Clinicopathological Significance of E-Cadherin Immunoexpression in Gastric Carcinoma

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ABSTRACT

Introduction: Gastric cancer remains the second commonest cancer in morbidity and mortality worldwide. Cadherin is a superfamily of calcium-mediated membrane glycoproteins, which are responsible for the homotypic cell to cell adhesion. These adhesion molecules may play an important role in carcinogenesis and metastasis. A cross sectional study aimed to find out the clinicopathological correlation of E- Cadherin by Immunohistochemistry staining (IHC) as a prognostic marker was carried out.

Material and Methods: Present study was a cross sectional study conducted for the period of two months. Data for the study was obtained by using Patient diagnosis, case details and examination of tissue sections. Cases were selected based on the inclusion and exclusion criteria. Permission is taken from IEC before starting the study. Tissue samples of gastric adenocarcinoma were obtained from gastrectomy and biopsy specimens who were analysed using immunohistochemical staining. Statistical analysis is done using SPSS 23 version.

Results: Study population was represented by 30 patients with a mean age of 59.34 years (Ranging from 30 Years. to 80 Years.). We have noted aberrant, negative or heterogeneous expression of the E-Cadherin for 14 of the cases (46.67%). Our results showed no existence of a relation between E-Cadherin expression and the tumours localization, being observed negative immuno-histochemical or heterogeneous reactions in 43.8% of the gastric antral carcinomas, 43.75% of the gastric body carcinomas and 50% of the cardial carcinomas, 66.7% of the pangastric carcinomas.

Conclusion: Abnormal expression of E-Cadherin is associated with the malignant behaviour of gastric carcinoma and is seen more frequently in diffuse type of gastric carcinoma along with advance gastric carcinoma cases. Therefore, it might serve as a marker of differentiation.

Keywords: E-Cadherin, Immunohistochemistry, Clinicopathological

INTRODUCTION

Gastric cancer is the second leading cause of morbidity and mortality worldwide as far as cancer patients are concerned. According to the most recent estimates, gastric cancer accounts for 8% of the total cancer cases and 10% of the deaths for all cancers in the world.[1] Lauren has classified gastric cancer into diffuse and intestinal type that are different in regard to epidemiology, etiology, pathogenesis and behaviour.[2] Cadherin is a superfamily of calcium-mediated membrane glycoproteins. They binds to cytosolic proteins namely α- catenin, β- catenin, and, γ-catenin which in turn are linked to the actins to form the intracytoskeleton.[3] The cadherins are responsible for the homotypic cell-cell adhesion, Therefore, these play an important role in carcinogenesis and metastasis. E-Cadherin is expressed in all epithelial cell types. Underexpression of the E-Cadherin is found in gastric, hepatocellular, oesophageal, breast, prostatic, bladder and gynaecological carcinomas and correlates with infiltrative and metastatic ability.[4]

Currently there is no satisfactory tumour marker for diagnosis or monitoring the disease progression. The most frequently used tumour markers in gastric cancer are carcinoembryonic antigen (CEA) and CA19-9, but only a small proportion of patients have higher levels of these markers. With the current advancements in molecular biology, the prognostic and diagnostic indication for cancer has changed in the last few decades. In the present study, E-Cadherin, was chosen as an exemplifying molecular marker for gastric carcinoma. The present cross sectional study aimed to investigate the clinicopathological significance of E- Cadherin by Immunohistochemistry staining (IHC) as a prognostic marker.

MATERIAL AND METHODS

The study was a cross sectional study conducted during May and June 2015 in a tertiary care hospital. Ethical approval was obtained from Institutional Ethics Committee prior to conducting the study and informed consent was obtained from all the cases. Sample size was 30 cases, which was calculated using the data from previous available literature and convenient sampling scheme. All diagnosed cases of gastric carcinoma and suspected gastric carcinoma cases were included in the study and all cases of lymphoma, squamous cell carcinoma, undifferentiated carcinomas and GIST (Gastro Intestinal Stromal Tumour) were excluded from the study. Tissue samples of gastric adenocarcinoma were obtained from gastrectomy and biopsy specimens which were formalin fixed, paraffin embedded. The normal gastric mucosa adjacent to tumour has been used as an internal positive control. Tumour staging is done in accordance with the unified TNM criteria for gastric cancer.

Standard immunohistochemical staining procedure was used for staining slides. Staining was scored independently by two observers and a high level of concordance was achieved. In case of disagreement, the slides were reviewed and a consensus view is achieved. The E-Cadherin expression in gastric carcinomas was levelled depending on the positive cells proportion found:

(I) Uniformly positive (+): Over 90% out of the tumoral cells are Immunostained with E- Cadherin at membranous level.

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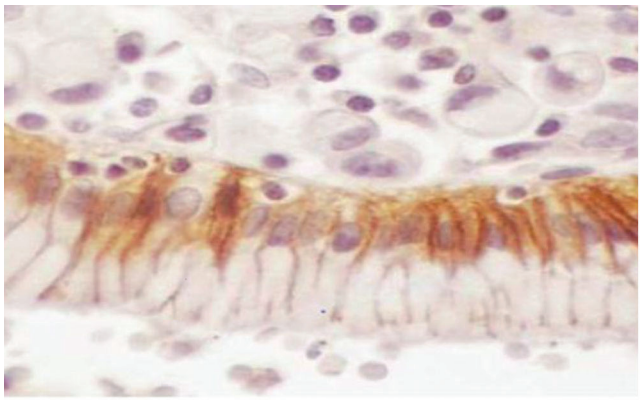
Clinico-morphological factors		E-Cadherin immunoexpression	
		Normal (n= 16)	**Aberrant (n=14)**
Lauren's classification	Intestinal type	12 (75%)	05 (36%)
	Diffused type	03 (19%)	07 (50%)
	Mixed type	01 (06%)	02 (14%)
Tumor grade	G_1	03 (19%)	01 (07%)
	G_2	07 (44%)	08 (57%)
	G_3	06 (37%)	05 (36%)
Lymphovascular invasion	Present	09 (56%)	08 (57%)
	Absent	07 (44%)	06 (43%)

Table-1: E-Cadherin immunoexpression in gastric carcinomas



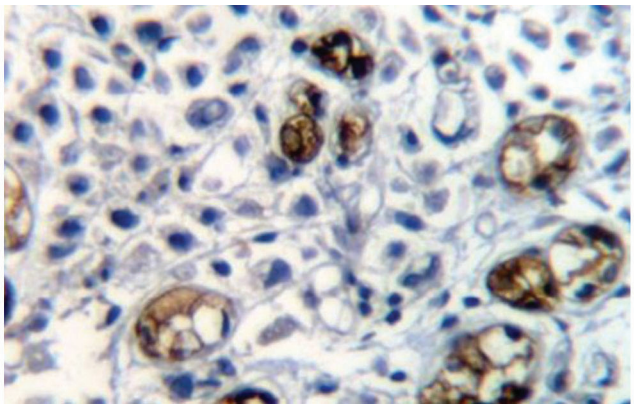


Figure-1: Normal gastric mucosa stained with E-Cadherin; **Figure-2:** Complete loss of E-Cadherin in diffused variety of gastric carcinoma

Socio-demographic factors		Gastric carcinoma cases (n=30)
Dietary Habits	Veg. diet	12 (40%)
	Non veg diet	18 (60%)
Previous history of any carcinoma	Yes	06 (20%)
	No	24 (80%)
Alcohol Intake	Yes	16 (53%)
	No	14 (47%)
Tobacco Chewing	Yes	08 (27%)
	No	22 (73%)
Family history of gastric carcinoma	Yes	04 (14%)
	No	26 (86%)
Family history of any carcinoma	Yes	17 (56%)
	No	13 (44%)

Table-2: Showing relation of socio-demographic factors with the incidence of gastric carcinoma

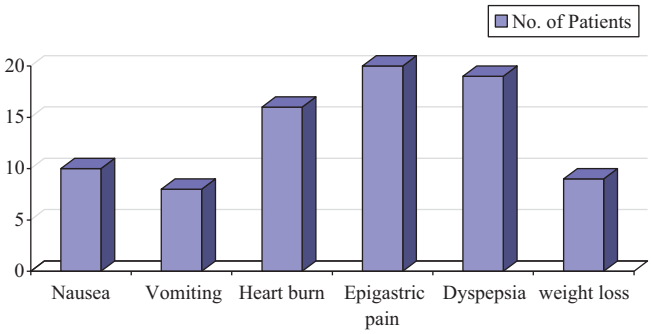


Figure-3: Showing relation of symptoms observed in gastric carcinoma patients

(II) Heterogeneous (±): Between 05 and 80% of the tumoral cells are immunostained at membranous and cytoplasmic level.

(III) Negative (-): Between 0 and 5% of the tumoral cells are immunostained.

STATISTICAL ANALYSIS

The data collected was analyzed using descriptive statistics for finding out the clinicopathological significance using Statistical Package for the Social Sciences (SPSS) Version 23.0.

RESULTS

Study population comprised of 30 patients (17 males and 13 females) with a mean age of 59.34 years (Ranging from 30 years to 76 years). In our study we observed that the homogeneous and intense stain for E-Cadherin of the epithelial cells membranes in the normal gastric mucosa, situated in the carcinomas' vicinity, which reflects the normal location of this molecule of intercellular adhesion. The immunostained normal mucosa had served as an internal positive control. We have noted aberrant, negative or heterogeneous expression of the E-Cadherin for 14 of the cases (46.67%). The aberrant E-Cadherin expression was noticed in close proportions in men (47.06%) and women (46.16%). We have also seen 44% carcinomas with aberrant immunohistochemical expression in patients with age ≤60 years and 60% carcinomas in patients ≥61 years of age. Our results showed no existence of a relation between E-Cadherin expression and the tumours localization, being observed negative immuno-histochemical or heterogeneous reactions in 43.8% of the gastric antral carcinomas, 43.75% of the gastric body carcinomas and 50% of the cardial carcinomas, 66.7% of the pangastric carcinomas. The E-Cadherin aberrant immunoexpression have been observed significantly more frequently in the diffuse type carcinomas in comparison to the intestinal type carcinomas.

Epigastric pain was the most common presenting symptom

followed by dyspepsia and heart burn. The findings of the study are summarized in Tables 1 and 2.

DISCUSSION

E Cadherin is an important molecule in cell adhesion and loss of E-Cadherin will disrupt proliferation inhibition and lead to more scattered types of tumor like diffuse type which have more malignant behaviour with poorly differentiated cells. We have demonstrated a significant correlation between E-Cadherin expression and tumor histology. In this study E-Cadherin influenced tumor depth of invasion but it was not significantly associated with lymph node metastasis. This reveals that preserved E-Cadherin expression does not necessarily lead to intact cell adhesion mechanisms. It might be a result of malfunctioned E-Cadherin protein despite normal staining in some cases

In the present study, as in many previously reported studies, abnormal or absent E-Cadherin immunoreactivity was observed in gastric adenocarcinomas, and the proportion of cases displaying abnormal E Cadherin immunoreactivity was greater in diffuse adenocarcinomas. The identification of E-Cadherin in the cytoplasm and not on the membrane is consistent with the notion that loss of membrane E-Cadherin promotes tumor disaggregation and dissemination. Since the normal role of E-Cadherin is to maintain homotypic adhesion in epithelial cells, the abnormal E-Cadherin expression leads to discohesion of cancer cells and there by facilitating their permeation into the gastric stroma. This is particularly relevant to diffuse adenocarcinoma, which spreads extensively and has a considerably greater likelihood to express little or no E-Cadherin[5] This preliminary immunohistochemical examination of E-Cadherin raises interesting questions that warrant further study. Analysis of these cases for mutations in the E-Cadherin gene sequence may yield information that better defines the molecular basis of the E-Cadherin alteration responsible for the paranuclear distribution. Although some studies have shown the reduction or absence of E-Cadherin in gastric carcinomas, the results regarding the correlations between the aberrant expression of E-Cadherin, the clinicopathological factors and gastric cancer patients' survival are contradictory.[6] In our study, we have proposed to investigate the E-Cadherin immunohistochemical expression in gastric carcinomas, as well as in the peritumoral mucosa. We noticed that homogeneous and intense immunostaining for E-Cadherin of the epithelial cells' membranes of the gastric mucosa situated near the carcinomas, which reflects the normal localization of this intercellular adhesion molecule. The immuno-marked areas of normal mucosa served as positive internal control. The atrophic chronic gastritis areas and the E Cadherin aberrant immunoreactions have been observed significantly more frequently in the diffuse-type carcinomas in comparison to the intestinal-type carcinomas, thus these data emphasize the strong relation between the Lauren's classification of the gastric carcinomas and the immunohistochemical expression of the E-Cadherin cellular adhesion molecule. The E-Cadherin aberrant immunohistochemical expression was noted more frequently in weakly differentiated carcinomas in comparison to the moderately differentiated and well differentiated carcinomas. The significant correlation between the E-Cadherin atypical immunoreaction and the tumoral grade is also signaled by other authors.[6-8]

CONCLUSION

The results obtained in our study suggest the important role of E-Cadherin in the development of differentiated forms of gastric carcinoma, in this case being a histological differentiation marker. However, there is no significant clinicopathological correlation between clinical presentation symptoms and pathological grading.

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