J Oral Med Oral Surg 2022;28:36
https://doi.org/10.1051/mbcb/2022017

https://www.jomos.org

JOMOS
Journal of Oral Medicine and Oral Surgery

Educational Article

Oral potentially malignant disorders: advice on management in primary care

Katherine Eccles[1], Barbara Carey[1], Richard Cook[2], Michael Escudier[2], Marcio Diniz-Freitas[3], Jacobo Limeres-Posse[3], Luis Monteiro[4], Luis Silva[4], Jean-Cristophe Fricain[5], Sylvain Catros[5], Giovanni Lodi[6], Niccolò Lombardi[6], Vlaho Brailo[7], Bozana Loncar Brzak[7], Raj Ariyaratnam[8], Rui Albuquerque[1,2,*]

[1] Oral Medicine, Guy's and St Thomas' NHS Foundation Trust, United Kingdom
[2] Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom
[3] School of Medicine and Dentistry, University Santiago de Compostela, Spain
[4] Oral Pathology and Rehabilitation Research Unit UNIPRO, University Institute of Health (IUCS), CESPU, Gandra, Portugal
[5] University of Bordeaux, France
[6] Università degli Studi di Milano, Italy
[7] Oral Medicine, School of Dental Medicine, University of Zagreb, Croatia
[8] University of Manchester, United Kingdom

(Received: 17 May 2022, accepted: 25 May 2022)

Keywords:
Oral potentially malignant disorders / OPMD / premalignant disorders

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

* Correspondence: rui.albuquerque@gstt.nhs.uk

(OEB), chronic hyperplastic candidiasis (CHC) and exophytic verrucous hyperplasia were removed from the classification of OPMDs [1]. With regards to terminology, the group deemed the use of the terms 'premalignant' or 'precancerous' indicated a definite transformation into malignancy [1].

The prevalence of OPMDs varies significantly in the literature and has been estimated to be 4.47%, ranging from 0.11% in North American populations to 10.54% in Asian populations [4].

With the emergence of the COVID pandemic, there was reduced clinical activity within hospital settings across Europe with redeployment of staff to other services. In the primary care setting, there was more pressure to accurately identify and refer OMPDs [5]. The Royal College of Surgeons of England produced recommendations for general dental practitioners (GDPs) for triaging and managing patients during the COVID-19 pandemic [6].

For GDPs in primary dental care, literature is available on the recognition and initial referral of suspected OPMDs or suspected malignant lesions. However, less guidance exists on how to review patients after a diagnosis of an OPMD is made and in those who have been discharged from Oral Medicine or Oral and Maxillofacial units for routine surveillance. Given the high morbidity associated with oral squamous cell carcinoma (OSCC) treatment, regular surveillance by GDPs to establish an early diagnosis and allow for timely treatment is vital [7]. In addition, the scope of practice for GDPs in Europe varies from country to country. In countries such as Portugal, Spain and Italy, it is routine for GDPs to undertake soft tissue biopsy procedures. In the United Kingdom, and Croatia, this tends to be undertaken in a specialist or secondary care setting.

The objective of this paper was to provide advice on management to GDPs on the topic of OPMDs with an overview of management in primary dental care, when to request urgent or routine review. The information provided represents an overall consensus between Oral Medicine clinicians across several units in Europe including Guy's and St Thomas's NHS Foundation Trust/King's College London (England), CESPU University (Portugal), University of Zagreb (Croatia), University of Bordeaux (France), University of Milan (Italy) and University of Santiago de Compustela (Spain). This article will provide an overview of OPMDs and give recommendations on monitoring of OPMDs in primary dental care. Following a consensus mapping methodology, the overall management of OPMDs in primary care was proposed by Guy's and St Thomas' institution and then disseminated by the lead author to all other authors. Principles and ideas were narrowed, reaching an overall consensus on management.

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 a histopathological description, unless being used for clinically accepted terminology, such as frictional keratosis [1].

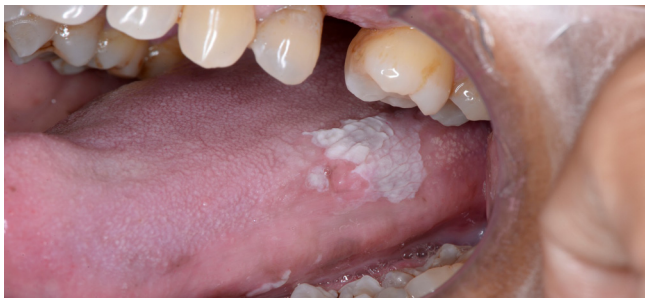

Fig. 1. Homogenous leukoplakia involving the left dorsal/lateral tongue (image provided by Guy's and St Thomas').

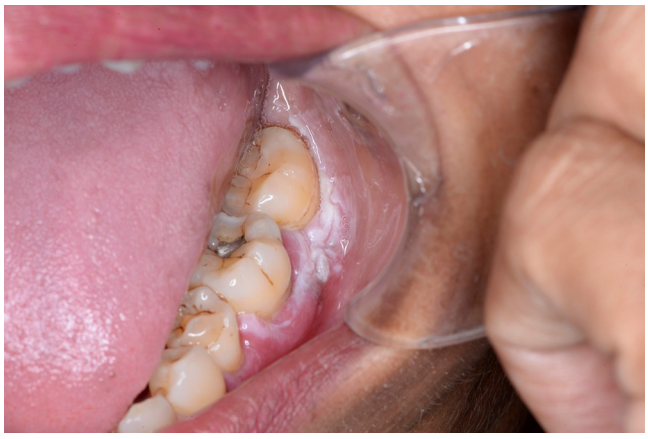

Fig. 2. Nodular leukoplakia involving the LL6/7 buccal gingivae (moderate dysplasia detected on histopathology) (image provided by Guy's and St Thomas').

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

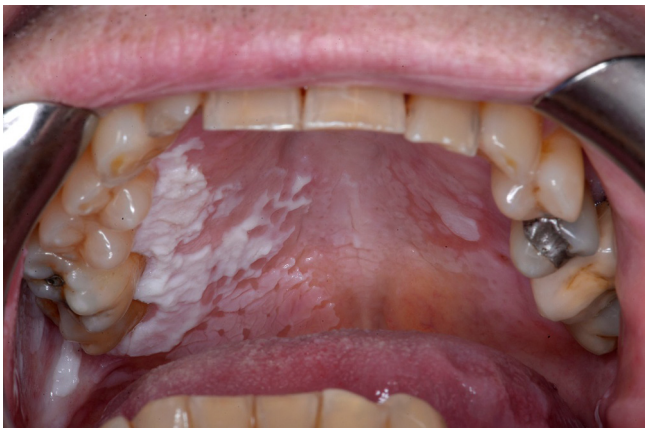

Fig. 3. Extensive verrucous leukoplakia involving the right palate and faint areas of leukoplakia involving the left palate (image provided by Guy's and St Thomas').

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].

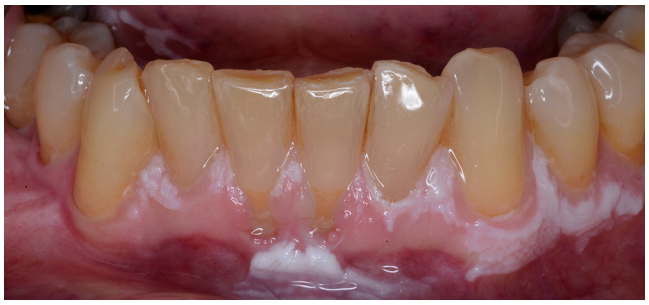

Fig. 4. Proliferative verrucous leukoplakia involving the marginal gingival of the lower anterior labial gingiva and lower lingual sulcus (image provided by Guy's and St Thomas').

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

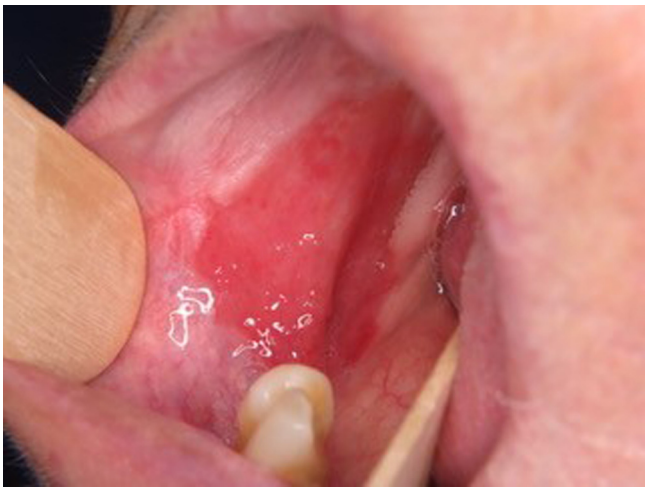

Fig. 5. Erythroplakia of the right buccal mucosa (image provided by University of Bordeaux).

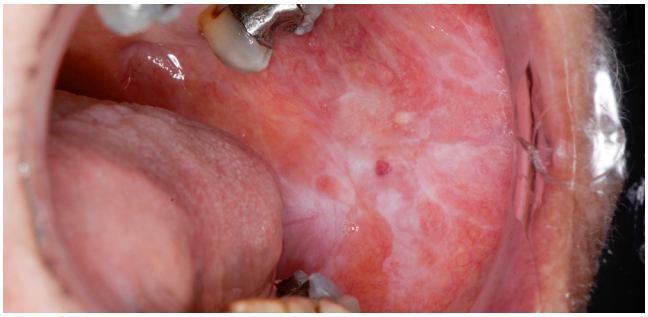

Fig. 6. White lichenoid striations with background erythema involving the left buccal mucosa consistent with oral lichen planus (mild dysplasia on histology) (image provided by Guy's and St Thomas').

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].

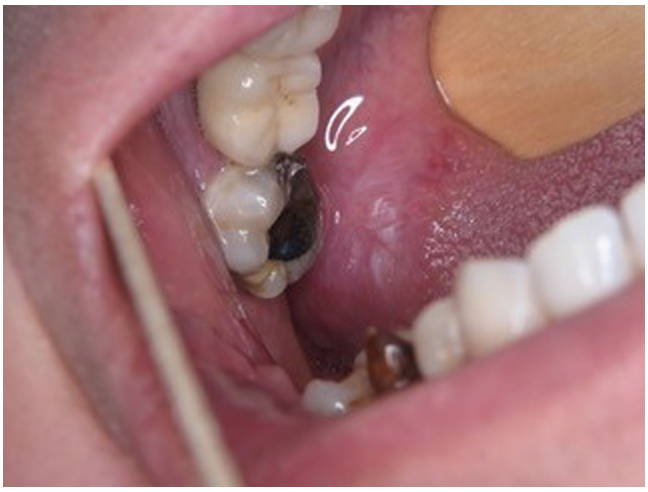

Fig. 7. Oral lichenoid reaction: white lichenoid striations with background erythema on the right lateral tongue opposing an amalgam restoration (image provided by University of Bordeaux).

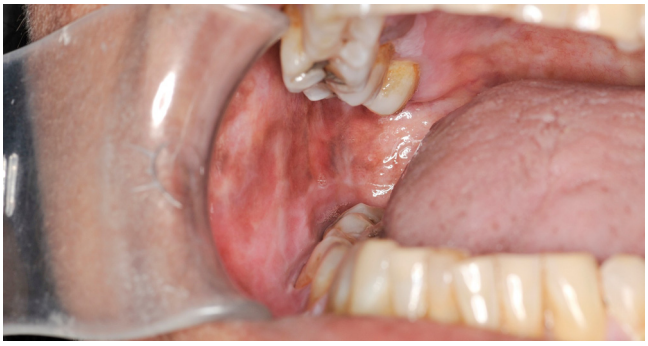

Fig. 8. Oral submucous fibrosis: Whitening with areas of mild background erythema and pigmentation involving the right buccal mucosa (image provided by Guy's and St Thomas').

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 síndrome [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 malignancies [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 apperance are usually reviewed in secondary care. Some patient's presenting with a reticular white striaes appearance and no active or worrying features as highlited 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

Katherine Eccles: writing – original draft, writing – review & editing, Barbara Carey: writing – original draft, writing – review & editing, Richard Cook: writing – review & editing, Michael Escudier: writing – review & editing, Marcio Freitas: writing – review & editing, Jacobo Limeres: writing – review & editing, Luis Monteiro: writing – review & editing, Luis Silva: writing – review & editing, Jean-Cristophe Fricain: writing – review & editing, Giovanni Lodi: writing – review & editing, Niccolò Lombardi: writing – review & editing, Vlaho Brailo: writing – review & editing, Bozana Loncar Brzak: writing – review & editing, Raj Ariyaratnam: writing – review & editing, Rui Albuquerque: conceptualization, writing – original draft, writing – review & editing.

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.

Funding

Co-funded by the Erasmus+ Programme of the European Union

This project is co-funded by the European Union's Erasmus +programme "Oral Potentially Malignant Disorders: Training of Healthcare Professionals", grant number 2020-1-UK01-KA202-078917. The European Commission supports the production of

this publication, does not constitute an endorsement of the contents which reflects the views only of the authors, and the Commission cannot be held responsible for any use which may be made of the information contained therein.

References

1. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, *et al.* 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 Dis 2020 (in press)
2. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa: potentially malignant disorders. J Oral Pathol Med 2007;36:575–580.
3. Liu W, Wu L, Zhang Y, Shi L, Yang X. Bibliometric analysis of research trends and characteristics of oral potentially malignant disorders. Clin Oral Investig 2020;24:447–454.
4. Mello FW, Miguel AFP, Dutra KL, *et al.* Prevalence of oral potentially malignant disorders: a systematic review and meta-analysis. J Oral Pathol Med 2018;47:633–640.
5. Dziedzic A, Varoni EM. Challenges of oral medicine specialists at the time of COVID-19 pandemic. Oral Dis 2022;28:904–907.
6. Royal College of Surgeons of England. COVID-19. Online information available at: https://www.rcseng.ac.uk/dental-faculties/fds/coronavirus/ (accessed September 2021).
7. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia – a systematic review and meta-analysis: Treatment and Follow-Up of Oral Dysplasia. Head Neck 2009;31:1600–1609.
8. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. J Oral Pathol Med 2016;45:155–166.
9. Warnakulasuriya S, Kovacevic T, Madden P, Coupland VH, Sperandio M, Odell E, *et al.* Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England: Malignant transformation in OPMD. J Oral Pathol Med 2011;40:677–683.
10. Iocca O, Sollecito TP, Alawi F, *et al.* Potentially malignant disorders of the oral cavity and oral dysplasia: a systematic review and meta-analysis of malignant transformation rate by subtype. Head Neck 2020;42:539–555.
11. Reibel J, Gale N, Hille J, *et al.* Oral potentially malignant disorders and oral epithelial dysplasia. In: el-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ, *et al.*, editors. WHO classification of tumours of the head and neck. 4th ed. Lyon: IARC Press; 2017.
12. Ho MW, Field EA, Field JK, *et al.* Outcomes of oral squamous cell carcinoma arising from oral epithelial dysplasia: rationale for monitoring premalignant oral lesions in a multidisciplinary clinic. Br J Oral Maxillofac Surg 2013;51:594–599.
13. Hankinson PM, Mohammed-Ali RI, Smith AT, Khurram SA. Malignant transformation in a cohort of patients with oral epithelial dysplasia. Br J Oral Maxillofac Surg 2021 59: 1099–1101. doi: 10.1016/j.bjoms
14. Warnakulasuriya S, Reibel J, Bouquot J, Dabelsteen E. Oral epithelial dysplasia classification systems: predictive value, utility, weaknesses and scope for improvement: Oral epithelial dysplasia classification systems. J Oral Pathol Med 2008;37: 127–133.
15. Odell EW. Aneuploidy and loss of heterozygosity as risk markers for malignant transformation in oral mucosa. Oral Dis. 2021;27: 1993–2007.
16. Alaizari NA, Sperandio M, Odell EW, Peruzzo D, Al-Maweri SA. Meta-analysis of the predictive value of DNA aneuploidy in malignant transformation of oral potentially malignant disorders. J Oral Pathol Med 2017;47:97–103.
17. Diniz Freitas M, Albuquerque R, Monteiro L, Fricain JC (eds). Oral Cancer Prevention. Birmingham: Clinical Photography & Design, Birmingham Dental Hospital; 2019.
18. Brouns E, Baart J, Karagozoglu K, Aartman I, Bloemena E, van der Waal I. Malignant transformation of oral leukoplakia in a well-defined cohort of 144 patients. Oral Disease. 2013;20:e19–e24.
19. Capella DL, Gonçalves JM, Abrantes AAA, Grando LJ, Daniel FI. Proliferative verrucous leukoplakia: diagnosis, management and current advances. Braz J Otorhinolaryngol 2017;83:585–593.
20. Torrejon-Moya A, Jané-Salas E, López-López J. Clinical manifestations of oral proliferative verrucous leukoplakia: a systematic review. J Oral Pathol Med 2020;49:404–408.
21. Van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. Oral Oncol 2010;46:423–425.
22. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: an update and implication for clinicians: Oral cancer and oral erythroplakia. Aust Dent J 2011;56:253–256.
23. Kalavrezos N, Scully C. Mouth cancer for clinicians part 6: Potentially malignant disorders. Dent Update 2015;42:866–888, 871–874, 877.
24. Eisen D. The clinical features, malignant potential, and systemic associations of oral lichen planus: A study of 723 patients. J Am Acad Dermatol 2002;46:207–214.
25. González-Moles MÁ, Ruiz-Ávila I, González-Ruiz L, Ayén Á, Gil-Montoya JA, Ramos-García P. Malignant transformation risk of oral lichen planus: A systematic review and comprehensive meta-analysis. Oral Oncol 2019;96:121–130.
26. Rotaru D, Chisnoiu R, Picos AM, Picos A, Chisnoiu A. Treatment trends in oral lichen planus and oral lichenoid lesions (Review). Exp Ther Med 2020;20:198.
27. Lucchese A, Dolci A, Minervini G, *et al.* Vulvovaginal gingival lichen planus: report of two cases and review of literature. Oral Implantol (Rome) 2016;9:54–60.
28. Lodi G, Manfredi M, Mercadante V, Murphy R, Carrozzo M. Interventions for treating oral lichen planus: corticosteroid therapies. Cochrane Database Syst Rev 2020;2:CD001168.
29. Kaplan I, Ventura-Sharabi Y, Gal G, Calderon S, Anavi Y. The Dynamics of Oral Lichen Planus: A Retrospective Clinicopathological Study. Head and Neck Pathology 2011;6:178–183.
30. McParland H, Warnakulasuriya S. Oral lichenoid contact lesions to mercury and dental amalgam – a review. J Biomed Biotechnol 2012;2012:589569.
31. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:582–590.
32. Suter VGA, Warnakulasuriya S. The role of patch testing in the management of oral lichenoid reactions. J Oral Pathol Med 2016;45:48–57.
33. Montebugnoli L, Venturi M, Gissi DB, Cervellati F. Clinical and histologic healing of lichenoid oral lesions following amalgam removal: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;113:766–772.
34. Kerr AR, Warnakulasuriya S, Mighell AJ, *et al.* A systematic review of medical interventions for oral submucous fibrosis and future

research opportunities: Oral submucous fibrosis, medical management. Oral Dis 2011;17:42–57.
35. Kujan O, Mello FW, Warnakulasuriya S. Malignant transformation of oral submucous fibrosis: a systematic review and meta-analysis. Oral Dis 2021;27:1936–1946.
36. Ray JG, Chatterjee R, Chaudhuri K. Oral submucous fibrosis: a global challenge. Rising incidence, risk factors, management, and research priorities. Periodontology 2000-2019;80:200–212.
37. Chourasia N, Borle R, Vastani A. Concomitant association of oral submucous fibrosis and oral squamous cell carcinoma and incidence of malignant transformation of oral submucous fibrosis in a population of central India: a retrospective study. J Maxillofac Oral Surg 2015;14:902–906.
38. Odell EW. Cawson's essentials of oral pathology and oral medicine. 9th ed. Elsevier; 2017.
39. Arvanitidou I-E, Nikitakis NG, Georgaki M, Papadogeorgakis N, Tzioufas A, Sklavounou A. Multiple primary squamous cell carcinomas of the lower lip and tongue arising in discoid lupus erythematosus: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:e22–e30.
40. Fava A, Petri M. Systemic lupus erythematosus: diagnosis and clinical management. J Autoimmun 2019;96:1–13.
41. Dancyger A, Heard V, Huang B, Suley C, Tang D, Ariyawardana A. Malignant transformation of actinic cheilitis: A systematic review of observational studies. J Investig Clin Dent 2018;9:e12343.
42. Bongiorno M, Rivard S, Hammer D, Kentosh J. Malignant transformation of oral leukoplakia in a patient with dyskeratosis congenita. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124: e239–e242.
43. Elad S, Zadik Y, Caton JG, Epstein JB. Oral mucosal changes associated with primary diseases in other body systems. Periodontol 2000-2019;80:28–48.
44. Atsuta Y, Suzuki R, Yamashita T, Fukuda T, Miyamura K, Taniguchi S, *et al.* Continuing increased risk of oral/esophageal cancer after allogeneic hematopoietic stem cell transplantation in adults in association with chronic graft-versus-host disease. Ann Oncol 2014;25:435–441.
45. Chang J, Sunwoo JB, Shah JL, Hara W, Hong J, Colevas AD, *et al.* Association between immunosuppression and outcomes in oral cavity squamous cell carcinoma. Otolaryngol Head Neck Surg 2021;164:1044–1051.
46. Engels EA, Pfeiffer RM, Fraumeni JF Jr, *et al.* Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011;306:1891–1901.
47. Warnakulasuriya S. Oral potentially malignant disorders: a comprehensive review on clinical aspects and management. Oral Oncol 2020;102:104550.
48. Sankari SL, Gayathri K, Balachander N, Malathi L. Candida in potentially malignant oral disorders. J Pharm Bioallied Sci 2015;7:s162–s164.
49. Vail M, Robinson S, Condon H. Recognition of oral potentially malignant disorders and transformation to oral cancer. JAAPA 2020;33:14–18.
50. Walsh T, Liu JLY, Brocklehurst P, Glenny A-M., Lingen M, Kerr AR, *et al.* Clinical assessment to screen for the detection of oral cavity cancer and potentially malignant disorders in apparently healthy adults. Cochrane Database Syst Rev 2013; CD010173.