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Case Report

Leukoplakia in HIV patients and risk of malignancy: A case report

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ABSTRACT

Background: *Oral potentially malignant disorder (OPMD) was defined by the World Health Organization (WHO) as an oral lesion which shows abnormalities with potential to become malignant. Leukoplakia is one such OPMD that may present in patients with human immunodeficiency virus (HIV), with the condition of HIV presenting a heightened risk of malignancy.* ***Purpose:*** *This case report aims to describe the initial finding and case management of an oral lesion that was suspected as leukoplakia in an HIV-positive patient on antiretroviral therapy (ART).* ***Case:*** *A 34-year-old male patient was referred to the Oral Medicine Division from an HIV clinic at Dr. Cipto Mangunkusumo General Hospital, Jakarta, with a chief complaint of dental caries. The patient was HIV and hepatitis C positive and already undergoing ART.* ***Case Management:*** *During the intraoral examination, we found multiple caries, poor oral hygiene and a single thin white plaque lesion on the right buccal mucosa around the second and third mandibular molar region. The white plaque was painless, irregular, clearly demarcated, could not be rubbed off and did not disappear when stretched. History of trauma in this area was non-contributory and the lesion had gone unnoticed prior to oral examination. The patient had an existing smoking habit of 25 years. As clinical examination suggested leukoplakia, a biopsy was arranged.* ***Conclusion:*** *Leukoplakia is defined as a potentially malignant lesion. The risk of shifting into malignancy can be higher for patients who are HIV positive. Especially in HIV-positive patients, special measures are needed to prevent shifting into malignancy, such as early detection, elimination of risk factors, performing excisional biopsy and regular intraoral examination.*

Keywords: *HIV; leukoplakia; oral potentially malignant disorder*

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INTRODUCTION

In conjunction with a workshop with the Centre for Oral Cancer/Precancer, the World Health Organization (WHO), in 2007, outlined the characteristics of patients who have the potential to develop malignant disorders, or what is called a potentially malignant disorder, classifying potentially malignancy disorders into subgroups as follows. The first subgroup includes precancerous lesions which are benign with morphologically altered tissue and have a greater risk becoming malignant than normal lesions.[1,2] The second group describes a precancerous condition in which a disease or patient's oral hygiene habits do not necessarily alter the clinical appearance of local tissues, but are associated with greater than normal risk of a precancerous lesion or the development of cancer in the affected tissue.[1,3]

Leukoplakia is defined as a white plaque lesion that cannot be clinically or histologically characterised by other conditions or diseases.[4] The prevalence of leukoplakia is estimated at 2% of the global population, with this condition known to occur in individuals who have a habit of smoking and drinking alcohol.[1,4] Leukoplakia can occur in all parts of the oral mucosa and is clinically divided into two types, namely homogenous lesions, which are flat, thin and a uniform white in colour, and non-homogenous lesions,

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which have a white-red appearance and can have irregular surface texture (speckled) or be nodular.[4,5]

Human immunodeficiency virus (HIV) is a viral infection that attacks the immune system, with its main target being $CD4^+$ T cells, causing the body to lose its ability to fight infection.[6] Based on the latest report from the Indonesian Ministry of Health regarding the spread of human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) from 1987 to June 2018, infection rates continue to rise.[7] To date, the reported number of people living with HIV/AIDS in Indonesia is 301,959.[7]

Leukoplakia falls into the category of precancerous lesions. As HIV is considered a precancerous condition, both leukoplakia and HIV have the potential to become malignant.[1] In this case report, the authors describe the management of leukoplakia in HIV-positive patients undergoing antiretroviral therapy (ART), with case management carried out with the aim of implementing preventive measures that will reduce the risk of transformation into malignancy.

CASE

On 25 February 2019, a 34-year-old male patient was referred from the HIV Clinic to the Oral Medicine Devision of Dr. Cipto Mangunkusumo General Hospital, with a working diagnosis of dental caries and a request for evaluation and management of the condition.

CASE MANAGEMENT

The patient was HIV positive and had been on ART since 2005. He was also known to have had chronic hepatitis C infection since 2003. During the first visit, the patient reported that the hepatitis C virus was at such a level that it was no longer detectable. The ART taken was a combination of Nevirapine and Duviral with a prescribed dosage frequency of two times per day. During the patient history, it was confirmed that the patient had actively smoked for the past 25 years, with an amount given of one pack of cigarettes per day. Upon undertaking oral examination using a light-emitting diode light, white plaque lesions were detected on the right buccal mucosa of the second and third mandibular molars. The white plaque lesion was painless, irregular, clearly demarcated, could not be rubbed off, did not disappear when stretched and was around 5mm in diameter. The white plaque lesion had gone unnoticed prior to oral examination and the patient denied history of trauma due to tooth friction in the area.

Based on the patient history and clinical examination, it was determined that the white lesion was suspected leukoplakia. Thus, an excisional biopsy (Figure 1) was scheduled. As shown in the panoramic radiograph (Figure 2),

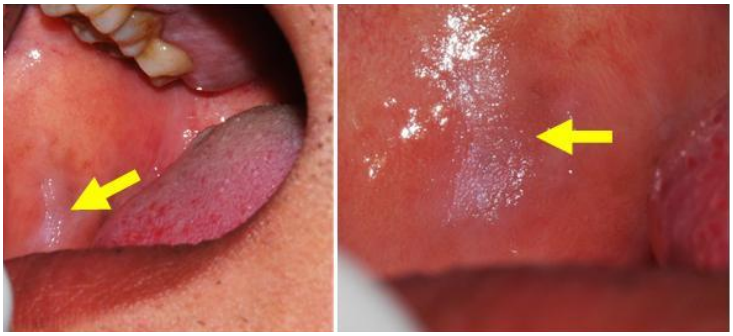

Figure 1. Clinical finding of white lesion on right buccal mucosa (see yellow arrow).

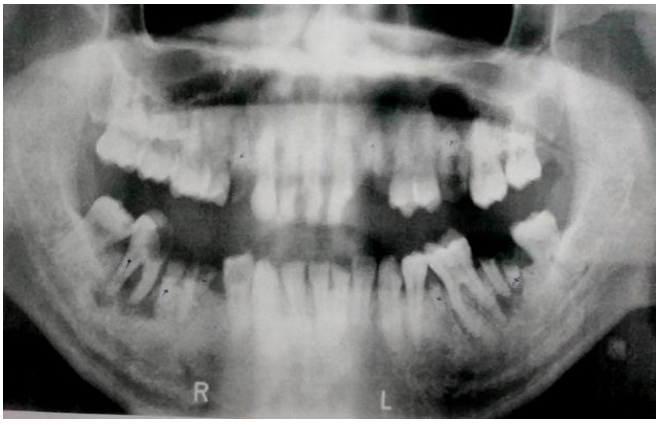

Figure 2. Panoramic radiograph.

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poor oral hygiene was evident in the form of sub- and supragingival calculus, tooth radices and pulp necrosis. An improvement of oral hygiene, multiple dental extraction and scaling were subsequently planned. Prior to the excisional biopsy, the white plaque lesion was treated with topical application of 100,000 IU vitamin A three times a day, with the additional suggestion that the patient take a once-daily dose of antioxidant supplement. We informed the patient of the oral findings, the aetiological factor of leukoplakia and the risk of malignant transformation of leukoplakia in HIV-positive patients, moreover recommending that the patient make changes toward a healthier lifestyle, including stopping smoking.

The complete blood count on 26 February 2019 showed erythrocyte levels, activated partial thromboplastin time (aPTT), blood creatinine and blood urea below normal range, while mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH) and mean corpuscular haemoglobin concentration (MCHC) levels were above normal range. An hepatitis C virus ribonucleic acid test had shown undetectable levels of the virus on 25 January 2019, while the February 2019 blood test indicated absolute lymphocyte count (CD45+), percentage of T cells (CD3+), T cells absolute (CD3+) and T cell absolute (CD4+) all above normal range (6629/μL, 74%, 4876 cell/μL and 1627 cell/μL respectively). Only the percentage of CD4 T cells was below normal range (25%).

The patient underwent an excisional biopsy for the white plaque lesion and multiple tooth extraction on 6 March 2019. The specimen from the excisional biopsy was then sent to the anatomical pathology laboratory for histopathological examination (Figure 3). On 15 March 2019, the patient came for a follow-up visit post-biopsy, in which they were advised of good hygiene practices and informed of the histopathological examination result. They were instructed to cease application of the topical ointment but continue to take the antioxidant supplement at a dose of one tablet per day, with a routine follow-up visit scheduled for every three months going forward. They were also informed of the need for a repeat biopsy at the same area one year after the first, especially should the white plaque lesion reappear.

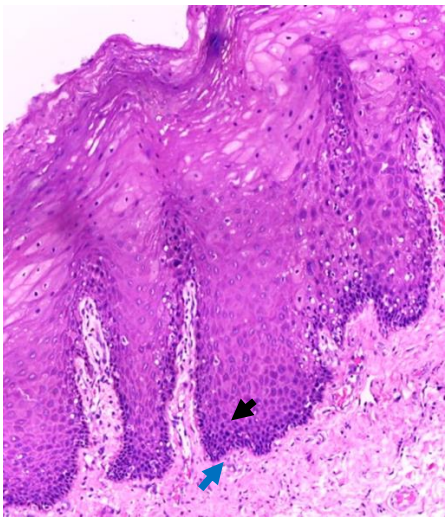

Figure 3. Histopathological result with haematoxylin eosin (H&E) staining. Squamous epithelium hyperkeratosis, spongiotic gingivitis, acanthosis and elongated rete ridges (see black arrow) are present, while the basal membrane is still intact and there is no sign of dysplasia (see blue arrow). Furthermore, there is an infiltration of lymphocyte cell in the subepithelial area.

DISCUSSION

In the above case, the patient was initially unaware of the white lesion, which was only found during intraoral examination by an oral medicine specialist. The white lesion was only present on the right buccal mucosa and persisted even when blanched. Furthermore, it could not be rubbed off. The patient denied history of trauma due to tooth friction in the area. Based on the clinical appearance, the history of heavy smoking for the past 25 years to date and the level of patient alcohol consumption, the white lesion was identified as suspected leukoplakia.

According to Lima et al.[8] individuals with a smoking habit have a six times higher risk of leukoplakia compared to those who do not smoke, with the most common location in which leukoplakia occurs being the buccal mucosa. This supports the conclusion that the white lesion identified on the buccal mucosa of the patient, who was a heavy smoker of one pack of cigarettes per day over the preceding 25 years, was highly suggestive of leukoplakia.

The causes of leukoplakia are attributed to several factors, with smoking being the main one. Leukoplakia can present as single or multiple lesions, with any oral site having the potential to be affected. Clinically, leukoplakia is divided into two types: homogenous and non-homogenous.[5,9] Homogenous lesions can be flat, thin and a uniform white in colour, while non-homogenous legions can be white or red and may be either of irregular surface texture (speckled), nodular or verrucous, the latter variety of which has an elevated, proliferative or corrugated surface appearance.[10]

Leukoplakia is categorised as a lesion with the potential to become malignant.[10] The estimated rate of change toward malignancy is 1–2%.[10,11] The causes of leukoplakia are divided into two categories: idiopathic leukoplakia and leukoplakia associated with habitual use of tobacco.[10,11] While leukoplakia can occur in all parts of the oral cavity, occurrences located at the base of the mouth, soft palate and tongue have a high risk of becoming malignant, whereas leukoplakia in other areas such as the buccal mucosa have a low risk of such transformation.[11]

In this case report, the patient was HIV positive. Based on the EC Clearinghouse on Oral Problems Related to HIV Infection study of 1992,[9] manifestations of HIV/AIDS

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in the oral cavity were divided into three groups: first, lesions that were strongly associated with HIV infection; second, lesions with a strong association with HIV; and third, lesions that could found in HIV-positive patients.[9,10] Leukoplakia is not included in the EC Clearinghouse categorisation. In terms of the white lesion examined in this study, an excisional biopsy was planned to confirm its nature. The choice to perform an excisional biopsy was made due to the relatively small size of the lesion (less than 6mm). Once the procedure was complete, the biopsy specimen was taken to the anatomy pathology laboratories for histopathological examination.

Histopathological features of leukoplakia have various appearances, including epithelial hyperkeratosis and hyperplasia, and can be accompanied by the presence or absence of dysplasia as well as carcinoma in situ.[12] Dysplasia is a histopathological change that is characterised by a loss of architectural form of epithelial cells and can be associated with impaired cell proliferation and impaired cell maturation.[10] In this case report, the histopathological features present in the specimen were hyperkeratosis, prolonged rete ridges, presence of acanthosis, hyperplasia in the basal cell area and an infiltration of subepithelial lymphocyte cells. However, there was no dysplasia found in the histopathology examination.

Although leukoplakia located on the buccal area has a low risk of becoming malignant when compared that on other locations, the presence of an HIV infection leads to the persistent assumption of a possibility that lesion may still be malignant, as HIV patients have a higher risk of malignancy when compared to general population.[13] Referring to Farah et al.'s[14] examination of several previous studies, it can be seen that, due to immune system deficiency issues, patients who are HIV positive have a high risk of developing cancer, including lip cancer, oral cancer, pharyngeal cancer and oesophageal cancer, compared to the general population. Immunodeficiency contributes to malignancy because an impaired immune system can reduced immune surveillance for malignant cells and also impair the ability to suppress oncogenic factors.[13,15] In HIV patients, the risk of developing oral cancer is increased by immune deficiency and can also be related to tobacco use.[14] We therefore informed the patient that risk of oral cancer may not be eliminated by excision of the lesion, recommending regular follow-up visits every three months. We also informed the patient that the lesion may recur within a matter of time, ranging from weeks, months to several years.

Management of leukoplakia can be accomplished through surgical excision, pharmacological therapy with drugs or a combination of both. For the patient described in this study, both pharmacological therapy and surgical excision were used. Prior to the excisional biopsy, we prescribed a topical application of 100,000 IU vitamin A cream to aid cellular growth and differentiation of epithelial cells after modulating cellular gene expression.[16] Retinoids are also a class of antioxidant compound that are responsible for the balance of cellular growth, differentiation and apoptosis, and have the capacity to prevent recurrence of leukoplakia.[16,17] Topical rather than systemic vitamin A was selected due to the lower side effects of topical versus systemic consumption. In addition to this topical application of vitamin A, an antioxidant supplement containing lycopene was also prescribed. Lycopene not only has antioxidant properties, but is also able to modify the intercellular exchange junction, meaning it functions as an anti-cancer mechanism.[17] The purpose of the treatment was to prevent the lesion from becoming malignant.

As leukoplakia has the potential to become malignant, it is important for clinicians to facilitate early diagnosis and remove possible contributing factors such as smoking, thus reducing the rate of malignant transformation. In conclusion, leukoplakia is categorised as a potentially malignant disorder, while in patients with HIV, the risk of becoming malignant can be even higher. Thus, in order to reduce the rate of malignant transformation, early detection and treatment, as well as patient education to avoid all risk factors, are of great importance. Furthermore, due to the potential recurrence of leukoplakia, it is highly recommended that patients have regular follow-up visits.

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