Oral potentially malignant disorders

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Abstract

Worldwide oral squamous cell carcinoma (OSCC) is one of the most frequent malignancies, with a mortality rate of 1.9 deaths per 100,000 per year. Most cases of OSCC are preceded by clinical lesions referred to as oral potentially malignant disorders (OPMDs). The World Health Organization defines OPMDs as "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa". These disorders include leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis, palatal lesion of reverse cigar smoking and oral lichen planus. In this review we discuss the clinical, pathologic and molecular features of OPMDs.

Keywords erythroplakia; erythroleukoplakia; leukoplakia; oral cavity; squamous cell carcinoma; squamous dysplasia; tongue

Introduction

Worldwide oral squamous cell carcinoma (OSCC) is one of the most frequent malignancies, and it carries a bad prognosis with a global mortality rate of 1.9 deaths per 100,000 per year.[1,2] Most cases of OSCC are preceded by asymptomatic clinical lesions collectively referred to as oral potentially malignant disorders (OPMDs).[3,4] According to the new classification of the World Health Organization, OPMDs are defined as "clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal oral mucosa".[5] The disorders of concern are leukoplakia, erythroplakia, erythroleukoplakia, oral submucous fibrosis, palatal lesion of reverse cigar smoking and oral lichen planus,[5] although the malignant potential of lichen planus remains controversial.[6] The purpose of this review is to discuss the clinical, pathologic and molecular features of OPMDs, with a focus on leukoplakia and erythroplakia.

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Clinical features

Leukoplakia is a clinical term used to describe white plaques of questionable risk, once other specific conditions and OPMDs have been rule out. In its clinical appearance, oral leukoplakia can be homogeneously white and flat, or predominantly white with nodular, verrucous, or red areas[5] (Figure 1). Erythroplakia is defined similarly to a leukoplakia but as a red patch instead of white. When patches have a mixed red and white appearance they are referred to as erythroleukoplakia[5] (Figures 2 and 3).

Among OPMDs, oral leukoplakia is the most commonly encountered entity in clinical practice.[4] The incidence of leukoplakia is highly variable with a global prevalence of 2–3%.[5] On the other hand, oral erythroplakia is a rare lesion, with prevalence between 0.02% and 0.83%.[5]

Oral leukoplakia is a multifactorial lesion, but in many cases it is idiopathic.[7] The most commonly associated risk factor is tobacco use (smoking and/or chewing),[5,7,8] with a direct relationship between the frequency and the duration of smoking and the prevalence of oral leukoplakia.[9] The use of areca (betel) nut, either alone or in combination with tobacco, is a significant risk for the development of oral leukoplakia and submucous fibrosis (Figure 3). The use of areca (betel) nut is seen mostly in south and southeast Asia.[7,8] Regarding HPV, many studies have reported the presence of HPV DNA in oral leukoplakias.[10–12] Nevertheless, the association between HPV and the development of oral leukoplakia is not clear.[13]

Males are affected at least three times more often than females[14] and the lesion is usually diagnosed in their middle years[7] although a systematic review by Petti showed that there was no difference in prevalence between adults aged 50 years or older and those aged less than 50 years.[14] Leukoplakia and erythroplakia can affect any intraoral site and may present as solitary or multiple lesions. The distribution depends on the specific associated disorder and on other etiological factors.[5,8] Leukoplakia is most frequently seen on the buccal mucosa and in case of reverse smoking habit the palate is the most affected site.[8] Erythroplakia is found most commonly on the soft palate, floor of the mouth, and buccal mucosa.[5]

Pathologic features

Oral leukoplakia is characterized by hyperkeratosis of the stratified squamous epithelium, with or without acanthosis and/or epithelial dysplasia (Figures 4 and 5). Oral erythroplakia shows a lack of keratin production with epithelial atrophy and a high probability for epithelial dysplasia[15] (Figure 5). Chronic inflammation is frequently observed in the connective tissue for both lesions.[15] According to the WHO classification, oral epithelial dysplasia "is a spectrum of architectural and cytological epithelial changes caused by accumulation of genetic changes, associated with an increased risk of progression to squamous cell carcinoma".[5]

The cellular alterations that are used to diagnose oral epithelial dysplasia are: abnormal variation in nuclear and/or cell size and shape, increased nuclear/cytoplasmic ratio, enlarged nuclei and cells, hyperchromatic nuclei, increased mitotic figures, abnormal mitotic figures (shape or localization), and increased number and size of nucleoli. The architectural

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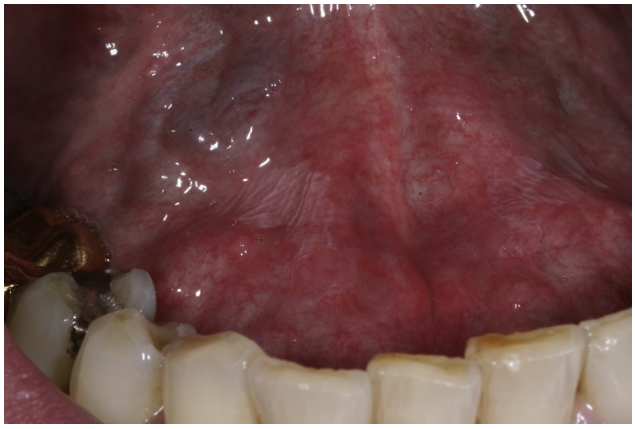

Figure 1 Bilateral homogeneous leukoplakia with flat and well-defined white patches on the floor of the mouth.

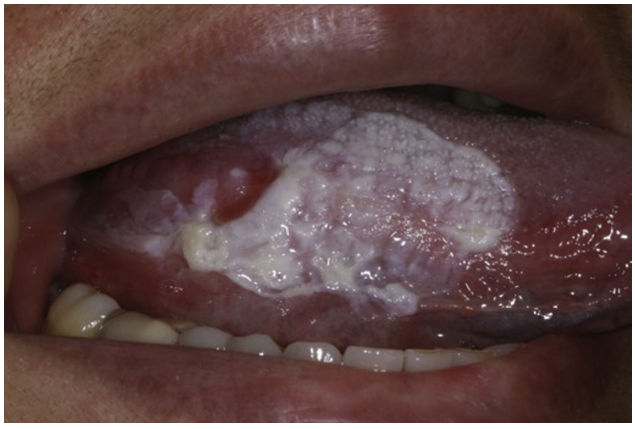

Figure 2 Erythroleukoplakia on the lateral tongue present for 15 years and histopathology of multiple biopsies showed mild dysplasia.

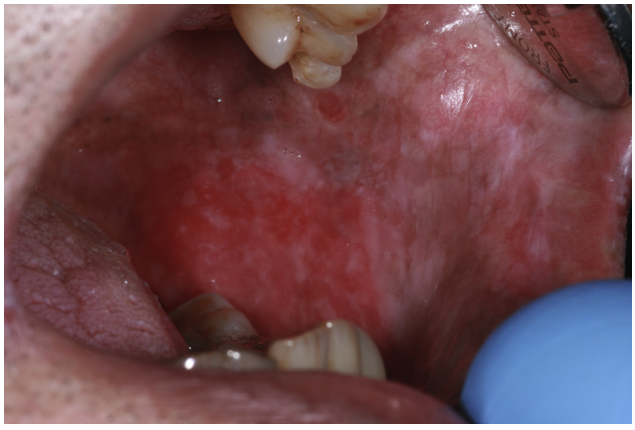

Figure 3 Erythroleukoplakia on the buccal mucosa in a patient with submucosal fibrosis as a result of paan (betel nut) use. Biopsy of the lesion showed severe dysplasia on histology.

changes are: loss of polarity, disordered epithelial maturation, increased cellular density, basal cell hyperplasia, dyskeratosis, bulbous drop shaped rete pegs and secondary extensions on rete tips.[5,16]

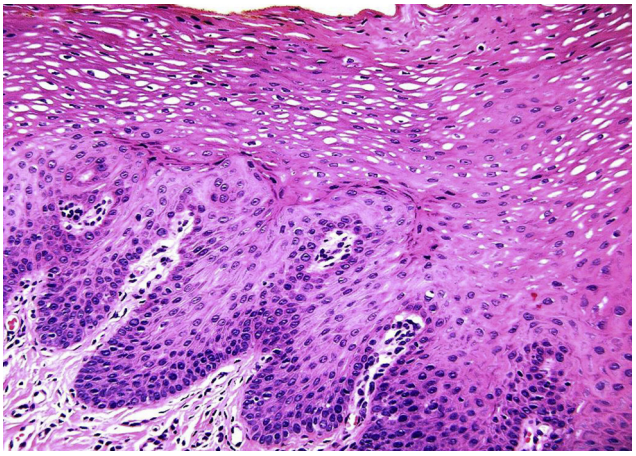

Figure 4 Biopsy of leukoplakia showing squamous hyperplasia with parakeratosis and hypercellularity of basal and suprabasal layers.

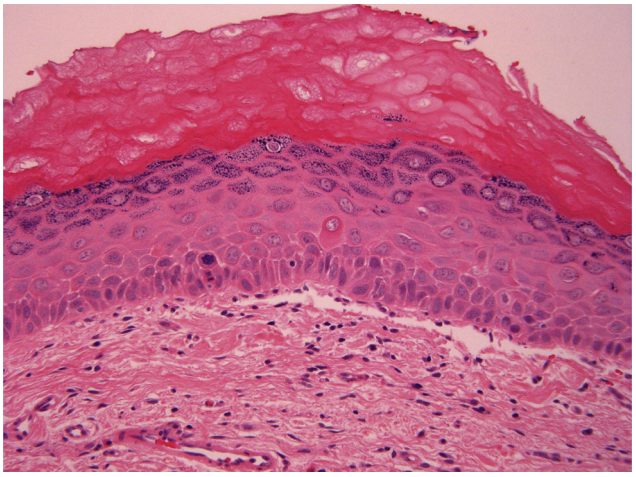

Figure 5 Biopsy of leukoplakia revealing mild dysplasia characterized by increased cellularity of the lower third of the squamous epithelium accompanied by dyskeratosis, nuclear irregularities (anisonucleosis), and suprabasal mitoses.

Oral epithelial dysplasia can be classified as mild, moderate and severe, according to the extent of architectural and cytologic abnormalities. In mild dysplasia, proliferation of cells involving the basal and parabasal layers is observed extending to no more than to the lower third of the epithelium, with minimum cytological and architectural changes[16] (Figure 5). Moderate dysplasia shows a proliferation of atypical cells extending to the middle one-third of the epithelium (Figure 6). Hyperchromatism, pleomorphism (nuclear and/or cellular), loss of basal polarity, hyperplasia leading to bulbous rete pegs can be found in moderate dysplasia.[16] Severe dysplasia is characterized by abnormal proliferation of the basal layer into the upper third of epithelium (Figure 7). Cytological and architectural changes are evident and all categories of atypia could be present[16] in severe dysplasia. This classification is highly subjective and it has been the subject of significant inter- and intraobserver variations when classifying

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