ORIGINAL RESEARCH

Expressions of CD 138 and CD43 in Oral Leukoplakia

Anand Siddappa Tegginamani[1], Vanishree Halasagundhi Shivakumar[1], Siti Mazlipah Ismail[2], Mannil Thomas Abraham[3], Priyadarshini Ramamurthy Hesarghatta[1], Ahmad Termizi Bin Zamzuri[1]

Abstract

Introduction: Oral Leukoplakia is the second most common oral potentially malignant disorder encountered in day-to-day clinical practice, with an overall global prevalence of 4.11%. The rate of its malignant transformation varies worldwide.

Aims & Objectives: The aim of the study was to assess CD 138 and CD43 immunoreactivity in oral epithelial dysplasia.

Materials & Methods: Immunohistochemistry was performed on fifteen formalin-fixed oral epithelial dysplasia tissues for CD 43 (n=15) and CD 138 (n=15) which were obtained from archives at Oral cancer research and coordinating centre, Malaysia.

Results: The expression of CD 43 in non-hematopoietic tissues was negative in all cases, but epithelium with dysplastic alterations had low or weak CD 138 expression between dysplastic tissue and non-dysplastic epithelium, there was a substantial difference in staining intensity.

Conclusion: Oral carcinogenesis is a multistep process, and cancer driver genes have been shown to have vastly diverse effects in various tissues. CD 138 expression was shown to be lower in tissues undergoing dysplastic alterations, which could be a sign of oral epithelial dysplasia with a high risk of malignancy.

Keywords: CD138, CD43, Immunohistochemistry, Malignant transformation, Oral dysplasia

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Introduction

A wide range of oral mucosal disorders present as white or red, or mixed white and red patches. In the literature they have been described as Oral submucous fibrosis, Oral leukoplakia, Erythroleukoplakia, Erythroplakia, Oral lichen planus, Oral lichenoid reactions, Palatal lesions in reverse smokers, Graft-versus-host disease, Oral lupus erythematosus which are included in the spectrum of oral potentially malignant disorders (OPMDs).[1] World Health Organization WHO in 2017 defined oral leukoplakia as clinical presentations that carry a risk of cancer development in the oral cavity, whether in a clinically definable precursor lesion or in clinically normal mucosa.[2] In 2018, potentially premalignant oral epithelial lesions [PPOELs] were proposed as a new term replacing OPMDs with the concept that these lesions have the potential to become malignant, in their current state.[1] Oral Leukoplakia (OL) is the second most common OPMD after oral submucous fibrosis with an overall global prevalence of 4.11%, OL presents as a white oral plaque with a questionable risk of malignant transformation (MT).[3,4] The process from normal mucosa to premalignant or dysplastic mucosa and to malignant is a complex interaction between the host genetics & immune system function and the environmental factors exposure to carcinogens like betel liquid, tobacco, alcohol. Certain factors are also indicative of the possible malignant transformation of OL like age/gender, clinical appearance, size exceeding > 2cm, location, type of lesion non-homogeneous, and most importantly, the degree of epithelial dysplasia. Potentially the malignant oral mucosal disease has some ability to give rise to malignancy of the oral epithelium, but it is still not known what percentage of oral squamous cell carcinoma (OSCC) develops from OPMDs as the rate of malignant transformation varies between 0.13% to 34.0% worldwide.[5-10] It has not been possible to predict the malignant potential of PPOELs merely based on their clinical characteristics and/or histologic characterization of which lesion or persons are at higher risk of MT. As a result, it's critical to establish predictive indicators that can identify lesions that are more likely to advance to cancer.[3,9]

[1] Faculty of Dentistry, SEGi University, Kota Damansara, Malaysia; [2] Faculty of Dentistry, University of Malaya, Kuala Lumpur, Malaysia; [3] Department of Dentistry, Sentosa Specialist Hospital, Taman Sentosa Perdana, Klang, Selangor, Malaysia.

Corresponding Author: Anand Siddappa Tegginamani, Faculty of Dentistry, SEGi University, Kota Damansara, Malaysia. E mail Id: anandsiddappa@segi.edu.my

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Conflict of Interest: None

Materials and Methods

Immunohistochemistry was performed on fifteen formalin-fixed oral epithelial dysplasia tissues for CD 43 (n=15) and CD 138 (n=15) which were obtained from the oral cancer research and coordinating centre (OCRCC). Malaysian oral cancer database and tissue bank system (MOCDTBS), University of Malaya, Malaysia. Immunohistochemistry was performed on 5 µm thick sections from 15 formalin-fixed and paraffin-embedded tissue samples after deparaffinization and rehydration procedures, epitope retrieval was executed in heated citrate buffer for 30 min as recommended. The primary antibodies CD138, CD43, DAKO Corporation, USA, immunohistochemical staining was done according to the manufacturer's instructions, counterstained with Mayer's hematoxylin, and the slides were coverslipped with DPX. The immunostained sections were examined using a light microscope to assess the localization of immunostaining within the epithelial tissue. Tonsil and SCC were used as a positive control and negative controls were carried out by omission of the primary antibody. The proportion of positive cells Grade I: 0% <25%, Grade II: 25–50%, Grade III: 50–75%, and grade IV: 75–100%, staining localization cytoplasmic, membranous or both, and stain intensity mild, moderate, strong were recorded. The present study was approved by the institutional Ethical Committee.

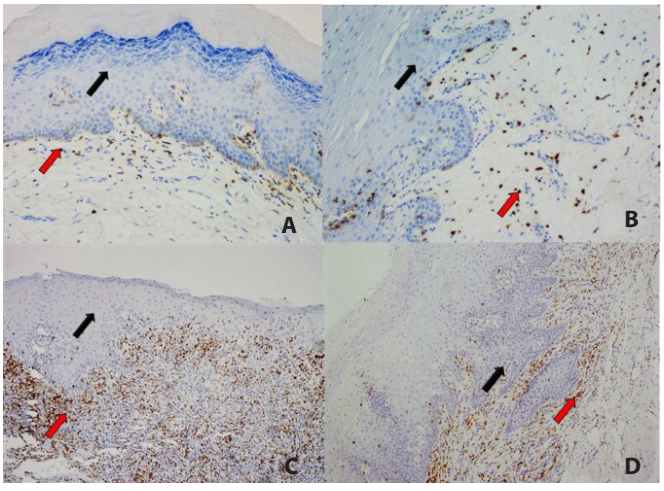
Results

The expression of CD 43 in non-hematopoietic tissues was negative in all cases examined (Fig 1 A to D) & the immune system cells served as internal controls for CD43. In normal epithelium, CD 138 expression was predominantly cytoplasmic and membranous, but in dysplastic alterations, it was missing or faint (Fig.2 A to D). Between dysplastic tissue and non-dysplastic epithelium, there was a substantial difference in staining intensity.

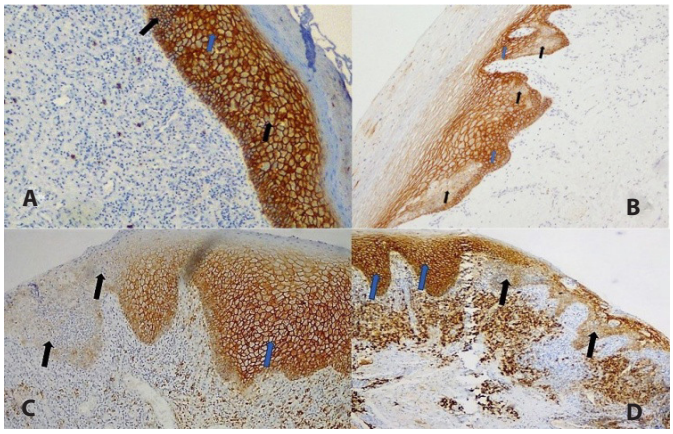
Discussion

Many researchers consider that most oral cancers arise from OPMDs of which oral leukoplakia is the most prevalent and well known. Epithelial carcinogenesis is a multistep process and recent studies on genomic analyses have shown that most of cancer driver genes are mutated in a tissue-dependent manner, i.e, they are altered in some cancers but not in others.[11-14] The basal stem cell layer of normal oral mucosa is a self-perpetuating reservoir of cells with a mechanism for self-renewal and this is referred to as clonogenicity or stemness, which means the integrity of the basal stem cell layer is thus extremely important for epithelial homeostasis, the breakdown in cell cycle turnover is a precursor to the development of oral potentially malignant disorders OPMDs.[15] The gold standard for determining malignant transformation MT risk is the microscopic assessment for the degree of dysplasia, and this histopathological assessment has been an area of controversy. It is generally believed that the more severe the epithelial changes, the more likely the lesion progresses to cancer. However, the progression of OL to malignancy does not always depend on the degree of dysplasia. Studies have reported that approximately 3% of hyperplastic lesions D0 and up to 30% of mildly dysplastic lesions D1 have shown MT. The MT rate of OL into an OSCC ranges between 0.13% to 34.0%.[16-20] The reported annual MT rate of OL varies between 1.36% - 2.9%, in the recent long-term follow-up study has shown that there was a 4.9% rate of MT annually.[21] The rates of MT are varied from study to study because of differences in the underlying pathology and differences in the use of putative carcinogens such as tobacco & alcohol, however, the effect of these on malignant transformation of OL remains controversial.[22-24] Presently, there are no microscopic or molecular methods that can predict which individual dysplasia, irrespective of the grade of epithelial dysplasia will progress to carcinoma, cumulative experience has shown that carcinoma can arise from all grades of dysplasia. Clinical and/or histologic biomarkers are exigently needed to improve the ability to distinguish lesions that may progress to cancer from those that may not. [21,25]

Cancer stem cells (CSCs)have been expressed in various solid tumors, including oral squamous cell carcinoma. Various proteins have been tested as molecular biomarkers that can identify the subset of lesions that are likely to progress to cancer in oral mucosal precancerous lesions. The CSC hypothesis, the likely explanation is that each marker labels only a distinct subset of stem cell-like cancer cells, leaving other unique subpopulations of cancer cells



Figs. 1 A to D: CD43 reveal negative expression for in epithelial dysplasia (A to D) (black arrows) the cells of the immune system serving as internal controls for CD43 (red arrows). (IHC magnification 10x)



Figs. 2 A to D: CD 138 shows a predominantly uniform strong membrane and cytoplasmic expression in non-dysplastic epithelium (blue arrow) and decreasing expression/weak in intensity of staining (black arrow) was observed in epithelium with a dysplastic change. (IHC magnification (10x)

with stem cell characteristics unidentified. Therefore, proper screening and profiling for each case with respect to different CSC markers are necessary[26,27] as it is arduous to find out the malignant potential of OPMDs based on a single marker investigation. The use of multiple biomarkers might help to differentiate between low and high-risk OPMDs. Until now, it continues to be the greatest challenge for a clinician to predict which OL lesion will progress to malignancy.[12,28-30]

CD43 is a sialoglycoprotein, also known as Leukosialin, Lialophorin which is normally expressed on the surface of leukocytes and is a sensitive and specific marker for hematopoietic cells and malignancies of its derivatives. CD43 plays a role in locomotion, apoptosis modulation, differentiation, and immune homeostasis. In both nonhematopoietic and hematopoietic cancers, CD43 expression may aid oncogenic cell survival.[31-33] Evidence suggests its role in epithelial neoplasms, but its contribution to tumor development is still not clear and it is hypothesized that CD43 activation via Wnt/APC/β-catenin signaling pathway can promote the development of tumor.[31,34,35] However, several studies have demonstrated CD43 expression in different solid tumors of non-hematopoietic origin including lung, breast, colon adenocarcinoma, salivary gland tumors, and small cell lung carcinoma, it is undetectable in normal tissues and benign lesions.[31-36] In a recent study with 307 non-hematopoietic neoplasms including pancreatic ductal adenocarcinomas, breast invasive ductal carcinomas, and papillary thyroid carcinomas, most of the non-hematopoietic neoplasms were negative for CD43 expression or with weak focal nuclear positivity. It was concluded that adenocarcinomas tend to be more often positive for CD43 compared to squamous cell carcinomas irrespective of the tissue of origin while the uniform and strong membranous staining of CD 43 expression are more specific to hematopoietic neoplasms. The literature data on expression with CD 43 in non-hematopoietic tumors is variable & contradictory.[37]

CD 138 also known as SDC1, Syndecan-1 is a family of integral membrane proteoglycans that participate in cell-matrix interactions and growth factor binding. They are deregulated during carcinogenesis and are related to angiogenesis, apoptosis, cell proliferation, and tumor invasion. In-vitro studies have shown their role in MT as they are associated with the maintenance of epithelial morphology, anchorage-dependent growth, and inhibition of invasiveness.[38,39] A recent study has shown high levels of cell membrane immunoreaction expressed on various epithelial cell types including normal squamous epithelial cells of the lip, oral cavity, tonsil.[40,41] CD138 has been extensively investigated in various human tumors including squamous cell carcinoma of the lung, head & neck, gastric, renal, colorectal, cholangitis, breast carcinoma, ovarian carcinoma, adrenal cortical carcinoma, urothelial carcinomas, and ameloblastoma, reduced CD 138 expression is thought to be a precursor to malignant transformation, as it has been seen in precancerous oral lesions, uterine cervix, colorectal adenoma, and oral squamous cell carcinoma. The changes in CD 138 expression reflect changes in its behaviour, shape, growth, migration, and cytoskeletal organization of the cells, suggesting the reduced or decreased CD 138 expression in epithelial cells associated with tumor aggressiveness and poor survival. 42-50 Recent study has concluded that CD 138 can be a useful biomarker for the detection of micro-invasion of oral verrucous carcinoma as its expression was reduced in the epithelium which is undergoing dysplastic or neoplastic changes.[51,52] The strong CD 138 expression was observed in normal epithelium and intermediate or decreasing expression with oral epithelial dysplasia and almost absent in the malignancy.[53] Studies have shown that the immunopositivity was lost as the extent of the epithelial dysplasia increased in both oral submucous fibrosis OSF & oral leukoplakia.[54] The expression was decreased significantly in oral squamous cell carcinoma, cutaneous squamous cell carcinoma[55], and cervical cancers[56] suggesting that CD 138 can be as a prognostic marker for malignant transformation.[38,53,54,57]

In the present study, the negative immunostaining with Leukosialin CD 43 for non-hemopoietic oral epithelial dysplasia samples assessed, which was in accordance with results of other studies in the literature.[34-37] Reduced SDC-1 CD138 expression was found in some parts of the epithelium with dysplastic changes in oral epithelial dysplasia samples, which was consistent with the findings of other studies in the literature. Reduced SDC-1/CD138 expression is thought to be a step toward malignant transformation or the likelihood of progression to malignancy.[38,53,54,57] Only a few studies have investigated CD 138 and CD 43 immunoreactivity in oral leukoplakia. CD43 was negative in non-hemopoetic tissue of oral epithelial dysplasia, while CD 138 appears to have a potential utility in assessing for oral epithelial dysplasia with low and high risk for cancer.

No single antibody/marker is sensitive and specific for a particular tumor, screening and profiling of each case with respect to several CSC markers might be essential as cancer cells are highly heterogeneous at genetic, epigenetic, and phenotypic levels, moreover, differences in results of markers worldwide may be attributed to the technique sensitivity of Immunohistochemistry.[29,36,37,57,58] It's well known that all dysplastic lesions will not transform to malignancy.[59] This is a retrospective study with small sample size and only oral leukoplakia tissues were examined, which could be a major drawback. More research with bigger samples, including other potentially malignant oral diseases as OSMF and Lichen planus, is needed.

Conclusion

CD43 appears to be a more sensitive and specific marker for hematopoietic cells and cancers of their derivatives, while CD138 expression is reduced or absent, allowing for the differentiation of low-risk oral leukoplakia from high-risk lesions that are more likely to progress to malignancy.

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