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REVIEWS

ORAL LEUKOPLAKIA AND CERVICAL LYMPHADENOPATHY—LITERATURE REVIEW AND PRESENT DATA

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ABSTRACT

INRTODUCTION: Current epidemiological data clearly indicate a steady rise in the incidence of malignant diseases. Although advances in surgical techniques, radiotherapy, and chemotherapy have improved treatment outcomes, overall cancer-related mortality continues to show an upward trend. For this reason, research in oncology must emphasize not only early detection and therapeutic interventions but also preventive strategies. One effective preventive approach is the management of oral preneoplastic conditions. Among these, leukoplakia is recognized as the most frequent precancerous lesion of the oral cavity and is frequently associated with enlargement of cervical lymph nodes.

MATERIALS AND METHODS: This review synthesizes information obtained from an in-depth analysis of 56 peer-reviewed, full-text publications in English.

DISCUSSION: Oral leukoplakia is clinically identified as a white mucosal lesion resulting from abnormal keratinization. It carries malignant potential and is defined by the World Health Organization as "a white plaque of questionable risk, excluding other conditions that are not associated with an elevated risk of cancer." The etiology is complex, often multifactorial, and in many instances remains idiopathic. Clinically, leukoplakia is classified into homogeneous and non-homogeneous forms, which differ in their presentation and malignant potential. Given its prevalence and potential severity, optimal management requires collaboration within an interdisciplinary medical team. Monitoring for cervical lymphadenopathy should always include detailed clinical examination supported by imaging modalities. In cases where malignancy is suspected, fine-needle aspiration cytology should be performed, supplemented by incisional or excisional biopsy of suspicious nodes to confirm the diagnosis.

CONCLUSION: Recognizing the early manifestations of oral preneoplastic lesions, particularly leukoplakia, the most common entity, is of paramount importance. Early intervention not only reduces the likelihood of malignant transformation but also represents a vital step in minimizing the long-term impact of cancer.

Keywords: *leukoplakia, dysplasia, oral cancer, oral cavity, cervical lymph nodes, oral preneoplasias*

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INTRODUCTION

Epdemiological data consistently demonstrate a rise in the incidence of malignant diseases worldwide. Despite substantial advances in surgical management, radiotherapy, and chemotherapy, mortality rates linked to neoplasms continue to increase (1). Consequently, cancer-related research must extend beyond diagnostics and treatment to include effective preventive strategies (2). A key preventive approach is the management of oral preneoplastic lesions, among which leukoplakia is considered the most prevalent condition within the oral cavity (1,2).

MATERIALS AND METHODS

This article is a review based on a comprehensive analysis of 56 contemporary full-text articles in English. The information from these sources was thoroughly reviewed, analyzed, and systematized to create a complete full-text publication on the characteristics of oral leukoplakia.

DISCUSSION

Epidemiological data consistently demonstrate a rise in the incidence of malignant diseases worldwide. Despite substantial advances in surgical management, radiotherapy, and chemotherapy, mortality rates linked to neoplasms continue to increase. Consequently, cancer-related research must extend beyond diagnostics and treatment to include effective preventive The term *leukoplakia*, introduced by Hungarian dermatologist Ernő Schwimmer in 1877, literally translates to *white plaque*. Clinically, it is described as a white lesion of the oral mucosa caused by abnormal keratinization and carrying malignant potential. According to the World Health Organization, it is defined as "a white premalignant plaque of uncertain risk, excluding other conditions that are not associated with a higher likelihood of cancer" (2,3). Leukoplakia is a clinical diagnosis that requires histopathological confirmation.

The etiology of leukoplakia is multifactorial, with some cases remaining idiopathic (4). Key risk factors include tobacco use, betel nut chewing, particularly prevalent in parts of Asia, chronic candidiasis (especially linked to non-homogeneous leukoplakia), excessive alcohol intake, chronic mechanical irritation, galvanic or electrical effects, ultraviolet exposure (notably on the lips), immunosuppression, and a prior history of cancer (5–7). Human papillomavirus (HPV) DNA can be identified in approximately one-quarter of lesions using polymerase chain reaction methods (8).

Leukoplakia affects men more commonly than women, at a ratio of about 2:1, and most cases are diagnosed between the ages of 40 and 70. In fact, 80% of patients are older than 40 at presentation (9). Risk factors for malignant transformation include female sex, idiopathic leukoplakia, long-standing persistence of the lesion, localization on the tongue or floor of the mouth, lesion size exceeding 200 mm^2, non-homogeneous morphology, concomitant candidiasis, and the presence of epithelial dysplasia (10).

Clinically, lesions are classified as homogeneous or non-homogeneous. Homogeneous leukoplakias present as thin, flat, and uniformly white plaques, often with well-demarcated borders, and usually have a relatively low malignant potential. In contrast, non-homogeneous lesions exhibit irregularities such as erythematous, speckled, nodular, or verrucous areas and are associated with a higher risk of malignant transformation (11). Proliferative verrucous leukoplakia, a rare and aggressive subtype, tends to occur more frequently in women, affects multiple areas of the oral cavity, and demonstrates the highest rate of malignant progression (12–14).

Oral leukoplakia begins its development as a fine uniform lesion and dysplasia during this initial period is not characteristic. As it progresses in its development, it thickens and becomes uneven, forming verrucas. This stage is called non-homogeneous leukoplakia. In the presence of dysplasia or invasive carcinoma, careful monitoring over time is necessary if it is impossible to remove them. In lesions that are nodular or ulcerated, a biopsy is required. Speckled leukoplakia is a clinical term describing the simultaneous presence of white and red areas in a lesion. It is considered more malignant because the red areas are less differentiated (15).

Elimination of causative factors can lead to regression of lesions within several weeks to months. If regression is absent after 2–4 weeks, biopsy is indicated (16). High-risk anatomical sites include the lateral and dorsal tongue, the soft palate, and the floor of the mouth (17). Diagnosis is based on a combination of history, clinical examination, and histopath-

ological evaluation, often supported by exclusion of other conditions (18). Adjunctive diagnostic aids include toluidine blue vital staining, brush cytology, autofluorescence and chemiluminescence-based devices, and biomarker testing from saliva, serum, or exfoliated cells (19,20).

The differential diagnosis encompasses a wide range of entities, including oral candidiasis, chemical burns, leukoedema, lichen planus, lupus erythematosus, chronic cheek biting, psoriasis, and inherited conditions such as white sponge nevus (21). Histopathological outcomes range from benign hyperkeratosis and parakeratosis (with or without acanthosis, atrophy, or inflammation) to epithelial dysplasia, carcinoma in situ, or invasive carcinoma (22).

Management depends on histological severity. Lesions with moderate to severe dysplasia or carcinoma in situ should be excised with clear margins (23). Although mild dysplasia may regress spontaneously, vigilant follow-up is required. Recurrence rates after excision vary between 0% and 35% (24–28). In cases of recurrence, re-excision with a 2–3 mm margin is recommended, and patients require lifelong monitoring at intervals of 3–6 months.

Alternative or adjunctive therapies include topical or systemic medications, risk factor elimination, and laser-based or photodynamic treatments. CO_2 laser excision is well-documented as an effective method, with recurrence and malignant progression rates ranging between 0% and 15% (32). Photodynamic therapy has also shown variable responses, from complete resolution to persistence of lesions (33). Dysplastic lip lesions may be managed with topical 5-fluorouracil (2–5% ointment, applied twice daily for 2–4 weeks) or imiquimod (5% ointment, applied 2–3 times weekly for up to 4 months), with 5-fluorouracil demonstrating superior efficacy (34,35). Other proposed therapies, such as β-carotene, vitamin A, bleomycin, ketorolac, or green tea extracts, have not demonstrated significant impact on malignant transformation risk (36). Elderly or medically compromised patients may be managed with observation, whereas younger or healthier patients benefit more from active lesion removal.

When histopathology confirms squamous cell carcinoma, referral to a multidisciplinary oncology board is required for further evaluation and management, including surgery, radiotherapy, or chemotherapy (37,38). Reported malignant transformation rates of leukoplakia vary between 1% and 9%. Even after lesion excision, recurrence and malignant progression may occur, and spontaneous regression is not uncommon, complicating outcome assessment. The unpredictability of dysplastic changes highlights the need for close and continuous follow-up (39).

Oral leukoplakia is a clinically common disease, and the best approach to it is an interdisciplinary team collaboration that includes an oral and maxillofacial surgeon, an otorhinolaryngologist, a dentist, a general practitioner, a pathologist, and a nurse. Patient education and the removal of predisposing factors are key.

In patients with oral leukoplakia, cervical lymphadenopathy is not a common sign, as the typical clinical presentation includes painless white or grey plaques without significant lymph node swelling (40). However, when cervical lymph nodes are clinically detected, especially in association with high-risk features such as non-homogeneous morphology, advanced dysplasia, lingual or sublingual localization, or lesions larger than 10 mm, suspicion for malignant transformation should be raised (41). While lymphadenopathy itself is not a characteristic sign of leukoplakia alone, this symptom can signal an ongoing malignant process, most often squamous cell carcinoma (42,43). In oral cancer, tumors often metastasize to cervical lymph nodes. According to published data, metastases occur in about 40% of patients, and in many of these cases, they remain clinically hidden and are only discovered through imaging (44).

Regional metastases in squamous cell carcinoma most frequently affect levels II and III of the cervical lymph node chain (45,46). For T1-T2 stage tumors, the percentage of metastases is around 30%, while for T3-T4, this percentage reaches up to 60% (47). A histopathological assessment shows a statistically significant link between the degree of malignancy, the type of keratinization, and the method of invasion with the likelihood of metastasis to the cervical lymph nodes (48).

Ultrasound, combined with fine-needle aspiration biopsy, achieves sensitivity and specificity above 90% for detecting nodal metastases. Suspicious fea-

tures include a short-to-long axis ratio below 0.5, loss of the echogenic hilum, internal heterogeneity, and abnormal vascularization. Roughly 25% of metastases remain clinically undetectable but can be identified through imaging (49).

Cervical lymphadenopathy carries a broad differential, ranging from infectious conditions (tonsillitis, stomatitis, tuberculosis) and autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis) to malignant causes such as lymphomas and squamous cell carcinoma (50–54). In patients over 50, newly detected cervical nodes should immediately prompt evaluation for possible head and neck or upper aerodigestive tract malignancy (55). Painless, persistent nodes without systemic symptoms such as fever, night sweats, or weight loss are more suggestive of malignant than infectious etiologies (56). In such cases, a combination of a clinical examination, imaging (ultrasound, computed tomoraphy, or magnetic resonance imaging), and fine needle aspiration biopsy or an incisional/excisional biopsy is recommended.

Proliferative verrucous leukoplakia, the multifocal progressive subtype, represents the most aggressive and high-risk variant (55,56). This form often presents with multiple lesions that are resistant to treatment, prone to recurrence, and undergo gradual transformation. This subtype requires especially strict monitoring with periodic biopsies and ultrasound evaluation of cervical nodes.

During a clinical examination of a patient with leukoplakia, a systematic palpation of all cervical lymph nodes is necessary to evaluate their size, consistency, mobility, and any signs of invasion, such as hardness, fixation to surrounding tissues, and lack of hilar structure (56). Suspicious findings mandate immediate further diagnostic evaluation. In studies of patients with leukoplakia that progressed to squamous cell carcinoma, nodal metastases were reported in up to 45% of cases (45). In other studies, the sensitivity of ultrasound diagnostics for detecting metastases reached up to 66%, highlighting its importance in early diagnosis (47).

CONCLUSION

Knowing the early symptoms of preneoplasias, especially oral leukoplakia as the most common among them, is crucial for cancer prevention and for mitigating its severe consequences. Despite the immense technological and therapeutic progress in medicine, prevention remains the primary method for dealing with this socially significant disease.

The presence of cervical lymphadenopathy in a patient with oral leukoplakia should always be considered a potential warning sign of malignant transformation. A complete clinical evaluation is necessary, including imaging and a biopsy of both the lesion and any suspicious lymph nodes. For patients with risk factors (smoking, alcohol consumption, advanced age), follow-up is recommended every 3 to 6 months. If there is high-grade dysplasia or a progressive clinical presentation, the intervals between examinations should be even shorter, requiring repeat biopsies and additional imaging methods to monitor the cervical lymph node status.

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