International Journal of Enhanced Research in Medicines & Dental Care
ISSN: 2349-1590, Vol. 7 Issue 5, May-2020, Impact Factor: 5.375

Pre-cancerous lesions in the oral and maxillofacial region: A review

Surbhi Chugh[1], Ishika Garg[2], Amit Dahiya[3], Arun Kumar[4]

[1] Dental Surgeon,
[2]Post Graduate StudentDeptt of Pedodontics, PGIDS Rohtak, Haryana
[3]Ex- Senior Resident Deptt of Pedodontics, PGIDS Rohtak Haryana
[4]Associate Professor Deptt of Pedodontics, PGIDS Rohtak, Haryana

ABSTRACT

Oral cancer is the most common head and neck cancer accounting for approximately 3% of all malignancies worldwide. Some cancers develop from precancerous lesions; however, there is no definitive clinico-pathological factor or biomarker that reliably enables malignant transformation to be predicted in an individual patient. The most common oral precancerous lesions are oral leukoplakia, oral submucous fibrosis (OSMF), and oral erythroplakia. Early detection and early treatment of oral cancer are important for improving the survival rate of patients. Therefore, correct diagnosis and timely treatment of premalignant lesions with high risk of malignant transformation may help to prevent malignant transformation.

INTRODUCTION

Cancer of oral and maxillofacial region accounts for approximately 3% of all malignancies and is a significant worldwide health problem.[1,2] Squamous cell carcinoma, which arises from the oral mucosal lining, is the most common cancer and constitutes over 90 percent of these tumors.[3]

The etiology of precancerous lesions of oral mucosa is not well known.[4] Some risk factors such as tobacco chewing, tobacco smoking, and alcohol play an important role in development of potentially malignant oral conditions. While tobacco chewing is a major risk factor for oral leukoplakia, oral submucous fibrosis and erythroplakia, tobacco smoking may be a risk factor for oral leukoplakia. Alcohol drinking may increase the risk by 1.5-fold for oral leukoplakia, by 2-fold for oral submucous fibrosis, and 3-fold for erythroplakia.[5] According to Thomas *et al*, while alcohol drinking and tobacco chewing may possibly be risk factors for multiple oral premalignant lesions, smoking was not associated with the risk of multiple oral premalignant lesions.[6]

Malignant transformation is a genetic process, which makes a phenotyping change at the cellular level.[7] Some cancers such as oral squamous cell carcinomas (OSCCs) develop from pre-malignant lesions and conditions.[8] Development of the oral cancer is a multistep process including genetic, epigenetic, and metabolic alterations.[9] Despite advances in the treatment of OSCC, the 5-year survival rate remains approximately 50% due to inability of early detection of OSCC and precursor lesions.[8] Early detection of a malignancy, especially in the pre-malignant stage, can significantly decrease mortality and morbidity.[10]

The most common oral precancerous lesions are oral leukoplakia, oral submucous fibrosis (OSMF), and oral erythroplakia. Actinic cheilitis, some miscellaneous inherited diseases such as xeroderma pigmentosum and Fanconi's anemia, and immunodeficiency are another potentially malignant disorders for oral carcinoma.[6,10]

This article reviews pre-cancerous lesions and conditions of the oral and maxillofacial region.

Leukoplakia

According to WHO definition, leukoplakia is a white patch or plaque that cannot be characterized clinically or pathologically as any other disease.[11] Smokeless tobacco is associated with developing a leukoplakia in 8.4% of cases.[12] Clinically, leukoplakia presents in different views including thin, thick or homogeneous, granular or nodular and proliferative verrucous leukoplakia.[13] The risk of malignant transformation significantly increases among people aged 60-70 years.[14] Leukoplakias on the floor of mouth, lateral tongue, and lower lip show more dysplasia or malignant

transformation.[14,15,16] The possible risk factors for malignant transformation are female gender, idiopathic leukoplakia (in non-smokers) larger than 200 mm^2, long duration, non-homogenous type, presence of Candida species, and epithelial dysplasia.[10]

Different molecular markers have been detected regarding dysplastic changes and malignant transformation of oral leukoplakia. For example, accumulated p53 protein has been shown in 89% of oral leukoplakias, mainly in basal layers.[17] Mutated TP53 in premalignant oral lesions was assumed to predict malignant progression.[18] TP53 and Mdm2 are highly expressed in the leukoplakia cancer group compared to the normal group.[19] Another study has reported the association between a higher expression of SMAD4 and increased rate of malignant transformation.[20]

Leukoplakia has no specific histopathological feature and is only a clinical term.[21] However, histopathologic findings are hyperkeratosis with or without epithelial dysplasia. Although the presence of epithelial dysplasia is the gold standard for the detection of malignant transformation of the lesions, but there are three major problems as follows: (1) as the diagnosis is subjective it cannot be standardized; (2) not only all lesions with dysplasia do not become a malignant lesion but also some of them even regress; and (3) in some cases carcinoma develops from lesions without any previous history of epithelial dysplasia.[22]

Other oral white lesions such as frictional keratoses, morsicatio buccarum are not considered as leukoplakia as they are not premalignant lesions, and are reversible after elimination of suspected etiological factors. Additionally, other oral white lesions such as candidiasis, lichen planus, leukoedema should not be considered as leukoplakia as they have specific microscopic features.[13]

Proliferative verrucous leukoplakia

Proliferative verrucous leukoplakia (PVL) is a rare lesion. In the early stage it is similar to conventional leukoplakia, both clinically and histopathologically,[23] but in the advance stage it appears clinically as verrucous carcinoma.[24] PVL is classified as a potentially malignant lesion in the oral cavity.[22] In the clinic, the lesion initially develops as a focal hyperkeratosis, which gradually progresses to form an exophytic multifocal lesion.[25] Therefore, it is characterized by 4 phases: 1) focal early development; 2) geographic expansion over time; 3) development of a verrucoid/warty appearance; and 4) malignant transformation.[26]

PVL shows variable microscopic features. In early stages, it shows a benign hyperkeratosis. With time, it appears as a papillary and exophytic mass. In later stages the papillary proliferation exhibits down-growth of well-differentiated squamous epithelium with blunt and broad rete ridges, which invades into the underlying lamina propria. In the final stages the invading epithelium transforms to SCC.[27] There are no specific histologic criteria, therefore, diagnosis is based on the histopathologic and clinical features along with the behaviour.[28]TP53 mutation has not been identified in PVL.[12]

Erythroplakia

Erythroplakia is an uncommon fiery red patch, which cannot be classified as any other condition clinically and histopathologically.[11] Clinically, the lesions present as flat to slightly raised red lesions with irregular borders.[24] TP53 mutation has been detected in 46% of oral erythroplakias.[29] The histopathological characteristics include the lack of excess surface keratinization, some degree of dysplasia, and even carcinoma in situ or SCC.[24,30]

Verrucous hyperplasia

Oral verrucous hyperplasia (OVH) appears as a white or pink single or multifocal plaque or nodule with a verrucous or papillary surface, resembling as a large wart.[31] Moderate dysplasia is predominant than mild dysplasia and is correlated with consumption of different tobacco preparations.[32] Verrucous hyperplasia can develop a malignancy, mostly SCC and in a lesser number a verrucous carcinoma.[33]

Histopathologic features include sharp and keratotic projections with keratin-filled invaginations without obvious fibrovascular cores. It never extends below that of the adjacent normal epithelium. In 68% of cases heavy inflammatory cell infiltration including lymphocytes, plasma cells and histiocytes can be observed.[34] Lateral and downward growth, broadened and bulbous-like rete ridges are formed. If a broad-front invasion occurs, it can be designated as a verrucous carcinoma. A verrucous carcinoma can be distinguished from a verrucous hyperplasia by a peripheral buttress/shoulder and extension below the lower border of the normal epithelium.[35]

Tobacco pouch keratosis; Smokeless tobacco keratosis; Smokeless tobacco-induced keratosis; **Snuff dipper's keratosis**

This lesion mostly occurs on the buccal or labial vestibule where the tobacco is held, however, the extension of the lesion into the adjacent gingiva and buccal mucosa has been reported.[36] In the early stage, it appears as a white wrinkled lesion disappearing by stretching. In the advanced stage, the lesion exhibits as a thickened grayish white zone with folds and fissures. Most of the lesions resolve within 2-6 weeks after cessation of the habit, otherwise, an incisional biopsy should be performed.[13] In the microscopic examination, hyperkeratinized and acanthotic epithelium with parakeratin chevrons can be seen. The epithelial dysplasia is not a common finding. Although a significant dysplasia or SCC may be seen, it is usually mild in degree.[27]

Reverse smoking

In some countries, due to placing of the lit end of the cigarette or cigar in the mouth, reverse smoking (RS) can develop, and is associated with increased risk of malignant transformation.[37] Among 497 patients with leukoplakia, 91.7% of the palatal leukoplakias were found in reverse smokers, and out of 10 oral cancer cases, 9 were located on the palate.[38] Keratosis associated with reverse smoking is a precancerous lesion.[39] Histopathological findings include marked hyperorthokeratosis in 80% of cases associated with epithelial hyperplasia in 73.1% of cases.

Oral submucous fibrosis

Oral submucous fibrosis (OSF) is a chronic lesion, which mostly develops in Indians.[40] The possible mechanisms in the development of the lesion are increased collagen synthesis or reduced collagen degradation.[41] Areca nut contact with epithelial cells induces transforming growth factor beta **(**TGF-β) signaling, which in turn induces inflammation and fibrosis in the underlying connective tissue. In addition, TGF-β produced by epithelial cells can diffuse into the connective tissue.[42] The characteristic clinical features of OSF are burning sensation, blanching and stiffening of the oral mucosa such as the lips, tongue, and palate.[41] A previous study has indicated that among 371 patients with oral cancer, 30% had OSF. Additionally, the patients with both oral cancer and OSF were younger than patients with oral cancer (45.11 vs 50.07 yr). Oral cancer with OSF was also more common in men (male: female ratio= 10:1) compared with oral cancer (male to female ratio=3.2:1). The tongue was the most common site of involvement in oral cancer-OSF group.[43]

In early stages of OSF, the microscopic examination shows a juxtra-epithelial inflammation, followed by hyalinization. Later, the atrophy of epithelium with focal para-keratosis or hyperkeratosis along with imbalance between degradation and synthesis of extracellular matrix (ECM), mainly collagen occurs. Finally, marked collagen accumulation in the lamina propria, submucosa, and superficial muscle layer can be seen.[41,44]

Oral Lichen Planus and Oral Lichenoid Reaction

Oral Lichen Planus (OLP) is a chronic inflammatory disease.[45] It is suggested that OLP is a T cell–mediated autoimmune disease. Induction of apoptosis of the basal cells of epithelium by $CD8^+$ T cells is the possible mechanism of developing of OLP.[46] WHO considers OLP as a precancerous lesion especially in the presence of dysplasia.[47]*Candida albicans*, Hepatitis C virus (HCV) infection, and immune-suppression are considered as the possible risk factors in OLP malignant transformation. Besides, *H. pylori* was detected in 59.2% of OLP tissue samples in a previous study.[48] Different sites of the oral cavity have been reported as the preferred site for malignant transformation. While some studies have reported the tongue as the preferred site of malignancy,[49] some others had indicated the midline of the palate, gingiva and lips.[50,51] The buccal mucosa had been reported as the highest risk site for malignant transformation.[52] The presence of a well-defined band-like infiltration of inflammatory cells dominantly lymphocytes, hydropic degeneration of epithelial basal layer, and absence of epithelial dysplasia are the histopathological criteria for OLP diagnosis.[53]

Oral Lichenoid Reactions (Lesions) (OLRs) are lesions similar to OLPs with different etiology.[54] On the lateral border of the tongue, dental materials such as amalgam and composite restorations may be associated with OLR.[55] Graft–vs-host disease, seen mainly in bone marrow transplant recipients, is another lichenoid reaction with the potential of developing an oral cancer. A systematic review on the malignant transformation of OLP and OLR found that 85 cases of SCC developed in OLP lesions and 4 cases of SCC arose in OLRs. Malignant transformation rate for OLP was between 0 and 3.5% and that for OLR was 3.2%.[56]

Lichenoid dysplasia

The term lichenoid dysplasia (LD) was introduced in 1985, used in cases of lichenoid stomatitis with dysplasia. Etio-pathogenesis of LD is different from that of OLP. In OLP, lichenoid infiltration represents cell-mediated immune response provoked by different antigens, whereas in LD, lichenoid infiltration occurs against atypical epithelial cells.[57] Lichenoid dysplasia mostly appears as an erythematous or leukoplakic area on the buccal mucosa or gingiva and is not a symmetrical lesion as can be found in OLP. Microscopic findings of these lesions consist of hyperparakeratosis or

hyperorthokeratosis, epithelial dysplasia and band-like lymphocyte infiltration. The basal cell hyperplasia and atypia rather than degeneration is the important histological feature.[58]

Epidermolysis bullosa

Epidermolysis bullosa (EB) is a heterogeneous group of inherited diseases, characterized by trauma-induced blistering of the skin and mucous membranes.[59] Three major EB types are simplex, junctional and dystrophic.[60] Infants with EB have generalized recurrent blistering, resulting in ulceration, pseudosyndactyly with mitten-like deformities of hands and feet, nail loss, as well as scarring or strictures of the oral mucous membrane, and esophagus.[61] Oral lesions have been reported in the junctional and dystrophic forms.[62] Although malignancy mostly occurs on the skin, it can also occur on the oral cavity, especially the lingual mucosa.[63,64]

Chronic Discoid Lupus Erythematous

Chronic Discoid Lupus Erythematous **(**CDLE) is a chronic form of cutaneous lupus which clinically presents as an erythematous, scaly and depigmented plaque.[65] Head and neck area is affected in 41% of all cases.[66] Oral lesions are asymmetrically distributed affecting the palate, buccal mucosa and tongue. The buccal mucosa can be affected in 15% of the patients and may transform to leukoplakia.[67]

Dyskeratosis Congenita

Dyskeratosis Congenita (DC) is a rare inherited bone marrow failure syndrome characterized by the triad of oral leukoplakia (80%), dystrophy of nails (90%), and reticular skin pigmentation (90%).[68] Mutations have been identified in TERC (telomerase RNA component), which provide a direct link between DC, telomerase, and DKC1 gene.[69,70] Malignancies develop in 10% of patients, typically in the third decade of life. The most common malignancy is SCC, and typically develops in areas of leukoplakia.[71]

Actinic cheilitis

Actinic cheilitis (AC) is a chronic inflammatory lesion.[72] In the clinical examination, the lesion is characterized by the darkening of the lip and atrophy of the vermilion border at the borders. Over time, scaly areas develop and become thick by extending to the wet line of the lip. Chronic focal ulcers as well as leukoplakic lesions can occur.[73] AC may transform into SCC,[73] but SCC arising on AC rarely metastasizes to cervical lymph nodes. A malignancy develops in patients older than 50 years of age who use tobacco and are exposed to the sun chronically.[74]Histopathologically, AC presents a variety of changes including varying degrees of keratosis, epithelial hyperplasia or atrophy, solar elastosis, and the presence or absence of dysplasia.[72]

Some inherited cancer syndromes

In patients with xeroderma pigmentosum and Fanconi's anemia, incidence of oral cancer has increased.[10]

Immunodeficiency

In patients with prolonged use of immunosuppressive drugs after solid organ transplants, human immunodeficiency virus patients, and chronic graft versus host disease after stem cell transplantation are the patients in risk group for oral cancer development.[10]

DISCUSSION

Not always a benign squamous hyperplasia progresses to a malignancy, therefore, some genetic alterations develop cancers.[75] Identification of early genetic alterations, tumor suppressor genes and proto-oncogenes provides necessary information in cancer treatment. Close observation of cases with dysplasia/neoplasia has an impact on patient's life but there is always a limitation due to the clinical differences between inflammatory benign lesions and true dysplastic/neoplastic changes. Slaughter proposed the concept of field cancerization in 1953.[76] According to this hypothesis, the entire epithelium of upper aero-digestive tract is exposed to carcinogens, therefore, there is a higher incidence of multiple genetic alterations to cause cancer development. In the oral cavity, some etiological factors have been identified. Tobacco smoking and alcohol consumption play important roles in oral cancer. Components of cigarette smoke, including nicotine can stimulate the proliferation of various normal and cancerous cells[77] by increasing the levels of both growth factors such as VEGF, VEGF-C, TGF-b, and growth factor receptors like VEGFR-2, PDGFR, HGFR and EGFR. Moreover, *Ras (Rat sarcoma)* mutation has been demonstrated in tobacco chewers.[78] Ethanol becomes oxidized into acetaldehyde, which is a carcinogen. Marked levels of acetaldehyde can be detected in saliva after taking ethanol. The oral microbiota may contribute in cancer development due to acetaldehyde production.[79]

Angiogenesis has been detected in oral pre-malignant lesions, which persist during progression of carcinogenesis. Increased level of VEGF was found in oral pre-malignant conditions.[80] Hyperactivity of the EGFR/ERK, and PI3K/AKT/mTOR signaling pathways has been found in OSCC and premalignant cell lines.[81] Amplification of proto-oncogene, *cyclin D1*, is another finding in head and neck squamous cell carcinoma (HNSCC).[78] Laminin-5$_\gamma$2 positivity distinguishes truly oral premalignant lesions from those that are not.[82] Podoplanin expression can be used as a predictor of the risk of cancer development in oral precancerous lesions.[83]

CONCLUSION

Oral cancer is very common with high mortality rate, therefore, the knowledge about precancerous lesions and their behaviour has a crucial impact on patients' life. Extra oral and intraoral examination of the head and neck region along with careful observation of the clinical and histological changes followed by early diagnosis can give lower morbidity and mortality.

REFERENCES

[1]. Kademani D. Oral cancer. Mayo Clin Proc 2007;82(7):878-87.
[2]. Silverman S Jr. Demographics and occurrence of oral and pharyngeal cancers. The outcomes, the trends, the challenge. J Am Dent Assoc 2001;132:7S-11S.
[3]. Irani S. Pre-Cancerous Lesions in the Oral and Maxillofacial Region: A Literature Review with Special Focus on Etiopathogenesis. Iran J Pathol 2016;11(4):303-22.
[4]. Vlková B, Stanko P, Minárik G, Tóthová L, Szemes T, Baňasová L et al. Salivary markers of oxidative stress in patients with oral prema- lignant lesions. Arch Oral Biol 2012; 57:1651-6.
[5]. Yardimci G, Kutlubay Z, Engin B, Tuzun Y. Precancerous lesions of oral mucosa. World J Clin Cases 2014;2(12):866-72.
[6]. Thomas G, Hashibe M, Jacob BJ, Ramadas K, Mathew B, Sankaranarayanan R et al. Risk factors for multiple oral premalignant lesions. Int J Cancer 2003;107:285-91.
[7]. Epstein JB, Zhang L, Rosin M. Advances in the diagnosis of oral premalignant and malignant lesions. J Can Dent Assoc 2002;68(10):617–21.
[8]. Silverman S Jr, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation A follow-up study of 257 patients. Cancer 1984;53(3):563–8.
[9]. Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. N Engl J Med 2001;344(17):1323–6.
[10]. 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.
[11]. Kramer IR, Lucas RB, Pindborg JJ, Sobin LH. Definition of leukoplakia and related lesions: an aid to studies on oral pre-cancer. Oral Surg Oral Med Oral Pathol 1978;46(4):518–39.
[12]. Agbor MA, Azodo CC, Tefouet TS. Smokeless tobacco use, tooth loss and oral health issues among adults in Cameroon. Afr Health Sci 2013;13(3):785–90.
[13]. Neville BW, Day TA. Oral cancer and precancerous lesions. CA Cancer J Clin. 2002;52(4):195–215.
[14]. Waldron CA, Shafer WG. Leukoplakia revisited A clinicopathologic study 3256 oral leukoplakias. Cancer 1975;36(4):1386–92.
[15]. Pogrel MA. Sublingual keratosis and malignant transformation. J Oral Pathol 1979;8(3):176–8.
[16]. Kramer IR, El-Labban N, Lee KW. The clinical features and risk of malignant transformation in sublingual keratosis. Br Dent J 1978;144(6):171–80.
[17]. Lippman SM, Shin DM, Lee JJ, Batsakis JG, Lotan R, Tainsky MA et al. p53 and retinoid chemoprevention of oral carcinogenesis. Cancer Res 1995;55(1):16–9.
[18]. Graveland AP, Bremmer JF, de Maaker M, Brink A, Cobussen P, Zwart M et al. Molecular screening of oral precancer. Oral Oncol 2013;49(12):1129–35.
[19]. Cui JJ, Han XL, Wang WM. Expression and significance of p53 and mdm2 in patients with leukoplakia cancer. Asian Pac J Trop Med 2013;6(10):831–4.
[20]. Xia RH, Song XM, Wang XJ, Li J, Mao L. The combination of SMAD4 expression and histological grade of dysplasia is a better predictor for the malignant transformation of oral leukoplakia. PloS One 2013;8(6):e66794.
[21]. Shafer WG, Waldron CA. A clinical and histopathologic study of oral leukoplakia. Surg Gynecol Obstet 1961;112:411–20.
[22]. Schepman KP, van der Meij EH, Smeele LE, van der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from The Netherlands. Oral Oncol 1998;34(4):270–5.
[23]. Shopper TP, Brannon RB, Stalker WH. Proliferative verrucous leukoplakia: an aggressive form of oral leukoplakia. J Dent Hyg. 2004;78(3):7.
[24]. Summerlin DJ. Precancerous and cancerous lesions of the oral cavity. Dermatol Clin 1996;14(2):205–23.
[25]. Hansen LS, Olson JA, Silverman S Jr. Proliferative verrucous leukoplakia A long-term study of thirty patients. Oral Surg Oral Med Oral Pathol 1985;60(3):285–98.
[26]. Bagan J, Scully C, Jimenez Y, Martorell M. Proliferative verrucous leukoplakia: a concise update. Oral Dis 2010;16(4):328–32.
[27]. Neville B, Dam D, Allen C, Bouquot J. Oral and Maxillofacial Pathology. 3rd ed. . China: Saunders Elsevier; 2009.
[28]. Barnes L EJ, Reichart P, Sidransky D. World Health Organization Classification of Tumours.Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press; 2005.
[29]. Qin GZ, Park JY, Chen SY, Lazarus P. A high prevalence of p53 mutations in pre-malignant oral erythroplakia. Int J Cancer. 1999;80(3):345–8.
[30]. Shafer WG, Waldron CA. Erythroplakia of the oral cavity. Cancer 1975;36(3):1021-8.

[31]. Wang YP, Chen HM, Kuo RC, Yu CH, Sun A, Liu BY et al. Oral verrucous hyperplasia: histologic classification, prognosis, and clinical implications. J Oral Pathol Med 2009;38(8):651–6.
[32]. Hazarey VK, Ganvir SM, Bodhade AS. Verrucous hyperplasia: A clinico-pathological study. J Oral Maxillofac Pathol 2011;15(2):187–91.
[33]. Hsue SS, Wang WC, Chen CH, Lin CC, Chen YK, Lin LM. Malignant transformation in 1458 patients with potentially malignant oral mucosal disorders: a follow-up study based in a Taiwanese hospital. J Oral Pathol Med 2007;36(1):25–9.
[34]. Shear M, Pindborg JJ. Verrucous hyperplasia of the oral mucosa. Cancer 1980;46(8):1855–62.
[35]. Woolgar JA, Triantafyllou A. Squamous cell carcinoma and precursor lesions: clinical pathology. Periodontol 2000 2011;57(1):51–72.
[36]. Somatunga LC, Sinha DN, Sumanasekera P, Galapatti K, Rinchen S, Kahandaliyanage A et al. Smokeless tobacco use in Sri Lanka. Indian J Cancer 2012;49(4):357–63.
[37]. Ortiz GM, Pierce AM, Wilson DF. Palatal changes associated with reverse smoking in Filipino women. Oral Dis 1996;2(3):232–7.
[38]. 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.
[39]. Axell T, Pindborg JJ, Smith CJ, van der Waal I. 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.
[40]. Pindborg JJ. Is submucous fibrosis a precancerous condition in the oral cavity? Int Dental J 1972;22(4):474–80.
[41]. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. Oral Oncol 2006;42(6):561–8.
[42]. Khan I, Kumar N, Pant I, Narra S, Kondaiah P. Activation of TGF-beta pathway by areca nut constituents: a possible cause of oral submucous fibrosis. PloS One 2012;7(12):e51806.
[43]. Chaturvedi P, Vaishampayan SS, Nair S, Nair D, Agarwal JP, Kane SV et al. Oral squamous cell carcinoma arising in background of oral submucous fibrosis: a clinicopathologically distinct disease. Head Neck 2013;35(10):1404–9.
[44]. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis--a collagen metabolic disorder. J Oral Pathol Med 2005;34(6):321–8.
[45]. Ebrahimi M, Nylander K, van der Waal I. Oral lichen planus and the p53 family: what do we know? J Oral Pathol Med 2011;40(4):281–5.
[46]. Eversole LR. Immunopathogenesis of oral lichen planus and recurrent aphthous stomatitis. Semin Cutan Med Surg 1997;16(4):284–94.
[47]. Holmstrup P. The controversy of a premalignant potential of oral lichen planus is over. Oral Surg Oral Med Oral Pathol 1992;73(6):704–6.
[48]. Irani S, Monsef Esfahani A, Sabeti Sh, Bidari Zerehpoush F. Detection of Helicobacter pylori in Oral Lichen Planus and Oral Lichenoid Reaction. Avicenna J Dent Res 2014;6(2):e23213.
[49]. Irani S. Squamous Cell Carcinoma arising in Oral Lichen Planus: A case report. DJH 2010;1(2):1–6.
[50]. Lanfranchi-Tizeira HE, Aguas SC, Sano SM. Malignant transformation of atypical oral lichen planus: a review of 32 cases. Med Oral 2003;8(1):2–9.
[51]. Mignogna MD, Lo Muzio L, Lo Russo L, Fedele S, Ruoppo E, Bucci E. Clinical guidelines in early detection of oral squamous cell carcinoma arising in oral lichen planus: a 5-year experience. Oral Oncol 2001;37(3):262–7.
[52]. Rajentheran R, McLean NR, Kelly CG, Reed MF, Nolan A. Malignant transformation of oral lichen planus. Eur J Surg Oncol 1999;25(5):520–3.
[53]. Larsson A, Warfvinge G. Malignant transformation of oral lichen planus. Oral Oncol 2003;39(6):630–1.
[54]. Van der Waal I. Oral lichen planus and oral lichenoid lesions; a critical appraisal with emphasis on the diagnostic aspects. Med Oral Patol Oral Cir Bucal 2009;14(7):E310-4.
[55]. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management and malignant transformation. J Oral Sci 2007;49(2):89–106.
[56]. 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.
[57]. Krutchkoff DJ, Eisenberg E. Lichenoid dysplasia: a distinct histopathologic entity.Oral Surg Oral Med Oral Pathol 1985;60(3):308–15.
[58]. Muller S. Oral manifestations of dermatologic disease: a focus on lichenoid lesions. Head Neck Pathol 2011;5(1):36–40.
[59]. Fine JD, Johnson LB, Weiner M, Li KP, Suchindran C. Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006.J Am Acad Dermatol 2009;60(2):203–11.
[60]. Fine JD, Eady RA, Bauer EA, Bauer JW, Bruckner-Tuderman L, Heagerty A et al. The classification of inherited epidermolysis bullosa (EB): Report of the Third International Consensus Meeting on Diagnosis and Classification of EB. J Am Acad Dermatol 2008;58(6):931–50.
[61]. Sawamura D, Nakano H, Matsuzaki Y. Overview of epidermolysis bullosa. J Dermatol 2010;37(3):214–9.
[62]. Reichart PA. Oral precancerous conditions--an overview. Mund Kiefer Gesichtschir 2003;7(4):201–7.
[63]. Wright JT, Fine JD, Johnson LB. Oral soft tissues in hereditary epidermolysis bullosa. Oral Surg Oral Med Oral Pathol 1991;71(4):440–6.
[64]. Martinez L, Goodman P, Crow WN. Squamous cell carcinoma of the maxillary sinus and palate in epidermolysis bullosa: CT demonstration. J Comput Assist Tomogr 1992;16(2):317–9.
[65]. Gupta U, Barman KD, Saify K. Squamous cell carcinoma complicating an untreated chronic discoid lupus erythematosus (CDLE) lesion in a black female. J Dermatol 2005;32(12):1010–3.
[66]. Aviles Izquierdo JA, Cano Martinez N, Lazaro Ochaita P. Epidemiological characteristics of patients with cutaneous lupus erythematosus. Actas Dermosifiliogra 2014;105(1):69–73.
[67]. Schiodt M, Andersen L, Shear M, Smith CJ. Leukoplakia-like lesions developing in patients with oral discoid lupus erythematosus. Acta Odontol Scand 1981;39 (4):209–16.
[68]. Nelson ND, Bertuch AA. Dyskeratosis congenita as a disorder of telomere maintenance. Mutat Res 2012;730(1-2):43–51.

[69]. Dokal I. Dyskeratosis congenita. Hematology Am Soc Hematol Educ Program 2011:480–6.
[70]. Vulliamy T, Marrone A, Goldman F, Dearlove A, Bessler M, Mason PJ et al. The RNA component of telomerase is mutated in autosomal dominant dyskeratosis congenita. Nature 2001;413(6854):432–5.
[71]. Holman JD, Dyer JA. Genodermatoses with malignant potential. Curr Opin Pediatr 2007;19(4):446–54.
[72]. Cavalcante AS, Anbinder AL, Carvalho YR. Actinic cheilitis: clinical and histological features. Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons 2008;66(3):498–503.
[73]. Vieira RA, 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(1):105–14.
[74]. Moy RL. Clinical presentation of actinic keratoses and squamous cell carcinoma. J Am Acad Dermatol 2000;42:8–10.
[75]. Califano J, van der Riet P, Westra W, Nawroz H, Clayman G, Piantadosi S et al. Genetic progression model for head and neck cancer: implications for field cancerization. Cancer Res 1996;56(11):2488–92.
[76]. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953;6(5):963–8.
[77]. Gotti C, Clementi F. Neuronal nicotinic receptors: from structure to pathology. Prog Neurobiol 2004;74(6):363–96.
[78]. Arora S, Aggarwal P, Pathak A, Bhandari R, Duffoo F, Gulati SC. Molecular genetics of head and neck cancer (Review) Mol Med Rep 2012;6(1):19–22.
[79]. Gainza-Cirauqui ML, Nieminen MT, Novak Frazer L, Aguirre-Urizar JM, Moragues MD, Rautemaa R. Production of carcinogenic acetaldehyde by Candida albicans from patients with potentially malignant oral mucosal disorders. J Oral Pathol Med 2013;42(3):243–9.
[80]. Raica M, Cimpean AM, Ribatti D. Angiogenesis in pre-malignant conditions.Eur J Cancer 2009;45(11):1924–34.
[81]. Degen M, Natarajan E, Barron P, Widlund HR, Rheinwald JG. MAPK/ERK-dependent translation factor hyperactivation and dysregulated laminin gamma2 expression in oral dysplasia and squamous cell carcinoma. Am J Pathol 2012;180(6):2462–78.
[82]. Nordemar S, Hogmo A, Lindholm J, Auer G, Munck-Wikland E. Laminin-5 gamma 2: a marker to identify oral mucosal lesions at risk for tumor development?Anticancer Res 2003;23(6d):4985–9.
[83]. Inoue H, Miyazaki Y, Kikuchi K, Yoshida N, Ide F, Ohmori Y et al. Podoplanin expression during dysplasia-carcinoma sequence in the oral cavity. Tumour Biol 2012;33(1):183–94.