Oral Hairy Leukoplakia: A Predictor and Prognostic Factor of HIV Infection

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Abstract: Introduction: Oral hairy leukoplakia (OHL), also known as benign hyperplasia of oral mucosa, is an asymptomatic white corrugated plaque that is most commonly found on the lateral borders of the tongue. This condition is caused by Epstein-Barr Virus (EBV). OHL is commonly found in immunocompromised patient, with the prevalence around 20-25% among HIV patients and indicates decline of CD4 counts. Case: A 29 year-old-male came to the Dermato-Venereology Outpatient Clinic of Dr. Soetomo General Hospital Surabaya with complaint of persistent asymptomatic whitish color on lateral side of his tongue. From history taking, the lesion was first appeared all over the tongue, and after consumption of antifungal treatment, the lesion subsided and persisted only on lateral border of the tongue. There were history of diarrhea, fever and cough for almost 1 month. He also has multiple sexual partners. From physical examination, we found painless white demarcated plaque with corrugated appearance on the left lateral border of the tongue. Further examination on HIV panels using three methods showed reactive result. Based on history taking, clinical and laboratory findings, the patient was diagnosed with OHL and HIV. The patient was treated with Acyclovir 800 mg, 5 times daily, and HAART (Duviral 2x1 tab + Neviral 1x1 tab). After 2 weeks of treatment, the lesion disappeared. Conclusion: The appearance of OHL is commonly associated with immunocompromised condition. The establishment of OHL has a diagnostic value for HIV infection. Systemic antiviral therapy and prevention of recurrence using antiretroviral medication showed satisfying result.

1 INTRODUCTION

Oral Hairy Leukoplakia (OHL) which also known as benign epithelial hyperplasia of oral mucosa, is an oral mucosal lesion associated with infection and replication of the Epstein-Barr virus (EBV) (Murtiastutik et al., 2008). The clinical presentation of OHL is a painless, white proliferative oral epithelial lesion that usually occured on the lateral margins of the tongue. This white patch is non-removable, with wide variation in size, severity, and surface characteristics.

OHL has been listed in the classification of oral lesions as a Group I lesion strongly associated with HIV infection (Classification and diagnostic criteria for oral lesions in HIV infection, 1993; Uihlein et al., 2011). It is also considered as a marker of poor prognosis that frequently precedes the onset of acquired immunodeficiency syndrome (Kreuter & Wieland, 2011). The lesion usually presents itself when the CD4 cell counts fall below $0.3x10^9$/L (Bravo et al., 2006). However, OHL is also found in other immunosuppressive non-HIV condition, such as transplant recipients, in patients with hematological malignancies, and in patients required under systemic steroid treatment (Piperi et al., 2010).

HIV is a lymphotropic human retrovirus, which is predominantly transmitted through sexual contact. HIV is also transmitted through exposure to infected blood (i.e needles shared by injecting drug users) and transmission from infected mother to her infant during pregnancy, delivery or breastfeeding (Uihlein et a., 2011). OHL has been associated with more rapid progression to AIDS with HIV viral loads exceeding 20.000 copies/ml, and with CD4+ counts below 200/mm^8 or $0.3x10^9$/L (Bravo et al., 2006).
A case of OHL in 29-year-old patient who was later diagnosed with HIV positive is reported. The diagnosis was established by history taking, physical

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examination, and later the establishment of HIV diagnose. This report discusses the clinical manifestation, diagnosis and treatment of this condition.

2 CASE

A twenty-nine-year-old Javanese male came to the Outpatient Clinic of Dermato-Venereology Department at Dr. Soetomo General Hospital Surabaya with the chief complaint whitish color all over the tongue since 2 months before visitation. He went to see doctor and was diagnosed with fungal infection and then prescribed ketoconazole 1 x 200 mg daily for 4 weeks. The whitish color on the middle part has gone, but parts on the borders still persist. The patient tried to remove the whitish color with tooth brush but there was no result.

The patient also complained of cough and fever for more than 2 weeks. There was also complaint of watery stool for 1 month and report of weight loss and loss of appetite. There was history of sexual relationship with multiple partners. History of sexual transmitted disease was denied. Patient has homosexuality preference.

The dermatological examination on his tongue showed bilateral painless white well demarcated plaque with corrugated appearance on the lateral borders of the tongue. The lesion can not be scrub off. Other physical examinations revealed normal findings.

The patient was consulted to the UPIPI outpatient clinic to have Voluntary Counseling and Testing (VCT) for HIV, and was told to do Rapid test and blood and urine examination. The HIV test result for all three methods (Imunochromatography, Imunodot, ELISA) were reactive.

The patient was then consulted to the internal department, and was diagnosed with s HIV stage 3. Complete blood count examination was conducted and the result was within normal limit. The absolute CD4 count was performed, and it was obtained that the absolute CD4 count was 1 cells/uL and CD4 percentage was 0.05%, considered as a very low CD4 count. The patient was also consulted to pulmonology department, and based on chest x ray and acid fast stain there was no abnormalities found, so the assessment of tuberculosis can be excluded.

A cytopathology examination was performed by scrapping of the lateral border of the tongue. From the examination, there was squamous epithelial and mononuclear inflammatory cells present. There was no dysplasia cell founded. Based on those result, it concluded that this condition caused by microorganism infection, and not a malignancy process.

Based on history taking, clinical findings and the laboratory examination, the patient was then diagnosed with Oral Hairy Leukoplakia and AIDS. The diagnosis of AIDS in this patient was obtained from the presence of OHL, reactive results of HIV panel test, and the CD4 cell count below 200/μL.

The patient was then treated with acyclovir 800 mg, administered 5 times a day, along with the administration of cotrimoxazole 1 times 960 mg as a Cotrimoxazole Prevention Treatment 2 weeks before starting the HAART. After 1 week of treatment, the lesion on the lateral border had subsided, the therapy was then continued for another week to make sure the lesion has totally disappeared. Clinical progression of the lesion

After outpatient clinic visit until the end of February 2017, patient no longer came to Dermato-venerology outpatient clinic. When we tried to contact the patient, he said he already moved to Papua for business affairs, and never come back to Surabaya ever since.

3 DISCUSSION

Oral hairy leukoplakia is a specific lesion in HIV infection caused by Epstein Barr virus, and has been reported in over more than 28% patients and is a sign of disease progression (Murtiastutik et al., 2008) OHL appear clinically as an asymptomatic, white or grayish white, well demarcated plaque with corrugated texture. The “hairy” surface vary in size and typically occurs on the lateral tongue. The lesion is painless and irremovable by blunt manipulation (Triantos et al., 1997).

In our case, the patient complaint loss of appetite regarding the lesion on his tongue. He was first treated with ketoconazole 1 x 200 mg. After given treatment for 4 weeks, the lesion subsided, but the lesion on both lateral borders persist. No pain, wound or swelling was reported.

EBV primarily transmitted through saliva as infected cells are shed into the surface of the oral mucosa. Primary infection activates the innate and adaptive immune systems, and the virus remains latent lifelong by living in circulatory B lymphocytes, which serve as the cellular reservoir (Walling et al., 2003). Severe immunosuppressive condition can lead into reactivation of EBV replication in the oropharynx of EBV-seropositive patients (Cruchley et al., 1989).

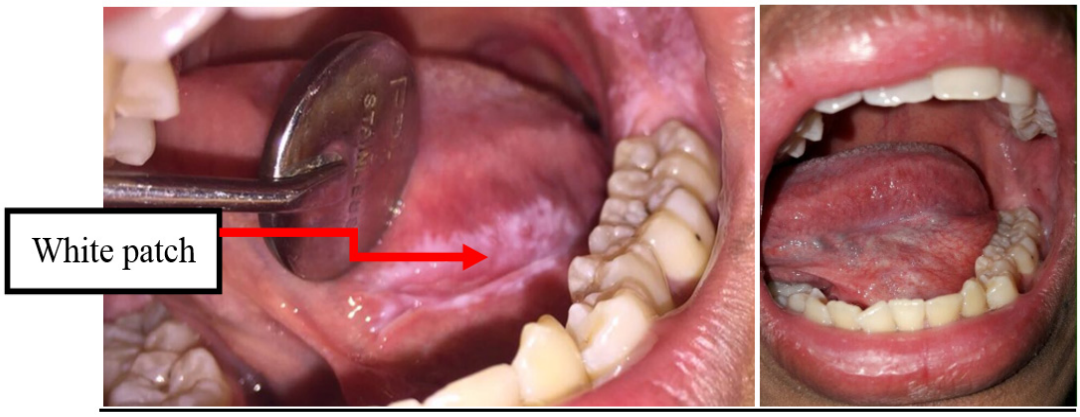

Figure 1: Patient's clinical condition before (left) and after 2-weeks-treatment (right).

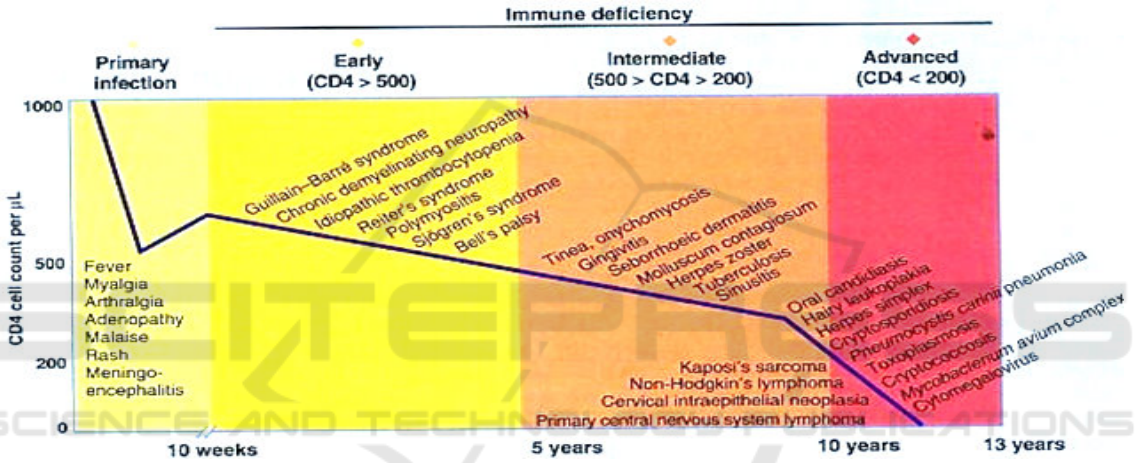

Figure 2: Opportunistic Infections Correlating with CD4+ Cell Count[11].

The lateral border of the tongue is the most common location of OHL. The development of on the tongue may be due to the accumulation of saliva in the floor of the mouth (Piperi et al., 2010). The lateral border of the tongue is also an area which prone to trauma, thus becomes a predilection area. Another explanation is the decreased number of Langerhans cells in OHL lesions compared with non lesional oral mucosa. A comparative study of normal mucosa revealed that the lowest density of Langerhans cells was found on the lateral border of the tongue and the sublingual region. Thus normal epithelium of the lateral and ventral sides of the tongue is more susceptible to EBV infection (Cruchley et al., 1989).

In our patient, from physical examination we found bilateral painless white well demarcated plaque with corrugated appearance on the lateral borders of the tongue, in accordance with the usual location of OHL, which is on the lateral borders of the tongue.

The importance of OHL as an indicator of immunosuppressive condition was recognized soon after it was first described in 1984 (Greenspan et al., 1984). OHL has been listed in the classification of oral lesions as a Group I lesion strongly associated with HIV infection (Classification and diagnostic criteria for oral lesions in HIV infection, 1993).

In this patient, after the initial diagnosis of OHL, the patient was then referred to do VCT. The HIV panel test result was reactive, which explain the immunocompromised condition as predisposing factor of OHL. OHL findings in patients with HIV can also provide some predictive immunity condition of how progressive the infection is, as it is believed to have correlation with CD4 T cell counts. The absolute CD4 count of the patient was 1 cells/uL (N = 410-1590 cells/uL) and CD4 percentage was 0.05% (N = 31-60%), which

considered as a very low CD4 count.This is in accordance with data provided in figure 2, where OHL is correlated with CD4 T cell counts <200/μL.

According to WHO clinical staging of HIV/AIDS for Adults and Adolescents, patient with OHL is classified as HIV stage 3, (WHO, 2007) but CDC stated that when the number of CD4 cells falls below 200 cells/mm, the patient is considered as AIDS. (Greenspan et al., 1984). Diagnosis of AIDS can also be established when one or more opportunistic infection occured, regardless of the CD4 count. Therefore the patient was diagnosed with OHL and AIDS.

In order to diagnosed patient with EBV infection, further examination to obtain EBV in the lesion needed. This can be done by performing histopathology, exfoliative cytology, *in situ* hybridization (ISH), or PCR examination. The most common histopathological features of OHL include hyperparakeratosis, epithelial hyperplasia, koilocyte-like cells within the prickle cell layer and minimal or complete absence of inflammatory cells in the lamina propria. A band-like layer of cells with clear cytoplasm (ground glass appearance) with basophilic nuclear inclusions, ballooning of cytoplasm and intracellular edema can also be seen in the upper spinous layer (Davis et al., 2017).

In our patient, the result of cytopathology examination does not specific for OHL. A study revealed that only 50% of HIV patients with clinical OHL had nuclear change (Reginald et al., 2017). Suggestive clinical findings, the typical involvement of lateral borders, the lack of response to ketoconazole treatment and the patient's HIV status is sufficient to make the diagnosis.

The differential diagnosis of OHL include oral candidiasis, lichen planus, tobacco-associated leukoplakia, frictional keratosis, human papilloma virus–induced oral intraepithelial neoplasia, and oral squamous cell carcinoma (Radwan Ozcko & Mendak, 2011). In most instances, OHL can be diagnosed clinically and does not require a confirmatory biopsy (Triantos et al., 1997).

OHL is a disease of minimal morbidity that does not always require intervention. Therapy is indicated when symptoms become troubling or when it is associated with HIV infection. Treatments for OHL when required consist of varying options. Usually the institution of highly active antiretroviral therapy (HAART) will reduced viral load and increased CD4 count which help decreasing prevalence of OHL significantly. Other therapeutic options including systemic antiviral agents such as acyclovir and valacyclovir, topical podophyllin, topical retinoids, cryotherapy and surgical excision (Triantos et al., 1997; Uihlein et al., 2011).

In our case, the patient was administered acyclovir 800 mg oral 5 times daily, which is corresponding with guidelines in the literature, for 2 weeks.After the 1st week, the lesion on the lateral borders had subsided, the therapy was then continued for another week to make sure the lesion has totally disappeared. The institution of HAART could also prevent the recurrence of OHL in this patient.

4 CONCLUSION

Oral hairy leukoplakia is a predictor and prognostic factor of HIV infection. It cannot be occured in immunocompetent patient so immunocompromised condition which can be caused by HIV must be ruled out before considering other immunocompromised etiologies. Oral manifestations are the earliest and most important indicators of HIV infection. OHL is often misdiagnosed and thus proper treatment is delayed.

In early diagnosis of OHL, health care provider must be cautious for and perform further examination to establish the diagnosis of HIV infection. Institution of HAART on HIV-related OHL patient significantly decline the prevalence of OHL. Other treatments such as systemic antiviral accelerate the resolution process. The ability to recognize early OHL manifestation in patient with HIV is key to providing optimal and appropriate care, administer early medical intervention and thus prolonging patient's life and improve their quality of life.

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