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Dilemmas in managing oral dysplasia: a case report and literature review

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Abstract

Oral epithelial dysplasia (OED) is a premalignant lesion which has an unpredictable course of progression. Its management has remained controversial due to a lack of high-quality prospective studies evaluating the different treatment modalities.[1] We present a patient with a long history of OED which subsequently transformed into malignancy. The clinical features of OED and the controversies surrounding its management, as they present in the current literature, will also be reviewed and discussed.

OED is a chronic, often progressive premalignant disorder of the oral mucosa. It is a term used to describe the histopathological changes seen in the oral mucosa and may be graded histologically along a continuum of cellular change as mild, moderate or severe ('carcinoma *in situ*'), where lesions with more cellular disorganisation are generally believed to have a greater risk of malignant change.[1] Clinically it may present as leukoplakia (white lesion), erythroplakia (red lesion), or leukoerythroplakia (mixed lesion).[2]

Erythroplakia is defined as bright red velvety plaque or patch which cannot be characterised clinically or pathologically as being due to any other condition[3]. It is associated with a significantly higher rate of dysplastic change than leukoplakia.[4]

Leukoplakia is a clinical diagnosis and describes an oral white lesion that cannot be rubbed off or characterised as any other definable lesion.[5] The term has been more recently defined as a predominantly white lesion with premalignant potential.[6] Clinical variants are classified into two groups: homogeneous and non-homogenous leukoplakia.

Homogeneous leukoplakia is defined as a lesion of uniform flat appearance that may exhibit superficial irregularities, but with consistent texture throughout. Non-homogeneous leukoplakia is a predominantly white or mixed white and red lesion with an irregular texture that may be characterised by a flat, nodular, or exophytic appearance.[7]

The clinical appearance of leukoplakia is important as homogeneous lesions are reported to have a lower rate of malignant transformation than lesions which are speckled, erosive, ulcerative, or verrucous in appearance.[2]

The rate of malignant transformation of oral leukoplakia into oral mucosal squamous cell carcinoma (OMSCC) varies from 2.2–17.5%.[8–10]

Despite advances in surgery, radiotherapy, and chemotherapy, the 5-year survival rate for oral cancer has not improved significantly over the past decades and remains at around 50%.[11]

Case report

A 52-year-old Caucasian woman presented to an oral and maxillofacial surgeon complaining of an intermittently uncomfortable white patch on her left lateral tongue of 2 years duration. She was generally fit and well and was not taking any regular medications. There was no history of tobacco use, but she had a weekly consumption of 1–2 units of alcohol.

On examination, a 1cm-diameter white lesion was present on left lateral surface of the tongue adjacent to a sharp amalgam restoration on her lower left first molar. As she was a clarinet teacher it was thought that her tongue movement against the sharp amalgam restoration may be causing the lesion. The amalgam restoration was smoothed and the lesion was monitored regularly.

At the 4-month review, the lesion had grown to 2.5 cm diameter. A biopsy of the left tongue was carried out (Figure 1 and Figure 2), and histopathology indicated a squamous dysplasia with an associated candidal infection. Amphotericin B was prescribed to treat the candidal infection, and the lesion was monitored.

Figure 1. Low-magnification photomicrograph showing squamous dysplasia

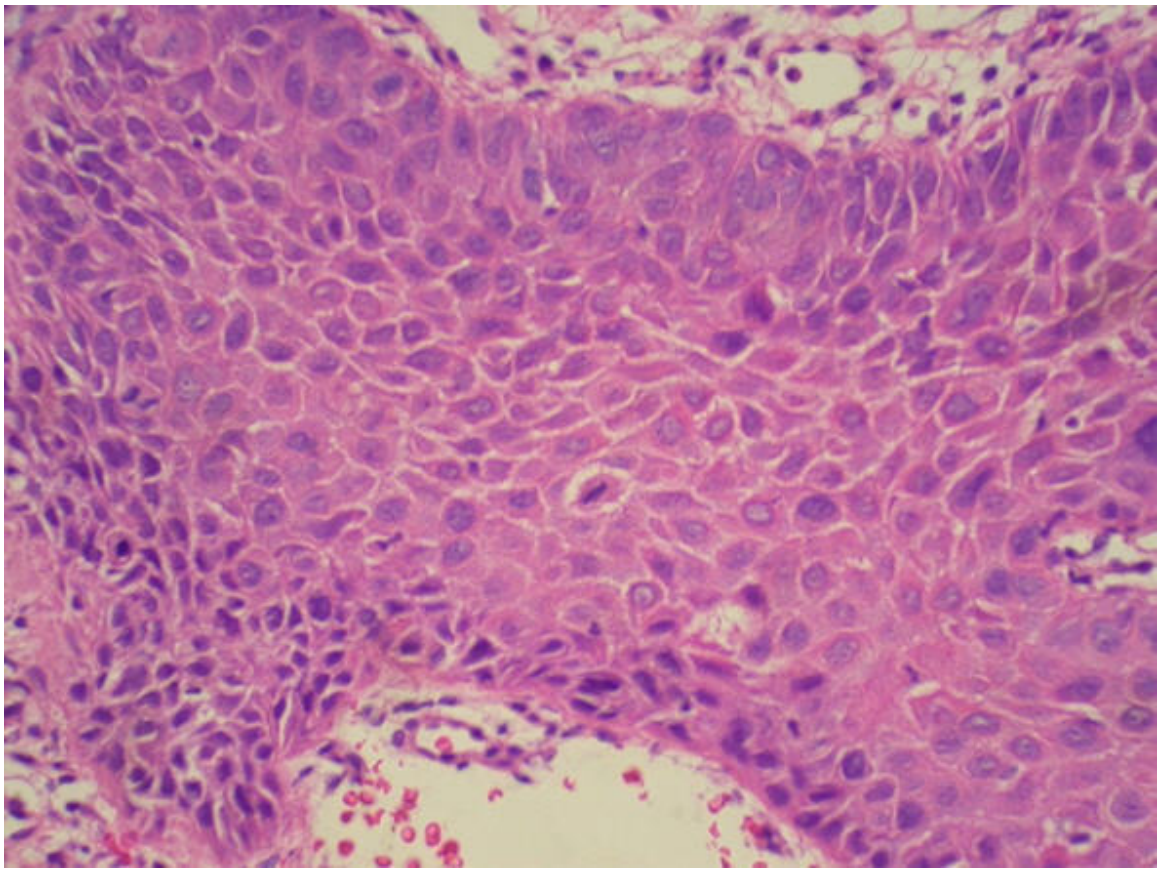
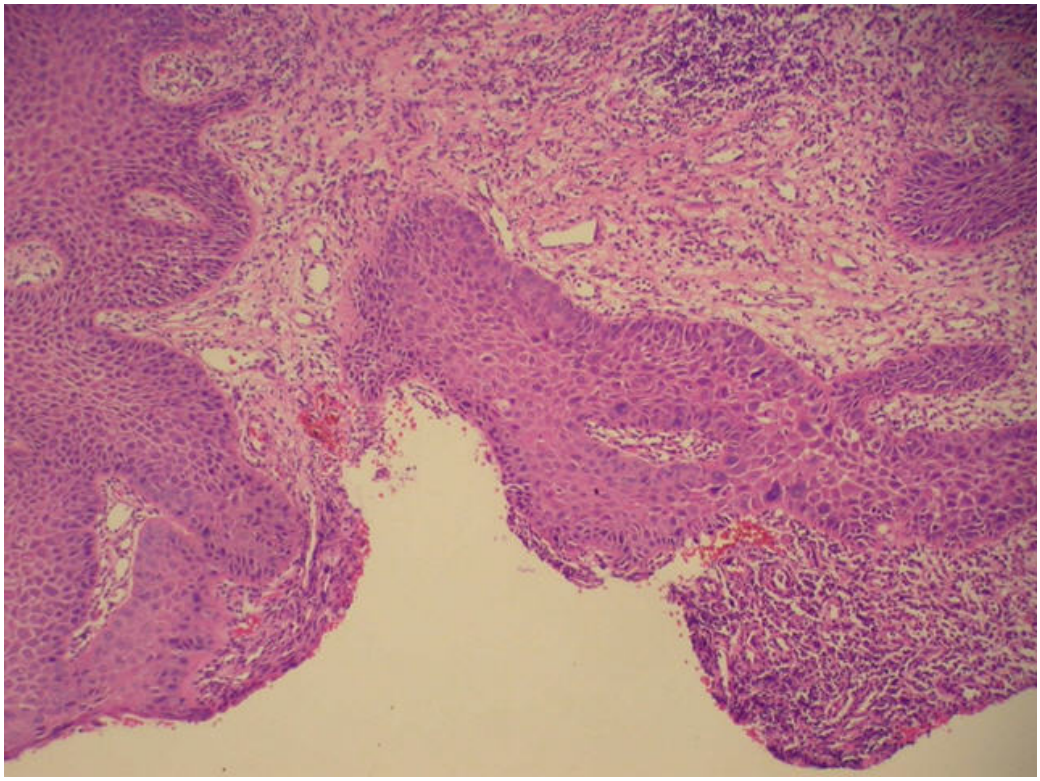


Figure 2. High-magnification photomicrograph showing cellular atypia and architectural disturbance in the epithelial layer

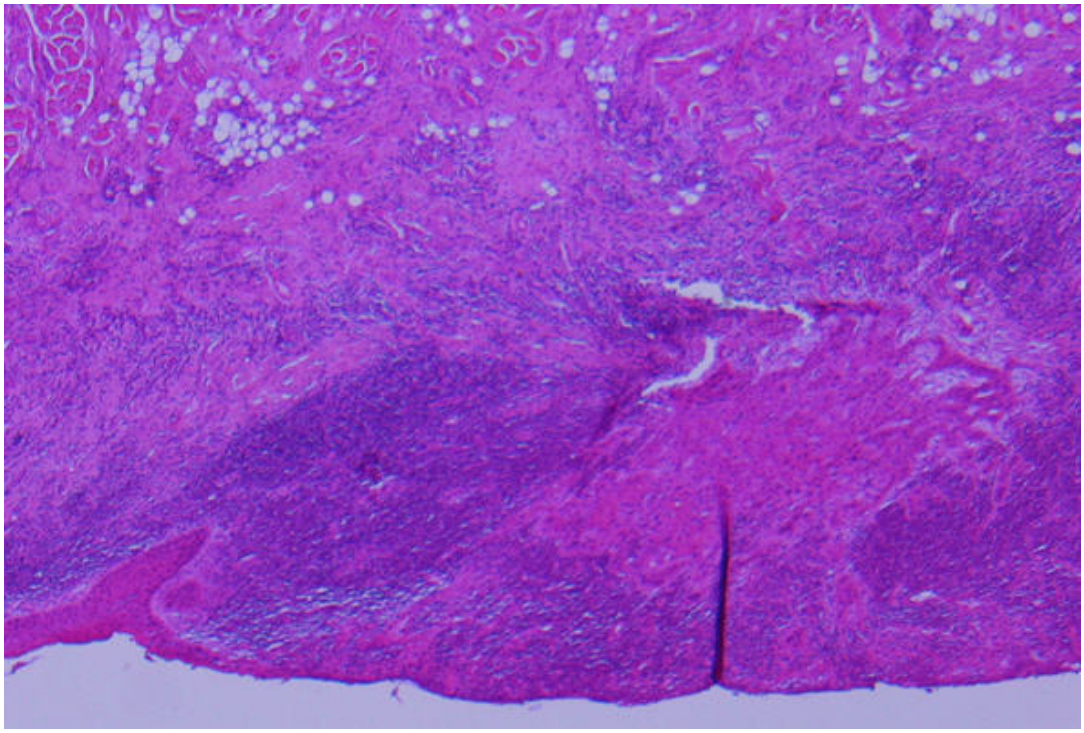


At the 2 months review, the lesion had not resolved, and the patient was referred to the Oral and Maxillofacial Surgery/Oral Medicine Clinic for further management. A diagnosis of OED secondary to chronic dental trauma was made based on the lesion's clinical and histological features.

She was referred to her private dentist for a crown on the heavily restored tooth, and was instructed to return to the Oral Medicine Clinic should the lesion not resolve.

After 2 years she presented again to the Oral Medicine Clinic. There had not been any improvement in the lesion which was still 2.5 cm in diameter and had developed a granular leukoerythroplakic appearance. An incisional biopsy at this stage diagnosed a poorly differentiated squamous cell carcinoma (Figure 3). A primary diagnosis of T2N0M0 was made. There was no palpable neck node and the computed tomography scan did not reveal regional disease.

Figure 3. High-magnification photomicrograph showing a poorly differentiated squamous cell carcinoma



The patient was then referred to the Multidisciplinary Head and Neck Oncology Clinic. Subsequent surgery involved a left partial glossectomy and pandescopy to exclude concurrent lesions. The histology of the tumour demonstrated an adequate clear surgical margin, but there was a maximum tumour thickness of 10 mm, which correlated to a high risk of occult metastasis.

A left supraomohyoid neck dissection was performed 3 weeks later to determine the presence of neck disease and ensure elimination of such pathology. A small biopsy of her posterior tongue was also performed at this stage, as she had complained of discomfort in this area and there was some subtle induration on palpation.

The neck dissection yielded one positive node without extracapsular spread. Histopathology from the tongue biopsy confirmed the diagnosis of a poorly differentiated squamous cell carcinoma under the mucosa of the posterior tongue, with perineural invasion evident.

A further excisional biopsy of the posterior tongue squamous cell carcinoma was undertaken, and a 1.5 cm wedge of tissue was taken from the posterior end of the scar which identified the site of the previous partial glossectomy. The tonsillar pillar and inferior portion of the tonsil were included in the resection.

Histopathology from the tongue biopsy confirmed the diagnosis of a poorly differentiated squamous cell carcinoma under the mucosa of the posterior tongue, with clear margins of the surgical specimen. This was believed to be an area of metastatic spread, rather than a primary site.

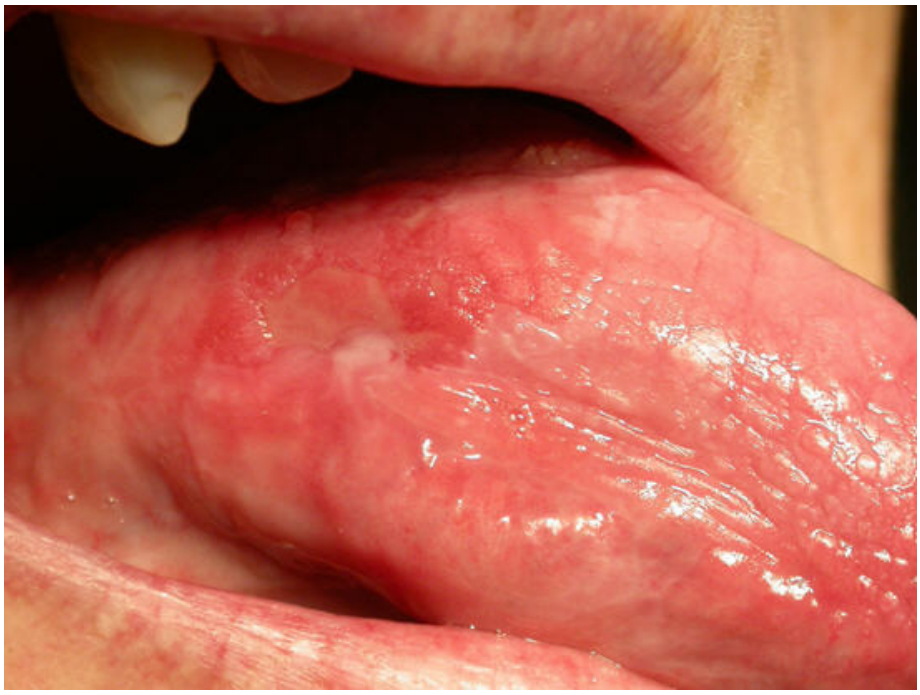
Due to the narrow excisional margin around the tumour, as well as the development of a metastatic lesion, the patient underwent postoperative radiation therapy receiving 60 Gy in 30 fractions.

The patient is currently being reviewed in the multidisciplinary head and neck oncology clinic and has remained disease-free 6 months post treatment.

Discussion

This case study presented a patient with chronic OED who was lost to follow-up and subsequently developed malignancy in the lesion. The difficulty for practitioners when managing OED is not only to identify a malignant lesion (Figure 4), but also to monitor the progressive changes in a dysplastic lesion and act appropriately.

Figure 4. An example of OMSCC right lateral border of the tongue



Histological examination of tissue from a biopsy is the only definitive method of diagnosing OED.[12] It has been reported that only 25% of leukoplakias undergo biopsy,[13] so clinicians must be aware of the of clinical features which are associated with a higher risk of malignant transformation (Table 1) and systemic risk factors for development of OMSCC (Table 2).

A patient with one dysplastic lesion also has a higher risk of developing dysplastic lesions elsewhere in their mouth. This is due to field changes within the oral mucosa, which involves cellular changes due to environmental and genetic influences, such as tobacco use, which render the whole mucosa susceptible to malignant change.[29] It is possible that these patients may have multiple areas of oral mucosa which are at risk

of malignant transformation. This makes regular examination of the whole mouth important, as these patients may develop multiple dysplastic lesions.

In the early stages, OMSCC may appear as a small area of induration with localised change, such as erosion, erythema, or keratosis.[13] The changes are often subtle and asymptomatic. It is important for the clinician to maintain a high index of suspicion, especially if risk factors such as tobacco or alcohol use are present.[31]

Due to the lack of a predictable natural history, there is no general consensus regarding the management of premalignant lesions.[4] Several strategies have been used including observation, non-surgical treatment, cryotherapy, laser vaporisation, and/or excision and scalpel excision.[29]

Management of suspicious lesions should begin with the removal of any obvious associated factors such as trauma from adjacent teeth or prostheses. Candidal infection should be treated with a suitable antifungal medication, and any nutritional deficiencies addressed. Other risk factors such as tobacco and alcohol use should be eliminated.[31]

Any oral lesion that does not respond to initial therapeutic measures within 2 weeks should undergo biopsy.[31] While monitoring patients with leukoplakia, any changes in signs and/or symptoms indicate that the lesion should be re-biopsied.[12]

If the lesion persists, or shows moderate to severe dysplasia, treatment by excision is generally recommended.[29] This applies in particular to lesions in high risk sites (Table 1), or in patients who are at high risk for cancer development due to associated risk factors (Table 2).[18] Research shows that 20–35% of oral leukoplakias recur after surgical excision, so ongoing review of these patients is vital.[4,32]

Table 1. Clinical features associated with malignant transformation of leukoplakia

Feature	Studies	Description
Clinical type	Silverman et al[4]	Speckled leukoplakia and leukoplakia with histological evidence of dysplasia have a higher rate of malignant transformation than homogeneous leukoplakia.
Site	Silverman et al[4] Kramer, El Labban, Lee[14] Waldron, Shafer[15]	Leukoplakia of the floor of mouth or ventral surface of the tongue are at a higher risk of malignant transformation.
Demarcation	Saito et al[16]	Patients with multiple oral leukoplakias have a higher rate of developing OMSCC than patients with localised lesions.
Size	Holmstrup et al[13]	Lesions larger than 200mm^2 are 5.4 times more likely to undergo malignant transformation.
Candida infection	Bánóczy, Sugar[17]	A higher malignant transformation rate has been reported in leukoplakias with associated chronic candidal infections.
Human papilloma virus (HPV)	Reibel[18] Miller, Johnstone[19]	HPV has been linked as a risk factor, especially HPV 16 and 18. The likelihood of detecting HPV was 4–5 times higher in OMSCC than in normal oral epithelium.
Epithelial dysplasia	Silverman et al[4]	Leukoplakia with pre-existing oral dysplasia has a shorter interval of time to malignant transformation compared to leukoplakia without dysplasia.

Table 2. Systemic risk factors for malignant transformation of leukoplakia

Risk factor	Studies	Description
Tobacco consumption	Hashibe et al[20] Balaram et al[21] Lewin et al[22]	The risk of developing oral cancer is 2.5–6.5 times greater for smokers than non-smokers. Betel nut or quid chewing is also associated with a higher risk of OMSCC.
Alcohol consumption	Hashibe et al[20] Mashberg et al[23]	Moderate to heavy alcohol drinkers have a 2–8 times greater risk of developing OMSCC. The harmful effect of alcohol and smoking is synergistic.
Diet	Petridou et al[24] Maserejian et al[25]	A diet high in vitamin C, carotene, thiamine, vitamin B6, folic acid, potassium, and iron has been found to have a decreased risk of developing OMSCC.
Genetic factors	Ichikawa et al[26]	p53 is a tumour suppression gene which mediates the cellular response to DNA damage. It is frequently mutated in OMSCC.
Female gender	Silverman[27] Bánóczy[28]	Although leukoplakia is more common in men, it has been found that women with leukoplakia have a higher rate of malignant transformation than men.

There is a lack of randomised controlled clinical trials analysing the effectiveness of surgical treatment in preventing the progression of these premalignant lesions to OMSCC.[7] However, it remains the most commonly practiced approach in managing leukoplakia for many clinicians,[33] as it provides a biopsy specimen which can be examined for the extent of dysplasia or malignancy. A split thickness skin grafting or mucosal grafting may be necessary in a large defect to prevent restriction of oral function.[29]

Carbon dioxide laser is an alternative method of carrying out ablation or excision of the lesion. The main criticism of laser ablation is that the tissue is vaporised and not available for histological examination.

Multiple biopsies need to be taken of the affected area before ablation to determine the histopathology of the lesion.[35] For this reason, the laser should be used to excise rather than ablate the lesion to allow for histological evaluation of the entire lesion. The disadvantage of this technique is that epithelial migration is delayed and wounds may take slightly longer to heal than if the lesion is surgically excised.[29]

Another surgical approach to treating OED is liquid nitrogen cryotherapy, which involves the use of extreme cold to destroy abnormal cells. It has been shown that malignant transformation of oral leukoplakia is higher amongst patients who receive cryosurgery or cryosurgery and excision when compared with patients who have only surgical excision.[35]

At present there is no evidence of effective nonsurgical treatments in preventing progression of dysplasic lesions to OMSCC. Interventions with topical bleomycin, systemic cis-retinoic acid, and systemic lycopene may help to resolve oral epithelial dysplastic lesions in the short term, but there is no evidence that these treatments are effective in preventing the malignant transformation of dysplastic lesions.[36]

Conclusion

There is a lack of consensus on the management of oral dysplasia. It is essential to remove any possible aetiological factors, and all dysplastic lesions require regular follow-up.

A surgical approach has not been shown to consistently prevent malignant change; however, it may be useful in moderate-to-severe dysplasia as it removes the bulk of the lesion and allows for histological assessment. Randomised controlled trials are required to determine the effectiveness of surgical and non-surgical treatment in preventing malignant transformation.

We recommend a 6-monthly review by the GP or specialist to ensure early detection of malignant transformation. The importance of clinical photographs to accurately document any lesion progression can not be overstated. If there is any uncertainty regarding the diagnosis or screening of these patients, a specialist opinion should be promptly sought.

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