A Brief Review of Common Oral Premalignant Lesions with Emphasis on Their Management and Cancer Prevention

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Abstract Long-term outcomes associated with oral cancer and its management over the past several decades has caused concern and the value of mass oral cancer screenings has come under scrutiny. Though not all oral carcinomas are preceded by premalignant lesions as clinically visible morphological alterations occur secondary to the cellular or molecular changes, certain high risk lesions have been identified. Their management remains controversially polarized between surgical excision to prevent malignant change and conservative medical or surveillance techniques. Though oral cancer is one of the “major killers” of modern times, there seem to be no widely accepted criteria for decision making in clinical practice, the evidence base is scanty and uncertainty persists throughout investigation, diagnosis, and treatment. In this article, we have briefly discussed the common premalignant

lesions, with an emphasis on their evidence based management and prevention.

Keywords Premalignant lesions · Oral cancer · Surgery, radiotherapy · Chemoradiation

Introduction

A premalignant lesion is a disease, syndrome, or finding that, if left untreated, may lead to cancer. The term was coined in 1875 by Romanian physician Victor Babeş. Oral premalignant lesions (OPMLs) are relatively common, occurring in about 2.5% of the general population and are an important target for cancer prevention. Two most important lesions are leukoplakia and erythroplakia or erythroleukoplakia (when both occur in the same lesion) and represent clinical rather than histological diagnoses, but their importance derives from the high proportion of cases in which biopsy reveals dysplasia or even frank carcinoma [1]. They can be detected visually, are easily amenable for screening and diagnosis and there is enough evidence to indicate that the cascade of premalignancy is triggered by tobacco (smoking, smokeless or inhaled, tobacco substitutes like pan masala or betel nut quid) and thus is considered as the strongest risk factor for majority of the oral lesions, followed by alcohol ingestion, poor oral, and dental hygiene [2]. Though researchers are proposing a genetic theory for OPMLs, similar changes seem to be caused by tobacco and alcohol as well [3]. Detection of OPMLs at an early stage, especially in high risk groups is of utmost importance to prevent further morbidity as they have shown a rate of progression and cancer transformation of up to 17% within a mean period of 7 years after diagnosis. The highest transformation rate is seen in

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heterogeneous erythroplakia and erythroleukoplakia with dysplastic changes [4]. Management modalities, like removal of exposures, chemoprevention, and ablative therapies have significantly reduced the mortality rates from 87% to 23% worldwide [3]. The treatment approach depends on numerous factors, like the size, clinical appearance, and histology of the lesion. Field cancerization too, leads to the formation of multiple OPMLs of different stages. The quality of life is significantly affected by morbidity in these patients and is a major economic burden on healthcare [5].

Common OPMLs

- Leukoplakia and erythroplakia or erythroleukoplakia, when both coexist are two very common clinical lesions
- Oral submucous fibrosis (OSMF)
- Lichen planus (very low risk of turning malignant)
- Other lesions (smokeless tobacco keratosis, leukoedema, and leukoderma)

Varied appearances of these lesions make it extremely difficult to classify them into a said group and are likely to be interpreted subjectively by the clinician. A histopathologic diagnosis is generally more indicative of premalignant change than clinically apparent alterations [6].

Leukoplakia

The World Health Organization (WHO) group has defined leukoplakia as “a white patch or plaque that cannot be characterized, clinically or pathologically, as any other disease”. These lesions are potentially premalignant and vary in size, shape, and consistency, and macroscopically said to be homogenous and nodular (Fig. 1). There is usually no relationship between morphologic appearance and histologic diagnosis. Histologic examination may reveal hyperkeratosis, dysplasia, carcinoma-in-situ (CIS) or invasive squamous cell carcinoma. Dysplasia occurs in

Fig. 1 Nodular leukoplakia

as many as 30% of leukoplakic lesions, whereas a small percentage of lesions show invasive SCC on pathologic examination. It is important to note that 60% of oral mucosa carcinomas are present as white, keratotic lesions [7].

Proliferative Verrucous Leukoplakia

Proliferative verrucous leukoplakia (PVL) is a distinct clinical form of oral leukoplakia defined by its progressive clinical course, changing clinical and histopathological features, and a great potential to develop into cancer (Fig. 2). PVL behaves in a more aggressive and relentless manner than the more innocuous white oral lesions that it can resemble clinically. PVL is seen more frequently in females and most often diagnosed after the sixth decade of life [8]. An interesting feature to note is that tobacco use is not strongly linked to the presence of PVL, though most patients with PVL progress to oral cancer [9, 10]. As this is a persistent and progressive lesion, it requires a very close follow-up along with early and aggressive treatment to increase the chances of a favourable outcome [11].

Erythroplakia

Erythroplakia (Fig. 3) and/or erythroleukoplakia is a red or erythematous patch of the oral mucosa and is associated with significantly higher rates of dysplasia, CIS, and invasive carcinoma than leukoplakia [4].

Oral Submucous Fibrosis

Oral submucous fibrosis (OSMF) (Fig. 4) is a chronic, debilitating disease characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues) [12]. It results in marked rigidity and an eventual inability to open the mouth.

Fig. 2 Proliferative verrucous leukoplakia of the tongue

Fig. 3 Erythroleukoplakia of the buccal mucosa

The buccal mucosa is the most commonly involved site, but any part of the oral cavity can be involved, even the pharynx. The condition is well recognized for its malignant potential and is particularly associated with areca nut chewing, the main component of betel quid. The mixture of this quid or chew is a combination of the areca nut (fruit of the *Areca catechu* palm tree, erroneously termed betel nut) and betel leaf (from the *Piper betel*, a pepper shrub), tobacco, slaked lime (calcium hydroxide), and catechu (extract of the *Acacia catechu* tree) [13]. The pathogenesis of OSMF is not well established and hence is believed to be multifactorial. The cascade begins with a juxtaepithelial inflammatory reaction in the oral mucosa, interspersed with healing and fibrosis, with trismus being the end result [14].

Lichen Planus

The premalignant potential of lichen planus (Fig. 5), a relatively common oral mucosal lesion, is in dispute. Pathologists seem to believe that the occasional epithelial dysplasia or carcinoma found in patients may be either coincidental or evidence that the initial diagnosis of lichen

Fig. 5 Lichen planus

planus was erroneous [15]. It is frequently difficult to differentiate lichen planus from epithelial dysplasia; one study found that 24% of oral lichen planus cases had 5 of the 12 WHO diagnostic criteria for epithelial dysplasia and only 6% had no histologic features suggestive of that disorder [16]. However, a few reports on lichen planus patients followed over time indicate a higher than expected rate of malignant transformation. Hence, it is worthwhile to biopsy the lesion at the initial visit to lay all doubts to rest [17].

Other Lesions

Premalignant changes arising in other oral lesions are uncommon. White lesions, such as linea alba, leukoderma, and leukoedema are common in the oral cavity but have no propensity for malignant transformation, while frictional keratosis has a small risk of transforming into cancer if local irritants are not removed [18]. The health professional can usually identify them by patient history and clinical examination.

Clinical Features of Oral Premalignancy

Clinical presentation and appearance of a lesion is a poor tool to determine premalignant changes. A diagnostic biopsy should be considered for any mucosal lesion that persists for more than 14 days after obvious irritants are removed [6]. A few patient-related factors predisposing/contributory to the occurrence of OPMLs are discussed below.

- 1) **Age:** Age by itself is not considered a risk factor for OPMLs, as it takes time to accumulate genetic changes that cause dysplasia and oral SCC. Hence, these lesions are common in middle aged and older individuals. The mean age at diagnosis of oral premalignancy is 37–

Fig. 4 Oral submucous fibrosis

- 59 years; only 5% under 30 years of age are seen to have OPMLs [5].
- 2) **Sex:** Epithelial dysplasia has a predilection for males. But the overall scenario is fast changing with a reversal of the M:F ratio and is due to the increased use of tobacco and alcohol among women [19].
  - 3) **Anatomic location:** Studies relating premalignant tissue changes to anatomic sites have produced varying results. One such study found 21.8% of oral epithelial dysplasias occurred on the buccal mucosa, 13.7% on the palate, and 12.3% on the floor of the mouth [20]. Another study on leukoplakia revealed that the mandibular mucosa and sulcus were involved in 25.2% of their cases and on the buccal mucosa in 21.9% [21]. Interestingly, the distribution of locations is much different from that of SCC of the oral cavity, for which the tongue, oropharynx, lip, and floor of mouth are the most common sites.
  - 4) **Clinical presentation:** Majority of the lesions are asymptomatic to start with and is the reason why are neglected, only to present with a frank cancer. Although most premalignant lesions are white (leukoplakia), they vary considerably in their initial presentation. The development of pain and soreness may be associated with malignant change.
  - 5) **Probability of malignant change:** It has been documented that about 5–18% of epithelial dysplasias turn malignant. Though diagnosed, many times these lesions are kept under surveillance. A systematic follow-up is crucial in these patients. A greater risk of malignant change in an epithelial dysplasia has been associated with these factors: (a) erythroleukoplakia, (b) a proliferative verrucous appearance, (c) location at a high-risk anatomic site, such as the tongue or floor of mouth, (d) the presence of multiple lesions, and (e) a history of not smoking cigarettes [22–24].

Diagnosis and Treatment

Though biopsy is a must to verify the premalignant status of an oral lesion, a noninvasive test, the topical application of toluidine blue to a suspicious area that helps identify the presence of dysplastic or carcinomatous lesions, is available. Zhang et al. [25] reported that proper use of toluidine blue yielded false-positive and false-negative rates less than 10%. The agent is believed to bind selectively to the DNA and RNA in cells. As this test can be done in an out-patient department, it helps clinicians to identify lesions more likely to have premalignant or malignant changes, select an appropriate biopsy site within a large lesion or monitor high-risk patients who have been previously diagnosed with a premalignant or malignant lesion. But when doubtful of

the result, a biopsy should be performed. Toluidine blue is an adjunct to biopsy, not a replacement!

All leukoplakic lesions should undergo biopsy, if there is a strong suspicion of malignancy or when they do not respond to conservative therapy. For small areas of leukoplakia, excisional biopsy is usually appropriate. For larger lesions, incisional biopsy is generally preferable: it is important to obtain an adequate-size biopsy specimen, in that varying degree of hyperplasia and dysplasia may occur within the same specimen. Hyperkeratotic lesions may be followed on a long-term basis, with rebiopsy performed if there are any changes in size or appearance. Lesions characterized by dysplasia and CIS should be completely excised to clear margins when possible [7, 11].

Erythroplakia is managed in much the same fashion as leukoplakia. Complete surgical excision is indicated if either a premalignancy or malignancy is suspected and confirmed with a close follow-up [12].

The treatment of patients with OSMF depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with OSMF present with moderate-to-severe disease, which is irreversible. Medical treatment is symptomatic and aimed at improving mouth movements and includes administration of steroids, placental extracts, hyaluronidase, and IFN-gamma [26, 27]. Drugs, like lycopene, pentoxifylline, and collagenase have been recently used with rewarding results [28, 29]. Surgical treatment is indicated in patients with severe trismus and/or biopsy results revealing dysplastic or neoplastic change. Surgical modalities that have been used include simple excision of the fibrous bands, split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy, and nasolabial flaps and lingual pedicle flaps [30, 31].

Surgical excision is the treatment of choice for oral epithelial dysplasia and can be accomplished with a scalpel or a CO₂ laser [32]. The latter provides a relatively bloodless surgical field. Once an incisional biopsy has established the diagnosis of epithelial dysplasia, the remainder of the lesion should be removed completely, as the probability of malignant change although unknown, must be considered substantial. Reported recurrence rates for premalignant lesions are as high as 34.4%. Chandu et al. [33] found a 18% recurrence rate in cases of severe epithelial dysplasia or CIS in which the lesion had been excised with a 3–5 mm margin of normal tissue. Whether recurrence relates to continued exposure to risk factors or to an underlying mechanism that initiated the original lesion is unclear, but patients should be closely monitored for recurrence.

The hyperkeratotic lesion can pose difficulties in management as it has a small potential for malignant change. It calls for removal of any local irritants first if

present, and then if after 2 weeks the hyperkeratosis is still present, excision should be considered, especially if the lesion is in a high-risk site (e.g., floor of mouth, ventral tongue) or if the patient has been exposed to established risk factors for oral cancer.

Problems in Treatment

The management of patients with OPMLs can present problems. The potentially invasive nature of premalignant lesions together with their large extent influences the treatment. The common modalities of treatment of these lesions are CO₂ laser surgery, surgical excision, cryotherapy, electrosurgery, and radiotherapy. Less pain, little bleeding, minimal post-operative edema, reduced risk of infection, and low recurrence rates are advantages observed following CO₂ laser surgery in the mouth when compared to other modalities of treatment. Healing following CO₂ laser surgery progress well with little postoperative scarring and re-epithelialization is complete after 4–6 weeks. The newly formed epithelium appears normal and is soft on palpation [34].

Chemoprevention

“Chemoprevention” should be considered in a patient if the size of the lesion, its location, or the medical status would make surgical removal difficult to try to prevent progression to carcinoma [35]. However, although antioxidant supplements have shown promise, they have an uncertain success rate and no long-term results.

Beta-carotene and the retinoids are the most commonly used antioxidant supplements for chemoprevention of oral cancer. Beta-carotene is a carotenoid found primarily in dark green, orange, or yellow vegetables. Clinical trials have found that treating oral leukoplakia solely with beta-carotene supplements is associated with clinical improvement; rates have ranged from 14.8% to 71% [33]. No side effects have been reported in patients given beta-carotene supplements; but there is little information about recurrence following discontinuation of this substance. Retinoids are compounds consisting of natural forms or synthetic analogues of retinol. Of the more than 1,500 synthetic analogues of vitamin A, 13-cis-retinoic acid (13-cRA) has generated the great interest and has been shown to cause temporary remission of oral leukoplakia, but with side effects in a high percentage of patients. Kaugars et al. [36] followed up 44 patients with oral leukoplakias who were treated with 1–2 mg/kg/day of 13-cRA for 3 months; nearly 67% of the patients had more than a 50% reduction in lesion size, but 79% experienced a variety of side effects. Other studies have noted that lowering the 13-cRA dose

reduced the incidence and severity of side effects, but there have been numerous reports of recurrence after discontinuation [31]. To date, no combination of antioxidants has demonstrated its clear superiority. Beta-carotene with ascorbic acid and/or alpha tocopherol is attractive because of lack of side effects, but clinical improvement typically takes several months. 13-cRA requires a shorter time to produce a clinical response, but use of this substance necessitates baseline and periodic serologies, and close monitoring for side effects; women using it must also avoid becoming pregnant.

Emerging Trends

Many human papilloma viruses (HPVs) are associated with papillary and verrucous lesions of skin and mucous membranes [37]. Oncogenic HPVs have been identified in many oral precancerous dysplastic and squamous carcinoma tissues; HPV 16 has been localized in normal oral mucosa as well. In an investigation of head and neck SCC using polymerase chain reaction methods, over 80% were found to harbour HPV 16 [38]. Mutations are also prevalent in both precancerous and overtly malignant oral tumours. However, determining the role these gene products and other oncogenes play in oral cancer causation and understanding their interplay with other carcinogens, such as tobacco products require further trails. Finally, identifying an accurate biomarker for the premalignant state would aid in diagnosis and also allow premalignancy rather than carcinoma to be an end point in clinical trials, and usher new hope to these patients.

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