Oral Potentially Malignant Disorders and Cancer Transformation

Naglaa M. Kamal*

Abstract:

Oral potentially malignant disorders (OPMDs) are a set of disorders that affect the oral mucosa and are associated with increased malignant risk. During their progression, visible alterations in the color or thickness of the oral mucosa can be found, and these changes may be observed throughout the oral examination.

Their clinical manifestations vary, and their natural history is poorly described. In clinical practice, the most frequent OPMD is oral leukoplakia. When stratifying their risk, the presence of red areas, a size greater than 200 mm2, and a higher grade of dysplasia in the pathology report are taken into consideration. Up to one-third of OPMDs can progress to squamous cell carcinoma.

Keywords: Premalignant, Oral cancer, Leukoplakia, Erythroplakia, Lichen planus.

Introduction:

A precancerous lesion was defined by the World Health Organization in 1973 as "a morphologically altered tissue in which oral malignancy is more prone to develop than its apparently healthy analogue."

A precancerous condition, on the other hand, is defined as "a generalized condition that is linked to a significantly increased risk of cancer." [1]

Because not all premalignant lesions progress to cancer, the WHO Workshop in 2005 recommended the term "oral potentially malignant disorders OPMDs" to encompass both lesions and conditions. [2]

Definition, prevalence, etiology, and clinical features

OPMDs are a set of lesions and conditions that have a variable elevated risk of developing lip and oral cavity malignancies. [3]

It is crucial to be aware that a person with any of these OPMDs has a greater risk of acquiring mouth cancer than an individual with healthy

* *A. Professor of Oral Pathology, Faculty of Dentistry, Ahram Canadian University, Egypt.*

mucosa. ***The risk of malignancy*** in an OPMD patient varies based on many factors, though it has been estimated to be 5-100 times higher than in the general population. It was observed that ***prevalence may vary*** between populations and was generally higher in Asians and men. [4]

The etiology of these disorders ranges from pure genetic aberrations predisposing for altered tissue regeneration, disorders caused by exogenous factors such as tobacco (both smoked and smokeless), excess alcohol consumption, chewing betel quid containing areca nut, immune-mediated disorders, and those associated with rare inherited diseases.[5]

OPMDs have a wide range of clinical features including color variations (white, red, and mixed white and red), topographic changes (plaque, smooth, corrugated, verrucous, granular, atrophic) and may be of variable size. [6]

Some OPMDs, particularly oral leukoplakia may superficially ulcerate due to abrasion of the surface by trauma from teeth or appliances. OPMDs can involve any anatomical site in the oral cavity.[7]

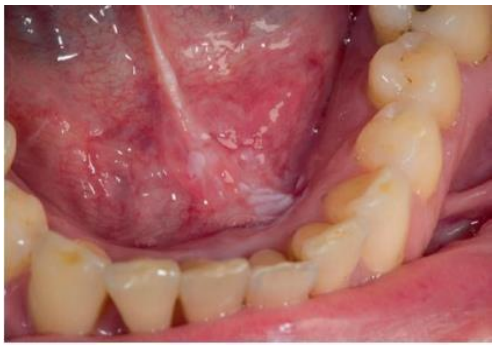
OPMDs have an unpredictable clinical course, they may remain static or may demonstrate progression or regression. The majority of patients with OPMDs are diagnosed in middle-aged or elderly patients, predominantly males. [8]

Diagnosis and investigations

A systematic oral visual examination and palpation of affected areas of the oral cavity and the neck is recommended to make a provisional clinical diagnosis.

Based upon current knowledge, the gold standard for the confirmation of the clinical diagnosis is to submit a representative biopsy sample for microscopic examination. Pathology diagnosis following a biopsy minimizes misclassification and assists in the management decisions. Microscopic examination of a biopsy specimen also gives the opportunity to exclude any occult malignancy as a small proportion of squamous cell carcinomas may clinically present as white and red patches. For white and red patches, a biopsy would allow to ascertain whether epithelial dysplasia is present or not and to assess the grade of dysplasia. The standard practice is to use the three-grade system (mild, moderate, or severe) as set out in the WHO guidelines for pathology reporting.[4]

Leukoplakia



©Association of Oral and Maxillofacial Surgeons of India

Fig. 1 Leukoplakia

A predominantly white patch or plaque that cannot be characterized clinically or pathologically as any other disorder. It cannot be rubbed off and generally asymptomatic.

Clinical presentation

Homogeneous leukoplakia: Uniformly white, flat, and thin, have a smooth surface and may exhibit shallow cracks.

Nodular leukoplakia: Small polypoid or rounded outgrowths, red or white excrescences.

Verrucous leukoplakia: The surface is raised, exophytic, wrinkled or corrugated.

Erythroleukoplakia: Mixed white and red (speckled) but retaining predominantly white character. [9]

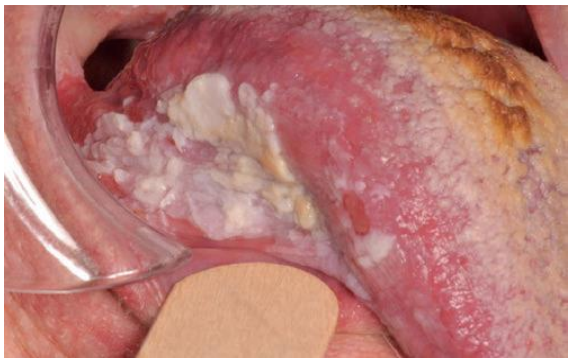
Almost all initial biopsies show hyperkeratosis without dysplasia or verrucous hyperplasia.

A systematic review of the literature by Warnakulasuriya et al. showed that the overall malignant transformation rate of leukoplakia was 3.5%, however, the rate varied in studies between 0.13% and 34%. Histopathological features of leukoplakia are hyperkeratosis of ortho- or parakeratotic type and acanthosis of the epithelium. Moreover, different degrees of epithelial dysplasia may occur.[9]

Clinical conditions to exclude in the diagnosis.

White sponge naevus, Frictional keratosis, Chemical injury, pseudomembranous candidosis, Leukoedema, Fordyce's spots, Hairy leukoplakia.[5]

Proliferative verrucous leukoplakia (PVL)



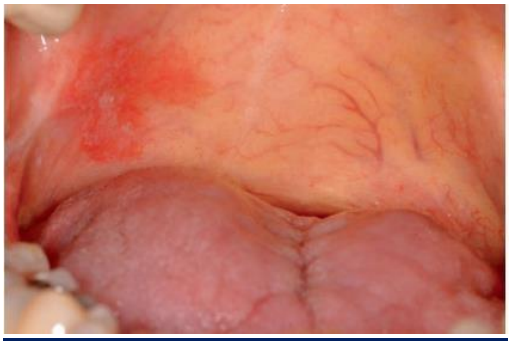
©Association of Oral and Maxillofacial Surgeons of India

Fig. 2 Proliferative verrucous leukoplakia

Leukoplakia that tends to spread and become multifocal. PVL is slow-growing, persistent, and irreversible, and in time areas become exophytic and wartlike. Frequently found in the gingiva, alveolar process, and palate. [10]

It is a distinct and aggressive form of leukoplakia with one of the highest known malignant transformation rates. It is typically diagnosed in elderly women (4:1 female ration) without a history of tobacco use. Etiology is thus largely unknown. PVL has a malignant transformation rate of 61.0% in an average follow-up period of 7.4 years. [5]

Erythroplakia



©Association of Oral and Maxillofacial Surgeons of India

Fig. 3 Erythroplakia

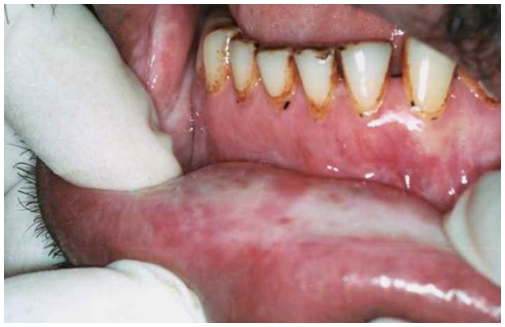
A red velvety patch that cannot be characterized clinically or pathologically as any other definable disease. [4]

Clinical conditions to exclude in the diagnosis.

Erythematous candidiasis, denture-associated stomatitis on palate, erythema migrans, erosive lichen planus, and vascular malformations. [9]

Upon histological analysis, 51% of erythroplakic lesions have been shown to demonstrate invasive squamous cell carcinoma (SCC), with 40% demonstrating carcinoma in situ, and 9% exhibiting mild-moderate dysplasia.[11]

Oral submucous fibrosis (OSF)



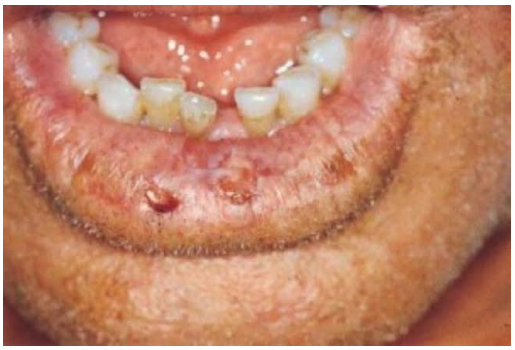
©Association of Oral and Maxillofacial Surgeons of India

Fig. 4 Oral submucous fibrosis

Oral submucous fibrosis is a chronic disease that affects the lamina propria of the oral mucosa, and as the disease advances, it involves tissues deeper in the submucosa of the oral cavity with resulting loss of fibro-elasticity and inability to open the mouth. [12] later, the mucosa develops marble-like pallor. It is linked to the use of betel quid.

Clinical signs develop within 3–5 years following chewing betel quid. Patients are 19 times as likely to develop oral cancer particularly with betel quid containing tobacco. Epithelial dysplasia has been described in 7-26% of OSF tissues. [9]

Actinic Cheilitis (AC)



©Association of Oral and Maxillofacial Surgeons of India

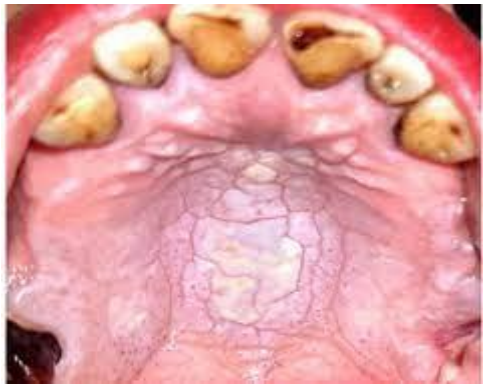
Fig. 5 Actinic Cheilitis

A disorder that results from sun damage and affects exposed areas of the lips, most commonly the vermilion border of the lower lip with a variable presentation of atrophic and erosive areas and white plaques. AC is one of the main risk factors for lip cancer, which is regarded as the fifteenth most common cancer worldwide in men. [13]

About 6-10% of AC cases undergo malignant transformation over time. In a study by Kwon et al., lip SCC originating from AC was demonstrated to have a greater risk for metastasis than SCC arising from other cutaneous parts.[14]

Histopathological features of AC range from atrophy to hyperplasia of the squamous cell epithelium of the vermilion border, with varying degrees of keratinization and cytological atypia. The underlying connective tissue shows basophilic degeneration. [5]

Palatal lesions associated with reverse smoking



©Association of Oral and Maxillofacial Surgeons of India

Fig. 6 Palatal lesions associated with reverse smoking

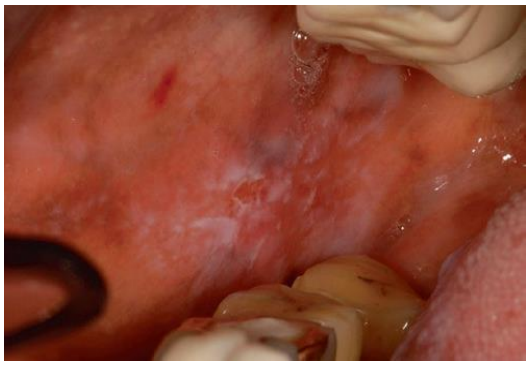
The palatal lesion of reverse smokers is unique to individuals who place the lit end of a cigarette inside the mouth.

The resulting palatal lesion may appear clinically as a red, white, patch or papule. [15]

Epithelial dysplasia and oral SCC occur in 83% and 13%, respectively, of reverse smokers.

Palatal keratosis associated with reverse smoking is characterized by different histopathological features including atypical changes in the epithelium and orifices of the ducts of the glands.[5]

Oral lichen planus (OLP)



©Association of Oral and Maxillofacial Surgeons of India

Fig. 7 Oral lichen planus

Oral lichen planus (OLP) is a common chronic, immunologically mediated mucocutaneous disease.

OLP ranges from asymptomatic reticular white lesions in the atrophic mucosa to erosive-ulcerative areas, while the most characteristic feature is the presence of a lace-like network of fine white lines. Lesions are frequently bilaterally symmetrical.

OLP is an immune-mediated disease, and some reports suggest it is associated with viral infection, such as herpes simplex, Epstein–Barr virus, human papillomavirus, and hepatitis C).[16]

Most patients with lichen planus are middle-aged (over 40 years) and females account for at least 65% of patients.[17]

The risk of malignant transformation in OLP has been controversial for a long time and is estimated to be between 0.4% and 3.7%. Histopathological features of OLP are hyperkeratosis with saw-toothed rete pegs, liquefaction degeneration of the basal cell layer, and a dense subepithelial band of lymphocytes.[18]

Disorders with limited epidemiological evidence of malignant potential.

Chronic hyperplastic candidosis/candidiasis (CHC), Discoid lupus erythematous, epidermolysis bullosa and dyskeratosis congenita. Although classified as potentially malignant conditions, the data regarding progression to malignancy for these conditions is controversial. Because of the difficulty in classifying and clinically distinguishing the varied lesions associated with these conditions, the potential for malignant transformation remains unclear.[11]

Syndromes that may potentiate cancer development in the oral cavity

Close to 20 familial cancer syndromes are described and people born with inherited genetic predispositions develop hematological malignancies and solid cancers at a younger age and with a relatively high frequency. Important examples are Fanconi anemia, xeroderma pigmentosum, Bloom's syndrome and Cowden syndrome. Many of these syndromes are caused by alterations in tumor suppressor genes, or DNA repair genes. [11]

Conclusion:

The "gold standard" for identifying and diagnosing oral malignancies is the proper clinical examination and histopathology examination of potentially malignant disorders. Hence it is of prime importance for every clinician to perform accurate clinical examination of oral cavity to diagnose premalignant lesions. Thus, accurate diagnosis and timely treatment may help prevent the transformation of potentially malignant disorders into OSCC thus saving patients' lives.

References:

1- World Health Organization. Report of a meeting of investigators on the histological definition of precancerous lesions. Geneva: World Health Organization. 1973;731.

2- Goyal D, Goyal P, Singh HP, Verma C. An update on precancerous lesions of oral cavity. International Journal of Medical and Dental Sciences. 2013 Jan 1:70-5.

3- Warnakulasuriya S, Johnson NW, Van der Waal I. Nomenclature, and classification of potentially malignant disorders of the oral mucosa. Journal of oral pathology & medicine. 2007 Nov;36(10):575-80.

4- Warnakulasuriya S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral oncology. 2020 Mar 1; 102:104550.

5- Ganesh D, Sreenivasan P, Öhman J, Wallström M, Braz-Silva PH, Giglio D, Kjeller G, Hasseus B. Potentially malignant oral disorders, and cancer transformation. Anticancer research. 2018 Jun 1;38(6):3223-9.

6- Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral surgery, oral medicine, oral pathology and oral radiology. 2018 Jun 1;125(6):612-27.

7- Farah CS, Woo SB, Zain RB, Sklavounou A, McCullough MJ, Lingen M. Oral cancer and oral potentially malignant disorders. International Journal of Dentistry. May 7;2014.

8- Farah CS, Shearston K, Nguyen AP, Kujan O. Oral carcinogenesis and malignant transformation. InPremalignant conditions of the oral cavity 2019 (pp. 27-66).

9-Mustafa E, Parmar S, Praveen P. Premalignant lesions, and conditions of the Oral Cavity. In Oral and Maxillofacial Surgery for the Clinician 2021 (pp. 1845-1852).

10- Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV. Oral potentially malignant disorders: A consensus report from an international seminar on nomenclature and classification, convened by the WHO

Collaborating Centre for Oral Cancer. Oral diseases. 2021 Nov;27(8):1862-80.

11- Steele T. Premalignant Conditions of the Oral Cavity.2009.

12- Ashvini Kishor V. Identifying Premalignant Lesions & Conditions of Oral Cavity. J Dental Sci 2019, 4(1): 000219.

13- Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015 Mar 1;136(5): E359-86.

14- Kwon NH, Kim SY, Kim GM. A case of metastatic squamous cell carcinoma arising from actinic cheilitis. Annals of Dermatology. 2011 Feb 1;23(1):101-3.

15-Alvarez Gomez GJ, Alvarez Martinez E, Jimenez Gomez R. Reverse smokers and changes in oral mucosa. Department of Sucre, Colombia. Med Oral Patol Oral Cir Bucal. Jan 1 2008;13(1): E1-8.

16-Mattila R, Rautava J and Syrjanen S: Human papillomavirus in oral atrophic lichen planus lesions. Oral Oncol 48: 980-984, 2012.

17-Parashar P: Oral lichen planus. Otolaryngol Clin North Am 44: 89-107, 2011.

18-Kanemitsu S: Oral lichen planus: Malignant potential and diagnosis. Oral Sci Int 11: 1-7, 2014.

Acknowledgement for: Mina Gehad, Odai Khaled, Makarious Gad, Nourhan Mahmoud, Mariem Ashraf , Marsilino Maged, Mohamed Gamal, Abdellah Montaser and Habiba Shuraim, for collecting data and analyzing it.