Importance of various oral manifestations regardless of CD4 cell count in HIV/AIDS patients

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In Berberi and Aoun's article[1], the results and conclusion stated that the CD4+ count was <200 cells/mm^{3} in 45 cases (60.0%), between 200-500 cells/mm^{3} in 18 cases (24.0%), and >500 cells/mm^{3} in 12 cases (16.0%). The mean CD4+ count was 182.18 cells/mm^{3} and the mean ratio of CD4+/CD8+ cells was 0.26. All patients exhibited at least one oral manifestation. There was no correlation between the CD4+/CD8+ cell ratio and the presence of oral lesions. The severity of the lesions was more pronounced when the CD4+ cell count was less than 200 cells/mm^{3}.

Although this original article was well written and provided a great deal of information regarding the presence of oral lesions in human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) patients according to the clusters of differentiation 4 (CD4) cell count including the CD4/CD8 cell ratio, a few additional recommendations regarding CD4 cell count related clinical studies should be included on the importance of oral manifestations.

1. CD4 enumeration timing in HIV/AIDS patients

In Berberi and Aoun's article[1], there was no information about the CD4 cell count enumeration timing in patients living with HIV/AIDS (PLWHA). CD4 cell count is more sensitive to sudden changes in a person's immunity and thus, is a better indicator of HIV/AIDS progression. CD4 cell count can also differ among individuals depending on their age, gender, and immune status. A known characteristic of HIV/AIDS pathogenesis is the targeting of human immune cells that bear the CD4 surface marker. HIV infections cause a gradual decrease in CD4+ cells, the most important being the T-helper cells (CD4 T-cells), B lymphocytes, macrophages, and natural killer cells. CD4 cell count (the amount of CD4 lymphocyte cells per milliliter) and viral RNA load (quantity of HIV-1 RNA copies per milliliter) are currently the most reliable laboratory indicators of HIV progression[2].

HIV-positive patients with CD4 lymphocyte-cell count <200 per milliliter are considered severely immune depressed and HIV-positive patients with viral RNA loads >10,000 copies per milliliter are considered to have active viremia. From previous studies[2] and related reviews[3,4], highly active antiretroviral therapy (HAART) could be implemented in HIV/AIDS patients with a CD4 cell count higher than 350 cells/mL. Common lesions among outpatients had a significant relationship with declining CD4 cell count from 290 to 140 cells/mL. This is finding consistent that specific clinical presentations appear as immunity declines in Ghanaian PLWHA patients[2]. This pattern is likely comparable to presentation patterns in other HIV-prevalent populations[2,3]. Some patients with HAART from urban populations exhibited minimal oral findings because of their ideal accessibility to treatment and education about HIV infections. Patients who were on long-standing HAART treatment also exhibited minimal oral manifestation such as pigmentation and xerostomia[2].

Therefore, whether all HIV/AIDS-positive patients who had not yet started HAART are enrolled or not, their CD4 cell count should be confirmed first in any clinical study. The median duration of antiretroviral therapy (ART)-mediated viral suppression was 3 years and 3 months to 4 years in Berberi and Aoun's article[1]. This situation could have resulted from the fact that the CD4 cell counts from most patients in

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the study were already increased due to ART. Therefore, oral manifestations could not be correlated in these circumstances.

2. Analysis methods of CD4

In Berberi and Aoun's article[1], their results showed that the CD4+ count was <200 cells/mm^{3} in 45 cases (60.0%), between 200-500 cells/mm^{3} in 18 cases (24.0%), and >500 cells/mm^{3} in 12 cases (16.0%). The mean CD4+ count was 182.18 cells/mm^{3}, and the mean ratio of CD4+/CD8+ cells was 0.26. There was no correlation between the CD4+/CD8+ cell ratio and the presence of oral lesions. The severity of the lesions was more pronounced when the CD4+ cell count was less than 200 cells/mm^{3}. The examination methods of CD4 or CD8 enumeration were not clearly expressed in the article, just the involvement of medical records, physical examinations, demographic data, and laboratory tests. Flow cytometry has been recognized as the representative method, but the Western blot technique[2] or other methods should be considered based on the laboratory's economic facility and skillset of the examiners[3,5,6].

Information on variability in the CD4+ T cell count in the absence of HIV infection is very important for interpreting the result of CD4+ T cell count enumeration. Reference values are therefore necessary for the given population as the values may vary from population to population depending upon the age, gender, and race of the population and the instruments used to perform the tests. The range is usually defined as a set of values 95% of the normal population fall within and is commonly referred to the normal range or normal values. Quality management is also an important factor in any laboratory involvement with HIV in order to ensure that the overall quality of the results from the services or products is reliable, reproducible, traceable, and auditable[5]. Even if population values or quality management standards are excluded, the basic analyzing methods should be expressed in any CD4 cell count related clinical study.

Immunofluorescence analysis by flow cytometry is known as the gold standard for CD4 T lymphocyte measurements with an enzyme immuno-assay on serum. The flow cytometry may be mainly performed using dual-platform and single-platform methods. In the dual-platform approach, T cell gating, CD45 gating, and Paneucogating are known. Many single-platform technologies have been developed commercially with fluorescence-activated cell sorting (FACS) microbeads-based systems and Dynabeads CD4/CD8 T lymphocytes quantitation as representative methods[3,5-8].

3. Sialadenitis and/or xerostomia the representative oral manifestation in HIV/AIDS patients

In Berberi and Aoun's article[1], the most frequent oral lesion detected was oral pseudomembranous candidiasis (80.0%), followed by periodontal disease (40.0%), herpetic lesions (16.0%), hairy leukoplakia (16.0%), gingivitis (20.0%), oral ulceration (12.0%), Kaposi's sarcoma (8.0%), and non-Hodgkin's lymphoma (4.0%). All of the patients exhibited at least one oral manifestation. In one related article[3] regarding oral lesions among 50 HIV/AIDS patients, all patients exhibited at least one oral manifestation and the most common of which was pseudomembranous candidiasis accounting for 76% (38/50) of the patients, followed by periodontal disease at 34% (17/50), herpetic lesions and hairy leukoplakia at 10% each (5/50), gingivitis at 8% (4/50), oral ulceration at 8% (4/50), Kaposi's sarcoma at 6% (3/50), and non-Hodgkin lymphoma at 2% (1/50)[9,10].

Unfortunately, there are no comments or findings about sialadenitis with and without xerostomia in the oral cavity. Due to the basic immunodepression nature of HIV/AIDS, related oral manifestations had been classified as oral infections, including fungal, viral, and bacterial, and HIV-associated malignancies or other lesions, academically[7]. Candidiasis and histoplasmosis in the fungal infection, herpes family viruses with other human papilloma virus, molluscum contagiosum, and hepatitis viruses in viral infection, and gingivitis with or without periodontitis were known in the bacterial infection. Kaposi's sarcoma, non-Hodgkin's lymphoma, and squamous cell carcinoma are representative HIV-associated malignancies in the oral cavity. In other HIV-associated oral lesions, recurrent aphthous lesion, lichen planus, sialadenitis, xerostomia, and melanotic hyperpigmentation could be considered. A significant relationship with CD4 cell counts with representative orofacial lesions has been determined including an association with xerostomia in many previous articles[2,7]. The authors also described that all the patients exhibited at least one oral manifestation without revealing more than one lesion. Therefore, xerostomia could be one of several oral manifestations.

4. Importance of oral manifestations regardless of CD4 cell count in HIV/AIDS patients

Oral manifestations are generally an early sign of HIV infection, but could also be used to predict the progression of HIV/AIDS in patients[3,7,11]. CD4 cell count is known as an

indicator of the immune system including the body's natural defense system against pathogens and illness. CD4 cells coordinate many immunological functions; as cell numbers decrease, the risk and severity of opportunistic infections (OI) increase and can become deadly. Previous research has indicated that the absolute number of CD4 lymphocytes in HIV-infected people falls from a normal level of 800-900 cu/mm to 60-100 within one year[2,11].

Oral manifestations could provide an opportunity for early clinical diagnoses because of the underlying association of CD4 cell counts. Such clinical tools are particularly important in low-social economic environments characterized by a deficient or even no examination facility. In our manual western blot enumeration procedure, the presence of oral lesions may lead to a positive diagnostic of HIV in rural Ghana[2]. The relationship between lesion presentation and cell count was significant for cell counts between 138.80 and 292.48 cells/mL, with oral hairy leukoplakia being the most common at the lowest end of the cell count range and melanotic hyperpigmentation at the highest. None of the patients examined were known to be on HAART. Nevertheless, it is important to note that some patients were on at least one type of medication at the time of examination, such as antifungals, antibiotics, antituberculosis therapy, or hematinics for the treatment of OI. It is therefore possible that these medications could have masked or affected the presence of any of these manifestations.

Oral lesions are among the early signs of HIV infection and can predict the progression to AIDS. The lesions commonly associated with the infection include oral candidiasis, herpes simplex infection, oral Kaposi's sarcoma, oral hairy leukoplakia, parotid gland enlargement, gingival disease, xerostomia, and recurrent oral ulcerations. The introduction of HAART has changed the epidemiology of some of the oral diseases associated with HIV infection[4,11].

In conclusion, from findings mentioned in the commentary, we can suggest that oral manifestations such as fungal infections, viral infections, bacterial infections, HIV-associated malignancies, and other lesions including sialadenitis and aphthous ulcers, are important clinical findings in HIV/AIDS patients. Oral manifestations are very important indicator among the early signs of HIV/AIDS infection and could predict the progression to AIDS regardless of the CD4 cell count under the influence of HAART.

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Authors' Contributions

S.M.K. participated in reference collection and wrote the manuscript. J.H.L. helped to draft and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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