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AIDS: An Epidemiological Study on Correlation between HIV- Related Oral Lesions and Plasma Levels of CD4, CD8 T Lymphocytes Counts and Ratio among 50 Patients

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Authors' contributions

This work was carried out in collaboration between all authors. Author AB designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author ZN managed the literature searches, and edited the final draft. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The aim of the study was to evaluate oral manifestations of HIV /AIDS patients and to correlate their occurrence with plasma levels of CD4+, CD8+ counts and CD4/CD8 ratio.
Study Design: A descriptive cross-sectional study.
Place and Duration: Odontology Unit, St-Antoine Hospital, a two- year study.
Methodology: In a descriptive cross-sectional study, 50 patients infected with human immunodeficiency virus (HIV) were assessed. The relationships between oral lesions and CD4+, CD8+ cell counts and CD4/CD8 ratio were evaluated.
Results: The mean CD4+ counts and CD8+ counts were 167.12 cells/mm^3 and 979.66 cells/mm^3 and the mean CD4/CD8 ratio were 0.25. All patients displayed at least one oral manifestation. The most common identified oral lesion was pseudo- membranous candidiasis, accounting for 76%

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(38/50) followed by periodontal disease 34% (17/50), herpetic lesions, and hairy leukoplakia 10% for each (5/50), gingivitis 8% (4/50), oral ulceration 8% (4/50), Kaposi's sarcoma 6% (3/50), and Non-Hodgkin lymphoma 2% (1/50).

Conclusion: The CD4+ count was decreasing and the presence of oral lesions were increasing in this study. No relation was found between the presence of oral lesions and CD4/CD8 ratio. Progression to AIDS was characterized by increased prevalence of some oral lesions such as candidiasis, hairy leukoplakia and Kaposi's sarcoma. The clinical appearance of oral lesions was more pronounced when CD4+ count was low.

Keywords: AIDS; CD4+; CD8+; HIV; oral lesions.

1. INTRODUCTION

Acquired Immune Deficiency Syndrome (AIDS) is the last evolution and progression of an infection with Human Immunodeficiency Virus (HIV).

It gradually destroys the immune system and makes the body predisposed to opportunistic infections [1].

HIV attacks immune system and patients become vulnerable not only to opportunistic infections, but to neurologic disorders, and malignancies as well [2].

HIV/AIDS is a worldwide endemic [1,2]. In 2013, approximately 35.3 million people have been declared HIV positive, with more than 2.1 million new patients per year.15 countries account more than 75% new HIV infections. Distribution of HIV treated patients is in Western Europe and North America, at 51% in Latin America, at 45%, and in the Middle East and North Africa 11% [3].

The main target of HIV infection is a complete damage of the immune system, related to a partial or total destruction of the CD4. [4] Circulating CD4 cell level serves as a marker of disease progression [1,4]. Within six months of sero-conversion, the CD4 count generally decreases about 30% and the CD8 count may increase about 40%, resulting in an inverted ratio that is generally less than 1 (normal ratio value may vary between 0.9 and 3.7) [5,6,7].

The European Economic Community classified more than 40 recognized oral manifestations of AIDS [6-7].

Oral candidiasis is the most shared manifestation of AIDS in the oral cavity, with a prevalence of 70% [5,8-11].

Non-Hodgkin's lymphoma and Kaposi's sarcoma are the common tumors observed in the final stage of disease [5,12-14].

Oral manifestations may play an important role in the prognosis and development of AIDS and can serve as clinical correlates with CD4+, CD8 + counts [11,15,16].

HIV destroys first the CD4 and limits the host response capacity [17].

When equilibrium between production and destruction of CD4+ is stopped, immune system fail and leads to occurrence of AIDS [4,18,19].

Oral lesions are identified during oral examination and the counts of CD4+, CD8+ are measured by flow-cytometry after a blood sample and laboratory analysis.

The aim of the study was to correlate the oral manifestations of HIV /AIDS patients with the CD4+, CD8+ count, and CD4/CD8 ratio.

2. MATERIALS AND METHODS

50 HIV-infected patients were followed and evaluated within a two-year descriptive cross-sectional study that aimed to investigate the relationship between HIV-related lesions and CD4+, CD8+ cell counts, and CD4/CD8 ratio. Each participant in the study signed informed consent. For each participant, a comprehensive medical history, including a history of present illness-HPI, was taken, together implemented with a physical examination, including an oral, maxillofacial, and head and neck one; all obtained records were available at Odontology unit of St-Antoine Hospital and all patients were instructed to visit the Unit for further observation and evaluation.

The variables investigated included medical history, physical examination, demographic data, and laboratory tests. Only one qualified and certified oral surgeon examined all participants and, for that, he took into consideration the site and type of oral lesions using the criteria of

European Community Clearing house/World Health Organization, 1993 on oral problems related to HIV [7].

When multiple lesions were observed in the same patient at the time of clinical evaluation, each lesion was considered independently for observation, evaluation and analysis.

CD4+ and CD8+ count levels were analyzed by the flow cytometer method. Based on the WHO classification [3], CD4+ cell counts ≥500 cells/mm^3 was classified as "class I", CD4+ cell count of > 201 to <499 cells/mm^3 as "class II" and CD4+ cell count of ≤ 200 cells/mm^3 as "class III". The ratio of CD4/CD8 was distributed according to WHO classification of the CD4+ cell count.

Other systemic conditions that could lead to low CD4+ count such as tuberculosis, autoimmune diseases, and use of immunosuppressant were considered as co-morbidities for CD4+ evaluation.

Data obtained from the study were analyzed using the Statistical Package for Social Sciences (SPSS; version 16.0, Chicago, USA). Statistical variables and data analyzed were the bio data of the recruited population, the types of oral lesions present, the level of CD4+, CD8+ count and CD4/CD8 ratio and its relationship with oral lesions.

3. RESULTS

Fifty patients were enrolled in this study, with a mean age of 39.9 years (28-57). Forty-five participants were male and five were female.
Contamination was related to homosexuality for twenty-eight cases, shared intravenous needles for eight cases, bisexuality for five cases, heterosexuality for five cases, blood transfusion for three cases, and one case of a combination of shared intravenous needles and homosexuality (Table 1).

The CD4+ count (cells/mm^3) was < 200, 201-499, and > 500 in 32 cases (64%), 16 cases (32%) and 2 cases (4%) respectively, and the mean CD4+ count (cells/mm^3) was 167.12 (Table 2).

All patients showed at least one oral manifestation. Identified oral lesions were pseudo- membranous candidiasis accounting for 76% (38/50) followed by periodontal disease 34% (17/50), herpetic lesions, hairy leukoplakia 10% for each (5/50), gingivitis 8% (4/50), oral ulceration 8% (4/50), Kaposi's sarcoma 6% (3/50) and Non-Hodgkin lymphoma 2% (1/50) (Fig. 1).

Distribution of oral lesions based on the CD4+ count of HIV- infected patients showed that 62% of oral lesions occurred at CD4+ count <200 cells/ mm^3 (mean CD4+ count 65.31, mean CD8+ count 607.25 and mean CD4/CD8 ratio 0.14), about 26% oral lesions were depicted at CD4+ count of 201-499 cells/ mm^3 (mean CD4+ count 318.81, mean CD8+ count 804.12 and mean CD4/CD8 ratio 0.39) whereas 12% cases of oral lesions were observed at CD4+ count >500 cells/ mm^3 (mean CD4+ count 582.5, mean CD8+ count 1528.5 and mean CD4/CD8 ratio 0.22) (Table 3).

Table 1. Distribution regarding the route of contamination and gender

Contamination	Male	Female
Homosexual	28	0
Heterosexual	4	1
Bisexual	5	0
Drug use, needle-sharing injection	4	4
Blood transfusion	3	0
Combination of drug use and homosexual	1	0

Table 2. Average of CD4+, CD8+ counts and CD4/CD8 ratio

CD4 classification	CD4 + counts	CD8 + counts	CD4 / CD8 ratio
> 500 Cells/mm3	65.31	1528.5	0.22
201 - 499 Cells/mm3	318.81	804.1	0.39
< 200 Cells/mm3	582.5	607.25	0.14

Table 3. Distribution of oral manifestations related to CD4+, CD8+ and CD4/CD8 ratio

	CD4 Counts	CD8 Counts	CD4/CD 8 Ratio	Gingivitis	Periodontitis	Herpes	Candidiasis	Hairy Leukoplakia	Kaposi's Sarcoma	Non-Hodgkin Lymphoma	Ulceration
< 200	65.31	607.25	0.14	3	7	3	28	4	3	1	1
>201<499	318.81	804.12	0.39	2	9	2	9	1	0	0	3
>500	582.5	1528.5	0.22	0	1	0	1	0	0	0	0

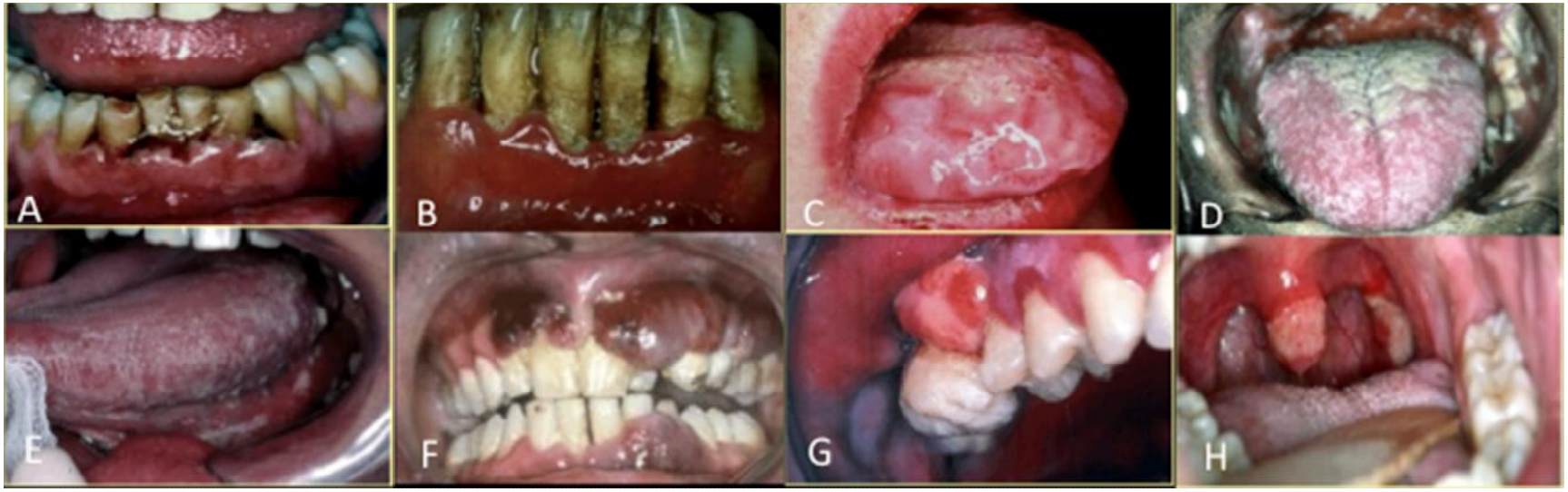

Fig. 1. Clinical appearance of the oral lesions; A: Gingivitis; B: Periodontal disease; C: Herpetic lesion; D: Pseudo-membranous candidiasis; E: Hairy Leukoplakia; F: Kaposi's Sarcoma; G: Non-Hodgkin Lymphoma; H: Ulceration

4. DISCUSSION

Oral lesions are fairly common in HIV-infected patients, the most common ad frequent oral hairy leukoplakia, xerostomia, recurrent aphtous ulcers, neutropenic ulcers, gingival erythematous candidiasis, oropharyngeal candidiasis, angular cheilitis, herpetic gingiva-stomatitis, parotid swelling (enlargement), linear gingival erythema, necrotizing ulcerative gingivitis.

The less frequently encountered HIV-AIDS related lesions are leukoplakia, papilloma, necrotizing ulcerative periodontitis, hard and soft palate Kaposi's sarcoma and Burkit's lymphoma.

Predictive value of plasma levels of CD4+ and CD8+ lymphocyte counts was investigated on 50 HIV-infected patients, knowing that relationship between oral lesions of HIV infection and CD4+/CD8+ cell ratios is high relevance in the clinical assessment of immune suppression. Indeed, these oral lesions develop in parallel to immune system depletion, specifically with low CD4+ cell counts (<200 cells/mm^3 and mean CD4+/CD8+ < 0.39 [20].

In the particular case of HIV-infected children, oral manifestations of immunosuppression usually take the form of either opportunistic infections or neoplasia, and they are considered as serious indicators of the progression of HIV infection [21]. Also low blood CD8+ T-lymphocytes and high circulating monocytes have a predictive value for HIV-associated progressive encephalopathy that can shorten life expectancy in HIV-infected Children [22]. Infection with HIV is characterized by a progressive depletion in the absolute number of circulating CD4+ and a decrease in the CD4/CD8 ration. In this epidemiological descriptive cross-sectional study, we were not able to find a correlation between CD4/CD8 ratio and the occurrence of oral lesions. However, a strong one was proven between the CD4+ count and oral manifestations. One explanation of these specific findings could be related to the anti-retroviral treatment (ART) of our patients. Indeed, during untreated HIV infection, CD8+ counts increase as CD4+ counts decrease [23] and during ART-mediated viral suppression, some patients with CD4+ counts > 500 cell/mm^3 display a simultaneous decline in CD8+ counts, leading to an almost normalization of CD4/CD8 ratio. On the other hand, some patients were able to maintain high levels of circulating CD8+ T cells, and consequently a persistently low CD4/CD8 ratio, this is related to the effects of ART and at the same time, may identify patients with persistent innate and adaptive immune activation at greater risk of serious non HIV/AIDS events [24,25,26].

Serrano-Villar and associates (2014) hypothesized that earlier ART initiation might also accelerate the rate of CD4/CD8 ratio normalization: using data from our distinct clinical cohorts and three clinical trials, they showed that a low CD4/CD8 in HIV-infected adults during effective ART (after CD4 count recovery above 500 cells/mm^3) is associated with immunological anomalies, including higher levels of CD8+ T cell activation and skewed T cell phenotype from naïve toward terminally differentiated CD8+ T cells. They concluded that a persistently low CD4/CD8 ratio during otherwise effective ART is associated with a higher risk of non HIV-AIDS morbidity/mortality and immunosenescent phenotype [24].

Among elderly HIV-uninfected adults, inversion of CD4/CD8 ratio (1.0) predicts all cause mortality and is considered part of the immunosenescent phenotype [24-29]. Impact of inversion of the CD4/CD8 ratio on natural history of HIV-infection was analyzed by Margolick and co-workers [26] who concluded that time from HIV seroconversion to inversion of Cd4/CD8 ratio independtly predicted time to AIDS.

The mean age of the participants in this study was approximately 39 years, demonstrating prevalence for infection among young population.

The mean age of males was significantly higher than that of females (40.7 vs. 32.4). The main route of HIV transmission was sexual intercourse (76% of cases) followed by shared intravenous needles (18%) and blood transfusion (6%). Shared intravenous needles infected the majority of females and males were infected through sexual contact. A predilection for sexual contamination was observed in our study, which is a characteristic of the most common transmission route of HIV, followed by shared intravenous needles.

Earlier studies reported that HIV patients with a CD4+ count of < 200 cells/ml had more oral lesions [11,16,19]. A similar finding was recorded in this study in which 62% of total HIV-related oral lesions were in the group of patients with CD4+ count of < 200 cells/mm^3.

The inverse relationship between CD4+ counts and prevalence of oral mucosal lesions in HIV-infected patients has been previously reported [8,11,19,27,28]. Similarly, this study lead to a significant inverse relationship between CD4+ counts and prevalence of oral lesions in HIV-infected patients.

Our findings indicate that occurrence of oral lesions in HIV-infected patients could be a useful indicator in determining a depletion of immunological status of HIV-infected patients. This agrees with reports supporting that CD4+ depletion is strongly associated with a high level of viral load [16]. Therefore, clinicians and researchers are advocating oral lesions as a useful tool for the diagnosis and detection of the progression of HIV infection [16,28].

The main factor associated with the development of oral opportunistic lesions is the CD4+ count [16]. The onset of oral candidiasis and oral hairy leukoplakia is heralded by a sustained reduction in the CD4+ blood cell count associated with a sharp increase in viral load [12]. An earlier study [30] stated that oral lesions found among a cohort of 737 HIV-infected in Italy were significantly associated with CD4+ count of < 300 cells/mm^3. In a study done on a population of 43 subjects in Greece [31], oral hairy leukoplakia was found to be associated with CD4+ counts < 200 cells/mm^3. Analysis of oral lesions in 81 HIV-positive subjects and 31 HIV-negative subjects and their CD4+ counts in a study done at Oyo, Nigeria, has shown that CD4+ counts < 500 cells/mm^3 were significantly associated with occurrence of pseudo- membranous candidiasis and angular cheilitis [29].

Similarly, this study revealed that oral candidiasis and hairy leukoplakia were associated with CD4+ counts < 200 cells/ml.

Thus far, CD4+ cell count is recognized and widely used as a marker for HIV-related disease progression. Accordingly, the Centers for Disease Control and Prevention in USA proposed a revised classification system and AIDS case surveillance definition that incorporates both clinical signs and symptoms as well as one laboratory marker, the CD4+ cell count [7].

5. CONCLUSION

As CD4+ count decreases, presence of oral lesions increases in this study. The ratio of CD4/CD8 is not related to the presence of oral lesions.

Disease progression is characterized by increased prevalence of some oral lesions such as candidiasis, hairy leukoplakia, and Kaposi's sarcoma. The clinical intensity of oral lesions was more pronounced with a CD4+ count <200 cells/mm^3.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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