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Review

Potentially Malignant Oral Disorders and Cancer Transformation

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Abstract. *Cancer in the oral cavity is often preceded by precursor lesions. Nine oral mucosal disorders are known to have an increased risk of malignant transformation. The etiology varies from disorders caused by exogenous factors such as tobacco and autoimmune inflammation to idiopathic or inherited genetic aberrations. In this review, these potentially malignant disorders (PMDs) are described regarding clinical presentation and histopathological architecture. Special attention is paid to the underlying etiologies of PMDs and the potential pathways leading to cancer. The clinical perspective focuses on the importance of accurate and timely diagnosis.*

Cancer is the second most common cause of death in developed countries and the third leading cause of mortality in developing countries (1). The cancer incidence is estimated to rise to 26 million cases and 17 million deaths per year in 2030 and is, therefore, a major global health issue (2). Lip and oral cavity cancer accounted for 145,000 deaths worldwide in 2012 (2% of total cancer cases). The incidence of lip and oral cavity cancer in different regions in the World. Western Africa had the lowest incidence both among males and females (1.7 and 1.4 per 100,000, respectively) in 2012, while Melanesia had the highest incidence both among males and females (22.9 and 16.0 per 100,000, respectively) in 2012 (3). Among the continents, Asia has the highest incidence of lip and oral cancer and 168,850 cases were reported in 2012 (4).

Oral squamous cell carcinoma (OSCC) constitutes 92-95% of all oral cancer (1). Most oral SCC is preceded by precancerous lesion (5, 6). Oral mucosal disorders with increased risk of cancer transformation are termed potentially malignant disorders (PMDs) of the oral mucosa by the World Health Organization (6).

Oral PMDs are categorized into leukoplakia, erythroplakia, actinic cheilosis, oral submucous fibrosis, palatal keratosis associated with reverse smoking, oral lichen planus, discoid lupus erythematosus, dyskeratosis congenita and epidermolysis bullosa (6). The etiology of the aforementioned disorders ranges from pure genetic aberrations predisposing for altered tissue regeneration (7), disorders caused by exogenous factors such as tobacco and immune-mediated disorders, and those associated with rare inherited diseases.

Genetically-acquired Potentially Malignant Disorders

Leukoplakia. Leukoplakia present as white patches or plaques that cannot be rubbed off, cannot be characterized clinically or histologically as any other condition (Figure 1A). The diagnosis is defined as "white plaques of questionable risk having excluded (other) known diseases" or "disorders that carry no increased risk for cancer" (6). Depending on the clinical presentation, leukoplakia can be divided into homogeneous and non-homogeneous forms. The homogenous form displays a uniform pattern of reaction throughout the lesion, with a uniform white patch with shallow ridges in the epithelium. The non-homogeneous

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form is of three types: i) speckled with mixed white and red appearance on the surface but predominantly white; ii) nodular with small polypoid outgrowths which are rounded red or white outgrowths; and iii) verrucous with a wrinkled or corrugated surface appearance (6). Leukoplakia is mostly caused from consumption of tobacco, alcohol, and betel quid; a few cases occur genetically and are referred to as idiopathic leukoplakia (6, 8).

Leukoplakia is commonly observed in middle-aged and older men (9, 10). Of those diagnosed with leukoplakia, fewer than 1% were males under 30 years of age (10). The global prevalence of leukoplakia has been estimated at 2.60% (95% confidence interval (CI) 1.72-2.74%) (11). Proliferative verrucous leukoplakia (PVL) is a rare subset of non-homogenous leukoplakia that generally affects several sites, frequently the gingival and buccal mucosa, and progressively involves contiguous or non-contiguous areas (Figure 1B). Almost all initial biopsies show hyperkeratosis without dysplasia or verrucous hyperplasia (12, 13). A possible etiological role of human papillomavirus in PVL remains controversial (14). PVL has a malignant transformation rate of 61.0% in an average follow-up period of 7.4 years (15).

A systematic review of the literature by Warnakulasuriya *et al*. showed that the overall malignant transformation rate of leukoplakia was 3.5%, however, the rate varied in studies between 0.13% and 34% (16). Histopathological features of leukoplakia are hyperkeratosis of ortho- or parakeratotic type and acanthosis of the epithelium. Moreover, different degrees of epithelial dysplasia may occur (17, 18). However, histopathological features *per se* are not sufficient to establish the diagnosis; clinical features combined with histopathological changes establish the diagnosis.

Erythroplakia. Erythroplakia is defined as "a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease" (Figure 1C) (19). All other possible diagnoses should be excluded before the diagnosis is established (20). The etiology of oral erythroplakia has a strong association with consumption of tobacco and alcohol (21).

Villa *et al*. reported the global mean prevalence of oral erythroplakia as 0.11% (ranging from 0.01 to 0.21%) (22). Erythroplakia most frequently occurs in males aged 50-70 years (10). According to Shafer and Waldron, 51% of oral erythroplakia transformed into oral SCC (21). Carcinoma *in situ* and mild to moderate dysplasia are observed in 40% and 9% respectively, of erythroplakia lesions (23). Malignant transformation rates of erythroplakia are very high ranging from 14% to 50% (20). Because of this high rate, early detection and immediate surgical excision are recommended. Histopathological features of erythroplakia show at least some degree of dysplasia and even carcinoma *in situ* or invasive carcinoma (23).

Actinic cheilitis. Actinic cheilitis (AC) is a pathological condition with mottling of the lip with atrophic areas or shallow erosions and rough, scaly, flaky keratotic patches on some parts, or on the entire exposed portion of the lip, sometimes with small wrinkles in the vermilion border (Figure 1E). AC affects most frequently the vermilion border of the lower lip, but the upper lip may also be affected in bimaxillary protrusion. In persons with everted lower lips (as a racial characteristic or as an inherited trait) the mucosal surface of the lower lip exposed to sunlight may also be affected (23-26). UVA and UVB can contribute to aging of the skin by damaging collagen, breaking down vitamin A (27), by causing local immunosuppression and by ionization, which releases hydroxyl and oxygen radicals and thus contributes indirectly to DNA damage (28). AC frequently involves the lower lip with a high risk of developing into SCC. AC is one of the main risk factors for lip cancer, which is regarded as the fifteenth most common cancer worldwide in men (3). About 6-10% of AC cases undergo malignant transformation over time (17, 29, 30). In a recent study by Kwon *et al*., lip SCC originating from AC was demonstrated to have a greater risk for metastasis than SCC arising from other cutaneous parts (31). Histopathological features of AC range from atrophy to hyperplasia of the squamous cell epithelium of the vermilion border, with varying degrees of keratinization and cytological atypia. Drop-shaped epithelial pegs are often present, but the basement membrane is intact. The underlying connective tissue shows basophilic degeneration (32, 33).

Tobacco-induced Potentially Malignant Disorders

Oral submucous fibrosis. Oral submucous fibrosis (OSF) is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx and esophagus (Figure 1D). It is characterized by a mucosal rigidity of varying intensity due to fibroelastic changes of the juxta-epithelial layer, resulting in a progressive inability to open the mouth (9, 23). OSF is more common in young Indian adults (20-40 years of age) (9). It has been suggested that consumption of chillies, nutritional deficiency, tobacco chewing of areca nut, genetic susceptibility, altered salivary constituents, autoimmunity and collagen disorders may be involved in the pathogenesis of this condition (34).

Patients with OSF are at least 19 times more likely to develop OSCC than healthy people (20). OSSC originating from OSF occurs at a mean age of 46 years, and occurs more commonly in men (male to female ratio 32.1:1), is more invasive and has a greater risk of metastasis than OSSC originating from other lesions (35). The risk of malignant transformation of OSF is 2-8% (36). Histopathological features of OSF show an atrophic epithelium with juxta-epithelial hyalinization and collagen of varying density (37).

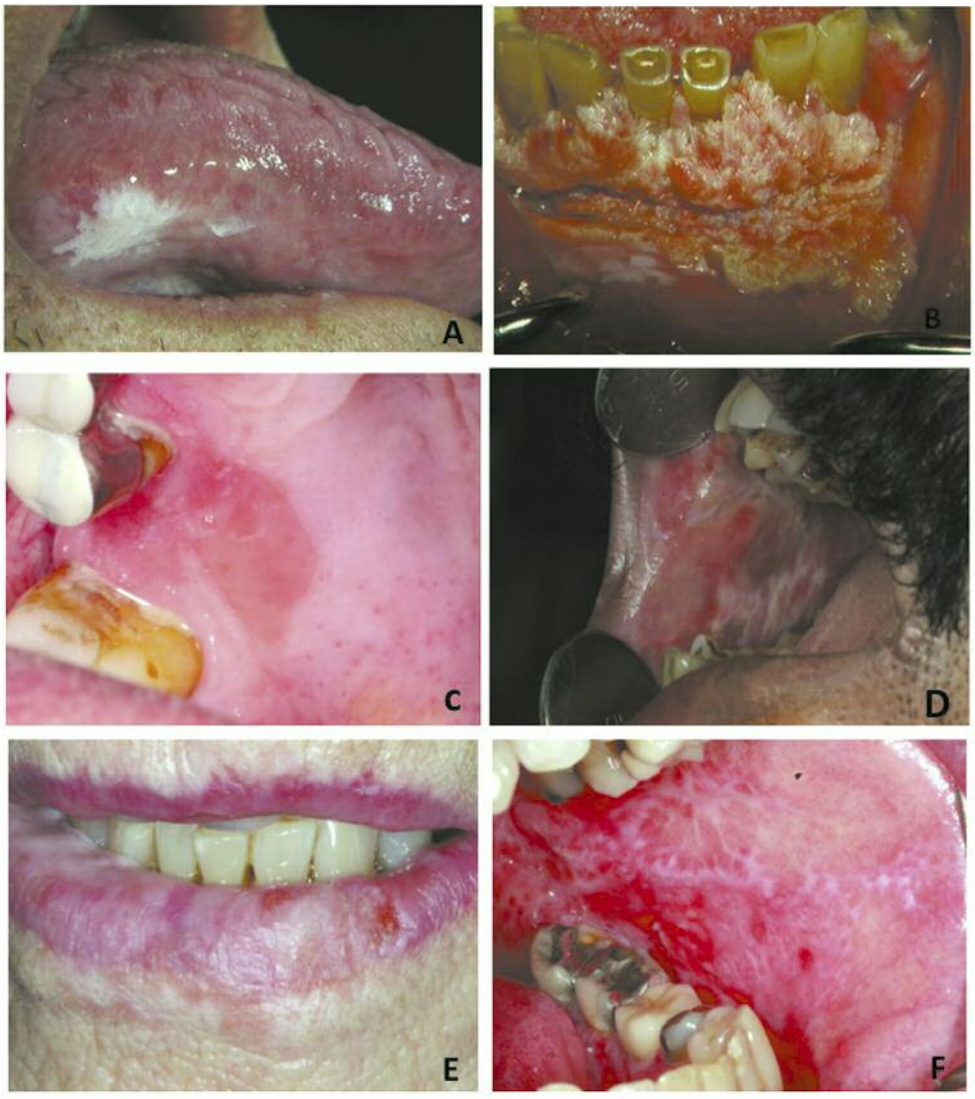

Figure 1. *Clinical aspects of potentially malignant oral disorders. A: Leukoplakia at the right border of the tongue. B: Proliferative verrucous leukoplakia in the anterior gingiva of the mandible. C: Erythroplakia in the hard palate. D: Oral submucous fibrosis in the right buccal mucosa. E: Actinic cheilitis in the lower lip. F: Oral lichen planus in the left buccal mucosa.*

Palatal keratosis associated with reverse smoking. In reverse smoking, the burnt end of a rolled tobacco leaf is put in the mouth instead of the unburnt end. This habit is practiced by people in South America (Columbia, Panama, Venezuela, the Caribbean Islands), Asia (India, the Philippines) and Europe (Sardinia) (38). Reverse smoking is seen in patients of low socioeconomic class and is more common in females (39). The palate and tongue are commonly affected areas in reverse smokers (40). Lesions associated with this habit range from palatal keratosis, excrescences, leukoplakia, and ulcerations to frank malignancy (40). Epithelial dysplasia and oral SCC occur in 83% and 13%, respectively, of reverse smokers (41). Palatal keratosis associated with reverse smoking is characterized by different histopathological features including atypical changes in the epithelium and orifices of the ducts of the glands, and papules with umbilication are due to hyperplasia of the mucous glands and micro-invasive carcinoma (42).

Immune-mediated Potentially Malignant Disorders

Oral lichen planus. Oral lichen planus (OLP) is a common chronic, immunologically-mediated mucocutaneous disease. OLP ranges from asymptomatic reticular white lesions in

the atrophic mucosa to erosive-ulcerative areas, while the most characteristic feature is the presence of a lace-like network of fine white lines (Figure 1F) (9). OLP is an immune-mediated disease and some reports suggest it is associated with viral infection, such as herpes simplex, Epstein–Barr virus, human papillomavirus, and hepatitis C (43-46). Most patients with lichen planus are middle-aged (over 40 years) and females account for at least 65% of patients (20). The worldwide prevalence rates of OLP range from 0.5% to 2.6% (47-49).

The risk of malignant transformation in OLP has been controversial for a long time and is estimated to be between 0.4% and 3.7% (9, 50). Histopathological features of OLP are hyperkeratosis with saw-toothed rete pegs, liquefaction degeneration of the basal cell layer, and a dense sub-epithelial band of lymphocytes (51).

Discoid lupus erythematosus. Discoid lupus erythematosus (DLE) is a chronic, scarring, immunological and mucocutaneous disease characterized by white keratinized plaques with elevated borders, radiating white striae, and telangiectasia (52, 53). The prevalence of DLE is fewer than 5 per 10,000 individuals and is more common in women, with a female to male ratio of 1.8:1 (54). Malignant transformation is rare in DLE (55), however, epithelial dysplasia and prolonged exposure to UV light are risk factors associated with an enhanced risk of malignant transformation in DLE (56, 57). It was reported that high-risk dysplasia was associated with a 19-fold increased risk of malignant transformation when compared to low-risk dysplasia (52). Histopathological features of DLE are hyperkeratosis, atrophy of rete processes, superficial and deep inflammatory infiltrate, edema in the *lamina propria* and thick continuous or patchy periodic acid–Schiff-positive deposits in the basement membrane zone (58).

Genetically-inherited Potentially Malignant Disorders

Dyskeratosis congenita. *Dyskeratosis congenita* (DC), also called Cole–Engman syndrome or Zinsser–Cole–Engman syndrome, is a rare inherited disease which is characterized by the classic triad of nail dystrophy, reticular skin pigmentation and oral leukoplakia (59). DC is very rare and affects one in 1,000,000 persons (62). The most common mode of inheritance is the X-linked recessive form which affects mainly males and is caused by mutation of the dyskerin pseudouridine synthase 1 (*DKC1*) gene at the Xq28 site (60, 62). It mainly occurs in men, with a male to female ratio of 13:1, and manifests between 5 and 13 years of age (59). DC significantly increases the risk of malignant transformation (63). Oral and dental abnormalities have been reported in a few cases which include hypodontia, short blunted roots, hypocalcification, thin enamel, gingival recession, gingival inflammation with gingival bleeding, alveolar bone loss, periodontitis, extensive caries, smooth atrophic tongue mucosa, leukoplakia, and lichen planus (64). The majority of patients with DC develop leukoplakia, approximately 87% (65).

Epidermolysis bullosa. Epidermolysis bullosa (EB) is a rare inherited blistering disease of the skin and mucosa. Approximately 500,000 individuals are affected worldwide (66). The four major EB groups include intraepidermal (simplex), junctional, dermolytic (dystrophic), and mixed (Kindler syndrome) (67). The simplex subtypes are caused by mutations in the plakophilin 1 (*PKP1*), desmoplakin (*DSP*), keratin 5 (*KRT5*), keratin 14 (*KRT14*), plectin (*PLEC1*), and integrin subunit 6 (*ITGA6*) genes (67). The junctional forms of EB are caused by mutations in laminin subunit alpha 3 (*LAMA3*), laminin subunit beta 3 (*LAMB3*), laminin subunit gamma 3 (*LAMC3*), collagen type XVII alpha 1 chain (*COL17A1*), integrin alpha 6a (*ITG6A*), and integrin subunit beta 4 (*ITGB4*) (67-69). The dystrophic EB types are also caused by mutations in collagen type VII alpha 1 chain (*COL7A1*) gene (70). Kindler syndrome is an autosomal recessive genodermatosis caused by mutations in the fermitin family member 1 (*KIND1*) gene (71). Common oral manifestation in EB is oral blistering, oral scarring, microstomia and enamel defects (72). Junctional EB develops into SCC in 25% of cases (73). Moreover, patients with EB are at a higher risk of developing basal cell carcinoma and malignant melanoma (74), a risc that has also been suggested for the month (6).

Conclusion

Development of potentially malignant disorders and oral SCC are multistep processes involving genetic changes due to exogenous or indigenous factors (57). Importantly, several potentially malignant disorders are related to tobacco use and subsequently preventable with tobacco cessation programmes. Those related to inflammatory disorders such as OLP and DLE may also be preventable to some extent by reducing the level of inflammation. Chronic inflammation is a well-known risk factor for malignant disorders (75-77). The etiological factors are unknown to idiopathic genetic damage in epithelial keratinocytes leading to the development of leukoplakia and are, therefore, a clinical challenge. Since there is currently no molecular or even histopathological pathognomonic hallmark that can predict malignant transformation of potentially malignant disorders, the analysis of the clinical aspects of these lesions remains the best way to control and prevent the development of oral SCC. Thus, accurate diagnosis and timely treatment may help prevent the transformation of potentially malignant disorders into OSCC (4).

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