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Original Article

Pathology Section

E-cadherin Immunoexpression Patterns in Gastric Carcinoma Histological Subtypes: A Hospital-based Descriptive Study

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ABSTRACT

Introduction: Gastric carcinoma is the second common Gastrointestinal (GIT) malignancy. Based on Global Cancer Observatory (GLOBOCAN) 2020 data, it is the 5th most common neoplasm and the 4th most common cause of death. Epithelial-cadherin (E-cadherin) is a transmembrane glycoprotein which plays a crucial role in maintaining cell-cell adhesion. Loss of E-cadherin contributes to enhanced invasion and metastasis in human cancers.

Aim: To study E-cadherin immunohistochemical expression in tumour cells and its association with gastric carcinoma histotypes.

Materials and Methods: It is a hospital-based descriptive study conducted at Department of Pathology, Osmania General Hospital, Hyderabad, Telangana, India from January 2010 to December 2012 as it was my dissertation. Routine histopathology and immunohistochemistry for E-cadherin were done on the sections. E-cadherin immunohistochemical staining and expression in tumour cells were evaluated according to the study by Jawhari A et al., Scores (0-3) were applied: 0-No staining; 1-Only cytoplasmic staining; 2-Cytoplasmic and membranous staining in the same case, 3-Normal membranous immunoexpression. Staining was evaluated based on absence of membranous expression scores (0 and 1) versus the presence of membranous expression (scores 2 and 3). Statistical analysis of the data was done by Chi-square test using Epi Info software.

Results: Total 70 cases were studied, of which 48 were gastric biopsies and 22 were gastrectomies. Gastric adenocarcinomas were classified as intestinal 40 cases (57.14%) and diffuse 30 cases (42.85%) according to Lauren's classification. Membranous staining of E-cadherin was seen in 34/40 cases (85%) of intestinal gastric cancer and 9/30 cases (30%) of diffuse intestinal cancer whereas non membranous or absent E-cadherin was seen in 6/40 cases (15%) of intestinal gastric cancer and 21/30 cases (70%) of diffuse gastric cancer. In this study, significant association was found between membranous E-cadherin expression (score 2 or 3) and intestinal histotype and absence of membranous expression (scores 0 or 1) and the diffuse histotype of gastric cancer.

Conclusion: Normal gastric mucosa shows strong membranous E-cadherin positivity. There is a change in the pattern of E-cadherin expression from membranous in intestinal type gastric adenocarcinoma to non membranous expression of E-cadherin in diffuse type of gastric carcinoma.

Keywords: Adenocarcinoma, Epithelial cadherin, Immunohistochemistry

INTRODUCTION

Gastric carcinoma is the fourth most common cause of cancer related deaths worldwide, according to GLOBOCAN data 2020 [1]. The most common histological type is adenocarcinoma which accounts for about 90-95% of gastric cancer [2,3]. Gastric adenocarcinoma is histologically classified into intestinal and diffuse type by the Lauren classification system [4]. The most important prognostic factor includes stage followed by histologic type [5]. Patients in the same stage and histologic type may have varied prognosis, therefore additional parameters have to be identified in order to better classify the biological subsets of the disease [6]. Early symptoms of both types of gastric adenocarcinoma resemble those of chronic gastritis and peptic ulcer disease including dyspepsia, dysphagia and nausea. As a result, these tumours are often diagnosed at advanced stages when symptoms such as weight loss, anorexia, early satiety, anaemia and haemorrhage trigger further diagnostic evaluation. Gastric cancer is more common in lower socio-economic groups and in individuals with multifocal mucosal atrophy and intestinal metaplasia. Gastric dysplasia and adenomas are recognisable precursor lesions associated with gastric adenocarcinoma [7].

A better understanding of the molecular basis of cancer has led to the development of molecular targeted therapies that interferes with signaling cascade involved in cell differentiation, proliferation, and survival.

E-cadherin (CDH1) is a Ca2+ dependent cell-to-cell adhesion molecule located on long arm of chromosome 16 (q22.1) [8,9]. It forms a multiprotein complex with catenins (α and β-catenin) which interact with the actin cytoskeleton [8]. It is a 120 kD transmembrane glycoprotein that is responsible for calcium-dependent intercellular adhesion by homotypic interactions [10-12]. It is expressed on the surface of epithelial cells, at the level of the intercellular junction and is important for establishing cell polarity, maintaining epithelial integrity and cellular differentiation [13,14]. It is an intercellular adhesion molecule which plays an essential role in the complex process of invasion and metastasis [15-18]. Mutations in the CDH1 gene have been observed in 50% of sporadic diffuse-type gastric cancers [19,20]. Altered E-cadherin expression due to genetic mutations is commonly seen in diffuse type gastric carcinomas and emphasises the significance of E-cadherin in early diffuse type tumours [21,22].

Hence, the present study aimed to study the pattern of E-cadherin expression in gastric adenocarcinoma by immunohistochemistry and to characterise gastric carcinoma histotypes based on E-cadherin immunoexpression.

MATERIALS AND METHODS

The study was done in the Department of Pathology, at Osmania General Hospital, Hyderabad, Telangana, India, from January

2010 to December 2012. Out of 70 specimens, of which 48 endoscopic biopsies and 22 gastrectomies, which were confirmed as adenocarcinoma in histopathological examination were included in the study. No ethical issues were involved in the study, as it is not involving subjects directly and being a part of dissertation work, the study was approved by the Head of Department.

Inclusion criteria:

- Histopathologically confirmed gastric adenocarcinoma was included.
- No prior treatment.
- Adequate tumour tissue for analysis.
- Complete clinicopathologic data (age, sex, histopathological diagnosis) was collected.

Exclusion criteria: Cases with extensive tumour necrosis without sufficient viable tumour cells for an accurate evaluation of the immunohistochemical results were excluded.

Study Procedure

Gastrectomy's and small biopsy specimens were received in 10% neutral buffered formalin. Detailed clinical history of each case including age, gender, clinical presentation, nature of specimen, location of the tumour were noted. The specimens were grossed, and sections were taken from representative sites. The sections were then processed in automated tissue processor and embedded in paraffin wax, 4 microns thick sections were cut, stained with Haematoxylin and Eosin (H&E), mounted and then examined by light microscopy. These H&E stained slides were studied for the tumour histology and classified into intestinal and diffuse according to Lauren's classification [4].

In addition, 4 µm sections were cut from a paraffin block of tumour tissue and taken on a poly-L-lysine coated glass slide for Immunohistochemistry (IHC) to detect E-cadherin expression. E-cadherin immunostaining was done with monoclonal mouse anti-human E-cadherin clone NCH-38 (DAKO). Staining was done according to the manufacturer's protocol.

Gastric and colonic normal mucosal sections away from the site of the tumour, and normal gastric glands between tumour cells, were used as positive controls. The fibroblasts and lymphocytes in these distant samples and inside tumour areas were considered as negative controls.

The slides are then examined under microscope and intensity of E-cadherin staining was graded according to study by Jawhari A et al., [23].

Scoring and evaluation:

Abnormal expression:

Score 0- No staining.

Score 1- Cytoplasmic staining without membranous staining.

Score 2- Cytoplasmic and membranous staining in the same case.

Normal expression:

Score 3- Normal membranous immunoexpression.

Jawhari scores were evaluated as absence of membranous expression (scores 0 and 1) versus the presence of membranous expression (scores 2 and 3) in intestinal and diffuse adenocarcinoma [23,24].

STATISTICAL ANALYSIS

Statistical analysis of the data was done by Chi-square test using Epi Info software. The p-value is 0.00001. Probability value of <0.05 was considered significant.

RESULTS

Out of 70 cases, which were confirmed as gastric adenocarcinoma, out of which 48 were gastric biopsies and 22 were gastrectomy specimens. The age of the patients ranged from 25-75 years and majority of cases 30 (42.85%) were seen in 5th to 6th decade [Table/Fig-1]. Out of 70 cases, 48 (68.57%) were males, and 22 (31.42%) were females with male to female ratio of 2.18:1 [Table/Fig-1]. Most of the cases 38 (54.28%) in the present study were located in the pyloric antrum [Table/Fig-2]. The common symptom observed in our study was weight loss (40%) followed by anorexia (34.2%) [Table/Fig-3]. Of the total 70 cases, 40 cases (57.14%) are intestinal and 30 cases (42.85%) are diffuse type [Table/Fig-4]. Most of the intestinal type gastric carcinoma 24/40 (60%) showed score 3 E-cadherin positivity, whereas diffuse type gastric carcinoma 14/30 (47%) showed score 0 E-cadherin staining [Table/Fig-4]. Membranous staining of E-cadherin was seen in 34 cases (85%) of intestinal gastric cancer, whereas non membranous staining of E-cadherin was seen in 21 cases (70%) of diffuse gastric cancer [Table/Fig-5-9].

Age group (years)	Male n (%)	Female n (%)	Total n (%)
<25	-	-	-
25-35	1 (2.08)	1 (4.54)	2 (2.85)
36-45	6 (12.5)	3 (13.63)	9 (12.85)
46-55	8 (16.66)	2 (9.09)	10 (14.28)
56-65	19 (39.58)	11 (50)	30 (42.85)
66-75	14 (29.16)	5 (22.72)	19 (27.14)
Total	48 (68.57)	22 (31.42)	70

[Table/Fig-1]: Age and gender-wise distribution of cases (N=70)

Location	Cases	Percentage
Cardia	13	18.57
Fundus	05	7.14
Corpus	14	20
Pyloric antrum	38	54.28

[Table/Fig-2]: Distribution of cases according to location.

Symptoms	No. of Cases (%)
Abdominal pain	5 (7.14)
Nausea/vomiting	8 (11.42)
Weight loss	28 (40)
Anorexia	24 (34.28)
Early satiety	3 (4.28)
Dysphagia	2 (2.85)

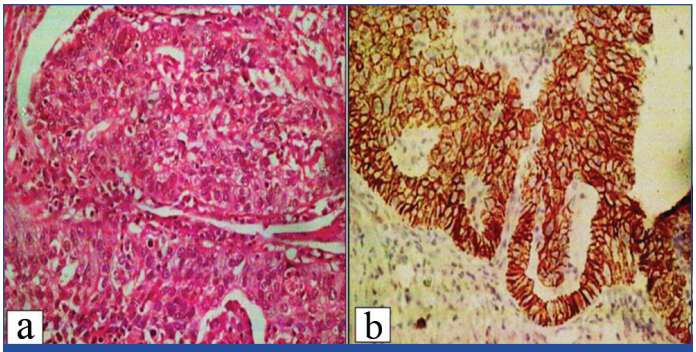
[Table/Fig-3]: Symptom analysis in patients of gastric cancer.

E-cadherin Score		Intestinal n (%)		Diffuse n (%)		p-value
0	Abnormal expression	2 (5%)	16 (40%)	14 (46.66%)	26 (86.65%)	<0.05
1		4 (10%)		7 (23.33%)		
2		10 (25%)		5 (16.66%)		
3	Normal expression	24 (60%)		4 (13.33%)		
Total		40 (57.14%)		30 (42.85%)		

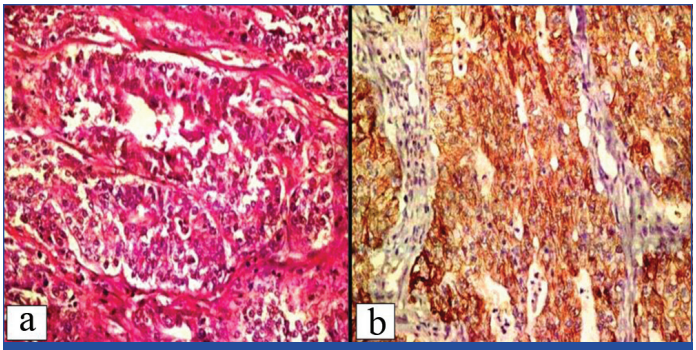
[Table/Fig-4]: Expression of E-cadherin (by score) in gastric cancer by histological type.

E-cadherin expression	Intestinal	Diffuse
Membranous staining	34 (85%)	9 (30%)
Non membranous staining	6 (15%)	21 (70%)

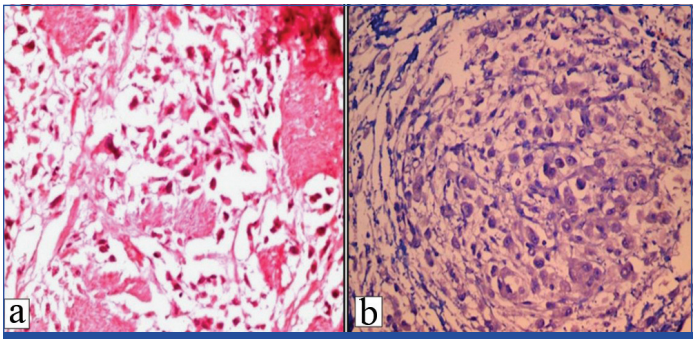
[Table/Fig-5]: E-cadherin expression (Membranous versus non membranous staining) in gastric cancer according to histological types.



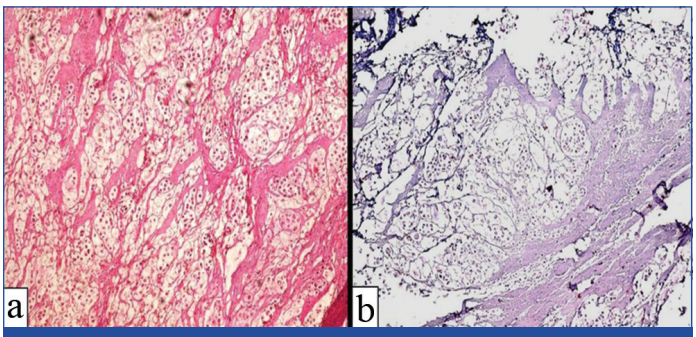
[Table/Fig-6]: Intestinal type gastric adenocarcinoma 40X: a) H&E showing tumour cells arranged in glandular pattern; b) E-cadherin membranous staining.



[Table/Fig-7]: Intestinal type gastric adenocarcinoma 40X: a) H&E showing tumour cells arranged in focal glandular and nesting pattern; b) E-cadherin membranous staining and cytoplasmic.



[Table/Fig-8]: Diffuse type adenocarcinoma stomach 40X: a) H&E showing poorly cohesive and singly scattered tumour cells; b) E-cadherin cytoplasmic expression.



[Table/Fig-9]: Diffuse type adenocarcinoma stomach 10X: a) H&E showing poorly cohesive and singly scattered tumour cells; b) E-cadherin absent expression.

DISCUSSION

E-cadherin, a transmembrane glycoprotein has an essential role in the homotypical cell-cell adhesion and involved in the complex process of invasion and metastasis [25-27]. Reduced or absent expression of E-cadherin causes dissociation of the cells by loosening of cell junctions and in a way acts as a tumour suppressor [28]. According to many studies, the role of E-cadherin in carcinogenesis is not only limited to invasion and metastasis, but also involved in modulating intracellular signalling, and thus promoting tumour growth [29,30]. The presence or absence of membranous staining is the most valuable criteria in evaluating E-cadherin expression and gastric carcinoma histotypes [31-33]. In the present study, we want to see the association of E-cadherin membranous or non membranous expression with gastric carcinoma histotypes in our local population.

The Jawhari scoring system is an effective qualitative approach to evaluate E-cadherin expression in gastric cancer [23]. Abnormal expression of E-cadherin has been found to have a wide range of variation in different series, from 24% to75% [23,25,34]. Abnormal expression corresponds to score 0,1,2 of Jawhari scoring [23] which implies to absent or cytoplasmic or cytoplasmic and membranous staining. Abnormal expression was found in 16/40 cases (40%) of intestinal type and 26/30 cases (86.65%) of diffuse type [Table/Fig-4]. The present study findings correlate well with observations of Almeida PR et al., and Zhou Y-N et al., Sundarama S et al., Sisodiya N and Jagani R; Sridevi C et al., Kishan J and Moula MC; Sadanandan A and Arunraj CN [Table/Fig-10] [6,24,25,35-38], so abnormal expression was found in total 42 cases (60%) of our samples including both intestinal and diffuse types. Normal expression corresponds to score 3, which implies membranous staining seen in 24/40 cases (60%) of intestinal type gastric cancer and 4/30 cases (13.33%) of diffuse type gastric cancer.

Study	E-cadherin staining			
	Normal expression		Abnormal expression	
	Intestinal	Diffuse	Intestinal	Diffuse
Present study	24/40 (60%)	4/30 (13.33%)	16/40 (40%)	26/30 (86.65%)
Almeida PR et al., 2010 [24]	36/40 (90%)	0	4/40 (10%)	34/34 (100%)
Zhou Y-N et al., 2002 [25]	72/108 (66.66%)	11/40 (27.5%)	36/108 (33.33%)	29/40 (72.5%)
Sundarama S et al., 2010 [35]	0	0	10 /10 (100%)	10/10 (100%)
Sisodiya N and Jagani R, 2016 [36]	12/17 (70.58%)	3/10 (30%)	5/17 (29.41%)	7/10 (70%)
Sridevi C et al., 2019 [37]	14/42 (33.33%)	0	28/42 (66.66%)	18/18 (100%)
Kishan J and Moula MC, 2019 [38]	20/40 (50%)	5/39 (12.82%)	20/40 (50%)	34/39 (87.17%)
Sadanandan A and Arunraj CN, 2020 [6]	35/43 (81.4%)	1/22 (4.54%)	8/43 (18.6%)	21/22 (95.45%)

[Table/Fig-10]: Comparison of normal and abnormal E-cadherin expression in intestinal and diffuse type gastric adenocarcinomas in similar studies [6,24,25,35-38].

Most important consideration in E-cadherin expression is presence of E-cadherin in cellular membranes (Jawhari A et al., [23] scores 2 or 3) versus absence (scores 0 or 1) of E-cadherin in cellular membranes, which is the site where this adhesion molecule acts.

In present study, correlation was found between membranous E-cadherin expression (score 2 or 3) and the intestinal histotype 34 cases (85%) and absence of membranous expression (scores 0 or 1) and the diffuse histotype 21 cases (70%) of gastric cancer. Similar expression was also found in studies done by Almeida PR et al., Sridevi C et al., Carpenter PM et al., Lazar D et al., and Wu ZY et al., [Table/Fig-11] [24,37,39-41].

The identification of E-cadherin in the cytoplasm (abnormal expression) and not on the membrane (normal expression) is consistent with the notion that loss of membrane E-cadherin promotes tumour disaggregation and dissemination. Abnormalities of E-cadherin implicated in tumour spread include complete absence of expression, which prevents any E-cadherin-mediated adhesion between affected tumour cells, and mutation of the E-cadherin molecule [41-43].

Authors	E-cadherin staining			
	Membranous staining		Non membranous staining	
	Intestinal	Diffuse	Intestinal	Diffuse
Sridevi C et al., [37]	28 (66.66%)	3 (16.66%)	14 (33.33%)	15 (83.33%)
Almeida PR et al., [24]	36 (90%)	23 (67.64%)	4 (10%)	11 (32.35%)
Carpenter PM et al., [39]	60 (69%)	25 (45%)	27 (31%)	31 (55%)
Lazar D et al., [40]	26 (92.87)	3 (17.64)	12 (42.85)	14 (82.35)
Wu ZY et al., [41]	9 (81.8)	7 (36.8)	2 (18.2)	12 (63.2)
Present study	34 (85%)	9 (30%)	6 (15%)	21 (70%)

[Table/Fig-11]: Comparison of membranous and non membranous E-cadherin expression in intestinal and diffuse type gastric adenocarcinomas in similar studies [24,37,39-41].

Limitation(s)

In the present study, expression of E-cadherin was studied based on histological subtype of gastric carcinoma. E-cadherin expression based on histological grade of the tumour and lymphnode status was not done in the present study.

CONCLUSION(S)

Immunohistochemical expression of E-cadherin showed membranous positivity in normal gastric mucosa. In gastric carcinoma, the expression gradually changed from membranous to cytoplasmic or absent staining from intestinal to diffuse histological subtypes. Since abnormal expression of E-cadherin is associated more with diffuse type gastric cancers. This can be used as a negative prognostic factor, if tumour staging, grading and lymph node status are correlated with the IHC expression and histological subtypes in future studies. Adequate patient follow-up to allow comparison of prognosis and survival rate between tumour subgroups and their IHC profiles, needs to be done in future studies.

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