Invited Review

Clinical Aspects of Oral Cancer and Potentially Malignant Disorders with Special Relevance to South Asia

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Abstract

Early identification of oral potentially malignant disorders (OPMDs) is utmost important to minimise oral cancer incidence as most oral cancers develop from OPMDs. Leucoplakia and oral submucous fibrosis (OSMF) are the most common OPMDs encountered. Erythroplakia is rare but is more serious as it has a very high malignant transformation rate. Clinical presentation of OPMDs can vary according to the type of the disorder as well as with the aetiological agents. OSMF is much prevalent in South and South Asian countries whereas leucoplakia is prevalent all over the world but with differences in clinical presentation. Identification of OPMD with clinical features at its early change is challenging and may require histopathology through a biopsy for confirmation. This review provides clinical descriptions of the wide range of OPMDs encountered in the oral cavity with emphasis on changes in clinical presentation in different populations.

Keywords: Erythroplakia, oral leucoplakia, oral potentially malignant disorder, oral submucous fibrosis

Introduction

Incidence and mortality of cancer is increasing all over the world, and oral cancer is no exception. According to the GLOBOCAN data for 2020, 377,713 new cases of lip and oral cavity cancers have been reported with 177,757 new deaths.[1] Oral cavity cancer is not equally distributed in the world and mostly prevalent in South and Southeast Asian countries, which can be attributed to the prevalence of tobacco chewing patterns associated with socio-cultural behaviours. Most oral cavity cancers in this region start as an oral potentially malignant disorder (OPMD), which provides an opportunity for early detection and prevention of oral cancer development. Even though the oral cavity is an easily detectable anatomical site, there is a considerable delay in the diagnosis resulting in poor prognosis. The delay in the diagnosis can be attributed to the factors related to the patient or to the healthcare provider, which is usually a dentist or the healthcare system. One of the major reasons for the diagnostic delay by the healthcare provider is the lack of awareness of the signs and symptoms presenting with early-stage oral squamous cell carcinomas (OSCCs) and OPMDs.[2,3] Therefore, it is critical for every oral health care provider to have significant knowledge on the clinical features of OPMDs and OSCCs.

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The World Health Organization (WHO) has defined OPMD as an altered epithelium with an increased likelihood for progression to squamous cell carcinoma.[4] Even though there are a variety of disorders of OPMDs, they vary in their prevalence, geographical distribution, clinical presentation and malignant transformation. Leucoplakia, erythroplakia, oral submucous fibrosis (OSMF), oral lichen planus (OLP) and oral lichenoid reactions (OLRs) are some of the most important types of disorders whereas some others may appear occasionally. Special emphasis has been placed on the premalignant nature of OLP/OLR.

Leucoplakia

Leucoplakia is not a simple white patch and is defined as a 'white patch of questionable risk having excluded (other)

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known diseases or disorders that carry no increased risk of cancer'.[5] Leucoplakias are not just confined to oral mucosa and may affect any site of the oral/oropharyngeal mucosa. The term oral leucoplakia (OL) is used at times to identify the leucoplakia confined to the oral mucosa. Most of the times, OL presents as either an asymptomatic lesion or with the appearance of a simple benign condition causing diagnostic challenges clinically.[6] OL is commonly seen in middle-aged and elderly people and more common in middle-aged/elderly males and among tobacco users. Even though most cases of OLs are associated with tobacco use, human papillomavirus is an important risk factor to consider.[7] Some of the OLs are idiopathic while majority is associated with a risk factor. Buccal mucosa and buccal sulcus are the common sites of presentation in Asian populations in contrast to the lateral border of the tongue and the floor of the mouth in the western world.[6] These site differences of OL are mainly due to chewing tobacco and keeping the quid on buccal sulcus and the pouch by Asian population resulting lesions in buccal mucosae and sulcus. Smoking and the use of alcohol are the common risk factors in individuals in western countries lead to OL on the tongue and the floor of the mouth. Gingival involvement is rare and is mostly associated with proliferative verrucous leucoplakia (PVL).

An interesting type of OL is observed in the palatal mucosa of people who practise reversed smoking which is an endemic tobacco smoking habit which is still practised by the people in coastal rural Andhra Pradesh, India. This lesion presents with palatal changes associated with reverse smoking or palatal keratosis associated with reverse smoking. These mucosal changes in the palate, can be physiological/adaptive changes to potentially malignant changes. Hyperpigmentation and excrescence can be considered adaptive changes whereas depigmented areas are representing transition regions between the adaptive and potentially malignant changes, which can present as leucoplakia and erythroplakia.[8] Three stages of OL have been described. Earliest lesion is a non-palpable, faintly translucent white lesion. Intermediate lesion is a localised or diffuse, slightly elevated, opaque white plaque with an irregular outline with a fine and granular texture. Advanced lesion of leucoplakia presents clinically as a white lesion with thickened, raised surface, with induration, grooving, fissuring or ulceration. Clinically two distinct types of lesions have been identified.[9] OL can present as homogeneous lesion or as non-homogeneous lesion. Homogeneous leucoplakia [Figure 1a] is essentially a white lesion of uniform flat, thin appearance. Lesion has a smooth, wrinkled or corrugated surface with a homogeneous texture throughout and may exhibit shallow cracks. These lesions cannot be rubbed off. The earliest lesions are homogeneous lesions.

Non-homogeneous lesions [Figure 1b] can manifest as three different clinical types. Speckled lesions are a mixture of red and white areas. Combination of white and red colour can vary from lesion to lesion, but white component is prevalent. These lesions are also called erythroleucoplakia. Nodular lesions

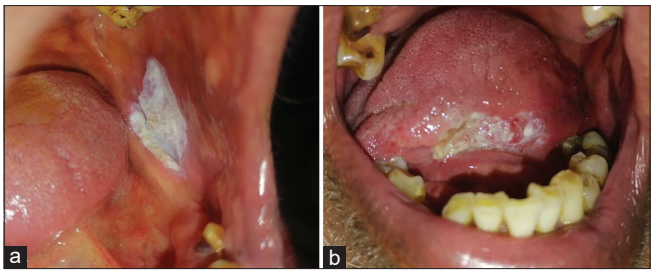

Figure 1: (a) Homogeneous leucoplakia, (b) Non-homogeneous leucoplakia

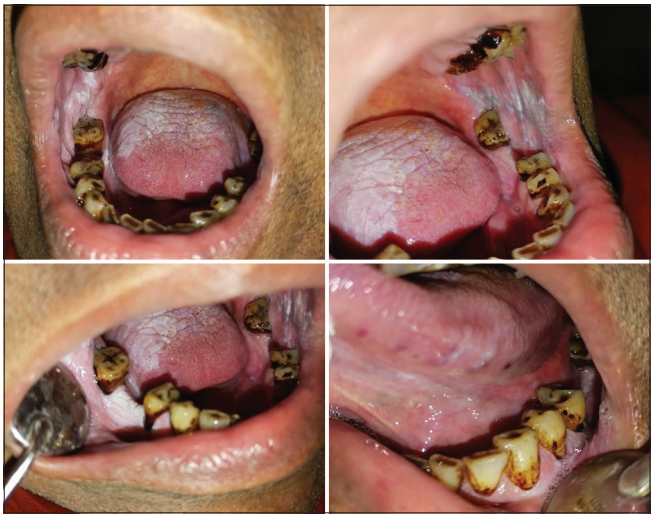

Figure 2: A patient presented with proliferative verrucous leucoplakia having lesions on bilateral buccal mucosae, tongue and gingiva

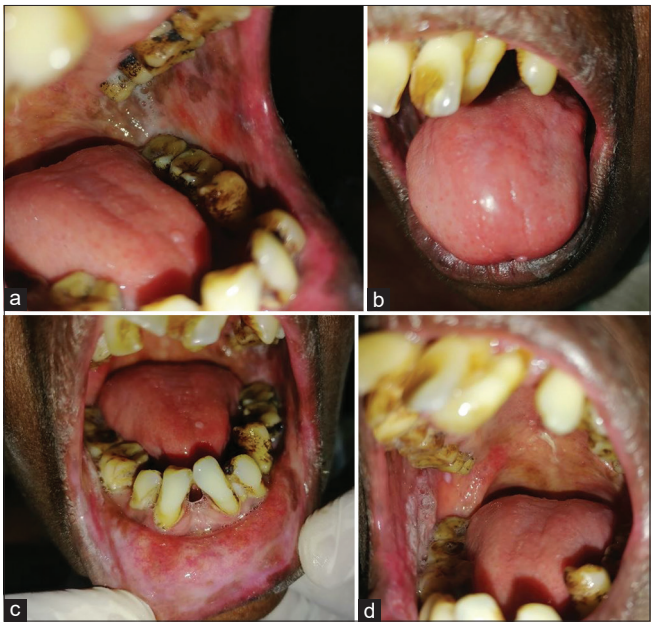

Figure 3: Clinical presentation in oral submucous fibrosis (OSMF). (a) Depigmented buccal mucosa, (b) Depapillated tongue, (c) Lower lip, (d) leucoplakia in the background of OSMF

appear with small, polypoid, rounded nodules. The third type is the verrucous/exophytic type, which presents clinically with

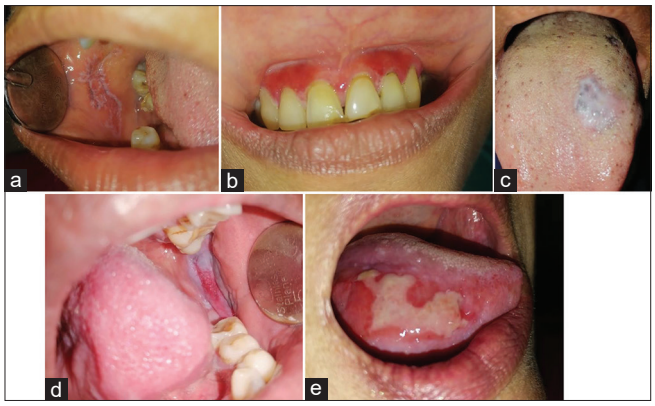

Figure 4: Different clinical presentations of oral lichen planus. (a) Reticular, (b) Desquamative gingivitis, (c) Plaque, (d) Erosive/atrophic, (e) Bullous

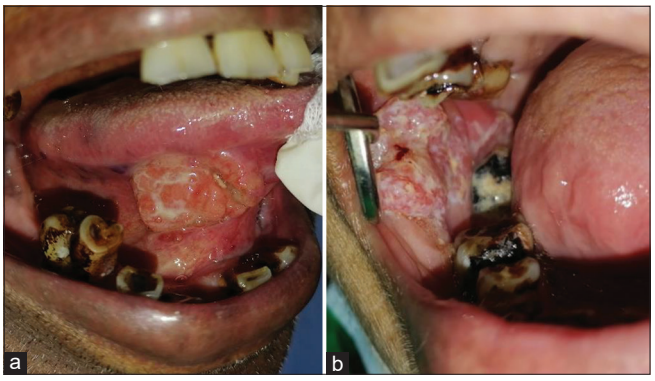

Figure 5: Clinical presentation of oral squamous cell carcinoma. (a) Lesion in the ventral surface of the tongue extending to floor of the mouth, (b) Lesion on buccal mucosa

a wrinkled or corrugated appearance.[6] Most OLs do not have any clinical symptoms and may rarely present with mild pain, discomfort or burning sensation for spicy food.

Other White Lesions of Oral Cavity Mimicking Oral Leucoplakia

Leucoplakia is not the only white lesion that can occur in the oral cavity. Different other white lesions can appear in the oral cavity causing difficulties in identification clinically as well as histopathologically. Anatomical site of the lesion, aetiological agent (tobacco and areca nut vs. idiopathic), size and number of lesions need to be considered in arriving at a diagnosis.

Other common white lesions [Table 1] include, various infections (candidosis – pseudomembranous or hyperplastic type, papilloma and hairy leucoplakia), developmental conditions (white sponge nevus), reactive/traumatic lesions (frictional keratosis/lesion, alveolar keratosis/lesion, leukoedema, smoker's palate and snuff-induced keratosis), immune-mediated/autoimmune (lupus erythematosus, plaque type OLP, lichenoid reaction, graft versus host disease (GVHD).[9,10] As the diagnosis of leucoplakia is by exclusion, it is important to exclude these conditions not only clinically but also histopathologically.

Acute pseudomembranous candidosis (oral thrush) presents as white, curd-like (creamy) patches or plaques, most frequently occurring on the buccal mucosa and tongue, but also seen on the palate, floor of mouth and gingiva. Clinically, this white plaque can be easily rubbed off with pieces of cotton/gauze, leaving a tender, red, raw/bleeding area beneath. Chronic hyperplastic candidosis (CHC)/candidal leukoplakia can present as white patches mainly on the commissural areas and/or on the tongue in smokers. Lesions in CHC cannot be rubbed off and are often asymptomatic. Differentiation of CHC from *Candida*-associated leucoplakia is difficult to distinguish clinically as well as histologically.[11]

Hairy leucoplakia is a characteristic white lesion, which occurs on the lateral border of the tongue with a corrugated or hairy appearance. The term hairy leucoplakia is a misnomer as it is not always hairy or a type of leucoplakia, but is well leucoplakia accepted in the literature as there is no better term described yet. It is not a potentially malignant disorder. This should be distinguished by its characteristic appearance on this specific location and should not be confused with leucoplakia. It usually occurs in patients who are immunocompromised, especially those with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS). White sponge nevus (WSN) is a rare hereditary dyskeratotic hyperplasia of mucous membranes. It is a genetically determined, autosomal dominant disorder with variable penetrance. WSN is characterised by the formation of white patches of tissue that appear as thickened, velvety, sponge-like tissue. The disease is noted in early life usually with a family history and involves larger areas including genital mucosa. There is no malignant transformation potential.

Betel chewer's mucosa (BCM) is present as brownish-red discolouration of oral mucosa with irregular epithelial surface that tends to desquamate or peel off. Buccal mucosa is the most frequently affected site. BCM is mostly seen in women. It may be found together with other oral mucosal lesions such as leukoedema, leucoplakia and ulceration. The aetiology of BCM is traumatic and possibly chemical. It is not an OPMD. Frictional lesion/keratosis is another possible reversible white lesion caused by mechanical irritation. It is at times referred to as 'frictional keratosis', but the term 'lesion' is preferred because 'keratosis' is actually a histopathological term. There is some overlap with alveolar ridge keratosis. Final diagnosis can only be applied to cases where lesion disappeared after the elimination of the possible mechanical cause.

Restoration-associated lesions are similar to frictional lesions as in 'contact lesion', caused by direct prolonged contact with large amalgam restorations with a buccal or lingual extension of the restoration. Final diagnosis should only be applied when the lesion has disappeared after replacement/removal of amalgam provided that there are no symptoms from a biopsy within 4–8 weeks. Definitive diagnosis of amalgam-associated lesion can only be made in retrospect.[11]

Table 1: White lesions other than oral leucoplakia that can appear in oral mucosa

Cause	Lesion	Main clinical feature helps in differentiation from OL
Infection	Pseudomembranous candidosis	Can be rubbed off
	CHC	Responds to antifungal treatment
	Viral wart/papilloma and other HPV lesions	Medical history, characteristic clinical appearance
	Hairy LPK	Lateral border of the tongue, medical history
Reactive/traumatic lesions	Frictional keratosis/lesion	Presence of trauma/irritation
	Alveolar keratosis/lesion	Missing teeth, presence of trauma/irritation
	Leukoedema	Disappearance with stretching of mucosa
	Linear alba	Linear appearance, attrition of teeth
	Smoker's palate	Inflamed minor salivary gland openings
	Snuff induced keratosis	Only in sulcus, in the place where snuff is kept
	Chemical burn	History, pain
	Restoration associated lesion	Presence of restoration in contact with the lesion
Immune-mediated/ autoimmune	LE	Mostly symptomatic
	OLP	Bilateral, mostly symptomatic
	Lichenoid reaction	Medical/drug history
	GVHD	Medical history
Developmental/ genetic conditions	WSN	From childhood, family history
	DC	Extraoral manifestations
	Hereditary benign intraepithelial dyskeratosis	From childhood
Inflammatory	Benign migratory glossitis	Migratory lesions

LPK: Leucoplakia, OL: Oral LPK, HPV: Human papillomavirus, OLP: Oral lichen planus, CHC: Chronic hyperplastic candidosis, WSN: White sponge nevus, LE: Lupus erythematosus, GVHD: Graft versus host disease, DC: Dyskeratosis congenita

Leukoedema is a normal anatomical variation seen mainly in dark-skinned people and smokers. It usually appears as a white opalescence/grey colour lesion of the bilateral buccal mucosa but rarely may present on the labial mucosa or soft palate as well. Characteristically, the lesion disappears or becomes less prominent when the mucosa is stretched and reappears upon relaxation, which helps to differentiate it from OL.[12] OLP-plaque type presents as solitary, slightly raised or flat white lesions commonly on the dorsum of the tongue. Usually, these plaques are non-tender and non-scrapable on palpation. Other clinical subtypes of OLP, especially reticular pattern, may be seen in association and/or in other parts of the oral cavity (especially in the bone marrow), which may confirm the clinical diagnosis of OLP.

Malignant Transformation of Oral Leucoplakia

The malignant transformation rate of OL is low (1%–4%).[13] Clinical features that may predict malignant transformation include verrucous type, proliferative type, erosive or ulcerative, presence of a nodule, lesion that is hard in its periphery, leucoplakia of the floor of the mouth and ventral surface of the tongue, female gender, long duration, idiopathic leucoplakia, size more than 200 mm^2 and presence of candidal superinfection. In all cases of OL, the relative risk of malignant transformation potential is determined by the presence of epithelial dysplasia upon histological examination. OL is typically managed by surgical excision or laser excision and in some cases by follow-up only. Currently, the management of OL is moving from traditional surgical methods to medical methods. Treatment decisions must be based on clinical appearance, risk factors and severity of dysplasia in the biopsy. Evidence on excision of leucoplakia in preventing malignant transformation is not clear.[13] There are cases, which regress without any treatment and there are some cases, which recur or transform into a malignancy even after surgical removal.

To reduce the malignant transformation in OPMDs, it is important to eliminate modifiable risk habits and to be followed up at regular intervals. However, there is no agreement on the follow-up interval. Most people prefer a 3-month interval, but this is not evidence-based and entirely based on the clinician, clinical appearance and degree of dysplasia in the biopsy. As the malignant transformation risk is highest within the first two years, shorter intervals are recommended for the first two years.

Proliferative Verrucous Leucoplakia

All leucoplakias do not behave in the same manner, and one such entity with a different clinical presentation and behaviour is PVL. It is a rare condition. It begins as a simple slow-growing, persistent hyperkeratosis which tends to spread and become multifocal [Figure 2]. Later, it develops into exophytic, wart-like or erythroplakic areas and appears to resist all attempts at therapy. They often recur.[14] High rate of malignant transformation is the main feature of the condition. Clinical presentation of PVL is variable, and at times, differentiation of it from multifocal OL is difficult. Multiple criteria have been developed to diagnose PVL. The criteria developed by Cerero-Lapiedra *et al*., for the diagnosis of PVL are widely used. It includes clinical features as well as histopathological features and consists of major criteria and minor criteria, and the diagnosis of PVL is dependent on the fulfilment of a

combination of features. Major criteria include the presence of a leucoplakia lesion with more than two different oral sites, presence of a verrucous area, spreading or engrossing of the lesion during development and recurrence in a previously treated area.[15] González-Moles *et al*., in 2021, developed newer diagnostic criteria and defined PVL as 'an OPMD that presents in the form of multifocal white plaques, which have expanded throughout its evolution, persistent and resistant to treatment, which is diagnosed in people in the second half of life, although it probably begins in earlier stages, and which has a very high risk of developing into oral cancer'.[16] Not everyone agrees with the definition of PVL, and some do not consider it as a separate entity and even call for its removal.[17]

PVL is commonly seen in older women, in non-smokers/non-habitual drinkers, and is most seen in gingiva followed by buccal mucosa and tongue.[18] They do have a high recurrence rate and malignant transformation potential and hence long-term follow-up is recommended. Most cases of PVL are with a non-homogeneous clinical appearance. It can have a verrucous or nodular appearance or red and white area combination giving an appearance of an erythroleucoplakia. Confusion can occur between OLP and erythroleucoplakia form of PVL as both are multifocal and bilateral.[10] Oral verrucous hyperplasia and PVL are two clinically interrelated oral mucosal lesions where the former is part of the developmental spectrum of the latter.[19-21] Oral verrucous hyperplasia is a histopathological entity and is part of the spectrum of verrucopapillary lesions.[22]

Oral Submucous Fibrosis

OSMF is a well-documented potentially malignant disorder, which is a chronic progressive inflammatory condition affecting primarily the oral epithelium and the submucosa. At the 11th International Dental Congress, London, Schwartz presented a paper on '*Atropica idiopathica mucosae oris*' in 1952. Joshi (1953) first described the clinical features of this condition, and in 1961, Prof. Rao presented a paper analysing 46 cases at the Institute of Laryngology and Otology, London.[23] In his lecture, he described cases from India as idiopathic palatal fibrosis ranging from moderate to severe cases and majority 34.7% and 32.6% of them were between 11–20 and 21–30 years, respectively. They were unable to trace the cause. However, they concluded that the condition is a localised collagen disease that responds to cortisone and its derivatives.[1] Subsequently, researchers proposed it could be due to mild chronic irritants, like chilli or areca nut chewing. Following application of arecoline in rat oral mucosa by Sirsat and Khanolkar, concluded that there was no significant role of arecoline as the aetiology of oral submucous fibrosis.[2,24] Although the aetiopathogenesis of the OSMF is multifactorial, areca nut chewing in any form is considered the main causative agent.

Diagnosis of OSMF is mainly based on clinical signs and symptoms. Features vary from early to advanced stages.[25] Burning sensation, blanching of the mucosa, blister formation, leathery mucosa and, in some cases, losses of pigmentation are the early signs and symptoms followed by gradual reduction of mouth opening, palpable fibrous bands on buccal mucosa and labial mucosa, depapillation of the tongue and shrunken uvula.[16] More advanced stage of OSMF is characterised by fibrous bands, both vertical and horizontal restricting of mouth opening and causing difficulty in oral functions such as mastication, speech and swallowing [Figure 3]. Restricted mouth opening together with burning sensation, reduced elasticity and ulcerations cause difficulties in maintaining oral hygiene. When fibrosis involves the nasopharynx or oesophagus, patients may experience referred pain to the ear, nasal voice and dysphagia to solid foods. Advanced cases of OSMF can be associated with hearing deficits. This is due to the decrease in the patency of the Eustachian tube by the involvement of palatal muscles resulting in conductive hearing loss.[26] Restricted mouth opening interferes with examination of the oral mucosa and makes early diagnosis of cancer in the case of malignant transformation difficult.

Depigmentation is an important and early manifestation in children with OSMF. Most of the children were diagnosed with OSMF at very early stage and were without classic clinical features of OSMF. Only manifestation in such children can be the depigmentation of lips.[27] Most patients with OSMF present to the clinic with symptoms that are unrelated and only about 25% of the patients visit with OSMF-related complaints.[28] Progressively reduced mouth opening has been reported as the main symptom in Indian patients,[28] whereas burning sensation is the comments complaint in Sri Lankan patients with OSMF.[29] Involvement of buccal mucosa with palpable fibrous bands is seen in almost 70% of the Sri Lankan patients whereas restricted tongue movements are seen in only 25% of them.[29] Among the Chinese population with OSMF, buccal mucosa is the most common site followed by tongue, lip and palate and their main clinical manifestations include pale mucosa, restricted mouth opening, burning sensation and fibrous bands.[30] Although the diagnosis can be made clinically, it is essential to perform diagnostic biopsy to exclude any dysplastic changes.

OSMF is an OPMD itself and provides a base to develop other OPMDs such as verrucopapillary lesions with dysplasia, leucoplakia and erythroplakia. Patients with OSMF have been reported to have a higher risk of developing OSCC (7.6%), compared to other OPMDs. Patients who have other OPMDs in the background of OSMF have double the risk of developing OSCC.[4]

Erythroplakia and Erythroplakia-like Lesions

Clinically erythroplakia is often a symptomatic, fiery reddish, sharply demarcated, shallow lesion that cannot be characterised clinically or pathologically as any other definable disease. It is relatively rare with a prevalence of 1%–2%; however, its malignant transformation rate varies from 14% to 50%.[5] These types of lesions are commonly seen in the middle-aged and elderly population. Common sites are the soft palate, the

floor of the mouth and the buccal mucosa, and the tongue is rarely affected.[6]

These reddish velvety surfaced lesions are irregular in shape with well-defined outlines.[7] Other similar lesions that need to be differentiated from erythroplakia have been described in the literature;[6,7] however, the most common lesions are erythematous candidosis, desquamative gingivitis and erosive and atrophic types of OLP. Erythema migrans and other inflammatory conditions also fall under differential diagnosis. A pathologist's opinion is important with an incisional biopsy as it is a high-risk lesion that may harbour dysplasia ranging from mild to severe.

Oral Lichen Planus and Oral Lichenoid Reactions

The diagnosis of OLP is initially based on the clinical presentation of bilateral white striations (Wickham striae), white patches with or without erosions, ulcers or blisters. Some cases are present in the background of blackish pigmentation. It can be classified according to the clinical presentation such as reticular/annular, atrophic/erythematous, erosive/ulcerative, plaque, papular and bullous types [Figure 4].

The reticular type is the most common and presents with asymptomatic, fine, white, linear and lace-like lesions of the buccal mucosa, tongue and gingiva. The whitish appearance is due to hyperkeratosis and is usually asymptomatic. The papular type is a rare form of OLP and mostly asymptomatic. It contains small white raised areas (papules) and occasionally it can generate whitish fine striae. Atrophic/erythematous type manifests as lesions with erythematous areas in the background of white radiating striae at the periphery with burning sensation. The erosive variant of lichen planus involves chronic and painful ulceration of the mucosal surfaces. Plaque-type OLP can mimic OL. It is usually present as thick white patches present in the buccal mucosa and dorsum of the tongue. This type is also asymptomatic. However, some cases may have burning sensation. The bullous type of OLP clinically presents with fibrin-coated ulcers surrounded by erythematous zone frequently displaying radiating white striae. However, it is crucial to differentiate erosive type and bullous type clinically. The most common presentation is desquamative gingivitis which is a clinical term used to name the gingival involvement with OLP, pemphigus, pemphigoid, linear immunoglobulin A disease and dermatitis herpetiformis. OLP presented in the background of pigmentation: degenerative changes in basal keratinocytes frequently led to pigmentary incontinence. The melanin pigment is ingested by macrophages in the superficial corium, resulting in a brownish-pigmented area in the mucosa, which can persist long after the OLP has resolved.

Lesions of OLRs/oral lichenoid lesions (OLLs) are clinically like OLP. They are probably due to certain medications (anti-diabetic drugs), dental restorative materials (e.g. amalgam), following graft versus host reaction in transplant patients, liver pathologies and betel quid induced (quid-induced lichenoid reaction). OLLs have recently been included as an OPMD.[5,8] Clinically, these lesions commonly present as unilateral, OLP types (described above). Majority are asymptomatic except atrophic/reddish lesions which may be sore. Combined findings from history, clinical features and histopathology are helpful in the diagnosis of OLPs/OLRs/OLLs. Pure histology cannot differentiate each type since all show similar features. However, there are evidence that there is a potential risk of malignant transformation x of OLP to OSCC.[9]

Other Uncommon Oral Potentially Malignant Disorders

Actinic cheilitis

Like the actinic keratosis of the skin, a premalignant lesion of the vermilion border of the lower lip occurs due to sunburn, mostly in light-complexioned persons. Initial alterations are non-inflammatory and are due to alterations induced by the ultraviolet components (ultraviolet B) of the sunlight. Outdoor workers are at higher risk and most of them are over 50 years of age. Following prolonged exposure, the risk of developing squamous cell carcinoma has been increased 2.5-fold.[31] It is necessary to take biopsies to exclude any dysplastic changes and OSCC.

Oral lupus erythematosus (OLE)

Lupus erythematosus (LE) is an immunologically mediated connective tissue disorder, some of which are confined to the mucosa or skin while others systemically affect any organ in the body. Oral manifestations of LE (OLE or oral discoid lesions) usually occur on the labial mucosa, buccal mucosa and vermillion border as white papules, reddish centred lesion radiating white striae with peripheral telangiectasia giving symptoms such as tenderness, burning sensation, dryness and pain.[20] However, OLE can occur without involvement of the skin. A study analysing 21 cases showed that 10% were without skin lesion while 90% were with skin involvement.[21] Discoid lupus erythematosus (DLE) -related malignant transformation is commonly seen related to the lower lip, hence DLE has been recognised as a potentially malignant disorder.[31,32] For diagnosis, clinicopathological correlation is essential as histological features are very much similar to OLP.

Oral Graft versus Host Disease (GVHD)

GVHD is triggered by the reactivity of donor-derived immune cells against allogeneic recipient tissues and usually occurs following allogeneic haematopoietic stem cell transplantation, or it may arise after blood transfusion or face or intestine transplants. Diagnosis is mainly clinical based. Development of clinical signs in the skin such as erythema, maculopapular rash, jaundice and symptoms such as nausea, diarrhoea and anorexia is diagnostic. However, oral lesions are rare and mainly non-specific erythema with or without ulcerations on the buccal mucosa and lips. Malignant transformation has been documented in the literature.[15]

Dyskeratosis Congenita

This condition was identified with a triad: dystrophic nails, oral whitish lesion (white spots on the tongue and oral mucosa) and abnormal skin pigmentation. The classic pattern for the triad is nail dystrophy at the age of 6 years, oral white lesions by the age of 7 years and abnormal reticulate skin pigmentation at 8 years of age. The earliest sign could be either anaemia or thrombocytopenia.[16] Oral manifestations are leucoplakia, atrophy of the tongue mucosa and OLP other than dental and periodontal problems. Leucoplakia is unusual in children and early presentation with white patches is an eye-opener to suspect dyskeratosis congenita (DC). These leucoplakic patches in patients with DC have a significantly increased risk of developing SCC.[5]

Palatal Keratosis in Reverse Smokers

Smoking of 'Chutta' (home-grown, semi-dried tobacco leaf is rolled crudely around a dried twig) a home-made cigar in - reversed direction is more popular in Andhra Pradesh, India. It is a practice of placing the lit end of the cigar inside the mouth while the other end is in between the lips keeping it wet to enjoy a longer time smoking.[17] Palate and tongue are the commonly affected intraoral sites. Initially, reddish circular areas develop followed by whitish papular lesions, which later increase in size forming ulcerations and ultimately lead to OSCC in the palate.[18]

Clinical Features of Oral Cancer

Oral cancer is defined as a malignant neoplasm arising in the oral cavity or on the lip. Some had used the term mouth cancer instead of oral cancer, which automatically includes lips. Cancers occurring in the oral mucosa excluding the skin side of the lip and posterior mouth are termed as oral cavity cancer. Although the clinical term oral cancer is synonymously used with the histopathological term OSCC, not all oral cancers are OSCCs. There are various other malignancies such as melanoma, different types of sarcomas, salivary gland malignancies and malignancies with odontogenic origin, which account for a small proportion of all oral cancers.

Even though oral cancer has high mortality and morbidity, it is easily preventable and detectable. It is easily preventable because the primary aetiological agents such as tobacco products, heavy use of alcohol, use of areca nut and combination of these are identified as carcinogens responsible for the development of oral cancer in most patients. Planning preventive strategies are not difficult even though the implementation and success of those depend on multiple factors. More than 90% of patients diagnosed with oral cancer give a history of some form of tobacco use. All forms of tobacco are responsible for carcinogenesis, including the use of smokeless tobacco. Smoking is prevalent all over the world, but smokeless tobacco use is confined to unique geographical areas such as South and Southeast Asia. Betel quid usage very much blends with the South Asian culture and this traditional betel quid contains both carcinogenic substances, tobacco and areca nut. Prognosis of the oral cancer depends on the stage at the time of diagnosis. Early detection of oral cancer allows a 5-year survival rate of 90%. Unfortunately, most oral cancers are diagnosed at advanced stages where the 5-year survival rate is 20%. Oral cancer has one of the worst prognoses of all major cancers because of the late diagnosis and the possibility of second primaries. No specialised techniques are required to examine the oral cavity for the presence of OPMDs or early oral cancers. Conventional oral examination with support from other diagnostic aids can assist in identifying the lesions at an early stage, yet most cases are diagnosed only at an advanced stage. Prevention and early diagnosis are therefore of utmost importance.

Oral cancer is commonly seen in middle-aged and elderly males. It is commonly seen in people with poor socio-economical backgrounds and may be associated with lack of awareness about the risk factors.[33,34] The most common anatomical site is buccal mucosa followed by the tongue, alveolar mucosa and floor of the mouth, especially in South Asia.[35] Buccal mucosa is the most common site of involvement in patients from South Asian countries and is attributed to the betel chewing habit.[34] Even South Asians residing in developed countries including the US have a higher incidence of buccal mucosal and buccal sulcus cancers. This finding suggests that the high incidence of cancers in buccal mucosa/sulcus is due to habit rather than racial susceptibility.[36] Clinical presentation, tumour characteristics and outcome in oral cancer appear to be different in developing and developed countries.[37]

Early lesions are usually painless and appear as small, apparently harmless areas of induration, erosion or keratosis, but advanced lesions present as a persistent painless ulcer with indurated and rolled margins. The most common complaints include ulceration, pain and swelling.[38] Oral cancer may present with different forms and at its early stage causes considerable challenge to the diagnosis. Early lesions can be present as small areas of erosion with variable induration. Oral cancer can present clinically as erosion, ulceration, granular or exophytic lesion [Figure 5]. Even though OSCC can present as exophytic lesion, this appearance is more common with verrucous carcinoma. Margins are indurated, and the base can be necrotic. Clinical presentation can vary with the site involved and histological type. Gingival carcinomas appear to be more whitish and exophytic that ulcerated.[38] Verrucous carcinoma is relatively larger, mostly seen in commissural area of smokers and has an exophytic appearance.

Clinically, malignant ulcers appear as single, chronic, non-healing ulcer with rolled, raised borders. Patients with advanced disease present with trismus or impaired tongue movement. At this stage, tumour may spread into the surrounding areas, fixed to underlying soft tissues or adjacent bone and it speared to regional lymph nodes easily resulting in cervical lymphadenopathy. Involved lymph nodes are usually painless unless secondarily infected. Involvement of

lymph node indicates poor prognosis. Rarely, patients present with persistent, severe pain, especially in the tongue due to involvement of nerves. Warning signs and symptoms of oral cancer include, but are not limited to red or red and white lesions, ulcers lasting for more than three weeks, swellings, lumps or thick patches anywhere in the mouth, numbness, pain or tenderness without any identifiable cause, pain in one of the ears without any hearing loss, difficulty with moving the lower jaw or tongue or with chewing, swallowing or speaking and mobility of teeth without any evidence of periodontal disease.[9,39]

Oral cancer is subjected to the 'field cancerisation phenomenon', having the highest risk of development of second primary tumours out of any cancer. Other than the late presentation, this is considered an important reason for poor prognosis. In addition to the possibility of occurrence of second primary, oral cancers can present as multiple tumours in multiple sites at the same time. They are called synchronous tumours. Surprisingly, single primary tumours have a poor prognosis than synchronous tumours.[40] All chronic painless ulcers present in the mouth are not oral cancers. Infections such as deep fungal infections or TB, trauma, major aphthous ulceration and many other conditions can mimic oral cancer clinically. Therefore, confirmation of the clinical diagnosis with histopathology is essential.

Summary

Oral cancer has a poor prognosis and results in serious physical, functional and psychological disabilities and social implications. Most oral cancers arise from OPMDs, which can be diagnosed easily with their characteristic clinical presentations. Clinical features of these OPMDs vary with the type of lesion, area of involvement as well as the population involved. Knowledge of clinical features and the inquisitive mind of a healthcare professional can reduce the delays associated with the diagnosis and management of these patients.

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Conflicts of interest

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