

Correlation Linear Gingival Erythema, Candida Infection and CD4+ Counts in HIV/AIDS Patients at UPIPI RSUD Dr. Soetomo Surabaya, East Java, Indonesia

Alexander Patera Nugraha¹, Diah Savitri Ernawati^{2*}, Adiastruti Endah P.², Bagus Soebadi²,
Erwin Asta Triyono³, Remita Adya Prasetyo⁴, Sulistyowati Budi⁴

1. Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

2. Undergraduate Student, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

3. Department of Internal Medicine, Faculty of Medicine Airlangga University, Surabaya, Indonesia.

4. Department of Oral Medicine, Instalation of Dental and Oral Health, RSUD. Dr. Soetomo, Surabaya, Indonesia.

Abstract

East Java has been 2nd highest province with HIV/AIDS cases in Indonesia on 2013. Oral manifestations are among the earliest and most important indicator of HIV infection progression. Linear Gingival Erythema (LGE) is the one of seven oral manifestation which associated with HIV Infection. Clinical feature of LGE is a distinctive fiery red band along the margin of the gingiva. The etiology and pathogenesis of LGE are still questionable, but a candidal infection and decreased of CD4+ counts has been suggested.

The aim of this study was to investigate LGE with its correlation with Candida infection and decreased level of CD4+ in HIV/AIDS patient.

This study was an analytical observational research with cross-sectional and total sampling method. The samples consisted of 88 HIV/AIDS patients treated in UPIPI RSUD Dr. Soetomo Surabaya from July-August 2014 were recruited for Candida microbial screening on LGE lesion. Clinical specimens including oral swabs were collected. Diagnosed of LGE by clinical appearance, the oral cavity of research subjects examined by oral medicine specialist. CD4+ counts obtained from patient's medical record.

88 HIV/AIDS patients were examined, there were 7 cases (5,83%) LGE, 7 from 7 gingival margin found Oral Candidiasis (OC) (100%). LGE was found to be significantly correlated to OC and decreased CD4+ counts < 200 cells/mm³ (p<0.05).

LGE related to candida infection and decreased CD4+ counts in HIV/AIDS patients.

Clinical article (J Int Dent Med Res 2017; 10(2): pp. 322-326)

Keywords: Gingival Erythema, Oral Candidiasis, Oral Manifestation, HIV/AIDS, CD4+.

Received date: 21 March 2017

Accept date: 01 May 2017

Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a syndrome caused by *Human Immunodeficiency Virus* (HIV).¹ In recent years, HIV infection rates have been increased rapidly, many people were alive with HIV infection in the world.² East Java province was the second highest with HIV infection cases between 19,249 peoples and 8,976 peoples with AIDS infection^{3,4}.

RSUD Dr. Soetomo was the largest

hospital in eastern Indonesia as one of the tertiary referral hospitals in Indonesia. RSUD Dr Soetomo is one from seven hospitals that appointed by the Ministry of Health as a Pilot Project Services and HIV/AIDS Prevention since 2010 centered in *Unit Perawatan Intermediate Penyakit Infeksi* (UPIPI)⁵.

Oral health is the important thing to identify quality systemic health of HIV/AIDS patients⁶. HIV/AIDS patients have 60% to 90% oral manifestation as opportunistic infection⁷. Detail history taking and examination the oral cavity of HIV/AIDS patients are important parts of the physical examination⁸. Dentist must do a proper management of oral manifestation in HIV/AIDS to improve the Quality of Life (QoL). Medical clinicians must able to recognize HIV-associated oral disease⁹.

*Corresponding author:

Diah Savitri Ernawati

Department of Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga. Jl. Mayjen. Prof. Dr. Moestopo No. 47 Surabaya 60132, Indonesia.

E-mail: diah-s-e@fkg.unair.ac.id

Linear Gingival Erythema (LGE) also one of the seven oral manifestations that commonly associated with HIV infection. LGE referred as HIV/AIDS gingivitis is the most common form of HIV/AIDS-associated periodontal disease¹⁰. It is considered resistant to conventional plaque-removal therapies, being considered nowadays as lesion of fungal etiology. Some data indicate a relationship between LGE and colonization of Candida species that can be conclude that LGE is another variant type form candidiasis in HIV/AIDS patients¹¹. LGE characterized clinically by a red fired, linear band 2 to 3 mm wide on the marginal gingival accompanied by petechiae-like or diffuse red lesions on the attached gingival on the oral mucosa may be accompanied by bleeding¹². The prevalence of this lesion varies widely in different studies, ranging from 0 to 48%, although LGE was often misdiagnosed as chronic gingivitis marginalis¹³.

The aim of this study was to investigate LGE with its correlation with Candida infection and CD4+ counts in HIV-infected patient in UPIPI RSUD Dr. Soetomo 2014.

Materials and methods

This an analytical observational research with cross-sectional and total sampling method. All patients has been agreed to join this study by filled informed consent. This study was approved by the institutional ethics committee, RSUD Dr. Soetomo Surabaya (301/Panke. KKE/VI/2014 20 June 2014).

The samples consisted of 88 HIV/AIDS HIV seropositive patients treated in UPIPI RSUD Dr. Soetomo Surabaya from July-August 2014. Diagnosis of HIV infection have been done by Internal Medicine Department Tropic Disease Division and Clinical Pathology RSUD Dr. Soetomo Surabaya following the standard protocol at Integrated Counselling and Testing Centre that employs pretest and posttest counselling and filled informed consent before HIV testing. Three different rapid tests were used to detect HIV-1 and HIV-2 antibodies (CombAids (Span Diagnostics Ltd.), Retrocheck HIV (Qualpro Diagnostics), and Tri-Line (Rapid Diagnostics) following the manufacturer's instructions. CD4+ counts obtained from patient's medical record.

All the patients were recruited for Candida microbial screening. Clinical specimens including

oral swabs were collected. Diagnosed of LGE by fungal test and clinical appearance, the oral cavity of research subjects examined by dentists specialized in Oral Medicine from Instalation of Dental and Oral Health, RSUD. Dr. Soetomo Surabaya and Department Oral Medicine, Faculty of Dental Medicine, Universitas Airlangga Surabaya

The samples were subjected to direct microscopy Potassium Hydroxide (KOH) preparation. In KOH-Calcofluorescent-stain method fungal characteristics like hyphae, yeast cells, and other fungal elements will fluorensce. Fungal culture was done on Sabouraud dextrose agar (SDA). Specimens were streaked and incubated at 37°C. Fungal growth was identified by colony morphology. Candida species identification based on carbohydrate utilization.

Correlation LGE, Candidia Infection, and CD4+ counts was determined using Pearson's test with $p < 0.05$. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) 17.0 software for windows 8.1 by SPSS Inc, Chicago, United State.

Results

In this study, there were 7 HIV/AIDS Patient with LGE cases (7.95%) associated with positive candida infection. Most of LGE cases can be found 26-35 years old patients group (57%) and most of them are male (86%) that can be seen in Figure 1, 2 and 3. In this study, there were Candida species in 7 LGE cases.

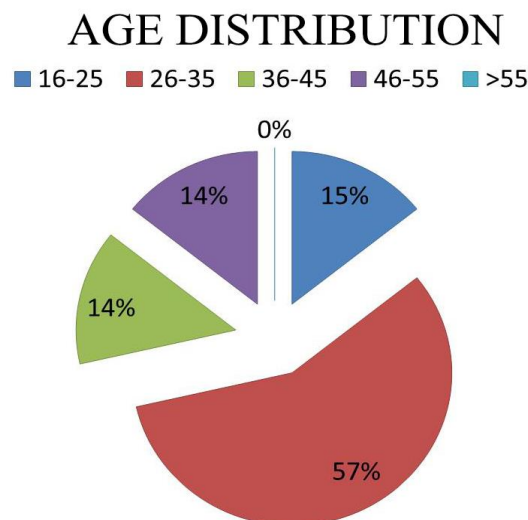


Figure 1. Age distribution of HIV/AIDS patients with LGE.

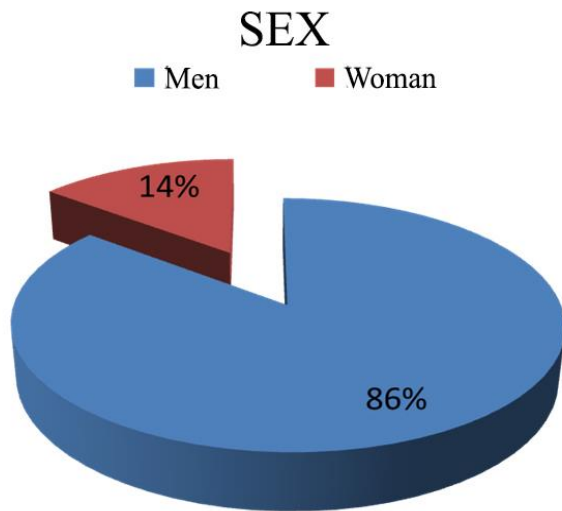


Figure 2. Sex distribution of HIV/AIDS patients with LGE.

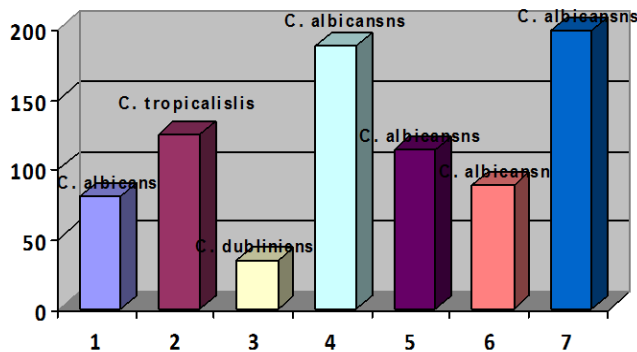


Figure 3. Candida species in seven LGE lesion with decreased CD4+ count <200 cells/mm³.

Most of them are *C. albicans* (71.43%) with decreased CD4+ count <200 cells/mm³, that can be seen in Figure 4. Pearson's Correlation Test showed that there was a correlation between the LGE and Candida infection on a significant level of 0,0092 ($p < 0.05$) and decrease of CD4+ counts on a significant level of 0,0045 ($p < 0.05$).



Figure 4. (A) 28 years old male, (B) 30 years old, (C) 35 years old, (D) 45 years old patients with LGE and OC, (E) 25 years old in fixed orthodontic treatment with LGE.

Discussion

HIV/AIDS is a serious universal health problem and most common example of an emerging infectious disease. Indonesia on 3rd highest country in Asia Pacific with the most widely HIV/AIDS cases, around 610.000².

The cases of LGE in this study are greater than the number that shown in previous study at UPIPI in 2011 found 5 cases of LGE (11%)¹². Periodontal lesion as oral manifestations tend to increase, it was not caused by plaque and calculus conditions but caused by immunodeficiency condition that occur in HIV/AIDS¹³.

LGE occur because of Candida infection in the subgingiva plaque. The microflora of LGE are similar with other periodontal lesions such as gingivitis and periodontitis¹⁴. The correlation of oral candidiasis and LGE were suspected. Microscopic examination of LGE shown *C. Dubliniensis* in 4 HIV/AIDS patient which had administered sytemic antifungal. The Etiology of LGE and its corelation with Candida infection are not clear yet.¹⁵

The previous study shown a subgingival plaque of HIV/AIDS patients with high viral load and low level of CD4⁺. *Saccharomyces cerevisiae* as the only fungal species that were detected in LGE, while *C. albicans* are not. *C. albicans* were detected in microbiology examination of LGE lesion from HIV/AIDS patients with low viral load and high level of CD4⁺¹⁶. The pathobiogenesis of LGE are unexplained yet¹⁷.

LGE mostly found in patients of HIV/AIDS with CD4⁺ < 200 cells/mm³¹³. The decrease of CD4⁺ lymphocytes cells cause decreased of imunne system and may cause the risk of opportunistic infection increased. This symptoms of opportunistic infections depend on the etiology of the infections^{17,18,19}.

There were significant correlation between LGE and OC ($p < 0,05$). The occurence of Candida infection always associated with OC in patiens of HIV/AIDS. Candida actually comensal, but the decrease of sIgA (secretory Immunoglobulin A) and also the decrease of lymphocytes T cell become patogen²⁰.

In the previous study, *C. albicans* was the most frequent species found from the isolation in five from seven patients, which confirm that the main etiologic agent of oral candidiasis. A mixed

culture of *C. albicans* and *C. Tropicalis* confirmed the association with other species rather than *C. albicans* isolated from oral candidiasis. One patient exhibited positive growth for *C. dubliniensis* indicating that this species is also present. Previous study also demonstrated the presence of *C. dubliniensis* in subgingival of HIV-positive patients indicating that this species has emerged as another pathogen in vitro potential for azole resistance and enhanced adherence to human buccal epithelial cells^{15,18,21}.

Pathobiogenesis of OC strongly correlated with HIV/AIDS due to TAT (Trans-Activating Transduction or Activator Transcription) that have been produced in early cycle of viral replication^{22,23}. Interaction between HIV TAT protein with *C. albicans* cell's wall allows the transduction of gen that form specific pathway of hyphae (Hypal Spesific Genes, HSG)²⁴.

Conclusions

LGE has a significant correlation with Candida infection and decreased level of CD4+ counts in HIV/AIDS patients at UPIPI RSUD Dr Soetomo.

Acknowledgements

The authors would like to thank the Universitas Airlangga (UNAIR), Faculty of Medicine and Faculty Dental Medicine, RSUD Dr. Soetomo Surabaya doctor, dentist, all paramedic and patients of UPIPI RSUD Dr. Soetomo who participated in data collection.

Declaration of Interest

The authors report no conflict of interest.

References

1. Nasronudin. HIV&AIDS pendekatan biologi molekuler, klinis dan sosial. 1st ed. Airlangga University Press. Surabaya: 2007,5:215.
2. Join United Nations Programme on HIV/AIDS (UNAIDS). 2013 Global Report on the Global AIDS epidemic. Journal of Epidemiology 2013;1(3): 5-6.
3. Kementrian Kesehatan RI. Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan. Pedoman nasional Tatalaksanaan Klinis Infeksi HIV dan Terapi Antiretroviral pada Orang dewasa. Jakarta. 2014; 1-2.
4. Spiritia. Infeksi HIV/AIDS. Jurnal Penyakit Dalam. 3(3) 5-7. Available atspiritia.or.id/li/bacali.php?lino=508. Accessed September 21, 2014.
5. Unit Perawatan Intermediet Penyakit Infeksi (UPIPI). Laporan Triwulan I 2014 HIV/AIDS. RSUD Dr. Soetomo Surabaya Press. Surabaya. 2014:1.

6. Coogan MM., Greenspan J., Challacombe S.J. Oral Lesion in Infection with Human Immunodeficiency Virus. *Bulletin of the World Organization*. 2010; 83:700-706.
7. Ramadian E.E, Pradono S.A, Wimardhani Y.A., Successful Treatment of Persistent Oral Ulcers in Patients with HIV / AIDS. *Journal of International Dental and Medical Research*. 2016; 9 (Special Issue, U.I. 1st International Workshop on Dental Research): 98-402.
8. Vaseliu N., Kamiru H., Kabue M. Oral Manifestation of HIV Infection. HIV Curriculum for the Health Professional. Available hivdent.org. Accessed May 2th, 2014. *J Stomatology*. 2011;7(6):53-55.
9. Ukpebor M., Braimoh O.B. HIV/AIDS; Oral Complications And Challenges, The Nigerian Experience. Nigeria. *Research Article Issue*. Benin City-Nigeria. 2012; 4: 44.
10. Lamster IB, Grbic JT, Mitchell-Lewis DA, Begg MD, Mitchell A. New concepts regarding the pathogenesis of periodontal diseases in HIV infection. *An Periodontal* 2008; 3: 62-75.
11. Swastika N., Gawande M., Chaudhary M., Patil S., Oral Candidal Carriage In Subgingival Sites And Its Subspecies Identification In Diabetic And Non-Diabetic Patients With Periodontitis. *Journal of International Dental and Medical Research*. 2013;6(2):69-73.
12. Hartanto B., Hendarti HT., Soebadi B. Prevalensi lesi oral yang terkait erat dengan HIV pada penderita HIV/AIDS di UPIPI RSUD Dr. Soetomo Surabaya. *Oral Medicine Dental Journal*. 2011; 3(1):1.
13. Portella BM., Cerqueira DF., Soares. Candida Spp in linear gingival erythema lesions in HIV-infected children : reports of six cases. Available <http://www.ijosd.uff.br/index.php/n37/article/viewFile/117/83>. Accessed November 24, 2014.
14. Chaurasia A., CD4+ counts and Oral Lesions in HIV infected/AIDS patients- an Indian Perspective. *Juniper Online Journal Case Study*. Juniper Publisher. 2017;1(5):1-3.
15. Portela MB, Souza IP, Costa EM, Hagler AN, Soares RM, Santos AL. Differential recovery of Candida species from subgingival sites in Human Immunodeficiency Virus-Positive from Rio de Janeiro, Brazil. *J Clin Microbiol* 2004; 42: 5925-7.
16. Aas JA., Barbuto SM., Alpagot T., Olsen I., Dewhirst FE., Paster BJ. Subgingival plaque microbiota in HIV positive patients. *Journal of Clinical Periodontology*. Havard. 2007;34:189-195.
17. Frimpong P., Amponsah E.K, Abebrese J., Kim S.M., Oral manifestations and their correlation to baseline CD4 count of HIV/AIDS patients in Ghana. *Korean Assoc Oral Maxillofac Surg*. South Korea. 2017; 43(1): 29–36.
18. Mukherjee P.K., Patton C.H, Evans L.L, Anthony S.L., Hakim K.J., Gaerolwe J.M., Frederick S., Pho M.T., Kenneth A.F., Shiboski C.H., Ghannoum, M.A., Salata R.A., Topical gentian violet compared with nystatin oral suspension for the treatment of oropharyngeal candidiasis in HIV-1-infected participants. The Oral HIV/AIDS Research Alliance (OHARA) AIDS Clinical Trials Group (ACTG) 5265 Team AIDS. 2017; 31(1): 81–88.
19. Alimonti JB., Ball TB., Fowke KR. Mechanism of CD4+ T Lymphocyte cell Death in Human Immunodeficiency Virus Infection and AIDS. *Journal of General Virology*. 2003; 84:1649-1661.
20. Kartono AF., Soebadi B., Radithia D. Prevalensi Angular Cheilitis pada Waria Penderita HIV/AIDS di PERWAKOS. *Oral Medicine Dental Journal* Vol. 6 No. 2 July-December. 2014; 6(2):40-47.
21. Knights H.D.J. A Critical Review of the Evidence Concerning the HIV Latency Reversing Effect of Disulfiram, the Possible Explanations for Its Inability to Reduce the Size of the Latent Reservoir In Vivo, and the Caveats Associated with Its Use in Practice. <https://doi.org/10.1155/2017/8239428>. *AIDS Research and Treatment*. 2017; 7.
22. Perfettini JL., Castedo M., Roumien T., Andreau K., Nardacci R., Piacentini M., Kroemer G. Mechanism of Apoptosis Induced by The HIV-1 Envelope. doi:10.1038/sj.cdd.4401584. *Cell Death and Differentiation*. 2005;5(12):916-923.
23. Vaags, A.K, Campbell, T.N. & Choy, F.Y.M. HIV TAT Variants differentially influence the production of glucocerebrosidase in Sf9 cells. *Online Journal: Genetic and Molecular Research*. 2005; 4(3): 10-12.
24. Harper, Kristin N. HIV-altered gut microbiome may be driving disease progression AIDS. The Oral HIV/AIDS Research Alliance (OHARA) AIDS Clinical Trials Group (ACTG) 5265 Team AIDS. 2017; 31(2): N1.