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Clinico-Pathological Perspectives on Potentially Malignant and Malignant Lesions of the Oral Cavity: A Comprehensive Review

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KEYWORDS

Oral cancer, potentially malignant disorders, oral cavity lesions, clinico-pathological correlation, dysplasia, early detection.

ABSTRACT:

Background: Oral potentially malignant disorders (OPMDs) and oral malignancies contribute significantly to global morbidity, especially in regions with high tobacco and areca nut use. Early detection and accurate clinico-pathological assessment are crucial for improving outcomes.

Aim: To comprehensively review the epidemiology, etiopathogenesis, clinical features, histopathological characteristics, diagnostic advancements, and management approaches of OPMDs and oral malignancies.

Methods: Relevant literature on clinical presentation, pathological evaluation, molecular alterations, and diagnostic innovations in oral cavity lesions was critically examined to highlight current understanding and evolving concepts.

Results: OPMDs such as leukoplakia, erythroplakia, oral submucous fibrosis, and lichen planus show variable malignant transformation potential influenced by lifestyle habits, genetic factors, and environmental exposures. Histopathology remains the gold standard for assessing dysplasia and malignancy, while emerging techniques—such as optical imaging, cytopathological adjuncts, biomarkers, and artificial intelligence—offer promise for early detection. Effective management requires a multidisciplinary approach combining risk assessment, clinical monitoring, and timely intervention.

Conclusion: Strengthening clinico-pathological correlation, improving early detection strategies, and integrating advanced diagnostic tools are essential for reducing the burden of oral cancer. Preventive measures, public health awareness, and personalised management approaches can significantly enhance patient outcomes.

INTRODUCTION

Oral cancer is a major global health concern, ranking as the sixth most common cancer worldwide and contributing significantly to morbidity and mortality, particularly in developing countries [1]. Oral squamous cell carcinoma (OSCC) constitutes nearly 90% of all oral malignancies and frequently arises from pre-existing oral potentially malignant disorders (OPMDs), which are clinically identifiable lesions with an increased likelihood of malignant transformation [2,3]. Despite advances in diagnostic and therapeutic modalities, the prognosis of oral cancer remains poor due to late-stage presentation, delayed diagnosis, and inadequate screening practices in high-risk populations [4].

OPMDs—including leukoplakia, erythroplakia, oral submucous fibrosis (OSMF), and oral lichen planus—exhibit substantial clinical and biological heterogeneity. Their transformation potential depends on several risk factors, such as tobacco use, betel nut chewing, alcohol consumption, chronic irritation, genetic susceptibility, and infections like human papillomavirus (HPV) [5–7]. Among these, tobacco and areca nut are the most significant contributors in South and Southeast Asia,

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where oral cancer incidence is among the highest globally [7,8].

Histopathological evaluation continues to be the gold standard for assessing epithelial dysplasia and malignant risk. The degree of dysplasia correlates strongly with transformation rates and is integral to guiding clinical management [9]. While newer diagnostic approaches—such as optical adjuncts, brush cytology, molecular biomarkers, and artificial intelligence—are gaining prominence, clinico-pathological correlation remains essential for early detection and prognosis [10,11].

Given the rising global burden of oral cancer and the recognized importance of identifying high-risk lesions at an early stage, a comprehensive understanding of clinical patterns, pathological characteristics, and determinants of malignant transformation is crucial. This review synthesizes current knowledge on the epidemiology, etiopathogenesis, clinical features, histopathology, diagnostic advancements, and management strategies pertaining to OPMDs and oral malignancies. The goal is to strengthen integrated diagnostic approaches that can improve early detection, optimize therapeutic outcomes, and reduce disease burden.

2. Epidemiology of OPMDs and Oral Cancer

Oral cancer is a global public health concern, with significant geographic variation in incidence and mortality. The highest burden is observed in South Asia, particularly India, Sri Lanka, and Pakistan, where cultural habits such as tobacco chewing, betel quid use, and areca nut consumption are prevalent [12]. Globally, oral cancer ranks among the top ten cancers in men and shows increasing incidence in younger populations [13]. According to GLOBOCAN estimates, more than 400,000 new oral cancer cases are reported annually, with mortality exceeding 50% due to late-stage diagnosis and inadequate early screening programs [14].

OPMDs exhibit similar epidemiological trends, with leukoplakia being the most common, affecting 1–3% of the global population, while erythroplakia, although less common, carries a higher malignant transformation potential [2,15]. OSMF shows particularly high prevalence in India due to widespread areca nut consumption, especially among the youth [7]. These epidemiological patterns emphasise the urgent need for early identification and preventive strategies.

3. Etiopathogenesis

3.1 Tobacco and Areca Nut Use

Tobacco (smoked and smokeless) remains the most significant etiological factor for OPMDs and OSCC, accounting for nearly 50–60% of oral cancer cases globally [16]. Areca nut, the primary causative agent for OSMF, induces fibroelastosis and epithelial atrophy, significantly raising cancer risk [7,11].

3.2 Alcohol Consumption

Alcohol synergistically enhances the carcinogenic effects of tobacco by increasing mucosal permeability and promoting the formation of carcinogenic metabolites such as acetaldehyde [17].

3.3 Viral Aetiology (HPV)

High-risk HPV subtypes, especially HPV-16 and HPV-18, are implicated in a subset of oral and oropharyngeal cancers. HPV-positive tumours often show better prognosis and distinct molecular characteristics compared to HPV-negative cancers [6,18].

3.4 Genetic and Epigenetic Alterations

Oral carcinogenesis progresses through a series of genetic events, including TP53 mutations, loss of heterozygosity at 3p and 9p, and epigenetic changes such as promoter hypermethylation of tumour suppressor genes [19]. These alterations underpin the concept of field cancerization.

3.5 Chronic Trauma and Irritation

Chronic mechanical irritation from sharp teeth, dental appliances, or habits like tobacco chewing may promote epithelial dysplasia and malignant progression through sustained inflammation and tissue remodelling [20].

4. Classification of OPMDs

4.1 Leukoplakia

Defined as a “white patch of questionable risk” without an identifiable cause, leukoplakia remains the most common OPMD. Non-homogeneous leukoplakias show higher rates of dysplasia and transformation [2,21].

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4.2 Erythroplakia

Although less prevalent, erythroplakia is associated with severe dysplasia, carcinoma in situ, or early invasive carcinoma in up to 50% of cases at initial presentation [15].

4.3 Oral Submucous Fibrosis (OSMF)

OSMF is characterised by progressive fibrosis of the oral mucosa leading to restricted mouth opening and significant malignant transformation risk (7–13%) [11].

4.4 Oral Lichen Planus (OLP)

OLP presents as reticular, plaque-like, erosive, or ulcerative lesions. The malignant transformation rate ranges from 0.1% to 1%, especially in the erosive form [22].

4.5 Dysplastic Lesions

The WHO grading of epithelial dysplasia—mild, moderate, severe—is crucial for risk assessment and guiding treatment decisions [9].

5. Clinical Features

5.1 Clinical Presentation of OPMDs

Leukoplakia manifests as white plaques with variable texture, whereas OSMF is characterised by burning sensation, mucosal blanching, and progressive trismus [7,11]. OLP typically presents as bilateral white striations (Wickham's striae), especially on the buccal mucosa [22].

5.2 Clinical Features of Oral Cancer

OSCC commonly presents as an ulceroproliferative lesion with induration, pain, dysphagia, bleeding, or neck node enlargement. The tongue, buccal mucosa, and floor of the mouth are the most frequently involved sites [1,14].

6. Histopathology

6.1 Histological Features of OPMDs

– Leukoplakia: hyperkeratosis, acanthosis, variable dysplasia
– Erythroplakia: almost always severe dysplasia or carcinoma in situ
– OSMF: epithelial atrophy, dense fibrosis, hyalinization
– OLP: band-like lymphocytic infiltrate and basal cell degeneration [22]

6.2 Epithelial Dysplasia

Architectural and cytological abnormalities, such as nuclear pleomorphism, basal cell hyperplasia, and increased mitotic activity, classify lesions into mild, moderate, or severe dysplasia [9].

6.3 Oral Squamous Cell Carcinoma

OSCC demonstrates invasion beyond the basement membrane, keratin pearl formation, and varying degrees of differentiation. Broders' grading—well, moderately, and poorly differentiated—helps predict prognosis [23].

7. Diagnostic Approaches

7.1 Clinical Examination

Detailed visual and palpatory examination forms the cornerstone of early detection. Opportunistic screening significantly increases detection rates in high-risk populations [24].

7.2 Histopathological Examination (Gold Standard)

Incisional biopsy with histopathology remains the definitive diagnostic method for evaluating dysplasia and malignancy [9].

7.3 Cytological Techniques

Oral brush biopsy and liquid-based cytology serve as minimally invasive screening tools, especially in resource-limited settings [25].

7.4 Adjunctive Diagnostic Tools

–Toluidine blue staining
–Autofluorescence imaging
–Chemiluminescence
These techniques help identify suspicious lesions but should not replace biopsy [26].

7.5 Molecular Biomarkers

Biomarkers like p53, Ki-67, EGFR, and miRNAs show promise in predicting malignant transformation [19,27].

7.6 Emerging AI and Digital Pathology

AI-based systems aid early detection by analyzing cytological and histological images with high accuracy [28].

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8. Malignant Transformation Risk

OPMDs show variable transformation rates depending on lesion type, dysplasia grade, anatomical site, and etiological factors. Non-homogeneous leukoplakia, erythroplakia, and OSMF carry higher risks compared to homogenous lesions [2,15]. Lesions on the tongue and floor of mouth show higher transformation rates [21]. Continuous follow-up is essential due to the unpredictable nature of malignant progression [29].

9. Management Strategies

9.1 Management of OPMDs

– Lifestyle modification: cessation of tobacco, alcohol, and areca nut
– Surgical excision: recommended for non-homogeneous lesions with dysplasia
– Pharmacological therapy: topical steroids for OLP; antioxidants and intralesional steroids for OSMF [30]

9.2 Management of OSCC

Multimodal treatment includes surgery, radiotherapy, and chemotherapy depending on stage and patient factors. Early-stage cancers benefit primarily from surgery, while advanced cases often require combined therapy [31].

10. Prevention and Public Health Measures

10.1 Tobacco and Areca Nut Cessation

Public health policies targeting tobacco and areca nut use remain central to reducing OPMDs and oral cancer burden [7].

10.2 Community Screening Programs

Population-based visual inspection screening reduces mortality from oral cancer, especially among high-risk groups [24,32].

10.3 Education and Awareness

Health education focusing on early warning signs significantly improves early detection and prognosis [33].

11. Future Directions

Advancements in molecular diagnostics, genomic profiling, and artificial intelligence are expected to transform early detection and risk prediction. Integrating biomarkers into routine screening, adopting digital pathology, and personalised therapy will shape the future landscape of oral cancer control [27,28].

CONCLUSION

Oral potentially malignant disorders and oral malignancies remain major health concerns, particularly in high-risk populations. Early recognition, supported by strong clinico-pathological correlation, is essential for preventing malignant transformation and improving outcomes. Despite advances in diagnostic technologies, histopathology remains the gold standard for assessment. Strengthening awareness, promoting habit cessation, and enhancing early detection strategies are key to reducing the burden of oral cancer. An integrated, multidisciplinary approach will continue to play a crucial role in improving patient care and prognosis.

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