Orocutaneous Manifestations as Markers of Disease Progression in HIV Infection in Indian Setting

Brig YK Sharma*, Col MPS Sawhney⁺, Lt Col DS Bhakuni[#], Maj V Gera^{**}

Abstract

CD4, CD8 and absolute lymphocyte counts (ALC) were carried out by flowcytometry in 36 HIV-infected cases with various orocutaneous manifestations, 50 asymptomatic HIV infected individuals and 50 HIV-negative controls. Average CD4 counts and CD4 : CD8 ratio in symptomatic HIV-infected cases were found to be 245.39/cmm and 0.27 respectively, significantly lower than that of HIV-infected asymptomatic individuals (622.4 and 0.45 respectively) and HIV-negative controls (798.81 and 1.03 respectively). Patients with one (77.78%), two (19.44%) and three (2.78%) orocutaneous manifestations had average CD4 counts of 280.25, 131.3 and 68/cmm respectively. All the 7 cases with oral mucosal candidiasis had CD4 counts lower than 200/cmm (average 105.28/cmm), thus fulfilling AIDS-defining criteria. Although 6 (85.71%) of the 7 cases had CD4 counts less than 200, *Herpes zoster* should not be considered as an AIDS-defining illness, as the HIV-infected who had had *H zoster* in the past had higher CD4 count (average 299/cmm). Dermatoses like seborrhoeic dermatitis and lichen planus, and some infections and infestations like scabies, bacillary angiomatosis, human papilloma virus infection, molluscum contagiosum and dermatophytosis cannot be considered as AIDS-defining illnesses per se.

MJAFI 2004; 60 : 239-243

Key Words: CD4 counts; HIV infection; Orocutaneous manifestations

Introduction

Except the rash of its acute infection, HIV infection causes skin changes indirectly through altered immune function. The affected individuals have a significantly increased incidence of skin complaints as their HIV infection progresses [1]. Common disorders present during the asymptomatic phase, but with atypical features. They may be widespread, have an unusual character or a more prolonged course and be more resistant to treatment. Infections occur with common as well as unusual organisms e.g. *Varicella zoster* virus (VZV), warts, oral hairy leukoplakia due to *Epstein-Barr* virus, etc. Seborrhoeic dermatitis, pityrosporum folliculitis, eosinophilic folliculitis, bacillary angiomatosis, fungal infections, penicilliosis, etc, are also well recognised [2]. In addition, during the later symptomatic stage, *Mycobacterium tuberculosis* and atypical mycobacterium, candida species, *Trichophyton rubrum*, *Malassezia furfur*, chronic *Herpes simplex*, florid molluscum contagiosum and rarely *Cytomegalovirus* (CMV) - caused skin ulcerations should be looked for. Neoplastic processes, especially Kaposi's sarcoma, also make their appearance at this time [2].

The main target of HIV being the CD4 cell population, a progressive reduction in their number and function is

one of the most striking and consistent immunological feature of HIV-related disorders [3]. Hence, CD4 cell count is one of the most important investigations in the clinical evaluation of the HIV-infected as it helps to decide the stage of the disease, the initiation of antiretroviral therapy and the prophylaxis for opportunistic infections [4]. CD4 counts also have prognostic significance and are used as markers for assessing progression for HIV infection to AIDS [5].

Many studies of various designs have been carried out in the West correlating orocutaneous manifestations of HIV and CD4 counts, thus highlighting the probable use of cutaneous manifestations of HIV as markers of disease progression [6-11].

In India, information on reference CD4 counts in healthy individuals, HIV-infected and AIDS patient is insufficient. A study from South India among AIDS patients, HIV-seropositives and healthy controls reported a very wide distribution of lymphocyte phenotypes and CD4 counts [12]. Further, a study conducted in the Department of Dermatology, Christian Medical College and Hospital, Vellore concluded that the pattern of skin lesions in the Indian patients with HIV infection may be different from that seen in the West [13].

Flowcytometry, a standard method of CD4 enumeration is expensive and requires sophisticated

*Commandant, Military Hospital, Roorkee, ⁺Senior Advisor (Dermatology), Base Hospital Barrackpore, [#]Classified Specialist (Medicine & Immunology), Command Hospital (Central Command), Lucknow, ^{**}Graded Specialist (Dermatology), Military Hospital, Ramgarh Cantt.

laboratory with necessary equipment and expertise. Hence, it may not be possible to perform this test in all the cases and at desired intervals. Thus, with increasing load of HIV-infected patients, most of whom have slow progression of the disease over many years, it is desirable to identify certain easily diagnosable orocutaneous markers of disease progression and correlate these to CD4 cell counts in the Indian setting. Therapeutic interventions can thus be undertaken to benefit the patients without waiting for specialised and expensive investigations [14,15]. This prompted us to undertake this study of correlation between CD4 count and orocutaneous manifestations in HIV infection.

Material and Methods

All cases of HIV infection between Jan 2001 to Dec 2001 were screened for presence of disease-related orocutaneous manifestations. The diagnosis was based on clinical criteria in most of the cases. In cases of doubt, appropriate laboratory tests like scraping for fungus / candida, culture and skin biopsy were performed. CD4, CD8 and ALC counts were performed in 36 (all males) HIV-infected cases with orocutaneous manifestations, 50 normal healthy HIV-negative blood donors and 50 asymptomatic HIV-positive male patients by using 2-colour EPICS-XL Coulter flowcytometry. The results were analysed using appropriate statistical analysis.

Results

The average age of 36 cases was 35.11 (range 21-53) years, of HIV-positive asymptomatic controls 34.1 (24-51) years and those of HIV-negative controls 33.7 (16-54) years. The probable duration of illness was known in only 24 of the symptomatic cases with average duration of illness being 33.5 months, while in asymptomatic controls it was known in 20 with average duration of illness being 57 months. The average CD4, CD8, ALC and CD4:CD8 ratio in the three groups above is shown in Table 1.

Table 1

CD4, CD8, absolute lymphocyte count and CD4:CD8 ratio in HIV-positive patients with orocutaneous manifestations, HIV-positive asymptomatic controls and HIV-negative controls

Cases	No.	CD4/ cmm (%)	CD8/ cmm (%)	ALC/ cmm (%)	CD4:CD8
HIV-positive cases with orocutaneous manifestations	36	245.39 (11.80)	921.05 (44.30)	2079.20 (100)	0.27
HIV-positive asymptomatic controls	50	622.4 (22.15)	1391 (49.53)	2810 (100)	0.45
HIV-negative healthy controls	50	798.81 (32.21)	776.63 (31.32)	2480 (100)	1.03

CD4 cell count was significantly lower in patients with orocutaneous manifestations than in healthy HIV-negative controls (SD 166.16 and 356.77, SE 90.85, $p < 0.05$).

CD4 cell counts in patients with orocutaneous

manifestations were also significantly lower than HIV-positive asymptomatic controls (SD 166.16 and 184.27, SE 64.51, $p < 0.05$).

CD4:CD8 ratio was also significantly lower in patients with orocutaneous manifestations, as compared to those of HIV-positive asymptomatic controls (χ^2 36.11, df-1, $p < 0.001$) and HIV-negative healthy controls (χ^2 250.10, df-1, $p < 0.001$)

3 (8.33%) of the patients with orocutaneous manifestations had CD4 counts less than 50, 17 (47.22%) between 51-200, 11 (30.56%) from 201-500 and 5 (13.89%) above 500.

28 (77.78%) had solitary orocutaneous manifestation, 7 (19.44%) had two, one (2.78%) had three manifestations, with mean CD4 counts of 280.25, 131.3 and 68/cmm respectively.

10 cases who in addition had pulmonary or extrapulmonary tuberculosis had a mean CD4 count of 172.2/cmm, as compared to 273.54/cmm in 26 patients without it. The difference, was however, not statistically significant (SD 83.29 and 182.61, SE 76.44, $p > 0.05$)

Various orocutaneous manifestations and CD4 count

CD4, CD8, ALC and CD4:CD8 ratio in cases of HIV infection with various orocutaneous manifestations is given in Table 2.

Seborrhoeic dermatitis and CD4 count

Average CD4 count in 11 cases of seborrhoeic dermatitis was 333.09/cmm (range 44-625). In 3 (27.27%), it was above 500, in 6 (54.54%) between 201-500 and in only one (9.09%) each, between 50-200 and below 50 respectively. The lowest CD4 count was found in an HIV case without any other AIDS-defining illness and thus was quite interesting. The dermatitis was also not very widespread or severe and restricted to head and neck. Another patient with CD4 count of 123/cmm also had pityrosporum folliculitis.

Herpes zoster and CD4 count

Average CD4 count in 7 cases with *H zoster* was 217.57/cmm (range 121-600). 6 (85.7%) had CD4 counts between 50-200. Two (28.57%) cases with multidermatomal zoster, one with molluscum contagiosum and another case, who also had tinea cruris, had average CD4 counts of 172/cmm, 121/cmm and 158/cmm respectively. 3 (42.86%) patients with associated pulmonary tuberculosis had CD4 count of 163.66/cmm, in contrast to 255.5/cmm in those without it. Apart from these 7 cases, 4 other patients who gave past history of *H zoster* had an average CD4 count of 299/cmm.

Oral candidiasis and CD4 count

Mean CD4 count in 7 patients with oral mucosal candidiasis was 105.28/cmm (range 46-163). In 2 (28.57%), the count was less than 50 and in rest (71.43%) it was between 50-200. Three (42.86%) with associated tuberculosis (two disseminated and one pulmonary) had an average CD4 count of 129.3/cmm, in contrast to 112.25 cmm in those without it. One each of these patients also had tinea imbricata, papular urticaria, seborrhoeic dermatitis, psoriatic nails and past history of *H zoster* with CD4 counts of 102, 128, 163, 124 and 46/cmm respectively.

Table 2**CD4, CD8, ALC and CD4:CD8 ratio in various orocutaneous manifestations in HIV infected cases**

Disease	No (%)	Mean CD4 (%)	Mean CD8 (%)	Mean ALC (%)	CD4:CD8
Seborrhoeic dermatitis	11 (30.55)	333.09 (15.81)	843.91 (40.05)	2107.27 (100)	0.39
Herpes zoster	7 (19.44)	217.57 (9.08)	1237.57 (51.67)	2395 (100)	0.18
Oral candidiasis	7 (19.44)	105.28 (7.0)	801.14 (53.28)	1503.71 (100)	0.13
Dermatophytosis	3 (8.33)	272.33 (14.85)	733.67 (40.01)	1833.33 (100)	0.37
Condylomata acuminata	2 (5.56)	245.5 (13.6)	1099 (61.05)	1800 (100)	0.22
Bacillary angiomatosis	1 (2.75)	68 (1.74)	140 (3.59)	3900 (100)	0.44
Irritant contact dermatitis	1 (2.78)	441 (18.38)	1248 (52)	2400 (100)	0.30
Lichen planus hypertrophicus	1 (2.78)	500 (20)	1650 (66)	500 (100)	0.35
Molluscum contagiosum	1 (2.78)	330 (16.5)	1050 (52.5)	2000 (100)	0.31
Scabies	1 (2.78)	174 (7.57)	564 (24.52)	2300 (100)	0.31
Tubercular sinus with infective eczema	1 (2.78)	89 (4.68)	519 (27.32)	1900 (100)	0.17

Discussion

Average CD4, CD8, ALC and CD4:CD8 ratio in HIV-negative healthy controls was found to be 798.81, 776.63, 2480 and 1.03 respectively. These findings are similar to the study conducted by Uppal et al [16], where the corresponding figures were 865, 552, 2114 and 1.7. The readings also fall within the reference range of values recommended by Coulter Corporation, the manufacturers of the EPICS-XL flowcytometer, which was used for the study (Table 3).

Table 3**Reference range and study values of CD4, CD8 and CD4:CD8 ratio in normal controls**

Cell type	Normal percentage		Normal cells/cmm	
	Reference range	This study	Reference range	This study
CD4	20-65	32.21	500-2000	798.81
CD8	5.0-55.0	31.32	350-1750	776.63
CD4:CD8 ratio	1.0-2.0	1.03		

CD4 count as well as CD4:CD8 ratio was significantly lower in cases of HIV infection with orocutaneous manifestations, as compared to healthy HIV-negative controls and asymptomatic HIV-positive patients. This indicates that appearance of orocutaneous manifestations in a case of HIV infection is sinister and indicates advanced disease. Others have also made similar observations [6-11,17].

While in the present study the patients with orocutaneous manifestations had CD4 counts less than

50, 50-200 and more than 200/cmm in 8.33%, 47.22% and 44.45% respectively, the corresponding percentages by Goldstein et al [11] were 63%, 22% and 15% and by Mignard et al [17] were 15.8%, 33.6% and 50.6% respectively. Thus our findings are closer to those of Mignard et al, whereby about half the patients with orocutaneous manifestations will fulfill the criteria of AIDS as per the new CDC case definition [18], in contrast to more than four-fifth of the patients as described by Goldstein et al.

It was also found that more numerous the cutaneous manifestations, more severe was the immune suppression, as the mean CD4 count with one (77.78%), two (19.44%) and three (2.78%) cutaneous manifestations was 280.25, 131.3 and 68/cmm respectively. The corresponding percentages of patients by Mignard et al [17] with one, two, three and four manifestations were 60.8%, 21.3%, 12.6% and 5% respectively. This also concluded that the frequency of skin lesions was inversely related to the CD4 count.

The patients who in addition had other AIDS-defining criteria, viz. pulmonary or extra-pulmonary tuberculosis, had a lower mean CD4 count. However, this difference was not found to be statistically significant.

Seborrhoeic dermatitis and CD4 count

Seborrhoeic dermatitis is the most common non-infectious skin disorder associated with HIV. The incidence and the severity of HIV-associated seborrhoeic dermatitis are closely related to the stage

of the disease and, as a result, are inversely correlated with the absolute CD4+ helper cells [19]. Only two (18.18%) of our patients were in the group of AIDS-defining criteria with CD4 counts < 200/cmm. Hence seborrhoeic dermatitis should not be considered as an AIDS-defining condition, as has also been reported by others [8,20]. In one series, excessive *Pityrosporum* organisms were found in only a minority of biopsy specimens from AIDS patients with seborrhoeic dermatitis [21]. However, in another study, a correlation between the severity of clinical disease and the number of *Pityrosporum* organisms was observed on Giemsa-stained smears [22]. One of our patients of seborrhoeic dermatitis, who in addition had *Pityrosporum* folliculitis, had a very low CD4 count of 123/cmm.

Herpes zoster and CD4 count

H zoster in adults may be a predictor of HIV infection. In one of the studies, 91% of the cases of *H zoster* referred were seropositive for HIV [23]. Some authors are of the opinion that there is an increased risk of development of AIDS in those patients who develop *H zoster* [24,25]. Others feel that it is not a reliable sign of profound immunodeficiency as it can occur at any stage of HIV-1 disease [26]. Although 6(85.71%) of our patients with *H zoster* had CD4 counts < 200/cmm, thus fulfilling AIDS case definition, another four patients who gave past history of *H zoster* and in addition had other orocutaneous manifestations had mean CD4 count of 299/cmm. This suggests that during the attack of *H zoster*, there is a transient fall in the CD4 cell count, as VZV may be acting as a co-factor in HIV replication.

Oral candidiasis and CD4 count

Oral candidiasis is the most common opportunistic infection in HIV-infected individuals [8,14]. It is a category B condition, and by itself does not fall in AIDS case definition [18]. Further, the median CD4 count in cases of oropharyngeal candidiasis in a study from India was found to be 420-578 per cmm [14]. However, in our study all the 7 cases with oral candidiasis had CD4 counts less than 200, with a mean of 105.28 per cmm, thus fulfilling the AIDS case definition. Thus, the development of oropharyngeal candidiasis shows an advance degree of immunosuppression, as has also been suggested by Munoz-Perez et al [8].

Bacillary angiomatosis and CD4 count

A single case of bacillary angiomatosis with CD4 cell count of 68 per cmm also had oral candidiasis and plantar warts. Though, not an AIDS-defining illness, it is a cutaneous sign of advanced immunosuppression, with reported CD4 count of less than 200 per cmm [20].

Molluscum contagiosum, human papilloma virus (HPV) infection, dermatophytosis, lichen planus, scabies and CD4 count

Average CD4 count in cases of molluscum contagiosum, HPV infection, dermatophytosis and lichen planus was found to be 330, 243, 272.33 and 500/cmm respectively. One case of scabies with CD4 count of 174/cmm, also had pulmonary tuberculosis. Hence, these conditions cannot be considered as AIDS-defining illnesses per se as has been reported by others as well [8,20]. However, increased incidence of molluscum contagiosum has been reported with CD4 counts < 200/cmm [20] and proximal subungual onychomycosis due to *T rubrum* is said to be common in patients with CD4 count less than 100 per cmm [27]. However, no such case figured in our study.

To conclude, patients with disease related infective and non-infective orocutaneous manifestations of HIV infection have significantly lower CD4 counts than HIV-positive asymptomatic controls (even though the average duration of illness may be longer in the latter), as well as HIV-negative healthy controls. Patients with two or more orocutaneous manifestations are more likely to be having CD4 counts less than 200/cmm. Though all the cases of oral mucosal candidiasis in our small study had CD4 counts less than 200/cmm, suggesting it to be an AIDS-defining illness, further validation by larger, multicentric studies is required before its recommendation as a category 'C' AIDS defining illness. *H zoster* should not be considered as an AIDS-defining illness, although it may cause transient fall in CD4 counts during the acute episode, VZV acting as a cofactor in HIV-replication, which rises again on subsidence of the disease. Hence, it is suggested that CD4 counts, if at all done to monitor the progression of the disease, should be performed few months after the episode of *H zoster*. Seborrhoeic dermatitis, scabies, HPV infection, molluscum contagiosum, dermatophytosis, bacillary angiomatosis and lichen planus cannot be considered as AIDS-defining illnesses per se.

References

1. Stern RS. Epidemiology of the skin disease in HIV infection : a cohort study of health maintenance organisation members. *J Invest Dermatol* 1994;102:834-7.
2. Sterling JC, Kurtz JB. Viral Infections. In: Champion RH, Burton JL, Burns DA, Breathnach SM, editors, *Rook/Wilkinson/Ebling Textbook of Dermatology*. 6th ed, Oxford, Blackwell Science Ltd 1998:995-1095.
3. Taylor JM, Fahey JL, Detels R, Gorge JV. CD4 percentage, CD4 number and CD4, CD8 ratio in HIV infection. *J Acquir Immune Defic Syndr* 1989;2:114-24.

4. Quinn TC. Laboratory tests in the medical management of HIV infection. *Bartlett Journal* (editorial) 1997;20:30.
5. Phillips AN, Lee CA, Elford J et al. Serial CD4 lymphocyte counts and development of AIDS. *Lancet* 1991;337:389-92.
6. Uthaya Kumar S, Nandwani R, Drinkwater T, Nayagam AT, Darley CR. Prevalence of skin disease in HIV infection and its relationship to the degree of immuno-suppression. *Br J Dermatol* 1998;139:155-6.
7. Reynaud P, Janier M, Gerbaka J et al. Dermatologic findings in HIV-1 infected patients : A prospective study with emphasis on CD4 + cell count. *Dermatology* 1996;192:325-58.
8. Munoz-Perez MA, Rodriguez-Pichardo A, Camacho F, Colmenero MA. Dermatological findings correlated with CD4 lymphocyte counts in a prospective 3 years study of 1161 patients with human immunodeficiency virus disease predominantly acquired through intravenous drug abuse. *Br J Dermatol* 1998;139:33-9.
9. Schaub N, Gilli L, Ruffli T et al. Epidemiology of skin diseases in HIV-infected patients: A prospective cohort study. *Schweiz Rundsch Med Prax* 1996;85:1162-6.
10. Garbe C, Husak R, Orgfanos CE. HIV associated dermatosis and their prevalence in 456 HIV-infected patients. Relation to immune status and its importance as a diagnostic marker. *Hautarzt* 1994;45:623-9.
11. Goldstein B, Berman B, Sukenik E, Frankel SJ. Correlation of skin disorders with CD4 lymphocyte counts in patients with HIV/AIDS. *J Am Acad Dermatol* 1997;36:262-4.
12. Babu DG, Zachariah A, Mathai D, John JJ. Flowcytometric analysis of lymphocyte subsets in AIDS patients, asymptomatic HIV seropositive patients and HIV seronegative controls in Vellore region. Proceedings of the International conference on AIDS, Vancouver, Canada. 7-12 July 1996;18:24-7.
13. Rajagopalan B, Jacob M, George S. Skin lesions in HIV-positive and HIV-negative patients in South India. *Int J Dermatol* 1996;35:489-92.
14. Giri TK, Pande I, Mishra NM, Kailash S, Uppal SS, Kumar A. Spectrum of clinical and laboratory characteristics of HIV infection in Northern India. *J Communicable Dis* 1995;27:131-41.
15. Kaur A, Babu PG, Jacob M et al. Clinical and laboratory profile of AIDS in India. *J Acquir Immune Defic Syndr* 1992;5:883-9.
16. Uppal SS, Tewari SC, Parasher PK. Evaluation of immunological status in patients of tuberculosis and advanced chronic renal failure by flowcytometric enumeration of T-lymphocyte subsets. DGAFMS, Ministry of Defence, New Delhi, AFMRC Project No.2158/97,1997:1-38.
17. Mignard M, Spira RM, Morlat P, Dabis F, Doutre MS. Correlation of the skin disorders with CD4 counts in patients with HIV/AIDS. *J Am Acad Dermatol* 1998;39:298-9.
18. Centers for Disease Control. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR* 1992;41:1-19.
19. Kaplan MH, Sadick N, McNutt NS, Meltzer M, Sarnagadharan MG, Pahwa S. Dermatological finding and manifestations of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1987;16:485-506.
20. Jung AC, Paauw DS. Diagnosing HIV-related disease: using the CD4 count as a guide. *J Gen Intern Med* 1998;13:131-6.
21. Soeprono FF, Schinella RA, Cockerell CJ, Comite SL. Seborrheic-like dermatitis of acquired immunodeficiency syndrome. A clinicopathological study. *J Am Acad Dermatol* 1986;14:242-8.
22. Grossier D, Bottone EJ, Lebwohl M. Association of *Pityrosporum orbiculare* (*Malassezia furfur*) with Seborrheic dermatitis in patients of acquired immunodeficiency syndrome (AIDS). *J Am Acad Dermatol* 1989;20:770-3.
23. Colebunders R, Mann JM, Francis H et al. *Herpes zoster* in African patients: A clinical predictor of Human Immunodeficiency Virus infection. *J Infect Dis* 1981;157:314-8.
24. Friedman-Kein AE, Lafluer FL, Gendler FC et al. *Herpes zoster* : a possible early clinical sign for the development of acquired immunodeficiency syndrome in high risk individuals. *J Am Acad Dermatol* 1986;14:1023-8.
25. Melbye M, Grossman RJ, Goedert JS, Eyster ME, Bigger RJ. Risk of AIDS after *Herpes zoster*. *Lancet* 1987;1:728-31.
26. Birchbinder SP, Katz MH, Hessol NA et al. *Herpes zoster* and Human Immunodeficiency Virus infection. *J Infect Dis* 1992;166:1153-6.
27. Domp Martin D, Domp Martin A, Deluol AM, Grosshans E, Coulaud JP. Onychomycosis and AIDS: clinical and laboratory findings in 62 patients. *Int J Dermatol* 1990; 29: 337-9.