Malignant Transformation of Oral Leukoplakia to Squamous Cell Carcinoma in a Patient with HIV: A Case Report

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Abstract

Oral leukoplakia is a potentially malignant lesion found more in the middle-aged and elderly, with an estimated global prevalence of 2.60%. Most oral squamous cell carcinomas develop on the background of oral leukoplakia. The risk of malignant transformation increases with the clinical type of leukoplakia, affected sites, immunosuppressive states of affected patients, alcohol and tobacco consumption, human papilloma virus infection, and chewing betel leaf and areca nut. Regular monitoring of patients with oral leukoplakia is very important for early detection of any mucosal and dysplastic change. This will aid early intervention and improve patient's survival.

Keywords*: Oral leukoplakia, potentially malignant, malignant transformation.*

Introduction

Oral leukoplakia (OL) refers to white plaques on the oral mucosa that cannot be characterized as any other specified disease, clinically or histologically[1], having excluded other known diseases or disorders that carry no increased risk for cancer[2]. Common intra-oral sites include the gums, buccal mucosa, lower lip, tongue, and floor of the mouth. The white lesions of OL in the affected sites cannot be scraped off, and it may contain speckles of reddish discoloration (erythroleukoplakia)[3,4]. OL is usually asymptomatic, but some areas of the OL may be sensitive to heat, touch, or spicy food[5]**.** The pathogenesis of OL is not well known; however, some factors have been found to play some roles in the development and progression of leukoplakia. They include *candida albicans* infection, *human papilloma* virus infection, immunosuppressive state like Human immunodeficiency virus (HIV) infection, poor oral hygiene, nutritional deficiency (vitamin A,B complex, C, Beta-carotene) repeated cheek or tongue biting, chewing betel leaf and areca nut, smoking, and alcohol consumption [3,6,7].

OL is considered the most common potentially malignant lesion with a global prevalence estimated at 2.60%[8]. Most oral squamous cell carcinomas (OSCC) occur on the background of oral leukoplakias,[9] with a malignancy conversion rate of 0.1%-17.5%[10] occurring within 15 years[11]. OSCC accounts for more than 90% of head and neck tumors.[12] Oral leukoplakia can occur years before a diagnosis of cancer.[13] Clinical evidence exists for the role of the immune system in malignant transformation in immunosuppressed patients.[9] Other factors that can also be considered risk factors for malignant transformation of oral leukoplakia include: female sex, advanced age, long duration of leukoplakia, alcohol, tobacco consumption, site of lesion (tongue and/or floor of the mouth), clinical types of the lesion (verrucous leukoplakia, leukoplakia exceeding 200mm, non-homogenous type), and presence of epithelial dysplasia—especially high grade dysplasia [8,14,15].

Routine monitoring of patients with OL is very important for early detection of any mucosal change, with strict instructions on avoidance of major risk factors for oral epithelial dysplasia like alcohol and tobacco[7]. OL rarely undergoes spontaneous regression[16], although cessation of most habits like tobacco may result in regression of leukoplakia. In the presence of persisting leukoplakia, treatment may be instituted to prevent malignant transformation.[17] Treatment of OL is usually non-specific as the predisposing factors, patient's clinical presentation and medical history, are important factors that are of utmost consideration.

This is a report of a malignant transformation of oral leukoplakia in a patient with HIV infection, who had the lesion for two years prior to the diagnosis of cancer. This report also reviews the likely risk factors for malignant transformation of oral leukoplakia, and outcome of regular monitoring.

Case report

A 56-year-old widow reported at the Oral medicine clinic, University of Benin Teaching Hospital, on account of white plaques on the lateral borders of her tongue of two years duration. There was no history of tobacco use and alcohol consumption. The patient is a known retroviral disease (RVD) patient and has been on Highly Active Antiretroviral Therapy (HAART) for about 10 years. The white plaques had been asymptomatic but persistent, with the recent appearance of a small swelling on the right lateral border the tongue which was first noticed about four months before presentation. This was of concern to her, hence her presentation at the clinic.

Upon physical examination, patient was apparently healthy looking, no evidence of pallor, not cyanosed and anicteric. The submandibular and cervical lymph nodes were not tender and palpable and there was no evidence of any associated cutaneous lesions. Intra-oral examination revealed fair oral hygiene status, with presence of homogenous white plaques on the lateral borders of the tongue

measuring 3cm by 2cm, and could not be scraped off. (fig. A). And the cusps of the posterior teeth were devoid of sharp edges. However, a small swelling with a smooth surface and which was associated with mild pain was seen on the lateral border of the tongue. Tongue swab was taken for mycology and patient placed on warm saline oral rinse 8 hourly/day for a week, with a plan for tissue biopsy of the swelling.

A week later, the result of the mycology showed presence of *candida albican spp* and the patient commenced nystatin (1:150,000 IU) oral rinse 3 times daily and fluconazole 100mg daily for 2 weeks. Exfoliative cytology of the lesion was done which revealed a reactive lesion showing hyperkeratosis-hyperplastic squamous epithelial lesion (fig. B). Patient was reassured, counselled on good nutrition and good oral hygiene, and encouraged to keep up with the HAART. Patient was also placed on chlorhexidine oral rinse 8 hourly/day for 1 week to optimize her oral hygiene. Following this, patient was placed on monthly review. Patient, however, did not keep her appointment and presented about 8 weeks later. At this point, the swelling was observed to have increased in size, presenting as a nodular lesion with marked pain (fig. C). Patient was then referred to the Oral Surgery clinic for an incisional biopsy of the lesion. An incisional biopsy of the nodular lesion was taken, and the result revealed the presence of dysplastic changes (fig. D) with a definitive diagnosis of squamous cell carcinoma made. Patient was promptly referred to the oncology team of the same hospital for treatment, and placed on monthly reviews at the oral medicine clinic.

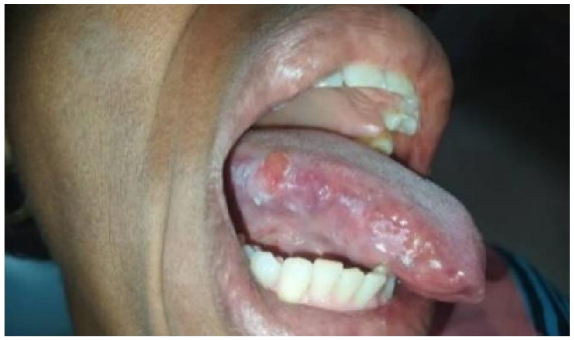

Figure A: Intraoral picture showing lesion at initial presentation

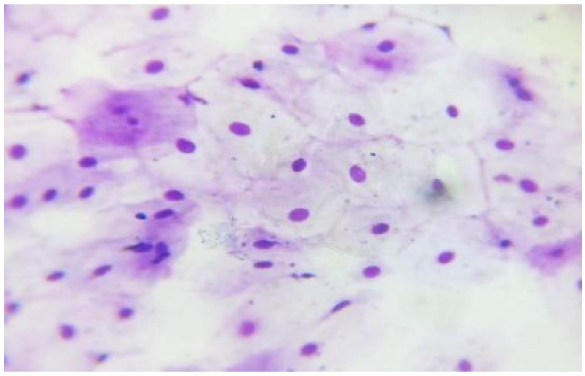

Figure B: Cytology showing clusters and disco-hesive squamous cells with neutrally placed small nuclei, with uniform nuclear chromatin, and abundant cytoplasm with dark staining granules. The background is loose with infiltrates of lymphocytes and necrotic debris (H&E stainx400)

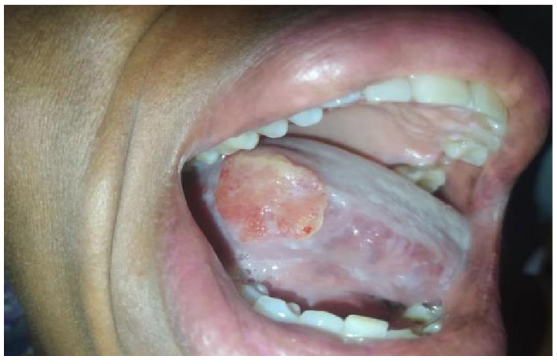

Figure C: Intraoral picture showing an increased size of the lesion on a background of leukoplakia

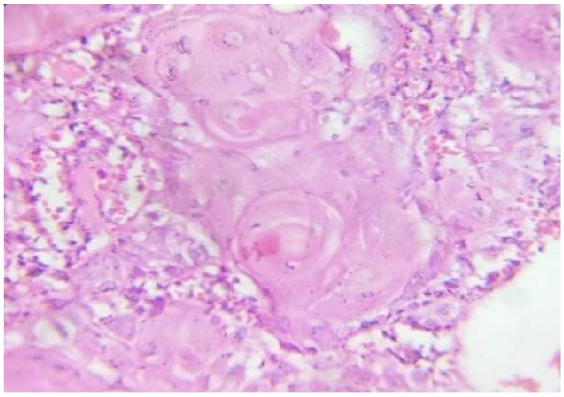

Figure D: Histological section showing numerous dysplastic squamous cells arranged in nests with keratin pearls, individual cell keratinization with presence of mixed chronic inflammatory cells infiltrates (H&E stainx400)

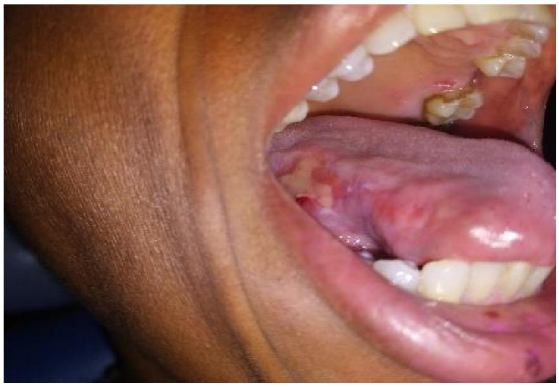

Figure E

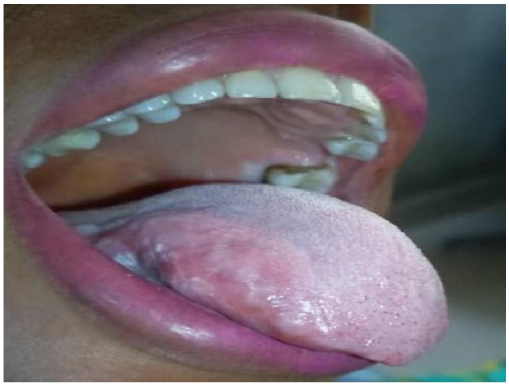

Figure F

Intraoral pictures showing marked regression of the lesion after commencement of chemotherapy. (Fig E) after 1st session of chemotherapy; (Fig F) after 4th session of chemotherapy.

Discussion

Oral leukoplakia (OL) is considered the most common potentially malignant lesion[8] which requires close monitoring to detect any clinical and histological changes. Most cases of OL may be asymptomatic for years. This was the case of our patient who had the white plaques for two years prior to presentation, without pain or discomfort. The cause of the swelling in the region of the OL on the right border of the tongue could not be ascertained. However, some strong indicators of leukoplakia transforming to cancer include appearance of ulceration, nodules, and bleeding[11]. In line with this, the appearance of a swelling in the region of the leukoplakia called for a closer monitoring of the patient.

An exfoliative cytology was initially done because the lesion was small, and the result showed a reactive lesion devoid of dysplastic cells. An increase in the size of the initial swelling to a nodular lesion weeks later was the reason an incisional biopsy was done. Studies have reported epithelial dysplasia to be a strong

indicator of malignant transformation,[8,11] hence, the dysplastic changes seen on the histology of this patient confirmed a diagnosis of OSCC. The likely factors that may have contributed to the malignant change have been considered thus. The first is the patient's immunosuppressive state.[3,9] The patient has been a known RVD patient, on HAART for about 10 years. Oral lesions are often the first signs and symptoms of HIV infection[18], and are considered high predictive markers of immunosuppression [19]. Some oral lesions associated with HIV infection include oral candidiasis, linear gingival erythema, periodontitis, oral hairy leukoplakia, oral warts, and Kaposi's sarcoma[20], and they can have a negative impact on the patients' quality of life.[20] The advent of HAART has however been associated with a decrease in the incidence of some these oral diseases[21]. While the immunosuppressive state of HIV can cause the development of opportunistic infections,[21] it has also been reported to be associated with an increased risk of oral cancers caused by human herpes viruses and human papilloma virus.[22]

The HIV-induced immunosuppression can hinder the control of cancer- associated viruses. [23] In immunocompetent people, these viruses are often carried asymptomatically. However, in immunocompromised states caused by illness, age, or HIV infection, the viruses can manifest to produce diseases. A study by Speicher on the role of HIV in the pathogenesis of oral cancer has reported possible mechanisms to include the following: (1) increasing the immune-suppression, and (2) immune activation with resultant chronic inflammation and subsequent carcinogenic effects. This can also result in an altered microbiome and loss of local immune surveillance.[22] The immunosuppressive state caused by HIV can be further complicated by the presence of co-factors for head and neck cancers (e.g. smoking and alcohol).[24] A study by Chen et al[25] also reported that HIV-infected patients were at a significant risk for oral cancer. The use of HAART, while improving the survival of HIV-infected persons, also resulted in long-term morbidities like cancers.[25,26] This reckons with our patient who has been on HAART for about 10 years.

OL that develop as a result of conditions like HIV infection may clear upon institution of antiviral therapy[3]. The OL in this patient, however, persisted despite the HAART. Patient was counseled on improved nutrition and oral hygiene, as poor oral hygiene and nutritional deficiency have been implicated in the transformation of OL to oral cancer.[3,27] Studies by Warnakulasuriya[8,15] observed factors that stand out as significant determinants contributing to the malignant potential of cancer, to include advanced age, the female gender, and leukoplakia exceeding 2cm. Barfi et al[28] reported that in female patients over 50 years of age, malignant transformations were associated with lesions located on the tongue as opposed to the males where the tongue and buccal mucosa were common sites for malignant change. These reports align with our patient who is a 56-year-old female, with lesion on the tongue.

The site of the lesion in this patient is considered a high risk for malignant change, as a study by Castagnola et al [29] reported that lesions on the ventrolateral surface of the tongue show a greater risk of aneuploidy and loss of heterozygosity which are features associated with a higher risk of malignant transformation. Barfi et al [28] also reported that most female patients with malignant transformation were non-smokers compared to male patients with malignant transformation who were mostly smokers. Our patient neither smokes nor takes alcohol, which are risk factors for malignant transformation. Non-homogenous leukoplakia (erythroleukoplakia) has been reported to be more associated with malignant transformation[8,13]. Our patient, however, had homogenous leukoplakia for two years before the appearance of the swelling in which the dysplastic changes were found. Monthly review of this patient aided the early diagnosis of OSCC. Early detection of OSCC and its preceding lesions is therefore very vital in improving patients' survival,[30] as OSCC is curable with reduced morbidity and disfigurement if detected at an early stage.[31]

Various studies have reported the treatment modalities for oral cancers to include chemotherapy, radiotherapy, and surgery. These can be employed singly or in combination.[32–34] The stage of the disease and the histologic cell type determine the choice of treatment.[35] Treatment upon late diagnosis is, however, associated with considerable morbidity as well as functional impairment and poor prognosis[9]. With the diagnosis of OSCC made in this case, the patient was immediately referred to the oncology team for treatment. Chemotherapy as the choice of treatment was promptly instituted, and the lesion was seen to have regressed remarkably (fig E) and (fig F). This was comparable to a report by Remco de Bree et al,[36] which observed frequent and significant regressions in head and neck squamous cell carcinoma after chemotherapy alone. The patient is still on routine follow-up at the oral medicine clinic.

Conclusion

This study reported a case of malignant transformation of oral leukoplakia in a known RVD patient on HARRT. Regular patient monitoring is very key in the early detection of mucosal changes, institution of appropriate therapy in the presence of dysplasia, and improved survival rate of patients.

References

1. Hong WK, Hittelman WN, Mao L, et al. Predicting cancer development in oral leukoplakia: ten years of translational research. Clinical Cancer Research. Published 2000. Accessed February 8, 2023. http://ovidsp.ovid.com?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=med4&AN=10815888%5Cnhttp://library.newcastle.edu.au:4550/resserv?sid=OVID:medline&id=pmid:10815888&id=&issn=1078-0432&isbn=&volume=6&issue=5&spag

e=1702&pages=1702-10&date=2000&title=Clinical+Cancer

2. Warnakulasuriya S, Johnson NW, Van Der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med*. 2007;36(10):575-580. doi:10.1111/J.1600-0714.2007.00582.X
3. Jennifer H. Leukoplakia: Symptoms, causes, and prevention. Published 2019. Accessed February 10, 2023. https://www.medicalnewstoday.com/articles/317689
4. Vlad R, Panainte I, Stoica A, Monea M. The Prevalence of Oral Leukoplakia: Results From a Romanian Medical Center. *Eur Sci Journal, ESJ*. 2016;12(27):12.
5. Leukoplakia - Cancer Care of Western New York. Accessed May 15, 2023.
6. Shiu MN, Chen THH, Chang SH, Hahn LJ. Risk factors for leukoplakia and malignant transformation to oral carcinoma: a leukoplakia cohort in Taiwan. *Br J Cancer*. 2000;82(11):1871-1874.
7. Erugula S, Umar Farooq M, Jahagirdar D, Srija C, Meruva S, Venkata G. Oral Leukoplakia Etiology , Risk Factors , Molecular Pathogenesis , Prevention and Treatment : A Review. *Int J Contemp Med Res*. 2020;7(11):5-9.
8. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies | Request PDF. *J oral Pathol Med*. 2019;45(155). Accessed January 31, 2023. https://www.researchgate.net/publication/337656720_Malignant_transformation_of_oral_leukoplakia_a_systematic_review_of_observational_studies
9. Weber M, Wehrhan F, Baran C, et al. Malignant transformation of oral leukoplakia is associated with macrophage polarization. *J Transl Med*. 2020;18(1):1-18. doi:10.1186/S12967-019-02191-0/TABLES/4
10. Srivastava VK. To Study the Prevalence of Premalignancies in Teenagers having Betel, Gutkha, Khaini, Tobacco Chewing, Beedi and Ganja Smoking Habit and Their Association with Social Class and Education Status. *Int J Clin Pediatr Dent*. 2014;7(2):86-92. doi:10.5005/JP-JOURNALS-10005-1243
11. Clevelandclinic. Leukoplakia; Causes, Symptoms, Management & Treatment. Published 2017. Accessed May 11, 2023.
12. Attar E, Dey S, Hablas A, et al. Head and Neck Cancer in a Developing Country: A Population-Based Perspective Across 8 Years. *Oral Oncol*. 2010;46(8):591. doi:10.1016/J.ORALONCOLOGY.2010.05.002
13. Sudbø J, Reith A. Which putatively pre-malignant oral lesions become oral cancers? Clinical relevance of early

targeting of high-risk individuals. *J Oral Pathol Med*. 2003;32(2):63-70.

14. Sun Z, Gong Y, Huang J. Analysis of relationship between risk factors of malignant transformation of oral leukoplakia and the LSCP system. Zhonghua kou qiang yi xue za zhi = Zhonghua kouqiang yixue zazhi = Chinese journal of stomatology. Published 2001. Accessed January 31, 2023.
15. Aguirre-Urizar JM, Lafuente-Ibáñez de Mendoza I, Warnakulasuriya S. Malignant transformation of oral leukoplakia: Systematic review and meta-analysis of the last 5 years. *Oral Dis*. 2021;27(8):1881-1895.
16. Waal I. Oral Leukoplakia : Present Views on Diagnosis , Management , Communication with Patients , and Research. Published online 2019:9-13.
17. Amagasa T, Yamashiro M, Ishikawa H. Oral Leukoplakia Related to Malignant Transformation. *Oral Sci Int*. 2006;3(2):45-55.
18. Ottria L, Lauritano D, Oberti L, et al. Prevalence of HIV-related oral manifestations and their association with haart and CD4+ T cell count: A review. *J Biol Regul Homeost Agents*. 2018;32(2):51-59.
19. Sharma G, Pai KM, Setty S, Ramapuram JT, Nagpal A. Oral manifestations as predictors of immune suppression in a HIV-/ AIDS-infected population in south India. *Clin Oral Investig*. 2009;13(2):141-148.
20. Lomelí-Martínez SM, González-Hernández LA, Ruiz-Anaya A de J, et al. Oral Manifestations Associated with HIV/AIDS Patients. *Med*. 2022;58(9).
21. El Howati A, Tappuni A. Systematic review of the changing pattern of the oral manifestations of HIV. *J Investig Clin Dent*. 2018;9(4):e12351.
22. Speicher DJ, Ramirez-Amador V, Dittmer DP, Webster-Cyriaque J, Goodman MT, Moscicki AB. Viral infections associated with oral cancers and diseases in the context of HIV: A workshop report. *Oral Dis*. 2016;22:181-192.
23. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens--Part B: biological agents. *Lancet Oncol*. 2009;10(4):321-322.
24. Gupta B, Johnson NW. Systematic review and meta-analysis of association of smokeless tobacco and of betel quid without tobacco with incidence of oral cancer in south asia and the pacific. *PLoS One*. 2014;9(11).
25. Chen CH, Chung CY, Wang LH, Lin C, Lin HL, Lin HC. Risk of cancer among HIV-infected patients from a population-based nested case-control study: Implications for cancer prevention. *BMC Cancer*. 2015;15(1):1-9.
26. Detels R, Muñoz A, McFarlane G, et al. Effectiveness of potent antiretroviral

therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators. *JAMA*. 1998;280(17):1497-1503.

27. Zain RB. Cultural and dietary risk factors of oral cancer and precancer - A brief overview. *Oral Oncol*. 2001;37(3):205-210.
28. Barfi Qasrdashti A, Habashi MS, Arasteh P, Ardakani MT, Abdoli Z, Eghbali S. Malignant Transformation in Leukoplakia and Its Associated Factors in Southern Iran: A Hospital Based Experience. *Iran J Public Heal*. 2017;46(8):1110-1117. Accessed January 31, 2023.
29. Castagnola P, Malacarne D, Scaruffi P, Maffei M, Donadini A. Chromosomal aberrations and aneuploidy in oral potentially malignant lesions : distinctive features for tongue. *BMC Cancer*. 2011;11(1):445.
30. Bettendorf O, Piffkò J, Bànkfalvi A. Prognostic and predictive factors in oral squamous cell cancer: important tools for planning individual therapy? *Oral Oncol*. 2004;40(2):110-119.
31. Baykul T, Yilmaz HH, Aydin Ü, Aydin MA, Aksoy MÇ, Yildirim D. Early diagnosis of oral cancer. *J Int Med Res*. 2010;38(3):737-749.
32. Haddad R, Annino D, Tishler RB. Multidisciplinary approach to cancer treatment: focus on head and neck cancer. *Dent Clin North Am*. 2008;52(1):1-17.
33. Aa O, Ao A, To A, et al. Orofacial Cancers : Pattern and Management in. 2018;45(4):179-188.
34. Awodutire PO, Ilori OR, Uwandu C, Akadiri OA. Pilot study of new statistical models for prognostic factors in short term survival of oral cancer. *Afr Health Sci*. 2022;22(2):310-317.
35. da Lilly-Tariah OB, Somefun AO, Adeyemo WL. Current evidence on the burden of head and neck cancers in Nigeria. *Head Neck Oncol*. 2009;1:14. doi:10.1186/1758-3284-1-14
36. de Bree R, Wolf GT, de Keizer B, et al. Response assessment after induction chemotherapy for head and neck squamous cell carcinoma: From physical examination to modern imaging techniques and beyond. *Head Neck*. 2017;39(11):2329-2349.