OPMDcare
Healthcare Professional Training

Oral Potentially Malignant Disorders

Healthcare Professional Training

KING'S College LONDON

USC UNIVERSIDADE DE SANTIAGO DE COMPOSTELA

UNIVERSITÀ DEGLI STUDI DI MILANO

Sveučilište u Zagrebu
University of Zagreb

université de BORDEAUX

CESPU
COOPERATIVA DE ENSINO SUPERIOR POLITÉCNICO E UNIVERSITÁRIO

Oral Potentially Malignant Disorders: Healthcare Professional Training (1st edition).

London, 2022

ISBN: 978-84-09-39243-8

Disclaimer

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.

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

Preface

Dear colleagues,

Despite commendable progress in the prevention, detection, and treatment of a wide variety of solid tumour types, oral squamous cell carcinoma (OSCC) remains a significant health burden across the globe. OSCC is often first diagnosed at a late stage of the disease with advanced locoregional disease and/or distant metastases.

In clinical practice, opportunities exist to identify patients with oral potentially malignant disorders (OPMDs), which precede the development of cancer. Although multiple sources of information exist, the majority focus on diagnosis and use older guidance, with little reference to overall management of the conditions. This book forms part of a European project directed at European healthcare professionals and aims to provide updated guidance to clinicians who encounter patients with head and neck pathology, to recognise, investigate, diagnose and manage OPMDs. The contents of the book has been extensively reproduced from the published work of the WHO Collaborating Centre (UK) that has held two expert workshops and reported their findings in 2007 and 2020. This learning tool also brings together experience from a number of Oral Medicine units throughout Europe through the respective universities of the partners involved (www.OPMDcare.com).

Dr Rui Albuquerque
Coordinator
Consultant in Oral Medicine & Honorary Clinical Senior Lecturer

Guy's Hospital,
Faculty of Dentistry, Oral & Craniofacial Sciences
King's College London
Department of Oral Medicine,
Floor 22, Tower Wing,
Guy's Hospital,
Great Maze Pond,
London SE1 9RT

Edited by

Rui Albuquerque, DMD, MS, DAS, PhD, PGCME, FHEA, FDS RCS(OM)
Department of Oral Medicine
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom
Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

Vlaho Brailo, DMD, PhD
Department of Oral Medicine
Clinic for Dentistry, University Clinical Hospital Zagreb, Zagreb, Croatia
School of Dental Medicine, University of Zagreb, Zagreb, Croatia

Barbara Carey BDS, MB BCh BAO BA, FDS(OM) RCSI, FFDRCSI (Oral Medicine), FHEA
Department of Oral Medicine
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

Márcio Diniz-Freitas, DDS, MSc, PhD
Special Care Dentistry Unit
School of Medicine and Dentistry, University of Santiago de Compostela, Spain

Jean-Christophe Fricain, DDS, PhD, HDR
Department of Oral Surgery
University Hospital Bordeaux, France

Giovanni Lodi DDS, PhD
Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche
Università degli Studi di Milano, Italy

Luis Monteiro DDS, MSc, PhD, Oral Surg Spec, Dip Oral Med
Oral Medicine and Oral Surgery Department
Oral Pathology and Rehabilitation Research Unit (UNIPRO – IUCS)
University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

Senathirajah Ariyaratnam, BDS, MDS (MAN), FDSRCS (ENG), FFGDP (UK), FCGDent (UK), SFHEA (UK), NTF (UK)
Department of Oral Medicine
School of Medical Sciences, The University of Manchester, United Kingdom

Authors

Rui Albuquerque, DMD, MS, DAS, PhD, PGCME, FHEA, FDS RCS(OM)
Department of Oral Medicine
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom
Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

Ana Andabak Rogulj, DMD, PhD
Department of Oral Medicine
Clinic for Dentistry, University Clinical Hospital Zagreb, Zagreb, Croatia
School of Dental Medicine, University of Zagreb, Zagreb, Croatia

Eduardo Barreira, DDS
Oral Medicine Post-graduation Course
University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

Franck Boralevi, MD PhD HDR
Paediatric Dermatology Department
University Hospital Bordeaux, France

Vlaho Brailo, DMD, PhD
Department of Oral Medicine
Clinic for Dentistry, University Clinical Hospital Zagreb, Zagreb, Croatia
School of Dental Medicine, University of Zagreb, Zagreb, Croatia

Barbara Carey, BDS, MB BCh BAO BA, FDS(OM) RCSI, FFDRCSI (Oral Medicine), FHEA
Department of Oral Medicine
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

Lisette Collins, BSc BDS MSc MFDS RCS (Eng) FRCPath
Oral and Maxillofacial Pathology
Guy's & St Thomas' NHS Foundation Trust/ Viapath LLC, London, United Kingdom

Richard James Cook, BDS (Hons) FDS RCS Eng MBChB MRCS Ed PhD FDS (OM) RCS Ed FHEA
Department of Oral Medicine
Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

Márcio Diniz-Freitas DDS, MSc, PhD
Special Care Dentistry Unit
School of Medicine and Dentistry, University of Santiago de Compostela, Spain

Michael Escudier, MD, MBBS, FRCS (Hon.), BDS, FDS RCS (Eng.), FDS RCPS (Glas.), FFD RCSI, FDS (OM) RCS, FFGDP (UK), FHEA
Department of Oral Medicine
Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom
Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

Emma Fribourg, DDS
Department of Oral Surgery
University hospital Bordeaux, France

Jean-Christophe Fricain, DDS, PhD, HDR
Department of Oral Surgery
University Hospital Bordeaux, France

Lucía García-Caballero, DDS, MsC, PhD
Department of Morphological Sciences
School of Medicine and Dentistry, University of Santiago de Compostela, Spain

Sandeep Joshi, BDS, MBBS, MFDS
Department of Oral Medicine
Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

Lucía Lago-Méndez, DDS, MSc, PhD
Oral Health Department
Galician Health Service (SERGAS), Santiago de Compostela, Spain

Jacobo Limeres-Pose, DDS, MSc, PhD
Special Care Dentistry Unit
School of Medicine and Dentistry, University of Santiago de Compostela, Spain

Giovanni Lodi DDS, PhD
Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche
Università degli Studi di Milano, Italy

Niccolò Lombardi DDS, Oral Surg Spec
Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche
Università degli Studi di Milano, Italy

Božana Lončar Brzak, DMD, PhD
Department of Oral Medicine
School of Dental Medicine, University of Zagreb, Croatia

Luis Monteiro, DDS, MSc, PhD, Oral Surg Spec, Dip Oral Med
Oral Medicine and Oral Surgery Department
Oral Pathology and Rehabilitation Research Unit (UNIPRO – IUCS)
University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

Alexander Morrell, BSc, PhD
Centre for Oral, Clinical & Translational Sciences
Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, London, United Kingdom

Vignesh Murthy, BA, BDentSc, Dip PCD, MFDS (RCSI), PGCME
Department of Oral Medicine
Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

Alberto Pispero DDS, PhD, Oral Surg Spec
Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche
Università degli Studi di Milano, Italy

Luis Silva, DDS, PhD
Oral Medicine and Oral Surgery Department
Oral Pathology and Rehabilitation Research Unit (UNIPRO – IUCS)
University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal
Polytechnic Institute Health Sciences (IPSN), CESPU, Gandra, Portugal

Ivana Škrinjar, DMD, PhD
Department of Oral Medicine
Clinic for Dentistry, University Clinical Hospital Zagreb, Zagreb, Croatia
School of Dental Medicine, University of Zagreb, Zagreb, Croatia

Selvam Thavaraj BDS, PhD, FDSRCS (Eng), FRCPath
Oral and Maxillofacial Pathology
Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom
Centre for Clinical, Oral & Translational Science, King's College London, United Kingdom

Elena Varoni DDS, PhD
Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche
Università degli Studi di Milano, Italy

Ana Catarina Vasconcelos, DDS
Oral Medicine and Oral Surgery Department
University Institute of Health Sciences (IUCS), CESPU, Gandra Portugal

Saman Warnakulasuriya, OBE, BDS (Hons), FDSRCS (Eng), FDSRCS (Edin), FDSRCPS (Glasg),Dip Oral Med, PhD (Glasg), DSc, FKC
King's College London, United Kingdom and WHO collaborating Centre for Oral Cancer, United Kingdom

External reviewer

Senathirajah Ariyaratnam, BDS, MDS (MAN), FDSRCS (ENG), FFGDP (UK), FCGDent (UK), SFHEA (UK), NTF (UK)
Department of Oral Medicine
School of Medical Sciences, The University of Manchester, United Kingdom

Correspondence:

Dr Rui Albuquerque
Oral Medicine Department, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom
Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom
Email: rui.albuquerque@gstt.nhs.uk

Contents

1

Oral potentially malignant disorders

Luis Silva[1]
Eduardo Barreira[1]
Rui Albuquerque[2,3]
Luis Monteiro[1,4]

1. Oral Medicine and Oral Surgery Department, Oral Pathology and Rehabilitation Research Unit (UNIPRO), University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

2. Department of Oral Medicine. Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom.

3. Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

4. Oral Medicine and Oral Surgery Department, University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

1.1. Introduction

Despite commendable progress in the prevention, detection, and treatment of a wide variety of solid tumour types, oral cancer remains a significant worldwide health burden. Unfortunately, the mortality rate associated with oral cancer in Europe is >50% in most countries [1, 2]. Oral squamous cell carcinoma (OSCC) is the most common histological subtype of oral cancer and is often diagnosed at a late stage, with advanced regional disease and / or metastasis at the time of diagnosis [2–4]. Delayed diagnosis has the potential to preclude successful treatment and favourable outcomes [1, 2, 5, 6]. Tobacco and alcohol misuse, in addition to having a synergistic effect, are the most important risk factors for the development of oral cavity cancers, and exposure to sunlight for development of lip cancers [7–9]. A causal role for human papillomavirus (HPV), primarily type 16, has been established particularly in cancers arising in the base of the tongue and tonsils. The rate of HPV positivity among oral cavity cancers is approximately 11% [10, 11].

Many cases of OSCC may be preceded by oral potentially malignant disorders (OPMDs), previously referred to as potentially premalignant oral epithelial lesions. Patients presenting with OPMD are at increased risk of developing an oral cancer [12].

To reduce the morbidity and mortality associated with oral cancers, OPMDs should be identified and managed appropriately. The oral cavity is well suited for early detection of OPMDs because these lesions can be readily visualised and examined by a healthcare professional. Despite this, only ~34% of oral malignancies are diagnosed at an early stage when the cancer is localised and has not yet spread [2]. General medical / dental practitioners often encounter patients who present with OPMDs in their routine practice, reinforcing the importance of increasing awareness and knowledge on these disorders in these groups of healthcare professionals.

This book forms part of a European project directed at European Union healthcare professionals, to provide E-learning tools and resources to enhance knowledge in the diagnosis and management of patients presenting with OPMDs.

With this book, we aim to provide guidance to clinicians who encounter patients with head and neck pathology, to recognise, investigate, diagnose and manage OPMDs. This innovative learning tool brings together experience from a number of Oral Medicine units throughout Europe through the respective universities of the partners involved. It covers an array of topics including: leukoplakia, erythroplakia, oral submucous fibrosis, actinic cheilitis, chronic hyperplastic candidiasis, lichen planus, discoid lupus erythematosus, systemic lupus erythematous, inherited disorders and oral biopsy techniques and the use of diagnostic adjuncts. Each chapter includes a resume identifying the main key learning points, along with a list of references to promote further reading.

1.2. Oral potentially malignant disorders (OPMDs) – Definitions and classifications

Oral potentially malignant disorders (OPMDs) are defined as a group of disorders where the clinical presentation may precede the diagnosis of an oral squamous cell carcinoma (OSCC) [12].

Many oral cancers arise in areas of abnormal mucosa in the oral cavity. In addition, several of these abnormal lesions share similarities at a morphological, cytological, genomic and molecular level as those observed in epithelial malignancies [13].

The term OPMDs was first introduced at the World Health Organisation (WHO) Workshop in 2005, leading to the disuse of many other terms previously used including ‘precancer’, ‘epithelial precursor lesions’, ‘premalignant’, ‘precancerous’, and ‘intra-epithelial lesion’ [13].

‘Precancer’ is one of the oldest terms initially described in 1805 to describe benign diseases that may develop into invasive malignancy if followed over a long period of time [12]. In 1978, the term ‘precancerous lesions’ was adopted by the WHO working group, with a division into precancerous lesions (e.g. leukoplakia, erythroplakia) and precancerous conditions (e.g. oral submucous fibrosis, actinic keratosis, oral lichen planus, or discoid lupus erythematosus) [14].

It was implied that oral cancers arose in the same site of a previous oral precancerous lesion and precancerous condition [13].

In the WHO 2005 OPMD Workshop, the working group made two observations. The first was that this association or risk is *potential* during the lifetime of the patient, and only a minority progress to oral cancer (and not all as a 'precancerous' terminology would suggest). The second was that an oral cancer could not only appear in the same location of a previous OPMD, but also in another location of the oral cavity of a patient with a lesion or condition identified as an OPMD [13]. This led to two important changes. 'Potentially malignant' became a more comprehensive term than 'precancerous' to indicate patients having these mucosal abnormalities are at risk of developing an oral cancer, but not necessarily. The second important change was merging the terms 'lesions' and 'conditions' into the category of 'disorders', where oral cancers could be detected in patients with any of these previously detected mucosal alterations and at any site of oral mucosa. This recognised the fact that environmental carcinogens could affect any part of the upper aero-digestive tract and the presence of these disorders could indicate an increased risk ('potential') of developing an oral cancer elsewhere in the oral cavity [15-17]. With this in mind, patients with a defined lesion, such as leukoplakia, are at risk of developing a malignancy anywhere in the oral cavity as a result of field change ('field cancerization'), even in clinically normal appearing mucosa [18]. This terminology has been adopted by the latest WHO classification on Head and Neck Tumours [19].

The WHO Collaborating Centre Consensus Workshop on OPMDs in 2020, updated the definition of an OPMD as 'any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer' [12]. It has put an emphasis not only directly to the disorder itself, but also to the patient who may carry genomic and other molecular abnormalities in the oral mucosa, promoting the existence of an OPMD and, potentially, an oral cancer [15, 17]. Therefore, patients diagnosed with OPMDs have an increased susceptibility to develop oral cancer in their lifetime [12].

1.3. Demographic and clinical aspects of OPMDs

The worldwide prevalence of OPMD had been estimated at 4.47% (95% CI = 2.43–7.08). This may vary between populations and is higher in Asian populations and males [12, 20].

The majority of patients with OPMDs are middle-aged or elderly [18]. Ethnicity and cultural habits influence the type and pattern of OPMDs reported in specific populations due to the dominance of particular risk factors. For example, betel quid/areca nut chewing habits are widely prevalent in South Asian populations resulting in a greater prevalence of OPMDs [20, 21]. Reverse smoking habit is also known to induce specific mucosal changes on the palate in some geographic regions [22].

OPMD encompass a heterogeneous group of clinically distinctive disorders (Table 1.1) including leukoplakia, proliferative verrucous leukoplakia, erythroplakia, oral submucous fibrosis, oral lichen planus, actinic keratosis (actinic cheilitis), palatal lesions in reverse smokers, discoid lupus erythematosus, dyskeratosis congenita, oral lichenoid lesion, and oral graft versus host disease [12].

OPMD´s classification according to the WHO Collaborating Centre 2020 [12]
Leukoplakia
Proliferative Verrucous Leukoplakia (PVL)
Erythroplakia
Oral submucous fibrosis (OSF)
Oral lichen planus (OLP)
Actinic Keratosis (Actinic Cheilitis) (AK/AC)
Palatal lesions in reverse smokers
Discoid lupus erythematosus (DLE)
Dyskeratosis congenita
Oral lichenoid lesion
Oral graft vs host disease (OGVHD)

Table 1.1. OPMD included in the WHO Collaborating Centre 2020 classification.

The clinical manifestations of OPMDs are heterogeneous with variations in colour (white, red, and mixed white and red), texture (plaque/plateau, smooth, corrugated, verrucous, granular, atrophic), and with variable size [18, 23]. In some cases, a superficial microinvasive carcinoma may already be present and revealed by histopathology. The clinical presentation can remain static, or may show clinical changes, or demonstrate progression or regression over time [18, 24].

OPMD can involve any anatomical site in the oral cavity (and oropharynx and larynx) and can present at a single or multiple sites [24].

The rate in which patients with previous OPMDs present with oral malignancy (often referred to as malignant transformation rate) varies worldwide and is closely related with the type of disorder and with other clinical, pathological or molecular factors including the type, colour, location, size, gender, and the presence and grade of dysplasia [25-27].

A recent systematic review reported an OPMD overall malignant transformation rate of 7.9% (99%CI 4.9%-11.5%) although with high heterogeneity test values (28). This study reported separate meta-analysis for specific OPMD subgroups including for leukoplakia 9.5% (99% CI 5.9%-14.00%), lichen planus 1.4% (99% CI 0.9%-1.9%), oral lichenoid lesions 3.8% (99% CI 1.6%-7.00%), oral submucous fibrosis 5.2% (99% CI 2.9%-8.00%), oral erythroplakia 33.1% (99% CI 13.6%-56.1%), and proliferative verrucous leucoplakia 49.5% (99% CI 26.7%-72.4%). This will be further addressed in later chapters of this book. We will use the terminology of the WHO Collaborating Centre Consensus Workshop on OPMDs held in Glasgow in 2020 in the next chapters [12].

Improved knowledge and better detection of OPMD is important to provide the best management but also to improve the patient's quality of life. It also ensures close follow-up of these patients facilitating prevention and early diagnosis of an invasive carcinoma involving the oral mucosa.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941-53.
2. Monteiro LS, Antunes L, Santos LL, Bento MJ, Warnakulasuriya S. Survival probabilities and trends for lip, oral cavity and oropharynx cancers in Northern Portugal in the period 2000-2009. Ecancermedicalscience. 2018;12:855.
3. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009;45(4-5):309-16.
4. Albuquerque R, López-López J, Marí-Roig A, Jané-Salas E, Roselló-Llabrés X, Santos JR. Oral tongue squamous cell carcinoma (OTSCC): alcohol and tobacco consumption versus non-consumption. A study in a Portuguese population. Braz Dent J. 2011;22(6):517-21.
5. Borsetto D, Higginson JA, Aslam A, Al-Qamachi L, Dhanda J, Marioni G, et al. Factors affecting prognosis in locoregional recurrence of oral squamous cell carcinoma. J Oral Pathol Med. 2019;48(3):206-13.
6. Gómez I, Seoane J, Varela-Centelles P, Diz P, Takkouche B. Is diagnostic delay related to advanced-stage oral cancer? A meta-analysis. Eur J Oral Sci. 2009;117(5):541-6.
7. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, et al. Tobacco smoking and cancer: a meta-analysis. Int J Cancer. 2008;122(1):155-64.
8. Hashibe M. Risk Factors for Cancer of the Mouth: Tobacco, Betel Quid, and Alcohol. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of Oral Cancer: Prevention, Diagnosis and Management. Cham: Springer International Publishing; 2020. p. 23-30.
9. Mello FW, Melo G, Pasetto JJ, Silva CAB, Warnakulasuriya S, Rivero ERC. The synergistic effect of tobacco and alcohol consumption on oral squamous cell carcinoma: a systematic review and meta-analysis. Clin Oral Investig. 2019;23(7):2849-59.
10. Fakhry C, Lacchetti C, Rooper LM, Jordan RC, Rischin D, Sturgis EM, et al. Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement of the College of American Pathologists Guideline. J Clin Oncol. 2018;36(31):3152-61.
11. Varoni EM, Lombardi N, Franchini R, D'Amore F, Noviello V, Cassani B, et al. Oral Human Papillomavirus (HPV) and sexual behaviors in a young cohort of oral cancer survivors. Oral Dis. 2021;27(4):919-23..
12. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, 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. 2021;27(8):1862-80.
13. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575-80.
14. World Health Organization. Report of a meeting of investigators on the histological definition of precancerous lesions. Geneva: World Health Organization, 1973, Can/731.
15. Johnson NW. Cancer Biology and Carcinogenesis: Fundamental Biological Processes and How They Are Deranged in Oral Cancer. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of Oral Cancer: Prevention, Diagnosis and Management. Cham: Springer International Publishing; 2020. p. 399-425.
16. Monteiro L & Warnakulasuriya S. Molecular and signalling pathways during oral carcinogenesis. In: JS WSaG, editor. Textbook of Oral Cancer - Prevention, Diagnosis and Management. 1 ed. Switzerland AG: Springer Nature 2020.
17. Johnson NW. The Biology and Pathology of Squamous Cell Carcinomata in the Head and Neck. In. Squamous Cell Carcinoma-Molecular Therapeutic Targets. Warnakulasuriya S & Khan Z. Springer ed. Berlin: Springer; 2017. p. pp 1-36
18. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):612-27.
19. Reibel J, Gale N, Hille J. Oral potentially malignant disorders and oral epithelial dysplasia. In A. K. El-Naggar, J. K. C. Chan, J. R. Grandis, T. Takata, & P. P. J. Slootweg (Eds.), WHO classification of head and neck tumours, (4th ed.; pp. 112–115). IARC, 2017.

20. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, et al. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J Oral Pathol Med. 2018;47(7):633-40.
21. Lee CH, Ko AMS, Yen CF, Chu KS, Gao YJ, Warnakulasuriya S, et al. Betel-quid dependence and oral potentially malignant disorders in six Asian countries. Br J Psychiatry. 2012;201(5):383-91.
22. Warnakulasuriya S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral Oncol. 2020;102:104550.
23. Williams PM, Poh CF, Hovan AJ, Ng S, Rosin MP. Evaluation of a suspicious oral mucosal lesion. J Can Dent Assoc. 2008;74(3):275-80.
24. Farah CS, Woo SB, Zain RB, Sklavounou A, McCullough MJ, Lingen M. Oral Cancer and Oral Potentially Malignant Disorders. Int J Den. 2014;2014:853479.
25. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck. 2009;31(12):1600-9.
26. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. J Oral Pathol Med. 2016;45(3):155-66.
27. 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. J Oral Pathol Med. 2011;40(9):677-83.
28. Iocca O, Sollecito TP, Alawi F, Weinstein GS, Newman JG, De Virgilio A, 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(3):539-55.

2

Oral Biopsy and Adjuncts Techniques

Luis Monteiro[1,2]
Luis Silva[1]
Eduardo Barreira[1]
Alexander Morrell[3]
Ana Catarina Vasconcelos[2]

1. Oral Pathology and Rehabilitation Research Unit (UNIPRO), University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

2. Oral Medicine and Oral Surgery Department, University Institute of Health Sciences (IUCS), CESPU, Gandra, Portugal

3. Centre for Oral, Clinical & Translational Sciences, Faculty of Dentistry, Oral and Craniofacial Sciences, King's College London, London, United Kingdom

2.1. Introduction

Biopsy has become a gold standard method for the diagnosis of many lesions and diseases including the investigation of oral malignancy or potentially malignant disorders [1].

Biopsy is defined as a surgical procedure where tissue from a living patient is removed for microscopic examination. It can confirm a provisional diagnosis, make a definitive diagnosis or may exclude other possible diagnoses. Additionally to diagnostic proposes, biopsy may contribute to the assessment of the efficacy of a treatment and help with determining prognosis in malignant or premalignant lesions. Biopsy and the histopathological report also constitute a document with medico legal value [2, 3].

2.2. Indications and non-indications for oral biopsy

The indications for performing an oral biopsy depend on multiple factors including the clinical and macroscopic characteristics of a lesion, such as evolution of a lesion, macroscopic presentation or refractory response to standard treatments. Biopsy is also indicated if there is suspicion of a malignant process. In Table 2.1, we detail the indications and clinical presentations that warrant undertaking a biopsy [4-6].

The contraindications to biopsy are primarily related to the general health status of the patient. Biopsy of normal variations of anatomical structures (e.g. lingual varix, racial pigmentation, geographic tongue, linea alba, lingual indentations, or Fordyce spots), irritative/traumatic lesions that respond to the removal of a local irritant, inflammatory or infectious lesions that respond to specific local treatments, is not indicated [4, 6].

Main indication	Example of particular cases
Suspected malignant lesion	• Persistent ulcerated, veruccous or mixed lesions • White, red or mixed areas, plaques, nodules or lumps • Induration or fixation of lesion to deep layers of tissue • Significant change in appearance of previous OPMD
Suspected potentially malignant disorder	• White, red, or mixed plaques • Veruccous, granular, atrophic or erosive persistent lesions and recent focal pigmented lesions • Suspicion of any OPMD (e.g. actinic cheilitis, erythroplakia, leukoplakia, lichen planus)
Chronic or persistent lesions of uncertain aetiology	• Ulcer or apparently inflammatory lesions that do not heal or improve within two weeks after treatment (e.g. removal of local irritants). • Lesions of unclear aetiology, particularly when associated with increasing pain, paraesthesia or anaesthesia
Systemic disorders where histopathological diagnosis is need to confirm or could complement a clinical or provisional diagnosis	• Includes lupus, amyloidosis, sarcoidosis, scleroderma, or Sjögren's syndrome, mucocutaneous diseases affecting the oral mucosa, such as pemphigus or pemphigoid, Crohn's disease • infectious diseases such as lesions suggestive of syphilis, tuberculosis etc
Lesions that interfere with oral function	• e.g. papilloma, fibrous hyperplasia, fibroma, lipoma, osteoma.
Radiolucent or radio-opaque osseous lesions where histopathological diagnosis or treatment is needed	• e.g. maxillary cysts and odontogenic tumours, ossifying fibroma, fibrous dysplasia, giant cell granulomas, or similar lesions
Lesions that are causing the patient extreme concern	• Patients may prefer biopsy or excisional biopsy of a persistent red, white or pigmented lesions or lump

Table 2.1. Main Indications for Oral Biopsy.

In some cases, a biopsy may be indicated for lesions that are causing extreme concern for a patient, but non-suspicious to the healthcare professional. Patient expectation should be acknowledged and the basic principle of 'cause no harm' should be followed to provide the best option for the patient.

2.3. Classification and types of oral biopsies

Biopsies may be classified into several subtypes [2, 3]. They may be incisional (only a representative part of the lesion is removed) or excisional (complete excision of the lesion) depending on the amount or area of tissue that is surgically removed.

Biopsy may be direct (located superficially, with easy access) or indirect (when the lesion lies deeper, covered by normal-appearing mucosa, which suggests an access flap may be required before removal of the lesion in question) depending on the anatomic location of the lesion.

Further categorizations may be used depending on the instruments and specific technique employed (scalpel, punch, core needle), processing of the tissue sample (e.g. fresh, frozen, formalin-fixed paraffin-embedded), type of tissue removed (soft tissue, hard tissue or blood). In next part of the chapter, we will focus on the most common types of biopsies used in the context of an OPMD [2, 3].

Soft tissue biopsies

For soft tissue biopsy, the removal of tissue is performed using a scalpel, a punch or forceps. Lasers or electroscalpels may also be used [2]. For diagnostic purposes, the use of a conventional scalpel or punch is preferable over lasers (diode or Nd:YAG, CO_2 lasers) or electroscalpel that may produce some histological artefacts leading to difficulties in diagnosis [7-10]. The Er:YAG laser has shown the least amount of tissue artefact [7, 11]. Lasers are useful in vascular abnormalities or in patients with bleeding disorders because of their coagulative effect [11]. The instrument selected should be the one with the most benefit for the patient with the objective of obtaining a diagnostically useful tissue. The most utilised methods for biopsy in the context of OPMD are the incisional biopsy, excisional biopsy and punch biopsies.

2.3.1. Incisional Biopsy

The incisional technique involves the removal of a representative area of the lesion (Table 2.2). The biopsy should include a representative area and, ideally, adjacent normal tissue. The importance of taking more abnormal or normal depends on the nature of the lesion (e.g. in cases suspicious for malignancy, abnormal tissue is preferred, in blistering disorders, 'normal' adjacent tissue is preferred) [2, 4, 12, 13].

In the case of extensive or large lesions (a long axis greater than ~1-2 cm) and in multiple lesions, incisional or mapping biopsies may be indicated. In heterogeneous lesions (in colour, texture or consistency), multiple incisional biopsies should be performed obtaining different representations of the lesion, with precise identification of each and placed in different identified specimen pots. Incisional biopsy is considered the gold standard when malignancy is suspected and for oral potentially malignant lesions [2, 3, 14].

Biopsy of vascular lesions or lesions close to neurovascular bundles (carry a risk of bleeding or numbness) or in difficult-to-access sites, may have to be undertaken in a hospital setting. Incisional biopsy should avoid damage to the tissues and be sufficient for histopathological evaluation [2-4, 13].

The technique should start with undertaking a comprehensive clinical history and intraoral examination. The most suspicious part of the lesion (speckled, red, indurated, or verrucous) should be biopsied. The use of diagnostic adjuncts tools may be helpful to identify the most representative area to include in the biopsy (described below) [2-4].

Informed consent should be obtained, discussing the risks and merits of undertaking a biopsy.

Adequate instruments should be selected to prevent damage to the tissues. Local analgesia should be administered more than half a centimetre from the lesion in question to avoid artefacts. Retractors may be used to provide a clear surgical field.

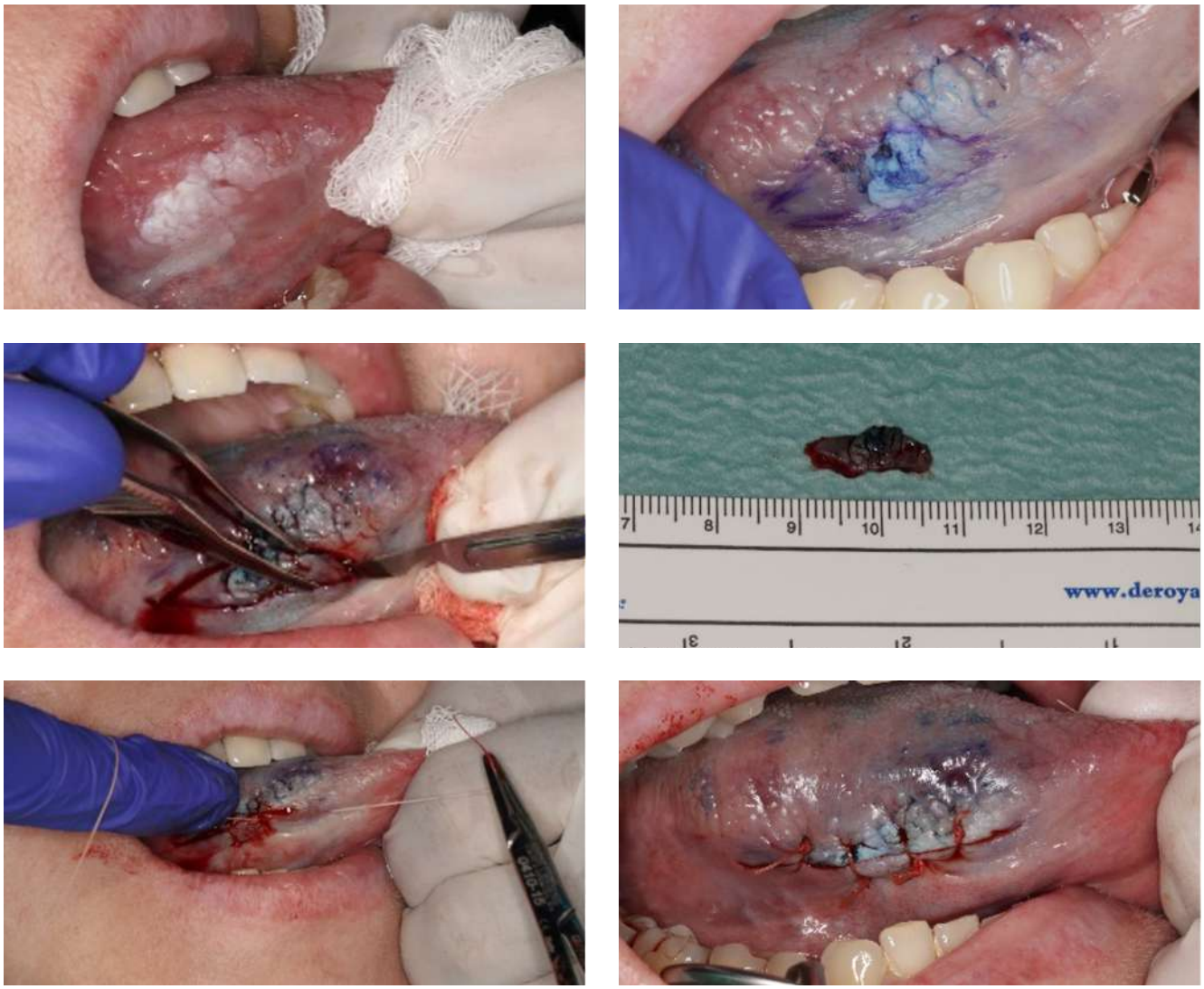

Figure 2.1. An incisional biopsy is performed in a white patch of the border of the tongue.

Using a scalpel, usually number 15-blade, two incisions are made at a 45º angle to the epithelial surface, converging in a V-shape at both ends and in an ellipse shape. The ratio of the length to width should be approximately 3:1, to promote better closure and healing without significant scarring.

The long axis of the elliptical incision should be parallel to the direction of normal stretching (lower tension) of the mucosa, in order to prevent wound dehiscence. The incisions should not be perpendicular to structures, such as neurovasular branches, to reduce the risk of damage. Necrotic tissue or the central part of ulcers should be avoided. For tissue removal, an Adson forceps or suture could be used.

The suture can be used to orientate the specimen [2-4]. Non-resorbable sutures are rarely indicated in the oral cavity.

The specimen should be placed in a specimen pot with fixing solution (10% formalin) with a volume that should exceed 10 to 20-fold the volume of the specimen. A patient identification label should be placed on the specimen pot and enclosed with a pathology request form, and sent to the Pathology lab. In case of samples for immunofluorescence, the specimen should not be fixed, and placed in Michel's medium or sent fresh in a container and transported in a freezing bag. Fresh samples should be sent as soon as possible to the laboratory [2-4].

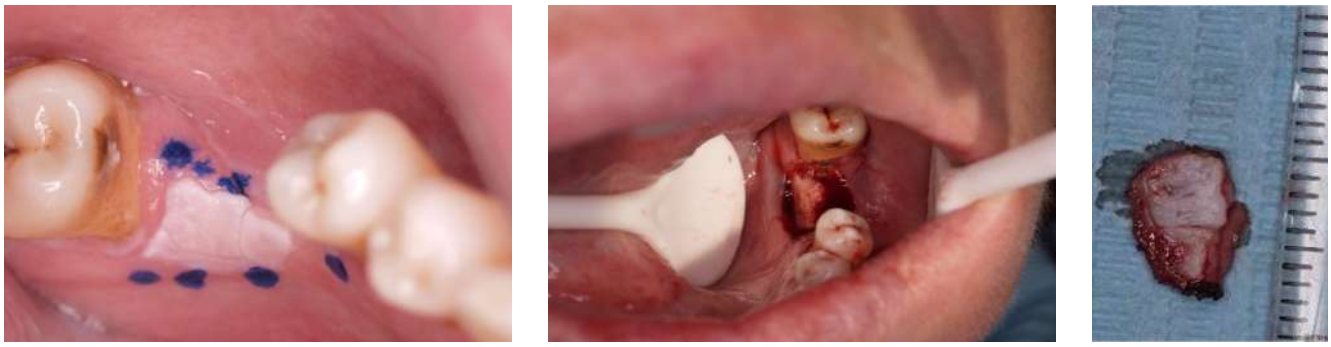

Figure 2.2. An excisional biopsy is performed in a white patch on alveolar bridge of 3º quadrant.

The pathology request form should include information of the lesion and patient medical history factors including a brief history of the lesion, clinical features, risk factors (smoking, alcohol, betel nut) and a provisional diagnosis, along with orientation of the specimen and type of biopsy undertaken (incisional or excisional).

2.3.2. Excisional Biopsy

Excisional biopsy involves removal of the entire lesion, with a margin of normal tissue peripherally and at the deeper margin (Figure 2.2). It is indicated for small lesions (~1cm), such as papillomas, fibromas, granulomas, or in cases of focal pigmented or vascular lesions additionally to the cases of small OPMD´s. This type of biopsy not only allows histological examination, but also allows treatment with complete removal of the lesion [2-4].

The technical principals of excisional biopsy are similar to those for incisional biopsy with regard to anaesthesia, instruments and incision orientation. However, special and attention should be given to the margins.

The incision should be performed on normal tissue in length and depth with clear margin. A greater size of clear margin is necessary for malignant lesions. Removal of the base of the lesion is important for papilloma to prevent recurrence. All lesions should be palpated carefully, determining the depth [2-4].

Orientation of the specimen may be needed in cases suspicious for malignancy.

2.3.3. Biopsy with biopsy forceps or punch

These instruments are designed to facilitate the removal of superficial lesions.

Biopsy forceps resemble a tweezers with an active cutting point (in the shape of a bird's beak) that allow incisional biopsy of superficial lesions and often not requiring closure withs suture. It is useful for lesions in difficult access sites.

A punch has an active cutting part similar to a circular scalpel. It is a single use instrument and is available in variety of diameters (2-10mm). Punches 4 to 6mm in size are usual for OPMDs. In most cases, it is an incisional type of biopsy but for small lesions, it can be used for excisional removal of a lesion.

The technique for a punch biopsy is like those described above for incisional biopsies (Table 2). However, for a punch, the cutting is performed in the most representative part of the lesion, with gentle pressure using circular cutting movements in a perpendicular axis to the mucosa (Figure 2.3). The target tissue can be extracted within the cylinder of the punch but most often, it is necessary to cut the base of the biopsy. A suture may not be required, with healing by secondary intention occurring in most cases. If haemostasis is difficult, a single suture is usually adequate [2-4, 15].

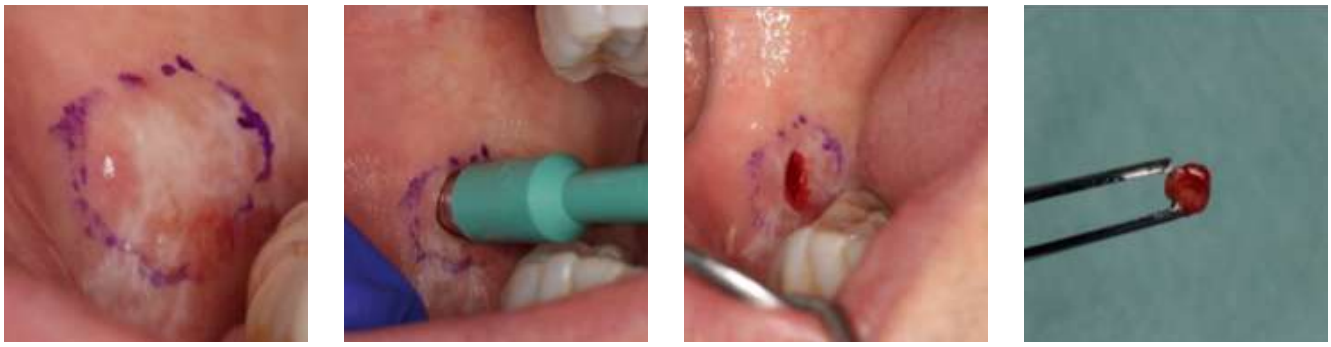

Figure 2.3. A punch biopsy is performed in a reticular white lesion on right buccal mucosa.

This type of biopsy is easy to use in single or multiple representative biopsies. Depending on the size of the punch, a smaller size of tissue may be available for diagnosis.

A punch biopsy is difficult to use in large lesions, lesions closely to vascularised or innervated areas, and in areas with difficult access, such as the hard palate [2-4].

Step	Description
Initial clinical observation and selection of the area to biopsy	• The type of biopsy should be selected according to clinical history, examination and suspected provisional diagnosis. Adjunct tools may help select the most representative area(s). Inform consented must be obtained.
Preparation of the surgical field	• The surgical area can be disinfected with an antiseptic topical agent, for example with a 0.12-0.20% chlorhexidine solution.
Local anaesthesia	• Local anaesthetic with vasoconstrictor and infiltrated away from the lesion to avoid introducing artefacts in the sample.
Incision	• After immobilization of oral tissues, an incision is performed (e.g. blade number 15) to obtain a slice of tissue in a 'V' wedge and elliptical shave, in a length to width 3:1 ratio. This ellipse is then excised by gently holding one end of the ellipse with tissue forceps or suture and dissecting it out using the scalpel. For incisional samples, a representative part of the lesion and some adjacent normal tissue should be included, and for excisional, a normal margin should be achieved. • Incision may also be performed with a punch biopsy technique, applying continuous rotational pressure perpendicular to the tissue.
Handling of the specimen	• The specimen must be handled gently to avoid artefacts and introduced in the fixing solution, usually 10% formalin solution inside a specimen pot. The specimen could be placed on sterile paper with the mucosal surface facing upwards (to avoid distortion and curling of the sample margins) and is gently placed in the 10% formalin container.
Suture of the resulting wound	• The suture should achieve good haemostasis, facilitate healing and should be removed after 1 week in the case of a non-resorbable suture. Deliver post-operative instructions.
Identification and information on pathology request form	• Identification of the patient should be placed on specimen pot and on the pathology request form information on clinical characteristics and provisional diagnosis.

Table 2.2. Biopsy technique.

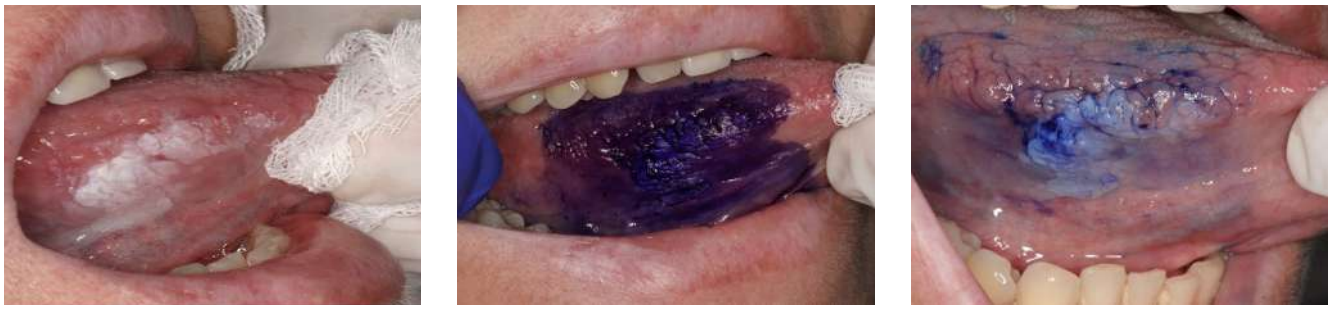

Figure 2.4. The use of toluidine blue in a white patch of the border of the tongue.

2.4. Diagnostic Adjuncts

Diagnostic adjunct tools involve the use of materials and/or devices to facilitate the detection of the most abnormal part of an oral lesion to assist the clinician in choosing a biopsy site [16-18]. These techniques are predominately non-invasive and are also used for identifying surgical margins for an excisional biopsy and in a surveillance setting to monitor high-risk patients.

In a primary care setting, diagnostic adjunct tools could be used to detect a potentially abnormal oral lesion permitting referral to establish a definitive diagnosis of an OPMD or oral cancer. In a secondary or tertiary care setting, diagnostic adjuncts tools could be used allow more detailed characterization or mapping of disease in patients with OPMDs and are especially helpful in extensive, multiple or heterogeneous lesions. They facilitate biopsy site selection at baseline and in a surveillance setting and may reduce the propensity for positive margins following excision of an OSCC or dysplastic lesion [16].

Several types of diagnostic adjunct tools are clinically available including vital staining, optical or light-based systems, cytology and saliva methods and are discussed below. Promising research into new diagnostic adjunct tools using vibrational spectroscopy is also discussed.

2.4.1. Vital Staining

Vital staining involves applying a biocompatible dye, in the form of mouth rinse or topical application directly to the selected area of the oral mucosa. Application of the stain could provide information on different lesion properties, identify non-evident lesions and help select the best site for a biopsy. The most routine vital stain used in oral medicine is toluidine blue, however alternatives are described below [4, 15, 16].

Toluidine Blue

Toluidine blue (TB) (or tolonium chloride) has been used as vital staining for more than half of a century in oral medicine. TB is a cationic metachromatic dye with a high affinity for acidic tissue components, such as nuclei acids. Areas of the mucosa that potentially show abnormalities or dysplastic or anaplastic cells can retain more stain, manifesting as a dark blue region (Figure 2.4). This could allow detection of satellite lesions, as well as non-detectable lesions to the naked eye [16, 18-20]. It is helpful for selecting the area of choice for biopsy, as well as margins of the lesion (in cases of an excision), and in the management of high-risk patients with a history of OSCC or previous OPMD [15, 16].

It is used as a 1% or 2% solution or in available commercial packs. It is used with 1% acetic acid solution to remove excess dye that is not bound to the tissues [15, 16, 19].

In a recent meta-analysis toluidine blue used as a single stain, revealed a sensitivity of 87% (95% CI: 80–94%) and a specificity of 71% (95% CI: 61–0.82%) [21]. False positives could be expected (in inflamed tissue, ulcerative lesions). False negatives can also occur when the epithelium is thick and the dye cannot enter such as in hyperkeratotic lesions [16). TB may be used as an aid to accompany a conventional oral examination (COE) and is best regarded as complementing a diagnostic plan.

Methylene blue

Methylene blue (MB) (also known as methylthionine chloride or tetramethylthione chloride) is an aromatic heterocyclic compound, similar as TB. MB has acidophilic properties that facilitate the retention of dye in cells with dysplastic characteristics similar to TB [16, 22, 23]. MB is used for screening of several cancers including prostate, bladder, and gastrointestinal lesions. It can be used in the treatment of some diseases as an antiseptic topical agent. In oral medicine, MB is commonly used for staining prior to contact endoscopy. It is also used in some photodynamic therapy methods [16, 22-25)].

The indications and method of application is similar to TB but it may be more economic and less toxic than TB [17, 18]. There is lack of evidence on the use of this dye in oral cancer screening and more studies are needed.

Lugol's Iodine

Lugol's iodine stain (LI) (or markodine) reacts with glycogen in the cytoplasm of the normal non-keratinized cells giving a brown-orange colour alteration. When LI stain is applied on an OPMD, the normal adjacent oral mucosa stains brown and abnormal tissues do not stain at all. It may be used in combination with TB where the abnormal tissues would stain dark blue and LI would stain the normal area. However, there no strong studies that demonstrate the usefulness of LI stain in the diagnosis of OPMDs [16, 26].

Rose Bengal

Rose Bengal (RB) (or tetraiododerivative of fluorescein) is a xanthene dye that has photo-sensitive properties. It is mainly used to detect ocular surface damage and could be used with light for photodynamic therapy or with sound-technology with ultrasound methods [16, 27, 28]. RB stains dead or degenerated cells, or even dysplastic and malignant cells, but not healthy epithelial cells, helping to demark corneal and conjunctive neoplastic lesions. Data on the usefulness of this stain in OPMD is scarce [16, 27, 28].

2.4.2. Optical and light-based systems

These constitute a group of approaches which rely on specific interactions between the incident radiation and tissue such as absorption, reflection, fluorescence, or scattering which could suggest carcinogenesis. Devices used clinically may be useful as a wide-field visualization adjunct in oral cancer screening, as a diagnostic adjunct in lesion characterization or as a narrow-field visualization adjunct directed to a specific site of a lesion. Techniques such as confocal microscopy, high-resolution microendoscopy, elastic-scattering spectroscopy, differential path-length spectroscopy, diffuse reflectance spectroscopy, time-resolved autofluorescence spectroscopy, and optical coherence tomography have received attention to supplement diagnostic adjuncts of OPMD and oral cancers [16].

Chemiluminescence approaches

Chemiluminescence is based on the proportion of light that a mucosal surface is capable of reflecting. Possible changes in mucosal tissues, such as in OSCC or oral epithelial dysplasia (OED), could demonstrate different absorption and reflectance [15, 16]. This technique was first used as a diagnostic adjunct in cervical mucosa for the detection of neoplastic lesions. Cervical and oral mucosa share common features, so this technique was adapted for oral medicine use [15, 16].

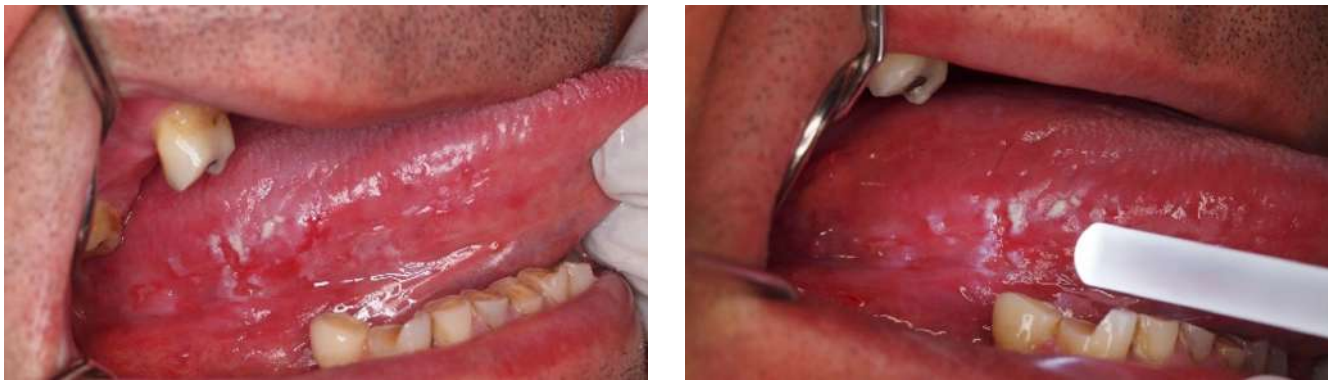

Figure 2.5. The use of the Microlux/DL enhancing a redwhite lesion on the right border of tongue.

This technique consists in two steps. Firstly, a mouth rinse with a 1% acid acetic (or direct mucosal application) to remove the glycoprotein barrier and dries the oral mucosa. The mucosa is subsequently illuminated with a blue or white light. Healthy epithelial cells absorb the light and show up blue (or white), while cells with nuclei alterations reflect light and appear bright white or 'acetowhite' [15, 16] There are several commercial devices available including ViziLite, Vizilite Plus or Microlux/DLÒ (Figure 2.5).

A recent meta-analysis yielded pooled sensitivity and specificity compared with histopathological outcomes of 72% (95% CI: 62–81%) and 31% (95% CI: 25–36%) respectively, which do not support its routine use in oral mucosal examination [21]. Devices using chemiluminescence are capable of highlighting lesion characteristics such as colour and demarcation of margins [15, 16, 29-31].

Autofluorescence approaches

Autofluorescence is a phenomenon whereby cells can produce fluorescence when subjected to specific wavelength of light. Tissue autofluorescence devices often consist of an instrument that generates blue/or violet light (400 – 460 nm wavelength) that excites endogenous fluorophores such as Flavin Adenine Dinucleotide (FAD) and Nicotinamide Adenine Dinucleotide (NADH). These fluorophores are present in the epithelium, collagen, and elastin of oral mucosa and emit a visible green coloured fluorescence [15, 16].

Abnormal variations in the structure of cells can change the distribution of key endogenous markers which emit fluorescence light. Premalignant or malignant cells that typically demonstrate cellular or nuclear pleomorphism and altered metabolism are not capable of emitting autofluorescence and therefore manifest as a dark spot. This gives the characteristic 'loss of fluorescence visualization' (FVL) in contrast to normal tissue which exhibits a 'retained fluorescence visualization' (FVR).

This technique can help identify lesions that are not visible to the naked eye (occult clinical lesion), and could be used to detect a suspicion area of a lesion and for determining adequate surgical margins (Figure 2.6). It has the advantages of being non-invasive and easy to use and allowing real time examination [15, 16, 32, 33].

Tissue autofluorescence devices have been used and evaluated in OPMD and oral cancer detection with promising results [15-17, 21, 30, 32, 33]. A recent meta-analysis yielded pooled sensitivity and specificity compared to histopathological outcomes of 90% (95% CI: 76–100%) and 72% (95% CI: 35–100%), respectively [21]. These devices may be useful as diagnostic adjuncts for OPMDs by experienced clinicians. It must be noted blood haemoglobin and melanin can reduce fluorescence, conversely keratin, fibrin and porphyrin can increase fluorescence. Therefore, it is difficult to discriminate between inflammatory conditions such as lichen planus, pemphigus or non-inflammatory vascular changes, or pigmented lesions, as these types of lesions tend to absorb light and do not reflect it [16].

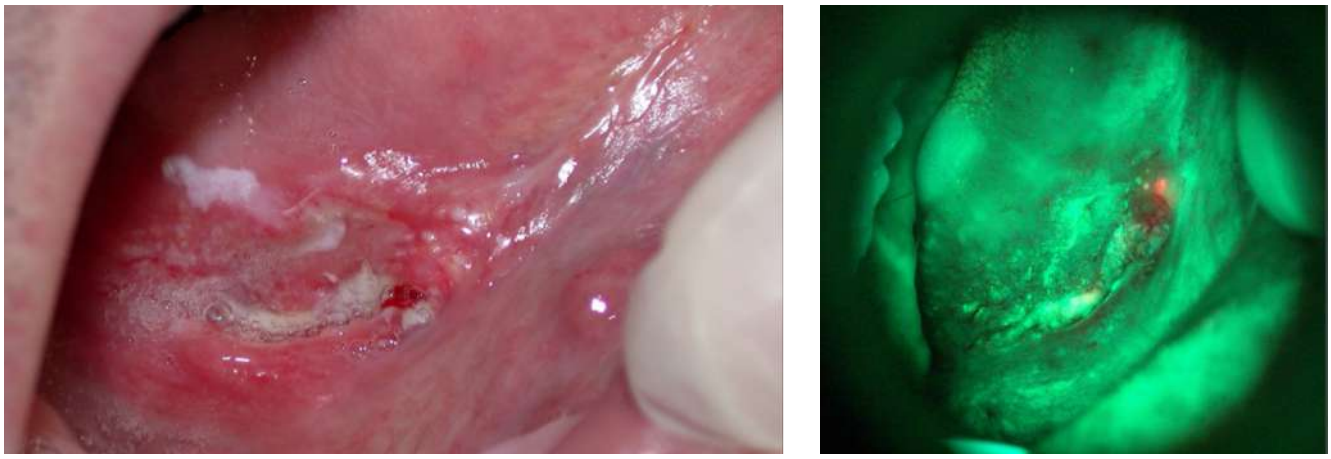

Figure 2.6. The use of the VELscope (Visually Enhanced Lesion Scope) in a redwhite ulcer on the right border of the tongue.

There are multiple commercial optical handheld devices available including the VELscope (Visually Enhanced Lesion Scope), Vizilite Pro and Identafi. The latter contains three-light emissions sources including a white light, violet light (405nm) to direct autofluorescence examination, and a green-amber light (540-575nm) to show vascular changes [15, 16]. Further studies and evaluation on usefulness of these devices are needed.

Laser-induced fluorescence examination

Laser-induced fluorescence examination (LIFE) or laser-induced autofluorescence (LIAF) is an autofluorescence technique that has a similar mechanism to autofluorescence devices previously described. The protocol is based on the activation of the fluorophores on oral mucosa inducing their fluorescence. The tissues that are not capable of emitting light (show loss of fluorescence visualization) are more likely to have dysplastic features [17, 34, 35).

The emission of light comes from a laser device that uses a diode laser with a wavelength between 375 and 405nm oriented to oral mucosa through an optic fibre and a handpiece. A pair of glasses with a yellow filter will demonstrate a white/blue light in healthy tissues and dark area in abnormal tissues. This method can be used on keratinised and non-keratinised tissues [17, 34-36].

This is a very promising tool as it highlights potential malignant areas and highlights lesions not visible to the human eye. The available data suggest a sensitivity between 95 and 100% and a specificity between 86 and 96% [17, 35]. Further investigations are needed to on the use of these methods in OPMD and oral cancer.

Narrow-Band Imaging

Narrow band imaging (NBI) is an optical imaging endoscopic technique first described in 2001 and has been used in aerodigestive tract mucosal tissue, pulmonology, gynaecology, and urology for evaluation of PMD. The NBI endoscope emits two wavelengths of light, one between 400–430nm blue light that is capable of imaging superficial vasculature in the mucosa (blood vessels appear brown), and a green light ranging 525 from 555nm that accentuates denser vessels in the submucosa (blood vessels appear as cyan) [16, 37, 38] (Figure 2.7). The process of carcinogenesis is characterised by neoangiogenesis, with abnormalities in the vascular architecture. NBI could allow the detection of premalignant or malignant changes at an early stage. The scientific evident on the use of NBI in OPMD and oral cancer diagnosis is sparce but with some interesting results suggesting the utility of NBI as an adjunct method in the detection of OPMDs or neoplastic lesions in the oral cavity and oropharynx [39, 40].

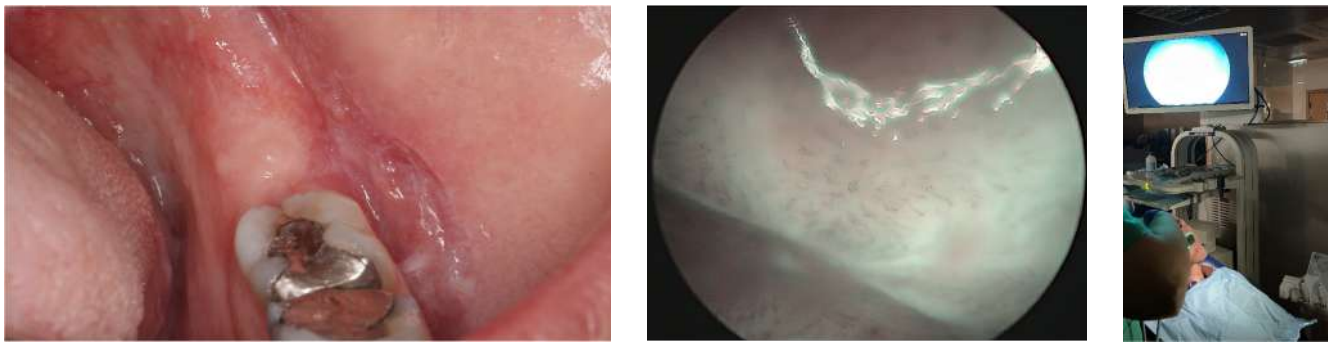

Figure 2.7. The use of the narrow band imaging (NBI) enhancing blood vessesls anatomy in a redwhite ulcer on the left buccal mucosa.

A recent systematic review and meta-analysis showed a sensitivity of 75.7% (95% CI 65.1%-83.9%) and a specificity of 91.5% (95% CI 81.8%-96.3%) [41].

Contact Endoscopy (direct stomatoscopy)

Contact endoscopy (CE) is a minimally-invasive imaging technique that was first described in 1979 by Hamou to study epithelial cells of the uterus, and was reported as a diagnostic tool in head and neck epithelial tumours in 1990 [42, 43]. CE uses a rigid endoscope in contact with the oral mucosa at low pressure and generates magnified images of high resolution (e.g. of 60x, 150x times or more) that demonstrate cellular architecture and vascular structures [44]. The images are displayed in a video system that processes the images in real time. This allows an *in vivo* cytological evaluation of oral mucosa (Figure 2.8) [24, 25, 42-45].

As part of the technique and for better visualization of cells, a vital stain is usually used, typically methylene blue, applied directly to the oral mucosa before CE observation. Some authors prefer to not stain the mucosa to better observe the vascular patterns. Saliva or blood may interfere with the capture and visualization of the images [24, 43, 44].

This is interesting for OPMD and oral cancer screening because it reveals in real time the number of cells per view, the size and contour of the cells, mitotic figures, nuclear/cytoplasmic ratio, hyperchromatism and heterochromatism that could suggest features of OPMD or oral carcinoma [24, 25, 42-45]. There are very few studies evaluating the efficacy of this method in oral cancer screening. Dowthwaite et al [43] report a sensitivity and specificity of 89% and 100% respectively in the evaluation of malignant lesions. CE is an expensive tool and requires experienced clinicians. Necrotic or oedematous tissues do not pick up the dye well and patients who undergo radiotherapy show cytomegaly and a smaller nuclear membrane, features that might be confused as part of carcinogenesis [24, 42-44]. It could be problematic for deep lesions with no superficial damage or in very thick lesions. It requires more studies to evaluate its potential as an oral cancer screening adjunct.

Vibrational spectroscopy

Vibrational spectroscopy including Raman has received significant attention as an approach for distinguishing between healthy and dysplastic oral tissues [46-54].

Figure 2.8. The use of the contact endoscopy showing the epithelial cellular composition of a white patch of ventral tongue.

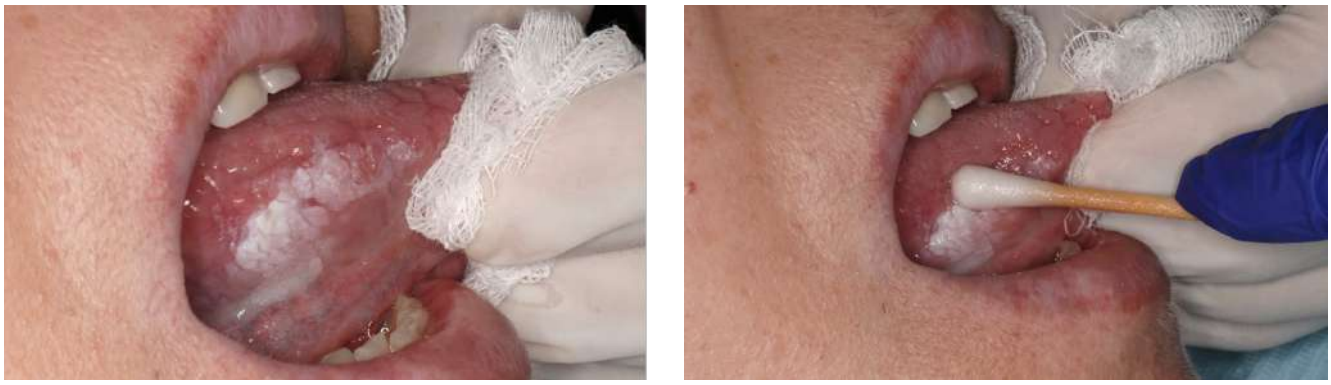

Figure 2.9. An exfoliative cytology is performed in a white patch of the border of the tongue.

The technique has significant potential for intra-operative use due to its non-destructive nature and does not require pre-treatment or labelling of tissues. Raman relies on scattering events with the incident light (ultraviolet, visible or near infrared) with chemical bonds within the target. Most light scatters at the same wavelength (or colour) known as Rayleigh or elastic scattering, however a small portion of light loses energy (or increases wavelength) due to its interactions with bonds in the sample [55]. Detecting this scattered light known as Raman or inelastic scatter can help identify the presence of specific molecules and their respective intensities. In the case of oral tissues, research has identified key characteristics of 'normal' tissues including a high lipid content and malignant tissues containing specific protein features [48-50]. These characteristic peaks can be analysed 'real-time' at chair side as the clinician moves the endoscope and could return information regarding tissue health. This can therefore guide sites to take a biopsy and inform correct tumour margins. At present no commercial system is available for distinguishing oral cancers using Raman spectroscopy. However, due to its promising results in *in vitro* and *in vivo* reports at many cancer locations, including oral tissues, it is anticipated this modality will be seen in routine clinical practise in the future [56].

2.4.3. Oral Cytology

Oral cytology refers to the study of cells for the purpose of microscopic diagnosis and an oral cytology exam is regarded as an auxiliary diagnostic procedure. As only isolated or small group of cells are observed, an incisional or excision biopsy should be performed to confirm a positive result.

Exfoliative cytology was first described by George Papanicolau who studied cervical cancer and it became a useful screening method [16, 57]. The sensitivity of oral cytology is inferior to any type of tissue biopsy. A wide range of sensitivities and specificities have been reported in the literature due to differences in the techniques used for collection of cells, the examination and interpretation (e.g. smear versus liquid-based cytology; microscopic examination versus molecular studies). A recent meta-analysis reported a pooled sensitivity and specificity of 96% (95% CI: 81–100%) and 90% (95% CI: 79–97%), respectively [16, 21]. It is an easy and non-invasive technique. Confirmation of a positive result must be obtained by conventional gold standard biopsy.

The three most common types are exfoliative cytology, transepithelial biopsy (Brush cytology biopsy) and fine-needle aspiration cytology (FNAC).

Exfoliative cytology and transepithelial (brush) cytology

Exfoliative cytology (EC) consists of the analysis of cells in the saliva (mouthwash sampling) or cells obtained from the oral mucosal surfaces by brushing or scrapping techniques that can be undertaken with a brush (preferable), wooden spatula, blunt instrument or sharp instrument. Oral exfoliative cytology is a painless, minimally invasive, simple procedure (Figure 2.9) [16, 58].

The technique presents some disadvantages as it scraps only the superficial layers of epithelium. The method may not be helpful in some inflammatory and reactive disorders because of lack of specificity.

Considering that most of the dysplastic cells appear deeper in the epithelium and not be represented in the sample obtained by scraping the surface [16, 57-59].

This has led to the development of extended methods that include an automated cytometric analysis or evaluation of molecular markers that could be present in oral cells or saliva [60]. A vigorous brushing of the oral epithelium (almost to the point bleeding could be observed) was observed in some studies, leading to the emergence of the transepithelial cytology technique. Some available commercial tools use this transepithelial cytology technique, including the OralCDX test, which is a computer assisted device that uses an algorithm to detect malignant cells, using a circular brush with hard bristles to collect the total depth of the epithelium (superficial, intermediate, and basal).

A positive result should be confirmed with a scalpel biopsy and histological evaluation [16, 58, 59].

2.4.4. Salivary adjuncts

Other diagnostic adjunct tools use saliva for the study of several molecular markers e.g. antibodies, cytokines, human and microbial nucleic acids (DNA, RNA, microRNA), growth factors, and a range of proteins, in particular, tumour biomarkers. Many of these are in a research phase or are commercially available (such as CD44 and 'total protein' levels or mRNA biomarkers), but with insufficient scientific evidence for their routine use in OPMD and oral cancer detection [61, 62].

References

1. Nezelof C, Contesso G, Guinebretière JM. [The biopsy: a neologism coined by Ernest Besnier]. Bull Cancer. 2001;88(8):719-23.
2. Kannan R. Oral Biopsy: Principles and Practice. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of Oral Cancer: Prevention, Diagnosis and Management. Cham: Springer International Publishing; 2020. p. 81-98.
3. Seoane JM, González-Mosquera A, Velo-Noya J. La biopsia oral en el contexto del precáncer y del cáncer oral. Avances en Odontoestomatología. 2008;24:89-96.
4. Márquez A, Castillo I, Fuentes M. La biopsia oral en el diagnóstico del cáncer. In Cáncer Oral Para Dentistas. López-Jornet and Seonane-lestón J. Primera Edición. ed Fundacion Dental Española – Consejo Dentistas. 2019:97-104.
5. Kumaraswamy KL, Vidhya M, Rao PK, Mukunda A. Oral biopsy: oral pathologist's perspective. J Cancer Res Ther. 2012;8(2):192-8.
6. Mota-Ramírez A, Silvestre FJ, Simó JM. Oral biopsy in dental practice. Med Oral Patol Oral Cir Bucal. 2007;12(7):E504-10.
7. Monteiro L, Delgado ML, Garcês F, Machado M, Ferreira F, Martins M, et al. A histological evaluation of the surgical margins from human oral fibrous-epithelial lesions excised with CO_2 laser, Diode laser, Er:YAG laser, Nd:YAG laser, electrosurgical scalpel and cold scalpel. Med Oral Patol Oral Cir Bucal. 2019;24(2):e271-e80.
8. Seoane J, Caballero TG, Urizar JM, Almagro M, Mosquera AG, Varela-Centelles P. Pseudodysplastic epithelial artefacts associated with oral mucosa CO_2 laser excision: an assessment of margin status. Int J Oral Maxillofac Surg. 2010;39(8):783-7.
9. Seoane J, González-Mosquera A, García-Martín JM, García-Caballero L, Seoane-Romero JM, Varela-Centelles P. Pseudoepitheliomatous hyperplasia after diode laser oral surgery. An experimental study. Med Oral Patol Oral Cir Bucal. 2015;20(5):e554-9.
10. Vescovi P, Corcione L, Meleti M, Merigo E, Fornaini C, Manfredi M, et al. Nd:YAG laser versus traditional scalpel. A preliminary histological analysis of specimens from the human oral mucosa. Lasers Med Sci. 2010;25(5):685-91.
11. Suter VGA, Altermatt HJ, Bornstein MM. A randomised controlled clinical and histopathological trial comparing excisional biopsies of oral fibrous hyperplasias using CO(2) and Er:YAG laser. Lasers Med Sci. 2017;32(3):573-81.
12. Saccucci M, Di Carlo G, Bossù M, Giovarruscio F, Salucci A, Polimeni A. Autoimmune Diseases and Their Manifestations on Oral Cavity: Diagnosis and Clinical Management. J Immunol Res. 2018;2018:6061825-.
13. Jeong W-J, Paik JH, Cho S-W, Sung M-W, Kim KH, Ahn S-H. Excisional biopsy for management of lateral tongue leukoplakia. Journal of Oral Pathology & Medicine. 2012;41(5):384-8.
14. Tudor-Green B. Surgical Biopsy Techniques and Adjuncts. In: Brennan PA, Aldridge T, Dwivedi RC, editors. Premalignant Conditions of the Oral Cavity. Singapore: Springer Singapore; 2019. p. 209-27.
15. Perks A, Forna D, Barreira E, Fricain JC, Monteiro L, Diniz-Freitas M, Escudier M, Forna N, Dios PD, Das P, Cook R, Albuquerque R, Warnakulasuryia S. Oral Cancer Prevenction. Diniz-Freitas M, Albuquerque R, Monteiro L, Fricain JC, Cook R, Escudier M, Warnakulasuryia S. European Regional Organization (ERO) of the Federation of Dentaire Internationale (FDI) and the Romanian Association of Dental Education (ADRE) 2019.
16. Ross Kerr A. Diagnostic Adjuncts for Oral Cavity Squamous Cell Carcinoma and Oral Potentially Malignant Disorders. In: Warnakulasuriya S, Greenspan JS, editors. Textbook of Oral Cancer: Prevention, Diagnosis and Management. Cham: Springer International Publishing; 2020. p. 99-117.
17. Giovannacci I, Vescovi P, Manfredi M, Meleti M. Non-invasive visual tools for diagnosis of oral cancer and dysplasia: A systematic review. Med Oral Patol Oral Cir Bucal. 2016;21(3):e305-15.
18. Macey R, Walsh T, Brocklehurst P, Kerr AR, Liu JL, Lingen MW, et al. Diagnostic tests for oral cancer and potentially malignant disorders in patients presenting with clinically evident lesions. Cochrane Database Syst Rev. 2015;2015(5):Cd010276.
19. Chainani-Wu N, Madden E, Cox D, Sroussi H, Epstein J, Silverman S, Jr. Toluidine blue aids in detection of dysplasia and carcinoma in suspicious oral lesions. Oral Dis. 2015;21(7):879-85.
20. Zhang L, Williams M, Poh CF, Laronde D, Epstein JB, Durham S, et al. Toluidine blue staining identifies high-risk primary oral premalignant lesions with poor outcome. Cancer Res. 2005;65(17):8017-21.
21. Lingen MW, Tampi MP, Urquhart O, Abt E, Agrawal N, Chaturvedi AK, et al. Adjuncts for the evaluation of potentially malignant disorders in the oral cavity: Diagnostic test accuracy systematic review and meta-analysis-a report of the American Dental Association. J Am Dent Assoc. 2017;148(11):797-813.e52.

22. Chen YW, Lin JS, Fong JH, Wang IK, Chou SJ, Wu CH, et al. Use of methylene blue as a diagnostic aid in early detection of oral cancer and precancerous lesions. Br J Oral Maxillofac Surg. 2007;45(7):590-1.
23. Lejoy A, Arpita R, Krishna B, Venkatesh N. Methylene Blue as a Diagnostic Aid in the Early Detection of Potentially Malignant and Malignant Lesions of Oral Mucosa. Ethiop J Health Sci. 2016;26(3):201-8.
24. Galrito M, Santos A, Monteiro L, Salvado F, Macor C. Contact endoscopy and laser treatment of oral leukoplakia - A new protocol proposal. 2019;48(S1):5-83.
25. Andrea M, Dias O, Macor C, Santos A, Varandas J. Contact endoscopy of the nasal mucosa. Acta Otolaryngol. 1997;117(2):307-11.
26. Petruzzi M, Lucchese A, Baldoni E, Grassi FR, Serpico R. Use of Lugol's iodine in oral cancer diagnosis: An overview. Oral Oncology. 2010;46(11):811-3.
27. Du GF, Li CZ, Chen HZ, Chen XM, Xiao Q, Cao ZG, et al. Rose bengal staining in detection of oral precancerous and malignant lesions with colorimetric evaluation: A pilot study. International Journal of Cancer. 2007;120(9):1958-63.
28. Vanerio N, Stijnen M, de Mol B, Kock LM. Biomedical Applications of Photo- and Sono-Activated Rose Bengal: A Review. Photobiomodul Photomed Laser Surg. 2019;37(7):383-94.
29. Lingen MW, Abt E, Agrawal N, Chaturvedi AK, Cohen E, D'Souza G, et al. Evidence-based clinical practice guideline for the evaluation of potentially malignant disorders in the oral cavity: A report of the American Dental Association. J Am Dent Assoc. 2017;148(10):712-27. e10.
30. Awan KH, Morgan PR, Warnakulasuriya S. Utility of chemiluminescence (ViziLite™) in the detection of oral potentially malignant disorders and benign keratoses. J Oral Pathol Med. 2011;40(7):541-4.
31. Patton LL, Epstein JB, Kerr AR. Adjunctive techniques for oral cancer examination and lesion diagnosis: a systematic review of the literature. J Am Dent Assoc. 2008;139(7):896-905; quiz 93-4.
32. Meleti M, Giovannacci I, Vescovi P, Pedrazzi G, Govoni P, Magnoni C. Histopathological determinants of autofluorescence patterns in oral carcinoma. Oral Dis. 2020 in press.
33. Vescovi P, Giovannacci I, Otto S, Manfredi M, Merigo E, Fornaini C, et al. Medication-Related Osteonecrosis of the Jaw: An Autofluorescence-Guided Surgical Approach Performed with Er:YAG Laser. Photomed Laser Surg. 2015;33(8):437-42.
34. Ganga RS, Gundre D, Bansal S, Shirsat PM, Prasad P, Desai RS. Evaluation of the diagnostic efficacy and spectrum of autofluorescence of benign, dysplastic and malignant lesions of the oral cavity using VELscope. Oral Oncol. 2017;75:67-74.
35. Mallia RJ, Thomas SS, Mathews A, Kumar R, Sebastian P, Madhavan J, et al. Laser-induced autofluorescence spectral ratio reference standard for early discrimination of oral cancer. Cancer. 2008;112(7):1503-12.
36. Tozar T, Andrei IR, Costin R, Pascu ML, Pirvulescu R. Laser induced autofluorescence lifetime to identify larynx squamous cell carcinoma: Short series ex vivo study. J Photochem Photobiol B. 2020;202:111724.
37. Shibahara T, Yamamoto N, Yakushiji T, Nomura T, Sekine R, Muramatsu K, et al. Narrow-band imaging system with magnifying endoscopy for early oral cancer. Bull Tokyo Dent Coll. 2014;55(2):87-94.
38. Aloisi A, Sonoda Y, Gardner GJ, Park KJ, Elliott SL, Zhou QC, et al. Prospective Comparative Study of Laparoscopic Narrow Band Imaging (NBI) Versus Standard Imaging in Gynecologic Oncology. Ann Surg Oncol. 2018;25(4):984-90.
39. Vu A, Farah CS. Narrow band imaging: clinical applications in oral and oropharyngeal cancer. Oral Dis. 2016;22(5):383-90.
40. Vu AN, Farah CS. Efficacy of narrow band imaging for detection and surveillance of potentially malignant and malignant lesions in the oral cavity and oropharynx: a systematic review. Oral Oncol. 2014;50(5):413-20.
41. Ansari UH, Wong E, Smith M, Singh N, Palme CE, Smith MC, et al. Validity of narrow band imaging in the detection of oral and oropharyngeal malignant lesions: A systematic review and meta-analysis. Head Neck. 2019;41(7):2430-40.
42. Carta F, Sionis S, Cocco D, Gerosa C, Ferreli C, Puxeddu R. Enhanced contact endoscopy for the assessment of the neoangiogenetic changes in precancerous and cancerous lesions of the oral cavity and oropharynx. Eur Arch Otorhinolaryngol. 2016;273(7):1895-903.
43. Dowthwaite S, Szeto C, Wehrli B, Daley T, Whelan F, Franklin J, et al. Contact endoscopy as a novel technique in the detection and diagnosis of oral cavity and oropharyngeal mucosal lesions in the head and neck. J Laryngol Otol. 2014;128(2):147-52.
44. Kumar S, Mishra AK, Galagali JR, Sethi A, Malik A. Contact endoscopy for detection of residual or recurrent disease after radiotherapy for squamous cell carcinoma of the upper aerodigestive tract. J Laryngol Otol. 2020;134(4):344-9.
45. Negoro A, Umemoto M, Fukazawa K, Terada T, Sakagami M. Observation of tongue papillae by video microscopy and contact endoscopy to investigate their correlation with taste function. Auris Nasus Larynx. 2004;31(3):255-9.
46. Cals FL, Schut TCB, Hardillo JA, De Jong RJB, Koljenović S, Puppels, GJ. Investigation of the potential of Raman spectroscopy for oral cancer detection in surgical margins. Laboratory Investigation. 2015; 95(10):1186-1196.
47. deVeld DCG, Bakker Schut TC, Skurichina M et al. Autofluorescence and Raman microspectroscopy of tissue sections of oral lesions. Lasers Med Sci. 2005;19:203–209
48. Deshmukh A, Singh SP, Chaturvedi P et al. Raman spectroscopy of normal oral buccal mucosa tissues: study on intact and incised biopsies. J Biomed Opt 2011;16:127004
49. Guze K, Pawluk HC, Short M et al. Pilot study: Raman spectroscopy in differentiating premalignant and malignant oral lesions from normal mucosa and benign lesions in humans. Head Neck 2014;37:511–517.
50. Guze K, Short M, Zeng H et al. Comparison of molecular images as defined by Raman spectra between normal mucosa and squamous cell carcinoma in the oral cavity. J Raman Spectrosc 2011;42:1232–1239.
51. Malini R, Venkatakrishna K, Kurien J et al. Discrimination of normal, inflammatory, premalignant, and malignant oral tissue: a Raman spectroscopy study. Biopolymers 2006;81:179–193.
52. Oliveira AP, Bitar RA, Silveira L et al. Near-infrared Raman spectroscopy for oral carcinoma diagnosis. Photomed Laser Surg 2006;24:348–353.
53. Singh SP, Deshmukh A, Chaturvedi P et al. In vivo Raman spectroscopic identification of premalignant lesions in oral buccal mucosa. J Biomed Opt 2012;17:105002.
54. Su L Sun YF, Chen Y et al. Raman spectral properties of squamous cell carcinoma of oral tissues and cells. Laser Phys 2012;22:311–316.
55. Baker MJ, Hughes CS, Hollywood KA, 2016. Biophotonics: Vibrational Spectroscopic Diagnostics. Morgan & Claypool Publishers.
56. Bergholt MS, Zheng W, Ho KY, Teh M, Yeoh KG, So JBY, et al. Fiber□ optic Raman spectroscopy probes gastric carcinogenesis in vivo at endoscopy. Journal of biophotonics, 2013;6(1), pp.49-59.
57. A HA, Kujan O, Farah CS. The utility of oral brush cytology in the early detection of oral cancer and oral potentially malignant disorders: A systematic review. J Oral Pathol Med. 2018;47(2):104-16.
58. Velleuer E, Dietrich R, Pomjanski N, de Santana Almeida Araujo IK, Silva de Araujo BE, Sroka I, et al. Diagnostic accuracy of brush biopsy-based cytology for the early detection of oral cancer and precursors in Fanconi anemia. Cancer Cytopathol. 2020;128(6):403-13.
59. Pandey P, Agarwal S, Ralli M, Dixit A, Singh D. Oral Brush Liquid-Based Cytology: A Study of Concordance between a Cytotechnologist and a Cytopathologist. Acta Cytol. 2018;62(2):121-9.
60. Odell EW. Aneuploidy and loss of heterozygosity as risk markers for malignant transformation in oral mucosa. Oral Dis. 2021;27(8):1993-2007.
61. Franzmann EJ, Reategui EP, Pereira LH, Pedroso F, Joseph D, Allen GO, et al. Salivary protein and solCD44 levels as a potential screening tool for early detection of head and neck squamous cell carcinoma. Head Neck. 2012;34(5):687-95.
62. Martin JL, Gottehrer N, Zalesin H, Hoff PT, Shaw M, Clarkson JH, et al. Evaluation of Salivary Transcriptome Markers for the Early Detection of Oral Squamous Cell Cancer in a Prospective Blinded Trial. Compend Contin Educ Dent. 2015;36(5):365-73.

3

Histological Aspects of Oral Potentially Malignant Disorders

Lisette Collins[1]

Selvam Thavaraj[1,2]

1 Head and Neck Pathology, Guy's & St Thomas' NHS Foundation Trust, London, UK

2 Centre for Clinical, Oral & Translational Science, King's College London, London, UK

3.1. Introduction

This chapter is intended as a general introduction to histopathological diagnosis of selected oral potentially malignant disorders (OPMDs) for physicians, surgeons, and allied health professionals. It is anticipated that the key aspect discussed in this chapter will provide clinical healthcare professionals with insight into the process of histological diagnosis in order to contextualise the role of the pathologist in the multidisciplinary management of OPMDs. It is not intended as a comprehensive text and will discuss the more common histological features of clinical OPMDs, namely oral lichenoid lesions (OLL) and oral epithelial dysplasia. Histological features of other OPMDs are covered elsewhere in this book.

Accurate histological diagnosis is context dependent since there are several overlapping and non-specific microscopic features. Some microscopic features gain relevance in certain clinical contexts which may otherwise be disregarded as incidental. Prior to microscopic evaluation, the pathologist requires 1) salient patient demographic information, 2) the clinical history and appearance of the OPMD, 3) serological findings (if applicable) 4) details of previous biopsies and, perhaps most importantly, 5) a clinical differential diagnosis including the degree of clinical suspicion of malignancy transformation. This highlights the importance for clear and comprehensive clinical information on the pathology request form which accompanies the specimen. Conversely, clinicians should always consider the pathology report in its clinical context; the histological diagnosis should complement, not contradict, the clinical impression. Clear and open communication between clinician and pathologists underpins effective management.

3.2. Oral Lichenoid Lesions

The oral lichenoid lesions (OLLs) are a diverse group of oral inflammatory conditions including, but not limited to, oral lichen planus (OLP), lichenoid reaction (LR), lupus erythematosus (LE) and Graft vs. Host disease (GVHD), which are grouped together on their shared histological features [1, 2].

Individually seen in many different conditions, it is the combination of hyperkeratosis, basal cell degeneration, apoptotic (Civatte) bodies, a sub-epithelial inflammatory infiltrate and lymphocyte exostosis that form the histological foundation for this group [3] (Figure 3.1). Additional findings may include a disturbed rete peg architecture, hyalinization of the basement membrane and pigmentary incontinence. It is the alteration in the keratin layer, and not the type nor amount, which is important. The keratin layer may present as either ortho- or para-keratin and extent may vary dependent on the oral cavity site. Liquefaction of the basal cells leads to basal squamoid change (apparent extension of the spinous cell layer to the basement membrane). The inflammatory infiltrate is usually predominated by lymphocytes with very few plasma cells unless ulceration or Candida is present. Typically, it is dense and band-like with varying degrees of lymphocyte epithelial tropism into the basal cell layers.

Analysis of the histological differences between OLLs have been shown to be non-significant, however some features are often regarded as favouring a specific OLL. Oral lichenoid drug and contact reactions may demonstrate a more diffuse mixed inflammatory infiltrate with a greater frequency of plasma cells. Lymphocyte exocytosis may also be noted extending both further into the suprabasal layers and into the deeper lamina propria with demonstration of perivascular inflammation and lymphoid follicles. Rete peg hyperplasia with flame shaped rete processes is associated with LE, occasionally extensive enough to form areas of pseudoepitheliomatous hyperplasia. Deep keratin plugging seen in LE skin lesions is not present in oral cavity lesions, however downwards extension of keratin can be present, giving the appearance of low-level keratinisation. Oral graft-versus-host disease may show identical histological features to oral lichen planus. The only feature regularly considered to be more suggestive of OGVHD is that the lymphocytic infiltrate is not as intense and, in many cases, resembles more of a 'burnt out' appearance.

Two histological exclusion criteria for all the oral lichenoid lesions are the presence of dysplasia as well as the presence of a verrucous epithelial architecture.

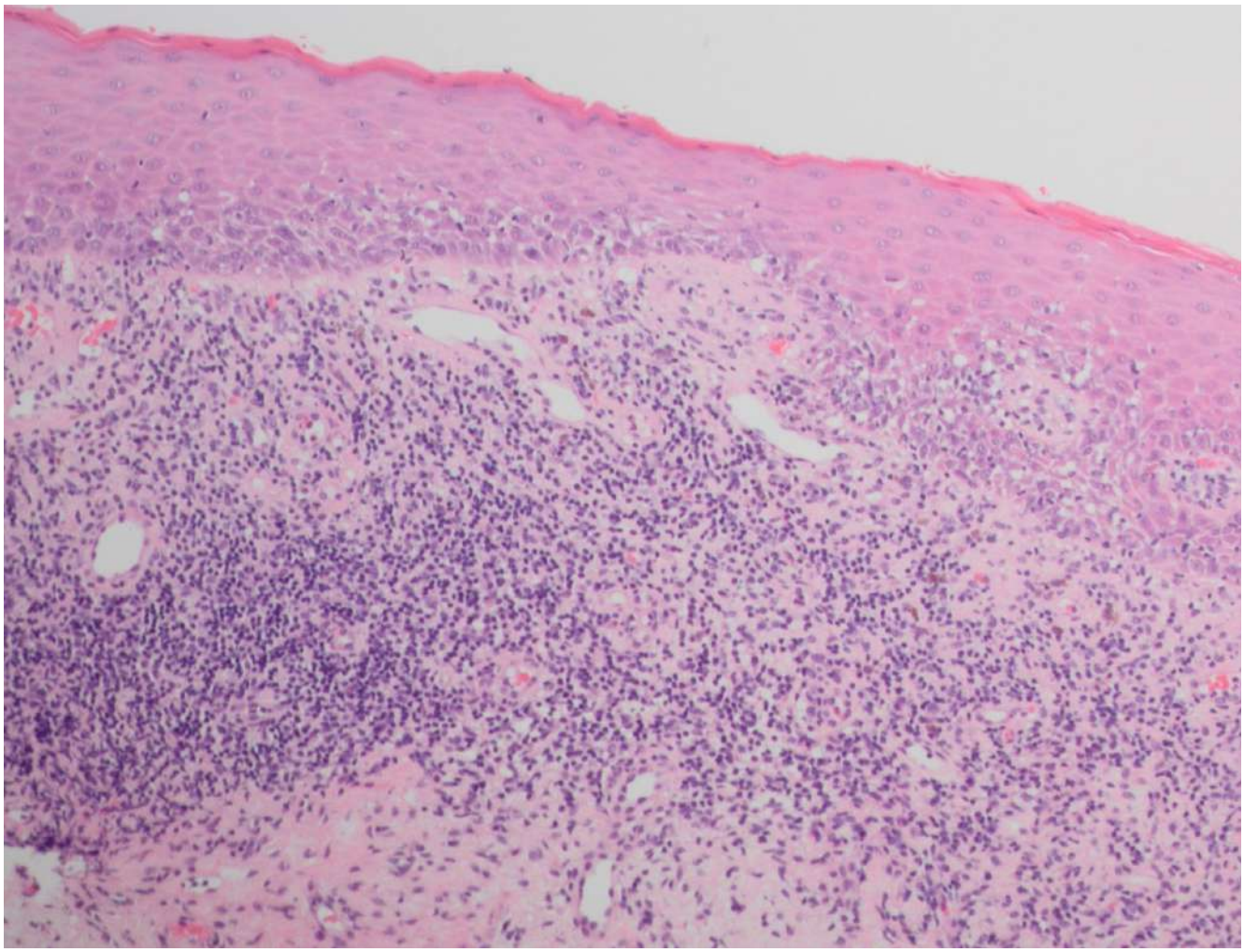

Figure 3.1. A photomicrograph showing the typical histological characteristics shared amongst the oral lichenoid lesions including hyperkeratosis, epithelial atrophy with basal cell degeneration and a dense 'band-like' lymphocytic inflammatory infiltrate with lymphocyte exocytosis.

OLLs as OPMDs have long been a controversial topic. The rationale behind this is that many dysplastic lesions show concurrent lichenoid inflammation and many lichenoid lesions cannot accurately be assessed for the presence of dysplasia, due to the altered basal cell layers and intermingled lymphocyte infiltrate [4]. Therefore, it is essential to always consider the presence of dysplasia in any lichenoid lesion. Lichenoid inflammation is also a common finding in oral epithelial dysplasia (OED), in particular those demonstrating verrucous architecture [5]. It has been suggested that this is likely in response to dysplasia within these lesions rather than a true association with an underlying lichenoid lesion. In a study of known proliferative verrucous leukoplakia cases, 59% had received an initial clinical diagnosis of OLP and 43% of biopsies had shown lichenoid features [6].

Although OLLs share many clinicopathological features, it is their differences which are exceedingly important in their diagnosis and only through understanding of the clinical presentation alongside additional findings can correct diagnosis be made. Interpretation of histological assessment should never be made without appreciation for the full clinical context.

3.3. Oral Submucous Fibrosis

The characteristic histological feature of oral submucous fibrosis is the presence of dense fibrosis with reduced vascularisation of the lamina propria. Early lesions can be challenging to diagnose before the fibrosis is marked. Special stains, such as Van Gieson, can aid visualization of the parallel arrangement of collagen fibres [7].

Hyperkeratosis and epithelial atrophy have also been reported as epithelial changes. The inflammatory infiltrate can be variable and may even show a lichenoid inflammatory pattern. Importantly, biopsies should be assessed for the presence of epithelial dysplasia, which is seen in up to 15% of cases [8].

3.4. Oral Epithelial Dysplasia (OED)

The World Health Organisation (WHO) defines OED as 'a spectrum of architectural and cytological changes associated with an increased risk of progression to squamous cell carcinoma' [9]. Whereas OPMD is ascribed to clinical presentations, OED is histomorphologically defined. Therefore, in addition to the identification of histological features associated with particular disorders, the pathologist will also consider the presence of dysplasia in any OPMD biopsy specimen.

Architectural changes refer to disordered tissue organisation, while cytological changes indicate individual cell abnormality (Table 3.1). The WHO recognise several features of OED but it should be noted that these features remain subjective since there are no agreed morphometric defining criteria. Furthermore, when taken in isolation, each individual feature may also be present in reactive oral mucosal conditions. Nevertheless, these features serve as diagnostic criteria and highlight to the pathologist that the lesion may contain potential for malignant transformation. In addition to the features detailed in Table 3.1, many would also add verrucous surface morphology, subdividing or budding rete processes, spontaneous apoptosis in the absence of intraepithelial inflammatory cells, ortho- or para-keratosis with abrupt lateral demarcation and a subepithelial lymphocytic infiltrate mimicking OLLs [10, 11]. Some groups also utilise the term 'differentiated dysplasia', namely expansion of the suprabasal compartment by large cells with abundant eosinophilic cytoplasm and intercellular oedema [12, 13]. These latter architectural features are frequently mistaken for reactive hyperplastic changes.

Architectural changes	Cytological changes
Irregular stratification	Abnormal variation in nuclear size
Loss of polarity of basal cells	Abnormal variation in nuclear shape
Bulbous rete ridges	Abnormal variation in cell size
Increased number of mitotic figures	Abnormal variation in cell shape
Premature keratinization in a single cell	Increased nuclear:cytoplasm ratio
Squamous eddies within rete ridges	Atypical mitotic figures
Loss of intracellular cohesion	Increased number and size of nucleoli
	Hyperchromasia

Table 3.1. Modified WHO morphologic criteria of OED [9]. Verrucous surface morphology, subdividing rete pegs, spontaneous apoptosis, abruptly demarcated pattern of keratosis and bulky suprabasal proliferation are also increasingly accepted features.

Currently, there is lack of evidence to indicate that any single feature should carry greater significance in predicting malignant transformation. Moreover, there seems to be relatively poor correlation between genetic aberrations and morphologic changes [14]. Therefore, when evaluating dysplasia, rather than applying any points-based algorithmic approach, pathologists undertake a global overview of the epithelial changes, taking into account the intraoral subsite and its clinical presentation [15].

There is a positive correlation between the likelihood and time to malignant transformation with increasing degrees of dysplasia [16]. However, published predictive values of malignant transformation have wide confidence intervals due to poor inter-observer reproducibility, methodological heterogeneity, and variable follow-up periods [17]. Predictive values may be improved using ploidy and loss of heterozygosity analyses as adjuncts to histological grading, but these are not currently available beyond highly specialised or research centres [18].

Since OED is a spectrum of morphological changes, histological grading of dysplasia is essential to inform subsequent management of any given OPMD. Most centres utilise a three-tier grading system for OED of mild, moderate and severe dysplasia (Figure 3.2) with carcinoma in situ being synonymous with the last [9]. This system is partly guided by the epithelial thickness in thirds affected by architectural and cytological change. However, it should be emphasised that mild, moderate, and severe dysplasia do not necessarily equate to changes limited to the basal, middle, and superficial thirds of the epithelium, respectively. For example, it is possible for the dysplasia to be graded as severe despite changes being limited to the basal third, highlighting how grading a global assessment of morphologic changes. Nevertheless, since the cut-offs between each grade are poorly defined, suboptimal interobserver reproducibility is compounded. To overcome this, some authorities advocate a binary grading system (high- versus low-grade) and suggest cut-off criteria between the grades [19, 20]. In future, reproducibility may be enhanced by incorporating artificial intelligence platforms [21]. Ultimately however, the goal of any grading system is not reproducibility, but to inform clinical management within a multidisciplinary context. To this end, the pathologist's intent in assigning a grade should be clear to the clinician regardless of the system used, further emphasising the need for good multidisciplinary working relationships for effective management of OPMDs [15].

Hyperkeratotic lesions frequently contain concurrent *Candida spp.* infections. The reactive (and therefore reversible) squamous epithelial response to fungal hyphae results in phenotypic changes which are indistinguishable from dysplasia. In such circumstances, it would be prudent to consider definitive histological grading of OED following elimination of candida infection, clinical re-assessment and/or re-biopsy.

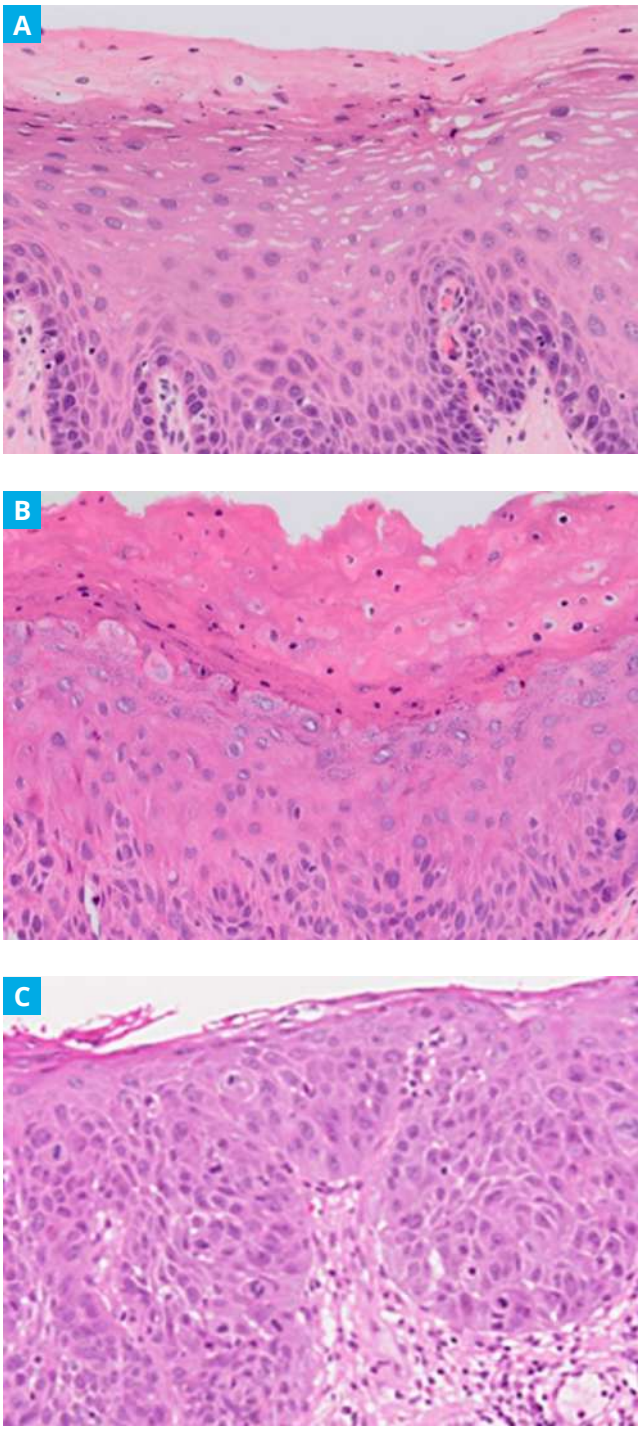

Figure 3.2. Examples of **A)** mild dysplasia demonstrating hyperchromasia and focally increased nuclear to cytoplasm ratio limited to the basal and parabasal layers; **B)** moderate dysplasia highlighted by disordered stratification and maturation affecting half the epithelial thickness; and **C)** severe dysplasia featuring full-thickness architectural and cytological atypia.

3.5. Human Papillomavirus-Associated Oral Epithelial Dysplasia (HPV OED)

A subset of OED is known to be associated with high-risk types of human papillomavirus (HPV), mainly HPV-16 [22-26]. The virus induces somewhat distinct histomorphological epithelial changes, namely karryorhexis, isolated suprabasal apoptotic keratinocytes, abortive mitotic forms (mitosoid bodies) and variable koilocyte-like cells within the superficial strata [22]. These morphological features on their own are insufficiently specific to confirm a virus-driven aetiology necessitating testing for transcriptionally active high-risk HPV.

The presence of biologically significant high-risk HPV may be demonstrated by strong and diffuse block positivity for p16 (often with sharp lateral demarcation) followed by in situ hybridisation for viral DNA or RNA [22, 25]. It should be noted that HPV testing by consensus PCR alone, in the absence of viral cytopathic changes, is insufficiently specific for HPV OED. Anecdotal reports of progression to carcinoma in HPV OED have been reported in small case series, but the overall malignant transformation rates currently remain unknown. Since there is no accepted grading system, HPV OED should for the present be graded and clinically managed according to conventional criteria [27].

References

1. Lu R, Zhou G. Oral lichenoid lesions: Is it a single disease or a group of diseases?. Oral Oncology. 2021;117:105188.
2. Alberdi-Navarro J, Marichalar-Mendia X, Lartitegui-Sebastián MJ, Gainza-Cirauqui ML, Echebarria-Goikouria MA, Aguirre-Urizar JM. Histopathological characterization of the oral lichenoid disease subtypes and the relation with the clinical data. Med Oral Patol Oral Cir Bucal. 2017;22(3):e307-e13.
3. Cheng YS, Gould A, Kurago Z, Fantasia J, Muller S. Diagnosis of oral lichen planus: a position paper of the American Academy of Oral and Maxillofacial Pathology. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(3):332-54.
4. Müller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Mod Pathol. 2017;30(s1):S54-S67.
5. Davidova LA, Fitzpatrick SG, Bhattacharyya I, Cohen DM, Islam MN. Lichenoid Characteristics in Premalignant Verrucous Lesions and Verrucous Carcinoma of the Oral Cavity. Head Neck Pathol. 2019;13(4):573-9.
6. McParland H, Warnakulasuriya S. Lichenoid morphology could be an early feature of oral proliferative verrucous leukoplakia. J Oral Pathol Med. 2021;50(2):229-35.
7. Nishat R, Kumar H. Collagen fibers in oral submucous fibrosis - A polarizing microscopy study using two special stains. Indian J Pathol Microbiol. 2019;62(4):537-43.
8. Cai X, Yao Z, Liu G, Cui L, Li H, Huang J. Oral submucous fibrosis: A clinicopathological study of 674 cases in China. J Oral Pathol Med. 2019;48(4):321-5.
9. Reibel J, Gale N, Hille J, Hunt JL, Lingen M, Muller S, et al. Oral potentially malignant disorders and oral epithelial dysplasia. In: ElNaggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. WHO Classification of head and neck tumours. 4th ed, Lyon. International Agency for Research on Cancer. 2017;112-5.
10. Woo SB. Oral Epithelial Dysplasia and Premalignancy. Head Neck Pathol. 2019;13(3):423-39.
11. Fitzpatrick SG, Honda KS, Sattar A, Hirsch SA. Histologic lichenoid features in oral dysplasia and squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol. 2014;117(4):511-20.
12. Wils LJ, Poell JB, Evren I, Koopman MS, Brouns EREA, de Visscher JGAM, et al. Incorporation of differentiated dysplasia improves prediction of oral leukoplakia at increased risk of malignant progression. Mod Pathol. 2020;33(6):1033-40.
13. Arsenic R, Kurrer M. Differentiated dysplasia is a frequent precursor or associated lesion in invasive squamous cell carcinoma of the oral cavity and pharynx. Virchows Archiv. 2013;462(6):609-617.
14. Fonseca-Silva T, Diniz MG, de Sousa SF, Gomez RS, Gomes CC. Association between histopathological features of dysplasia in oral leukoplakia and loss of heterozygosity. Histopathology. 2016;68(3):456-60.
15. Mehanna HM, Rattay T, Smith J, McConkey CC. Treatment and follow-up of oral dysplasia - a systematic review and meta-analysis. Head Neck. 2009;31(12):1600-9.
16. Iocca O, Sollecito TP, Alawi F, Weinstein GS, Newman JG, De Virgilio A, 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(3):539-55.
17. Odell EW. Aneuploidy and loss of heterozygosity as risk markers for malignant transformation in oral mucosa. Oral Dis. 2021;27(8):1993-2007.
18. Kujan O, Oliver RJ, Khattab A, Roberts SA, Thakker N, Sloan P. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncol. 2006;42(10):987-93.
19. Nankivell P, Williams H, Matthews P, Suortamo S, Snead D, McConkey C, et al. The binary oral dysplasia grading system: validity testing and suggested improvement. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(1):87-94.
20. Mahmood H, Shaban M, Indave BI, Santos-Silva AR, Rajpoot N, Khurram SA. Use of artificial intelligence in diagnosis of head and neck precancerous and cancerous lesions: A systematic review. Oral Oncol. 2020;110:104885.
21. Lerman MA, Almazrooa S, Lindeman N, Hall D, Villa A, Woo SB. HPV-16 in a distinct subset of oral epithelial dysplasia. Mod Pathol. 2017;30(12):1646-54.
22. McCord C, Xu J, Xu W, Qiu X, McComb RJ, Perez-Ordonez B, et al. Association of high-risk human papillomavirus infection with oral epithelial dysplasia. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;115(4):541-9.
23. Khanal S, Trainor PJ, Zahin M, Ghim SJ, Joh J, Rai SN, et al. Histologic variation in high grade oral epithelial dysplasia when associated with high-risk human papillomavirus. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017;123(5):566-85.
24. Hendawi N, Niklander S, Allsobrook O, Khurram SA, Bolt R, Doorbar J, et al. Human papillomavirus (HPV) can establish productive infection in dysplastic oral mucosa, but HPV status is poorly predicted by histological features and p16 expression. Histopathology. 2020;76(4):592-602.
25. de la Cour CD, Sperling CD, Belmonte F, Syrjänen S, Kjaer SK. Human papillomavirus prevalence in oral potentially malignant disorders: Systematic review and meta-analysis. Oral Dis. 2021;27(3):431-8.
26. Odell E, Gale N, Thavaraj S, Nadal A, Zidar N, Gnepp D. Precursor lesions for squamous carcinoma in the upper aerodigestive tract. D. Gnepp and B.J. A., Editors. 2020, Elsevier.

4

Oral Lichen Planus and Oral Lichenoid Lesions

Márcio Diniz Freitas[1]
Lucía García Caballero[2]
Jacobo Limeres Pose[1]

1. Special Care Dentistry Unit. School of Medicine and Dentistry. University of Santiago de Compostela, Spain.

2. Department of Morphological Sciences, School of Medicine and Dentistry, University of Santiago de Compostela, Spain.

Oral lichen planus (OLP) and oral lichenoid lesions (OLLs) include a group of oral mucosal disorders that likely represent a pattern of common reactions in response to extrinsic antigens, altered autoantigens and superantigens [1]. Historically, there have been debates and controversies, which are still unresolved, regarding the terminology for OLP and OLLs, and we still lack definitive clinical diagnostic and histological criteria to differentiate OLP from OLLs. There is also no consensus on the possible clinical and behavioural differences regarding the risk of malignant transformation between OLP and OLLs [2].

OLP was included as a potentially malignant disorder in the 2005 classification and was recently confirmed in the World Health Organization Collaborating Centre for Oral Cancer Workshop held in the United Kingdom in 2020. This workshop added OLLs and graft-versus-host disease (GVHD) within the classification of the potentially malignant disorders [3].

4.1. Oral lichen planus

4.1.1. Definition

OLP has been defined as 'a chronic inflammatory disorder of unknown etiology with characteristic relapses and remissions, displaying white reticular lesions, accompanied or not by atrophic, erosive and ulcerative and / or plaque-type areas.' Lesions are frequently bilaterally symmetrical. Desquamative gingivitis may be a feature [3].

4.1.2. Epidemiology

OLP is a relatively common mucocutaneous disease, with an estimated prevalence of 1–3% of the population. OLP is the most common mucocutaneous disease of the oral cavity [4].

A recent systematic review and meta-analysis found a global prevalence of OLP of 1.01%, with marked geographical differences. The highest prevalence was noted in Europe (1.43%) and the lowest in India (0.49%). A preference for the female sex has also been reported, as well as an increased risk of development after 40 years of age [5] with a mean age of presentation of 50–55 years [6].

4.1.2.a. Potential for malignant transformation

Although OLP is considered a potentially malignant disorder, there are still no clear diagnostic criteria, and conflicting findings have been reported on its malignant potential. While a number of studies have questioned the true potential of the malignant transformation of OLP and have attributed a greater risk of malignancy to OLLs [7], more recent studies seem to confirm the malignant transformation potential of OLP and do not allow OLP to be differentiated from OLLs as different entities in relation to their ability to progress towards oral cancer (Table 4.1).

A systematic review [8] of 16 observational studies reported a mean malignant transformation rate of 1.09%, with an annual malignant transformation rate of 0.36–0.69%. Subsequently, another systematic review [9] of 57 studies confirmed a malignant transformation rate of 1.1%.

A recently published systematic review and meta-analysis of follow-up studies focused on the risk of malignant transformation of OLP and OLLs and on the factors affecting this risk. The results showed an incidence rate for malignant transformation of 1.14% (CI 0.84–1.49) and 1.88% (CI 0.15–4.95) among cases of OLP and OLLs, respectively, although this difference was not statistically significant (p=0.561) [10]. After the publication of new studies on the malignant transformation of OLP (n=5) and OLLs (n=2), the authors repeated the analysis and found a malignancy rate of 1.21% (95% CI 0.89–1.56) and 2.02% (95% CI 0.30–4.78) for OLP and OLLs, respectively, though these differences were not significant (p=0.375) [11]. In a subsequent analysis that exclusively included those publications that met strict quality criteria, the authors observed a malignant transformation rate of 2.28% for OLP (CI 1.49–3.20) [12].

It is the opinion of other authors that the malignant potential of OLP has been exaggerated in the scientific literature. In their systematic review and meta-analysis, Idrees et al. initially identified a total of 33 studies with a total of 12,838 patients with OLP. Initially, the authors found 151 cases of OLP that had progressed to oral squamous cell carcinoma (OSCC) (1.2%).

Malignant Transformation of OLP and OLLs			
Articles	**Malignant transformation rate% (confidence interval)**		
	OLP	**OLLs**	**Difference (p)**
Fitzpatrick et al. (2014)	1.8%	3.2%	
Aghbari et al. (2017)	0.9% (-)	2.5% (-)	
González-Moles et al. (2019)	1.14% (0.84–1.49)	1.88 (0.15–4.95)	0.561
González-Moles et al. (2020) (let-ter)	1.21% (0.89–1.56)	2.02% (0.30–4.789)	0.375
González-Moles et al. (2020)*	2.28 (1.49–3.20)		
Giuliani et al. (2019)	1.37% (-)	2.43 (-)	
Idrees et al. (2020)	1.2% 0.44%*		
Ioca et al. (2020)	1.4 (0.9–1.9)	3.8 (1.6–7.0)	

* After applying stricter selection criteria

Table 4.1. Systematic Reviews of the Malignant Transformation Potential of Oral Lichen Planus and Oral Lichenoid Lesions Conducted in the Past 10 Years.

After applying stricter inclusion criteria, however, the authors considered that only 56 of these cases of OLP had undergone malignant transformation (0.44%). The main reasons for exclusion were a) lack of a confirmed diagnosis of OLP, b) development of an OSCC in a location unrelated to the site of previous OLP, c) a short latency period between the diagnosis of OLP and that of OSCC and d) the presence of epithelial dysplasia in the diagnostic histopathology of OLP [13].

To date, various risk factors for malignant transformation have been identified, including lingual location [8,10), the presence of atrophic/erosive lesions [9,10), tobacco and alcohol consumption [9,10), human papillomavirus [9], hepatitis C virus (HCV) [10] and the presence of aneuploidy [14].

The mean interval between the initial diagnosis of OLP and that of oral cancer can vary from 20.8 months to 10.1 years, although the maximum risk is between 3 and 6 years after first diagnosis [15].

Patients with OLP and OLLs can develop multiple malignant lesions, which do not always develop at the site of pre-existing lesions, a finding in agreement with the well-known concept of field cancerization [16].

Moreover, the OSCC that develops in patients with OLP and OLLs shows favorable prognostic parameters, especially in terms of mortality rate [17].

4.1.3. Clinical presentation

The clinical manifestations of OLP varies from patient to patient; however, the distinctive clinical characteristics of OLP are represented by the presence of white papules that enlarge and fuse to form a reticular, annular or plaque-like pattern, so-called Wickham striae.

Classically, 6 clinical subtypes of OLP have been described, which can be observed individually or in combination: reticular, plaque-like, atrophic, erosive/ulcerative, papular and bullous [18, 19]. Other authors have simplified these 6 subtypes into 3 (reticular, atrophic and erosive [20, 21] or 2 subtypes (keratotic [white] and erythematous [red] (6).

4.1.3.a. Keratotic oral lichen planus (white)

The keratotic subtype is the most recognised form of OLP and is characterised by symmetrical white reticular lesions (Wickham striae) and less frequently as white papules or plaques (Fig. 4.1).

The plaque form of OLP appears as a homogeneous, slightly elevated, multifocal white plaque, which typically affects the tongue and buccal mucosa (Fig. 4.2c).

The keratotic form is generally asymptomatic and is usually an incidental finding during routine examination of the oral cavity by dental practitioners [22].

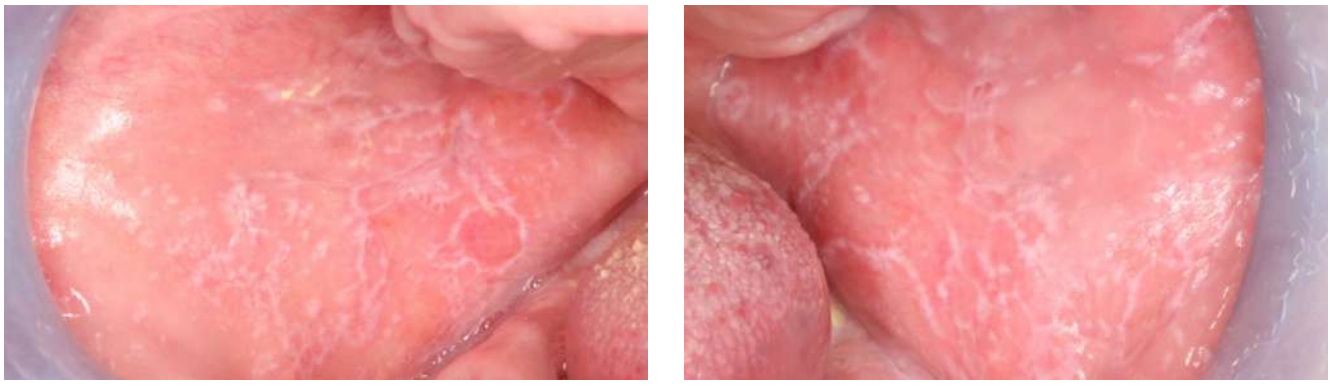

Figure 4.1. Reticular oral lichen planus.

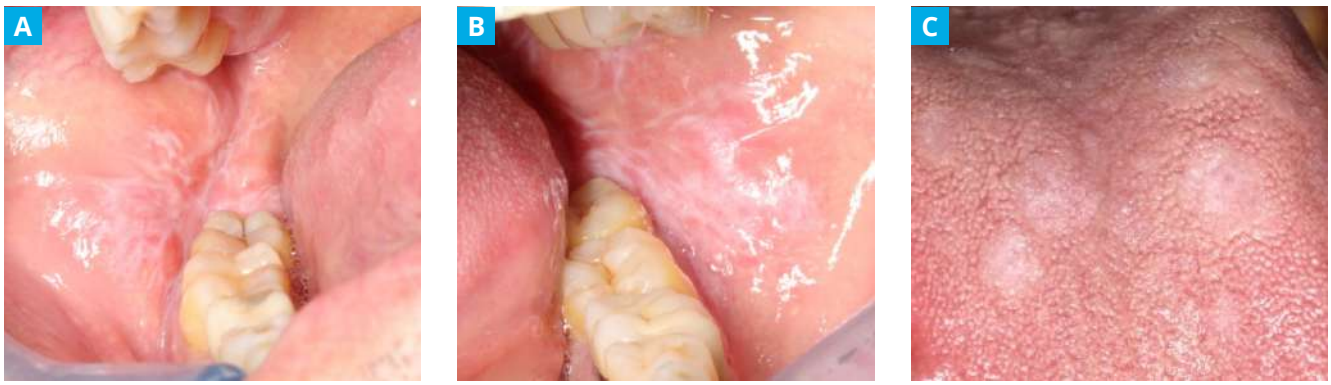

Figure 4.2. A, B) Reticular; and C) plaque-like lesions of oral lichen planus in the same patient.

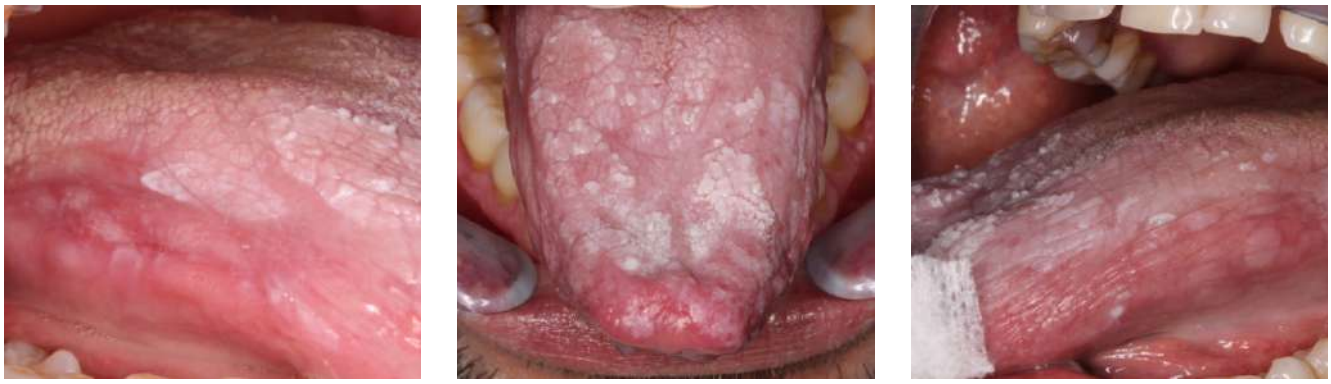

Figure 4.3. Plaque-like lesions of the dorsum and lateral tongue. Histopathologically confirmed as oral lichen planus with no epithelial dysplasia.

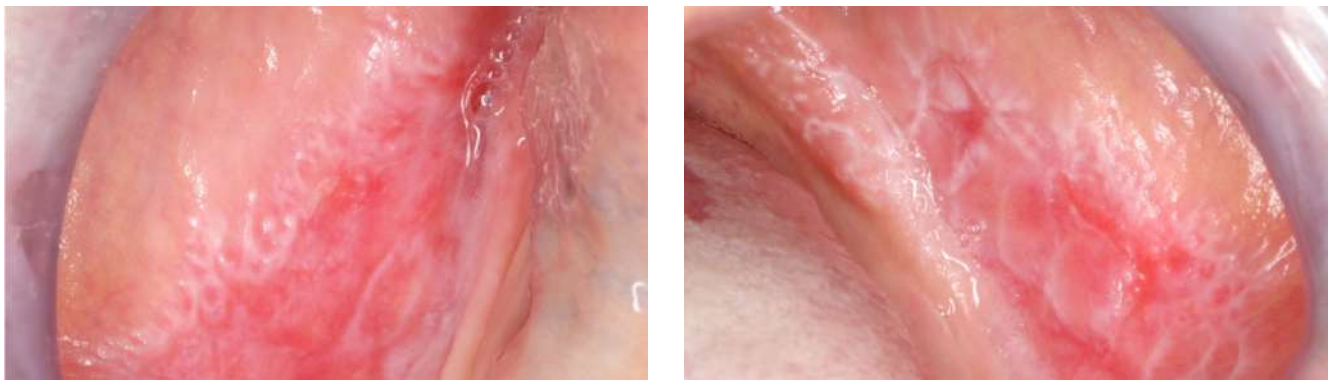

Figure 4.4. Bilateral atrophic/erosive oral lichen planus of the buccal mucosa.

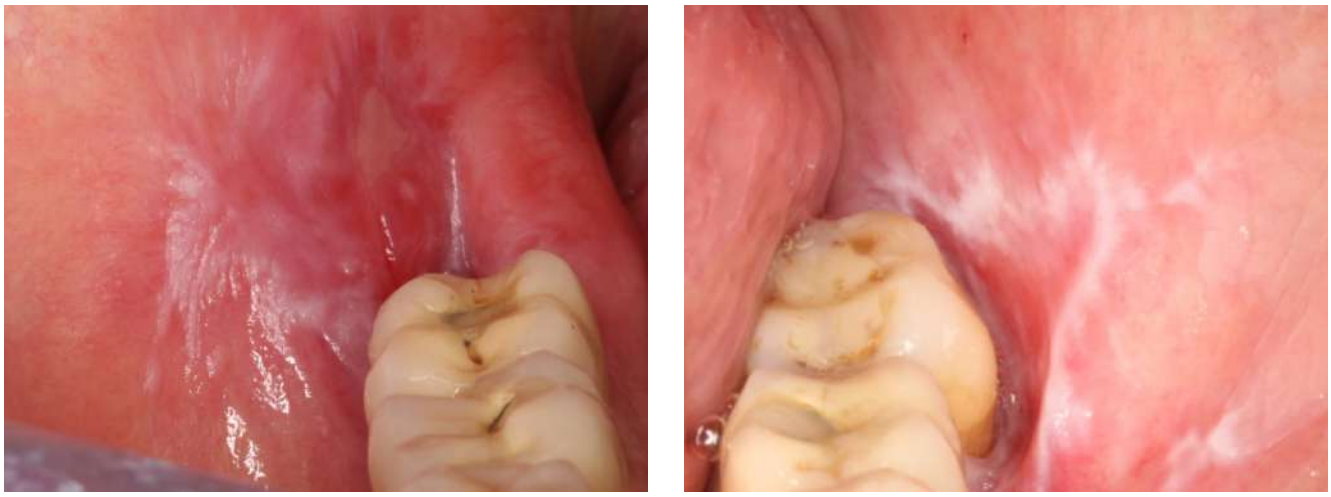

Figure 4.5. Bilateral atrophic/erosive oral lichen planus of the buccal mucosa.

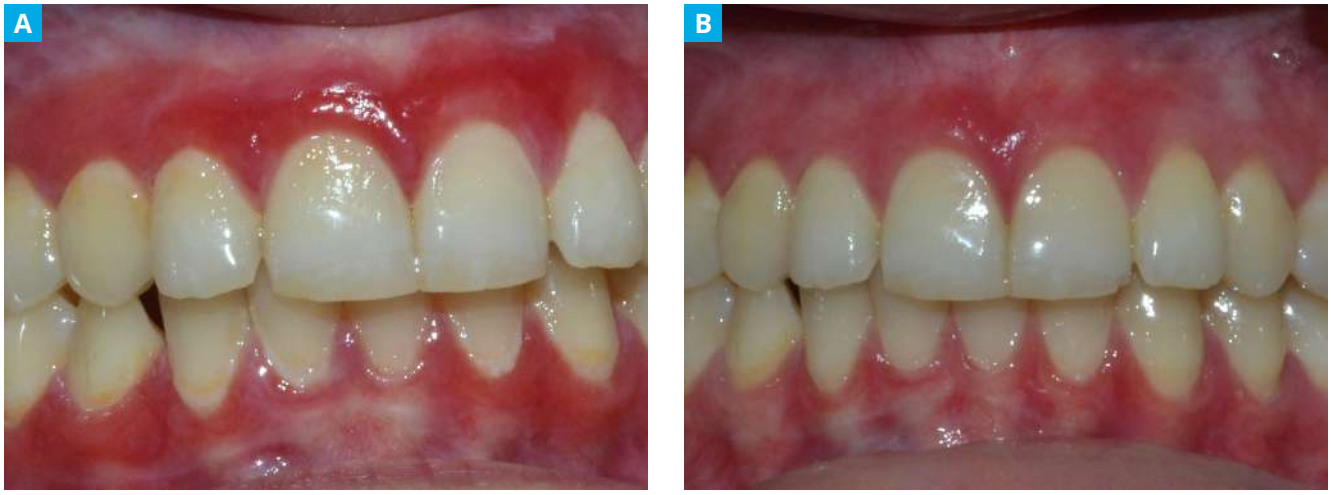

Figure 4.6. Desquamative gingivitis in a patient with oral lichen planus a) before and b) after treatment with 0.3% triamcinolone acetonide in individual custom trays.

4.1.3.b. Erythematous oral lichen planus (red)

The erythematous subtype can present as an area of atrophic mucosa or as red lesions due to hyperemia of the oral mucosa (6). These areas of erythema can be accompanied by ulceration and are often associated with white keratotic striae [21] (Fig. 4.4).

There are a variety of symptoms, from a mild burning sensation to debilitating pain, depending on the extent of lesions and areas involved. The lesions can interfere with speech, chewing and swallowing.

Erosive lichen planus located on the gums presents as desquamative gingivitis (Fig. 4.6). OLP is the most common cause of desquamative gingivitis, followed by pemphigoid and pemphigus [23].

The buccal gingiva is the most commonly affected; in severe cases, however, the palatal and lingual gingiva can be involved (24). In approximately 10% of cases, OLP presents only involvng the gingiva [25].

Patients usually present with lesions of more than one subtype simultaneously, and lesions usually undergo changes with time [26]. The most commonly affected locations are the buccal mucosa, the lateral and dorsum of tongue and the gingiva, while the palate (hard and soft), lips and floor of the mouth are affected less frequently. There is almost always a bilateral distribution, which is more or less symmetrical. The course of OLP is characterised by relapses and remission, with intervals of several weeks or months, both of the clinical signs and symptoms [26].

Clinical presentation of OLP		
Type	**Clinical presentation and most common locations**	**Comments**
Keratotic oral lichen planus (white)		
Reticular/plaque	White striae (Wickham striae), papules or plaques in buccal mucosa, dorsal surface and edges of the tongue, gums and labial mucosa. Typically asymptomatic.	Most common clinical manifestations of OLP
Erythematous oral lichen planus (red)		
Atrophic	Erythematous areas. When it affects the gums (desquamative gingivitis), it can be painful.	Typically associated with reticular lesions
Erosive/ulcerative	Single or multiple ulcers afecting the buccal mucosas. Can cause significant pain and functional disability.	Typically associated with erythematous and reticular lesions

Table 4.2. Most common clinical manifestations of oral lichen planus.

Extraoral manifestations

Patients with OLP can develop lesions that affect the skin and other mucous membranes. Although only a minority (15%) of patients with OLP develop cutaneous lichen planus, up to 60% of patients with cutaneous lichen planus have oral manifestations [25]. Cutaneous lichen planus typically presents as a papulosquamous rash with purplish, flat-topped bumps, of varying size, often described using the '6 Ps' (purple, pruritic, polygonal, planar, papules and plaques), characterised by the classic Wickham striae [27].

Cutaneous lichen planus is typically located on the extremities (Fig. 4.7) but occasionally presents with generalised involvement and can include the scalp (which results in cicatricial alopecia) and nails.

Other anatomical locations that can be affected include the genital mucosa (penile-gingival and vulvovaginal-gingival syndromes have been described in up to 20% of patients with OLP [28]. Esophageal involvement can occur with OLP but is unusual [29]. The ocular, urinary, nasal, laryngeal, otic, gastric and anal mucosa are rarely involved [25]. A thorough history and examination should undertaken to investigate the potential extraoral manifestations for all patients with OLP [30].

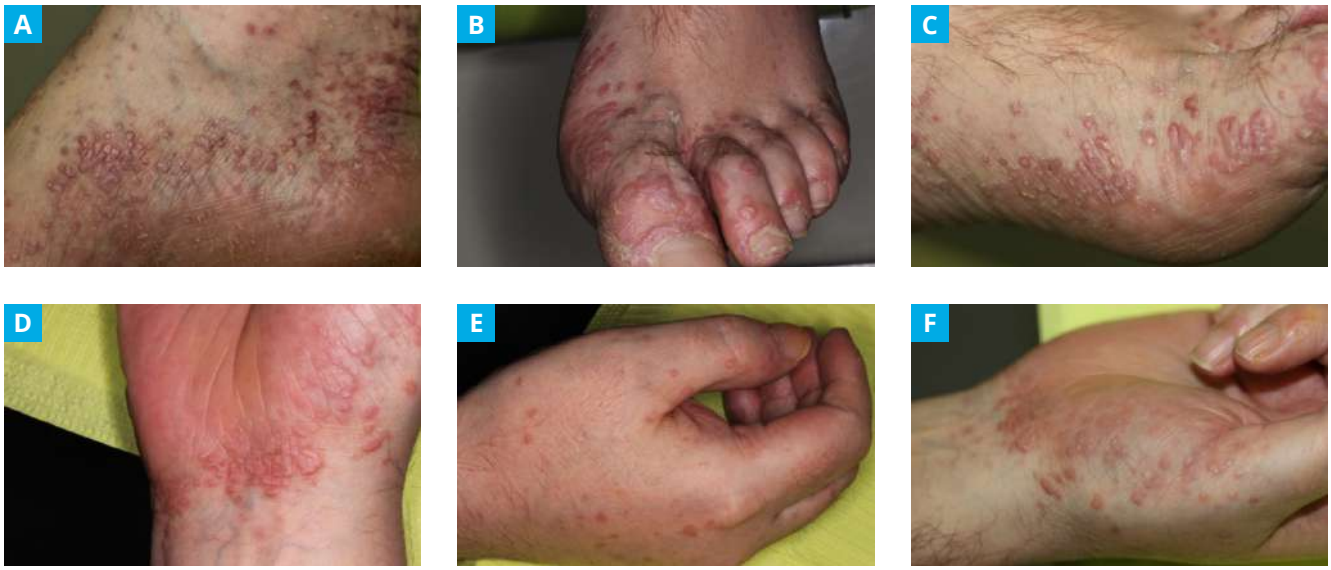

Figure 4.7. Cutaneous involvement in a patient with oral lichen planus (Figure 4.1). Papular lesions in A-C) feet; and D-F) wrist and hands. After the clinical diagnosis of the mucocutaneous lesions, an HCV determination was requested (due to the patient's clinical history), which was positive.

Association with systemic diseases

Due to its chronic nature, OLP has been associated with various systemic diseases, including hepatitis C, hypertension, diabetes and thyroid diseases [31]. Among these diseases, there is solid and persuasive evidence that HCV is associated with OLP and is possibly involved in its pathogenesis; however, there are no clinical guidelines that recommend if all patients with OLP should be screened for HCV [32]. From a practical perspective, it would be prudent to at least ask patients with OLP about risk factors associated with HCV and to request an HCV antibody determination (using an enzyme-linked immunosorbent assay) for those patients with significant risk factors [33].

4.1.4. Differential diagnosis

There are different lesions that resemble OLP, both at clinical and histopathological levels, which should be considered in the differential diagnosis. The differential diagnosis of reticular and erythematous lesions include OLLs and discoid lupus erythematosus. The atrophic and ulcerative forms are usually accompanied by reticulation, differentiating it from other mucocutaneous diseases, such as pemphigus vulgaris, pemphigoid and liner immunoglobulin (Ig)-A disease. When the erosive form is associated with severe ulcers, however, it can mask the typical white striae. A careful clinical examination, however, often shows this recognizable characteristic of OLP [24,34].

When the disease presents in plaque form, the differential diagnosis of oral leukoplasia should be considered. Occasionally, the initial clinical manifestation of proliferative verrucous leukoplakia (PVL) can resemble OLP or OLLs that subsequently develops multiple leukoplakic lesions [35,36]. Regardless of their initial diagnosis, these patients with white multifocal lesions should be carefully monitored for early malignant transformation [37].

4.1.4.a. Diagnosis

The diagnosis of OLP is reached by first noting the lesions' clinical appearance (bilateral distribution and classical reticular pattern). A biopsy and pathology study should always be performed to confirm the clinical suspicion, and to differentiate other entities of clinically similar appearance.

Although the clinical manifestations, particularly when they present the 'classical' bilateral keratotic pattern (in reticular or papular form), can allow for the diagnosis, performing a confirmatory biopsy is a prudent clinical practice, given the chronic course, pleomorphic clinical manifestations, the need for long-term treatment and follow-up, and the risk of malignant transformation [2]. The histopathological aspects of OLP are not always diagnosed by themselves, and there may be a discrepancy between the clinical diagnosis and histopathological diagnosis of OLP [38]. The diagnosis of OLP is therefore based on the correlation between the clinical presentation and the histopathological findings (Table 4.3).

Clinical criteria	• Presence of bilateral, more or less symmetrical white lesions affecting the buccal mucosa, tongue, lips, and/or gingiva. • Presence of white papular lesions and a lace-like network of slightly raised white lines (reticular, annular, or linear pattern) with or without erosions and ulcerations. • Sometimes presents as desquamative gingivitis.
Erosive/ ulcerative	• Presence of a well-defined band-like predominantly lymphocytic infiltrate that is confined to the superficial part of the connective tissue. • Signs of vacuolar degeneration of the basal and/or suprabasal cell layers with keratinocyte apoptosis. • In the atrophic type, there is epithelial thinning and sometimes ulceration caused by failure of epithelial regeneration as a result of basal cell destruction. A mixed inflammatory infiltrate can be found.

Table 4.3. Diagnostic criteria for oral lichen planus (Adapted from Warnakulasuriya et al., 2020).

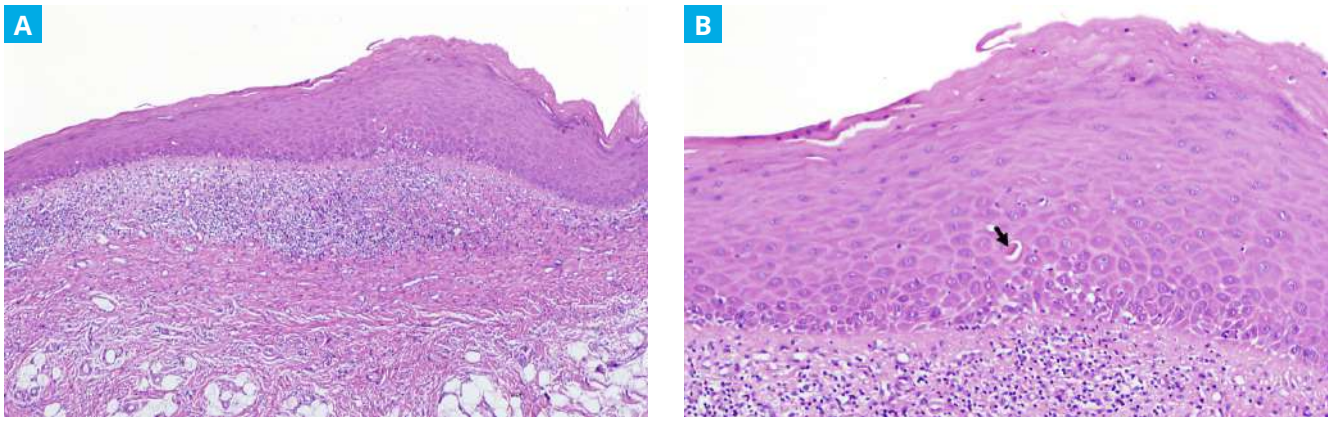

Figure 4.8. Oral lichen planus histopathological findings A) Acanthosis, thickening of the basal membrane and lymphocytic band at the interface (H&E, x4); B) At higher magnification, the epithelium shows squamatization of the basal layer, slight spongiosis, leukocyte exocytosis and occasional colloid (Civatte) bodies formation (arrowhead) (H&E, x10).

A number of authors use the term 'lichenoid dysplasia' to describe a dysplastic superficial epithelium accompanied by a band-like lymphocytic infiltrate in the underlying lamina propria. These findings would be indicative of a premalignant process and should not be misinterpreted as lichen planus with dysplastic characteristics [39, 40].

Under certain conditions, diagnosing OLP can be challenging because the histopathological characteristics can be influenced by a variety of factors, including the clinical subtype and disease severity at the time of the biopsy [22, 34]. Direct immunofluorescence, although non-specific for OLP, might be necessary to differentiate OLP from ot lupus erythematosus, pemphigoid and pemphigus [41], and is of particular importance in the case of OLP that presents only as desquamative gingivitis [42]. The direct immunofluorescence technique requires transporting the tissue sample in Michel's solution instead of 10% formalin used for transporting tissue for routine staining with hematoxylin-eosin. For this purpose, 2 samples should be obtained or the sample should be divided into two [34].

The fluorescence pattern described for OLP includes the linear deposits of fibrinogen or the 'shaggy pattern' over the area of the basement membrane with or without positive fluorescence for IgM in the Civatte bodies (apoptotic cells). Other patterns include the deposit of IgM and complement 3 in the basement membrane and IgA, IgG and complement 3 in the Civatte bodies [41].

Referral to a dermatologist or gynecologist may be considered depending on the extraoral signs and symptoms. Occasionally, patient referral might be indicated to exclude the presence of associated comorbidities such as HCV infection, diabetes mellitus and thyroid disease [6].

4.1.5. Management

The main objective of OLP treatment is symptom relief. Typically, patients with reticular lesions and other asymptomatic lesions need no treatment [2]. First, the triggers and aggravating factors (sharp or broken teeth, poorly fitted prosthesis, etc.) should be identified and excluded. Patients should be advised to cease tobacco and alcohol consumption because they can increase the risk of malignant transformation [40]. Patients should also be instructed to maintain good oral hygiene, because reducing dental plaque can have a beneficial effect on gingival lesions [42]. The use of rinses with chlorhexidine can occasionally be indicated for the chemical control of dental plaque [43]. Sodium-lauryl sulphate (SLS) is a foaming agent added to toothpastes that may exacerbate symptoms and SLS-free toothpastes can be used in preference.

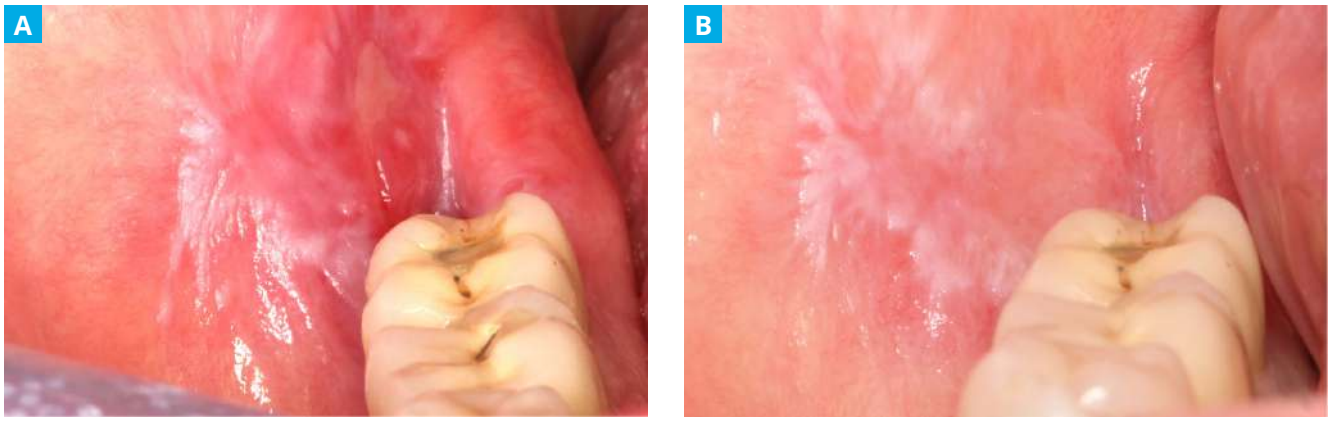

Figure 4.9. Atrophic/erosive lichen planus, A) before; and B) after 7 days of topical treatment with 0.3% triamcinolone in Orabase.

Occasionally, an assessment of the patient's psychological profile might be justified for patients with symptomatic OLP in whom there is no topographical relationship between the lesion location and location of the pain, given that a higher prevalence of anxiety, depression and sleep disorders has been reported in patients with OLP [44].

Various treatments have been proposed for symptomatic control of OLP. Symptomatic relief can be obtained by using topical anaesthetic agents such as benzydamine hydrochloride 0.15% (as a spray or mouthwash) or lidocaine gel.

Topical agents are usually the first-line treatment because they have fewer secondary adverse effects [2, 45]. However, the use of systemic agents might be necessary for extensive lesions or if recalcitrant to topical treatments [2].

Topical corticosteroids (administered as gels, adhesives or similar preparations) are the first line agents for treating OLP, and their effectiveness in reducing the pain of symptomatic OLP has been demonstrated [46]. A number of preparations are available to be used as mouthwashes: Betamethasone sodium phosphate 500microgram tablets dissolved in 10ml of water up to four times daily, prednisolone 5mg tablets dissolved in 10ml of water or Flixonase 400mcg nasules added to 10ml of water twice daily. Fluticasone propionate spray (50microgram/puff) directed at affected areas 3-4 times daily is useful for isolated lesions.

Triamcinolone formulations can be applied at initial visits [45]. If there is no response (greater than 50% remission of symptoms), however, more powerful formulations such as 0.05% clobetasol propionate should be applied to the lesion 3 times a day [6]. When regularly using superpotent corticosteroids, the patient should have their serological 9am cortisol levels measured every 3 months to monitor for systemic absorption [6].

For desquamative gingivitis, preparations with corticosteroids in the form of gel applied in individual custom trays are employed, made in soft clear resin or silicone to increase the contact time [47]. For refractory and symptomatic localised ulcerative lesions, intralesional injections of triamcinolone acetonide (10 to 40 mg/mL) may be employed [34]. However, the evidence on the efficacy of intralesional injections of corticosteroids in OLP is scarce, as are standardised protocols regarding various factors such as the need for local anesthesia and application intervals [48].

The use of topical corticosteroids can increase the risk of developing candidiasis and requiring concomitant therapy with antifungals, although studies have observed that the risk of candidiasis after treatment with less potent topical corticosteroids (0.3–0.5% triamcinolone acetonide) is relatively low (approximately 11%) [45].

The use of other immunosuppressive such as topical tacrolimus (a calcineurin inhibitor) has been reported, which a number of studies have shown are more effective for resolving pain than corticosteroids, although there is uncertainty regarding the adverse effects and clinical response to tacrolimus [46].

Topical/systemic corticosteroids frequently employed for treating OLP		
Medication	**Instructions**	**Comments**
Topical corticosteroids		
• 0.05% clobetasol propionate • 0.01–0.05% fluocinolone acetonide • 0.1–0.5% triamcinolone acetonide	• 2–3 times/day. • Monitor to assess response.	• The use of creams or ointments is preferred for managing localised intraoral lesions. • Mouthwashes for extensive and multiple lesions or those inaccessible to gel applications. • Gingival lesions can be treated using individual custom trays.
Intralesional corticosteroids		
• Triamcinolone acetonide 10–40 mg/mL	• Inject directly into the subepithelial connective tissue just below the lesion through the adjacent healthy mucosa. • Consider the use of local anesthesia (0.5 mL of 2% lidocaine) in the solution. • Repeat every 1–4 weeks.	• Refractory and symptomatic localised ulcerative lesions.
Systemic corticosteroids		
• Prednisone 0.5–1.0 mg/kg/day	• Prednisone 0.5–1.0 mg/kg/day Until a therapeutic response is achieved*	• OLP with highly severe initial presentation and/or generalised ulceration and erythema; • Treatment of resistant/ recalcitrant OLP or the treatment of resistant/ recalcitrant lichen planus that involves numerous locations, including the oral cavity.

*If used for more than 2 weeks, a tapering regimen is required.

Table 4.3. Management of symptomatic oral lichen planus. (Adapted from Kuten Shorrer et al., 2020 [34]).

Systemic corticosteroids are usually indicated for treating lichen planus with extensive involvement of the skin and mucous membranes (genital, oral, esophageal) and in severe symptomatic forms of OLP that have not responded to therapy with topical agents [49].

Systemic prednisone (1 mg/kg/day) is usually effective and should be employed for the shortest time possible with the aim of mitigating the potential adverse effects. If used for more than 2 weeks, a tapering regimen is required [34].

Alternative systemic therapy includes hydroxychloroquine, azathioprine, mycophenolate mofetil and methotexate. Hydroxychloroquine is a useful agent in treating severe erosive OLP. Eisen et al., [50] reported 9 out of 10 patients had an excellent response to a trial of hydroxycholorquine.

The most notable side-effect requireing urgent attention is retinal toxicity. Azathioprine can be used to treat severe oral lichen planus, resulting in resolution in up to 75% of cases [51]. Mycophenolate mofetil is another immunosuppressive agent which is effective in recalcitrant cases of OLP [52]. Methotrexate has also been shown to be of benefit in recalcitrant and erosive forms of OLP, though it is not widely used [53].

In any case, once the disease has been well controlled, efforts should be made to gradually reduce any systemic agent to the lowest effective dose possible while maximising the effects of the topical treatment [54].

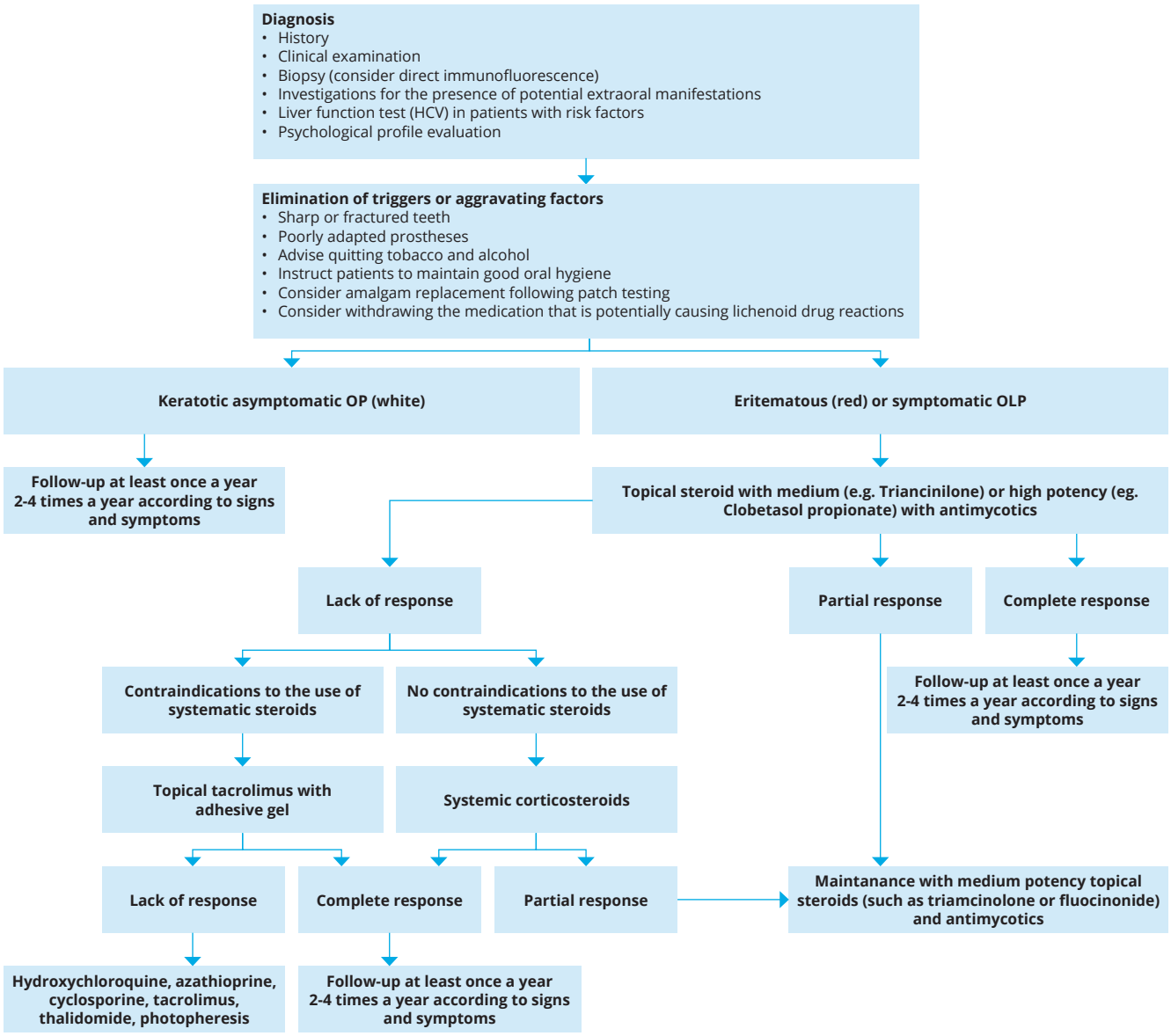

Figure 4.8. Decision making in the management of patients with lichen planus and oral lichenoid lesions (Adapted from Gonçalves et al., 2019; [48]).

4.1.6. Follow-up

Due to the risk of malignant transformation, regular follow-up should be conducted to assess for relapse, given that approximately 1% of cases can undergo malignant transformation within 5–10 years [6]. The frequency of follow-up visits increases proportionally to the disease activity and symptoms (34). At a minimum, the recommendation is an annual follow-up and preferably 2 to 4 annual check-ups based on the signs and symptoms of OLP [40,55]. If changes in a lesion are observed during the follow-up visits, a biopsy should be performed and follow-up intervals should be shortened [56].

4.2. Oral Lichenoid Lesions

4.2.1. Definition

Lichenoid lesions are red/white intraoral lesions with a reticular striated appearance similar to OLP but are associated with different known stimuli. The lesions can be divided into oral lichenoid contact lesions (OLCLs), drug-induced OLLs and GVHD-induced OLLs [40].

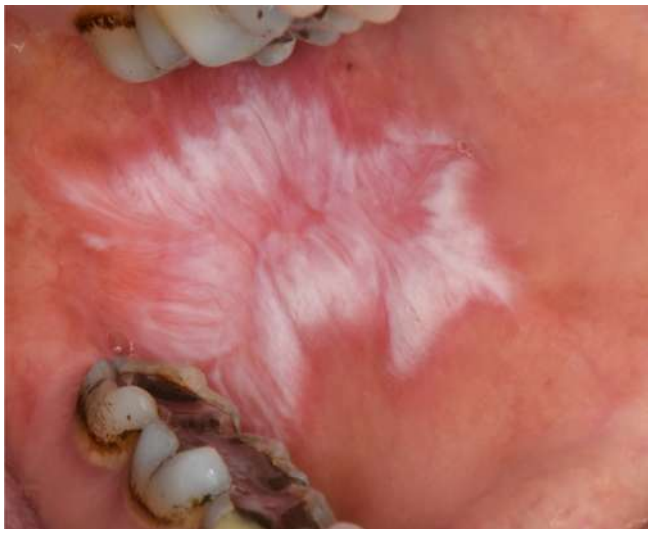

Figure 4.10. Oral lichenoid lesion in close contact with amalgam dental restoration.

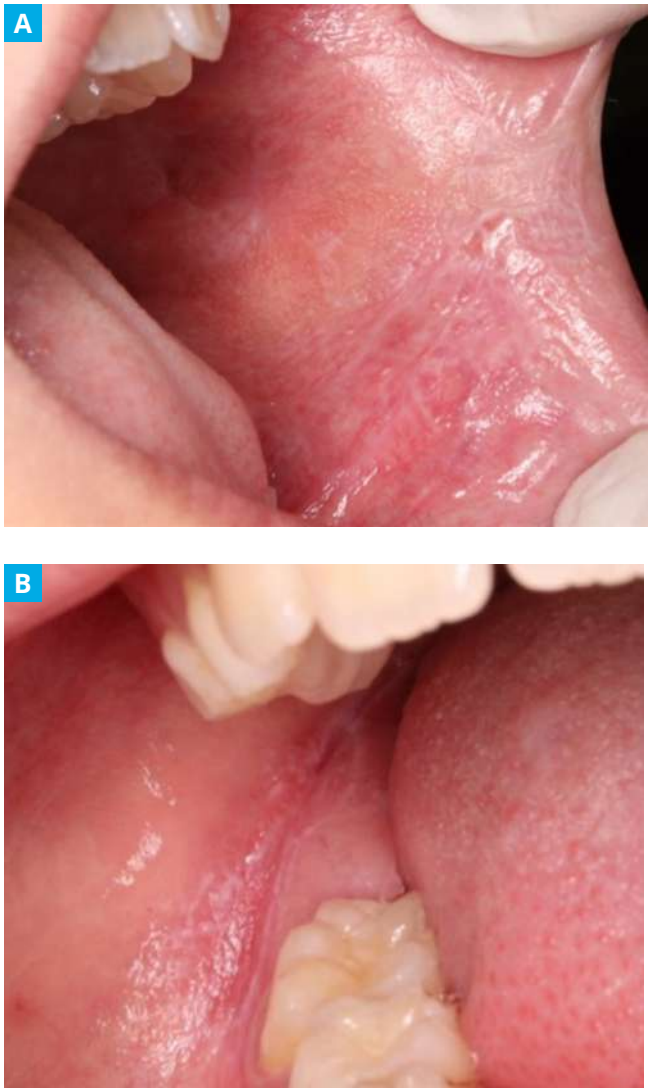

Figure 4.11. A, B) Lichenoid contact lesion after the placement of a removable acrylic orthodontic apparatus in an 11-year-old male patient.

4.2.1a. Oral lichenoid contact lesions

The term OLCL is used to describe oral lesions that resemble lichen planus, both clinically and histopathologically, but are believed to be caused by a localised hypersensitivity reaction (hypersensitivity mediated by delayed immunity) to a dental restorative material, mainly amalgam, or other contact agents (e.g. cinnamon) [2,40]. Other dental restorative materials, such as gold, nickel and acrylic resin, can also be related to the onset of lichenoid lesions [57,58].

OLCLs present as white lesions or mixed red/white lesions, occasionally ulcerated. It is believed that OLCLs are less symmetrical and more often unilateral than OLP and can lack the typical reticular appearance of OLP, more typically presenting in the plaque or atrophic form [2].

Clinically and histologically, OLCLs can be indistinguishable from OLP. The diagnostic characteristic is the topographical location directly related to the suspected causal agent. The most frequently involved locations are the lateral tongue and the buccal mucosa (2). OLP lesions can also present in locations close to dental restorative materials, but in this case are usually more extensive and affect other locations. The duration of the contact between the causal agent and the oral mucosa appears to be an important factor in the development of OLCLs [40].

The diagnosis is usually based on the clinical findings, and the disappearance of the lesion after the elimination/replacement of the restorative material or possible causal agent establishes the diagnosis. A biopsy is performed when the clinical manifestations are atypical and to rule out a possible malignant process (59). Histopathology can help the diagnosis if it reveals the presence of a subepithelial infiltrate of mixed cells and a deeper diffuse distribution in the lamina propria. However, OLCLs are usually indistinguishable from other OLLs and OLP lesions depending on the histopathology [2].

A common practice is to perform a patch test to identify potential hypersensitivity reactions; however, studies on its usefulness for diagnosing OLCLs have shown conflicting results [2]. Performing a patch test can also be of assistance for determining the alternative restorative material [40]. Moreover, positivity to the patch test is inconsistent and a generally weak predictor of improvement of the lesion following the elimination of the amalgam restorations [32]. The removal of nearby amalgam restorations or those in contact can lead to complete healing in 39–89% of the lesions, compared with 0–29% of the lesions adjacent to amalgam restorations that are not removed [32]. In any case, clinicians should discuss the potential benefits and risks of removing the amalgam restorations with the patients, describing the cyclic nature of the disease, characterised by periods of exacerbation and spontaneous remission, and the unpredictability of the amalgam removal procedure for resolving the lesions [32].

4.2.1.b. Drug-induced oral lichenoid lesions

Drug-induced OLLs are caused or associated with exposure to particular drugs and are uncommon, unlike cutaneous OLLs. There is a long list of systemic drugs associated with the onset of OLLs, which includes non-steroidal anti-inflammatory drugs, anti-hypertensives, oral hypoglycemic agents, antibiotics, antifungals and monoclonal antibodies [2, 56]. There is usually a temporal association between the onset of oral and/or skin lesions and taking certain drugs [40]; however, the drug reaction can occur at any moment, including years after its introduction [60]. The clinical appearance is unclear, especially compared with other lichenoid lesions, although the unilateral location can help the diagnosis.

At the histopathological level, drug-induced OLLs can present as a subepithelial inflammatory infiltrate that contains eosinophils and/or plasma cells and is more diffuse and extends more deeply than OLP or has a perivascular appearance [61]. However, other OLLs can present similar histopathologic characteristics, such as discoid lupus erythematosus [60].

There are no well-defined clinical and histological characteristics that help differentiate drug-induced OLLs from OLP and other lichenoid lesions of the oral cavity.

The diagnosis is confirmed when there is a regression of the lesion after discontinuing or changing the possible causal drug and after reappearance when restarting the treatment with the same drug [40].

However, the drug should be discontinued only after consulting the patient's physician, and this practice is not always feasible in polymedicated patients [62]. Through a systematic review, Fortuna et al. [63] recently demonstrated that there is no solid scientific evidence to support a causal relationship between any drug and OLLs.

Graft-Versus-Host Disease

GVHD is a complication that occurs in bone marrow or hematopoietic stem cell transplant recipients (64). GVHD is a systemic condition with a considerable variety of signs and symptoms and affects multiple locations and organs, including the skin, oral cavity, eyes, gastrointestinal tract and liver, as well as other systems such as the lungs, joints and genitourinary tract.

The oral involvement of GVHD in its acute form is extremely rare; however, the oral cavity is one of the most commonly affected locations in chronic GVHD. When chronic GVHD affects the oral mucosa, it is clinically characterised by a lichenoid inflammation that frequently involves the tongue and oral mucosa but can affect any location in the oral cavity and can vary from a limited disease with only mild changes to a more extensive and symptomatic disease. The clinical changes include papules, white plaques and hyperkeratotic striae that resemble the Wickham striae found in OLP, as well as erythema and pseudomembranous ulcers (65). Other clinical characteristics include xerostomia and pain (6). The clinical characteristics by themselves are often sufficient for establishing the diagnosis, provided that they are present in the context of a patient who has undergone allogeneic hematopoietic stem cell transplantation.

The clinical presentation, epidemiology, diagnosis and treatment of GVHD will be addressed elsewhere.

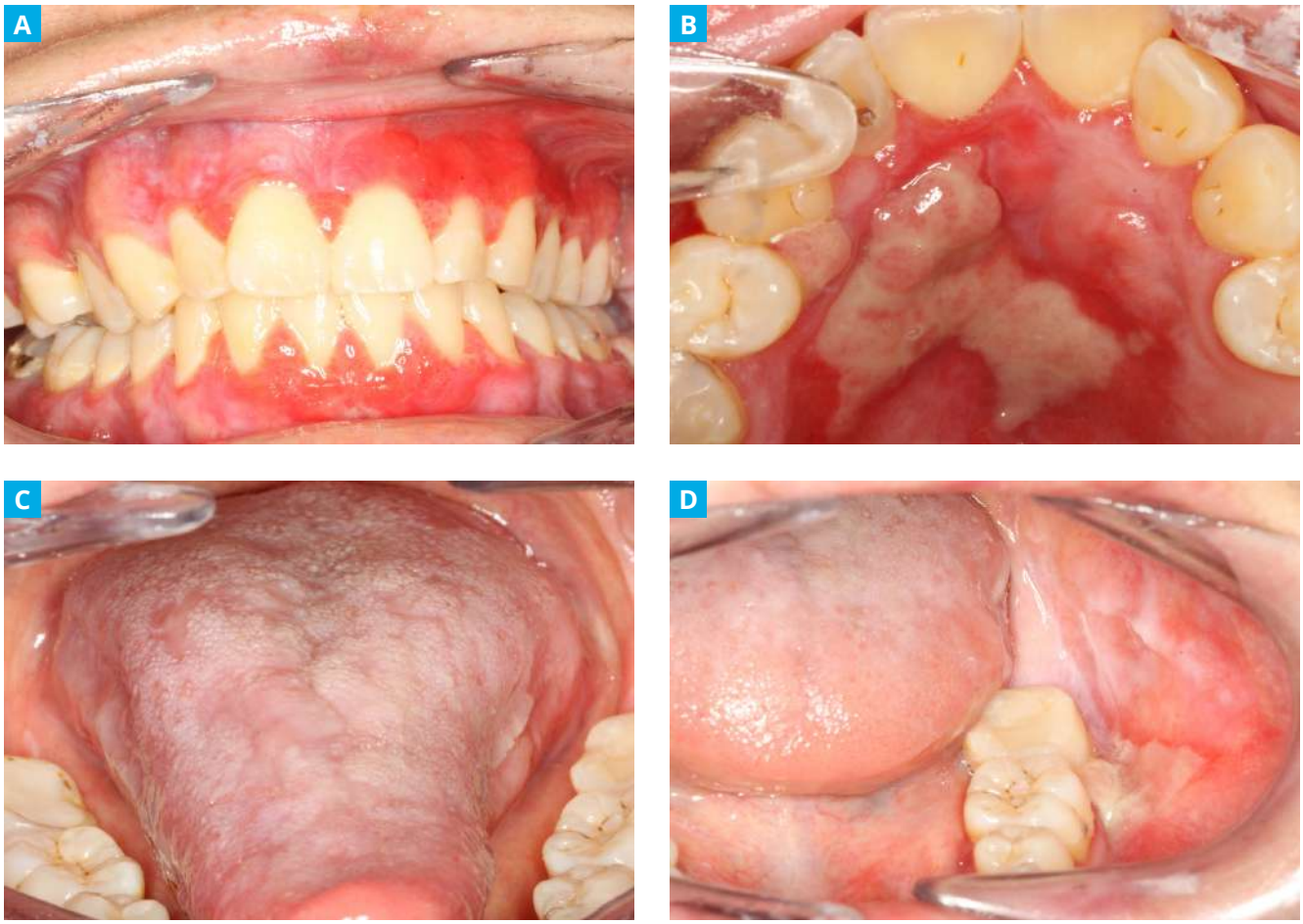

Figure 4.12. Chronic graft-versus-host disease in a patient with a history of hematopoietic stem cell transplantation due to Hodgkin's lymphoma. A) Erythema and reticular lesions in the upper and lower gums; B) erythema and ulceration in the hard palate; C) white lesions in plaque in the lingual dorsum; and D) erythema, ulceration and white lesions in the left jugal mucosa.

References

1. Khudhur AS, Di Zenzo G, Carrozzo M. Oral lichenoid tissue reactions: diagnosis and classification. Expert Rev Mol Diagn. 2014;14:169-184.
2. Carrozzo M, Porter S, Mercadante V, Fedele S. Oral lichen planus: A disease or a spectrum of tissue reactions? Types, causes, diagnostic algorhythms, prognosis, management strategies. Periodontol 2000. 2019;80(1):105-125.
3. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, 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. 2021;27(8):1862-1880.
4. McCartan BE, Healy CM. The reported prevalence of oral lichen planus: a review and critique. J Oral Pathol Med 2008;37(8):447–53.
5. González-Moles MA, Warnakulasuriya S, González-Ruiz I, González-Ruiz L, Ayén Á, Lenouvel D, Ruiz-Ávila I, Ramos-García P. Worldwide prevalence of oral lichen planus: A systematic review and meta-analysis. Oral Dis 2021;27(4):813-828.
6. Warnakulasuriya S. White, red, and mixed lesions of oral mucosa: A clinicopathologic approach to diagnosis. Periodontol 2000 2019;80(1):89-104.
7. van der Meij EH, Mast H, van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective five-year follow-up study of 192 patients. Oral Oncol. 2007;43(8):742-748.
8. Fitzpatrick SG, Hirsch SA, Gordon SC. The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. J Am Dent Assoc. 2014;145(1):45-56.
9. Aghbari SMH, Abushouk AI, Attia A, Elmaraezy A, Menshawy A, Ahmed MS, Elsaadany BA, Ahmed EM. Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. Oral Oncol. 2017;68:92-102
10. 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
11. González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, González-Ruiz L, Ayén Á, Lenouvel D, et al. Clinical interpretation of findings from a systematic review and a comprehensive meta-analysis on clinicopathological and prognostic characteristics of oral squamous cell carcinomas (OSCC) arising in patients with oral lichen planus (OLP): Author's reply. Oral Oncol. 2021;113:105036.
12. González-Moles MÁ, Ramos-García P, Warnakulasuriya S. An appraisal of highest quality studies reporting malignant transformation of oral lichen planus based on a systematic review. Oral Dis. 27(8):1908-1918.
13. Idrees M, Kujan O, Shearston K, Farah CS. Oral lichen planus has a very low malignant transformation rate: A systematic review and meta-analysis using strict diagnostic and inclusion criteria. J Oral Pathol Med. 50(3):287-298.

14. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):612-627.
15. Gonzalez-Moles MA, Scully C, Gil-Montoya JA. Oral lichen planus: controversies surrounding malignant transformation. Oral Dis 2008;14:229–243.
16. Mignogna MD, Fedele S, Lo Russo L, Mignogna C, de Rosa G, Porter SR. Field cancerization in oral lichen planus. Eur J Surg Oncol. 2007;33(3):383-389.
17. González-Moles MÁ, Warnakulasuriya S, González-Ruiz I, González-Ruiz L, Ayén Á, Lenouvel D, Ruiz-Ávila I, Ramos-García P. Clinicopathological and prognostic characteristics of oral squamous cell carcinomas arising in patients with oral lichen planus: A systematic review and a comprehensive meta-analysis. Oral Oncol. 2020;106:104688.
18. Andreasen JO. Oral lichen planus. 1. A clinical evaluation of 115 cases. Oral Surg Oral Med Oral Pathol 1968;25(1):31–42.
19. Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res. 2016;308(8)539-561.
20. Silverman S Jr, Gorsky M, Lozada-Nur F. A prospective follow-up study of 570 patients with oral lichen planus: persistence, remission, and malignant association. Oral Surg Oral Med Oral Pathol. 1985;60(1):30-34.
21. Au J, Patel D, Campbell JH. Oral lichen planus. Oral Maxillofac Surg Clin North Am. 2013 Feb;25(1):93-100, vii.
22. De Rossi SS, Ciarrocca K. Oral lichen planus and lichenoid mucositis. Dent Clin North Am 2014;58: 299–313.
23. Leao JC, Ingafou M, Khan A, Scully C, Porter S. Desquamative gingivitis: retrospective analysis of disease associations of a large cohort. Oral Dis. 2008;14(6):556-560.
24. Müller S. Oral lichenoid lesions: distinguishing the benign from the deadly. Mod Pathol. 2017 Jan;30(s1):S54-S67.
25. Scully C, Carrozzo M Oral mucosal disease: lichen planus. Br J Oral Maxillofac Surg 2008;46:15–21.
26. Robledo-Sierra J, van der Waal I. How general dentists could manage a patient with oral lichen planus. Med Oral Patol Oral Cir Bucal. 2018;23(2):e198-e202
27. Tziotzios C, Lee JYW, Brier T, Saito R, Hsu CK, Bhargava K, Stefanato CM, Fenton DA, McGrath JA. Lichen planus and lichenoid dermatoses: Clinical overview and molecular basis. J Am Acad Dermatol. 2018;79(5):789-804.
28. Parashar P. Oral lichen planus. Otolaryngol Clin North Am 2011;44:89–107.
29. Fox LP, Lightdale CJ, Grossman ME. Lichen planus of the esophagus: what dermatologists need to know. J Am Acad Dermatol. 2011;65(1):175-183.
30. Eisen D. The evaluation of cutaneous, genital, scalp, nail, esophageal,and ocular involvement in patients with oral lichen planus.Oral SurgOral Med Oral Pathol Oral Radiol Endod 1999;88:431-436.
31. Cassol-Spanemberg J, Rodríguez-de Rivera-Campillo ME, Otero-Rey EM, Estrugo-Devesa A, Jané-Salas E, López-López J. Oral lichen planus and its relationship with systemic diseases. A review of evidence. J Clin Exp Dent. 2018;10(9):e938-e944.
32. Baccaglini L, Thongprasom K, Carrozzo M, Bigby M. Urban legends series: lichen planus. Oral Dis. 2013;19(2):128-43
33. Bigby M. The relationship between lichen planus and hepatitis C clarified. Arch Dermatol 2009;145: 1048–1050.
34. Kuten-Shorrer M, Menon RS, Lerman MA. Mucocutaneous Diseases. Dent Clin North Am. 2020 Jan;64(1):139-162.
35. Lopes MA, Feio P, Santos-Silva AR, Vargas PA. Proliferative verrucous leukoplakia may initially mimic lichenoid reactions. World J Clin Cases. 2015 Oct 16;3(10):861-3
36. McParland H, Warnakulasuriya S. Lichenoid morphology could be an early feature of oral proliferative verrucous leukoplakia. J Oral Pathol Med. 2020 (In press)
37. Gilligan G, Garola F, Piemonte E, Leonardi N, Panico R, Warnakulasuriya S. Lichenoid proliferative leukoplakia, lichenoid lesions with evolution to proliferative leukoplakia or a continuum of the same precancerous condition? A revised hypothesis. J Oral Pathol Med. 2021;50(2):129-135.
38. Van der Meij EH, Van der Waal I. Lack of clinicopathologic correlation in the diagnosis of oral lichen planus based on the presently available diagnostic criteria and suggestions for modifications. J Oral Pathol Med. 2003;32:507-512.
39. Eisenberg E. Clinical controversies in oral and maxillofacial surgery: part one. Oral lichen planus: a benign lesion. J Oral Maxillofac Surg 2000;58:1278-1285.
40. Al-Hashimi I, Schifter M, Lockhart PB, Wray D, Brennan M, Migliorati CA, et al. Oral lichen planus and oral lichenoid lesions: diagnostic and therapeutic considerations. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103 (suppl):1-12.
41. Yamanaka Y, Yamashita M, Innocentini LMA, Macedo LD, Chahud F, Ribeiro-Silva A, Roselino AM, Rocha MJA, Motta AC. Direct Immunofluorescence as a Helpful Tool for the Differential Diagnosis of Oral Lichen Planus and Oral Lichenoid Lesions. Am J Dermatopathol. 2018;40(7):491-497.
42. Salgado DS, Jeremias F, Capela MV, et al. Plaque control improves the painful symptoms of oral lichen planus gingival lesions. A short-term study. J Oral Pathol Med. 2013;42: 728-732.
43. Holmstrup P, Schiøtz AW, Westergaard J. Effect of dental plaque control on gingival lichen planus. Oral Surg Oral Med Oral Pathol.1990;69:585590.
44. Adamo D, Calabria E, Coppola N, Lo Muzio L, Giuliani M, Bizzoca ME, et al. Psychological profile and unexpected pain in oral lichen planus: a case-control multicenter SIPMO study. Oral Dis. 2021 (In press)
45. González-García A, Diniz-Freitas M, Gándara-Vila P, Blanco-Carrión A, García-García A, Gándara-Rey J. Triamcinolone acetonide mouth rinses for treatment of erosive oral lichen planus: efficacy and risk of fungal over-infection. Oral Dis. 2006;12(6):559-565.
46. Lodi G, Pellicano R, Carrozzo M. Hepatitis C virus infection and lichen planus: a systematic review with meta-analysis. Oral Diseases. 2010;16:601-612.
47. Gonzalez-Moles MA, Ruiz-Avila I, Rodriguez-Archilla A, Morales-Garcia P, Mesa-Aguado F, Bascones-Martinez A, Bravo M. Treatment of severe erosive gingival lesions by topical application of clobetasol propionate in custom trays. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95(6):688-692.
48. Gonçalves S., Dionne R.A., Moses G., Carrozzo M. Pharmacotherapeutic Approaches in Oral Medicine. In: Farah C., Balasubramaniam R., McCullough M, (eds). Contemporary Oral Medicine. A comprehensive approach to clinical practice. Springer, Switezerland, 2019.
49. Carbone M, Goss E, Carrozzo M, et al. Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. J Oral Pathol Med. 2003;32:323-329.
50. Eisen D. Hydroxychloroquine sulfate (Plaquenil) improves oral lichen planus: An open trial. J Am Acad Dermatol 1993;28:609–12.
51. Ho JK, Hantash BM. Systematic review of current systemic treatment options for erosive lichen planus. Expert Rev Dermatol 2012;7:269-282.
52. Wee JS, Shirlaw PJ, Challacombe SJ, Setterfield JF. Efficacy of mycophenolate mofetil in severe mucocutaneous lichen planus: a retrospective review of 10 patients. Br J Dermatol 2012;167:36–43.
53. Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus: a case series with emphasis on therapy. Arch Dermatol 2007;143:511-515.
54. Bruch JM, Treister NS. Immune-Mediated and Allergic Conditions. In: Bruch JM, Treister NS, (eds). Clinical Oral Medicine and Pathology. Humana Press, 2009.
55. Mignogna MD, Fedele S, Lo Russo L. Dysplasia/neoplasia sur-veillance in oral lichen planus patients: a description of clinical criteria adopted at a single centre and their impact on prognosis. Oral Oncol. 2006;819-824.
56. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Sci 2007;49:32-37.

57. Epstein JB, Wan LS, Gorsky M, Zhang L. Oral lichen planus: progress in understanding its malignant potential and the implications for clinical management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96 (1):32–7.
58. Elhadad MA, Gaweesh Y. Hawley retainer and lichenoid reaction: a rare case report. BMC Oral Health. 2019;19(1):250.
59. Larsson A, Warfvinge G. Oral lichenoid contact reactions may occasionally transform into malignancy. Eur J Cancer Prevention 2005;14:525-529.
60. McCartan BE, McCreary CE. Oral lichenoid drug eruptions. Oral Dis 1997;3:58-63.
61. Den Haute VV, Antoine JL, Lachapelle JM. Histopathological discriminant criteria between lichenoid drug eruption and idiopathic lichen planus: retrospective study on selected samples. Dermatology. 1989;179:10-13.
62. Schmidt-Westhausen AM. Oral lichen planus and lichenoid lesions: what's new? Quintessence Int. 2020;51(2):156-161.
63. Fortuna G, Aria M, Schiavo JH. Drug-induced oral lichenoid reactions: a real clinical entity? A systematic review. Eur J Clin Pharmacol. 2017;73(12):1523-1537.
64. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 ;125(6):582-590.
65. Kuten-Shorrer M, Woo SB, Treister NS. Oral graft-versus-host disease. Dent Clin North Am. 2014;58(2):351-368.

5

Actinic Keratosis

Lucía Lago Méndez[1]
Lucía García Caballero[2]
Márcio Diniz Freitas[3]

1. Oral Health Unit, Galician Health Service (SERGAS), Santiago de Compostela, Spain.

2. Department of Morphological Sciences, School of Medicine and Dentistry, University of Santiago de Compostela, Spain.

3. Special Care Dentistry Unit, School of Medicine and Dentistry, University of Santiago de Compostela, Spain.

5.1. Definition

Actinic Keratosis (AK), also known such as Actinic Cheilites of the lips and solar cheilitis [1], is a potentially malignant disorder resulting from long-term exposure to ultraviolet (UV) rays [2].

5.2. Epidemiology

AK is a potentially malignant disorder of the lips caused by long-term exposure to solar radiation. Its frequency is higher in geographical areas with high ultraviolet (UV) radiation, in open-air workers and in those with fairer skin types. The highest rates are reported in Brazil, with rates of 28.4% - 39.6% among agricultural workers [3, 4]. Data from Europe is scarce and mixed. Tortorici et al (2016) reported a prevalence of 0.8% in the Sicilian population [5]. In Greece, Ntomouchtsis et al (2010) reported a prevalence of 17% [6]. In contrast, a recent study showed a prevalence of 31.3% in the population > 45 years in the northwest of Spain [7].

Although it can occur at any age, the disease is more common among individuals >50 years with long periods of exposure to solar light (8,9). Other factors that have been associated with an increased prevalence of AK include low educational level, a precarious socioeconomic status, genetic predisposition and unhealthy lifestyles such as smoking and poor diet [10, 11].

Although numerous studies have assessed the association between AK and squamous cell carcinoma (SCC), the rates of malignant AK transformation have not been definitively established. A number of studies have estimated the rate at approximately 17% [12]. In a recent systematic review which analysed the evidence on malignant transformation, only one article satisfied the inclusion criteria and determined that the malignant transformation rate for AK was 3.07%. [13]

Up to 95% of cases of SCC of the lips are preceded by AK [14]. Therefore, diagnosis and early treatment of AK are vital for preventing the development of SCC [15].

5.3. Clinical presentation

Actinic cheilitis most commonly affects the lower lip and presents with a broad range of clinical characteristics. Initially, it is characterised by erythema, flaking, induration, erosion and/or cracks or ulcers on the vermilion. Repeated exposure to UV radiation produces chronic tissue changes including hyperkeratosis, loss of elasticity and effacement of the cutaneous-mucous labial border (Figure 5.1) [16]. These manifestations can be localised or diffuse [12].

The first clinical signs of AC can be subtle, and patients may attribute these changes to normal aging. As a result, the time to initial presentation is often delayed until more advanced changes or SCC is already present [11].

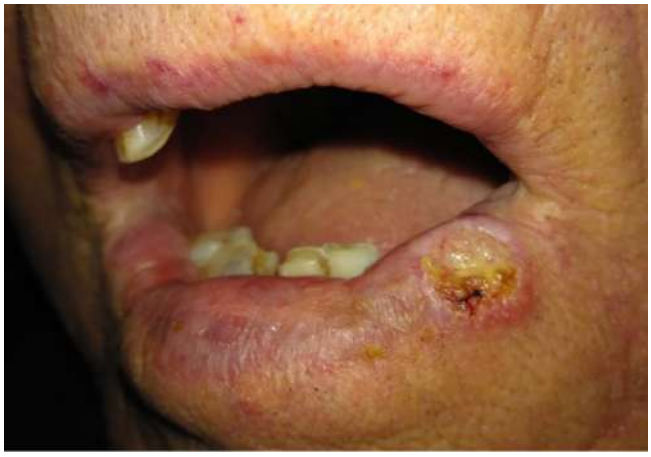

Figure 5.1. Squamous cell carcinoma with background actinic cheilitis involving the lower lip. The lips appear dry and cracked with loss of the vermilion border. An ulcer with everted edges and indurated on palpation is noted on the left lower lip.

5.4. Differential diagnosis

In the differential diagnosis, we should consider the following: herpes simplex infection, lichen planus, oral lichenoid lesions, erythema multiforme, pemphigus vulgaris, leukoplakia, SCC, basal cell carcinoma, malignant melanoma and other forms of cheilitis such as exfoliative cheilitis and contact cheilitis [17, 18]. The medical history, employment history, social history and intraoral manifestations will help to differentiate AK from the entities mentioned above (Table 5.1).

Disease	Symptoms
Herpes labialis	Erythema, followed by vesicles around the mucocutaneous junction of the lip. Spontaneous healing in 7–10 days.
Oral lichen planus	White striae (Wickham striae), erythema, erosion, ulcers. The in-traoral lesions are preferentially located in the buccal mucosa and tongue and are usually symmetrical.
Discoid lupus ery-thematosus	Intense red macules and papules that usually progress leaving scars, atrophy and hyperpigmentation; the clinical appearance of the le-sions varies with solar exposure. There can be systemic signs and symptoms.
Pemphigus vulgaris	Characterised by blisters, erosion and ulcers that affect the lips and oral mucosa. More than 85% of cases of oral pemphigus vulgaris are preceded by a skin lesion.
Angular cheilitis	Erythema and flaking of the labial commissures. Associated with loss of vertical dimensionality, Candida infection, vitamin B12 deficien-cy or HIV infection.
Exfolia-tive/factitious cheilitis	Thick hemorrhagic crusts, induration, ulceration, comorbid anxiety / depression
Con-tact/eczematous cheilitis	History of allergic reactions or exposure to known antigens (e.g. toothpaste, cosmetic products and exposure to an extreme cli-mate). Characterised by flaking and erythema throughout the ver-milion border of the lips with detachment of the superficial epithe-lium.
Granulomatous cheilitis	Episodic and painless enlargement of one or both lips, firm and nodular to palpation. Usually associated with systemic diseases such as Crohn's disease, sarcoidosis and Melkersson-Rosenthal syndrome.
Glandular cheilitis	Chronic inflammatory condition that manifests as hypersecretion of the minor salivary glands, with ductal ectasia, lip swelling, nodular growth, everted labial mucosa and ulceration.
Squamous cell car-cinoma	Red or white papule or persistent indurated ulcer. Usually back-ground AK changes. May be accompanied by lymph node metastasis at the submandibular and/or cervical level.

Table 5.1. Differential diagnosis of actinic cheilitis (modified from Jadotte and Schwartz, 2012 (19).

5.5. Diagnosis

The diagnosis of AK is based on the demographic history, clinical findings and histopathology [12]. Effacement of the vermilion border is a relevant clinical characteristic but can be difficult to identify due to the loss of support of the labial structures in older patients [20]. The accuracy of the clinical diagnosis can be increased with non-invasive imaging techniques such as dermatoscopy and confocal microscopy [7, 21].

On palpation, AK is often perceived as fine sandpaper when sliding a gloved finger over the surface of the lip. Palpation is also important to differentiate AK from SCC of the lips [8]. The neck should also be examined for the presence of lymphadenopathy (unilateral v. bilateral, mobile vs. fixed) [20].

Although the diagnosis is usually clinical, a confirmatory biopsy should be undertaken, especially on lesions that demonstrate substantial changes, such as induration, ulceration, and suspicious of an SCC [22–24].

A sample should be obtained from a representative area, as well as from lesions with atrophy, ulceration or induration [19].

Histologically, AK causes changes at an epithelial level and in the underlying connective tissue. The epithelium in AK can present hyperkeratosis, hyperparakeratosis, atrophy, acanthosis or loss of polarity of the basal keratinocytes. Varying degrees of dysplasia is frequent. In the connective tissue, the presence of elastosis may be observed, corresponding to a basophilic degeneration of the extracellular matrix, which is replaced by amorphous elastic fibers. A chronic inflammatory infiltrate of distinct intensity can be observed, as well as the presence of telangiectatic blood vessels [8].

Most cases of AK have some degree of epithelial dysplasia and, in some cases, carcinoma *in situ* [24]. Studies have shown a poor correlation between clinical appearance and grade of epithelial dysplasia [8, 25].

The histological changes are not uniform throughout the labial vermilion, even in cases with a homogenous clinical appearance. Multiple biopsies may be required, particularly in patients with diffuse AK changes [26].

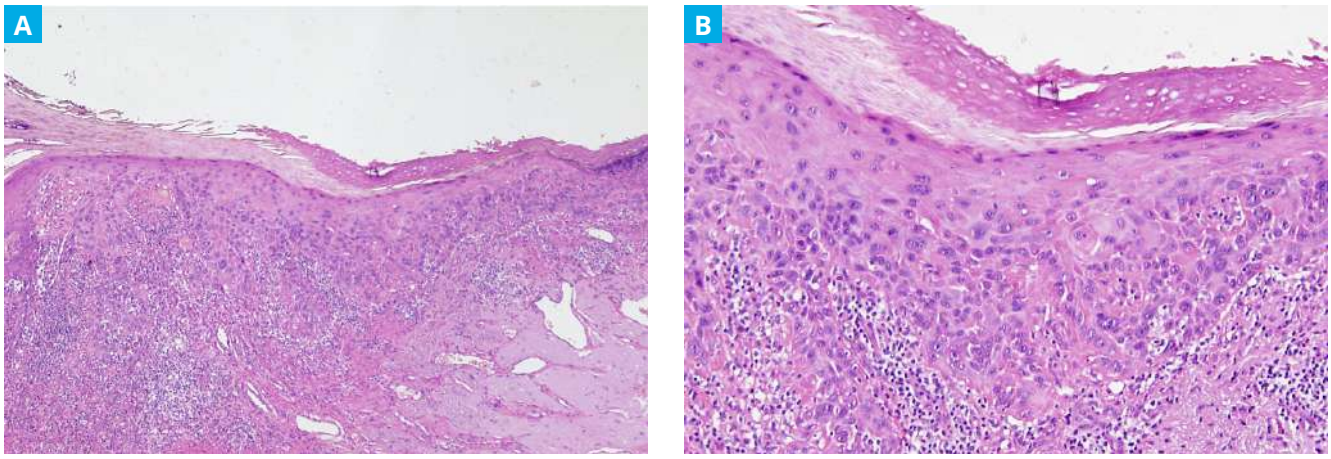

Figure 5.2. A) Epithelial hyperplasia with dysplasia, moderate chronic inflammatory infiltrate, and prominent solar elastosis and vascular telangiectasia at the submucosa (bottom right) (H&E, x4); B) At higher magnification, alternating areas of parakeratosis and orthokeratosis are observed, as well as epithelial dysplasia, lymphocytic infiltrate and elastosis. (H&E, x10).

5.6. Management

Prevention

Adequate photoprotection is the important preventative measure for AK. Specific recommendations for protection in high-risk populations should be reinforced [24, 27]. Photoprotection measures include 1) limiting exposure to the sun between 10 am and 2 pm (or between 11 am and 3 pm in summer), 2) wearing a protective wide-brimmed hat, 3) using water-resistant lip balm with broad-spectrum UVA and UVB protection (SPF30+), applied generously and reapplied at least every 2 hours. This advice is applicable to all patients with a diagnosis of AK and for prevention in those individuals with fair skin who spend long periods exposed to the sun e.g. fishermen, farmers, athletes [16].

Treatment

The aim of treatment is to reduce the risk of malignant transformation while maintaining functionality and aesthetics. Various surgical and non-surgical therapeutic options have been employed aimed at eliminating dysplastic epithelium. Determining the best therapy available remains a subject of debate in the scientific community [28] (Table 5.2).

The type of therapeutic modality should depend on the individual case and based on the clinical (size, location) and pathology findings (degree of epithelial dysplasia), taking into account side effects, potential aesthetic sequelae and evidence base [12,29].

The most common non-surgical therapies include topical applications of fluorouracil (5-FU), 5% imiquimod, 3% diclofenac with 2.5% hyaluronic acid, and 0.015% ingenol mebutate [15].

Photodynamic therapy, which consists of combining a light source (400-700 nm) and a photosensitizer (5–20% 5-aminolevulinic acid or methyl aminolevulinate), produces free oxygen radicals that destabilize the membranes and cell organelles, inducing cell death [19, 28].

Non-surgical therapies are less invasive and have fewer side effects than surgical modalities [31]. However, they are less effective in terms of clinical and histological control of the lesion and associated with higher relapse rates [29, 31] Topical therapies can improve results when used in conjunction with surgical therapeutic options [29].

Surgical options include vermilionectomy by excision, laser ablation, cryotherapy and electrocauterization [10]. Vermilionectomy is the surgical method most often employed and consists of total extirpation of the affected lip, although its magnitude can vary depending on the thickness of the tissue to be removed.

Vermilionectomy with cold scalpel is the only technique that allows for histopathology analysis of all extirpated tissue [30]. This is important because discrepancies have been shown between the histological diagnosis of the incisional biopsy and that of the final specimen obtained after performing a complete vermilionectomy [26].

It is an aggressive technique that can cause complications such as pain, oedema, delayed healing, infections, paresthesia and scarring [28].

Current evidence suggests that surgical treatments using vermilionectomy with a cold scalpel or laser ablation with carbon dioxide are the treatments of choice, especially for high-risk patients [32].

Treatment modality	Indications	Adverse ef-fects	Advantages	Disadvantages
Surgical therapies				
Vermilionectomy / Surgical excision with a cold scalpel	First treatment of choice for circumscribed lesions and diffuse lesions with moderate/severe dysplasia.	Pain, oedema, delayed healing, infection, paresthesia, scars, restricted oral functionality.	• High healing rates (approaching 100%) and few relapses. • Allows for the complete histological analysis of the lesion.	• Can cosmetically disfigure compared with other treatment options.
Vaporization with CO_2 laser	Diffuse or multicentric Lesions with mild dysplasia.	Pain, hypertrophic scars.	• Good healing rates. • Minor cosmetic effects compared with cold scalpel vermilionectomy.	• Does not allow for histological analysis.
Non-surgical therapies				
5-fluorouracil (5-FU) • 5% solution - 3 times a day / 9–15 days • 0.5% cream - 2 times day / 2–4 weeks	Treatment of choice for patients with diffuse lesions with mild to no dysplasia and those for whom surgery is contraindicated or who prefer medical treatment. Can be administered in addition to surgical treatment.	Pain, crusting, inflammation, poorly tolerated by some patients.	• Easy to apply. • Full healing at 2–3 weeks post-treatment.	• Does not allow for histological analysis of the lesion. Affected by the patient's or their caregivers' degree of compliance. • The healing rates are inconsistent.
5% imiquimod	An alternative to 5-FU	Irritation, erythema, erosion, induration and superficial ulceration.	• Easy to apply. • Fewer side effects than 5-FU.	• Does not allow for histological analysis of the lesion. Affected by the patient's or their caregivers' degree of compliance. • The healing rates are inconsistent.
Photodynamic therapy	Has not been established	Pain, erythema, swelling	• Few esthetic sequelae. Faster healing than with other non-surgical therapies.	• Does not allow for histological analysis of the lesion. Lower healing rates than with vermilionectomy but higher when used in combination with other therapies (e.g. Er:YAG laser) • High cost.
Photoprotection	Supplementary to all other treatment modalities.		• Reduces the progression of the lesions.	• Depends on patient compliance.

Table 5.2. Main Treatment Modalities for Actinic Cheilitis.

In summary, localised lesions suspicious for malignancy should undergo excision or vaporization if moderate to severe dysplasia is detected, or complete surgical excision if an SCC is diagnosed (Figure 3). Vermilionectomy techniques should be reserved for diffuse AK with moderate to severe dysplasia, while laser vaporisation techniques should be employed for diffuse or multisite lesions with mild dysplasia [29].

Follow-up

Regardless of the therapeutic modality, AK treatment should be supplemented with sun protection creams and periodic clinical reviews [10]. Patients should undergo a post-therapy follow-up regimen, with visits at least every 6 months during the first 2 years and subsequently annually [31]. If changes are detected during follow-up, re-biopsy should be performed, and follow-up intervals shortened.

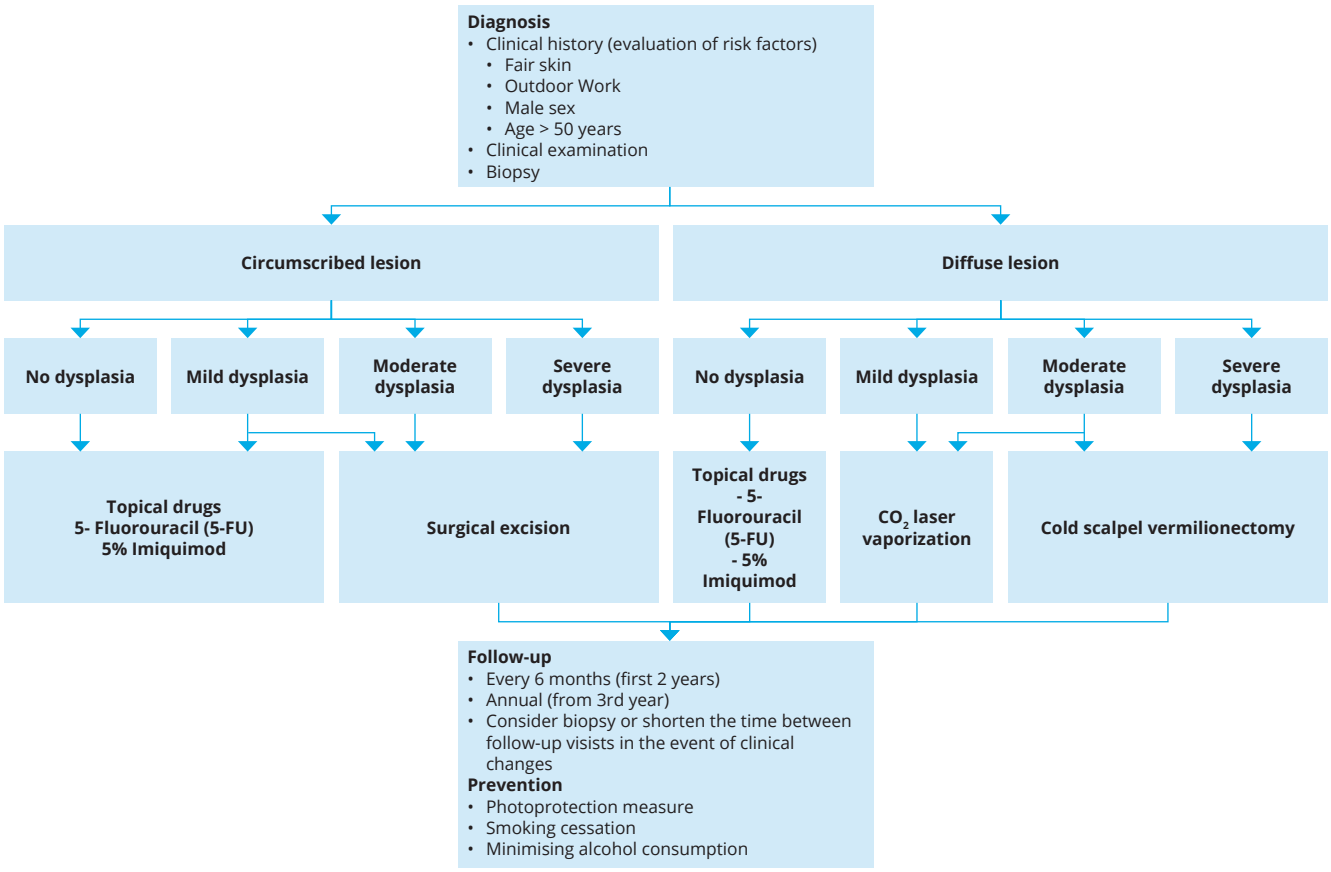

Figure 5.3. Decision making in the management of patients with actinic cheilitis.

References

1. Cataldo E, Doku HC. Solar cheilitis. J Dermatol Surg Oncol. 1981 Dec;7(12):989-895.
2. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, Lodi G, Mello FW, Monteiro L, Ogden GR, Sloan P, Johnson NW. 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. 2021;27(8):1862-1880.
3. Junqueira JL, Bönecker M, Furuse C, Morais Pde C, Flório FM, Cury PR, Araújo VC. Actinic cheilitis among agricultural workers in Campinas, Brazil. Community Dent Health. 2011;28(1):60-63.
4. Ferreira AM, de Souza Lucena EE, de Oliveira TC, da Silveira É, de Oliveira PT, de Lima KC. Prevalence and factors associated with oral potentially malignant disorders in Brazil's rural workers. Oral Dis. 2016;22(6):536-542.
5. Tortorici S, Corrao S, Natoli G, Difalco P. Prevalence and distribution of oral mucosal non-malignant lesions in the western Sicilian population. Minerva Stomatol. 2016; 65(4):191-206.
6. Ntomouchtsis A, Karakinaris G, Poulolpoulos A, Kechagias N, Kittikidou K, Tsompanidou C, Vahtsevanos K, Antoniades K. Benign lip lesions. A 10-year retrospective study. Oral Maxillofac Surg. 2010;14(2):115-118.

7. Rodríguez-Blanco I, Flórez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I, Pereiro-Ferreirós M. Actinic Cheilitis Prevalence and Risk Factors: A Cross-sectional, Multicentre Study in a Population Aged 45 Years and Over in North-west Spain. Acta DermVenereol. 2018;98(10):970-974.
8. Kaugars GE, Pillion T, Svirsky JA, Page DG, Burns JC, Abbey LM. Actinic cheilitis: a review of 152 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;88(2):181-186.
9. de Souza Lucena EE, Costa DC, da Silveira EJ, Lima KC. Prevalence and factors associated to actinic cheilitis in beach workers. Oral Dis. 2012;18(6):575-579.
10. Vieira R, Minicucci EM, Marques ME, Marques SA. Actinic cheilitis and squamous cell carcinoma of the lip: clinical, histopathological and immunogenetic aspects. An Bras Dermatol. 2012;87:105-114.
11. Jadotte YT, Schwartz RA. Solar cheilosis: an ominous precursor: part I. Diagnostic insights. J Am Acad Dermatol. 2012;66(2):173-184.
12. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: clinical and pathologic characteristics in 65 cases. Oral Dis. 2004;10(4):212-216.
13. Dancyger A, Heard V, Huang B, Suley C, Tang D, Ariyawardana A. Malignant transformation of actinic cheilitis: A systematic review of observational studies. J InvestigClinDent. 2018;9(4):e12343.
14. Gomes JO, de Vasconcelos Carvalho M, Fonseca FP, Gondak RO, Lopes MA, Vargas PA. CD1a+ and CD83+ Langerhans cells are reduced in lower lip squamous cell carcinoma. J Oral Pathol Med. 2016;45(6):433-439.
15. Lai M, Pampena R, Cornacchia L, Pellacani G, Peris K, Longo C. Treatments of actinic cheilitis: A systematic review of the literature. J Am Acad Dermatol. 2020 Sep;83(3):876-887.
16. Savage NW, McKay C, Faulkner C. Actinic cheilitis in dental practice. Aust Dent J. 2010;55 Suppl 1:78-84.
17. Van der Waal. Queilitis Actínica. In: Bascones A, Seoane JM, Aguado A, Suárez-Quintanilla JM. Cáncer y precáncer oral: Bases clínico-quirúrgicas y moleculares. Ediciones Avances Médico-Dentales S.L., Madrid, 2003.
18. Muse ME, Crane JS. Actinic Cheilitis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
19. Jadotte YT, Schwartz RA. Solar cheilosis: an ominous precursor part II. Therapeutic perspectives. J Am Acad Dermatol. 2012;66(2):187-189.
20. Greenberg SA, Schlosser BJ, Mirowski GW. Diseases of the lips. Clin Dermatol. 2017 Sep-Oct;35(5):e1-e14.
21. Ulrich M, González S, Lange-Asschenfeldt B, Roewert-Huber J, Sterry W, Stockfleth E, Astner S. Non-invasive diagnosis and monitoring of actinic cheilitis with reflectance confocal microscopy. J Eur Acad Dermatol Venereol. 2011;25(3):276-284.
22. Kahn MA, Hall JM. The ADA practical guide to soft tissue oral disease. 2nd edition. Wiley, 2018.
23. Warnakulasuriya S (2000). Lack of molecular markers topredict malignant potential of oral precancer. J Pathol 190:407–409.
24. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, Rivero ERC. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J Oral Pathol Med. 2018;47(7):633-640.
25. Onofre MA, Sposto MR, Navarro CM, Motta ME, Turatti E, Almeida RT. Potentially malignant epithelial oral lesions: discrepancies between clinical and histological diagnosis. Oral Dis 1997; 3: 148–152.
26. Menta Simonsen Nico M, Rivitti EA, Lourenço SV. Actinic cheilitis: histologic study of the entire vermilion and comparison with previous biopsy. J Cutan Pathol. 2007;34(4):309-314.
27. Rodriguez-Blanco I, Florez Á, Paredes-Suárez C, Rodríguez-Lojo R, González-Vilas D, Ramírez-Santos A, Paradela S, Suárez Conde I, Pereiro-Ferreirós M. Use of lip photoprotection in patients suffering from actinic cheilitis. Eur J Dermatol. 2019;29(4):383-386.
28. Salgueiro AP, de Jesus LH, de Souza IF, Rados PV, Visioli F. Treatment of actinic cheilitis: a systematic review. Clin Oral Investig. 2019;23(5):2041-2053.
29. Varela-Centelles P, Seoane-Romero J, García-Pola MJ, Leira-Feijoo Y, Seoane-Romero JM. Therapeutic approaches for actinic cheilitis: therapeutic efficacy and malignant transformation after treatment. Int J Oral Maxillofac Surg. 2020;49(10):1343-1350.
30. Calcaianu N, Popescu SA, Diveica D, Lascar I. Surgical attitude in premalignant lesions and malignant tumors of the lower lip. J Med Life. 2015;8(1):109-111.
31. Carvalho MV, de Moraes SLD, Lemos CAA, Santiago Júnior JF, Vasconcelos BCDE, Pellizzer EP. Surgical versus non-surgical treatment of actinic cheilitis: A systematic review and meta-analysis. Oral Dis. 2019;25(4):972-981.
32. Trager MH, Farmer K, Ulrich C, Basset-Seguin N, Herms F, Geskin LJ, Bouaziz JD, Lebbé C, de Masson A, Bagot M, Dobos G. Actinic cheilitis: a systematic review of treatment options. J Eur Acad Dermatol Venereol. 2021;35(4):815-823.

6

Dyskeratosis Congenita

Emma Fribourg[1]
Franck Boralevi[2]
Sandeep Joshi[3]
Jean-Christophe Fricain[1]

1. Oral Surgery Department, University Hospital Bordeaux (France)

2. Pediatric Dermatology, University Hospital Bordeaux (France)

3. Oral Medicine, Guy's & St Thomas' NHS Foundation Trust (United Kingdom)

6.1. Definition

Dyskeratosis congenita (DC) is a rare multisystem inherited genodermatosis leading to reduced telemerase function impairing chromosomal stability [1]. Also known as Zinsser-Cole-Engman syndrome, it was first described in 1906 [2]. Telemeres form the ends of chromosomes and telemerase is an enzyme responsible for the synthesis of telomeres [3]. A reduction in or impaired function of telemerase leads to a reduction in genetic material and subsequent activation of 'DNA damage response pathways' resulting in cell death [4].

Bone marrow failure occurs as the bone marrow is dependent on telomere function due to its high cell turnover. In addition, DC also commonly manifests with mucocutaneous signs, pulmonary and/or hepatic fibrosis [1].

6.2. Aetiology

Dyskeratosis congenita is one of a few inherited marrow failure syndromes which has inheritance patterns including X-linked, autosomal dominant and autosomal recessive. The specific genetic defect DKC1 mutation associated with X-linked DC, the most severe form of DC, leads to absence of functioning dyskerin, severely impairing telemerase function [5]. A number of genetic mutations have been identified resulting in different clinical manifestations including RTEL1 and TINF2 which have cerebellar hypoplasia and retinal disease as prominent features, respectively [6, 7]. Recessive mutations in NOP10, CTC1, NHP2, PARN and WRAP53 are rarer and lead to differing clinical presentations [8].

6.3. Epidemiology

Dyskeratosis congenita is rare, typically presenting clinically between 5-12 years and has a male predominance [9]. An estimated incidence of 1 in 1,000,000 people has been reported [10].

6.4. Clinical presentation

The presentation of DC is typically early in life, in contrast to acquired forms of aplastic anaemia and are the consequence of the genetic mutations [11]. Zinsser in 1906 [2] first described the characteristic triad of DC which includes the following:

- Reticular atrophy and cutaneous hyperpigmentation. (Figure 6.1)
- Nail dystrophy (Figure 6.2)
- Oral leukoplakia

In addition, features of bone marrow failure include fatigue, dyspnoea, tachycardia, pallor, easy bruising and infection may become apparent as pancytopenia develops. Approximately 80% of patients with DC develop bone marrow failure by 30 years of age [1]. However, cutaneous and nail changes typically manifest earlier, before the age of 10 years. Variations in timeline of signs and symptoms can occur deviating from the classical early cutaneous changes [1].

The disease process can also impair other organs such as the pulmonary system causing interstitial lung disease leading to deterioration of respiratory function and hepatic system leading to steatosis, cirrhosis and portal hypertension [12,13]. Moreover, other clinical manifestations include microcephaly, short stature, hypogonadism, enteropathy, liver disease, oesophageal and urethral stenosis, osteoporosis, avascular necrosis of the hips and shoulders [14].

In patients with DC as a result of chromosomal instability, there is an increased risk of developing cancer affecting various bodily systems. It has been reported that children with DC have a 100-fold increased risk of developing Acute Myeloid Leukaemia (AML) [15]. There is also an increased risk of developing squamous cell carcinomas of the head and neck, cervix and anogenital region [15]. Cancers of the skin, aerodigestive tract and pancreas have also been reported and majority of all cancers occur in third decade of age [16].

Oral Manifestations

A number of intraoral changes have been reported to present in patients with DC including oral leukoplakia, which is the most common feature found in up to 80% of patients [1, 17].

In a cross-sectional study of 17 patients with DC, oral leukoplakia was found in 11 patients with the most common sites involved being the tongue, buccal mucosa, palate and gingivae [18]. Atkinson et al. [18] also described soft tissue changes including erythema, particularly in the buccal mucosa and tongue, brown pigmentation, and depapillation of the tongue. In addition, altered sensation described as burning of the tongue has been reported [19].

The rate of malignant transformation of oral leukoplakia has been documented to range between 0.13-34% depending on multiple risk factors such as age, sex, homogeneity and size of the lesion [20]. In DC, the rate of progression of such lesions to cancer is approximately 30% between 10-30 years [21]. Moreover, in DC due to early telomere shortening, cancers have been reported to present earlier in patients as young as 5 years [22]. Therefore, close surveillance is essential and frequently require biopsies. Case reports of SCC manifesting intraorally have been documented [19, 23].

Cannell et al in 1971 [24] described the sequential stages according to age in the development of oral leukoplakia:

- Age 5-14: white patches of necrotic epithelium or possible candida infection. Patches always preceded by vesicles and ulceration.
- Age 14-20: recurrent ulceration and erythroplakia
- Age 20-30 erosive leukoplakia and carcinoma

Gingival inflammation and periodontal disease are frequently seen in patients with DC due to a combination of early destruction of periodontal tissues as a result of anomalies in ectodermal derived structures, and a poor response to this secondary to neutropenia [25]. In one study of 79 patients with aplastic anaemia, common intraoral features included petechiae in the buccal and labial mucosa, gingival hyperplasia, spontaneous gingival bleeding and herpetic ulceration [26]. Though periodontal disease of varying severity has been reported in patients with DC [27] it is not always an identified feature [18,28]. Gingivitis presenting in young patients always requires further investigation, once local causes have been excluded, to ascertain if an underlying causative process such as aplastic anaemia is responsible [29]. Lichen planus&Lichenoid reaction has been reported to be associated with DC but remains a relatively rare finding [30]. (Figure 6.3)

Dental caries is frequently identified in patients with DC with one study of 73 patients reporting 'extensive caries' in 13 patients [31] and these findings have been supported elsewhere [32, 33]. In addition, other dental anomalies seen in patients with DC include hypodontia, short blunted roots, thinned enamel [25,33], taurodontism, decreased crown/root ratio, hypocalcification and gingival recession [18,32].

6.5. Differential diagnosis

Aplastic anaemia can be classified into two broad categories; acquired and inherited. The acquired causes include idiopathic, which is the most common cause, drug induced, viral, pregnancy and connective tissue diseases. Inherited causes include Fanconi anaemia, Shwachman- Diamond Syndrome and GATA2 syndrome [11]. Though Fanconi anaemia remains the most common differential diagnosis.

Differential diagnoses oral white lesions involve infective processes such as candidiasis and non-infective causes including oral lichen planus, lichenoid lesions, white sponge naevus, frictional keratosis and graft-versus-host disease GVHD [34].

6.6. Diagnosis

The diagnostic criteria for DC as outlined by Dokal 2011 [1] states that at least 2 of 4 major features (BM failure, abnormal skin pigmentation, nail dystrophy and leukoplakia] must be present along with a minimum of at least two other identified somatic features. These are shown in the table 6.1 [1].

The diagnosis of DC can be confirmed by performing blood tests including full blood count (FBC] and reticulocyte count to establish if pancytopenia is present. A bone marrow biopsy may reveal a hypocellular marrow. Further investigations would include specialised tests such as genetic sequencing, measurement of telomere length by flow cytometry fluorescence in situ hybridisation (FISH) and computed tomography (CT) scans to determine if pulmonary and/or hepatic involvement [11]. In the case of a positive family history, prenatal genetic diagnosis by chorionic villus sampling or preimplantation genetic diagnosis may be available.

Ogden et al., examined the cytokeratin profiles of lingual keratosis by immunocytochemistry. They found an unusual immature or disturbed keratin pattern [35]. Electron microscopy studies have shown that cells in DC have an embryonic immature nucleus, which have a higher chance of undergoing malignant transformations [36].

6.7. Management

A multidisciplinary (MDT) approach is required in the care of patient's diagnosed with DC and the health care professionals involved will be governed by the bodily systems involved. However, haematologists will have a focal role as bone marrow failure is a primary cause of early morbidity and mortality [37]. Androgenic therapy has been found to cause haematological improvement in up to 70% of patients with DC [38]. However, allogenic haematopoietic stem cell transplantation is the only definitive treatment option though it has its own risks such as GVHD [37].

Oral leukoplakia particularly in patients with DC has the potential to transform into oral cancer and therefore attentive surveillance is required. Oral and maxillofacial surgeons may decide to surgically intervene if atypia or squamous cell carcinoma is detected [23]. Resections of oral soft and hard tissue will often require reconstruction with prosthesis, therefore necessitating detailed planning with a prosthodontist to achieve a satisfactory functional and aesthetic result [23].

Non-surgical management of oral leukoplakia with topical tretinoin 0.1% solution resulted in partial improvement in two siblings aged 10 and 15 years old [39]. Chemotherapeutic agents such as bleomycin and cyclophosphamide have been reported to be effective but similar results have not shown to be consistent in improving oral leukoplakia [40]. Another reported etretinate, a vitamin A derivative, was effective for oral leukoplakia in DC [41].

A holistic approach in preventing and managing dental disease through optimised preventative advice and interventions are essential in improving quality of life for patients with DC.

Clinical features/abnormality
Major/common features
Clinical features/abnormality
Abnormal skin pigmentation
Nail dystrophy
Bone marrow failure
Leukoplakia
Other recognised somatic features
Epiphora
Learning difficulties/developmental delay
Pulmonary disease
Short stature
Extensive dental caries/loss
Oesophageal stricture
Premature hair loss/greying/sparse eyelashes
Hyperhidrosis
Malignancy
Intrauterine growth retardation
Liver disease/peptic ulceration/enteropathy
Ataxia/cerebellar hypoplasia
Hypogonadism/undescended testes
Microcephaly
Urethral stricture/phimosis
Osteoporosis/aseptic necrosis/scoliosis
Deafness

Table 6.1. Clinical features used in the diagnostic criteria of DC as described by Dokal (2001) [1].

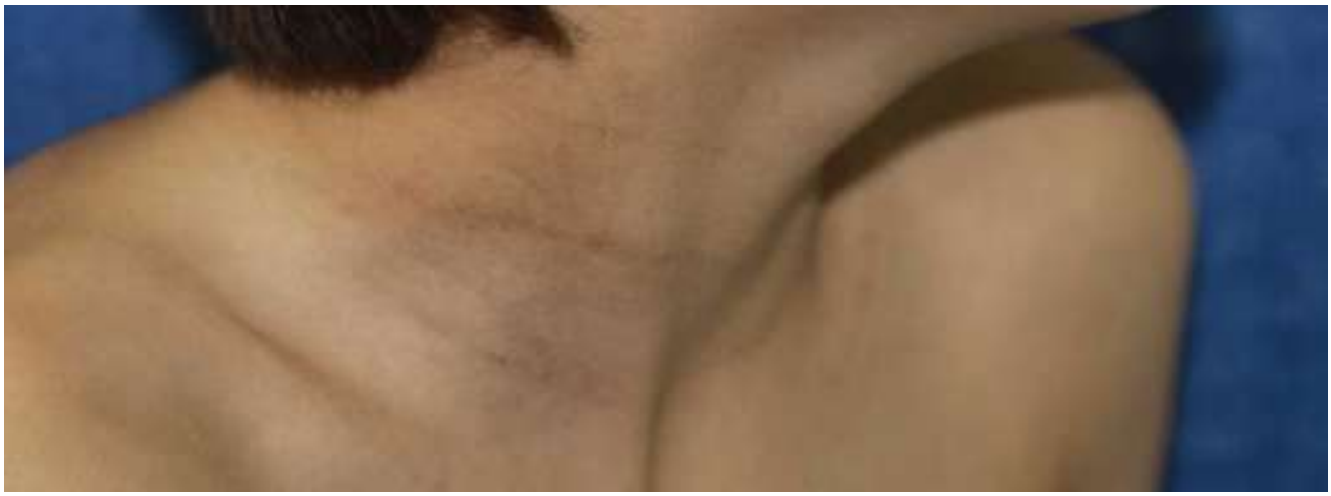

Figure 6.1. Cutaneous Hyperpigmentation of the neck.

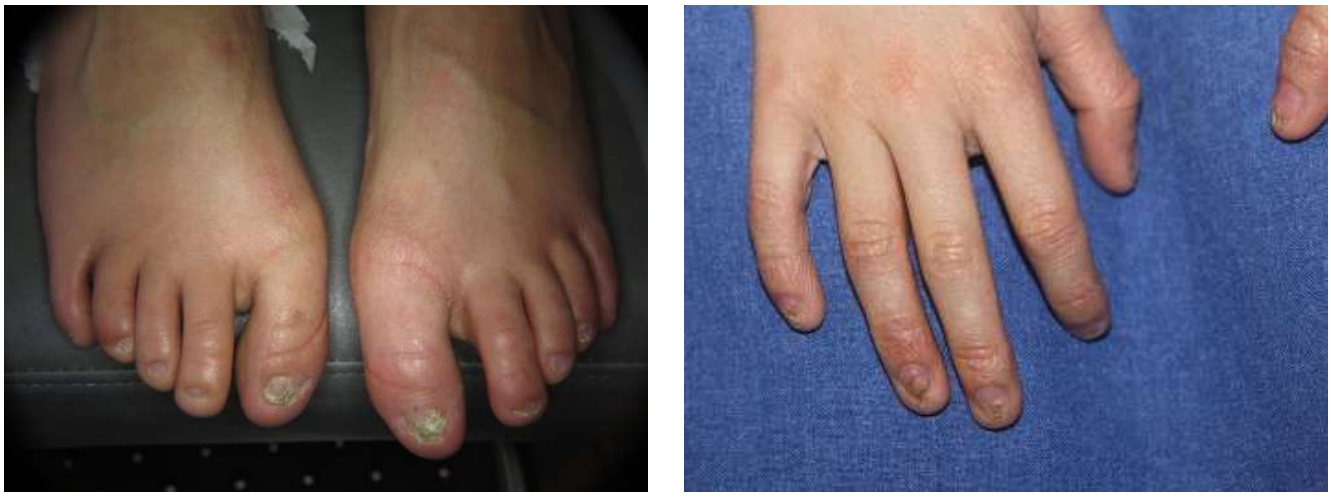

Figure 6.2. Dystrophic nails in patient with Dyskeratosis Congenita (DKC).

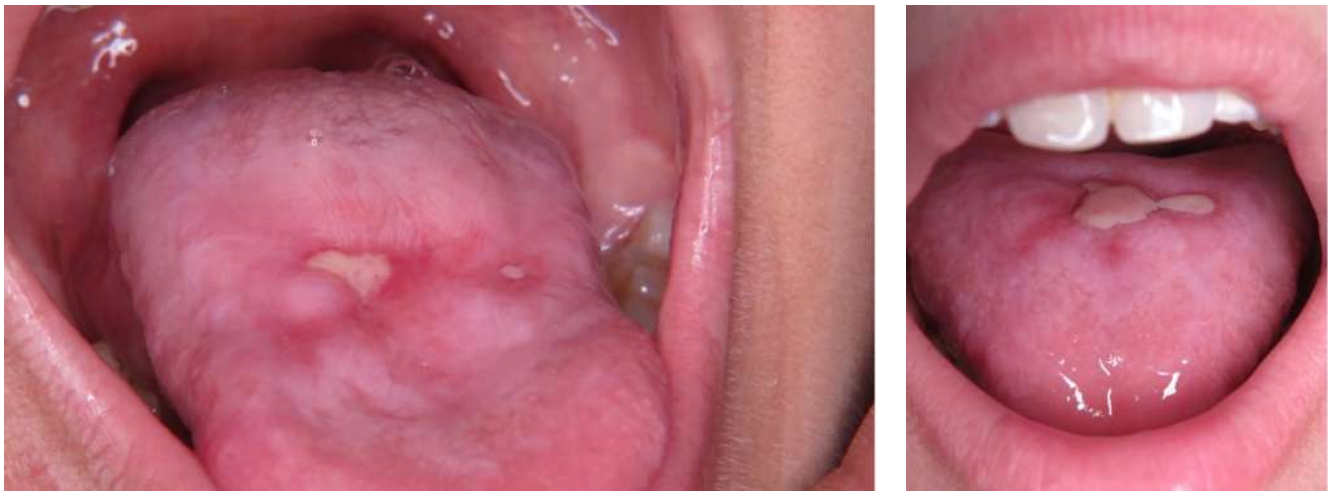

Figure 6.3. Ulceration and mild Keratosis affecting the dorsum of the tongue.

References

1. Dokal I. Dyskeratosis Congenita. Hematology. Am Soc Hematol Educ Program;2011(1):480-486.
2. Zinsser F. Atropha cutis reticularis cum pigmentatione, dystrophia ungiumet leukoplakia oris. Ikonogr Dermatol (Hyoto) 1906 (5):219–23.
3. Szostak J, Blackburn E. Cloning yeast telomeres on linear plasmid vectors. Cell. 1982;29(1):245-255.
4. Townsley D, Dumitriu B, Young N. Bone marrow failure and the telomeropathies. Blood. 2014;124(18):2775-2783.
5. Angrisani A, Vicidomini R, Turano M, Furia M. Human dyskerin: beyond telomeres. Biological Chemistry. 2014;395(6):593-610.
6. Walne A, Vulliamy T, Kirwan M, Plagnol V, Dokal I. Constitutional Mutations in RTEL1 Cause Severe Dyskeratosis Congenita. The American Journal of Human Genetics. 2013;92(3):448-453.
7. Savage S, Giri N, Baerlocher G, Orr N, Lansdorp P, Alter B. TINF2, a Component of the Shelterin Telomere Protection Complex, Is Mutated in Dyskeratosis Congenita. The American Journal of Human Genetics. 2008;82(2):501-509.
8. Walne A, Vulliamy T, Marrone A, Beswick R, Kirwan M, Masunari Y et al. Genetic heterogeneity in autosomal recessive dyskeratosis congenita with one subtype due to mutations in the telomerase-associated protein NOP10. Human Molecular Genetics. 2007;16(13):1619-1629.
9. Sinha S, Trivedi V, Krishna A, Rao N. Dyskeratosis Congenita-Management and Review of Complications: A Case Report. Oman Medical Journal. 2013;28(4):281-284.
10. Mitre C, Corda D, Dunca F, Iancu C. Anesthesia in a patient with dyskeratosis congenita presenting for urgent subtotal gastrectomy. Journal of Clinical Anesthesia. 2015;27(7):612-615.
11. Marsh J, Kulasekararaj A. Aplastic anaemia in adults [Internet]. 1st ed. England: British Medical Journal; 2021 [cited 10 July 2021].
12. Parry E, Alder J, Qi X, Chen J, Armanios M. Syndrome complex of bone marrow failure and pulmonary fibrosis predicts germline defects in telomerase. Blood. 2011;117(21):5607-5611.
13. Calado R, Regal J, Kleiner D, Schrump D, Peterson N, Pons V et al. A Spectrum of Severe Familial Liver Disorders Associate with Telomerase Mutations. PLoS One. 2009;4(11):e7926.
14. Nelson N, Bertuch A. Dyskeratosis congenita as a disorder of telomere maintenance. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. 2012;730(1-2):43-51.
15. Alter B, Giri N, Savage S, Peters J, Loud J, Leathwood L et al. Malignancies and survival patterns in the National Cancer Institute inherited bone marrow failure syndromes cohort study. British Journal of Haematology. 2010:179-188.
16. Hoareau-Aveilla C, Henry Y, Leblanc T. La dyskératose congénitale. médecine/sciences. 2008;24(4):390-398.
17. Calado R, Young N. Telomere Diseases. New England Journal of Medicine. 2009;361(24):2353-2365.
18. Atkinson J, Harvey K, Domingo D, Trujillo M, Guadagnini J, Gollins S et al. Oral and dental phenotype of dyskeratosis congenita. Oral Diseases. 2008;14(5):419-427.
19. Bongiorno M, Rivard S, Hammer D, Kentosh J. Malignant transformation of oral leukoplakia in a patient with dyskeratosis congenita. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology. 2017;124(4):e239-e242.
20. Warnakulasuriya S, Ariyawardana A. Malignant transformation of oral leukoplakia: a systematic review of observational studies. Journal of Oral Pathology & Medicine. 2015;45(3):155-166.
21. Karunakaran A, Ravindran R, Arshad M, Ram M, Laxmi M. Dyskeratosis Congenita: A Report of Two Cases. Case Reports in Dentistry. 2013;2013:1-3.
22. JH K, CS K. Squamous cell carcinoma of the tongue in 5-year-old girl with dyskeratosis congenita. International Journal of Oral and Maxillofacial Surgery. 2021:1013-1023
23. Le J, Kase M, Morlandt A. A case of dyskeratosis congenita with squamous cell carcinoma of the maxilla: A case report and review of the literature. Oral and Maxillofacial Surgery Cases. 2020;6(1):100140.
24. Cannell H. Dyskeratosis congenita. British Journal of Oral Surgery. 1971;9(1):8-20.
25. Yavuzyilmaz E, Yamalik N, Yetgirr S, Kansu O. Oral-dental findings in dyskeratosis congenita. Journal of Oral Pathology and Medicine. 1992;21(6):280-284.
26. Brennan M, Sankar V, Baccaglini L, Pillemer S, Kingman A, Nunez O et al. Oral manifestations in patients with aplastic anemia. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2001;92(5):503-508.
27. Davidovich E, Aker M, Shapira J, Peretz B. Dyskeratosis congenita: dental management of a medically complex child. Paediatric dental. 2005;27(3):244-248.
28. Koruyucu M, Barlak P, Seymen F. Oral and Dental Findings of Dyskeratosis Congenita. Case Reports in Dentistry. 2014;2014:1-5.
29. Luker J, Scully C, Oakhill A. Gingival swelling as a manifestation of aplastic anemia. Oral Surgery, Oral Medicine, Oral Pathology. 1991;71(1):55-56.
30. Loh H, Koh M, Giamj Y. Dyskeratosis congenita in two male cousins. British Journal of Oral and Maxillofacial Surgery. 1987;25(6):492-499.
31. Knight S, Vulliamy T, Copplestone A, Gluckman E, Mason P, Dokal I. Dyskeratosis Congenita (DC) Registry: identification of new features of DC. British Journal of Haematology. 1998;103(4):990-996.
32. Wald C, Diner H. Dyskeratosis congenita with associated periodontal disease. Oral Surgery, Oral Medicine, Oral Pathology. 1974;37(5):736-744.
33. Boeck K, Degreef H, Verwilghen R, Corbeel L, Casteels-Van Daele M. Thrombocytopenia: first symptom in a patient with dyskeratosis congenita. Paediatrics. 1981;67(6):898-903.
34. Scully C, Porter S. Orofacial Disease: Update For The Dental Clinical Team: 3. White Lesions. Dental Update. 1999;26(3):123-129.
35. Ogden G, Chisholm D, Leigh I, Lane E. Cytokeratin profiles in dyskeratosis congenita: an immunocytochemical investigation of lingual hyperkeratosis. Journal of Oral Pathology and Medicine. 1992;21(8):353-357.
36. McKay G, Ogden G, Chisholm D. Lingual hyperkeratosis in dyskeratosis congenita: ultrastructural findings. Journal of Oral Pathology and Medicine. 1991;20(4):196-199.
37. Feldstein J, Fernandez Garcia S. The diagnosis and treatment of dyskeratosis congenita: a review. Journal of Blood Medicine. 2014:157.
38. Khincha P, Wentzensen I, Giri N, Alter B, Savage S. Response to androgen therapy in patients with dyskeratosis congenita. British Journal of Haematology. 2014;165(3):349-357.
39. Coelho J, Lestre S, Kay T, Lopes M, Fiadeiro T, Apetato M. Dyskeratosis Congenita-Two Siblings with a New Missense Mutation in the DKC1 Gene. Pediatric Dermatology. 2011;28(4):464-466.
40. Matsui T, Itho K. Cole-Engman syndrome. Acta Derm Kyoto. 1974;1(1):69-99. Tanaka A, Kumagai S, Nakagawa K, Yamamoto E. Cole-Engman syndrome associated with leukoplakia of the tongue: A case report. Journal of Oral and Maxillofacial Surgery. 1999;57(9):1138-1141.

7

Oral Leukoplakia

Niccolò Lombardi[1]
Elena Varoni[1]
Barbara Carey[2]
Giovanni Lodi[1]

1. Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi di Milano, Italy

2. Department of Oral Medicine, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

7.1. Definition

Several definitions have been suggested for oral leukoplakia (OL) and this has continuously evolved over the last 40 years (Table 7.1). The most recent and widely accepted definition was proposed by WHO Collaborating Centre for Oral Cancer in 2007 and re-confirmed in 2020. Leukoplakia is defined as 'A predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer' [1]. Another definition for OL was suggested in 2015 by van der Waal: 'A predominantly white patch or plaque that cannot be characterised clinically or pathologically as any other disorder; oral leukoplakia carries an increased risk of cancer development either in or close to the area of the leukoplakia or elsewhere in the oral cavity' [2].

Meeting	Definition
Denmark 1978	Leukoplakia now is defined as a white patch or plaque that cannot be characterised clinically or pathologically as any other disease, and again it must be emphasised that this use of the term is unrelated to the absence or presence of dysplasia
Malmo, Sweden 1983	Leukoplakia is a whitish patch or plaque that cannot be characterised clinically or pathologically as any other disease and it is not associated with any physical or chemical causative agent except the use of tobacco
Uppsala, Sweden 1994	Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion; some oral leukoplakias will transform into cancer.
London, UK* 2005	Leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer
Glasgow, UK* 2020	Leukoplakia is a predominantly white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer

Table 7.1. Definitions of leukoplakia as proposed by the meetings organised by the WHO Collaborating Centre for Oral Cancer UK*.

The term leukoplakia is used when any other condition of the oral mucosa that may present as a white lesion has been excluded (e.g. frictional keratosis, lichen planus, white sponge nevus, hairy leukoplakia etc.) [3]. By definition leukoplakia is a clinical entity, diagnosis by exclusion and it does not have a specific histopathological component [4].

7.2. Epidemiology and Risk Factors for Development of Oral Leukoplakia

Oral leukoplakia is commonly diagnosed in middle-aged to elderly patients. It is globally more commonly identified in males. OL is six times more common among smokers than non-smokers [5–8]. OL rarely occurs in the first two decades of life, and the condition is usually diagnosed after the fourth decade [5, 9].

OL may arise anywhere in the oral cavity and may be uni- or multifocal [1]. However, in Western industrialised populations, the most common sites of involvement are the lateral border of the tongue and floor of the mouth [5]. In Asian populations, due to the frequent consumption of betel quid, the buccal mucosa and the labial mucosa are often affected [5].

The prevalence of OL varies significantly with geographical variations due to different risk factors, such as betel nut chewing in South East Asia [6].

OL is one of the most common lesions included in the group of Oral Potentially Malignant Disorders (OPMDs) [10]. The pooled global prevalence of OL is estimated to be between 1.5% (95% confidence interval [CI], 1.4%–1.6%) and 2.6% (95%CI, 1.7%–2.7%) with no gender predilection in one systematic review [11, 12]. A recent systematic review on the prevalence of different types of OPMDs, reported a higher prevalence of 4.11% (95% CI = 1.98-6.97) [13]. Moreover, the prevalence of OL among Asian studies was estimated to be 7.77% (95% CI = 2.86-14.80), among South America and the Caribbean countries 3.32% (95% CI = 2.06-4.88), while in Europe 1.20% (95% CI = 0.57-2.06) [13]. The variation in prevalence of OL between the two reviews may be related to different methodology used in the inclusion criteria: diagnostic center-based populations are not ideal for investigating disease prevalence and most studies included in the most recent review included this cohort [13].

For this reason, the data should be interpreted with caution as it may differ from the real prevalence in the general population [13].

However, OL is associated with various risk factors, similar to those observed in oral cancer, such as tobacco (both smoked and smokeless), heavy alcohol consumption, betel quid chewing (especially in South Asian countries) and, for lesions involving the lip, ultraviolet (UV) light exposure [5, 10, 12, 14–16]. Alcohol consumption is an independent risk factor [5]. It has been established that these factors may have an aetiological role in the development of OL in more than 75% of the affected individuals [14]. Leukoplakias without a known cause are termed 'idiopathic leukoplakias' [1]. Moreover, immunosuppression (e.g. HIV/AIDS, post-organ transplantation), personal or family history of cancer (60%–70%) and selected syndromes (e.g. dyskeratosis congenita, Fanconi anaemia), may be considered risk factors for OL [5, 17, 18]. Leukoplakia which develops in a patient with no pre-disposing factors is considered to have un underlying genetic basis for development [5, 6, 8, 14]. Several studies have evaluated the role of human papillomavirus (HPV) in the development of OL and a possible correlation has been identified [5, 10, 19]. However, the aetiological role of HPV in OL and OSCC development remains controversial [15, 20].

7.3. Clinical Presentation

Clinically, leukoplakia show a wide range of variable features in appearance (white, red, and mixed white and red, plaque/plateau granular, atrophic) texture (smooth, corrugated, verrucous granular, soft, firm or hard), and size and shape [1, 7].

The clinical extension of oral leukoplakia may vary in size from a relatively small and well circumscribed lesion to extensive involving a large area of the oral mucosa [5].

Leukoplakia can be clinically sub-classified into two types: homogenous and non-homogenous. Figures 7.1 & 7.2.

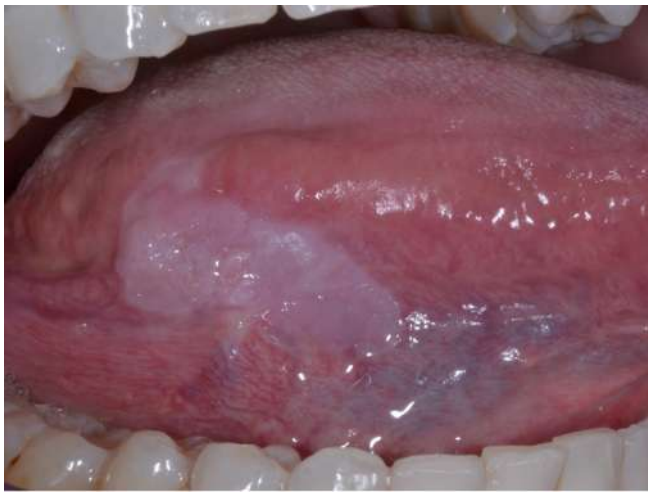

Figure 7.1. Homogenous Leukoplakia of the mid right lateral tongue.

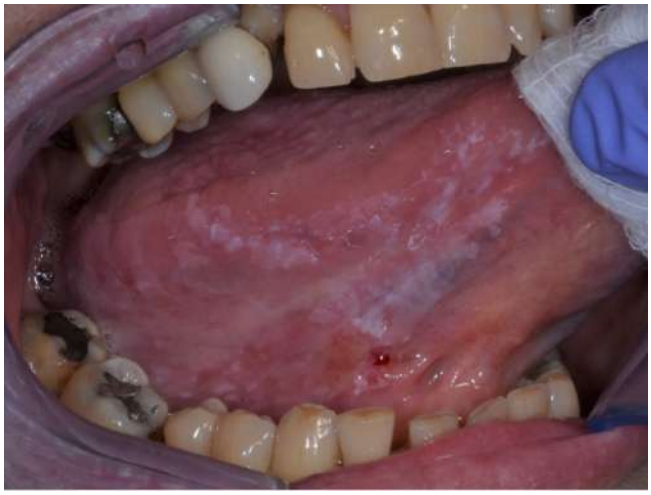

Figure 7.2. Non-homogenous leukoplakia involving the right lateral and ventral surfaces of the tongue.

This distinction is purely clinical, based on distinct features such as surface, colour and texture [1,21,22]: homogenous leukoplakia and non-homogenous leukoplakia (Table 7.2).

Oral Leukoplakia	
Homogenous leukoplakia	**Non-homogenous leukoplakia**
• Uniform flat and thin white plaque/patch with well-defined margins, smooth surface associated with shallow cracks/fissures. • Cannot be scraped off.	• *Speckled*: mixed white and red colour • *Nodular*: small polypoid outgrowths, rounded, red or white nodules • *Verrucous* or *exophytic:* wrinkled or corrugated surface. • Cannot be scraped off.

Table 7.2. Classification of the oral leukoplakia based on the distinct clinical features

Homogenous leukoplakia is characterised by a uniform flat and thin white plaque/patch with well-defined margins and smooth surface which may be associated with shallow cracks/fissures of the surface keratin [1, 5, 7, 10, 12, 17, 23]. Further illustrated in Figure 7.3.

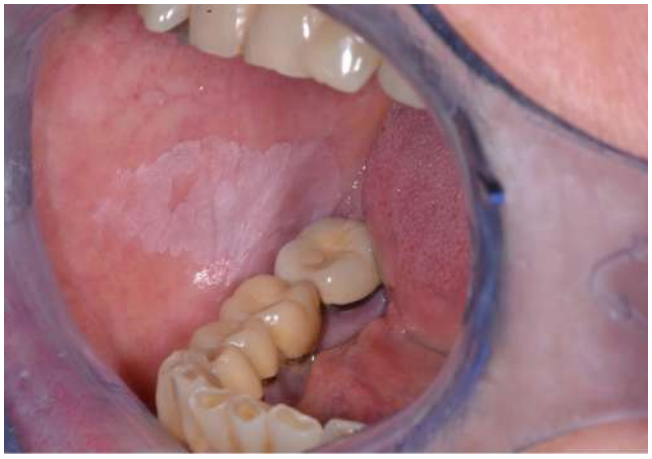

Figure 7.3. Homogenous Leukoplakia of the right buccal mucosa.

Non-homogenous leukoplakia is characterised by irregular texture, which can include focal superficial ulceration, and ill-defined margins [10, 12, 21, 23]. Non-homogenous leukoplakia may be associated with different clinical appearances used for their description [1, 5, 7, 10, 22]: Further illustrated in Figure 7.4 & 7.5.

- **Speckled:** mixed white and red colour but maintaining predominantly white coloration (also defined as erythroleukoplakia)
- **Nodular:** small polypoid projections, rounded, red or white excrescences
- **Verrucous** or **exophytic:** wrinkled or corrugated surface appearance

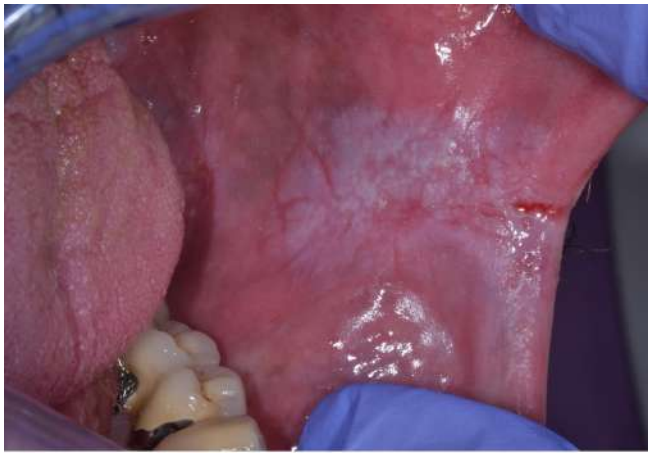

Figure 7.4. Non-homogenous leukoplakia with verrucous and nodular components affecting the left buccal mucosa.

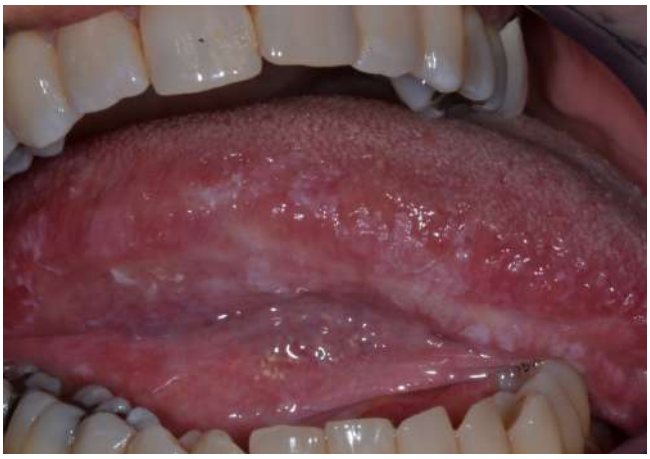

Figure 7.5. Non-homogenous leukoplakia involving the encompassing largely the right lateral tongue with more prominent keratotic areas seen, not exophytic.

The term **erythroleukoplakia** identifies lesions characterised by mixed white and red colour and it should not be confused with the term erythroplakia, which should only be used to describe lesions that are uniformly red [7]. In the proposed classification in 2007, erythroleukoplakias were considered a separate entity, but the consensus of the 2020 working group classified these lesions under the group of non-homogeneous leukoplakia [1,22].

Leukoplakias are generally asymptomatic and are often identified during routine general examination [5]. Homogenous leukoplakias are typically asymptomatic [1]. Symptoms are rare, and if present, are usually associated with the non-homogeneous forms which may show focal superficial ulceration [1, 5]. In these cases, the symptoms more frequently reported are discomfort, tingling, and sensitivity to touch, hot beverages, or spicy foods [5].

Oral **proliferative verrucous leukoplakia** (PVL), a subset of non-homogenous leukoplakia, may be defined as a distinct form of multifocal leukoplakia characterised by a progressive clinical course and changing in clinical appearance and histopathologic features [1, 12]. PVL may involve a single area, but is more frequently multifocal affecting the gingiva, buccal mucosa, and tongue in both contiguous and non-contiguous sites of the oral cavity [12, 22, 24]. PVL is more common in females with mean age of 70 years, and is usually not associated with tobacco smoking [12, 25].

The original report by Hansen et al. in 1985, coined the term PVL associated with the following definition; 'Leukoplakias that tend to spread and become multifocal. PVL is slow-growing, persistent, and irreversible, and in time areas become exophytic and wartlike' [15, 26].

The terms 'proliferative multifocal leukoplakia' and 'proliferative leukoplakia' have also been proposed in the literature [27,28]. The most recent definition, approved by WHO Collaborating Centre for Oral Cancer 2020, described PVL as a 'progressive, persistent, and irreversible disorder characterised by the presence of multiple leukoplakias that frequently become warty' [1].

Clinically, PVL often presents as one or more leukoplakias, eventually presenting in multiple locations with gradual spread of an individual focus or resulting from fusion over time of several adjacent foci [27]. Figure 7.6 illustrates mild PVL of the gingiva. Chapter 12 further elaborates on Proliferative Verrucous Leukoplakia

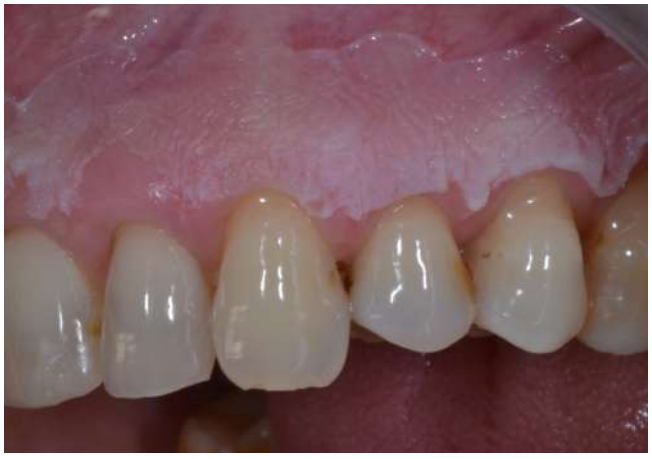

Figure 7.6. Mild Proliferative Verrucous leukoplakia involving the gingiva from the Upper left central incisor extending to and past the upper left first molar.

Risk of Cancer Onset

Oral squamous cell carcinoma is the most common neoplasia affecting the oral cavity [29,30]. OSCC typically affects males over 60 years, however, recently prevalence has increased in those younger than 40-years [30, 31]. OSCC may present as a non-healing ulcer, growing mass with irregular surface and red or white lesions of the oral epithelium [29, 30].

Leukoplakias are classified as oral potentially malignant disorders predisposing affected individuals to an increased risk of development of oral squamous cell carcinoma [30]. OL shows variable percentages of progression to OSCC, varying from 0% to 36.4% [16]. The annual rate of transformation ranged from 0.3% to 6.9% per year as reported by a recent review of observational studies [32].

Risk factors, which have shown statistical significance, for cancer development in individuals affected by OL are listed in table 4 [3,30,33,34]. Figure 7.7 illustrates a leukoplakia of the floor of mouth, considered a high risk site due to pooling of carcinogens.

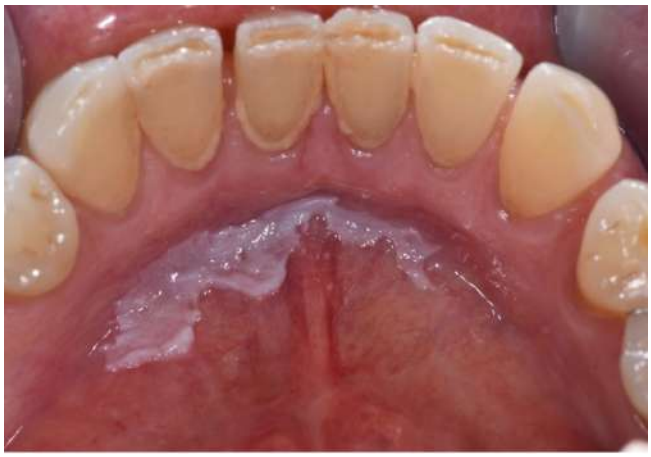

Figure 7.7. Largely Homogenous Leukoplakia of the floor of mouth.

Oral leukoplakia – Risk factor of malignant transformation
Non-homogeneous clinical appearance
Female gender
Long-standing leukoplakia
Idiopathic leukoplakia (non-smoking/non-drinking/non-chewing status)
Location: lateral tongue and/ or floor of the mouth
Size > 200 mm^2
Presence of epithelial dysplasia
Presence of Candida albicans (chronic hyperplastic candidosis or candida leukoplakia) [35]

Table 7.3. Risk factors of malignant transformation for oral leukoplakia.

Leukoplakias with different clinical, histological or molecular characteristics may have different risks of transforming into OSCC. It is difficult to compare data between studies because of the different locations and different methods of reporting malignant transformation [7].

Non-homogenous leukoplakias carry a higher risk of OSCC development compared to homogeneous leukoplakias [7,36]. One systematic review reported a malignant transformation rate of 1.36% per year [7, 11], while another calculated an overall transformation rate of 3% for homogeneous lesions and 14.5% for non-homogeneous lesions [32]. Others have reported non-homogeneous leukoplakias carry a 20-25% risk of cancer progression versus 0.6%–5% in homogeneous lesions [8, 17, 37].

It has been estimated that there is an approximately 7-fold increase risk for malignant development with non-homogeneous leukoplakia compared with homogeneous leukoplakia and a 5-fold increase in risk when the lesion size is greater than 200 mm^2 [4, 38, 39].

A systematic review reported that the buccal mucosa was the most common affected site (18.4% of lesions), however showed the lowest rate of progression to cancer (3.35%) [7, 32]. In this review, the tongue accounted for 16.14% of all lesions, however, was the most common site for malignant transformation (24.22%) [7, 32].

Non-smokers with OL localised to the floor of mouth presented a 38-fold increased risk of progression to cancer compared to smokers [40]. It is important to emphasise that idiopathic OL, which affect never smokers, may show a more aggressive clinical course [1]. The malignant transformation rates of idiopathic leukoplakia in non-smoking individuals are reportedly higher [32]. In Western populations, elderly females with long-standing idiopathic leukoplakia, with no risk factors, paradoxically, have an increased risk of progression to cancer probably due to an endogenous risk factor rather than environmental factors [1].

Redness in an OL lesion (non-homogeneous lesion) indicates potential colonisation by *Candida* species and also an increased risk for dysplasia and/or malignancy [5, 41].

The oral cancer incidence in the presence of oral dysplasia, has been reported in 6.6-36.4% of cases [42–44]. Less than 5% of the malignant transformation is associated with mild epithelial dysplasia whereas, with moderate and severe dysplasia, rates of 3-15% and 7-50% are reported, respectively [42, 45]. Oral epithelial dysplasia is widely evaluated with a three-tiered classification (mild, moderate and severe dysplasia) according to the presence and severity of cellular atypia and architectural features [46]. A new binary classification of low-grade and high-grade dysplasia has been developed for histopathological analysis of OL however this scale awaits validation [47].

The presence of epithelial dysplasia may be considered a risk factor for development of malignancy. The risk of cancer may increase with the severity of dysplastic changes and it is assumed that more severely dysplastic lesions have the greatest risk of transformation [48]. Oral epithelial dysplasia in non-smokers show a greater than 2-fold increase of progression to cancer [40].

The grade of dysplasia, is accepted a strong predictor of future malignant transformation in OL and remains the best aid to assess the risk of oral cancer development [5, 35, 43, 49]. Non- homogeneous leukoplakia more often exhibit severe dysplasia or superficially invasive OSCC at the time of baseline biopsy [31, 50, 51]. The risk of cancer development is closely related to the type of lesion and the grade of dysplasia [7, 17].

PVL is associated with a high malignant transformation rate compared with other OPMDs [17, 30, 52, 53]. A recent systematic review estimated the risk to be 49.5% (CI 26.7%-72.4%) [53]. Multiple primary carcinomas of gingival sites have also been documented in a case series of patients affected by PVL [25, 30, 54].

7.4. Diagnosis of Leukoplakia

A systematic intraoral examination, with palpation of cervical lymph nodes, is mandatory [5]. As described above, the term leukoplakia is a clinical diagnosis having excluded other clinically recognizable white or white/red lesions [15, 61].

The following criteria should be considered when making a clinical diagnosis of oral leukoplakia [1]:

- white patch/plaque that cannot be rubbed off
- does not disappear on retracting the tissue
- homogeneous leukoplakia usually has well-demarcated borders
- non-homogeneous leukoplakia often presents red or nodular components and more diffuse borders
- no evidence of related chronic traumatic irritation
- is not reversible on elimination of apparent traumatic causes
- exclusion of other white or white/red lesions

Carrard and van der Waal recently proposed a list of parameters, some of which are reported in the table, that may be relevant when establishing a clinical diagnosis of oral leukoplakia (Table 7.4) [9].

Feature	Role and relevance during the clinical diagnosis of oral leukoplakia
Age	OL rarely occurs in the first two decades of life.
Medical history	Important for the diagnosis of several leukoplakia-like diseases, such as oral manifestations of genodermatoses, syphilis and HIV-infection.
Tobacco habits of any type	More common in tobacco users
Symptoms	Most OL are asymptomatic, but pain or itching may occur.
Onset of the disease	OL arise slowly, over several months or years.
Course of the disease	Has a stable clinical course.
Morphology	
Size	Size is not relevant with regard to a clinical diagnosis of OL.
Color	The colour may vary from homogeneous white to a mixed white-and-red appearance.
Texture	The texture may vary from smooth, wrinkled to verrucous. Ulceration may be indicative of malignancy.
Induration	Palpation is a very important examination tool, induration being a sign of potential malinancy.

Table 7.4. A list of some features, modified from Carrard and van der Waal, which may be useful in the clinical diagnosis and assessment of leukoplakia.

Leukoplakia is a clinical term in which a clinicopathological correlation is necessary in order to establish a definitive diagnosis and prognosis [6]. OL is considered a provisional clinical diagnosis which can be made after excluding other disorders [1]. Though, the histopathological features of OL are not pathognomonic and are non-specific, the diagnosis and prognosis of OL and PVL is based on a combination of clinical and histological features [1, 26]. Several adjuncts, which evaluate tissue autofluorescence, have been proposed as a visual diagnostic aid for potentially malignant disorders and malignant lesions of the oral mucosa [59]. Optical fluorescence imaging may be an adjunct to complete oral examination in clinical settings, however, these devices should be considered as clinical adjuncts and not as diagnostic tool [60].

The gold standard procedure to confirm the clinical diagnosis of oral leukoplakia is to perform a representative incisional biopsy of the white patch lesion and send tissue for histopathological analysis [1, 17]. Diagnostic biopsy is mandatory to confirm or refute the diagnosis of OL. The biopsy, and the subsequent histopathological examination, allow one to exclude other pathologies which may present as a white patch and assess for candida colonisation within the epithelium [5]. Biopsy is necessary to exclude the diagnosis of oral squamous cell carcinoma (OSCC) and to evaluate the presence of and degree of epithelial dysplasia [5,6]. Histopathological findings associated with oral leukoplakia can range from simple epithelial hyperplasia with hyperparakeratosis or hyper(ortho) keratosis, the presence or absence of and degree of epithelial dysplasia [3, 55, 56].

Though a binary classification for oral dysplasia (low-grade and high-grade) has been proposed, the three-grade system (mild, moderate or severe) is still widely used in clinical practice around the world [15, 46, 47,57].

In order to achieve uniformity in classification and reporting, the WHO Collaborating Centre for Oral Cancer recommends the following pathology report as histopathological confirmed diagnosis of OL: 'keratosis with no / mild / moderate / severe dysplasia, consistent with oral leukoplakia' [1]. This minimizes misclassification and assists in the subsequent management and treatment decisions [15].

Microscopic examination also gives the opportunity to exclude the presence of malignancy as a small area of OSCC may be clinically difficult to identify, especially in white and red patches [1, 15].

In non-homogeneous OL and extensive PVL lesions, it is important to select the correct site (or sites) for incisional biopsy to avoid underdiagnosis. Histopathological examination may lead to variable results within the field of the same lesion [15].

Errors during biopsy procedures, often linked to taking samples from non-representative sites, may also contribute to misdiagnosis [15]. This common error may underestimate epithelial dysplasia or miss a diagnosis of squamous cell carcinoma [15].

Therefore, in non-homogeneous white and red patches, multiple incisional biopsies may be indicated to achieve complete mapping of the lesion [1, 5, 15]. Multiple and periodic mapping biopsies may be indicated in PVLs to detect different grades of dysplasia or OSCC [12, 18]. However, it must be noted that multiple and frequent biopsy may alter the natural history of the disease and interventions may significantly increase the chances of developing a malignancy. In non-homogeneous OL and PVL, approximately 10%–17% of cases may be missed by undertaking only a single biopsy [12, 50, 58].

7.5. Differential Diagnosis of White Patches

During clinical examination of a white lesion, it is important to evaluate any potential local traumatic causes and, if identified, the white patch should be designated as frictional keratosis [1]. Frictional keratosis is not regarded an OPMD and on removing the putative frictional source, they should resolve [1].

In the following table is a detailed list of the most relevant white lesions and disorders which should be excluded prior to making a clinical diagnosis of oral leukoplakia (Table 7.5) [1, 9, 15].

Differential diagnosis with OL	Description
White sponge nevus	Noted in early life, often family history, bilateral presentation, often extensive in the mouth, genital mucosa may be affected.
Linea alba	The diagnosis is clinical, almost always bilateral along the plan of occlusion
Leukoedema	Clinical diagnosis of a bilateral veil-like aspect on buccal mucosa, and disappears stretching the tissues. Predilection among some racial groups: middle-aged dark-skinned people.
Fordyce's spots/ granules	1-2mm diameter spots/papules distinctly demarcated from the normal surrounding lining mucosa, elevated, circular, white or yellow-white in color
Morsicatio buccarum	A condition characterised by chronic irritation or injury to the buccal mucosa, commissures or cheeks, caused by habitual and repetitive chewing or biting. Irregular whitish-yellowish flakes with jagged out line are observed; often bilateral.
Frictional keratosis	Positive clinical history for friction or other mechanical trauma. Mostly reversible after removal of the etiological cause.
Keratotic lesions	Include: reversed smoking keratosis, alveolar ridge keratosis (ARK), frictional keratosis, sanguinaria-associated keratosis, tobacco pouch keratosis and keratosis of unknown significance (KUS). Reversed smoking keratosis and tobacco pouch keratosis have malignant potential.
Chemical injury	History of prolonged exposure to a chemical agent (e.g. an aspirin tablet) or to a caustic agent (e.g. sodium hypochlorite). The lesion is painful, but usually it resolves rapidly
Nicotinic stomatitis (smoker's palate)	Greyish-white palate with red spots related to inflamed minor salivary glands. Usually, a clinical diagnosis associated with smoking history.
Uremic stomatitis	White, sharply demarcated, adherent plaques of fibrinous exudate with some desquamated epithelial cells. Diagnosis is associated with positive history for renal disease.

Differential diagnosis with OL	Description
Actinic cheilitis	Inferior lip is the most affected area with white lesion. The typical clinical presentation may vary and leukoplakia-like changes may occur.
Oral lichen planus (OLP)	In the typical forms white papules are joined up with lines to form a reticular appearance on the surface of variably inflamed mucosa. Often bilateral presentation. OLP may also present as desquamative gingivitis. Several clinical subtypes of lichen planus may occur: • Reticular: lace-like white lines • Linear, annular, papular: various presentations as lines, ring-like or white dots • Plaque-type: white patch with striae at margins • Atrophic, and ulcerative: red and frankly ulcerated • Bullous: vesicular OLP plaque-type may be very difficult to distinguish from oral leukoplakia. OLP is included in the group of oral potentially malignant disorders [1]
Direct contact lichenoid lesion	Caused by prolonged direct contact of the oral mucosa with an amalgam or other types of restoration. The lesion should disappear in an arbitrarily chosen period of 2-3 months after removal of the restoration.
Acute pseudomembranous Candidiasis	Generally widespread infection of oral, and sometimes oropharyngeal mucosa. The white membrane can be scraped off sometimes revealing an erythematous/raw footprint. Associated with local (e.g. inhaled spray steroids) or systemic (e.g. immunodeficiency) underlying causes
Chronic hyperplastic candidiasis (Candidal Leukoplakia)	An adherent white or white and red patch caused by a chronic fungal infection, usually Candida albicans. Mainly located in the retro-commissures area, often bilateral. Antifungal treatment is used for evaluate regression of the lesions and establish the diagnosis.
Hairy leukoplakia	Keratosis with vertical streaking, caused by opportunistic Epstein Bar virus, which is often bilateral and most common on the lateral borders of the tongue. History of immunosuppression for HIV-disease or drugs (e.g. after organ transplantation/long term steroids).
Syphilis, secondary	The diagnosis should evaluate the medical history and demonstrate serology positivity for Treponema Pallidum. The clinical presentation may be various: • multiple 'mucous patches' • whitish lichenoid and leukoplakia-like changes of the oral mucosa • multiple red lesions on the dorsal tongue and palate
Papilloma and HPV-related lesions (e.g. condyloma acuminatum, multifocal epithelial hyperplasia, verruca vulgaris)	The diagnosis is based on the clinical appearance of the lesions and on the medical history. A biopsy, associated with HPV typing, is usually helpful

Table 7.5. A detailed list of the main white lesions, conditions or diseases that should be excluded before making a clinical diagnosis of oral leukoplakia (modified by [1,9]).

Misdiagnosis and misclassification of leukoplakias have made data reporting regarding prevalence and malignant transformation of OL difficult [1, 62]. Misclassifying a 'frictional keratosis' as a 'leukoplakia' may generate confusion and could lead to underestimated malignant transformation rate of real OL.

The term keratosis is often misused to clinically describe a white lesion. A number of oral lesions exist with 'keratosis' in their name [1]:

- *Tobacco pouch keratosis:* It is a white patch found on the lower buccal mucosa related to the use of smokeless tobacco which is retained for long period in the same site [63]. The discontinuation of the habit often leads to resolution of the lesion. However, those patients who persist in the smokeless tobacco habit, should be included within the group of oral leukoplakias. An incisional biopsy is usually indicated at baseline [1].
- *Sublingual keratosis:* This term was used by Kramer's group for describe a white patch localised on the floor of the mouth or at inferior surface of the tongue [64]. Any white patch on the floor of mouth should be clinically considered a leukoplakia and warrants careful follow-up [1].
- *Sanguinaria-associated keratosis:* This form of a white patch is related to the use of a dentifrice and/or mouth rinse containing the herbal additive sanguinaria (now banned) [65]. It is not considered a leukoplakia because it has a well-established cause and resolves with discontinuation of the causative agent [1].
- *Palatal keratosis in reverse smokers:* This condition is associated to reverse smoking, a particular practice in which the burning end of a cigarette or cigar is held inside the mouth. It is classified as a separate entity and is not considered as a leukoplakia [1]. This condition has a high risk of malignant transformation. It was first described in 1980 by Gupta et al. as thickened white plaques involving the palate, with mucosal nodularity, excrescences around orifices of minor salivary glands, yellowish brown staining, erythema and ulceration. Lesions may present as red, white or mixed red and white, on a background of tobacco staining [66]. A more recent study on reverse smokers identified 32% of subjects affected by white and red patches on the palate [67].
- *Keratosis of unknown significance (KUS):* This term refers not to a specific clinical context, but to an histological picture of hyperkeratosis with minimal to no epithelial dysplasia or cellular atypia [68, 69]. The use of this term is not recommended [1].

7.6. Management

The primary aim in the management of oral leukoplakia should be to monitor and prevent the oral cancer onset. In a shared attempt to reduce the chances of cancer development, a number of different treatments and management protocols have been proposed [3, 70]. The main approaches in the management of OL can be divided into three groups:

- medical treatment (topical or systemic)
- clinical observation (leave and review); no intervention but strict clinical and histological surveillance)
- surgery: performed with different techniques (scalpel, laser surgery (excision and vaporization, cryosurgery)

There is no consensus on the most appropriate approach for OL [71, 72].

Medical Treatment

None of the medical and complementary treatments studied (vitamin A, beta carotene, bleomycin) have been shown to be effective in preventing cancer onset in individuals with OL [3]. Several studies on chemo-prevention have also shown considerable toxicity of the drugs used [73]. Medical treatment of leukoplakia may be effective in reducing or resolving oral leukoplakia in the short term, but have been associated with a high risk of relapse [73, 74].
The use of chemo-preventive methods in clinically controlled trials have yet to show their effectiveness in the prevention of malignant transformation and of subsequent recurrence [75].

Wait and see (Leave and Review) approach

Another approach may be to keep a leukoplakia under strict clinical and histological surveillance, with frequent clinic visits (examination) and biopsies with the aim to detect malignant transformation as early as possible, thus providing the best possible prognosis [70].

This approach is based on the concept of 'field cancerization', proposed by Slaughter in 1957 whereby if a carcinogen has led to a clinically detectable premalignant or malignant change in one part of the oral cavity, there is equal risk to other parts of the oral cavity because of a field effect [76]. OL can be considered an indicator of risk for the whole oral mucosa rather than for a site-specific area [21].

A recent RCT evaluated the effectiveness of surgical excision, compared with standard care in the prevention of OSCC in 260 subjects with non-dysplastic OL. Two patients, one in each arm, developed OSCC and the authors concluded regular clinical follow-up could be considered a reliable standard of care among patients with non-dysplastic OLs [77].

Surgery

A single Randomised Controlled Trial (RCT) exists, which compared the effect of surgical excision versus no treatment or placebo [3, 77]. Despite this, surgical treatments are, for most clinicians, are the treatment of choice in the management of oral leukoplakia [3]. Surgical excision is frequently performed and there is some evidence to suggest that this reduces the risk of malignant transformation when compared with active surveillance [78]. Only data from observational studies has compared rates of cancer incidence in people who did or did not undergo surgical treatment for oral leukoplakias with differences in diagnostic and inclusion criteria, follow-up intervals, participant characteristics and surgical techniques employed. These studies showed highly variable results and were conflicting in their conclusions [79].

The largest longitudinal study investigating severe dysplasia showed that surgical removal of the severe dysplasia significantly reduced the progression into cancer [80]. There is little controversy regarding the need for intervention in high-grade dysplastic lesions, however the opinion on management of low or medium-grade dysplasia [81] still differs.

Some dysplastic areas are extensive or involve multiple sites, or even the whole oral mucosa, therefore, excision would be impractical [25, 82] Excision without reconstruction causes harm, and is probably why many clinicians choose regular observation and biopsy, or laser ablation as an alternative to excision [82].

Laser ablation vaporizes the dysplastic area and causes less scarring than excision, but does not provide tissue for histological assessment [82].

Surgical intervention with cold knife excision and/ or CO_2 laser is usually performed for non-homogeneous leukoplakia or erythroplakia that are associated with moderate to severe dysplasia [3, 83, 84].

Summary

Surgery remains the treatment option favored by most, however the efficacy of surgery compared with regular clinical observation has not been assessed in RCTs for prevention of cancer development [3]. To date, just one RCT compared surgical treatments to no treatment. In the absence of robust RCTs, clinical practice continues to vary [3, 18, 21, 36, 82].

References

1. Warnakulasuriya, S.; Kujan, O.; Aguirre-Urizar, J.M.; Bagan, J. V.; González-Moles, M.Á.; Kerr, A.R.; Lodi, G.; Mello, F.W.; Monteiro, L.; Ogden, G.R.; 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, odi.13704,.
2. van der Waal, I. Oral leukoplakia, the ongoing discussion on definition and terminology. Med. Oral Patol. Oral Cir. Bucal 2015, 20, e685–e692, .
3. Lodi, G.; Franchini, R.; Warnakulasuriya, S.; Varoni, E.M.; Sardella, A.; Kerr, A.R.; Carrassi, A.; Macdonald, L.C.I.; Worthington, H. V. Interventions for treating oral leukoplakia to prevent oral cancer. Cochrane Database Syst. Rev. 2016.
4. Amagasa, T.; Yamashiro, M.; Uzawa, N. Oral premalignant lesions: From a clinical perspective. Int. J. Clin. Oncol. 2011, 16, 5–14.
5. Warnakulasuriya, S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 125, 582–590.
6. Staines, K.; Rogers, H. Oral leukoplakia and proliferative verrucous leukoplakia: A review for dental practitioners. Br. Dent. J. 2017.
7. Speight, P.M.; Khurram, S.A.; Kujan, O. Oral potentially malignant disorders: risk of progression to malignancy. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 25(6):612-627.
8. Napier, S.S.; Speight, P.M. Natural history of potentially malignant oral lesions and conditions: An overview of the literature. J. Oral Pathol. Med. 2008, 37, 1–10.
9. Carrard, V.; van der Waal, I. A Clinical Diagnosis of Oral Leukoplakia . Med Oral Patol Oral Cir Bucal 2018, 23(1):e59-e64
10. Sundberg, J.; Korytowska, M.; Holmberg, E.; Bratel, J.; Wallström, M.; Kjellström, E.; Blomgren, J.; Kovács, A.; Öhman, J.; Sand, L.; et al. Recurrence rates after surgical removal of oral leukoplakia-A prospective longitudinal multicentre study. PLoS One 2019, 14.
11. Petti, S. Pooled estimate of world leukoplakia prevalence: A systematic review. Oral Oncol. 2003, 39, 770–780.
12. Villa, A.; Sonis, S. Oral leukoplakia remains a challenging condition. Oral Dis. 2018, 24, 179–183.
13. Mello, F.W.; Miguel, A.F.P.; Dutra, K.L.; Porporatti, A.L.; Warnakulasuriya, S.; Guerra, E.N.S.; Rivero, E.R.C. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J. Oral Pathol. Med. 2018, 47, 633–640.

14. Jayasooriya, P.R.; Dayaratne, K.; Dissanayake, U.B.; Warnakulasuriya, S. Malignant transformation of oral leukoplakia: a follow-up study. Clin. Oral Investig. 2020, 24(12):4563-4569.
15. Warnakulasuriya, S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral Oncol. 2020, 102.
16. Arduino, P.; Bagan, J.; El-Naggar, A.; Carrozzo, M. Urban legends series: Oral leukoplakia. Oral Dis. 2013, 19, 642–659.
17. Villa, A.; Celentano, A.; Glurich, I.; Borgnakke, W.S.; Jensen, S.B.; Peterson, D.E.; Delli, K.; Ojeda, D.; Vissink, A.; Farah, C.S. World Workshop on Oral Medicine VII: Prognostic biomarkers in oral leukoplakia: A systematic review of longitudinal studies. Oral Dis. 2019, 25, 64–78.
18. Villa, A.; Woo, S. Bin Leukoplakia—A Diagnostic and Management Algorithm. J. Oral Maxillofac. Surg. 2017, 75, 723–734.
19. Syrjänen, S.; Lodi, G.; von Bültzingslöwen, I.; Aliko, A.; Arduino, P.; Campisi, G.; Challacombe, S.; Ficarra, G.; Flaitz, C.; Zhou, H.; et al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: A systematic review. Oral Dis. 2011, 17, 58–72.
20. Varoni, E.M.; Lombardi, N.; Franchini, R.; D'Amore, F.; Noviello, V.; Cassani, B.; Moneghini, L.; Sardella, A.; Lodi, G. Oral Human Papillomavirus (HPV) and sexual behaviors in a young cohort of oral cancer survivors. Oral Dis. 2020, 27(4):919-923.
21. Awadallah, M.; Idle, M.; Patel, K.; Kademani, D. Management update of potentially premalignant oral epithelial lesions. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 125, 628–636.
22. Warnakulasuriya, S.; Johnson, N.W.; Van Der Waal, I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J. Oral Pathol. Med. 2007, 36, 575–580.
23. van der Waal, I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. Oral Oncol. 2010, 46, 423–425.
24. Pentenero, M.; Meleti, M.; Vescovi, P.; Gandolfo, S. Oral proliferative verrucous leucoplakia: Are there particular features for such an ambiguous entity? A systematic review. Br. J. Dermatol. 2014, 170, 1039–1047.
25. Lombardi, N.; D'amore, F.; Elli, C.; Pispero, A.; Moneghini, L.; Franchini, R. Gingival lesion in proliferative verrucous leukoplakia. Dent. Cadmos 2020, 88, 647–648.
26. Hansen, L.S.; Olson, J.A.; Silverman, S. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surgery, Oral Med. Oral Pathol. 1985, 60(3):285-98.
27. Villa, A.; Menon, R.S.; Kerr, A.R.; De Abreu Alves, F.; Guollo, A.; Ojeda, D.; Woo, S.B. Proliferative leukoplakia: Proposed new clinical diagnostic criteria. Oral Dis. 2018, 24, 749–760.
28. Aguirre-Urizar, J.M. Proliferative multifocal leukoplakia better name that proliferative verrucous leukoplakia. World J. Surg. Oncol. 2011, 9.
29. Lombardi, N.; Varoni, E.M.; Moneghini, L.; Lodi, G. Submucosal oral squamous cell carcinoma of the tongue. Oral Oncol. 2020, 105121.
30. Lodi, G.; Tarozzi, M.; Baruzzi, E.; Costa, D.; Franchini, R.; D'Amore, F.; Carassi, A.; Lombardi, N. Odontoiatria e cancro della bocca: dai fattori di rischio alla riabilitazione - Modulo 1: Epidemiologia e fattori di rischio. Dent. Cadmos 2021, 89, 01.
31. Lombardi, N.; Sorrentino, D.; D'amore, F.; Moneghini, L.; Franchini, R.; Sardella, A. Oral erythroleukoplakia on the lateral border of the tongue in a young patient. Dent. Cadmos 2020, 88, 277–278.
32. Warnakulasuriya, S.; Ariyawardana, A. Malignant transformation of oral leukoplakia: A systematic review of observational studies. J. Oral Pathol. Med. 2016, 45, 155–166.
33. Ho, M.W.; Risk, J.M.; Woolgar, J.A.; Field, E.A.; Field, J.K.; Steele, J.C.; Rajlawat, B.P.; Triantafyllou, A.; Rogers, S.N.; Lowe, D.; et al. The clinical determinants of malignant transformation in oral epithelial dysplasia. Oral Oncol. 2012, 48, 969–976.
34. Field, E.A.; McCarthy, C.E.; Ho, M.W.; Rajlawat, B.P.; Holt, D.; Rogers, S.N.; Triantafyllou, A.; Field, J.K.; Shaw, R.J. The management of oral epithelial dysplasia: The Liverpool algorithm. Oral Oncol. 2015, 51, 883–887.
35. van der Waal, I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol. 2009.
36. Diz P, Gorsky M, Johnson NW, Kragelund C, Manfredi M, Odell E, et al. Oral leukoplakia and erythroplakia: a protocol for diagnosis and management. EAOM – Diagnostic Ther. Protoc. 2011, 1, 1-8.
37. Van der Waal, I.; Axéll, T. Oral leukoplakia: A proposal for uniform reporting. Oral Oncol. 2002, 38, 521–526.
38. Reddi, S.P.; Shafer, A.T. Oral Premalignant Lesions: Management Considerations. Oral Maxillofac. Surg. Clin. North Am. 2006, 18, 425–433.
39. Pereira, J.D.S.; Carvalho, M.D.V.; Henriques, Á.C.G.; De Queiroz Camara, T.H.; Miguel, M.C.D.C.; Freitas, R.D.A. Epidemiology and correlation of the clinicopathological features in oral epithelial dysplasia: Analysis of 173 cases. Ann. Diagn. Pathol. 2011, 15, 98–102.
40. Rock, L.D.; Rosin, M.P.; Zhang, L.; Chan, B.; Shariati, B.; Laronde, D.M. Characterization of epithelial oral dysplasia in non-smokers: First steps towards precision medicine. Oral Oncol. 2018, 78, 119–125.
41. Dilhari, A.; Weerasekera, M.M.; Siriwardhana, A.; Maheshika, O.; Gunasekara, C.; Karunathilaka, S.; Nagahawatte, A.; Fernando, N. Candida infection in oral leukoplakia: an unperceived public health problem. Acta Odontol. Scand. 2016, 74, 565–569.
42. Speight, P.M. Update on oral epithelial dysplasia and progression to cancer. Head Neck Pathol. 2007, 1, 61–66.
43. Warnakulasuriya, S.; Kovacevic, T.; Madden, P.; Coupland, V.H.; Sperandio, M.; Odell, E.; Møller, H. Factors predicting malignant transformation in oral potentially malignant disorders among patients accrued over a 10-year period in South East England. J. Oral Pathol. Med. 2011, 40, 677–683.
44. Arduino, P.G.; Surace, A.; Carbone, M.; Elia, A.; Massolini, G.; Gandolfo, S.; Broccoletti, R. Outcome of oral dysplasia: A retrospective hospital-based study of 207 patients with a long follow-up. J. Oral Pathol. Med. 2009, 38, 540–544.
45. Watabe, Y.; Nomura, T.; Onda, T.; Yakushiji, T.; Yamamoto, N.; Ohata, H.; Takano, N.; Shibahara, T. Malignant transformation of oral leukoplakia with a focus on low-grade dysplasia. J. Oral Maxillofac. Surgery, Med. Pathol. 2016, 28, 26–29.
46. Kujan, O.; Oliver, R.J.; Khattab, A.; Roberts, S.A.; Thakker, N.; Sloan, P. Evaluation of a new binary system of grading oral epithelial dysplasia for prediction of malignant transformation. Oral Oncol. 2006, 42(10):987-93.
47. El-Naggar A.K., Chan J.K.C., Grandis J.R., Takata T., S.P.J. WHO classification of Head and Neck tumors; 4th ed.; IARC Press: Lyon, 2017; ISBN 9789283224372.
48. Thomson, P. Oral Precancer; Thomson, P., Ed.; John Wiley & Sons, Ltd.: West Sussex, UK, 2012; ISBN 9781118702840.
49. Warnakulasuriya, S.; Reibel, J.; Bouquot, J.; Dabelsteen, E. Oral epithelial dysplasia classification systems: Predictive value, utility, weaknesses and scope for improvement. J. Oral Pathol. Med. 2008, 37, 127–133.
50. Pentenero, M.; Carrozzo, M.; Pagano, M.; Galliano, D.; Broccoletti, R.; Scully, C.; Gandolfo, S. Oral mucosal dysplastic lesions and early squamous cell carcinomas: Underdiagnosis from incisional biopsy. Oral Dis. 2003, 9, 68–72.
51. Lee, J.J.; Hung, H.C.; Cheng, S.J.; Chen, Y.J.; Chiang, C.P.; Liu, B.Y.; Jeng, J.H.; Chang, H.H.; Kuo, Y.S.; Lan, W.H.; et al. Carcinoma and dysplasia in oral leukoplakias in Taiwan: Prevalence and risk factors. Oral Surgery, Oral Med. Oral Pathol. Oral Radiol. Endodontology 2006, 101, 472–480,.
52. Cabay, R.J.; Morton, T.H.; Epstein, J.B. Proliferative verrucous leukoplakia and its progression to oral carcinoma: A review of the literature. J. Oral Pathol. Med. 2007, 36, 255–261.
53. Iocca, O.; Sollecito, T.P.; Alawi, F.; Weinstein, G.S.; Newman, J.G.; De Virgilio, A.; Di Maio, P.; Spriano, G.; Pardiñas López, S.; Shanti, R.M. 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.
54. Bagan, J.; Murillo-Cortes, J.; Poveda-Roda, R.; Leopoldo-Rodado, M.; Bagan, L. Second primary tumors in proliferative verrucous leukoplakia: a series of 33 cases. Clin. Oral Investig. 2020, 24, 1963–1969.
55. Reibel, J.; Gale, N.; Hille, J.; Hunt, J.; Lingen, M.; Muller, S.; Sloan, P.; Tilakaratne, W.; Westra, W.; Williams, M.; et al. Oral potentially malignant disorders and oral epithelial dysplasia. In WHO classification of head and neck tumours; IARC, Ed.; Lyon France, 2017; pp. 112–115 ISBN 9789283224389.

56. Ranganathan, K.; Kavitha, L. Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders. J. Oral Maxillofac. Pathol. 2019, 23, 19–27.
57. Barnes, L.; Eveson, J.W.; Reichart, P.; Sidransky, D. World Health Organization Classification of Tumours. Pathology & Genetics. Head and Neck Tumours. International Agency for Research on Cancer (IARC). WHO Classif. Tumours (3rd Ed. 2005, 177–80.
58. Lee, J.J.; Hung, H.C.; Cheng, S.J.; Chiang, C.P.; Liu, B.Y.; Yu, C.H.; Jeng, J.H.; Chang, H.H.; Kok, S.H. Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions. Oral Surgery, Oral Med. Oral Pathol. Oral Radiol. Endodontology 2007, 104, 217–225,.
59. Meleti, M.; Giovannacci, I.; Vescovi, P.; Pedrazzi, G.; Govoni, P.; Magnoni, C. Histopathological determinants of autofluorescence patterns in oral carcinoma. Oral Dis. 2020, (in press).
60. Tiwari, L.; Kujan, O.; Farah, C.S. Optical fluorescence imaging in oral cancer and potentially malignant disorders: A systematic review. Oral Dis. 2020.
61. Warnakulasuriya, S. White, red, and mixed lesions of oral mucosa: A clinicopathologic approach to diagnosis. Periodontol. 2000 2019, 80, 89–104.
62. Auluck, A.; Pai, K.M. (Mis)interpretations of leukoplakia. J. Can. Dent. Assoc. (Tor). 2005, 71(4):237-8.
63. Müller, S. Frictional Keratosis, Contact Keratosis and Smokeless Tobacco Keratosis: Features of Reactive White Lesions of the Oral Mucosa. Head Neck Pathol. 2019, 13, 16–24.
64. Kramer, I.R.; El, L.; Lee, K.W. The clinical features and risk of malignant transformation in sublingual keratosis. Br. Dent. J. 1978, 144, 171–180.
65. Eversole, L.R.; Eversole, G.M.; Kopcik, J. Sanguinaria-associated oral leukoplakia: Comparison with other benign and dysplastic leukoplakic lesions. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 2000, 89, 455–464.
66. Gupta, P.C.; Mehta, F.S.; Daftary, D.K. Incidence rates of oral cancer and natural history of oral precancerous lesions in a 10-year follow-up study of Indian villagers. Community Dent. Oral Epidemiol. 1980, 8, 287–333.
67. Sreenivasa Bharath, T.; Govind Raj Kumar, N.; Nagaraja, A.; Saraswathi, T.R.; Suresh Babu, G.; Ramanjaneya Raju, P. Palatal changes of reverse smokers in a rural coastal Andhra population with review of literature. J. Oral Maxillofac. Pathol. 2015, 19, 182–187.
68. Woo, S. Bin; Grammer, R.L.; Lerman, M.A. Keratosis of unknown significance and leukoplakia: A preliminary study. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2014, 118, 713–724.
69. Villa, A.; Hanna, G.J.; Kacew, A.; Frustino, J.; Hammerman, P.S.; Woo, S. Bin Oral keratosis of unknown significance shares genomic overlap with oral dysplasia. Oral Dis. 2019, 25, 1707–1714.
70. Lodi, G.; Porter, S. Management of potentially malignant disorders: Evidence and critique. J. Oral Pathol. Med. 2008, 37, 63–69.
71. Kanatas, A.N.; Fisher, S.E.; Lowe, D.; Ong, T.K.; Mitchell, D.A.; Rogers, S.N. The configuration of clinics and the use of biopsy and photography in oral premalignancy: A survey of consultants of the British Association of Oral and Maxillofacial Surgeons. Br. J. Oral Maxillofac. Surg. 2011, 49, 99–105.
72. Kumar, A.; Cascarini, L.; McCaul, J.A.; Kerawala, C.J.; Coombes, D.; Godden, D.; Brennan, P.A. How should we manage oral leukoplakia? Br. J. Oral Maxillofac. Surg. 2013, 51, 377–383.
73. Dionne, K.R.; Warnakulasuriya, S.; Zain, R.B.; Cheong, S.C. Potentially malignant disorders of the oral cavity: Current practice and future directions in the clinic and laboratory. Int. J. Cancer 2015, 136, 503–515.
74. Diajil, A.; Robinson, C.M.; Sloan, P.; Thomson, P.J. Clinical Outcome Following Oral Potentially Malignant Disorder Treatment: A 100 Patient Cohort Study. Int. J. Dent. 2013, 2013, 1–8.
75. Ribeiro, A.S.; Salles, P.R.; da Silva, T.A.; Mesquita, R.A. A Review of the Nonsurgical Treatment of Oral Leukoplakia. Int. J. Dent. 2010, 2010, 1–10.
76. Jaiswal, G.; Jaiswal, S.; Kumar, R.; Sharma, A. Field cancerization: concept and clinical implications in head and neck squamous cell carcinoma. J. Exp. Ther. Oncol. 2013, 10(3):209-14.
77. Arduino, P.G.; Lodi, G.; Cabras, M.; Macciotta, A.; Gambino, A.; Conrotto, D.; Karimi, D.; El Haddad, G.; Carbone, M.; Broccoletti, R. A Randomised Controlled Trial on Efficacy of Surgical Excision of non-dysplastic Leukoplakia to Prevent Oral Cancer. Cancer Prev. Res. 2020, canprevres.0234.2020, 14(2):275-284.
78. Mehanna, H.M.; Rattay, T.; Smith, J.; McConkey, C.C. Treatment and follow-up of oral dysplasia - A systematic review and meta-analysis. Head Neck 2009, 31(12):1600-9.
79. Saito, T.; Sugiura, C.; Hirai, A.; Notani, K.I.; Totsuka, Y.; Shindoh, M.; Fukuda, H. Development of squamous cell carcinoma from pre-existent oral leukoplakia: With respect to treatment modality. Int. J. Oral Maxillofac. Surg. 2001, 30, 49–53.
80. Zhang, L.; Lubpairee, T.; Laronde, D.M.; Rosin, M.P. Should severe epithelial dysplasia be treated? Oral Oncol. 2016, 60, 125–129.
81. Balasundaram, I.; Payne, K.F.B.; Al-Hadad, I.; Alibhai, M.; Thomas, S.; Bhandari, R. Is there any benefit in surgery for potentially malignant disorders of the oral cavity? J. Oral Pathol. Med. 2014.
82. Thomson, P.J.; McCaul, J.A.; Ridout, F.; Hutchison, I.L. To treat...or not to treat? Clinicians' views on the management of oral potentially malignant disorders. Br. J. Oral Maxillofac. Surg. 2015, 53, 1027–1031.
83. Kuribayashi, Y.; Tsushima, F.; Morita, K.; Matsumoto, K.; Sakurai, J.; Uesugi, A.; Sato, K.; Oda, S.; Sakamoto, K.; Harada, H. Long-term outcome of non-surgical treatment in patients with oral leukoplakia. Oral Oncol. 2015, 51, 1020–1025.
84. Mogedas-Vegara, A.; Hueto-Madrid, J.A.; Chimenos-Küstner, E.; Bescós-Atín, C. Oral leukoplakia treatment with the carbon dioxide laser: A systematic review of the literature. J. Cranio-Maxillofacial Surg. 2016, 44(4):331-6.

8

Oral Erythroplakia

Vignesh Eswara Murthy[1]
Barbara Carey[1]
Rui Albuquerque[1,2]

1. Department of Oral Medicine. Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom.

2. Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

8.1. Definition

The World Health Organisation (WHO) originally defined erythroplakia as 'any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterised clinically or pathologically as any other recognizable condition' [1]. There is no universally accepted definition of oral erythroplakia, however, the majority of modern definitions, are more or less reductive of the original WHO definition. The most frequently used definition in the literature described as oral erythroplakia as a 'a fiery red patch that cannot be characterised clinically or pathologically as any other definable lesion' (Pindborg et al., 1977). The majority of definitions are based upon the principle that the diagnosis of erythroplakia is by exclusion, similar to definitions used to describe oral leukoplakia (OL) [2]. Defining the condition on this principle, similarly to OL, is considered inadequate, as the above definitions provide no commentary on the condition's aetiology and histopathology or describe the premalignant potential of erythroplakia.

Additional terminology such as erythroleukoplakia, leukoerythroplakia and speckled erythroplakia, have been used to describe a mixture of red and white patches [2]. Some authors have described erythroplakia as a deficient description, as clinically the condition does not present with plaques and often presents with a depression of the surrounding mucosa, when compared to leukoplakia. The term 'erosive leukoplakia' has also been used [2]. Reichart and Philipsen, in 2005, first described 'true' erythroplakia lesions as homogenous, adding another possible term to the growing list of descirptors, without a global consensus on the correct terminology [2].

There is much deliberation in the literature regarding the adequacy of the existing definitions and terminology surrounding erythroplakia. However, it is worth noting, the mostly widely used definition is that by Pindborg et al and the most widely used and accepted term [4].

The first description of erythroplakia is not well reported. A correlation between erythroplakia and oral cancer development was not documented until the 1960s [3, 4].

8.2. Aetiopathogenesis

Several studies have mentioned many of the main aetiological factors in oral cancer as contributory or aetiological factors in the development of erythroplakia. It has been observed that these factors are contributory to the malignant transformation of erythroplakia, however, their role in the aetiopathogenesis of erythroplakia is poorly understood. These factors are primarily betel quid chewing, tobacco chewing, tobacco smoking and alcohol consumption [2]. Other implicated possible aetiological factors include BMI and nutritional status [2, 3, 5].

Human papillomavirus (HPV) has also been elucidated as a possible contributory factor or aetiological cofactor. However, there is a paucity of research in the area and the associations are based on observational cross-sectional studies [6, 7].

Superimposed candida infections have also been observed in erythroplakia and the role of candida has also been investigated. There is a dearth of research to comment on the role candida and other microorganisms play in the development of erythroplakia [2, 8].

Histopathological analysis reveals dysplasia (varying from mild to severe), carcinoma in situ or squamous cell carcinoma in 60-90% of cases. These microscopic descriptions would explain the deep red colour of the lesions. There is lack of surface keratin which would normally disperse and reduce the intensity of the red colour [2].

There is also a reduction in the depth of the epithelial layer; therefore, vasculature present in the connective tissue are more visible from the surface. Finally, the number of vascular structures appears to increase in response to the inflammation (Sapp and Wysocki, 2004).

Molecular markers, such as the p53, may be a predictor of malignant transformation [2]. Immunohistochemical analysis has been performed in a study investigating the role of HPV in erythroplakia [6].

8.3. Epidemiology

There is a lack of large-scale epidemiological studies investigating the prevalence of oral erythroplakia [2]. The prevalence rate varies from approximately 0.02 to 2%. A large-scale study (500) completed on hospital inpatients in India found a prevalence of 0.6% [9]. The prevalence amongst a similar sized study in Saudi Arabia (559) was 0.7% [10]. An Irish study consisting of 210 addiction treatment centre residents found a prevalence as high as 1.9% [11]. Population-based samples have found considerably lower prevalence rates. Studies involving larger samples with more equal gender distribution completed in Brazil and India have found a prevalence of 0.3% and 0.24%, respectively [12].

Much lower incidence rates have been found in larger scale epidemiological studies conducted from 1971 to 2000, with sample sizes in some of the studies in excess 60,000. The incidences varied from 0.02 to 0.2 % [13–15]. A systematic review conducted in 2018 found a worldwide prevalence of 0.17% and this was considerably lower when compared to other OPMDs [16].

It is widely accepted that the prevalence of erythroplakia is less than other OPMDs and oral leukoplakia [2].

There appears to be no gender predilection, despite earlier studies reporting a male predominance [2].

Erythroplakia appears to occur mainly in middle aged and elderly [2]. A recent systematic review assessing oral leukoplakia and erythroplakia in younger patients found there was a lack of studies to comment but found the frequency of oral leukoplakia to be lower in younger patients (patients younger than 40 years of age) [17].

There is no known geographical distribution of erythroplakia, however, the prevalence is observably higher in populations with a preexisting smoking and betel nut chewing habit [2].

8.4. Clinical Presentation

Erythroplakia presents as fiery red macule or patch with a soft velvety texture. Erythroplakia is typically soft to palpate with induration only being observed in cases of malignancy. Lesions are usually irregular in outline, though, well defined. Occasionally, however, the surface may appear granular [18].

There are usually no symptoms. Patients may report non-specific soreness or burning from the area. Metallic taste have also been reported [5].

In erythroleukoplakia, red areas show atrophy or thinning of epithelium and unlike erythroplakia or leukoplakia, may present with an irregular margin. Erythroleukoplakia is more commonly symptomatic [18].

The floor of the mouth, ventral tongue, soft palate, tonsillar fauces and the buccal mucosa are the sites reported to be the most commonly affected. The mostly commonly cited area varies from study to study, with the tongue rarely being reported as affected. Typically, lesions are small (less than 1.5cm) though larger lesions have been reported (>4cm). Rarely erythroplakia affects multiple sites [2].

In cases of malignant transformation, patients may present with signs and symptoms of oral squamous cell carcinoma (OSCC).

There is no widely accepted classification of erythroplakia.

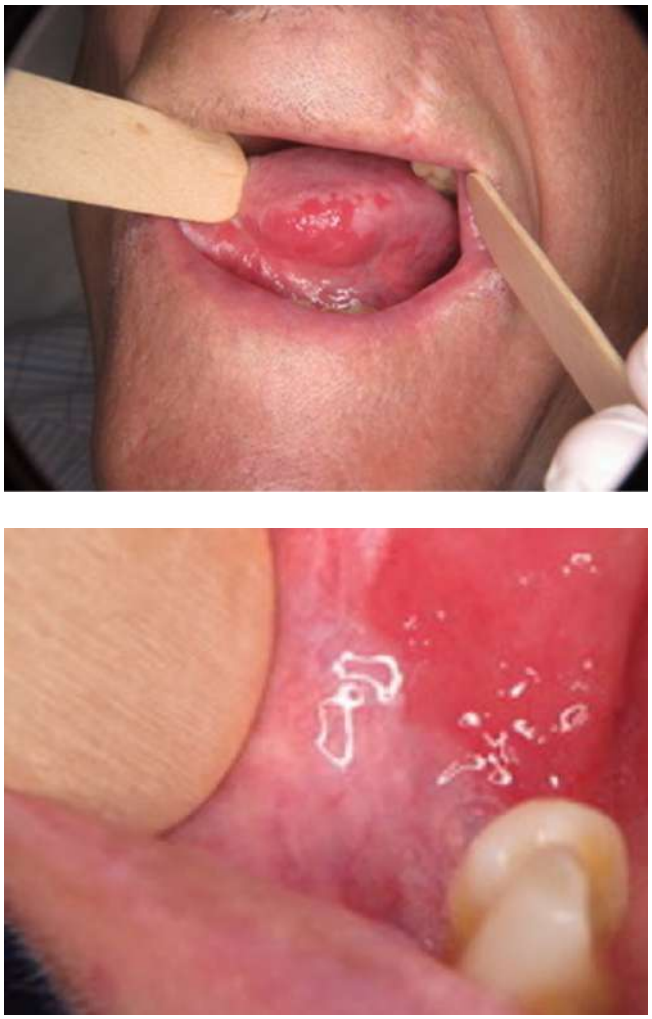

Figure 8.1. Widespread Erythroplakia homogenously affecting the left lateral border of the tongue and homogenous erythroplakia homogenously affecting the right buccal mucosa posteriorly.

8.5. Differential Diagnosis

The list of differentials includes those lesions presenting with erythematous oral mucosa. Erythematous candidiasis and atrophic lichen planus are frequently cited as the most common. Erythematous candidiasis and denture stomatitis can be differentiated from erythroplakia, as frequently these erythematous areas resolve with denture/oral hygiene instruction and treatment with antifungals, both systemic and topicals agents. Erythematous candidiasis may present asymptomatically, with central erythematous areas affecting the dorsal surface of the tongue, with a reflective lesion affecting the palate [2]. Other microbial infections may present with oral manifestations such as red patches affecting the oral mucosa, including histoplasmosis and tuberculosis [2, 3].

Atrophic lichen planus tends to present symptomatically, with other features of OLP such as white striations affecting other areas of the oral mucosa. Oral manifestations of systemic lupus erythematous (SLE) are frequently encountered and may include non-specific erythema [2, 3, 5].

Erythematous lesions affecting the oral mucosa, may also present after trauma or local irritation (e.g. burns), however, these areas tend to be painful and resolve after a few weeks after removal of the noxious stimulus/i. Oral Kaposi's sarcoma may also present with erythematous patches affecting the oral mucosa. However, Oral Kaposi's Sarcoma may present as a non-pigmented to brownish red/violaceous macule, as opposed to a flat or depressed lesion [19]. The various oral immunobullous disorders such as pemphigus and pemphigoid, after vesicle rupture, result in erythematous areas affecting the oral mucosa. However, these disorders can be differentiated from erythroplakia on the basis of the history and other special tests, including immunofluorescence studies [2]. Arteriovenous malformations such as dilated capillaries and haemangiomas may also present with erythematous areas. Finally, and most importantly early squamous cell carcinoma should be included in the list of differentials.

8.6. Diagnosis

A solitary lesion with well demarcated borders aids the practitioner to clinically distinguish erythroplakia from other disorders. These solitary lesions may be discovered incidentally by the general dental practitioners prompting referral. Urgent biopsy is essential to exclude neoplastic change. The histopathological features that may be found have been described above, thin and atrophic epithelium, lack of keratin and hyperplasia. Hematoxylin and eosin is the most common staining used by histopathologists in the diagnosis of erythroplakia [2].

The rate of malignant transformation varies from 14 to 50%. Many red lesions may present with carcinoma in situ or invasive disease at the time of diagnosis. The presence of moderate to severe dysplasia indicates a considerably higher risk of malignant transformation [2, 3, 5, 20].

A recent systematic review calculated the overall risk of malignant transformation as 33.1% and a malignant transformation rate per year at 2.7%. However, there was high degree of heterogeneity amongst the studies included [21].

The malignant transformation rate is observably higher in cohorts with other known risk factors for oral cancer, such as betel quid chewing, tobacco habits, alcohol consumption and poor nutritional status. Currently, there is no reliable diagnostic tool to identify which lesions will undergo malignant transformation. Hypothesised sites that undergo the highest rate of malignant transformation include the floor of mouth and ventral tongue regions. The exact mechanism causing malignant transformation remains unknown [2]. Image cytometry DNA ploidy analysis combined with grade of dysplasia has been shown to have the highest predictive value, when considering malignant transformation and OPMDs [22].

Destructive and abhorrent patterns of intraepithelial papillary capillary loop of Narrow Band Images (NBI) have been implicated as indicators for high-grade dysplasia, carcinoma in situ and invasive carcinoma in erythroplakia. NBI is not routinely used and the application of this optical technique will remain to be seen [23].

Recently, optical techniques utilising light-based imaging, such as tissue autofluorescence and chemiluminescence have been developed to facilitate the early detection of mucosal changes indicating changes for oral cancer. Other adjuncts include oral exfoliative cytology (brush biopsies), and the use of contrast agents/vital dyes. However, the efficacy of these when used solely to differentiate between benign and potentially malignant/malignant disorders has yet to be demonstrated and conventional oral examination with biopsy remains the gold standard [24].

8.7. Management

Owing to the highest risk of malignant transformation early treatment is crucial. Surgical excision is the treatment of choice. There is lack of studies on follow-up following surgical excision and treatment outcomes. There are no guidelines on the exact margin to excise, this is often dictated by the degree of cellular atypia identified. Carbon dioxide laser excision has been used recently, as an alternative to scalpel excision. This has been associated with more favourable healing of the area and post-operative comfort. The rate of recurrence following excision is unknown, however, the size of the excised lesion has been shown to be a significant predictive factor [25]. Other therapies including vitamin A, retinoids, bleomycin and mixed tea have not yielded favourable results to advocate their use. Cessation of recreational habits associated with higher risk of malignant transformation should be recommended [2].

There is no suggested follow-up interval for erythroplakia. An increase in size, high risk recreational habits (smoking/alcohol), high risk sites (ventral tongue and floor of mouth), change in clinical appearance and the development of symptoms may dictate re-biopsy of a lesion. A clinical photograph taken at subsequent appointments is useful to objectively assess for any changes in appearance of the lesion [2].

Summary

The most widely accepted definition of erythroplakia is ‘any lesion of the oral mucosa that presents as bright red velvety plaques which cannot be characterised clinically or pathologically as any other recognizable condition’. Smoking, alcohol, betel nut chewing and genetic mutations may all play role in aetiology. Erythroplakia is the OPMD with the lowest prevalence rate and one of the highest malignant transformation rate. Considering the high malignant transformation rate, early incisional biopsy is advocated to identify early neoplastic changes. The treatment of choice for high-risk lesions (severe dysplasia and carcinoma in situ) is surgical excision. Regular follow is necessary and the threshold to for re-biopsy is low.

Despite the high malignant transformation rate amongst OPMDs, erythroplakia remains the OPMD that is most poorly understood. The lack of research leaves many unanswered questions regarding aetiology, prevalence, diagnosis and management of erythroplakia.

References

1. Kramer IR, Lucas RB, Pindborg JJ, Sobin LH. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. Oral Surg Oral Med Oral Pathol. 1978;46(4):518-39.
2. Reichart PA, Philipsen HP. Oral erythroplakia--a review. Oral Oncol. 2005;41(6):551-61.
3. Holmstrup P. Oral erythroplakia-What is it? Oral Dis. 2018;24(1-2):138-43.
4. Pindborg JJ, Renstrup G, Poulsen HE, Silverman S Jr. Studies in oral leukoplakias. V. Clinical and histologic signs of Malignancy. Acta Odontol Scand. 1963;21:407-14.
5. Villa A, Villa C, Abati S. Oral cancer and oral erythroplakia: an update and implication for clinicians. Aust Dent J. 2011;56(3):253-6.
6. Nielsen H, Norrild B, Vedtofte P, Praetorius F, Reibel J, Holmstrup P. Human papillomavirus in oral premalignant lesions. Eur J Cancer B Oral Oncol. 1996;32B(4):264-70.
7. Holmstrup P, Pindborg JJ. Erythroplakic lesions in relation to oral lichen planus. Acta Derm Venereol Suppl (Stockh). 1979;59(85):77-84.
8. Bouquot JE, Ephros H. Erythroplakia: the dangerous red mucosa. Pract Periodontics Aesthet Dent. 1995;7(6):59-67; quiz 8.
9. Thavarajah R, Rao A, Raman U, Rajasekaran ST, Joshua E, R H, et al. Oral lesions of 500 habitual psychoactive substance users in Chennai, India. Arch Oral Biol. 2006;51(6):512-9.
10. Al-Attas SA, Ibrahim SS, Amer HA, Darwish Zl-S, Hassan MH. Prevalence of potentially malignant oral mucosal lesions among tobacco users in Jeddah, Saudi Arabia. Asian Pac J Cancer Prev. 2014;15(2):757-62.
11. O'Sullivan EM. Prevalence of oral mucosal abnormalities in addiction treatment centre residents in Southern Ireland. Oral Oncol. 2011;47(5):395-9.
12. Ferreira AM, de Souza Lucena EE, de Oliveira TC, da Silveira É, de Oliveira PT, de Lima KC. Prevalence and factors associated with oral potentially malignant disorders in Brazil's rural workers. Oral Dis. 2016;22(6):536-42.
13. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer. 1975;36(3):1021-8.
14. Lumerman H, Freedman P, Kerpel S. Oral epithelial dysplasia and the development of invasive squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995;79(3):321-9.
15. Hashibe M, Mathew B, Kuruvilla B, Thomas G, Sankaranarayanan R, Parkin DM, et al. Chewing tobacco, alcohol, and the risk of erythroplakia. Cancer Epidemiol Biomarkers Prev. 2000;9(7):639-45.
16. Mello FW, Miguel AFP, Dutra KL, Porporatti AL, Warnakulasuriya S, Guerra ENS, et al. Prevalence of oral potentially malignant disorders: A systematic review and meta-analysis. J Oral Pathol Med. 2018;47(7):633-40.
17. Roza ALOC, Kowalski LP, William WN, de Castro G, Chaves ALF, Araújo ALD, et al. Oral leukoplakia and erythroplakia in young patients: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2021;131(1):73-84.
18. Warnakulasuriya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125(6):582-90.
19. Fatahzadeh M, Schwartz RA. Oral Kaposi's sarcoma: a review and update. Int J Dermatol. 2013;52(6):666-72.
20. Abati S, Bramati C, Bondi S, Lissoni A, Trimarchi M. Oral Cancer and Precancer: A Narrative Review on the Relevance of Early Diagnosis. Int J Environ Res Public Health. 2020;17(24):9160.
21. Iocca O, Sollecito TP, Alawi F, Weinstein GS, Newman JG, De Virgilio A, 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(3):539-55.
22. Zaini ZM, McParland H, Møller H, Husband K, Odell EW. Predicting malignant progression in clinically high-risk lesions by DNA ploidy analysis and dysplasia grading. Sci Rep. 2018;8(1):15874.
23. Yang SW, Lee YS, Chang LC, Hwang CC, Luo CM, Chen TA. Clinical characteristics of narrow-band imaging of oral erythroplakia and its correlation with pathology. BMC Cancer. 2015;15:406.
24. Kim DH, Lee J, Lee MH, Kim SW, Hwang SH. Efficacy of chemiluminescence in the diagnosis and screening of oral cancer and precancer: a systematic review and meta-analysis. Braz J Otorhinolaryngol. 2020;29:S1808-8694(20)30110-5.
25. Yang SW, Lee YS, Chang LC, Hsieh TY, Chen TA. Outcome of excision of oral erythroplakia. Br J Oral Maxillofac Surg. 2015;53(2):142-7.

9

Oral Graft-Versus-Host Disease

Božana Lončar Brzak[1]
Barbara Carey[2]
Vlaho Brailo[1]

1. Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia

2. Department of Oral Medicine, Guys & St Thomas' NHS Foundation Trust, London, United Kingdom

9.1. Definition

Graft-versus-host disease (GVHD) is an immunologic condition which develops following allogeneic hematopoietic stem cell transplantation (HSCT) [1, 2]. It is a major cause of non-relapse morbidity and mortality in this group of patients [3, 4]. The incidence and prevalence of GVHD are increasing due to the extension of clinical indications for HSCT treatment and more prolonged patient survival and follow-up [2]. GVHD is an indicator of treatment success because due to graft-versus-tumor (GVT) effect, there is a lower risk of malignancy relapse [5-8]. Therefore, there is a balance between GVT and chronic GVHD for optimal transplantation results [7, 8]. The aim of this chapter is to present readers with information on the epidemiology, clinical characteristics, diagnosis and management of oral graft-versus-host disease.

9.2. Epidemiology

GVHD develops in 40-60% of patients following allogeneic HSCT [1, 2]. The incidence is higher in pediatric patients. It is a major cause of morbidity [3,4] and is fatal in approximately 15% of patients [3]. Both acute (aGVHD) and chronic GVHD (cGVHD) may have oral manifestations. The incidence of chronic GVHD is varies from 25-80% [5].

Oral lesions are rarely seen in acute GVHD, and the incidence is therefore, unknown. In over 70% of patients with cGVHD, the oral cavity is affected [9, 10].

9.3. Clinical presentation

GVHD is a mult-isystem disease with acute and chronic presentations. It requires multidisciplinary management [5]. Earlier classification systems of GVHD documented the type depending on time to presentation of symptoms which in the case of acute GVHD, developed within the first 100 days following HSCT. The National Institute of Health (NIH) consensus criteria (2005) suggested the diagnosis of acute or chronic GVHD should be based on clinical findings and pathologic features [11, 12]. Acute GVHD may be classified as classic (which occurs in the first 100 days after HSCT) and late, recurrent or persistent (if it occurs after this period) which may be seen in patients on non-myeloablative conditioning [5, 13].

Likewise, cGVHD may also manifest as classic cGVHD (without overlapping but with some features of aGVHD) or as an overlap syndrome (with distinctions of both acute and chronic GVHD at the same time, for example in patients who receive donor lymphocyte infusions) [5, 12].

Acute GVHD primarily affects the skin, liver and the gastrointestinal (GI) tract. Skin lesions are often the earliest visible sign of the disease [14]. The oral mucosa is rarely involved in aGVHD and the lesions are non-specific [15]. Lesions may also be visible on the oral mucosa or lips, as gingivitis, mucositis, erythema or ulceration [12]. In the case of overlap syndrome, oral lesions may be seen as lichen planus-like hyperkeratotic changes.

The severity of aGVHD is graded from I to IV depending on the combination of the degree of involvement of the skin, liver and the GI tract. Grade I of aGVHD gives the best prognosis for survival [16, 17].

Chronic GVHD can manifest as one of three models: 1) de novo onset in a patient who did not have previous aGVHD lesions; 2) quiescent onset after the lesions of aGVHD have completely resolved; and 3) progressive onset when cGVHD immediately follows aGVHD [18, 19]. The disease can affect one or multiple organs. The skin, eyes, oral cavity, GI tract, liver and lungs are among the preferred sites involved [5].

In the oral cavity, cGVHD can be classified as oral mucosal cGVHD, salivary gland disease and sclerotic disease [2, 10, 20].

Oral mucosal disease presents with white striae, erythema and ulcers, most frequently affecting buccal mucosa and lateral tongue (Figure 9.1). The lesions are painful and limit food and beverage intake. In the gingiva, the lesions manifest as erythema and desquamation, with or without the presence of white striations (Figure 9.2). Gingival lesions are also painful and may impede oral hygiene [10, 20].

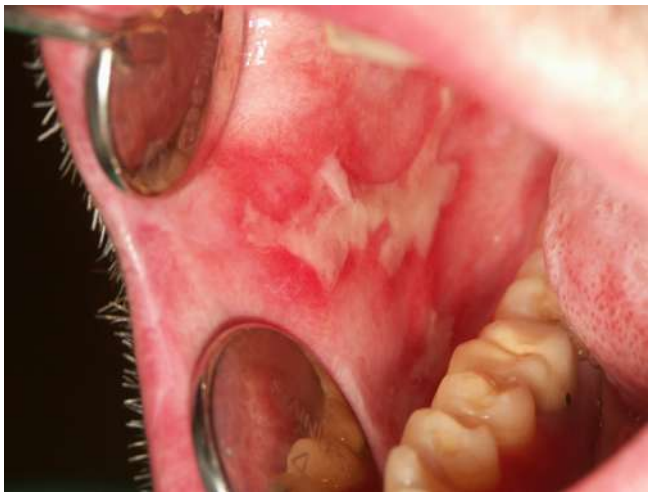

Figure 9.1. Ulcerative lesion involving the buccal mucosa in a patient with cGVHD.

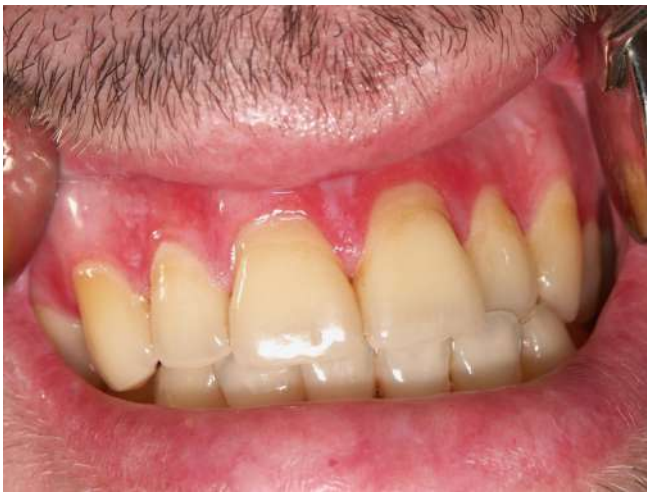

Figure 9.2. Gingival involvement presenting with erythema and striations in a cGVHD patient.

Salivary gland cGVHD can affect minor and major salivary glands. Multiple mucoceles, usually small in size, in clusters and not precipitated by trauma, are typically localised to the soft palate, but other parts of the oral mucosa can also be affected. After mucoceles rupture, they may leave erosions which may be sensitive. Chronic GVHD in major salivary glands leads to quantitative and qualitative changes in saliva, often resulting in marked hyposalivation [10, 21]. Salivary gland swelling and pain may occur [15].

The sclerotic form of cGVHD affecting facial skin and the oral cavity, may manifest with restriction of mouth opening and loss of elasticity of the lips and restricted tongue movements.

Severe fibrosis may result in shallow vestibules and periodontal defects which greatly deteriorates oral function. Oral hygiene and dental procedures can be severely compromised [2, 10, 20].

Assessment of oral cGVHD is important for clinical practice and clinical research. The National Institute of Health (NIH) cGVHD Task Force proposed a scoring system in 2005 [21] which was revised in 2014 [22]. The NIH scale includes three types of oral manifestations (erythema, lichenoid and ulcers) which can be graded in three activity levels (mild, moderate and severe) (Table 9.1).

Erythema	None	0	Mild or moderate erythema (<25%)	1	Moderate (≥25%) or severe (≤25%) erythema	2	Severe erythema (≥25%)	3
Lichenoid	None	0	Lichen-like changes (<25%)	1	Lichen-like changes (25-50%)	2	Lichen-like changes (>50%)	3
Ulcers	None	0			Ulcers involving (≤20%)	3	Severe ulce-rations (>20%)	6
Total score for all mucosal changes								

Table 9.1. Scoring of oral cGVHD lesions (adapted from Lee et al, 2015 [22]).

9.4. Diagnosis

The diagnosis of aGVHD is established based on the history and clinical examination with skin, liver and gastrointestinal tract involvement within the first 100 days of HSCT and not meeting the dagnostic criteria for cGVHD. The diagnosis is based on the exclusion of other conditions and the coexistence of aGVHD in other organs (skin, liver, intestines) [15]. These patients are classified as classic aGVHD. Some patients may develop signs of aGVHD beyond 100 days of HSCT without diagnostic signs of cGVHD. These patients are classified as persistent, recurrent or late aGVHD.

Patients with at least one distinctive sign of cGVHD without signs of aGVHD are classified as classic cGVHD. Patients with signs of both aGVHD and cGVHD are classified as overlap syndrome [23]. Diagnostic distinction between aGVHD and cGVHD is presented in Table 9.2.

If the lesions of oral cGVHD have a typical lichenoid presentation, the diagnosis is established clinically. In cases presenting as erythema, ulceration or as a white plaque, with an absence of typical white striations, a biopsy is needed to establish the diagnosis [11, 22] and to exclude other conditions. The differential diagnosis of oral GVHD may include viral and fungal infections (usually HSV, candidosis), erythema multiforme [10], lichen planus, lichenoid reactions and discoid lupus. Histopathological findings of oral mucosal cGVHD include lichenoid interface inflammation, leukocyte exocytosis and keratinocyte apoptosis.

Histopathological findings of salivary gland cGVHD demonstrates intralobular periductal lymphocytic infiltration (frequently seen with fibrosis) and exocytosis of lymphocytes into intralobular ducts and acini [24].

9.5. Management

The aim of oral GVHD treatment is to alleviate symptoms to enable uninterrupted oral function. Topical treatment is the same for acute and chronic GVHD. In cases of cGVHD with oral cavity involvement, topical therapy is the treatment of choice. Topical therapy may be an adjunct to systemic therapy. The treatment of choice for systemic therapy are corticosteroids with or without the use of cyclosporine [25]. New treatment options include ibrutinib, ruxolitinib, imatinib, rituximab and sirolimus [15, 26].

9.6. Mucosal cGVHD

First-line treatment of oral mucosal cGVHD lesions include topical corticosteroids and calcineurin inhibitors such as tacrolimus. Topical corticosteroids of varying potency can be applied as solutions, gels, creams or ointments several times a day. Intralesional injections of corticosteroids (e.g. triamcinolone acetonide) for localised ulceration are helpful for persistent lesions resistant to treatment. Topical tacrolimus may be used as add-on therapy. Tacrolimus ointment (available as 0.03% and 0.1%) is recommended for lesions involving the lips, while tacrolimus solution is a better choice for intraoral involvement [5].

Acute GVHD		Chronic	
• Rash • Nausea and Vomiting • Loss of appetite • Diarrhoea • Cholestatic hepatitis		• Typical lichenoid features • Erythema • Ulceration • Leukoplakia • Dry mouth • Limited mouth opening	
Classic: Occurs within 100 days	**Persistent / Recurrent / Late acute:** Beyond 100 days	**Classic:** At least one diagnostic / distinctive manifestation, no time restriction	**Overlap syndrome:** Features of acute and chronic, no time restriction

Table 9.2. Acute and chronic GVHD [15].

Oral pain can be controlled with topical anesthetic agents such as viscous lidocaine, or systemic analgesics, including opioids [27]. Maintaining oral hygiene is difficult. Patients should be advised to use neutral-pH toothpastes and to avoid mint flavouring which may act as an irritant. Ultra-soft toothbrushes are recommended in the case of painful oral lesions [15].

Limited data from the literature have shown that low level laser therapy, CO2 laser therapy and phototherapy with intraoral PUVA or UVB are effective in treating pain associated with oral cGVHD lesions [5, 15, 28]. Further studies are necessary to determine the efficiency of these treatments.

9.7. Salivary gland cGVHD

Treatment is aimed at gustatory and mechanical stimulation of salivary glands and the use of oral lubricants as a saliva replacement. Systemic treatment with cholinergic agonists may be helpful (e.g. pilocarpine 5-10mg three to four times daily; or cevimeline 15-30mg two to three times daily) [29]. Topical fluoride application should be recommended to prevent demineralization of teeth. Patients should be educated regarding the importance of non-cariogenic nutrition and instructed to rinse after meals [10, 15].

9.8. Sclerotic oral cGVHD

Sclerotic changes tend to be progressive and non-reversible. Patients should be instructed to undertake physiotherapy exercises daily to enhance flexibility of the perioral tissues. Systemic cGVHD treatment may be warranted, and in some cases, surgical treatment may be necessary.

The treatment of oral cGVHD is summarised in Table 9.3.

Oral mucosal cGVHD		
Topical corticosteroids		
• 0.05% clobetasol propionate • 0.01–0.05% fluocinolone acetonide • 0.1–0.5% triamcinolone acetonide • Tacrolimus 0.1% solution • Tacrolimus 0.1% ointment, 2 times/day 2–3 times/day	• 2–3 times/day. • Check-ups every 15 days to assess the response.	• The use of creams or ointments is preferred for managing localised intraoral lesions. • Mouthwashes for extensive and multiple lesions or those inaccessible to gel applications. • Gingival lesions can be treated using individual custom trays.
Intralesional corticosteroids		
• Triamcinolone acetonide 10–40 mg/mL	• Inject directly into the subepithelial connective tissue just below the lesion through the adjacent healthy mucosa. • Consider the use of local anesthesia (0.5 mL of 2% lidocaine) in the solution. • Repeat every 1–4 weeks.	• Refractory and symptomatic localised ulcerative lesions.
Systemic corticosteroids		
• Prednisone 0.5–1.0 mg/kg/day	• Until a therapeutic response is achieved*.	• Severe initial presentation and/or generalised ulceration and erythema; • Treatment of resistant/recalcitrant lesions or the treatment of resistant/ recalcitrant disease that involves numerous locations, including the oral cavity.

Salivary gland cGVHD		

• Xerostomia
• Dental caries
• Candidosis
	• Salivary stimulants (gum/candy) Oral-moisturising agents Sialogogue therapy
	  • Pilocarpine 5 mg tid
	  • Cevimeline 30 mg tid
	• Good oral hygiene
	• Avoid sugary foods/drinks
	• Topical fluoride therapy Remineralization therapy
	• Regular dental visits
	• Fluconazole
	• Disinfect removable prosthesis nightly
		• Sugar-free or xylitol-containing gum/candy
		• Sialogogues may take 8-12 wks for full efficacy
		• Avoid sialogogues in patients with pulmonary disease
		• Topical corticosteroid therapy increases risk of candidisis
		• Antifungal prophylaxis for recurrent candidiasis

Sclerotic cGVHD		
	• Physiotherapy exercises • Intralesional steroid therapy • Surgery to disrupt mucosal bands	• Condition is generally progressive and requires ongoing therapy

Table 9.3. Summary of treatment options for GVHD.

9.9. Complications

Patients frequently develop oral candidosis due to dry mouth, immunosuppression and antimicrobial prophylaxis. Prophylactic antifungal therapy should be given to patients with predisposing factors. In cases where oral candidosis develops, it should be treated with systemic antifungal therapy, usually fluconazole [10].

Recurrent HSV infections are also possible, often with atypical presentations. Systemic antivirals (acyclovir) are the treatment of choice.

After HSCT, patients have an increased risk of a second primary cancer. The risk for oral cancer in cGVHD patients is 6 times higher compared to the general population. The longer the time since transplantation, the risk of cancer arising increases.

The average time for oral cancer development following HSCT is 6-8 years. NIH recommendations suggest patients are screened twice a year [30]. In cases of oral cancer development, the follow-up time should be prolonged due to risk of recurrence [31].

Summary

Most patients with cGVHD present with oral manifestations of the disease. Treatment is symptomatic and aimed at preserving function and improving quality of life. Due to the increased risk for dental caries development and risk of oral cancer, long-term follow-up and screening of oral mucosa every 6 months is recommended.

References

1. Treister N, Schubert MS, Fall-Dickson JM. Oral chronic graft vs host disease. In: Vogelsang GB, Pavletic SZ, eds. Chronic Graft-Versus-Host Disease: Interdisciplinary Management. New York: Cambridge University; 2009:182–198.
2. Mays JW, Fassil H, Edwards DA, Pavletic SZ, Bassim CW. Oral chronic graftversus-host disease: current pathogenesis, therapy, and research. Oral Dis. 2013;19(4):327–346.
3. Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. Blood 2012;119(1):296–307.
4. Atkinson K, Horowitz MM, Gale RP, et al. Risk factors for chronic graft-versus-host disease after HLA-identical sibling bone marrow transplantation. Blood 1990;75(12):2459–64.
5. Kuten-Shorrer M, Woo SB, Treister NS. Oral graft-versus-host disease. Dent Clin North Am. 2014;58(2):351-68.
6. Blazar BR, Murphy WJ, Abedi M. Advances in graft-versus-host disease biology and therapy. Nat Rev Immunol 2012;12(6):443–58.
7. Weiden PL, Sullivan KM, Flournoy N, et al. Antileukemic effect of chronic graftversus-host disease: contribution to improved survival after allogeneic marrow transplantation. N Engl J Med 1981;304(25):1529–33.
8. Schubert MM, Correa ME. Oral graft-versus-host disease. Dent Clin North Am 2008;52(1):79–109 viii-ix.
9. Treister NS, Cook EF Jr, Antin J, et al. Clinical evaluation of oral chronic graftversus-host disease. Biol Blood Marrow Transplant 2008;14(1):110–5.
10. Treister N, Duncan C, Cutler C, et al. How we treat oral chronic graft-versus-host disease. Blood 2012;120(17):3407–18.
11. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus host disease: I. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 2015;21(3):389–401.e1.
12. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graftversus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 2005;11(12):945–56.
13. Mielcarek M, Martin PJ, Leisenring W, et al. Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. Blood 2003;102(2):756–62.
14. Elad S, Aljitawi O, Zadik Y. Oral graft-versus-host disease: a pictorial review and a guide for dental practitioners. Int Dent J. 2020 Jun 28. doi: 10.1111/idj.12584.
15. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995;15(6):825–8.
16. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graftversus-host disease. Br J Haematol 2012;158(1):30–45.
17. Shulman HM, Sale GE, Lerner KG, et al. Chronic cutaneous graft-versus-host disease in man. Am J Pathol 1978;91(3):545–70.
18. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant 2003;9(4):215–33.
19. Imanguli MM, Alevizos I, Brown R, et al. Oral graft-versus-host disease. Oral Dis 2008;14(5):396–412.
20. Meier JK, Wolff D, Pavletic S, et al. Oral chronic graft-versus-host disease: report from the International Consensus Conference on Clinical Practice in cGVHD. Clin Oral Investig 2011;15(2):127–39.
21. Pavletic SZ, Martin P, Lee SJ, et al. Measuring therapeutic response in chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: IV. Response Criteria Working Group report. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow. Transplantation 2006;12(3):252–66.
22. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. national institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group Report. Biol Blood Marrow Transpl 2015;21(6):984–99.
23. Margaix-Muñoz M, Bagán JV, Jiménez Y, Sarrión MG, Poveda-Roda R. Graft-versus-host disease affecting oral cavity. A review. J Clin Exp Dent. 2015;7(1):e138-45.
24. Shulman HM, Kleiner D, Lee SJ, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II. Pathology working group report. Biol Blood Marrow Transplant 2006;12(1):31–47.
25. Fall-Dickson JM, Cordes S, Berger AM. Oral complications. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 11th ed. Philadelphia: Wolters Kluwer; 2019:2094–2108.
26. Jaglowski SM, Blazar BR. How ibrutinib, a B-cell malignancy drug, became an FDA-approved second-line therapy for steroid-resistant chronic GVHD. Blood Adv. 2018;2(15):2012–2019.
27. Fall-Dickson JM, Pavletic SZ, Mays JW, Schubert MM. Oral Complications of Chronic Graft-Versus-Host Disease. J Natl Cancer Inst Monogr. 2019;2019(53): lgz007.
28. Treister N, Li S, Lerman MA, et al. Narrow-band UVB phototherapy for management of oral chronic graft-versus-host disease. Photodermatol Photoimmunol Photomed 2015;31(2):75–82.
29. Elad S, Jensen SB, Raber-Durlacher JE, et al. Clinical approach in the management of oral chronic graft-versus-host disease (cGVHD) in a series of specialised medical centers. Support Care Cancer 2015;23(6):1615–22.
30. Carpenter PA, Kitko CL, Elad S, et al. National institutes of health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. The 2014 Ancillary Therapy and Supportive Care Working Group Report. Biol Blood Marrow Transpl 2015;21(7):1167–87.
31. Elad S, Zadik Y, Zeevi I, et al. Oral cancer in patients after hematopoietic stem-cell transplantation: long-term follow-up suggests an increased risk for recurrence. Transplantation 2010;90(11):1243–4.

10

Oral Submucous Fibrosis

Vignesh Eswara Murthy[1]
Barbara Carey[1]
Richard Cook[2]
Michael Escudier[2]
Rui Albuquerque[1,2]

1. Department of Oral Medicine, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

2. Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

Oral Submucous Fibrosis (OSMF) is a chronic, progressive scarring condition affecting the oral mucosa and often, the upper oesophagus. The condition was first described by Schwartz in 1952 as 'atrophic idiopathic mucosa oris'. The term OSMF was first used by Joshi in 1953. The first cases were reported in the Indian subcontinent in the mid twentieth century [1]. The aim of this review is to provide a comprehensive overview of OSMF including the epidemiology, clinical features, diagnosis, and management of the disease.

10.1. Definition

There is no universally accepted definition of OSMF, and more recent definitions aim to provide commentary on the disease's aetiology, epidemiology and clinical features. Pindborg in 1966 defined OSMF as 'an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx' [2]. Brad (2019) defined OSMF as a 'chronic, precancerous and often debilitating condition characterised by slowly progressive fibrosis of the oral cavity and oropharynx' and Langdon (2007) described OSMF as 'a progressive disease in which fibrous bands form beneath the oral mucosa' (Brad, 2019) (Langdon, 2007). The aforementioned definitions are similar in some respect and highlight certain ubiquitous themes in the diseases clinical pattern and aetiology, in particular, the progressive and chronic nature of the disease. A more comprehensive definition defines OSMF as 'a chronic, progressive disease that alters the fibroelasticity of the oral submucosa, prevalent in India and Southeast Asia but rare elsewhere, and characterised by burning and pain in the oral cavity, loss of gustatory sensation, the presence of blanched fibrous bands and stiffening of the oral mucosa and oro-pharynx (leading to trismus and a progressive reduction in mouth opening) and an increased risk of developing oral squamous cell cancer (3-19%) [2]. It is usually associated with the chewing of the areca nut (an ingredient in betel quid) but the exact etiology is unknown and there is currently no effective treatment.

10.2. Aetiopathogenesis

OSMF is primarily caused by chewing an Areca nut. Areca or betel nut is the name for the nut derived from the Areca plant. A dose dependent relationship for both frequency and duration of chewing has been noted in the development of OSMF [4]. Areca, betel or paan chewing is a common recreational habit in the Indian subcontinent and its consumption is becoming increasingly more common in Western communities due to migration. Certain preparations of Areca nut include tobacco and other known carcinogens. Areca nut in isolation is a recognised carcinogen, as it contains certain tannins and alkaloids, which have a cytotoxicity and genotoxicity. Slaked lime, which is another common ingredient in Areca nut preparations has elevated concentrations of arsenic. In the Hindu religion, Areca nut is believed to be divine and it is consumed due to the perceived medicinal value. It has also been perceived as an aphrodisiac, an agent that improves oral hygiene and reduces halitosis, a salivary stimulant that improves digestion and, within the Indian subcontinent, it is believed to have a stabilising effect on glycemic control in patients with diabetes. Arecoline, a byproduct after metabolism of Areca nut, is an alkaloid that readily crosses the blood brain barrier and has been implicated in the addictive potential of the Areca nut chewing habit. The subsequent physiological effects are often described as euphoric, users also describe heightened awareness and improved productivity. The International Agency for Research on Cancer has categorised Areca nut as a Group 1 carcinogen [5, 6].

There may also be a genetic predisposition, with association with certain HLA subtypes and haplotypes (A10/DR3). Malnutrition, anaemia and haematinic deficiencies are associated with atrophy of the oral mucosa and increased potential for collagen synthesis [3]. Capsaicin, an active component of chili peppers, may incite an allergic or hypersensitivity reaction, which may contribute to fibrosis [3].

OSMF is characterised by abnormal collagen deposition. Areca alkaloids, such as arecoline, cause fibroblast proliferation. Flavourings within areca nut preparations, such as tannins, may also inhibit collagenase activity. The progression of the disease is associated with replacement of the easily degradable type 1 collagen, with more resistant type 3 collagen. There is also inhibition of collagen phagocytosis. Arecoline is the main aetiological factor in this inhibition as it causes suppression of T-cell activity. Copper released during the chewing of Areca nut causes upregulation of lysyl oxidase enzyme which leads to increased cross-linking of collagen and elastin molecules. There is increased expression of fibrogenic cytokines, and many consider the activation of TGF-Beta the main molecular event, leading to the increased collagen production and fibrosis [7]. Occasionally, the development of OSMF is associated with the formation of vesicles, however, the characteristic changes are a juxtaepithelial inflammatory reaction followed by fibroelastic changes and atrophy of the oral epithelium, leading to the classic clinical sequelae [5, 7, 8].

Histopathological specimens will exhibit certain features of OSMF, such as atrophy or thinning of the epithelium and juxtaepithelial hyalinization and collagen of varying density, along with a fibrosed lamina propria and anchoring fibrils [9].

10.3. Epidemiology

OSMF occurs predominantly in the Indian subcontinent and South East Asia including India, Taiwan, China, Bangladesh, Malaysia, Singapore, Thailand and Sri Lanka. It has also been reported in South Africa and Saudi Arabia. OSMF is found in Asian populations in the USA, United Kingdom and developed countries and therefore the condition exhibits a global health burden. The number of global cases in 1996 was estimated to be 2.5 million. OSMF symptoms tend to develop in the 4th - 5th decade of life, but cases have been reported in the patients as young as eleven [10, 11]. The disease has a female preponderance for unknown reasons.

10.4. Clinical Presentation

OSMF has been clinically categorised into four stages by More (2012), encompassing an eruptive and then fibrotic phase. The eruptive phase may be associated with vesicle formation, with burning sensation and discomfort in the oral cavity being common. The texture of the oral mucosa begins to change, losing its suppleness. Pallor of the mucosa progresses, and the mucosa begins to blanch. Mucosal petechia may develop, as well as melanotic mucosal pigmentation, mucosal ulceration and erythematous areas [3, 12].

In stage two, fibrosis occurs in the vesicles and ulcers when they heal. Vertical and circular palpable fibrous bands in the buccal mucosa and/or oropharynx develop with or without stomatitis. Thinner bands may be present in the earlier stages when compared to these palpable bands [4].

In stage three, palpable fibrous bands may be present in any part of the oral cavity with or without stomatitis [3]. Stage four encompasses all of the above with the development of a potentially malignant disorder or frank oral squamous cell carcinoma [3].

Specific findings in stages two to four include trismus, depigmentation of the gingiva, atrophic uvula and depapillation of the tongue. Changes in facial aesthetics may also be observed with sinking of the cheeks which does not correlate to age or nutritional status. In severe cases, speech and hearing deficits may develop. OSMF has been reported to have a significant impact on quality of life in the later stages.

More also described a functional staging of OSMF based on interincisal mouth opening; Stage 1 (greater than or equal to 35 mm), stage 2 (between 25 and 35 mm), stage 3 (15 and 25mm) and stage 4 (less than 15mm).

There have been further classifications, however, the 2012 classification has been readily adapted across the Indian subcontinent and serves as an effective communication tool amongst clinicians [13].

Paymaster in 1956 first reported the premaligant potential of the condition [14]. There are significant geographical variations in the reported malignant transformation rates.

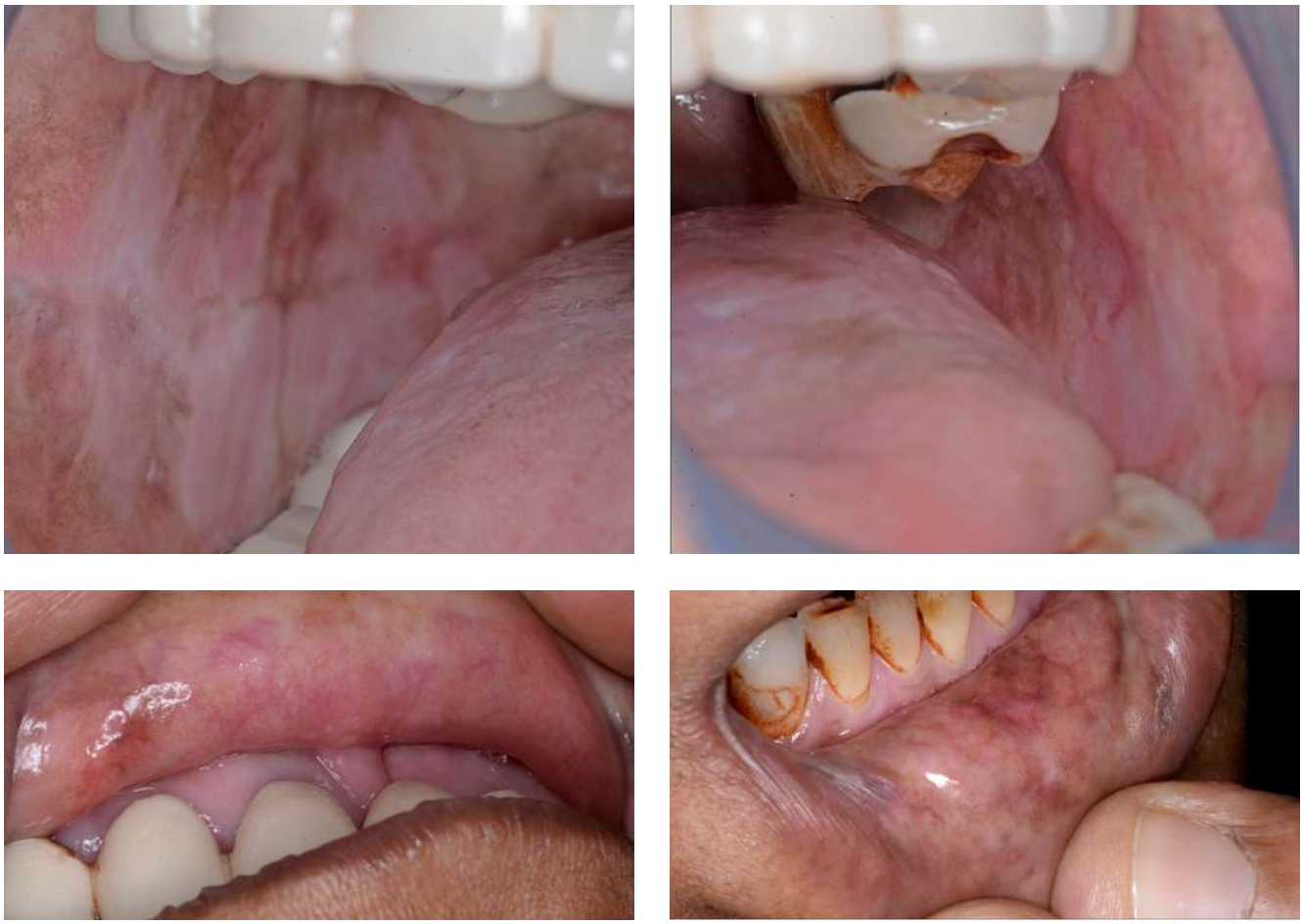

Figure 10.1. Showing Blanching of the left and right buccal mucosa with leukoplakia and some evidence of fibrous banding visible, more prominent on the right buccal mucosa. Loss of pallor is evident on the upper and lower labial mucosa.

The rate is generally higher in India, when compared to other countries. A potential explanation of this is the way areca nut is prepared with additional additives. Taiwanese studies found that tobacco products are generally not used in conjunction with areca nut products and this could account for the lower rate of malignant transformation in this population. The rate of malignant transformation has been estimated to be between 1 and 9%. A higher malignant transformation rate has been observed in those with a concurrent oral leukoplakia. Oral cancers originating from OSMF have also been reported to be both less and more aggressive when compared to Oral Cancer originating from other lesions within the oral cavity [15, 16]. Many studies have attempted to correlate potential molecular markers in the development of oral cancer, to better understand the mechanism of malignant transformation [16].

10.5. Differential Diagnosis

In the early stages, OSMF may be misdiagnosed. Patients complaining of a burning sensation with mucosal atrophy may be diagnosed with Oral Dysaesthesia, with or without an underlying contributing factor such as a haematinic deficiency or anaemia. Careful history taking and enquiry into recreational habits is fundamental. OSMF may present with features similar to other oral potentially malignant disorders, such as oral lichen planus [3].

Scleroderma is an autoimmune condition affecting the skin, internal organs and blood vessels. It is characterised by diffuse sclerosis of the skin and other connective tissue. Scleroderma may present with fibrous bands in the oral mucosa and progressive trismus. Patients with scleroderma will also have extraoral complaints. Microvascular imaging, testing for autoantibodies help establish the diagnosis of scleroderma [17].

Amyloidosis is characterised by the deposition of amyloid proteins (fibrillar protein) in tissues. Systemic amyloidosis may present with macroglossia or progressive trismus. Careful history taking, blood and biopsy help establish the diagnosis [18]. In its later stages, OSMF may present as frank oral SCC, leukoplakia and erythroplakia

10.6. Diagnosis

Careful enquiry into recreational habits will strongly suggest a diagnosis of OSMF. As OSMF is a potentially malignant condition, incisional biopsies are necessary. Histopathological analysis is helpful in clinical staging of the disease however trauma from the biopsy procedure can potentially induce a degree of fibrosis which can contribute to worsening trismus. Certain biomarkers, such as mRNA, can influence the staging of disease and genetic analysis of specimens may predict future malignant transformation. Hematoxylin and eosin is the most common stain used in the diagnosis of OSMF although special stains e.g. van gieson, may be used to demonstrate collagen in the lamina propria and submucosa [19].

Biochemical and biomolecular techniques are not routinely recommended. Serum copper levels have been correlated with the severity of OSMF. Blood investigations may be required to exclude certain differential diagnoses, for example anaemia or scleroderma [19].

Conventional oral examination, followed by biopsy remains the gold standard for diagnosis [20].

10.7. Management

Patients should be counselled on the continued use of Areca nut chewing and its role in the aetiopathogenesis and risk of malignant transformation and should be encouraged to stop the habit.OSMF carries a significant global disease burden and primary prevention is a key focus of government strategy in countries within the Indian subcontinent.

Approaches such as banning Areca plant products and their preparations, as well as education on the harmful effects of Areca nut chewing have been demonstrated to be useful in primary prevention at both individual and population levels [3]. OSMF often presents late creating a management dilemma.

10.7.1. Conservative management:

In the moderate to severe stages of OSMF, the degree of fibrosis is irreversible, and treatment is primarily symptomatic. Conservative management for progressive reduction of mouth opening involves physical therapy. Various exercises aimed at stretching the tissues and strengthening the muscles of mastication are advised. Custom made devices may also be useful in reducing trismus. Patients are encouraged to massage the muscles of mastication. Oral hygiene should be reinforced as patients with OSMF display higher levels of dental diseases such as periodontal disease, dental caries and halitosis [21, 22].

Patients complaining of general oral discomfort can be prescribed anesthetic. In more advanced stages of OSMF, intralesional corticosteroid injections have been useful in reducing trismus but with limited success [21].

Other topical treatments such as hyaluronidase may be useful and have a synergistic effect when used in combination with other topical treatments. Hyaluronidase catalyses the degradation of hyaluronic acid, a component of collagen. Other fibrinolytic therapies include the use of chemotrypsin and collagenase. Interferon gamma is a recognised antifibrotic cytokine and intralesional injection has demonstrated therapeutic effect. Intralesional application of placental extracts has also been demonstrated to be efficacious [21].

Other therapies aim to promote oral mucosal blood flow. Pentoxyphyline is a drug that alters fibroblast physiology and also improves tissue oxygenation by improving peripheral blood flow. It has been shown to provide symptomatic relief to patients with OSMF. Agents such Beta-adrenergic agonist drugs have a vasodilatory effect and also have been demonstrated to provide symptomatic relief [21].

The use of antioxidants, nutrients, micronutrients therapy (AONMT) are aimed at improving the nutritional status of patients with OSMF and are used in combination with vitamin and mineral supplementation. Agents such as Beta-carotene and lycopene are used to promote cellular health and have a protective effect with regards to the carcinogenic process [21].

There exists no globally accepted conservative management technique/s for OSMF. Kerr et al. [23] found a low grade of evidence to support recommendations for the management of OSF.

10.7.2. Surgical Management:

Surgical treatment may be indicated in severe cases of trismus and aims to improve mouth opening and masticatory and oral health [21]. The surgical approach usually involves removal of the fibrosed tissue and after care is aimed at maintaining opening after removal and muscle release [21].

Simple excision of the fibrosed bands exacerbates the condition, as iatrogenic trauma from the surgical process leads to subsequent fibrosis [21]. Chronic trismus as a result of OSMF can lead to physiological changes in the temporalis tendon and skin grafting procedures may help to resolve this, for example a Split-thickness skin grafting following bilateral temporalis myotomy or a coronoidectomy [21]. These are extensive surgical procedures and should not be undertaken lightly, but may alleviate the symptoms of trismus [21]. Myotomy of other masticatory muscles may also be considered [21].

Various flaps such as the nasolabial flap and its modifications (the extended nasolabial flap/ winged nasolabial flap/ facial artery-based nasolabial flap) are used to resurface intraoral defects after the above procedures [21]. These procedures result in aesthetically compromising facial scarring, however, in the Indian subcontinent it is widely applied due the simplicity of the procedure and the high success rate [21].

Free flaps are extensive surgical procedures primarily used in the management of oral squamous cell carcinoma [21]. The radial forearm free flap involves harvesting tissue from the forearm and is considered to be the gold standard surgical approach in the management of severe recalcitrant OSMF [21].

To avoid recurrence following surgery, postoperative physiotherapy is essential to maintain mouth opening. Physical therapy methods post-operatively are similar to those involved in the conservative management of OSMF [21]. Preoperative planning involves clinical, radiological and histopathological screening 21].

Summary

OSMF is chronic, progressive condition that results in fibrosis of the oral mucosa and, occasionally, the upper oesophagus, as a result of Areca nut chewing. Areca nut and its metabolites are both fibrogenic and carcinogenic and various preparations of Areca nut may include other carcinogens. The malignant transformation rate varies geographically and ranges from 1-9%. The rate of malignant transformation is dose dependent and correlated with the duration and intensity of Areca nut chewing habit and when used in combination with alcohol and tobacco consumption. There is no universally accepted management protocol.

Globally, knowledge of the condition amongst the general population and healthcare professionals is low. This may contribute to the late diagnosis of these patients. All healthcare professionals have a role in the primary prevention and recognition of the disease [3].

References

1. Rajendran R. Oral submucous fibrosis: etiology, pathogenesis, and future research. Bull World Health Organ. 1994;72(6):985-96.
2. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764-79.
3. Rao NR, Villa A, More CB, Jayasinghe RD, Kerr AR, Johnson NW. Oral submucous fibrosis: a contemporary narrative review with a proposed inter-professional approach for an early diagnosis and clinical management. J Otolaryngol Head Neck Surg. 2020;49(1):3.
4. Angadi PV, Rao SS. Areca nut in pathogenesis of oral submucous fibrosis: revisited. Oral Maxillofac Surg. 2011;15(1):1-9.
5. Arakeri G, Rai KK, Hunasgi S, Merkx MAW, Gao S, Brennan PA. Oral submucous fibrosis: An update on current theories of pathogenesis. J Oral Pathol Med. 2017;46(6):406-12.
6. Garg A, Chaturvedi P, Gupta PC. A review of the systemic adverse effects of areca nut or betel nut. Indian J Med Paediatr Oncol. 2014;35(1):3-9.
7. Yoithapprabhunath TR, Maheswaran T, Dineshshankar J, Anusushanth A, Sindhuja P, Sitra G. Pathogenesis and therapeutic intervention of oral submucous fibrosis. J Pharm Bioallied Sci. 2013;5(Suppl 1):S85-8.
8. Rai A, Ahmad T, Parveen S, Faizan MI, Ali S. Expression of transforming growth factor beta in oral submucous fibrosis. J Oral Biol Craniofac Res. 2020;10(2):166-70.
9. Pandya S, Chaudhary AK, Singh M, Mehrotra R. Correlation of histopathological diagnosis with habits and clinical findings in oral submucous fibrosis. Head Neck Oncol. 2009;1:10.
10. Cox SC, Walker DM. Oral submucous fibrosis. A review. Aust Dent J. 1996;41(5):294-9.
11. Gupta PC, Warnakulasuriya S. Global epidemiology of areca nut usage. Addict Biol. 2002;7(1):77-83.
12. More C, Gupta S, Joshi J, Varma S. Classification system for oral submucous fibrosis. Journal of Indian Academy of Oral Medicine and Radiology. 2012;24(1):24-9.
13. Passi D, Bhanot P, Kacker D, Chahal D, Atri M, Panwar Y. Oral submucous fibrosis: Newer proposed classification with critical updates in pathogenesis and management strategies. Natl J Maxillofac Surg. 2017;8(2):89-94.
14. PAYMASTER JC. Cancer of the buccal mucosa; a clinical study of 650 cases in Indian patients. Cancer. 1956;9(3):431-5.
15. Murti PR, Bhonsle RB, Pindborg JJ, Daftary DK, Gupta PC, Mehta FS. Malignant transformation rate in oral submucous fibrosis over a 17-year period. Community Dent Oral Epidemiol. 1985;13(6):340-1.
16. Arakeri G, Patil SG, Aljabab AS, Lin KC, Merkx MAW, Gao S, et al. Oral submucous fibrosis: An update on pathophysiology of malignant transformation. J Oral Pathol Med. 2017;46(6):413-7.
17. Ali FM, Patil A, Patil K, Prasant MC. Oral submucous fibrosis and its dermatological relation. Indian Dermatol Online J. 2014;5(3):260-5.
18. Silva WP, Wastner BF, Bohn JC, Jung JE, Schussel JL, Sassi LM. Unusual presentation of oral amyloidosis. Contemp Clin Dent. 2015;6(Suppl 1):S282-4.
19. Shih YH, Wang TH, Shieh TM, Tseng YH. Oral Submucous Fibrosis: A Review on Etiopathogenesis, Diagnosis, and Therapy. Int J Mol Sci. 2019;20(12).
20. Kim DH, Lee J, Lee MH, Kim SW, Hwang SH. Efficacy of chemiluminescence in the diagnosis and screening of oral cancer and precancer: a systematic review and meta-analysis. Braz J Otorhinolaryngol. 2020;29:S1808-8694(20)30110-5.
21. Arakeri G, Rai KK, Boraks G, Patil SG, Aljabab AS, Merkx MAW, et al. Current protocols in the management of oral submucous fibrosis: An update. J Oral Pathol Med. 2017;46(6):418-23.
22. Rai S, Rattan V, Gupta A, Kumar P. Conservative management of Oral Submucous Fibrosis in early and intermediate stage. J Oral Biol Craniofac Res. 2018;8(2):86-8.
23. Kerr A, Warnakulasuriya S, Mighell A, Dietrich T, Nasser M, Rimal J, Jalil A, Bornstein M, Nagao T, Fortune F, Hazarey V, Reichart P, Silverman S. and Johnson N. A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. Oral Diseases 2011; 17:42-57.

11

Palatal Lesions in Reverse Smokers

Vignesh Eswara Murthy[1]
Barbara Carey[1]
Rui Albuquerque[1,2]

1. Department of Oral Medicine, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom

2. Faculty of Dentistry, Oral & Craniofacial Sciences, King's College London, United Kingdom

Reverse smoking is an unusual form of smoking in which smokers place the lit end of the cigarette into the oral cavity and inhale the smoke. This particular form of smoking is prevalent on the Indian subcontinent [1]. When the cigarette is held by the teeth and lips, the seal provided by the lips allows for a slower inhalation of the cigarette fume. In addition, moisture from the lip on the opposite end of the cigarette may allow for the cigarette to be consumed over a longer time period. Cigarette ashes are often swallowed in the process. The intraoral temperature can reach up to 120 degrees Celsius and the products of combustion increase the frequency of lesions inside the oral cavity when compared to conventional smoking. There is a relative paucity of epidemiological and controlled studies assessing these lesions [1].

11.1. Definition

In 2020, the World Health Organization (WHO) collaborating centre for oral cancer, defined palatal lesions in reverse smokers (PLRS) as 'white and / or red patches affecting the hard palate in reverse smokers, frequently stained with nicotine' [2]. These lesions were first described in the Indian state of Andhra Pradesh in the 1970s [3]. While it is useful to have consistent nomenclature regarding PLRS, the definition does not describe the full spectrum of clinical presentations of the disease. Some of the changes in the palatal mucosa have a recognised malignant potential and PLRS are classified as an oral potentially malignant disorder (OPMDs) [2].

11.2. Aetiopathogenesis

The palatal mucosa, when continuously exposed to higher temperatures in reverse smoking results in thermal injury. In combination with the products of combustion, this thermal injury leads to increased frequency of palatal lesions when compared to conventional smoking. The lips act as a seal that prolongs contact time. The carcinogenic effects of cigarette smoking are well reported and have been described throughout this series [1].

Thermal injury along with prolonged contact with many of the carcinogens result in the likely changes in the palatal mucosa [4].

11.3. Epidemiology

Reverse smoking is a smoking habit observed around the world, however, there is a distinct lack of epidemiological studies evaluating the geographic distribution. Reverse smoking is most frequently observed in warm and tropical climates in the developing world, in countries such as Columbia, Venezuela, Panama and India [5]. The habit has also been observed in the developed world, for example it is known to be common on the Italian island of Sardinia. In India, reverse smoking appears to be a traditional habit amongst older woman in the southern state of Andhra Pradesh [6]. The type of cigarette used in these areas are often called *chutta*. A *chutta* is a coarse preparation of cheroot of varying length which can be prepared by the consumer or in factories. A study investigating the psychosocial factors associated with reverse smoking found that the habit is derived or *inherited* maternally or from other people in the family or social circle. The study found a profound psychological aetiology as there is no apparent physical benefit to perpetuating the habit [1, 5, 6].

11.4. Clinical Presentation

Bharath et al. [5], separated the palatal changes induced by reverse smoking into the following:

- Hyperpigmentation, in which well-defined diffuse or focal greyish black pigmentation is observed, as a result of melanocyte initiation. Typically, the margins are irregular, when compared to physiological racial pigmentation which presents as asymptomatic dark brown macules with less well-defined borders.

- Depigmentation, presents as pale areas in the oral mucosa, often surrounded by areas of hyperpigmentation. Bharath et al [5], hypothesised that melanocytes act as an antioxidant that scavenge the toxic products produced by tobacco during combustion. Prolonged reverse smoking may deprive this melanin defense barrier causing a reduction of melanin production. Depigmentation may also be described as palatal keratosis.

- Excrescences describe approximately 1-3mm elevated areas with central dots which mark the orifices of minor salivary gland in the palatal mucosa. These represent the initial palatal reaction in reverse smokers. Excrescences have been often historically used synonymously with nicotina palatini observed in conventional smokers, however, carry a higher malignant potential. The orifices are often referred to as central umbilications.

- Potentially Malignant Lesions: These areas are clinically indistinguishable from leukoplakia and erythroplakia. These conditions have been described in chapters in this series.

- Ulceration: These represent a 'burn' type reaction of the palatal mucosa from thermal injury, these ulcers are often crater-like. Ulceration may be the direct result of thermal injury, however, may also represent frank carcinoma [5].

In addition, multimorphic lesions with all the above have been described where all or some the above palatal changes coexist in a single lesion [1].

11.5. Differential Diagnosis

Specific conditions such as oral lichen planus, oral candidiasis and oral lupus may present with clinical features such as those listed above. These can be excluded on careful history taking and enquiry into a reverse smoking habit. Oral candidiasis can be excluded by taking a swab for culture and the patient may also have other risk factors for oral candidiasis, such as coexistent immunosuppression. Differentiation of leukoplakia and erythroplakia has been described elsewhere in this series [1].

11.6. Diagnosis

Careful enquiry into recreational habits and a history of long-standing reverse smoking should lead to a high degree of clinical suspicion when changes are observed in the palatal mucosa. Conventional oral examination with appropriate lighting should be sufficient to detect palatal oral mucosal changes.

Gomez et al., proposed a grading system for these lesions:

- Grade 0 in which no palatal changes are observed
- Grade 1 in which mild palatal changes are observed such as 'red circular areas over a slightly raised blanched mucosa of the glandular zone of the hard palate.'
- Grade 2 represent moderate palatal changes such as 'papules of 2-4mm with central umbilication less than 2mm of diameter. Moderate changes include hyperkeratinization and premalignant changes like leukoplakia.'
- Grade 3 represent severe palatal changes such as 'papules greater than 4-5mm in size with central umblicus 2-4 mm in size or characterised by crater like ulcerations surrounded by keratinization'.
- Grade 4 lesions represent palatal carcinoma [4].

Due to the malignant potential of PLRS, biopsy of these lesions is paramount and may show varying grades of dysplasia or carcinoma. Specifically, excrescences, histologically show hyperplasia of ductal epithelium [5].

11.7. Management

Management is dependent on the histological diagnosis. Lesions with moderate to severe dysplasia may undergo surgical excision. Similarly, carcinoma is treated by surgical excision, with or without neck dissection and radiotherapy, depending on lesion size and depth of invasion. The exact malignant transformation rate of PLRS is unknown due to the lack of studies. Similarly, the recurrence rates after treatment are also unknown. Van Der Eb et al. [7], concluded that reverse chutta smoking was one of the major determinants for palatal cancer [7]. A dose frequency relationship is assumed, however cannot be confirmed due to the paucity of studies.

Summary

Multiple pictures are available on Bharath et al. [8] Reverse smoking is a rare and peculiar tobacco smoking habit which results in variety of changes in the palatal mucosa, which can range from hyperpigmentation to frank palatal carcinoma.

Due to a lack of studies assessing this unique disease entity, there are many unanswered questions with regards to epidemiology, management, and malignant transformation rate.

References:

1. Dharmavaram AT, Nallakunta R, Reddy SR, Chennoju SK. Demystifying the Enigma of Smoking - An Observational Comparative Study on Tobacco Smoking. J Clin Diagn Res. 2016;10(4):ZC94-9.
2. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles M, Kerr AR, 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.
3. Pindborg JJ, Mehta FS, Gupta PC, Daftary DK, Smith CJ. Reverse smoking in Andhra Pradesh, India: a study of palatal lesions among 10,169 villagers. Br J Cancer. 1971;25(1):10-20.
4. Alvarez Gómez GJ, Alvarez Martínez E, Jiménez Gómez R, Mosquera Silva Y, Gaviria Núñez AM, Garcés Agudelo A, et al. Reverse smokers's and changes in oral mucosa. Department of Sucre, Colombia. Med Oral Patol Oral Cir Bucal. 2008;13(1):E1-8.
5. Bharath TS, Kumar NG, Nagaraja A, Saraswathi TR, Babu GS, Raju PR. Palatal changes of reverse smokers in a rural coastal Andhra population with review of literature. J Oral Maxillofac Pathol. 2015;19(2):182-7.
6. Harini G, Krishnam Raju KV, Raju DV, Chakravarthy KK, Kavya SN. Psychosocial factors associated with reverse smoking: A qualitative research. J Int Soc Prev Community Dent. 2016;6(6):529-34.
7. van der Eb MM, Leyten EM, Gavarasana S, Vandenbroucke JP, Kahn PM, Cleton FJ. Reverse smoking as a risk factor for palatal cancer: a cross-sectional study in rural Andhra Pradesh, India. Int J Cancer. 1993;54(5):754-8.
8. Bharath TS, Kumar NG, Nagaraja A, Saraswathi TR, Babu GS, Raju PR. Palatal changes of reverse smokers in a rural coastal Andhra population with review of literature. J Oral Maxillofac Pathol. 2015;19(2):182-187.

12

Proliferative Verrucous Leukoplakia (PVL)

Niccolò Lombardi[1]
Elena Varoni[1]
Alberto Pispero[1]
Barbara Carey[2]
Vignesh Eswara Murthy[2]
Giovanni Lodi[1]

1. Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche Università degli Studi di Milano, Italy

2. Department of Oral Medicine, Guy's Hospital, London

12.1. Definition

Proliferative verrucous leukoplakia (PVL) was first defined in 1985, when Hansen and colleagues first described a particular form of leukoplakia, characterised by slow-growth and persistence, with a tendency to spread, become multifocal, and exophytic or wart-like with time [1]. More recently, alternative terms 'Proliferative Multifocal Leukoplakia' and 'Proliferative Leukoplakia' have been suggested. 'Proliferative Multifocal Leukoplakia' was proposed by Aguirre-Urizar, to emphasize the proliferative and multifocal nature rather than the verrucous appearance [2]. 'Proliferative Leukoplakia', proposed by Villa and colleagues, was based on data demonstrating an absence of a verrucous appearance in almost 40% of cases [3].

In 2020, the Working Group of the WHO Collaborating Centre for Oral Cancer acknowledged that 'despite the imperfection of the term PVL to capture an expanded group of patients with multifocal disease, the term is widely reported, and the Working Group recommended retaining this term'. The same group proposed the following definition: 'a progressive, persistent, and irreversible disorder characterised by the presence of multiple leukoplakias that frequently become warty' [4].

PVL can be considered a distinct form of oral leukoplakia (OL) characterised by multifocal lesions, progressive clinical course and changes in clinical appearance and histopathologic features [4, 5]. However, such a position to classify PVL as a separate entity is not universally agreed, since large, widespread leukoplakias, and not only PVLs, carry a distinct risk of malignant transformation [6].

12.2. Epidemiology and Risk of Cancer

The overall prevalence of OL is estimated to range between 1.5% and 2.6% [7]. PVL is less common than standard leukoplakia and data on its prevalence is not available [3].

The aetiology of PVL remains unknown. PVL is more common in elderly females without a racial predilection [3, 5, 8] and it is not associated with the traditional risk factors for OL and oral squamous cell carcinoma (OSCC), i.e. tobacco and alcohol consumption [9]. Approximately two-thirds of PVL cases are in never-smokers and patients who do not report alcohol abuse [3, 5, 8].

The putative role of human papillomavirus (HPV) has not yet been established [3, 10]. The reported HPV prevalence in PVL ranges from 0-88% based on the results from studies with small patient numbers [9, 11, 12]. A study investigating the prevalence of HPV in 58 patients showed no significant differences between patients affected by PVL and those with conventional OL (24% versus 25%) [9, 13].

On the first histopathological examination, the majority of PVL lesions (52.5%) show hyperkeratosis without dysplasia or verrucous hyperplasia [3]. Nevertheless, PVL is associated with the highest incidence of oral cancer amongst OPMDs, either verrucous carcinoma or squamous cell carcinoma [14–20]. Approximately 61% of patients with PVL develop oral cancer over an average period of 7.4 years [21], though a recent systematic review estimated malignant transformation occurs in 49.5% (CI 26.7%-72.4%) of PVL cases [4,15]. The annual incidence is estimated to be 10.0% per year [22].

Multiple primary carcinomas of gingival sites have been reported in the literature in patients affected by PVL, evidenced in recent case series [8,17,23]. PVL is associated with an overall mortality of 40% [21, 24].

12.3. Clinical Presentation

Clinically, PVL may involve a single large area of the oral mucosa, but more frequently, it is multifocal, affecting the gingiva, buccal mucosa, and tongue in both contiguous and non-contiguous sites of the oral cavity [3, 5, 21, 25]. The oral sites more frequently involved by PVL are the gingiva (62.7%), the buccal mucosa (59.8%) and the tongue (49.1%) [9, 21]. Figures 12.1-12.3 illustrate PVL affecting multiple sites within the oral cavity.

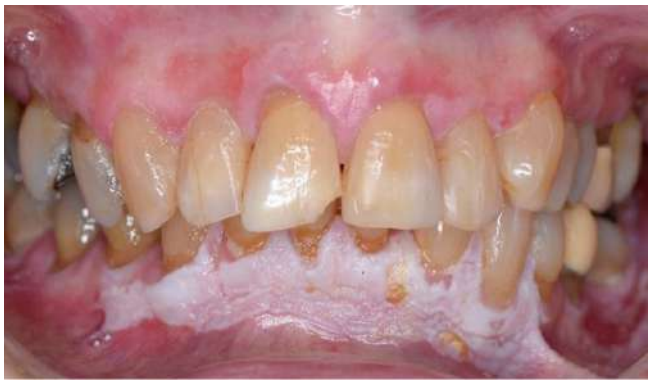

Figure 12.1. Dense PVL affecting the buccal gingiva in the lower anterior sextant, with nodular components, a speckled patch can also be seen in the lower left buccal sulcus.

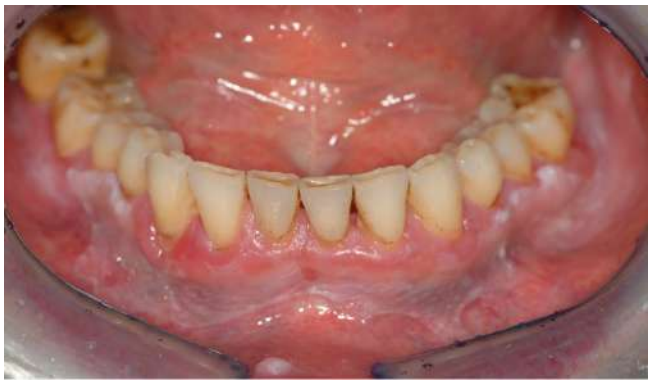

Figure 12.2. Mild PVL affecting the edentulous ridges.

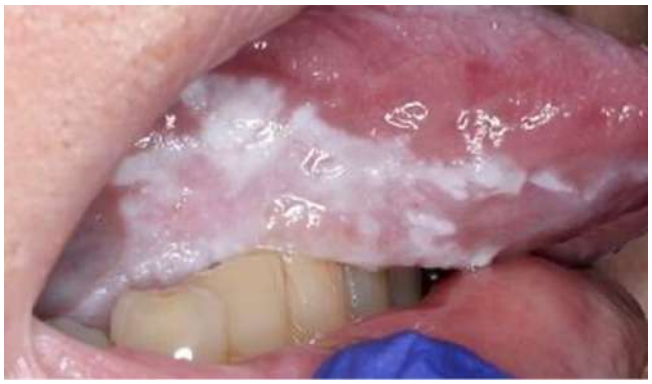

Figure 12.3. A dense multifocal area of PVL on the encompassing the right lateral tongue.

Multifocality and progressive clinical course are the main features which characterize PVL [4]. The oral lesions in PVL are often associated with ongoing changes in the clinical and histopathological picture [4]. Table 12.1 reports the characteristic clinical features of PVL as described in the recent report on OPMDs prepared by the WHO Collaborating Centre for Oral Cancer [4].

PVL clinical presentation
Multiple, thick, white patches in more than two different oral sites, frequently found on the gingiva, alveolar processes, and palate
Majority of the lesion presents a verrucous pattern
Lesions spread and coalesce during development
Recurrence in a previously treated area

Table 12.1. Clinical presentation of PVL according with WHO Collaborating Centre for Oral Cancer 2020 [4].

PVL usually begins as a homogenous leukoplakia with no dysplasia on histological examination and progressively evolves to verrucous lesions in single or multiple area of the oral mucosa [3,26]. At the beginning, PVL manifests as one or more leukoplakias which progressively affect multiple locations with gradual spread of a single lesion or multiple lesions coalescing [3, 4]. At the initial stages, PVL may present as a multifocal lesion lacking the typical verrucous appearance [3, 27]. In addition, the initial lesion can be white and flat, sometimes demonstrating a lichenoid appearance, making the distinction between it and oral lichen planus (OLP) difficult [3, 4, 28, 29]. In such cases, PVL may be erroneously treated as OLP for long periods with the subsequent risk of missing or delaying the diagnosis of a potential OSCC [4,29].

PVL has also been characterised by prominent erythema (19% in the series by Villa et al) with a malignant transformation rate (MTR) of 100% when compared to those PVL lesions without an erythematous component (MTR 62.5%) [3].

12.4. Diagnosis

The histopathological features of PVL are not pathognomonic and are non-specific, ranging from hyperkeratosis in the early stages, to verrucous hyperplasia, and different grades of dysplasia [5, 9]. In addition, PVL cases characterised clinically by an inflammatory component or lichenoid appearance may show a 'lichenoid' lymphocytic band, and be misdiagnosed as OLP [4]. For this reason, the definitive diagnosis of PVL is made on the basis of a combination of clinical and histopathological findings [1, 4, 9]. Every white lesion, which becomes warty and exophytic, with spread over time and recurrence after treatment, should be considered as PVL [27].

Since the first definition in 1985, other authors have proposed alternative diagnostic criteria [3]. In 2010, Cerero-Lapiedra et al proposed five major and four minor criteria, and specific combinations of them, to establish an early diagnosis of PVL (Tab.12.2) [20].

Major Criteria	Minor Criteria
Oral leukoplakia affecting more than two different oral sites (more frequently gingiva, palate, and alveolar ridge)	The lesions cover a mucosal extension that exceeds 3 cm (adding all the affected areas)
Verrucous clinical appearance	Female gender
Lesions show clinical progression and spreading	Never-smoker (regardless of gender)
Recurrence in a previously treated area	Disease evolution longer than 5 years
Histopathological picture of oral epithelial hyperkeratosis or verrucous hyperplasia, verrucous carcinoma, or squamous cell carcinoma.	
Diagnosis of PVL can be made when: • three major criteria (histopathological criterion being one) or • two major (histopathological criterion being one) and two minor criteria	

Table 12.2. PVL diagnostic criteria according to Cicero-Lapiedra et al. (Modified by [3,20]).

Carrard et al proposed to simplify the diagnostic criteria of PVL omitting the distinction between major and minor criteria, and suggested four criteria which should be met (Table 12.3) [30].

Modified diagnostic criteria for PVL: all four criteria should be met.

1. Leukoplakia showing the presence of verrucous or wartlike areas, involving more than two oral subsites. The following oral subsites are recognised: dorsum of the tongue (unilateral or bilateral), border of the tongue, cheek mucosa, alveolar mucosa or gingiva upper jaw, alveolar mucosa or gingiva lower jaw, hard and soft palate, floor of the mouth, upper lip and lower lip.
2. Adding all involved sites, the minimum seize should be at least three centimeters.
3. A well-documented period of disease evolution of at least five years, being characterised by spreading and enlarging and the occurrence of one or more recurrences in a previously treated area.
4. The availability of at least one biopsy in order to rule out the presence of a verrucous carcinoma or squamous cell carcinoma.

Table 12.3. Simplified diagnostic criteria for PVL [30].

When obtaining a biopsy from a suspected PVL lesion, as well as non-homogeneous OL, it is important to choose the most representative parts to avoid underdiagnosis [31]. Histopathological examination may lead to a variable diagnosis within the same lesion [31]. For this reason, multiple mapping biopsies are often recommended [5, 22]. Multiple and periodic mapping biopsies are indicated in PVL to detect different grades of dysplasia or to exclude OSCC [5, 22]. It has been reported in PVL and non-homogeneous OL that approximately 10%–17% of OSCC cases may be missed by performing only a single biopsy [5, 32, 33].

12.5. Management

The management and treatment of PVL is particularly challenging [5]. In the last decade, different approaches have been proposed to reduce the high incidence of oral cancer among patients affected by PVL. To date, none of the treatments, (surgery, laser ablation, retinoids, photodynamic therapy and chemo¬therapy) have proven to be effective in reducing oral cancer development in these patients [19, 34].

Despite the lack of evidence on efficacy, surgical treatment is the most frequent intervention adopted in the management of PVL [24]. When PVL is characterised by small lesions, and if the area is discrete, excision may be attempted, but the patient should be aware that ongoing follow-up will be necessary due to high oral cancer risk and risk of lesion recurrence (71%) [3, 24]. Most PVL cases demonstrate large lesions and involve multifocal non-contiguous areas. A recent systematic review reported the overall recurrence rate of PVL to all treatment modalities is approximately 85% [19], without any reduction in cancer incidence [19]. For all these reasons, surgical excision in extensive PVL may be considered an impractical and unnecessary aggressive treatment option [35].

Many clinicians choose a 'wait and see' approach, based on periodical multiple biopsies and regular clinical examination [35]. The aim of this approach is to identify very early onset of oral carcinoma, giving the best treatment outcome and prognosis.

In conclusion, considering the high cancer incidence in PVL patients, multiple biopsies and strict clinical follow-up is mandatory (every 3-6 months depending on clinical features) [24]. The timing of malignant transformation is unpredictable, therefore lifelong follow-up is necessary [3].

References

1. Hansen, L.S.; Olson, J.A.; Silverman, S. Proliferative verrucous leukoplakia. A long-term study of thirty patients. Oral Surgery, Oral Med. Oral Pathol. 1985, 60, 285–298.
2. Aguirre-Urizar, J.M. Proliferative multifocal leukoplakia better name that proliferative verrucous leukoplakia. World J. Surg. Oncol. 2011, 9, 122.
3. Villa, A.; Menon, R.S.; Kerr, A.R.; De Abreu Alves, F.; Guollo, A.; Ojeda, D.; Woo, S.B. Proliferative leukoplakia: Proposed new clinical diagnostic criteria. Oral Dis. 2018, 24, 749–760.
4. Warnakulasuriya, S.; Kujan, O.; Aguirre□Urizar, J.M.; Bagan, J. V.; González□Moles, M.Á.; Kerr, A.R.; Lodi, G.; Mello, F.W.; Monteiro, L.; Ogden, G.R.; 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. 2021, 27(8):1862-1880..
5. Villa, A.; Sonis, S. Oral leukoplakia remains a challenging condition. Oral Dis. 2018, 24, 179–183.
6. van der Waal, I. Oral leukoplakia; a proposal for simplification and consistency of the clinical classification and terminology. Med. Oral Patol. Oral y Cir. Bucal 2019, 24, e799–e803.
7. Petti, S. Pooled estimate of world leukoplakia prevalence: A systematic review. Oral Oncol. 2003, 39, 770–780.
8. Lombardi, N.; D'amore, F.; Elli, C.; Pispero, A.; Moneghini, L.; Franchini, R. Gingival lesion in proliferative verrucous leukoplakia. Dent. Cadmos 2020, 88, 647–648.
9. Staines, K.; Rogers, H. Oral leukoplakia and proliferative verrucous leukoplakia: A review for dental practitioners. Br. Dent. J. 2017, 223, 655–661.
10. Varoni, E.M.; Lombardi, N.; Franchini, R.; D'Amore, F.; Noviello, V.; Cassani, B.; Moneghini, L.; Sardella, A.; Lodi, G. Oral Human Papillomavirus (HPV) and sexual behaviors in a young cohort of oral cancer survivors. Oral Dis. 2021, 27, 919–923.
11. Bagan, J. V.; Jimenez, Y.; Murillo, J.; Gavaldá, C.; Poveda, R.; Scully, C.; Alberola, T.M.; Torres-Puente, M.; Pérez-Alonso, M. Lack of Association Between Proliferative Verrucous Leukoplakia and Human Papillomavirus Infection. J. Oral Maxillofac. Surg. 2007, 65, 46–49.
12. Palefsky, J.M.; Silverman, S.; Abdel□Salaam, M.; Daniels, T.E.; Greenspan, J.S. Association between proliferative verrucous leukoplakia and infection with human papillomavirus type 16. J. Oral Pathol. Med. 1995, 24, 193–197.
13. Campisi, G.; Giovannelli, L.; Ammatuna, P.; Capra, G.; Colella, G.; Di Liberto, C.; Gandolfo, S.; Pentenero, M.; Carrozzo, M.; Serpico, R.; et al. Proliferative verrucous vs conventional leukoplakia: No significantly increased risk of HPV infection. Oral Oncol. 2004, 40, 835–840.
14. Cabay, R.J.; Morton, T.H.; Epstein, J.B. Proliferative verrucous leukoplakia and its progression to oral carcinoma: A review of the literature. J. Oral Pathol. Med. 2007, 36, 255–261, doi:10.1111/j.1600-0714.2007.00506.x.
15. Iocca, O.; Sollecito, T.P.; Alawi, F.; Weinstein, G.S.; Newman, J.G.; De Virgilio, A.; Di Maio, P.; Spriano, G.; Pardiñas López, S.; Shanti, R.M. 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.
16. Villa, A.; Celentano, A.; Glurich, I.; Borgnakke, W.S.; Jensen, S.B.; Peterson, D.E.; Delli, K.; Ojeda, D.; Vissink, A.; Farah, C.S. World Workshop on Oral Medicine VII: Prognostic biomarkers in oral leukoplakia: A systematic review of longitudinal studies. Oral Dis. 2019, 25, 64–78.
17. Lodi, G.; Tarozzi, M.; Baruzzi, E.; Costa, D.; Franchini, R.; D'Amore, F.; Carassi, A.; Lombardi, N. Odontoiatria e cancro della bocca: dai fattori di rischio alla riabilitazione - Modulo 1: Epidemiologia e fattori di rischio. Dent. Cadmos 2021, 89, 01.
18. Lombardi, N.; Varoni, E.M.; Moneghini, L.; Lodi, G. Submucosal oral squamous cell carcinoma of the tongue. Oral Oncol. 2021, 115, 105121.
19. Capella, D.L.; Gonçalves, J.M.; Abrantes, A.A.A.; Grando, L.J.; Daniel, F.I. Proliferative verrucous leukoplakia: diagnosis, management and current advances. Braz. J. Otorhinolaryngol. 2017, 83, 585–593.
20. Cerero-Lapiedra, R.; Balade-Martinez, D.; Moreno-Lopez, L.; Esparza-Gomez, G.; Bagan, J. Proliferative verrucous leukoplakia: A proposal for diagnostic criteria. Med. Oral Patol. Oral y Cir. Bucal 2010, 15, e839–e845.
21. Pentenero, M.; Meleti, M.; Vescovi, P.; Gandolfo, S. Oral proliferative verrucous leucoplakia: Are there particular features for such an ambiguous entity? A systematic review. Br. J. Dermatol. 2014, 170, 1039–1047.
22. Villa, A.; Woo, S. Bin Leukoplakia—A Diagnostic and Management Algorithm. J. Oral Maxillofac. Surg. 2017, 75, 723–734.
23. Bagan, J.; Murillo-Cortes, J.; Poveda-Roda, R.; Leopoldo-Rodado, M.; Bagan, L. Second primary tumors in proliferative verrucous leukoplakia: a series of 33 cases. Clin. Oral Investig. 2020, 24, 1963–1969.
24. Abadie, W.M.; Partington, E.J.; Fowler, C.B.; Schmalbach, C.E. Optimal Management of Proliferative Verrucous Leukoplakia: A Systematic Review of the Literature. Otolaryngol. - Head Neck Surg. (United States) 2015, 153, 504–511.

25. Warnakulasuriya, S.; Johnson, N.W.; Van Der Waal, I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J. Oral Pathol. Med. 2007, 36, 575–580.
26. Ghazali, N.; Bakri, M.M.; Zain, R.B. Aggressive, multifocal oral verrucous leukoplakia: proliferative verrucous leukoplakia or not? J. Oral Pathol. Med. 2003, 32, 383–392.
27. Warnakulasuriya, S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 2018, 125, 582–590.
28. Garcia-Pola, M.; Llorente-Pendas, S.; Gonzalez-Garcia, M.; Garcia-Martin, J. The development of proliferative verrucous leukoplakia in oral lichen planus. A preliminary study. Med. Oral Patol. Oral y Cir. Bucal 2016, 21, e328–e334.
29. McParland, H.; Warnakulasuriya, S. Lichenoid morphology could be an early feature of oral proliferative verrucous leukoplakia. J. Oral Pathol. Med. 2021, 50, 229–235.
30. Carrard, V.C.; Brouns, E.R.E.A.; van der Waal, I. Proliferative verrucous leukoplakia; A critical appraisal of the diagnostic criteria. Med. Oral Patol. Oral Cir. Bucal 2013, 18, e411–e413.
31. Warnakulasuriya, S. Oral potentially malignant disorders: A comprehensive review on clinical aspects and management. Oral Oncol. 2020, 102, 104550.
32. Pentenero, M.; Carrozzo, M.; Pagano, M.; Galliano, D.; Broccoletti, R.; Scully, C.; Gandolfo, S. Oral mucosal dysplastic lesions and early squamous cell carcinomas: Underdiagnosis from incisional biopsy. Oral Dis. 2003, 9, 68–72.
33. Lee, J.J.; Hung, H.C.; Cheng, S.J.; Chiang, C.P.; Liu, B.Y.; Yu, C.H.; Jeng, J.H.; Chang, H.H.; Kok, S.H. Factors associated with underdiagnosis from incisional biopsy of oral leukoplakic lesions. Oral Surgery, Oral Med. Oral Pathol. Oral Radiol. Endodontology 2007, 104, 217–225.
34. Lodi, G.; Franchini, R.; Warnakulasuriya, S.; Varoni, E.M.; Sardella, A.; Kerr, A.R.; Carrassi, A.; MacDonald, L.C.; Worthington, H. V.; Mauleffinch, L.F. Limited evidence for interventions to treat oral leukoplakia. Evid. Based. Dent. 2017, 18, 92–93.
35. Thomson, P.J.; McCaul, J.A.; Ridout, F.; Hutchison, I.L. To treat□or not to treat? Clinicians' views on the management of oral potentially malignant disorders. Br. J. Oral Maxillofac. Surg. 2015, 53, 1027–1031.

13

Discoid Lupus Erythematosus

Vlaho Brailo[1,2]
Ana Andabak Rogulj[1]
Barbara Carey[3]
Ivana Škrinjar[1,2]

1 Department of Oral Medicine, School of Dental Medicine, University of Zagreb, Zagreb, Croatia

2 Department of Oral Medicine, Clinic for Dentistry, University clinical hospital Zagreb, Zagreb, Croatia

3 Department of Oral Medicine, Guy's and St Thomas's NHS Foundation Trust, London, UK

The aim of this chapter is to present readers with summarised information on the epidemiology, clinical characteristics, diagnostic procedure and management of oral lesions in discoid lupus erythematosus (DLE).

13.1. Definition

Discoid lupus erythematosus (DLE) is a chronic inflammatory condition affecting skin and oral mucosa (1). DLE is the most common variant of chronic cutaneous lupus comprising 80% of cases [2]. The pathophysiology of the disease is complex and involves multiple factors including genetics, environmental factors and the innate and adaptive immune system (2). The most common environmental triggers for DLE include UV irradiation, drugs, radiotherapy and smoking [4, 5].

13.2. Epidemiology

The prevalence of DLE ranges from 9-70 cases per 100,000 population [6,7]. DLE incidence in the general population varies from 0.8-4/100 000 person/years and is 3–5 times higher in Asian and Black ethnic groups compared to White ethnic groups [3, 6, 8]. DLE predominantly affects women with a female to male ratio of 3:1. Although DLE may occur at any age, it most often develops in persons aged 20-40 years. Oral lesions are present in 20% of DLE patients [9,10]. Occurrence of oral lesions in DLE patients without cutaneous involvement is rare and reported in 10% of cases [11].

13.3. Clinical presentation

The most common presentation of chronic cutaneous lupus is DLE which may occur as localised type (80%) with lesions presenting on the face, ears and scalp. Disseminated DLE (20% of cases) presents with lesions above and below the neck and is associated with an increased risk of progression to systemic lupus erythematosus [12]. DLE cutaneous lesions present on sun exposed areas of the face and neck with annular erythema and follicular hyperkeratosis. A characteristic plaque over the malar area of the face and the bridge of the nose in a butterfly pattern has been described. The skin lesions may be accompanied by an itching or burning sensation.

As the skin lesions progress, central atrophy, scarring, telangiectasia and hypopigmentation occur. Irreversible scarring alopecia on the scalp also occurs [13].

Oral lesions occur in approximately 20% of the cases and typically affect the lips, hard palate and buccal mucosa [14]. Oral DLE lesions are characterised by the presence of central erythema or ulceration surrounded by hyperkeratotic papules or radiating striae, and peripheral telangiectasia (Figures 13.1 and 13.2). The 'honeycomb' appearance occurs in long-standing lesions. Mucosal lesions may occur without involvement of the skin or prior to the development of skin lesions. Lip lesions may spread to involve the adjacent skin, obscuring the vermilion border. Desquamative gingivitis affecting lower and/or upper gingiva may also be present [15]. With healing, erosive lesions may leave post-inflammatory pigmentation. The most common symptoms of DLE include a burning sensation (66.6%), photosensitivity (57.1%), dryness (23.8%), tenderness (14.3%) and pain (4.8%) but lesions can be asymptomatic [11].

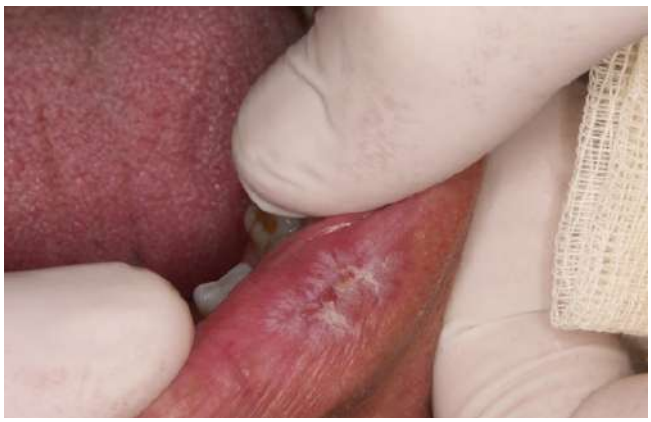

Figure 13.1. Lip lesion in DLE presenting with central atrophy surrounded by radiating hyperkeratotic striae (courtesy of Professor Ivan Alajbeg).

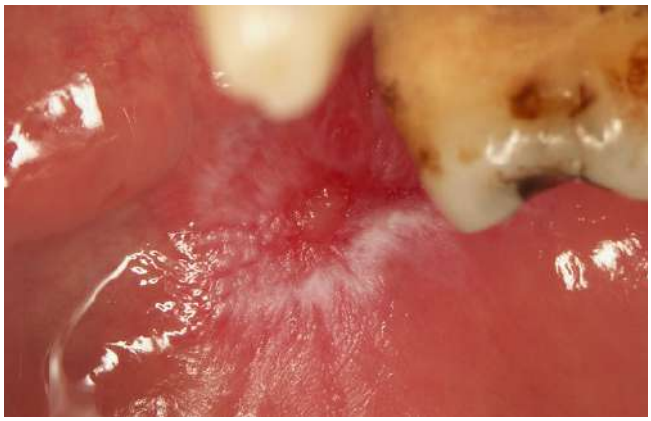

Figure 13.2. Oral mucosal lesion of DLE presenting with central atrophy and erosion surrounded by radiating hyperkeratotic striae (courtesy of Professor Ivan Alajbeg).

DLE patients have increased risk of cancer, including non-melanoma skin cancer and oral cancer, compared to the general population [16, 17]. The World Health Organization categorised DLE as an oral potentially malignant disorder though malignant transformation is rare [18, 19]. More commonly, malignant transformation occurs in DLE lesions localised to the vermilion border of the lip, with the lower lip more often affected. Long-term ultraviolet light exposure, chronic scarring, HPV infection and long-term immunosuppressive therapy may be predisposing factors for the development of SCC. The mean duration from the onset of DLE to the development of lip cancer is shorter compared to cancers originating from DLE lesions at other sites (10-13 years vs. 19-26 years) [20–24]. Furthermore, DLE-related cancers are more aggressive and have higher metastatic potential (10-25%), recurrence rates (27-29%) and mortality (19.4%) compared to non-DLE related cancers (20%, 0.5-6% and 1%, respectively) [20-24].

13.4. Differential diagnosis

The differential diagnosis of DLE oral lesions includes oral lichen planus (OLP), oral lichenoid lesions, oral leukoplakia and actinic cheilitis (when the lower lip is affected) [25].

In the case of OLP, lesions are more widespread and more symmetrically distributed, and the reticular pattern is more pronounced unlike in DLE oral lesions. Contact oral lichenoid lesions present as white striae in sites directly in contact with amalgam restoration. Following removal of the restoration, the lesion improves or resolves. Oral leukoplakia does not exhibit a radial pattern of hyperkeratotic striae and does not present with central atrophy. Actinic cheilitis usually involves the lower lip presenting with scabbing and without striae formation [25].

13.5. Diagnosis

The diagnosis of DLE can be challenging in light of the similarities with oral lichen planus on histopathology. Chapter 'Histological Aspects of Oral Potentially Malignant Disorders' discusses these challenges in greater detail.

Histological findings of oral DLE include hyperkeratosis with keratotic plugs, atrophy of the rete ridges, hydropic degeneration of the basal cell layer, interface mucositis with superficial or deep perivascular lymphocytic infiltrate, oedema in the lamina propria and PAS positive thickening of blood vessel walls [11, 26, 27]

Though the histology of oral DLE is characteristic, it may be difficult to distinguish from oral lichen planus. Direct immunofluorescence (DIF) may be helpful for further analysis [28]. DLE lesions demonstrate linear or granular deposition of IgM, IgG and complement 3 (C3) at the basement membrane zone – the so called 'lupus band' [28]. In contrast to DLE, fibrinogen deposits can be found in 90-100% of the OLP patients along the basement membrane [28]. Due to the marked difference in DIF findings between DLE and oral lichen planus, many authors believe DIF should be part of the diagnostic standard when it is suspected [26, 27].

Serological and haematological abnormalities may be detected in DLE patients [29]. In some cases, the erythrocyte sedimentation rate may be elevated [29]. Approximately 20% of patients have positive antinuclear antibody (ANA) and up to 20% have SS-A autoantibodies. Anti-Sm autoantibodies, usually seen in systemic lupus erythematosus, may occur in 5-20% of DLE patients [29].

13.6. Management

Patients should be made aware of the possibility of progressing to systemic disease. The risk of progression from DLE to SLE is 16.7% within 3 years of diagnosis and 17% within 8 years of diagnosis [3, 30]. Preventive measures include avoidance of UV exposure and smoking cessation.

While there appears to be some evidence on the use of topical fluocinonide cream, systemic hydroxychloroquine and acitretin in patients with DLE affecting the skin, the evidence for oral DLE management is scarce [31].

In cases of localised oral lesions, topical treatment is first-line. Topical corticosteroids (triamcinolone acetonide, betamethasone valerate, clobetasol diproprionate, hydrocortisone, fluocinolone acetonide) are the mainstay of therapy.

Calcineurin inhibitors (tacrolimus, pimecrolimus) may also be used. Intralesional injection of corticosteroids (triamcinolone acetonide) is useful for individual lesions. For recalcitrant lesions or widespread disease, systemic therapy is often needed. Antimalarials (hydroxychloroquine, chloroquine and quinacrine) alone or in combination with systemic corticosteroids are used as first-line systemic drugs. In more severe cases, immunomodulators (dapsone, thalidomide, lenalidomide) and/or oral retinoids (acitretin, isotretinoin, alitretinoin) and/or immunosuppressives (methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, mycophenolate sodium, cyclosporine) can be used. Biologic agents (rituximab, belimumab) are used in the most severe cases [27, 32].

Patients with DLE should be monitored at regular intervals. Response to therapy differs for each patient, varying from a few weeks to months.

Each patient should be managed on a case-by-case basis for the purposes of symptom control and surveillance for potential malignant transformation [19–24].

Summary

Oral lesions are detected in 20% of DLE patients. Lesions have a characteristic appearance with central atrophy surrounded by radial hyperkeratotic striae. Lesions can clinically and histologically resemble oral lichen planus. The diagnosis is made by histological examination and direct immunofluorescence. Topical corticosteroids form the first-line treatment. Malignant transformation of oral DLE lesions is rare. DLE-related cancers predominantly arise on the lower lip and show more aggressive behaviour with higher recurrence rates, metastatic potential and mortality compared to non-DLE related cancers.

References

1. Warnakulasurya S. Clinical features and presentation of oral potentially malignant disorders. Oral Surg Oral Med Oral Pathol Oral Radiol. 2018;125:582–90.
2. Stannard JN, Kahlenberg JN. Cutaneous lupus erythematosus: updates on pathogenesis and associations with systemic lupus. Curr Opin Rheumatol. 2016;28(5): 453–9.
3. Grönhagen CM, Fored CM, Granath F, Nyberg F. Cutaneous lupus erythematosus and the association with systemic lupus erythematosus: a population-based cohort of 1088 patients in Sweden. Br J Dermatol. 2011;164(6):1335-41.
4. Blake SC, Daniel BS. Cutaneous lupus erythematosus: A review of the literature. Int J Womens Dermatol. 2019;5(5):320-9.
5. Szczęch J, Samotij D, Werth DP, Reich A. Trigger factors of cutaneous lupus erythematosus: a review of current literature. Lupus. 2017;26(8):791-807.
6. Izmirly PM, Buyon JP, Belmont HM, Sahl S, Wan I, Salmon JE et al. Population-based prevalence and incidence estimates of primary discoid lupus erythematosus from the Manhattan Lupus Surveillance Program. Lupus Sci Med. 2019;6(1):e000344.
7. Jarukitsopa S, Hoganson DDD, Crowson CS, Sokumbi O, Davis MD, Michet CJ et al. Epidemiology of Systemic Lupus Erythematosus and Cutaneous Lupus in a Predominantly White Population in the United States. Arthritis Care Res. 2015; 67(6): 817–28.
8. Drenkard C, Parker S, Aspey LD, Gordon C, Helmick CG, Bao G, Sam Lim S. Racial disparities in the incidence of primary chronic cutaneous lupus erythematosus in the southeastern US: the Georgia lupus registry. Arthritis Care Res. 2019; 71:95–103.
9. Nico MMS, Apparecida M, Vileila C, Rivitti EA, Lourenco SV. Oral lesions in lupus erythematosus: correlation with cutaneous lesions. Eur J Dermatol 2008;18(4):376-81.
10. Menzies S, O'Shea F, Galvin S, Wynne B. Oral manifestations of lupus. Ir J Med Sci. 2018; 187:91–3.
11. Ranginwala AM, Chalishazar MM, Panja P, Buddhdev KP, Kale HM. Oral discoid lupus erythematosus: A study of twenty-one cases. J Oral Maxillofac Pathol. 2012;16(3): 368–73.
12. Lallas A, Apalla Z, Lefaki I, et al. Dermoscopy of discoid lupus erythematosus. Br J Dermatol 2013;168: 284–8.
13. McDaniel B, Sukumaran S,Tanner LS. Discoid Lupus Erythematosus. NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
14. Shafer WG, Hine MK, Levy BM. A textbook of oral pathology. 7th ed. Philadelphia: W B Saunders;1999. p. 8992.
15. Kranti K, Seshan H, Juliet J. Discoid lupus erythematosus involving gingiva. J Indian Soc Periodontol. 2012;16(1): 126–8.
16. Grönhagen CM, Fored CM, Granath F, Nyberg F. Increased risk of cancer among 3663 patients with cutaneous lupus erythematosus: A Swedish nationwide cohort study. Br J Dermatol 2012; 166: 1053–1059.
17. de Berker D, Dissaneyeka M, Burge S. The sequelae of chronic cutaneous lupus erythematosus. Lupus 1992;1:181-6.
18. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36:575-580.
19. Arvanitidou IE, 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.
20. Fernandes MS, Girisha BS, Viswanathan N, Sripathi H and Noronha TM. Discoid lupus erythematosus with squamous cell carcinoma: a case report and review of the literature in Indian patients. Lupus. 2015; 24: 1562–6.
21. Sherman RN, Lee CW, Flynn KJ. Cutaneous squamous cell carcinoma in black patients with chronic discoid lupus erythematosus. Int J Dermatol 1993; 32: 677–679.
22. Liu W, Shen ZY, Wang LJ, et al. Malignant potential of oral and labial chronic discoid lupus erythematosus: A clinicopathological study of 87 cases. Histopathology 2011; 59: 292–298.
23. Tao J, Zhang X, Guo N, et al. Squamous cell carcinoma complicating discoid lupus erythematosus in Chinese patients: Review of the literature, 1964–2010. J Am Dermatol 2012; 66: 695–696.
24. Makita E, Akasaka E, Sakuraba Y, Korekawa A, Aizu T, Kaneko T et al. Squamous cell carcinoma on the lip arising from discoid lupus erythematosus: a case report and review of Japanese patients. Eur J Dermatol. 2016;26(4):395-6.

25. Naik V, Prakash S. Oral Discoid Lupus Erythematosus: A Case Effectively Managed and Differentiated with other Overlapping Diseases. Indian J Dent Adv 2018;9(4): 221-5.
26. Del Barrio-Díaz P, Reyes-Vivanco C, Cifuentes-Mutinelli M, Manríquez J, Vera-Kellet C. Association between oral lesions and disease activity in lupus erythematosus. J Eur Acad Dermatol Venereol. 2020;34(2):349-356.
27. Martins da Costa Marques ER, Silva R, Hsieh R. Oral Mucosal Manifestation of Lupus Erythematosus: A Short Review. Dent Oral Biol Craniofac Res 2020.
28. Bhushan R, Agarwal S, Chander R, Agarwal K. Direct Immunofluorescence Study in Discoid Lupus Erythematosus. World Journal of Pathology 2017; 9:56-60.
29. Biazar C. Sigges J. Patsinakidis N. Ruland V. Amler S. Bonsmann G. Kuhn A. Cutaneous lupus erythematosus: first multicenter database analysis of 1002 patients from the European Society of Cutaneous Lupus Erythematosus (EUSCLE).Autoimmun Rev. 2013; 12(3):444-454.
30. Wieczorek I.T., Propert K.J., Okawa J, Werth V.P. Systemic symptoms in the progression of cutaneous to systemic lupus erythematosus. JAMA Dermatol. 2014; 150(3):291-6.
31. Jessop S, Whitelaw DA, Grainge MJ, Jayasekera P. Drugs for discoid lupus erythematosus. Cochrane Database Syst Rev. 2017;5(5):CD002954.
32. Okon LG, Werth VP. Cutaneous lupus erythematosus: diagnosis and treatment. Best Pract Res Clin Rheumatol. 2013;27: 391-404.

14

Genetic Disorders

Saman Warnakulasuriya

Emeritus Professor, King's College London,
Director, WHO Collaborating Centre for Oral Cancer

14.1. Familial or genetic predisposition

Sporadic case reports are found in the literature that proposed oral cancer could be familial [1]. The authors conducted a pedigree analysis of oral cancer patients registered in their Centre and reported a familial aggregation of oral cancer in 5 families. The familial cancers were 0.94 % of the total oral cancer cases. A case-control study from Italy and Switzerland confirmed a family history of oral, pharyngeal cancer or laryngeal cancer is a strong determinant of oral and pharyngeal cancer risk, independent from tobacco and alcohol [2] [multivariate OR: 2.6, 95% CI: 1.5–4.5], while the adjusted OR was much higher 7.1 (95% CI: 1.3–37.2) for those with 2 or more first-degree relatives affected. In this multicentre study, a family history of most other cancer sites was not associated with an increased risk of oral and pharyngeal cancer.

14.2. Genetic Predisposition

Of the many genetic cancer syndromes described patients with Fanconi anaemia, Dyskeratosis Congenita, xeroderma pigmentosum, Li Fraumeni syndrome, Blooms's syndrome, ataxia telangiectasia, and Cowden syndrome have shown an increased susceptibility to oral cancer due to genetic instability. Fanconi anaemia has the strongest evidence for a predisposition to cancer. Dyskeratosis Congenita (DKC) (also called Zinsser-Cole-Engman syndrome) is a rare hereditary condition with predisposition to oral leukoplakia of the tongue that could transform to cancer in early life.

In this chapter we describe susceptibility to oral cancer and oral potentially malignant disorders (OPMDs) in two cancer syndromes namely Fanconi anaemia and Dyskeratosis Congenita. OPMDs associated with these two syndromes are chronic graft vs host disease (cGVHD) (recently added to the OPMD classification in 2020), oral lichen planus and oral leukoplakia.

14.3. Fanconi anaemia

Fanconi anaemia (FA) is a multisystem disorder characterised by a spectrum of congenital abnormalities, progressive bone marrow failure and pancytopenia, high susceptibility to acute myeloid leukaemia (AML) and solid tumours. FA occurs worldwide and affects 1 in 100,000 births in the USA, and notably more common among Afrikaners (approximates 1 in 22,000), estimated at 1 in 45,000 in Israel and the Spanish Gypsy population is reported to having the highest prevalence.

FA is a clinically a heterogenous syndrome of bone marrow failure (BMF), congenital abnormalities that may affect all organ systems. Patients with FA may suffer from a variety of malformations. Congenital anomalies include skeletal malformations (short stature, microcephaly, or hypoplastic thumb), organ abnormalities (renal, ophthalmic, ear, cardiac, and genital), abnormal skin pigmentation, like café au lait patches (Table 14.1). So far, 23 genes have been implicated in FA caused by germline mutations in one of multiple FA genes (FANCA to FANCV). Mutations in FANCA are the most common, involved in 60–65% of reported cases. All mutations in FA genes are inherited in an autosomal recessive manner, except for FANCB and RAD51, which are inherited in an X-linked manner and autosomal dominant manner, respectively. FA proteins interact in a common cellular pathway and participate in various aspects of DNA repair, particularly DNA crosslink repair, genomic stabilization, and regulation of downstream proteins. Defects in any of these FA proteins result in genomic instability, defective DNA repair mechanisms and an increased risk of cancer. FA patients with hematopoietic dysfunction usually require bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT) which is the preferred treatment option. One of the most common complications after hematopoietic stem cell transplantation (HSCT) is the development of oral chronic graft-versus-host disease (cGVHD), which is also a risk factor for the development of cancer, particularly oral squamous cell carcinoma. cGVHD is now recognised as an oral potentially malignant disorder (OPMD) [3].

Given the wide range of clinical abnormalities, patients with FA require a comprehensive evaluation at diagnosis. FA may be grossly indistinguishable from other genetic syndromes, causing challenges to diagnosis. Variable expressiveness of FA makes early diagnosis difficult in certain cases. A detailed clinical description of most frequent alterations found in the different organs is given by Moreno et al (4). Laboratory diagnosis is made by positivity in the chromosome breakage test upon exposure to DNA-crosslinking agents. Other diagnostic methods used include western blotting, multiplex ligation-dependent probe amplification and next-generation sequencing. Once the diagnosis is confirmed lifelong surveillance of patients with FA is required to ensure early diagnosis of cancer. Genetic counselling is essential.

Craniofacial malformations
Developmental delay
Short stature
Hypodontia, small teeth
Oral bleeding
Swollen gums
VACTERL association
Abnormal thumb or radius
Osteoporosis
Progressive BMF
Cardiac defects
Genitourinary and gastrointestinal malformations
Renal ectopia or dysplasia
Endocrine dysfunction
Decreased fertility

Table 14.1. Clinical features of Fanconi anaemia (adapted from Nalepa and Clapp [5].

About a quarter of FA patients who develop solid tumours are diagnosed with FA only after discovery of their cancer. Therefore, FA should be considered in early-onset malignancies. Early-onset of oral cancer as described in several case reports (cited below) can serve as a pointer to consider the diagnosis of FA in young patients who develop HNSCC in the absence of risk factors.

FA may lead to bone marrow failure, hematopoietic stem cell transplantation may lead to cGVHD. Chronic graft versus host disease arising in patients who have received HSCT is considered a major risk factor for HNSCC and oral squamous cell carcinoma being the most common type. The estimated incidence is from 200-fold to 800-fold higher in patients with FA than in the general population. Recently, there has been renewed interest among researchers on development of OSCCs in FA. In a review of reported FA cases the median age of the 12 patients who developed oral carcinomas following a bone marrow transplant was 21 years which was significantly younger than the age of 28 for patients who had not received a bone marrow transplant ($P< 0.02$), suggesting a possible adverse effect of transplant ie cGVHD on the risk of developing an oral carcinoma [6]

Masserot et al., [7] described – the largest series so far of head and neck squamous cell carcinomas – 13 patients (8 in the oral cavity) with Fanconi anemia after hematopoietic stem cell transplantation (HSCT). The median age of the patients at time of HSCT was 9.7 years and HNSCC was diagnosed at a median interval of 10 years after HSCT, in numerous sites within the oral cavity, localised mainly on the tongue, gingivae or palate. Median age of HNSCC diagnosis was 20.6 years. Three patients had 2 tumour sites. Extensive chronic GVHD with lichen planus-like lesions occurred in all patients. Nine patients (69.2%) had potentially malignant lesions -mostly oral leukoplakia or oral lichen planus before the diagnosis of HNSCC was made. A single case similar to above of oral squamous cell carcinoma (OSCC) originating in the buccal mucosa of an 18-year-old female patient with chronic graft-versus-host disease(GVHD) 9 years after HLA-identical sibling bone marrow transplantation (BMT) for FA was reported by Millen et al [8] . In a systematic review, Furquim et al., [9] identified a total of 121 individuals affected by FA and OSCC among 47 published from 1970 to 2016. The tongue was the most affected site. The overall risk was estimated to increase 500- to 700-fold for head and neck cancer in FA patients compared to the general population [10] and the majority developed carcinomas at an early age. Therefore, young people who develop HNSCC must receive FA diagnostic tests. Patients with FA can present with potentially malignant disorders, especially oral leukoplakia [11] and CGVHD [12].

Among 138 Brazilian patients with FA who had not undergone hematopoietic stem cell transplantation (HSCT), 16 cases (12%) were diagnosed with oral leukoplakia, with a median age of 16.5 years [13].

Considering that patients with FA present a very high risk of developing OSCC regular screening to detect OPMDs or early cancers is an essential step in the overall management of FA patients. The risk of oral cancer in FA may become even higher as death from aplastic anemia is reduced and as patients survive longer after BMT. The occurrence of a squamous cell carcinoma of the tongue in a young person who does not smoke should prompt consideration of FA as the underlying medical condition and should lead to performance of a screening chromosome breakage test.

14.4. Dyskeratosis congenita

Dyskeratosis Congenita (DKC) (also called Zinsser-Cole-Engman syndrome) is a rare hereditary condition of dysfunctional telomere maintenance that is regarded as a potentially malignant disorder. A higher frequency of oral cancers is noted among patients affected by this condition [14]. The pathogenesis is attributed to mutations of several genes that help maintain telomere. Most cases are inherited and may be X-linked, autosomal dominant, or autosomal recessive, with variable penetrance [15]. Gopal Ray et al [16] described a sporadic case of DC with no related disorder in the siblings of the patient, or the first-degree and second-degree relatives. The condition often arises early and should always be considered and excluded in a child presenting with oral leukoplakia. It consists of the triad of oral Leukoplakia (usually on the dorsal tongue but can arise in any mucous membranes within the body), hyperpigmentation of the skin (usually with a reticular pattern on the Neck, face, chest and arms) and nail dystrophy [17]. Lichenoid-like lesions have also been reported [15]. The prognosis is often poor, due to either malignant change within the oral lesions or bone marrow failure resulting in overwhelming infection and death. Attempts have been made to identify potential markers for future cancerous change within these oral lesions. Evidence for disturbed cytokeratin, abnormal p53 expression and changes at an ultrastructural level (fetal/neonatal features) have been reported some 10 years before malignant change [18, 19]. The identification of a white patch (oral leukoplakia) within the mouth of a child, in the absence of any other obvious cause must arouse suspicion of this rare condition. DC patients have a recognised increased risk of malignancy from pre-existing oral leukoplakia, and the incidence of this transformation is in the order of approximately 35% [20]. DKC is further elaborated upon in the preceding chapter 6.

References

1. Ankathil R, Mathew A, Joseph F, Nair MK (1996). Is oral cancer susceptibility inherited? Report of five oral cancer families. Eur J Cancer B Oral Oncol. 32(1):63–7.
2. Garavello W, Foschi R, Talamini R, La Vecchia C, Rossi M, Dal Maso L, et al. (2008). Family history and the risk of oral and pharyngeal cancer. Int J Cancer. 122(8):1827–31.
3. Warnakulasuriya S, Kujan O, Aguirre-Urizar JM, Bagan JV, González-Moles MÁ, Kerr AR, Lodi G, Mello FW, Monteiro L, Ogden GR, Sloan P, Johnson NW. 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. 2021;27(8):1862-1880.
4. Moreno OM, Paredes AC, Suarez-Obando F, Rojas A. An update on Fanconi anaemia: Clinical, cytogenetic and molecular approaches (Review). Biomed Rep. 2021;15(3):74.
5. Nalepa G, Clapp DW. Fanconi anaemia and cancer: an intricate relationship. Nat Rev Cancer. 2018;18(3):168-185.
6. Alter BP. Cancer in Fanconi anemia, 1927-2001. Cancer. 2003 15;97(2):425-40.
7. Masserot C, Peffault de Latour R, Rocha V, Leblanc T, Rigolet A, Pascal F, Janin A, Soulier J, Gluckman E, Socié G. Head and neck squamous cell carcinoma in 13 patients with Fanconi anemia after hematopoietic stem cell transplantation. Cancer. 2008;15;113(12):3315-22.
8. Millen FJ, Rainey MG, Hows JM, Burton PA, Irvine GH, Swirsky D. Oral squamous cell carcinoma after allogeneic bone marrow transplantation for Fanconi anaemia. Br J Haematol. 1997;99(2):410-4.
9. Furquim CP, Pivovar A, Amenábar JM, Bonfim C, Torres-Pereira CC. Oral cancer in Fanconi anemia: Review of 121 cases. Crit Rev Oncol Hematol. 2018;125:35-40.
10. Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, Goberdhan A, Shah JP, Singh B. High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia. Arch Otolaryngol Head Neck Surg. 2003;129(1):106-12. doi: 10.1001/archotol.129.1.106. PMID: 12525204.
11. Amenábar JM, Torres-Pereira CC, Tang KD, Punyadeera C. Two enemies, one fight: An update of oral cancer in patients with Fanconi anemia. Cancer. 2019 15;125(22):3936-3946.
12. Grein Cavalcanti L, Fuentes Araujo RL, Bonfim C, Torres-Pereira CC. Oral manifestations compatible with chronic graft-versus host disease in patients with Fanconi anemia. Biol Blood Marrow Transplant. 2015;21:275-280
13. Grein Cavalcanti L, Lyko KF, Araújo RL, Amenábar JM, Bonfim C, Torres-Pereira CC. Oral leukoplakia in patients with Fanconi anaemia without hematopoietic stem cell transplantation. Pediatr Blood Cancer. 2015;62(6):1024-6..

14. Bongiorno, M., Rivard, S., Hammer, D., & Kentosh, J. Malignant transformation of oral leukoplakia in a patient with dyskeratosis congenita. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 2017; 124(4), e239–e24
15. Handley, T. P., & Ogden, G. R. Dyskeratosis congenita: Oral hyperkeratosis in association with lichenoid reaction. Journal of Oral Pathology and Medicine, 2006; 35(8), 508–512.
16. Ray JG, Swain N, Ghosh R, Richa, Mohanty SP. Dyskeratosis congenita with malignant transformation. BMJ Case Rep. 2011 11;2011:bcr0320102848.
17. Ogden, G. R., Connor, E., & Chisholm, D. M. Dyskeratosis congenita: Report of a case and review of the literature. Oral Surgery, Oral Medicine, Oral Pathology, 1988; 65(5), 586–591.
18. McKay, G. S., Ogden, G. R., & Chisholm, D. M. (1991). Lingual hyperkeratosis in dyskeratosis congenita: Ultrastructural findings. Journal of Oral Pathology and Medicine, 20(4), 196–199.
19. Ogden, G. R., Chisholm, D. M., Hopwood, D., & Lane, E. B. (1993). Evidence for field change in oral cancer based on cytokeratin expression. British Journal of Cancer, 67, 1324–1330.
20. Cannell H. Dyskeratosis congenita. Br J Oral Surg 1971;9: 8–10

Notes

Notes

OPMDcare
Healthcare Professional Training