Educational Article

Oral potentially malignant disorders: advice on management in primary care

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Abstract – Introduction: The diagnosis of and risks associated with oral potentially malignant disorders (OPMD) have been widely reported, but little has been published on the management of OPMDs in a primary dental care setting. Hospital services face ongoing pressures due to long-term follow-up, with a need for surveillance to be jointly undertaken with primary dental care clinicians. In a primary care setting, identification and surveillance of OPMDs can be challenging as no universal guidance exists on recommended recall intervals. Corpus: In this article, an update on OPMDs is provided and, based on the practices of six Oral Medicine units in Europe (London (United Kingdom), Milan (Italy), Bordeaux (France), Porto (Portugal), Zagreb (Croatia) and Santiago de Compostela (Spain)), aiming to provide guidance on monitoring in a primary care setting in Europe. Conclusion: Oral medicine clinicians can provide guidance to general dental practitioners (GDPs) on recommended recall intervals. It is important that they feel confident in monitoring these conditions and, when concerned, to arrange referral to a hospital or appropriate specialist. GDPs should document descriptions of lesions and, if possible, take clinical photographs. Patients should be counselled on modifiable lifestyle factors and directed to oral medicine society websites to access patient information leaflets.

Learning objectives

- To review oral potentially malignant disorders (OPMDs) nomenclature and classification.
- To provide advice to General Dental Practitioners on management of OPMDs, with an overview on management and follow-up in a primary dental care setting.

Introduction

The WHO Collaborating Centre for Oral Cancer Workshop in 2020 defined oral potentially malignant disorders (OPMDs) as “any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer” [1], a slight modification to the original definition by the same group in 2007 [2]. In March 2020, the workshop reviewed the terminology and agreed that although there were some discrepancies in the literature, OPMDs remained a well-recognised and understood term, used in hundreds of publications [1,3]. In addition, oral epidermolysis bullosa
Leukoplakia

Defined in 2007 by the WHO Collaborating Centre, leukoplakia is "a predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer" [1]. The WHO Collaborating Centre have set out criteria when establishing a clinical diagnosis of leukoplakia including: homogeneity, lack of chronic irritation, persistence if irritant factors are removed and cannot be rubbed away [1]. Leukoplakia can be described as white patches or plaques, the use of ‘keratosis’ should remain consistent with the histopathological description, unless being used for clinically accepted terminology, such as frictional keratosis [1].

Homogenous leukoplakias are uniformly white, flat and smooth (Fig. 1) [1]. Non-homogenous leukoplakia encompasses three sub-types: nodular (rounded exophytic lesions) (Fig. 2), verrucous (wrinkled or warty exophytic surface) (Fig. 3) and erythroleukoplakia (mixed red and white speckled lesions) [1]. Malignant transformation rate (MTR) has been reported at 3% for homogenous lesions and 14.5% for non-homogenous lesions [8].

Biopsy can confirm or modify a clinical diagnosis of leukoplakia [1], with specific reference to the presence and degree of dysplasia. The malignant transformation rate (MTR) of dysplastic lesions is variable. Studies have reported an overall MTR of 2.6–12.1% [9,10]. Others have reported 1.7–15.0% for mild, 0.0–32.1% for moderate and 0–50.0% for severe dysplasia [8–11]. As moderate and severe dysplastic lesions are often excised, the true transformation rates are more difficult to estimate. Time to transformation is also variable [12,13]. An alternative two-tier system of ‘low’ risk for no/questionable risk lesions or ‘high’ risk for moderate/severe.
risk lesions has been proposed, with a need for further longitudinal studies [14]. Patients should be advised regarding the risk of transformation and importance of risk factor modification.

Aneuploidy is a change from the normal DNA or chromosomal complement in a cell and is assessed by detecting specific chromosomal amplifications or deletions or non-specifically by measuring total cell DNA content [15]. A meta-analysis of the predictive value of DNA aneuploidy in malignant transformation of OPMDs, found aneuploidy was associated with a 3.12-fold increased risk of malignant transformation [16]. It was shown that DNA diploid and tetraploid status have negative predictive values [15]. Dysplasia grading, combined with ploidy analysis gives higher predictive values for malignant transformation compared to dysplasia grading alone [15].

In addition to the grade of dysplasia and ploidy analysis, risk factors such as smoking and alcohol consumption, non-homogenous appearance, size, localization on high risk sites will influence the frequency of recall appointments for surveillance of lesions [17].

When monitoring lesions in general dental practice, GDPs should follow advice from secondary care regarding frequency of review, with special attention to soreness in a previously asymptomatic lesion, a change in thickness or size of the lesion, colour changes, ulceration or induration [17]. The grade of dysplasia and ploidy analysis results are also important when evaluating lesions and deciding long-term follow-up [15]. In non-dysplastic lesions, follow up has been proposed and varies between 3 and 6 months [18]. GDPs should also direct patients to appropriate smoking cessation services and provide advice regarding moderation of alcohol consumption.

**Proliferative verrucous leukoplakia**

Proliferative verrucous leukoplakia (PVL) is defined as a distinct form of multifocal oral leukoplakia characterized by having a progressive clinical course, changing clinical, and histopathological features and is associated with the one of highest proportion of oral cavity cancer development compared with other OPMDs. The MTR is reported as 49.5% [1,10].

The aetiology remains unknown, though a lichenoid morphology has been associated with the initial presentation of PVL [19,20]. The high recurrence rate following excision and high MTR necessitates strict follow-up of these lesions.

Due to the high risk of malignant transformation, these lesions should be closely monitored in a secondary care setting. Between appointments, the GDP should document any textural changes (from a smooth lesion to a verrucous or warty texture), extent of lesion and change in colour (Figs. 3 and 4). Photographs are important for comparison when looking for subtle changes in PVL.

**Erythroplakia**

Erythroplakia is “a predominantly fiery red patch that cannot be characterised clinically or pathologically as any other definable disease” [1]. Its solitary nature can help discern it from other conditions [21]. There is variability in both outline (regular/irregular) and texture (velvety, granular) (Fig. 5) [17]. Most frequently affected sites include the soft palate, floor of mouth, ventral tongue and tonsillar fauces [22].

The reported global mean prevalence of oral erythroplakia has been reported as 0.11% (ranging from 0.01 to 0.21%) [22]. Malignant transformation rates of erythroplakia are high, ranging from 14% to 85% [23]. Early detection and surgical excision are recommended. Histopathological features of erythroplakia show at least some degree of dysplasia or even carcinoma *in situ* or invasive carcinoma [22]. These lesions are rarely monitored in a primary care setting.

**Oral lichen planus**

Oral lichen planus (OLP) is an autoimmune chronic inflammatory disease of unknown aetiology, characterized by the presence of white reticular lesions and/or erosive and/or atrophic lesions [23]. Clinically six types have been identified: reticular, plaque-like, papular, atrophic/erosive, ulcerative, and bullous (Fig. 6) [24]. Lichen planus is a dermatological
condition, and can have extra-oral manifestations, with almost 15% of OLP patients developing cutaneous lesions and 20% developing genital lesions [24,25].

The malignant transformation rate has been reported as 1.14% for OLP [25]. Malignant transformation risk is higher in atrophic and/or erosive lesions, with the tongue carrying the highest risk [25].

Management of oral lichen planus is aimed at reducing symptoms, healing ulcerated areas, and prolonging symptom-free periods [26]. In the UK, dentists in primary care are limited in the prescribing of topical therapies for the management of OLP. GDPs in Europe have access to a greater range of topical treatments. Topical anaesthetics, such as benzydamine hydrochloride (0.15%) or lidocaine gel, can be prescribed for symptomatic relief in primary care. Lifestyle advice is important and includes dietary advice to avoid spices/acidic foods that may exacerbate symptoms and the use of SLS-free toothpastes and maintenance of good oral hygiene. Patient should be encouraged to cease tobacco habits and moderate alcohol consumption.

Treatment for symptomatic and erosive lichen planus is variable. Topical corticosteroids are used as first-line treatment. Commonly prescribed to be used as mouthwash once mixed with water include betamethasone 500 mcg soluble tablets, prednisolone 5 mg soluble tablets and fluticasone 400 mcg nasules [26,27]. Clobetasol propionate ointment (0.05%) with Orabase paste, or fluticasone propionate inhaler are also commonly prescribed [26]. Triamcinolone acetonide can be injected to persistent localised erosive lesions [26]. In patients with an additional diagnosis of dysplasia on a background of lichen planus, moderate and severe dysplastic lesions tend to be excised in secondary care.

Systemic treatments include oral corticosteroids, hydroxychloroquine, azathioprine, mycophenolate mofetil, ciclosporin, methotrexate and retinoids [24,28].

Patients discharged to the primary care setting for routine follow-up should be aware of the potential for development of extraoral manifestations of lichen planus and advised to contact their general practitioner in the first instance. The increased risk of malignant transformation should be discussed. Patient information leaflets can be provided (for example, https://bisom.org.uk/clinical-care/patient-information/). Patients should be instructed on how to self-monitor the oral cavity. We recommend reticular oral lichen planus, with no erythema or ulceration, can be monitored every 6 months [29]. Signs including non-healing ulceration, surface texture changes, induration require urgent referral to secondary care.

Lichenoid lesions

Oral lichenoid lesions (OLLs) have features compatible with, but not typical of OLP [1]. They may not be symmetrical and may be unilateral. They often have an underlying causative agent; dental restoration [30,31], drugs (e.g. oral hypoglycaemic agents, anti-hypertensives), following intake of food substances or in association with chronic graft-versus-host-disease (GvHD) [31]. The term oral lichenoid reaction (OLR) is also used and in the literature refers to lesions caused by direct contact with a dental restoration or drugs. Lesions secondary to dental restorations are localized to the area in contact with the material (Fig. 7) [32].

Skin patch testing can be undertaken, which can help formulate a treatment plan with regards to recommendation of restoration replacement. Positive patch test rates of 24% [33] and 67.8% [32] have been reported in those with a confirmed diagnosis of OLR [32]. However, positive patch testing was unable to predict resolution of an OLR when a restoration has been replaced. Partial resolution or considerable improvement has been reported, particularly for patients with an amalgam restoration adjacent to OLR [32]. Patients should be aware that lesions may not resolve completely when discussing replacement of restorations. The restoration of choice is at the discretion of the GDP.

Drug reaction presentations vary, with a predilection for being erosive and unilateral [32]. MTR has been reported as 1.71% for OLRs, which may be underestimated [26].
Oral submucous fibrosis

Oral submucous fibrosis (OSMF) is a chronic, insidious disease that affects the oral mucosa resulting in loss of fibroelasticity of the lamina propria and ultimately, fibrosis of the lamina propria and the submucosa with epithelial atrophy [1]. It frequently, but not exclusively, affects the buccal mucosa in South and Southeast Asian populations [34,35]. Areca nut (areca catechu) and betel quid chewing play a well-established role in its development [36]. There is increasing evidence of genetic susceptibility to the condition [36]. The MTR has been reported as 4.2% [37]. Advanced cases may present with pallor and marbling of the mucosa, hypomobility of the tongue and soft palate, xerostomia, loss of the uvula and leukoplakia (Fig. 8) [35]. Patient often report a burning sensation. In primary dental care, routine dental treatment in patients with OSMF with restricted mouth opening, may prove difficult due to limited access. Surveillance is usually undertaken in secondary care. When GDPs are monitoring these cases, the same principles apply regarding early detection of worrying features.

Oral lupus erythematosus

Lupus erythematosus is a chronic autoimmune condition with systemic, discoid and drug-induced forms [1]. Approximately 20% of systemic lupus patients will have oral manifestations [1]. Orally lesions may present as ulceration and/or as areas with central atrophy and surrounding white striations — similar to those seen in oral lichen planus [38]. Lesions affect the palate more frequently than in oral lichen planus. Malignant transformation reports intraorally are rare, with most cases arising on the lip [1,39].

GDPs should follow the same principles described above regarding early identification of worrying features. There may be an overlap with Sjogren’s syndrome in patients with systemic lupus erythematosus [40].

Actinic cheilitis

This is chronic inflammation, resulting from chronic exposure to UV radiation (solar or artificial) affecting the lips, most frequently the lower lip. The prevalence varies from 0.45% to 2.4% [41]. Acute areas may be erythematous or ulcerated. The most common appearance in chronic cases is flaking and dryness associated with whitish discoloration. The MTR to squamous cell carcinoma was found to be 3.07% [41].

Sun safety advice should be given to patients, including the daily use of high factor sunscreen, avoiding direct sun exposure during peak times and to wear broad brimmed hats.

Palatal lesions in reverse smokers

Reverse smoking is when the lit end of a cigarette is placed inside the mouth and inhaled. It is a rare habit in the Western world and is seen mainly in Indian populations, the Caribbean Islands, Latin America and some Pacific Islands [1]. Lesions are typically seen on the palate appearing as white, red or mixed white and red [1].

GDPs should encourage cessation of the habit and make referrals to, or direct patients to, smoking cessation services.

Dyskeratosis congenita

This is a rare inherited bone marrow failure syndrome [42]. Leukoplakia is the most common presentation of this condition, frequently involving the tongue or buccal mucosa [43]. White patches orally in childhood are rare. Once candidal infection or trauma have been excluded, these lesions should be treated with suspicion and referred [42].

Oral GVHD

Oral graft versus host disease (GVHD) can occur following allogenic stem cell transplantation for haematological malignacies [44]. The oral lesions usually have a lichenoid
appearance with areas of ulceration, erythema and/or atrophic areas, similar to oral lichen planus [1]. Mucoceles may develop on the palate. The salivary glands may also be involved resulting in xerostomia. Multi-system chronic GVHD has been reported as a risk factor for development of oral SCC [17]. A fivefold increase in the incidence in oral cavity cancer has been reported in immunosuppressed populations [45]. Immunosuppression is also associated with poorer outcomes with regards recurrence and mortality, highlighting a need for close monitoring and early intervention in these patients [46, 47]. Patients with active oral GVHD with presenting with a lichenoid appearance are usually reviewed in secondary care. Some patient’s presenting with a reticular white striaes appearance and no active or worrying features as highlighted previously, having been discharged from the Haemathology department with regards the overall haemathology malignant condition, can potentially be followed up in primary care with 6 monthly interval.

Overall recommendations

Patients diagnosed with OPMDs have an increased susceptibility to develop oral cavity cancer during their lifetime [1]. The role of candida in OPMDs remains contentious [1,48].

Predicting malignant transformation is challenging. Many factors influence malignant transformation; patient demographics and lifestyle factors, the type of OPMD, appearance, size, anatomic location and presence/degree of dysplasia on histopathology [49]. The grade of dysplasia, when present, and ploidy analysis [16] provide valuable information when deciding on intervention or monitoring. There are no universal follow-up protocols for monitoring these lesions. Treatment and surveillance frequency is determined on a case-by-case basis. Oral medicine clinicians can provide guidance to GDPs on recommended recall intervals.

Patients should be encouraged to monitor lesions and to report any changes in appearance of lesions or change in symptoms. The role of mouth self-examination (MSE) is inconclusive [50]. A 2013 Cochrane review concluded there was insufficient evidence to determine the diagnostic test accuracy of MSE as part of an organised screening programme [50].

The GDP should keep up-to-date with guidance on OPMDs. Patients should be counselled on lifestyle factors and directed to oral medicine society websites to access patient information leaflets. GDPs should document descriptions of any lesions carefully and contemporaneously. Clinical photographs are advised. Patients should be reassured when lesions are unchanged in appearance.

Candidiasis can alter the appearance of lesions and may cause symptoms. If oral candidiasis is suspected, antifungal treatment should be prescribed and lesions reviewed 2 weeks later. Referral should be considered for biopsy to exclude dysplasia or malignancy.

Referral to secondary care for patients who have been discharged, should be undertaken when there are new lesions, or if there is a change in appearance of current lesions. The criteria for urgent referrals is widely reported in the literature [17].

For patients under the joint care of primary and secondary care settings, follow-up assessments should ideally be spaced out so ensure regular surveillance by a healthcare professional.

Conclusion

Information is becoming most widely available for the management of OPMDs. This will continue to influence clinical decision-making in determining recall intervals and surveillance of patients in a primary care setting. It is important that general dental practitioners feel confident in monitoring these conditions and when concerned to arrange referral to a hospital or appropriate specialist. Finally, GDPs are in a key position to advise patients regarding high-risk habits which can increase risk of malignancy. Patients should be educated to self-monitor lesions and to alert their clinician if any changes are detected.

Author contributions


Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

Informed consent

The authors declare that informed consent not required.

Ethical committee approval

The authors declare that Ethical approval not required.

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