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CORRELATION OF CD4 COUNTS AND CD4/CD8 RATIO WITH HIV-INFECTION ASSOCIATED ORAL MANIFESTATIONS

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F.M.A. BUTT, V.P. VAGHELA and M.L. CHINDIA

ABSTRACT

Background: The relationship between oral lesions arising from HIV infection and CD4/CD8 cell ratios is of relevance in clinical assessment of immune suppression.

Objective: To correlate the prevalence of oral manifestations arising from HIV infection and the levels of CD4/CD8 cell ratios.

Design: A cross-sectional study.

Setting: Kenyatta National Hospital, Nairobi, Kenya.

Subjects: Two hundred and seven HIV-infected patients in medical wards were recruited in the study.

Results: Seventy eight (37.7%) were male and 129 (62.3%) female, with an age range of 18-73 years (mean = 34.81 years). Oral manifestations encountered with highest prevalence in the oral cavity included: hyperplastic candidosis (labial mucosa) 15%, erythematous candidosis (gingival) 5%, angular cheilitis 32.4%, herpes simplex (corner of the mouth) 0.5%, persistent oral ulceration (labial mucosa) 0.5%, Parotid enlargement 2% and Kaposi sarcoma (hard/soft palate) 2.9%.

Conclusion: The prevalence of oral manifestations was higher with low CD4 count <200 cell/mm³ and mean CD4/CD8 <0.39 (95% CI 0.32-0.48).

INTRODUCTION

At the beginning of the HIV pandemic it was reported that 41% of patients with the acquired immunodeficiency syndrome (AIDS) had head and neck manifestations (1). However, as awareness of these lesions has increased it is now known that nearly 100% of patients with AIDS have head and neck manifestations (2). The presence of oral lesions is an indicator of progression to AIDS. They are strongly associated with immune suppression, as measured by CD4 cell counts. Oral lesions serve as potential markers of HIV viraemia and the consequent destruction of the immune system

with progressive HIV disease (3). The most widely available marker of immune system destruction in the HIV-infected subject is a reduction in the number of circulating CD4 cells. It provides a measure of the degree of damage to a patient's immune system and indicates the potential of the body to respond effectively to pathogens (4). Clinical symptoms appear as the virus destroys blood cells important for maintaining immunity.

The most serious consequence of HIV infection is a decline in the number and function of the helper-inducer (T4, CD4+) subset of lymphocytes. Progressive destruction of the immune function allows for the development of opportunistic infections and

neoplasms; and leads finally to the full-blown AIDS (5). Hence, the CD4 cell count is one of the most important investigations in the clinical evaluation of the HIV-infected patient as it helps to evaluate the stage of the disease, initiation of anti-retroviral therapy and prophylaxis for opportunistic infections (6). CD4 cell counts are also of prognostic significance and are used as markers for assessing progression from HIV infection to AIDS (7). Oral lesions cannot only indicate infection with HIV but are also among the early clinical features of infection and can predict progression of the HIV disease to AIDS. They can, therefore, be used as entry or exit points in therapy and vaccine-trials and can be determinants of opportunistic infection and anti-HIV therapy in addition to being used in staging and classification (8).

The occurrence of oral lesions has not been extensively evaluated in the context of the immunological changes that characterise HIV infection, with the majority of the focus on western populations (9). Nowhere is the HIV/AIDS crisis more profound than in sub-Saharan Africa where 28.1 million people are infected. Most of the countries in Africa lack the economic capacity and infrastructure to handle the economic and health costs of the disease (10). Accessibility and affordability of treatment options to HIV-infected individuals is questionable given the limited resources available in sub-Saharan Africa. In Kenya, very few studies have been done correlating oral manifestations with CD4 counts in those who are HIV infected; and therefore, little is known about their relationship with HIV-associated oral lesions. Hence, the purpose of this study was to correlate the CD4 cell count and CD4/CD8 ratio with oral manifestations in HIV-infected patients.

MATERIALS AND METHODS

This study was approved by the Kenyatta National Hospital and University of Nairobi (KNH-UoN) Ethics, Research and Standards Committee reference number KNH/ERC/01/810. This was a prospective cross-sectional survey including a random sample of 207 HIV-infected patients in the medical wards at the Kenyatta National Hospital in Nairobi, Kenya. The sample size was calculated using the Chi square formula with a population of 180 participants. The HIV serostatus was confirmed by two different enzyme-linked immunosorbent assay (ELISA) techniques.

Participation in the study included patients who were aged 18 years and above who had tested positive for HIV infection; and had not been previously on antiretroviral therapy. A specially designed chart was used to record demographic details, findings at examination of the patient and results of all the tests performed. Each chart was assigned a code, hence avoiding use of names, which ensured patient's confidentiality. All patients were subjected to a comprehensive standardised method of examination recommended by the World Health Organisation for both the extra- and intra-oral tissues of the head and neck (11). Examination was conducted with patients seated on their beds under artificial light and the clinically diagnosable lesions were recorded. Blood was drawn from each participant to repeat the ELISA test with a more sensitive fourth generation method and for determining the CD4 cell counts and CD4/CD8 ratios. All the tests were performed at the Aga Khan University Hospital (AKUH) laboratory for ELISA and CD4/CD8 T-lymphocyte count determinations. Incisional biopsies were performed on all lesions for histopathologic examination.

RESULTS

Of the 207 participants, complete sets of investigations were achieved for 190 patients with an age range of 18 to 73 years among whom 78 were male and 129 female. The average CD4 cell count was 214.3 cells/mm³ (95% CI 173.07–255.48). There was a wide (± 287.94) variation in the CD4 cell count with lowest count having been one cell/mm³ and the highest 1693 cells/mm³. However, the average CD4 cell counts for males was slightly lower than for females (Table 1). Table 2 shows a comparison of the CD4 cell count, total lymphocyte count (TLC) and CD4/CD8 ratio for males and females. From the results it appears that females (221.3 cells/mm³) had a higher CD4 count than males (202.8 cells/mm³) while the CD4/CD8 ratio was higher in males (0.44) than females (0.42). The mean TLC was higher in males 2662.5 cells/mm³ than females 1295.8 cells/mm³. There was, however, no significant statistical difference between the male and female values ($p > 0.05$).

In this study, approximately 66.8% of the participants had CD4 counts less 200 cells/mm³ with 12.6% having greater than 500 cells/mm³ (Figure 1). Further analysis showed that 50% of

the population had a CD4 cell count of greater than 100 cells/mm³. There was a higher prevalence of oral manifestation as the CD4 cell counts decreased especially with counts <200 cells/mm³ (Figure 2). Hyperplastic and erythematous candidiasis, and angular cheilitis were the most common oral fungal infections seen in decreasing order of frequency. All patients who presented with Herpes simplex had a CD4 cell count between 200–500 cells/mm³. More than 70% of the patients who presented with Kaposi's sarcoma and oral ulceration had CD4 cell counts of <200 cells/mm³. This is in contrast with those who had CD4 counts of >500 cells/mm³. The highest was a prevalence 3.4% for angular cheilitis followed by 2.9% for hyperplastic candidiasis with a 0%

for Kaposi's sarcoma, erythematous candidiasis, herpes simplex and oral ulceration.

A majority of the study participants (97.6%) had CD4/CD8 ratio of less than one with the minority (2.4%) having had a ratio of greater than two (Table 3). It is apparent that as the ratio decreased the prevalence of the manifestations escalated, the most common neoplastic lesion having been Kaposi's sarcoma and non-neoplastic, oral ulceration followed by hyperplastic candidiasis. All of the patients with Kaposi's sarcoma had a ratio of <1. Only three out of the 190 patients had parotid enlargement with CD4 cell counts of <200 cells/mm³ and with a CD4/CD8 ratio of <1. It was interesting to note that all of the patients who had a ratio of >2, developed herpes simplex.

Table 1

Average CD4 cell count, total lymphocyte count (TLC) and CD4/CD8 ratio for the population

Variable	Average	Minimum	Maximum	Confidence interval 95%
CD4 count (cells/mm ³)	214.8	1	1693	173.62-255.98
CD4/CD8 Ratio	0.43	0	3.05	0.34-0.52
TLC	1813.7	100	73200	1007.1-2620.25

Table 2

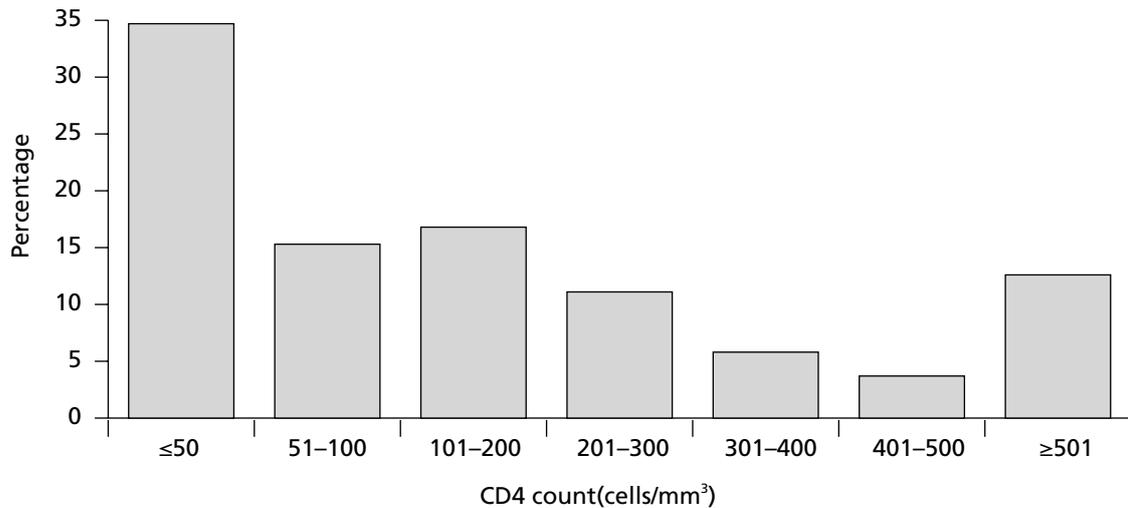
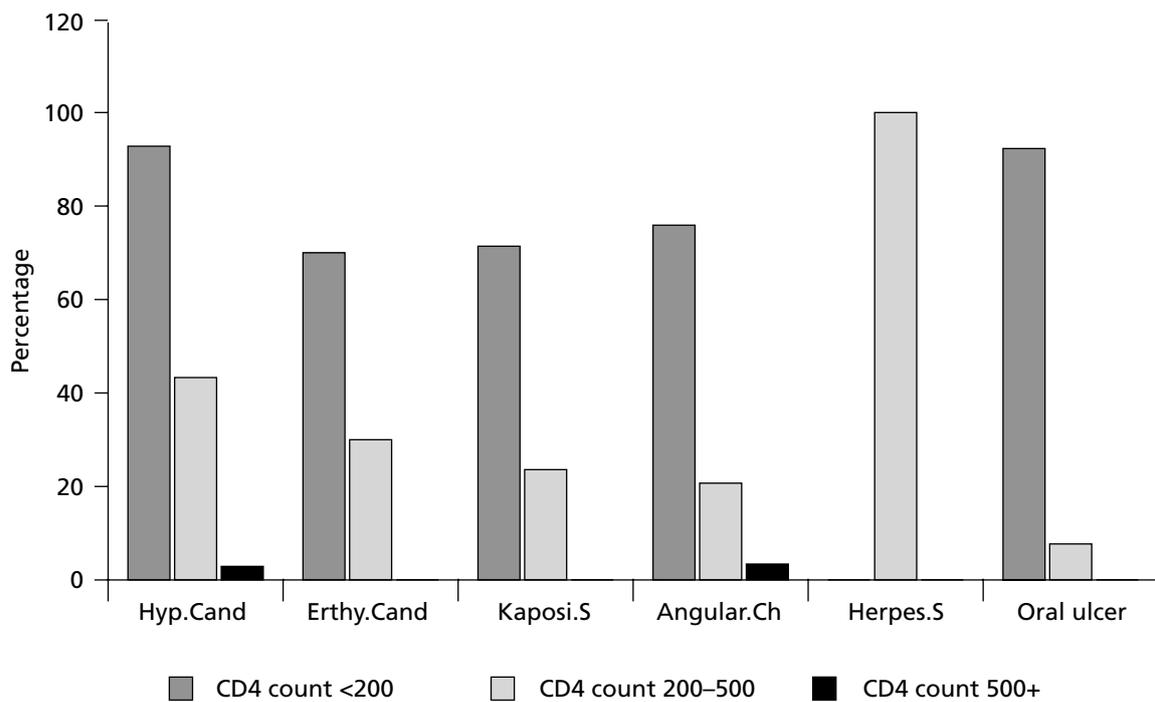
Comparison of CD4 cell count TLC and CD4/CD8 ratio in males and females

Patient gender	Mean	Confidence interval 95%	Minimum	Maximum
Males				
CD4 count	202.83	136.29 – 269.38	1	1693
TLC	2662.25	551.18 – 4773.82	100	73200
CD4/CD8 ratio	0.44	0.29 – 0.59	0	2.48
Females				
CD4 count	221.25	168.06 – 274.45	1	1363
TLC	1295.76	1664.32 – 1527	200	12400
CD4/CD8 ratio	0.42	0.31 – 0.53	0.01	3.05

Table 3

CD4/CD8 ratio and oral manifestations

CD4/CD8 ratio	Hyperplastic candidiasis (%)	Erythematous candidiasis (%)	Kaposi's sarcoma (%)	Angular cheilitis (%)	Oral ulcers (%)	Herpes simplex (%)
<1	97.6	94.7	100	96.6	100	0
1.0-2.0	1.8	5.3	0	34	0	0
>2	0.6	0	0	0	0	100

Figure 1*Classification of CD4 cell count into groups versus the percentage of patients***Figure 2***Frequency of oral manifestations versus CD4 count*

DISCUSSION

This study illustrates clearly that HIV-associated oral lesions are common in this study population as has been reported elsewhere (9-16). The frequency of candidiasis particularly hyperplastic, erythematous and angular cheilitis was high with CD4 cell counts of less than 200 cells/mm³ and CD4/CD8 ratio of less than one. Oral candidiasis, is one the most prevalent opportunistic infection in HIV-infected individuals

(17). The main factor associated with the development of oral lesions especially oral candidiasis is the low CD4+ T-lymphocyte count. Reductions in the CD4+ cell count and sharp increases in viral loads are preceded by the onset of oral candidiasis (18, 19). In Tanzania and Congo, oral mucosal lesions in particular, oral candidiasis was one of several clinical features related to HIV seroconversion. In Nigeria 27% of cases were due to advanced HIV-infection, highly predictive of low CD4+ cell

counts, with similar results in India and Thailand. In Zambia, erythematous candidiasis was the only lesion significantly associated with CD4 cell counts of <200 cells/ mm^3 . In Malawi and Uganda clinical signs strongly indicative of HIV infection included oral hairy leukoplakia (OHL), Kaposi's sarcoma and oral candidiasis. Oral KS is more common in Africa and Latin America, while HIV associated oral candidiasis is seen globally (20). It is interesting to note that some of these lesions are more prevalent in the developing countries in contrast to the developed ones (21).

A borderline association between the presence of intra-oral lesions and CD4 cell counts of <200 cells/ mm^3 has been shown in one study done in Dar-es-Salaam, Tanzania. However, the lack of absolute significance could be due to a large variety of lesions including squamous cell carcinoma (9). A recent study done in India, found that the more numerous the oro-facial manifestations, the more severe was the immune suppression (22). Similarly, the present study showed that 70% of the participants had CD4 cell counts of <200 cells/ mm^3 with 66.8% of them presenting with oral manifestations. The most prevalent having been, candidiasis (especially the hyperplastic and angular cheilitis type), Kaposi's sarcoma and oral aphthous ulceration.

From the preceding results it is clear that patients who presented with oral manifestations of HIV infection had significant reductions in the CD4 cell count and CD4/CD8 ratio, especially below <200 cells/ mm^3 and <1 respectively. Those who had low counts also presented with more than one manifestation and as the counts further dropped to <100 cells/ mm^3 developed two or more lesions with an increasing prevalence of malignancy particularly Kaposi's sarcoma. It was interesting to note that 34.7% of them had a count of <50 cells/ mm^3 despite having been in the AIDS clinical stage of the disease were stable. As the CD4/CD8 ratio decreases it is seen that the prevalence of oral manifestations increases with candidiasis, oral ulceration and Kaposi's sarcoma as the most frequent. According to studies conducted in some developed countries, pseudomembranous candidiasis is the most common clinical presentation (55.8 to 69.7%) of all candidal infections followed by the erythematous, angular and hyperplastic types (0-1.7%) (23-25).

According to the present study the most prevalent types of candidal infection were the hyperplastic, angular cheilitis, erythematous with very few cases of the pseudomembranous variant.

Paralleling early reports of the oral lesions of the HIV-infected patients in the developed world, there have been many reports of oral manifestations in the developing countries. Despite the differences in transmission risk behaviour, geographical location, gender distribution, ethnicity, nutritional status and endemic disease there are few striking examples particularly as regards to the prevalence and type of common oral lesions observed (26,27). Kaposi's sarcoma remains the most common AIDS-associated malignancy, with the oral cavity being commonly involved being the first clinical sign in 20% of cases found to occur concomitantly with skin and visceral involvement in up to 70% of patients (28-30). Kaposi's sarcoma was the most prevalent neoplastic manifestation in the study participants, with 71.4% frequency in those who had CD4 cell counts <200 cells/ mm^3 .

A larger multicentric study incorporating patient control groups to compare CD4 cell counts and CD4/CD8 ratio is recommended to monitor these values in the Kenyan population. Patients in this study with CD4 cell count as low as 50 cells/ mm^3 appeared to have been still coping with a challenged immunity. In resource poor countries, screening of patients with expensive laboratory tests of lymphocyte counts and viral loads in order to commence on anti-retroviral therapy is a financial burden on the patient. Oral examination is easy, non-invasive, does not require costly equipment and can be used for screening and to start anti-retroviral treatment. Future priorities in oral health care in HIV infection discussed at the 5th World Workshop on Oral lesions and HIV disease held in Phuket 2004 concluded a need to re-target research efforts to resource poor countries.

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