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Original Research Article

E-cadherin expression – Significance in gastric carcinoma

Prathipaa R[1], **Divya J**[1,*]

[1] *Dept. of Pathology, ACS Medical College, Chennai, Tamil Nadu, India*

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ABSTRACT

Introduction: Gastric carcinoma is aggressive cancer with poor prognosis. E-cadherin is 120 kD calcium mediated transmembrane glycoprotein that forms the cell adhesion molecule which maintains the integrity of epithelial cells by keeping it cohesive. E-cadherin down regulation in gastric cancer is of great significance in the dissociation of epithelial cells, alteration of tumor microenvironment, invasion, tumor genesis and metastasis.

Aims and Objective: To study the E-cadherin expression in gastric carcinoma and to correlate with the existing clinical and pathological parameters.

Materials and Methods: The study included 100 confirmed cases of adenocarcinoma from gastrectomy specimens. Immunostaining was done with E-cadherin mouse monoclonal antibody and expression studied based on the staining pattern and correlated with various clinico-pathological parameters. Data was statistically analysed by chi square test with calculation of p-value.

Results: E-cadherin expression showed aberrant staining in 87% cases. E-cadherin expression showed significant correlation with histological types, tumor grade, tumor depth of invasion, lymphovascular invasion and lymphnode involvement. The expression E-cadherin in gastric cancer was aberrant in 100 % of diffuse type and poorly differentiated tumors. 96.61% of lymph node positive cases showed aberrant expression. The cases with aberrant expression were comparatively more in T3 (100%) and T4 (93.75%) tumors.

Conclusion: The study highlights the significance of E-cadherin expression in gastric carcinoma that can be utilised as a potent bio marker for aggressiveness, metastasis and prognosis.

1. Introduction

Gastric carcinoma ranks fifth among cancers in the world and fourth among cancer deaths in the world in 2020.[1] The incidence of gastric cancer in 2020 was 1.1 million cases out of which 770,000 deaths were estimated.[2] Gastric adenocarcinoma constitutes 90% of malignancy of the stomach.[3,4] The gastric cancer is classified into cardia and non-cardia based on anatomical subsites. The common risk factors are smoking, alcohol, preserved salted foods. The strong association between Helicobacter pylori and non-cardia cancers were found in 90% cases while gastroesophageal reflux and obesity were associated with cardia cancer.[5,6]

The detachment of adhesion molecules between cancer cells forms the initial step in the process of penetration of tumor cells in to the stroma and metastasis. E-Cadherin is a calcium mediated transmembrane glycoprotein that maintains the cohesiveness of the epithelial cell.[7] Its is considered as tumor suppressor gene and its downregulation is associated with the dissociation and invasion of tumor cells in gastric carcinoma.[8–10] Recent studies postulated role of E-cadherin in cancer growth

* *Corresponding author*.
E-mail address: prathipaa.rl@gmail.com (Divya J).

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through modulation of intracellular signalling pathways. CDH 1 gene, on chromosome 16q22.1 codes E-cadherin protein and its mutation is associated with hereditary diffuse type gastric cancer.[11] The study aims to demonstrate the E-cadherin expression in gastric carcinoma and to correlate with the existing histopathological parameters.

2. Materials and Methods

The study included 100 case slides from the pathology department in a tertiary care hospital. 100 confirmed cases of gastric adenocarcinoma by histopathological examination from gastrectomy specimens during the period of 3 years from March 2019 to March 2022 were studied. The tissues were fixed in 10% neutral buffered formalin and subjected to routine histopathological processing. After embedding, the paraffin block made and tissues were cut into 4 to 5 micrometer thickness and sections were kept over the slide and stained with haematoxylin & eosin stain for routine histopathological examination. The variables studied were age, sex, tumor size and site, histological types, tumor grade, tumor depth of invasion, lymphovascular invasion and lymphnode status

To study the expression of E-cadherin in gastric carcinomas, immunostaining of E-cadherin was done using IgG1 monoclonal mouse antibody.

2.1. Interpretation of E-cadherin Expression on Immunohistochemistry

According to previous studies, positive staining was defined as strong golden brown membranous staining similar to normal epithelial cells. E -cadherin staining pattern was observed under light microscope and based on the pattern of staining, the expression of E cadherin was classified as normal and aberrant expression[12,13] (Table 1). Data analysis carried out statistically using Chi-square test with calculation of p-value.

3. Results

The study included 100 confirmed cases of gastric adenocarcinoma. The various clinco histopathological parameters included in our study were age, sex, tumor size and site, histological types, grade, depth of invasion, lymphnode status and lymphovascular invasion. E-cadherin expression studied with all the above parameters (Table 3). The mean age in our study was 57 years and grouped into two categories based on the mean age (< 57 & ≥57 years). The males were the predominant population in our study (61%). The most common location of adenocarcinoma in our study was antrum (53%) and least was cardia (17%). The cut-off for tumor size was taken as 5 cm and around 52% of tumors were ≥5cm. According to Lauren classification, gastric adenocarcinoma was classified into intestinal (76%) and diffuse (24%) histological types. Only 7 cases were well differentiated and predominant cases showed moderate differentiation (64%). Majority of the cases were in T2 (39%) and T3(42%) level of invasion. Only 3 cases were in T1 level of tumor invasion.

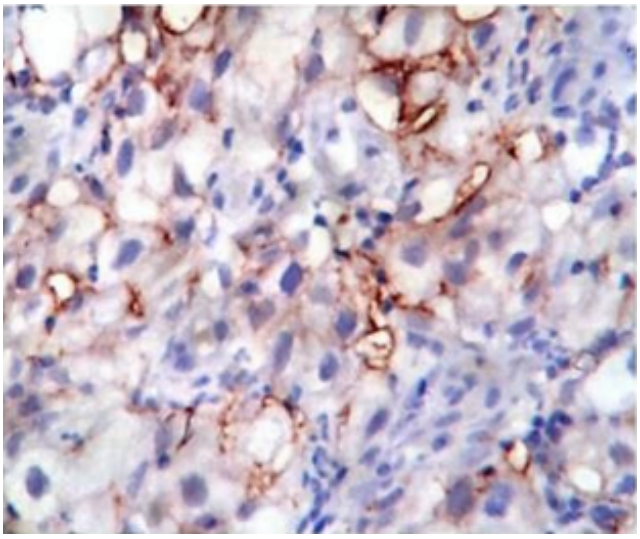

Fig. 1: IHCX400 -Aberrant expression (faint and loss of staining pattern) of E- cadherin in poorly differentiated tumors

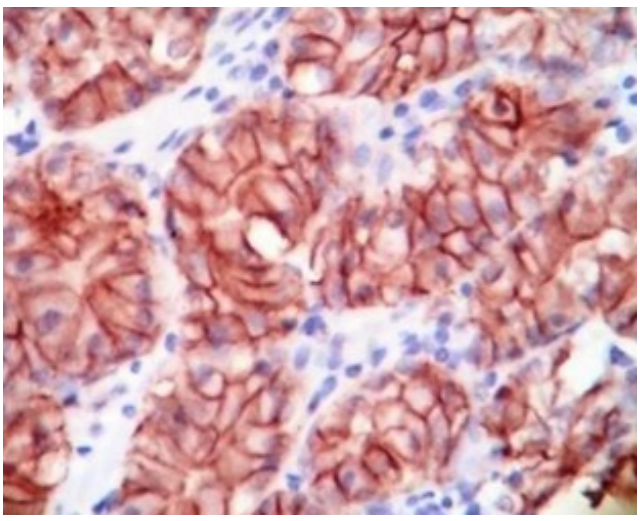

Fig. 2: IHCX400-Normal expression (strong membranous staining pattern) of E- cadherin

Out of 100 cases 87 of carcinoma showed aberrant expression and 13% showed normal expression (Figures 1 and 2). There expression of E-cadherin expression was not correlated significantly with the age, sex, tumor location, tumor size. The expression of E-cadherin was aberrant in 100% of diffuse gastric carcinoma and poorly differentiated tumors. Among 42 cases of T3 tumors, none showed normal expression and out of 16 cases of T4, 93.75% showed aberrant expression. In

Table 1: Interpretation of E-cadherin staining pattern.

Staining pattern	Expression of E cadherin
Strong and Membranous in >90 % of tumor cells	Normal
• Membranous and cytoplasmic • Reduced cytoplasmic, • Faint or absent staining	Aberrant

Table 2: Demographic features and expression of E-cadherin in gastric carcinoma

Demographic Features	No of cases (n=100)	Expression of E-cadherin		P value
		Normal (n=13)	Aberrant (n=87)	
Age				
<57 years	43	7(16.28%)	36(83.72%)	0.397
≥57 years	57	6(10.53%)	51(89.47%)	
Sex				
Male	61	9(14.75%)	52(85.25%)	0.513
Female	39	4(10.26%)	35(89.74%)	

Table 3: Histopathological features and expression of E-cadherin in gastric carcinoma

Histopathological features	No of cases (n=100)	Expression of E-cadherin		P value
		Normal (n=13)	Aberrant (n=87)	
Tumor size				
<5cm	48	7(14.58%)	41(85.42%)	0.445
≥5cm	52	5(9.62%)	47(90.38%)	
Tumor site				
Cardia	17	4(23.53%)	13(76.47%)	0.113
Body	30	1(3.33%)	29(96.67%)	
Antrum	53	8(15.09%)	45(84.91%)	
Histological Types				
Intestinal	76	13(17.11%)	63(82.89%)	0.29*
Diffuse	24	0	20(100%)	
Histological Grade				
Well differentiated	7	3 (42.86%)	4(57.14%)	0.005*
Moderately differentiated	64	10(15.62%)	54(84.38%)	
Poorly differentiated	29	0	29(100%)	
Tumor-Depth of Invasion				
T1	3	1(33.33%)	2(66.66%)	0.001*
T2	39	11(28.21%)	28(71.79%)	
T3	42	0	42(100%)	
T4	16	1(6.25%)	15(93.75%)	
Lymph Node				
Positive	59	2(3.39%)	57(96.61)	0.001*
Negative	41	11(26.83%)	30(73.17%)	
Lymphovascular invasion				
Present	67	4(5.97%)	63(94.03%)	0.002*
Absent	33	9(27.27%)	24((72.73%)	

our study 59 cases showed positive lymph nodes for adenocarcinoma out of which 96.61% showed aberrant expression. Among 67 cases with lymphovascular invasion, 94.03% of cases expressed aberrant E-cadherin. In our study there was no significant correlation of E cadherin expression with tumor histological type, tumor grade, tumor depth of tumor invasion, lymphovascular invasion and lymphnode metastasis (p value<0.05).(Table 3)

4. Discussion

Gastric carcinoma is an aggressive disease with increased morbidity and mortality. Gastric carcinoma is multifactorial with multistep carcinogenesis. E- cadherin is the prototype of all cadherins, located on the epithelial cell that forms tight adhesion between the cells. The E cadherin loss is the first step in the dynamic instability of tumor micro-environment such as epithelial cell dis

cohesiveness, motility of the cells, invasion into stroma and metastasis. The CDH1 that encodes E-cadherin is the most common gene mutated and responsible for loss or aberrant E- cadherin expression in gastric carcinoma. The decreased E-cadherin expression in gastric cancer plays major role in growth and development of tumor, invasion and metastasis. Studies showed the E-cadherin as tumor suppressor protein in gastric carcinoma and its downregulation was associated with diffuse gastric cancer.[14,15] Studies show H.pylori, a major carcinogen of gastric carcinoma, causes downregulation of E-cadherin in gastric cancer.[16]

In our study of 100 cases of gastric adenocarcinoma, 87% showed aberrant expression. Based on the lauren classification of histological types of gastric adenocarcinoma, E-cadherin expression was aberrant in 100% of diffuse gastric carcinoma compared to intestinal type(82.89%) and showed statistically significant correlation (p value=0.029). This finding is concordance with the studies by Sadanandan A et al and Sridevi C et al[17] in which aberrant E-cadherin expression in diffuse type were 95.50% and 83.33% respectively. This finding proved E-cadherin loss was associated with the diffuse histological type and hereditary diffuse gastric cancer.

A statistically significant difference between E-cadherin expression and grade of gastric carcinoma was noted in our study (p value=0.005). We found as a grade increases aberrant expression of E-cadherin also increases and 100% of poorly differentiated tumors in our study showed aberrant E -cadherin expression and it was similar to the study by Sadanandan A et al. The study by Joo Y E et al showed 79.3% of poorly differentiated tumors with aberrant expression.[18] This showed E-cadherin as cell-adhesion molecule in maintaining the cohesiveness of epithelial cells and its loss in dissociation of tumor cells.

On comparison of depth of invasion, aberrant E-cadherin expression was noted in 66.66%, 71.79%, 100%, 93.75% of T1, T2, T3, T4 cases respectively with statistically significant correlation (p value=0.001). This was similar to the study by Mayer et al.[19] Our study also showed a significant correlation of E- cadherin expression with lymph node involvement (p=0.001) and lymphovascular invasion (p=0.002). This suggested that the role of E-cadherin in tumor genesis and its decreased expression was associated with basement membrane breach, migration of tumor cells, stromal invasion and metastasis.

5. Conclusion

This study showed a statistically significant correlation of E-cadherin expression with histological types, grade of the tumor, depth of invasion of tumor, lymphovascular invasion and lymphnode status in gastric carcinoma. The E-cadherin expression changes from normal to aberrant with increase in grade of differentiation, depth of invasion of and lymph node metastasis. This highlights that E-cadherin expression could be used as a potential tool and novel bio marker for predicting aggressiveness, metastasis and prognosis in gastric carcinoma.

6. Conflict of Interest

There are no conflicts of interest in this article.

7. Source of Funding

None.

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Author biography

Prathipaa R, Associate Professor https://orcid.org/0000-0001-6873-9731

Divya J, Associate Professor https://orcid.org/0000-0003-2031-0666

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