

Skin in HIV

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Editor: Leelavathy Budamakuntla

Published by SM Online Publishers LLC

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ISBN: 978-0-9962745-2-4

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First published April, 2015

Online Edition available at <http://www.smgebooks.com>

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Neoplasia of the Skin in HIV

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Published Date: April 15, 2015

INTRODUCTION

People with HIV/AIDS are at high risk for developing some types of malignancies, such as Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical cancer. For people with HIV, these malignancies are often described as "AIDS- defining conditions", which means that, if a person with HIV has one of these cancers it can signify the development of AIDS. The association between HIV/AIDS and certain cancers is not completely deciphered, but it likely depends on the immune system. Most types of cancer start when normal cells begin to show changes and grow uncontrollably, forming a mass called tumor.

Both the incidence and clinical course of cutaneous malignancies are altered in the context of HIV infection. The mechanisms which lead to the observed increased rate of cancer in persons with HIV are poorly understood; however, such features as dysfunctional cell-mediated immunity, increased susceptibility to certain oncogenic viruses, preferential expression of Th2 cytokines, and the presence of HIV proteins known to promote oncogenesis are thought to contribute.

In HIV-infected persons, lympho-hematopoietic malignancies occur in great excess. These malignancies are typically more aggressive, diagnosed at more advanced stages, respond less

favourably to treatment, and are classically of T-cell phenotype.

Epidemic Kaposi sarcoma (KS) remains the most common cancer associated with HIV infection in the United States despite dramatically declining incidence rates since the advent of HAART.

Malignant melanoma appears to occur with an increased frequency, at an earlier age, and behaves more aggressively in HIV-infected persons than in the general population.

The risk of nonmelanoma skin cancers is approximately three- to fivefold elevated among patients with AIDS relative to the general population.

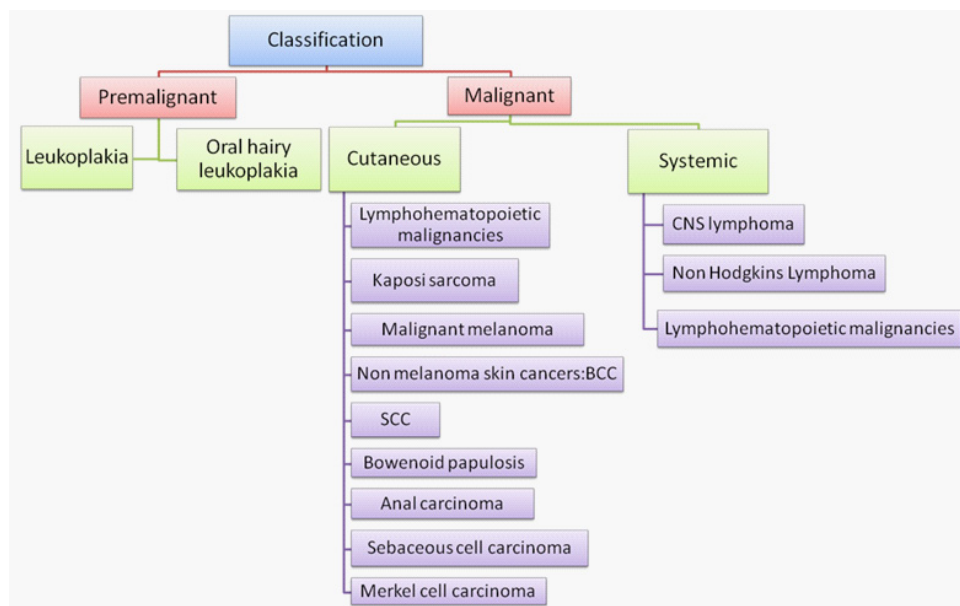
Bowenoid papulosis, generally regarded as a transitional state between condyloma and Bowen's disease that is induced by oncogenic HPV, occurs in excess in HIV seropositive individuals.

Anal carcinoma and its precursor lesions are associated with infection with certain oncogenic HPV subtypes, and occur with great excess among HIV-infected individuals. These lesions are often times asymptomatic, but may manifest as pruritic, bleeding, or painful, perianal masses.

In HIV-infected patients, sebaceous carcinoma may deviate from its classic presentation, and present in extraocular locations or achieve unusually large size.

As life expectancy of HIV infected person increases, cancers have become an important cause of morbidity and mortality. The types of cancer most common for people with HIV/AIDS are described in more detail below.

CLASSIFICATION



Lymphohematopoietic malignancies are diagnosed at greatly increased rates among HIV-seropositive versus HIV-seronegative persons. HIV-infected persons have a 100-fold higher

risk of developing NHL than that expected in the general population [1]. The majority of AIDS-associated lymphomas are of B-cell lineage with a predilection for such extranodal sites as the central nervous system and gastrointestinal tract.

In contrast, cutaneous NHLs are rare in patients with HIV infection and are typically of T-cell phenotype. In HIV disease, cutaneous lymphomas are characteristically more aggressive, diagnosed at more advanced stages, and less responsive to therapy [2].

Kerschmann et al. discovered two forms of HIV-associated cutaneous lymphomas: First an indolent, epidermotropic, CD30-lymphoma resembling mycosis fungoides (MF) or Sézary syndrome, and second, a lymphoma composed of large, CD30 cells that classically harbour the Epstein–Barr virus (EBV), with a typically grave prognosis [3].

MYCOSIS FUNGOIDES (MF)

MF rarely complicates HIV disease and tends to occur in individuals with a relatively intact immune system.

Etiopathogenesis

Etiopathogenesis of MF in HIV-seropositive patients is poorly understood. This predominantly occurs in adult males (2:1 male/female ratio), although children are occasionally affected. The natural history of mycosis fungoides is one of slow progression, with the patches and plaques giving rise over time to nodules that may eventually ulcerate. Clinical and histopathological manifestations are similar to those in the general population.

Clinical Features

Lesions initially present as erythematous scaling patches and plaques (Figure 7.1) that typically are resistant to anti-inflammatory therapy. Lesions are generally large (many centimeters in diameter), and may show arcuate or polycyclic configurations. Zones of alopecia may occur due to infiltration and mucinous degeneration of hair follicles (**alopecia mucinosa**). Occasional lesions may show epidermal atrophy, prominently dilated superficial dermal blood vessels, and patchy hyper- and hypo-pigmentation (**poikiloderma vasculare atrophicans variant**), while others may show excessive epidermal thickening and scaling.



Figure 7.1: Cutaneous T cell Lymphoma.

(Photocourtesy: Victoria Hospital, Bangalore)

Diagnosis

Histopathological parameters for the diagnosis are *pautrier's* microabscess, lymphocytes with a clear perinuclear halo, lymphocytes aligned along the basal layer, intraepidermal lymphocytes with hyperconvoluted nuclei, epidermal lymphocytes larger than the dermal lymphocytes and epidermotropism.

Treatment

HAART should be instituted if appropriate, and existing algorithms for the treatment of MF in immunocompetent individuals should be followed. Certain agents, such as denileukin diftitox (Ontak) and total skin electron beam therapy, have unknown safety in this population.

Bexarotene, a retinoid, approved for the topical treatment of KS patches, is currently under study for the treatment of HIV-associated cutaneous T-cell lymphoma (CTCL) [4].

ATYPICAL CUTANEOUS LYMPHOPROLIFERATIVE DISORDER (ACLD)

Synonyms

pseudo-Sézary, pseudo-CTCL, CTCL-simulant, and atypical cutaneous lymphoproliferative disorder (ACLD).

Introduction

An inflammatory, pruritic, lymphoproliferative eruption that histologically mimics MF has been described in HIV-seropositive individuals. The descriptive term ACLD is most appropriate as the dermatosis does not clinically resemble MF.

Clinical Features

ACLD typically occurs in patients with advanced HIV disease as evidenced by their low CD4

lymphocyte counts. ACLD classically manifests with an intensely pruritic, generalized, persistent eruption of poorly circumscribed erythematous papules and plaques. Less commonly, ACLD may present with nodules, pustules, hyperpigmentation, or lichenification. There are also reports of ACLD occurring as a morbilliform drug like eruption and as a photodistributed eruption [4].

Histopathology

ACLD may consist of a psoriasiform lichenoid infiltrate with exocytosis of lymphocytes and minimal spongiosis. More characteristically, however, the lesions show a superficial and deep perivascular and perifollicular infiltrate of atypical mononuclear cells admixed with eosinophils, plasma cells, and rare neutrophils. Atypical lymphocytes possess enlarged (and sometimes cerebriform) nuclei with prominent nucleoli, further complicating distinction from MF [5]. Immunohistochemistry demonstrates a predominance of CD8 cells.

Treatment

Since ACLD is not a true lymphoma, chemotherapy is not required. Treatment with potent topical steroids or phototherapy is usually effective.

CD30 LARGE-CELL LYMPHOMA

CD30 large-cell lymphoma may occur as either a visceral or a primary cutaneous malignancy. Whereas visceral CD30 lymphomas are classically of B cell lineage, the preponderance of cutaneous CD30 large-cell lymphomas in HIV disease originate from T-lymphocytes.

Clinical Features

Patients classically present with one to several rapidly growing nodule(s). These lymphomas develop in patients with profound HIV immunosuppression (Figure 7.2).



Figure 7.2: Lymphoma- Multiple erythematous nodules and crusting over abdomen and groin.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)

Diagnosis

Confirmed with a combination of routine histology and immunohistochemistry. The tumour cells are generally CD4++ and by definition CD30++ with expression of cytotoxic proteins [7,8]. There is variable loss of other T-cell antigens such as CD2, CD5 and CD3. Presence of the EBV genome is demonstrable either by staining with EVA latent membrane protein antiserum or in situ hybridization for EBV-encoded RNA (EBER-1).

Histopathology

Include dermal collections of cells with abundant, pale eosinophilic cytoplasm, and large, pleomorphic, vesicular nuclei with prominent nucleoli. Common additional features include multinucleate cells and occasionally bizarre mitotic figures. Epidermal involvement is variable. Epidermotropism is absent. Pyogenic cutaneous lymphoma- neutrophil-rich variant of CD30_ large-cell lymphoma, is described in some patients with HIV.

Prognosis

AIDS-associated CD30 large-cell lymphoma generally carries a grave prognosis [4]. Survival in one study was only 6.7 months [3]. CD30 large-cell lymphoma in association with HIV appears to be more aggressive than in immunocompetent hosts. However, in existing reports, very few patients died of metastatic lymphoma, while the majority died of opportunistic infections. It, therefore, remains possible that CD30 large-cell lymphomas are not intrinsically more aggressive in this population, but rather, that they represent a marker for more advanced immunosuppression.

Treatment

Both excision and localized radiotherapy are acceptable methods of treating isolated lesions [6]. The recurrence rate on the treated site is very low, but over time new lesions may develop elsewhere on the skin. Systemic chemotherapy, including CHOP, may be effective but cutaneous recurrence is likely, and chemotherapy is therefore not the treatment of choice for disease confined to the skin. Low-dose methotrexate may also be effective.

EPIDEMIC KAPOSI SARCOMA

Epidemiology

First recognized in 1979 [9,10] when an epidemic of Kaposi's sarcoma was identified in the homosexual community in New York. Since that time, it became firmly associated with the later stages of HIV infection. In United States, epidemic KS remains the most common cancer associated with HIV infection.

At the zenith of the HIV epidemic, approx 26% of HIV-infected men who have sex with men (MSM) but only 3% of intravenous HIV-infected heterosexual intravenous drug abusers presented with, or eventually developed KS.

With the introduction of highly active antiretroviral therapy (HAART) the incidence of Kaposi's sarcoma in HIV/AIDS has decreased dramatically in the Western world [11]. As a result of HAART it is rare to see patients presenting with widespread lesions of Kaposi's sarcoma and the latter may regress as a result of this therapy, making the clinical and histological diagnosis even more difficult.

Etiopathogenesis

In 1994, Chang et al. [12] identified the causative agent, a gamma herpesvirus, now known as human herpesvirus 8 (HHV-8) or KS associated herpesvirus (KSHV) which is responsible for Kaposi sarcoma. KS is transmitted sexually, commonly by the faeco oral route or the ejaculate than by blood, in HIV-positive homosexual Men [13–17]. It is also seen in non-homosexuals and in children arising from other routes of transmission, for example saliva [18,19]. The pathogenesis of KS is thought to involve angiogenic and proinflammatory effects on endothelial cells that proliferate to form characteristic spindle-cell tumour [20].

Clinical Features

Most commonly involved sites include the oral mucosa, head (Figure 7.3), trunk, penis, lower extremities, palms, and soles. The classical lesion in Epidemic KS is asymptomatic, mucocutaneous lesions that may comprise any combination of nontender, violaceous macules, patches, papules, plaques, and nodules. Lesions are often multiple, multifocal, and in a symmetrical distribution. The lesions grow larger and more numerous, especially in profoundly immunosuppressed patients. Large lesions uncommonly ulcerate. Phimosis may occur [21].



Figure 7.3: Kaposi's Sarcoma.

(Photocourtesy: Victoria Hospital, Bangalore.)

Histopathology

The histological features of KS are well described [22] and consist of dilated, irregularly shaped, vascular structures that are typically slit-like in a fully developed nodular lesion. The differential diagnosis may be clarified by immunohistochemical techniques that identify endothelial cells

(immunostaining for factor VIII-related antigen and *Ulex europaeus* lectin), which have been thought to be the cell of origin of KS.

Differential Diagnosis

KS should be differentiated from other conditions like naevi, histiocytoma and lymphangioma [23], although cryptococcosis [24,25], histoplasmosis [26], leishmaniasis [27,28], lesions due to *Pneumocystis* [29] and dermatophytosis [30] may also mimic and/or complicate KS.

Treatment

In HIV/AIDS regression of lesions may be seen with HAART [31].

Local treatments include cryotherapy, radiotherapy, intralesional chemotherapy, intralesional interferon and topical 5% imiquimod cream [32].

Liposomal doxorubicin may also be a useful treatment and interleukin-12, either alone or in combination with the latter, may also induce remission in AIDS patients with Kaposi's sarcoma who are on HAART [33].

Pegylated liposomal doxorubicin has been used with success on its own, as second line treatment of AIDS-related Kaposi's sarcoma and in advanced, classic Kaposi's sarcoma [34,35].

Biologic agents such as interferon alfa are now considered first-line therapy for some patients with epidemic cutaneous Kaposi's sarcoma. Subcutaneous, intravenous, or intralesional interferon- α resulted in remissions in 20 to 60 percent of patients.

MELANOMA

Epidemiology

Melanoma is probably more common [36-38] although one UK study has found a decreased incidence [39]. Melanoma patients who are HIV-seropositive are typically younger (with a median age of approximately 38 years) than those in the general population.

Pathogenesis

The reason for the altered behavior of malignant melanoma in persons with HIV has not yet been elucidated. Depressed CMI response appears to be important.

Clinical Features

Melanoma may present atypically, appearing as 'normal' naevi or 'benign macules' or multiple 'nevus lesions', and behave more aggressively with decreased disease-free and overall survival rates; low CD4 counts indicate a poorer prognosis although the Breslow thickness is unrelated to the CD4 count at presentation [4,40-42] (Figure 7.4).



Figure 7.4: Melanoma over right sole.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)

Treatment and Follow up

Wilkins et al. propose annual complete skin examination for all high-risk individuals (positive family history, history of blistering sunburns, people with 50 typical nevi, and 5 atypical nevi). Physicians should maintain a high index of suspicion, and have a low threshold for biopsy irrespective of CD4 count.

No formal guidelines exist for the management of primary cutaneous melanoma in persons with HIV. Surgical excision with margins depending on the depth is the recommended management. Some authors propose an expansion of the existing criteria for sentinel lymph node biopsy so as to incorporate tumors of lesser thickness among persons with HIV [4].

Prospective studies investigating this theory are lacking. Metastatic disease should be fervently sought at the time of diagnosis. Current guidelines regarding the frequency and content of follow-up fail to include infection with HIV as a factor to consider [43].

Wilkins et al recommend follow- up every 3 months for the first 2 years subsequent to diagnosis and twice annually thereafter [4]. Follow-up visits should include a comprehensive history and physical examination, including palpation for enlarged lymph nodes and hepatosplenomegaly. The appropriateness of such testing as chest radiography and routine serology (i.e., lactate dehydrogenase) awaits formal investigation.

Because of evidence suggesting improved outcomes among patients treated with HAART [44], initiation of combination antiretroviral agents is recommended unless contraindicated. Such immunotherapeutic interventions as IFN- α 2b and interleukin 2 (IL-2) warrant exploration in this population. Though not yet studied for melanoma, the relative safety of IFN- α 2b in this population for the treatment of unrelated conditions has been reported [45]. IL-2 is not contraindicated in HIV-infected persons, and has surfaced as an agent of interest in the treatment of HIV infection itself [4].

NON MELANOMA SKIN CANCERS

Patients with AIDS have a three- to fivefold increased risk of developing a basal cell carcinoma (BCC) or a squamous cell carcinoma (SCC). The ratio of SCC to BCC in HIV-seropositive patients approximates 1:7 [4]. Risk factors for developing nonmelanoma skin cancer in HIV-seropositive patients mimic those in immunocompetent, HIV-seronegative individuals, and include fair skin, actinic damage and family history [4]6. The incidence of these ultraviolet-induced skin cancers will expectedly increase, as survival in this population is prolonged by current and emerging antiretroviral agents.

BASAL CELL CARCINOMA (BCC)

Epidemiology

Persons living with HIV are at greatly increased risk for developing BCCs. This increased risk appears to be independent of CD4 lymphocyte counts [47]. In a prospective study involving 724 HIV-infected members of the military followed for 3 years with skin exams, BCC, with an incidence of 1.8%, ranked second only to KS [48]. A multicenter retrospective study of haemophiliacs demonstrated an 11.4-fold higher incidence of BCCs among HIV-seropositive haemophiliacs than that expected in the general population. In this study, BCCs developed at a lower mean age among HIV-infected than among HIV-seronegative haemophiliacs (40 years versus 55 years) [49].

Clinical Features

BCC characteristically presents as a dome-shaped, pearly papule or nodule with prominent telangiectasia and a tendency toward central ulceration, the so called nodular BCC. In immunocompromised patients who do not seek health care, the tumors can grow rapidly and can reach sizeable dimensions (Figure 7.5). Most BCCs occurring in HIV-immunocompromised patients are superficial type, multifocal, and located on the trunk [4].



Figure 7.5: BCC-A solitary well defined nodule with verrucous surface over right cheek.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)

Prognosis

BCC tends to be more aggressive in the context of HIV-induced immunosuppression. Aggressive subtypes, including multiple infundibulocystic BCC [50], metastatic BCC [51], and aggressive morpheaform BCC arising within a scar have been reported within this population [52].

Treatment and Follow-up

Both primary prevention, including diligent sunscreen use and sun avoidance, and secondary prevention, with regular, careful skin examination by a dermatologist, are critical, especially in patients with light skin types. Biopsy of any suspicious lesion should not be delayed. Adherence to standard treatment protocols for BCC achieves cure rates comparable with those achieved in the general population [49,53]. Use of the topical immunomodulator, imiquimod, for superficial tumors warrants further investigation in these patients [54]. Chemoprevention with acitretin (dosed 25 to 50 mg daily, as tolerated) for cases with multiple lesions may be considered, but the medication needs to be continued indefinitely as its beneficial effect ceases 2 to 3 months after treatment discontinuation. Following treatment, regular, semiannual follow-up is recommended [4]. Physical examination should include a search for both local and nodal recurrence.

SQUAMOUS CELL CARCINOMA SCC

Epidemiology

HIV-infected individuals have an elevated risk of developing mucocutaneous SCC. In a published report, the median age at which patients developed a cutaneous SCC was 44 years, compared with 70 years in the general population [56].

Pathogenesis

Specific high-risk HPV genotypes have been implicated in the development of anogenital, cervical, oral, and some nail unit SCCs. Epidermodysplasia verruciformis (EV)-type HPV refers to those subtypes, including HPV-5 and -8, whose DNA has been detected by PCR in SCC occurring in individuals with this rare disorder [57]. Suppressed CMI, as occurs with advancing HIV disease, alters susceptibility to viral infection. HPV is chief among the pathogenic viruses that infect the immunosuppressed host. Between 5 and 27% of HIV-infected persons develop HPV-associated mucocutaneous lesions. Additionally, the prevalence of common and plantar warts is increased in this population, and histopathological review of these lesions more commonly demonstrates atypia [58]. A pathogenic role for HPV in the development of cutaneous SCC in HIV-seropositive persons is certainly plausible, but awaits elucidation.

Clinical Features

SCC in the context of HIV is clinically indistinguishable from that which occurs in the general population. The typical presentation is an erythematous, scaly, and sometimes ulcerated plaque or nodule (Figure 7.6, 7.7).



Figure 7.6: SCC- Lymphedema with ill defined tumor over right dorsum of foot.

(Photo courtesy: Department of Dermatology, Bowring and Lady Curzon Hospital)



Figure 7.7: Squamous cell carcinoma of the penis in a 70 year old male.

(Photocourtesy: Bowring and Lady Curzon Hospital, Bangalore.)

Prognosis

Cutaneous SCCs appear to be more aggressive in HIV-seropositive persons. One retrospective series of 10 aggressive SCCs in HIV-infected persons demonstrated high rates of local recurrence and metastasis, and 50% mortality (6 months to 7 years). Poor outcomes did not correlate with the patients' histories of opportunistic infections or CD4 lymphocyte counts. Rather, morbidity and mortality were most closely linked to the initial control of local and metastatic disease.

Treatment and Follow-up

Primary and secondary prevention, including early biopsy of suspicious lesions, is essential
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in this population. A low threshold for biopsy of anogenital, periungual, or otherwise persistent verrucous lesions, particularly in those patients with a history of genital warts or of dysplasia, is prudent. In so far as initial control of local and metastatic disease has been demonstrated to be the principal predictor of morbidity and mortality, all tumors should be treated aggressively, irrespective of CD4 T-cell count. Evaluation for metastasis with high-resolution scans should be considered. Resection with margin control (i.e., Mohs' micrographic surgery) represents the most prudent approach, whereas ablative therapy without histologic control should be discouraged [56]. Sentinel lymph node procedures and local or regional adjuvant therapy should be considered for all high-risk tumors. Regular, careful follow-up including a search for local and metastatic recurrence should be conducted twice annually after treatment.

BOWENOID PAPULOSIS

Epidemiology

The incidence of bowenoid papulosis appears to be increased in men and women with HIV infection. This disease is predominantly seen in uncircumcised white men.

Etiology

The aetiology of BP is unknown. The neoplasm is considered to represent a transitional state between condyloma and Bowen's disease that is induced by oncogenic HPV (predominantly HPV-16) and HIV infection [59,60]. Voltz et al. [61] found anogenital warts in 16% of all HIV-positive males, nearly half of whom showed histological signs of intraepithelial neoplasia.

Risk Factors

Local carcinogenic factors such as poor hygiene, smegma, trauma, friction, heat, maceration, inflammation, phimosis, dermatoses such as lichen sclerosus and smoking (tar metabolites in urine) have been proposed as the risk of acquiring these lesions in uncircumcised men [62].

Clinical Features

The typical lesions are flesh-colored, reddish, or pigmented papules with a flat or verrucous surface on the anogenital (and less often oral) areas and resemble condyloma accuminata. Individual papules often coalesce into larger plaques (Figure 7.8).



Figure 7.8: Grouped verrucous papules over female genitalia – A case of bowenoid papulosis.

(Photo courtesy: Dr.Leelvathy B, Department of Dermatology, Bowring and Lady Curzon Hospital)

HIV Association

The neoplasm is assumed to have a nonaggressive nature; however, data regarding the course in HIV immunocompromised persons is scant. A case of orolabial bowenoid papulosis caused by HPV-32 is noted [63].

Histopathology

Reveals features of an intraepithelial carcinoma. Secondary amyloid deposition has been reported histologically in one case of BP [64].

Differential Diagnosis

Lichen planus, common warts, seborrhoeic warts, naevi and condylomata lata. A biopsy is indicated in instances where the clinical diagnosis is uncertain.

Treatment and Follow up

Treatment depends on many factors. Circumcision removes a major risk factor for cancer and provides extensive tissue for histology. Topical 5-fluorouracil as a 5% cream is a well established conventional option for the treatment of BP [65-67], but there have not been any clinical trials.

Other treatments include cryosurgery, curettage and electrocautery, excisional surgery, glans resurfacing, Mohs micrographic surgery, laser and photodynamic therapy [65-69]. Radiotherapy should be avoided. Topical imiquimod may help some patients [70-72]. Patients presenting with these conditions should be counselled and screened for HPV and other sexually transmitted diseases, including HIV infection. They should stop smoking. Sexual partners should be advised to seek assessment. Follow-up should be long term [66,67,73].

ANAL CARCINOMA

Synonyms

Anal dysplasia, anal intraepithelial neoplasia, and squamous intraepithelial lesions (SIL).

Epidemiology

AIN is frequently associated with homosexuality, anal warts, HPV and HIV, although it is not a prominent feature of other conditions involving immunosuppression. Before the HIV epidemic, the incidence of anal cancer among men who have sex with men (MSM) was estimated to be as high as 35 per 100,000, which is similar to that of cervical carcinoma before screening with PAP smears. Recent studies have estimated a twofold higher incidence among MSM who are HIV infected than among those who are HIV-seronegative [74]. The prevalence of SIL among HIV-seropositive MSM and women is reported to be 36 and 14%, respectively [4].

Risk Factors

Lower absolute T-cell counts, history of an AIDS-defining event, infection with high-risk HPV types, and infection with multiple HPV types [74].

Pathogenesis

Anal SCC and its precursor lesion, SIL, are associated with HPV infection by strains with high risk for oncogenicity (i.e., HPV-16, -18, -31, and -33) [4]. An etiologic role for HPV infection in the pathogenesis of anal SCC is strongly suggested by the detection of HPV DNA in anal cancer and SIL tissues. High-risk HPV-16 is detected in most cases of anal HSIL, whereas LSIL more commonly contains HPV-6 and -11, types known to have a low risk of oncogenicity in the cervix. Among HIV-seropositive persons, irrespective of sexual practices, the rate of anal HPV infection is elevated two- to sixfold. HIV-infected persons are at increased risk for infection with multiple different and high-risk HPV types.

Utilizing PCR, Palefsky et al. detected anal HPV DNA in the lesions of 93% of HIV infected and 61% of HIV-seronegative homosexual men. Multiple HPV types were detected in 73% of HIV-infected and 23% of HIV-seronegative cases. Both groups demonstrated a similar spectrum of HPV type, with HPV-16 representing the most common type. An apparent association between advanced immunosuppression and increased replication of more oncogenic HPV types was suggested by higher levels of group B HPV types, (including high-risk types HPV-16, -18, -31, and -33) among HIV-infected individuals with lower CD4 counts [75].

The HPV life cycle is only completed in fully differentiated squamous epithelia. HPV does not encode the machinery required for transcription or replication, and is therefore entirely dependent on co-opting the cellular machinery of the host. Productive infection is initiated when the virus enters its primary target, the proliferating basal epithelial cells. Within the mid epidermis, viral DNA is incorporated into host cells and viral proteins are expressed by host cells [76]. Early HIV disease is characterized by a nearly intact host immune response, and thus, low levels of HPV infection and anal SIL. Declining CD4 T-cell counts, and consequently, compromised CMI responses result in higher levels of HPV, increased risk for development of SIL, and subsequent progression to more advanced disease.

An improved understanding of the molecular biology of HPV has helped to elucidate a mechanism for its oncogenicity. Two viral oncoproteins, early (E) genes 6 and 7, have been identified and are expressed at high levels in HSIL. E6 facilitates destruction of p53, and thus, eliminates a break on cell-cycling. E7 binds the tumor suppressor gene Rb, thereby liberating growth factor E2F from its typical cell-cycle inhibition. Integration of viral DNA into host chromosomes induces chromosomal instability and cellular proliferation. Within this unchecked environment, other co-carcinogens may exert a deleterious effect, thereby promoting progression from dysplasia to invasive cancer [77]. Thus far, evidence to suggest that the introduction of HAART has led to a decreased incidence of SIL is lacking [78]. Conversely, several recent population based analyses have demonstrated increased rates of anal SCC among HIV seropositive persons during the past decade. Some investigators report that high mortality rates prior to the advent of HAART may have masked rising rates of anal SCC or its precursor lesions [79].

Clinical Features

The majority of anal carcinomas arise from squamous epithelium and columnar epithelium. Perianal cancers are SCCs. Anal dysplasia is generally asymptomatic and therefore identified only by targeted screening with cytologic anal smears and colposcopically guided biopsy. It can present relatively asymptotically as red, shiny or scaly patches like Bowen's disease, or as warty lesions like Bowenoid papulosis. Occasionally, anal cancer is readily visible as an erythematous, verrucous, and sometimes eroded perianal plaque. Patients may complain of such nonspecific symptoms as pruritus, discomfort, bleeding, or a perianal mass; however, these symptoms more commonly herald the presence of exophytic condylomata typical of infection with low-risk HPV subtypes.

Staging

T Stage

- Tis - Carcinoma in situ
- T0 - No evidence of primary tumor
- T1 - Tumor <2 cm in greatest dimension
- T2 - Tumor >2 cm but <5 cm in greatest dimension
- T3 - Tumor >5 cm in greatest dimension
- T4 - Tumor of any size that invades adjacent organs including the vagina, urethra, or bladder. Tumors that invade the anal sphincter only do not qualify as T4 tumors

N Stage

- N0 - No evidence of spread to the lymph node

- N1 - Spread of cancer to the lymph nodes directly adjacent to the rectum (perirectal lymph nodes)
- N2 - Spread of the cancer to lymph nodes of the inguinal or internal iliac lymph node chains on one side
- N3 - Spread of the cancer to lymph nodes of the inguinal or internal iliac lymph node chains on both sides OR cancer involvement of both the perirectal lymph nodes

M Stage

- M0 - No evidence of distant spread of the cancer
- M1 - Evidence of distant spread of the cancer including spread to lymph node chains other than the ones listed under “N Stage”

Prevention

Anal SCC is potentially preventable. As anal dysplasia is generally asymptomatic, anal cytologic screening is critical for the early detection of this cancer. Screening comprises regular cytologic (Papanicolaou) smears of the lower rectum, squamo columnar junction, and anal canal. Several experts have recommended anal cytologic screening irrespective of sexual history in all HIV-seropositive men, especially those with CD4 T-cell counts below

500×10^6 cells/L [74]. Abnormal Pap smear results warrant further investigation with high-resolution anoscopy (analogous to colposcopy) and biopsy of all visualized lesions [81]. Any lesion observed should be biopsied and HSIL lesions should be destroyed.

Treatment

Treatment depends on staging. Published guidelines for the treatment of SIL and anal cancer, including both surgical and nonsurgical modalities, should guide treatment once dysplasia is documented. Treatment of in situ lesions with topical 5-fluorouracil and/or imiquimod remains investigational [80]. Carcinoma in situ or small, well-differentiated anal cancers that have not invaded into the anal sphincter can be surgically resected. Radiation with or without chemotherapy is the mainstay of treatment for other tumors. A potential role for HPV vaccines (designed for cervical cancer-associated HPV infection) in the prevention of anal cancer in this population is under investigation [4].

SEBACEOUS CARCINOMA

Epidemiology

Sebaceous carcinoma is rare, comprising less than 1% of all skin malignancies. It may occur in immunosuppressed organ-transplant patients, and these tumours are associated with microsatellite instability [83]. Sebaceous carcinoma may be associated with the Muir–Torre syndrome [84].

Clinical Features

The face and scalp [82] are the commonest sites, especially the eyelid. Extraocular carcinomas occurring outside the head and neck area [85]. Characteristically, sebaceous carcinomas are present in the periocular region, specifically the upper eyelid. Only 25% are extraocular and the majority of these appear on the head and neck. One-half of periocular tumors arise from Meibomian glands. The neoplasm appears as a firm, skin-colored, or yellowish papule that slowly grows into a nodule. Metastasis occurs in 14 to 25% of patients. Several cases reported in HIV-infected patients achieved unusually large sizes and were not present on the face.

Treatment

Complete surgical excision is required [86,87]. Reports of excellent results with Moh's surgery suggest that this may be the treatment of choice [88]. Other destructive modalities such as cryotherapy are less definitive [89].

Prognosis and Follow-up

When detected early, survival rates are good for people who have SC. But SC can return or spread to other areas of the body, so follow-up is essential.

MERKEL CELL CARCINOMA

Epidemiology

This is a rare tumour of the elderly presenting mainly in Caucasians (0.23 annual age adjusted incidence per 100 000) [90], with a high concentration of primary tumours on sun-exposed sites. There are also a high number of cases in association with immunosuppression [91], including not only transplant patients but also those with HIV infection [92].

Risk Factors

AEIOU Features of MCC

- A Asymptomatic/lack of tenderness
- E Expanding rapidly
- I Immune suppression
- O Older than 50 years
- U Ultraviolet-exposed/fair skin

MCC and a Newly Discovered Polyomavirus

Recently, it has been suggested that a novel type of polyomavirus (named Merkel cell polyomavirus) may play a role in the aetiology of the neoplasm as clonal integration of the virus was demonstrated in eight out of 10 cases of Merkel cell carcinoma tested [93].

Clinical Features

Head and neck- 49%, Extremities -38% (lower extremities more frequently involved than the upper extremities),Trunk – 13%(mainly lower back and buttocks) .The lesions are described as raised, reddish-blue nodules, which may develop on anybody site, although the head and neck area is over-represented in terms of surface area. Tumors are asymptomatic in the majority of cases and grow rapidly with most lesions measuring between 0.5 and 2 cm. Spontaneous regression of Merkel cell carcinoma has occasionally been reported [94,95]. Partial regression has been reported as a result of withdrawal of azathioprine in an immunosuppressed patient [96], although rapid growth of a tumour was described after treatment with rituximab [97].

Histopathology

MCC is one of the small blue cell tumours. Tumor characteristically involves the dermis with sparing of the epidermis. Tumor cells form irregular trabeculae extending down into the subcutaneous tissue. The tumor may resemble lymphoma, carcinoid, oat cell carcinoma, sweat gland carcinoma, or neuroblastoma.

Ultrastructurally, the tumor cells contain membrane-bound, dense-core neurosecretory granules in the peripheral cytoplasm. These granules vary from 80 to 180 nm in diameter, and their presence is an important diagnostic feature. The cells also show characteristic perinuclear filament whorls.

Staging

Stage 1	Local Disease IA, confined to skin, <2 cm diameter
	Local Disease IB, confined to skin, > 2 cm diameter)
Stage 2	Locoregional Disease (node positive)
Stage 3	Distant Disease(metastasis positive)

Clinical stage at presentation is the strongest predictor of distant spread and the most significant prognostic factor for survival: node negative median survival is 40 months, whereas node positive is 13 months and distant metastatic disease is 6 months [102]. Overall 5-year survival for MCC is reported as 62- 74%, being 48% for node positive and 88% for node negative.

Diagnosis

Surgical excision is required [98], but metastases occur early and 30–50% of patients may die from metastases. Arterial limb perfusion has been used for lesions on limbs and may be beneficial [99]. Merkel cell tumours are considered to be radiosensitive, and trials of postoperative radiotherapy suggest a survival advantage [100]. Sentinel lymph node biopsy is a useful

procedure not only to demonstrate spread in patients that have been understaged by clinical and radiological (CT scan) examination but is also important in predicting prognosis and improving survival in patients with positive results who undergo lymph node dissection [101]. The detection of micrometastasis in sentinel lymph nodes is increased by the use of immunohistochemistry for cytokeratin 20 [102].

Treatment

The preferred treatment at present is surgical excision with sentinel lymph node biopsy followed by lymph node dissection if the latter is positive. Postoperative radiotherapy is also given and this approach improves locoregional control and also improves disease-free survival [103,104]. Treatment of involved regional lymph nodes, with or without lymphadenectomy, has also been found to increase survival [105]. Chemotherapy is not routinely recommended as there is lack of evidence that it increases survival, there is important morbidity and mortality associated with this modality of treatment and resistance to chemotherapy quickly develops in many patients [106].

CONCLUSION

Several malignancies that are more prevalent in HIV-infected individuals involve the skin. The mechanisms underlying the observed increased rate of malignancy in HIV-infected individuals remain poorly understood. Depressed cell-mediated immunity and increased susceptibility to certain oncogenic viruses (i.e., HHV-8 and HPV) are responsible in part. The clinical findings and course of several neoplasms differ dramatically in HIV-seropositive individuals. The introduction of effective antiretroviral therapy has led to marked reductions in the incidence of and mortality from certain malignancies, such as KS; however, the excess malignancy rate in this population has not normalized. It is essential for dermatologists to be aware of the diverse presentations, course, and management of cutaneous cancers in the context of HIV. Moreover, it is imperative to recognize that the standard of care for prevention, treatment, and follow-up of certain malignancies in HIV-infected individuals differ substantially from that set forth for immunocompetent populations.

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