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Review Article

Immunohistochemical Verification of Oral Dysplasia, Premalignant Lesions and Oral Cancer by Use of Varied Expression of Cytokeratins; A Review

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ABSTRACT

Oral cancer, predominantly squamous cell carcinoma, carries high morbidity and disease burden all over the world. Evaluation of the cellular basis of oral carcinogenesis has implied dysregulation in cytokeratins as one of the contributory factors. These intermediate filament proteins of the oral epithelium, guardian of cellular architecture, are known to maintain cellular interactions and are involved in various cell cycle regulation pathways. Oral premalignancy and neoplastic progression are often depicted by disturbed and/or haphazard expression of these cytokeratins. We present a summarized analysis of cytokeratins and explore their diagnostic potential using immunohistochemistry. CK 8/18 is a significant and reliable biomarker of oral precancer and cancer that can be utilized in addition to histopathology for early malignancy screening and intervention.

Moreover, dysplastic oral lesions are attributed to downregulation and/or gradual disappearance of CK 4/13, CK 5/14, and expression of CK 17. Increasing the diagnostic strategy using immunohistochemical techniques on specific cytokeratins and extensive sample studies on premalignant lesions, dysplasia, and oral squamous cell carcinoma can open up many possibilities. Utilizing the enhanced diagnostic spectrum of specific cytokeratins can help clinicians and dental specialists diagnose early, thus timely managing and alleviating suffering associated with oral cancer.

Keywords: Oral cancer, dysplasia, premalignant lesions, cytokeratins, CK 8/18, immunohistochemistry, oral squamous cell carcinoma, leukoplakia, oral epithelium, keratins, oral premalignant lesions, biomarker.

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INTRODUCTION

Oral cancer: squamous cell carcinoma belongs to 6thmalignancy amongst all cancers. According to WHO, with a 5-year survival rate of 45-60%, late diagnosis is one of the factors corresponding to increased mortality and morbidity.[1] The tongue and floor of the mouth are the most common sites affected. It is often preceded by oral potentially premalignant lesions, which include leukoplakia, erythroplakia, oral submucous fibrosis, lichen planus, actinic keratosis, and epidermolysis bullosa. Not all potentially malignant lesions run to the course of oral cancer, but it has been reported that 8-10% of premalignant lesions turn into oral cancer.[2,3]

Oral malignancy, with its wide and multifactorial aetiology including genetics, local risk factors, and various carcinogens, e.g., smoking, tobacco, betel and quid, is unpredictable in its behaviour right from a white patch lesion to dysplasia and invasive carcinoma, however, prevention is better than cure can hold in this case also as with other diseases.[1] Increasing diagnostics and screening methods before a lesion becomes malignant can help. Immunohistochemistry (IHC) to screen for molecular markers such as p53, Ki 67, and AE1 and AE3 early in a dysplastic oral lesion, which otherwise is clinically designated as leukoplakia, and therefore early excision of the lesion can somehow decrease the worst prognosis associated with oral malignancy.[4] AE1 and AE3, known as Pan-cytokeratin, detect keratins/cytokeratins in epithelium and carcinomas by immunohistochemistry. The multifaceted role of detection of these molecular markers helps detect metastases in lymph nodes, tumour invasion and budding in carcinomas, and epithelial origin of neoplasms. IHC for keratins also has prognostic differential when isolated tumour islands and micrometastasis are associated with poor prognosis in stage 1 lung adenocarcinoma, gastric cancer and squamous cell carcinoma of the tongue.[5]

THE BASICS ABOUT KERATINS IN THE ORAL CAVITY

The oral cavity with stratified squamous epithelium is resilient to thermal stimuli, mechanical pressure and chemical imbalances by the diversified

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distribution of these cytokeratins/keratins divided into high and low molecular-weight keratins. These keratins are part of cellular architecture's cytoskeleton/structural proteins, which have varying functions depending upon their distribution.[6] The epithelium in the oral cavity is keratinized and non-keratinized in differing distributions, henceforth the varied presence of keratin groups in these locations. Type 1 (Acidic 9-19) and Type 2 (Basic 1-8) are broadly divided into two groups. All sites in the oral cavity express CK 5 and 14 pairs in the basal layer, CK 10,1, 4, 13 in the suprabasal layer of epithelium. Buccal mucosa, a non-keratinized epithelium, has CK 5, 14 in the basal layer and 4, 13 in the suprabasal layer. Meanwhile, the keratinizing epithelium gingiva has CK 5, 14 in the basal layer and CK 1,10 in the suprabasal layer.

ORAL PATHOLOGIES RELATED TO ALTERED KERATINS

The beneficial effect of keratins in maintaining cellular architecture cannot be disregarded because various lesions, both inherited and acquired, of the oral cavity arise due to defects in their expression. White sponge naevus is a hereditary disorder of keratin expression where mutations in genes for CK 4,13 result in bilateral white plaques in the oral cavity, histopathological evidence of hyperparakeratosis, and keratin condensation around nuclei is present. Hyperkeratosis is inherent in various acquired keratitis disorders, e.g., lichen planus, frictional keratosis, tobacco-related keratosis, and hairy leukoplakia. Various premalignant and malignant lesions also have different appearances or disappearances of keratins in the epithelium, which, if diagnosed early, can be promptly identified and managed. Hyperkeratosis is present in leukoplakia and actinic cheilitis, whereas squamous cell carcinoma is characterized by dyskeratosis, aberrant distribution of normal keratin pairs, presence of keratin pearls, and presence of CK 8,18 in areas of dysplasia.[1,6,7]

IMMUNOHISTOCHEMISTRY, A DIAGNOSTIC TOOL

AE1/AE3, as a molecular marker in immunohistochemistry (IHC), detects all keratins in oral malignancies and other neoplasms without differentiating between their groups, finding about epithelial or glandular nature of various neoplasms as there is a significant difference between keratins expression in simple and glandular epithelium.[5,8] Various studies have pointed out variable expressions of CK 4, 13, 5, 6, 8, 18, 17, and 19 in the standard dysplastic, premalignant epithelium, and squamous cell carcinoma.[1,8] Focusing on one specific keratin by molecular diagnostics can give a possible clue as to when oral epithelium undergoes differentiation, dedifferentiation, or gets entirely phenotypically altered, as in carcinomas.

LOSS OR DOWN-REGULATION OF CYTOKERATIN 4 AND 13 IN DYSPLASIA

As mentioned earlier, CK 4, 13 is localized and diffusely expressed in the suprabasal epithelium of keratinized buccal mucosa in a healthy state. Its disappearance or downregulation is a common observation in dysplasia of the oral cavity, which is clinically visible as either a simple white patch or leukoplakia. Katsube *et al*. reported the decreased appearance of both CK 4 and 13 in epithelial dysplasia and squamous cell carcinoma by IHC with associated change in the appearance of the oral epithelium.[9] Another study investigating the role of cytokeratins in dysplasia revealed a significant difference between mild and moderate dysplasia. There was a difference in staining intensity for CK 13. Moderate dysplastic epithelium and dysplasia with Carcinoma in Situ (CIS) were weakly positive for CK 13 compared to mild dysplasia, where more epithelial cells were positive.[10] Kiani *et al*. reported decreased immunohistochemical expression of CK 13 with increased severity of dysplasia and invasive carcinoma.[11] This pair of keratins, i.e., CK 4 and 13, is related to cell differentiation in the stratified epithelium. Therefore, its loss is associated with severe dysplasia and poor prognosis in squamous cell carcinoma, as indicated by Dmello *et al*. in their study on cell differentiation type keratins.[12] Among other markers that have prognostic significance in oral dysplasia, e.g., p53 genomic marker Ki67 proliferation marker, which is mainly used to differentiate oral dysplasia from normal mucosa, only CK 13 is comparable to Ki67 as a cell differentiation marker where there is a loss of its expression beyond a certain degree of dysplasia.[13] In several studies comparing CK 13 expression in non-neoplastic and neoplastic mucosa, there has been evidence of a decrease and complete loss of expression of CK 13 in cellular atypia, severe dysplasia and invasive carcinomas, indicating that it can be used as a valuable immunohistochemical diagnostic tool in oral pathologies.[11,14]

ALTERATION IN CYTOKERATIN 5, 14 PROFILE

Cytokeratin 5 and 14 are usually present in the basal layer of oral epithelium in both keratinized and non-keratinized mucosa in a healthy state [7,15] and are related to the cell proliferation cycle.[12] Regarding its change in leukoplakia, oral submucous fibrosis and squamous cell carcinomas, this pair is completely lost, indicating its significance in cell cycle regulation.[1] CK 5 increases in intensity in some studies on dysplasia associated with smoking and tobacco, implying its intense staining with increasing grades of dysplasia is an essential additional marker to detect dysplasia early before it turns into squamous cell carcinoma.[16] In one of the studies on leukoplakia, in order to categorize it into high- and low-grade dysplasia, there was a progressive decrease in the number of cells positive for immunohistochemical expression for CK 14 in low-grade dysplasia, high-grade dysplasia and squamous cell carcinoma indicating that it can be used to early detect and possibly grade dysplasia in leukoplakia which is one of the premalignant lesion.[17]

Oral submucous fibrosis, another premalignant lesion of the oral cavity, characterized by progressive fibrosis, deposition of excessive collagen in the connective tissue beneath the epithelium, that can change into true malignant neoplasm in 1.5-15% of cases has been researched for CK 5 and 14 by IHC. There has been evidence of decreased CK 5 and 14 expressions compared to standard oral epithelium.[18, 19]

NEOEXPRESSION OF CYTOKERATIN 17

CK 17 is a keratin localized to basal and myoepithelial cells and glandular epithelium but not present in the stratified squamous epithelium of oral mucosa. It has been identified in basal cell carcinoma and expressed upon cell injury and inflammation.[20] Its expression in dysplasia and oral squamous cell carcinoma results from repeated alterations in cell cycle regulation involving various pathways that evade apoptosis and cause limitless growth of tumour cells. Keratin, whose expression is only related to dysplasia and various grades of squamous cell carcinoma not ubiquitously expressed in healthy oral epithelium, carries confirming potential in histopathology and molecular diagnostics.[21] Sanguansin and associates have summarized the increasing prevalence of CK 17 in invasive carcinoma as compared to in non-neoplastic cells and the proportional increase in no. of tumour cells positive for CK 17 (69% and 87% cells in samples of dysplasia and OSCC). Oral leukoplakia with dysplasia has also shown immunoreactivity to CK 17 in basal, parabasal and prickle cell layers compared to only the prickle cell layer in OL without dysplasia.[22]

RELEVANCE OF CYTOKERATIN 8 & 18 TO ORAL PREMALIGNANCY AND CARCINOGENESIS

CK 8/18, also called simple epithelium keratin, is part of cellular architecture in the normal glandular and transitional epithelium and is expressed by liver epithelial cells.[23] Various studies have emphasized CK 8/18's role in cell differentiation and transformation. It is related to the alpha6beta4 integrin pathway, a tumour promoter pathway that contributes to increased cellular invasion and enhanced oncogenic potential, leading to the progression of epithelial cells towards neoplasia.[24]

AMPLIFICATION OF NEOPLASTIC PROGRESSION

The downregulation of CK8/18 is associated with reduced neoplastic progression in cells derived from oral squamous cell carcinoma. Furthermore, artificial induction of CK 8 in cells derived from human buccal mucosa has resulted in transformed phenotype, malignant potential, dysplasia and carcinoma in rat lingual mucosa.[24,12] Comparative analysis of the presence of CK8/18 in various studies has found it to be prevalent in dysplasia, leukoplakia (premalignant lesions) and oral squamous cell carcinoma but not detected in benign inflammatory lesions of the oral mucosa, making it a promising biomarker for early detection of neoplastic change.[25,26,27]

PROGNOSTIC IMPLICATIONS OF CYTOKERATIN 8 & 18

CK 8/18 detection in histopathologically proven oral squamous cell carcinoma has various prognostic implications. Its enhanced expression in poorly differentiated tumours is a hallmark of poor prognosis, contrary to its normal appearance in the cellular architecture of the early embryonic phase. The developmental stage of cellular organization and differentiation when human buccal and tongue epithelium are positive for CK 8/18 is until 27 weeks of gestation.[1,28]

EFFECT OF CYTOKERATIN 8 & 18 EXPRESSION TO HISTOLOGICAL GRADE OF DYSPLASIA AND ORAL SQUAMOUS CELL CARCINOMA

The higher stage is associated with increased local recurrence and depth of invasion, and the higher stage is associated with increased expression of CK 8/18 in oropharyngeal squamous cell carcinoma, thereby

associated with poor prognostic potential.[29] True expression of CK 8 is also widely prevalent in all stages of dysplasia and malignancy, including its presence in lymph nodes and metastasis. It provides clues about the origin of neoplasia, except for the larynx and tongue in head and neck carcinogenesis.[30]

The suprabasal expression of CK 8/18 has also been a clue for the neoplastic transformation of mucosal epithelium in addition to its de novo expression in leukoplakia with dysplasia where it is more likely to turn into malignancy and, therefore, poor prognosis. Therefore, early adjunctive aid using IHC to grade leukoplakia can help with the prevention and progression of oral cancer.[31] Combining the histological grading and staging with molecular markers such as CK 1,8, and 18 in dysplasia and squamous cell carcinoma has been studied, and a consensus is there regarding their utility in determining the course of disease beforehand in oral premalignant lesions and oral cancer.[32,33]

ROLE OF CYTOKERATIN 8 AND 18 IN FIELD CANCERIZATION AND MONITORING RESPONSE TO THERAPY

The important diagnostic differential of cytokeratins is corroborated by the fact that their serum markers, such as Cytokeratin Fragment(CYFRA-21-1), Tissue Polypeptide Antigen (TPA), and Tissue Polypeptide Specific Antigen (TPS), have disinterred and recognized soluble fragments of CK 8, 18, and 19, disintegrated from tumour cells, in blood and body fluids and have 60% sensitivity and specificity in head and neck carcinomas. These serum markers for CKs also carry a potential for targeted immune and radiotherapy, monitoring efficacy and follow-up to various treatment modalities.[34] OfOf another mechanism involved in cancer pathogenesis is the presence of cancer stem cells, which is a group of cells in the uninvolved adjacent normal tissue responsible for cancer initiation and progression and are resistant to treatment likely to cause recurrence, owing to their demonstration of CK 8,18,19, by a process called field cancerization and therefore elucidating the role of cytokeratins in disease presentation in normal uninvolved buccal mucosa adjacent to neoplastic mucosa.[35]

ANALYSIS OF CYTOKERATIN 19 EXPRESSION

Cytokeratin 19, one of the smallest acidic group keratins, is a simple epithelial keratin that is expressed by the basal layer (non-keratinized), suprabasal layer in transitional oral epithelium, and ductal epithelium in salivary glands. This keratin is unique in its dual nature of being present in a healthy and diseased stratified oral epithelium.[36,15] Various studies pointing it to be used as a marker for evaluation of premalignancy and malignancy of oral epithelium have found it to be prevalent in all, i.e., inflammatory, hyperplastic and neoplastic lesions. Therefore, there is a consensus that its appearance alone cannot be regarded as a specific marker of the advent of malignancy in oral lesions.[1,15,28,29] One exception is its appearance in the suprabasal layer of oral epithelium, which correlates with various grades of dysplasia and early invasive squamous cell carcinoma lesions.[15,20] Ali *et al*. concluded in their study a gradual increase in staining of squamous cells with CK 19 in hyperplasia, dysplasia and well and poorly-differentiated squamous cell carcinoma, indicating a possible role of acidic keratins in oral carcinogenesis.[37] Smoking is one of the risk factors in the pathogenesis of neoplasia. However, its molecular effect in altered cells has been corroborated by this finding that there is an intense expression of CK19, 8,18, in the inflamed periodontium and gingiva of smokers, whereas less staining in PDL architecture with good oral health without any smoking history.[38] The prognostic differential of oral squamous cell carcinoma is also affected by changed keratin profile as discovered by Lee *et al*. when increased CK19 at the time of diagnosis also relates to more chance of higher stage or grade and metastasis due to increased disruption of extracellular matrix reflecting limitless replicating potential which is one of the hallmarks of cancer.[29,39] Henceforth, decreased expression of CK19 is associated with better 5-year survival and good prognosis in squamous cell carcinoma.[29]

RECOMMENDATIONS

While navigating the diagnostic dimension of cytokeratins using immunohistochemistry for premalignant lesions, leukoplakia, and oral squamous cell carcinoma, we suggest the following key elements of consideration:

1. For any suspicious oral lesion for which surgical biopsy is deemed necessary for histopathological diagnosis, screening for the molecular marker CK 8/18 is also recommended. The presence of this simple keratin in areas of oral mucosa where it is not normally present could indicate some disparity in cell cycle regulation, a probability of dysplasia, tumour invasion, and/or carcinogenesis.

2. Prospective large sample immunohistochemical studies for oral submucous fibrosis, leukoplakia, erythroplakia, and dysplasia for CK 8/18, 17 to further enhance the diagnostic utility and early mitigation of disease.
3. Loss or aberrant distribution of specific keratins CK 4/13 and CK 5/14 inherent to oral epithelium also indicates a transformed oral lesion.

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CONCLUSION

Keratins, owing to their unique function in cell proliferation, differentiation and specialization, can give a clue about altered cellular profiles. Immunohistochemical expression of CK 8/18 in leukoplakic and dysplastic lesions is an early sign of a transformed lesion. Therefore, adjunctive aid to histopathology in diagnosing oral premalignant and malignant pathologies, early management of excision of a small lesion or utilizing targeted drug therapies that work on molecular pathways, improving prognosis in malignancies. Likewise, gradual loss or disappearance of differentiation-specific keratins CK 4/13, 5/14 and expression of CK 17 by IHC can also give a clue about modified and switched over phenotype of oral lesions, including varying grades of dysplasia and invasion, which can be further used to classify oral lesions and treatment regime recommendations can be proposed according to the condition.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AW & TS: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

FK: Data acquisition, data analysis, approval of the final version to be published.

NZ: Critical review, concept, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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