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Original Research Article

HISTOPATHOLOGICAL STUDY OF GASTRIC CARCINOMA AND EVALUATION OF HER2/NEU AND E-CADHERIN EXPRESSION

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ABSTRACT

Background: Gastric carcinoma is the leading cause of cancer-related mortality worldwide. HER2/neu is a transmembrane receptor tyrosine kinase, and E-cadherin, which is a cell attachment molecule, has been reported as a tumor promoter, that is, connected to tumor progression and metastasis, and also in consideration of therapeutic response. Analysis of their expression patterns also gives information towards targeted therapy and prognostic evaluation. The current study aimed to assess the histopathological spectrum of gastric carcinoma and evaluate the expression of HER2/neu and E-cadherin in these cases. **Materials and Methods:** This retrospective study was done on 40 histologically proven cases of gastric carcinoma. Classification of the tumor samples was performed on the basis of the Lauren and WHO classification by means of hematoxylin and eosin staining. The IHC was done to evaluate HER 2 /neu (0-3+) and E-cadherin (membranous vs red / lost cell membrane, and cytoplasmic rearrangement). FISH was additionally used to analyse cases in which HER2 expression was equivocal (2+). Biomarker expression was correlated with clinicopathological characteristics and was analysed. **Result:** Of the 40 cases included in the study, 70% were above 50 years of age, and 65% were male. The antrum (45%) was the most frequent tumor site, and the intestinal type (60%) was predominant. HER2 positivity (IHC 3+) was observed in 15% of cases, mainly in intestinal-type carcinomas. E-cadherin loss was detected in 25% of cases, with a higher frequency in diffuse-type cancers. Cytoplasmic shift of E-cadherin occurred in 55%. Survival analysis showed significantly poorer outcomes with E-cadherin loss (20% 2-year survival, HR 2.9, p=0.004) and with combined HER2 positivity and E-cadherin loss (0% survival, HR 4.1, p<0.001). **Conclusion:** HER2/neu overexpression was associated predominantly with intestinal-type gastric carcinoma, while E-cadherin loss correlated strongly with diffuse-type cancers and adverse outcomes. Combined HER2 positivity and E-cadherin loss predicted the worst survival, suggesting that dual biomarker evaluation may improve prognostic accuracy and guide personalized treatment strategies in gastric carcinoma.

INTRODUCTION

Gastric carcinoma (GC) is one of the leading causes of cancer-related mortality worldwide. The incidence of GC is on the rise, and according to data from GLOBOCAN 2020, gastric cancer is rated as the fifth common cause of malignancy, and it is the fourth leading cause of cancer death globally. Its incidence is high in Eastern Europe, East Asia, and parts of South America.[1] The incidence of gastric carcinoma in India shows geographical variations with higher prevalence in Northeastern states and coastal regions in the South.[2] In many cases, the prognosis of gastric carcinoma is poor because of late-stage diagnosis; therefore, this highlights the importance of early detection and precise tumor characterization for treatment. Gastric carcinoma is heterogeneous in morphology, behavior, and molecular profile. The most commonly used classification for gastric carcinoma is Lauren's classification, which differentiates gastric carcinoma into intestinal and diffuse types.[3] The intestinal type is from glandular structures with a background of chronic gastritis and intestinal metaplasia. In diffuse type, there is

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predominance of poorly cohesive cells often with signet ring morphology and usually shows aggressive clinical behavior.[4] Accurate histological subtyping helps in clinical decision-making and prognosis. Molecular pathology has made significant contributions to our comprehension of gastric carcinoma. It is known that some biomarkers have prognostic and therapeutic significance. A proto-oncogene that codes a transmembrane tyrosine protein kinase receptor of cellular proliferation and survival pathways is found on chromosome 17q21, called the HER2/neu.[5] Approximately 7%-34% of gastric carcinomas have been shown to have HER2 overexpression and gene amplification, which is more common among the intestinal type and gastroesophageal junction tumors.[6] The clinical significance of HER2 as a gastric carcinoma marker was proven by the ToGA trial, which proved that advanced HER2-positive patients had better survival rates when using trastuzumab along with chemotherapy.[7] Therefore, HER2 testing is now an integral part of the pathological evaluation of advanced gastric carcinoma. Consequently, HER2 testing has become a standard component of pathological evaluation in advanced gastric carcinoma. E-cadherin is another major biomarker, which is a cell adhesion molecule that is calcium-dependent on chromosome 16q22.1. E-cadherin is important in epithelial integrity and polarity. Genetic or epigenetic loss of E-cadherin expression facilitates dissociation of tumor cells, invasion, and metastasis.[8] Such a change is specific to the pathologic morphology of the diffuse type of gastric carcinoma and is also linked with poor prognosis.[9] Germline CDH1 mutations also have an association with hereditary diffuse gastric cancer (HDGC), which is an autosomal dominant syndrome and penetrant.[10] Assessment of the HER2/neu and E-cadherin expression in gastric carcinoma not only helps prognosticate but also helps determine patients who are likely to respond to targeted therapies. Although HER2 positivity suggests that the patient might become a candidate for the anti-HER2 monoclonal antibody treatment, loss of E-cadherin expression means aggressive tumor biology and the possibility of losing control over the disease with intensive surveillance required. With this background, the present study aimed to evaluate the histopathological spectrum of gastric carcinoma and to evaluate HER2/neu and E-cadherin expression in gastric carcinoma cases.

MATERIALS AND METHODS

This was a retrospective, observational study carried out at the Department of Pathology, Mahavir Institute of Medical Sciences, Vikarabad, Telangana. Institutional ethical approval was obtained for the study in accordance with the Declaration of Helsinki. Written consent was obtained from all the participants of the study after explaining the nature of the study in the vernacular language.

Inclusion Criteria

- Adult patients with histologically confirmed primary gastric adenocarcinoma.
- Males and females
- Biopsy samples were received by the Department of Pathology
- Written consent signed by the patients.

Exclusion Criteria

- Recurrent gastric cancer,
- Neoadjuvant chemotherapy or radiotherapy before biopsy
- Inadequate or autolysed tissue,
- Cases with incomplete clinical data.

A total of (n = 40) consecutive, histologically confirmed cases of gastric carcinoma (endoscopic biopsies and gastrectomy specimens) were included for analysis during the study period.

Histopathology: All the samples received were fixed in 10% neutral buffered formalin, processed routinely, and embedded in paraffin. The blocks were prepared with sections of 4 µm and stained with hematoxylin and eosin. Lauren's classification was used for grading and typing of gastric carcinoma. Tumor grade and depth of invasion were recorded, and staging information was recorded from the surgical reports as per AJCC guidelines.

Immunohistochemistry (IHC): IHC was done for all the samples for HER2/neu and E-cadherin. The sections were deparaffinized, rehydrated, and then subjected to antigen retrieval. IHC was done using validated monoclonal antibodies against HER2/neu and E-cadherin with manual methods. A positive and negative control was used in each case.

HER2/neu interpretation criteria (Hofmann/ToGA modifications): 0 = no reactivity or membranous reactivity in <10% of tumor cells; 1+ = faint/barely perceptible membranous staining in ≥10% tumor cells; 2+ = weak to moderate complete, basolateral, or lateral membranous staining in ≥10% tumor cells (equivocal); 3+ = strong complete, basolateral, or lateral membranous staining in ≥10% tumor cells (positive). Cases with 2+ (equivocal) staining were recommended for HER2 gene amplification testing by fluorescence in situ hybridization (FISH), where material and resources permitted.

E-cadherin interpretation: E-cadherin expression was evaluated for membranous staining of tumor cells. Cytoplasmic staining was noted separately but not considered positive for membranous expression. Expression was classified as: preserved (strong continuous membranous staining in >70–80% of tumor cells), reduced/heterogeneous (variable membranous staining or discontinuous staining in 10–70% cells), or lost (absent membranous staining in >90% of tumor cells). Where available, correlation with morphological patterns (signet-ring cells) was documented.

Statistical Analysis: All the available data were refined, segregated, and uploaded to an MS Excel

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spreadsheet and analyzed by SPSS version 25 in Windows format. Continuous variables were represented as mean, standard deviation, frequency, and percentage. Categorical variables were calculated by the Chi-square test for associations between biomarker expression (HER2 positivity and E-cadherin loss). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 40 cases were studied during this study. Most of the patients 70% were aged above 50 years, and there was a male predominance with 65% of total cases. The anatomical location revealed that most often involved areas were the antrum (45%), body (30%), and cardia (25%). Histopathology showed that 60% of cases were intestinal-type carcinoma, followed by 35% diffused type and mixed-type 5%. As for tumor grade, the most frequent type was poorly differentiated (42.5%), moderately differentiated tumors included (37.5%), and well-differentiated 20%. This would imply that there is a high frequency of high-grade histology and intestinal-type morphology in the older personnel, where the majority of them are males with antrum as the most frequent site of tumor occurrence.

Table 1: Demographic and clinicopathological characteristics (n=40)

Characteristic	Category	Frequency	Percentage
Age	< 50 years	12	30.0
	> 50 years	28	70.0
Gender	Male	26	65.0
	Female	14	35.0
Tumor location	Antrum	18	45.0
	Body	12	30.0
	Cardia	10	25.0
Histopathological type	Intestinal type	24	60.0
	Diffuse-type	14	35.0
	Mixed-type	2	5.0
Tumor grade	Well documented	8	20.0
	Moderately differentiated	15	37.5
	Poorly differentiated	17	42.5

The expression of HER2/neu via the immunohistochemical method can be given in Table 2. In 45% of the cases, there was an HER2 score 0 (negative); 25% cases had a score 1+ (negative). Equivocal expression (2+) was observed in 15 percent of patients, and strong positive expression (3+) was also observed in 15 percent of patients. In sum, 15% of the patients were HER2-positive (3+ staining, or, when this was 2+, FISH also positive). This comparatively low HER2 positivity rate reflects that in this cohort, only a minority of gastric carcinomas are possible candidates to receive HER2-directed therapy, consistent with international evidence that there is also a diverse range of HER2 expression throughout the gastric cancer population and histological subgroups.

Table 2: HER2/neu Immunohistochemical Expression

HER2/neu Score	Interpretation	Frequency	Percentage
0	Negative	18	45
1+	Negative	10	25
2+	Equivocal	6	15
3+	Positive	6	15
Overall HER2+ (3+)		6	15
HER2 positivity defined as IHC 3+ or IHC 2+ with FISH confirmation			

The E-cadherin expression pattern of the cohort is presented in Table 3. The analysis of the table shows that a normal membranous pattern of staining (>70% tumor cells) was seen in 30% of cases. Reduced expression (10–69% cells) was observed in 45% of cells. Complete loss of E-cadherin expression was seen in (<10% cells) in 25%. The E-cadherin was shifted to the cytoplasm in 55% of the cases, whereas in 45% of the cases, it lacked this manifestation. There is a preponderance of decreased expression and cytoplasmic relocation, indicating that cell-to-cell adhesion is severely impaired in most gastric carcinomas, especially in aggressive variants. Amplification or mislocalization of E-cadherin may be central to invasion, metastasis, and poor outcome, particularly in diffuse-type gastric cancers.

Table 3: E-Cadherin Expression Patterns

E-Cadherin Staining	Pattern	Frequency	Percentage
Membranous Staining	Normal (>70% tumor cells)	12	30
	Reduced (10—69% cells)	18	45
	Lost (< 10% cells)	10	25
Cytoplasmic Shift	Present	22	55
	Absent	18	45

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Table 4 depicts the correlation between HER2/neu and E-cadherin changes and gastric carcinoma subtypes. The level of HER2 positivity was the highest in intestinal-type tumors (20.8%), intermediate in diffuse-type (7.1%), and non-existent in mixed-type tumors. Loss of e-cadherin was frequently found in the diffuse-type tumor (42.9%) as compared to the intestinal-type (16.7%) and none in the mixed-type. The extent of cytoplasmic shift of E-cadherin was high in diffuse-type (85.7%) and mixed-type (100%) compared with the intestinal-type (33.3%). These tendencies indicate that HER2 positivity has a higher connection with intestinal morphology, but the E-cadherin alteration, particularly loss and mislocalization, is closely related to the diffuse-type histology, which occurs due to their divergent pathogenetic pathways.

Table 4: Association of HER2/neu and E-Cadherin with Tumor Subtypes

Parameter	Intestinal-type (n =24)	Diffuse-type (n=14)	Mixed-type (n =2)
HER2+ (3+)	5 (20.8%)	1 (7.1%)	0 (0.0%)
E-Cadherin Loss	4 (16.7%)	6 (42.9%)	0 (0.0%)
Cytoplasmic Shift	8 (33.3%)	12 (85.7%)	2 (100%)

The 2-year survival analysis is shown in Table 5 along with the biomarker status. HER2-positive patients had a survival of 33.3%, and the resultant hazard ratio was 1.8 (p=0.08), which shows that there is a tendency for poor outcomes, although not statistically significant. There was a reduction in survival rate of 20% with a hazard ratio of 2.9 (p=0.004) with the loss of E-Cadherin. The cases that showed both positivity to HER2 and loss of E-cadherin had 0% survival rate at 2 years with a hazard ratio of 4.1 (p<0.001). This demonstrates that combined biomarker assessment is of prognostic value, with combined abnormalities indicating aggressive disease with very poor patient outcomes.

Table 5: Survival Analysis at 2-Year Follow-up

Biomarker Status	2-Year Survival Rate	Hazard Ratio (95% CI)	p-value
HER2+ (3+)	33.30%	1.8 (0.9 - 3.6)	0.08
E-Cadherin Loss	20.00%	2.9 (1.4 - 6.1)	0.004
Both Abnormal*	00.00%	4.1 (1.9 - 8.8)	<0.001*
Both abnormal = HER2+ (3+) and E-Cadherin loss			

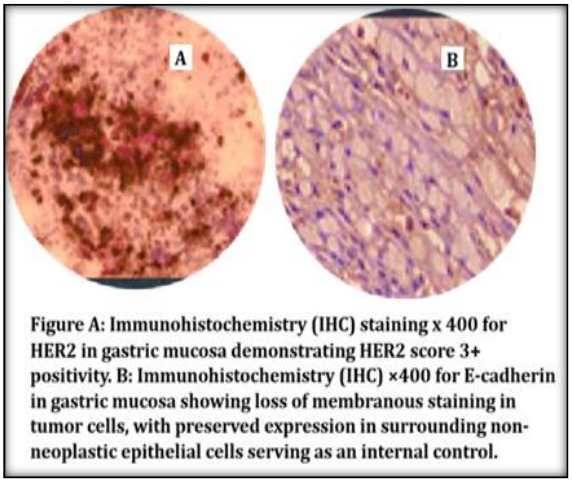

Figure A: Immunohistochemistry (IHC) staining x 400 for HER2 in gastric mucosa demonstrating HER2 score 3+ positivity. B: Immunohistochemistry (IHC) ×400 for E-cadherin in gastric mucosa showing loss of membranous staining in tumor cells, with preserved expression in surrounding non-neoplastic epithelial cells serving as an internal control.

DISCUSSION

In the current study, 40 cases of gastric carcinoma were studied in our tertiary care hospital. The results of this study showed that most of the patients (70%) were in the category of above 50 years age and this is in agreement with other studies that have stated that gastric cancer often involves older patients because of accumulation of exposures to environmental factors, chronic gastritis, and random genetic mutations over many years of life.[11,12] There was a male preponderance (65%) in our study. This is consistent with the epidemiology of the disease across the world and is believed to be associated with a greater incidence of underlying risk factors such as smoking, alcohol usage, and eating habits in men.[13] Most of the carcinomas (45%) occurred in the antrum, unlike other studies involving Indians and Asians, whose gastric cancers are still more prevalent than those affecting the proximal region, perhaps due to variation in the prevalence of Helicobacter pylori and different carcinogenic intake in various regions.[14] Histologically, the intestinal type (60%) prevailed over the diffuse type (35%), and this was consistent with the findings of areas with a high background of chronic gastritis and intestinal metaplasia.[15] About 42.5% of cases were made up of poorly differentiated tumors, which further indicates the aggressiveness of most of the lesions conducted in tertiary centers. In this study, the most common location of carcinoma was the antrum (45%). Similar trends have been found in Asian and Indian cohorts, where gastric cancers remained more frequently in distal regions as compared to proximal areas because of regional differences in Helicobacter pylori infections and dietary carcinogen exposure.[4] Histologically, the intestinal type (60%) prevailed over the diffuse type (35%), and this was consistent with the findings of regions with a high background of chronic gastritis and intestinal metaplasia.[15] In this study, 42.5% of cases comprised poorly differentiated tumors, which further indicates the aggressiveness of most of the lesions conducted in tertiary centers.

HER2/neu overexpression (IHC3+) was found in 15% of our cases, and most of them were intestinal type. These rates are within the range of global

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reports on gastric cancers, which reported (7 -34%) overexpression (IHC3+) in overall cases. Our results are comparable to Indian data, where the positivity rate is similar. The differences in the positivity rates of our cases with the global findings could be because of differences in scoring methods and heterogeneity of population.[16,17] In this study, we found a preferential association of the tumors with intestinal histology, which could be because of distinct molecular carcinogenesis pathways between Lauren subtypes.[18] Our results did not show the significance of HER2 positivity (p=0.008); however, there was a trend towards poorer outcomes, which is in agreement with previous studies that show that HER2 overexpression confers aggressiveness to gastric cancers.[19] In our study, we found E-cadherin loss in 25% of cases, which was mostly seen in diffuse type of tumors (42.5%) compared to intestinal type (16.7%). This shows that E-cadherin dysfunction plays a role in the pathogenesis of diffuse gastric carcinoma because of impaired cell-cell adhesion and also increases its invasiveness.[20,21] A cytoplasmic shift of E-cadherin was found in 55% of cases, which, because of functional alteration, even in the presence of preserved membranous staining as found by immuno-histochemical studies.[22] Notably, HER2 positivity and E-cadherin loss in patients yielded a poor prognosis, with no 2-year survivors and a hazard ratio of 4.1. The synergistic effect of this result has been hypothesized in earlier studies, where the synergy between changes in the growth factor signaling and adhesion pathway enhances the aggressiveness and metastasis of the tumor.[23,24] Such results demonstrate the possible benefit of evaluating two biomarkers in prognostication and treatment planning. Our findings support the fact that gastric carcinoma is heterogeneous and that stratification on the basis of biomarkers is essential. HER2 testing will continue to be necessary in selecting patients who are candidates to receive targeted therapy, and after all, E-cadherin testing can offer prognostic evaluations, particularly in diffuse-type cancers. These results should be confirmed by larger and multi-centered investigations and should be broadened to an investigation of combined biomarker panels as a subject of personalized management in the Indian population.

CONCLUSION

Within the limitations of the current study we found HER2/neu overexpression was associated predominantly with intestinal-type gastric carcinoma, while E-cadherin loss correlated strongly with diffuse-type cancers and adverse outcomes. Combined HER2 positivity and E-cadherin loss predicted the worst survival, suggesting that dual biomarker evaluation may improve prognostic accuracy and guide personalized treatment strategies in gastric carcinoma.

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