Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20174374

Original Research Article

Low current Cd4+T cell count: prediction, for persistent herpetic gingivostomatitis in HIV-positive patients under antiretroviral therapy

S. K. Narendra[1]*, N. C. Sahani[2], Upendra Das[3], S. Tripathy[4]

[1]Department of Periodontology, SCB Dental College, Cuttack, Odisha, India
[2]Department of Community Medicine, [3]Department of Biochemistry, [4]Department of Medicine, SCB Medical College, Cuttack, Odisha, India

Received: 29 July 2017
Revised: 19 August 2017
Accepted: 23 August 2017

***Correspondence to:**
Dr. S. K. Narendra,
Email: suryakantanarendra@yahoo.com

ABSTRACT

Background: Oral viral lesions associated with HIV infection are important since they affect the quality of life of the patient and are useful markers of disease progression and immunosuppression. The purpose of this study was to correlate the persistence of herpetic gingivostomatitis lesions with the current CD4+ T cell count for adherence of HIV-infected individuals to anti retroviral therapy (ART) and antiviral therapy.
Methods: 302 HIV +ve patients developing oral ulcers were included in this study. The herpes simplex viral infections associated with the oral manifestations were detected through Immuno histochemical staining. The quantitative analysis of oral ulceration was done by using mucositis index.CD4T cell count was correlated with clinical manifestations of extensiveness of oral ulcers, acute febrile condition and other constitutional symptoms during follow up of cases for the treatment with anti viral therapies.
Results: Association of herpes simplex viral infections was found in 72 out of 302 HIV+ ve cases. All the HSV +ve patients developed extensive oral mucsal lesions during the 1st week. Extensive lesions developed within 7 days in patients with CD4 count <200 due to HSV infection, remained more or less unchanged in the oral cavity up to 90 days although they were receiving antiretroviral and antiviral therapies. In HIV + patients with CD4 count >500, manifestation of mucosal ulcers due to acute herpetic gingivostomatitis was limited to a period of 1 to 2 weeks. Patients with CD4 count >200 <500 did not follow a definite pattern.
Conclusions: Persistent oropharyngeal mucosal ulcers along with acute febrile condition due to herpes simplex virus infection are associated with low CD4 T cell count in HIV + patients under antiretroviral therapy.

Keywords: Herpetic gingivostomatitis, Herpes simplex infections, HIV Infections

INTRODUCTION

Ulcers in oral mucosa persisting for a longer time in acquired immunodeficiency syndrome (AIDS) represent one associated disease entity caused by several factors. Persistent mucosal ulcers in patients suffering from AIDS are found to be associated with herpes simplex virus.[1] Several etiological factors responsible for the development of persistent ulcers in oral mucosa, in patients suffering from acquired immune deficiency syndrome, represent themselves as separate disease entity. Persistent mucosal ulcers due to herpes simplex virus are difficult to differentiate from other ulcerogenic diseases such as aphthous major, necrotizing stomatitis and other concurrent infections.[1] The common manifestations of the oral cavity in HIV infected patients are due to concurrent viral infections. They served as the clinical criteria for determining the disease progression. The viral manifestations found in HIV infected patients are usually due to Herpes virus type 1 and rarely type 2, Epstein-Barr virus (EBV), Cytomegalovirus and Human Papilloma Virus.[2] One of the classified Oral manifestations of HIV

associated infection declared by the WHO Collaborative Centre are viral in origin. A significant proportion of patients are found to develop oral viral lesions distributed in lip, buccal mucosa, tongue.[3] Co-infection of herpes simplex virus and cytomegalovirus presents persistent oral ulcers causing oral pain with non healing tendency on the palate, retro molar pad, tongue, lip, with non specific clinical appearance in HIV+ patients.[4] Concurrent oral herpes simplex virus gives rise to oral ulcerative lesion in patients with acquired immunodeficiency syndrome. Both immunocompetent and immunocompromised persons are found to suffer from recurrent oral herpes simplex virus lesions.[5] Intraoral herpes simplex virus infection presents clinical features, which varies from single ulcers to multiple lesions occurring on keratinized or nonkeratinized mucosa of the oral cavity with history of recurrences.[6] Cytomegalovirus (CMV) associated oral lesions in human immunodeficiency virus (HIV) infected patients also manifests oral ulcerations but not usually associated with features of recurrence.[7] Additional improvement in quality of life has been brought about by advances in the development and application of antiviral drugs for the HIV-infected individual. Acyclovir is the drug of choice for treatment of opportunistic infections due to Varicella zoster and Herpes simplex. Other antivirals like Ganciclovir or foscarnet are also recommended for HIV Infected patients for other common life-threatening oppurtunistic viral infection in patients suffering from AIDS.[8] Crawford KW et al, found in their observational study that high virological suppression is achieved in patients on first-line antiretroviral therapy (ART) with application of efavirenz or nevirapine+ zidovudine/ lamivudine through the assessment of viral load (HIV-1 RNA) and CD4 cell count. There was a positive association of virological suppression with efavirenz use and improvements in CD4 cell percentage and total lymphocyte count.[9] Oral health measures are to be effectively formulated for the HIV-infected individuals with the help of the reports from both developing and developed countries, as HIV infection is a major global health problem. Reports from developed countries on oral lesions in HIV infection are well-documented contrary to the inadequate reports of developing countries.[10] With this back ground of information we have planned this study to correlate the clinical features of oral ulcers associated with herpes simplex virus infection with the current CD4+ T cell count in HIV+ patients with application of anti retroviral therapy and other antiviral therapy.

METHODS

Study design

Non interventional clinical observational study was designed from amongst the HIV+ patients attending the anti retroviral therapy (ART) centre. Three hundred two HIV infected patients developing oral ulcers, referred from ART cenre for oral examination and prophylaxis were included in this study, which was conducted over a period of 1 year. Written informed consent from all the patients and necessary approval from institutional ethical committee were obtained.

Inclusion criteria

- All these patients were HIV+ patients developing oral ulcers.
- All of them were subjected to Immuno histochemical staining, to include the Herpes simplex viral infection + patients only.
- All these patients are following the standard treatment protocol of ART centre.

Exclusion criteria

- HIV+ patients developing manifestations of multiple oral viral infections were excluded from this study.

The Spijkervet's mucositis index was taken for quantitative analysis of oral ulceration due to the manifestation of herpetic gingivostomatitis.[11] The index is displayed in Table 1. The quantitative analysis of the compiled data was done using the measures of dispersion and paired t- test. Acute febrile conditions associated with the constitutional symptoms are analysed through qualitative analysis.

Table 1: Mucositis Index (Spijkervet's Mucositis index).[10]

Local sign	Score of local sign(K)	Length (E)	Final score
No mucositis	0		
White discolouration	1	1 cm	1
Erythema	2	1cm-2cm	2
Pseudomembrane	3	2cm-4cm	3
Ulceration	4	4cm	4

Indices for Local Mucositis Signs-K
Indices for length of areas-E
An area (The I^{th} area=1……..n) might include several sub areas
Key: n=number of areas, K=sign, E=length

The patients are divided into 3 groups as per their CD4 T cell count. Group 1 with CD4 count <200 treated with antiretroviral therapy and antiviral therapy, Group 2 with CD4 count >200 <500 treated with antiretroviral therapy and antiviral therapy, Group 3 with CD4count> 500 received no treatment. Degree of mucosal ulceration and associated constitutional symptoms ingroup1, group 2 and group 3 are monitored at 1 week, 1month, 2 months and 3 months interval for a period of 3months or till the reversal of the lesions, whichever is earlier.

RESULTS

Out of 302 HIV positive patients with oral ulcers, Herpetic gingivostomatitis was diagnosed in 72 patients, displayed in Table 2. Distribution of HSV+ patients among different

groups of HIV + patients are shown in the graph of Figure 1.

Table 2: Profile of base line characteristics.

Characteristics	Number (%)
A) Number of patients HIV+ patients with oral ulcers B) Number of patients +ve for HSV	302(100%) 72 (23.84%)
Sex wise distribution of the HSV + sample: C) Female D) Male	 21(29.17%) 51(70.83%)
Age wise distribution of the sample E) Range less than35Yrs More than 35 yrs	 18-54 yrs 40(55.6%) 32(44.4%)
Distribution according to CD 4 Count: A) Group1: CD4T cell count <200. B) Group2: CD4T cell count ≥200 to <500 C) Group3: CD4T cell count ≥ 500	 31 33 08

In group 1 (with CD4 count <200), the degree of involvement of herpetic gingivostomatitis lesions are analyzed in terms of their mucositis score from 1st week up to 3months in Table 3. Significant increase in degree of mucosal involvement was found between the base value and1st week (P <0.001). However, mucositis index was found to remain unchanged at that increased level after 1 week as observed during subsequent follow-ups at 1 month, 2 months and 3 months (p>0.05). In group 2 with CD4 count >200 <500, the scores of mucositis index increased significantly (p<0.001) during 1st week of observation, but the scores of mucositis index followed no definite trend in the subsequent follow up, even if the patients were under the cover of antiretroviral therapy and antiviral therapy as per the required dose schedule. In group 3 patients with CD4 count ≥500, the scores of mucositis index increased significantly (p<0.001) during 1st week of observation. During the follow up period of 3months it decreased with the antiviral therapy significantly when compared to the value at 1 week (P<0.001).

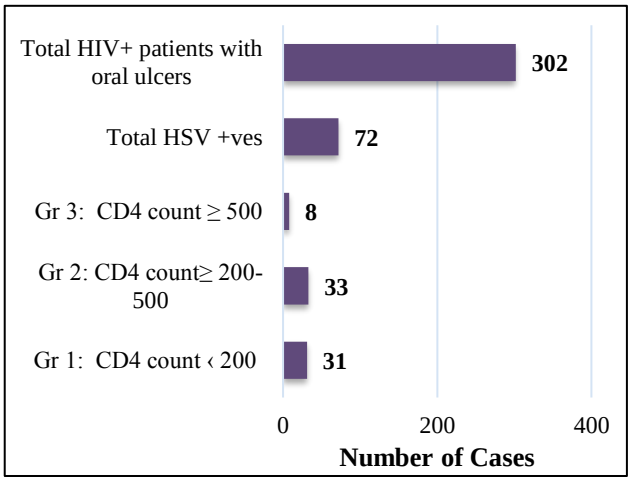

Figure 1: Distribution of HIV +ve and HSV+ve Oral ulcer patients.

The degree of mucosal manifestations of HSV Infection during follow up in all three groups is shown in the Figure 2.

Association of other constitutional symptoms like dysphagia, fever, anorexia and malaise were found all along during the observation period in majority of patients in group 1. Dysphagia was found in about the 90.3% of the patients in group 1 and other constitutional symptoms like fever/anorexia/ malaise was found in about 83.8% of the patients.

Table 3: Comparison of the degree of mucosal manifestation of HSV infection in different groups during the follow up period.

Group	No of patients	Base value At reporting	Follow up period			
			1 week	1 month	2 months	3 months
Group 1	31	1.1±0.2	4.4±0.78 *t=22.82, df=60 P <0.001	4.7±0.51 **t=1.79 df=60 P>0.05	4.6±0.61 **t =1.12 df=60 P>0.05	4.7±0.32 **t=1.982 df=60 P>0.05
Group 2	33	1.2±0.1	4.2±0.82 *t=20.86 df=64, P <0.001	3.9±1.62 **T=3.164 df=64, P <0.01	3.2±1.54 **T=3.292 df=64, P <0.01	3.1±1.72 ** t=8.486 df=64, P <0.001
Group 3	8	1.1±0.12	4.8±0.42 *t=23.96 df=14, P <0.001	0.85±0.35 **T=20.46 df=14, P<0.001	0.95±0.52 **T=16.29, df=14, P<0.001	0.55±0.25 **t=28.18 df=14, P<0.001

*value at 1week as compared to base values
**values as compared to that at 1week

In group 2, dysphagia was found in about 63.6% of the patients and other constitutional symptoms in about 60.6%, but for a shorter period up to 1 month. Other constitutional symptoms were found only in few i.e. 25% of the patients and for a short period of 1 to2 weeks in group 3.

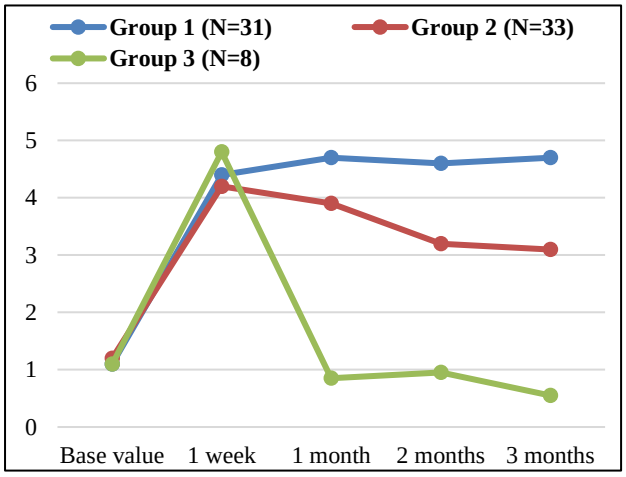

Figure 2: Degree of mucosal manifestation of HSV infection during follow up period in HIV+ patients.

Table 4: Symptomatic presentation of study subjects.

Group of the patients	Symptoms with duration	
	Dysphagia	Constitutional symptoms including fever/anorexia/ Malaise
Group1 (N=31)	28 (90.3%) Up to 3 months	26 (83.87%) Up to 3 months
Group2 (N=33)	21 (63.64%) ≤1 month	20 (60.6%) ≤1 month
Group3 (N=8)	2 (25%) 1-2 weeks	2 (25%) 1-2 weeks

DISCUSSION

The disease progression in HIV positive patients could be determined by the clinical criteria of concurrent viral infections of the oral cavity. Herpes virus infection was found as common opportunistic pathogen in HIV-infected individuals during the study of oral manifestations of AIDs patients. About 23% of oral lesions are viral in origin and distributed in lip, buccal mucosa, tongue and palate. Herpes simplex infection causing persistent mucosal ulcers, are difficult to differentiate from ulcerogenic diseases such as aphthous major, necrotizing stomatitis. The characteristic clinical feature of intraoral herpes simplex virus infection in a portion of HIV +ve patients attributed to oral ulcers with pain and non healing tendency. Con current infections with oral herpes simplex virus, cytomegalovirus and histoplasmosis in HIV-infected patients are also found to be associated with simultaneous extensive oral ulcerations. Improvement in quality of life for the HIV-infected individual has been brought about by application of antiviral drugs like Acyclovir, Ganciclovir or foscarnet. Spijkervet's mucositis index was used for quantifying the oral ulcerations and mucosal lesions.[1-11]

Patient morbidity could be reduced by early diagnosis of HSV infections and treatment of immunocompromised HIV patients with acyclovir. Thus in all HIV + patients, diagnostic culture should be recommended for herpes simplex virus for all oral ulcers regardless of their location.[12] Immune status and response determined by CD4+T cell count and plasma viral load decide the success and clinical outcome of antiretroviral therapy (ART).[13] The seroprevalence of HSV-1 infection being inversely related to socioeconomic background, triggers significance of such study in a developing country like India. HSV-1 infections are usually asymptomatic but give rise to mucocutaneous vesicular eruptions affecting primarily the lips, gingiva, buccal mucosa, tongue, hard and soft palate.[14] The morbidity caused especially by the herpes simplex virus could be reduced by antiviral drug regimens in immunocompromised patients. Herpes simplex virus is one ubiquitous infectious agent as it establishes latency and undergo subsequent recurrence, subjecting its cure, a far from reality and a concern for immunocompromised patients.[15] Herpes labialis can be effectively treated by Acyclovir (ACV) 5% cream and pencyclovir 1% cream. Widely accepted and effective treatment protocol for acute primary herpetic gingivostomatitis includes standard topical therapy and systemic antiviral therapy. Application of Acyclovir and famcyclovir in immunocompromised patients reduce the duration and recurrence of HSV-1 infection. The dosing and timing schedule of the treatment varies according to situation.[16] Diagnosis and treatment of primary and recurrent herpetic infections are more frequently initiated at dental office. During treatment on patients, dentists should use management strategies for prevention of spread of this infection. Adequate nutrition and maintenance of proper oral hygiene practices are of paramount importance.[17] Difficulties in distinguishing the precipitating factors of oral mucosal ulcerations one from the other leads to inappropriate therapeutic intervention. Better understanding of the virologic and local immunologic alterations within the oral mucosa improves the treatment strategies within the general practice setting.[18] Any alteration in 1993 ECC/WHO Classification of oral lesions associated with adult HIV infection could be possible by availing adequate data from developing countries regarding oral lesions associated with adult HIV infection.[19] Development of opportunistic infection constituting the clinical features of AIDS, due to profound immune deficiency, is elaborated gradually in HIV infected patients. Increased risk of autoimmune disease with destruction of the immune system by the virus leads to the development of opportunistic infection and malignancy. Primary illness within weeks after first exposure to HIV found to be manifested as the clinical symptoms of mononucleosis syndrome in about half of the total cases. The Progressive risk of developing

opportunistic infections like oral candidiasis, oral hairy leukoplakia, recurrent mucocutaneous herpes simplex virus (HSV), herpes zoster (VZV) and malignancies increases, when CD4 counts drop below 200 cells/mm3, as typical clinical feature of AIDS.[20] Randomized double blind trials for treatment of suppression of mucocutaneous HSV lesions by drugs like famciclovir, acyclovir and valaciclovir in HIV patients were shown to be effective.[21,22] The patients with immune compromised status adhered to anti retroviral therapy also suffers more or less with such resistant ulcers, Itin PH, et al.

With this background, the observations of this study can be summarized as follows. In HIV + patients with CD4 ≤200: the herpetic gingivostomatitis lesions are found to be at significant level at the end of the 1st week and remains more or less unchanged in the oral cavity up to 3 months. The immune compromised patients suffered from such resistant ulcers due to recurrent infections, even if they were on ART and antiviral therapy during that 3 months span of this study, whereas, the scores of mucositis index followed no definite trend in the subsequent follow up period of 3months after the significant rise of 1st week in group2.The reason attributed could be due to the uneven distribution of the CD4 count between the range of 200 to 500 in this group. As per the observations in the patients in group 3, acute herpetic gingivostomatitis in HIV + patients with adequate immune status in the patients with CD4 count ≥500 get manifested in the form of ulcers and other mucosal lesions for a period of 1week and remission was noticed within 2 weeks. The remission may be either due to the effect of antiviral drugs or due to the self-limiting character of this viral infection in patients with adequate immune status.

CONCLUSION

HIV+ Patients with CD4 count less than 200 behaved differently due to persistence of the extensive ulcers due to HSV infections affecting the quality of life irrespective of the treatment with ART and the antiviral treatment for HSV infection. On the other hand the manifestations in patients with higher CD4 count ,more than 500 were less morbid and satisfactory without the same anti retroviral therapy along with antiviral therapy. Oral lesions due to HSV infection in HIV+ patients are important, since they affect the quality of life of the patient and are useful markers of disease progression and immune suppression. However larger prospective studies are warranted with the goal of confirming our observations.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Garber A, Klein E, Bruce S, Sankoh S, Mohideen P. Metformin-glibenclamide versus Flaitz CM1, Nichols CM, Hicks MJ. Herpesviridae-associated persistent mucocutaneous ulcers in acquired immunodeficiency syndrome. A clinicopathologic study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;81(4):433-41.
2. Itin PH, Lautenschlager S. Viral lesions of the mouth in HIV-infected patients. Dermatology. 1997;194(1):1-7.
3. Tukutuku K, Muyembe-Tamfum L, Kayembe K, Odio W, Kandi K, Ntumba M. Oral manifestations of AIDS in a heterosexual population in a Zaire hospital. J Oral Pathol Med. 1990;19(5):232-4.
4. Regezi JA, Eversole LR, Barker BF, Rick GM, Silverman S. Herpes simplex and cytomegalovirus coinfected oral ulcers in HIV-positive patientsOral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996;81(1):55-62.
5. Heinic GS, Northfelt DW, Greenspan JS, Mac Phail LA, Greenspan D. Concurrent oral cytomegalovirus and herpes simplex virus infection in association with HIV infection. A case reports. Oral Surg Oral Med Oral Pathol. 1993;75(4):488-94.
6. Firth NA, Rich AM, Reade PC. Oral mucosal ulceration due to cytomegalovirus associated with human immunodeficiency virus infection. Case report and brief review. Aust Dent J. 1994;39(5):273-5.
7. Eisen D. The clinical characteristics of intraoral herpes simplex virus infection in 52 immunocompetent patients. - Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86(4):432-7.
8. Fletcher CV. Treatment of herpesvirus infections in HIV-infected individuals. Ann Pharmacother. 1992;26(7-8):955-62.
9. Crawford KW, Wakabi S, Magala F, Kibuuka H, Liu M, Hamm TE. Evaluation of treatment outcomes for patients on first-line regimens in US President's Emergency Plan for AIDS Relief (PEPFAR) clinics in Uganda: predictors of virological and immunological response from RV288 analyses. HIV Med. 2015 Feb;16(2):95-104.
10. Ranganathan K, Hemalatha R. Oral lesions in HIV infection in developing countries: an overview. Adv Dent Res. 2006;19(1):63-8.
11. Spijkervet FKL, van Saene HKF, Panders AK, Vermey A, Mehta DM. Scoring irradiation mucositis in head and neck cancer patients. Journal of Oral Pathology & Medicine. 1989;18(3):167-71.
12. Woo SB, Lee SF. Oral recrudescent herpes simplex virus infection.Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;83(2):239-43.
13. Pasternak AO, de Bruin M, Bakker M, Berkhout B, Prins JM. High Current CD4+ T Cell Count Predicts Suboptimal Adherence to Antiretroviral Therapy PLoS One. 2015 Oct 15;10(10):e0140791.
14. Arduino PG, Porter SR. Herpes Simplex Virus Type 1 infection: overview on relevant clinico-pathological features, J Oral Pathol Med. 2008;37(2):107-21.
15. Huber MA. Herpes simplex type-1 virus infection. Quintessence Int. 2003;34(6):453-67.

16. Arduino PG, Porter SR. Oral and perioral herpes simplex virus type 1 (HSV- 1) infection: review of its management. Oral Dis. 2006;12(3):254-70.
17. Siegel MA. Diagnosis and management of recurrent herpes simplex infections. J Am Dent Assoc. 2002 Sep;133(9):1245-9.
18. Sciubba JJ. Herpes simplex and aphthous ulcerations: presentation, diagnosis and management--an update. Gen Dent. 2003;51(6):510-6.
19. Patton LL, Phelan JA, Ramos-Gomez FJ, Nittayananta W, Shiboski CH, Mbuguye TL. Prevalence and classification of HIV-associated oral lesions. Oral Dis 2002;8(2):98-109.
20. Lloyd A. HIV infection and AIDS. P N G Med J. 1996;39(3):174-80.
21. Beyene MB, Beyene HB. Predictors of Late HIV Diagnosis among Adult People Living with HIV/AIDS, Who Undertake an Initial CD4 T Cell Evaluation, Northern Ethiopia: A Case-Control Study. PLoS One. 2015 Oct 8;10(10):e0140004.
22. Baccaglini L, Atkinson JC, Patton LL, Glick M, Ficarra G, Peterson DE. Management of oral lesions in HIV-positive patients. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007;103:S50.e1-23.

Cite this article as: Narendra SK, Sahani NC, Das U, Tripathy S. Low current Cd4+T cell count: prediction, for persistent herpetic gingivostomatitis in HIV-positive patients under antiretroviral therapy. Int J Basic Clin Pharmacol 2017;6:2446-51.