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Study of Expression of Vascular Endothelial Growth Factor In Breast Cancers At A Tertiary Care Centre

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Abstract

Aim

Breast Cancer is the most frequent cancer in India. Tumor angiogenesis has been considered as a crucial step in the cancer development and progression. Vascular endothelial growth factor (VEGF) is one important prognostic marker in patients with breast cancer. The aim of the study isto see the expression of VEGF in breast cancers by immune histochemistry..

Materials and methods

Formalin fixed paraffin embedded sections of 100 cases of malignant breast lesions were taken up for the study and subjected to immune histochemistryusing VEGF.

Results

The intensity of VEGF immunostaining in malignant breast lesions was evaluated and scoring was graded as 0,1+,2+,3+ and 4+. Statistical analysis was performed with Chi-Square test and significant differences were noted between these 3 groups (p value< 0.05).

Conclusion

VEGF expression correlated well with the grade and stage of tumor indicating that VEGF positive tumors are biologically aggressive and are associated with poor prognosis.

Keywords: VEGF, Immunohistochemistry.

Introduction

Breast cancer is the most frequent cancer in India and mortality rates associated with it is higher in India. Molecular mechanism are involved in its pathogenesis with many genetic alterations and oncogene protein products having a role to play which interfere with the mechanism of proliferation and differentiation of tumor growth. The prognostic biomarkers include raised levels of expression of Proliferation markers like Ki67, expression of Estrogen Receptor (ER) and Progesterone Receptor(PR), amplification and over expression of HER2, cyclin D1 etc. Recent studies have found tumor angiogenesis as a critical step in cancer development and progression. Among these, vascular endothelial growth factor (VEGF) has emegred as a prognostic marker with several type of cancer including breast cancer.[1]

VEGF is produced and secreted by a number of normal cells and is a polyfunctional molecule that has been implicated in vasculogenesis, endothelial cell proliferation and migration, vascular permeability, and stromal degradation by the activation of some proteolytic enzymes involved in tumor invasiveness and angiogenesis.[2]VEGF is required for the initial stages of breast cancer tumor genesis, and this initial effect is related to the formation of neovascular stroma. Keeping all these alterations in mind,

in this present study we have studied the VEGF expression in malignant breast lesions.

Materials and Methods

The study was conducted at a Tertiary Care Hospital with 100 cases of malignant breast lesions taken up for study. All females' patients irrespective of their age and other physical conditions during the period of June 2010 to January 2017 were taken up for the study. Females of ages ranging from 20 to 70 years were taken up for the study and all of them underwent modified radical mastectomy (MRM).The diagnosis were reconfirmed on Hematoxylin and Eosin (H&E) stained sections and the appropriate blocks were subjected to IHC using VEGF antibody.

Scoring system

Positive immunoreactions showed a dark brown precipitate (cytoplasmic for VEGF). The intensity of the staining was assessed by a scoring system laid by Sophia K. et al[2].

Scoring according to Sophia K. et al, at objective 40x: (Table 1)

Score	Results	Interpretation
0	Negative	None or <5% cells positive
1+	Weak or Mild staining	Weak or mild staining; 5-10% of tumor cells are positive
2+	Moderate staining	<25% of tumor cells are positive
3+	Strong staining	Strong staining; 25-50% of tumor cells are positive
4+	Highly strong staining	Highly strong staining; >50% of tumor cells are positive

Table1. Scoring for VEGF

Statistical analyses

Statistical analyses of all results were done by using Chi square test at level of significance $p \leq 0.05$ was done.

Results

The malignant lesions in the study were seen in all histological grades of the tumor with majority of the cases having a higher grade. These also presented with different stages with predominant cases having a higher stage with a presentation of Stage III being more common followed by Stage IV. None of the cases presented in Stage 0 or Stage I in our study. The axillary lymph nodes were involved in 70% of our cases (Table 2).

Features	Grade			Stage					Axillary Lymph Nodes	
	I	II	III	0	I	II	III	IV	Positive	Negative
No. of cases	10	40	50	0	0	20	60	20	70	30

Table 2. The characteristic features of all malignant breast lesions.

Out of the 100 cases of malignant breast lesions, expression of VEGF was noted 75% of cases in the current study (Figure 1).

Intensity of staining of VEGF in malignant breast lesions:

Among the 75 cases, 25 cases showed a weak (1+) positivity for VEGF wheras35 cases showed a moderate positivity (2+), 15 cases showed a strong (3+) positivity and none of the cases showed a highly strong (4+) positivity (<p=0.05) (Table 3).

Intensity of staining of VEGF	No. of cases	Percentage
1+	25	33
2+	35	47
3+	15	20
4+	0	0

Table 3. Percentage of expression of intensity of staining in malignant breast lesions for VEGF.

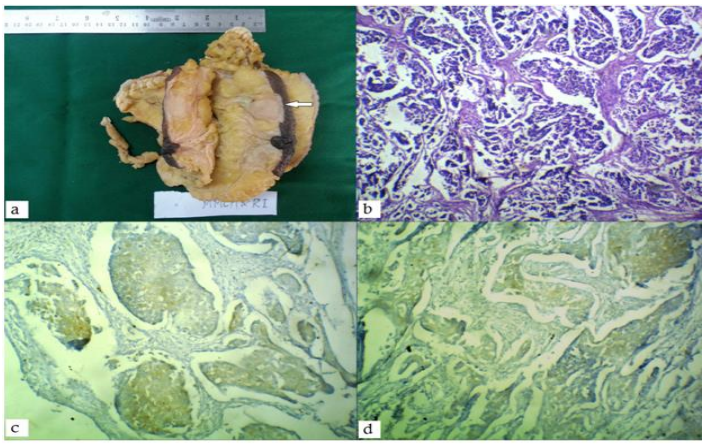

Figure 1. VEGF in IDC Breast. a) IDC breast with a large

firm grey white area. b) H & E of IDC breast. (10x) c & d) Positive Immunostaining of VEGF in IDC breast (10x).

VEGF overexpression and grade of tumor

VEGF immunohistochemical analysis in relation to grade of tumorrevealed that none of grade I was positive, 30 (75%) out of 40 cases of grade II were positive, 45 out of 50 (90%) cases of grade III were positive for VEGF. The detection rate of VEGF correlated well with the grade of tumor with higher grade tumor showing positivity in a higher proportion whereas the tumor with lower grade I, VEGF expression was not detected $p<0.05$ (Table 4).

Grade of Tumor	Positive Staining	Negative Staining	Total
I	0	10	10
II	30	10	40
III	45	5	50

Table 4. Expression of VEGF in relation to grade of the tumor

VEGF Overexpression and stage of tumor

VEGF immunohistochemical expression was reported in all 20 cases of stage IV with 45 out of 60 cases in stage III showing positivity and among the 20 cases in stage II, 10 cases were positive for VEGF. There was significant positive correlation between VEGF overexpressionand the stage of tumor (p value <0.05), and a higher proportion of cases were found in stage III and IV (Table 5).

Stage of Tumor	Positive Staining	Negative Staining	Total
I	0	0	0
II	10	10	20
III	45	15	60
IV	20	0	20

Table 5. Expression of VEGF in relation to the stage of the tumor

VEGF immunohistochemical expression and axillary lymph node involvement

65out of 70 cases of node-positive breast cancer found to have VEGF overexpression (92%),while only ten out of 30 cases of node-negative breast cancer showed VEGF overexpression (33%) ,with significant difference between these two groups. (p value <0.05)

Discussion

Expression of VEGF in malignant breast lesions

Overexpression of VEGF in infiltrating ductal carcinoma was found in 75% of cases. This finding is higher than those of Melanie Schmidt *et al* (2008)) who reported that 60% were VEGF positive[9]. It was higher than a study conducted by ES Al Harris *et al*who reported. 61.5% were VEGF positive[4]. It was lower than those of Anca Maria Cimpean *et al* (2008)who reported that 87.1% of primary breast carcinoma were VEGF positive[5].In this study VEGF overexpression was detected in 75% of breast cancer patients .

VEGF overexpression and grade of tumor

VEGF immunohistochemical analysis in relation to grade of tumor revealed that none of grade I was positive, 75% of grade II were positive, 90% of grade III were positive for VEGF. There was highly significant positive correlation between VEGF overexpression and grade of breast cancer($p<0.05$).This finding correlated well with studies conducted by Linderholm B *et al*.,(2000), Gottfried *et al*.,(2004), Shankar R *et al*.,2006) and AL-Harris E *et al*(2007) [4, 6-7]

VEGF overexpression and stage of tumor

VEGF immunohistochemical expression was reported in 10 out of 20 cases of stage II, in 45 out of 60 cases of stage III, and in all 20 cases of stage IV .There was significant positive correlation between VEGF overexpressionand the stage of tumor (p value <0.05), and a higher proportion of cases were found in stage III and IV.

These findings correlated well with Collagy G *et al.*, (2000), Bolat F *et al*.,(2006), AL-Harris E *et al*(2007) and Xu W *et al*., (2007).[4, 9-11]

VEGF is expressed more in those with advanced stage which reflects the aggressive behavior of the tumor.

VEGF immunohistochemical expression and axillary lymph node involvement

VEGF overexpression is higher in node positive breast cancer than in node negative breast cancer with significant difference between these two groups(p value <0.05).

This finding agreed with that reported by Yi WJ*et al*.,(2003), Gottfried *et al*., (2004), Wang X *et al*., (2006) [18, 1 2-13]

Conclusion

The pathogenesis of breast cancer is a multi-stage process involving progressive accumulation of genetic alterations.

In this study, VEGF overexpression was significant in all grades and stages of breast cancer (p<0.05).VEGF overexpression correlated well with the grade and stage of tumor indicating that VEGF positive tumors are biologically aggressive and are associated with poor prognosis.

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