International Journal Dental and Medical Sciences Research
Volume 2, Issue 1, pp: 96-104 www.ijdmsrjournal.com ISSN: 2582-6018

Oral Potentially Malignant Disorders: Clinico-Histopathological Correlation. A Review

[1]Pooja Sharma, [2]Amanpreet Kaur, [3]Gopikrishnan Vijayakumar
[1]*Consultant Oral Pathology and General dental practitioner*
[2]*Consultant Periodontist and general Gental practitioner*
[3]*Consultant Oral Pathology and general Gental practitioner*
*Corresponding Author: *Dr. Gopikrishnan Vijayakumar, Consultant Oral Pathology and general Gental practitioner*

Date of Submission: 17-07-2020 Date of Acceptance: 01-08-2020

ABSTRACT
Oral squamous cell carcinoma accounts for at least 90% of all oral malignancies. It exhibits significant mortality and morbidity rates. Virtually, all oral cancers exhibit a two-step process of cancer progression, i.e., an initial precancerous stage that subsequently evolves into final stage of oral cancer. The precancerous stages referred to as potentially malignant disorders of oral cavity namely the leukoplakia, erythroplakia, oral lichen planus, and oral submucous fibrosis. The early detection and treatment aid in an improved prognosis of cancer and is only possible with a proper knowledge of their clinical and histopathological features. Therefore, this mini review we aim to elaborate these features of potentially malignant disorders which will assist in early diagnosis and timely treatment.

KEYWORDS: Oral squamous cell carcinoma; potentially malignant disorders

I. INTRODUCTION

Oral cancer is a potentially fatal disease that usually presents late leading to poor prognosis. The most common oral cancer is squamous cell carcinoma (OSCC) which affects significant numbers of people around the world and represents more than 90% of head and neck cancers.[1] Recent studies shows that 4-10% of cases are reported in patients below the age of 40 years.[2,3] Approximately two thirds of such OSCCs seem to be diagnosed only at its advanced stages. The late diagnosis of a significant number of OSCCs is attributed to the delay in patient treatment seeking, lack of patient awareness, asymptomatic clinical states and/or inappropriate investigation.[4]

Despite the different treatment modalities for OSCCs, the five-year survival rate has not improved in recent years. OSCCs may arise from Potentially Malignant Disorders (PMDs), a term that has been recently introduced by the WHO to be used instead of premalignant or precancerous lesions/conditions.[5] PMDs mainly constitute leukoplakia, erythroplakia, erythroleukoplakia, lichen planus, submucous fibrosis and actinic cheilitis as well as inherited cancer syndromes. Most oral PMDs are asymptomatic or present with few symptoms and they are regarded as an intermediate stage between normal and malignant tissues.Hence, there is a vital need to detect OPMDs at an early stage. On literature analysis, in indexed journals in English literature for past twenty years very few review articles are available which provide histopathology of different PMDs under one roof which we aim to bring to literature by this review.

1. Oral potentially malignant disorders

PMD is the latest WHO recommended term for a group of disorders that carry an unpredictable risk of malignant transformation. They vary from a small well-defined white or red mucosal patch to a widespread and extensive involvement of oral mucosa.Examples of white, predominantly white or red disorders of the oral mucosa that carry an increased risk for oral cancer development are leukoplakia, erythroplakia, erythroleukoplakia, oral lichen planus, submucous fibrosis, actinic cheilitis, dyskeratosis congenita, xeroderma pigmentosusm, epidermolysis bullosa, DLE and Fanconi anemia. Leukoplakia and erythroplakia are the most common lesions.[5,7,]

1.1 Oral leukoplakia

The term ‘Leukoplakia’ was given by a Hungarian dermatologist, Schwimmer in 1977. Oral leukoplakia (OL) is defined as ‘‘a white plaque of questionable risk having excluded known diseases or disorders that carry no increased risk for cancer”.[8] OL is the most common PMD

International Journal Dental and Medical Sciences Research
Volume 2, Issue 1, pp: 96-104 www.ijdmsrjournal.com ISSN: 2582-6018

affecting 0.2- 4.9% of the world population.[9] The most common site affected by OLs varies in different studies and this variation may similarly be related to geographical differences, race, and individual habits.[10] The buccal mucosa, alveolar mucosa and lower lip were the common sites observed in a study conducted by Waldron and Shafer (1975), while buccal mucosa and the floor of mouth (FOM)were the most commonly affected oral sites, followed by lateral border of tongue, with gingiva and labial commissures least affected in a study carried out by Jaber et al (2003).[11,12]Clinically, OL is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion and may be seen in any part of the oral cavity and oropharynx. The different classification of OL is tabulated in table 1. The differentiation between them is entirely clinical, based upon surface, color and morphological features.. [13,14]

1.2 Staging of Oral Leukoplakia

According to the International Classification of Diseases Application to Dentistry and Stomatology (ICD-DA) codes for the oral cavity, three size categories have been proposed, analogous to the TNM system of oral cancer. L represents the size of single or multiple leukoplakias as follows:

Size:
L1 < 2 cm
L2 =2-4 cm
L3 > 4 cm
Lx size not specified.

P represents the pathology of leukoplakias as follows:

P0 No epithelial dysplasia
P1 Mild or moderate dysplasia
P2 Severe dysplasia
Px Absence or presence of dysplasia not specified

Accordingly, four stages have been proposed in this system which includes:

Stage I	L1P0
Stage II L2	P0
Stage III L3	P0 or L1 L2 P1
Stage IV L3	P1 or any LP2

1.3 Variants of Oral Leukoplakia

1. Proliferative verrucous leukoplakia (PVL)

First described by Hansen et al. (1985), more prevalent among elderly women with or without history of tobacco use.Clinically, PVL mostly appears as a flat white keratotic lesion with a verrucous surface and may be associated with an erythematous component. As the lesion progresses it becomes more exophytic, granular and verruciform ultimately becoming multifocal and developing a warty-type appearance (Figure 1a,1b).[16]

2. Candidal Leukoplakia

A secondary candida infection of the epithelium is found in about 10% of all leukoplakias. If the degree of dysplasia is also taken into account, the incidence of candidiasis increases with the degree of dysplasia reaching 38% in lesions showing a high degree of dysplasia. Fungal growth in leukoplakic lesions must therefore be regarded both as a risk factor and as a risk indicator (Figure 1c,1d**).**[17]

1.4 Epithelial dysplasia in Oral Leukoplakia

1. Leukoplakia without or with mild dysplasia

With this form of leukoplakia, whitish atrophy of the mucosa is due to increased keratinization (hyperkeratosis) at the surface and thickening of prickle cell layer (acanthosis) beneath. Mucosal keratinization may take the form of anucleate horny squames. (orthokeratosis) or of remnants of nuclei persisting in the keratinocytes (parakeratosis). Less common features are cells swollen with intracellular water or edematous enlargement of intracellular spaces. This group of harmless leukoplakias is not to be considered precancerous and accounts for 74% of oral leukoplakias.[18]

2. Leukoplakia with moderate dysplasia

These hold an intermediate position having more marked dysplasia and represent 17% of leukoplakias. Their behavior corresponds largely to that of the group with low-degree dysplasia.

3. Leukoplakia with severe dysplasia & carcinoma in situ

Leukoplakias with a high degree of dysplasia must be considered precancerous. They are identified by the fact that all the criteria of dysplasia are usually present in marked degree. Endophytic growth with downward extension of epithelial rete pegs is a common finding. Carcinoma in situ is characterized by the additional feature of complete loss of epithelial stratification. It may be regarded as an early form of oral cancer not showing invasive growth. 6% of leukoplakias show signs of extreme dysplasia, 3% of leukoplakias show carcinoma in situ.[18]

2.1 Oral erythroplakia

The current widely accepted WHO definition of oral erythroplakia is: “a fiery red patch that cannot be characterized clinically or

pathologically as any other definable disease".Previous studies have shown a prevalence range between 0.02% and 0.83%from research performed in South and Southeast Asia. OE is a rare disorder and is much less common than leukoplakia. It is a disease of middle age and elderly and more common in men.[19] Clinically, erythroplakias may have flat or depressed surfaces which may be smooth, granular or nodular with a well-defined demarcation adjacent to mucosa of normal appearance. Erythroplakia tends to present as solitary lesions and rarely affects widespread areas.[20]

2.2 Histopathology

Erythroplakia as a clinical term does not carry any histological connotation; however, histological biopsy of oral erythroplakia may show epithelial dysplasia, CIS or invasive carcinoma.[21] According to Reichart and Philipsen, all erythroplakias showed some degree of epithelial dysplasia: 51% showed invasive squamous cell carcinoma, 40% CIS or severe dysplasia and the remaining 9% demonstrated mild to moderate dysplasia.[22]Although oral erythroplakia is rare, its malignant transformation rate is the highest among all of the oral PMDs. Dysplasia and CIS or invasive carcinoma may be seen in more than 90% of OE cases (Figure 2a,2b).[19]

3.1 Oral lichen planus

Oral lichen planus (OLP) is a chronic inflammatory disorder of unknown etiology affecting up to 2% of the middle aged and elderly. [24] It is a cell mediated autoimmune condition associatedwith accumulation of an inflammatory infiltrate composed predominantly of T-lymphocytes beneath the epithelium of the oral mucosa which results in cell-mediated damage to basalkeratinocytes.There is an increased rate of differentiation of stratified squamous epithelium, resulting in hyperkeratosis and erythema with or without ulceration.[25] Clinically, OLP has six types: papular, reticular, plaque-like, atrophic, erosive (ulcerative) and bullous. It has characteristic clinical and histological appearancewhich usually allows distinction from OL. However, the plaque type of lichen planus may often resemble leukoplakia, emphasizing the importance of biopsy in diagnosis.[26]

3.2 Histological features

Hyperparakeratosis or hyperorthokeratosis with thickening of the granular layer, acanthosis with intracellular edema of the spinous cells in some instances, the development of a 'saw tooth' appearance of the rete pegs are typical features. Band-like subepithelial mononuclear infiltrate consisting of T-cells and histiocytes; increased numbers of intraepithelial T-cells; and degenerating basal keratinocytes that form colloid (Civatte, hyaline, cytoid) bodies, which appear as homogenous eosinophilic globules are consistently seen. Degeneration of the basal keratinocytes and disruption of the anchoring elements of the epithelial basement membrane and basal keratinocytes weakens the epithelial-connective tissue interface. As a result, histologic clefts (i.e. Max-Joseph spaces) may form, and blisters on the oral mucosa (bullous lichen planus) may be seen at clinical examination (Figure 2c,2d).[27,28]

3.3 Lichenoid Dysplasia

When dysplasia is seen in epithelium which otherwise has the microscopic features of lichen planus, the lichen planus features are essentially ignored and lesion is graded according to the criteria of epithelial dysplasia, although the term "lichenoid dysplasia" may be applied to the case.[29] Lichenoid dysplasia is fundamentally a precancerous process with lichenoid features. It is related to lichen planus and other lichenoid conditions only as far as superficial resemblance is concerned. It looks like lichen planus clinically and histopathologically.[30]

3.4 Eisenberg histopathological criteria for Oral Lichen Planus & Oral Lichenoid Lesion [31]

Essential feature

- Basal cell liquefaction
- Band-like lymphocytic infiltrate at epithelial-stromal junction with obfuscation of basal cell region
- Normal epithelial maturation pattern

- **Other nonrequisite features**
- "Candle-dripping," spindly rete ridges
- Parakeratosis
- Civatte bodies
- Ragged separation of epithelium from lamina propria due to basal cell destruction

- **Exclusionary features (rule out definitive diagnosis of LP)**
- Atypical cytomorphology
- Nuclear enlargement or hyperchromasia
- Prevalent dyskeratosis (abnormal keratinization or abundant individually keratinized cells)
- Increased numbers of mitotic figures; aberrant mitoses

International Journal Dental and Medical Sciences Research
Volume 2, Issue 1, pp: 96-104 www.ijdmsrjournal.com ISSN: 2582-6018

- **Topographic features**
  - Blunted, droplet-shaped rete ridges
  - Absence of basal cell liquefaction
  - Stratification disarray

- **Lichenoid infiltrate**
  - Heterogeneous population
  - (Deeper) submucosal extension of infiltrate beyond superficial stroma
  - Perivascular infiltration

4.1 Oral submucous fibrosis (OSF)

OSMF was first described three decades ago by Pindborg and Sirsat. It is regarded as a pre-cancerous condition. It is characterized by a juxtaepithelial inflammatory reaction followed by fibroelastic change in the lamina propria and associated epithelial atrophy. This leads to a restricted mouth opening, resulting as trismus leading to restriction of food consumption, difficulty in maintaining oral health, as well as impairs the ability to speak. The fibroelastic changes are almost entirely due to abnormal accumulation of collagen in the sub epithelial layers resulting in dense fibrous bands in the mouth.[32]

4.2 Histopathology

The epithelial changes in the different stages of OSF are predominantly hyperplasia (early) and atrophy (advanced), associated with an increased tendency for keratinizing metaplasia. The epithelial atrophy is the marked epithelial change in advanced OSF. Lesions involving the palate showed predominantly orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitotic count in parakeratotic epithelium, the association with parakeratotic leukoplakia and atrophic epithelial changes predisposes OSF to malignancy.On the basis of the histopathological appearance of stained (H&E) sections, OSF can be grouped into four clearly definable stages:very early, early, moderately advanced and advanced. The inflammatory cells seen are mainly lymphocytes and plasma cells. The connective tissue in advanced stages is characterized by the submucosal deposition of extremely dense and avascular collagenous tissues with variable numbers of chronic inflammatory cells (Figure 2e,2f).[33,34]

5.1 Actinic cheilitis

Actinic cheilitis (AC) is a clinical term for an ulcerative lesion, sometimes with crust formation on the mucosa, part or the entire vermilion border of the lip.It is a pathological condition that most frequently affects the vermilion border of the lower lip. When both the upper and lower lips are prominent, as in bimaxillary protrusion, the upper lip may also be more vulnerable to sunlight exposure. In the past, actinic cheilitis was regarded as being potentially malignant, with not infrequent transformation into invasive, metastasizing squamous cell carcinoma.[35] The exact mechanism of development of AC is unclear. The pathogenesis of AC is explained in broad terms that chronic exposure to UV radiation (sunlight) results in mutational changes in the keratinocytes and progressive degradation of epithelium and inflammatory responses in the lamina propria.

5.2 Histopathology

Histologically, the squamous epithelium of the lip vermilion may show hyperplastic or atrophic changes with disordered maturation, varying degrees of keratinization, cytological atypia and increased mitotic activity with the underlying connective tissue showing basophilic degeneration of collagen and elastosis.Apart from the clinical features, biopsy and histopathological examination is essential in the diagnosis of AC because it is consideredto be a potentially malignant disorder and exposure to sunlight is a predisposing factor for lip cancer**(**Figure 2g,2h).[36] Martínez et al. found using immunohistochemical methods that the epithelial expression of p53 and murine double minute (mdm2) genes was significantly increased in AC. As alterations in the expression of the p53/mdm2/p21 pathway are common features of oral squamous cell carcinoma (SCC), these markers in AC may be considered to predict premalignancy in the lip. Altered expression of β-catenin, a protein related to cell adhesion and expression, may be associated with AC.[37,38]

6.1 Hereditary disorders

There are a few known inherited disorders associated with an increased risk of malignancy in the oral cavity, such as Fanconi's anemia, Dyskeratosis congenita, Epidermolysis bullosa, Xeroderma pigmentosum and Bloom's syndrome.[39]

6.2 Fanconi's anaemia

Fanconi anaemia (FA) is a complex genetic syndrome which is associated with risk of congenital malformations, bone marrow failure and cancer. It is a rare autosomal recessive syndrome caused by defects in approximately 11

International Journal Dental and Medical Sciences Research
Volume 2, Issue 1, pp: 96-104 www.ijdmsrjournal.com ISSN: 2582-6018

genes involved in the detection and repair of DNA.Those types of patients are characterized by aplastic anaemia with progressive bone marrow failure, congenital abnormalities, and a high tendency to malignancies including head and neck cancer. In the absence of alcohol and tobacco exposure, 14% of anaemic patients develop head and neck squamous cell carcinomas by the age of 40s.[40,41]Orally, there is a manifestation of generalized black hyperpigmentation on the buccalmucosa, tongue and palate associated with severe generalized periodontitis reported in patients with Fanconi's anaemia.[42] Classical features of FA are short stature, thumb or radial ray abnormalities, microcephaly, and evidence of bone marrow dysfunction. FA has been diagnosed in adult patients with few or absent obvious classical clinical features, and can also be the diagnosis in severely affected newborns with the VACTERL spectrum of abnormalities (vertebral anomalies, anal atresia, cardiac malformations, tracheo-esophageal fistula with esophageal atresia, structural renal and limb anomalies).[43] The most important clinical features of FA are haematological; FA is the commonest type of inherited bone marrow failure syndrome and the incidences of aplastic anaemia, myelodysplastic syndrome, and acute myeloid leukaemia are all greatly increased in homozygotes. The affected FA patient may present with bleeding, pallor and recurring infections.[44]

6.3 Dyskeratosis congenita

Dyskeratosis congenita (DC) was first described by Zinsser in 1906 and was recognized as a clinical entity by Engman (1926) and Cole (1930).DC patients suffer premature morbidity most commonly from BMF, which affects 80%–90% of cases by age 30 years and is the leading cause of death.Pulmonary fibrosis and cancer are severe complications during the evolution of the disease. It is an inherited bone marrow failure (BMF) syndrome characterized by abnormal skin pigmentation, nail dystrophy, oral premalignant leukoplakia, BMF, and cancer predisposition, with increased risk for squamous cell carcinoma and hematolymphoid neoplasms.[45] DC is heterogeneous at the genetic level, depending on the affected gene. DC can be inherited in X-linked, autosomal dominant (AD), or autosomal recessive (AR) patterns.Oral leukoplakia has been reported in 80% of dyskeratosis congenita patients and it may affect any mucosal surface, but the oral mucosa is most commonly affected with the tongue the most frequently affected site. Severe periodontal destruction occurs due to anomalies in ectodermal derived structures and a poor response in the patient caused by neutropenia. In addition, there may be defects in decreased root/crown ratio and mild taurodontism. The evidence of multiple permanent teeth with decreased root/crown ratios may suggest a diagnosis of DC. These patients also may have more incidence of and more severe periodontal disease.[46] DC is a rare disease with an estimated annual incidence of 1 in 1 million, with multiple and variable clinical manifestations.The classic and initial form is usually characterized by the mucocutaneous triad of abnormal skin pigmentation, nail dystrophy, and leukoplakia.[47,48] Patients with dyskeratosis congenita have a recognised increased risk of malignancy from pre-existing mucosal leukoplakia with an incidence of approximately 35% with a peak in the third decade of life.There are no targeted therapies for DC. DC patients usually die of bone marrow failure due to deficient renewing capability of hematopoietic stem cells. Allogeneic hematopoietic stem cell transplantation is the only curative treatment.[49]

7.1 Other hereditary disorders

Epidermolysis bullosa

Epidermolysis bullosa is a hereditary disorder of skin and oral mucosa which is either autosomal dominant or recessive.Clinically, epidermolysis bullosa is characterized by an exceptional tendency of the skin and mucosae to form bullae and vesiclesafter minor friction and trauma, such as routine dental care or even normal tooth brushing.[50] Oral features include repeated blistering and oral tissue scarring leading to limited oral opening, ankyloglossia, obliteration of the oral vestibule, perioral stricture (microstomia), severe periodontal disease and alveolar bone resorption, atrophy of the maxilla with mandibular prognathism and an increased mandibular angle. Patients with epidermolysisbullosa have an increased risk for squamous cell carcinoma.[51]

Xeroderma pigmentosum

Xeroderma pigmentosum is a rare neurocutaneous disease with a recessive mode of inheritance which may affect all races worldwide and has an equal sex incidence. It is characterized by skin changes and neoplasia in exposed parts of the body due to UV radiation. The lips are the most frequently affected and show epithelia atrophy, telangiectasia and hyperpigmentation and this may occasionally be seen in oral mucosa.Most cases of Xeroderma pigmentosum start in early childhood and are fatal by 20 years of age due to multiple metastasis of squamous cell carcinoma and

melanoma, infection or neurological complications. There is an increased incidence ofmalignancies including oral cancer.[52]

II. CONCLUSION

OPMDs have an increased risk of developing into oral cancer. Several varieties are recognised. Some of them are solitary lesions while others referred to as conditions which are multifocal or widespread within the oral cavity. Leukoplakia is the most common oral PMD encountered in clinical practice. Overall malignant progression in these lesions is only of the order of 5%. A maximum of 50% of severe dysplasias, 30% of moderate dysplasias and very few (5%) mild dysplasia are thought to progress to cancer. Therefore, early understanding of their clinical as well as histopathological aspects is very essential for timely intervention of oral cancer.

Conflict of interest

All authors have indicated they have no potential conflicts of interest and no financial relationships relevant to this article to disclose. **"Declarations of Interest: none"**

Source of Funding: Nil

Author contribution: all authors have equally contributed in study

BIBLIOGRAPHY

[1]. Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol. 2009; 45(4-5): 309-16.

[2]. Bachar G, Hod R, Goldstein DP, Irish JC, Gullane PJ, Brown D, Gilbert RW, Hadar T, Feinmesser R and Shpitzer T. Outcome of oral tongue squamous cell carcinoma in patients with and without known risk factors. Oral Oncol. 2011; 47(1): 45-50.

[3]. Myers JN, Elkins T, Roberts D and Byers RM. Squamous cell carcinoma of the tongue in young adults: increasing incidence and factors that predict treatment outcomes. Otolaryngol Head Neck Surg. 2000; 122(1): 44-51.

[4]. Morse DE, Psoter WJ, Cuadrado L, Jean YA, Phelan J, Mittal K, Buxo CJ, Cruz GD and Elias A. A deficit in biopsying potentially premalignant oral lesions in Puerto Rico. Cancer Detect Prev. 2009; 32(5): 424-30.

[5]. Van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; terminology, classification and present concepts of management. Oral Oncol. 2009; 45(4-5): 317-23.

[6]. Warnakulasuriya S, Johnson NW, Van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med 2007;36:575-80.

[7]. Napier SS and Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature. J Oral Pathol Med. 2008; 37(1): 1-10.

[8]. Van der Waal I and Axell T. Oral leukoplakia: a proposal for uniform reporting. Oral Oncol. 2002; 38(6): 521-6.

[9]. Axell T, Pindborg JJ, Smith CJ and van der Waal. Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. International Collaborative Group on Oral White Lesions. J Oral Pathol Med. 1996; 25(2): 49-54.

[10]. Gupta PC, Mehta FS, Daftary DK, Pindborg JJ, Bhonsle RB, Jalnawalla PN, Sinor PN, Pitkar VK, Murti PR, Irani RR, Shah HT, Kadam PM, Iyer KS, Iyer HM, Hegde AK, Chandrashekar GK, Shiroff BC, Sahiar BE and Mehta MN. 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(6): 283-333.

[11]. Ishii J, Fujita K, Munemoto S and Komori T. Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. J Clin Laser Med Surg. 2004; 22(1): 27-33.

[12]. Jaber MA, Porter SR, Speight P, Eveson JW and Scully C. Oral epithelial dysplasia: clinical characteristics of western European residents. Oral Oncol. 2003; 39(6): 589-96.

[13]. Rajendran R. Oral leukoplakia (leukokeratosis): Compilation of facts and figures. J Oral Maxillofac Pathol 2004;8:58-68.

[14]. Waal IV. Oral leukoplakia; a proposal for simplification and consistency of the clinical classification and terminology. Med Oral Patol Oral Cir Bucal. 2019 Nov 1;24 (6):e799-803.

[15]. Schepman KP, Van der Waal I. A proposal for a classification and staging system for oral leukoplakia: a preliminary study. European Journal of Cancer Part B: Oral Oncology. 1995 Nov 1;31(6):396-8.

[16]. Richardson MS, Spruill L, Neville B. Proliferative Verrucous Leukoplakia:

Review of an Evolving Entity. AJSP: Reviews & Reports. 2016 May 1;21(3):132-7.
[17]. Wu L, Feng J, Shi L, Shen X, Liu W, Zhou Z. Candidal infection in oral leukoplakia: a clinicopathologic study of 396 patients from eastern China. Annals of diagnostic pathology. 2013 Feb 1;17(1):37-40.
[18]. Geetha KM, Leeky M, Narayan TV, Sadhana S, Saleha J. Grading of oral epithelial dysplasia: Points to ponder. Journal of oral and maxillofacial pathology: JOMFP. 2015 May;19(2):198.
[19]. Shafer WG and Waldron CA. Erythroplakia of the oral cavity. Cancer. 1975; 36(3): 1021-8.
[20]. Scully C. Cannabis; adverse effects from an oromucosal spray. Br Dent J. 2007; 203(6):E12; discussion 336-7.
[21]. Hashibe M, Mathew B, Kuruvilla B, Thomas G, Sankaranarayanan R, Parkin DM and Zhang ZF. Chewing tobacco, alcohol, and the risk of erythroplakia. Cancer Epidemiol Biomarkers Prev. 2000b; 9(7): 639-45.
[22]. Scully C. Oral and maxillofacial medicine: the basis of diagnosis and treatment. Edinburgh ; New York, Elsevier. 2004
[23]. Bouquot JE and Ephros H. Erythroplakia: the dangerous red mucosa. Pract Periodontics Aesthet Dent. 1995; 7(6): 59-67; quiz 68.
[24]. Axell T and Rundquist L. Oral lichen planus--a demographic study. Community Dent Oral Epidemiol. 1987; 15(1): 52-6.
[25]. Chitturi RT, Devy AS, Nirmal RM, Sunil PM. Oral Lichen Planus: A Review of Etiopathogenesis, Clinical, Histological and Treatment Aspects. J Interdiscipl Med Dent Sci. 2014; 2: 142. doi:10.4172/2376-032X.1000142
[26]. Roopashree MR, Gondhalekar RV, Shashikanth MC, George J, Thippeswamy SH, Shukla A. Pathogenesis of oral lichen planus–a review. Journal of Oral Pathology & Medicine. 2010;39(10):729-34.
[27]. Krupaa RJ, Sankari SL, Masthan K, Rajesh E. Oral lichen planus: An overview. J Pharm Bioall Sci 2015;7:S158-61.
[28]. Shirasuna K. Oral lichen planus: Malignant potential and diagnosis. Oral science international. 2014;11(1):1-7.
[29]. Eisenberg E. Clinicopathological patterns of oral lichenoid lesions. Oral and Maxillofacial Surgery Clinics of North America. 1994;6:445-63.
[30]. Thornhill MH, Sankar V, Xu XJ, Barrett AW, High AS, Odell EW, Speight PM and Farthing PM. The role of histopathological characteristics in distinguishing amalgam-associated oral lichenoid reactions and oral lichen planus. J Oral Pathol Med. 2006; 35(4): 233-40.
[31]. Van der Meij EH, Schepman KP and van der Waal I. The possible premalignant character of oral lichen planus and oral lichenoid lesions: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003; 96(2): 164-71.
[32]. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: Review on etiology and pathogenesis. Oral oncology. 2006; 42: 561-68.
[33]. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis–collagen metabolic disorder. J Oral Pathol Med. 2005; 34: 321-8.
[34]. Narwal A, Kamboj M, Gupta S, Singh E, Sharma P. Exemplary Delineation of Osmf Turning Malicious. Dental Journal of Advance Studies. 2017 Aug;5(02):104-9.
[35]. Wood NH, Khammissa R, Meyerov R, Lemmer J, Feller L. Actinic cheilitis: a case report and a review of the literature. European journal of dentistry. 2011; 5(1):101.
[36]. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: Clinical and histological features. J Oral Maxillofac Surg 2008;66:498-503.
[37]. Markopoulos A, Albanidou-Farmaki E, Kayavis I. Actinic cheilitis: Clinical and pathologic characteristics in 65 cases. Oral diseases 2004. Oral Dis 2004;10:212-6.
[38]. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: Clinical and histological features. J Oral Maxillofac Surg 2008;66:498-503.
[39]. Prime SS, Thakker NS, Pring M, Guest PG and Paterson IC (2001). "A review of inherited cancer syndromes and their relevance to oral squamous cell carcinoma." Oral Oncol 37(1): 1-16.
[40]. Thompson LH (2005). "Unraveling the Fanconi anemia-DNA repair connection." Nat Genet 37(9): 921-2.
[41]. Lustig JP, Lugassy G, Neder A and Sigler E (1995). "Head and neck carcinoma in Fanconi's anaemia--report of a case and review of the literature." Eur J Cancer B Oral Oncol 31B(1): 68-72.

[42]. Saleh A and Stephen LX (2008). "Oral manifestations of Fanconi's anaemia: a case report." SADJ 63(1): 028-31.
[43]. Kutler DI, Auerbach AD, Satagopan J, Giampietro PF, Batish SD, Huvos AG, Goberdhan A, Shah JP and Singh B (2003). "High incidence of head and neck squamous cell carcinoma in patients with Fanconi anemia." Arch Otolaryngol Head Neck Surg 129(1): 106-12.
[44]. Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anaemia pathway: new players and new functions. Nature reviews Molecular cell biology. 2016 Jun;17(6):337.
[45]. Handley TP, McCaul JA and Ogden GR (2006). "Dyskeratosis congenita." Oral Oncol 42(4): 331-6
[46]. Karunakaran A, Ravindran R, Arshad M, Ram MK, Laxmi MK. Dyskeratosis congenita: a report of two cases. Case Rep Dent. 2013;2013:845125.
[47]. Khincha PP, Savage SA. Genomic characterization of the inherited bone marrow failure syndromes. Semin Hematol. 2013;50(4):333–347.
[48]. García MS, Teruya-Feldstein J. The diagnosis and treatment of dyskeratosis congenita: a review. Journal of blood medicine. 2014;5:157.
[49]. Dokal I (2000). "Dyskeratosis congenita in all its forms." Br J Haematol 110(4): 768-79.
[50]. Das BB and Sahoo S (2004). "Dystrophic epidermolysis bullosa." J Perinatol 24(1): 41-7.
[51]. Sedano HO and Gorlin RJ (1989). "Epidermolysis bullosa." Oral Surg Oral Med Oral Pathol 67(5): 555-63.
[52]. Mehta C, Gupta CN and Krishnaswamy M (1996). "Malignant melanoma of conjunctiva with xeroderma pigmentosa--a case report." Indian J Ophthalmol 44(3): 165.

Figure captions:

Figure 1: Photomicrograph showing clinical as well as histopathological presentation of various PMDs respectively 1a,1b) Proliferative Verrucous Leukoplakia; 1c,1d) Candidal Leukoplakia.

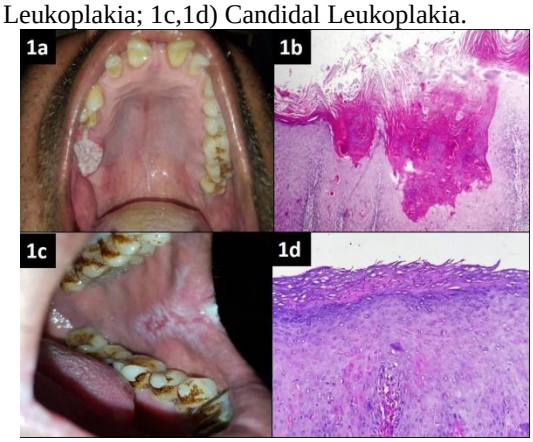
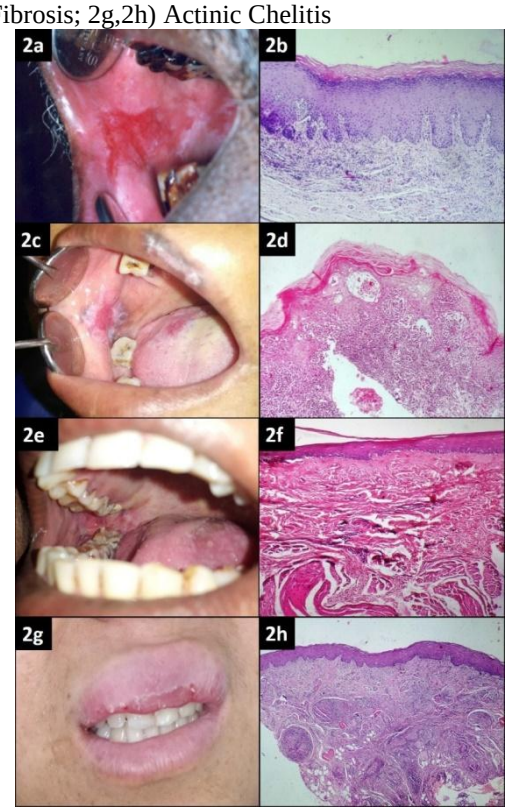


Figure 2: Photomicrograph showing clinical as well as histopathological presentation of various PMDs respectively 2a, 2b) oral erythroplakia; 2c,2d) Oral Lichen Planus; 2e,2f) Oral Submucous Fibrosis; 2g,2h) Actinic Chelitis



International Journal Dental and Medical Sciences Research
Volume 2, Issue 1, pp: 96-104 www.ijdmsrjournal.com ISSN: 2582-6018

Table 1: Various classifications of Leukoplakia

BANOCZY (1977)	
Type I	Leukoplakia Simplex
Type II	Leukoplakia Verrucosa
Type III	Leukoplakia Erosiva
PAPE et al (1994)	
Homogenous	Flat Corrugated Pumice like Wrinkled
Non-Homogenous	Proliferative & Verrucous Ulcerated Nodular Erythroleukoplakia
WHO (1998)	
Type I	Thin, smooth leukoplakia
Type II	Thick, fissured leukoplakia
Type III	Granular, verruciform leukoplakia
Type IV	Erythroleukoplakia
WHO (2002)	
Phase I	thin, smooth leukoplakia - better prognosis
Phase II	thick, fissured leukoplakia.
Phase III	proliferative verrucous leukoplakia (PVL) -higher malignant transformation rate.
Phase IV	erythroleukoplakia - poor prognosis
WARNAKULASURIYA et al (2007)	
Type I	Homogeneous leukoplakia
Type II	Non - Homogenous leukoplakia
Type III	Speckled leukoplakia
Type IV	Nodular leukoplakia
Type V	Verrucous leukoplakia