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**Research Article**

# ORAL ERYTHROLEUKOPLAKIA: A REVIEW OF ETIOPATHOGENESIS, DIAGNOSIS, AND MANAGEMENT WITH A CLINICAL ILLUSTRATION

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**Abstract**

Oral erythroleukoplakia, classified as a subtype of non-homogeneous leukoplakia, is a clinically significant oral potentially malignant disorder (OPMD) characterized by the coexistence of red and white components within the same lesion. Compared with homogeneous leukoplakia, these lesions show a higher prevalence of epithelial dysplasia and a greater risk of malignant transformation, which makes early recognition and timely management essential. This article reviews the current literature on oral erythroleukoplakia, covering its epidemiology, etiopathogenesis, clinical presentation, histopathology, diagnostic approaches, and contemporary management strategies, including habit cessation, surgical or laser excision, and long-term surveillance. We also report the case of a 48-year-old male with a 20-year history of tobacco and gutkha chewing. Intraoral examination revealed a non-homogeneous keratotic lesion with an irregular erythematous component on the left buccal mucosa, and a similar speckled lesion on the left lateral border of the tongue, a high-risk site. The clinical features suggested erythroleukoplakia, but because histopathological examination was not performed, a definitive diagnosis could not be established. The differential diagnosis includes candidal leukoplakia, oral lichen planus, proliferative verrucous leukoplakia, and early squamous cell carcinoma. Adjunctive techniques such as toluidine blue staining, tissue autofluorescence, narrow-band imaging, optical coherence tomography, salivary biomarkers, and artificial intelligence-assisted image analysis show promise for assessing OPMDs, but their sensitivity and specificity vary, and none can replace histopathology. Biopsy of the most clinically suspicious (erythematous) area remains the gold standard. Early detection, elimination of etiological risk factors, and appropriate management are essential to reduce progression to oral squamous cell carcinoma.

**Keywords:** Oral erythroleukoplakia, Speckled leukoplakia, Non-homogeneousleukoplakia, Erythroplakia, Oral potentially malignant disorder, Smokeless tobacco

## INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity, accounting for approximately 90% of oral cancers worldwide.[1] Despite advances in diagnostic and therapeutic approaches, the global burden of OSCC remains substantial, with many patients presenting with advanced-stage disease.[2] A substantial proportion of oral squamous cell carcinomas arise in the setting of oral potentially malignant disorders (OPMDs), a heterogeneous group of mucosal lesions and conditions associated with an increased risk of malignant transformation.[1] Early recognition, accurate diagnosis, and appropriate management of OPMDs are therefore essential for reducing the burden of invasive oral cancer and improving patient outcomes.[2] According to the World Health Organization (WHO) Collaborating Centre consensus, oral erythroplakia is defined as a predominantly fiery red patch that cannot be characterized clinically or histopathologically as any other definable disease.[1] Lesions exhibiting both red and white components have been described as oral erythroleukoplakia or speckled leukoplakia. The terminology surrounding mixed red-and-white lesions has historically been inconsistent, and their classification requires careful clinical and histopathological assessment.[3] Oral erythroplakia is relatively uncommon, with reported prevalence estimates ranging from 0.02% to 0.83%.[3,4] It is considered a high-risk OPMD because a substantial proportion of lesions demonstrate severe epithelial dysplasia, carcinoma in situ, or invasive squamous cell carcinoma at the time of biopsy.[3,5] A systematic review and meta-analysis published in 2022, which included 10 observational studies involving 441 patients, reported that 42.8% of oral erythroplakia lesions were already diagnosed as squamous cell carcinoma at the initial biopsy. The pooled malignant-development rate was 19.9%, although substantial heterogeneity was observed among the included studies.[5] The etiopathogenesis of oral erythroleukoplakia is multifactorial and remains incompletely understood. Tobacco smoking, smokeless tobacco use, areca nut and gutkha consumption, and alcohol use are important risk factors associated with the development of oral potentially malignant disorders.[2] Additional factors, including chronic candidal infection, nutritional deficiencies, genetic susceptibility, and molecular alterations, have also been implicated in the development and progression of potentially malignant oral lesions.[6] The present article reviews the current literature on oral erythroleukoplakia, with emphasis on its epidemiology, etiopathogenesis, clinical presentation, histopathological characteristics, diagnostic approaches, and contemporary management strategies. In addition, a clinical illustration of a patient with a lesion clinically suggestive of oral erythroleukoplakia is presented to emphasize the importance of meticulous oral examination, histopathological confirmation, timely intervention, and risk-factor modification in individuals with long-standing tobacco habits.

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Oral squamous cell carcinoma (OSCC) is the most common malignancy affecting the oral cavity and accounts for approximately 90% of all oral cancers worldwide.[1] Despite advances in diagnosis and treatment, its global burden remains significant because many patients present at advanced stages of the disease.[2] A substantial proportion of oral squamous cell carcinomas arise from oral potentially malignant disorders (OPMDs), a group of lesions and conditions associated with an increased risk of malignant transformation.[1] Early recognition and appropriate management of OPMDs are therefore essential to reduce the incidence of invasive oral cancer and improve patient prognosis. [2]

According to the World Health Organization (WHO), oral erythroplakia is defined as a predominantly fiery red patch that cannot be characterized clinically or histopathologically as any other definable disease.[1] Lesions exhibiting both red and white components are termed oral erythroleukoplakia or speckled leukoplakia and represent one of the highest-risk forms of OPMDs.[3] Oral erythroplakia is relatively uncommon, with a reported prevalence ranging from 0.02% to 0.83%.[3,4] Histopathological studies have demonstrated that nearly 80–90% of erythroplakic lesions exhibit severe epithelial dysplasia, carcinoma in situ, or invasive squamous cell carcinoma.[3] A recent systematic review reported a malignant transformation rate ranging from 55% to 65%, emphasizing the aggressive biological behaviour of these lesions.[5] The precise etiopathogenesis of oral erythroleukoplakia remains incompletely understood. Tobacco smoking, smokeless tobacco, areca nut, gutkha, and alcohol consumption are regarded as the principal risk factors associated with its development. [2] Additional contributing factors, including chronic candidal infection, nutritional deficiencies, genetic susceptibility, and molecular alterations, have also been implicated in disease progression.[6] The present article reviews the current literature on oral erythroleukoplakia, including its epidemiology, clinical presentation, histopathological characteristics, diagnostic advances, and contemporary treatment strategies. In addition, a clinical illustration of a patient with suspected oral erythroleukoplakia is presented to emphasize the importance of meticulous oral examination, timely diagnosis, and appropriate intervention in individuals with long-standing tobacco habits.

## Clinical Illustration

A 48-year-old male was reported to the Department of Oral Medicine and Radiology for a routine dental examination. The patient was asymptomatic and did not complain of pain, burning sensation, ulceration, bleeding, or difficulty in mastication. His medical history was non-contributory. Habit history revealed tobacco powder chewing three times daily and gutkha consumption five times daily for the past 20 years.

Extraoral examination revealed no facial asymmetry or palpable cervical lymphadenopathy. Intraoral examination revealed a non-scrapable, non-homogeneous white keratotic plaque involving the left buccal mucosa, extending from the left commissure of the mouth posteriorly to the region of tooth 37 (Figure 1). The lesion exhibited a characteristic cracked mud appearance. Interspersed within the keratotic plaque was an irregular erythematous area measuring approximately 2 × 2 cm, extending from the 36–37 region, resulting in a mixed red-and-white appearance clinically suggestive of an erythroleukoplakic lesion.



**Figure 1. Erythroleukoplakia on the left buccal mucosa**

Further intraoral examination revealed a non-scrapable white keratotic lesion involving the left lateral border of the tongue, with multiple interspersed erythematous areas producing a speckled appearance, also clinically suggestive of an erythroleukoplakic lesion (Figure2).



**Figure 2. Speckled leukoplakia on the lateral borders of the tongue**

In addition, multiple inflamed minor salivary gland duct openings were observed on the lower labial mucosa (Figure 3). Generalized extrinsic tobacco stains and cervical abrasions were also noted.



**Figure 3. Inflamed salivary gland openings on the lower labial mucosa**

Based on the patient's history and clinical findings, a provisional diagnosis of non-homogeneous leukoplakia with erythroleukoplakic changes involving the left buccal mucosa and left lateral border of the tongue was considered. The differential diagnosis included erosive oral lichen planus, chronic hyperplastic candidiasis, erythematous candidiasis, discoid lupus erythematosus, traumatic keratosis with secondary inflammation, and early oral squamous cell carcinoma. The patient was counselled regarding the potentially malignant nature of the lesion and was strongly advised to discontinue tobacco and gutkha use. Oral prophylaxis and habit cessation counselling were provided. An incisional biopsy from the erythematous component of the

buccal mucosal lesion was recommended to establish a definitive histopathological diagnosis, as the erythematous area is more likely to demonstrate epithelial dysplasia or malignant transformation. However, histopathological examination had not been performed because the patient did not undergo biopsy. The patient was advised periodic clinical follow-up for monitoring of the lesion and reinforcement of tobacco cessation.

## DISCUSSION

Oral erythroleukoplakia is an uncommon but clinically significant oral potentially malignant disorder (OPMD) characterized by the coexistence of erythematous and keratotic components within the same lesion. The World Health Organization (WHO) defines oral erythroplakia as a predominantly fiery red patch that cannot be characterized clinically or histopathologically as any other definable disease, while lesions exhibiting both red and white components are commonly referred to as oral erythroleukoplakia or speckled leukoplakia.[1,3] Compared with homogeneous leukoplakia, erythroleukoplakia carries a considerably higher risk of epithelial dysplasia and malignant transformation, warranting early recognition and prompt intervention.[3,5] The prevalence of oral erythroplakia has been reported to range between 0.02% and 0.83%.[3,4]Although uncommon, it is regarded as one of the oral potentially malignant disorders with the highest risk of malignant transformation.[5] Histopathological evaluation has demonstrated severe epithelial dysplasia, carcinoma in situ, or invasive squamous cell carcinoma in approximately 80–90% of lesions.[3] A recent systematic review reported a malignant transformation rate ranging from 55% to 65%, emphasizing the aggressive biological behaviour of these lesions.[4,5]

The precise etiopathogenesis of oral erythroleukoplakia remains incompletely understood. Chronic exposure to tobacco, smokeless tobacco, areca nut, gutkha, and alcohol is considered the principal etiological factor.[2] Additional factors, including chronic candidal infection, nutritional deficiencies, genetic susceptibility, and molecular alterations, have also been implicated in disease progression.[6] The present patient had a 20-year history of tobacco and gutkha consumption, which strongly correlates with the established risk factors reported in the literature. Clinically, oral erythroleukoplakia comprises an irregular red-and-white lesion with a distinct demarcation from the adjacent normal-appearing mucosa and frequently exhibits a velvety or granular surface texture.[7] The floor of the mouth is considered the most common site of occurrence, followed by the ventrolateral surface of the tongue, soft palate, and buccal mucosa.[3] Occasionally, islands of clinically normal-appearing mucosa may be observed within the lesion, a feature that has been attributed to the coalescence of multiple precancerous foci.Although erythroplakia has no apparent gender predilection, it is reported more frequently in individuals during the sixth and seventh decades of life.[4] Shafer and Waldron observed site-related differences between sexes, reporting the floor of the mouth as the most common site in men, whereas the mandibular alveolar mucosa, mandibular gingiva, and mandibular sulcus were more frequently affected in women.Most lesions remain asymptomatic and are detected incidentally during routine oral examination. [3] The differential diagnosis of oral erythroleukoplakia includes erosive oral lichen planus, erythematous candidiasis, chronic hyperplastic candidiasis, areas of mechanical irritation, vascular lesions,discoid lupus erythematosus, traumatic keratosis, and early oral squamous cell carcinoma.[7,8] Owing to the overlapping clinical appearance of these lesions, histopathological examination following an incisional biopsy remains the gold standard for definitive diagnosis.[8] Biopsy should preferably be obtained from the erythematous component of the lesion, as this area is more likely to exhibit epithelial dysplasia or malignant transformation.[9]

Recent advances in adjunctive diagnostic techniques have significantly improved the early detection of oral potentially malignant disorders. Toluidine blue staining is a simple and inexpensive chairside aid that facilitates identification of areas with increased cellular activity and assists in selecting the most appropriate biopsy site.[10] Autofluorescence imaging (VELscope) enables visualization of alterations in tissue fluorescence associated with epithelial dysplasia, whereas narrow-band imaging (NBI) enhances the visualization of abnormal mucosal vascular patterns. Optical coherence tomography (OCT) provides high-resolution cross-sectional imaging of the oral epithelium and has shown promising results in the non-invasive assessment of epithelial architecture.[11] Furthermore, salivary biomarkers, including microRNAs and inflammatory cytokines, together with artificial intelligence-assisted image analysis, are emerging as valuable adjuncts for the early detection and risk assessment of oral potentially malignant disorders.[12] Despite these advances, none of these modalities can replace conventional histopathological examination, which remains the diagnostic gold standard.[8]

| Diagnostic modality | Principle | Clinical application |
|---|---|---|
| Toluidine blue | Vital staining | Identifies high-risk areas for biopsy |
| VELscope | Tissue autofluorescence | Detects dysplastic mucosal changes |
| Narrow-band imaging | Enhanced vascular imaging | Identifies abnormal microvasculature |
| Optical coherence tomography | Cross-sectional optical imaging | Non-invasive assessment of epithelial architecture |
| Salivary biomarkers | Molecular analysis | Early detection and risk assessment |
| Artificial intelligence | Digital image analysis | Lesion classification and risk prediction |

The data in the table are adapted from the following sources: Farah CS et al .(2013), Kerr AR et al. (2021), Mehrotra R et al.(2011)

Management of oral erythroleukoplakia is guided by the histopathological severity of epithelial dysplasia. Complete cessation of tobacco, gutkha, areca nut, and alcohol consumption is fundamental in reducing disease progression.[2] Lesions exhibiting moderate or severe epithelial dysplasia generally require complete surgical excision. Conventional scalpel excision remains the standard treatment; however, $CO_2$ laser excision, diode laser surgery, Er:YAG laser therapy, and photodynamic therapy have demonstrated favourable outcomes with improved haemostasis, reduced postoperative discomfort, and satisfactory wound healing.[10,11] Long-term follow-up is mandatory because recurrence and malignant transformation may occur despite appropriate treatment. The present clinical illustration underscores the importance of meticulous oral examination in individuals with long-standing tobacco habits. Although the clinical findings were highly suggestive of an erythroleukoplakic lesion, histopathological confirmation was

unavailable because an incisional biopsy had not been performed. Nevertheless, this case highlights the need for early recognition, patient education, tobacco cessation, timely biopsy, and regular follow-up to reduce the risk of progression to oral squamous cell carcinoma.

**Conclusion**

Oral erythroleukoplakia is an uncommon yet clinically significant oral potentially malignant disorder with a high propensity for epithelial dysplasia and malignant transformation. Early recognition through meticulous clinical examination, particularly in individuals with long-standing tobacco habits, is essential for timely diagnosis and management. Although several adjunctive diagnostic modalities have emerged to facilitate early detection, histopathological evaluation following biopsy remains the gold standard for definitive diagnosis. The present clinical illustration emphasizes the importance of comprehensive oral screening, patient education, tobacco cessation, and regular follow-up in minimizing the risk of progression to oral squamous cell carcinoma.

**Limitation**

The major limitation of the present clinical illustration is the absence of histopathological confirmation, as an incisional biopsy had not been performed becausethe patient was lost to follow-up. Consequently, the diagnosis was based solely on clinical findings and should be considered provisional. Long-term follow-up findings were also unavailable. Future studies incorporating histopathological correlation and longitudinal follow-up would provide a more comprehensive understanding of the biological behaviour and clinical outcome of such lesions.

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