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An Insight into Field Cancerization Through basic Fibroblast Growth Factor in Radical Neck Dissection

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Abstract

In India Oral Squamous Cell Carcinoma(OSCC) contributes for about 40% of all the cancers. The delayed presentation or the tumor cell insensitivity to chemotherapy has resulted in less than 5 year survival rate. Most OSCCs develop within precancerized epithelium fields that contain keratinocytes at different stages of transformation. The persistence of such fields of precancerization, where there has previously been OSCC is considered as cause for the high-rate of occurrence of new tumors. basic Fibroblast Growth Factor (bFGF) is one such marker that regulates tumor growth, proliferation and metastasis. Evaluating bFGF during radical neck dissection for clear margins can provide better prognosis.

Methodology: 30 cases with OSCC that underwent radical neck dissection were included in the study. Tumor tissue along with apparently normal adjacent mucosa were stained with monoclonal bFGF antibody for immunoexpression.

Results: Study showed male predominance with 25:5 male: female ratio with mean age 56±4.95 years among females and 53.4±14.09 years among males. 10 cases showed positive lymph node metastasis. 5 cases showed recurrence within 3 years of radical neck dissection.

Conclusion: In our study the immunoexpression of bFGF in the epithelium and in the connective tissue stroma of the apparently adjacent normal mucosa showed either similar expression or reduced expression compared to the lesional tissue suggesting that the loss of bFGF expression could be because of the molecular changes occurring within, which might lead to more aggressive tumors and decreased disease free and total survival. Targeting bFGF in therapeutic aspects and evaluating bFGF during radical neck dissection for clear margins

could provide better prognosis and might increase the disease free state.

Introduction

OSCC accounts for about 90% of all the malignancies in the oral cavity. Despite diagnostic technical advances and improvement in treatment modalities, the poor prognosis of OSCC still continues. [1] The existence of transformed cells in areas that are adjacent to the primary tumor site is referred as Field Cancerization.[2] The relapse occurs due to field cancerization in most of the cases. The carcinogenic process involves various molecular events for the transformation of a normal cell into a cancer cell. In recent years different cancer biomarkers are of interest in research. Potential biomarkers for diagnosis and prognosis of OSCC have been reported in the literature. One such novel molecule is basic Fibroblast Growth Factor (bFGF) which is a strong mitogen. bFGF initiates proliferation of mesodermal and neuroectodermal cells. It stimulates hematopoeisis, angiogenesis, neuronal degeneration and remodelling. Also seen in tumor development and wound healing. bFGF is studied in various carcinomas and also as field cancerization biomarker in breast carcinoma. [3] However no studies have been conducted on the role of bFGF in field cancerization in oral mucosa in patients with OSCC. Hence the present study was conducted to evaluate the expression of bFGF and its role in OSCC and Apparently adjacent normal mucosa to aid in the evaluation of transformed cells in areas that are adjacent to the primary tumor site referred as field cancerization.

Materials and Methods

30 cases with OSCC that underwent radical neck dissection were included in the study. Tumor tissue along with apparently normal adjacent mucosa were stained with monoclonal bFGF antibody for immunoexpression for intensity, percentage and localization in epithelium and connective tissue.

Results

Demographic data shows male predominance with 5/30 patients being female and 25/30 being male. The mean age 56±4.95 years among females and 53.4±14.09 years among males was observed. These findings were in accordance with IARC database wherein the peak age of OSCC was noted in the 5^{th} - 6^{th} decade. 10 cases showed positive lymph node metastasis. 2 cases showed positive margins on histopathological observation. 1/30 cases recurred within 1year of post resection of primary tumor, 3/30 cases recurred within 2 years of post resection of primary tumor, 1/30 cases recurred within 3 years of post resection of primary tumor.

Table 1: Immunoexpression In The Epithelium:

Parameters	Scoring	OSCC No of Cases (%)	Apparently Adjacent Normal Mucosa No of Cases (%)
Intensity Fischer Exact Test- P Value .795	Mild	12(40)	13(43.3)
	Moderate	12(40)	13(43.3)
	Intense	12(40)	13(43.3)
% Of Positive Cells Fischer Exact Test: P Value of .769	1-25%	9(30)	9(30)
	25-50%	17(56.7)	15(50)
	>50%	4(13.3)	6(20)
Localization of Expression	Membrane	5(16.7)	5(16.7)

Fischer Exact Test: P Value of 1	Cytoplasm	16(53.3)	16(53.3)
	Membrane And Cytoplasm	9(30)	9(30)

Table 2: Immunoexpression In The Connective Tissue:

Parameters	Scoring	OSCC No Of Cases (%)	Apparently Adjacent Normal Mucosa No Of Cases (%)
Intensity Fischer Exact Test- P Value .789	Mild	12(40)	10(33.3)
	Moderate	12(40)	10(33.3)
	Intense	12(40)	10(33.3)
% Of Positive Cells Fischer Exact Test: P Value Of .924	1-25%	8(26.7)	7(23.3)
	25-50%	17(56.7)	17(56.7)
	>50%	5(16.7)	6(20)
Localization Of Expression Fischer Exact Test: P Value Of 0.721	Membrane	2(6.7)	3(10)
	Cytoplasm	18(60)	15(50)
	Membrane And Cytoplasm	10(33.3)	12(40)

Table 3: Correlation between the intensity, percentage of immunoexpression and localization of bFGF in epithelium and connective tissue among OSCC and apparently adjacent normal mucosa

	OSCC	apparently adjacent normal mucosa
Intensity	0.583 (p=0.001)	0.779 (p<0.001)
% of positive cells	0.652 (p<0.001)	0.576 (p=0.001)
Localization	0.720 (p<0.001)	0.524 =0.003)

Non Parametric correlation (Spearman's correlation) was done between the intensity, percentage of immunoexpression and localization of bFGF in epithelium and connective tissue among OSCC and apparently adjacent normal mucosa: Positive correlation was noted in the intensity, percentage of positive cells and localization of the expression of bFGF in the epithelium and connective tissue within the OSCC with p value of = 0.001, <0.001 and < 0.001 respectively suggesting it to be statistically significant. Positive correlation was noted in the intensity, percentage of positive cells and localization of the expression of bFGF in the epithelium and connective tissue within the apparently adjacent normal mucosa with p value of < 0.001, =0.001 and =0.003 respectively suggesting it to be statistically significant.

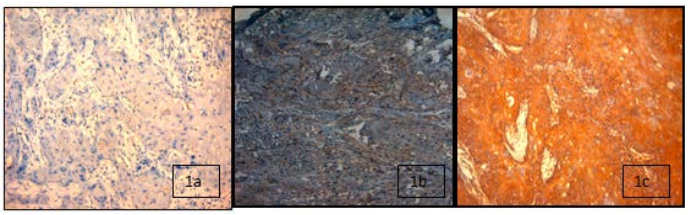

Fig1: Immunoexpression for bFGF in OSCC showing mild intensity (1a), moderate intensity (1b) and intense intensity (1c)

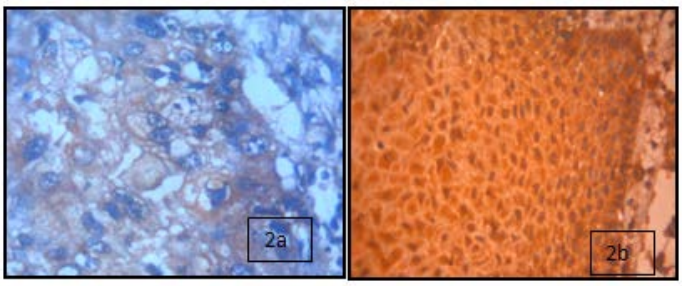

Fig2: Immunoexpression for bFGF in OSCC showing membranous localization (2a) and cytoplasmic and membranous localization (2b)

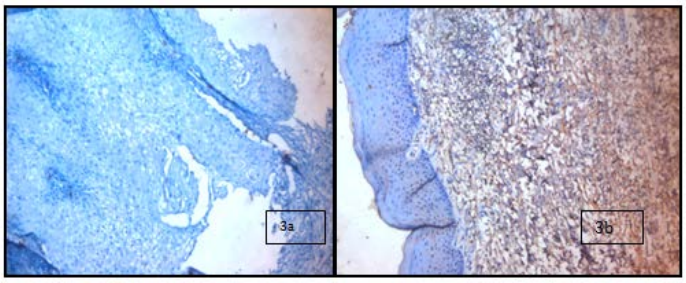

Fig 3: Immunoexpression for bFGF in OSCC with recurrence showing negative immunoexpression in OSCC (3a) and negative immunoexpression in Apparently adjacent normal mucosa

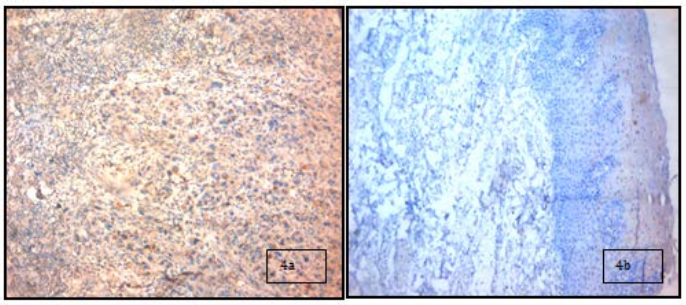

Fig 4: Immunoexpression for bFGF in OSCC with recurrence showing positive immunoexpression in OSCC (4a) and reduced expression in apparently adjacent normal mucosa (4b)

Discussion

Carcinogenesis is a multi step process with oral carcinoma being no exception. This multistep process involves alterations at molecular level. [4]A wide range of molecular markers and gene alterations are involved in cell cycle regulation, apoptosis, cell migration, cell adhesion and tumor microenvironment. Apart from molecular changes which may play a role in tumor progression and metastasis, clinical and histopathological parameters are also strongly associated with tumor progression, metastasis and prognosis. Clinical parameters such as mode of tumor invasion, presence of lymph node metastasis, extra-capsular spread, clear surgical margins, loco regional recurrence (LRR) and invasive tumor front grade are strongly associated with survival rate. [5] OSCC has a high propensity for local failure. It has been attributed to local recurrence at the primary site or by the occurrence of second primary tumors (SPT) due to field cancerization. In normal tissue, basic Fibroblast Growth Factor is present in basement membranes. It is detected in the sub endothelial extracellular matrix of blood vessels. Until no signal peptide is received it remains membrane bound. During both wound healing of normal tissues and tumor development, the action of heparin sulphate-degrading enzymes activates bFGF. This further monitors the formation of new blood vessels.[6]

All the cases of OSCC were positive for bFGF. Within the tumor tissue the immunopositivity varied greatly in the different areas from a scattered weak positivity to dense positivity suggesting that there are variation in distribution of receptors for proteoglycan binding. [7] Staining intensity for bFGF increases as the grade of malignancy increases.[8] 16/30 (53.3%) showed moderate positivity. 4 cases showing mild expression and 6 cases with moderate expression also had positive lymph node metastasis. 10/30 cases showed immunoexpression in basal and parabasal layers where it is normally expressed. Whereas 6/30 cases expressed in superficial 1/3rd suggesting that cells in the superficial 1/3rd are acquiring a different morphology and expression pattern of keratin and thus are suggestive of expressing bFGF.[9] The remaining cases showed immune positivity throughout the epithelium. 8/10 cases with

positive lymph node metastasis expressed bFGF particularly in basal , parabasal and in the superficial layers of epithelium. The number of positively stained cells with bFGF decreased as the grade of malignanacy increases.[7] Localization of immunoexpression of BFGF in epithelium of OSCC showed cytoplasmic staining in 16/30 cases that LMW(Low Molecular Weight) FGF2 decreased with increasing grades of tumor. Whereas 9/30 (30 %) of cases showed both membrane and cytoplasmic staining suggesting that there is no signal peptide with increasing grades of tumor. This also shows that tumors synthesizing bFGF are less aggressive than those which do not. None of the cases expressed bFGF in nucleus suggests that no HMW (High Molecular Weight)FGF2s were present and thus no intracrine effect. [9] Intensity of immunoexpression within the connective tissue , all the cases of OSCC were positive for bFGF. Only one case showed intense positivity for bFGF with positive lymph node metastasis. This suggests that intensity in stromal expression of bFGF is inversely associated with lymph node metastasis.[10] Percentage of positivity of cells increased with tumor grade as well as in tumor supporting stroma of the apparently adjacent normal mucosa. WDSCC groups show expression of bFGF in membrane suggesting that they still do not have a signal peptide suggesting it to be still less aggressive.[9]

Correlation between the intensity, percentage of positivity and localization of immunoexpression of bFGF in the epithelium and connective tissue within OSCC showed positive correlation. Positive correlation was noted in the intensity, percentage of positive cells and localization of the expression of bFGF in the epithelium and connective tissue within the apparently adjacent normal mucosa. This suggests that interactions between tumor cells and tumor allied stromal cells have cancer phenotypes that are aggressive.[11] In our study the immunoexpression of bFGF in the epithelium and in the connective tissue stroma of the apparently adjacent normal mucosa showed either similar expression or reduced expression compared to the lesional tissue. Study also suggests that the apparently adjacent normal mucosa which is clinically/histologically considered as clear margins may have undergone cellular biomolecular changes which may result in secondary primary tumors or recurrence of the existing primary tumor.

Conclusion

The immune expression of bFGF in the epithelium and in the connective tissue stroma of the apparently normal adjacent mucosa showed either similar expression or reduced expression compared to the lesional tissue suggesting that the loss of bFGF expression in apparently adjacent normal mucosa could be because of molecular changes occurring within, which might lead to more aggressive tumors and decreased disease free and total survival. However the current surgical practice includes wider excision margin than practised previously, still OSCC remained with an unfavorable prognosis. Targeting bFGF in therapeutic aspects and evaluating bFGF during radical neck dissection for clear margins could provide better prognosis and might increase the disease free state.

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