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INTEGRATED STUDY MASTER'S THESIS

Precancerous Lesions of Oral Cavity

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ABSTRACT

Oral potentially malignant disorders are a group of conditions characterized by changes in the oral mucosa that have the potential to transform into oral cancer if left untreated. The aim of this review is to gather and summarize the most recent data regarding the clinical manifestations, etiology, risk factors, currently available diagnostic methods and treatments of precancerous lesions in oral cavity. Electronic databases (PubMed and Google Scholar) were searched from 2018 to 2024. Studies assessing the malignant transformation rates of oral leukoplakia, erythroplakia, erythroleukoplakia, and chronic hyperplastic candidosis/candidal leukoplakia were identified. Among the 812 identified articles, 65 met the inclusion criteria and were included in this review. Oral leukoplakia and erythroplakia appeared to be the most prevalent oral potentially malignant disorders. Proliferative verrucous leukoplakia is a rare lesion but it carries a high risk of progression into oral cancer. Erythroplakia and erythroleukoplakia lesions present a higher incidence of carcinomatous transformation than leukoplakia lesions. Oral chronic hyperplastic candidiasis is an uncommon oral potentially malignant disorder. The rate of malignant transformation of this lesion is lower than that of erythroplakia, erythroleukoplakia and proliferative verrucous leukoplakia and comparable to that of oral leukoplakia. The transition from normal to premalignant or dysplastic mucosa, and eventually to malignancy, involves a complex interaction between genetics, immune system function, and exposure to carcinogens like betel quid, tobacco, alcohol, and human papillomavirus. Low-risk epithelial dysplasias need careful monitoring, with biopsies if any changes are seen. High-risk dysplastic lesions require surgery, followed by thorough patient follow-up.

KEYWORDS

Oral potentially malignant disorders, oral cancer, premalignant, leukoplakia, erythroplakia, erythroleukoplakia.

ABBREVIATIONS

AI - Artificial Intelligence
ALA-PDD - 5-Aminolevulinic Acid Photodynamic Diagnosis
ALA-PDT - 5-Aminolevulinic Acid Photodynamic Therapy
ANN - Artificial Neural Network

CHC - Chronic Hyperplastic Candidosis

CO2 - Carbon Dioxide

COE - Conventional Oral Examination

ctDNA - Circulating Tumor DNA

DNA - Deoxyribonucleic Acid

ED - Epithelial Dysplasia

FAD - Flavin Adenine Dinucleotide

HPV - Human Papillomavirus

IL-6 - Interleukin-6

LBC - Liquid-Based Cytology

LI - Lugol's Iodine

MT - Malignant Transformation

NADH - Nicotinamide Adenine Dinucleotide

NBI - Narrow-Band Imaging

OCT - Optical Coherence Tomography

OL - Oral Leukoplakia

OPMD - Oral Potentially Malignant Disorder

OSCC - Oral Squamous Cell Carcinoma

OVC - Oral Verrucous Carcinoma

PVL - Proliferative Verrucous Leukoplakia

SCC - Squamous Cell Carcinoma

TB - Toluidine Blue

UK - United Kingdom

VELscope - A brand name for a device used for oral tissue visualization

WHO - World Health Organization Introduction

1. INTRODUCTION

The World Health Organization (WHO) defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity" [1]. Quality of life is a crucial health outcome measure that encompasses various aspects of life, including physical, psychological, social, economic, spiritual, cognitive, and sexual dimensions. Disruptions in one aspect can impact other domains, influencing overall quality of life. Oral health is integral to overall health and

is vital for quality of life. Issues related to the oral cavity can lead to pain, challenges in eating, speaking, and appearance, ultimately affecting self-confidence and social interactions.

According to the 2020 Globocan report, approximately 0.37 million new cases of oral cancer were estimated, with the majority originating from the Asian continent [2]. Most oral cancer cases, approximately 80%, arise from oral potentially malignant disorders (OPMDs), and early detection has the potential to reduce the severity of the disease [2, 3]. Discrepancies in the oral presentation of precancerous lesions have consistently posed a challenge in clinical decision-making. The notion of 'pre-cancer' was introduced in 1805 when a group of European physicians proposed the idea that certain benign diseases could progress into invasive malignancy if observed over an extended period [4].

The World Health Organization has undergone multiple revisions of clinical and histological parameters to mitigate ambiguity and promote consistent reporting of oral potentially malignant disorders, which include oral leukoplakia, erythroplakia, erythroleukoplakia, and chronic hyperplastic candidosis/candidal leukoplakia. They represent a notable category of mucosal disorders that could precede the identification of oral squamous cell carcinoma [4]. These lesions typically manifest as white patches (leukoplakia) but can also appear as red (erythroplakia) or red and white (erythroleukoplakia) and can present alterations in morphology, including variations such as plaque/plateau, smooth, grooved, wrinkled, granular, and atrophic, can occur in various sizes and affect different anatomical sites within the oral cavity [2, 4]. Various risk factors are associated with the occurrence of an OPMD and the potential for malignant transformation. The global prevalence of OPMDs is 4.47%, with a higher frequency in males, and it varies among different populations [5]. The most common OPMD is leukoplakia presenting 2.6 % prevalence worldwide [6]. The overall rate of malignant transformation (MT) for OPMDs is 7.9%, underscoring the severity of the issue [2].

Despite having access to the oral cavity, potentially malignant lesions are frequently overlooked due to a substantial lack of knowledge among medical professionals. Certainly, gaining a more comprehensive understanding of the current status of diagnosis, prognosis, and therapeutic aspects of OPMDs is crucial for developing improved strategies. The purpose of this review is to provide an overview of clinical manifestations, etiology, risk factors, currently available diagnostic methods and treatments of precancerous lesions in oral cavity.

2. LITERATURE SEARCH STRATEGY

All searches were conducted up to January 1, 2018. Literature search and subsequent analysis were focused on papers reporting malignant transformation rates of oral leukoplakia, erythroplakia,

erythroleukoplakia, and chronic hyperplastic candidosis/candidal leukoplakia. The search strategy for relevant studies comprised the evaluation of electronic databases including PubMed and Google Scholar databases. The keywords and Boolean expression used in the search of the selected electronic databases included the following: ("oral precancerous lesion" OR "oral precancer" OR "oral premalignant" OR "oral premalignant disorders" AND "leukoplakia" OR "erythroplakia" OR "erythroleukoplakia" OR "chronic hyperplastic candidosis" OR "candidal leukoplakia"). Studies were excluded from the present review if they were non-English language articles and if their titles indicated a focus on topics outside the scope of our investigation. The exclusion of articles was based on a title review and a full-text assessment, with the aim of streamlining the inclusion of studies directly relevant to the primary focus of this review. The inclusion criterion was publications from 2018 to 2024 on the prespecified topics (Figure 1). If duplicate studies were identified, they were eliminated from the analysis.

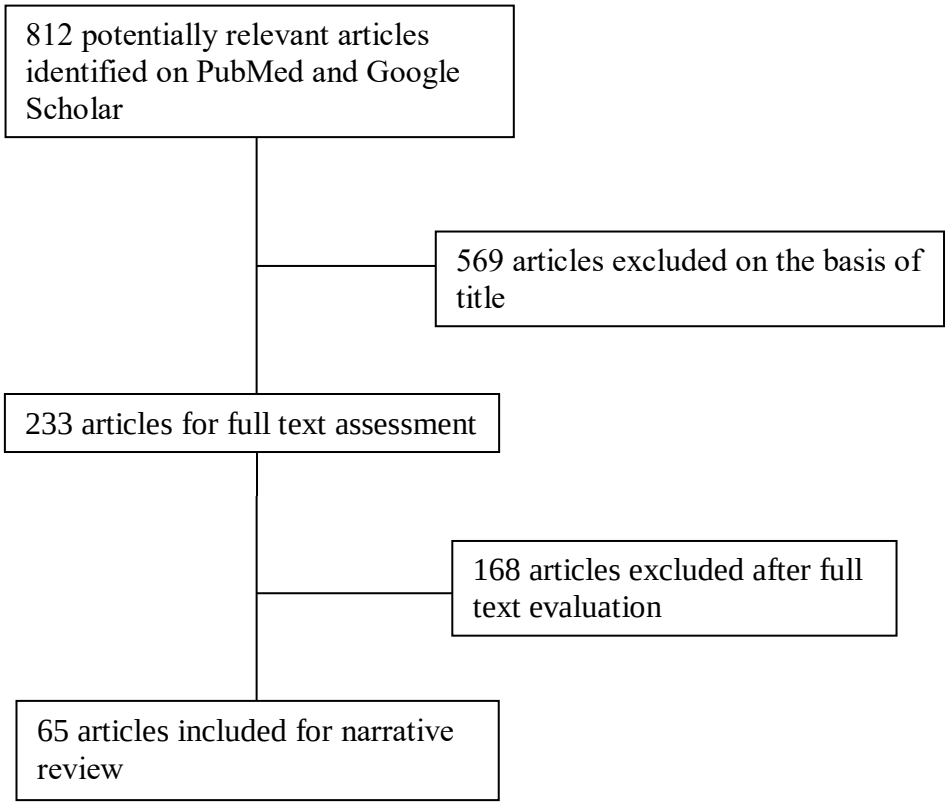

Figure 1. Flow chart for inclusion of studies

3. LEUKOPLAKIA

DEFINITION AND CLINICAL MANIFESTATION

Leukoplakia is the most common oral potentially malignant disorder. Various forms of leukoplakia have been identified, and subtyping them clinically may provide some limited insights into

prognosis prediction. In order to achieve an accurate diagnosis of this condition, it is crucial to consider the specific definition applied to oral leukoplakia (OL). Historically, the term leukoplakia was a clinical descriptor used to refer to any adherent white patch or plaque (keratosis). However, over the course of several decades, clinicians recognized that not all white patches appearing in the oral cavity should be categorized as oral leukoplakia. Multiple definitions of oral leukoplakia have been proposed in recent decades. The most current definition in use characterizes leukoplakia as 'predominantly white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer' [6, 7]. The primary method for clinical diagnosis relies on visual examination and manual palpation. The histopathological observations in leukoplakia span from hyperkeratosis without epithelial dysplasia to varying degrees of epithelial dysplasia, including carcinoma in situ, outright squamous cell carcinoma, and verrucous carcinoma [8]. Carcinoma-in-situ is the term employed when the entire epithelial thickness is implicated, with dysplasia extending from the basal layer to the mucosal surface above, without encroachment into the underlying connective tissue [9].

An oral leukoplakia patch can range from a small and well-defined area to a larger lesion that covers a significant portion of the mucosal surface [7]. In clinical practice, two primary clinical types of leukoplakia are commonly encountered: homogeneous and non-homogeneous leukoplakia. This differentiation is determined by surface color and morphological characteristics, which include thickness and texture [7].

Homogeneous leukoplakias display a consistent flatness and thinness, with a smooth surface and the possibility of shallow ridges in the epithelium (Figures 2, 3, 4) [6, 7, 10].

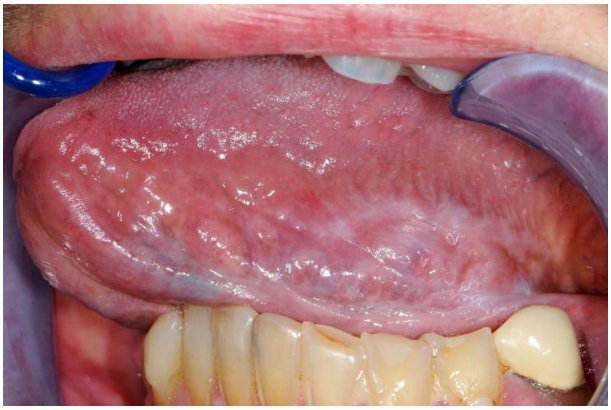

Figure 2. Homogeneous leukoplakia on the ventrolateral surface of the tongue [7]

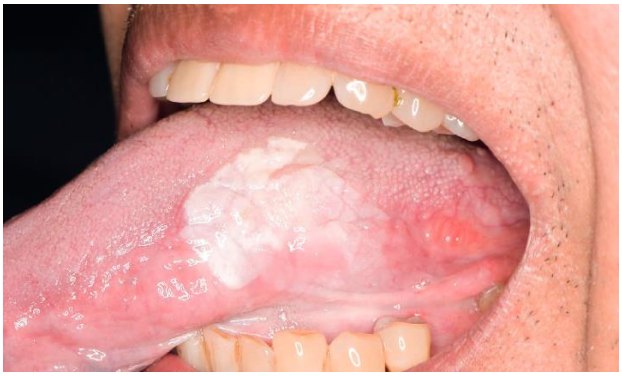

Figure 3. Homogeneous leukoplakia on the dorsolateral aspect of the tongue [10]

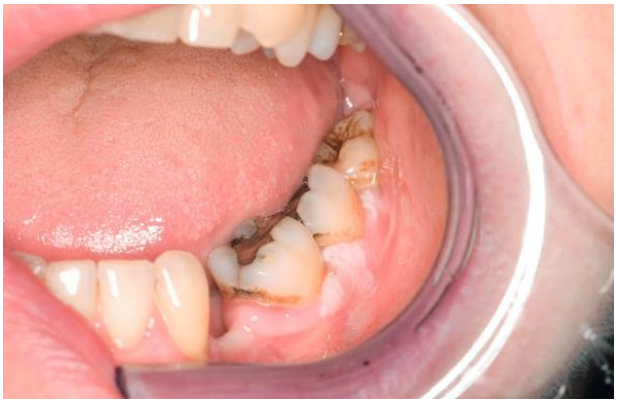

Figure 4. Homogeneous leukoplakia on the left mandibular buccal gingiva [10]

Non-homogeneous types consist of three clinical subtypes and typically present with symptoms:

(1) Speckled: mixed, white and red (also referred to as erythroleukoplakia), with white being the predominant feature.

(2) Nodular: characterized by small polypoid outgrowths that appear as rounded red or white excrescences.

(3) Verrucous or exophytic: exhibiting a wrinkled or corrugated surface appearance (Figure 5) [7].

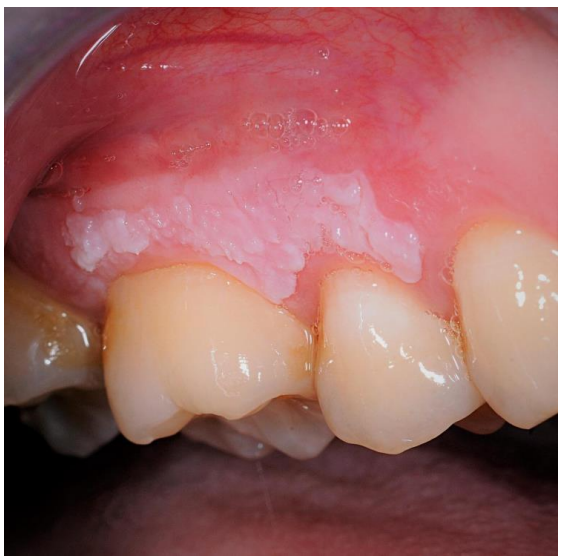

Figure 5. Verrucous leukoplakia [7]

Typically, the majority of leukoplakias do not cause symptoms and are discovered during routine visual examinations conducted by healthcare providers. If symptoms do occur, they are often associated with the non-homogeneous speckled variety. These symptoms may include discomfort, tingling, and heightened sensitivity to touch, hot beverages, or spicy foods [7]. The presence of a red component in the leukoplakia, known as erythroleukoplakia, suggests potential colonization by *Candida* organisms and an elevated risk of dysplasia and/or malignancy (Figure 6) [7]. Such condition can progress to carcinoma *in situ* (Figure 7) [7].

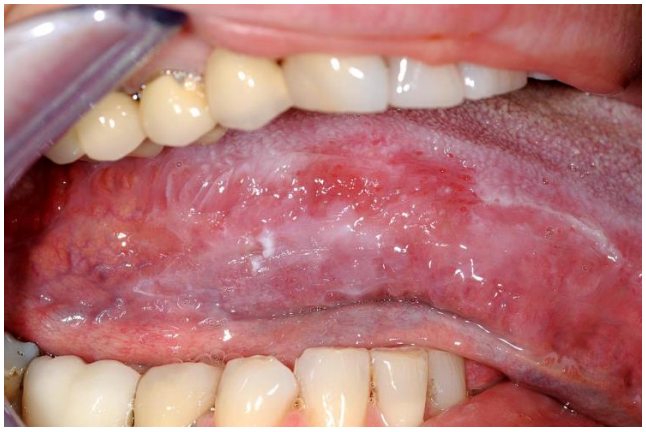

Figure 6. Erythroleukoplakia [7]

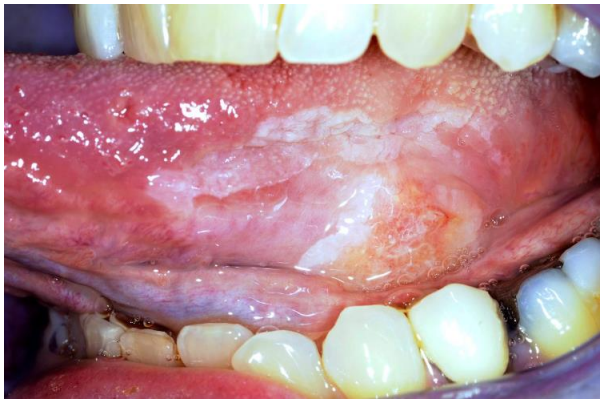

Figure 7. Carcinoma arising in a mixed, white and red lesion [7]

ETIOLOGY

Leukoplakias are six times more prevalent among individuals who smoke compared to non-smokers [7, 11]. Additionally, alcohol consumption is an independent risk factor [7].

Leukoplakia frequently appears on the buccal mucosa in individuals who use smokeless tobacco [11]. Leukoplakia is mainly linked to such causative agents as tobacco, alcohol, and betel quid but there are also other factors as mechanical irritation, dental restoration, low serum vitamin A and carotene [7, 12]. In a minority of cases, human papillomavirus (HPV) may play a potential role in the development of leukoplakia [13]. Some leukoplakias are of genetic origin or may not have a

known identifiable risk factor and are considered idiopathic [6, 7]. Chronic candidiasis has been associated with the emergence of leukoplakia, especially in cases of nonhomogeneous leukoplakia. This potential role may be connected to the elevated nitrosation potential observed in certain candidal strains, implying the possibility of endogenous nitrosamine production [9].

PREVALENCE

The occurrence of leukoplakia is more frequent among middle-aged and elderly men rather than women (62.2% versus 37.8%), typically manifesting after the age of 40, when compared to other demographic groups in research studies [7, 9, 14]. Leukoplakia's prevalence rises with advancing age. Among individuals diagnosed with leukoplakia, fewer than 1% were males under the age of 30 [6]. The worldwide prevalence of leukoplakia has been estimated at 2.6 %, and prevalence in developed countries is around 3% [6, 10, 11].

In Western industrialized populations, frequent areas of occurrence include the lateral margin of the tongue and the floor of the mouth [7]. However, among Asian individuals, the buccal mucosa and lower buccal grooves are commonly affected due to the placement of betel quid in these locations [7]. Although gingival leukoplakia (affecting the gums) is rare, it has predominantly been observed in the Japanese population [7]. In a systematic review, over half of the cases of oral leukoplakia with malignant transformation occurred on the tongue (56.3%), and among these, 98% were situated on the ventral or lateral borders [14].

A systematic review revealed that the overall rate of malignant transformation in leukoplakia was 3.5%, however, this rate displayed variations among studies, ranging from as low as 0.13% to as high as 34% [6, 9]. Furthermore, various levels of epithelial dysplasia can be present [6]. The clinical type of oral leukoplakia that progressed into squamous cell carcinoma was evaluated in 13 studies, involving a total of 525 lesions. Among these, 66.7% were classified as non-homogeneous oral leukoplakia, and 33.3% as homogeneous oral leukoplakia [14].

Statistical analyses conducted in various studies across the Indian subcontinent, with a specific focus on India, have yielded findings indicating a prevalence of leukoplakia ranging from 0.2% to 5.2% and a malignant transformation rate of 0.13% to 10%. This significant rise in the prevalence of leukoplakia in India is likely attributed to cultural, ethnic, and geographical factors [9]. An annual incidence rate of malignant conversion in leukoplakia ranging from 6.2 to 29.1 cases per 100,000 individuals has been found [9].

Idiopathic leukoplakia, as well as alterations in surface structure such as nodularity or verrucous changes, presence of regions with redness within the leukoplakia (referred to as erythroleukoplakia

or speckled leukoplakia), floor of mouth, ventrolateral tongue and soft palate involvement, lesions greater than 200 mm, advance age, female gender are known to be a predictive risk factor of malignant transformation [10, 14]. In a specific population of smokers, a higher prevalence of oral leukoplakia is anticipated; nevertheless, if oral leukoplakia emerges without identifiable causative factors, the risk of malignant transformation is elevated [10]. The likelihood of malignant transformation in predominantly white lesions located on the alveolar ridge (referred to as "alveolar ridge keratosis") and the buccal gingiva (known as "frictional keratosis") is lower than that observed in similar lesions situated on the borders of the tongue or the floor of the mouth [8].

DIFFERENTIAL DIAGNOSIS

A preliminary clinical diagnosis of leukoplakia is established when a white patch is observed after ruling out any local traumatic causes, confirming its non-removability, and noting that the color persists upon stretching the tissue [7]. It is essential to carefully evaluate and rule out other conditions that may present with a white appearance.

A biopsy is necessary to confirm the initial clinical diagnosis, and prompt referral to a specialist is recommended. Despite ongoing controversies surrounding interpretation, the grade of dysplasia reported by a pathologist continues to be the most reliable means of assessing the risk of malignant transformation in oral potentially malignant disorders [7].

For small lesions, excisional biopsy is recommended, while for larger lesions, an incisional biopsy is performed, encompassing the adjacent healthy tissue, for subsequent histopathological examination (Figures 8, 9) [9].

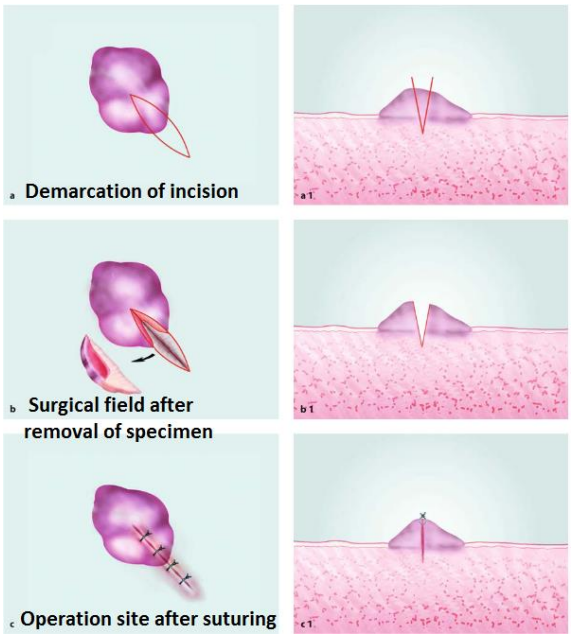

Figure 8. Incisional biopsy [15]

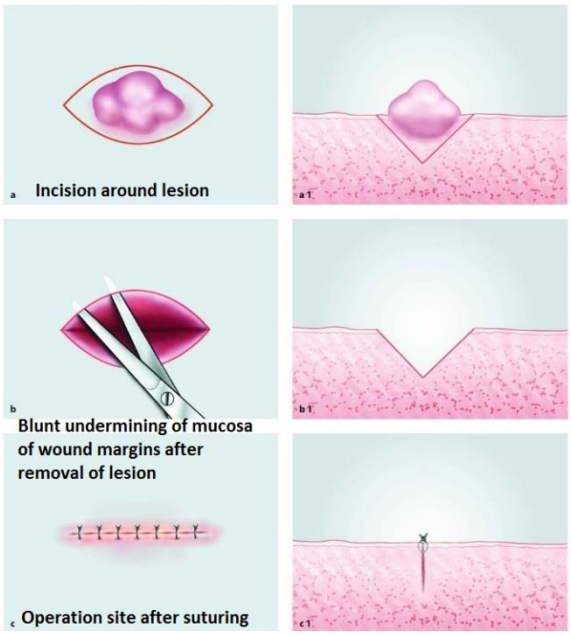

Figure 9. Excisional biopsy [15]

Additional traditional clinical diagnostic methods for early identification of leukoplakia encompass toluidine blue dye, oral brush biopsy kits, salivary diagnostics, and optical imaging systems [9]. Various benign white lesions that should be ruled out when diagnosing oral leukoplakia include conditions such as frictional keratosis (resulting from cheek biting), smoker's palate, as well as candidiasis, actinic cheilitis, lichen planus [7, 9, 16]. Table 1 represents these conditions and their characteristics [8, 10].

Table 1. Conditions affecting the oral mucosa that can be recognized and ruled out as part of a leukoplakia diagnosis [8, 10]

Diagnosis	Key features
Smoker's palate	Difuse keratotic changes on the hard palate, often with inflamed minor salivary gland orifices, typically improve upon smoking cessation
Frictional keratosis	Superficial keratotic changes, often caused by factors like sharp teeth, typically resolve upon removing the underlying cause.
Oral lichen planus	It affects oral mucosal surfaces, often with reticular keratosis or annular/plaque-like lesions. Atrophy or erosion may occur within these lesions, sometimes accompanied by desquamative or erythematous gingivitis
Actinic cheilitis	In actinic cheilitis on the lower lip, leukoplakia-

	like changes may develop, obscuring characteristic features.
Candidiasis, hyperplastic pseudomembranous	It is typically found in the corners of the mouth, as well as on the tongue's dorsum and lateral borders. Diagnosis may depend on response to antifungal treatment; otherwise clinically identical to leukoplakia. Easily removable

Distinguishing between leukoplakia and non-reticular lichen planus presents a significant challenge in the clinical diagnostic process. In theory, these lesions can either coexist or potentially transform into one another over time, such as lichen planus evolving into leukoplakia [8].

Proliferative verrucous leukoplakia frequently involves the attached gingiva and, as it advances, manifests as expansive, dense, white plaques with a wrinkled surface (Figure 10, A) [17]. This is distinct from oral lichen planus of the gingiva, which exhibits an erythematous component and lacks the thickened plaques (Figure 10, B) [17].

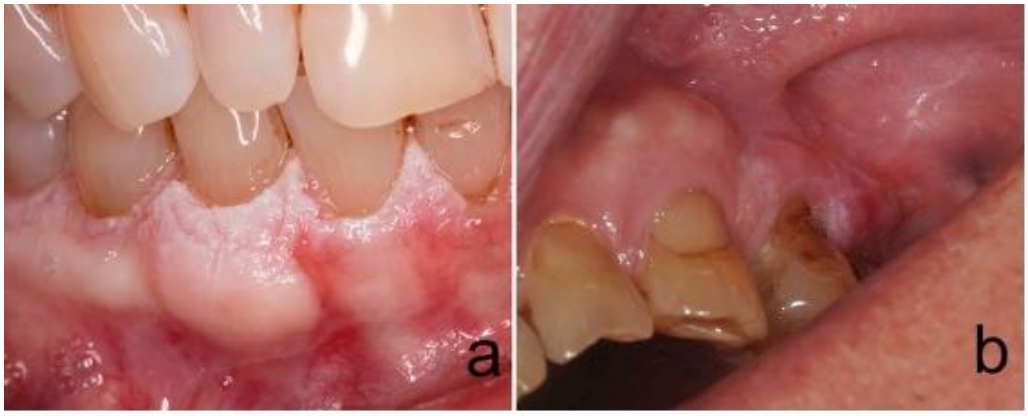

Figure 10. Proliferative verrucous leukoplakia (A) and oral lichen planus of the gingiva (B) [17]

Nearly all initial biopsies typically display hyperkeratosis without any signs of dysplasia or verrucous hyperplasia [6]. The term 'proliferative verrucous leukoplakia (PVL)' is employed when there is the observation of widespread or multiple patches of leukoplakia, often affecting the gingival and buccal mucosa, it progressively spreads to contiguous or non-contiguous areas [6]. This represents a unique condition associated with an elevated risk of malignant transformation and, fortunately, is uncommon [7]. Proliferative verrucous leukoplakia exhibits a malignancy transformation rate of 61.0% over an average follow-up period spanning 7.4 years [6].

Various tobacco-related conditions, including smoker's palate (lat. *Leukokeratosis nicotina palati*), palatal keratosis in reverse smokers, and snuff (or snus) dipper's lesions, have historically been distinguished from leukoplakia, despite their white appearance and their association with tobacco use [7].

TREATMENT

The approach to treating leukoplakia depends on its size and grade. Initially, patients are encouraged to discontinue any underlying habits. For lesions smaller than 2 mm, an excisional biopsy is recommended. For larger lesions, an initial incisional biopsy is conducted to confirm the diagnosis, followed by surgical excision, cryosurgery, or laser ablation, especially when the lesion is on the ventral and lateral borders of the tongue, soft palate, floor of the mouth, and oropharynx [9, 11].

Even after the removal of invasive lesions, recurrence is a frequent occurrence. Oral leukoplakia can exhibit spontaneous regression, making it challenging to assess their progress with treatment. In general, once dysplastic changes are evident, the prognosis becomes uncertain [9].

The occurrence of spontaneous regression in leukoplakia is extremely uncommon. Both surgical and non-surgical interventions have not demonstrated effectiveness in preventing potential future malignant transformation [8].

None of the studies indicated significant differences in malignant transformation based on the treatment approach. However, it is worth noting that one study reported a significant reduction in the risk of malignant transformation with photodynamic therapy, and they also observed a higher risk of malignancy in untreated oral leukoplakia cases (20.5%) [14]. Another study found a 11.6% malignant transformation rate among oral leukoplakia patients who underwent risk factor elimination, compared to a 10.1% malignant transformation rate among those who received surgical treatment [14].

4. PROLIFERATIVE VERRUCOUS LEUKOPLAKIA

DEFINITION AND CLINICAL MANIFESTATION

Proliferative verrucous leukoplakia (PVL) is an uncommon yet high-risk variant of leukoplakia [18]. The extensive nature of this condition can encompass multiple areas within the oral cavity, primarily affecting the gingiva, alveolar mucosa, tongue, and buccal mucosa. Bagan's group has outlined a set of diagnostic criteria for proliferative verrucous leukoplakia [7]. Their primary clinical criteria encompass the following: A leukoplakia lesion that affects more than two distinct oral sites, with a predilection for the gingiva, alveolar processes, and palate. B. The presence of a verrucous region. C. Evidence that the lesions have expanded or enlarged as the disease progressed, and D. The occurrence of recurrence in a previously treated area [7]. Not all cases of PVL exhibit a verrucoid appearance, especially in the early stages. Recently, a panel of experts in the United States has assigned a clinical diagnosis of proliferative verrucous leukoplakia to patients who

present with multifocal lesions lacking a verrucous appearance [19]. They argue that the involvement of multiple sites is a more critical criterion than a verrucous appearance. As a result, an alternative term "proliferative multifocal leukoplakia" was suggested for this condition [7]. According to Gonzalez-Moles et al. 2021, proliferative verrucous leukoplakia is an oral potentially malignant condition characterized by multifocal white plaques that progressively enlarge, resist treatment, and typically affect individuals in the latter half of life, although its onset may occur earlier [20]. Proliferative verrucous leukoplakia carries a significant risk of progressing into oral cancer [20]. In the initial stages, proliferative verrucous leukoplakia lesions manifest as small, well-defined, asymptomatic white patches or plaques, sometimes with surface thickening and sometimes without. As the condition advances, these lesions gradually increase in size and extend across various regions of the oral mucosa. Proliferative verrucous leukoplakia lesions transit from being flat patches to becoming progressively exophytic and verrucous. (Figure 11) [18].

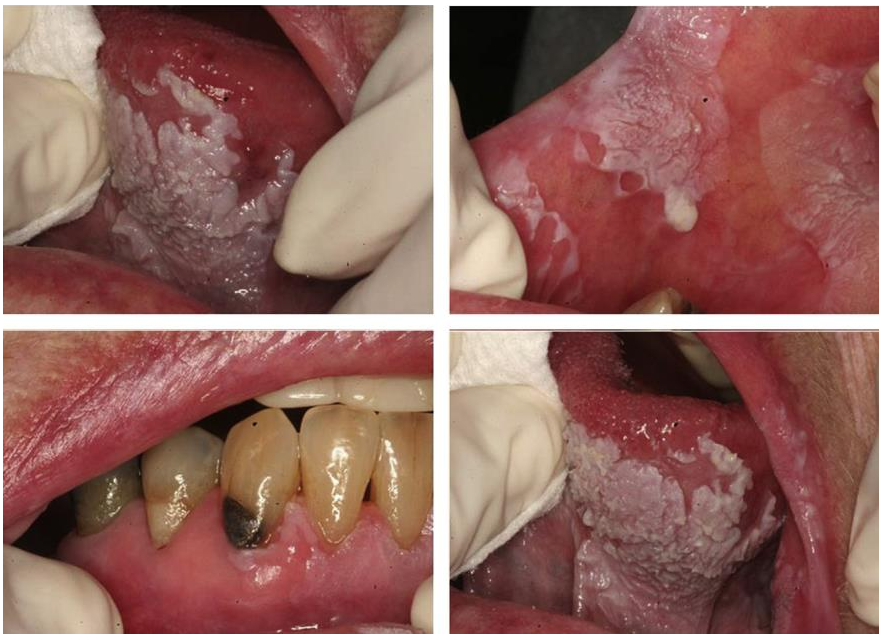

Figure 11. Manifestations of proliferative verrucous leukoplakia [18]

Proliferative verrucous leukoplakia can affect numerous oral cavity sites, such as the gingiva, alveolar mucosa, tongue, palate, and buccal mucosa (Figure 12) [7].

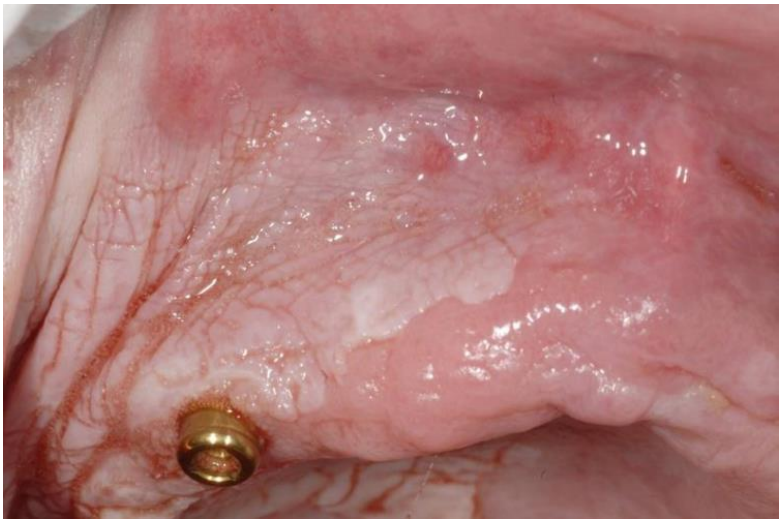

Figure 12. Proliferative verrucous leukoplakia extending from the gingiva and alveolar mucosa to the buccal mucosa [7]

The gingiva is the area most frequently impacted. Additionally, gingival and palatal lesions are the most common sites to undergo malignant transformation (Figure 13) [18].

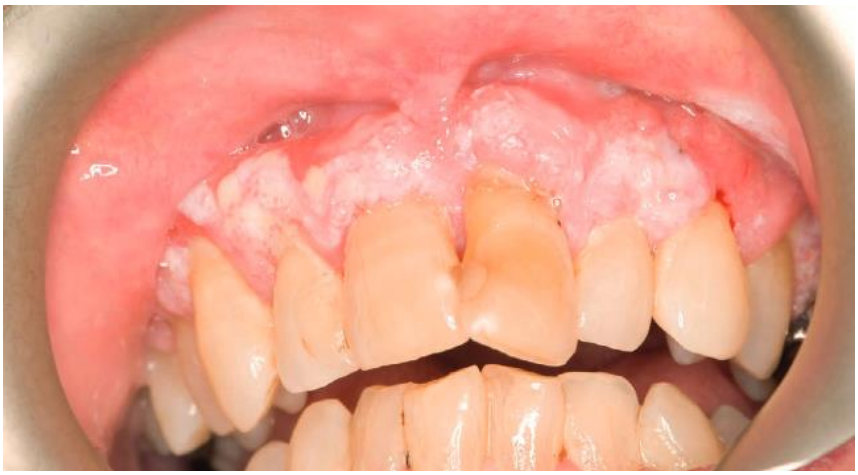

Figure 13. Proliferative verrucous leukoplakia with features of mild epithelial dysplasia in gingiva [18]

In a recent systematic review that aggregated data on the site distribution of proliferative verrucous leukoplakia, the most commonly affected sites were the gingiva (62.7%), followed closely by the buccal mucosa (59.8%), and the tongue (49.1%) [10].

ETIOLOGY

The etiology of proliferative verrucous leukoplakia is unknown. The consumption of tobacco (whether smoked or chewed) and alcohol does not appear to have a significant influence on the development of this condition. This differs from true leukoplakia, where tobacco is widely acknowledged as the primary risk factor [21]. It was observed that oral squamous cell carcinoma

(OSCC) related to proliferative verrucous leukoplakia exhibited more of the following characteristics: an early stage of development, smaller tumor size, an absence of lymph node metastases, predominant occurrence on the gingiva and buccal areas, higher instances of local relapses or second primary tumors, and a favorable 4-year survival rate (100%) [21]. Conversely, OSCC not associated with proliferative verrucous leukoplakia demonstrated more advanced stages of development with larger tumor sizes, a higher frequency of lymph node metastases (36.7%), prevalent locations on the lingual margin and mouth floor mucosa, and fewer instances of relapses or second tumors (12.2%) [21]. This hypothesis could have practical implications in determining treatment strategies and follow-up timing for OSCCs arising in these two different conditions.

PREVALENCE

The incidence rate of PVL is low and varies in different studies. For instance, it was found to be 0.1% in the UK population in one study and was diagnosed in 13.6% of patients with OPMDs in a cohort study of 590 patients [22]. Proliferative verrucous leukoplakia typically occurs in women over the age of 60 who do not have a documented history of tobacco or alcohol use [18]. There is no apparent ethnic predisposition [18]. Proliferative verrucous leukoplakia exhibits a higher likelihood of progressing to malignancy compared to OL. It can lead to the development of both OSCC and oral verrucous carcinomas (OVC). In a substantial case series involving 55 patients with proliferative verrucous leukoplakia, those who eventually developed proliferative verrucous leukoplakia were more commonly female and non-smokers [10]. In another study, a ratio of 4:1 female to male predominance was reported, and patients are usually older than 50 [18, 23]. The research also revealed that females exhibit not only a higher prevalence of proliferative verrucous leukoplakia and an elevated risk of its malignant transformation but also a statistically greater likelihood of proliferative verrucous leukoplakia progressing to OSCC compared to males [21]. The documented rate of malignant transformation for proliferative verrucous leukoplakia lesions ranges from 63.3% to 100% [18]. It is worth noting that patients with proliferative verrucous leukoplakia who go on to develop oral cancer experience at least one secondary tumor in a different intraoral location in 46.5% of cases [21]. In a systematic review published in 2020, it was noted that a malignancy transformation rate of 49.5% was documented [24].

DIFFERENTIAL DIAGNOSIS

Given the severity of proliferative verrucous leukoplakia, it is imperative to make an accurate diagnosis for the well-being of the patient. The diagnostic criteria for proliferative verrucous leukoplakia encompass the following:

1 Presence of a verrucous region
2 Involvement of more than two distinct sites
3 Lesions that have progressively grown in size and spread to other areas over a minimum of 5 years
4 Recurrence in a region previously treated
5 Microscopic examination of representative biopsy samples of lesional tissue, with the exclusion of invasive squamous cell carcinoma [18]

Despite these criteria, all proliferative verrucous leukoplakia lesions do not exhibit a verrucous surface [18].

Leukoplakia can be distinguished in differential diagnosis based on the following categories: congenital, infectious, inflammatory, and mucosal injury. Within the realm of congenital white lesions, there are instances such as leukoedema, characterized by mucosal stretching that causes the disappearance of white patches, and white sponge nevus, also known as Cannon disease or familial white folded dysplasia, which typically presents bilaterally in the buccal mucosa [18].

White lesions of infectious origin encompass conditions like pseudomembranous candidiasis, where a white membrane can be physically removed, revealing a raw erythematous mucosal base [18]. Another example is oral hairy leukoplakia, which occurs as a secondary manifestation in individuals with compromised immune systems infected with the Epstein Barr virus, also known as human herpesvirus 4 [18].

Inflammatory leukoplakic lesions display a lichenoid appearance and include conditions like lichen planus, lichenoid mucositis resulting from medication side effects and contact hypersensitivities, oral manifestations of systemic lupus erythematosus, and graft-versus-host disease in patients with a history of bone marrow transplant [18]. A comprehensive clinical history aids in distinguishing these inflammatory conditions from true leukoplakia.

Lastly, leukoplakia resulting from chemical and thermal mucosal burns, morsicatio (a habit of biting the oral mucosa), linea alba (a white line at the occlusal plane), and frictional keratoses all appear as white areas due to mucosal injury [18]. Diagnosing mucosal injury involves assessing the location of the injury and conducting thorough patient interviews.

A single histopathological characteristic that definitively confirms a diagnosis of proliferative verrucous leukoplakia is lacking, and typically, the diagnosis relies on the combination of both histological and clinical findings. Frequently, multiple biopsies are performed in clinically

suspicious areas. Histological findings may encompass a spectrum of features, ranging from hyperkeratosis in the early stages to epithelial hyperplasia and atypia. These changes can subsequently advance to verrucous hyperplasia, verrucous carcinoma, and, in some cases, squamous cell carcinoma (SCC). This progression and the various stages seen in proliferative verrucous leukoplakia highlight the importance of conducting multiple and repeated biopsies over time to monitor for dysplasia and the potential progression to SCC [10].

To diagnose proliferative verrucous leukoplakia, Cerero-Lapiedra et al. proposed major and minor criteria in 2010, which have been subsequently refined into four diagnostic criteria [10]. These criteria entail the presence of verrucous or wart-like leukoplakia affecting two or more sub-sites, a cumulative lesion size of at least 3 cm when considering all affected sites, a minimum disease duration of five years, and confirmation through at least one biopsy to exclude the presence of verrucous carcinoma or squamous cell carcinoma [10].

DNA (Deoxyribonucleic acid) ploidy is a measure of DNA content. Anomalies in DNA content, known as aneuploidy, serve as an indicator of chromosomal instability, resulting from genetic and epigenetic alterations in carcinogenesis. Aneuploidy has been proposed as an indicator of heightened risk for malignant progression, whether or not there are abnormalities in the epithelium [25]. The aggressiveness of PVL's did not show a correlation with various grades of aneuploidy. Nevertheless, aneuploidy successfully predicted malignant development in five out of nine SCC cases [25]. It was observed that in PVL patients, higher Interleukin-6 (IL-6) levels are associated with more verrucous areas, suggesting that IL-6 could serve as a valuable tool for monitoring PVL patients [25]. There were several studies on the association of monoclonal antibodies in PVL, expression of several biomarkers implicated in carcinogenesis in PVL but no reliable results have been obtained [25].

TREATMENT

An analysis of the available literature indicates that proliferative verrucous leukoplakia can exhibit resistance to various treatment methods, including surgery, laser ablation, retinoids, photodynamic therapy, and chemotherapy. Unfortunately, there is no treatment that seems to effectively reduce the risk of malignant transformation. Despite the lack of conclusive evidence, surgery tends to be the most commonly employed intervention for proliferative verrucous leukoplakia. However, a recent review of the literature discovered that the mean recurrence rate for all treatment modalities used to address this condition was as high as 85% [10, 18]. Additional treatment approaches that have been documented include laser removal, photodynamic therapy, and medical interventions. Nevertheless, none of these methods have demonstrated comprehensive effectiveness [19].

Numerous studies have investigated various treatment strategies for proliferative verrucous leukoplakia, yet the majority has shown limited effectiveness in halting the recurrence of lesions or their advancement into advanced invasive carcinoma [26].

5. ERYTHROPLAKIA

DEFINITION AND CLINICAL MANIFESTATION

Erythroplakia is described as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. The outline of the lesions is usually irregular and has a bright red smooth velvety non-scrapable surface which is sometimes granular, the lesions can be flat or depressed below the mucosal surface, can be soft or hard to palpation and may range in size from 1 cm to 4 cm in diameter [7, 27]. It can affect any oral and oropharyngeal region but the most commonly involved sub site is soft palate; other common sites of involvement are the ventral surface of the tongue and the floor of the mouth [7, 16, 27, 28]. Among 208 Thai patients screened from 1996 to 2015, tongue erythroplakia often manifested as a rough granular surface in the majority of cases (65.4%), as opposed to a smooth surface (34.6%), with a statistically significant difference [29]. Specifically, approximately 80% of erythroplakia cases were predominantly located at the tip and lateral border of the tongue. The second most common site for erythroplakia was the ventral surface of the tongue (Figure 14) [27]. Other localizations include hard palate, buccal mucosa (Figures 15-18) [6, 11, 30, 31].

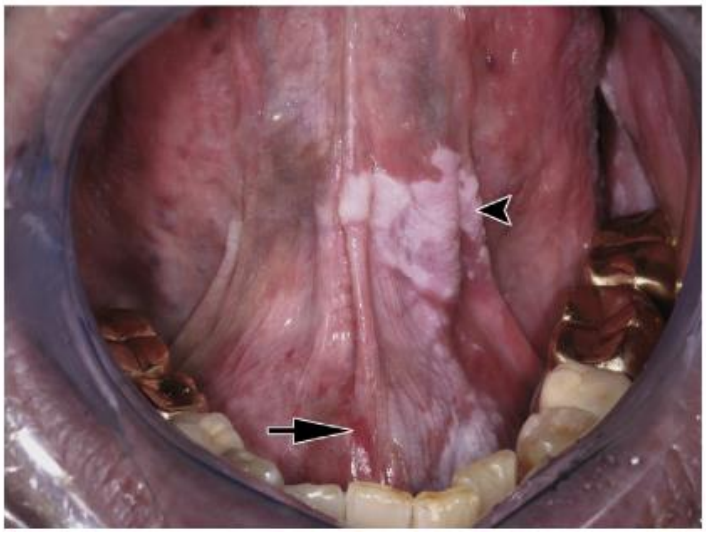

Figure 14. Erythroplakia (left arrow) and leukoplakia (right arrow) [27]

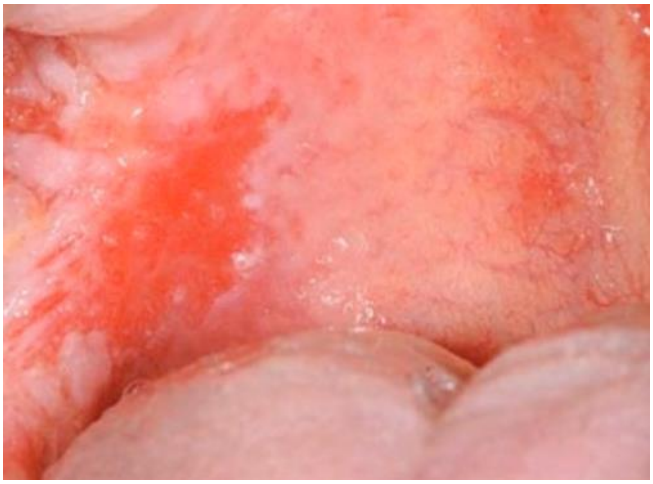

Figure 15. Erythroplakia in the hard and soft palate [30]

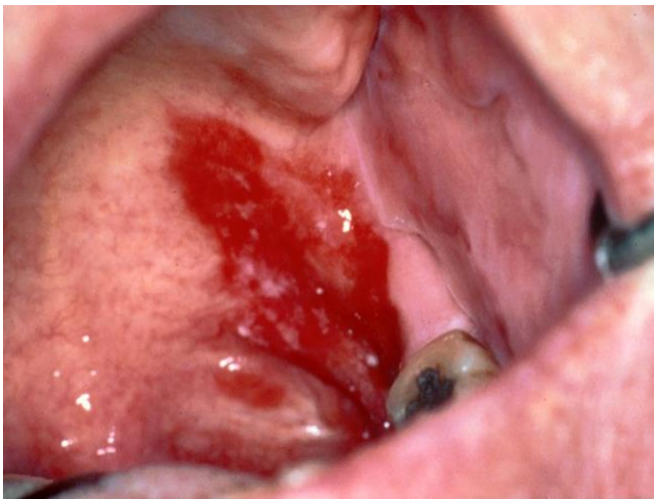

Figure 16. Case of erythroplakia and oral submucous fibrosis on the right buccal mucosa [11]

In terms of the presence of epithelial dysplasia, every erythroplakia case exhibited it [29]. The red color results from atrophy of the epithelium, which makes the microvasculature of the underlying tissue exposed [31]. The symptoms can be discomfort, tingling and sensitivity to touch, hot or spicy food, or the lesions can be asymptomatic which is less common [16, 27]. Keratin production is usually absent, and epithelial atrophy is commonly observed [31].

ETIOLOGY

The etiology of oral erythroplakia is strongly associated with tobacco and alcohol consumption, exhibiting a certain degree of correlation linked to the practice of betel quid chewing [6, 32]. Based on a cohort study, among 1,085 people using tobacco in different forms in Hazaribagh, 2.3% had erythroplakia [33]. Among 13,492 screened tobacco-using women in India, 9 people demonstrated

erythroplakia [34]. A diagnostic biopsy should be undertaken urgently as many erythroplakias are dysplastic or may harbour carcinoma *in situ* [7].

PREVALENCE

Erythroplakia is the least occurring oral potentially malignant disorder in Western countries. It mainly occurs in middle-aged and elderly individuals, most frequently in 50-70 year-old men [11], [29]. The mean prevalence of oral erythroplakia worldwide is 0.11% (ranging from 0.01 to 0.21%), it is common in South Asian countries, and from 14% to 50% of oral erythroplakia transforms into oral squamous cell carcinoma, and the rate does not decrease over the years [6, 11, 35]. A Swedish report showed that initial biopsies of erythroplakia lesions revealed mild dysplasia in 40% of cases and moderate dysplasia in 9% of cases [36]. Research conducted in the Netherlands found that in the initial biopsy of over 90% of erythroplakia patients, signs of oral carcinoma were already present, with 51% showing invasive carcinoma and 40% exhibiting carcinoma *in situ* [36]. In an Asian study focused on erythroplakia, it was reported that there was a transformation rate of 3.91% over a 5-year period, along with an annual malignant transformation rate of 9.75 per 1000 person-years [36].

Regarding the prevalence of erythroplakia among patients with diabetes mellitus, there is a rate of 20 per 100,000 patients with diabetes mellitus. No heterogeneity was found, neither subgroups meta-analyses nor meta-regression analyses were performed [23]. Erythroplakia in men smoking cigarettes and/or chewing areca nut was associated with a progressively higher risk of mortality from type 2 diabetes mellitus [37]. Based on a cohort study, patients with Fanconi Anemia are at high risk for head and neck malignancy (odds ratio 483.8), and erythroplakia was reported in 9% of the examined group among 233 patients with Fanconi Anemia [38]. Erythroplakia lesions present a higher incidence of carcinomatous transformation than leukoplakia lesions [11]. The presence of epithelial dysplasia in the initial biopsy is the worst prognostic factor [39]. Carcinoma *in situ* and mild to moderate dysplasia are observed in 40% and 9% of erythroplakia lesions respectively. Because of this high rate, early detection and immediate surgical excision should be performed.

DIFFERENTIAL DIAGNOSIS

The red patches that should be differentiated from erythroplakia are erythematous candidiasis, denture-associated stomatitis on palate, erythema migrans, erosive and inflammatory/infective disorders, desquamative gingivitis (Figure 17), discoid lupus, erosive lichen planus (Figure 18), pemphigoid and other inflammatory/ infectious conditions (Figure 19) [16, 40-42]. Two frequently encountered examples often confused by practitioners as erythroplakia include erythematous candidiasis (denture-associated stomatitis) and erythema migrans (Figure 20) [7, 43, 44]. Factors that help to clinically distinguish erythroplakia from these disorders is well-demarcated, solitary presentation [7].

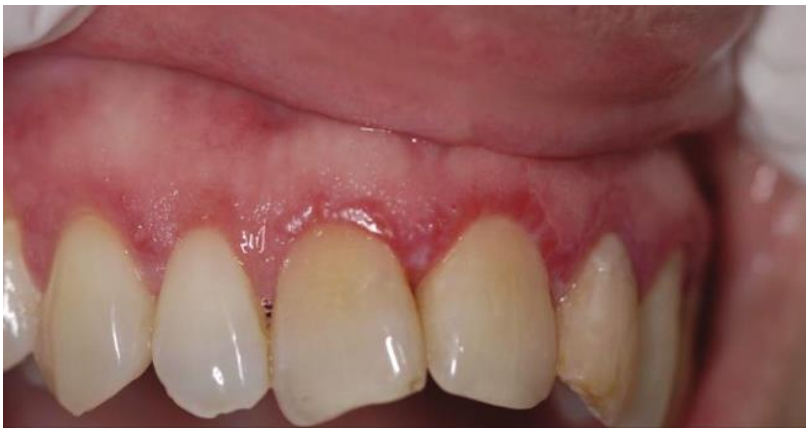

Figure 17. Desquamative gingivitis [40]

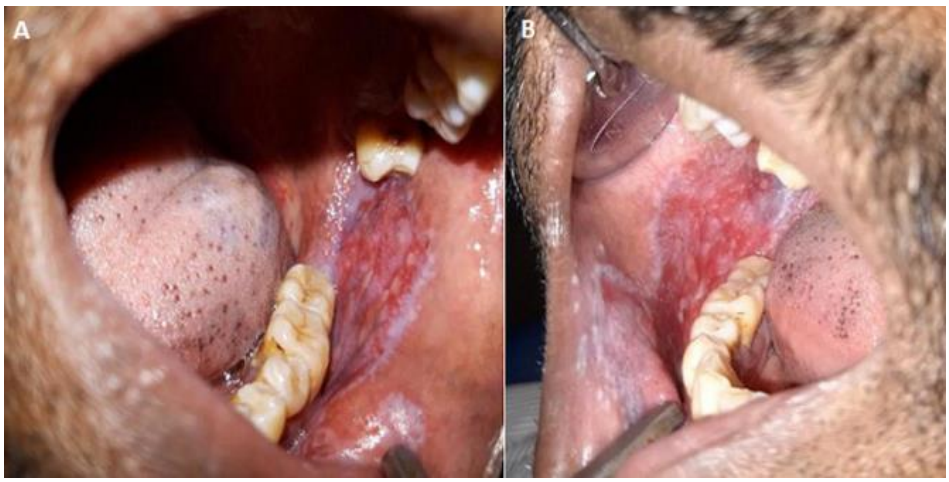

Figure 18. Erosive lichen planus [41]

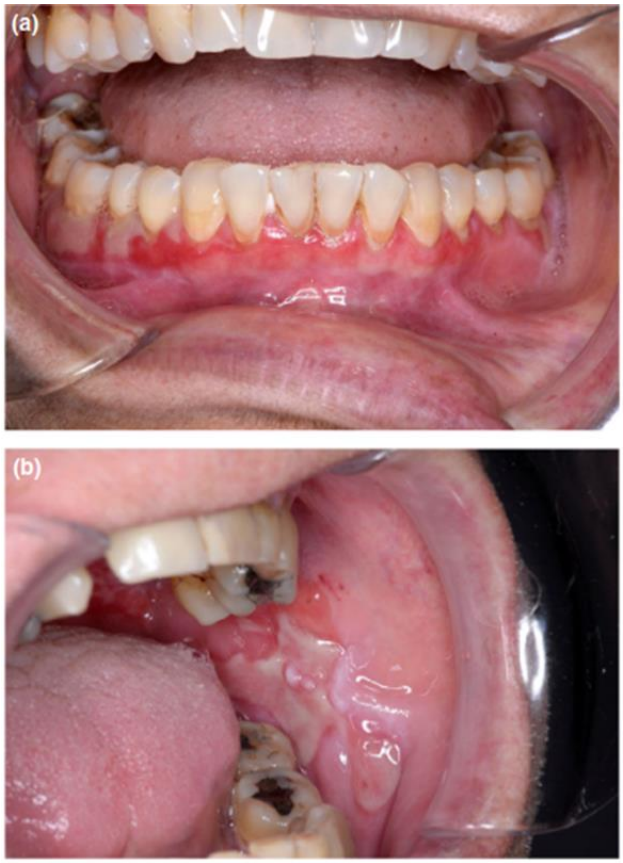

Figure 19. Mucous membrane pemphigoid: a) desquamative gingivitis of the attached gingiva with focal areas of ulceration, b) ulceration on the buccal mucosa, extending onto the palate [42]

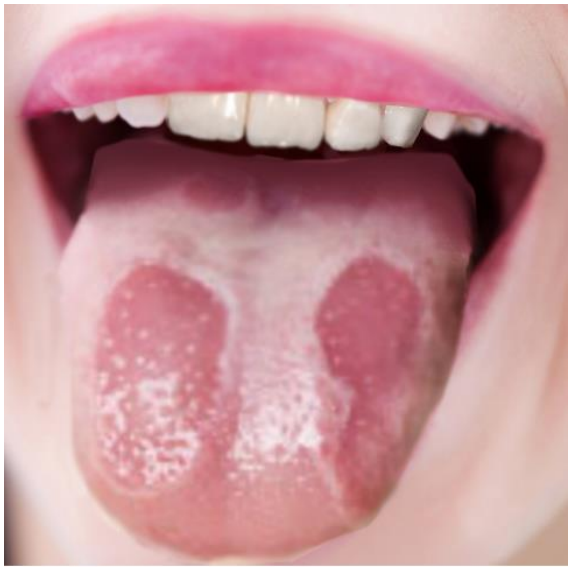

Figure 20. Erythema migrans [44]

A diagnostic biopsy is crucial for obtaining a pathologist's assessment to differentiate from the aforementioned specific and nonspecific inflammatory oral lesions. This should be conducted promptly, as many cases of erythroplakia exhibit dysplasia or may harbor carcinoma *in situ* or frank carcinomas [7].

TREATMENT

Erythroplakia tends to have a cautious prognosis, as the majority of them exhibit some degree of epithelial dysplasia upon presentation. The management of erythroplakia is determined based on a histopathological diagnosis. Treatment involves habit cessation, an incisional biopsy, and, once the diagnosis of the lesion is confirmed, surgical removal or laser excision [11]. The epithelium is thin and atrophic with visualization of the underlying microvasculature, it shows at least some degree of dysplasia and even carcinoma *in situ* or invasive carcinoma [6, 27]. The conclusive diagnosis entails toluidine blue staining entails toluidine blue staining before conducting an incisional biopsy. For cases exhibiting severe dysplasia or carcinoma *in situ*, excisional biopsy is advocated, whereas histologically moderate or non-dysplastic lesions warrant timely follow-up. The use of CO2 laser excision methods is deemed safe and effective, characterized by fewer postoperative complications such as absence of wound bleeding, trismus, or difficulties in chewing, swallowing, or articulation [2]. In some clinical situations, more than one potentially malignant lesion can be noted in the same patient [11].

6. ERYTHROLEUKOPLAKIA

DEFINITION AND CLINICAL MANIFESTATION

Lesions characterized by a combination of white and red areas, previously known as speckled leukoplakia, are now referred to as erythroleukoplakia. This condition, unlike leukoplakia or erythroplakia, may exhibit an irregular margin and the red component can show atrophy or speckling (Figure 21) [7].

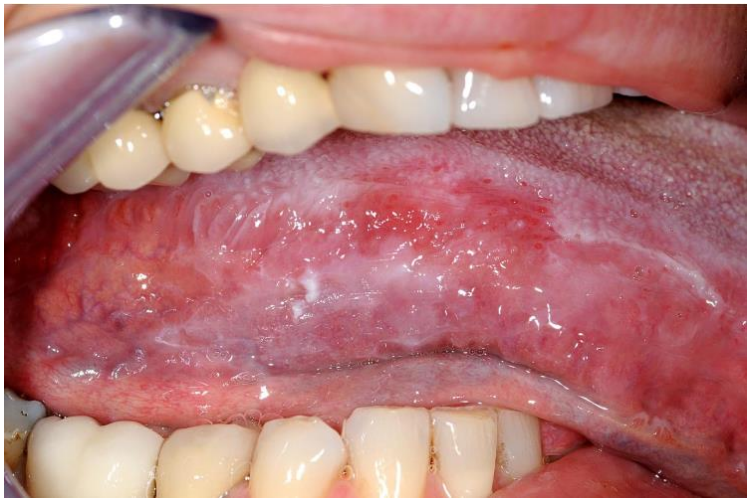

Figure 21. Erythroleukoplakia on the lateral surface of the tongue [7]

Patients with erythroleukoplakia may sometimes experience soreness, often attributed to the colonization of candidal hyphae [7].

ETIOLOGY

The etiology of erythroleukoplakia is similar to that of leukoplakia, including smoking, alcohol consumption, betel chewing, microorganisms, HPV.

PREVALENCE

The age, gender distribution, and common affected sites for erythroleukoplakia are similar to those for erythroplakia mentioned before [18].

DIFFERENTIAL DIAGNOSIS

Unlike erythroplakia, which typically exhibits clear boundaries, erythroleukoplakia often lacks a well-defined margin and tends to blend with the surrounding tissue. Clinically, erythroleukoplakia can manifest in two general patterns: either as numerous small and irregular leukoplakic areas within a red patch (Figure 22) or as an erythroplakia adjacent to a leukoplakia (Figure 23) [18]. In contrast to leukoplakia and erythroplakia, individuals with erythroleukoplakia often experience symptoms such as pain or soreness [18].

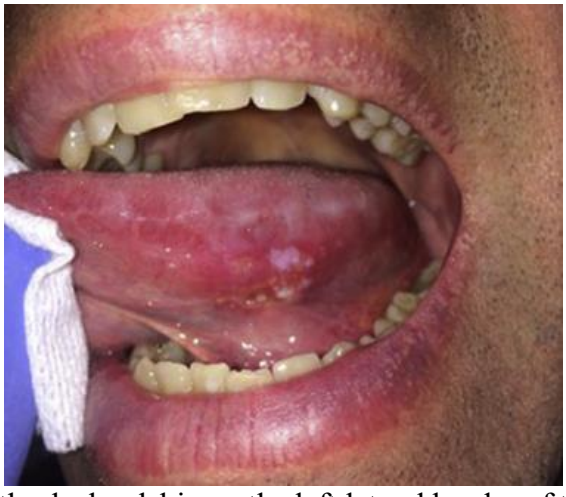

Figure 22. Erythroleukoplakia on the left lateral border of tongue [18]

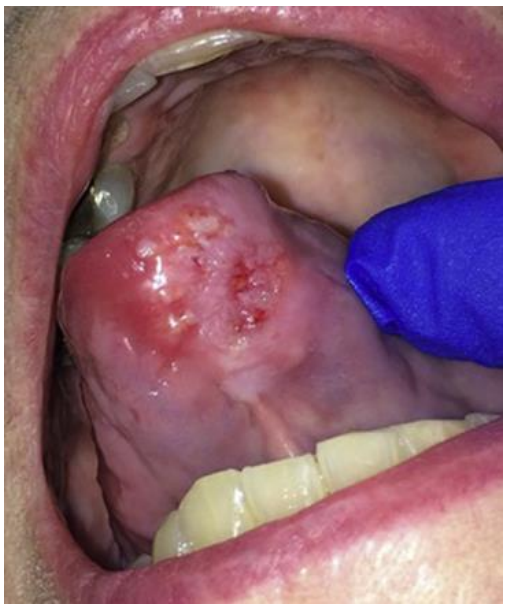

Figure 23. Erythroleukoplakia of the ventral tongue [18]

TREATMENT

Treatment methods of erythroleukoplakia are similar to those for erythroplakia and leukoplakia and include habit cessation, an incisional or excisional biopsy (depending on the size of the lesion), and, once the diagnosis of the lesion is confirmed, surgical removal or laser excision.

7. CHRONIC HYPERPLASTIC CANDIDOSIS

DEFINITION AND CLINICAL MANIFESTATION

Chronic hyperplastic candidosis, or candidiasis (CHC), is a specific type of oral candidosis, encompassing a clinical and pathological category that represents an intraoral white lesion caused by a persistent fungal infection, often *Candida albicans*. This entity exhibits two distinct clinical manifestations: a homogeneous variant characterized by a single, attached, and substantial white plaque (Figure 24), and a nodular/speckled form characterized by the presence of multiple white nodules on a reddened background (Figures 25 and 26) [45-48].

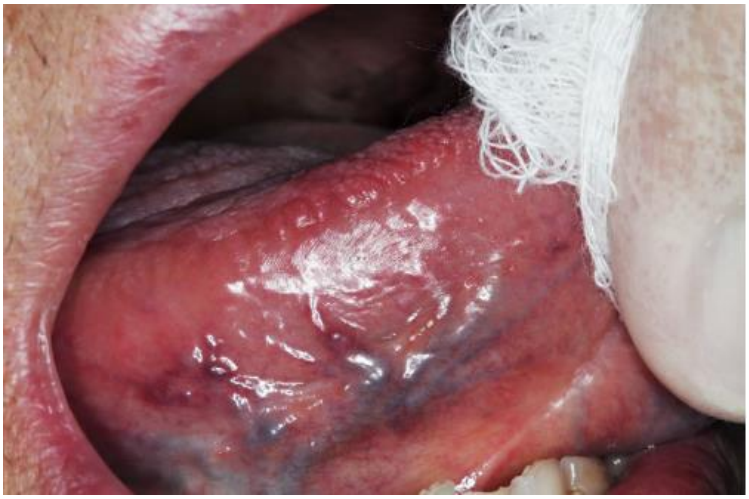

Figure 24. Chronic hyperplastic candidiasis on lateral edge of the tongue showing a white plaque [48]

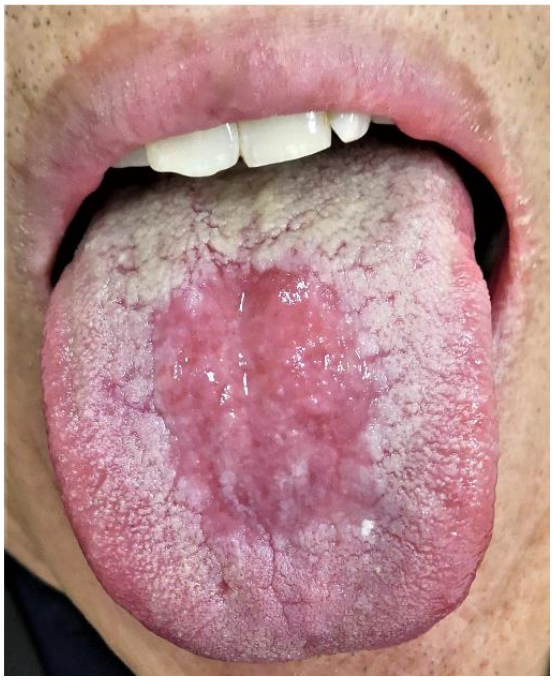

Figure 25. Oral nodular chronic hyperplastic candidiasis in the centre of the tongue [47]

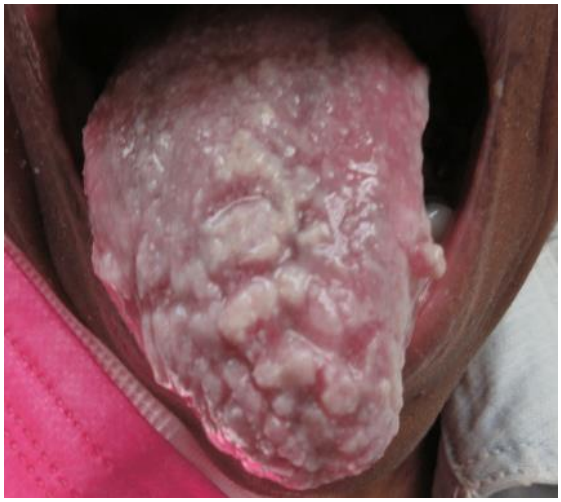

Figure 26. Oral nodular chronic hyperplastic candidiasis of the tongue [46]

ETIOLOGY

Candida albicans is reported to be the main factor of CHC [49, 50]. Some other *Candida* species that can be causal agents are *C. tropicalis, C. glabrata, C. pseudotropicalis, C. krusei, C. lusitaniae, C. parapsilosis, and C. stellatoidea* [49, 50]. CHC is frequently observed on the buccal mucosa beyond the commissures, the dorsal surface of the tongue, and the palate, particularly in individuals who wear dentures [45, 51]. Regarding preventive measures for CHC, the available evidence is of low quality. Patients are advised to abstain from smoking or using smokeless tobacco. Some authors also recommend that patients refrain from wearing their dentures at night and enhance their oral hygiene practices [45]. It is worth noting that certain systemic issues, such as anemia, vitamin deficiencies, and compromised immune function, can also contribute to the development of this type of candidiasis [45].

PREVALENCE

Oral chronic hyperplastic candidiasis is the most uncommon type of oral candidiasis, and it presents with various manifestations. Predominantly men in their 50s and 60s are affected [45]. The buccal mucosa has traditionally been the most common site for CHC, but it's worth noting that other areas, including the tongue and palate, can also be affected [45]. None of the recent studies provided confirmation that the presence of epithelial dysplasia (ED) is a direct risk factor for malignant transformation (MT) [45]. However, some authors argue that *Candida* infection is associated with more severe grades of ED, indirectly suggesting a higher risk of malignancy [45, 51]. The findings of a systematic review revealed that one out of every ten patients diagnosed with chronic hyperplastic candidiasis will eventually experience malignant transformation [45].

DIFFERENTIAL DIAGNOSIS

Testing for candidal colonization of an OPMD is advisable as an additional assessment. *Candida* has been found in 6.8% to 100% of leukoplakias, and three follow-up studies have reported malignant transformation rates of 2.5%, 6.5%, and 28.7% in *Candida*-infected leukoplakias [16].

TREATMENT

It is important to distinguish between reactive and pre-neoplastic epithelial changes. A group of researchers also emphasized the need to delay re-biopsy for at least 6 weeks after antifungal treatment, considering the turnover time of the oral mucosal epithelium. Resolution of CHC has been reported following systemic antifungal treatment, along with a reduction in ED [45]. Studies highlight that the potential for CHC to undergo malignant transformation is underestimated in current scientific literature, as some authors consider CHC to be a low-risk disorder [45]. Biopsy is recommended for the diagnosis of CHC [51]. A challenging case involved an 85-year-old female with chronic hyperplastic candidiasis, which was managed through a combination of photodynamic therapy and laser therapy, resulting in a notably positive clinical outcome was described in literature (Figure 27: Thick white verrucous plaque on the inner side of the upper lip; B. Only part of the lesion subsided after three times of ALA-PDT; C, D. The remaining lesion was removed by the semiconductor laser) [52].

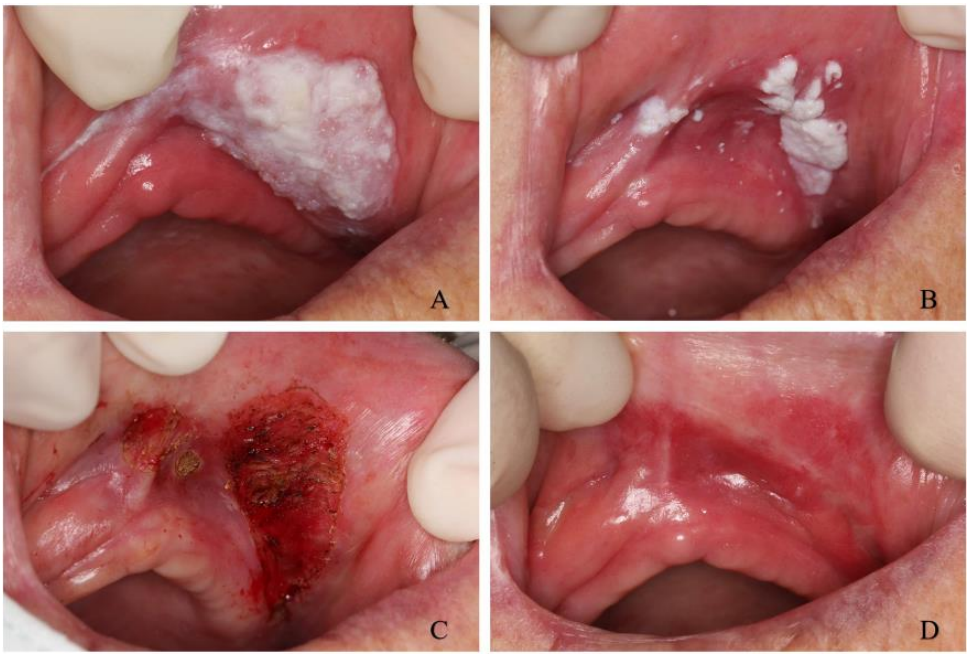

Figure 27. Chronic hyperplastic candidiasis on the inner side of the upper lip [52]

It is advisable to regularly monitor for *Candida* infection and to identify and reduce the risk factors associated with oral leukoplakia (OL). The management of OL should prioritize the maintenance of oral hygiene, oral health balance, salivation, and regular oral prophylaxis [53]. Additionally, it is essential to sustain dental, periodontal, and overall systemic health. Supporting individuals in their efforts to quit tobacco, areca nut, and alcohol use through counseling and consistent follow-up is a crucial aspect of the management plan [51, 53]. Antifungal therapy can be utilized to diminish the risk of super-infection and to address oral secretory problems associated with *Candida*-related OL. It can serve as both a therapeutic intervention and a prophylactic measure in the long-term care of *Candida*-associated OL [51, 53].

8. NEW TECHNIQUES OF EARLY DIAGNOSIS OF PRECANCEROUS LESIONS

According to current understanding, the preferred method to confirm a clinical diagnosis is to submit a representative biopsy sample for microscopic examination. In situations where facilities for scalpel biopsy are unavailable, cytologic testing using the brush biopsy technique may be considered [16]. Among various adjunctive techniques analyzed, cytologic testing appears to have the highest accuracy [16]. Screening aids encompass various methods, including 1) vital staining using toluidine blue (TB) and Lugol's iodine (LI), 2) devices utilizing autofluorescence, 3) devices employing chemiluminescence, 4) narrow-band imaging (NBI), 5) high-frequency ultrasounds, 6) optical coherence tomography (OCT), 7) *in vivo* confocal microscopy, and 8) biomarker assessment (derived from saliva, serum, or exfoliated cells) [2]. Being a noninvasive technique, optical coherence tomography (OCT) offers real-time, *in vivo*, and deep imaging capabilities. The texture information embedded in OCT images serves as a valuable adjunct in enhancing diagnostic accuracy. The superior classification results yielded an average accuracy of 98.17% [54]. Toluidine blue staining is a method valuable for identifying malignant lesions and those with high-grade dysplasia. A 1% toluidine blue solution is employed for staining. However, its sensitivity and specificity are limited for lesions that are benign or exhibit low to intermediate dysplasia. The reported sensitivity and specificity of toluidine blue in the literature vary, ranging from 57-81% for sensitivity and 56-67% for specificity [55]. The methylene blue staining system utilizes a dye composed of 1% methylene blue, 1% malachite, 0.5% eosin, glycerol, and dimethyl sulfoxide. Several studies have indicated that methylene blue exhibits high sensitivity but low specificity [11]. Lugol's iodine solution, comprising different concentrations of iodine and potassium iodide in water, leverages iodine's affinity to glycogen present in normal or healthy mucosa. A study revealed a 4% rate of intraepithelial neoplasia or dysplasia at the surgical margin when Lugol's iodine solution was utilized, compared to 32% at the surgical margin in the standard group where it was not employed [55]. Brush cytology/biopsy is a minimally invasive technique that involves using a brush to obtain a complete transepithelial specimen, capturing more than just the exfoliated superficial cells. The sensitivity of this technique in the literature varies from 73% to 100%, and its specificity ranges from 32% to 94%, respectively [55]. Exfoliative cytology comprises conventional and liquid-based cytology (LBC). In the conventional method, cells are scraped from the oral mucosa onto a glass slide, while LBC scatters cells in a fixative liquid, creating a thin cell layer on the slide. The study indicates that LBC outperforms conventional methods, leading to less discrepancy between histological diagnosis and cytological classification [56]. The identification

and examination of biomarkers in peripheral blood and saliva (including ctDNA, miRNAs, proteins, and exosomes) have the potential to enhance existing screening programs and diagnostic approaches. This could lead to improved early detection and real-time monitoring of diseases in the context of precision and personalized medicine. Despite numerous proposed technologies, the routine clinical implementation of liquid biopsy is currently constrained by issues related to sensitivity, specificity, and the absence of standardized protocols [57]. The general effectiveness of Artificial Intelligence (AI) methods seems to be on par with traditional light microscopic histopathological evaluation, offering the additional benefits of quicker, more objective, and reproducible assessments, the accuracy of AI methods was found to be between 79 and 100% [58]. Nonetheless, the incorporation of these methods into the digital pathology workflow necessitates thorough evaluation for each approach, relying on extensive multi-centric datasets. A recent systematic review focusing on optical fluorescence imaging, which analyzed data from twenty-seven studies, revealed that optical fluorescence imaging enhances the detection and visualization of lesions compared to relying solely on comprehensive oral examination in the clinical assessment of oral potentially malignant disorders [59]. An artificial neural network (ANN) method has demonstrated superior accuracy compared to traditional forecasting methods, with an accuracy rate exceeding 90% [60]. This algorithm proves capable of fulfilling the requirements for diagnosing high-risk groups of oral cancer lesions, leading to significantly improved diagnostic efficiency and patient survival rates. Autofluorescence-based systems, coupled with quantitative analysis, effectively differentiate oral cancer and dysplasia from benign lesions. Photodynamic Diagnosis using 5-Aminolevulinic Acid (ALA-PDD) is adept at detecting subtle changes or early malignant transformations in superficial mucosa lesions, providing earlier detection than conventional oral examinations (COEs). It demonstrates sensitivities and specificities of 83–90% and 79–89%, respectively, in distinguishing oral epithelial dysplasia from normal tissues [61, 62]. The combination of ALA-PDD and simple imaging processing enhances sensitivity and specificity for identifying high-risk dysplasia and cancer, facilitating objective discrimination between high-risk and low-risk OPMDs [62]. Recent advancements in risk assessment involve more sensitive approaches, such as evaluating DNA ploidy status, where aneuploid lesions suggest a higher risk. Additionally, testing for loss of heterozygosity has been implemented in a Canadian sample [16]. Chemiluminescence has demonstrated effective sensitivity in detecting various oral PMDs. However, a notable drawback is its tendency to favorably detect leukoplakia while sometimes overlooking erythematous patches. Additionally, the high associated cost limits its widespread utilization [11]. The VELscope, which utilizes narrow emission tissue fluorescence, is a portable device designed for direct visualization of the oral cavity and is promoted for oral cancer screening.

However, its effectiveness is a subject of controversy [11]. Consequently, it may not be considered a highly reliable tool for screening potentially malignant lesions and oral cancer. A two-channel autofluorescence test was developed in a study to detect oral cancer, focusing on exciting and detecting autofluorescence of reduced-form nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) at specific wavelengths. The study included 49 patients with oral cancer lesions, 34 with precancerous lesions, and 77 with healthy oral mucosa. The results suggest the potential for oral cancer screening, and possibly for other cancers, pending resolution of device issues such as size, water vapor, and the absence of a white-light reference in the same device. However, further long-term studies are needed to validate the clinical method's efficacy [63]. In a study evaluating the efficacy of fluorescent immunocytochemical diagnostics for oral mucosa precancerous diseases and cancer, 46 patients with squamous cell carcinoma, 35 with precancerous lesions, and 30 healthy individuals underwent traditional cytological examination along with additional immunocytochemical examination using direct immunofluorescence. The study assessed expression levels of tumor markers P53, P16, and Ki67, comparing the results with histological analysis. Findings revealed four times higher P53 expression in cancer patients than those with precancerous pathology. Co-expression of Ki67 and P16 was observed in 6.52% of cases [64]. Fluorescent immunocytochemical diagnostics offers non-invasive, timely, and remote result evaluation, enhancing accessibility and potential for population screening. The tongue microbiome has emerged as a non-invasive diagnostic and prognostic tool for disease detection, particularly cancer. Numerous studies have highlighted a higher abundance of specific microorganisms in pre-cancer or cancer groups compared to healthy individuals. These include *Firmicutes, Fusobacteria*, and *Actinobacteria* at the phyla level, as well as *Streptococcus, Actinomyces, Leptotrichia, Campylobacter*, and *Fusobacterium* at the genus level [65]. Thus, the tongue microbiome holds promise as a diagnostic tool and long-term monitoring tool in cases of precancerous or cancerous conditions.

These techniques, characterized by minimal invasiveness and virtually no morbidity, do come with notable false positive and false negative rates. As a result, diagnostic adjuncts should be employed cautiously and primarily as supplementary measures to the physical examination and tissue biopsy, which are still regarded as the gold standard for detection and diagnosis.

Despite attempts to enhance the management of OPMDs, numerous cases are still identified at a stage where a cure is exceedingly challenging, and interventions offer limited efficacy. Consequently, the early detection of OPMDs, particularly in high-risk groups, holds paramount importance in preventing their progression to malignancy. It is crucial to stratify patients based on various factors such as lesion size, clinical presentation, and histology to offer appropriate

counseling and screening for those at higher risk. Additionally, individuals with habits like tobacco chewing, areca nut consumption, alcoholism, smoking, and drug abuse face elevated risks. Therefore, public education regarding the hazards associated with these factors is of utmost importance.

9. CONCLUSIONS

Despite advancements in cancer therapeutics, the mortality rate for oral cancer remains high. A comprehension of the conditions leading to oral cancer and their prevention can significantly improve outcomes. Oral potentially malignant disorders are premalignant conditions encompassing a diverse range of oral lesions, that, if not detected and treated early, can transform into oral cancer in many cases, and leukoplakia and erythroplakia apear to be the most prevalent oral potentially malignant disorders. Proliferative verrucous leukoplakia is a rare lesion but it carries a high risk of progression into oral cancer. Erythroplakia and erythroleukoplakia lesions present a higher incidence of carcinomatous transformation than leukoplakia lesions. Oral chronic hyperplastic candidiasis is an uncommon oral potentially malignant disorder. The rate of malignant transformation of this lesion is lower than that of erythroplakia, erythroleukoplakia and proliferative verrucous leukoplakia and comparable to that of oral leukoplakia. The management of oral potentially malignant disorders is contingent on the conclusive diagnosis obtained from the biopsy specimen being the gold standard for detection. Various diagnostic adjuncts, such as vital staining with toluidine blue, methylene blue, and Lugol's iodine, along with methods like autofluorescence, chemiluminescence, immunocytochemical diagnostics, and others, show diverse success in diagnostics. Low-risk epithelial dysplasias require vigilant monitoring, with biopsies performed if any alterations to the lesion are observed. High-risk dysplastic lesions necessitate surgical excision, accompanied by thorough and prolonged patient follow-up. The progression from normal mucosa to premalignant or dysplastic mucosa and eventually to malignant transformation involves a complex interplay between the environment and the host. Host factors encompass genetics and immune system function, while environmental factors include exposure to carcinogens such as betel quid, tobacco, alcohol, and human papillomavirus.

10. RECOMMENDATIONS

Oral potentially malignant disorders require thorough examination. There are various additional methods of investigation, yet biopsy is the most reliable one and should be given primary

consideration. Patients should be encouraged to quit their habits of alcohol consumption, smoking, tobacco and betel quid chewing, areca nut consumption and drug abuse, as well as enhance oral hygiene. Mechanical irritation, sharp dental restoration, low serum vitamin A and carotene should also be considered as a possible causative factor and eliminated, if approved. Systemic diseases, such as anemia, vitamin deficiencies, and compromised immune function should be considered as a provocative factor and taken into consideration while suggesting a treatment plan. Lesions should be monitored for *Candida* infection as it may possess an increased risk of malignant transformation. Antifungal therapy can be used as both a therapeutic intervention and a prophylactic measure in the long-term care of Candida-associated oral leukoplakia. For oral leukoplakia lesions smaller than 2 mm, an excisional biopsy is recommended; for larger lesions, surgical excision, cryosurgery, or laser ablation should be used as a treatment method.

In case of erythroplakia, surgical or laser excision should be utilized.

In cases of erythroleukoplakia, the treatment methods are the same as for oral leukoplakia and erythroplakia.

Either surgical removal, laser removal, photodynamic therapy, retinoids, or chemotherapy should be used in treatment of proliferative verrucous leukoplakia, although their lack of effectiveness and high possibility of recurrence and malignant transformation of this lesion should be considered.

For chronic hyperplastic candidiasis, a combination of surgical or laser removal along with photodynamic therapy can be utilized.

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FIGURES

1. Flow chart for inclusion of studies
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TABLES

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