



Research article

Vimentin expression and its correlation with lymph node metastasis in oral squamous cell carcinoma

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ABSTRACT

Squamous cell carcinoma and Adenocarcinoma are common subtypes of carcinoma of oral cavity. More than six lakh cases of cancers of head and neck are being diagnosed globally every year and worldwide, it's the 6th most common cancer. Head and Neck cancers mostly take origin from epithelial lining of oral cavity, oropharynx, larynx and hypopharynx and 90% of them morphologically is predominantly squamous cell carcinoma. OSCC has a poor prognosis, the reason being metastasis to lymph nodes and its recurrence. So, the identification of specific markers with metastasis to lymph nodes should be done for early and specific diagnosis. Normal and neoplastic mesenchymal cells contain vimentin as major protein constituent of intermediate filaments. Vimentin does not show expression usually in non-neoplastic epithelial cells, but shows expression in mesenchymal cells. Vimentin as a marker of epithelial to mesenchymal transition is used in diagnosing lymph node metastasis in cases of OSCC.

Keywords: OSCC, Vimentin, Lymph Node Metastasis

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INTRODUCTION

Squamous cell carcinoma and Adenocarcinoma are two common subtypes of carcinoma of oral cavity. Carcinomas are malignant neoplasms, arising from epithelial cells and can be derived from any of the three germ layers¹.

Head and Neck cancers mostly take origin from epithelial lining of oral cavity, oropharynx, larynx and hypopharynx². Oral cavity is most common site of origin of approximately 95 % of all the squamous cell carcinomas of head and neck. Favored locations of squamous cell carcinoma to arise are ventral surface of tongue, floor of mouth, lower lip, soft palate and gingiva¹. Worldwide, sixth most common cancer is combined Head and Neck cancers².

EPIDEMIOLOGY

More than six lakh cases of cancers of head and neck are diagnosed globally every year.² Incidence is predominantly found in males. Male-Female ratio varies worldwide and regarding anatomical site with ratio 2.1 to 4.1.²

About 300000 new cases of OSCC have been reported each year.³ Prevalence of Oral cancers is 45 % in India. In males, the rate of morbidity and mortality is 6.6 per 1 lakh and 3.1 per 1 lakh respectively, while it is found to be 2.9 per 1 lakh and 1.4 per 1 lakh

respectively in females.²

Incidence of oral cancer in males is found to be 53842, where as in females, it is found to be 23161. It is found that men are 2-3 times more affected than females in India, due to change in behavioural and life style patterns.⁴

Predisposing Risk Factors

Risk factors include tobacco, slaked lime, Betel, Areca nut, actinic radiations, Consumption of alcohol, HPV 16, 18 infection, EBV, HSV, Candida and also associated with diet low in fruits and vegetables. Other risk factors include, family history, and for the cancers of lower lip, known predisposing influences are sunlight and pipe smoking and consumption of betel leaves and areca nuts in India.¹ Oral squamous cell carcinoma has not a good prognosis, the reason being spread to lymph nodes and recurrence.³

Pathogenesis⁵

Its pathogenesis is multifactorial. Various risk factors as mentioned above play a significant role in its pathogenesis. 70% of SCC involving the tonsils, the base of tongue, and the pharynx harbors HPV. HPV vaccine helps to reduce the risk of HPV associated head and neck SCC besides cervical cancer. It's a multi-step process involving the activation of tumor causing genes and inactivation of

the genes which suppress their growth activity, sequentially in a clonal population of cells. Loss of chromosomal regions of 3p and 9p21 is the first change. Then there is inactivation of the p16 gene resulting in the conversion from normal to increase in cell number due to loss of heterozygosity. Then loss of heterozygosity 17p occurs simultaneously in association with alteration in the p53 gene and it leads to the development of dysplasia. A common late event which can be seen as cyclin D1 gene' amplification and overexpression.

Diagnostic Tools

Important diagnostic tools being clinical examination, and lymph nodes palpation. Different diagnostic modalities include: vital staining (Rose Bengal, Methylene Blue, Toluidine Blue), Histopathology, Photospectrometry, FNAC, Liquid based cytology and Molecular Analysis. But HPE still remains as gold standard.⁶

Histopathological Grading

Various grading systems has been used in diagnosing oral squamous cell carcinomas: TNM staging, Broder's system (1920), Jakobsons, Fisher (1975), Lund (1975), Willen (1975), Crissman, Anneroth, Bryne (1989-92).⁷

Broder's system of classification:⁸

Well differentiated (Grade 1)	= <25% undifferentiated cells
Moderately differentiated	= <50% undifferentiated cells (Grade 2)
Poorly differentiated (Graded 3)	= <75% undifferentiated cells
Anaplastic (Graded 4)	= >75% undifferentiated cells

Because individual reporting variations influence the histological grade and predicting biological behavior is not possible.

Immunohistochemistry in Oral Squamous Cell carcinoma

IHC is used as a standard tool in making diagnosis and for prognosis of tumours with the beginning. It has been used to characterize the proteins within the cells, the other cell components in the tissues. Antigen-Antibody reaction is basic procedure in IHC. It is used to determine Antigens with the use of specific Antibodies which can be appreciated on staining by Immunohistochemistry.⁹ In a specific disease, IHC is used as an important use as monoclonal and polyclonal antibodies are used to find the specific Antigen.

The antibody binding site is seen using ordinary or fluorescent microscopy. With the help of markers like fluorescent dye, enzymes, radioactive elements, which is bind directly to primary antibody or to anspacificsecondary antibody? ¹⁰ Oral squamous cell carcinoma has not a good prognosis, the reason being spread to lymph nodes and recurrence. So, the identification of specific markers with metastasis to lymph nodes should be done for early and specific diagnosis. ³

Vimentin

Intermediate filaments are found approximately in each eukaryotic cell. ¹¹ In humans, intermediate filaments are made up of special intermediate filament proteins, encoded by more than seventy genes. The intermediate filaments are categorized into six gene

families based on the structure of proteins, homology sequence and the pattern of expression.¹² A part of the cytoskeleton is formed by Vimentin, which is around 57 k Da protein. ¹³ Vimentin is a multi-functional protein with 466 amino acids and its upregulation in epithelial cells results in some changes like in cell shape, loss of contact between cell to cell in addition to increasing cell motility. ¹⁴

Various intermediate filaments are distinguished from one another by their immunological specificities, chemical properties and distribution of cell-type. ¹⁵ Normal and neoplastic mesenchymal cells contain vimentin as major protein constituent of intermediate filaments. ¹ Vimentin does not show expression usually in normal epithelial cells, but shows expression in mesenchymal cells. ³

Cell migration is regulated by Vimentin in many cells. Vimentin filaments make matrix adhesions in fibroblasts. ¹⁷ Vimentin expression is seen in normal mesenchymal cells, and it maintains the structure of the cell and cohesion of the tissues. ¹⁸ Its expression can also be found in some other cells in specific conditions like cultured cells or in malignant effusions.¹⁹

Utility of Vimentin in Oral Squamous Cell Carcinomas

Its expression by epithelial malignancy is found to be linked with high invasiveness and is contemplated as a dependable marker of a process in which epithelial counterpart is transformed into mesenchymal counterpart. Vimentin expression has also found to be associated with high prevalence of metastasis in lymph nodes in OSCC. ¹⁹ So, Vimentin is used in diagnosing metastasis in lymph nodes in cases of OSCC.¹⁶

Epithelial Mesenchymal Transition

This is a crucial event in the process in which there is progression toward cancer spread. ¹⁷ In this process, epithelial cells attain fibroblast like properties, and become mobile and invasive.²⁰ In this event, many phenotypic features are lost by epithelial cells and gain features which are found in mesenchymal cells. In this process, there is transformation of the epithelial cells which were initially polarized into mesenchymal-like cells that show no polarization and high mobility, a characteristic sign of this process.¹⁹

Criteria for Immunohistochemistry used³

Vimentin expression is quantitated by determining the average percentage positive cells minimum in 5 random fields at high power.

The intensity of the vimentin-immunoreactivity

- 1 + as Mild
- 2 + as moderate
- 3 + as strong

At low power, selected positive cells over uniform distribution area, average percentage positive cells in at least 5 random fields at high power

Zero to Five percent as 0

Six to Twenty Five percent as 1

Twenty six to Fifty percent as 2

Fifty one to Seventy Four percent as 3

Immunoreactivity score is product of proportion positive score and intensity score

IHC Score >4: High Vimentin expression; High risk for lymph node metastasis

Correlation between Vimentin expression and Broder's grading system

In a study carried out by V.C.de Araujo et. al, researches concluded that vimentin positivity was associated with almost 60 % of the cases and this positivity was found mostly in high grade tumors and suggested that vimentin expression indicates bad prognosis in OSCC.¹¹

Jingping Zhou et. al. conducted a study and found that Vimentin had 25 %, 33.3% and 66.7% expression in Well, Intermediate and Poorly differentiated OSCC.²¹

So, fact can be stated that most studies tells about Vimentin expression having a poor outcome, mostly in high grades of differentiation but vimentin expression may also found to be high in low and medium grades of differentiation.

Correlation between Vimentin expression and Lymph Node Metastasis

JIN Hiroyuki et. al. conducted a study in which vimentin expression was identified in approximately 74% and the significantly higher incidence of metastasis in lymph nodes was seen in vimentin-positive cells.¹⁶

Jingping Zhou et. Al found in his study that positive expression of Vimentin was lower in tissues without lymph node metastasis.²¹

We also want to state the fact that many studies have found a direct correlation between high Vimentin expression and lymph node metastasis.

Role of Vimentin in other Carcinomas

It is known that Vimentin shows expression in carcinoma of prostate, breast, gastrointestinal tract, central nervous system, lung, and malignant melanomas of skin.²² EMT related with the invasive behavior is found in Pituitary macro adenomas and this process is related to expression of Vimentin.²³ In Colorectal carcinomas, it has been found that, vimentin gene expression is altered and revealing an association between its expression and tumor aggressiveness²⁴ and high expression of Vimentin is not having a good prognosis in colorectal malignancy.²⁵

A statistically significant correlation has been found between vimentin-positive Gastric Cancer cells and advanced clinical stage, macroscopic scirrhus-type, histological diffuse-type, lymph node metastasis and lymphatic invasion.²⁶ High expression of Vimentin has been seen in high-grade ductal carcinoma of the breast.²⁷ Its expression is also found to be high in medullary carcinomas of breast and associated with bad prognostic factors.

Increased vimentin expression is seen in breast carcinomas occurring in females in age less than 50 years and Vimentin-positive

cells are associated with high grade tumors, and increased tumor proliferation, however its expression has no correlation with tumor size, nodal metastasis, and survival status²². Also there is a diagnostic role of vimentin in urinary bladder carcinomas.²⁸ In Mucoepidermoid carcinomas of salivary glands, Vimentin expression is found to be high²⁹ Vimentin expression is also seen in benign and malignant salivary gland tumours.¹¹ Also association of high vimentin positivity with formation of tumor, spread and invasion in non-small cell cancer of lung³⁰.

CONCLUSION

OSCC is seen commonly, not having a good prognosis, mainly due to its metastasis in lymph nodes and recurrence. IHC analysis can be applied as an adjunct for grading oral squamous cell carcinoma in correlation with Broder's grading system.

Identification of specific markers of OSCC with metastasis to lymph nodes should be done for early and specific diagnosis. Mesenchymal markers like Vimentin will be valuable help in diagnosing metastasis in lymph nodes in patients of OSCC as its expression by epithelial malignancy is found to be associated with high invasiveness and is contemplated as a dependable marker of a process in which epithelial counterpart is transformed into mesenchymal counterpart

So, it will be very helpful in diagnosing the cases with poor outcome, and their management can be done early.

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