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New Ray of Hope in Prognosis-Significance of Clinical, Histopathological and Biological Characteristics among Potentially Malignant Disorders and Oral Cancer– Case Series

G. Sathees Chandramouli[1*], CH. Uma Reddy[1], A. Steffina Lydia Jascinth[1], M. Anitha[1] and B. R. Sathvikalakshmi[1]

[1]Department of Oral Medicine and Radiology, Best Dental Science College, Tamil Nadu Dr. M. G. R Medical University, Ultra Nagar, Madurai-625104,Tamil Nadu, India.

Authors' contributions

This work was carried out in collaboration between all authors. Author GSC designed the study, performed the statistical analysis, wrote the protocol and first draft of the manuscript. Authors CUR and ASLJ managed the analyses of the study. Author MA managed the literature searches. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Early detection of disease progression remains a challenging task mainly due to the lack of adequate early predictive markers. It is necessary to consider the biological behaviour and underlined molecular events while selecting treatment modalities in order to get the better outcome of oral potentially malignant disorders (OPMD) and oral cancer. The aim of the study was to evaluate Cytokeratin (CK) and vimentin expression in pre and post-treatment status of Oral leukoplakia, Oral sub mucous fibrosis (OSMF), Oral squamous cell carcinoma (OSCC) using Immunohistochemistry (IHC). These markers serve as prognostic indicators.

Keywords: Cytokeratins; vimentin; oral potentially malignant disorders.

**Corresponding author: E-mail: drsatheeschandra@yahoo.co.in;*

1. INTRODUCTION

The term "potentially malignant disorders" was defined by World Health Organization (WHO) as the risk of malignancy being present in a lesion or condition either during the time of initial diagnosis or at a future date. WHO also classified PMDs into two subgroups as follows: a) precancerous lesion, a benign lesion with morphologically altered tissue, which has a greater than normal risk of transforming into malignancy; b) precancerous condition, a disease or patients' habit that does not necessarily alter the clinical appearance of local tissues but is associated with a greater than normal risk of precancerous lesion or cancer development in that tissue. Many oral squamous cell carcinomas develop from potentially malignant disorders (PMDs) [1]. Ability of current clinical/histological methods to predict high-risk precursor lesions for the conversion of malignant transformation is limited. The existing imaging modalities are also not sensitive enough for the early diagnosis. Molecular biological markers have been suggested to be of value in the diagnosis and prognostic evaluation of OPMD [2]. Cytokeratin is an intermediate filament protein, which is found in most of the simple and non-keratinizing stratified epithelia. It has been shown as a useful marker of cellular atypia, associated with malignant lesions in the oral epithelium [3]. Vimentin is type III intermediate filament (IF) protein of mesenchymal cells and its expression has been correlated with poor prognosis in various types of carcinomas including OSCC [4]. Vimentin expression is significantly enhanced in cell growth, cell cycling, tumor differentiation, and during the process of tumorigenesis.

2. MATERIALS AND METHODS

The proposed research was submitted to the institutional board of review and ethical clearance was obtained. This study was conducted in the department of Oral Medicine and Radiology after obtaining informed consent from the participants. This study was done in three patients who were clinically diagnosed as oral leukoplakia, oral sub mucous fibrosis and oral squamous cell carcinoma with 18 years or above to consent for biopsy of lesions, to evaluate the expression of vimentin and CK as a prognostic indicator in pre and post-treatment using Immunohistochemistry.

Immuno-reactivity was divided into four categories and defined as follows:

<5% (/no), 6–30% (+/low), 31–50% (++/moderate) and >51% (+++/intense) [5].

2.1 Case 1

A male patient age of 33 years came with the complaint of burning sensation and restricted mouth opening for the past 7 months to the Department of oral medicine and Radiology. He gave a personal history of areca nut chewing habit for past 3 years and an alcoholic with the frequency of 3 days in a week. On intraoral examination mucosal pallor and marble-like appearance with blanching seen in both right and left buccal mucosa. Limitation in the opening of the mouth was noted with inter incisal width of 29 mm. Based on personal history, clinical features and clinical examination, a provisional diagnosis of Oral sub mucous fibrosis involving right and left buccal mucosa (Grade III) was made [6]. After histopathological examination it was confirmed that oral sub mucous fibrosis and pre-assessment was done. The patient was advised to quit the habit of betel nut chewing. He was given antioxidants with the combination of lycopene, micronutrients like zinc and selenium for 4 months. Intra lesional injection of hyaluronidase 1500 IU mixed with 1 ml of dexamethasone was given 2 times in a week for four weeks [7]. After 6 months of treatment his mouth opening was much improved (inter incisal width 33 mm) and burning sensation was completely resolved. Post-treatment, patient was assessed for tumour markers cytokeratin and Vimentin.

Results

Pre and post treatment Cytokeratins and Vimentin levels were compared and pretreatment specimen of cytokeratin was intense and post treatment specimen of cytokeratin was moderate and vimentin remained same.

2.2 Case 2

A male patient aged 42 years came with the complaint of burning sensation in his mouth for past 6 months. He had a smoking habit for past 12 years and he smokes 10 cigarettes per day in 1- hour interval. Based on clinical appearance and personal history it was provisionally diagnosed as speckled leukoplakia [8] on the left buccal mucosa. Histopathological examination showed epithelial hyperplasia with mild dysplasia favouring the diagnosis of leukoplakia. Further tissue specimen was subjected for assessment

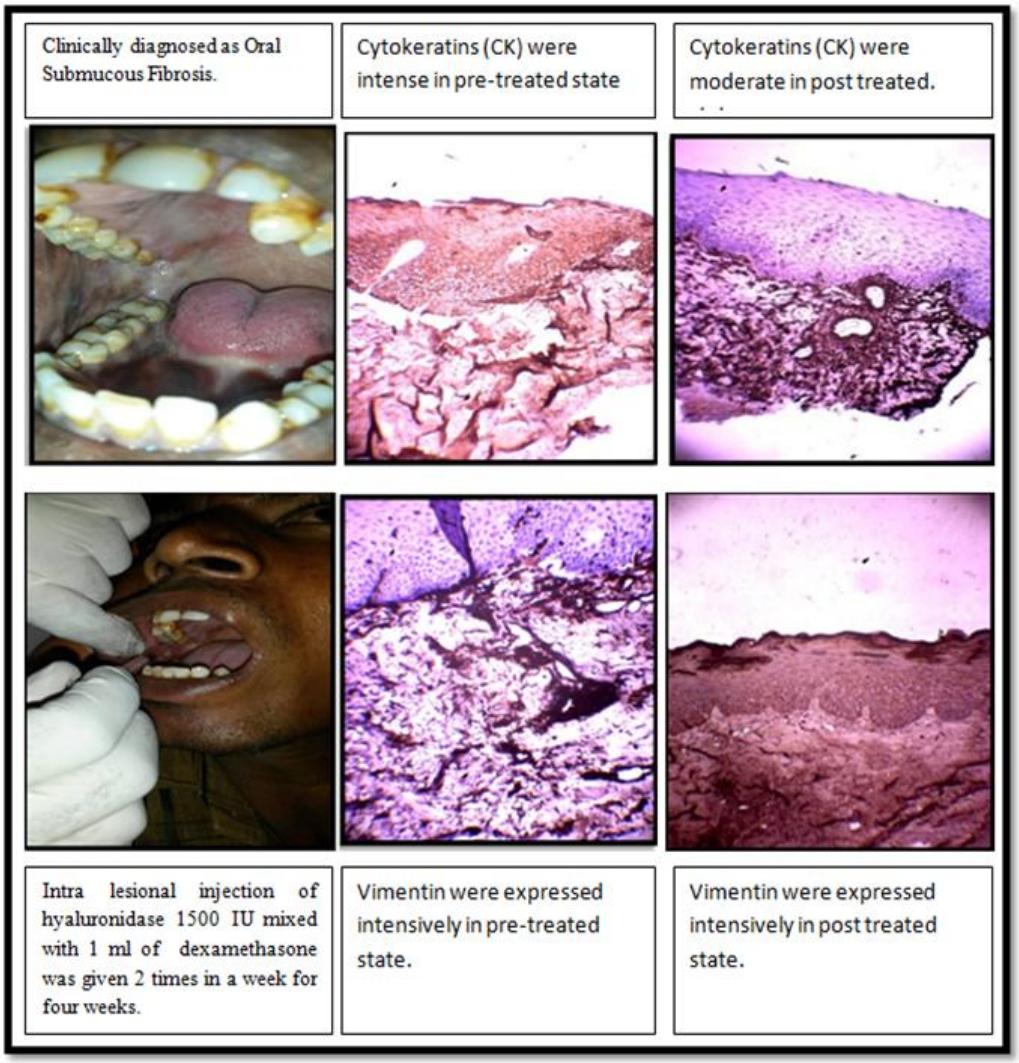

Fig. 1. Shows pre and post immunohistochemical appearance of OSMF under 4X

of cytokeratin and Vimentin. Cessation of smoking habit was carried out by the patient immediately and he was advised Clotrimazole mouth paint [4-6times/day for 1week] for superficial candidal infection. He was given antioxidants with micronutrients including zinc, selenium. After 5 months of treatment, his burning sensation was completely resolved. The patient was assessed for tumor markers following post-treatment.

Results

Pre and post treatment Cytokeratins and Vimentin levels were assessed. The pre-treatment specimen of CK was intense and post-treatment specimen of CK was moderate and vimentin remained same.

2.3 Case 3

A male patient aged 56 years came with the complaint of unusual growth in left cheek region for past 4 months. On clinical examination, an ulceroprolifertive growth was evident in left buccal mucosa which was diagnosed as well differentiated squamous cell carcinoma by histopathological examination. The clinical stage of the lesion fell into TNM staging of oral cancer stage II. [9] Pt had apprehension to undergo surgical management hence opted for Chemotherapy. Inj.cisplatin 20 mg for 3 days. Inj.

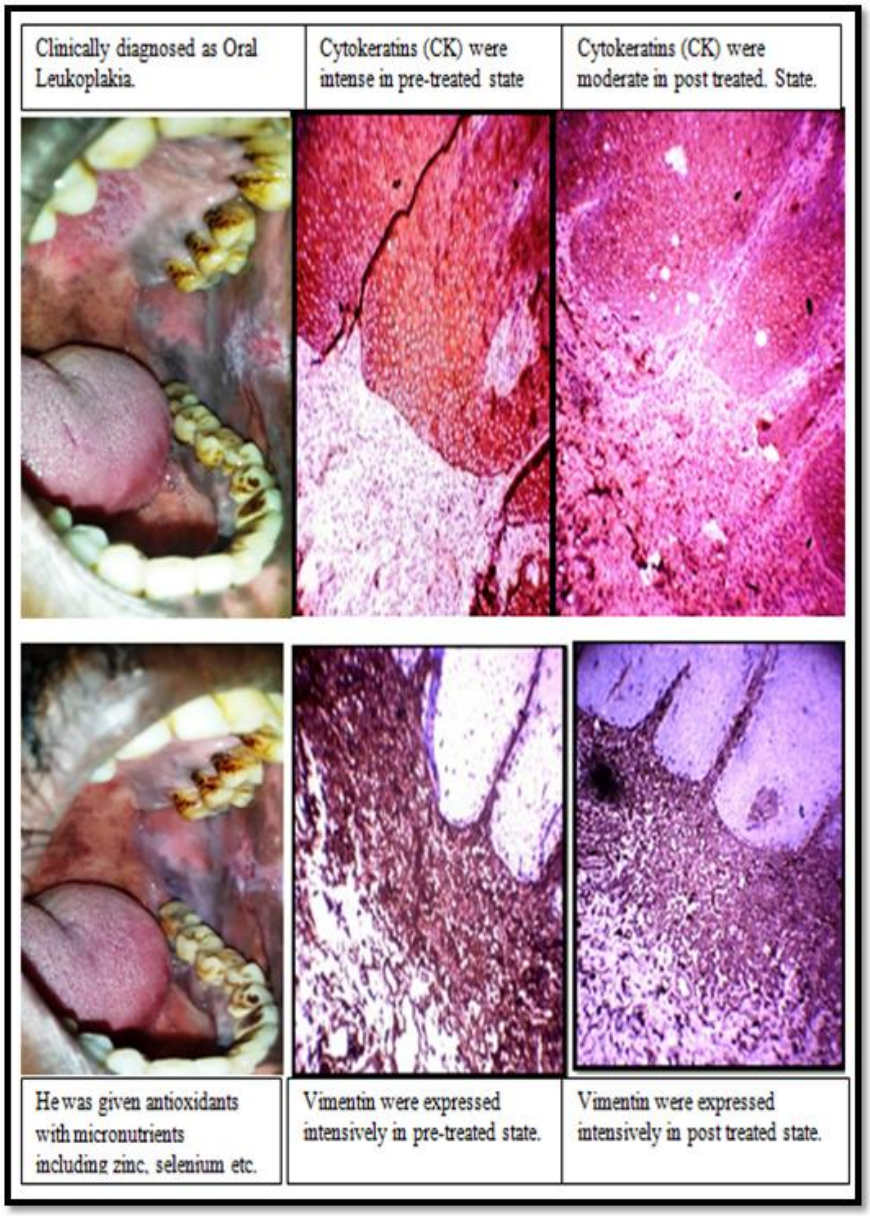

Fig. 2. Shows pre and post immunohistochemical appearance of SPECKLED leukoplakia under 4X

5 Fluorouracil 500 mg for 3 days for every 21 days next cycle of chemotherapy started. After completion of chemo cycles, IHC study was done.

Results

The pre and post results show intense immune reactivity for both CK and vimentin expression and negative vimentin expression in tumour cells.

3. DISCUSSION

Cytokeratins is an intermediate filament protein and its expression in the suprabasal layers of the oral mucosa may also be a useful marker in the identification of oral lesions, with a potential malignant transformation. [10] CKs are broadly classified on the basis of their molecular weight and isoelectric points into Type 1 -Acidic with low molecular weight CKs 9-23, and Type 2 - Basic

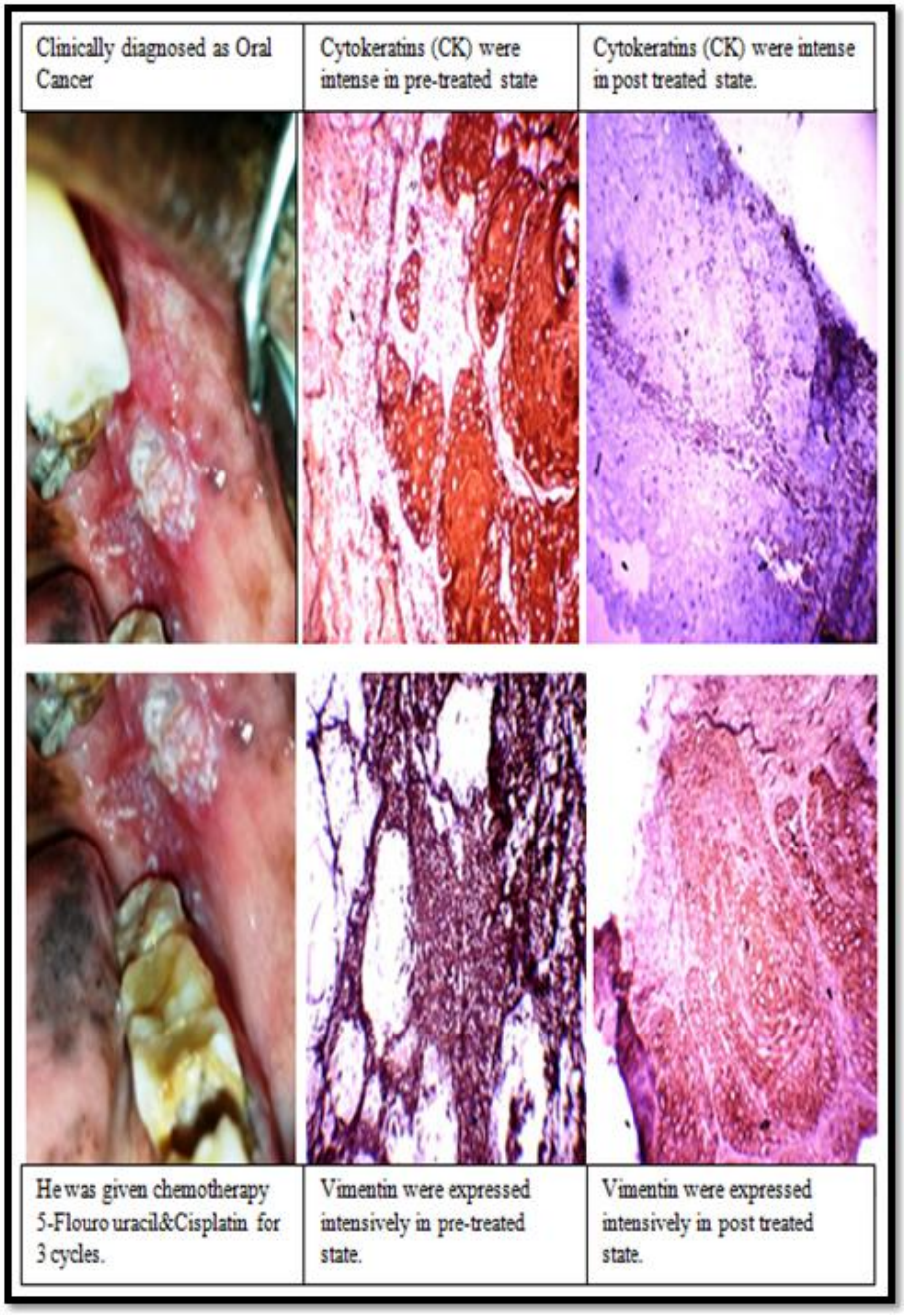

Fig. 3. Shows pre and post immunohistochemical appearance of SCC under 4X

or Neutral with high molecular weight CKs1-8 [11]. Vimentin is a type III intermediate filament (IF) protein of mesenchymal cells with molecular weight 54 KD. Vimentin is a mesenchymal-specific protein whose expression is not observed in normal epithelial cells. Although its expression has been shown in invasive and metastatic OSCC [12]. OSMF is a disorder of underlined connective tissue, it has been shown that keratinocyte play a major role in the pathogenesis of fibrosis, and on the other hand, fibroblasts have been shown to be responsible for the structural and functional alterations of oral mucosa [13]. It is known that the exposure of tobacco/areca nut causes epithelial cells to stimulate cytokines, and these cytokines are the

real initiator of fibrosis [13]. This suggests that both the compartments-connective tissue and epithelium have a mutual influence on their cellular and functional regulators. Hence, abnormal vimentin expression in epithelial cells could be the cause of early molecular changes occurring in both the epithelial and mesenchymal compartments during oral tumorigenesis. The percentage of samples positive for vimentin expression was much higher in clinically non-homogenous leukoplakia lesions as compared to homogeneous leukoplakia lesions. It has been reported that non-homogenous leukoplakia is more prone to malignant conversion over a period of time as compared to homogenous leukoplakia [14]. Tumourmarker is characterized as a promising tool if the reaction pattern in epithelial dysplasias is similar to that in carcinomas and/or if the aberrant reaction pattern is positively related to the grade of epithelial dysplasia [15]. Burkhardt et al. reported that mild, moderate and severe dysplasias have the malignant potential of about 3%, 4% and 43% respectively. Speight et al. [9] reported that moderate dysplasia have malignant transformation potential of 3-15%, whereas mild epithelial dysplasia show a very low risk (<5%). Murti et al. followed sixty-six patients with oral submucous fibrosis for a period of 17 yr (median observation 10 yr) in Ernakulam District, Kerala, India. Oral cancer developed in five (7.6%) patients. The malignant transformation rate in the same sample was 4.5% over a 15-yr observation period (median 8 yr). These findings impart a high degree of malignant potential to this condition. Anand Lalli et al., in 2008 found an increase of K1 and K10 in the suprabasal layers, induction of K6 in the basal layer and complete loss of K19 in the epithelium. They concluded that the altered keratin profiles could be useful as histological diagnostic markers, and these may provide important insights into the pathogenesis of the disease and its predisposition to malignancy [13].

In this study, we found a marked decrease in the expression of CK in post-treatment stages when compared with pre-treatment stage which was confirmed by immunohistochemical evaluation of the same patients, who were having OPMDs. The mild expression of vimentin in OPMDs, but there is no marked differences in vimentin expression among pre-treated and post-treated subjects and intense expression in OSCC is confirmed in this study. Also, we noted that there is marked, expression of both CK and vimentin, in pre- as well post-treated specimens we found no change in expression for the confirmed, case of oral squamous cell carcinoma. Hence it was found that there is a lesser expression of CK in potentially malignant lesions, it is a prognostic indicator for better management.

4. CONCLUSION

Various biological markers are used for the assessment of cancer risk. Identification of these molecular markers like CK, vimentin has shown promise as these are used for the diagnosis and future prognosis of malignancies. The recognition of some of the markers are thought to be important with reference to dysplasia since the reactivity and recognition of these molecules were positively related to different grades of epithelial dysplasia. An ideal tumour marker should be highly sensitive, specific and reliable with high prognostic value. In spite of few limitations CK have shown excellent clinical relevance in monitoring efficacy of different modes of therapy. This study throws light that these markers CK and Vimentin levels can be used as prognostic indicators in pre and post-treatment potential malignant and malignant lesions of the oral cavity.

This study has certain limitations with sample size and follows up time period. Hence further studies with a larger population and follow up are required to arrive at a conclusion.

CONSENT

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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