

Skin in HIV

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Papulosquamous Disorders in HIV

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A variety of inflammatory noninfectious skin conditions have been described in HIV-infected patients since the advent of the disease. Some of these skin conditions may be directly related to the presence of HIV infection. However, in other conditions, the exact mechanism and relationship between the cutaneous disorders and HIV infection cannot be elucidated. Most of these conditions are more prevalent and worsen in severity with diminishing CD4 counts induced by HIV.

The list of papulosquamous disorders that will be discussed in this chapter are:

- Psoriasis
- Reiter's syndrome
- Seborrhoeic dermatitis
- Pityriasis rubra pilaris
- Xerosis and ichthyosis
- Atopic dermatitis

PSORIASIS IN HIV

Psoriasis is a chronic papulosquamous skin disease that is thought to be a T-cell-mediated

autoimmune disorder of keratinocyte proliferation [1].

Psoriasis affects 2% to 5% of patients with HIV infection [2,3], as compared with its prevalence of 1% in the general population. The occurrence of psoriasis in the background of HIV immunodysregulation is an interesting prospect in terms of both pathogenesis and treatment.

Etiopathogenesis

The occurrence of these two conditions appears paradoxical as psoriasis is a Th1-mediated disorder and HIV shows Th2 immune predominance in advanced disease. It has been hypothesized that the immune dysregulation resulting from HIV infection may trigger psoriasis in genetically predisposed individuals (having CW* 0602 allele) [4].

The relationship between psoriasis and HIV-1 is also interesting because of the clinical observation that HIV-1 infection can exacerbate existing psoriasis or trigger new-onset psoriasis [1]. With the progression of HIV disease, CD4 cells decrease and this can worsen psoriasis [5,6]. This is puzzling because psoriasis is mediated by activation of T cells. The various explanations for this “psoriasis HIV-1 paradox” proposed, include HIV-1 induced destruction of regulatory CD4 cells [7], an increase in number of memory CD8+ T cells late in disease [8], HIV-1 proteins acting as superantigens [9], or co-stimulation through traditional antigenic presentation [7].

The pathogenesis of psoriasis in patients with HIV is considered a medical paradox that revolves around 3 main quandaries. First, this T-cell-mediated disease manages to flourish in an environment of decreasing T-cell counts [7]. Second, although various therapies targeting T lymphocytes are effective in psoriasis, the condition worsens with decreasing CD4 T-cell counts in patients with HIV [10,11]. Third, HIV is characterized by a strong helper T cells type 2 (TH2) cytokine profile and psoriasis is characterized by a strong helper T cells type 1 (TH1) secretion pattern [12,13].

The exacerbation of psoriasis in patients with HIV is largely mediated by memory CD8 T cells, a population of cells that are relatively and absolutely expanded in HIV infection. The IFN- γ produced by the memory CD8 T cells is capable of inducing keratinocytes to abnormally express HLA-DR, which predisposes these cells to become activated by bacterial superantigens that are more likely to be in excess in the immunocompromised patient. Once activated, these keratinocytes perpetuate the psoriatic phenotype by producing the proinflammatory cytokine, TNF- α [14].

The presence of HIV in keratinocytes and Langerhans cells could stimulate the proliferation of keratinocytes. Another hypothesis points out that psoriasis gets worse in AIDS due to an enhanced colonization of the skin by Gram-negative organisms, due to impaired immunity and exacerbated infections. Moreover the liberation of bacterial lipopolysaccharides (LPS) act as a proliferation factor for keratinocytes, which release TNF- α (Tumor Necrosis Factor) giving rise to deteriorating immune deficiency, therefore completing the disastrous circle. HIV infected

lymphocytes release substance P (associated to connective inflammatory processes), leading to keratinocyte proliferation and therefore causing psoriatic plaques to appear [15].

Clinical Features

Psoriasis in a classical patient presents as erythematous well demarcated plaques with silvery scale distributed more on the extensor surface of the limbs and body, also involving the scalp and nails.

Two main clinical forms can be found [16]: 1) psoriasis guttata or long plaques and sometimes both guttata and vulgaris forms can be observed in the same patient; 2) diffuse psoriasiform dermatitis, associated with palmoplantar keratoderma 3) The initial presentation can be atypical, manifesting in the form of inverse psoriasis [17] [Figure 3.1].

The HIV patients present mainly with plaque form while other forms like the inverse variant of psoriasis, with intense involvement of the scalp, armpits, and groin are also seen. Palmoplantar involvement and localized or generalized pustular forms were also more common.



Figure 3.1: Annular and polycyclic erythematous scaly plaques over abdomen.

[Photo courtesy: Department of dermatology, Bowring and lady Curzon hospital]

Severe exfoliative erythroderma may develop and is one of the common causes for admissions [18] [Figure 3.2]. Erythrodermic psoriasis in HIV-infected patients may be a sign of *S. aureus* septicemia, and the psoriasis may improve dramatically with only intravenous antibiotics [19]. Acral pustular lesions of keratoderma blenorrhagicum coexisting with psoriasis or sebopsoriasis have been observed. Psoriasis may show exacerbation with the development of HIV infection and be difficult to treat in HIV disease [20,21].



Figure 3.2: Psoriatic erythroderma seen in HIV positive male patient with CD4 count 30cells/cumm.

[Photo courtesy: Department of dermatology, Bowring and lady Curzon hospital]

Guttate psoriasis in HIV patients is refractory to antibiotic therapy unlike in seronegative patients. There is also an increased incidence of secondary infection with *staph.aureus* or *candida*, sometimes leading to sepsis also [22].

It has been reported that 10% of HIV-infected patients with associated psoriasis will also develop arthritis [23], higher than that found in the general population. Human retrovirus 5 is a recently described, partially characterized retrovirus that has been implicated in the pathogenesis of psoriatic arthropathy, though not psoriasis [4,23].

HIV-positive patients present with different types of spondyloarthropathy in which severe joint involvement is observed, with joint destruction; they are usually associated with nail involvement and palmoplantar lesions. Joint involvement in patients with psoriasis and HIV infection is aggressive and is more prevalent and clinically more florid than in HIV-negative patients [24] [Figure 3.3]. Unlike in Reiter disease, sacroiliac involvement is rare in these patients.

HIV infection should be suspected and a serologic diagnosis should be made whenever there is sudden exacerbation of extensive and severe inflammatory psoriasis.



Figure 3.3: Psoriatic arthritis in HIV positive male patient.

[Photo courtesy: Department of dermatology, Bowring and lady Curzon hospital]

Histologically psoriasis is essentially the same in immunocompetent and HIV positive individuals, with some differences being noted. Munro microabscesses are seen less frequently in HIV-related psoriasis, with more irregular acanthosis and less obvious thinning of the suprabasal plate [25,26]. The histologic features are seen to overlap with those of seborrheic dermatitis.

Table 3.1: Clinical characteristics of psoriasis in HIV patients

Sudden onset
Palmoplantar keratoderma
Severe nail dystrophy
Flexural involvement/ inverse variants
Pustular forms
Higher frequency of arthritis

Treatment

Therapy for psoriasis includes a wide range of topical and systemic agents. Topical steroids, anthralin, Ultraviolet Light B (UVB) with or without tar, psoralens plus ultraviolet A (PUVA), retinoids, and immunosuppressives (especially methotrexate) have been tried [27].

In general, psoriasis responds poorly to less than medium- or high-potency topical steroids. Using topical steroids over extensive areas leads to systemic absorption, adrenal axis suppression, and immunosuppression which are obviously undesirable effects in patients with HIV infection. Topical steroids reduce local immunity, increasing the likelihood of cutaneous infections.

Tar plus UVB (Goeckermann therapy) has been used with marginal success. Several patients develop Kaposi sarcoma KS while receiving this therapy, and there are reports of appearance of KS or worsening of HIV disease with UVB therapy [3]. KS, like psoriasis, is known to develop in areas of inflamed or traumatized skin (Koebner's phenomenon)

PUVA reduces T cell numbers in atypical infiltrates in the skin and may even eliminate circulating atypical T lymphocytes. PUVA is also carcinogenic for skin. The safety of PUVA in HIV-infected patients is yet to be established. Short-term treatment with PUVA has been used in early HIV disease without obvious complications.

Standard low-dose methotrexate therapy has been associated with progressive immunosuppression or rapid demise (or both) when used in some HIV-infected persons [3]. Methotrexate use in HIV-infected individuals is of high potential risk and should be considered a last resort.

Cyclosporine has shown moderate effectiveness in therapy but immunosuppressant actions precipitating opportunistic infections are a strong limiting factor.

Many HIV-infected patients with severe psoriasis have responded favourably to etretinate, a retinoid given in standard doses [3,28]. The frequency of past or current liver disease due to hepatitis B infection in patients with HIV disease has limited etretinate's usefulness [29]. Etretinate followed by Re-PUVA has been indicated as the most effective systemic therapy, with rare adverse effects [30].

Carbamazepine can be a good option in such patients as they do not suppress the immunity instead cause inhibition of the neuropeptide secretion leading to regression of the lesions and reduction of the erythema [31].

Significant improvement of psoriasis is seen with zidovudine therapy [29]. The response is described as dose related. Highly active antiretroviral therapy (HAART) should be encouraged in all HIV-infected patients with psoriasis. Studies on efficacy of HAART for psoriasis in HIV disease is lacking.

The introduction of biologic therapies is a ray of hope to the treatment of patients with psoriasis and HIV infection. There has been established data by other specialties on the safety & efficacy of these drugs in treatment of other systemic diseases in HIV patients [32]. Based on this; dermatologists have tried these drugs with encouraging results. Anti-TNF drugs were contraindicated by clinical guidelines until recently [33], the most recent literature indicates that their use does not significantly increase rates of morbidity and mortality in these patients [34]; nor does it appear that inhibiting TNF- α has a negative effect on the CD4 count or viral load [35]. Infliximab and efalizumab both seem to have similar efficacy in treatment. High levels of TNF- α are associated also with HCV infection, hence TNF- α inhibitors may be beneficial in moderate to severe psoriasis associated with HCV infection. Etanercept and other TNF- α blockers have been suggested as second line drugs for patients with psoriasis and HCV infection [36]. However, as the risk of using these drugs in HIV-positive patients has not been evaluated in controlled studies, during therapy it is essential to carry out optimal antiretroviral treatment, the recommended prophylaxis against infections, and a strict clinical and analytical follow-up.

REITER'S SYNDROME

Reiter's syndrome is characterized by a triad of polyarthrititis (particularly sacroilitis), urethritis and conjunctivitis [37]. It has been reported in 6 to 10% of HIV-infected patients [39].

Etiopathogenesis

Reiter's syndrome is more likely to occur in genetically predisposed individuals. Human leucocyte antigen (HLA)-B2, present in up to 90% of Reiter's syndrome patients, increases the risk of developing Reiter's syndrome by 25 times and is associated with a more severe course [39].

Clinical Features

The symptoms of HIV infection and Reiter's appear simultaneously or the HIV infection is symptomatic before the onset of Reiter's [27]. Palmoplantar pustular dermatosis is characteristically associated with nail dystrophy, periungual erythema, and hyperkeratosis [40]. The lesions initially present as erythematous macules and later progress to become hyperkeratotic, waxy papules associated with an erythematous halo. Multiple papules coalesce and eventually form thickened horny plaques. The lesions are mainly distributed over the palms and soles, less frequently over the trunk and extremities [Figure 3.4a,3.4b]. Reiter's syndrome usually has a relapsing course. The genitourinary system is involved with circinate balanitis, urethritis, prostatitis, seminal vesiculitis, as well as hemorrhagic cystitis. Cervicitis and vulvitis may be the presenting symptom in females [41]. Evanescent asymptomatic oral erosions and geographic tongue may be observed. Clinically and histologically, this is a close mimicker of psoriasis, hence presence of the triad is essential for definitive diagnosis.



Figure 3.4a: Reiter's disease-Multiple hypopigmented scaly plaques over dorsum of hand

[Photo courtesy: Department of dermatology, Bowring and lady Curzon hospital]



Figure 3.4b: Reiter's disease- Multiple well defined annular scaly plaques.

[Photo courtesy: Department of dermatology, Bowring and lady Curzon hospital]

Treatment

The therapeutical options for Reiter's are similar to that of psoriasis. Oral acitretin is considered the drug of choice in HIV patients [42].

SEBORRHOEIC DERMATITIS

Seborrheic dermatitis is a mild eruption, usually affecting the scalp and central areas of the face that occurs in up to 5% of the non-HIV-infected population [27].

The prevalence of SD in HIV-positive and AIDS patients is between 34% [43] and 83% [44] as opposed to 3% in the general population.

Seborrheic dermatitis may be the initial cutaneous manifestation of HIV disease. Seborrheic dermatitis like eruptions is observed in 83% of patients with AIDS [45] in a study conducted by Mathes et al.

Incidence in HIV Disease

One study found an 83% point prevalence of seborrheic dermatitis associated with advanced HIV disease and a 42% point prevalence with symptomatic HIV disease [46,47]. Other studies have reported rates in patients with advanced HIV disease ranging from 25 to 45% [48-50]. These percentages are far above those expected in a population on the basis of flare-ups from severe illness alone.

Etiopathogenesis

Its incidence and severity are closely related to the stage of HIV infection and inversely correlate

with the absolute CD4 and helper T cell counts [51]. The clinical picture seen in HIV infection-AIDS is termed as SD-like dermatitis of AIDS and is regarded as a distinctive entity. The exacerbated clinical picture is due to enhanced growth of yeasts secondary to immunosuppression [46].

Clinical Features

Seborrheic dermatitis in HIV-infected individuals ranges from typical seborrheic dermatitis to a widespread form like inverse psoriasis or sebopsoriasis [46]. The eruption, which is characterized by widespread inflammatory and hyperkeratotic lesions, may progress to erythroderma in some patients.

Clinically, typical HIV-related seborrheic dermatitis occurs predominantly on the scalp, usually with mild involvement on the face. Occasionally, seborrheic dermatitis will also occur on the chest, in the axillae and groin. Lesions are poorly defined, faint pink patches, with mild-to-severe fine, loose, waxy scales. In a small percentage of patients, the seborrheic dermatitis is more extensive and is present on the scalp and large areas of the face (Figure 3.5). The intertriginous lesions are clinically identical to those seen in Reiter's syndrome and psoriasis concurrent with HIV infection [27].



Figure 3.5: Seborrheic dermatitis

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

A small percentage of patients present with the most severe form of seborrheic dermatitis, which consists of typical severe seborrheic dermatitis of the face and scalp, plus extensive involvement of the intertriginous areas. The axillae and groin are bright red and covered by a fine scale. The eruption moves out from the intertriginous areas onto the trunk and neck and may involve large areas of the body. Like classic seborrheic dermatitis, pruritus is generally mild. This severe form of seborrheic dermatitis may also be seen in non-HIV-infected persons, although it is quite unusual. This form may be called sebopsoriasis or inverse psoriasis -- a cross between seborrheic dermatitis and psoriasis -- and may be the presenting manifestation of HIV infection [27].

Patients with HIV characteristically have more erythema and extensive involvement in the sebaceous areas of the scalp and nasolabial folds than those without HIV. Sites such as the chest, back, axillae and intertriginous zones are more commonly involved [52].

Treatment

Mild seborrheic dermatitis in HIV-infected patients is managed in the same manner as in non-HIV-infected patients: mild topical steroids (e.g., 1% hydrocortisone), coal tar, and twice daily application of imidazole creams (clotrimazole or ketoconazole), which is used for its anti-inflammatory rather than its antifungal effects. Patients respond poorly to treatment with topical imidazoles alone [27].

PITYRIASIS RUBRA PILARIS

Pityriasis rubra pilaris (PRP) is a papulosquamous disorder of uncertain etiology comprised of a spectrum of clinical variants.

It was first categorised into 5 types based on the type of skin lesions and patient age in the year 1980 [53]. An additional variant type 6 associated with HIV was added in 1995 [54].

Pathogenesis

The exact pathogenesis of type 6 PRP has not yet been put forth. It has been proposed that follicular inflammation caused by infection of the hair bulb region by the virus is responsible for the disease initiation and evolution [55]. There is no proven association between the degree of immunosuppression (CD4 counts) and occurrence of PRP. HIV was suspected only in cases of PRP with atypical cutaneous presentation. In few cases onset of PRP has been noticed within two to three months of detection of retropositive status [56].

Clinical Features

In classical adult onset PRP in immunocompetant patients, the eruption is seen as erythematous perifollicular papules with a central keratotic acuminate plug, appearing in groups and progressing in the cephalo-caudal direction. Later they become confluent to form sheets of orange desquamation with normal skin in between ('islands of sparing'). The nails are thickened and discoloured distally, showing splinter haemorrhages. Palms and soles become hyperkeratotic and yellow ('PRP sandal') [57].

On the contrary, type 6 PRP (HIV associated) is characterized by nodulocystic acne lesions, lichen spinulosus-like lesions, showing resistance to treatment. Prominent follicular plugging with formation of spicules, which is rarely seen in classic adult-onset PRP, is a common observation in HIV-associated PRP. The incidence of erythroderma occurring is higher compared to other types. There is an increased prevalence of follicular manifestations like lichen spinulosus [58] and acne conglobata [59] in such patients. Therefore, clinical researchers prefer to describe this under a spectrum of a unique and distinctive disease called HIV-associated follicular disorder [60]. This

group of disorders comprise of generalized follicular disease, including nodulocystic inflammatory folliculitis, prominent keratotic spines, and possibly generalized papulosquamous findings indistinguishable from PRP. It has also been referred to as HIV-associated follicular syndrome [60] or HIV-associated follicular occlusion triad [61]. The striking nodulocystic folliculitis sets this disorder apart from classic PRP.

Treatment

Many therapeutic modalities have been employed in the treatment of HIV-associated PRP. These include retinoids like etretinate, isotretinoin, minocycline, prednisolone, UVB phototherapy. These agents have been given in conjunction with ART drugs like zidovudine, stavudine, lamivudine, indinavir and saquinavir. The response with any of the drugs mentioned has not been consistent. Oral retinoids, which are very promising in treating classic PRP, seem to be ineffective in HIV-associated PRP.

It can be concluded that a middle-aged patient presenting with the classic triad of features of nodulocystic acne, lichen spinulosus, and psoriasiform lesions or isolated nodulocystic acne or lichen spinulosus-like lesions should be tested to detect early HIV infection in the backdrop of diagnosis of type 6 pityriasis rubra pilaris.

XEROSIS AND ICHTHYOSIS

HIV-infected patients commonly complain of increasing dryness of the skin or xerosis [62,63]. The exact pathogenesis of xerosis in the setting of HIV is unknown. Poor nutritional status, immunosuppression, and chronic illness have been implicated [64-66]. Xerosis is seen in approximately 30% of HIV-infected patients [64,66]. The xerosis is most prominent on the anterior lower legs, but it may become quite widespread. During winter, the xerosis is more severe and can lead to a severe form called asteatotic eczema, manifesting as itching and dryness with areas of erythematous plaques and fine scale on the posterior arms and shins. Thickened skin can be noticed over palms and soles (Figure 3.6)

Acquired ichthyosis (Figure 3.7) may begin on the lower extremities and disseminate in advanced HIV disease. Acquired ichthyosis may be a marker of concomitant infection with HIV-1 and human lymphotropic virus II in persons who use intravenous drugs and have profound helper T-cell depletion [67]. Acquired ichthyosis has been seen in association with a wasting syndrome. Treatment is the same as for xerosis [27].



Figure 3.6: Hyperkeratotic and thickened skin with fissuring over soles.

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



Figure 3.7: Acquired Ichthyosis

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

Excessive or frequent bathing with strong antibacterial soaps is a frequent precipitating factor and should be discontinued. Patients should apply mild topical steroid ointments (1.0 to 2.5% hydrocortisone or 0.025% triamcinolone) to the eczematous areas thrice a day and liberal application of emollients containing urea, lactic acid, salicylic acid done immediately after bathing and at bedtime.

ATOPIC DERMATITIS IN HIV

Patients with HIV infection commonly manifest atopic-like dermatitis and often have severe disease that is recalcitrant to therapy [68]. This may be explained by similar cytokine profiles in both Atopic Dermatitis (AD) and HIV. Patients with atopic dermatitis have a Th2 cytokine profile, which is similar to the cytokine profile seen in HIV disease. The Th2 cytokine profile is characterized by elevated IgE levels, increased eosinophils, and increased interleukin 4 and 5 [40].

Atopic dermatitis may appear in both children and adults infected with HIV. Adults with a previous history of atopic disease (been in remission) may also note recurrence of atopy in advanced HIV disease [69]. They may develop atopic dermatitis when previously they had only respiratory atopic symptoms. Few severe cases have developed erythroderma too [70]. AD is associated with pruritus that can lead to secondary skin changes such as lichenification or lichen simplex chronicus or secondary pyoderma.

Treatment includes emollients, topical steroids, oral antihistamines, and avoidance of irritants. Phototherapy has been used with success [68]. Systemic immunosuppressants should be avoided. It is thought that effective antiretroviral therapy reduces the prevalence and severity of HIV-related AD [71].

CONCLUSION

Papulosquamous disorders which are usually non infectious inflammatory dermatoses, constitute a major percentage of cutaneous disorders encountered in HIV infected patients. They can occur after detection of seropositivity, get flared up after onset of HIV infection or can sometimes serve as markers of underlying immunosuppression. The diseases usually run a course similar to that in an immunocompetent individual, with only few subtle differences. However, they are persistent and recalcitrant to regular treatment modalities making it challenging for the treating dermatologists.

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