22: Tinea corporis

[Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore]

In patients with HIV disease, epidermal dermatophytosis is usually not symptomatic. Pruritus may be experienced in some cases. Cosmetic disfigurement is seen when the infection occurs in such sites as the face, neck, or feet. Pain can occur at the involved site, usually with bacterial superinfection. Patients may present with moccasin-pattern tinea pedis that extends to the dorsum of the foot. In healthy individuals, epidermal dermatophytosis of the feet and hands usually involves both feet and one hand. In persons with HIV disease, both hands may be infected as well as the feet. Patients may also present with tinea incognito, ie, epidermal dermatophytosis that has been incorrectly diagnosed as an inflammatory dermatosis, such as psoriasis, and has been treated with a topical corticosteroid, resulting in exacerbation of the lesions. Tinea cruris

may be incorrectly diagnosed as *Candida* intertrigo and treated with nystatin, which is ineffective for dermatophyte infections. In the absence of immunocompromising factors, widespread non inflammatory (anergic) tinea corporis may be an indication for HIV testing.

Table 2.5: Tinea pedis and its clinical forms.

Clinical forms	Prevalence	Common agents
Interdigital	Common	<i>Trichophyton rubrum</i> , <i>Trichophyton mentagrophytes</i> , <i>Epidermophyton floccosum</i>
Vesicular	Occasional	<i>Trichophyton mentagrophytes</i>
Moccasin	Frequent	<i>Trichophyton rubrum</i>

In PSO, *T rubrum* extends proximally over the dorsal nail plate, over the matrix, and onto the under surface of the nail plate bed, resulting in white dystrophic changes. Tinea unguium (dermatophytic nail unit infection) or onychomycosis (nail unit infection caused by dermatophyte, *Candida*, or nondermatophytic mold) is often asymptomatic. Patients may present with cosmetic disfigurement, especially with fingernail onychomycosis but also with toenail onychomycosis. Pain associated with onychomycosis occurs with painful thickened toenails, with a *Staphylococcus aureus* paronychia associated, and with traumatic paronychia. HIV testing is indicated for patients noted to have PSO who have not recently had HIV testing and who do not have other immunocompromising conditions, because PSO is indicative of significant immunocompromise and most commonly HIV disease. PSO does not occur with HIV-seroconversion, but years afterward with diminished immune function. Children with HIV disease can present with severe, painful tinea capitis such as a kerion.

Dermatophytic folliculitis can occur on the scalp and other hair-bearing sites, caused by *T rubrum* and other dermatophytes. It may be complicated by Majocchi's granuloma and deep abscess formation.

Disseminated infection by *T rubrum* is extremely rare, even in immunosuppressed patients, with few reports of involvement of lymph nodes, bones, spleen, brain, and liver [17].

Differential diagnosis

Epidermal dermatophytosis: inflammatory disorders, such as eczematous dermatitis, seborrheic dermatitis, and psoriasis.

Chronic hyperkeratotic tinea pedis: psoriasis, keratoderma blennorrhagicum. DLSO of either the fingernails or toenails: subungual psoriasis. Paronychial infections of the fingernails: infection by *C albicans*, superinfection with *S aureus*.

Diagnosis

Wood's lamp examination of infected sites is rarely helpful, because dermatophytes that cause infections in patients with HIV do not fluoresce. Wood's light examination does show

bright green fluorescence of hair shafts infected by *M canis* or *M audouini*. A potassium hydroxide (KOH) preparation of epidermal scale, nail or nail bed keratin, or hair should be performed in all cases. To obtain scales for mycologic examination, the proximal part of the nail suspected of proximal onychomycosis or the borders of the lesions in cases suggestive of tinea corporis should be scraped and microscopically examined with KOH. This area is where viable hyphae are easily found. Specificity of a direct mycologic examination is variable. Culture in Sabouraud medium is frequently useful in cases of a negative direct mycologic examination and should be assessed in 4 to 6 weeks. Dermatophyte test medium is an alternative to the traditional culture media for fungi. Dermatophyte growth in dermatophyte test medium is diagnosed by a change from yellow to red due to the production of alkaline metabolites by the fungus. The reading can be made in 3 to 7 days, and the inconvenience is the lack of identification of the species involved [18]. Because of the high prevalence of onychomycosis in HIV patients, mycologic examination of ungual material is important, including special staining. Biopsy of the ungual bed and staining with periodic-acid Schiff (PAS) facilitates fungus visualization and can be useful to exclude other diseases, such as psoriasis [19]. Most cultures will reveal infection by *T rubrum* or *C albicans*.

Histopathologic examination reveals a granulomatous reaction with histiocytes, lymphocytes, and neutrophils in the dermis; hyphae may be absent in the horny layer. If present in the dermis, they can be shorter and thicker than those observed in superficial infections. Majocchi granuloma, also known as nodular granulomatous perifolliculitis, is an example of dermal fungal involvement.

Treatment

Simple topical therapy can often prevent dermatophytosis, especially of the feet. A benzoyl peroxide wash to the feet can be used after showering. An antifungal cream can be applied to the webspaces and feet after drying and before putting on socks. Antifungal powder is preferred by some individuals. Oral antifungal agents, such as terbinafine, itraconazole, or fluconazole are used in the treatment of dermatophyte infections in HIV.

Tinea unguium (Onychomycosis)

Oral terbinafine is effective for treatment of dermatophytosis and candidiasis. The usual dosage for oral terbinafine in the treatment of tinea unguium in patients infected with HIV is 250 mg/day, 6 weeks for fingernail and 12 weeks for toenail involvement [20]. Terbinafine can be taken fasting or with food. With advanced HIV disease (which is defined as a CD4 cell count of 50 to 0 cells/ μ L) and extensive onychomycosis, an additional 2 to 4 weeks of therapy may be indicated. Adverse events with terbinafine include gastrointestinal symptoms, rash, and transient loss of sense of taste [21].

Itraconazole in the capsule form is used to treat dermatophytosis. The capsules are approved for continuous therapy of onychomycosis at a dose of 200 mg/day for 6 weeks for fingernail infection and 12 weeks for toenail involvement. Pulse dosing is also used for toenail onychomycosis; 3 to 4 pulses are advised. To ensure optimal absorption, itraconazole capsules must be taken

with food, especially fatty food, or with acidic drink. Because a low gastric pH is essential for absorption of itraconazole capsules, they should not be taken with agents that raise the gastric pH. Hypochlorhydria or achlorhydria is relatively common in advanced HIV disease and may reduce absorption of itraconazole in capsules. In contrast, itraconazole oral solution or capsules must be taken fasting for optimal absorption. Because itraconazole inhibits the cytochrome P450 enzyme system, serious drug-drug interactions occur when it is given with astemizole, cisapride, mevinic acid-derivative antilipemic agents and benzodiazepines (lovastatin, simvastatin, midazolam, triazolam), and anti-HIV protease inhibitors. Itraconazole must not be given concomitantly with any of these agents. HAART therapy is associated with hyperlipidemia, which is treated with antilipemic drugs. The most common adverse effect is an exanthematous eruption, which occurs in 1% to 2% of individuals not infected with HIV and in up to 15% of individuals infected with HIV.

Fluconazole is effective in epidermal and nail dermatophytic infections. Once weekly intermittent dosing at 300 mg is continued until the nails have grown out normally.

It takes 2 to 6 months for clearing of fingernail onychomycosis and requires 10 months or longer for clearing of toenail onychomycosis [22].

Epidermal Dermatophytosis

Patients with tinea pedis and onychomycosis are best treated for toenail onychomycosis, because tinea pedis usually recurs unless strict secondary prophylaxis is maintained.

Itraconazole capsules 200 mg/day for 1 week for all epidermal sites except the feet; for tinea pedis, 200 mg twice daily is recommended

The recommended dosing for the treatment of epidermal dermatophytosis with terbinafine is 250 mg/day for 1 week for individuals with early HIV disease and for 2 weeks with more advanced HIV disease [22]. Fluconazole is also effective for epidermal dermatophytosis, but the dosing has not yet been established.

Dermatophytosis of Hair and Scalp

Ultramicrosized griseofulvin remains the drug of choice for tinea capitis - 10 to 15 mg/kg daily being administered for 6 to 8 weeks. Itraconazole capsules or solution, fluconazole tablets or solution, and terbinafine tablets have also been reported to be effective alternative drugs.

Phaeohyphomycosis

Phaeohyphomycosis is considered a rare fungal infection caused by a variety of pigment-producing fungi, known as dematiaceous fungi, that are present in nature [23]. More than 100 species have been implicated as causal agents, with *Exophiala*, *Alternaria*, *Bipolaris*, *Wangiella*, and *Curvularia* being the most frequent. *Phialophora* and *Scytalidium* are also frequently described as causes of the infection associated with immunosuppressive diseases such as AIDS [24].

Pathogenesis

Most infections are preceded by a traumatic event that leads to the fungus being implanted in the skin and subcutaneous tissue. The systemic form can occur by progression through the skin or inhalation of the fungus.

Clinical features: Phaeohyphomycosis is classified as cutaneous, subcutaneous, and systemic, with some authors recognizing only the last two [25]. Primary cutaneous phaeohyphomycosis in the immunocompromised patient most often presents as one or more, occasionally grouped, nodules that may be suppurative and often have a verrucous or ulcerating surface. The lesions are usually painless, with chronic indolent courses and smolder for weeks to months before being brought to medical attention. Sporotrichoid nodules are uncommon, but have been reported [26]. Other presentations include a subcutaneous cyst; a boggy verrucous plaque; a crusted erythematous nodule studded with pustules; superficial brown keratotic papules that resemble seborrheic keratoses; subcutaneous abscesses with sinus tracts, dermatomal hemorrhagic vesicles, and crusts; a fluctuant abscess with surrounding cellulitis; a necrotic ulcerated plaque with surrounding erythema resembling ecthyma gangrenosum; Subcutaneous phaeohyphomycosis (also referred to as phaeomycotic cyst or abscess) usually presents as a painless solitary subcutaneous firm or cystic nodule or abscess. Multiple, poorly encapsulated, or fistulizing lesions and satellite papules or nodules are more often seen in immunocompromised patients. Hands, feet, arms, and legs which are commonly exposed to trauma are the areas usually involved. Phaeomycotic abscesses often lack local or systemic signs of inflammation or associated lymphadenopathy or hematogenous spread of infection, and are attached to the skin, but not underlying muscle or bone. The overlying skin is usually intact. Rupture of the cyst onto the skin surface infrequently results in drainage of pus, ulceration, small sinus tracts, or verrucous plaques. When a purulent discharge is present or extracted from a lesion, direct microscopy with potassium hydroxide can reveal light brown spores and hyphae [27].

Secondary or disseminated cutaneous phaeohyphomycosis occurs almost exclusively in the immunosuppressed patient. Most patients have known pulmonary or other visceral involvement before hematogeneous spread to the skin, although dissemination from the skin has been reported [28]. Clinical presentations of disseminated phaeohyphomycosis vary and include tender erythematous subcutaneous nodules of *Bipolaris*; ulcerated papules and haemorrhagic pustules of *Alternaria* scaly hyperpigmented plaques of *Curvularia*; hyperpigmented buttock nodules with a purulent exudate and fistula formation of *Phialophora* [29]; Prognosis is good when the infection is localized, but a mortality rate of nearly 80% occurs with systemic involvement. Disseminated disease is rare, even in immunocompromised patients [24].

Diagnosis

Direct examination, culture, and histopathologic examination are required for the diagnosis. Brownish septated hyphae, with toruloid aspect and yeastlike cells, are seen on direct examination

[30]. The involved species will be identified in culture in a period of 5 to 30 days [38]. Staining with hematoxylin and eosin can help in the diagnosis, but special stains, such as Fontana-Masson, will improve fungus visualization [30].

Treatment

Treatment for localized forms consists basically in surgical procedures associated or not with oral antifungals such as itraconazole. Treatment duration and the dosage varies according to the severity of involvement. Itraconazole (200 to 400 mg/d), terbinafine (250 to 500 mg/d), fluconazole (200 to 400 mg/d), or a combination of the last two can be used, with collateral effects being monitored in immunodepressed patients [30]. For the systemic form or in lesions that are not surgically removed, amphotericin B, itraconazole, and 5-flucytosine are used with variable results [31]. In many cases, improvement of the immunosuppression causes the mycosis activity to decrease [1].

Hyalohyphomycosis

It is caused by non-*Aspergillus* fungi, such as *Fusarium*, *Paecilomyces*, and *Acremonium*. These organisms are more likely to lead to disseminated disease and a worse prognosis than those caused by *Aspergillus* spp. Other hyaline fungi, such as *Penicillium*, *Scedosporium*, and *Trichoderma*, are also causative agents [1]. They are saprophyte fungi dwelling in the soil, vegetal parasites, and degraders of organic material. They have limited pathogenicity and infection depends on the individual's immunologic status.

Clinical features

Most infections by *Paecilomyces* spp occur in immunosuppressed patients [32]. Transmission occurs generally after local trauma in localized forms and by inhalation and hematogenous dissemination in systemic cases. The lesions vary according to the type of infection. Localized infection can manifest as nodules or necrotic papules, cellulitis, subcutaneous abscesses, superficial or deep ulcers, and pustules. The disseminated form appears as multiple, erythematous, or grayish macules or painful papules, sometimes presenting central necrosis. Pustules and subcutaneous nodules, frequently affecting the extremities, can be observed [33]. The central ulceration results from invasion of the dermis by hyphae causing thrombosis. The cutaneous lesions caused by *Fusarium* spp can manifest in several evolutionary stages [33]. *Paecilomyces* spp occur frequently as laboratory contaminants. Despite their implication in human diseases being rare, some cases have been reported in immunodepressed patients, with the eyes being the most involved organ and the skin the least. Cellulitis, nodules, and erythematous plaques have been described [34]. *Penicillium marneffei* presents a preference for the reticuloendothelial system, and when the skin is involved, molluscum-like papules, necrotic nodules, and acneiform lesions appear, always accompanied by lymphadenopathy. The most affected sites are the face, followed by the arms and trunk [35].

Diagnosis

Hyaline-septated hyphae with or without clamydoconidia, arthroconidia, and yeast-like cells are observed on direct mycologic examination. Most cases are diagnosed by culture, and the fungus is easily cultured in Sabouraud medium in 7 to 14 days [36]. Identification of the species is useful, and the sensitivity to antifungals varies according to the involved genus [34]. Biopsy specimens of cutaneous lesions facilitate the diagnosis of the infection in most cases [33].

In histologic sections, PAS staining will show the hyphae as structures with irregular morphology and in 45° and 90° angles [36].

Treatment

The treatment of hyalohyphomycoses is not entirely defined due to the rarity of this infection. For localized forms, antifungals of the azole class and surgery are used [33]. The use of itraconazole (20 mg/d for 9 weeks) and imiquimod (5%) for treating cutaneous hyalohyphomycoses has been reported [37]. Oral voriconazole is a new triazole successfully used in cases of fusariosis, and some authors consider this the drug of first choice [11]. Voriconazole and liposomal amphotericin B could have similar efficacy against *Fusarium* spp, curing about 50% of infections [1]. Terbinafine has been considered a therapeutic alternative in patients with *P. marneffeii*, who have a high mortality rate when therapy is inadequate [35]. Fluconazole is considered ineffective in these infections [38].

Diseases Caused by *Malassezia* Spp

Malassezia (previously known as *Pityrosporum ovale* and *Pityrosporum orbiculare*) is a ubiquitous fungus of low pathogenicity that colonizes normal resident flora of the pilosebaceous units. *Malassezia furfur* is a dimorphic fungus that requires an exogenous source of medium- and long-chain fatty acids for growth. The skin of the human chest, back, and scalp are sebaceous regions rich in fatty acids, which is an exogenous source of lipids for *M. furfur*.

Clinical Manifestations

Malassezia is thought to play a role, or to be the causative factor, in the development of several skin diseases, such as seborrheic dermatitis, tinea versicolor, *Pityrosporum* folliculitis, and possibly atopic dermatitis, particularly in adults [39]. Pityriasis versicolor is a benign and chronic superficial mycosis characterized by brownish, pinkish or hypochromic patches with defined borders, which coalesce and affect extensive body areas [35]. The fungus is initially located in seborrheic areas, with the scalp and acoustic meatus being considered reservoirs. The palms and soles are spared. *Malassezia globosa* is a more frequently isolated species in cases of pityriasis versicolor [14]. The lesions of *Pityrosporum* folliculitis are predictable, distributed over the chest, shoulders, and upper back, where pilosebaceous units are most abundant. The erythematous follicular papules and pustules are minimally pruritic and may number from fewer than ten to hundreds. The pustular lesions of *Pityrosporum* folliculitis may mimic disseminated candidiasis,

bacterial folliculitis, or severe acne. The role of *Malassezia* spp in the pathogenesis of seborrheic dermatitis is uncertain. Its clinical presentation is similar to that of patients in general, but it can present extensively. Ungual involvement by the fungus exists, with a report of onychomycosis by *M furfur* (previously known as *P ovale*) in a patient with AIDS [40]. Severe systemic infections in immunosuppressed patients have also been reported. In recent years, yeast has been implicated in causing invasive disease in premature infants receiving lipid rich intravenous infusions and in severely immunocompromised patients with central venous access devices (CVAD). The fungus colonizes the skin and gains access to the CVAD causing fever and fungemia. Resolution of the infection follows removal of the CVAD, discontinuation of parenteral nutrition including intralipids, and may or may not require parenteral antifungal therapy.

Diagnosis

The clinical diagnosis can be confirmed by the use of Wood's lamp, with the characteristic pink-gold color [41], and by direct microscopic examination of the scales with 10% KOH, with the addition of Parker permanent ink [14]. An alternative is to add Calcofluor and analyze the specimen under the fluorescent microscope. Short, curved, and thick-walled filaments are observed with one or two septa, besides spherical oval yeasts, isolated or in bunches. Culture of *Malassezia* requires supplementation of the medium with a source of fatty acids such as sterile olive oil. Culture is not done routinely, and presently 11 different species can be identified by molecular biology [42].

Treatment

Topical treatment is generally efficient, and the frequency of recurrence is 60% to 80%. Sometimes prophylactic therapy is instituted. Ketoconazole (400 mg monthly or 200 mg for 3 days per month) has been suggested in addition to a shampoo-based ketoconazole or selenium sulphide solution to clean the scalp, acoustic meatus, and body³⁵. *Pityrosporum* folliculitis responds to treatment with ketoconazole (200 mg/d for 10-14 days).

White Piedra, Black Piedra and Trichosporonosis

Piedras are pure trichopathies caused by the fungus *T ovoides* (*T beigeli*) in white piedra and by the fungus *Piedraia hortae* in black piedra. These are asymptomatic and benign diseases of low frequency [14].

Clinical features

White piedra is characterized by small soft white yellowish or yellow-brownish nodules adhered to the hair shafts of the pubic and perianal area, armpits, beard, moustache, and, rarely the scalp. The incidence of white piedra in the pubic region has increased since the onset of the HIV epidemic [35]. In immunosuppressed patients, *T beigeli* can cause trichosporonosis, severe systemic infection with fungemia, fever, lung infiltrate, cutaneous lesions (papules and purple vesicles, usually with central necrosis), and kidney disease [43].

Black piedra is similar in HIV and non-HIV patients and is characterized by dark and hardened nodules in the scalp hair and, rarely, in other body hair. The nodules are usually located in the middle or third distal end of the hair and are well adhered [44]. This fungus can destroy the cuticular layer of the hair, penetrate into the cortex, and later lead to its destruction [45].

Trichosporonosis is an uncommon but frequently fatal emerging opportunistic fungal infection in immunocompromised patients. Trichosporon species, *T. cutaneum* and *T. asteroides* cause superficial infections; *T. ovoides*, white piedra of the scalp; *T. inkin*, white piedra of the pubic area; *T. asahii* and *T. mucoides*, white piedra and deep seated infections. They can cause invasive infections in patients with HIV. Trichosporonosis is associated with frequent visceral involvement and a poorer prognosis. Cutaneous involvement occurs in 30–43% of patients with disseminated trichosporonosis [44]. The most frequently documented skin lesions are purpuric papules and nodules with central necrosis and ulceration. The trunk, arms and face were most commonly involved. Pink nodules on the face and scalp is another manifestation in patients with AIDS [44].

Diagnosis

The diagnosis is easily attained by inspection. The affected hair can be examined after preparation with KOH (10% to 40%). At microscopy of the fungal nodules, hyaline hyphae, arthroconidia, and few blastoconidia are observed [35]. With the use of molecular biology techniques, six species associated with cutaneous infection were identified: *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin*, *T. mucoides*, and *T. ovoides* [46]. In Black piedra direct mycologic examination shows masses of pigmented hyphae adhered along the hair [14], and culture in Sabouraud complements the diagnosis. In Trichosporonosis, skin biopsy and culture gives a high yield. Close observation of biopsy specimens containing *T. beigeli* reveals pseudohyphae, numerous rectangular arthroconidia and a few blastoconidia permitting an accurate diagnosis. *Trichosporon* shares cross-reactive antigenicity with the capsular polysaccharide of cryptococcus that results in a positive cryptococcal antigen test. In invasive Trichosporon infection, antigen positivity to *Aspergillus* galactomannan may also be positive potentially leading to misdiagnosis and inadequate treatment [47]. Fungal cultures of cutaneous lesions are positive in greater than 90% of cases and can minimize the possibility of mistaken histologic identification.

Treatment

The treatment of the piedras consists of hygiene measures, cutting of hair, followed by application of topical antifungals. The use of shampoos with azoles is indicated [14]. Therapeutic options for white piedra are 2% formalin solution; topical imidazole derivatives twice daily for 15 days, and oral itraconazole (100 mg/d) [48]. For black piedra, the administration of terbinafine (250 mg/d) for 6 weeks was described as an efficient treatment. Disseminated Trichosporon infections are often fatal despite antifungal treatment. The death rate approaches 80%.

Cryptococcosis

Cryptococcosis, a disease caused by the yeast *Cryptococcus neoformans*, is considered one of the most common mycoses in immunosuppressed patients, particularly in those with AIDS [1], mainly affecting the central nervous system. Impairment of cellular immunity is considered the main predisposing factor for infection by this microorganism. Cryptococcosis associated with HIV is common in Africa and Southeast Asia [49], and it is a frequent cause of death in patients with AIDS in these regions. *C. neoformans* presents 5 serotypes (A, B, C, D, and AD). These are subdivided into 3 varieties: variety *grubii* (serotype A), which has been recently described, variety *neoformans* (serotypes D and AD), and variety *gattii* (serotypes B and C).

Serotypes A and D most commonly cause infection in humans and 90% occur in immunosuppressed hosts [50]. The distribution of *C. neoformans* var *neoformans* is worldwide.

It is found in bird droppings and contaminated soil, unlike the *gattii* variety, which has been isolated from various species of tree remains [49]. *C. neoformans* serotype D has been associated with a tendency toward skin lesions, when compared with serotypes A, B, or C [1]. Patients with AIDS with CD4 counts below 100 cells/mL are particularly at risk for this infection.

Clinical features

The disease is primarily pulmonary and, usually, subclinical. In immunocompromised individuals, it may rapidly become systemic, involving the central nervous system (CNS), skin and mucosa, bones, and a variety of other tissues. The most important manifestation is subacute or chronic meningoencephalitis expressed by headache and fever. The most common lesions of primary cutaneous cryptococcosis are ulcers, nodules, cellulitis, and a whitlow with or without phlegmon [51]. Disseminated cryptococcosis demonstrates cutaneous involvement in 10–20% of cases. Cutaneous manifestations may present 2–6 weeks prior to the onset of signs of systemic disease. As cutaneous signs may be the first manifestation of this potentially fatal disease, clinicians should have a high index of suspicion for cryptococcosis when a new rash develops in patients with a CD4 count below 100/cmm. Face, neck, and scalp are common areas of cutaneous involvement and include molluscum like lesions, cellulitis, erythematous papules, nodules, pustules, and oral ulcerations. A more acute onset of numerous papules, variation in size, and a central hemorrhagic crust may help the clinician distinguish cryptococcal lesions from molluscum contagiosum. Cryptococcal cellulitis, more often a sign of disseminated disease than primary cutaneous infection, presents with the same erythema, warmth, and tenderness as bacterial cellulitis. Vesicles, bullae, or subcutaneous abscesses may develop. Bullae may rupture to produce areas of ulcerations. Cystic or firm subcutaneous nodules that may ulcerate either spontaneously or after incision may be signs of systemic cryptococcosis. The nodules may be red, warm, and resemble staphylococcal abscesses or erythema nodosum. The cutaneous lesions of *Cryptococcus* may mimic other primary dermatologic disorders in addition to molluscum contagiosum (Figure 2.23) such as pyoderma gangrenosum, rhinophyma, herpes simplex, Kaposi sarcoma, follicular

or nummular eczema, ulcerated squamous cell carcinoma of the vulva, keratoacanthoma, keloid, and basal cell carcinoma. Acneiform papules and pustules with a predilection for the face and neck due to disseminated *Cryptococcus* may enlarge, ulcerate, and coalesce. Most simultaneous infections with multiple organisms in skin lesions occur in AIDS patients with low CD4 counts (<100 cells/mm³).

In the oral cavity, lesions occur with the disseminated form in the gingiva, hard and soft palate, pharynx, and tonsillar pillar, particularly following extractions, in the corresponding alveolus. Oral lesions have been described as having violaceous nodules, granulating tissue, edema, or ulcerations. Most oral cryptococcosis cases have been reported in HIV-positive patients [52]. Of note, cutaneous cryptococcosis may occur in the absence of demonstrable fungal infection in the lung or meninges [53]. Other locations that may be affected include the eyes, kidneys, prostate, adrenals, heart, liver, spleen, bone, muscle, lymph nodes, and thyroid. The definitive diagnosis is established by culture of fluid or affected tissue, with demonstration of the round or oval encapsulated yeast.



Figure 2.23: Cryptococcal lesions resembling Molluscum contagiosum.

[Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore]

Diagnosis

Tzanck smears which are performed by scraping the surface of a lesion, placing the material on a glass slide, fixing with methyl alcohol, and staining with rapid Giemsa technique, reveal multiple encapsulated and budding yeast forms (Figure 2.24). The fluid may be examined using India ink stain or with the specific latex agglutination test for the polysaccharide capsule of the cryptococcal antigen, which is highly sensitive and specific. This test can also be performed with serum and urine. Computerized brain tomography should precede lumbar puncture to exclude expansive lesions, causing obstructive hydrocephalus [49].

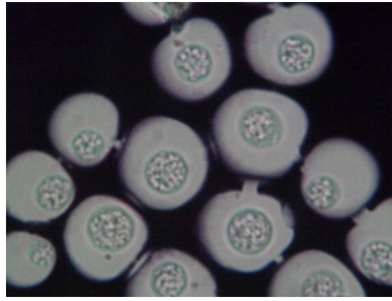


Figure 2.24: Cryptococcus- Capsulated yeast forms seen in Indian ink stain.

[Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore]

Histopathology may be performed in the tissues, and the fungus may be observed with routine or special staining, such as mucicarmine stain, methenamine silver stain or periodic acid Schiff (PAS) [53]. The spores of *Cryptococcus* will stain pink with PAS stain, black with Gomori methenamine-silver, and dark brown with Fontana-Masson. The capsule will not stain with either H&E or PAS stains, but will stain purple with methylene blue, blue with alcian blue and colloidal iron, and red with mucicarmine [54]. In patients with AIDS, histopathologic examination reveals loosely aggregated histiocytes and multinucleated giant cells of the foreign body type; Langhans giant cells are not typically seen. In addition, cryptococci are seen as extra- and intracellular yeast forms with budding.

Treatment

For nonmeningeal cryptococcosis, an induction phase of amphotericin B (0.7–1 mg/kg/day for 2 weeks) followed by fluconazole (400 mg/day) for a minimum of 10 weeks is recommended [55]. The addition of 5-flucytosine during the induction phase reduces the risk of relapse [56]. Untreated cryptococcal meningitis is uniformly fatal. The recommended initial treatment for acute cryptococcal meningitis is amphotericin B deoxycholate 0.7 mg/kg body weight/day IV with or without flucytosine 25 mg/kg PO QID for 2 weeks [57]. Aggressive treatment for elevated intracranial pressure via daily repeated lumbar punctures or CSF shunt placement in patients with meningoencephalitis may improve outcome [58]. Chronic suppressive therapy has now become the standard of care in patients with HIV-associated cryptococcosis, with oral fluconazole (200 mg/day) being the most widely used drug. Several studies have shown that it is acceptable to discontinue cryptococcal suppressive therapy after 6–12 months in patients who have a sustained immunologic response to HAART (with CD4 counts $>150 \times 10^6/l$) if they have had adequate initial antifungal treatment [59]. Maintenance therapy should be resumed if the CD4 counts decrease to <100 cells/ cmm^3 . Institution of HAART in patients with AIDS-associated cryptococcosis may be complicated by immune reconstitution inflammatory syndrome (IRIS), a potentially fatal outcome [60]. IRIS is a result of an exuberant inflammatory response towards incubating opportunistic pathogens. Risk factors for cryptococcosis-associated IRIS include

previously undiagnosed HIV infection, disseminated cryptococcosis, fungemia, lack of CSF sterilization after 2 weeks of antifungal treatment, and the introduction of HAART within 2 months after the diagnosis of cryptococcosis [60]. The most frequent signs of cryptococcosis-associated IRIS are enlarged necrotic lymph nodes and acute CNS related symptoms. Treatment for IRIS includes continuation of the primary therapy against the fungal pathogen as well as continuation of effective HAART and other supportive measures.

Fluconazole is effective prophylaxis in the prevention of cryptococcal meningitis in patients with AIDS. Surgical excision or debridement of cutaneous *Cryptococcus* may be used to remove localized or bulky areas of disease and certainly for the purpose of establishing a diagnosis.

Histoplasmosis

The etiologic agent of histoplasmosis associated with AIDS cases is *H. capsulatum* var *capsulatum*. The fungus inhabits acidic soils rich in organic matter, particularly with birds and bat droppings. Enclosed areas, such as caves or sheds inhabited by bats, are ideal sites for fungal development. Hyaline hyphae are present in the soil in the form of mycelium, branched, with pyriform macroconidia, measuring 3 to 5 μm and spherical macroconidia with thickened walls and spikes measuring 10 to 15 μm .

Clinical features

Three types of systemic disease occur: (1) acute pulmonary (self-limited asymptomatic or “flu-like” syndrome); (2) chronic cavitary; and (3) disseminated. Progressive disseminated disease is a complication of depressed cellular immunity and may occur as a primary infection, reinfection, or reactivation. Mucocutaneous lesions of histoplasmosis present in one of three forms: primary cutaneous inoculation (rarest), reactive erythema (erythema nodosum or erythema multiforme), or mucosal and/or cutaneous lesion(s) of disseminated disease [61].

Primary cutaneous histoplasmosis presents as a nodule or chancriform ulcer with or without lymphangitis or lymphadenopathy [62]. Mucocutaneous lesions of disseminated histoplasmosis occur on the face (Figure 2.25), extremities, and trunk. The morphologic appearance of the skin lesions in the immunosuppressed patient is protean, and more than one morphologic lesion may be present in the same patient. The lower the CD4 count, the more atypical the morphology. Uncommonly, mucocutaneous lesions present only after the initiation of anti-retroviral therapy and may be due to the immune reconstitution syndrome [63]. Rarely mucocutaneous histoplasmosis may be transmitted between HIV-infected partners [64]. Mucocutaneous lesions most commonly present as papules, nodules, or ulcers, but may also present as papules with or without necrotic centers [65]; erythematous macules and patches; maculopapular eruption [66]; follicular, pustular, rosacea-like, or acneiform lesions; vesicular herpetiform lesions; fistulae; verrucous, crusted, or vegetative plaques; pyoderma gangrenosum-like ulcers; molluscum contagiosum-like papules; erythema multiforme-like lesions; exfoliative dermatitis; vasculitic lesions; psoriasiform exanthematous eruptions; nodular purpuric lesions; panniculitis; cellulitis;

papules with transepidermal keratin elimination; and violaceous plaques mimicking Kaposi sarcoma. Disseminated histoplasmosis may present as a widespread morbilliform eruption mimicking a drug rash and examination of a peripheral blood smear for intracellular yeast forms can lead to a rapid diagnosis. Mucosal lesions, present in 26–58% of patients with disseminated disease, may be the presenting manifestation of disseminated histoplasmosis. Patients frequently have hoarseness, weight loss, painful ulcers, and sore throat. The most common locations include the tongue, palate, buccal mucosa, lips, gingiva, and oropharynx, but the epiglottis, nasal vestibule, submandibular salivary gland, perianal area, and genitalia may also be affected. Lesions described include ulcerated nodules and papules; deep or vegetating ulcers mimicking squamous cell carcinoma; palatal perforation; necrosis with heaped up margins; hemorrhagic plaques on the tongue; perianal and penile herpetiform lesions; painful, well-demarcated penile ulcers with yellow exudates with or without inguinal lymphadenopathy; and perforation of the prepuce.



Figure 2.25: Histoplasmosis of face

[Photo courtesy: Dr. Hanumanthayya K, Vydehi Institute of Medical Sciences, Bangalore]

Diagnosis

The diagnosis can be made by serology in the acute phase, histopathology, sputum culture (in chronic obstructive pulmonary disease), and blood culture [49]. The latter is performed by the lyses centrifugation method with 5% saponin, which has demonstrated positive results in more than 70% of histoplasmosis cases associated with AIDS [67]. Biopsy and bone marrow culture may be useful, and should be considered in patients with pancytopenia or a hematocrit less than 30% or a leukocyte count less than 4000/ μ L or a lactate dehydrogenase level greater than 600 U/L [68]. Microscopic observation of the fungus in venous blood leukocytes is considered useful for the diagnosis, but it is not routinely used. Scarification of ulcers and erosions are useful for performing the Tzanck cytodagnostic examination with Giemsa stain, which allows diagnosis of approximately 70% of cases [69]. The determination of glycoprotein antigen in blood and urine can be done by radioimmunoassay or enzyme-linked immunosorbent assay, achieving diagnosis in 90% of cases with a diagnostic and prognostic value [70].

Treatment

The frequency of histoplasmosis associated with AIDS has declined as a result of antiretroviral therapy. Treatment includes an initial phase of 0.5 to 1.0 mg/kg per day amphotericin B for 12 weeks or 600 mg itraconazole for 3 days, followed by 400 mg for 12 weeks. Clinical remission was achieved with 400 mg per day of itraconazole in 75% of patients treated [71]. Improvement begins within 10 to 15 days following treatment. Another option is 800 mg per day of fluconazole. This drug is less effective than itraconazole; however, it is indicated in cases of meningoencephalitis because of its ability to cross the blood-brain barrier.

Prophylaxis with 200 mg per day itraconazole must be considered in HIV-positive patients with a CD4 count lower than 150 or 100/mm³. Prophylaxis should be interrupted when the patient is asymptomatic, is on antiretroviral therapy with an improvement of immune status for more than 6 months, or when there is an undetectable viral load and the patient has a CD4 count higher than 150/μL. The mortality rate for untreated disseminated histoplasmosis is approximately 95% [72].

Coccidioidomycosis

This systemic mycosis is caused by the dimorphic fungus *Coccidioides immitis*. Its geographic distribution is limited to the southwestern United States, Mexico, and Central and South America [73]. *C. immitis* is found as a saprophyte in arid soils with high levels of salt and an alkaline pH. Infection occurs by inhalation of arthroconidia, an infectious form of the fungus that reaches the pulmonary alveoli. After 2 or 3 days, they become endospores. After about 3 weeks, specific cellular immunity causes the formation of epithelioid granulomas with activated macrophages. Acute coccidioidomycosis is associated with conditions that decrease cellular immunity, such as HIV/AIDS. In these individuals, there is a 50 to 200 times greater risk of disseminated disease [1]. In areas of high endemicity, the presence of coccidioidomycosis and AIDS must be considered in the differential diagnosis of severe conditions affecting the CNS and lungs.

Clinical features

The clinical picture is a community-acquired pneumonia with cough, fever, and focal pulmonary infiltrates [74]. In contrast, immunosuppressed patients with interstitial reticulonodular involvement often have general deterioration. Their evolution is usually severe, with a 70% mortality rate, even when treatment is started within the first 8 weeks. The most common fatal complications are respiratory failure and septic shock. Involvement of the meninges, lymph nodes, and skin have been reported, and osteoarticular involvement is rare [74].

The cutaneous manifestations of coccidioidomycosis can be divided into two categories: reactive, which includes erythema nodosum, acute generalized exanthem (toxic erythema), erythema multiforme-like eruptions, Sweet syndrome, and reactive interstitial granulomatous dermatitis; and due to the organism itself, either secondary to dissemination to the skin or, rarely, primary inoculation. Coccidioidomycosis is an acquired immune deficiency syndrome

(AIDS) defining disease, with CD4 counts less than 250/ m L predisposing to active infection [75].

Erythema nodosum and toxic erythemas represent cutaneous hypersensitivity reactions to coccidioidal infection. Disseminated coccidioidomycosis presents with systemic symptoms such as fever, cough, and night sweats. Dissemination to the skin, meninges, bones, and joints is common. Skin lesions of disseminated coccidioidomycosis, most commonly verrucous plaques (usually facial), subcutaneous cold abscesses, and ulcerations, are rarely seen in immunocompromised hosts. Specific skin lesions described in immunosuppressed patients include papulopustules; morbilliform eruption; an indurated, erythematous plaque on the thigh and erythema and edema of distal fingers after fomite transmitted coccidioidomycosis in an immunosuppressed child (skin biopsy not performed); abscess; necrotizing cellulitis; erythematous masses on the buttocks at the site of pentamidine injections in an HIVpositive patient (*locus minoris resistentiae*) [76].

Diagnosis

The diagnosis of coccidioidomycosis is based on histopathology, serology, and culture. *Coccidioides* species can be detected in tissues or clinical samples using a variety of standard staining techniques, including hematoxylin eosin. Tissue specimens can often be used for rapid diagnosis of coccidioidomycosis as detection of spherules with endospores from such specimens is pathognomonic. This technique can also be used on bronchoalveolar lavage fluid and sputum specimens. Cytological staining methods, especially Papanicolaou and Gomori methenamine, are useful for rapid detection in respiratory secretions [74]. In more than 40% of cases, *C immitis* is found by direct microscopic examination and in more than 90%, it is isolated in culture. Blood culture can be used in the diagnosis of severe pulmonary disease. Some patients with HIV present with seropositivity for *C immitis* antigens, especially by complement fixation. A complement fixation reaction with a titer of 1/32 or more should be considered reliable for diagnosing coccidioidomycosis. Culture is a very useful tool for diagnosis. The incubation period varies from 2 to 7 days [77].

Treatment

Treatment is based on the use of amphotericin B and azoles. Amphotericin B is used in severe cases, especially in the pulmonary form with diffuse reticular nodular involvement and meningitis. Almost 60% of patients with meningitis die after 2 years despite treatment. A long period of treatment with 800 mg daily of fluconazole is used as an alternative. Itraconazole 400 mg per day for 12 months has also been shown to be effective. Ketoconazole has been used successfully, but it has a higher incidence of adverse reactions. Voriconazole 800 mg per day is prescribed in cases of therapeutic failure [78]. Posaconazole is also described as effective therapy [79]. There is no consensus regarding secondary prophylaxis; recent studies support interruption after immune reconstitution with HAART. Others report that relapses are common and secondary prophylaxis with 200 mg per day fluconazole or itraconazole is indicated, even with antiretroviral therapy.

Aspergillosis

Aspergillosis is an opportunistic mycosis most commonly caused by *Aspergillus fumigatus* and *Aspergillus flavus* [1], although other species have been described, such as *Aspergillus glaucus*, *Aspergillus terreus*, and *Aspergillus niger*, which are saprophytic fungi. Contamination occurs by inhalation of spores, leading to bronchopulmonary aspergillosis. This systemic mycosis has been increasingly reported in HIV infected individuals. These saprophytic fungi cause primary cutaneous aspergillosis by direct posttrauma inoculation (intravenous catheters), or secondary skin lesions that result from invasive disease with hematogenous dissemination, usually seen in immunocompromised individuals [52].

Clinical features

Its clinical picture may have 3 clinical variants: saprophytic, allergic, and invasive infection [52]. The HIV-infected population generally develops the invasive form by the end of the course of the illness. Invasive disease may occur in individuals with severe immunodeficiency (CD4 <20 cells/mL) with an incidence of 10% [80]. Lung involvement is a sign of invasive disease. Other involved areas include the CNS, heart, kidneys, bones, face, larynx, eyes, ears, and oral cavity.

Among reported cases of HIV-related cutaneous aspergillosis, the majority have had *A. fumigates* infection. Skin involvement (5%-11%) has various clinical manifestations, including clam like lesions, verrucous plaques and pustules, ulcerated nodules, and thickened areas of overlying erythema. The lesions are found preferably in the extremities and the head, sparing the chest. The prognosis is much worse for patients with skin involvement secondary to disseminated disease.

Diagnosis

Diagnosis of aspergillosis is suspected when septate hyphae are seen in fungal stains of tissue. In some cases, a presumptive diagnosis of primary cutaneous aspergillosis can be made rapidly by staining the roof of a bulla or by examining a potassium hydroxide preparation of a biopsy specimen [81]. In general, however, diagnosis of cutaneous *Aspergillus* infections requires biopsy of a skin lesion taken for both culture and histopathology. Skin biopsy specimens for suspected fungal lesions should be taken from the center of the lesion and should reach the subcutaneous fat as *Aspergillus* tends to invade blood vessels of the dermis and subcutis, resulting in an overlying ischemic cone. In the microbiology laboratory, fungal hyphal structures can be stained directly from tissue specimens with the whitening agent calcofluor, which will fluoresce when exposed to UV light. On histopathologic examination with routine stains (such as H&E), *Aspergillus* hyphae may be seen in consequence of either staining the nucleus and cytoplasm of the fungus or revealing the cell wall by a negatively staining shadow. The Gomori methenamine silver (GMS) stain can clearly and reliably detect hyphae, as the hyphal cell wall stains black while the tissue background stains green. *Aspergillus* hyphae have acute angle branching with frequent septations. In cases of pulmonary disease, radiographic findings may include diffuse interstitial pneumonitis

or a localized wedge-shaped dense infiltrate representing pulmonary infarction, related to the organism's predilection for invasion of vascular endothelium [82].

Treatment

Lesions of primary cutaneous aspergillosis may require both surgery and antifungal therapy. The drug of choice for localized infection is voriconazole 6 mg/kg intravenously every 12 hours for 1 day, followed by 4 mg/kg intravenously every 12 hours; thereafter, oral doses of 200 mg every 12 hours are prescribed. In the context of invasive aspergillosis, voriconazole appears to be superior. In refractory infections, intravenous caspofungin (50 mg per day after an intravenous dose of 70 mg per day loading dose) or liposomal amphotericin B (3-5 mg/kg per day) may be useful rescue therapy. An alternative scheme includes posaconazole, itraconazole, or other echinocandins. Secondary prophylaxis is recommended in cases of chronic immunosuppression, using azoles such as voriconazole, posaconazole, or itraconazole [83].

Sporotrichosis

The etiologic agent of sporotrichosis, *Sporothrix schenckii*, is a dimorphic fungus found in the soil and in animal feces. It has a worldwide distribution, but it is most commonly found in temperate and tropical climates [84]. The infection generally results from cutaneous inoculation by trauma, but pulmonary infection may occur after spore inhalation. Cutaneous inoculation may occur from scratches from rose thorns, salt meadow hay, cactus plants, carnations, conifer needles, splinters, cuts from barbs, brushing against infected tree bark or contaminated mine timbers, sphagnum moss (especially associated with bonsai trees), or handling of certain animals (especially cats, armadillos, and fish). Predisposed to infection are farmers, florists, gardeners, forestry workers, veterinarians, and carpenters.

This organism has a mycelium phase that develops in the environment, and incubated culture at 28°C, developing rapidly growing gray-colored colonies with short aerial hyphae. Microscopic examination shows thin, branched, hyaline, septated mycelium with formation of asexual spores (conidia) that are located on both sides of the hyphae forming rosettes at the end of unbranched sporophores. In the tissues and in blood agar medium at 37°C, they form shell- or cigar-shaped unicellular elements.

Clinical features

The clinical presentations of sporotrichosis include lymphocutaneous (70%), fixed cutaneous (20%), disseminated (including disseminated cutaneous), and extracutaneous disease [85]. The classic cutaneous lesion of sporotrichosis begins at the inoculation site as a painless papule or pustule that develops into a nodule that ultimately enlarges, softens, ulcerates, and drains purulent fluid. Neighboring asymptomatic nodules develop, extend along lymphatics, and may or may not be accompanied by lymphangitis or lymphadenopathy (Figure 2.26). Fixed cutaneous sporotrichosis is a solitary lesion or group of lesions that remains localized to the inoculation site

and may present as facial cellulitis (children), pyodermatous erosions, verrucous or psoriasiform plaques, pyoderma gangrenosum-like ulcers, or an erythematous ulcerated nodule with rolled translucent borders and central eschar, mimicking a basal cell carcinoma [86]⁸⁶. Cutaneous lesions of disseminated sporotrichosis tend to be widely distributed, but the morphology is protean: necrotic ulcers; painful, ulcerated papules with a seropurulent exudates [87]; ulcers with rolled erythematous borders; nodules that may be umbilicated, ulcerated, crusted, irregular, or suppurative; ulcerating grayish black smooth papulonodules; psoriasiform plaques; have all been described.



Figure 2.26: Sporotrichosis- lesions along the lymphatic spread.

[Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore]

Mucosal lesions are rare, but laryngeal, conjunctival, pharyngeal, oral, and nasal involvement have been reported [87]. Lesions in the oral or nasal mucosa may present as ulcerations with a thin overlying granulomatous surface and erythematous borders or gingival hyperplasia with painful, erythematous, proliferative papules and plaques on the alveolar process or gingiva.

Involvement of the CNS, joints, spleen, face, and bone marrow has been described [88]. There are reports of pneumonia, arthritis, endophthalmitis, and meningitis in patients with HIV. Meningitis is very rare in patients with AIDS and is difficult to diagnose, as the cerebrospinal fluid (CSF) may be negative in culture.

Diagnosis

In patients with AIDS, biopsy and culture of skin lesions should always be performed. Numerous fungal cells are seen, sometimes within macrophages. After staining with Giemsa, they can be mistaken for *H. capsulatum*. Finding *S. schenckii* by direct microscopic examination (skin scrapings), isolation in blood sample cultures, material from needle puncture biopsy of nodules, and bronchoalveolar lavage may be useful in achieving the diagnosis.

Treatment

Amphotericin B is indicated for severe and disseminated infection at a dose of 0.7 mg/kg per day for 3 to 4 weeks. Classic treatment with potassium iodide is not recommended for patients with HIV/AIDS infection or other conditions associated with immunodeficiency. Itraconazole

has a high concentration in the skin and is generally more effective than fluconazole. Liposomal amphotericin B has been used when there is intolerance to ordinary amphotericin B [84]. For coinfecting patients, maintenance of therapy is recommended and itraconazole is the drug of choice, at a dosage of 200 mg per day 3.

Infection by *Penicillium Marneffei*

Penicillium marneffei is a dimorphic fungus that causes disease in both healthy and immunocompromised hosts. It has become an important opportunistic pathogen in HIV-positive patients, particularly in northern Thailand [52]. A significant increase in incidence was observed in Vietnam, Hong Kong, southern China, India, and Japan. Exposure to soil, especially during the rainy season, constitutes a high risk factor for penicilliosis [89]. In HIV infected patients, it occurs in the disseminated form. The clinical and histological features of the focal form simulates tuberculosis [52]. Penicilliosis was considered a late complication of AIDS with a CD4+ cell count below 100 cells/mm³.

Clinical features

The clinical picture is similar to disseminated mycosis involving the monocytic-histiocytic system with lymphadenopathy, hepatosplenomegaly, prolonged fever, weight loss, fatigue, anorexia, anemia, persistent cough, micronodular pulmonary infiltrates or interstitial pneumonia, clam like skin lesions, abscesses or subcutaneous nodules, and leucocytosis [90]. Skin lesions are usually located on the face, chest, and extremities, being present in 70% of disseminated cases [1].

Oral lesions are described as papules, ulcers, or shallow erosions of various sizes, covered with a yellow exudate. The palate, gingiva, lips, tongue, and throat are the most involved areas⁵². Genital ulcers may be present. A high index of suspicion is necessary for the diagnosis, including an appropriate history, especially outside of the endemic areas.

Diagnosis

The diagnosis is confirmed by histology and culture. *P. marneffei* has an intracellular parasitic stage, and within macrophages it has the same shape and size as *H. capsulatum*. Immunofluorescence with monoclonal antibodies, and DNA hybridization techniques have been successfully used for rapid diagnosis in infected tissues. In Sabouraud dextrose agar culture at 27°C, the organism produces velvet like colonies with red pigment that diffuses in the culture. The identification of cultures may be accelerated by the application of techniques such as exoantigen or hybridization (polymerase chain reaction) [91].

Treatment

P. marneffei has good sensitivity to amphotericin B, ketoconazole, itraconazole, and 5-flucytosine. Granulocyte-macrophage colony stimulating factor enhances the fungicidal ability of phagocytes against the fungus and can help in the treatment [92]. Although itraconazole is extremely effective, the initial treatment involves the use of amphotericin B followed by

itraconazole for up to 10 weeks [52]. Suppressive therapy is necessary with itraconazole. Prophylaxis is discontinued in patients with low or undetectable viral loads and when CD4 counts are greater than 150/ μ L [93].

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BACTERIAL SKIN INFECTIONS IN HIV

Bacterial skin and soft tissue infections (SSTIs) are seen frequently in HIV-infected individuals. The risk of bacteraemia and septicaemia goes up to 25% following cutaneous bacterial infection and therefore may signify systemic infection. Central lines, concomitant chemotherapy, injectable drug abuse and the presence of other skin diseases pose additional risks. Even normal skin flora can become systemically pathogenic in the HIV patient; so great care should be taken in skin antisepsis prior to surgery and instrumentation [1]. On the other hand systemic bacterial infection may display dermatological signs such as splinter haemorrhages and acral papulonecrotic lesions [1]. The common pathogens which cause bacterial cutaneous infections in HIV include *Staphylococcus aureus*, *Pseudomonas* spp., *Escherichia coli* and *Streptococcus pyogenes* in that order; polymicrobial infection may be present in up to 40% of cases.

Cutaneous Manifestations of *Staphylococcus Aureus*

Staphylococcus aureus is the most common cutaneous bacterial infection in persons with HIV disease. Approximately 50% of HIV-infected persons are nasal carriers of *S. aureus*, explaining in part the high rate of infection in contrast to 30 % of non HIV infected individuals [2,3]. Infection with *S. aureus* may occur before any other signs or symptoms of HIV infection. Upto 83% of patients suffer from *Staphylococcus aureus* at some time during the course of their illness and its incidence is more in children with AIDS compared to adults [4]. Morphologic patterns that may occur include: bullous impetigo, folliculitis, ecthyma, abscesses, cellulitis, hidradenitis-like plaques, and pyomyositis [5]. Folliculitis (Figure 2.27) and impetigo (Figure 2.28) may be recurrent and persistent in HIV disease, especially in children.

Bullous impetigo usually occurs in hot, humid weather, which presents as very superficial blisters or erosions, most commonly seen in the groin or axilla. Because the blisters are flaccid, they rupture early and leave erosions and crusts.

Ecthyma is an eroded or superficially ulcerated lesion with an adherent crust. Underneath the crust, there is often a plane of purulent material containing staphylococci. Hence removal of this crust is necessary to treat the lesion topically.

Folliculitis due to *S. aureus* occurs most commonly in the hairy areas of the trunk, groin, axilla, or face, especially in men who shave. The primary lesion is follicular pustules. Gram's stain and culture confirm the diagnosis and allow selection of appropriate antibiotic therapy. But in the context of HIV other causes of folliculitis should also be kept in mind.

Table 2.6: Differential diagnosis.

- Staphylococcal folliculitis
- Malassezia folliculitis,
- Dermatophyte folliculitis,
- Eosinophilic folliculitis,
- Demodex folliculitis
- Acne vulgaris or rosacea
- Cryptococcosis folliculitis
- Very rarely, micrococcus, Acinetobacter baumannii and Clostridium perfringens folliculitis, herpes simplex and zoster viral folliculitis.

Even cryptococcosis can present as a corporeal pseudofolliculitis. Flexural staphylococcal folliculitis may mimic candidosis [1]. HIV-infected persons with scabies have concurrent *S. aureus* folliculitis in about 50% of the patients. Occasionally, follicular lesions extend more deeply, forming abscesses. Rarely, there may be formation of a large, violaceous, hidradenitis-like plaque. Which may be studded with pustules and have deep tracts connecting infected follicles.

Community associated Methicillin resistant staphylococcus aureus (CA-MRSA) is also posing a serious threat to the HIV affected. It usually causes minor Skin and soft tissue infections (SSTIs) but it can progress rapidly to life-threatening infections like necrotizing fasciitis, osteomyelitis, pneumonia, and bacteremia [6,7]. Recent evidence has suggested that its prevalence may be on the increase, particularly among HIV-positive homosexual men, with studies showing an association with high-risk sex, drug-using behaviour, absence of co-trimoxazole prophylaxis, partners with skin infections, recent hospitalization, prior MRSA infection and recent receipt of β -lactam antibiotic. However, studies disagree on whether CD4 cell counts and antiretroviral therapy affect the likelihood of infection with MRSA [1,8].

Itchy folliculitis occurring in people with low CD4 cell counts is often not due to bacterial infection, but immune dysregulation. Persistent lesions should be biopsied to determine whether the problem has a bacterial source. Folliculitis which do not respond to antibiotics, an aspirate or biopsy of an infected lymphnode is done to rule out MRSA, mycobacterial infection, cat scratch disease and malignancy.



Figure 2.27: Multiple folliculitis over knee.

[Photo courtesy: Dr Hanumanthaiah, Vydehi Institute of Medical Sciences, Bangalore]



Figure 2.28: Impetiginized lesions over beard region

[Photo courtesy: Dr Hanumanthaiah, Vydehi Institute of Medical Sciences, Bangalore]

Cellulitis in HIV

Cellulitis and soft tissue infection (Figure 2.29, 2.30) are underestimated complications of HIV disease, but they have a broad etiological and clinical spectrum, are predominantly community-acquired, and are responsible for an appreciable morbidity, due to the supporting role of i.v. drug addiction, and the frequent hematogenous dissemination (which is significantly related to the progression of immunodeficiency and underlying disease) [9]. The frequent polymicrobial etiology requires a combination antimicrobial therapy (to be guided by in vitro susceptibility studies), which may avoid a complicated and recurrent disease course in the great majority of cases [9]. More than 90 pathogens have been isolated from cellulitis lesions in HIV and the most common agent is *S aureus*. Other bacterial causes include group A streptococci, group B streptococci, *H influenzae* type B, and *P aeruginosa* [10].

For facial cellulitis, if the patient is ill or a child, or if the cellulitic area has a purplish hue, ceftriaxone or cefotaxime should be used to cover for *H influenzae* type B. For gravely ill severely immunocompromised patients, antibiotic coverage should be extended to include gram-negative enteric bacteria and *P aeruginosa*. Culture from leading edge of cellulitis will help in making microbiological diagnosis. Based on isolation of an organism, therapy should be instituted accordingly.



Figure 2.29: Necrotising Fasciitis caused by *Pseudomonas aeruginosa*

[Photo courtesy: Bowring and Lady Curzon Hospital, Bangalore]



Figure 2.30: Fournier's Gangrene

[Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore]

CATHETER-RELATED SOFT TISSUE INFECTIONS

The most common bacteria causing catheter-related soft tissue infections are *S aureus* and *S epidermidis*. A wide variety of gram-positive cocci and gram-negative bacilli also can cause these infections. Initial treatment with vancomycin will provide coverage for *S aureus* and *S epidermidis*. Therapy can then be directed toward the bacteria isolated from the catheter tip and infected site. Because the infection is deep-seated, antibiotic treatment often must be continued for at least 7 days following catheter removal.

Using new materials such as covalently linked heparin on the central venous catheter surface, electrically charged central venous catheter, novel topical agents that interfere with bacterial colonization, antiadhesin molecules and agents that block the gene expression involved in the biofilm formation, are all being tried to reduce the high catheter-related infection risk among HIV+ patients [9].

Lymphadenitis

Adenitis may be caused by typical bacterial pathogens, such as *S aureus* and group A streptococci, but also can be caused by *S viridans*, *Enterobacter* spp, and *S epidermidis* [11]. The etiologic agent of cat-scratch disease, *Bartonella henselae*, also should be considered in the diagnosis. Initial treatment is to use antibiotics against *S aureus* and group A streptococci and then can be changed according to the culture and sensitivity report.

Peri Rectal Abscess

Peri rectal abscesses are seen more frequently in immunosuppressed patients, especially those with neutropenia [12]. The most frequently isolated bacteria include *Bacteroides* spp, *E coli*, *Peptostreptococcus* spp, *K pneumoniae*, *P melaninogenicus*, and *S aureus*. In addition, *Acinetobacter* spp and *Enterococcus* spp have been reported in HIV-infected children [11]. A combination of clindamycin or metronidazole plus an aminoglycoside, ceftriaxone, or cefotaxime

will be active against most of the bacteria associated with these infections. The non-neutropenic child should have prompt surgical drainage or aspiration of the abscess, even if local fluctuance is not palpable [13]. Material obtained from drainage or aspiration of the abscess should be sent for Gram stain and aerobic and anaerobic culture. Antibiotics should be tailored to the bacterial isolates obtained from the infected material. In severe neutropenic HIV infected child, drainage often is not attempted because of the lack of pus formation. Intravenous antibiotics are given for 2-3 weeks in such cases. Later, surgical drainage or aspiration can be performed if there is abscess formation.

Treatment for bacterial skin infections includes keeping the lesions clean with soap and water. Parents should be instructed in good hand washing to prevent the spread of lesions. *Staphylococcus aureus* often colonizes the nails, nares, and anogenital areas of patients. Antibacterial creams, such as mupirocin, should be applied to these sites twice daily for 3-4 weeks to prevent spread of infection to other cutaneous sites and to household contacts. Antibacterial washes, such as chlorhexidine, or vinegar baths (add 1 cup of plain white vinegar to the bath water) may be used to treat impetigo and folliculitis, as well as prevent recurrence of any of these superficial bacterial infections.

Dermatologic Manifestations of *Pseudomonas aeruginosa* Infection

Chronic ulcerations and macerated skin are susceptible to colonization by gram-negative bacteria, especially *P. aeruginosa*. Skin lesions caused by *P. aeruginosa* infection are more common in advanced stages of HIV infection and include ecthyma gangrenosum, (Figure 2.31) erythematous macular or maculopapular lesions, and violaceous nodules [14]. *P. aeruginosa* can be cultured from these lesions and, often, from the blood. Ecthyma gangrenosum is a round, indurated, painless, ulcerated lesion covered by a central black eschar. It usually occurs during *P. aeruginosa* bacteremia, but may occur following folliculitis. The manifestation of disseminated *P. aeruginosa* infection presents as erythematous and macular, maculopapular, or nodular lesions [15]. In patients with advanced HIV disease there is potential danger for sepsis and even death resulting from a seemingly benign infection. Treatment with 2 antipseudomonal antibiotics for at least 2 weeks should be instituted. Drainage of purulent material or wide surgical excision may be needed for recovery [16,17].



Figure 2.31: Ecthyma gangrenosum over right leg.

[Photocourtesy: Department of Dermatology, Bowring and Lady Curzon Hospital]

Dermatologic Manifestations of Bartonella: Bacillary Angiomatosis

Bacillary angiomatosis is a treatable opportunistic infection, was initially reported as epithelioid angiomatosis, atypical subcutaneous infection in patients with advanced HIV disease. Initially causative agents were designated as *Rochalimaea* which has been reclassified as *Bartonella*. The infectious agents causing this condition have been identified as two species of *Bartonella* - *B. henselae* and *B. Quintana* [18]. Cat exposure and cat scratches are risk factors for acquiring bacillary angiomatosis [19]. Bacillary angiomatosis initially was considered primarily a disorder of the skin, but systemic involvement is common.

The most characteristic cutaneous lesions of bacillary angiomatosis resemble pyogenic granulomas -- fleshy, friable, protuberant papules-to-nodules that tend to bleed very easily. In addition, deep cellulitic plaques and subcutaneous nodules may occur. Lesions range from a few to hundreds. Clinically, the skin lesions mimic as vascular tumors, especially Kaposi's sarcoma (KS) [19]. A prominent vascular proliferation that forms an elevated papule histologically characterizes the lesions. In the interstitium neutrophilic leukocytes are prominent. Adjacent to the vascular lumina, bacterial aggregates are found which represent collections of the bacterium. Diagnosis is confirmed by identifying the causative organism in affected tissue using silver stains or electron microscopy.

Fever, night sweats, weight loss, and anemia are common systemic findings in patients with bacillary angiomatosis. Mucosal lesions of the conjunctiva and upper respiratory tract have also been reported. Visceral lesions may be more common than cutaneous lesions. The most common visceral organs involved are liver and spleen with or without skin lesions [18]. They present with abdominal pain, hepatosplenomegaly, fevers, and elevated levels on liver function tests. Biopsy of Liver and spleen may show a pattern called peliosis which is large ectatic vascular spaces. Abundant bacilli are adjacent to these vascular spaces. Osseous lesions may precede the appearance of skin lesions and manifestations as bone pain [17]. Routine radiographs reveal a lytic lesion at the site of pain. Isolated lymph node enlargement can also be present at times [20]. The diagnosis of visceral disease is made on the basis of biopsy of the affected organ and examination with silver stains or electron microscopy. In the untreated patient, fatal widespread visceral disease including cerebral involvement may occur [21].

Treating affected patients with erythromycin in full doses (500 mg orally 4 times daily) resolves the lesions. It also responds to doxycycline (100 mg orally twice daily). In 3 to 4 weeks cutaneous lesions usually resolve, but therapy should continue for at least 8 weeks. Patients with visceral disease should receive at least 4 months of therapy. Relapses can occur if treatment is not continued appropriately. In vitro sensitivities as currently performed do not correlate well with clinical response. Bacillary angiomatosis lesions do not respond to radiation therapy [19].

Syphilis in HIV - Cutaneous Manifestations

Cutaneous presentations of primary and secondary syphilis in HIV-infected persons are

usually similar to those in non-HIV-infected persons. However, syphilis seroconversion may be delayed, and standard serologic tests that aid in diagnosing syphilis may be unreliable [22]. Also, in primary syphilis, presentation with multiple ulcers is more common in HIV-infected patients. Rapid progression of secondary syphilis to tertiary syphilis and syphilis maligna has been reported in patients infected with HIV [23,24]. Dermatologists should regard all genital, perianal and oral ulceration and any papulosquamous eruption with great suspicion and handle them with circumspection. Rarer manifestations of syphilis which are not encountered in the post penicillin era, such as keratoderma, lues maligna (necrotic red nodules) and nodular syphilis (simulating lymphoma) have been reported in association with HIV [1].

Lyme borreliosis pseudolymphoma [25] and a persistent erythema chronicum migrans (with meningoradiculitis) have occurred [26].

Dermatological Manifestations of Mycobacterial Infections

Mycobacterium tuberculosis; *M. avium-intracellulare* complex (MAC); and, rarely, *M. kansasii* may present with cutaneous lesions in HIV patients. The commonest mode of presentation is acneiform papules and indurated crusted plaques [27].

Cutaneous tuberculosis can be seen as a part of reinfection with, or reactivation of, *Mycobacterium tuberculosis* which occurs early in HIV infection. The clinical presentation is diverse, including scrofula, scattered violaceous papules, acute miliary tuberculosis of the skin, keratotic papules, nodules and palmar/plantar keratoderma and tuberculides [28].

Atypical mycobacterial skin disease in patients infected with HIV is usually due to *Mycobacterium avium-intracellulare*. This occurs as part of a disseminated infection in up to one-third of patients at CD4 T-cell counts below $50 \times 10^6/L$ (rare below $200 \times 10^6/L$). Cutaneous manifestations thus far reported include the scaling plaques, crusted ulcers, ecthyma like lesions, verrucous ulcers, inflammatory nodules, panniculitis, pustular lesions and draining sinuses [29]. Primary cutaneous MAC infection manifesting as sporotrichosis like lesions was described in a patient with AIDS [29].

The possibility of co infections, which may be multiple, should be kept in mind. Co infection with *B. quintana*, MAC, and Cytomegalovirus (CMV) has been reported in an AIDS patient [30].

In patients with HIV, *M. haemophilum* can also present as violaceous draining nodules and superficial ulcers on the extremities, trunk, head, and genitalia. Skin involvement has also been reported with *M. kansasii*, *M. haemophilum*, *M. fortuitum*, *M. lentiflavum* and *M. marinum* [1].

The diagnosis of mycobacterial infection can be problematic because characteristic histopathological features such as caseating granuloma may be absent due to diminished cell-mediated immunity [31]. All biopsies where tuberculosis and/or atypical mycobacterial infection are suspected should be stained for acid-fast bacilli (which may be very numerous because of

diminished cell-mediated immunity) and a separate portion sent for mycobacterial culture under appropriate laboratory conditions.

HAART and specific conventional antituberculous drugs are used. Atypical mycobacterial infection is treated with a macrolide and ethambutol.

Unlike other mycobacterial disease, the epidemiological and clinical features of leprosy have not been significantly altered by the HIV infection with the exception of IRIS (Immune Reconstitution Inflammatory Syndrome) [32].

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CUTANEOUS PARASITIC INFESTATIONS IN HIV

Parasitic infections which can present as cutaneous manifestations in an HIV patient can be classified into arthropod borne, protozoal and helminthic infections.

Arthropod Borne Infections

Scabies

Scabies occurs frequently in HIV-infected patients and usually presents with the typical pattern of pruritic papules with accentuation in the intertriginous areas, genitalia, and finger webs. They may also have unusual clinical features for example the skin of the head and neck is often involved, which is highly unlikely in non-HIV-infected adults. The infestation exaggerates with advancing immunosuppression, becoming refractory to treatment, and sparing the characteristic areas. Transmission is by sexual intercourse, nursing, comforting and massage [1].



Figure 2.32: Norwegian scabies.

[Photo courtesy: Dr Hanumanthaiah, Vydehi Institute of Medical Sciences]

Gamma-benzene hexachloride (lindane) applied from the neck down for 8 to 24 hours is usually curative. But lindane may result in peripheral neuropathies in HIV-infected patients, with low CD4 count (< 200) [2]. 5% permethrin cream, used in the same method as lindane, is safe and effective for HIV infected persons over 2 months of age. Extremely aggressive housekeeping procedures and fumigation must be undertaken to eliminate fomite transmission of infestation.

In rare cases, true crusted (Norwegian) scabies (Figure 2.32) may occur in patients with advanced HIV disease. Norwegian scabies is non pruritic and appears as thick crusts over some areas of the body. Crusted scabies in HIV infection may be localized to the soles or the genitals. These crusts teem with mites and are highly contagious. Isolation of patients with Norwegian scabies is a must until therapy is complete as it is highly contagious. Treatment is difficult. Permethrin is repeated at least weekly until cutaneous manifestations clears. Additionally, Ivermectin, 6% precipitated sulfur ointment daily may be added to the therapy. Ivermectin orally

has been successful in treating Norwegian scabies [3,4]. Norwegian scabies can lead to sepsis and death as a result of secondary bacterial infection [5].

Demodicidosis

The hair follicle mite *Demodex folliculorum* and *D. brevis* are ubiquitous obligatory ectoparasites of man. They are cigar shape mites and are resident in human pilosebaceous follicles (nasolabial folds, nose, forehead and perioral region). They do not give rise to eruptive lesions in normal healthy individuals with good personal hygiene. Demodicidosis in patients infected with HIV is reported both in adults and in children [6].

Most authors believe that the altered immune system, which is characteristic of the acquired immunodeficiency syndrome, favors the growth of this usually saprophyte agent so that the latter eventually causes a skin disorder. On the other hand, some authors suspect an unusual hypersensitivity against the mite itself [7]. The latter view is based on the pathological findings of demodicidosis showing a dermal infiltrate of lymphocytes and eosinophils and typical granulomas prevalently composed by CD4+ T helper lymphocytes, which are often distributed around a *Demodex* body [8].

The skin disorders due to these parasites includes papular and pustular eruptions of the scalp, follicular pityriasis, acne rosacea, perioral dermatitis, some cases of blepharitis, pustular folliculitis and hyperpigmented plaques.

The treatment with topical metronidazole and erythromycin per mouth is effective in most patients with *Demodex* infestation. Other options include topical crotamiton or topical benzyl peroxide and systemic ivermectin [9].

Protozoal Infections

Leishmaniasis

The impact of HIV/AIDS pandemic is not only changing the natural history of leishmaniasis but also increasing the risk (100 to 1,000 times) of developing Visceral Leishmaniasis (VL) in endemic areas, reducing the therapeutic response, and increasing the possibility of relapse cases [10]. Leishmaniasis in HIV-infected patients is mainly Visceral Leishmaniasis, however, some cases of Cutaneous Leishmaniasis have also been reported.

Leishmaniasis can have varied presentations in the HIV-infected patient and may mimic Kaposi Sarcoma and dermatofibroma. Cutaneous nodules and ulcers, digital necrosis, linear brown macules of the digits and palms, ulceration of the tongue, a tattoo reaction and cutaneous hyperpigmentation and atypical disseminated leishmaniasis resembling post kala-azar dermal leishmaniasis have been described. IRIS -associated leishmaniasis is recognized [11]. Patients have a higher rate of recurrence or reinfection and their disease is more difficult to treat when compared with HIV-negative individuals. Since the introduction of HAART, the numbers of *Leishmania*-HIV co-infected cases are rapidly declining [10].

Miscellaneous

Reactivation of American trypanosomiasis (Chagas' disease) in AIDs may manifest with skin lesions [12].

Pneumocystis carinii (now jiroveci) pneumonia is common in HIV infection but disseminated disease and cutaneous involvement are rare with only scattered case reports. Lesions masquerading as Kaposi Sarcoma have also been described [13].

Cryptosporidiosis and microsporidiosis can cause skin lesions occasionally [14,15].

Disseminated amoebiasis may rarely cause skin manifestations like cutaneous ulceration and disseminated skin lesions and in such cases dermatological involvement can point to diagnosis of the systemic illness [15]. Anogenital ulceration due to amoebiasis should lead to the suspicion of underlying HIV infection [17].

Helminthic Infections

Helminth and Human Immunodeficiency Virus co-infection is widespread but skin lesions due to them are not so common. Helminth coinfection has been associated with an increased risk for mother-to-child transmission of HIV infection. HIV positive pregnant mothers with chronic intravascular helminth coinfection were found to have sevenfold greater odds of transmitting HIV to their offspring. That increased risk was attributed to the in utero priming of T cells by soluble parasite antigens [18,19,20].

Onchocercal skin disease may be worse in patients with HIV infection with HIV-positive patients with having higher onchocercal skin scores than those who are not HIV infected. However there is no treatment differences with ivermectin in HIV-infected patients [21]. A few studies have suggested a significant association of lymphatic filariasis with HIV infection [22]. Urogenital schistosomiasis can increase susceptibility to HIV infection [22]. The sensitivity of skin testing for Strongyloidiasis decreases in HIV [23].

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