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Oral Potentially Malignant Disorders: Current Insights and Emerging Treatment Strategies

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Abstract

Oral potentially malignant disorders (OPMDs) are a group of conditions requiring early diagnosis due to their high risk of malignant transformation. The most prevalent OPMD are leukoplakia, erythroplakia, lichen planus, and oral submucous fibrosis, all associated with a high risk of oral squamous cell carcinoma (OSCC) progression. This literature review provides a comprehensive overview of advances in treating these lesions, highlighting the necessity for efficient prevention and early detection to lower cancer incidence and improve survival outcomes. Leukoplakia, the most common OPMD, is associated with tobacco use and manifests in homogeneous and non-homogeneous forms, with the latter having a higher malignant transformation risk. Management includes surgical excision, laser therapy, photodynamic therapy, cryotherapy, and chemo preventive agents. Erythroplakia, characterized by a high malignant potential, primarily appears in the floor of the mouth, soft palate, and ventral tongue, and is managed with surgical methods and long-term monitoring. OSMF is a chronic, progressive scarring disease primarily linked to areca nut chewing, characterized by oral mucosal stiffness and restricted mouth opening. Its management includes drug therapy, mouth-opening exercises, and elective surgery. Recent advancements in OSMF treatment, such as sesame oil pulling, drug-loaded micro needle patches, and combined drug regimens, show promising results. Surgical interventions focus on improving mouth opening and preventing re-fibrosis. The review emphasizes the critical importance of early detection and advanced treatment methodologies in reducing cancer incidence and improving patient outcomes. Despite extensive research, no single

treatment modality has proven universally effective for OPMDs, highlighting the need for continued research and innovation in treatment strategies. Future studies should focus on identifying reliable biomarkers for early detection and developing personalized treatment approaches to enhance the management and outcomes of patients with potentially malignant disorders.

Keywords: Multistage process, Oral leukoplakia, premalignant, Oral submucous fibrosis.

Introduction

The transformation of oral mucosa into cancer is a complex, multistage process, with a significantly increased risk of oral squamous cell carcinoma (OSCC) in patients diagnosed with specific oral lesions termed oral potentially malignant disorders (OPMDs).[1] OPMDs are defined as “any oral mucosal abnormality that is associated with a statistically increased risk of developing oral cancer”. [2] The reclassification of "premalignant" as 'Potentially Malignant Disorders (PMD)' by the WHO in London in May 2005 marks a pivotal shift in understanding the progression of oral mucosal conditions towards cancer.[3] Although OPMDs do not invariably lead to oral cancer, approximately 7% of SCCs are preceded by these types of lesions.[4] Efficient prevention and early detection of OPMDs have the dual benefit of lowering incidence rates and improving survival outcomes for those affected by oral cancer.[3] A recent systematic review indicated that fewer than half of medical practitioners are aware of the common risk factors for OPMD or oral carcinoma. Furthermore, most medical practitioners demonstrate a limited understanding of common PMD in the oral cavity. Consequently, there is a critical need to improve understanding and recognition of the symptoms, pathophysiology, and management of these conditions. The most prevalent OPMD are leukoplakia, erythroplakia, lichen planus, and oral submucous fibrosis.[5] Among these lesions, erythroplakia has the highest malignant potential.[6]

Oral leukoplakia (OL) is the most common OPMD of the oral cavity often linked to tobacco chewing and smoking. The malignant potential of OL was first suggested by Sugar and Banoczy in 1957.[7] The malignant transformation rates of oral leukoplakia lesions vary significantly: 1% to 7% for homogeneous thick leukoplakia, 4% to 15% for granular or verruciform leukoplakia, and 18% to 47% for erythroleukoplakia.[8] These high rates underscore the critical importance of early detection and prompt treatment of these lesions.

Oral submucous fibrosis (OSF) is a precancerous condition of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues, leading to significant rigidity and restricted mouth opening (trismus).[9] Causative factors contributing to OSF include deficiencies in vitamins B, C, and iron, along with the habitual chewing of areca nut, consumption of spicy foods, human papillomavirus (HPV) infection, and genetic mutations. Epidemiological studies highlight chewing areca nut as one of the foremost risk factors for OSF. Areca nut, commonly chewed with betel leaf, lime, and other spices, contains arecoline, a stimulant implicated in the onset of OSF and potential malignancy.[10] The rate of malignant transformation in OSF ranges from 3% to 19%.[7]

This article emphasizes key aspects of the prevalent potentially malignant lesions—leukoplakia, erythroplakia, and oral submucous fibrosis (OSF)—particularly focusing on recent advancements in their treatment.

Methodology

A literature review was conducted to provide a comprehensive overview of current knowledge regarding advances in the treatment of potentially malignant oral lesions. Studies were selected from PubMed, Cochrane, Scopus, and Google Scholar, focusing on publications from 2008 onwards. The review aimed to evaluate recent developments in the treatment of three prevalent potentially malignant lesions: leukoplakia, erythroplakia, and oral submucous fibrosis. The search terms included "Leukoplakia," "Erythroplakia," "Oral submucous fibrosis," "Oral Potentially Malignant Disorders," "Recent Advances," "Tobacco," "Disease Management," and "Treatment Outcome." The review included articles written in English and covered case reports, clinical studies, and systematic reviews on the treatment of leukoplakia, erythroplakia, and OSMF, with a focus on recent advancements in treatment methodologies.

Leukoplakia

Shanbhag et al.[11] defined leukoplakia as "a predominantly white, irreversible, non-scrapable lesion of the oral mucosa that cannot be characterized clinically or histopathologically as any other lesion/disease and has increased risk of cancer occurrence than its normal counterpart and is usually associated with consumption of tobacco, betel quid, and alcohol, but otherwise can be of idiopathic in nature". It comprises about 80% of oral lesions categorized as potentially malignant.[12] The definitive cause of leukoplakia remains ambiguous, but it is primarily associated with tobacco use, both smoking and smokeless forms, along with chronic alcohol consumption.[13]

Clinical Presentations

Leukoplakia manifests clinically in two main forms: homogeneous, which appears uniformly flat with occasional superficial irregularities but consistent texture, and non-homogeneous (including erythroleukoplakia), characterized by a predominantly white or white and red lesion with an irregular texture that may include ulceration, often presenting with a speckled, nodular, or verrucous appearance.[14] Proliferative verrucous leukoplakia, a subtype of verrucous leukoplakia, was first described by Hansen et al. in 1985. It is characterized by multifocal presentation and exhibits resistance to treatment, along with a strong potential for malignant transformation. Non-homogeneous leukoplakias carry a higher propensity for malignant transformation compared to homogeneous variants.[15] The risk of malignant transformation in nonhomogeneous leukoplakia is estimated to be between 23.4% and 38%.[16] Dysplastic leukoplakia has a greater risk of malignant transformation than non-dysplastic leukoplakia, particularly with the risk increasing to between 36.3% and 43% in the presence of epithelial dysplasia.[13, 16] Additional, significant risk factors linked to cancer development in individuals with leukoplakia include female gender, prolonged duration of the lesion, non-smoking status, location on the lateral tongue or floor of the mouth, lesion size greater than 200 mm^2, and the presence of Candida albicans. Aneuploid lesions, characterized by abnormal DNA content, are more prone to cancer transformation compared to diploid lesions with normal DNA content.[14]

Management and Treatment

The diagnosis and treatment of leukoplakia are crucial due to its premalignant nature. Currently, there is no well-defined clinical management guideline for leukoplakia. Treatment necessity is primarily determined by the characteristics of the lesions.[13] The primary objective in managing leukoplakia is to prevent its progression to cancer. Various surgical and nonsurgical treatment modalities are available for its management.

Surgical Treatment

The rationale for surgical excision is to remove clinically abnormal tissue, aiming to prevent the onset of oral cancer.[14] Surgical excision is recommended for histopathologically identified white lesions showing dysplasia (grades 1 and 2) or carcinoma in situ (grade 3), especially in cases of moderate to severe epithelial dysplasia where margins are unclear.[13] The surgical interventions include excision using various methods like scalpel, cryosurgery, photodynamic therapy, laser surgery, and vaporization.[14]

The two most preferred treatment modalities are CO2 laser therapy or surgical excision.[15]

Tambuwala A et al.[16] compared CO2 laser excision of leukoplakia to traditional scalpel methods in thirty patients with bilateral lesions (60 lesions on the right and left buccal mucosa) requiring excision for biopsy. Their study concluded that CO2 laser excision offers superior intra-operative precision and reduced scarring compared to conventional scalpel excision.

OL has been treated using different vaporization or excision techniques with a range of lasers, such as carbon dioxide (CO2), Nd, and KTP lasers. Laser therapy provides significant advantages over alternative treatments for OL, such as effective hemostatic effects and the potential to reduce tissue contraction and scarring after treatment, particularly beneficial for managing larger lesions.[17] Additionally, it is associated with fewer postoperative complications like scarring, pain, and secondary infections, and lower recurrence rates. The CO2 laser, in particular, provides the added benefit of controlling bleeding through thermal coagulation, enabling operators to detect any remaining tissue abnormalities, such as white or gray areas in the connective tissues, after the removal of carbonized sections.[18]

For extensive lesions, photodynamic therapy (PDT) can be considered.[15] PDT is a minimally invasive treatment method for OL involving the activation of a photosensitizer with a specific wavelength of light. D. Di Stasio et al.[19] treated fifteen cases of leukoplakia with 2.5% toluidine blue (TB) and an LED source of 630 nm wavelength, reporting that 40% of the lesions had a complete response, 47% had a partial response, and 13% showed no response at the end of the treatment cycles. Upon re-evaluation after a 1-year follow-up, a complete remission was observed in one patient who initially had a partial response, and one previously unresponsive patient showed an improvement to a partial response.

Cryotherapy serves as an effective alternative treatment modality for oral leukoplakia lesions alongside surgical excision, laser surgery, and photodynamic therapy.[8] Cryotherapy involves the controlled and targeted destruction of diseased tissue by applying a cold substance in situ. The benefits of cryotherapy include reduced discomfort and pain (due to decreased nerve conduction speed), absence of bleeding (vasoconstriction), minimal scarring, ease of application, preservation of inorganic structures of bone, low infection risk (reduced metabolic rate lowers oxygen dependency), and localized treatment action.[20] The efficacy of cryotherapy and photodynamic treatment was compared, with complete responses obtained in 72.9% of patients treated with photodynamic therapy and 89.2% of patients treated with cryotherapy.[15]

Non-surgical treatment modalities for leukoplakia include chemo preventive agents such as carotenoids (β-carotene, lycopene), vitamins [L-ascorbic acid (vitamin C), α-tocopherol (vitamin E), retinoic acid (vitamin A), and fenretinide (Vitamin A analog)], bleomycin, protease inhibitors, anti-inflammatory drugs, green tea, and curcuma.[15, 12] Chemoprevention refers to the use of

natural or synthetic chemical agents, applied either topically or systemically, to prevent the progression or development of oral cancer.[4]

The rationale for medical treatments is based on the specific mechanisms of action of the agents used. Retinoids, vitamin A, and carotenoids potentially influence epithelial turnover; non-steroidal anti-inflammatory drugs (NSAIDs) block cyclooxygenase activity, modulating specific prostaglandins possibly involved in carcinogenesis; and chemotherapeutic agents act directly on early neoplastic cells.[14] Non-surgical intervention advocates the use of topical bleomycin, systemic retinoids, and systemic lycopene to treat dysplasia.[13] Among patients treated with topical retinoic acid, complete response rates ranged from 10% to 27%, while partial response rates varied between 54% and 90%. However, recurrence of leukoplakia was reported in approximately 50% of patients after withdrawing topical retinoic acid.[15]

Oral Erythroplakia

Oral erythroplakia (OE) is defined as 'A fiery red patch that cannot be characterized clinically or pathologically as any other definable disease'.[21] Its reported prevalence ranges between 0.02% and 0.2%.[22] Alcohol consumption, cigarette smoking, and betel quid chewing, with or without tobacco, are recognized as primary causes of OE. Among these, chewing tobacco may pose a greater risk for OE than smoking. Dose-response relationships indicate that individuals who keep tobacco in their mouth overnight or swallow the tobacco fluid are at a higher risk of developing erythroplakia compared to those who do not. Tobacco is primarily consumed as part of betel quid or pan, which also includes betel leaves, areca nut, and lime. A distinct type of oral erythroplakia (OE) is found among chutta smokers in India. This practice involves reverse cigar smoking, where the burning end is placed inside the mouth, resulting in red patches on the palate mucosa.[23]

Clinical Presentations

Erythroplakia lesions can appear clinically as either flat or depressed, and they may co-occur with leukoplakia (erythroleukoplakia).[22] These lesions typically have irregular but distinct outlines, with a bright red velvety surface, occasionally appearing granular.[24] OE primarily appears in the floor of the mouth, soft palate, ventral tongue, and tonsillar fauces. It is characterized by dysplastic features and frequently presents as either carcinoma in situ or invasive carcinoma upon biopsy. While often asymptomatic, some patients may experience symptoms such as a burning sensation or soreness.[22]

Management

The high malignant transformation rate associated with erythroplakia highlights the necessity for effective treatment strategies. Surgical methods, such as cold knife or CO2 laser procedures, are recommended as the primary treatment options.[25] Long-term monitoring and follow-up are essential requirements.[26]

Oral submucous fibrosis

Oral submucous fibrosis (OSMF) is a chronic progressive scarring oral disease characterized by a burning sensation in the oral cavity, oral ulceration, vesiculation, blanching and stiffening of the oral mucosa and oropharynx and trismus. The primary etiological factor in the development of OSMF is areca nut chewing. Other contributing factors include the consumption of commercial smokeless tobacco products, high dietary intake of chillies, the presence of harmful copper traces in food, micronutrient deficiencies, and genetic predisposition. It is primarily affect individuals from Southern Asian countries or Southern Asian immigrants living in other parts of the world.[27] In rural

India, the condition affects 4/1,000 adults, with an estimated 5 million young Indians suffering from OSMF. Recent reports indicate a prevalence rate as high as 6.42% in India, predominantly among males aged 20 to 40 years. A case-control study conducted in Chennai, South India, involving 185 subjects, revealed a male-to-female ratio of 9.9:1.[28]

Clinical Presentation

OSMF is characterized by the progressive buildup of constricting collagen bands in the cheeks and adjacent structures of the mouth.[28] The most frequently affected area is the buccal mucosa, followed by the palate, the retro molar region, the faucial pillars, and the pharynx.[27] The typical clinical symptoms include progressive bleaching, burning sensation, increased mucosal stiffness, and the presence of characteristic fibrous bands, which restrict oral movements and make chewing and swallowing challenging.[29] Initially, the mucosa feels leathery with palpable fibrotic bands. In advanced stages, the oral mucosa becomes blanched and slightly opaque, with white fibrous bands in the buccal mucosa, lips, soft palate, faucial pillars, and tongue. Additional features of OSMF include xerostomia, recurrent ulcers, oral mucosa pigmentation, burning sensation, and reduced mouth opening and tongue protrusion.[28]

More et al.[30] classifications:

I: Clinical staging: Stage 1 (S1): Stomatitis and/or blanching of oral mucosa.

Stage 2 (S2): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis.

Stage 3 (S3): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, and in any other parts of oral cavity, with/without stomatitis.

Stage 4 (S4): A: Any one of the above stage along with other potentially malignant disorders, e.g., oral leukoplakia and oral erythroplakia. B: Any one of the above stage along with oral carcinoma.

II: Functional staging:

M1: Inter-incisal mouth opening up to or >35 mm

M2: Inter-incisal mouth opening between 25 to 35 mm

M3: Inter-incisal mouth opening between 15 to 25 mm

M4: Inter-incisal mouth opening <15 mm

Management

The key objective of treating OSF is to reduce its severity in terms of morbidity and to prevent its progression to cancer.[7] Treatment of OSF is based on severity of disease. Early detection of OSF enables effective intervention, with cessation of betel quid chewing at this stage often resulting in complete remission of the disease.[31] Current treatment approaches for OSF are categorized into drug therapy, mouth opening exercises, and elective surgery.[32]

Table 1: The common drugs in clinical drug treatment of OSF[32]

Drug Name	Drug type	Effect
Hydrocortisone, Triamcinolone, Dexamethasone Betamethasone	Corticosteroid	Anti-inflammation
IFN-γ	Cytokines	Anti-inflammation
Collagenase, Hyaluronidase	Enzymes	Breaking down the ground substance in connective tissue
Pentoxifylline	Vasodilator	Hampered mucosal vascularity
Isoxsuprine	Vasodilator	Hampered mucosal vascularity
Vitamin A, B, C, D, E	Adjuvant	Deactivate free radicals
Iron,	Adjuvant	Relief the symptom

Recent advancements in the treatment of oral submucous fibrosis OSF have shown promising results through

various therapeutic approaches. Shrivastava S et al.[33] conducted a prospective interventional study with 62 patients to evaluate the efficacy of sesame oil pulling in managing OSF. They observed significant clinical improvements in parameters such as mouth opening, tongue protrusion, speech difficulty, deglutition, and burning sensation. These findings suggest that oil pulling may offer a beneficial adjunctive approach in managing OSF symptoms. Cheng et al.[34] developed an innovative double-layered, drug-loaded, mucoadhesive micro needle patch that demonstrated superior mechanical strength, facilitated effective triamcinolone release, and provided enhanced wet adhesion. This drug delivery system ensures targeted delivery to lesion sites and holds significant promise for managing OSF.

Shah, S. U. et al.[35] demonstrated that combining pentoxifylline and triamcinolone substantially alleviates symptoms associated with OSF. This regimen, leveraging a hemorrheologic agent and steroid, improves pain management and reduces inflammation, ultimately enhancing mouth opening.

Ahmad et al.[7] inferred from their study that oral curcumin at 300 mg twice daily resulted in significant improvements in mouth opening, burning sensation, and cheek flexibility compared to placebo. Similarly, oral lycopene at 8 mg twice daily showed significant improvements in these parameters compared to placebo. The study suggests that oral curcumin and lycopene are effective, safe, and cost-effective options for treating OL and OSF.

Mouth Exercising Devices

Therapeutic conventional exercises are widely used as a non-invasive treatment for patients with OSF.[36, 37] These exercises utilize devices that can either be prefabricated, such as EZBite, or custom-made oral stents.[32] Mouth exercising devices lead to a notable increase in mouth opening, typically by about 10.5 mm and maintain these improvements for 12 weeks to 6 months.[38] Additionally, commercially available devices such as Thera Bite®, Malmö, Sweden Jaw Motion Rehabilitation System™, and Dynasplint Trismus System® (DTS) have shown to increase mouth opening by up to 14 mm.[39]

Elective surgery

Surgical intervention is recommended for patients with severe trismus characterized by an inter-incisal mouth opening of less than 25 mm.[40] Procedures such as fibrotomy, coronoidectomy, or myotomy may be performed.[41] The primary aim of these surgeries is to restore articulation, mastication, and oral hygiene by improving mouth opening (40)Scalpel blades, electrocautery, and lasers are used to cut the fibers that restrict mouth opening, and coronoidectomy is performed to reconstruct soft tissue to increase mouth opening.[32] Various flaps and graft techniques are incorporated to fill the created gap, prevent re-fibrosis and promote healing without excessive scarring.[41] Soft tissue reconstruction involves various types of flaps including the fat flap, nasolabial flap, tongue flap, mandibular mucoperiosteal flap, palatal flap, and platysma myocutaneous flap.[42] These techniques are utilized to restore tissue integrity and function. Post-flap transplantation, medical treatment includes the administration of a vasodilator with antioxidant, anti-inflammatory, and immune-modulatory properties to support healing and reduce complications.[43]

Conclusion

Early detection and advanced treatment methodologies for OPMDs are crucial in lowering cancer incidence and improving patient outcomes. Diagnosing these conditions early significantly enhances prognosis. Timely treatment and regular monitoring are essential to prevent malignant transformation. Despite extensive

research over the years, no single treatment modality has proven universally effective for OPMDs. Therefore, there is a pressing need for continued research and innovation in treatment strategies. Future studies should focus on understanding the identifying reliable biomarkers for early detection and developing personalized treatment approaches. By addressing these gaps, we can improve the management and outcomes of patients with potentially malignant disorders.

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