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Original Article

Potentially Malignant Disorders of Oral Cavity – A Review of Etiology and Clinicopathological Correlation

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Abstract

Background: Oral cancer is the most life threatening of all oral diseases and may be preceded by oral potentially malignant disorders (OPMD). Oral potentially malignant disorders show visible clinical changes in the oral mucosa in the form of white or red patch which may resemble each other clinically making biopsy mandatory for confirmation.

Purpose: This article is an attempt to classify oral potentially malignant disorders, correlate the clinical appearance and malignant transformation of these disorders for clinician's understanding of OPMD, which in turn can be helpful to take appropriate measures in patient management.

Methodology: In the systematic review process, 40 articles and 5 textbooks were reviewed. Literature search was done using Google search engine. Textbook references were done from institutional library.

Conclusion: Data from 5 textbooks and 27 articles were considered and it was concluded that clinical aspects of OPMD are of prime importance in predicting and preventing malignant transformation.

Key words: Etiology, Malignant transformation, Oral cancer, Potentially malignant

INTRODUCTION

Oral cancer is the most life threatening of all oral diseases. It has a prolonged natural history with oral potentially malignant disorders (OPMD) which were earlier termed as precancerous lesions and precancerous conditions. The recognition and diagnosis of OPMD will help in early treatment, patient survival and in reducing morbidity related to treatment of oral cancer. The most common oral cancer which is squamous cell carcinoma is correlated to OPMD. It has been well established that oral cancers are preceded with visible clinical changes in the oral mucosa usually in the form of white or red patch. Sometimes these oral lesions resemble each other clinically hence making biopsy mandatory for confirmation.[1] The clinical characteristics of OPMDs can show remarkable variations within the same histopathologically defined lesions which may be critical in assessing malignant transformation potential and thus may serve as an important prognostic marker.[2] Surgical treatment of oral cancer and effects of radiation may produce difficulty in speech, mastication, swallowing, and reduced ability for social interaction along with economic burden.[3] Correct diagnosis and timely treatment of OPMDs will help in preventing it's malignant transformation.[4] This article is an attempt to correlate the etiology, clinical appearance, and malignant transformation of these disorders and help clinicians in better understanding of OPMD for its early diagnosis and management.

In the systematic review process, 40 articles and five textbooks were reviewed. Data from five textbooks and 27 articles were considered. Other articles were excluded

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because there was repetition of information. Literature search was done using Google search engine. Textbook references were done from institutional library.

Concept of OPMD

Concept of malignant transformation in oral mucosa has been proposed for more than 100 years.[4] Clinical observation indicates that in a proportion of cases of squamous cell carcinoma in the mouth, they are preceded by or coexist with other distinctive oral mucosal lesion which are considered to be precancerous. It is suggested that these associated lesions occur more frequently than would be expected to arise and the implication is that these may be precursors of malignancies.[5]

Two stage mechanism hypothesis of carcinogenesis suggests that cells are first changed from normal to dormant tumor cells by some carcinogenic influence. At this phase of initiation tissue may be clinically and histologically normal. As there is subsequent exposure of initiated tissues to these carcinogenic agents, proliferation of dormant tumor cells results and a visible tumor is produced. Initiating agent causes carcinogenic alteration but not morphological change. Morphological alteration is caused by promoting action of same carcinogenic agent. It is unlikely that a single sudden event is responsible for malignant neoplasm. A progressive loss or diminished effectiveness of normal control mechanism on cell growth and division seems to be the more likely cause. It is reasonable that a stage would exist in which the epithelium was demonstrably abnormal, but had not invaded the underlying connective tissue. This stage is called as premalignancy or precancer.[5] Histological connotation to premalignancy is denoted by aberrant and uncoordinated cellular proliferation depicted basically at cellular level (atypia) and reflections of which could be seen at tissue level (dysplasia). Histopathological features of epithelial dysplasia as explained by Krammer in 1978 are as follows:[6]

- Loss of polarity of basal cells.
- Presence of more than one layer of cells having basaloid appearance.
- Increased nuclear to cytoplasmic ratio.
- Drop shaped rete processes.
- Irregular epithelial stratification.
- Increased number of mitotic figures.
- Presence of mitotic figures in superficial half of epithelium.
- Cellular pleomorphism.
- Nuclear hyperchromatism.
- Enlarged nucleoli.
- Reduction in cellular cohesion.
- Keratinization of single cells or cell groups in prickle cell layer.

Oral pathologists use this term epithelial dysplasia to describe the histopathological features of a tissue specimen which is associated with risk of malignant change and assign a grade of severity.[6] Dysplasia is graded as mild, moderate, severe, and carcinoma *in situ*. Mild epithelial dysplasia refers to alterations confined to basal and parabasal layers of epithelium. Moderate epithelial dysplasia shows involvement of basal layer and spinous layer up to its mid portion. Severe grade is given when epithelial dysplasia involves whole of basal and spinous layer. Carcinoma *in situ* refers to involvement of entire thickness of epithelium from basal to superficial most layer.[7]

Certain lesions denoted as premalignant are based on evidence that:

- In longitudinal studies areas of lesion identified as precancerous at first assessment have undergone malignant change during follow-up.
- Some of these alterations such as red and white mucosal changes are seen to coexist with squamous cell carcinoma at its margins.
- A proportion of these may share morphological and cytological changes observed in epithelial malignancies, but without frank invasion.
- Some of the molecular and genomic changes seen in oral cancers are detected in these precancerous or premalignant phases.[1]

Evolution of Terminologies

The term precancer was first described by Victor Babes in 1875. However, the concept of precancer was present since 1805 as suggested by a European panel of scientists. They described precancer as certain benign lesion which will always develop into invasive malignancy. Sir James Paget described a lesion of oral mucosa termed leukokeratosis of palate and tongue in smokers with an increased risk of conversion into malignant tumor. Later on various terminologies such as premalignancy, preneoplastic, carcinoma prone, and intraepithelial neoplasia were evolved and used by many researchers. The World Health Organization (WHO) workshop in 1978 proposed the term precancer for such lesions and classified them into precancerous lesions and conditions. The WHO defined precancerous lesion as morphologically altered tissue in which cancer is more likely to occur than its apparently normal counterpart and precancerous condition as a generalized state associated with significantly increased risk of cancer. Recent workshop of the WHO in 2005 proposed the term OPMD instead of classifying them as precancerous lesions and conditions since all these lesions may not transform into oral cancer. They also used the terminology "epithelial precursor lesion" to describe the same.[1]

Working Classification of OPMD

A comprehensive classification helps clinicians to develop a treatment algorithm. The working classifications

Table 1: Classification of OPMD based on clinical presentation

Red lesions	White lesions	Mixed red and white lesions
Erythroplakia	Leukoplakia	Speckled leukoplakia
Erosive lichen planus	Proliferative verrucous leukoplakia (PVL)	Oral submucous fibrosis
	Candidal leukoplakia	

OPMD: Oral potentially malignant disorders

Table 2: Classification of OPMD based on etiology

i. OPMDs related to habits	
1. Tobacco induced	Leukoplakia and its variants Erythroplakia Palatal lesion associated with reverse smoking
2. Areca nut induced	Oral submucous fibrosis
ii. OPMDs with no related habits	
1. Autoimmune diseases	Oral lichen planus Discoid lupus erythematosus Graft versus host disease
2. Nutritional deficiencies	Plummer Vinson syndrome Oral epithelial atrophy associated with Vitamin B deficiency
3. Infections	Hyperplastic candidiasis Syphilis
4. UV radiation induced	Actinic cheilitis Keratoacanthoma
5. Immunodeficiency diseases	Blooms syndrome Fanconi's anemia
6. Genodermatosis	Epidermolysis bullosa Dyskeratosis congenita Xeroderma Pigmentosum
7. Immunosuppressive states	Solid organ transplantation AIDS

OPMD: Oral potentially malignant disorders

formulated in this article is an attempt to categorize OPMD based on etiopathogenesis, clinical presentation, and risk of malignant transformation [Tables 1-3].

Discussion of Various OPMD

A clinician comes across various OPMD in their routine practice. Clinical presentation and its correlation with risk of malignant transformation of these commonly encountered OPMD are discussed below:

1. Leukoplakia

It is a precancerous white lesion defined by the WHO as "white plaque of questionable risk having excluded other known diseases or disorders that carry no increased risk for cancer."[8] Use of the term "disorder" is preferred than "lesion" since malignant transformation does not always take place in leukoplakia areas. It has an increased prevalence among adult males and the most common etiologic factor is tobacco use. Leukoplakia may occur in non-users of tobacco as well.[9] Clinically, this disorder can be classified as homogenous and non-homogenous. The homogenous type is thin, flat, and uniform white plaque which is demarcated from surrounding normal appearing tissues.[8] Non-homogenous type is characterized by well demarcated raised white areas interspersed with erythematous areas.[7] Proliferative verrucous leukoplakia, considered as a form of non-homogenous leukoplakia, has a different clinical presentation. It is more common in elderly females; only < 40% of cases are associated with tobacco and has a significantly increased risk of malignant transformation than other forms of leukoplakia. Erythematous areas, areas of firmness, or induration and ulcerated areas should always be submitted for biopsy.[8] Leukoplakia is a clinical term and histologically it is reported with note on presence or absence of epithelial dysplasia. Dysplasia is graded based on the extent and degree of cytological atypia. The WHO 2005 grading of dysplasia based on architectural disturbances and cytological atypia is as follows:[10]

Grade 1: Squamous hyperplasia
Grade 2: Mild dysplasia
Grade 3: Moderate dysplasia
Grade 4: Severe dysplasia
Grade 5: Carcinoma in situ

Risk of malignant transformation in homogenous leukoplakia is only 0.6–5%, whereas in non-homogenous leukoplakia it is high as 20–25%.[2] Proliferative verrucous leukoplakia shows higher risk of malignant transformation between 70% and 100%.[8]

2. Erythroplakia

Erythroplakia refers to a red patch that cannot be categorized clinically or pathologically as any other condition. It is considered as the most severe form of OPMD because of its high malignant transformation potential.[11] Shear classified erythroplakia into three variants.

- Homogenous erythroplakia – flat, velvety lesion with uniform red appearance.
- Granular erythroplakia – red lesion with granular appearance.
- Speckled erythroplakia – predominantly red lesion speckled with white spots.[3]

Table 3: Classification of OPMD based on risk of malignant transformation

High risk OPMD	Intermediate risk OPMD	Low risk OPMD
Erythroplakia	Non homogenous leukoplakia	Homogenous leukoplakia
Proliferative verrucous leukoplakia	Palatal lesion associated with reverse smoking	Erosive lichen planus
	Oral submucous fibrosis	Discoid lupus erythematosus
	Candidal leukoplakia	Oral epithelial atrophy associated with nutritional deficiency

OPMD: Oral potentially malignant disorders

Erythroplakia possess a malignant transformation risk of 90%. According to Shafer and Waldron, 51% of erythroplakia at the time of diagnosis were squamous cell carcinoma histologically, 40% were carcinoma *in situ*, and 9% were mild-to-moderate dysplasias.

3. Oral submucous fibrosis

It is a chronic progressive potentially malignant disorder predominantly seen in people of Asian descent with areca nut chewing being the most important etiologic factor. Clinically, patient presents with trismus along with restricted movement of tongue, lips, and palate which can be attributed to presence of fibrosis histologically. Initial signs and symptoms include vesicle formation, blanching of mucosa and intolerance to spicy food stuffs. Arecoline is the most abundant alkaloid in areca nut and these alkaloids undergo nitrosation and give rise to N-nitrosamines, which might have a cytotoxic effect on cells. Arecoline has been demonstrated to promote collagen synthesis due to its effect on TGF-β. Arecoline activates TGF-β thus stimulating collagen synthesis.

Three main events that are modulated by TGF-β, which favors the collagen production are:

1. Activation of procollagen genes.
2. Elevation of procollagen proteinases levels: (a) Procollagen C-proteinase (PCP)/bone morphogenetic protein1 (BMP1) and (b) procollagen N-proteinase (PNP).
3. Upregulation of lysyl oxidase (LOX) activity.[12]

TGF-β activates the genes for Tissue Inhibitor of Matrix Metalloproteinases (TIMP), thereby more TIMP is formed. This inhibits the activated collagenase enzyme that is necessary for the degradation of collagen. Thus, TGF-β also causes fibrosis by its influence on collagen degradation pathway. Lysyl oxidase, the enzyme required for collagen cross linking is activated by copper. Arecanut is rich in copper, thus increasing the collagen crosslinking and organization of extracellular matrix. Malignant potential of OSF was first described by Paymaster in 1956. Risk of transformation into oral squamous cell carcinoma was found to be 7–13%.[13]

4. Palatal lesion associated with reverse smoking

In reverse smoking habit, cigarette is placed in reverse direction inside the mouth which leads to certain changes in palate which are considered to be potentially malignant. Clinically, it may present with keratosis, excrescence, patches, redness, ulcerations, and non-pigmented areas.[6] Histopathological findings include hyperorthokeratosis, dysplasia, and increased melanin containing cells in basal layer.[14] According to Alvarez Gomez, 12.5% cases showed squamous cell carcinoma histologically.[4]

5. Oral lichen planus

Lichen planus is a chronic, immune mediated mucocutaneous disorder. It involves skin and oral mucosa commonly and can also occasionally involve genital mucosa, nails, and scalp. The prevalence of oral lichen planus worldwide is 0.5–2.6%. The lesion carries a female predilection and is common after fifth decade of life. Clinically, oral lichen planus exhibits reticular, white plaques which are characteristically seen symmetrically on bilateral buccal mucosa. Reticular appearance is due to the presence of interlacing white lines termed as Wickham's striae. It may also show erosive or ulcerative lesions which may be symptomatic. Based on clinical appearance, different types of lichen planus are described which include reticular lichen planus, erosive lichen planus, bullous lichen planus, atrophic lichen planus, papular lichen planus, and plaque like lichen planus.[15]

Cell mediated immunity plays an important role in pathogenesis of lichen planus. Lichen planus antigen induces CD8+ T lymphocytes which are recruited and retained in the subepithelial connective tissue. These lymphocytes induce basal keratinocyte apoptosis by release of cytokines. Thus, histologically lichen planus shows basal cell degeneration producing civatte/hyaline/cytoid bodies and subepithelial band of lymphocytes.[16] Other histological features include hyperkeratosis, focal thickening of spinous layer of epithelium (responsible for Wickham's striae clinically), and saw toothed rete pegs.[15]

Malignant potential of lichen planus is much debated in recent years. The erosive lichen planus possess malignant transformation potential of 1–2%. Even though the etiology of malignant transformation is uncertain, it is thought to be due to the genetic alteration in epithelial cells as a result of persistent increase in levels of cytokines.[15]

6. Candidal leukoplakia (Chronic hyperplastic candidiasis)

Chronic hyperplastic candidiasis is the least common of all variants of candidiasis comprising only 5%.[17] Clinically, it appears as a white nonscrapable plaque on buccal mucosa, tongue, and oral commissures bilaterally and is classified under OPMD in recent WHO classification.[18] Carcinogenic nitrosamines and acetaldehyde which are released by candida albicans are the probabale explanation of malignant transformation in chronic hyperplastic candidiasis. A microenvironment of chronic inflammation will also favor carcinogenesis. Malignant transformation is described in 10% of reported cases.[19] Tobacco use along with candidiasis may increase this risk due to reduction of IgA levels in saliva and impaired neutrophil function.[17]

7. Actinic cheilitis

Actinic cheilitis appears clinically as an ulcerative crust forming lesion of vermilion border of lower lip and

histologically as hyperkeratosis with or without dysplasia.[7] Risk of the development of dysplasia and squamous cell carcinoma of lip in actinic cheilitis is found to be 6–10%.[4]

8. Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is an auto immune collagen vascular disease characterized by scaly patches which heal with atrophy, scarring, and pigmentation. DLE represents cutaneous form in which systemic symptoms are not seen whereas systemic lupus erythematosus shows systemic symptoms. Somatic mutations in genes coding for lymphocytic stem cells resulting in production autoantibodies are implicated in pathogenesis of DLE.[20]

Oral lesions of DLE are mostly identical to lichen planus characterized by ulcerated or atrophic central zone with radiating white striae on periphery. However, it is rarely seen in oral mucosa in the absence of skin lesions unlike lichen planus. Histopathologically, DLE shows hyperkeratosis, alternate atrophy, and thickening of spinous layer, basal cell degeneration, diffuse lymphocytic infiltrate, PAS positive material in basement membrane zone, and subepithelial edema.[7]

Carcinoma of skin from cutaneous DLE and its healed scar (both squamous cell carcinoma and basal cell carcinoma) is between 3.3 and 3.4%. Malignant transformation may be as late as 20 years after the occurrence of DLE. Neoplastic transformation of DLE to malignant fibrous histiocytoma and atypical fibroxanthoma is also reported.[20,21]

9. Plummer–Vinson syndrome

Plummer–Vinson syndrome is a severe form of iron deficiency anemia characterized by esophageal webs, koilonychia, and glossitis.[6] Deficiency of iron dependent enzymes and high turnover rate in epithelium of esophagus makes it vulnerable to DNA damage resulting in epithelial changes and malignant transformation especially in young individuals.[22] It possesses 3–15% risk of development of squamous cell carcinoma of the upper gastrointestinal tract.[23]

10. Syphilitic glossitis

Syphilis is bacterial infection caused by spirochete, *Treponema pallidum*. Lesion on tongue in secondary syphilis occurs as spirochetes have affinity to mobile tissues and these lesions possess increased risk malignant transformation. This risk may be attributed to vasculitis and obliterative endarteritis caused by *Treponema pallidum* resulting in circulatory deficiency of lingual papillae leading to its atrophy. Atrophic epithelium may predispose to the development of oral leukoplakia which, in turn, can transform into squamous cell carcinoma.[24] Arsenic agents used for the treatment of syphilis in the past were also thought to be an etiology for malignant transformation.[7]

11. Graft versus host disease (GVHD)

GVHD is a common complication of allogenic bone marrow transplant. Oral GVHD predisposes to oral cancer and is unrelated to tobacco exposure. The reason for malignant transformation into squamous cell carcinoma is attributed to immunological injury of chronically inflamed oral epithelium which may arise after many years of post-transplantation unlike secondary hematological malignancies which are immediate complications associated with GVHD.[25]

12. Epidermolysis bullosa

It is blistering genodermatosis which exhibit oral involvement in two of its types which are junctional and dystrophic epidermolysis bullosa. These types also exhibit malignant potential and in oral cavity epidermolysis bullosa affecting tongue possess an increased risk of malignant transformation.[4] Similar genodermatosis such as dyskeratosis congenita also predispose to oral leukoplakia and carcinoma.[26]

Various immunosuppressant states also predispose oral mucosa to squamous cell carcinoma. Immunosuppression due to use of immunosuppressant drugs following organ transplantation leads to DNA mutation in epithelial cells.[27] Even though HIV infection also causes immunosuppression, oral and laryngeal cancer in HIV patients is suggested to be due to their synergistic interaction with HPV and HSV viruses.[28]

Vitamin B deficiencies cause epithelial atrophy which in rare instances is prone to develop epithelial dysplasia.[5,29]

Apart from the lesions discussed above, other lesions like long standing tobacco pouch keratosis which does not regress even after tobacco habit cessation does show significant epithelial dysplasia with a risk for malignant transformation. Hence, these lesions should also be considered as OPMD and biopsy should be performed.[30]

Risk Factors for Malignant Transformation

Risk of malignant transformation varies greatly between various above discussed OPMD. Clinical variables that may determine malignant transformation are summarized below:[31,32]

- Site – OPMD if present on ventral surface of tongue and floor of mouth may show greater malignant transformation potential when compared to other sites.
- Increasing age and female gender can contribute to increased risk of malignancy.
- OPMD that occurs in non-users of tobacco possess greater risk of oral cancer.
- Synergistic effects of tobacco and alcohol carry higher risk of cancerous changes when compared to use of tobacco alone.
- Changes such as erythema and ulceration may be indications to probable malignant transformation.

CONCLUSION

Dental professionals play a key role in early identification of both habit related and non-habit related mucosal disorders. Development of OPMD and oral cancer is multistep process involving genetic changes due to exogenous and endogenous factors. Since there is currently no molecular and even histopathological pathognomonic hallmark that can predict malignant transformation of OPMD, the analysis of clinical aspect of these lesions remains the best way to control and prevents the development of oral squamous cell carcinoma.

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