REVIEW

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The use of autofluorescence for screening and early detection of oral potentially malignant disorders – A narrative review

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ABSTRACT

Premalignant lesions of the oral cavity encompass a broad range of pathology and are often comorbid in a variety of patient populations. Prompt diagnosis and management of these lesions are essential to prevent patient morbidity and mortality. The purpose of this article is to summarize and review the evaluation, screening and early detection of premalignant lesions of the oral cavity and to highlight the role of the dental team in recognizing and treating patients with these conditions, that may progress to oral cancer. In addition, a review of a non-invasive detection technique that is currently being marketed to aid general dentists and other healthcare providers for early diagnosis of potential cancerous lesions is presented. Although many studies have assessed the diagnostic accuracy of autofluorescence in oral potentially malignant disorders (OPMDs), there has been a paucity of such information in high-risk populations.

Keywords: oral cancer, oral epithelial dysplasia, autofluorescence, oral potentially malignant disorders, early detection

INTRODUCTION

Oral cancer is a major public health problem, and there is an increasing trend for oral cancer to affect young men and women. Public awareness is poor, and many patients present with late-stage disease, contributing to high mortality. Oral cancer is often preceded by a clinical premalignant phase accessible to visual inspection, and thus there are opportunities for earlier detection and to reduce morbidity and mortality [1].

The oral potentially malignant disorders (OPMDs) or premalignant oral disorders is a blanket term for a variety of pathologies that can arise in the oral cavity and represent a significant group of mucosal disorders that may precede the diagnosis of oral squamous cell carcinoma (OSCC) [2]. Their early recognition and prompt management are key to optimal outcomes. However, there remains a significant knowledge gap in this area among dental practitioners [3,4]. A recent systematic review revealed that less than half of medical practitioners were aware of common risk factors of premalignant oral lesions or oral carcinoma; further, a low level of awareness was noted among most medical practitioners of common premalignant oral cavity lesions. Thus, there remains a significant need to understand and recognize the presentation, pathophysiology, screening modalities and management of these conditions [5,6].

OPMDs represent tissue with more or less distinctive clinical appearances at initial assessment, and where a proportion within each clinical category has been documented to have subsequently developed a cancer during follow-up; tissues within

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these categories have enhanced malignant potential. "Potentially malignant" implies that not all patients diagnosed with any of these mucosal abnormalities will develop an oral malignancy [7,8]. It does not imply that a carcinoma will arise exactly at the site where an OPMD was previously diagnosed, but some of these clinical alterations, red and white patches in particular are some of the several factors increasing the risk for cancer development [9].

Patients diagnosed with OPMDs may have an increased susceptibility to develop cancer anywhere in their mouth during their lifetime. The majority of these OPMDs may not progress to carcinoma, but rather they provide a field of abnormality in which cancer development is more likely than in their clinically normal mucosa and more likely than in patients without such disorders. Cancer does not necessarily occur in the site of the visibly altered mucosa. An important challenge faced by clinicians managing patients with OPMDs is to be able to identify the small proportion of patients most likely to develop a future malignancy [10].

The oral potentially malignant disorders (OPMDs) are asymptomatic, clinically evident, early oral lesions, which usually precede oral cancer [8]. Malignant transformation of these lesions is attributed to multiple factors, with the presence of oral epithelial dysplasia (OED) on histopathological examination, posing the most significant risk [9].

The early detection of oral cancer results in better survival rates, better treatment outcomes, reduced treatment- associated problems, and lower healthcare costs [11,12]. The routine oral cancer screening method (inspection and palpation) may miss many lesions and may be unable to differentiate between benign, premalignant, and malignant lesions. This is because premalignant and malignant lesions may lurk in the mucosa, appearing clinically normal on routine screening. In addition, the clinical presentation of the lesions (e.g., ulcer, white patch, red patch, etc.) can be misdiagnosed as any other condition. The gold standard for diagnosing oral premalignant and malignant lesions remains biopsy with histological assessment [13]. However, this method is invasive, which makes the need for non-invasive techniques necessary for early diagnosis and screening.

Currently, direct visual oral examination is the most common method used for the screening and surveillance of oral mucosal lesions, however, misdiagnoses is common due to the multiple variations observed in normal mucosa, benign and neoplastic oral lesions. The most commonly used technique, autofluorescence is based on the fluorescence of inherent molecules in the tissues called fluorophores [14]. Understanding the characteristics and implication of these techniques will help dental professionals in choosing the apt technique for screening, early detection, management of OPMDs and oral cancer

A variety of new and emerging non-invasive imaging techniques are used as adjuncts in screening and early diagnosis of OPMDs. Several non-invasive detection techniques for detecting OPMDs are available. These include staining with a solution, optical diagnostics, salivary biomarkers, and light-based detection [12,14]. Optical-based imaging detects the mucosal tissues undergoing abnormal metabolic or structural changes.

The autofluorescence-based diagnostic technique is an emerging method widely used in screening for oral and non-oral premalignant and malignant lesions, differentiating types of lesions, and reducing the need for invasive biopsies [13]. The diagnostic strength of autofluorescence is based on its ability to detect alterations in the structure and metabolism of tissues that occur during premalignant and malignant changes [14]. Endogenous fluorophores in cells produce fluorescent emissions when exposed to the light of a specific wavelength, resulting in autofluorescence [15]. Normal cells show a pale green fluorescence when examined through a filter at these excitation wavelengths, whereas diseased cells lose their auto-fluorescence and appear dark [14,15]. The autofluorescence technique is a rapid, easy-to-operate, chairside autofluorescence OPMD screening device.

MATERIAL AND METHODS

A PubMed search was performed using keywords related to " oral potentially malignant disorders," "autofluorescence", "oral premalignant lesions", "oral cancer" and "oral squamous cell carcinoma" results and selected relevant references. As this field is still developing, and there is a certain heterogeneity in terms used within the field, this article is a narrative review intended to provide an overview of the topic in and identify gaps for future research. Studies adopting autofluorescence devices, evaluating the efficacy of comprehensive oral examination and optical autofluorescence imaging in detection, visualization of potentially malignant disorders, as well as discriminating oral epithelial dysplasia from other mucosal lesions, were included in the literature search across bibliographic databases until December 2022.

TYPES OF ORAL PREMALIGNANT LESIONS

Stratified squamous epithelium lines the majority of the oral cavity, and aberrancy in this epithelium is often what gives rise to premalignant oral lesions. The definition of OPMDs is above all a clinical description, but morphological confirmation is the most important procedure, not only to identify the

correct lesion. In cases where the lesions persist, change or progress, biopsy is mandatory, and histological examination represents the most complete and useful tool to exclude or confirm the presence of dysplasia in order to assess the risk of malignant transformation. Unfortunately, histological findings only indicate that a given lesion may have malignant potential (dysplasia), and cannot be used for the prediction of malignant changes. Thus, the presence of dysplasia only indicates that an oral lesion may have an increased risk of malignant transformation [16,17].

The most common entities which are diagnosed and described are oral leukoplakia (OL), oral erythroplakia (OE), oral lichen planus (OLP) and oral submucous fibrosis (OSF), each of them with diverse risks of malignant transformation.

Oral Leukoplakia (OL)

To precisely diagnose oral leukoplakia, it is important to consider its definition. Historically, the term leukoplakia was used clinically to denote any adherent white patch or plaque (keratosis). Over several decades, clinicians realized that all white patches arising in the oral cavity should not be labeled oral leukoplakia. Several definitions of oral leukoplakia have been put forth in the past few decades. The most recent definition in use refers to leukoplakia as "predominantly white plaques of questionable risk, having excluded (other) known diseases or disorders that carry no increased risk for cancer." Examples of other benign white lesions that should be excluded to arrive at the diagnosis of oral leukoplakia are frictional keratosis (cheek biting), alveolar ridge kera- tosis, leukoedema, white sponge nevus, and Fordyce granules, which are usually buff colored [16,17].

Oral leukoplakia may be asymptomatic or display a benign clinical appearance making it difficult for the clinician to sometimes differentiate it from common reactive or inflammatory (benign) disorders of the oral mucosa [16,17].

With a prevalence of 0.02%, leukoplakias are usually diagnosed after the fourth decade of life. They are more common in males and are 6 times more common among smokers than among nonsmokers. Alcohol consumption is an independent risk factor. Leukoplakia is not associated with any chemical or physical causative agents except tobacco, alcohol, or betel quid. In a minority of leukoplakias, human papillomavirus may have a potential role. Some leukoplakias are idiopathic and may not have a known risk factor [18,19].

Common sites of involvement include the lateral margin of the tongue and the floor of mouth. However, among other locations being the buccal mucosa and the lower buccal grooves are commonly affected because of placement of betel quid at these locations. Gingival leukoplakia (affecting gums) is uncommon [20].

A patch of oral leukoplakia may vary in size from a quite small and circumscribed area to an extensive lesion involving a large area of the oral mucosa.

Two main clinical types of leukoplakia are encountered in clinical practice: homogeneous and nonhomogeneous leukoplakia. The distinction is based on surface color and morphologic (thickness and texture) characteristics. Homogeneous leukoplakias are uniformly flat and thin, have a smooth surface, and may exhibit shallow cracks. Nonhomogeneous varieties comprise 3 clinical types and are usually symptomatic:

Speckled—mixed, white and red in color (also termed erythro-leukoplakia), but retaining predominantly white coloration

Nodular—small polypoid outgrowths, rounded, red or white excrescences

Verrucous or exophytic—wrinkled or corrugated surface appearance [18,19]

Generally, most leukoplakias are asymptomatic and are found during a routine visual examination. Symptoms, if present, are associated with the nonhomogeneous speckled variety and might include discomfort, tingling, and sensitivity to touch, hot beverages, or spicy foods. A red component in the leukoplakia (erythroleukoplakia) indicates possible colonization by Candida species and an increased risk for dysplasia and/or malignancy [18,19]

Non-homogenous OL presents a higher risk for malignant transformation. These two distinct appearances may be seen as dysplastic or non-dysplastic leukoplakia. Prevention and treatment of OL include clinical surveillance and risk factors elimination as first step [20].

Oral Erythroplakia (OE)

OE represents a single erythematous oral mucosal lesion with high malignant trans- formation rate. Is it associated with tobacco and alcohol abuse and high-risk HPV, and its prevalence is between 0.02% and 0.83%, affecting adults of middle age [21].

The term erythroplakia is used analogously to leukoplakia and has been defined as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease." The lesions of erythroplakia are usually irregular in outline, although well defined, and have a bright red velvety surface. Occasionally, the surface is granular [21]. The most commonly involved subsite is the soft palate. Just as there are many oral lesions that present clinically as white patches on the mucosa, there are a number of conditions that appear as red areas. Examples of other red patches that need to differentiate from erythroplakia have been out-

lined. Two common examples of entities often mistaken by practitioners as erythroplakia are erythematous candidiasis (denture-associated stomatitis) and erythema migrans. Other conditions to include in the differential diagnosis are erosive disorders, desquamative gingivitis, discoid lupus, erosive lichen planus, pemphigoid, and other inflammatory/infectious conditions. Well- demarcated, solitary presentation of erythroplakia helps clinically distinguish it from the other more wide- spread disorders listed above [22].

A diagnostic biopsy is essential to obtain a pathologist's opinion to distinguish erythroplakia from the above- mentioned specific and nonspecific inflammatory oral lesions. This should be undertaken urgently because in many cases, the erythroplakia is dysplastic or may harbor carcinoma in situ or even frank carcinomas. Due to the high malignant transformation rate, early diagnosis and treatment are mandatory [21].

Oral Lichen Planus (OLP)

The oral manifestations of lichen planus (OLP) vary from patient to patient. Oral mucosal lesions are usually multiple and have a symmetric distribution. Several factors have been proposed to be able to produce this kind of lesion, but the etiology remains unclear. OLP is more frequent in women in middle age, and the malignant transformation rate is low (<1–6%). Typically, lesions are localized in the buccal mucosa, bilaterally, and usually asymptomatic. Clinical aspect present different type of OLPs, such as reticular, plaque-like, bullous, atrophic or erosive. The most common is the reticular subtype characterized by thin white plaques called "Wickham's striae". Atrophic and erosive patterns are associated with significant pain. Bullous pattern is the least common type of OLP that is characterized by bullae formation. Plaque-like type is frequently observed in smokers. Lesions may have a combination of characteristics [23]. The diagnosis of OLP is typically made clinically and confirmed histologically. Treatment of OLP is generally palliative and not curative. The principal goal of management is to reduce inflammation and alleviate symptomatology with topical steroids [24].

Oral submucous fibrosis (OSF)

OSF is a chronic, insidious 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. History of chewing betel quid and areca nut in an Asian patient who has limited mouth opening should arouse suspicion of this condition. The disease is characterized by the presence leathery mucosal texture and palpable fibrous bands in the oral mucosa, ultimately leading to limitation of mouth opening and rigidity of the tongue [25]. Early features include blanching of mucosa, loss of normal pigmentation, and a burning sensation in the mucosa when spicy food is eaten. On clinical examination, sunken cheeks and limitation of mouth opening may be obvious. In addition, the tongue may be small, exhibit limited mobility, and show marked loss of papillae. The palate may appear pale, with horizontal bands across the soft palate, and the uvula may be shrunken or de- formed tongue [26]. The severity and permutations of the signs and symptoms of OSF are highly variable. The severity of the disease is generally measured objectively by assessing mouth opening and by the presence of leukoplakia or erythroplakia as multiple lesions [27]. Progressive limitation of mouth opening is a hallmark feature of OSF, and this disease has a significant impact on quality of life of affected individuals. Among betel quid users, a new lesion with malignant potential, particularly in association with OSF, has been described as "oral verrucous hyperplasia." [28].

Importance of early detection and oral epithelial dysplasia (OED)

There is general consensus that the clinical stage at the time of diagnosis is the most important predictor of recurrence and mortality in oral cancer patients. The time to diagnosis is influenced by multiple clinical and sociodemographic variables, including patient reluctance to consult a health-care professional due to lack of access to health care, especially in patients with low socioeconomic status, as well as professional delay in diagnosing and treating the disease [29]. Clinicians can improve patients' survival rates if a malignant lesion is detected at an early stage, or if an early dysplasia is discovered and treated prior to malignant progression [30]. A major challenge for early diagnosis of the at-risk tissue is our limited ability to differentiate oral premalignant lesions at high risk of progressing into invasive OSCC from those at low risk [31]. Early detection and screening for oral cancer has the potential to decrease the morbidity and mortality of disease, but methods for screening have not been proven successful. Although a typical routine oral cancer examination requires a 90 seconds visual and tactile examination, too dentists in particular are conducting these exams [32].

The preferred term for the histopathological changes in oral epithelium that indicate a risk of malignant transformation is epithelial dysplasia, simply meaning abnormal growth. Epithelial dysplasia describes histological changes only and has no clinical morphological equivalent [34]. However, there is clinical and molecular evidence, that the changes are not neoplastic, rather they are harbin-

gers of neoplasia as evidenced by the fact that epithelial dysplasia has molecular changes distinct from those in carcinoma, often persists for decades without progression and sometimes resolves with conservative treatment or spontaneously equivalent [35].

While OPMD is ascribed to clinical presentations, oral epithelial dysplasia (OED) is histomorphologically defined as a spectrum of epithelial changes associated with an increased risk of transformation to carcinoma. Several morphological features of OED are classified as either "architectural" (disordered tissue organization) or "cytological" (individual cell abnormality) [37]. Grading of dysplasia is essential to inform subsequent management of any given OPMD. The overall evidence indicates a positive correlation between the likelihood and time to malignant transformation with increasing degrees of dysplasia. The most widely utilized grading system is that which utilizes three-tiers (mild, moderate and severe dysplasia) [38]. This system takes into account, but is not limited to, the epithelial thickness in thirds affected by dysplastic changes.

Oral potentially malignant disorders are recognized and defined clinically and dysplasia may or may not be present in them. For this reason, the term potentially malignant, derived and is used to describe the clinical changes [3,33]. Even when dysplasia is present, it still only indicates a risk of malignant transformation; most dysplastic lesions never transform in the life of the patient and the time to transformation in those that do is highly variable. The common histopathological changes of epithelial dysplasia in OPMDs, the majority of which present as leukoplakia, erythroplakia or mixed red and white mucosal changes [4].

Autofluorescence tools for early detection and screening of OPMDs

Attempts to expose tissues at specific wavelengths of light have resulted in the discovery of differences between the autofluorescence properties of different tissues Fluorophores are the parts of molecules that are responsible for fluorescence; therefore, the loss of fluorescence is characteristic of tissues in which the internal fluorophore environment has changed. Tissue absorbs fluorescent light and can take on a color ranging from brown to black. This is unlike healthy tissue, which emits pale green autofluorescence light [42].

Using the tissue autofluorescence concept for diagnosis of dysplastic lesions in the oral cavity hinges on the changes in the structure and metabolism of the epithelium and the subepithelial stroma when interacting with light. Specifically, loss of autofluorescence in dysplastic and cancerous tissue is believed to reflect a complex mixture of alterations, due to tissue remodeling such as the breakdown of the collagen matrix and elastin composition as well as alterations to metabolism such as the decrease in flavin adenine dinucleotide concentration, and increase the reduction form of nicotinamide adenine dinucleotide associated with progression of the disease [38,39].

Further, these structural changes in tissue morphology are associated with alterations not only in the epithelium but also in the lamina propria (e.g., thickening of the epithelium, hyperchromatin and increased cellular/nuclear pleomorphism, or increased microvascularity). The latter changes lead to increased absorption and/or scattering of light, which in turn reduces and modifies the detectable autofluorescence signal [40].

In the past decade, several forms of autofluorescence technology have been developed for inspection of the oral mucosa. It is a simple hand-held fluorescence visualization tool for the direct visualization of tissue fluorescence, and it is quick and easy to use. The site of interest is viewed through the instrument eye piece. Normal oral mucosa appears pale green due to the tissue autofluorescence resulting from stimulation with intense blue light excitation at 400–460 nm wavelength. In contrast, dysplastic and malignant lesions will appear darker than the surrounding healthy tissues as they have decreased autofluorescence [41,42,43].

The most commonly used device that can detect the loss of fluorescence in tissues is the VELscope® (Visually Enhanced Lesion Scope; LED Dental Inc., White Rock, BC, Canada), which emits waves at a length of 400–460 nm. Research has shown that the most effective light color is from red to green, with a wavelength of approximately 405 nm. The sensitivity of this method is 97–98%, and its specificity is 94–100% [44,45].

Two studies emphasized the controversial use of this system for early diagnosis. One study, demonstrated that VELscope examination did not provide a definitive diagnosis regarding the presence of epithelial dysplasia, and that loss of autofluorescence is not useful in diagnosing epithelial dysplasia without relevant clinical interpretation [46]. While the other study showed that the VELscope was useful in confirming the presence of oral leukoplakia and erythroplakia and other oral mucosal disorders, but the device was unable to discriminate high-risk from low-risk lesions [14].

An early observation for the use of autofluorescence as a diagnostic tool for oral and cervical cavities has been the autofluorescence identification of lesions that under white light inspection were clinically occult [47]. This ability is yet to be entirely explored; however, it encourages three potential clinical directions for the use of this evaluation method:

early diagnosis of premalignant lesions and cancers that are clinically occult; early identification of recurrent disease, either as a second primary tumor situated elsewhere in the oral cavity or as a recurrence at treated lesion site; better delineation of the surgical margin in malignant lesions [48].

CONCLUSION

The knowledge and education in detecting oral cancer at its premalignant phase is the key to prevent its progression to later stages. In order to improve early detection, it is imperative to increase the health-care providers' depth of knowledge about oral cancer, their risk factors and the most common oral premalignant conditions. Future research can also be directed towards establishing appropriate clinical practice standards for early detection examinations. All in all, one can suggest, that autofluorescence devices could supplement clinical oral examination and aid the identification of OPMDs during biopsy procedures, potentially improving oral cancer screening among patients seeking care. Currently, the new innovative visual-based techniques show promising results, but lack strong evidence to support their effectiveness in early detection. Their utilization in clinic practice is still anecdotal.

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