

Dermatological manifestations in human immunodeficiency virus infected patients: Morphological spectrum with CD4 correlation

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Abstract

Background: More than 90% of human immunodeficiency virus (HIV) infected patients develop skin lesions at some time throughout the course of the disease. Several skin diseases have proved to be sensitive and useful indicators of progression of HIV infection. Although these conditions may be seen in general healthy population, their occurrence in patients with acquired immunodeficiency syndrome is often atypical, more severe and explosive. **Aims:** The present study was carried out to categorize the skin lesions by histopathology using punch biopsy or cytology when feasible in HIV infected patients and to see the correlation for various skin lesions with CD4 counts. **Materials and Methods:** In total 110 known HIV positive patients with the symptomatic skin lesions, cytology and punch biopsy was correlated with CD4 counts. **Results:** Maximum patients were between 31 and 40 years. 53 (48.18%) patients had infectious and 37 (34.55%) patients had non-infectious lesions. Out of 110 patients, CD4 counts were available in 70 patients. The spectrum of various non-infectious and infectious lesions such as viral, bacterial, fungal, protozoa and their association with CD4 counts is discussed. **Conclusions:** CD4 counts below 200 were associated with the maximum infectious lesions, whereas CD4 counts more than 350 showed more of the non-infectious lesions. Most common infectious lesion was *Molluscum contagiosum*. The most common non-infectious lesion was pruritic papular eruptions.

Key words: CD4, human immunodeficiency virus, pruritic papular eruptions, punch biopsy, skin lesions

INTRODUCTION

Diseases of skin and mucous membranes are common clinical manifestations of acquired immunodeficiency syndrome (AIDS). Cutaneous disorders are not only associated with terminal immunodeficiency, but also occur throughout the course of human immunodeficiency virus (HIV)

infection. More than 90% of patients develop skin lesions at some time during the disease. In some patients, skin is the first organ affected.^[1] Skin diseases have proved to be sensitive and useful measures by which HIV progression can be monitored. Impaired skin immune system occurring early in HIV disease is believed to be responsible for the frequent occurrence of both infectious and non-infectious skin diseases even before the development of full blown HIV infection.^[2] Although skin lesions may be seen in the general healthy population, their occurrence in HIV infected patients is often atypical and more severe, explosive, extensive or resistant to therapy. The unusual histology of some of the diseases in AIDS may contribute to misdiagnosis. Thus, proper histological

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diagnosis of skin manifestations is very important as it may serve as the earliest manifestation to suspect a case of HIV infection. Infectious agents can produce skin lesions even though the classic organ of involvement for that the agent does not include the skin.

MATERIALS AND METHODS

This was a prospective observational study of 2 year duration carried out in the Department of Pathology of a tertiary referral center. Total 110 known HIV positive patients of all ages with symptomatic skin lesions attending skin and venereal disease out-patient department and Anti Retroviral Therapy Clinic at this center were included in the study. Patient's HIV positivity was confirmed by three different sets of Ag systems (HIV comb-AIDS Rapid test, Rapid spot test-Pareekshak and Tridot). The complete clinical details, in particular skin lesions were noted along with CD4 counts when available. Irrespective of any other systemic involvement or presence of other STDs, only skin lesions were sampled after taking informed written consent. The lesions were sampled using the punch biopsy or cytology and the diagnosis was made with the help of special stains as and when required. Of the total 110 patients, 106 punch biopsies were taken and cytology was done in 25 cases. (Four cases were diagnosed only on cytology. In 21 cases, both punch biopsy and cytology was done.) The type of cytology sample varied depending upon the nature of the lesions, i.e., in nodular lesions, fine needle aspiration cytology (FNAC) was done, scrape smears were taken in ulcerative lesions and in vesiculobullous lesions, Tzanck smears were taken. In few cases with scaly pruritic skin lesions, wet and potassium hydroxide mount preparation was done. Many of the lesions were eruptions or a rash or maculopapular type where cytology was not possible, in such lesions only punch biopsy was done using sterilized disposable skin biopsy punches. The fresh and active lesions were considered for sampling. All universal aseptic precautions according to National AIDS Control Organization guidelines were followed. The biopsy obtained was processed by standard formalin fixing paraffin embedding method. Serial sections and special stains were studied as and when required.

RESULTS

Out of total 110 known HIV infected patients, 74 were males and 36 were female patients. Maximum numbers of cases were seen in between 31 and 40 years of age group. Average age in the study was 34 years. CD4 counts were correlated in 70 cases.

Out of 70 HIV infected patients, 42 (59%) patients had CD4 counts <200, 10 patients showed CD4 counts between 200 and 350, 11 patients had counts from 350 to 500 and 7 (10%) patients had CD4 count >500 [Table 1]. Different diagnostic categories with different clinical diagnoses having proportionate clinical morbidity were observed in the study [Table 2]. As two biopsies were inadequate, diagnosis was possible in 108 cases, out of which, 53 (48%) had infectious pathology, whereas 37 (35%) patients had non-infectious pathology. Three patients had infectious as well as non-infectious pathology. Few patients had more than one infectious lesion. A total of 11 patients had Miscellaneous and other skin pathology. Variety of infectious skin lesions were observed such as viral, bacterial, fungal and parasitic (Arthropod) infections. Total 30 (27.28%) patients showing viral pathology included *Molluscum contagiosum* (15), human papilloma virus (HPV) (8), herpes zoster (6) and herpes simplex virus (HSV) (1). Total 14 (12.72%) patients had bacterial infections, which included leprosy (4), cutaneous tuberculosis (4), folliculitis (3), syphilis (1), donovanosis (1) and furunculosis (1). Total 7 (6.36%) cases of parasitic infections were seen which included demodicidosis (6) and scabies (1). Total fungal infections were 6 (5.45%), which included candidiasis (2), dermatophytoses-tinea (2), cryptococcosis (1) and histoplasmosis (1) [Table 3].

In non-infectious category, majority of patients (25) had pruritic papular eruptions (PPE) followed by seborrheic dermatitis (5), psoriasis (4), eosinophilic folliculitis (3) and prurigo (3). Total eight patients

Table 1: Correlation of CD4 count with skin lesions

CD4 count	<200 (%)	200-350 (%)	350-500 (%)	>500 (%)
Infectious	36 (85.7)	5 (50)	4 (36.4)	2 (28.5)
Non-infectious	4 (9.5)	4 (40)	7 (63.6)	5 (71.4)
Mixed	2 (4.7)	1 (10)	0	0
Total 70	42	10	11	7

CD=Cluster of differentiation

Table 2: Different diagnostic categories in the study

Diagnosis	Total	%
Infectious	53	48.18
Non-infectious	37	34.55
Miscellaneous and others	11	10.00
Infectious, non-infectious	3	2.73
Non-infectious, miscellaneous	3	1.82
Inadequate	2	1.82
Infectious, miscellaneous	1	0.90
Grand total	110	100.00

had non-specific pathology, whereas two patients had neutrophilic dermatitis. Cytology was done in total 25 patients who included infective lesions such as viral (18), bacterial (3), fungal (2) and parasitic (2). Out of 108 patients, mixed lesions were found in 19 (18%) patients.

DISCUSSION

Although a lot of literature regarding the etiology of cutaneous manifestations in HIV patients is available in Western world and some parts of Asia; very few case studies in Indian patients are available. No such type of study has been carried out in Central India. Most of the patients in our study were from 31 to 40 years age group with youngest patient, 3 year of age and oldest was 60 year. Average age was 34 years. A study by Kumarasamy *et al.* had 50% patients between 18 and 30 years age group.^[3] In the present study; we found 67% male patients as compared with 33% females. Most of the patients had itching as the main symptom.

In our study of 110 HIV infected patients, CD4 correlation was done in 70 patients. Maximum patients, i.e., 42 (59%) had CD4 count below 200, followed by 21 (31%) patients with CD4 counts between 200 and 500, whereas 7 (10%) patients had CD4 counts above 500. The category of 200-500 was further subdivided into two, (between 200-350 and 350-500) Maximum number of infective lesions were seen in patients with CD4 counts below 350 whereas patients with CD4 count above 350 showed minimum infective, but most of the non-infectious lesions [Table 1]. Previous studies showed that CD4 counts <200 cells/cumm were associated with more number of infectious lesions.^[2,4-7] Muñoz-Pérez (1998)

stated that various dermatoses such as genital herpes, tinea, Kaposi's sarcoma, xerosis, HSV, drug eruptions, candidial folliculitis, *M. contagiosum*, psoriasis, abscess, verruca vulgaris, PPE, oral hairy leukoplakia and seborrheic dermatitis could be used as clinical markers of disease progression due to their strong association with CD4 counts.^[8]

We found that 57 out of 110 (52%) patients had infectious lesions. Unusual clinical presentations of common skin infections or florid, unusual forms had been described in these patients by various authors.^[5] In these patients, infectious agents can produce skin lesions even though the classic organs of involvement for that agent do not include the skin, e.g., cryptococcosis, *Cytomegalovirus* and histoplasmosis. We found 30 (27.28%) patients with viral lesions. Out of 15 cases of *M. contagiosum*, 2 cases had giant *Molluscum* all over the body diagnosed first on FNAC [Figures 1 and 2]. Maximum patients showed CD4 counts <200 as studied by other authors. Few cases were associated with demodex infection. The HPV related lesions



Figure 1: Photograph showing multiple giant *Molluscum contagiosum*

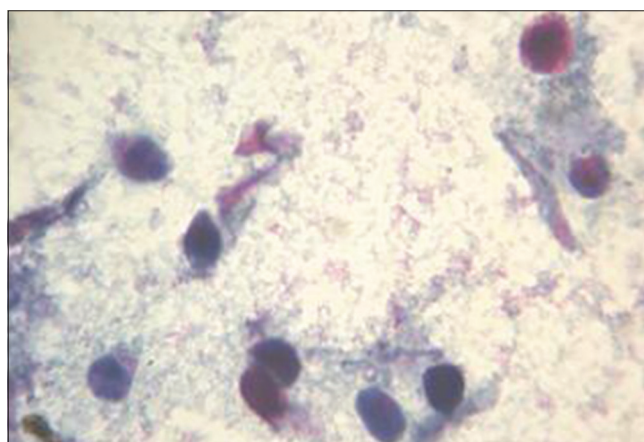


Figure 2: Papanicolaou stained cytology smears showing *Molluscum* bodies (x400)

Table 3: Infectious lesions in the study

Category	Infectious lesions	No. of cases
Viral	<i>Molluscum contagiosum</i> (15), Human papilloma virus (8), Herpes zoster (6) Herpes simplex (1)	30
Bacterial	<i>Mycobacterium Leprae</i> , BT (3) TT (1) <i>Mycobacterium Tuberculosis</i> PNT Papulo Necrotic Tuberculid (2) scrofuloderma (1) TB cutis orificialis (1) folliculitis (3), syphilis (1), donovanosis (1) furunculosis (1)	14
Parasitic (arthropod)	Demodicidosis (6) scabies (1)	7
Fungal	Dermatophytoses (Tinea) (2), candidiasis (2) cryptococcosis (1), histoplasmosis (1)	6
	Total infectious lesions	57

PNT=Papulo necrotic tuberculid; TB=Tuberculosis; BT=Bordertline tuberculoid; TT=Tuberculoid

were verruca vulgaris, verruca plana and bowenoid papulosis and condylomata acuminata. Muñoz-Pérez *et al.* found no significant difference between the incidence of condyloma acuminata or verruca vulgaris in stage III and stage IV disease or with CD4 counts.^[8] Smith *et al.* also failed to find consistent increased occurrence of HPV infection with advancing stage.^[9] Present study showed no significant difference in the occurrence of HPV related lesions in patients with <200 or >200/cumm CD4 counts. Muñoz-Pérez *et al.* in their study mentioned that HIV infection itself predisposes to an increased risk of HPV infection that is not directly related to the degree of immunosuppression.^[8] We found six cases of herpes zoster infection, one of which was perianal extensive ulcer with secondary infection, which was diagnosed on cytology. Another case was multidermatomal infection and one had associated candidiasis. Friedman-Kien *et al.* had mentioned a strong association between the occurrence of herpes zoster and incidence of AIDS.^[10]

Nichols *et al.* stated that bacterial infections in AIDS were often under represented.^[11] In our study we found 14 (12.72%) cases of bacterial infection including Mycobacterium infections. Dermatological lesions of tuberculosis (TB) infection are rarely found in Western countries.^[12] Various mycobacterium lesions in our study were leprosy (three cases of borderline tuberculoid and one case of tuberculoid leprosy), papulonecrotic tuberculid (2), scrofuloderma and TB cutis orificialis one each. Later two were diagnosed first on cytology and confirmed on histology. CD4 counts were not available in all TB cases except scrofuloderma (95) and TB cutis orificialis (81). Frommel *et al.* found no association between leprosy and HIV-1 infection; he had mentioned that it does not seem to alter its course.^[13]

We found six cases of fungal lesions which included two cases of dermatophytoses and candidiasis each and one case each of histoplasmosis and cryptococcosis, first diagnosed on FNAC; thus recommending the cytodiagnosis of these lesions for early diagnosis and early institution of therapy [Figures 3-6]. All fungal infections were seen in CD4 counts below 350 cells/cumm. We found 7 (6.36%) cases of parasitic infection, which included six cases of demodicidosis and one case of scabies. One interesting finding in scabies was that it was not detected histologically; but only wet preparation and scrape cytology showed the parasite. Kaplan *et al.* reported four cases of scabies who presented with pruritic dermatitis. Clinically,



Figure 3: Nodulo-ulcerative lesion over nose in a patient with cutaneous histoplasmosis

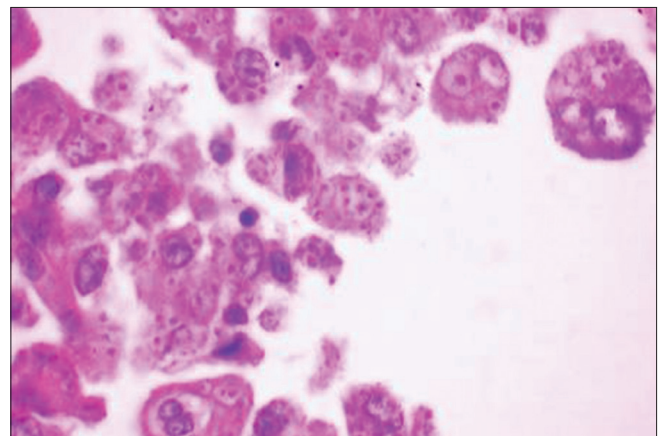


Figure 4: Cytology smears showing macrophages containing intracytoplasmic tiny capsulated histoplasma organisms (H and E, ×1000)



Figure 5: Nodule over lower lid in a patient with cutaneous cryptococcosis

the lesions of scabies may resemble psoriasis vulgaris or Darier's disease.^[5,14] The most common non-infectious skin manifestation found in our study was PPE. They were intensely pruritic, papular lesions more on the trunk and extremities with a predominance of eosinophils as described by Francis.

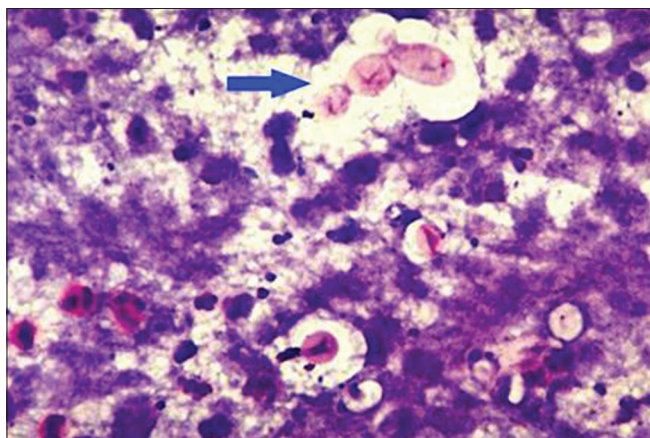


Figure 6: May-Grunwald-Giemsa stained cytology smears showing budding forms of *Cryptococcus* in necrotic inflammatory background ($\times 1000$)



Figure 7: Skin lesion in a patient with psoriasis

The severe form of similar eruptions is seen in African and Haitian patients.^[4] Hevia *et al.* (1991) mentioned histological and clinical criteria for the diagnosis of these lesions.^[15] Most of the cases of PPE in our study were seen with CD4 counts more than 350 cells/cumm. We have found only 4.54% cases, which was similar to other studies in India (Mumbai 3%) and Asia (Thailand 4.7%) indicating low incidence in Asian patients.^[16,17] We found three cases of eosinophilic folliculitis. Rosenthal *et al.* found its association in patients with CD4 counts between 200 and 500 cells/cumm.^[18] It could be an important clinical marker of HIV infection, particularly in patients at increased risk of developing opportunistic infection. The clinical and histological differential diagnoses of eosinophilic folliculitis include demodicidosis and PPE. We found three cases of psoriasis and one case of Reiter's syndrome [Figure 7]. Incidence of psoriasis as high as 70% had been reported by Duvic *et al.*^[19] We found 4 cases of seborrheic dermatitis. Although, it is mentioned that the incidence of seborrheic dermatitis is very high from 40% to 83% in Western literature; and in some other studies.^[20] We found one case each of drug eruption, keratosis pilaris, porokeratosis, Reiter's syndrome, seborrheic keratosis, lichen planus and papular urticaria. Miscellaneous group included 8 cases of non-specific dermatitis, two cases of neutrophilic dermatitis and one case each of chronic dermatitis, interface dermatitis, pityriasis rosea, panniculitis/vasculitis and abscess. We did not get any case of neoplastic lesion, i.e., Kaposi's sarcoma, lymphoma or any other cutaneous malignancies. Wiwanitkit (2004) and D. N. Lanjewar (2011) also found striking low prevalence of cutaneous and other malignancies in these patients.^[6,21] Histological variations from normal were noted in certain lesions.

In many biopsies, we observed myxoid change in dermis not related with lesion. It was seen in both infectious and non-infectious conditions. In cases of herpes zoster, specific nuclear changes were seen not only in the epidermis and adnexal structures, but in fibroblasts of the granulation tissue and vascular endothelial cells giving pseudosarcomatous appearance. Periadnexal and perivascular inflammatory infiltrate, i.e., lymphocytic infiltration was seen in most of the lesions irrespective of histological diagnosis. Epidermal hyperplasia in the form of acanthosis, irregular parakeratosis or hyperkeratosis was seen in most of the lesions. None of the lesions showed normal epidermis.

To summarize, in the present study on skin lesions in HIV infected individuals, infectious skin lesions were seen more commonly with CD4 counts below 350 and non-infectious skin lesions were seen more commonly with CD4 counts more than 350. The most common infectious lesion was *M. contagiosum* and most common non-infectious lesion was PPE. In ulceronodular lesions, cytology was useful for early diagnosis, especially in infectious lesions. Strikingly low occurrence or absence of cutaneous malignancies was seen in the present study.

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