Cutaneous manifestations of HIV—a detailed study of morphological variants, markers of advanced disease, and the changing spectrum

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ABSTRACT

BACKGROUND

Cutaneous manifestations are early and easily identifiable markers of human immunodeficiency virus (HIV) infection. They can help in predicting severity and progress of the disease and can be correlated well with CD4 counts. This study was undertaken to study the cutaneous manifestations of HIV infection and to correlate them with CD4 counts. It also aimed to study the changing spectrum of these manifestations and describe cutaneous manifestations seen in advanced disease.

METHOD

A total of 234 HIV-positive patients not on anti-retroviral therapy, who attended the outpatient department or were admitted as inpatients at Military Hospital, Shillong during the period between May 2008 and October 2009 were included. Cutaneous, mucosal, and genitourinary manifestations in these patients were studied in detail and were correlated with CD4 counts.

RESULTS

Infections were the most common group of mucocutaneous manifestations, while onychomycosis was the commonly observed individual manifestation. A different set of cutaneous markers for advanced HIV disease was observed and new parameters for therapy were also arrived at.

CONCLUSION

Specific morphological variants of cutaneous markers may provide a better clue to early diagnosis of HIV and can help in diagnosing advanced stages of the disease. Fresh cutaneous markers are required for indicating cut-off levels of CD4 count at 350/μL for starting therapy.

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Key Words: AIDS; CD4 count; cutaneous manifestations; HIV

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INTRODUCTION

Diseases of the skin and mucous membranes were among the first recognised clinical manifestations of acquired immune deficiency syndrome (AIDS) in the early 1980s. In some patients, skin findings may be the earliest and the only sign of human immunodeficiency virus (HIV) presentation, and can thus alert one to an early diagnosis and treatment.¹ The dermatological manifestations increase both in frequency and severity with the progression of HIV and decline in CD4+ cell counts and thus can serve as important markers of disease progression especially in countries with poor resources.

This study was commenced to study the cutaneous and genitourinary manifestations in HIV in an Indian population and their correlation to CD4 counts. It also aimed to study the changing spectrum of these manifestations and describe cutaneous features of advanced disease, which may act as markers for initiating therapy. Only few such studies have been carried out earlier in an Indian population.^{2,3} Sharma et al reports a single study comprising 36 patients carried out in a military setting encompassing a detailed description of morphological variants of cutaneous manifestations and their correlation with CD4 counts.⁴

MATERIALS AND METHOD

This descriptive study was conducted at Military Hospital, Shillong, which is the HIV referral centre as well as the information, education, and counselling (IEC) node for armed forces and paramilitary personnel of North East India, between May 2008 and October 2009. All HIV-positive patients attending outpatient departments (OPDs) and admitted as inpatients during the above period were included in the study. Initial screening for HIV was done by the rapid test and, if positive, was confirmed by two different types of enzyme-linked immunosorbent assay (ELISA). Patients already on anti-retroviral therapy (ART) were not included. Age, weight, probable time of first high-risk behaviour and CD4+ counts were noted. A complete medical history and physical examination of patients was carried out for optimal evaluation and diagnosis of dermatological and venereological lesions. The diagnosis was based on clinical criteria in most of the cases. Appropriate laboratory tests like scraping for fungus/candida, culture, skin biopsy,

Venereal Disease Research Laboratory (VDRL) test and *Treponema pallidum* haemagglutination assay (TPHA) were performed in certain cases to confirm the diagnosis. The CD4 counts were performed in all cases using fluorescence activated cell sorter (FACS) flow cytometry. Chi-square test was used to determine the significance of cutaneous manifestations in relation to CD4 counts.

RESULTS

A total of 234 HIV-positive patients were enrolled in the present study. All patients were males and average age of the patients was 36.35 ± 11.15 (range 23–52 years of age). The predominant mode of transmission was heterosexual contact (200/234, 85% patients). The average period from probable onset to detection of disease was 7.5 ± 5.2 years (range six months–22 years). A total of 581 cutaneous and genitourinary manifestations were found in these patients with an average of $2.48 (\pm 1.16)$ manifestations per patient. The prevalence of cutaneous manifestations in the present study was 216 patients (92.3%). Maximum number of manifestations in a single patient was eight while 18 patients (7.7%) did not have a single manifestation. The most common HIV-related dermatological manifestations both group-wise and individually are given in Table 1.

A total of 176 fungal infections were found in 114 patients, indicating that many patients had more than one type of fungal infection (Table 2). The type of nail involvement commonly seen was total dystrophic onychomycosis (38 patients, 16.2%) followed by distal and lateral subungual onychomycosis

(DLSO) in 22 patients (9.4%) (Figure 1A). White superficial onychomycosis was present only in two patients (<1%) (Figure 1B). Only two of the nail fungal infections were found to be candidial in origin. Corresponding tinea pedis was found in eight patients (3.4%), with the moccasin leather variety more

Table 1 Prevalence of common cutaneous manifestations, groupwise, and individual.

Manifestation	No. of manifestations in patients	Prevalence (%)
Groupwise		
Infections	306	56.41
Disorders with dry skin	42	17.95
Pigmentary abnormalities	40	17.09
Sexually transmitted diseases	32	10.68
Miscellaneous	78	23.08
Individual manifestations		
Onychomycosis	62	26.5
Warts	39	16.67
Xerosis	39	16.67
Tinea corporis	35	14.96
Papular eruptions	27	11.54
Furuncles	27	11.54
Herpes zoster	26	11.11
Oral candidiasis	26	11.11
Tinea cruris	24	10.26
Seborrhoeic dermatitis	23	9.83

Table 2 Infections and relation with CD4 counts.

Type of illness	Cutaneous manifestation	Total no. of patients	Average CD4 count (range)	CD4 <200	CD4 >200 and <350	CD4 >350
Fungal	Onychomycosis	62	291 (77–692)	12	35	15
	Tinea corporis	35	296 (85–631)	3	22	10
	Oral candidiasis	26	233 (30–697)	16	7	3
	Tinea cruris	24	224 (118–532)	1	14	9
	Tinea pedis	17	300 (115–576)	2	9	6
	Pityriasis versicolor	5	313 (107–543)	1	3	1
	Genital candidiasis	4	226 (67–398)	1	2	1
	Tinea manuum	3	358 (221–492)	–	2	1
Viral	Warts	39	241 (5–864)	6	24	9
	Herpes zoster	26	208 (34–497)	9	14	3
	Molluscum contagiosum	12	211 (5–465)	5	5	2
	Herpes labialis	2	218 (162–274)	1	1	–
	Oral hairy leukoplakia	1	108	1	–	–
Sexually transmitted disease	Herpes genitalis	11	239 (83–431)	3	5	3
	Syphilis	10	157 (54–358)	8	1	1
	Chancroid	5	262 (92–384)	1	3	1
	Urethritis	5	241 (102–387)	2	2	1
	LGV	1	566	–	–	1

LGV: lymphogranuloma venereum.

Figure 1 Fungal infections: (A) distal and lateral superficial onychomycosis, (B) white superficial onychomycosis, (C) Tinea manuum, and (D) Tinea pedis moccasin leather type.

Figure 2 Oral candidiasis: (A) atrophic type and (B) pseudohypertrophic variety.

common than the others (Figure 1C). Tinea manuum was found in only three patients (Figure 1D). In oral candidiasis, atrophic variety (Figure 2A) was more common than the classic pseudohypertrophic variety (Figure 2B).

Viral manifestations were present in 80 patients (34.19%) and the spectrum of these manifestations is as given in Table 2. Condyloma acuminata (Figures 3A and B) and molluscum

contagiosum (Figure 3C) continue to be widespread in HIV. Herpes zoster was present in 26 patients (11.11%) and was the presenting complaint in each one of them. Complicated cases included one each of disseminated, multi-dermatomal, and ulcerated variety (Figure 3D).

Furuncles (27 patients, 11.54%) was the common bacterial infection followed by folliculitis (5 patients, 2.14%), and one

Figure 3 Viral manifestations: (A) giant penile warts, (B) perianal warts, (C) ulcerated herpes zoster, and (D) giant molluscum contagiosum.

Figure 4 Rare manifestations: (A) oral hyperpigmentation, (B) clubbing, (C) prurigo nodularis, and (D) keratosis pilaris.

Table 3 Cutaneous manifestations with CD4 < 200/ μ L.

S. no.	Manifestation	Total no. of patients	Average CD4 (range)	Patients with CD4 $\leq$ 200	Patients with CD4 > 200
1	Hyperpigmentation on dorsum of tongue	5	161 (21–179)	5	–
2	Atrophic oral candidiasis	20	147 (30–328)	14	6
3	Extensive tinea corporis	3	114 (85–164)	3	–
4	Latent syphilis	9	151 (54–267)	8	1
5	Perianal warts	4	146 (5–289)	3	1
6	Molluscum-extragenital	7	114 (5–167)	5	2
7	Complicated herpes zoster	3	119 (35–187)	3	–
8	Ophthalmic zoster	1	34 (28–40)	1	–
9	Extensive xerosis	3	115 (30–199)	3	–
10	Extensive seborrhoeic dermatosis	3	103 (29–203)	3	–
11	Brittle hair	3	58 (36–106)	3	–
12	Finger nail onychomycosis	12	167 (77–276)	10	2
13	Bullous tinea pedis	1	80	1	–
14	Sebopsoriasis	1	32	1	–

patient each had sty, paronychia, and impetigo lesions. The common site for furuncles was the thighs followed by the buttocks, while that of folliculitis was the beard area. Staphylococcus was the common organism responsible, while rest were mixed infections.

The spectrum of various sexually transmitted diseases (STDs) in this study was as given in Table 2. Most patients with herpes genitalis had recurrent episodes and responded well to oral acyclovir. In two of the patients who had VDRL reactivity, TPHA was found to be negative, confirming their false positivity.

Xerosis was the commonly observed dry skin disorder affecting 39 patients (16.67%) of which three had extensive involvement. Ichthyosis was present in three patients and 23 patients (9.83%) alone had seborrhoeic dermatosis of which three were severe. The average CD4 count in these patients was 376/ μ L.

Recurrent large aphthae were present in three patients and herpes labialis in two patients. None of these patients had CD4 counts <200/ μ L. Another finding was that five patients had hyperpigmentation on the dorsum of tongue (Figure 4A), with no other aetiology found for their occurrence.

Generalised hyperpigmentation was present in eight patients (3.42%) of which one had predominant pigmentation on dorsum of hands and feet. Average CD4 count in these patients was 246/ μ L. Thirty-two patients had malar hyperpigmentation with an average CD4 count of 364/ μ L.

A total of four patients in the present study had photodermatoses of which two had photosensitivity and one each had tropical acne and actinic reticuloid. The average CD4 count was 217/ μ L.

Two patients had drug reactions. One of them developed maculopapular rash to cotrimoxazole and the second patient had a fixed drug eruption to tinidazole. The average CD4 count in these patients was 241/ μ L.

Dry lustreless hair was present in four patients, three had generalised hair loss, two had canities, and three patients had brittle hair. Melanonychia was present in six patients who also had generalised hyperpigmentation. Two patients had loss of cuticles. An interesting finding was that clubbing was present in seven patients (Figure 4B).

Pruritic papular eruptions were very common affecting 27 patients (11.54%). Keratosis pilaris was another interesting finding found in five patients (Figure 4C). Prurigo nodularis (Figure 4D) was found in four patients. Other rare mucocutaneous manifestations which were noticed include: Shamberg's purpura, atrophoderma of face, rosacea, palmoplantar keratoderma, anetoderma, acne keloidalis, and lichen nitidus.

The average CD4 count was 249/ μ L ($\pm$ 132). A total of 120 patients (51.3%) had CD4 counts <200/ μ L. Cutaneous manifestations with CD4 counts <200/ μ L were as given in Table 3.

DISCUSSION

Human immunodeficiency virus infection can lead to a variety of cutaneous manifestations in approximately 80–95% of those affected.⁵ The prevalence of manifestations in our study was similar to those reported worldwide. In the 1990s STDs were the commonly seen associated manifestations with HIV.⁶ The syndromic approach in the management of STDs and self or primary healthcare treatment of STDs with antibiotics have reduced the number of STD patients reaching the hospitals. Seborrhoeic dermatitis and oral candidiasis have been reported as the most common dermatological disorders among HIV patients in various studies in the past decade.^{7,8} In our study, dermatophytosis was more common than candidiasis or seborrhoeic dermatitis. A single study earlier has reported dermatophytosis as the most common manifestation.⁹

Fungal infections are an early manifestation of immunosuppression and they are more frequent when the CD4 cell count approaches 450 cells/ μ L,¹⁰ which could explain the higher incidence in our study as most patients had higher CD4 counts. The prevalence of onychomycosis was similar to the other studies, in the range of 15–40%.¹¹ However, the type of nail involvement was at odds with earlier studies in which proximal subungual onychomycosis (PSO)¹² and DLSO constituted the predominant variety.¹³ Proximal subungual onychomycosis which is pathognomonic of HIV infection was not present in any of the patients, thus underlying its rarity in the Indian setting.¹⁴ Trauma could be a significant risk factor for the increased incidence of distal and lateral onychomycosis and total dystrophic varieties. Oral candidiasis is a common feature of HIV infection and occurs in as many as 75% of the HIV-infected patients.¹⁵ The decreased prevalence of oral candidiasis in the present study could be attributable to increased awareness about the condition and early treatment. Atrophic variety of candidiasis is a subtle manifestation which occurs early in the disease and could be missed with only a cursory examination.

Oral hairy leukoplakia can have a prevalence as great as 42%,^{16,17} but only one case had this manifestation in the present study, suggesting the rarity in Indian population. Approximately 25% of HIV patients experience herpes zoster, which has been described as an early indicator of the infection.¹⁸ Our study showed a similar prevalence too.

Bacterial infections are on the wane mainly due to early antibiotic treatment. The CD4 correlation showed all bacterial manifestations occurring with CD4 counts >200/ μ L, which is similar to most of the other studies.

Although the data regarding the overall incidence of scabies and HIV infection are not well determined, in one study it was reported as 20%.¹⁹ Some authors suggest that an extremely high mite burden with atypical presentations such as crusted scabies occur in HIV-infected patients, but no such case was present in this study probably due to the early treatment of scabies.

Incidence of herpes genitalis has risen above the bacterial STDs because of the early treatment of genital ulcers and urethritis with antibiotics before the cases reach the hospital. In recent times, as many as 70% of HIV-infected patients have histories or serologic evidence of syphilis but only a few have described active syphilis,²⁰ which was true in the present study also.

A study done in South India had shown a prevalence of 23.6% for oral pigmentation.²¹ Stimulation of melanocytes in association with immunopathologic changes in the oral mucosa has been thought of as a possible explanation.

Other studies report up to 85% of HIV-infected individuals experiencing seborrheic dermatitis at some point during their illness.²² Increasing awareness about dryness and seborrheic dermatitis have led to patients taking better care of their skin and scalp have possibly contributed to lesser incidence seen in our study.

Surprisingly no patient had psoriasis, lichen planus or Reiter's disease. Further studies are required to confirm the

fact that these disorders really have an increased incidence with HIV.

Few studies have described an association of HIV with clubbing.^{23,24} Factors blamed for the presentation include chronic HIV infection, HIV-related arthropathy, infections associated with HIV infection and so on. None of the patients in the present study had any other associated risk factor.

Interesting Findings of the Study

Cutaneous manifestations occurring at average CD4 counts <200/ μ L in the present study are in sharp contrast to the studies from the west which only list systemic manifestations as AIDS defining illnesses, with Kaposi's sarcoma being the lone exception. A study conducted in the Department of Dermatology, Christian Medical College and Hospital, Vellore had come to the same conclusion that the manifestations are distinctly different across different countries.²⁵ Specific markers of AIDS like bacillary angiomatosis, Kaposi's sarcoma, eosinophilic folliculitis, and proximal subungual onychomycosis were not at all present in this study. Even oral hairy leukoplakia (OHL) was present in only one patient. Hence, different markers may be required in an Indian setting and the manifestations given in Table 3 are being proposed as potential candidates.

Another interesting aspect was that the variants of different cutaneous manifestations occurring in HIV were studied in detail. This is important for the fact that specific morphological variants of certain cutaneous manifestations, e.g. atrophic oral candidiasis, may be markers of advanced disease and these may be missed if they are considered group-wise. An effort in this direction has been taken in this study.

It is also presently seen that therapeutic guidelines advocate CD4 counts <350/ μ L as benchmark for starting ART. So, a separate list of cutaneous manifestations in addition to those given in Table 3 have been described, which may provide clues for diagnosing patients with CD4 count <350/ μ L (Table 4).

Certain interesting manifestations like clubbing, keratosis pilaris, and keratolysis exfoliativa, which have rarely been reported earlier in association with HIV, were observed to be present in the study.

A change in the spectrum of cutaneous manifestations was also observed. An ever increasing incidence of HIV-2 infection, early reporting of cases with higher CD4 counts, early treatments of bacterial infections, and STDs and awareness of patients about common manifestations leading to early seeking of medical advice are factors which bring about changes in the spectrum of cutaneous manifestations in HIV. A comparison of the common orocutaneous manifestations over a period of two decades is as given in Table 5.

In patients with CD4 <200/ μ L, hyperpigmentation of dorsum of tongue, latent syphilis, and finger nail onychomycosis were the only manifestations to have a statistically significant correlation, while in those with CD4 <350/ μ L, dermatophyte infection, and herpes zoster were the statistically significant correlations. A *P* value of <0.05 was considered significant for the calculations.

Table 4 Cutaneous manifestations with CD4 < 350/ μ L.

S. no.	Cutaneous manifestation	Total no. of patients	Average CD4 count (range)	Patients with CD4 $\leq$ 350	Patients with CD4 > 350
1	Dermatophyte infection	114	281 (84–619)	97	17
2	Pityriasis versicolor	5	313 (107–543)	4	1
3	Genital candidiasis	5	226 (67–398)	4	1
4	Furuncles	27	211 (62–631)	19	8
5	Tuberculosis skin	2	222 (154–290)	2	–
6	Warts	39	241 (42–864)	30	9
7	Molluscum	12	211 (76–465)	10	2
8	Herpes zoster	26	205 (28–497)	23	3
9	Herpes labialis	2	218 (176–262)	2	–
10	Herpes genitalis	11	239 (83–431)	9	2
11	Chancroid	5	262 (92–384)	4	1
12	Urethritis	5	241 (102–387)	4	1
13	Scabies	12	213 (84–657)	11	1
14	Pruritic papular eruption	27	238 (154–465)	21	6
15	Photodermatoses	4	217 (121–367)	3	1
16	Keratosis pilaris	5	218 (76–334)	4	1
17	Drug reactions	2	241 (213–269)	2	0
18	Xerosis	39	237 (34–623)	31	8
19	Ichthyosis	3	251 (46–723)	2	1

Table 5 Comparison of commonest orcutaneous manifestations of human immunodeficiency virus over two decades.

Study	1	2	3	4	5
Khopkar et al, 1992 ⁶	Sexually transmitted diseases	Alopecia	Bacterial infections	Herpes zoster	Seborrhoeic dermatitis
Kumarasamy et al, 2000 ²⁶	Oral candidiasis	Herpes zoster	Dermatophytosis	Herpes genitalis	Papular pruritic dermatitis
Kaviarasan et al, 2002 ²⁷	Sexually transmitted diseases	Oral candidiasis	Papular pruritic eruptions	Bacterial infections	Herpes zoster
Shobhana et al, 2004 ²⁸	Oral candidiasis	Dermatophytosis	Gingivitis	Herpes zoster	Herpes simplex
Sharma et al, 2004 ⁴	Seborrhoeic dermatitis	Herpes zoster	Oral candidiasis	Dermatophytosis	Warts
Attili et al, 2008 ²⁹	Oral candidiasis	Drug reactions	Dermatophytosis	Seborrhoeic dermatitis	Recurrent herpes zoster
Singh et al, 2009 ²	Seborrhoeic dermatitis	Xerosis	Generalised hyperpigmentation	Onychomycosis	Pruritic papular eruption

The study has inherent limitations of being carried out in a modest sample size and will have to be carried out in a larger cohort of patients to see the significance of the individual manifestations.

CONCLUSION

Dermatologic disease in HIV-infected patients may be severe, atypical, and difficult to treat. Because dermatologic manifestations may be the first clue to HIV infection, offering HIV testing

to affected individuals can lead to early diagnosis and treatment as well as a decrease in disease progression and transmission. Since the cutaneous manifestations differ in an Indian setting from the west, we have herein described a set of cutaneous markers seen in advanced HIV infection, which may act as markers to initiate therapy.

Intellectual Contributions of Authors

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CONFLICTS OF INTEREST

None identified.

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