ejpmr, 2020,7(6), 324-330

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

STUDY OF IMMUNOHISTOCHEMICAL EXPRESSION OF E-CADHERIN AND VIMENTIN IN PREMALIGNANT AND MALIGNANT SQUAMOUS LESIONS OF ORAL CAVITY AND OROPHARYNX AT A TERTIARY CARE CENTRE IN NORTH INDIA

Dr. Indira Sahu*, Dr. Kusum Mathur and Dr. Mukta Meel

Department of Pathology, Sms Medical College, Jaipur, Rajasthan, India.

***Corresponding Author: Dr. Indira Sahu**

Department of Pathology, Sms Medical College, Jaipur, Rajasthan, India.

Article Received on 05/04/2020 **Article Revised on 26/04/2020** **Article Accepted on 17/05/2020**

ABSTRACT

Background: Oral squamous cell carcinoma accounts for high morbidity and mortality despite the improvement in surgical treatment and adjunctive therapy. This necessitates the use of molecular markers to identify the high risk cases for invasion and metastasis. Loss of epithelial morphology and acquisition of mesenchymal characteristics, termed epithelial-to-mesenchymal transition (EMT) are typical for dysplastic epithelium to become tumorigenic and correlate with local invasiveness and metastatic potential. **Objectives:** To study EMT by observing the expression of E-cadherin and vimentin in precancerous and cancerous lesions of the oral cavity and oropharynx and to know the specific pattern of expression and hence predict invasiveness. **Methods:** This cross-sectional study looked at 96 cases of oral and oropharyngeal lesions obtained between 2018 - 2019 & Immunohistochemical expression of epithelial marker E-cadherin and mesenchymal marker vimentin was evaluated. **Results:** There were 36 premalignant and 60 malignant cases in this study. Majority of malignant cases were seen in the fifth and sixth decades of life while most of the premalignant lesions were seen in a decade earlier. The majority of premalignant lesions showed strong E-cadherin expression and low expression of vimentin while dysplasias showed reduced E cadherin and gain in expression of vimentin intensifying with increase in grade. E-cadherin expression was significantly reduced in carcinomas compared to dysplasias and the difference in immunoreactivity was statistically significant ($p < 0.003$). Vimentin expression increased as the tumor progressed from dysplasias to carcinomas ($p < 0.001$). **Conclusions:** This study highlighted the role of expression of E-cadherin and vimentin where decreased or loss of E-cadherin and increased vimentin expression proved the predictor of high risk cases for invasion and distant metastasis in oral dysplasia and squamous cell carcinoma patients who can be picked by clinician for further follow up and targeted therapy.

KEYWORDS: Premalignant, Malignant, Cadherin, Vimentin.

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common head and neck cancer and ranks as one of the top ten cancers worldwide. Oral cancer is among top three types of cancer in India and accounts for 16.1% of all cancers among men and 10.4% of all cancers in women.[1] Squamous cell carcinoma of oral cavity and oropharyngeal region is considered as an aggressive malignant neoplasm, by means of high mortality and morbidity, commonly occurring in middle-aged males and older individuals. Prognosis of oral cancer is generally poor, with a five year survival less than 50%. Local recurrence as well as lymph node metastasis occur in a significant percentage of patient.[2]

Oral squamous cell carcinogenesis is a multistep process that involves genetic events leading to modification of the normal function of oncogenes and tumour suppressor genes. The earliest morphologic changes that could be detected are the appearance of premalignant lesions that includes leukoplakia and erythroplakia.[3] Fifty Percent of leukoplakia exhibit dysplasia and the changes of dysplasia is more in erythroplakic lesions than in homogenous leukoplakia and overall malignant transformation potential is about 0.3-2.19% per year.[4] High incidence of oral cancer has been correlated with prevalence of risk factors like tobacco chewing and smoking habits. India ranks 2nd in consumption of tobacco and 3rd largest producer of tobacco among of the world as per GATS (Global Adult Tobacco Survey report) 2016-2017.[5]

The chances for simple hyperplastic lesions to turn malignant is 0.9%, for oral leukoplakic lesion without dysplasia malignant transformation rate is 16% whereas moderate and severe dysplasia have 36% incidence rate of malignant transformation.[3],[4] Epithelial malignancies manifest various phenotypic, invasive and biologic

patterns during cancer development and progression. It has been reported that some lower grades of dysplasia progress to cancer, whereas the higher grades may remain static or even regress; irrespective of the environmental factors.[3] Thus, it is almost impossible to accurately predict which lesions have higher malignant potential. This could be explicated by the fact that cancer development is a multistep process characterized by accumulation of genetic defects and mutations reflected by changes evident at the molecular level. These changes at the molecular level are apparent before the appearance of clinical or histological changes. Identification of these molecular characteristics can assist in defining the biologic aggressiveness and malignant potential.

The crucial factor for the homeostatic maintenance of oral mucosa is the interface between the epithelium and lamina propria. Loss of epithelial morphology and acquisition of mesenchymal characteristics, termed epithelial-to-mesenchymal transition (EMT) are typical for dysplastic epithelium to become tumorigenic and correlate with local invasiveness and metastatic potential of the tumor.[6] In our study, we looked at the role of EMT in precancerous and cancerous lesions of the oral cavity and oropharynx (specifically decreased expression of E-cadherin and increased expression of vimentin) and sought to determine if the specific pattern of E-cadherin and vimentin expression could be used to predict invasiveness.

A combination of relevant clinical data, adequate sampling, detailed histopathological examination & techniques like immunohistochemistry are important to identify the neoplastic lesions with high malignant potential of invasion and metastasis. Hence detection of high risk cases for distant metastasis at an early stage is mandatory for the better prognosis of the individual.

METHODS

This cross-sectional descriptive observational study looked at 96 cases of oral and oropharyngeal lesions from the Department of Pathology, SMS Medical College, Jaipur, Rajasthan, India. Study began after approval by ethical committee May 2018 and continued till the required sample size was attained till October 2019. 78 biopsies from the buccal mucosa, tongue, and pharynx and 18 resected oral specimens were evaluated for all premalignant and malignant lesions using routine hematoxylin and eosin staining and E-cadherin (HECD-1 IgG1 ready to use mouse monoclonal antibodies for E-cadherin, Biocare), and vimentin (V9-IgG1/kappa monoclonal antibodies for Vimentin, Biocare) immunohistochemical stains, wherever possible. Immunohistochemical analysis was performed on the serial sections. Slides were examined for the pattern (cytoplasmic or membrane), proportion and intensity of staining of tumor cells. Grading of E-cadherin immunostaining was based on the percentage of cells stained[7]; 1+/negative: < 10% positive cells; 2+: 10 to 20% positive cells; 3+: >20 to 50% positive cells; and 4+: > 50% positive cells. Grading of E-cadherin was also evaluated based on the location and intensity of staining; 1+: absent membrane staining; 2+: weak/heterogeneous membranous staining; and 3+: strong/homogeneous membrane staining. Grading of vimentin was done on the basis of the stain intensity: 1+/ negative: weak and focal staining; 2+: strong and focal staining; 3+: weak and diffuse staining; and 4+: strong and diffuse staining.

Data Management and Statistical Analysis

The collected data were entered in Microsoft excel spreadsheet and analysed using SPSS version 17.0 for Windows. Qualitative data were presented as mean and standard deviation (median in case of skewed data). Normally distributed quantitative data were analysed using student t-test. Qualitative variables were analysed using chi-square test (Fisher exact test where n<5). Point of statistical significance was considered when p value was less than 0.05 ($p<0.05$).

RESULTS

There were 36 premalignant and 60 malignant cases in our study. Seventy eight cases (81.3%) were seen in males and 18 (18.7%) in females. Both premalignant and malignant cases were more prevalent in males compared to females. The majority of malignant cases, (n = 24; 40%) were seen in the fifth and sixth decades of life while most of the premalignant lesions (n = 14; 38.9%) were seen in the fourth and fifth decade. The number of malignant cases increased with advancing age. Most of the lesions were found in tongue followed by buccal mucosa. Majority of malignant lesions presented with ulceroproloiferative growth pattern. Risk of OSCC in smoking and tobacco chewing was found in 56.7% and 61.7% respectively. Amongst the 36 premalignant oral lesions studied, leucoplakia and lichen planus comprised of 7 cases (07.2%), 7 cases were of Verrucous hyperplasia (7.2%), and there were 22 cases (22.9%) of different grades of dysplasias. Most of the premalignant lesions studied showed strong (4+) and moderate (3+) membranous immunostaining of E-cadherin ($p = 0.003$) [Table 1]. In Oral Epithelial Dysplasia(OED) , Only 2 cases of mild & moderate dysplasia showed strong (4+) expression of E-cadherin, 11 cases of dysplasia showed 3+ expression and 6 cases showed 2+ expression while E cadherin expression was negative to 1+ in 3 cases of moderate & severe dysplasia**.** The majority of premalignant lesions also showed weak (1+ or 2+) cytoplasmic immune-expression for vimentin ($p = <0.001$). In verrucous hyperplasia only 1 out of 7 cases (14.28%) showed weak 2+ vimentin expression rest were negative for Vimentin. In case of leucoplakia and other lesions 2 cases out of 7 (28.57%) expressed weak 2+ vimentin positivity, while 10 (45.5%) showed weak 2+ vimentin positivety [TABLE 2,,3]**.** Although none of premalignant lesion showed strong Vimentin expression but percentage positivity for vimentin increased from 1+ to 2+ as we proceeded to dysplasias [Figure 1a,b,c]. In our study, a total of 60 cases of OSCC were studied with 20 cases each of Well,Moderate and Poorly

Differentiated Squamous Cell Carcinoma but none of the OSCC showed 4+ E cadherin expression. Out of 20 cases of well differentiated carcinoma(WDSCC), four (20%) cases showed moderate (3+) staining intensity of E-cadherin and thirteen (65%) cases showed weak (2+) immunoexpression of E-cadherin while it was lost in 3 cases (15%). Only three (15%) cases of moderately differentiated carcinomas(MDSCC) showed moderate (3+) expression of E-cadherin and negative to 1+ expression was observed in 10 (50%) cases. While in case of poorly differentiated carcinoma(PDSCC) E cadherin negative expression was seen in 8 (40%) cases and 9 (45%) cases showed weak 2+ E cadherin expression [Figure 2a,b,c]. We concluded that E-cadherin expression was significantly reduced in carcinomas compared to dysplasias .(p=0.003) [Table 1].

Four out of twenty (20.0%) cases of WDSCC showed negative(1+) vimentin staining, while three out of twenty (15.0%) cases of PDSCC showed strong (4+) staining and three (15.0%) cases had moderate (3+) staining. Only one cases was negative for vimentin [Table 3]. Our study showed an increased expression of vimentin as the tumor progressed from dysplasias to carcinomas (p < 0.001) [Table 1].

E cadherin intensity scoring showed maximum (50%) cases of premalignant lesions in grade 3 (strong membranous) but as proceeded to malignancy 43 cases (71.7%) showed grade 2 intensity (weak/ heterogenous) while only 1 case (1.7%) showed grade 3 intensity. This correlation of E cadherin intensity with type of lesion was found statistically significant (p value=<0.001) [Table 4]. Among various grades of tumor WDSCC showed 18 cases with grade 2 intensity, MDSCC showed 7 cases (35%) with grade 1 and rest 13 cases (65%) with grade 2 intensity and PDSCC showed 8 cases (40%) with grade 1 intensity and rest 12 cases (60%) showed grade 2 intensity [Table 5].

DISCUSSION

The shift in cancer research from the histopathological to the molecular and genetic levels was brought about by many new technologies, one among them is immunohistochemical study and is believed that understanding the molecular basis of cancer will lead to precise diagnosis and better treatment. EMT is an important biological event in which cohesive and polarized epithelial cells switch to mesenchymal-like cells exhibiting no polarization and high mobility. This acquired migratory phenotype is important, particularly during tumor invasion and metastasis.[8],[9] The altered expression of EMT markers such as E-cadherin and vimentin have been studied in various malignant epithelial tumors.[8] Our study showed positivity of different intensity of E-cadherin and vimentin expression in premalignant and malignant lesions. We observed a significant decrease in E-cadherin membrane expression from dysplasia to invasive carcinoma and a significant increase in vimentin expression with progression of the tumor. Loss of E-cadherin and gain of vimentin is a hallmark of tumor progression and E-cadherin is a good prognostic marker whereas vimentin expression indicates a poor prognosis.

In case of oral epithelial dysplasia, 86.4% of OED cases were found Positive for E cadherin, this expression was comparable with Akhtar K study done on OED.[7] 45.5% of OED cases were found Positive for Vimentin. Results were found comparable with study results done by Fernandez A where expression was found in 37.5% cases which was slightly higher in present study.[10]

E cadherin expression was found in 65% (n=39/60) of malignant cases. This is comparable to study done by De freista Silva (2014)[11] where E cadherin expression was found in 65% of OSCC cases which was higher than study done by Kaur J (2013)[12] where E-cadherin expression was seen in 42% cases of OSCC only. Here we noted that, Degree of E-cadherin expression decreased as the grade of the tumor was increased which is comparable with study done by Akhtar K concluding that the loss of E-cadherin mediated cell adhesion is prominent. The difference in expression for different grades was found statistically significant. (p value=0.006).

There were 60 malignant cases where Vimentin positive expression was found in 85 % (n=51/60) of malignant cases. It was comparable with study of Fernandez A (2017)[10] who found Vimentin positive expression in 89.1% of OSCC cases. There was found increased expression of vimentin with increase in grade of tumor. The difference in expression for different grades was found statistically significant. (p value=<0.001).

Kaur G (2009) studied E-cadherin expression in different histological grades of oral squamous cell carcinoma and reported E-cadherin immunoreactivity to be inversely related with loss of cell differentiation. Strong expression in 90% well differentiated, 92.9% moderately differentiated and 15.4% poorly differentiated carcinoma. E cadherin membranous positivity decreased and cytoplasmic positivity increased as the tumour grade increased from well to poorly differentiated squamous cell carcinoma, leading to poor prognosis. E-cadherin was negative in majority of metastatic lymph nodes.[13]

Zhou J (2015) reported progressive reduction of E-cadherin with grade of OSCC i.e. WDSCC (83.3%), MDSCC (61.9%) and PDSCC (33.3%) which was associated with increased Vimentin reactivity with differentiation i.e. WDSCC (25%), MDSCC (33.3%), & PDSCC (66.7%). This expression of low E-cadherin and high vimentin were associated with lymph node metastasis (p<0.05). Further, E-cadherin positivity was more in the center of the tumor as compared to the infiltrative margin while contrastingly vimentin expression was higher in the infiltrative margin as compared to the central areas (p<0.05). Thus, there was

negative correlation between E-cadherin and vimentin in OSCC which is suggestive of EMT.[14]

Akhtar K (2016) studied diagnostic and prognostic significance of E-Cadherin and Vimentin in oral cancer metastasis. He found decrease degree of E cadherin expression as grade of tumor was increased. E-cadherin staining showed 6/10 (60%) cases of well differentiated carcinoma with 4+ degree of expression while 0/10 case of poorly differentiated carcinoma showed 4+ and only a single case showed 3+ degree of expression with 8/10 (80%) cases of well differentiated carcinoma depicting strong staining intensity of E-cadherin. 6/10(60%) cases of well differentiated oral squamous cell carcinoma showed 1+ degree of expression of vimentin while 6/10(60%) cases of poorly differentiated carcinoma showed 4+ degree of expression. 1(1.6%) case of positive lymph node metastasis showed strong positive staining for E-cadherin and 4 (66.6%) cases showed absent staining pattern of E-cadherin. The differences in the immunoreactivities were statistically significant between CIS and mi-croinvasive or invasive carcinomas ($p<0.001$) in the study.[7]

Alejandra Fernandez (2017) studied 56 samples of oral cavity to compare immunoexpression of endothelial markers in normal oral mucosa,oral epithelial dysplasia and oral squamous cell carcinoma and found the extent & intensity of ECadherin was high in normal oral mucosa (NOM)-100% and in oral squamous cell carcinoma (OSCC)-36%. Reciprocally intensity expression of vimentin was also found statistically significant that is 81.25% of NOM samples were negative for marker while 37.5% of oral epithelial dysplasia (OED) samples showed medium intensity and 36.04% of OSCC showed higher intensity.[10]

The expression of E cadherin was negative in 44.5% tumors with lymph node metastasis**.**. The results were comparable (although with greater % positivity) with Fan HX[15] studies thus showing a correlation between invasiveness and decrease in e cadherin expression. The expression of vimentin was seen in 100% cases with Lymph node metastasis while those without lymph node metastasis showed Vimentin expression in 66.7% cases only. The results were comparable with Zhou J[14] & Liu KL[16] studies (75% in +LN and 64.75% in -LN) thus showing a correlation between invasiveness and increase in Vimentin expression. Although the correlation was not found statistically significant (p value =0.205) [Table 6].

Table 1: Association of Lesion with E-cadherin and Vimentin expression

Lesion	**E-cadherin Positive**	**Negative**	**Vimentin Positive**	**Negative**
Premalignant (36)	33 (91.7%)	3 (8.3%)	13 (36.1%)	23 (63.9%)
Malignant (60)	39 (65.0%)	21 (35.0%)	51 (85.0%)	9 (15.0%)
Total	69	27	64	32

Chi square test,for E cadherin p-value=0.003, Vimentin p-value=<0.001.

Table 2: E cadherin proportion grade expression in various oral lesions.

Lesions (n=96)	**+1**	**+2**	**+3**	**+4**
Mild Dysplasia (n=7)	0	2	4	1
Moderate dysplasia (n=8)	1	1	5	1
Severe Dysplasia (n=7)	2	3	2	0
Verrucous lesion (n=7)	0	1	3	3
Leukoplakia& others (n=7)	0	1	3	3
Well differentiated Squamous cell Carcinoma (n=20)	3	13	4	0
Moderately differentiated Squamous cell Carcinoma (n=20)	10	7	3	0
Poorly differentiated Squamous cell Carcinoma (n=20)	8	9	3	0

Table 3: Vimentin expression in various oral lesions.

Lesions (n=96)	**+1**	**+2**	**+3**	**+4**
Mild Dysplasia (n=7)	3	4	0	0
Moderate dysplasia (n=8)	5	3	0	0
Severe Dysplasia (n=7)	4	3	0	0
Verrucous lesion (n=7)	6	1	0	0
Leukoplakia& others (n=7)	5	2	0	0
Well differentiated Squamous cell Carcinoma (n=20)	4	14	2	0
Moderately differentiated Squamous cell Carcinoma (n= 20)	4	11	4	1
Poorly differentiated Squamous cell Carcinoma (n=20)	1	13	3	3

Table 4: Association of E-cadherin intensity grade with type of Lesion.

	Grade 1	Grade2	Grade3	% total
Premalignant	2 (5.6%)	16 (44.4%)	18 (50%)	36 (37.5%)
Malignant	16 (26.7%)	43 (71.7%)	1 (1.7%)	60 (62.5%)
Overall	18	59	19	96

Chi square test, p-value=<0.001

Table 5: Association of E-cadherin intensity grade with OSCC type.

	+1	+2	+3	Total
WDSCC	1 (5%)	18 (90%)	1 (5%)	20
MDSCC	7 (35%)	13 (65%)	0	20
PDSCC	8 (40%)	12 (60%)	0	20
Total	16 (26.7%)	43 (71.7%)	1 (1.7%)	60

Chi-square test, p-value=0.066

Table 6: Association of Lymph node metastasis with E-cadherin and Vimentin expression (%).

Lymph node metastasis	E-cadherin Positive	Negative	Vimentin Positive	Negative
Yes (n=9)	5 (55.5%)	4 (44.5%)	9 (100%)	0
No	9 (100%)	0	6 (66.7%)	3 (33.3%)
Total	11	7	15	3

Fisher exact test, E cadherin p-value=0.082, Vimentin p value=0.205.

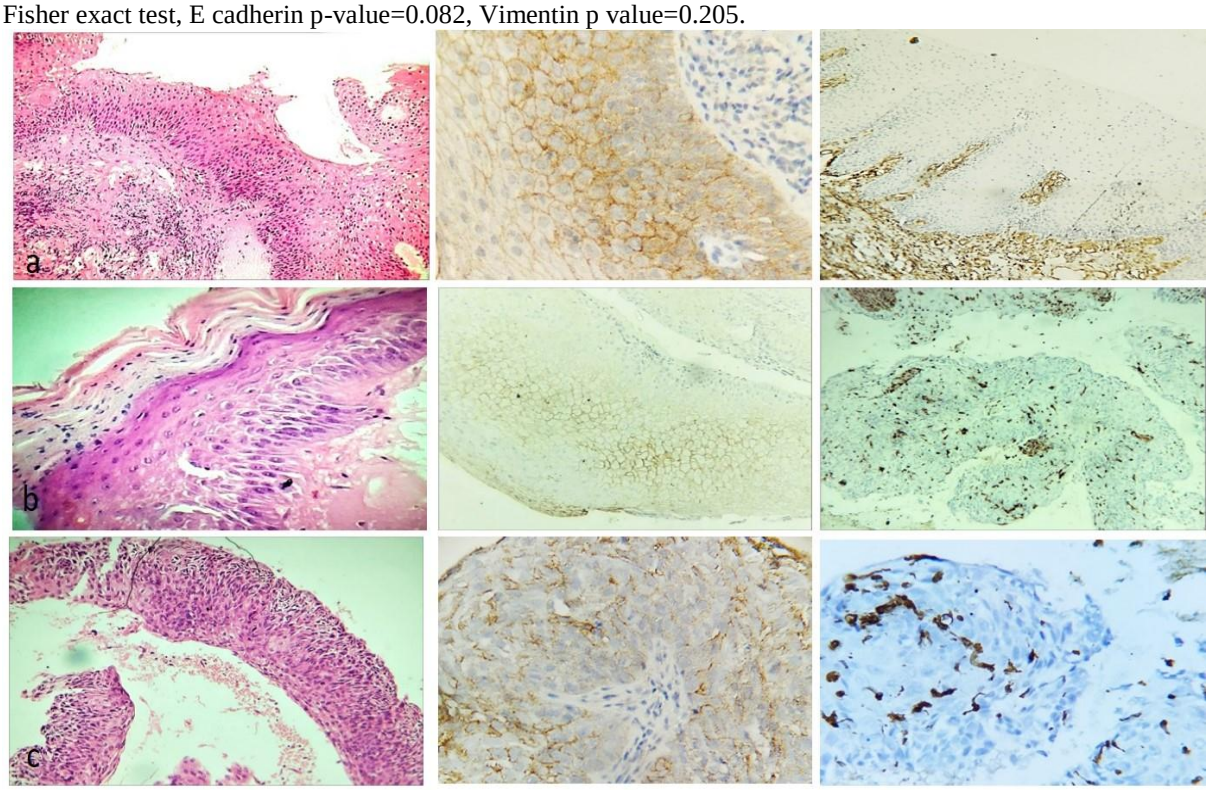

Figure 1 a,b,c.

Figure Legend 1

a) Mild dysplasia- loss of differentiation with basaloid cell in lower 1/3rd of epithelium,(H&E,100X), reduced E cadherin(3+) in lower 1/3rd of epithelium (IHC stain,400X) , Vimentin (1+) expression appearing in lining (IHC stain,100X).

b) Moderate dysplasia - loss of differentiation with basaloid cell in lower 2/3rd of epithelium (H&E,100X), reduced E cadherin(2+) in lower 2/3rd of epithelium (IHC stain,100X),strong but focal cytoplasmic expression of Vimentin (2+) seen in lining (IHC stain,100X).

c) Severe dysplasia -loss of differentiation seen with basaloid cells replacing the entire thickness of epithelium (H&E,40X), reduced E cadherin (2+) in lower 2/3rd of epithelium (IHC stain,400X), strong but focal cytoplasmic expression of Vimentin (2+) seen in lining (IHC stain,400X).

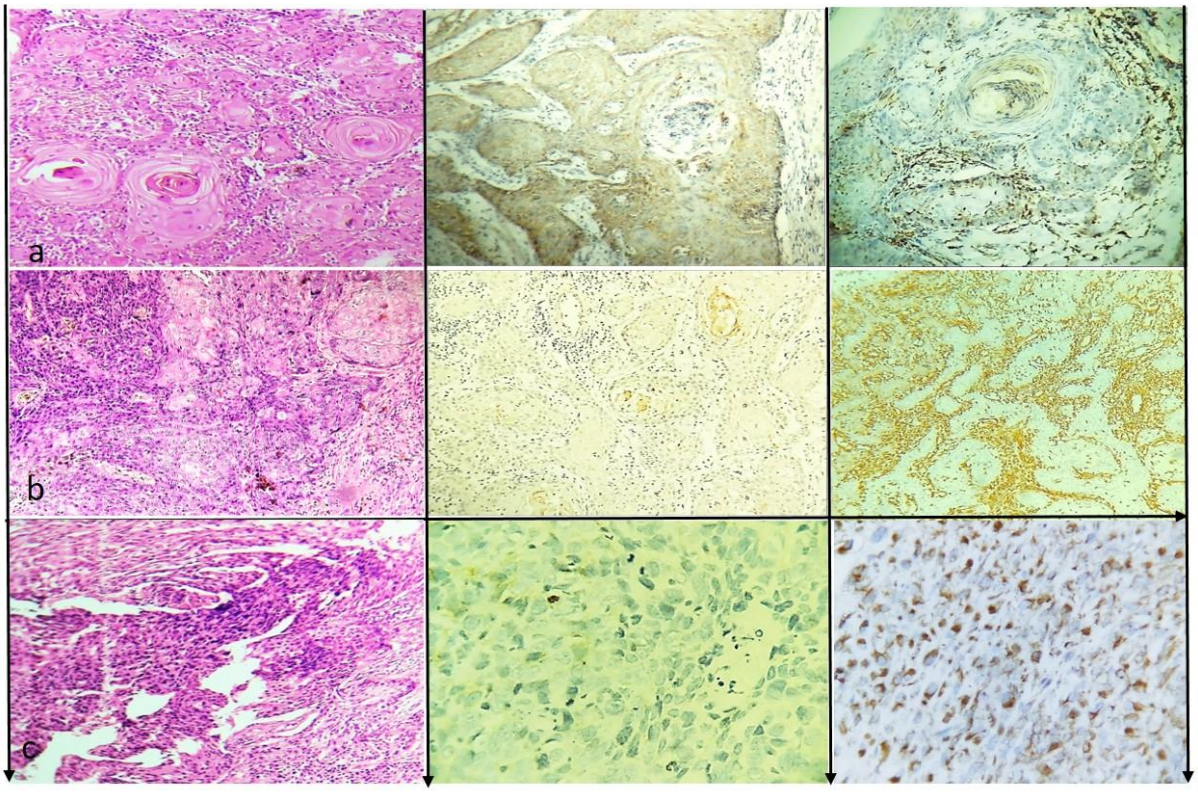

Figure 2 a,b,c.

Figure Legend 2

a) Well differentiated squamous cell carcinoma - shows many keratin pearls with tumor cells. E cadherin (3+) positive expression and +2 intensity in cell membrane of tumor cells and keratin pearls (IHC stain,100X), Vimentin expression is detected focally in tumor cells (2+) (IHC stain,100X).

b) Moderately differentiated squamous cell carcinoma -broad trabeculae and sheets of pleomorphic cells are noted (H&E,100X). reduced E cadherin expression observed with cytoplasmic positivity (2+) (IHC stain,400X), diffuse Vimentin expression detected in cytoplasm of tumor cells (3+) (IHC stain,100X).

c) Poorly differentiated squamous cell carcinoma - diffuse sheets of pleomorphic cells are noted (H&E,100X), negative E cadherin expression (1+) (IHC stain,400X). strong and diffuse cytoplasmic Vimentin expression (4+) (IHC stain,400X)

CONCLUSION

This study highlighted the role of expression of E-cadherin and vimentin where decreased or loss of E-cadherin and increased vimentin expression proved the predictor of high risk cases for invasion and distant metastasis in oral dysplasia and squamous cell carcinoma patients who can be picked by clinician for further follow up and targeted therapy. The present study has shown the existence of Epithelial Mesenchymal Transition phenotype in oral premalignant and malignant lesions i.e. Leukoplakia/Oral Epithelial Dysplasia, and Oral Squamous Cell Carcinoma (OSCC). This suggests that EMT is an early change evident in the premalignant stage and can predisposes to invasion and tumorigenesis in OSCC hence its molecular identification may aid in recognition of high risk lesions with enhanced malignant potential.

REFRENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin, 2018 Nov-Dec; 68(6): 394–424.
2. Elango JK, Gangadharan P, Sumithra S, Kuriakose MA.Trends of head and neck cancers in urban and rural India. Asian Pac J Cancer Prev, 2006 Jan-Mar; 7(1): 108-12.
3. Speight PM, Khurram SA, Kujan O. Oral potentially malignant disorders: Risk of progression to malignancy. Oral Surg Oral Med Oral Pathol Oral Radiol, 2018 June; 125(6): 612-27.
4. Silverman S Jr, Gorsky M, Lozada F. Oral leukoplakia and malignant transformation. A follow-up study of 257 patients. Cancer, 1984 Feb; 53(3): 563-8.
5. Global Adult Tobacco Survey (GATS 2) Fact Sheet 2016-2017. WHO.
6. Hollier BG, Evans K,Mani SA. The epithelial-to mesenchymal transition and cancer stem cells: a coalition against cancer therapies. J Mammary Gland Biol Neoplasia, 2009 Mar; 14(1): 29-43.
7. Akhtar k, Ara A, Siddiqui SA, Sherwani R. Transition of immunohistochemical expression of e cadherin

and vimentin from premalignant to malignant lesions of oral cavity and oropharynx. Oman Med J, 2016 May; 31(3): 165-9.
8. Guarino M, Rubino B, Ballabio G. The role of epithelialmesenchymal transition in cancer pathology. Pathology, 2007; 39: 305-18.
9. Scanlon CS, van Tubergen EA, Inglehart RC, D'Silva NJ. Biomarkers of epithelial-mesenchymal transition in squamous cell carcinoma. J Dent Res, 2013; 92: 114-21.
10. Fernandez A, Marshall M, Santibanez N, Martinez C, Fernandez J, Martinez R. Comparing the Immuno-Expression of Endothelial Markers in Normal Oral Mucosa, Oral Epithelial Dysplasia and Oral Squamous Cell Carcinoma: Relationship between ECadherin, Vimentin, CD31, CD117 and Epithelial-Mesenchymal Transition. MOJ Anat Physiol, 2017 Sept; 4(2): 301-6.
11. De Freitas Silva BS, Yamamoto-Silva FP, Pontes HR, Pinto DS. E-cadherin down regulation and Twist overexpression since early stages of oral carcinogenesis. J Oral Pathol Med, 2014 Feb; 43(2): 125–31.
12. Kaur J, Sawhney M, DattaGupta S, Shukla NK, Srivastava A, Walfish PG,. Clinical significance of altered expression of ß-catenin and E-cadherin in oral dysplasia and cancer: Potential link with ALCAM expression. PLoS One, 2013; 8(6): e67361.
13. Kaur G, Carnelio S, Rao N, Rao L. Expression of E-cadherin in primary oral squamous cell carcinoma and metastatic lymph nodes: an immunohistochemical study. Indian J Dent Res, 2009 Mar; 20(1): 71-6.
14. Zhou JP, Tao D, Xu Q, Gao Z, Tang D. Expression of e cadherin and vimentin in oral squamous cell carcinoma. Int J Clin Exp Pathol, 2015 Mar; 8(3): 3150-4.
15. Fan HX, Wang S, Zhao H, Liu N, Chen D, Sun M, Zheng JH. Sonic hedgehog signaling may promote invasion and metastasis of oral squamous cell carcinoma by activating MMP-9 and E-cadherin expression. Med Oncol, 2014 Jul; 31(7): 41-3.
16. Liu LK, Jiang XY, Zhou XX, Wang DM, Song XL, Jiang HB. Upregulation of vimentin and aberrant expression of E cadherin in oral squamous cell carcinomas: correlation with the clinicopathological features and patient outcome. Mod pathol, 2010 Feb; 23(2): 213-224.