

Journal of Dentistry Indonesia 2016, Vol. 23, No.2, 54-58
doi:10.14693/jdi.v23i2.992

CASE REPORT

Oral Hairy Leukoplakia: Clinical Indicator of an Immunosuppressive Condition and Challenges in Patient Management

Yohana Alfa Agustina¹, Indriasti Indah Wardhany², Yuniardini Septorini Wimardhani², Ening Krisnuhoni³, Anak Iamaroon⁴

¹*Oral Medicine Residency Program, Faculty of Dentistry, Universitas Indonesia, Jakarta 10430, Indonesia*

²*Department of Oral Medicine, Faculty of Dentistry, Universitas Indonesia, Jakarta 10430, Indonesia*

³*Department of Anatomical Pathology, Faculty of Medicine, Faculty of Dentistry, Universitas Indonesia, Jakarta 10430, Indonesia*

⁴*Department of Oral Biology and Diagnostic Sciences, Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand*

Correspondence e-mail to: yohanaalfa@yahoo.co.id

ABSTRACT

Oral hairy leukoplakia (OHL) is defined as an asymptomatic white patch with vertical corrugation pattern the lateral borders of the tongue, that is associated with Epstein-Barr Virus (EBV) infection. Generally, it is related to immunosuppressive condition found in HIV-positive patients and patients undergoing immunosuppressive therapy. Sometimes, its clinical appearances could mimic other white lesions. Although most OHL cases are found in HIV seropositive individuals, finding in the immunocompetent individuals has also been reported. Appropriate clinical evaluations and laboratory investigations are important for patient's comprehensive management. **Objective:** To report a finding of oral hairy leukoplakia as a clinical indicator of an immunosuppressive condition in otherwise a clinically healthy-looking individual and to discuss the challenges on patient management. **Case Report:** A 40 year-old man presented with asymptomatic, bilateral homogenous white hyperkeratotic plaques with a hairy appearance located on the dorsal of the tongue, extended to the lateral tongue mucosa. The patient failed to remember the lesion's first appearance, until three weeks before a visit. Working diagnosis of OHL was made with differential diagnoses including white sponge nevus, leukoplakia and oral lichen planus. Histopathological assessment was consistent with OHL. Challenges on patient management include identifying possible risk factors and assuring patient for HIV testing. **Conclusion:** This case reported findings of OHL as the first clinical indicator of immunosuppressive condition that might be related to HIV-infection.

Keywords: Acquired Immunodeficiency Syndrome, Epstein-Barr Virus, Human Immunodeficiency Virus, oral hairy leukoplakia

INTRODUCTION

Oral hairy leukoplakia (OHL) is a white lesion commonly found in individuals with immunodeficiency. OHL is a unique white lesion presenting as an asymptomatic white patch with a vertical corrugation pattern on the lateral border of the tongue and associated with Epstein-Barr Virus (EBV) infection.¹ OHL could be an early indicator of immunosuppression such as hematologic malignancies, long-term uses of systemic steroid, undiagnosed HIV/AIDS. It is an indicator

of those who in the progression of state of AIDS for example seropositive homosexual men.² In general, OHL is recognized as a form of an opportunistic infection associated with HIV infection. The ability to recognize the manifestations of systemic conditions is a key in providing a comprehensive care with an early appropriate medical intervention in order to reduce the mortality rate of patients and enhancing the quality of life.^{3,4}



Figures 1(a)-(d). The homogenous hairy white patches along the dorsolateral border and ventral tongue surfaces.

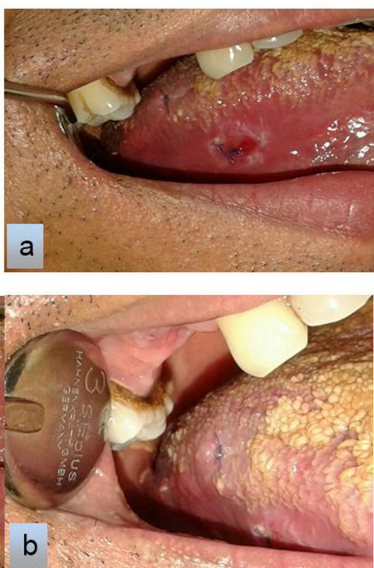


Figure 2. (a) The clinical feature reveals the lesion on the right dorsolateral surface of the tongue where the biopsy was performed; (b) The clinical feature showed a completely healed wound on the following visit.

OBJECTIVE

The objective of this case report was to present a finding of OHL as a clinical indicator of an immunosuppressive condition in a clinically healthy-looking individual and to discuss the challenges on patient management.

CASE REPORT

A 40 year-old man who looked apparently healthy came to the Dental Hospital Universitas Indonesia, complaining of the appearance of asymptomatic bilateral white plaques located on the dorso lateral

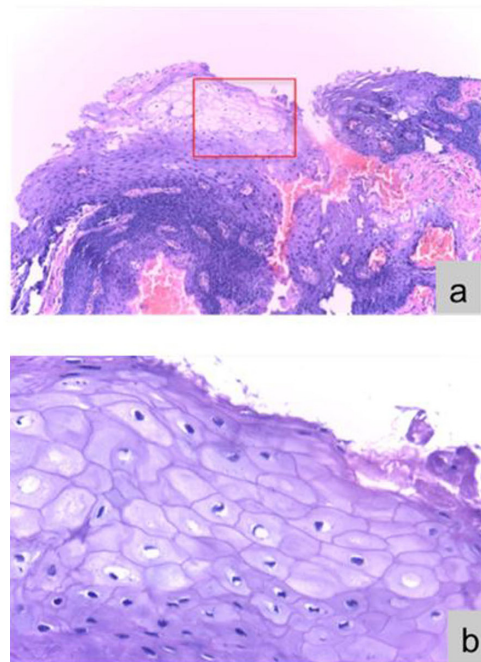


Figure 3. (a) Ballooning degeneration of the epithelial cells in the stratum spinosum was demonstrated (H&E, original magnification x100); (b) Higher magnification showed perinuclear halos and peripheral margination of the chromatin in the nuclei of the spinous cells (H&E, original magnification x400).

borders of his tongue. The patient failed to remember the lesion's first appearance, until three weeks before this visit. The patient was worried that the appearance of white patches on the tongue was a sign of malignancy especially cancer of the tongue or HIV infection. He had never been tested for HIV before. He denied any medical problems, risks or lifestyles associated with HIV infection. The patient reported no fever or pain when swallowing or chewing. Numbness and a burning sensation on the tongue were also denied. The intraoral examination showed bilateral white hyperkeratotic homogenous patches on the lateral borders of the tongue along the region of teeth 34-37 and 44-47. The lesions appeared to spread downwards to the ventral surfaces of the tongue and were unscrapable, painless, hairy or corrugated in appearance and showed no induration or erythema (Figure 1 a-d).

The working diagnosis of oral hairy leukoplakia was made with differential diagnoses of white sponge nevus, leukoplakia and oral lichen planus. In order to obtain the definitive diagnosis, the patient was scheduled for biopsy for histopathology examination. On the following visit, the intraoral examination revealed white patches with erythematous borders that could be scrapped off on the soft palate and both sides of buccal mucosae. These clinical appearances were consistent with pseudomembranous candidiasis.

On that visit, the patient was prescribed with nystatin oral suspension four times daily for two weeks. He was scheduled for biopsy and basic blood laboratory tests in two-week time at the Department of Oral and Maxillofacial Surgery.

On the day of the biopsy, intraoral examination showed that the pseudomembranous candidiasis lesion did not completely disappear. The patient admitted that he was not properly adhered on taking medication prescribed. He was then prescribed with twice daily 50 mg of Fluconazole orally for 7 days. Biopsy was performed (Figure 2a) and the specimen was sent for histopathological assessment at the Department of Anatomic Pathology, Faculty of Medicine, University of Indonesia. On the following visit, intraoral examination showed complete healing of the wound at the operation site (Figure 2 a,b). Finally, the histopathological assessment confirmed that the white lesion was consistent with OHL exhibiting the ballooning spinous cells without any sign of dysplastic changes (Figure 3 a,b).

Two weeks after the biopsy, the patient was scheduled for private consultation about the results of the histopathologic assessment of OHL. The patient was concerned about the definitive diagnosis of the lesion and its connection with HIV infection. The patient was then given explanations about OHL as an indicator of HIV infection and a lifestyle related to the lesion. Unexpectedly, the patient became uneasy and worried about what he was told. He decided to leave the clinic and asked for another appointment. We informed the patient that the diagnosis of HIV infection could not be done only by having a clinical examination. In fact, he still needed some tests to confirm the diagnosis. In addition, it was essential for him to have pre- and post-counseling about HIV infection and referral to the internal medicine when the definitive diagnosis was made. Reassurance and supports were given to the patient continuously. Although the patient did not decide to be scheduled for another appointment, he promised he would receive the treatment when he was ready. In fact, for two months, we got communication by phone, for consulting the test and assuring medication. Then after 3 months, the patient came to the Dental Hospital, and give the result of the test. He told us that he was positive HIV, in which CD4 is 38. He also took the ARV medication. On the oral examination, the lesion of OHL was remission after he consumed ARV medication. The manajement of this patient was completely resolved, with the remission of the OHL lesion, and the patient was under ARV treatment by internist.

The lesion of OHL can be diagnosed by clinically and histopathological examination. We confirm that in most cases, oral hairy leukoplakia can be diagnosed clinically and does not require a confirmatory biopsy. It does not require specific treatment and frequently

resolves under HAART or ARV medication, if associated with HIV infection.

DISCUSSION

Oral hairy leukoplakia is one of the most common early lesions in immunocompromised patients. OHL is a flat, corrugated or hairy lesion usually located on the lateral border of the tongue, unilaterally or bilaterally. OHL cannot be removed by scraping.^{5,6} Generally, OHL is related to immunosuppressive conditions found in HIV-positive patients and patients undergoing immunosuppressive therapy. Although most OHL cases are found in HIV-seropositive individuals, finding in the absence of immunosuppression has also been reported. Previous studies have suggested that OHL is an early indicator of HIV infection and be related to the progression of AIDS.¹ Although typically, the clinical feature of OHL is unique, its clinical appearances in some cases may mimic other oral white lesions suggesting a confirmation of the diagnosis by histopathologic examination in those cases. Oral white lesions that could have similar appearances to OHL include oral white sponge nevus, chronic hyperplastic candidiasis, pseudomembranous candidiasis, oral lichen planus, idiopathic oral leukoplakia, frictional keratosis, geographic tongue and “galvanic” lesions.^{3,6}

Etiologically, OHL is believed to be associated with an infection with EBV, a double-stranded DNA virus that can replicate in the epithelial cells as a primary site. Based on the histopathological examination, an absence or a high reduction of Langerhans cells in the lesion was reported. Langerhans cells are the antigen-presenting immune cells that are responsible for viral infection.⁷ Detection of EBV DNA in the epithelial cells was studied in 25 OHL cases by using noninvasive diagnostic techniques, the filter in situ hybridization (FISH) and cytospin in situ hybridization (CISH). The results showed that all cases were EBV-positive by FISH, and 23 cases were EBV-cases by CISH.⁸ By combined methods of immunohistochemistry, DNA in situ hybridization, and lectin histochemistry, the life cycle of EBV in the keratinocytes, in which both EBV protein and DNA were found, was identified.⁹ Moreover, the pathogenesis of OHL was suggested to be involved in a migration of the EBV-infected monocytes/macrophages from the submucosa into the spinosum or granulosum layer of the oral epithelium.¹⁰

As the AIDS disease progresses, reflected by a continual loss of CD4 lymphocytes, the oral cavity becomes more susceptible to various oral lesions as shown in Table 1.¹¹ Candidiasis was the most common lesion seen in patients with CD4+ counts less than 200 (28 cases), followed by periodontitis (7 cases). OHL was found in three patients with CD4+ counts less than 200, and one patient with CD4+ counts at the range of 200- 499.¹¹

Table 1. Oral manifestations related to CD4+ counts

CD4+ count cell/mm ³	Periodontitis	Gingivitis	Herpes	Candidiasis	Hairy Leukoplakia	Ulceration	Kaposi's Sarcoma	Non Hodgkin Lymphoma
<200	7	3	3	28	3	1	3	1
>200 <499	9	2	2	9	1	3	0	0
>500	1	0	0	1	0	0	0	0

The histology examination of OHL shows acanthotic parakeratinized stratified squamous epithelium with finger-like projections, giving a clinical feature of a corrugated or hairy appearance. Typically, the upper spinous cell layer reveals the presence of the koilocytes occurred by ballooning degeneration of the epithelial cells.^{12,13} Microscopically, the koilocytes are the vacuolated spinous cells with pyknotic nuclei and perinuclear halos.

There is a specific patient's management of OHL especially for undiagnosed HIV infection, especially good communication by giving the right information about the risk factors of OHL including HIV infection. The dentists who are get involved need to be skillful in interviewing patients and good listeners to get the information about patient's lifestyle that might be related to a risk factor for HIV infection. For undiagnosed HIV-infected persons, the principal patients' management focuses on restoring the patient's comfort, eliminating secondary infections of bacteria, viruses and fungi, and preventing the possibility of other oral diseases.⁵ The pre-test counseling for undiagnosed HIV patients with a consideration of the human rights is also needed.¹⁴

There are three principles of HIV testing, (the "three Cs") are established as norms: *counseling* and information providing about HIV/AIDS before and after the test; *consent* to tests by suspicious individuals in an informed, specific, and voluntary way; and *confidentiality* of the test results and the fact of seeking a test.¹⁴ Moreover, the strategies of relaxing counseling by reducing stigma and discrimination related to HIV infection or AIDS would give patient's confidence to talk about history of his/her life style and lead to patient's decision making to have a test for HIV infection.¹⁴ There are rapid HIV screening tests for antibodies against the HIV in individuals who have initially infected within a month and a half to up to six months. It is important to note that during the initial infection before the development of the antibodies, a stage known as "acute HIV infection," those individuals will not have a positive test result and could make a greater risk of transmission.¹⁵ It was reported that undiagnosed HIV infection is a major drive of the transmission of HIV causing the incidence of HIV infection in the United States of over 50,000 annually. It was described that 18 % of infected persons nationally are unaware of their HIV status. In fact, 44-66 % of new HIV infections are attributed to this modest proportion of individuals with undiagnosed

HIV.¹⁶ Therefore, to eliminate the global HIV/AIDS epidemic, there is a need for an action to promote the "seek, test, treat, and retain" (STTR) strategy. This strategy consists of seeking people at risk who have not been recently tested for HIV infection (seeking), engaging them in HIV testing (testing), initiating, monitoring, and maintaining treatment for those testing positive (treating) and retaining patients in care (retaining).¹⁶ One of the seeking strategies is to detect the oral lesion that could show a clinical sign of the immunodeficiency status of HIV. In 2009, the Government of Canada initiated the Seek and Treat Strategic for Optimal Prevention of HIV/AIDS in BC (STOP HIV/AIDS in the British Columbia province, BC). As a result, the morbidity, mortality, and new HIV diagnoses have continued to decrease steadily in BC.¹⁷ In China, the number of people being tested for HIV had increased almost four folds b 2007 to 101 million in 2012, between 2007 to 2012. The number of newly identified HIV cases had increased from 48,074 to 82,434 cases. Subsequently, started in 2011, China has taken further steps to promote HIV testing and treatment particularly targeting people at risk of HIV infection in each province across the nation. This effort has significantly improved the identification of infected individuals and the number of new patients receiving earlier treatment has increased, leading to a reduction in the mortality rate of patients.¹⁷ In an Asia-Pacific region, there were 350000 newly HIV-infected individuals especially who were the drug users and homosexuals or transgender persons. HIV-infected homosexuals in Indonesia, India, Malaysia and some certain other Asian countries are considered inaccessible and victimized because of the stigma, discrimination, and injustice against.⁴ Collectively, a proper management and counselling in newly HIV-infected individuals have to be established and a screening of the oral cavity of HIV-infected persons is suggested to be regularly performed.⁴

In Indonesia, the Ministry of Health of Indonesia reported that there were totally 150,296 HIV-infected individuals and 55,799 patients with AIDS from 1987 until September 2014 and 7335 HIV-infected individuals and 176 patients with AIDS during the quarter of July to September 2014. The modes of transmission include heterosexual (34,305), homosexual/bisexual (1,366), Injecting Drug Users (IDU) (8,462), blood transfusion (130) and perinatal transmission (1,506), and unknown (9,536).¹⁸ The AIDS epidemic in Indonesia (2007) showed the prevalence of HIV infection among different groups of people

as follows; 10.4% among direct sex workers; 4.6% among indirect sex workers; 24.4% among transgender; 0.8% among the clients of female sex workers; 5.2% among MSM; and 52.4% among IDU. Interestingly, it was found that the transmission of HIV infection is rising among MSM.¹⁹ To eliminate the rising of the transmission, the interventions of Government of Indonesia is needed by providing supportive policies to the key populations, promoting the use of condoms, and reducing stigma and discrimination against HIV-infected individuals and patients with AIDS especially the MSM group.¹⁹

CONCLUSION

In summary, OHL could be an early sign of undiagnosed immunosuppression, particularly who might be undergoing the progression of HIV infection as reported here. The goal of the patient's management was to establish the definitive diagnosis and to assure the patient to immediately have tests for HIV infection and CD4 counts.

CONFLICT OF INTEREST

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias the conduct and findings of this study.

REFERENCES

1. Brasileiro CB, Abreu MH, Mesquita RA. Critical review of topical management of oral hairy leukoplakia. *World J Clin Cases*. 2014;2:253-6.
2. Coogan MM, Greenspan J, Challacombe SJ. Oral lesions in infection with human immunodeficiency virus. *Bull World Health Organ*. 2005;83:700-6.
3. Reginald A, Sivapathasundharam B. Oral hairy leukoplakia: An exfoliative cytology study. *Contemp Clin Dent*. 2010;1:10-3.
4. Sharma G, Oberoi SS, Vohra P, Nagpal A. Oral manifestations of HIV / AIDS in Asia : Systematic review and future research guidelines. *J Clin Exp Dent*. 2015;7:e419-27.
5. Bravo IM, Correnti M, Escalona L, Perrone M, Brito A, Tovar V, et al. Prevalence of oral lesions in HIV patients related to CD4 cell count and viral load in a Venezuelan population. *Med Oral Pathol Oral Cir Bucal*. 2006;11:E33-9.
6. Greenspan JS, Greenspan D, Webster-Cyriaque J. Hairy leukoplakia; lessons learned: 30-plus years. *Oral Dis*. 2016;22Suppl 1:120-7.
7. Daniels TE, Greenspan D, Greenspan JS, Lennette E, Schiødt M, Petersen V, et al. Absence of Langerhans cells in oral hairy leukoplakia, an

- AIDS-associated lesion. *J Invest Dermatol*. 1987;89:178-82.
8. De Souza YG, Freese UK, Greenspan D, Greenspan JS. Diagnosis of Epstein-Barr virus infection in hairy leukoplakia by using nucleic acid hybridization and noninvasive techniques. *J Clin Microbiol*. 1990;28:2775-8.
9. Rabanus J, Greenspan D, Petersen V, Leser U, Wolf H, Greenspan JS. Subcellular distribution and life cycle of Epstein-Barr Virus in keratinocytes of oral hairy leukoplakia. *Am J Pathol*. 1991;139:185-97.
10. Tugizov S, Herrera R, Veluppillai P, Greenspan J, Greenspan D, Palefsky JM. Epstein-Barr Virus (EBV)-infected monocytes facilitate dissemination of EBV within the oral mucosal epithelium. *J Virol*. 2007;81:5484-96.
11. Berberi A, Noujeim Z. Epidemiology and relationships between CD4+ counts and oral lesions among 50 patients infected with Human Immunodeficiency Virus. *J Int Oral Health*. 2015;7:18-21.
12. Moffat M, Jauhar J, Jones ME, MacDonald DG, Felix DH. Oral hairy leukoplakia in an HIV-negative, immunocompetent patient. *Oral Biosci Med*. 2005;4:249-51.
13. Dias EP, Rocha ML, Silva Júnior A, Spyrides KS, Ferreira SM, Polignano GA, et al. Oral hairy leukoplakia. Histopathologic and cytopathologic features of a subclinical phase. *Am J Clin Pathol*. 2000;114:395-401.
14. Jürgens=R, Cohen J, Girard F, Beyrer C. Increasing access to HIV testing and counselling while respecting human rights. *HIV AIDS Policy Law Rev*. 2007;12:63-6.
15. Ka Cyrilliciriazova TK, Neduzhko OO, Kang Dufour M, Culiba RJ, Myers JJ. Evaluation of the effectiveness of HIV voluntary counseling and testing trainings for clinicians in the Odessa region of Ukraine. *AIDS Behav*. 2014;18 Suppl 1:S89-95.
16. Gwadz M, Cleland CM, Hagan H, Jenness S, Kutnick A, Leonard NR, et al. Strategies to uncover undiagnosed HIV infection among heterosexuals at high risk and link them to HIV care with high retention: a "seek, test, treat, and retain" study. *BMC Public Health*. 2015;15:481.
17. Gustafson R, Montaner J, Sibbald B. Seek and treat to optimize HIV and AIDS prevention. *Can Med Assoc J*. 2012;184:1971.
18. Indonesian General Directorate of Communicable Disease Control and Environmental Health. [Cases of HIV/AIDS in Indonesia Reported through September 2014] [internet] Available from: <http://spiritia.or.id/Stats/StatCurr.pdf>
19. National AIDS Commission. National HIV and AIDS Strategy and Action Plan 2010 – 2014. [internet]. Available from: http://www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/legaldocument/wcms_173075.pdf

(Received February 21, 2016; Accepted May 12, 2016)